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Associations of proteomics with kidney function and blood pressure in the general population

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Jiesheng Lin

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Ludwig-Maximilians-Universität München

Erstes Gutachten:	Prof. Dr. Barbara Thorand
Zweites Gutachten:	Prof. Dr. Annette Peters
Drittes Gutachten:	Priv. Doz. Dr. Stefanie Steiger
Viertes Gutachten:	Prof. Dr. Claudia Veigel
Dekan:	Prof. Dr. med. Thomas Gudermann
Tag der mündlichen Prüfung:	13.11.2024

Affidavit

LMU
LUDWIG-MAXIMILIANS-UNIVERSITÄT MÜNCHEN
Promotionsbüro Medizinische Fakultät
MMRS

Affidavit

Lin, Jiesheng
Surname, first name

Ingolstädter Landstraße 1
Street

85764, Neuherberg, Germany
Zip code, town, country

I hereby declare, that the submitted thesis entitled:

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Promotionsbüro
Medizinische Fakultät

MMRS

Confirmation of congruency between printed and electronic version of the doctoral thesis

Lin, Jiesheng
Surname, first name

Ingolstädter Landstraße 1
Street

85764, Neuherberg, Germany
Zip code, town, country

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is congruent with the printed version both in content and format.

Munich, November 19, 2024
place, date

Jiesheng Lin
Signature doctoral candidate

Table of content

List of abbreviations

BP	Blood pressure
CKD	Chronic kidney disease
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
eGFR	Estimated glomerular filtration rate
eGFRcr	Creatinine-based eGFR
eGFRcys	Cystatin C-based eGFR
eGFRcr-cys	Combined creatinine and cystatin C-based eGFR
ESKD	End-stage kidney disease
FDR	Benjamini–Hochberg False-discovery rate
GFR	Glomerular filtration rate
GWAS	Genome-wide association studies
KORA	Cooperative Health Research in the Region of Augsburg
MONICA	Monitoring of Trends and Determinants in Cardiovascular Diseases
MR	Mendelian randomization
MR-proADM	Mid-regional pro-adrenomedullin
MR-proANP	Mid-regional pro-atrial natriuretic peptide
NT-proBNP	N-terminal pro-B-type natriuretic peptide
RAAS	Renin–angiotensin–aldosterone system
SBP	Systolic blood pressure
SD	Standard deviation
SNP	Single nucleotide polymorphism
TNF	Tumor necrosis factor

Full names of the proteins can be found in Table S1 in Paper I or Paper II

List of publications

Publications included in the cumulative thesis

1. **Lin JS**, Petrera A, Hauck SM, Muller CL, Peters A, Thorand B. Associations of Proteomics With Hypertension and Systolic Blood Pressure: KORA S4/F4/FF4 and KORA Age1/Age2 Cohort Studies. Hypertension, 2024, 81(5): 1156-1166.
2. **Lin JS**, Nano J, Petrera A, Hauck SM, Zeller T, Koenig W, Muller CL, Peters A, Thorand B: Proteomic profiling of longitudinal changes in kidney function among middle-aged and older men and women: the KORA S4/F4/FF4 study. BMC Med, 2023, 21(1): 245.
3. **Lin JS**, Zeller T, Koenig W, Jousilahti P, Kee F, et al. Longitudinal and cross-sectional associations of myocardial stress markers with kidney function and chronic kidney disease: the BiomarCaRE project. Under review

Other publications during Ph.D. study

1. **Lin JS,** Chan FY, Leung J, Yu B, Lu ZH, Woo J, Kwok T, Lau KK. Longitudinal association of built environment pattern with DXA-derived body fat in elderly Hong Kong Chinese: a latent profile analysis. Int J Obes, 2021, 45: 2629–2637.
2. **Lin JS**, Leung J, Yu B, Lu ZH, Woo J, Kwok T, Lau KK. Association of green space with bone mineral density change and incident fracture in elderly Hong Kong Chinese: Mr. OS and Ms. OS study. Environ Res, 2021:201:111547.
3. **Lin JS**, Leung J, Yu B, Lu ZH, Woo J, Kwok T, Lau KK. Socioeconomic status as an effect modifier of the association between built environment and mortality in elderly Hong Kong Chinese: A latent profile analysis. Environ Res, 2021:195, 110830.
4. Nano J, Schöttker B, **Lin JS,** et al. Novel biomarkers of inflammation, kidney function and chronic kidney disease in the general population. Nephrol Dial Transplant, 2022, 37(10):1916-1926.
5. Li Y, Feng Y, Zhong Y, Li S, **Lin JS**, Fang P, Wan J, Zhao M. The Atherogenic Index of Plasma is a Predictor for Chronic Total Occlusion and Coronary Collateral Circulation Formation in CTOs Patients. Rev Cardiovasc Med, 2023, 24(10).
6. Li Y, Feng Y, Li S, Ma Y, **Lin JS**, Wan J, Zhao M. The atherogenic index of plasma (AIP) is a predictor for the severity of coronary artery disease. Front Cardiovasc Med, 2023, 10:1140215.
7. Zhang B, Li Y, Peng A, Liu C, **Lin JS**, Feng Y, Wan J. Association between the pan-immune-inflammation value and coronary collateral circulation in chronic total coronary occlusive patients. BMC Cardiovasc Disord, 2024;24(1):458.

Contribution to the publications

Contribution to paper I

As the first author of paper I, I drafted the research proposal and the analysis plan, which laid the groundwork for this study, with support from my supervisor. Following this, I applied for the necessary data and performed the statistical analysis. As the next step, I interpreted the results in collaboration with my TAC members. I then wrote the first draft of the manuscript and prepared supplemental materials, as well as created all tables and figures to present our findings. I revised the manuscript according to comments from my co-authors. Finally, I submitted the manuscript to the journal, addressed the comments from peer reviewers, and prepared a detailed response letter for the revised manuscript.

Contribution to paper II

Similarly, as the first author of paper II, I drafted the research proposal and the analysis plan, which laid the groundwork for this study, with support from my supervisor. Following this, I applied for the necessary data and performed the statistical analysis. Then I interpreted the results in collaboration with my TAC members. I then wrote the first draft of the manuscript and prepared supplemental materials, as well as created all tables and figures to present our findings. I revised the manuscript according to comments from my co-authors. Finally, I submitted the manuscript to the journal, addressed the comments from peer reviewers, and prepared a detailed response letter for the revised manuscript.

Contribution to paper III (Appendix)

As the first author of paper III, I began by developing the research question together with my supervisor and drafting the research proposal and the analysis plan, which laid the groundwork for this study. Following this, I applied for the necessary data, performed the statistical analysis, and interpreted the results. I then wrote the first draft of the manuscript and prepared supplemental materials, as well as created all tables and figures to present our findings. I revised the manuscript according to comments from my co-authors. Finally, I submitted the manuscript to the target journal and will address the comments from peer reviewers, and will prepare a detailed response letter for the revised manuscript once I receive the comments.

1. Introduction

1.1 Chronic kidney disease

The kidneys are some of the most vital organs that perform numerous functions, such as filtering waste products and excess fluid from the blood, maintaining a stable balance of water, salts, and minerals, as well as regulating blood pressure (BP).[1] Kidney function refers to the kidneys' ability to perform their tasks effectively. One of the optimal assessments of kidney function is the glomerular filtration rate (GFR), which measures the rate at which the kidneys filter blood. GFR can vary among individuals, influenced by factors such as age, sex, and body size.[2-6] In healthy adults, GFR is approximately 120 ml/min/1.73 m^2, with a gradual decline of approximately one unit per year starting around the ages of 30 to 40 years.[7,8] However, direct measurement of GFR is complex, making it impractical for routine clinical use. Thus, estimated GFR (eGFR), which is calculated using serum creatinine and/or cystatin C, in combination with other factors such as age and sex, is commonly used in clinical practice.[2-6] One of the most commonly used estimations of GFR is based on the equations developed by the Chronic Kidney Disease-Epidemiology Collaboration, which calculate eGFR from creatinine (eGFRcr), cystatin C (eGFRcys), and a combination of creatinine and cystatin C (eGFRcr-cys).[2-4]

Chronic kidney disease (CKD) is a condition where the kidneys progressively lose their functionality over a prolonged duration, and it is defined clinically as eGFR less than 60 ml/min/1.73 m^2, maintained at this level for a period extending three months or more.[9,10] A recent study, gathering CKD prevalence data from 161 countries, estimated a global median CKD prevalence of 9.5%, with Eastern and Central Europe exhibiting the highest prevalence at 12.8%.[11] The global burden of CKD is escalating, posing significant challenges in healthcare costs for many countries. CKD has many known causes, such as older age, diabetes, hypertension, and obesity.[12] Given the increasing prevalence of these risk factors, the incidence of CKD is estimated to rise continuously.

CKD can lead to severe complications, such as the development and progression of cardiovascular disease (CVD). One of the most severe consequences of CKD is its progression to end-stage kidney disease (ESKD), characterized by an eGFR below 15 mL/min/1.73m^2, where the kidneys lose their effectiveness and typically require kidney replacement therapy.[13] However, CKD often develops silently and progresses asymptomatically in its early stages, leading to missed opportunities for early detection and intervention. Additionally, the pathophysiological mechanism of CKD involves a complex interplay of different components, such as the renin-angiotensin-aldosterone system (RAAS), inflammation, oxidative stress, and endothelial dysfunction.[12,14,15] Despite these understandings, the pathophysiology leading to CKD remains incompletely understood, resulting in very limited specific therapeutic targets for CKD, and consequently, current treatment strategies for CKD primarily focus on managing its risk factors to delay its progression.[10] Given these challenges, there is an urgent need to address issues related to its underlying pathophysiology, early diagnosis, and treatment targets. Addressing these issues is crucial to reducing the burden of CKD on individuals and healthcare systems.

1.2 Hypertension

Hypertension, characterized by high BP persistently exceeding normal levels, includes both primary and secondary types. Primary hypertension, also known as essential hypertension, is predominant, affecting approximately 90% of patients with hypertension, with no identifiable cause, while secondary hypertension is caused by specific medical conditions, such as adrenal disease and thyroid problems.[16,17] Conventionally, hypertension is defined as systolic BP (SBP) $\geqslant$ 140 mm Hg and/or diastolic BP (DBP) $\geqslant$ 90 mm Hg, or reported use of antihypertensive medications.[16] According to this definition, the worldwide prevalence of hypertension in 2019 among adults aged 30–79 years was 32% in women and 34% in men, impacting 1.28 billion individuals in this age group.[18]

BP is also regulated by a complex interplay of various pathophysiological mechanisms, such as the RAAS, endothelial function, oxidative stress, inflammation, the sympathetic nervous system, and the immune system.[19] BP can naturally change with age, but the patterns of change differ between SBP and DBP. As a result of arterial stiffening and other aging processes, DBP generally increases until around the age of 50 and then declines, whereas SBP continues to increase with age.[20-23] BP can also be influenced by a variety of factors, such as unhealthy diets, physical inactivity, smoking, and obesity.

Despite often being asymptomatic, hypertension can cause damage to multiple organs, such as the heart, kidneys, brain, and eyes, and serves as a major risk factor for CVD and kidney disease, contributing significantly to morbidity and mortality worldwide.[24,25]

Hypertension is a disease in its own right with possible acknowledged mechanisms, but the cut-off value of BP to define hypertension is closely linked to its complications. The cut-off value is mainly determined by evaluating observational evidence that shows continuous associations between a wide range of BP and CVD outcomes, along with evidence from randomized controlled trials examining the effects of lifestyle modifications and antihypertensive medications on BP levels and CVD.[17,26,27] The cut-off value for hypertension has changed over time and varies across different guidelines. For instance, the 2017 American College of Cardiology/American Heart Association guideline redefined the cut-off value as 130/80 mm Hg.[26]

Given the complexity of hypertension, which involves multiple pathophysiological mechanisms and affects various target organs, it is inadequate to define it solely relying on a BP reading. Consequently, there is an increasing demand to refine the definition and assessment of hypertension to better capture its multifaceted nature. One promising approach is the incorporation of new biomarkers, offering deeper insights into underlying mechanisms, enabling better prediction of hypertension development and progression, and providing valuable information regarding monitoring of treatment responses.

1.3 Interplay between CKD and hypertension

CKD and hypertension frequently coexist, exhibiting a complex and bidirectional interplay. Hypertension is not only an independent risk factor for the development and progression of CKD but also a common complication of CKD, with a prevalence ranging from 60-90%.[28] Persistently high BP can damage the blood vessels and filters in the kidneys, gradually impairing kidney function over time and potentially leading to CKD.[29] Conversely, kidney dysfunction resulting from CKD can elevate BP levels through mechanisms such as dysregulated activation of the RAAS and impaired volume regulation.[30]

Moreover, CKD and hypertension share common risk factors, complications, and pathophysiological mechanisms. Risk factors such as age, obesity, and diabetes are common to both conditions. Both CKD and hypertension are significant risk factors for CVD and ESKD, and the coexistence of both conditions further amplifies the risk of CVD.[12,31-33] In terms of pathophysiology, mechanisms such as RAAS, endothelial dysfunction, oxidative stress, and inflammation play key roles in the development and progression of both CKD and hypertension.

Understanding the intricate interplay between CKD and hypertension is crucial for implementing integrated approaches for effective prevention, early detection, and comprehensive management of both conditions. This understanding can guide healthcare professionals in providing optimal care to patients, potentially slowing disease progression and improving overall health outcomes.

1.4 Proteomics

Proteomics, which is the large-scale study of the proteome (the entire compilation of proteins expressed by an organism), has emerged as a valuable tool in medical research.[34,35] The rapid advancements in high-throughput proteomics technology have enabled simultaneous measurement of a vast number of proteins, thereby opening new possibilities for the study of disease mechanisms, biomarker discovery, and identification of therapeutic targets.[35-38]

In general, proteins are the products of both genetic information and environmental factors, making the proteome more dynamic and complex than the genome, and thus, proteomics can provide a more comprehensive view of biological systems.[35] As proteins are the primary effectors of biological function, carrying out diverse cellular functions, changes in protein levels can reflect the functional status of organisms, providing information on the underlying mechanisms of disease.[39,40] Moreover, proteomic approaches can reveal protein-protein interactions, shedding light on the complex cellular networks contributing to disease pathophysiology. By identifying proteins and pathways associated with disease pathophysiology, proteomics could unveil potential therapeutic targets for intervention.

In terms of biomarker discovery, the proteomic approach allows for the identification of disease-specific protein profiles by detecting changes in protein expression in response to disease. These protein changes can serve as potential biomarkers for risk stratification, disease diagnosis, prognosis, and response to treatment.

1.5 Proteomic studies on CKD and hypertension

1.5.1 Proteomics and CKD

Over the past decade, a growing number of studies have utilized proteomics to identify new biomarkers for kidney disease. In 2010, a set of 273 urinary peptides was identified to exhibit differential expression between 230 patients with kidney disease and 379 healthy controls.[41] When these 273 peptides were utilized in a classification model within the same study, a sensitivity of 98.7% and a specificity of 100% were reported, and upon validation in a separate group of individuals (110 patients with kidney disease and 34 controls), the sensitivity and specificity were 85.5% and 100%, respectively.[41] This peptide panel is now known as the CKD273 classifier. The CKD273 classifier has furthermore been linked to kidney function decline and has shown potential in predicting the development and progression of various types of kidney diseases, such as diabetic kidney disease.[42-47] Two prospective studies have also found that CKD273 could predict early-stage CKD, even when accounting for baseline eGFR and albuminuria.[48,49] In 2016, the US Food and Drug Administration issued a letter of support for CKD273 to encourage its development in early-stage CKD.[50] The CKD273 classifier not only contributes to the early detection of CKD but also opens the door to the field of proteomic studies on CKD.

Recent studies have increasingly focused on blood-based proteomics, such as serum and plasma, since circulating proteomics can provide a more comprehensive view of the body’s physiological condition and better reflect systemic changes compared to urinary proteomics. This shift has also been facilitated by advancements in proteomic technology, enabling large-scale circulating proteomics studies.[51-64] For instance, a cross-sectional study discovered 80 out of 1095 plasma proteins associated with kidney function among 995 general Europeans and successfully validated 57 proteins among three independent studies with 1887 individuals of mixed ancestry, including several well-known biomarkers of kidney function.[51] Longitudinal studies have also investigated proteomics with kidney function decline and incident CKD during follow-up among the general population[54-56] and individuals with diabetes.[57-60] Several other longitudinal studies have concentrated on the progression of CKD.[61-64] For example, a recent cohort study, investigating the associations of 4638 plasma proteins with a composite outcome of more than 50% eGFR decline or ESKD over 10 years in 3235 patients with CKD, identified 330 proteins and externally validated 76 of them in 578 patients with CKD, and uncovered several pathways that may be involved in CKD progression.[61]

Despite the increasing amount of studies on circulating proteomics, the number of longitudinal studies conducted among the general population remains limited, particularly those with a long follow-up period. Moreover, while new potential biomarkers have been identified and externally validated in some of the studies, it is still crucial to replicate and confirm the findings in independent studies, which should be ideally conducted among diverse populations to ensure the generalizability of the results. Another challenge is the variability in proteomic measurements across different studies due to the use of different technologies, such as mass spectrometry, the SomaScan platform, and the Olink platform. These platforms vary in their protein detection and quantification capabilities, which have been reported to impact the findings of proteomic studies.[65,66] However, the superiority of one platform over the others remains unclear. While recent studies have identified certain circulating proteins associated with kidney function and kidney disease, these current biomarkers may not fully capture the complexity of CKD. Therefore, there is a pressing need to explore additional biomarkers.

1.5.2 Proteomics and hypertension

In contrast to the increasing number of proteomic studies on CKD, proteomic studies on primary hypertension and BP are scarce. To our current knowledge, only three cross-sectional studies with small sample sizes[67-69] and one longitudinal study[70] have investigated proteomics in primary hypertension. Two of these cross-sectional studies examined the different levels of circulating proteins between 118/20 hypertensive patients and 85/20 normotensive controls.[67,68] Another cross-sectional study investigating urinary proteomics among 56 patients with hypertension and 19 controls, found that urinary uromodulin, a protein involved in the regulation of water and salt balance, was significantly higher among patients with hypertension.[69] The only longitudinal proteomic study to date conducted a discovery-validation approach of 79 plasma CVD-related proteins, identifying a positive association between renin levels and BP progression over 5 years in a discovery cohort of 804 participants, but this was not replicated in a larger validation cohort of 2659 participants.[70] It is worth noting that their longitudinal analysis included only 79 proteins and two repeated BP measurements with a relatively short follow-up duration, highlighting the need for more comprehensive and long-term large-scale proteomic studies in this area.

1.5.3 Mendelian randomization analysis

It is of significant interest for some of the proteomic studies to determine whether their observed associations are causally related. A two-sample bidirectional Mendelian randomization (MR) analysis conducted by Matias-Garcia et al.[51] suggested potential causal associations of 4 proteins with kidney function, i.e., testican-2, melanoma inhibitory activity, carbonic anhydrase III, and cystatin-M. Similarly, Dubin et al.[61] found 3 proteins, including two druggable targets (i.e., interleukin-1 soluble receptor type II and matrix metalloproteinase 7), that were casually associated with rapid kidney function decline in their MR analysis. Lin et al.[70] identified an association between renin and BP change but were unable to conduct further MR as planned due to the lack of adequate genetic instruments for renin. Presently, the increasing availability of protein quantitative trait loci studies and genome-wide association studies (GWAS) on kidney function and hypertension has enhanced the feasibility of using two-sample MR to infer causal relationships in observed associations.

2. Aims of the thesis

Given the global burden of both CKD and hypertension, there is a pressing need to address challenges related to early diagnosis, treatment targets, and enhancing assessment for CKD and hypertension. One of the promising approaches in this context is the utilization of proteomics. Furthermore, considering the interplay among CVD, CKD, and hypertension, this cumulative thesis aims to identify and validate biomarkers from a pool of 233 CVD- and inflammation-related proteins. Figure 1 provides an overview of the topics included in this thesis.

Paper I aimed to identify proteins associated with longitudinal decline in kidney function and development of CKD in a general population-based prospective cohort, while also exploring the pathways involved in these processes and examining potential causality by using a two-sample MR design.[71] Paper III further validated longitudinal and cross-sectional associations of three CVD-related proteins with kidney function and CKD based on the Biomarkers for Cardiovascular Risk Assessment in Europe (BiomarCaRE) Consortium.

Paper II aimed to discover and validate proteins associated with hypertension and SBP across two general population-based prospective cohorts. A similar two-sample MR design was used to explore potential causality.[72]

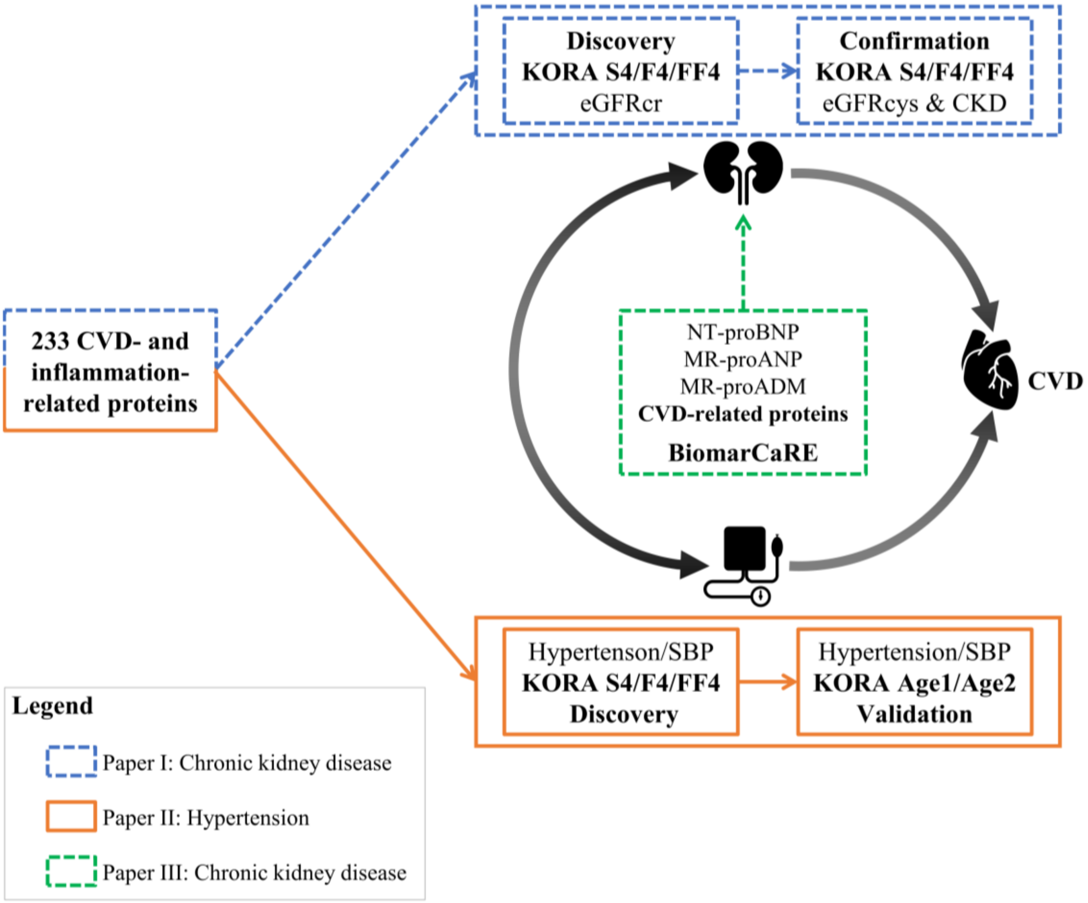

Figure 1. Overview of the research projects incorporated in this cumulative thesis.

Abbreviations: BiomarCaRE, Biomarkers for Cardiovascular Risk Assessment in Europe; CKD, chronic kidney disease; CVD, cardiovascular disease; eGFRcr, creatinine-based estimated glomerular filtration rate; eGFRcys, cystatin C-based eGFR; KORA, Cooperative Health Research in the Region of Augsburg cohort study; MR-proADM, mid-regional pro-adrenomedullin; MR-proANP, mid-regional pro-atrial natriuretic peptide; NT-proBNP, N-terminal pro-B-type natriuretic peptide; SBP, systolic blood pressure.

3. A brief overview of methods

Detailed descriptions of the methods of the present thesis are included in the respective papers, with a brief overview in this section.

3.1 Study design and population

The Monitoring of Trends and Determinants in Cardiovascular Diseases (MONICA) study conducted three health surveys (S1 to S3) from 1984 to 1995 (Figure 2). These surveys targeted the population aged between 25 and 74 years residing in Augsburg, Germany. The Cooperative Health Research in the Region of Augsburg (KORA) study, extended MONICA by conducting a 4th survey (S4) between 1999-2001.[73] In Paper I regarding CKD, 1566 participants with measurement of both proteomics and eGFRcr at KORA S4 were included. Among them, 1120 and 658 participants were followed up at KORA F4 and FF4, respectively, with 1140 having at least one follow-up eGFRcr measurement. Paper II focusing on hypertension, included 1560 participants with measurement of both proteomics and BP at KORA S4, as well as 1115 at F4, and 657 at FF4 for discovery analysis. Validation analysis in Paper II included a random subset of 1024 participants at KORA-Age1, which contained participants aged 65 years or older in 2009 from MONICA/KORA S1-S4, and 786 participants at KORA-Age2 were included. Paper III, further investigated associations of three CVD-related proteins (mid-regional pro-adrenomedullin [MR-proADM], mid-regional pro-atrial natriuretic peptide [MR-proANP], and N-terminal pro-B-type natriuretic peptide [NT-proBNP]) with kidney function and CKD, included 4205 participants with at least one follow-up eGFRcr measurement from MONICA/KORA S3/S4 and their follow-up surveys for longitudinal analysis and 61830 participants from the BiomarCaRE Consortium[74] for cross-sectional analysis. Seven studies/cohorts (including MONICA/KORA S3/S4) from the BiomarCaRE Consortium were included in this thesis.

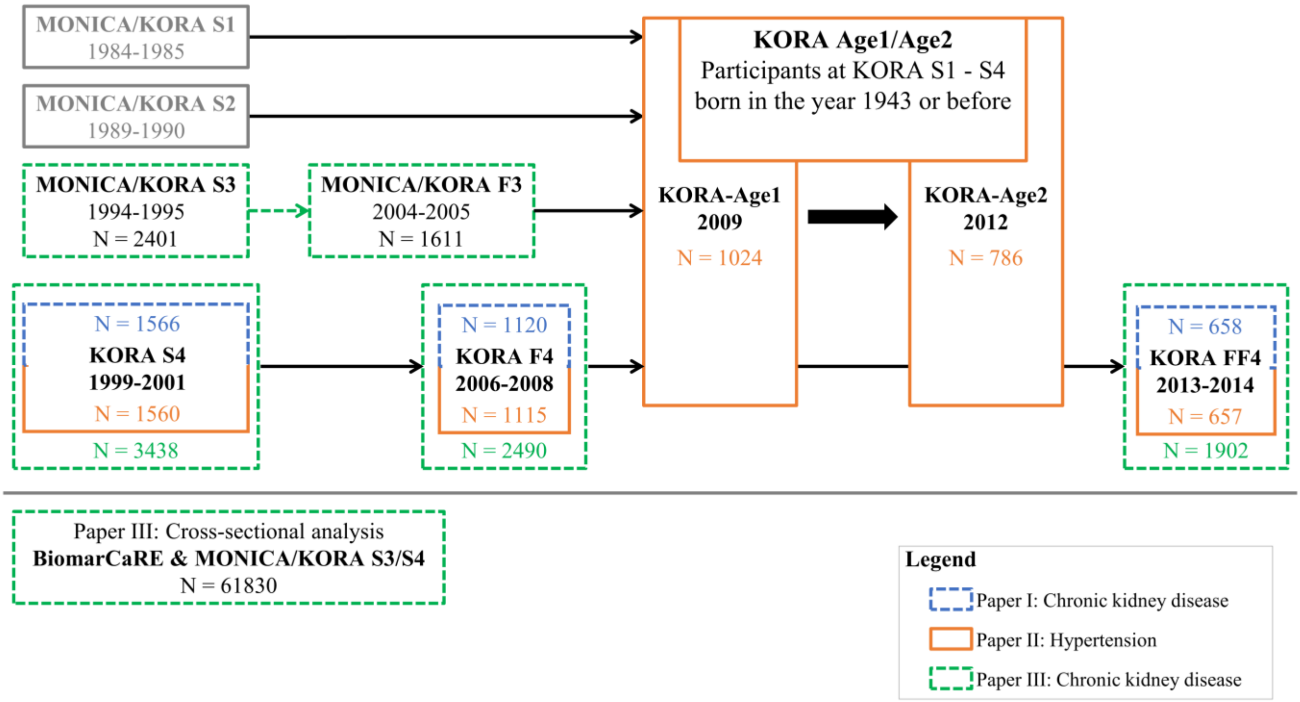

Figure 2. Overview of the studies included in this thesis.

Abbreviations: BiomarCaRE, Biomarkers for Cardiovascular Risk Assessment in Europe; KORA, Cooperative Health Research in the Region of Augsburg cohort study; MONICA, Monitoring of Trends and Determinants in Cardiovascular Diseases.

3.2 Measurement of proteins

In Paper I and Paper II, relative concentrations of plasma proteins were measured by the Olink platform at both KORA S4 and KORA-Age1.[75,76] At KORA S4, 233 proteins were selected after quality controls, and out of these, 231 proteins were available at KORA-Age1. Z-score transformations were conducted for all proteins in participants at KORA S4 and KORA-Age1, respectively, to compare the magnitude of associations given one standard deviation (SD) increase in proteins.

In Paper III based on the BiomarCaRE, absolute concentrations of plasma MR-proADM (N = 9327) and MRproANP (N = 9499) were measured using immunoluminometric assays, and serum NT-proBNP (N = 61830) was measured using an electrochemiluminescence immunoassay. The three markers were log-transformed, followed by Z-score transformations for comparability between markers. Additionally, original marker levels were categorized into four groups (G1, G2, G3, and G4) using the following cut-off values: NT-proBNP (< 48, 48 to < 125, 125 to < 300, and ⩾ 300 pg/ml), MR-proANP (< 40, 40 to < 80, 80 to < 120, and ⩾120 pmol/l), and MR-proADM (< 0.425, 0.425 to < 0.609, 0.609 to < 0.766 and ⩾ 0.766 nmol/l).[77]

3.3 Assessment of kidney function and blood pressure

Kidney function was assessed from creatinine (i.e., eGFRcr), cystatin C (i.e., eGFRcys), and a combination of creatinine and cystatin C (i.e., eGFRcr-cys) using Chronic Kidney Disease-Epidemiology Collaboration equations.[2-4] In Paper I, the primary outcome focused on the annual rate of change in eGFR, computed as β coefficients from linear regression of eGFR against age at S4/F4/FF4 for each participant. CKD was defined as eGFR < 60 ml/min/1.73 m^2.

BP was measured by an automatic digital oscillometer three times with a 3-minute interval between measurements following standard protocols, and the mean of the 2nd and 3rd measurements was used for analysis.[78,79] Sociodemographic variables, lifestyle factors, and medication use were gathered.[73,80] Hypertension was defined based on the cut-off value of 140/90 mm Hg or antihypertensive medication use given that participants were aware of having hypertension.[16]

3.4 Statistical analysis

Figure 3 shows the overview of the statistical strategies of the three papers included in this thesis.

3.4.1 Paper I: Proteomics and CKD

Discovery analysis utilized linear regression to assess the associations between 233 proteins and the annual rate of change in eGFRcr, adjusted for age, sex, eGFRcr, and various health and lifestyle factors at baseline. Sixty-six proteins significantly linked with the annual eGFRcr change rate were further examined for their associations with eGFRcys change rate. A false-discovery rate (FDR) was applied for multiple testing correction, with FDR < 0.05 deemed statistically significant.[81] The 66 eGFRcr change-associated proteins were also examined for their associations with incident CKD, using interval-censored Cox regression models adjusted for the same covariates. The proteins consistently associated with the annual rate of change in eGFRcr, eGFRcys, and incident CKD were taken to MR analysis and pathway enrichment analysis. A two-sample MR design was employed using the most extensive GWAS results available. Single nucleotide polymorphisms (SNPs) for proteins were selected and SNP-eGFR decline associations were extracted from large European population-based GWAS.[82,83] SNPs that did not meet the MR assumptions were excluded, resulting in 17 proteins with a single SNP for MR analysis. Gene ontology enrichment analyses were conducted to identify biological pathways.

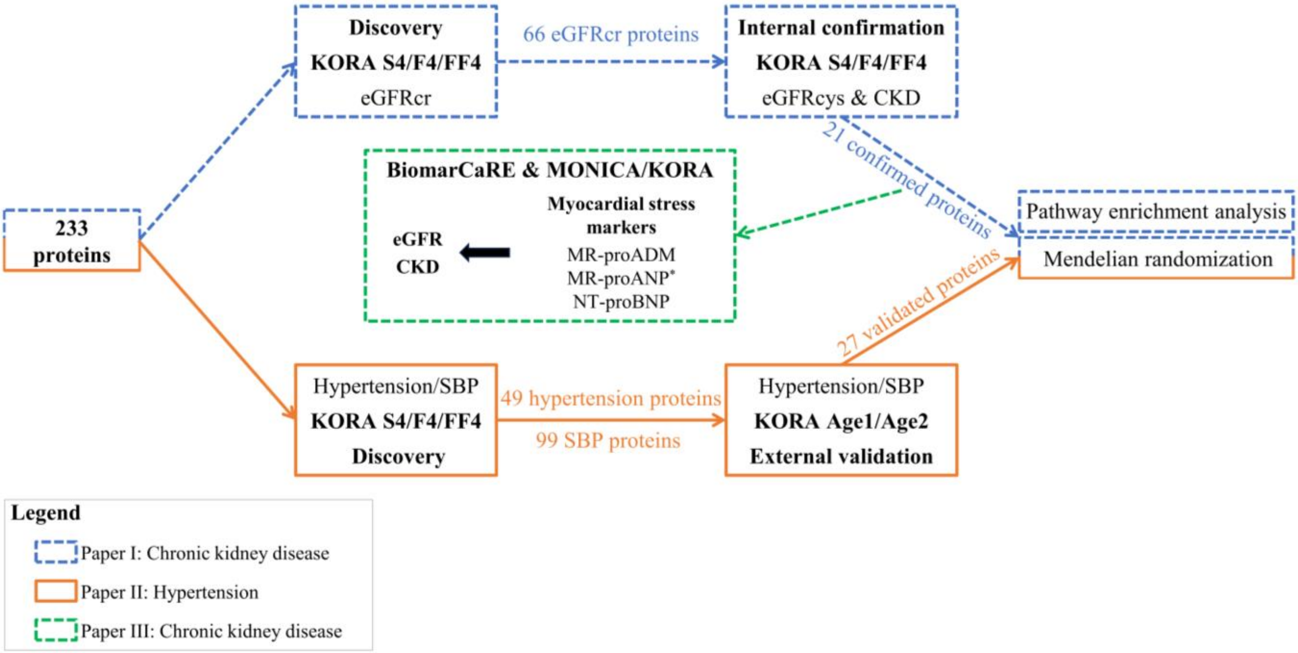

Figure 3. Flowchart of statistical strategies of the three research projects.

Abbreviations: BiomarCaRE, Biomarkers for Cardiovascular Risk Assessment in Europe; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; eGFRcr, creatinine-based eGFR; eGFRcys, cystatin C-based eGFR; KORA, Cooperative Health Research in the Region of Augsburg cohort study; MONICA, Monitoring of Trends and Determinants in Cardiovascular Diseases; MR-proADM, mid-regional pro-adrenomedullin; MR-proANP, mid-regional pro-atrial natriuretic peptide; NT-proBNP, N-terminal pro-B-type natriuretic peptide; SBP, systolic blood pressure. *MR-proANP is not included in the 233 included proteins.

3.4.2 Paper II: Proteomics and hypertension

In the KORA S4/F4/FF4 study, discovery analyses utilized generalized estimating equations to identify proteins associated with hypertension and SBP out of a pool of 233 proteins, accounting for various factors such as age, sex, lifestyle factors, health conditions, and medication use (antihypertensive medication for SBP outcome only), with significance set at an FDR below 0.05. Proteins significantly associated with hypertension or SBP were validated in the KORA Age1/Age2 study using the same analyses. Proteins were considered validated if they demonstrated significant associations at P-value below 0.05. A two-sample MR design was performed to explore the potential causality of 27 validated proteins with SBP using large European population-based GWAS.[83,84] The selected SNPs were further refined to meet the MR assumptions, resulting in 26 proteins with 1-17 SNPs for MR analysis.

3.4.3 Paper III: Myocardial stress markers and CKD

Cross-sectional analyses utilized linear regression to assess the β coefficients and 95% confidence intervals (CIs) of eGFR and utilized logistic regression to assess odds ratios of prevalent CKD per 1 SD increase in log-transformed markers and across G2-G4 compared with G1, adjusting for age, sex, study, and various health and lifestyle factors. Longitudinal analyses within the MONICA/KORA study utilized linear mixed-effects models to assess β (95% CIs) of a 10-year decline in repeatedly measured eGFR for per 1 SD increase in log-transformed NT-proBNP or grouped NT-proBNP, considering both random intercept and random slope in the model. Interval-censored Cox regression models were utilized to investigate associations with incident CKD. Longitudinal analyses also adjusted for baseline eGFR.

4. Key findings

4.1 Key findings from Paper I:

Discovered and confirmed 21 proteins associated with kidney function decline and incident CKD, with tumor necrosis factor receptor superfamily member 11A (TNFRSF11A) further showing a potential causal relationship with kidney function decline.

Discovery analyses identified 66 proteins that showed inverse associations with annual eGFRcr change rate (FDR < 0.05), suggesting that participants with higher levels of these proteins at the start of the study experienced a more rapid decline in eGFRcr. Kidney injury molecule 1 (KIM1), NT-proBNP, interleukin-18-binding protein (IL-18BP), TNF receptor superfamily member 9 (TNFRSF9), and ephrin type-B receptor 4 (EPHB4) were the top 5 proteins with the strongest associations (β coefficients ranged from -0.292 to -0.233 ml/min/1.73 m^2 per year). Confirming their associations with eGFRcys decline, 38 out of 66 proteins showed consistent inverse associations (FDR < 0.05). For associations with incident CKD, 28 out of 66 proteins were positively associated with risk of incident CKD (FDR < 0.05), with TNF-related apoptosis-inducing ligand receptor 2 (TRAIL-R2), TNFRSF9, TNFRSF11A, KIM1, and interleukin-15 receptor subunit alpha (IL-15RA) being the top 5 proteins with the highest hazard ratios (ranged from 1.41 to 1.52). Twenty-one proteins were consistently associated with more rapid declines in both eGFRcr and eGFRcys, as well as higher incident CKD risk.

The MR analysis suggested a potential causal positive association relationship between TNFRSF11A and eGFR decline (P-value = 0.030), although significance was not maintained after multiple corrections (FDR > 0.05). Finally, pathway enrichment analysis using the 21 biomarkers identified 254 significant pathways, with the top 15 pathways primarily involved in TNF stimulus-response and T cell proliferation.

4.2 Key findings from Paper II:

Discovered and validated 27 hypertension/SBP-associated proteins, with robust associations observed for KIM1, NT-proBNP, and osteoprotegerin (OPG). MR analysis identified 5 proteins showing potential causal associations with SBP, including NT-proBNP and OPG.

Of the 233 proteins discovered in KORA S4/F4/FF4, 49 proteins were identified for hypertension and 99 for SBP (FDR < 0.05), with 31 proteins showing associations with both hypertension and SBP. Of these 31 proteins, the top 5 for hypertension were NT-proBNP, hepatocyte growth factor (HGF), carcinoembryonic antigen-related cell adhesion molecule 8 (CEACAM8), KIM1, and transforming growth factor alpha (TGF-α), with odds ratios ranging from 1.24 to 1.33. The top 5 proteins for SBP were KIM1, OPG, NT-proBNP, HGF, and chitinase-3-like 1 (CHI3L1), with β coefficients ranging from 2.66 to 3.95 mm Hg. In the validation phase within KORA Age1/Age2, 7 out of 49 hypertension-associated proteins and 23 out of 99 SBP-associated proteins were validated. Among these, NT-proBNP, KIM1, and OPG were associated with both outcomes, resulting in a total of 27 validated proteins.

MR analysis on SBP identified 5 out of 26 validated proteins (excluding 1 protein due to lack of genetic instruments) with potential causal associations. NT-proBNP and interleukin-10 receptor subunit beta (IL-10RB) exhibited inverse associations, while tissue inhibitor of metalloproteinases 4 (TIMP4), programmed cell death 1 ligand 1 (PD-L1), and OPG showed positive associations.

4.3 Key findings from Paper I & II

Among the 21 proteins associated with kidney outcomes and the 27 proteins associated with BP outcomes, 5 proteins overlapped, including adrenomedullin (ADM), KIM1, NT-proBNP, PD-L1, and thrombomodulin (TM) (Figure 4).

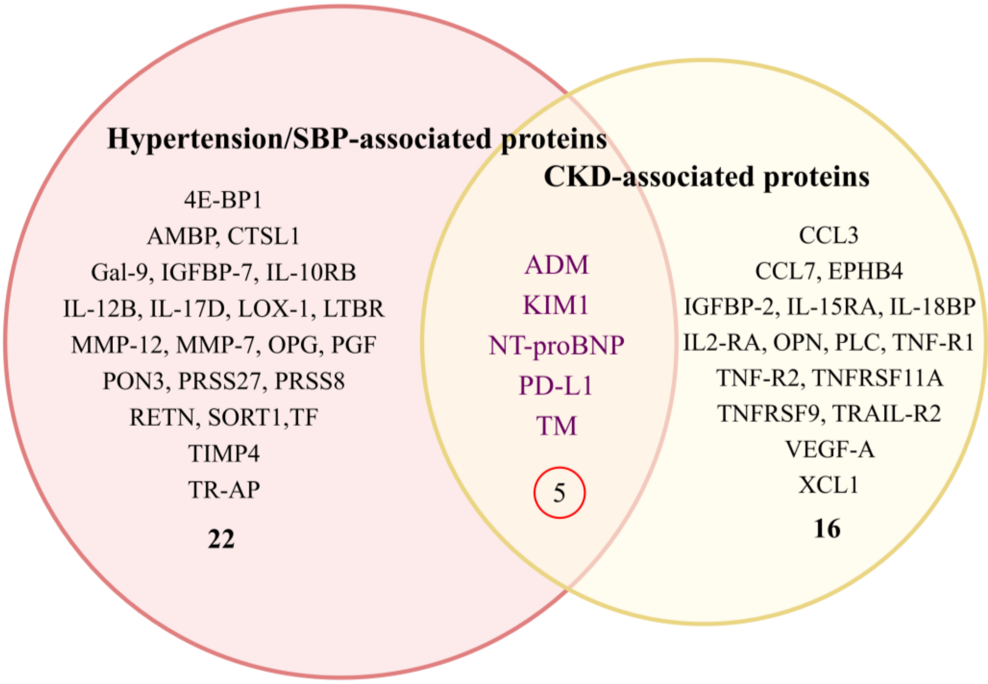

Figure 4. Overlap of proteins associated with kidney outcomes and blood pressure outcomes.

Abbreviations: CKD, chronic kidney disease; SBP, systolic blood pressure. The complete protein names are in Supplemental Table 1 in Paper I or Paper II.

4.4 Key findings from Paper III:

Higher levels of MR-proADM, MR-proANP, and NT-proBNP were cross-sectionally associated with lower kidney function and a greater CKD prevalence, with the associations being stronger among patients with CVD and diabetes. Higher NT-proBNP levels were further associated with a more rapid kidney function decline and a greater CKD incidence.

In the BiomarCaRE studies, higher levels of MR-proADM, MR-proANP, and NT-proBNP demonstrated consistent cross-sectional associations with lower eGFR and a greater CKD prevalence across all three eGFR/CKD assessments. For example, for every 1 SD increase in log-transformed MR-proADM, MR-proANP, and NT-proBNP, the multivariate-adjusted β (95% CIs) of eGFRcr were -2.88 (-3.32, -2.45) ml/min/1.73m^2, -1.45 (-1.90, -1.00), and -1.06 (-1.18, -0.93), respectively. Corresponding odds ratios (95% CIs) of CKDcr were 1.73 (1.56, 1.92), 1.31 (1.18, 1.45), and 1.49 (1.42, 1.57), respectively. Results using categories of markers were similar. For instance, β (95% CIs) of eGFRcr for G2-G4 compared to G1 of NT-proBNP were -0.10 (-0.35, 0.14), (-1.49, -0.74), and -6.92 (-7.51, -6.34), respectively. Stratified analyses observed that the associations with eGFR were stronger among patients with CVD and diabetes. In longitudinal analyses within the MONICA/KORA study, participants with higher baseline NT-proBNP experienced more rapid eGFR declines. Multivariate-adjusted β (95% CIs) for a 10-year eGFRcr decline were -1.39 (-1.80, -0.99) units/10-year for 1 SD increase in log-transformed NT-proBNP, while for G2-4 compared to G1 were -0.81 (-1.66, 0.04), -3.19 (-4.51, -1.88), and -8.51 (-11.2, -5.77). Hazard ratios of incident CKDcr were 1.16 (1.00, 1.32) per 1 SD increase in log-transformed NT-proBNP and 1.09 (0.80, 1.48), 1.14 (0.79, 1.63), and 1.86 (1.15, 3.01) for G2-4 compared to G1.

5. Discussion

In this cumulative thesis, Paper I discovered and internally confirmed 21 proteins linked to kidney function decline and incident CKD within a general population-based cohort study, while Paper II discovered and externally validated 27 hypertension/SBP-associated proteins across two cohort studies. Notably, among these proteins, 5 proteins showed consistent associations with both kidney function and BP outcomes, including ADM, KIM1, NT-proBNP, PD-L1, and TM. Paper III further validated longitudinal (NT-proBNP only) and cross-sectional associations of MR-proADM (surrogate of ADM), MR-proANP, and NT-proBNP with kidney function and CKD among a large European dataset comprising several population-based studies. The presence of overlapping proteins further underscores the interplay between kidney function and BP, suggesting shared pathophysiological mechanisms underlying the regulation of both kidney function and BP. Additionally, these findings may indicate potential targets for interventions aimed at managing patients with both CKD and hypertension, thereby offering valuable insights for future clinical management strategies.

While some key findings have been thoroughly discussed in the respective papers, the following discussion primarily focuses on new insights or briefly revisits some crucial points previously discussed in the included papers.

5.1 Role of several key proteins

Among the 5 proteins showing consistent associations with both kidney and BP outcomes in proteomic analyses, KIM1 and NT-proBNP exhibited the strongest associations. Furthermore, when measured by absolute concentrations, NT-proBNP and another natriuretic peptide (i.e., MR-proANP) demonstrated consistent associations with kidney outcomes. KIM1, a novel biomarker of kidney injury, plays a role in kidney repair[85], while MR-proANP/NT-proBNP, inactive peptides released along with active peptides ANP/BNP in response to atrial/ventricular wall stretch, serve as key biomarkers in heart failure diagnostics and prognostication.[77,86] Both ANP and BNP can counteract the effects of the RAAS and the sympathetic nervous system. ANP and BNP promote vasodilation, diuresis, and natriuresis, which decrease vascular resistance, increase blood flow, and reduce blood volume through the excretion of sodium and water by the kidneys, leading to an increase in eGFR and a decrease in BP.[87,88] Comprehensive discussions on KIM1, MR-proANP, and NT-proBNP have been included in the respective papers comprising this cumulative thesis.

Similarly, ADM/MR-proADM, another heart failure-related biomarker, has multiple biological functions like ANP and BNP, such as promoting vasodilatation, diuresis, and natriuresis. It has been found to be positively associated with the development and progression of CKD[57,62,89-92] and plays a pathophysiological role in kidney disease.[93] It has also been reported to be positively associated with the development of hypertension.[94,95]

TM, a glycoprotein expressed primarily on the surface of endothelial cells, plays a crucial role in regulating blood coagulation, anti-inflammation, and endothelial function.[96,97] TM is released into the circulation following endothelial injury or stress, serving as a biomarker for endothelial dysfunction[96,97], a common pathological mechanism underlying both CKD and hypertension.[12,19] Several proteomic studies have reported positive associations of TM with rapid declines in kidney function.[55-57] For instance, a study consisting of two cohorts (N = 687/360) exploring associations of 80 proteins with decline in kidney function over 5 years found that TM was associated with kidney function decline and incident CKD.[55] A cross-sectional study including 59 children with CKD also reported an inverse association of TM with kidney function.[98] As for hypertension and BP, given the key role of TM in coagulation and endothelial function, TM should also closely link to hypertension and BP. While epidemiological evidence is limited, several cross-sectional studies in hypertensive patients have reported that severe hypertension is associated with higher levels of TM.[99-101] For example, a cross-sectional study consisting of 132 hypertensive patients found that patients with complications such as heart diseases and kidney dysfunction had higher levels of plasma TM than patients without complications, suggesting an association of TM with hypertension progression.[99] A similar association was also observed in another cross-sectional study consisting of 120 patients with grade 1-3 hypertension and 40 controls.[100]

Lastly, PD-L1 and its receptor PD1 are regulatory proteins that influence immune responses and play a critical role in the immune system.[102,103] Overexpression of PD-L1 allows cancer cells to evade the immune system by inhibiting T cell activity, making PD-L1/PD1 druggable targets for cancer treatment and reliable treatment response biomarkers.[102,103] PD-L1 also exhibited consistent associations with both outcomes and further demonstrated a positive causal association with SBP in MR analysis. Previous proteomic studies have also reported associations of higher levels of PD-L1 with lower kidney function in cross-sectional studies[54,59] and with kidney disease progression in a cohort study.[62] PD-L1 may have direct protective effects on kidney function, potentially influencing processes like kidney inflammation and tissue damage, and thus, an overexpression of PD-L1 levels may be indicative of kidney dysfunction.[104,105] While there is limited epidemiological evidence linking PD-L1 and BP, the established role of the immune system in regulating BP[19] implies that PD-L1 could potentially have an impact on BP regulation.

5.2 Implications in clinical practice

In considering the implications of the findings from this thesis, it is important to note that the direct application of these findings to clinical practice is not immediate and requires future research. Nonetheless, our findings may have implications on the aspects of early diagnosis, risk stratification, underlying mechanisms, therapeutic targets, and personalized management strategies for CKD and hypertension.

The proteins identified in this thesis may improve the early detection and refine assessment of CKD and hypertension, which is important for preventing disease progression and complications. For instance, in the recently updated KDIGO 2024 CKD evaluation and management guideline, several novel urinary biomarkers such as KIM1, interleukin-18, uromodulin, and neutrophil gelatinase-associated lipocalin are recommended for CKD evaluation in future research.[10] Regarding hypertension management, in the latest 2023 European Society of Hypertension Guidelines, measurements of biomarkers such as lipoprotein (a), NT-proBNP, and high-sensitivity troponins are recommended in patient work-up.[17] Given the asymptomatic nature of both conditions in early stages, our identified proteins could serve as early biomarkers, leading to earlier treatment and minimizing adverse outcomes. These proteins could also be used as biomarkers for risk stratification, especially for patients with both conditions, which helps identify individuals with higher risks.

Beyond their diagnostic utility, these proteins offer insight into the molecular mechanisms underpinning both CKD and hypertension. For instance, we found a role of TNF signaling pathways in the pathophysiology of CKD[71] and identified a key endothelial dysfunction indicative biomarker, TM, among both outcomes. Furthermore, a deeper understanding of pathophysiological mechanisms may pave the way for targeted therapeutic interventions aimed at modulating these pathways to slow disease progression and improve patient outcomes.[106,107] Additionally, these proteins could serve as potential indicators of treatment response. The identification of proteins could improve the development of personalized management strategies for CKD and hypertension.

5.3 Strengths and limitations

Key strengths of this cumulative thesis lie in the fact that the three included papers were based on large general population-based prospective cohorts and cross-sectional studies. Additionally, the utilization of large-scale proteomics and the approach of internal confirmation or external validation of discovered proteins enhance the reliability of the findings.

However, several limitations should also be acknowledged. First, as the measurement of proteins was limited to baseline assessments, the evaluation of dynamic changes in protein over time is not accounted for in the analysis. Moreover, the utilization of relative rather than absolute protein concentrations in proteomic analyses may affect the interpretation of results, as relative values may not provide a complete picture of the protein levels in the body. However, when measured by absolute concentrations, three CVD-related proteins show consistent associations. Second, the study population for longitudinal analyses was primarily from Germany and we did not validate the findings in diverse ethnic populations, which may limit the generalizability of our findings. Third, both CKD and hypertension were determined based on a single assessment, without subsequent confirmations in each survey, which may lead to misclassification bias. Lastly, participants lost to follow-up may introduce a potential selection bias in longitudinal analyses.

5.4 Future studies

The field of proteomic technology is in a state of continuous evolution, driving a new era of medical research. Platforms like SomaScan and Olink enable the measurement of an extensive breadth of proteins from minimal sample volumes. For instance, as of now, SomaScan can measure up to 11000 proteins from just a 55-µL sample[108], while Olink's Explore HT solution enables the measurement of more than 5400 proteins from a mere 2-µL sample[109], and these numbers are continually growing. This ongoing progress is not only enhancing further understanding of the complex biological systems but also uncovering potential biomarkers that were previously hidden. On the other hand, advancements in high-throughput proteomics technology could potentially make the absolute quantification of proteins more precise, less time-consuming, and more cost-effective in the near future. Therefore, the developing proteomic technology offers exciting opportunities for future studies on CKD and hypertension.

The integration of multi-omics data, including genomics, transcriptomics, proteomics, and metabolomics, is another promising direction for future studies.[110,111] The integration of multi-omics data can uncover more complex biological interactions and provide a more comprehensive understanding of biological processes underlying CKD and hypertension. Besides, with the integration of multi-omics data, superior predictive models could be developed to more accurately forecast the development and progression of both conditions. Furthermore, the integration of multi-omics data paves the way for precise and personalized medical management of CKD and hypertension.

As previously mentioned, our findings do not directly translate into clinical practice, suggesting the importance of clinical translation in future studies. This includes validating our findings among diverse ethnic populations, including clinical populations, as well as developing therapeutic targets based on the identified proteins. Additionally, future studies should develop standardized protocols for biomarker measurement and establish clinical guidelines for incorporating these proteins into routine clinical practice to improve diagnostic accuracy, prognostication, and treatment strategies for patients with CKD and hypertension.

5.5 Conclusions

In conclusion, this thesis provides insight into the complex interplay between kidney function and BP from a proteomic perspective. Through comprehensive analyses of large-scale proteomics from prospective general population-based cohort studies, proteins associated with kidney function/CKD, and SBP/hypertension were identified and validated. Some of these identified proteins were found to have causal associations. These findings illuminate potential biomarkers and pathways underlying the pathophysiology of CKD and hypertension, providing valuable insights for risk stratification, early diagnosis, and personalized management strategies. Moving forward, future research should focus on validating our findings among diverse populations, integrating multi-omics data, and translating these findings into clinical practice.

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Paper I

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Authors:	Jie-sheng Lin, Jana Nano, Agnese Petrera, Stefanie M. Hauck, Tanja Zeller, Wolfgang Koenig, Christian L. Müller, Annette Peters, Barbara Thorand
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Proteomic profiling of longitudinal changes in kidney function among middle-aged and older men and women: the KORA S4/F4/FF4 study

Jie-sheng Lin[1,2], Jana Nano[1,3], Agnese Petrera[4], Stefanie M. Hauck[4], Tanja Zeller[5,6], Wolfgang Koenig[7,8,9], Christian L. Müller[10,11,12,13], Annette Peters[1,3,14] and Barbara Thorand[1,14*]

Abstract

Background Due to the asymptomatic nature of the early stages, chronic kidney disease (CKD) is usually diagnosed at late stages and lacks targeted therapy, highlighting the need for new biomarkers to better understand its pathophysiology and to be used for early diagnosis and therapeutic targets. Given the close relationship between CKD and cardiovascular disease (CVD), we investigated the associations of 233 CVD- and inflammation-related plasma proteins with kidney function decline and aimed to assess whether the observed associations are causal.

Methods We included 1140 participants, aged 55–74 years at baseline, from the Cooperative Health Research in the Region of Augsburg (KORA) cohort study, with a median follow-up time of 13.4 years and 2 follow-up visits. We measured 233 plasma proteins using a proximity extension assay at baseline. In the discovery analysis, linear regression models were used to estimate the associations of 233 proteins with the annual rate of change in creatinine-based estimated glomerular filtration rate (eGFRcr). We further investigated the association of eGFRcr-associated proteins with the annual rate of change in cystatin C-based eGFR (eGFRcys) and eGFRcr-based incident CKD. Two-sample Mendelian randomization was used to infer causality.

Results In the fully adjusted model, 66 out of 233 proteins were inversely associated with the annual rate of change in eGFRcr, indicating that higher baseline protein levels were associated with faster eGFRcr decline. Among these 66 proteins, 21 proteins were associated with both the annual rate of change in eGFRcys and incident CKD. Mendelian randomization analyses on these 21 proteins suggest a potential causal association of higher tumor necrosis factor receptor superfamily member 11A (TNFRSF11A) level with eGFR decline.

Conclusions We reported 21 proteins associated with kidney function decline and incident CKD and provided preliminary evidence suggesting a potential causal association between TNFRSF11A and kidney function decline. Further Mendelian randomization studies are needed to establish a conclusive causal association.

Keywords Proteomics, Glomerular filtration rate, Chronic kidney disease, Cohort study, Mendelian randomization

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*Correspondence:
Barbara Thorand
thorand@helmholtz-muenchen.de
Full list of author information is available at the end of the article

Background

Chronic kidney disease (CKD), which is characterized by a progressive loss in kidney function over months or years [1], affected approximately 9.1% of the general population globally in 2017 [2]. Estimated glomerular filtration rate (eGFR), together with albuminuria and blood urea nitrogen, are the most commonly used indicators to evaluate kidney function and diagnose CKD in clinical practice. Kidney function declines with aging, while early stages of CKD remain asymptomatic, resulting in CKD usually being diagnosed in late stages. Besides, there is no targeted therapy for CKD beyond the management of its risk factors, such as diabetes and hypertension. The pathophysiology leading to CKD is not completely understood, and thus, there is a pressing need to identify new biomarkers that may provide new insight into the underlying pathophysiology of CKD, help in early diagnosis, and potentially be used as therapeutic targets.

It has been well documented that CKD is strongly related to cardiovascular diseases (CVD), and they share common mechanisms such as oxidative stress and inflammation [3, 4]. Thus, targeting CVD- and inflammation-related biomarkers may provide a valuable opportunity to identify biomarkers likely to be involved in the pathophysiology of CKD. Advances in proteomics technology, such as proximity extension assay technology using the Olink platform [5], make it possible to measure a large number of targeted biomarkers simultaneously.

An increasingly large number of studies investigating the associations of urinary and circulating proteomic biomarkers with kidney function and the progression of kidney disease have been published in the past decade [6–16]. We have previously identified and replicated 42 proteins associated with kidney function from a panel of inflammatory proteins, and revealed several pathophysiological pathways related to kidney disease using pathway analysis, highlighting the importance of investigating proteomics profiling in the general population [15]. A longitudinal study applying a large proteomics approach also identified novel biomarkers of progression to kidney failure in diabetic patients [16].

The present study aimed to investigate the associations of 233 CVD- and inflammation-related plasma proteins with longitudinal changes in kidney function in a community-based prospective cohort of middle-aged and older adults to uncover biomarkers and pathways involved in longitudinal kidney function decline and CKD development. Furthermore, we aimed to investigate whether the observed associations were potentially causal by using a two-sample Mendelian randomization (MR) design.

Methods

Study population

This study was based on the Cooperative Health Research in the Region of Augsburg (KORA) S4/F4/FF4 cohort study [17, 18]. A total of 4261 adults, aged 25–74 years, were included at baseline between 1999 and 2001 (S4) in Germany. Follow-up examinations were conducted after 7 years (F4) and after 14 years (FF4). The present analysis was restricted to participants aged 55–74 years at S4 ($N=1653$). The flow chart of study participants is presented in Fig. 1. Participants without data on creatinine-based estimated glomerular filtration rate (eGFRcr, $n=19$) or complete proteomics measurements ($n=68$) at KORA S4 were excluded, leaving a total of 1566 participants at baseline. For the longitudinal analysis, participants without follow-up information on eGFRcr at both F4 and FF4 ($n=426$) were further excluded. Finally, a total of 1140 participants were included, with a median follow-up time of 13.4 (25^{th} percentile: 7.1, 75^{th} percentile: 13.5) years (Fig. 1A). Among these 1140 participants, 638 participants were both followed up at F4 and FF4, 482 participants were only followed up at F4, and 20 participants were only followed up at FF4 (Fig. 1B). Participants with eGFRcr-based CKD at baseline ($n=54$) were further excluded when investigating the associations of proteomic biomarkers with incident CKD. The KORA S4, F4, and FF4 studies were approved by the local ethical committee (Number: 99186) and all participants gave written informed consent.

Measurement of proteomic biomarkers

Plasma samples of baseline participants aged 55–74 years were used to measure proteomic biomarkers. Three Olink panels, including the Proseek Multiplex CVD II, CVD III, and Inflammation panels (Olink, Upsala, Sweden), each covering 92 proteins, were measured using proximity extension assay technology [5]. The assay allows the relative quantification of analyte concentrations and was given as normalized protein expression values on a log2 scale, with higher expression values corresponding to higher protein levels. Details of the measurement process and exclusion of the proteins (e.g., proteins with more than 25% of all data below the limit of detection were excluded) have been reported elsewhere [19, 20]. A total of 233 proteins were included in this study (Additional file 1: Table S1). The Z-score transformation was conducted for all values of proteins in 1566 participants with complete proteomics measurements at baseline, which allows comparing the magnitude of the effect sizes across proteins and Z-score transformation was appropriate for most of our proteins after evaluating the distribution of each protein.

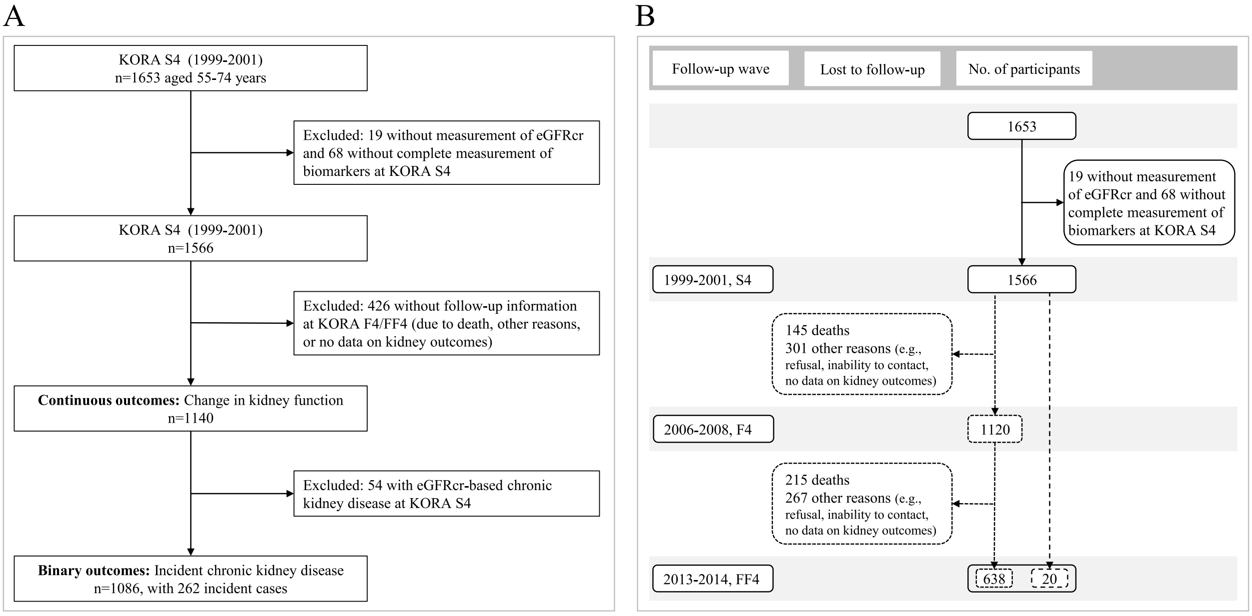

Fig. 1 Flowchart of study participants. Abbreviations: eGFRcr, creatinine-based estimated glomerular filtration rate; KORA S4/F4/FF4, the Cooperative Health Research in the Region of Augsburg (KORA) cohort study at baseline (S4), first follow-up (F4) and second follow-up (FF4)

Measurement of kidney function and CKD

The primary outcomes in the present study were the annual rate of change in eGFRcr and incident eGFRcr-based CKD, given their availability at KORA S4, F4, and FF4. Creatinine was assessed in fresh serum using an enzymatic method at S4 (CREA plus, Boehringer, Mannheim, Germany), a modified kinetic rate Jaffe method at F4 and the first part of FF4 (CREA Flex, Dade Behring / Siemens Healthcare Diagnostics Products GmbH), and a Jaffe method for the second part of FF4 (Cobas 8000 instrument, Roche Diagnostics, Mannheim, Germany). Serum creatinine at KORA F4 and FF4 (part 1) were Isotope-Dilution Mass Spectrometry standardized. Kidney function was primarily assessed by eGFRcr calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) Eq. 2009 [21]. A CKD case was defined as eGFRcr < 60 ml/min per 1.73m^2 [1]. Participants free of CKD at S4 who had CKD at F4 or FF4 were defined as incident cases. In addition, the new race-free CKD-EPI Eq. 2021 [22] was used to calculate eGFRcr for supplementary analyses. Cystatin C-based eGFR (eGFRcys) was calculated using CKD-EPI cystatin C Eq. 2012 [23] and used for confirmation of significant associations. In comparison to eGFRcr, there were 278, 5, and 17 missing values on eGFRcys at S4, F4, and FF4, respectively, and imputation of missing values of eGFRcys was conducted by using a linear mixed-effects model. Additionally, urine albumin to creatinine ratio (UACR) was also available at F4. Details on measurements of UACR and cystatin C and imputation of missing values of eGFRcys are presented in Additional file 2: Text S1.

Covariates

In all surveys, standardized face-to-face interviews were conducted by trained staff [17], gathering the following information: age, sex, physical activity (active/inactive), smoking status (never/former/current smoker), alcohol consumption (0/0–20.0/ > = 20 g/d), use of antihypertensive medication (yes/no), use of lipid-lowering medication (yes/no), prevalent diabetes (yes/no), prevalent cardiovascular diseases (yes/no), and fasting status (fasting for 8 h or more before blood was taken, yes/no) [24, 25]. Participants who were non-fasting before blood was taken were predominantly participants with diabetes. Anthropometric indices and blood pressure were measured based on standard protocols. High-density lipoprotein-cholesterol and triglycerides were measured in serum on Hitachi 717/917 (Boehringer, Mannheim, Germany), respectively.

Statistical analysis

Continuous variables were reported as mean (standard deviation, SD) for normally distributed data and median (interquartile range) for skewed data. Categorical variables were presented as total numbers with the corresponding percentage.

Identification and confirmation of change in eGFR-associated proteins

For participants with eGFR measured at more than one visit (*n* = 1140), the annual rate of change in eGFR was calculated as β coefficients from linear regression of eGFR regressed against age at the time of eGFR measurement for each participant, and thus, each participant had 1 annual rate of change in eGFR (Additional file 2: Figure S1). Additional file 2: Figure S2 shows the flowchart of statistical analyses. In the discovery analysis, linear regression models were used to estimate the associations of the 233 proteins with the annual rate of change in eGFRcr. Two models were constructed: model 1 adjusted for age, sex, and eGFRcr at baseline; model 2 further adjusted for body mass index, physical activity, smoking status, alcohol consumption, systolic blood pressure, use of antihypertensive medication, triglycerides (naturally log-transformed), high-density lipoprotein cholesterol, use of lipid-lowering medication, prevalent diabetes, prevalent cardiovascular diseases, and fasting status at baseline. The 66 biomarkers significantly associated with the annual rate of change in eGFRcr were taken to investigate their associations with the annual rate of change in eGFRcys. Given the high proportion of missing values at FF4, we did not use linear mixed-effect models. Benjamini–Hochberg false-discovery rate (FDR) was performed for multiple testing correction, and FDR < 0.05 was considered statistically significant [26]. FDR seemed to be more appropriate to correct for multiple testing in our large-scale proteomics exploratory study, because it controls the rate of false positives while still allowing for the identification of a number of potential biomarkers.

Several sensitivity analyses of associations between the 66 significant biomarkers and the annual rate of change in eGFRcr were conducted based on model 2 described above. The analyses were repeated after exclusion of participants who were non-fasting at the time of blood sampling (*n* = 113), exclusion of participants who had CKD at baseline (*n* = 54), exclusion of participants who had an increase in eGFRcr during follow-up (*n* = 151), or further adjusted for UACR at F4 to control for the confounding effect of albuminuria (UACR values were unavailable at S4). To partially address bias caused by loss to follow-up (due to death or other reasons, Fig. 1B), the inverse probability weighting method [27] was used to calculate a weight for each participant. Each participant's probability of loss to follow-up (P1) was estimated by logistic regression with loss to follow-up (yes/no) as outcomes, including baseline covariates in the above model 2 as predictors. Inverse probability weighting-weight was calculated as 1/(1-P1) and these weights were applied in model 2 (details are presented in Additional file 2: Text S2).

To further assess the robustness of our results on the annual rate of change in eGFRcr, rapid decline in eGFRcr (yes/no), which was defined as the annual rate of change in eGFRcr < -3 ml/min/1.73 m^2/year [28], was used to investigate associations with the 66 eGFRcr-associated biomarkers in logistic regressions, adjusting for the same covariates as in the above model 2.

Identification of incident CKD-associated proteins

The 66 proteins significantly associated with the annual rate of change in eGFRcr were taken to investigate their associations with eGFRcr-based incident CKD, using interval-censored Cox regression models (500 bootstrap samples were used to construct 95% confidence intervals), adjusted for the same covariates in the above model 2, using R package "icenReg v.2.0.15" [29]. Cox proportional hazards models were not appropriate, because we did not know the exact time point of CKD occurrence. In sensitivity analyses, incident eGFRcr-based CKD cases were redefined as follows: Participants free of CKD at S4 or F4, respectively, had to have more than 25% decline in eGFRcr together with eGFRcr < 60 ml/min per 1.73m^2 at the following follow-up (i.e., F4 or FF4), or participants free of CKD at S4 had to have more than 50% decline in eGFRcr together with eGFRcr < 60 ml/min per 1.73m^2 at FF4 [28]. The controls were defined as eGFRcr ≥ 60 ml/min per 1.73m^2 at S4, F4, and FF4.

The proteins consistently associated with the annual rate of change in eGFRcr, the annual rate of change in eGFRcys, and incident CKD were further investigated regarding their associations with UACR at F4 using linear regression. To annotate druggable targets of the identified proteins, related information (e.g., known drugs, corresponding diseases or indications, and clinical trials status) was gathered from Open Targets Platform (https://platform.opentargets.org/) [30] based on their UniProt_IDs. In order to examine the novelty of the identified proteins, relevant publications were searched to check whether the identified proteins had been previously reported to be associated with kidney function and/or CKD.

Mendelian randomization analysis

We applied a two-sample MR design using the largest genome-wide association studies (GWAS) results to date. Additional file 2: Figure S3 shows the process of MR analysis, and details of MR analysis are described in Additional file 2: Text S3 [31–37]. Briefly, selection of single nucleotide polymorphisms (SNPs) for proteins [31] and extraction of SNPs-eGFR decline associations [32] were from European ancestry population-based GWAS. To test the assumption of MR that instrumental variables are not associated with confounders, associations between selected SNPs and other traits were searched for in the PhenoScanner V2 [33]. One SNP (rs198389) was excluded given its associations with blood pressure (Additional file 1: Table S2), leaving 17 proteins for MR analysis (Additional file 1: Table S3). Wald ratio was calculated since only one SNP was available for each protein. MR analyses were performed using R package "TwoSampleMR v.0.5.6" [34].

Pathway enrichment analysis

To characterize biological pathways that are enriched for the identified proteins, a Gene Ontology enrichment analysis was performed, using R package "clusterProfiler v.4.0.5" [38]. To investigate the potential biological pathways linking identified biomarkers and kidney function, the analysis was limited to the biological process subontology, using Fisher's exact test.

All analyses were conducted by R version 4.1.0 (R Development Core Team, Vienna, Austria) and RStudio version 1.4.1717 (RStudio, Boston, MA, USA).

Results

Characteristics of the study population

Table 1 shows the baseline characteristics of participants. The 1140 participants had a mean age of 63.3 (SD, 5.36) years. The median annual rate of change in eGFRcr was -1.04 ml/min/1.73 m^2/year (Additional file 2: Figure S4A). Characteristics and kidney function of all participants over the study period are shown in Additional file 1: Table S4. The mean eGFRcr was 82.9 (SD, 12.2) ml/min/1.73 m^2 at S4 and declined to 67.6 (SD, 15.3) ml/min/1.73 m^2 at FF4. Figure 1B shows the number of participants and reasons for loss to follow-up and Additional file 1: Table S5 shows baseline characteristics for participants with and without follow-up information on eGFRcr. Participants lost to follow-up tended to be older,

Table 1 Baseline characteristics of participants

	Total (*N* = 1140)	**Non-CKD cases (*N* = 824)[b]**	**Future CKD cases (*N* = 262)[b]**
	Mean (standard deviation) or number (%)		
Age (years)	63.3 (5.36)	62.3 (5.17)	65.5 (5.01)
Sex, N(%) female	556 (48.8)	400 (48.5)	125 (47.7)
Body mass index (kg/m^2)	28.4 (4.25)	28.2 (4.22)	28.7 (4.45)
Smoking status, N (%)			
Never smoker	560 (49.1)	304 (36.9)	112 (42.7)
Former smoker	440 (38.6)	415 (50.4)	118 (45.1)
Current smoker	140 (12.3)	105 (12.7)	32 (12.2)
Alcohol consumption			
No alcohol consumption	291 (25.5)	194 (23.5)	76 (29.0)
> 0 and < 20 g/day	462 (40.5)	343 (41.7)	98 (37.4)
≥ 20 g/day	387 (33.9)	287 (34.8)	88 (33.6)
Physically active, N (%)	509 (44.6)	362 (43.9)	126 (48.1)
Systolic blood pressure (mmHg)	135.1 (19.8)	133.8 (19.3)	138.5 (21.3)
Use of antihypertensive medication, N (%)	388 (34.0)	228 (27.7)	126 (48.1)
Hypertension, N (%)	615 (53.9)	405 (49.2)	175 (66.8)
Triglycerides (mmol/L) [a]	1.35 (0.93)	1.31 (0.97)	1.35 (0.90)
High-density lipoprotein cholesterol (mmol/L)	1.50 (0.43)	1.52 (0.43)	1.45 (0.42)
Use of lipid-lowering medication, N (%)	127 (11.1)	84 (10.2)	31 (11.8)
Type 2 diabetes, N (%)	94 (8.20)	53 (6.40)	32 (12.2)
Cardiovascular diseases, N (%)	135 (11.8)	84 (10.2)	37 (14.1)
Fasting status, N (%)	1027 (90.1)	760 (92.2)	221 (84.4)
eGFRcr (ml/min/1.73 m^2)	82.9 (12.2)	86.6 (9.83)	77.1 (9.87)
eGFRcys (ml/min/1.73 m^2)	81.1 (15.2)	84.9 (13.7)	73.6 (13.2)
Annual rate of change in eGFRcr (ml/min/1.73 m^2/year) [a]	-1.04 (1.35)	-0.86 (1.06)	-2.05 (1.36)
Annual rate of change in eGFRcys (ml/min/1.73 m^2/year) [a]	-1.13 (1.47)	-0.93 (1.44)	-1.78 (1.40)

Abbreviations*: *CKD Chronic kidney disease, *eGFRcr* Creatinine-based estimated glomerular filtration rate; *eGFRcys* Cystatin C-based estimated glomerular filtration rate

[a] Reported as median (interquartile range)

[b] Participants with eGFRcr-based CKD at baseline (*n* = 54) were excluded

were more frequently smokers, consumed less alcohol, were less physically active, and had higher systolic blood pressure and prevalence of diabetes.

Associations of proteomic biomarkers with kidney function decline

After adjustment for age, sex, and baseline eGFRcr in model 1, 95 out of 233 biomarkers were inversely associated with the annual rate of change in eGFRcr ($FDR < 0.05$), which means that in comparison to participants with lower levels of biomarkers at baseline, participants with higher levels of biomarkers had a faster decline in eGFRcr (Additional file 1: Table S6). After adjustment for additional covariates in model 2, 66 biomarkers showed inverse associations with change in eGFRcr (62 of these were also significant in model 1) (Additional file 1: Table S6 & Fig. 2). The top 3 biomarkers with the lowest FDR were KIM1 ($FDR = 9.51E\text{-}09$, $\beta = -0.292$), NT-proBNP ($FDR = 1.62E\text{-}06$, $\beta = -0.249$), and EPHB4 ($FDR = 1.62E\text{-}06$, $\beta = -0.233$). The β coefficients for biomarkers significantly associated with eGFRcr decline ranged from -0.292 to -0.098 ml/min/1.73 m^2/year. When calculating eGFRcr using the 2021 equation, the correlation coefficient between the annual rate of change in eGFRcr-2009 and eGFRcr-2021 was 0.998 (Additional file 2: Figure S4D). Among the 233 biomarkers, 67 biomarkers were associated with eGFRcr-2021 decline ($FDR < 0.05$, β ranged from -0.301 to -0.104, Additional file 1: Table S7), and 65 out of these 67 were associated with eGFRcr-2009 decline. In 3 sensitivity analyses removing participants with non-fasting status, CKD, or increase in eGFRcr, 60, 62, and 63 of the 66 biomarkers remained significant, respectively (Additional file 1: Table S8 & Additional file 2: Figure S5). In sensitivity analyses model 2d (further adjusted for UACR) and 2e (inverse probability weighting-weight was applied), all 66 biomarkers remained significant, indicating that albuminuria and bias caused by loss to follow-up may not affect our associations (Additional file 1: Table S8). When investigating associations with rapid eGFRcr decline defined as the annual rate of change in eGFRcr < -3 ml/min/1.73 m^2/year, 61 out of 66 biomarkers were positively associated with rapid eGFRcr decline, with odds ratios ranging from 1.29 to 2.09 (Additional file 1: Table S9).

When investigating their associations with the annual rate of change in eGFRcys, 38 out of 66 biomarkers were inversely associated with change in eGFRcys at levels of $FDR < 0.05$ (Additional file 1: Table S10 & Additional file 2: Figure S6), and associations of the total 233 biomarkers with the annual rate of change in eGFRcys are presented in Additional file 1: Table S11. Associations between baseline characteristics and the annual rate of change in eGFRcr and eGFRcys are presented in Additional file 1: Table S12.

Associations of proteomic biomarkers with eGFRcr-based incident CKD

Among 1086 participants free of eGFRcr-based CKD at baseline, 262 cases of incident CKD were identified during 11,849 person-years of follow-up. Twenty-eight out of the 66 eGFRcr change-associated biomarkers were associated with incident CKD in model 2 ($FDR < 0.05$, Additional file 1: Table S10 & Additional file 2: Figure S7). The hazard ratios (HRs) for biomarkers with significant associations with incident CKD ranged from 1.16 to 1.52. The top 3 biomarkers with the highest HRs and lowest FDR for the associations were TRAIL-R2 (HR, 1.52), TNFRSF9 (HR, 1.51), and TNFRSF11A (HR, 1.49). In sensitivity analyses using the alternative definition of incident cases, 166 cases were identified and 30 out of 66 biomarkers were associated with incident CKD ($FDR < 0.05$, HRs ranged from 1.21 to 1.67), with 27 biomarkers overlapping with the initially identified 28 biomarkers (Additional file 1: Table S9).

We found that 21 proteins were consistently associated with faster decline in eGFRcr, faster decline in eGFRcys, and higher risk of incident CKD (Table 2, Additional file 1: Table S10 & Fig. 3). Among these 21 biomarkers, 17 were also positively associated with higher levels of UACR at F4 (Additional file 1: Table S13). In the discovery of their potential to serve as drug targets, we found 10 out of 21 have been used as drug targets for drugs to treat a wide range of diseases or indications, and IL2-RA has been used as drug target for kidney failure and CKD treatment (Additional file 1: Table S14). All 21 identified biomarkers have been reported in previous proteomic studies (Additional file 1: Table S15). The pairwise correlations of these 21 biomarkers are shown in Additional file 2: Figure S8. After correction for multiple testing, 199 out of 210 pairs of correlations were significant, with a mean correlation coefficient of 0.35 (range 0.14 to 0.88) for significant correlations.

Mendelian randomization analysis

The MR analysis results show a potential causal association of a higher level of TNFRSF11A ($\beta = 0.024$, $P\text{-value} = 0.030$) with faster eGFR decline ($\beta > 0$ means a positive association with eGFR decline [32]). However, no significant associations were observed for any of the proteins after multiple corrections ($FDR > 0.05$, Table 3).

Pathway enrichment analysis

A total of 254 pathways that reached statistical significance ($FDR < 0.05$) were identified when using 21 biomarkers (Table 2 & Fig. 3). The top 15 enriched pathways

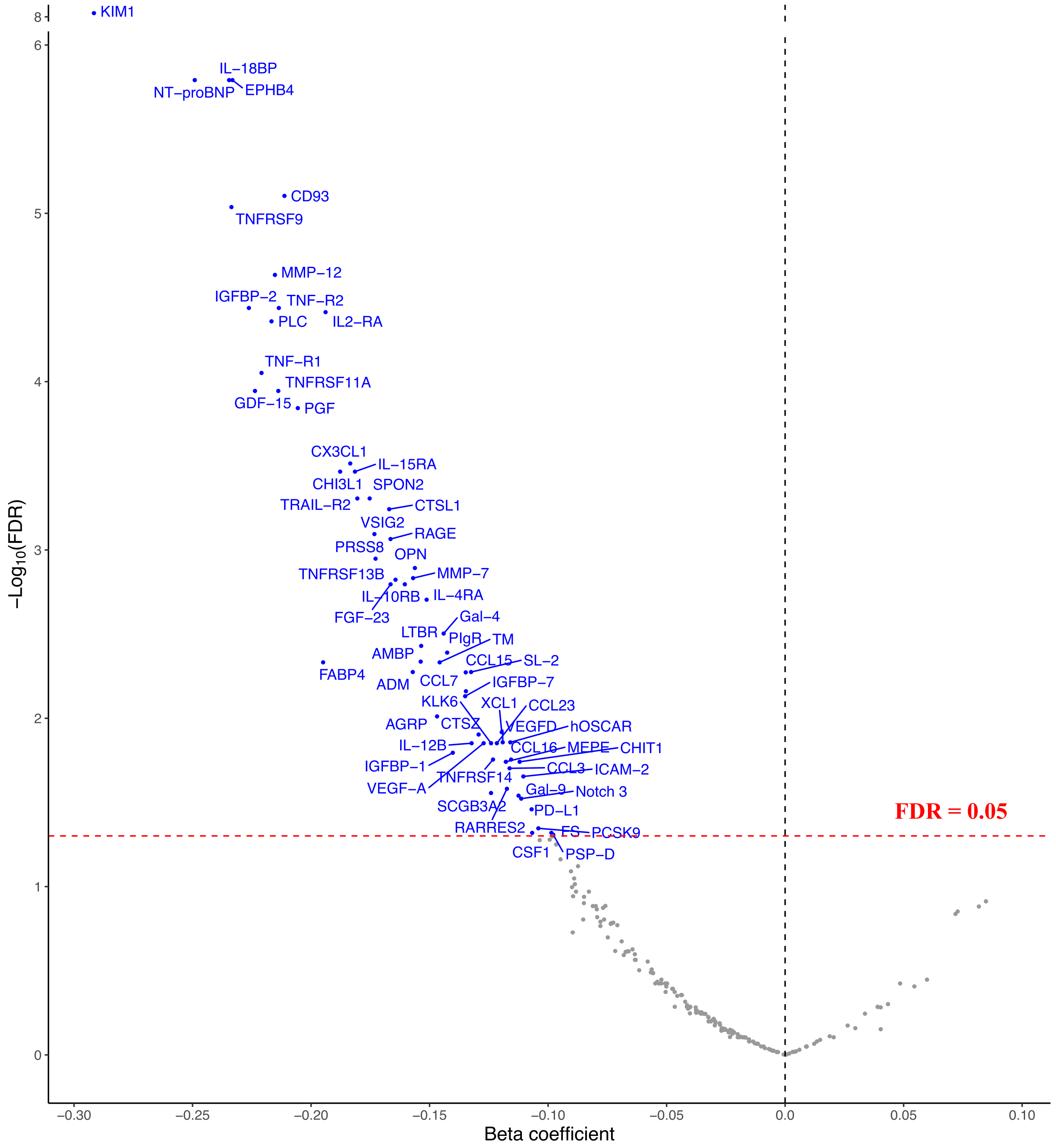

Fig. 2 Association of 233 proteomic biomarkers with the annual rate of change in eGFRcr. Detailed results of beta coefficients and FDR for the association of 233 proteins with change in eGFRcr are presented in Additional file 1: Table S6 for model 2. Abbreviations: eGFRcr, creatinine-based estimated glomerular filtration rate; FDR, Benjamini–Hochberg false-discovery rate. Full names of the biomarkers can be found in Additional file 1: Table S1

were characterized by processes relating to the response of a tumor necrosis factor (TNF) stimulus, T cell proliferation, monocyte chemotaxis, and regulation of lymphocyte and leukocyte chemotaxis (Table 4 & Additional file 2: Figure S9).

Discussion

In this prospective cohort study, we investigated the associations of 233 proteins with longitudinal change in kidney function and incident CKD among 1140 participants. A total of 66 biomarkers were associated with the annual

Table 2 Significant associations of 21 proteomic biomarkers with the annual rate of change in eGFR and CKD incidence [a]

Biomarker	UniProt_ID	Associations with change in eGFRcr ($N = 1140$)			Associations with change in eGFRcys ($N = 1140$)			Associations with CKD incidence ($N = 1086$; cases = 262, controls = 824)		
		β (95%CI)	P	FDR	β (95%CI)	P	FDR	HR (95%CI)	P	FDR
ADM	P35318	-0.157 (-0.249, -0.065)	8.67E-04	5.31E-03	-0.138 (-0.238, -0.038)	6.78E-03	2.13E-02	1.29 (1.07, 1.55)	6.92E-03	2.28E-02
CCL3	P10147	-0.116 (-0.197, -0.036)	4.77E-03	1.98E-02	-0.101 (-0.186, -0.016)	1.98E-02	4.21E-02	1.24 (1.08, 1.42)	2.05E-03	1.13E-02
CCL7	P80098	-0.135 (-0.216, -0.053)	1.19E-03	6.91E-03	-0.095 (-0.181, -0.010)	2.88E-02	4.99E-02	1.25 (1.09, 1.44)	1.78E-03	1.12E-02
EPHB4	P54760	-0.233 (-0.313, -0.153)	1.46E-08	1.62E-06	-0.184 (-0.273, -0.095)	5.18E-05	8.57E-04	1.29 (1.10, 1.52)	2.25E-03	1.14E-02
IGFBP-2	P18065	-0.226 (-0.318, -0.135)	1.36E-06	3.65E-05	-0.168 (-0.268, -0.068)	1.01E-03	6.56E-03	1.29 (1.08, 1.54)	5.37E-03	2.07E-02
IL-15RA	Q13261	-0.181 (-0.266, -0.097)	2.59E-05	3.42E-04	-0.138 (-0.231, -0.044)	4.03E-03	1.48E-02	1.41 (1.20, 1.65)	3.13E-05	3.44E-04
IL-18BP	O95998	-0.235 (-0.317, -0.152)	2.70E-08	1.62E-06	-0.161 (-0.252, -0.069)	6.13E-04	5.06E-03	1.24 (1.05, 1.47)	1.08E-02	2.98E-02
IL2-RA	P01589	-0.194 (-0.273, -0.115)	1.66E-06	3.87E-05	-0.108 (-0.193, -0.022)	1.40E-02	3.18E-02	1.21 (1.04, 1.40)	1.26E-02	3.32E-02
KIM1	Q96D42	-0.292 (-0.377, -0.206)	4.08E-11	9.51E-09	-0.138 (-0.229, -0.047)	3.08E-03	1.32E-02	1.45 (1.23, 1.71)	9.94E-06	3.01E-04
NT-proBNP	P16860	-0.249 (-0.336, -0.162)	2.77E-08	1.62E-06	-0.238 (-0.331, -0.145)	5.66E-07	3.74E-05	1.30 (1.10, 1.54)	1.87E-03	1.12E-02
OPN	P10451	-0.156 (-0.236, -0.076)	1.37E-04	1.28E-03	-0.101 (-0.188, -0.014)	2.36E-02	4.59E-02	1.23 (1.06, 1.42)	6.15E-03	2.13E-02
PD-L1	Q9NZQ7	-0.107 (-0.187, -0.026)	9.24E-03	3.47E-02	-0.106 (-0.191, -0.022)	1.36E-02	3.18E-02	1.30 (1.13, 1.51)	3.44E-04	2.84E-03
PLC	P98160	-0.217 (-0.306, -0.128)	2.07E-06	4.38E-05	-0.142 (-0.240, -0.044)	4.58E-03	1.59E-02	1.31 (1.10, 1.57)	2.82E-03	1.33E-02
TM	P07204	-0.146 (-0.230, -0.061)	7.13E-04	4.65E-03	-0.105 (-0.195, -0.015)	2.24E-02	4.49E-02	1.26 (1.07, 1.49)	5.65E-03	2.07E-02
TNF-R1	P19438	-0.221 (-0.315, -0.127)	4.57E-06	8.88E-05	-0.174 (-0.279, -0.070)	1.09E-03	6.56E-03	1.24 (1.05, 1.47)	1.31E-02	3.33E-02
TNF-R2	P20333	-0.214 (-0.300, -0.127)	1.41E-06	3.65E-05	-0.197 (-0.294, -0.101)	6.49E-05	8.57E-04	1.31 (1.12, 1.54)	7.94E-04	5.82E-03
TNFRSF11A	Q9Y6Q6	-0.214 (-0.306, -0.121)	6.37E-06	1.14E-04	-0.208 (-0.308, -0.109)	4.37E-05	8.57E-04	1.49 (1.23, 1.79)	2.95E-05	3.44E-04
TNFRSF9	Q07011	-0.234 (-0.322, -0.145)	2.36E-07	9.18E-06	-0.170 (-0.269, -0.070)	8.59E-04	6.30E-03	1.51 (1.30, 1.75)	4.12E-08	2.72E-06
TRAIL-R2	O14763	-0.180 (-0.267, -0.094)	4.24E-05	4.94E-04	-0.105 (-0.198, -0.013)	2.61E-02	4.78E-02	1.52 (1.26, 1.84)	1.45E-05	3.01E-04
VEGF-A	P15692	-0.127 (-0.211, -0.043)	2.96E-03	1.41E-02	-0.142 (-0.230, -0.054)	1.56E-03	8.55E-03	1.27 (1.08, 1.50)	3.21E-03	1.41E-02
XCL1	P47992	-0.120 (-0.196, -0.043)	2.23E-03	1.21E-02	-0.103 (-0.183, -0.022)	1.27E-02	3.11E-02	1.16 (1.03, 1.31)	1.54E-02	3.75E-02

Abbreviations: *CI* Confidence interval, *CKD* Chronic kidney disease; *eGFRcr* Creatinine-based estimated glomerular filtration rate; *eGFRcys* Cystatin C-based estimated glomerular filtration rate, *FDR* Benjamini–Hochberg false-discovery rate, *HR* Hazard ratio. Full names of the biomarkers can be found in Additional file 1: Table S1

[a] The 66 biomarkers significantly associated with the annual rate of change in eGFRcr were used to investigate their associations with the annual rate of change in eGFRcys using linear regressions and eGFRcr-based incident CKD using interval-censored Cox regressions. Detailed information and results are presented in Additional file 1: Table S10. The 21 biomarkers significantly associated with both the annual rate of change in eGFRcys and incident CKD ($FDR < 0.05$) are presented in this table

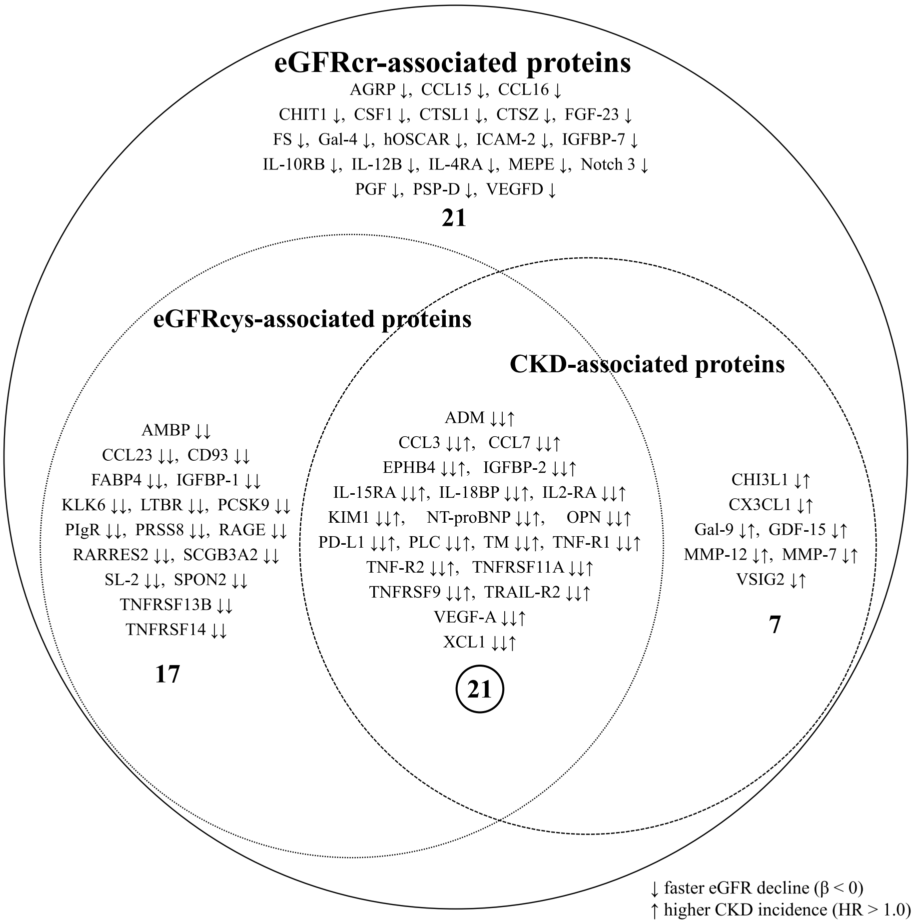

Fig. 3 Overlap of proteomic biomarkers associated with kidney function decline and incident CKD. Kidney function decline includes both the annual rate of change in eGFRcr and the annual rate of change in eGFRcys. Detailed results are presented in Additional file 1: Table S10. Abbreviations: CKD, chronic kidney disease; eGFRcr, creatinine-based estimated glomerular filtration rate; eGFRcys, cystatin C-based estimated glomerular filtration rate; HR, hazard ratio. Full names of the biomarkers can be found in Additional file 1: Table S1

rate of change in eGFRcr in discovery analysis, and 21 biomarkers out of these, were found to be also associated with both the annual rate of change in eGFRcys and incident CKD. Using a two-sample MR approach, we provided preliminary evidence suggesting a potential causal association between TNFRSF11A and kidney function decline (P-value = 0.030, FDR = 0.463).

All 21 biomarkers that we identified were associated with greater kidney disease risk, probably because we targeted 233 CVD- and inflammation-related biomarkers. Our results were consistent with previous studies investigating proteomic biomarkers measured by the same Olink panels and kidney function [8, 12, 15]. Some of the proteins that we identified are well-known biomarkers of kidney function, such as kidney injury molecule (KIM1), TNF-R1, TNF-R2, and TNF-related apoptosis-inducing ligand receptors 2 (TRAIL-R2), supporting the feasibility of proteomic analysis to identify biomarkers of kidney function decline. In the present study, KIM1 was the biomarker with the strongest association with kidney function decline. KIM1 has been extensively studied and represents a potential biomarker of tubular injury in both animals and humans [39, 40]. Longitudinal studies have also reported that urinary and blood KIM1 are positively associated with kidney function decline, incident CKD, and CKD progression in both diabetic patients and the general population [8, 13, 14, 39, 41, 42]. When investigating the associations with incident CKD, TRAIL-R2 was the biomarker with the strongest association in our study. The best-understood function of TRAIL-R2 is the induction of apoptosis [43]. TRAIL-R2 has been found to be associated with kidney function decline in several proteomic studies [8, 10, 11, 13]. For example, TRAIL-R2 was the biomarker with the strongest association with kidney function decline among 80 CVD-related plasma proteins in a longitudinal study [10]. Several other TNF superfamily receptors (TNFRSF)

Table 3 Results of the two-sample Mendelian randomization analysis between 17 proteins and eGFR decline

Biomarkers	MR_Method	No. IVs	% variance explained by SNP[a]	β (95%CI)	SE	*P*-value	FDR
ADM	Wald ratio	1	1.32	0.033 (-0.026, 0.092)	0.030	0.279	0.694
CCL7	Wald ratio	1	0.61	-0.022 (-0.105, 0.061)	0.042	0.610	0.845
EPHB4	Wald ratio	1	1.23	-0.015 (-0.070, 0.041)	0.028	0.609	0.845
IGFBP-2	Wald ratio	1	0.20	0.008 (-0.133, 0.150)	0.072	0.908	0.965
IL-15RA	Wald ratio	1	2.92	-0.028 (-0.065, 0.010)	0.019	0.147	0.626
IL2-RA	Wald ratio	1	14.8	-0.004 (-0.022, 0.013)	0.009	0.646	0.845
OPN	Wald ratio	1	0.44	0.065 (-0.035, 0.165)	0.051	0.202	0.687
PD-L1	Wald ratio	1	4.61	0.010 (-0.018, 0.038)	0.014	0.488	0.829
PLC	Wald ratio	1	1.27	-0.054 (-0.110, 0.002)	0.029	0.058	0.463
TM	Wald ratio	1	1.21	-0.008 (-0.062, 0.046)	0.028	0.767	0.884
TNF-R1	Wald ratio	1	0.31	0.020 (-0.122, 0.162)	0.072	0.780	0.884
TNF-R2	Wald ratio	1	1.24	0.022 (-0.029, 0.073)	0.026	0.394	0.744
TNFRSF11A	Wald ratio	1	11.2	0.024 (0.002, 0.046)	0.011	**0.030**	0.463
TNFRSF9	Wald ratio	1	1.21	0.048 (-0.006, 0.103)	0.028	0.082	0.463
TRAIL-R2	Wald ratio	1	5.58	-0.001 (-0.028, 0.027)	0.014	0.968	0.968
VEGF-A	Wald ratio	1	24.2	0.006 (-0.006, 0.019)	0.006	0.317	0.694
XCL1	Wald ratio	1	22.4	0.006 (-0.006, 0.019)	0.006	0.327	0.694

Abbreviations: *CI* Confidence interval, *eGFR* Glomerular filtration rate, *IVs* Instrumental variables, *FDR* Benjamini–Hochberg false-discovery rate, *MR* Mendelian randomization, *SE* Standard error, *SNP* Single nucleotide polymorphism. Full names of the biomarkers can be found in Additional file 1: Table S1

[a] The proportion of proteomic biomarkers' variance explained by the SNP [31]

Table 4 Pathway enrichment analysis of the 21 identified biomarkers showing top biological processes related to kidney function [a]

Gene Ontology	Description	Gene	FDR
GO:0071356	Cellular response to tumor necrosis factor	TNFRSF11A, XCL1, CCL3, CCL7, TNFRSF9, TNFRSF1A, TNFRSF1B	2.01E-05
GO:0034612	Response to tumor necrosis factor	TNFRSF11A, XCL1, CCL3, CCL7, TNFRSF9, TNFRSF1A, TNFRSF1B	2.01E-05
GO:0035747	Natural killer cell chemotaxis	XCL1, CCL3, CCL7	7.27E-05
GO:0002548	Monocyte chemotaxis	TNFRSF11A, XCL1, CCL3, CCL7	1.87E-04
GO:0042129	Regulation of T cell proliferation	XCL1, CD274, IGFBP2, IL2RA, TNFRSF1B	1.87E-04
GO:0032496	Response to lipopolysaccharide	ADM, THBD, TNFRSF11A, CCL3, CD274, TNFRSF1B	1.87E-04
GO:0007565	Female pregnancy	ADM, THBD, VEGFA, IGFBP2, SPP1	1.87E-04
GO:0140131	Positive regulation of lymphocyte chemotaxis	XCL1, CCL3, CCL7	1.87E-04
GO:0002237	Response to molecule of bacterial origin	ADM, THBD, TNFRSF11A, CCL3, CD274, TNFRSF1B	1.95E-04
GO:0042098	T cell proliferation	XCL1, CD274, IGFBP2, IL2RA, TNFRSF1B	2.21E-04
GO:0050727	Regulation of inflammatory response	TNFRSF11A, XCL1, CCL3, IL2RA, TNFRSF1A, TNFRSF1B	2.21E-04
GO:0044706	Multi-multicellular organism process	ADM, THBD, VEGFA, IGFBP2, SPP1	2.29E-04
GO:0002690	Positive regulation of leukocyte chemotaxis	XCL1, CCL3, CCL7, VEGFA	2.29E-04
GO:1,901,623	Regulation of lymphocyte chemotaxis	XCL1, CCL3, CCL7	2.29E-04
GO:0097529	Myeloid leukocyte migration	TNFRSF11A, XCL1, CCL3, CCL7, VEGFA	2.29E-04

Abbreviations: *CKD* Chronic kidney disease, *eGFRcr* Creatinine-based estimated glomerular filtration rate, *eGFRcys* Cystatin C-based estimated glomerular filtration rate, *FDR* Benjamini–Hochberg false-discovery rate

[a] The 21 biomarkers significantly associated with the annual rate of change in eGFRcr, the annual rate of change in eGFRcys, and incident CKD (Table 2 & Fig. 3), were included in the pathway enrichment analysis. The y-axis signifies the top 15 biological processes in kidney function. The x-axis is the -log10 of the FDR

were found to be related to kidney function decline in our study, including TNF-R1, TNF-R2, TNFRSF9, and TNFRSF11A. In our pathway enrichment analysis, TNF response- and inflammatory response-related pathways were in the top 15 pathways related to kidney function and CKD (Table 4 & Additional file 2: Figure S9). Thus, our study provides additional evidence that TNF signaling pathways and inflammation may play a role in the pathophysiology of CKD. Similarly, a previous study identified a panel of 17 proteins from 194 plasma inflammatory proteins to be associated with end-stage kidney disease (ESKD) risk in diabetic patients, and these 17 proteins were enriched for TNF superfamily receptors [9]. The findings supported the involvement of immune response mechanisms in the development of CKD, which is also consistent with our pathway analysis, implicating T cell proliferation-related mechanisms involved in kidney function pathophysiology. Three chemokines, including C–C motif chemokine 3 (CCL3), C–C motif chemokine 7 (CCL7), and lymphotactin (XCL1), were involved in more than half of the top 15 pathways, and have been reported to be inversely associated with kidney function in previous studies [8, 10, 12, 13, 15]. Chemokines may play a key role in guiding inflammatory cells into the sites of inflammation in kidneys and recruiting immune cells such as T cells and monocytes during the development of chronic kidney injury [44]. Increasing evidence suggests that chemokines and their receptors may be potential targets for anti-inflammatory therapy in CKD [45].

Another important biomarker we identified was N-terminal prohormone brain natriuretic peptide (NT-proBNP), which has been shown to be a reliable biomarker for diagnosis of heart failure and prognostic evaluation among patients with heart failure [46]. In the present study, NT-proBNP was the second strongest biomarker associated with kidney function decline, which is in line with findings from other KORA cohort-based studies [47, 48]. Similarly, a recent proteomic study found that higher plasma NT-proBNP was associated with worsening kidney function among 5131 patients with type 2 diabetes [8]. Community-based longitudinal studies have also found that blood NT-proBNP is positively associated with kidney function decline and incident CKD [49, 50]. The exact mechanisms explaining the link between NT-proBNP and kidney function decline remain unclear. Several pathways have been proposed to explain the association. The increase in blood NT-proBNP can result from cardiac stretch, volume overload, and venous congestion, which in turn, are potential risk factors of kidney function decline. For example, volume overload or venous congestion can lead to an increase in central venous pressure, which has been reported to be associated with impaired kidney function [51, 52]. On the other hand, NT-proBNP is partially dependent on kidney clearance for elimination, so the concentration of NT-proBNP accumulates with impaired kidney function [53, 54]. Thus, NT-proBNP could be only a marker for other kidney-damaging risk factors rather than a causal risk factor itself. Further studies are warranted to explore the underlying mechanisms. In addition to NT-proBNP, we also identified another heart failure-related biomarker, adrenomedullin, which has previously been found to play a pathophysiological role in kidney disease [55].

A similar previous study by Grams et al. [14] investigated associations of 4877 proteins measured by the SomaScan platform with a composite outcome of more than 50% eGFR decline or ESKD among 3 American-based cohorts, including 2 kidney disease-related cohorts (1 of them was an African American cohort). However, our study was based on a community-based cohort of a relatively healthy European population. As differences in dietary habits and genetic background between ethnically diverse populations may affect both levels of protein expression and kidney function, it is important to verify observed associations in independent populations from various regions. Furthermore, most of the CKD cases we identified did not yet progress to ESKD (only 2 out of 262 incident cases had ESKD, i.e., eGFRcr $<$ 15 ml/min per 1.73m^2). Thus, we mainly focused on the annual rate of kidney function decline as an outcome rather than severe eGFR decline (e.g., $\geq$ 50% decline) or ESKD. Of note, our sensitivity analyses on rapid kidney function decline and redefinition of incident CKD cases show robust results (Additional file 1: Table S9). In our study, we targeted 233 CVD- and inflammation-related proteins measured by the Olink platform based on prior knowledge of close CKD-CVD relations, providing a more targeted approach to uncover pathways and mechanisms underlying kidney disease compared to the more comprehensive SomaScan platform used in the previous study [14]. However, it is worth noting that the smaller number of proteins measured by the Olink platform may be seen as a disadvantage compared to the SomaScan platform [56]. In a study by Rooney et al. [57] comparing correlations of 417 proteins that overlapped between the Olink and SomaScan platforms in 427 participants, the median Spearman correlation coefficient was 0.53 (range -0.21 to 0.97) and only 19% of the correlation coefficients were higher than 0.8. When Rooney et al. [57] further investigated associations of the overlapping proteins with eGFR, Olink platform-based proteins demonstrated more associations with eGFR, particularly in the group of proteins with Spearman correlation coefficients less than 0.3. Katz et al. [56] reported similar results and showed that the median Spearman correlation coefficient of proteins that overlapped between the two platforms was 0.45. These results show that findings from proteomic studies can be affected by the used platform, but the superiority of one platform over the other has not been clearly established yet. Thus, proteomic studies based on different platforms are important and our study adds to the existing literature in the field.

In MR analysis, our results show preliminary evidence suggesting a potential causal association of TNFRSF11A with eGFR decline (P-value = 0.030). A previous GWAS in 583 coronary patients observed an association of a polymorphism located within the genomic region of TNFRSF11A with kidney function decline [58]. In line with these associations, longitudinal studies that examined proteomics of kidney function also reported that plasma TNFRSF11A was positively associated with kidney function [8, 11]. MR is an effective approach to provide a robust and less biased estimate of causal associations, but our MR analysis was limited by the availability of GWAS, especially GWAS of proteins measured using the Olink platform. As GWAS by Sun et al. [31] reported only cis-SNPs with significance at the level $p < 3.4E\text{-}11$, each protein had only 1 cis-SNP as instrument, which limited the possibility to test the robustness of our results in sensitivity analyses and may have reduced our statistical power [59]. Additionally, the presence of overlapping participants in the 2 GWAS used in the present MR analysis may have caused bias [35], although this potential bias did not significantly change our MR results when using a maximum likelihood method to address it (details in Additional file 2: Text S3 & Additional file 1: Table S16). Further MR analyses based on multiple instruments GWAS summary statistics from larger populations are warranted.

Study strengths include the assessment of a large number of proteomic biomarkers and the use of a large prospective cohort study, with a median follow-up time of 13.4 years and two follow-up visits for most participants. The Strengthening the Reporting of Observational Studies in Epidemiology checklists for cohort studies and MR studies are presented in Additional file 1: Table S17 & 18, respectively. However, several limitations should also be considered. First, we used FDR to correct for multiple testing, which is less conservative and may increase the risk of false positives compared to Bonferroni correction. Furthermore, we did not validate the identified biomarkers in external cohorts since all our 21 identified biomarkers have been reported in previous proteomic studies (Additional file 1: Table S15). Second, there may be misclassification resulting from measurement errors due to different measurement methods of serum creatinine and cystatin C at S4/F4/FF4, and imputation of missing value of eGFRcys. Additionally, we defined CKD cases based on a single creatinine measurement, which does not fulfill the diagnosis of CKD in clinical practice that the presence of eGFRcr < 60 ml/min per 1.73m^2 persists for more than 3 months. Thus, because our data may not be ideally suited for predictive analysis due to various limitations, such as a suboptimal CKD diagnosis and lack of external validation cohorts, we did not develop a prediction model for the development and progression of CKD. Our primary aim was to identify potential biomarkers related to kidney function decline, which may contribute to the development of predictive models, diagnostic strategies, and therapeutic targets in the future. Third, there may be selection bias due to loss to follow-up, but the results of sensitivity analysis with inverse probability weights suggest that this may not affect our result remarkably. Finally, although we adjusted for multiple confounders, we were unable to adjust for albuminuria at baseline due to lack of data.

Conclusions

In conclusion, we found 21 known proteins to be associated with kidney function decline and incident CKD in a Caucasian community-based population and provided further evidence regarding new diagnostic or prognostic biomarkers and therapeutic targets for CKD. Although the current underpowered MR analysis failed to find convincing evidence for causal associations of the 21 proteins with kidney function decline, our results provide preliminary evidence suggesting a potential causal association between TNFRSF11A and kidney function decline and a role of TNF signaling pathways in the pathophysiology of CKD. Further MR studies are needed to establish and validate a conclusive causal association.

Abbreviations

CKD	Chronic kidney disease
CVD	Cardiovascular disease
eGFR	Estimated glomerular filtration rate
eGFRcr	Creatinine-based estimated glomerular filtration rate
eGFRcys	Cystatin c-based estimated glomerular filtration rate
ESKD	End-stage kidney disease
FDR	Benjamini–Hochberg false-discovery rate
GWAS	Genome-wide association study
HR	Hazard ratio
KORA	Cooperative Health Research in the Region of Augsburg
MR	Mendelian randomization
SD	Standard deviation
SNP	Single nucleotide polymorphism
TNF	Tumor necrosis factor
UACR	Urine albumin-creatinine ratio

Supplementary Information

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Additional file 1: Table S1. Normalized expressionvalues for proteomic biomarkers at baseline; **Table S2.** SNPs-traitsassociations retrieved from PhenoScanner V2 for proteins-related SNPs; **Table S3.** Harmonized summary statisticsused in Mendelian randomization analysis; **TableS4.** Characteristics of participants over the study period; **Table S5.** Baseline characteristics forparticipants with and without follow-up information on eGFRcr; **Table S6.** Longitudinal associationsbetween 233 proteomic biomarkers and the annual rate of change in eGFRcr; **Table S7.** Longitudinal associations between 233 proteomicbiomarkers and the annual rate of change in CKD-EPI Equation 2009-based andCKD-EPI Equation 2021-based eGFRcr;**Table S8.** Sensitivity analyses oflongitudinal associations between 66 proteomic biomarkers and the annual rateof change in eGFRcr; **Table S9.** Sensitivityanalyses of association of 66 proteomic biomarkers with rapid decline in eGFRcrand CKD incidence; **Table S10.** Associationof 66 proteomic biomarkers with the annual rate of change in eGFRcys and CKDincidence; **Table S11.** Longitudinalassociations between 233 proteomic biomarkers and the annual rate of change ineGFRcys; **Table S12.** Longitudinal associationsbetween baseline characteristics and the annual rate of change in eGFRcr andeGFRcys; **Table S13.** Association of 21 proteomic biomarkers with UACR; **Table S14.** Summary of druggable targetsand their corresponding disease of the 21 identified proteins; **Table S15.** Proteomic biomarkersassociated with kidney function and/or chronic kidney disease in previouscross-sectional or longitudinal proteomic studies; **Table S16.** Evaluation of bias due to participant overlap intwo-sample Mendelian randomization analysis; **Table S17.** STROBEStatement—checklist of items in reports of observational studies; **Table S18.** STROBE-MR checklist of recommended items in reports of Mendelianrandomization studies.

Additional file 2: Text S1. Assessment of kidneyoutcomes; **TextS2.** Inverse probabilityweighting; **Text S3.** Mendelianrandomization analysis; **Figure S1.** Exampleof the annual rate of change in eGFR for each participant; **Figure S2.** Flowchart of statistical analyses; **Figure S3.** Genetic instrument selection and data harmonization forMendelian randomization analysis; **FigureS4.** Distribution and correlation between the annual rate of change ineGFRcr and eGFRcys; **Figure S5.** Overlapof proteomic biomarkers between biomarkers associated with the annual rate ofchange in eGFRcr in several sensitivity analyses; **Figure S6.** Longitudinal associations between 66 proteomicbiomarkers and the annual rate of change in eGFRcys; **Figure S7.** Association of 66 proteomic biomarkers with eGFRcr-basedCKD incidence; **Figure S8.** Pairwisecorrelation matrix between the 21 identified proteomic biomarkers; **Figure S9.** Pathway enrichment analysisof the 21 identified biomarkers showing top biological processes related tokidney function.

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Authors' contributions
JSL drafted the analysis plan, performed the statistical analysis, interpreted the data, and wrote the first draft of the manuscript. JN, CM, and AnP contributed to the analysis plan and data interpretation. BT designed the study, contributed to the analysis plan and data interpretation. AgP, SH, TZ, WK, AnP, and BT contributed data. All authors read and approved the final manuscript. JSL and BT had primary responsibility for the final content.

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Availability of data and materials
The informed consent given by KORA study participants does not cover data posting in public databases. Cooperation partners can obtain permission to use KORA data under the terms of a project agreement (https://helmholtz-muenchen.managed-otrs.com/external).

Declarations

Ethics approval and consent to participate
The KORA S4, F4, and FF4 studies were approved by the local ethical committee (Number: 99186) and all participants gave written informed consent.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

Author details
[1]Institute of Epidemiology, Helmholtz Zentrum München, German Research Center for Environmental Health (GmbH), Ingolstädter Landstraße 1, 85764 Neuherberg, Germany. [2]Institute for Medical Information Processing, Biometry, and Epidemiology (IBE), Faculty of Medicine, LMU Munich, Pettenkofer School of Public Health, Munich, Germany. [3]Chair of Epidemiology, Institute for Medical Information Processing, Biometry, and Epidemiology (IBE), Ludwig-Maximilians-Universität München, Munich, Germany. [4]Metabolomics and Proteomics Core, Helmholtz Zentrum München, German Research Center for Environmental Health (GmbH), Neuherberg, Germany. [5]University Center of Cardiovascular Science, University Heart and Vascular Center, University Medical Center Hamburg-Eppendorf, Hamburg, Germany. [6]German Center for Cardiovascular Research (DZHK), Partner Site Hamburg, Hamburg, Germany. [7]Deutsches Herzzentrum München, Technische Universität München, Munich, Germany. [8]German Center for Cardiovascular Research (DZHK), Partner Site Munich Heart Alliance, Munich, Germany. [9]Institute of Epidemiology and Medical Biometry, University of Ulm, Ulm, Germany. [10]Institute of Computational Biology, Helmholtz Zentrum München, German Research Center for Environmental Health (GmbH), Neuherberg, Germany. [11]Helmholtz AI, Helmholtz Zentrum München, German Research Center for Environmental Health (GmbH), Neuherberg, Germany. [12]Department of Statistics, Ludwig-Maximilians-Universität München, Munich, Germany. [13]Center for Computational Mathematics, Flatiron Institute, New York, USA. [14]German Center for Diabetes Research (DZD), Partner München-Neuherberg, Neuherberg, Germany.

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Publisher's Note

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Table S1. Normalized expression values for proteomic biomarkers at baseline (N = 1140)

Full name	Biomarker	Mean (SD)	UniProt_ID	Panel
Eukaryotic translation initiation factor 4E-binding protein 1	4E-BP1	9.15 (1.22)	Q13541	Inflammation
Angiotensin-converting enzyme 2	ACE2	4.21 (0.72)	Q9BYF1	CVD II
Adenosine deaminase	ADA	6.31 (0.77)	P00813	Inflammation
A disintegrin and metalloase with thrombospondin motifs 13	ADAM-TS13	6.30 (0.13)	Q76LX8	CVD II
Adrenomedullin	ADM	6.86 (0.47)	P35318	CVD II
Agouti-related	AGRP	5.05 (0.49)	O00253	CVD II
CD166 antigen	ALCAM	7.09 (0.31)	Q13740	CVD III
Protein AMBP	AMBP	8.12 (0.22)	P02760	CVD II
Angiopoietin-1	ANG-1	9.56 (1.04)	Q15389	CVD II
Aminopeptidase N	AP-N	4.82 (0.33)	P15144	CVD III
Axin-1	Axin-1	6.18 (1.64)	O15169	Inflammation
Tyrosine-kinase receptor UFO	AXL	8.77 (0.37)	P30530	CVD III
Bone morphogenetic	BMP-6	5.08 (0.58)	P22004	CVD II
Brother of CDO	BOC	4.27 (0.29)	Q9BWV1	CVD II
Carbonic anhydrase 5A, mitochondrial	CA5A	2.29 (0.98)	P35218	CVD II
Caspase-3	CASP-3	7.46 (1.45)	P42574	CVD III
Caspase-8	CASP8	2.66 (1.01)	Q14790	Inflammation
Eotaxin	CCL11	6.48 (0.59)	P51671	Inflammation
Monocyte chemotactic protein 4	CCL13	12.5 (1.07)	Q99616	Inflammation
C-C motif chemokine 15	CCL15	6.65 (0.52)	Q16663	CVD III
C-C motif chemokine 16	CCL16	6.15 (0.58)	O15467	CVD III
C-C motif chemokine 17	CCL17	8.49 (1.14)	Q92583	CVD II
C-C motif chemokine 19	CCL19	7.55 (1.28)	Q99731	Inflammation
Monocyte chemotactic protein 1	CCL2	11.5 (0.51)	P13500	Inflammation
C-C motif chemokine 20	CCL20	4.38 (1.22)	P78556	Inflammation
C-C motif chemokine 23	CCL23	9.20 (0.56)	P55773	Inflammation
C-C motif chemokine 24	CCL24	4.81 (0.94)	O00175	CVD III
C-C motif chemokine 25	CCL25	5.95 (0.57)	O15444	Inflammation
C-C motif chemokine 28	CCL28	2.14 (0.39)	Q9NRJ3	Inflammation
Macrophage inflammatory protein-1alpha	CCL3	5.00 (0.62)	P10147	Inflammation
C-C motif chemokine 4	CCL4	6.12 (0.72)	P13236	Inflammation
Monocyte chemotactic protein 3	CCL7	1.88 (0.62)	P80098	Inflammation
Scavenger receptor cysteine-rich type 1 M130	CD163	7.94 (0.56)	Q86VB7	CVD III
Natural killer cell receptor 2B4	CD244	7.43 (0.59)	Q9BZW8	Inflammation
T-cell surface glycoCD4	CD4	5.37 (0.51)	P01730	CVD II
CD40L receptor	CD40	12.1 (0.64)	P25942	Inflammation
CD40 ligand	CD40-L	6.42 (1.52)	P29965	CVD II
T-cell surface glycoprotein CD5	CD5	5.71 (0.80)	P06127	Inflammation
T cell surface glycoprotein CD6 isoform	CD6	6.28 (0.98)	P30203	Inflammation
SLAM family member 5	CD84	5.28 (0.55)	Q9UIB8	CVD II
T-cell surface glycoprotein CD8 alpha chain	CD8A	9.91 (0.69)	P01732	Inflammation
Complement component C1q receptor	CD93	10.6 (0.36)	Q9NPY3	CVD III
CUB domain-containing protein 1	CDCP1	3.68 (0.66)	Q9H5V8	Inflammation
Cadherin-5	CDH5	4.30 (0.39)	P33151	CVD III
Carcinoembryonic antigen-related cell adhesion molecule 8	CEACAM8	4.25 (0.78)	P31997	CVD II
Chitinase-3-like 1	CHI3L1	3.96 (0.97)	P36222	CVD III
Chitotriosidase-1	CHIT1	5.18 (1.45)	Q13231	CVD III

Table S1. Normalized expression values for proteomic biomarkers at baseline (N = 1140)

Full name	**Biomarker**	**Mean (SD)**	**UniProt_ID**	**Panel**
Contactin-1	CNTN1	4.43 (0.39)	Q12860	CVD III
Collagen alpha-1(I) chain	COL1A1	2.79 (0.41)	P02452	CVD III
Carboxypeptidase A1	CPA1	5.66 (0.72)	P15085	CVD III
Carboxypeptidase B	CPB1	5.53 (0.69)	P15086	CVD III
Macrophage colony-stimulating factor 1	CSF1	10.1 (0.24)	P09603	Inflammation
Cystatin D	CST5	5.43 (0.54)	P28325	Inflammation
Cystatin-B	CSTB	4.40 (0.78)	P04080	CVD III
Chymotrypsin C	CTRC	9.64 (0.76)	Q99895	CVD II
Cathepsin L1	CTSL1	6.94 (0.32)	P07711	CVD II
Cathepsin Z	CTSZ	5.44 (0.45)	Q9UBR2	CVD III
Fractalkine	CX3CL1	5.75 (0.43)	P78423	Inflammation
C-X-C motif chemokine 1	CXCL1	9.26 (1.21)	P09341	Inflammation
C-X-C motif chemokine 10	CXCL10	8.91 (0.95)	P02778	Inflammation
C-X-C motif chemokine 11	CXCL11	7.33 (1.27)	O14625	Inflammation
C-X-C motif chemokine 16	CXCL16	4.86 (0.33)	Q9H2A7	CVD III
C-X-C motif chemokine 5	CXCL5	11.1 (1.48)	P42830	Inflammation
C-X-C motif chemokine 6	CXCL6	8.20 (1.03)	P80162	Inflammation
C-X-C motif chemokine 9	CXCL9	7.17 (0.76)	Q07325	Inflammation
Decorin	DCN	5.11 (0.28)	P07585	CVD II
2,4-dienoyl-CoA reductase, mitochondrial	DECR1	8.69 (1.48)	Q16698	CVD II
Dickkopf-related 1	Dkk-1	8.98 (0.80)	O94907	CVD II
delta homolog 1	DLK-1	5.86 (0.64)	P80370	CVD III
Delta and Notch-like epidermal growth factor-related receptor	DNER	9.26 (0.25)	Q8NFT8	Inflammation
Epidermal growth factor receptor	EGFR	2.97 (0.23)	P00533	CVD III
Protein S100-A12	EN-RAGE	2.22 (0.89)	P80511	Inflammation
Epithelial cell adhesion molecule	Ep-CAM	5.12 (1.04)	P16422	CVD III
Ephrin type-B receptor 4	EPHB4	5.43 (0.34)	P54760	CVD III
Fatty acid-binding, intestinal	FABP2	9.11 (0.74)	P12104	CVD II
Fatty acid-binding, adipocyte	FABP4	5.35 (0.77)	P15090	CVD III
Tumor necrosis factor receptor superfamily member 6	FAS	5.84 (0.49)	P25445	CVD III
Fibroblast growth factor 19	FGF19	7.82 (0.96)	O95750	Inflammation
Fibroblast growth factor 21	FGF21	5.84 (1.16)	Q9NSA1	Inflammation
Fibroblast growth factor 23	FGF-23	3.86 (0.56)	Q9GZV9	CVD II
Fms-related tyrosine kinase 3 ligand	FLT3L	9.28 (0.41)	P49771	Inflammation
Follistatin	FS	11.9 (0.42)	P19883	CVD II
Galectin-4	Gal-4	3.69 (0.51)	P56470	CVD III
Galectin-9	Gal-9	8.86 (0.37)	O00182	CVD II
Growth/differentiation factor 15	GDF-15	5.25 (0.55)	Q99988	CVD III
Growth/differentiation factor 2	GDF-2	8.90 (0.56)	Q9UK05	CVD II
Growth hormone	GH	8.19 (2.08)	P01241	CVD II
Gastric intrinsic factor	GIF	7.95 (1.03)	P27352	CVD II
Lactoylglutathione lyase	GLO1	6.82 (1.15)	Q04760	CVD II
Human GPVI Antibody	GPVI	2.93 (0.98)	Q9HCN6	CVD III
Granulins	GRN	5.24 (0.34)	P28799	CVD III
Gastrotropin	GT	1.75 (0.65)	P51161	CVD II
Hydroxyacid oxidase 1	HAOX1	5.36 (1.42)	Q9UJM8	CVD II
Proheparin-binding EGF-like growth factor	HB-EGF	6.33 (0.67)	Q99075	CVD II

Table S1. Normalized expression values for proteomic biomarkers at baseline (N = 1140)

Full name	**Biomarker**	**Mean (SD)**	**UniProt_ID**	**Panel**
Hepatocyte growth factor	HGF	8.89 (0.47)	P14210	Inflammation
Heme oxygenase 1	HO-1	11.5 (0.40)	P09601	CVD II
Osteoclast-associated immunoglobulin-like receptor	hOSCAR	10.8 (0.24)	Q8IYS5	CVD II
Heat shock 27 kDa	HSP 27	10.3 (0.35)	P04792	CVD II
Intercellular adhesion molecule 2	ICAM-2	4.93 (0.42)	P13598	CVD III
Alpha-L-iduronidase	IDUA	6.39 (0.48)	P35475	CVD II
Interferon-gamma	IFNG	6.80 (0.94)	P01579	Inflammation
Insulin-like growth factor-binding 1	IGFBP-1	5.26 (1.04)	P08833	CVD III
Insulin-like growth factor-binding 2	IGFBP-2	7.42 (0.72)	P18065	CVD III
Insulin-like growth factor-binding 7	IGFBP-7	7.38 (0.40)	Q16270	CVD III
Low affinity immunoglobulin gamma Fc region receptor II-b	IgG Fc receptor II-b	3.64 (0.92)	P31994	CVD II
Interleukin-10	IL-10	3.38 (0.68)	P22301	Inflammation
Interleukin-10 receptor subunit beta	IL-10RB	5.85 (0.33)	Q08334	Inflammation
Interleukin-12 subunit beta	IL-12B	5.46 (0.68)	P29460	Inflammation
Interleukin-15 receptor subunit alpha	IL-15RA	1.23 (0.34)	Q13261	Inflammation
Pro-interleukin-16	IL-16	7.83 (1.23)	Q14005	CVD II
Interleukin-17D	IL-17D	2.50 (0.39)	Q8TAD2	CVD II
Interleukin-17 receptor A	IL-17RA	4.12 (0.69)	Q96F46	CVD III
Interleukin-18	IL-18	8.24 (0.71)	Q14116	CVD II
Interleukin-18-binding protein	IL-18BP	6.15 (0.37)	O95998	CVD III
Interleukin-18 receptor 1	IL-18R1	8.43 (0.42)	Q13478	Inflammation
Interleukin-1 receptor antagonist	IL-1RA	5.11 (0.81)	P18510	CVD II
Interleukin-1 receptor-like 2	IL1-RL2	5.06 (0.45)	Q9HB29	CVD II
Interleukin-1 receptor type 1	IL-1RT1	6.33 (0.31)	P14778	CVD III
Interleukin-1 receptor type 2	IL-1RT2	5.55 (0.37)	P27930	CVD III
Interleukin-27	IL-27	6.15 (0.39)	Q8NEV9	CVD II
Interleukin-2 receptor subunit alpha	IL2-RA	3.36 (0.44)	P01589	CVD III
Interleukin-4 receptor subunit alpha	IL-4RA	2.29 (0.36)	P24394	CVD II
Interleukin-6	IL-6	2.80 (0.91)	P05231	Inflammation
Interleukin-6 receptor subunit alpha	IL-6RA	11.7 (0.39)	P08887	CVD III
Interleukin-7	IL-7	3.33 (0.78)	P13232	Inflammation
Interleukin-8	IL-8	5.41 (0.79)	P10145	Inflammation
Melusin	ITGB1BP2	7.31 (1.63)	Q9UKP3	CVD II
Integrin beta-2	ITGB2	6.16 (1.05)	P05107	CVD III
Junctional adhesion molecule A	JAM-A	6.14 (1.21)	Q9Y624	CVD III
Kidney injury molecule 1	KIM1	7.28 (0.82)	Q96D42	CVD II
Kallikrein-6	KLK6	2.19 (0.37)	Q92876	CVD III
Low-density liporeceptor	LDL receptor	4.31 (0.57)	P01130	CVD III
Leptin	LEP	7.54 (1.20)	P41159	CVD II
Leukemia inhibitory factor receptor	LIFR	3.85 (0.32)	P42702	Inflammation
Tumor necrosis factor ligand superfamily member 14	LIGHT	5.00 (1.04)	O43557	Inflammation
Lectin-like oxidized LDL receptor 1	LOX-1	6.59 (0.82)	P78380	CVD II
Lipolipase	LPL	9.52 (0.48)	P06858	CVD II
Lymphotoxin-beta receptor	LTBR	3.62 (0.43)	P36941	CVD III
Macrophage receptor MARCO	MARCO	6.07 (0.20)	Q9UEW3	CVD II
Myoglobin	MB	7.51 (0.58)	P02144	CVD III
Monocyte chemotactic protein 2	MCP-2	8.52 (0.74)	P80075	Inflammation

Table S1. Normalized expression values for proteomic biomarkers at baseline (N = 1140)

Full name	**Biomarker**	**Mean (SD)**	**UniProt_ID**	**Panel**
Matrix extracellular phosphoglyco	MEPE	5.32 (0.45)	Q9NQ76	CVD III
Tyrosine-kinase Mer	MERTK	6.07 (0.42)	Q12866	CVD II
Matrix metalloproteinase-1	MMP-1	11.3 (1.25)	P03956	Inflammation
Matrix metalloase-12	MMP-12	6.87 (0.68)	P39900	CVD II
Matrix metalloase-2	MMP-2	3.82 (0.37)	P08253	CVD III
Matrix metalloase-3	MMP-3	7.46 (0.72)	P08254	CVD III
Matrix metalloase-7	MMP-7	10.1 (0.70)	P09237	CVD II
Matrix metalloase-9	MMP-9	4.82 (0.87)	P14780	CVD III
Myeloperoxidase	MPO	3.75 (0.83)	P05164	CVD III
NF-kappa-B essential modulator	NEMO	8.01 (1.30)	Q9Y6K9	CVD II
Neurogenic locus notch homolog 3	Notch 3	5.02 (0.42)	Q9UM47	CVD III
Neurotrophin-3	NT3	2.24 (0.43)	P20783	Inflammation
N-terminal pro-B-type natriuretic peptide	NT-proBNP	3.47 (1.13)	P16860	CVD III
Osteoprotegerin	OPG	10.0 (0.37)	O00300	Inflammation
Osteopontin	OPN	7.17 (0.53)	P10451	CVD III
Oncostatin-M	OSM	3.48 (0.90)	P13725	Inflammation
Plasminogen activator inhibitor 1	PAI	6.39 (0.88)	P05121	CVD III
ase-activated receptor 1	PAR-1	9.38 (0.64)	P25116	CVD II
Poly [ADP-ribose] polymerase 1	PARP-1	5.65 (2.05)	P09874	CVD II
Proconvertase subtilisin/kexin type 9	PCSK9	3.36 (0.39)	Q8NBP7	CVD III
Platelet-derived growth factor subunit A	PDGF subunit A	3.98 (1.03)	P04085	CVD III
Platelet-derived growth factor subunit B	PDGF subunit B	10.6 (1.08)	P01127	CVD II
Programmed cell death 1 ligand 1	PD-L1	7.21 (0.48)	Q9NZQ7	Inflammation
Programmed cell death 1 ligand 2	PD-L2	2.92 (0.39)	Q9BQ51	CVD II
Platelet endothelial cell adhesion molecule	PECAM-1	5.57 (0.87)	P16284	CVD III
Placenta growth factor	PGF	7.67 (0.38)	P49763	CVD II
Peptidoglycan recognition 1	PGLYRP1	6.86 (0.51)	O75594	CVD III
Polymeric immunoglobulin receptor	PIgR	6.86 (0.15)	P01833	CVD II
Perlecan	PLC	7.88 (0.33)	P98160	CVD III
Paraoxonase	PON3	6.07 (0.69)	Q15166	CVD III
Prolargin	PRELP	8.58 (0.24)	P51888	CVD II
Serine protease 27	PRSS27	8.91 (0.45)	Q9BQR3	CVD II
Prostasin	PRSS8	8.84 (0.39)	Q16651	CVD II
P-selectin glycoligand 1	PSGL-1	4.81 (0.37)	Q14242	CVD II
Pulmonary surfactant-associated D	PSP-D	3.07 (0.72)	P35247	CVD III
Pentraxin-related PTX3	PTX3	4.68 (0.46)	P26022	CVD II
Receptor for advanced glycosylation end products	RAGE	13.5 (0.43)	Q15109	CVD II
Retinoic acid receptor responder 2	RARRES2	11.3 (0.34)	Q99969	CVD III
Renin	REN	6.81 (0.83)	P00797	CVD II
Resistin	RETN	5.97 (0.60)	Q9HD89	CVD III
Stem cell factor	SCF	8.87 (0.45)	P21583	CVD II
Secretoglobin family 3A member 2	SCGB3A2	2.12 (0.87)	Q96PL1	CVD III
E-selectin	SELE	11.8 (0.61)	P16581	CVD III
P-selectin	SELP	10.7 (0.94)	P16109	CVD III
Serpin A12	SERPINA12	2.72 (1.07)	Q8IW75	CVD II
Tyrosine-phosphatase non-receptor type substrate 1	SHPS-1	3.52 (0.52)	P78324	CVD III
SIR2-like protein 2	SIRT2	6.28 (1.74)	Q8IXJ6	Inflammation

Table S1. Normalized expression values for proteomic biomarkers at baseline (N = 1140)

Full name	**Biomarker**	**Mean (SD)**	**UniProt_ID**	**Panel**
Matrix metalloproteinase-10	SL-2	8.46 (0.61)	P09238	Inflammation
Superoxide dismutase [Mn], mitochondrial	SOD2	10.1 (0.11)	P04179	CVD II
Sortilin	SORT1	9.11 (0.35)	Q99523	CVD II
Spondin-2	SPON2	8.65 (0.26)	Q9BUD6	CVD II
Proto-oncogene tyrosine-kinase Src	SRC	8.23 (0.83)	P12931	CVD II
Sulfotransferase 1A1	ST1A1	3.95 (1.14)	P50225	Inflammation
Protein ST2	ST2	4.14 (0.57)	Q01638	CVD III
STAM-binding protein	STAMBP	7.52 (1.57)	O95630	Inflammation
Serine/threonine-kinase 4	STK4	6.19 (1.00)	Q13043	CVD II
Tissue factor	TF	5.53 (0.32)	P13726	CVD II
Tissue factor pathway inhibitor	TFPI	8.46 (0.39)	P10646	CVD III
Transforming growth factor alpha	TGF-α	2.93 (0.44)	P01135	Inflammation
Latency-associated peptide transforming growth factor beta-1	TGF-β1	7.98 (0.58)	P01137	Inflammation
Protein-glutamine gamma-glutamyltransferase 2	TGM2	8.88 (0.53)	P21980	CVD II
Thrombospondin-2	THBS2	6.36 (0.21)	P35442	CVD II
Thrombopoietin	THPO	3.41 (0.45)	P40225	CVD II
Angiopoietin-1 receptor	TIE2	8.14 (0.25)	Q02763	CVD II
Tissue inhibitor of metalloproteinases 4	TIMP4	3.22 (0.53)	Q99727	CVD III
Trem-like transcript 2	TLT-2	5.19 (0.47)	Q5T2D2	CVD III
Thrombomodulin	TM	10.7 (0.32)	P07204	CVD II
Tumor necrosis factor receptor 1	TNF-R1	6.45 (0.43)	P19438	CVD III
Tumor necrosis factor receptor 2	TNF-R2	5.91 (0.43)	P20333	CVD III
Tumor necrosis factor receptor superfamily member 10A	TNFRSF10A	3.78 (0.45)	O00220	CVD II
Tumor necrosis factor receptor superfamily member 10C	TNFRSF10C	6.50 (0.54)	O14798	CVD III
Tumor necrosis factor receptor superfamily member 11A	TNFRSF11A	5.88 (0.48)	Q9Y6Q6	CVD II
Tumor necrosis factor receptor superfamily member 13B	TNFRSF13B	10.1 (0.38)	O14836	CVD II
Tumor necrosis factor receptor superfamily member 14	TNFRSF14	4.96 (0.57)	Q92956	CVD III
Tumor necrosis factor receptor superfamily member 9	TNFRSF9	7.22 (0.46)	Q07011	Inflammation
TNF-related apoptosis-inducing ligand	TNFSF10	8.08 (0.31)	P50591	Inflammation
Tumor necrosis factor ligand superfamily member 13B	TNFSF13B	6.93 (0.40)	Q9Y275	CVD III
Tumor necrosis factor-alpha	TNF-α	2.79 (0.51)	P01375	Inflammation
Tumor necrosis factor-beta	TNF-β	4.67 (0.46)	P01374	Inflammation
Tissue-type plasminogen activator	t-PA	6.44 (0.93)	P00750	CVD III
Transferrin receptor 1	TR	5.71 (0.56)	P02786	CVD III
TNF-related apoptosis-inducing ligand receptor 2	TRAIL-R2	5.66 (0.39)	O14763	CVD II
TNF-related activation-induced cytokine	TRANCE	4.54 (0.57)	O14788	Inflammation
Tartrate-resistant acid phosphatase type 5	TR-AP	3.39 (0.41)	P13686	CVD III
Tumor necrosis factor Ligand superfamily member 12	TWEAK	9.04 (0.33)	O43508	Inflammation
Urokinase-type plasminogen activator	uPA	9.96 (0.33)	P00749	Inflammation
Urokinase plasminogen activator surface receptor	U-PAR	5.40 (0.73)	Q03405	CVD III
Vascular endothelial growth factor A	VEGF-A	10.5 (0.45)	P15692	Inflammation
Vascular endothelial growth factor D	VEGFD	8.15 (0.41)	O43915	CVD II
V-set and immunoglobulin domain-containing 2	VSIG2	4.85 (0.53)	Q96IQ7	CVD II
von Willebrand factor	vWF	7.54 (0.71)	P04275	CVD III
Lymphotactin	XCL1	4.87 (0.60)	P47992	CVD II

Abbreviations: CVD II, Cardiovascular II Olink panel; CVD III, Cardiovascular III Olink panel; SD, standard deviation.

Table S2. SNPs-traits associations retrieved from PhenoScanner V2 for proteins-related SNPs [a]

SNP	hg38_coordinates	a1	a2	trait	efo	pmid	ancestry	year	beta	se	p	direction	n	n_cases	n_controls	n_studies	unit	dataset
rs12722497	chr10:6053965	C	A	Interleukin 2 receptor antagonist levels	EFO_0008332	27989323	European	2017	0.6279	0.04844	2.00E-38	+	-	-	-	-	SD	NHGRI-EBI_GWAS_Catalog
rs198389	chr1:11859214	A	G	N terminal signal peptide of pro B type natriuretic peptide blood level	NCIT_C139088; NCIT_C119205	21273288	European	2011	NA	NA	1.70E-12	NA	1325	-	-	-	-	GRASP
rs198389	chr1:11859214	A	G	B type natriuretic peptide	-	25561047	African	2015	-0.18	0.02946	1.00E-09	-	-	-	-	-	unit	NHGRI-EBI_GWAS_Catalog
rs198389	chr1:11859214	A	G	NT proBNP levels in acute coronary syndrome	EFO_0005278	26908625	Mixed	2016	-0.153	0.01906	1.00E-15	-	-	-	-	-	ng/L	NHGRI-EBI_GWAS_Catalog
rs198389	chr1:11859214	A	G	Diastolic blood pressure	EFO_0006336	UKBB	European	2017	0.019	0.002506	3.44E-14	+	317756	0	317756	1	IVNT	Neale-B_UKBB_EUR_2017
rs198389	chr1:11859214	A	G	Self-reported hypertension	EFO_0000537	UKBB	European	2017	0.007665	0.001086	1.68E-12	+	337159	87690	249469	1	risk diff	Neale-B_UKBB_EUR_2017
rs198389	chr1:11859214	A	G	Systolic blood pressure	EFO_0006335	UKBB	European	2017	0.01989	0.002505	2.01E-15	+	317754	0	317754	1	IVNT	Neale-B_UKBB_EUR_2017
rs198389	chr1:11859214	A	G	Vascular or heart problems diagnosed by doctor: high blood pressure	EFO_0004325	UKBB	European	2017	0.0077	0.001101	2.65E-12	+	336683	91033	245650	1	risk diff	Neale-B_UKBB_EUR_2017
rs198389	chr1:11859214	A	G	Vascular or heart problems diagnosed by doctor: none of the above	-	UKBB	European	2017	-0.006837	0.00113	1.47E-09	-	336683	236530	100153	1	risk diff	Neale-B_UKBB_EUR_2017
rs2403310	chr11:10341724	C	G	Hematocrit	EFO_0004586	27863252	European	2016	-0.02068	0.003541	5.25E-09	-	173480	0	173480	2	IVNT	Astle-W_Blood-Cell-Traits_EUR_2016
rs2403310	chr11:10341724	C	G	Hemoglobin concentration	EFO_0004586	27863252	European	2016	-0.02094	0.003557	3.91E-09	-	173480	0	173480	2	IVNT	Astle-W_Blood-Cell-Traits_EUR_2016
rs2403310	chr11:10341724	C	G	Red blood cell count	EFO_0004586	27863252	European	2016	-0.02151	0.003567	1.64E-09	-	173480	0	173480	2	IVNT	Astle-W_Blood-Cell-Traits_EUR_2016
rs314361	chr7:100815383	G	A	Pulse rate	EFO_0004326	UKBB	European	2017	0.0235	0.002504	6.34E-21	+	317756	0	317756	1	IVNT	Neale-B_UKBB_EUR_2017
rs6921438	chr6:43957870	A	G	Serum vascular endothelial growth factor VEGF	EFO_0003276	21757650	European	2011	NA	NA	0.00E+00	NA	3527	-	-	-	-	GRASP
rs6921438	chr6:43957870	A	G	Vascular endothelial growth factor levels	EFO_0004762	26910538	Mixed	2016	0.64	NA	0.00E+00	+	-	-	-	-	unit	NHGRI-EBI_GWAS_Catalog
rs6921438	chr6:43957870	A	G	Vascular endothelial growth factor levels	EFO_0004762	27989323	European	2017	-0.49	0.01756	2.00E-171	-	-	-	-	-	SD	NHGRI-EBI_GWAS_Catalog

[a] Associations of SNPs with traits with genome-wide significance at the level P < 5E-8 were selected.

Abbreviations: SNPs, single nucleotide polymorphisms.

Table S3. Harmonized summary statistics used in Mendelian randomization analysis

SNP	exposure	effect_allele.E	other_allele.E	effect_allele.O	other_allele.O	beta.E	beta.O	eaf.E	eaf.O	chr.O	pos.O	se.O	pval.O	N.O	chr.E	pos.E	se.E	pval.E	N.E	UniProt_ID
rs2403310	ADM	C	G	C	G	0.160	0.005	0.473	0.450	11	10363271	0.005	2.81E-01	246851	11	10363271	0.007	1.80E-116	35571	P35318
rs9907136	CCL7	T	C	T	C	0.111	-0.002	0.645	0.655	17	32516245	0.005	6.12E-01	306950	17	32516245	0.007	9.13E-50	35571	P80098
rs314361	EPHB4	G	A	G	A	0.151	-0.002	0.520	0.509	7	100413005	0.004	6.16E-01	343032	7	100413005	0.007	2.57E-99	35571	P54760
rs4674100	IGFBP-2	A	G	A	G	-0.072	-0.001	0.293	0.282	2	217480424	0.005	9.01E-01	311421	2	217480424	0.008	1.95E-17	35571	P18065
rs3136630	IL-15RA	T	C	T	C	-0.258	0.007	0.296	0.283	10	5997820	0.005	1.50E-01	340451	10	5997820	0.008	1.00E-200	35571	Q13261
rs12722497	IL2-RA	A	C	A	C	0.945	-0.004	0.089	0.079	10	6095928	0.009	6.44E-01	304499	10	6095928	0.013	1.00E-200	35571	P01589
rs56254643	OPN	C	T	C	T	-0.114	-0.007	0.192	0.186	4	88858885	0.006	1.97E-01	306950	4	88858885	0.009	1.24E-36	35571	P10451
rs822340	PD-L1	G	A	G	A	0.340	0.003	0.745	0.748	9	5453260	0.005	4.94E-01	342922	9	5453260	0.008	1.00E-200	35571	Q9NZQ7
rs6684152	PLC	G	A	G	A	-0.171	0.009	0.294	0.289	1	22147764	0.005	5.96E-02	306950	1	22147764	0.008	1.00E-102	35571	P98160
rs1042579	TM	A	G	A	G	0.195	-0.002	0.191	0.227	20	23028724	0.005	7.71E-01	304061	20	23028724	0.009	9.98E-104	35571	P07204
rs4149584	TNF-R1	T	C	T	C	-0.307	-0.006	0.017	0.019	12	6442643	0.022	7.80E-01	82525	12	6442643	0.028	1.27E-28	35571	P19438
rs5746026	TNF-R2	A	G	A	G	-0.391	-0.009	0.040	0.053	1	12253062	0.010	3.95E-01	337190	1	12253062	0.018	1.97E-99	35571	P20333
rs113339733	TNFRSF11A	A	G	A	G	-0.592	-0.014	0.193	0.153	18	60018329	0.007	3.20E-02	223123	18	60018329	0.009	1.00E-200	35571	Q9Y6Q6
rs2493214	TNFRSF9	G	A	G	A	-0.195	-0.009	0.190	0.239	1	7994420	0.005	8.14E-02	307054	1	7994420	0.009	3.30E-100	35571	Q07011
rs1105944	TRAIL-R2	G	A	G	A	0.536	0.000	0.896	0.903	8	22885109	0.007	9.64E-01	342316	8	22885109	0.011	1.00E-200	35571	O14763
rs6921438	VEGF-A	A	G	A	G	-0.683	-0.004	0.490	0.489	6	43925607	0.004	3.22E-01	303905	6	43925607	0.007	1.00E-200	35571	P15692
rs4656599	XCL1	T	C	T	C	0.831	0.005	0.190	0.212	1	168503386	0.005	3.29E-01	343336	1	168503386	0.009	1.00E-200	35571	P47992

Only part of columns in Table S3 are presented in the thesis. Full content of Table S3 is available on:
https://bmcmedicine.biomedcentral.com/articles/10.1186/s12916-023-02962-z#Sec21

Abbreviations: E, exposure; O, outcome; SNPs, single nucleotide polymorphisms.

Table S4. Characteristics of participants over the study period [a]

	KORA S4, 1999-2001 (N = 1140)	KORA F4, 2006-2008 (N = 1120)	KORA FF4, 2013-2014 (N = 658)
	Mean (standard deviation) or number (%)		
Age (years)	63.3 (5.36)	70.3 (5.38)	76.0 (4.92)
Sex, N(%) female	556 (48.8)	546 (48.8)	312 (47.4)
Body mass index (kg/m^2)	28.4 (4.25)	28.7 (4.50)	28.2 (4.49)
Smoking status, N (%)			
Never smoker	560 (49.1)	549 (49.0)	329 (50.0)
Former smoker	440 (38.6)	487 (43.5)	294 (44.7)
Current smoker	140 (12.3)	84 (7.50)	35 (5.30)
Alcohol consumption			
No alcohol consumption	291 (25.5)	360 (32.2)	185 (28.1)
>0 and <20 g/day	462 (40.5)	426 (38.0)	270 (41.0)
≥ 20 g/day	387 (33.9)	334 (29.8)	203 (30.9)
Physically active, N (%)	509 (44.6)	559 (49.9)	328 (49.8)
Systolic blood pressure (mmHg)	135.1 (19.8)	128.8 (19.7)	123.3 (19.0)
Use of antihypertensive medication, N (%)	388 (34.0)	642 (57.3)	429 (65.2)
Hypertension, N (%)	615 (53.9)	706 (63.0)	433 (65.8)
Triglycerides (mmol/L), median (IQR)	1.35 (0.93)	1.29 (0.85)	1.23 (0.64)
High-density lipoprotein cholesterol (mmol/L)	1.50 (0.43)	1.44 (0.36)	1.72 (0.48)
Use of lipid-lowering medication, N (%)	127 (11.1)	271 (24.2)	221 (33.6)
Type 2 diabetes, N (%)	94 (8.20)	179 (16.0)	140 (21.3)
Cardiovascular diseases, N (%)	135 (11.8)	179 (16.0)	126 (19.1)
Fasting status, N (%)	1027 (90.1)	1110 (99.1)	655 (99.5)
eGFRcr (ml/min/1.73 m^2), CKD-EPI equation 2009	82.9 (12.2)	75.9 (14.8)	67.6 (15.3)
eGFRcr (ml/min/1.73 m^2), CKD-EPI equation 2021	87.2 (12.3)	80.3 (15.2)	71.9 (16.0)
eGFRcys (ml/min/1.73 m^2)	81.1 (15.2)	75.8 (17.9)	65.5 (18.3)

[a] eGFRcr was calculated using the CKD-EPI equation 2009 and equation 2021.

Abbreviations: CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFRcr, creatinine-based estimated glomerular filtration rate; eGFRcys, cystatin C-based estimated glomerular filtration rate; IQR, interquartile range.

Table S5. Baseline characteristics for participants with and without follow-up information on eGFRcr

	With follow-up (N = 1140)	Lost to follow-up (N = 426)	*P* -value [a]
	Mean (standard deviation) or number (%)		
Age (years)	63.3 (5.38)	65.8 (5.32)	<0.001
Sex, N(%) female	556 (48.8)	205 (48.1)	0.863
Body mass index (kg/m^2)	28.4 (4.25)	28.9 (4.62)	0.023
Smoking status, N (%)			0.001
Never smoker	560 (49.1)	189 (44.4)	
Former smoker	440 (38.6)	83 (19.4)	
Current smoker	140 (12.3)	154 (36.2)	
Alcohol consumption			<0.001
No alcohol consumption	291 (25.5)	148 (34.7)	
>0 and <20 g/day	462 (40.5)	134 (31.5)	
≥ 20 g/day	387 (33.9)	144 (33.8)	
Physically active, N (%)	509 (44.6)	147 (34.5)	<0.001
Systolic blood pressure (mmHg)	135.1 (19.8)	139.7 (21.9)	<0.001
Use of antihypertensive medication, N (%)	388 (34.0)	187 (43.9)	<0.001
Hypertension, N (%)	615 (53.9)	269 (63.1)	0.001
Triglycerides (mmol/L), median (IQR)	1.35 (0.93)	1.42 (0.93)	0.093
High-density lipoprotein cholesterol (mmol/L)	1.50 (0.43)	1.46 (0.41)	0.094
Use of lipid-lowering medication, N (%)	127 (11.1)	55 (12.9)	0.384
Type 2 diabetes, N (%)	94 (8.20)	54 (12.7)	0.010
Cardiovascular diseases, N (%)	135 (11.8)	56 (13.1)	0.539
Fasting status, N (%)	1027 (90.1)	354 (83.1)	<0.001
eGFRcr (ml/min/1.73 m^2)	82.9 (12.2)	81.2 (15.8)	0.019
eGFRcys (ml/min/1.73 m^2)	81.1 (15.2)	74.2 (16.7)	<0.001

[a] P-value was estimated by t-Test (continuous variables) or chi-squared test (categorical variables).

Abbreviations: eGFRcr, creatinine-based estimated glomerular filtration rate; eGFRcys, cystatin C-based estimated glomerular filtration rate; IQR, interquartile range.

Table S6. Longitudinal associations between 233 proteomic biomarkers and the annual rate of change in eGFRcr (N=1140) [a]

Biomarker	UniProt_ID	Model 1				Model 2		
		β (95%CI)	P	FDR		β (95%CI)	P	FDR
4E-BP1	Q13541	-0.043 (-0.120, 0.034)	2.77E-01	3.67E-01		-0.009 (-0.087, 0.069)	8.19E-01	8.92E-01
ACE2	Q9BYF1	**-0.120 (-0.201, -0.038)**	**4.15E-03**	**1.49E-02**		-0.072 (-0.159, 0.016)	1.09E-01	2.41E-01
ADA	P00813	-0.076 (-0.155, 0.003)	5.84E-02	1.15E-01		-0.046 (-0.125, 0.034)	2.62E-01	4.46E-01
ADAM-TS13	Q76LX8	-0.005 (-0.082, 0.072)	9.01E-01	9.19E-01		0.015 (-0.062, 0.092)	7.06E-01	8.14E-01
ADM	P35318	**-0.201 (-0.289, -0.114)**	**6.30E-06**	**5.88E-05**		**-0.157 (-0.249, -0.065)**	**8.67E-04**	**5.31E-03**
AGRP	O00253	**-0.164 (-0.249, -0.079)**	**1.64E-04**	**9.53E-04**		**-0.147 (-0.239, -0.055)**	**1.76E-03**	**9.75E-03**
ALCAM	Q13740	**-0.102 (-0.184, -0.019)**	**1.56E-02**	**4.19E-02**		-0.088 (-0.170, -0.006)	3.55E-02	1.07E-01
AMBP	P02760	**-0.187 (-0.273, -0.101)**	**2.11E-05**	**1.69E-04**		**-0.154 (-0.242, -0.065)**	**6.72E-04**	**4.61E-03**
ANG-1	Q15389	-0.006 (-0.083, 0.070)	8.69E-01	8.96E-01		0.000 (-0.076, 0.077)	9.94E-01	9.94E-01
AP-N	P15144	-0.053 (-0.132, 0.025)	1.82E-01	2.74E-01		-0.041 (-0.120, 0.038)	3.04E-01	5.07E-01
Axin-1	O15169	0.020 (-0.057, 0.096)	6.13E-01	6.84E-01		0.026 (-0.050, 0.103)	4.97E-01	6.69E-01
AXL	P30530	**-0.100 (-0.178, -0.022)**	**1.23E-02**	**3.37E-02**		-0.073 (-0.153, 0.006)	6.88E-02	1.65E-01
BMP-6	P22004	-0.051 (-0.128, 0.027)	1.98E-01	2.89E-01		-0.031 (-0.108, 0.047)	4.38E-01	6.22E-01
CA5A	Q9BWV1	**-0.137 (-0.215, -0.058)**	**6.52E-04**	**2.97E-03**		-0.079 (-0.162, 0.003)	5.93E-02	1.52E-01
CASP-3	P35218	-0.004 (-0.081, 0.073)	9.15E-01	9.27E-01		0.002 (-0.075, 0.078)	9.64E-01	9.81E-01
CASP8	P42574	-0.062 (-0.141, 0.018)	1.32E-01	2.10E-01		-0.018 (-0.100, 0.064)	6.67E-01	7.86E-01
CCL11	Q14790	**-0.102 (-0.180, -0.023)**	**1.12E-02**	**3.12E-02**		-0.074 (-0.153, 0.006)	7.01E-02	1.67E-01
CCL13	P51671	-0.037 (-0.114, 0.040)	3.45E-01	4.32E-01		-0.029 (-0.106, 0.047)	4.53E-01	6.33E-01
CCL15	Q99616	**-0.163 (-0.242, -0.084)**	**5.97E-05**	**3.98E-04**		**-0.135 (-0.214, -0.055)**	**8.93E-04**	**5.34E-03**
CCL16	Q16663	**-0.128 (-0.206, -0.049)**	**1.40E-03**	**5.82E-03**		**-0.116 (-0.194, -0.037)**	**4.00E-03**	**1.76E-02**
CCL17	O15467	-0.084 (-0.161, -0.006)	3.43E-02	7.32E-02		-0.071 (-0.148, 0.006)	7.21E-02	1.70E-01
CCL19	Q92583	-0.041 (-0.122, 0.040)	3.16E-01	4.07E-01		-0.010 (-0.091, 0.071)	8.06E-01	8.90E-01
CCL2	Q99731	-0.084 (-0.161, -0.006)	3.49E-02	7.32E-02		-0.064 (-0.142, 0.014)	1.05E-01	2.36E-01
CCL20	P13500	-0.044 (-0.120, 0.033)	2.67E-01	3.59E-01		-0.003 (-0.081, 0.074)	9.32E-01	9.60E-01
CCL23	P78556	**-0.113 (-0.193, -0.032)**	**5.98E-03**	**1.93E-02**		**-0.122 (-0.202, -0.041)**	**2.97E-03**	**1.41E-02**
CCL24	P55773	-0.030 (-0.107, 0.047)	4.47E-01	5.35E-01		-0.038 (-0.114, 0.038)	3.31E-01	5.22E-01
CCL25	O00175	-0.075 (-0.153, 0.003)	6.00E-02	1.17E-01		-0.072 (-0.150, 0.005)	6.68E-02	1.64E-01
CCL28	O15444	-0.064 (-0.142, 0.013)	1.01E-01	1.70E-01		-0.077 (-0.154, 0.000)	5.00E-02	1.34E-01
CCL3	Q9NRJ3	**-0.145 (-0.225, -0.065)**	**3.72E-04**	**1.90E-03**		**-0.116 (-0.197, -0.036)**	**4.77E-03**	**1.98E-02**
CCL4	P10147	**-0.094 (-0.173, -0.015)**	**2.03E-02**	**4.97E-02**		-0.079 (-0.159, 0.001)	5.15E-02	1.36E-01
CCL7	P13236	**-0.187 (-0.267, -0.107)**	**5.50E-06**	**5.34E-05**		**-0.135 (-0.216, -0.053)**	**1.19E-03**	**6.91E-03**
CD163	P80098	-0.075 (-0.154, 0.003)	5.92E-02	1.16E-01		-0.025 (-0.107, 0.056)	5.47E-01	7.09E-01
CD244	Q86VB7	-0.054 (-0.130, 0.023)	1.68E-01	2.54E-01		-0.035 (-0.112, 0.041)	3.66E-01	5.57E-01
CD4	Q9BZW8	-0.070 (-0.150, 0.010)	8.70E-02	1.58E-01		-0.019 (-0.101, 0.062)	6.46E-01	7.84E-01
CD40	P01730	-0.067 (-0.144, 0.010)	8.89E-02	1.61E-01		-0.050 (-0.127, 0.027)	2.05E-01	3.76E-01
CD40-L	P25942	-0.005 (-0.083, 0.072)	8.94E-01	9.17E-01		0.003 (-0.074, 0.080)	9.36E-01	9.60E-01
CD5	P29965	-0.076 (-0.153, 0.002)	5.61E-02	1.12E-01		-0.035 (-0.113, 0.044)	3.88E-01	5.69E-01
CD6	P06127	-0.023 (-0.101, 0.054)	5.54E-01	6.30E-01		0.006 (-0.072, 0.084)	8.79E-01	9.32E-01
CD84	P30203	-0.008 (-0.085, 0.069)	8.33E-01	8.74E-01		-0.001 (-0.078, 0.076)	9.88E-01	9.94E-01
CD8A	Q9UIB8	**-0.120 (-0.198, -0.042)**	**2.52E-03**	**9.61E-03**		-0.080 (-0.159, -0.001)	4.76E-02	1.31E-01
CD93	P01732	**-0.211 (-0.290, -0.131)**	**2.17E-07**	**3.89E-06**		**-0.211 (-0.290, -0.132)**	**1.69E-07**	**7.88E-06**
CDCP1	Q9NPY3	**-0.119 (-0.201, -0.036)**	**4.73E-03**	**1.62E-02**		-0.085 (-0.168, -0.002)	4.41E-02	1.25E-01
CDH5	Q9H5V8	**-0.092 (-0.167, -0.016)**	**1.72E-02**	**4.41E-02**		-0.087 (-0.163, -0.012)	2.34E-02	7.57E-02
CEACAM8	P33151	-0.028 (-0.111, 0.055)	5.14E-01	5.96E-01		0.060 (-0.028, 0.148)	1.83E-01	3.57E-01
CHI3L1	P31997	**-0.216 (-0.299, -0.133)**	**3.54E-07**	**5.15E-06**		**-0.188 (-0.275, -0.100)**	**2.65E-05**	**3.42E-04**
CHIT1	P36222	**-0.105 (-0.183, -0.028)**	**7.50E-03**	**2.27E-02**		**-0.112 (-0.189, -0.035)**	**4.20E-03**	**1.81E-02**
CNTN1	Q13231	-0.055 (-0.135, 0.026)	1.86E-01	2.76E-01		-0.054 (-0.135, 0.027)	1.91E-01	3.68E-01
COL1A1	Q12860	-0.025 (-0.103, 0.052)	5.18E-01	5.97E-01		-0.056 (-0.133, 0.021)	1.52E-01	3.11E-01

Table S6. Longitudinal associations between 233 proteomic biomarkers and the annual rate of change in eGFRcr (N=1140) [a]

Biomarker	UniProt_ID	Model 1				Model 2		
		β (95%CI)	P	FDR		β (95%CI)	P	FDR
CPA1	P02452	-0.050 (-0.131, 0.030)	2.22E-01	3.14E-01		-0.040 (-0.121, 0.041)	3.32E-01	5.22E-01
CPB1	P15085	-0.087 (-0.168, -0.005)	3.65E-02	7.59E-02		-0.067 (-0.149, 0.015)	1.11E-01	2.42E-01
CSF1	P15086	**-0.149 (-0.232, -0.065)**	**4.90E-04**	**2.28E-03**		**-0.107 (-0.191, -0.022)**	**1.34E-02**	**4.80E-02**
CST5	P09603	-0.055 (-0.139, 0.028)	1.94E-01	2.84E-01		-0.067 (-0.151, 0.016)	1.13E-01	2.44E-01
CSTB	P28325	**-0.106 (-0.187, -0.025)**	**1.02E-02**	**2.91E-02**		-0.063 (-0.146, 0.019)	1.31E-01	2.73E-01
CTRC	P04080	0.043 (-0.039, 0.124)	3.07E-01	3.99E-01		0.043 (-0.038, 0.125)	2.98E-01	4.99E-01
CTSL1	Q99895	**-0.209 (-0.289, -0.129)**	**3.36E-07**	**5.15E-06**		**-0.167 (-0.248, -0.086)**	**5.16E-05**	**5.73E-04**
CTSZ	P07711	**-0.175 (-0.257, -0.093)**	**2.89E-05**	**2.25E-04**		**-0.129 (-0.213, -0.046)**	**2.36E-03**	**1.25E-02**
CVD II BOC	Q9UBR2	-0.066 (-0.145, 0.013)	1.01E-01	1.70E-01		-0.056 (-0.134, 0.023)	1.63E-01	3.26E-01
CX3CL1	P78423	**-0.171 (-0.255, -0.086)**	**8.30E-05**	**5.22E-04**		**-0.183 (-0.268, -0.099)**	**2.10E-05**	**3.06E-04**
CXCL1	P09341	-0.051 (-0.127, 0.025)	1.84E-01	2.75E-01		-0.044 (-0.119, 0.032)	2.56E-01	4.41E-01
CXCL10	P02778	-0.057 (-0.135, 0.020)	1.49E-01	2.29E-01		-0.040 (-0.118, 0.038)	3.14E-01	5.18E-01
CXCL11	O14625	-0.073 (-0.151, 0.004)	6.17E-02	1.19E-01		-0.052 (-0.129, 0.025)	1.84E-01	3.57E-01
CXCL16	Q9H2A7	**-0.111 (-0.191, -0.032)**	**6.18E-03**	**1.97E-02**		-0.081 (-0.161, -0.001)	4.76E-02	1.31E-01
CXCL5	P42830	0.010 (-0.067, 0.086)	8.05E-01	8.51E-01		0.013 (-0.062, 0.089)	7.27E-01	8.32E-01
CXCL6	P80162	-0.063 (-0.138, 0.012)	1.01E-01	1.70E-01		-0.044 (-0.119, 0.032)	2.57E-01	4.41E-01
CXCL9	Q07325	-0.081 (-0.162, -0.001)	4.83E-02	9.87E-02		-0.069 (-0.150, 0.012)	9.35E-02	2.12E-01
DCN	P07585	-0.027 (-0.110, 0.057)	5.35E-01	6.11E-01		-0.022 (-0.106, 0.061)	6.02E-01	7.50E-01
DECR1	Q16698	0.030 (-0.048, 0.107)	4.54E-01	5.39E-01		0.039 (-0.038, 0.116)	3.20E-01	5.18E-01
Dkk-1	O94907	-0.022 (-0.100, 0.057)	5.89E-01	6.67E-01		-0.007 (-0.085, 0.071)	8.63E-01	9.23E-01
DLK-1	P80370	**-0.107 (-0.187, -0.027)**	**8.99E-03**	**2.65E-02**		-0.095 (-0.175, -0.014)	2.10E-02	6.89E-02
DNER	Q8NFT8	0.040 (-0.040, 0.119)	3.29E-01	4.19E-01		0.005 (-0.076, 0.085)	9.12E-01	9.52E-01
EGFR	P00533	0.017 (-0.061, 0.096)	6.65E-01	7.30E-01		0.009 (-0.071, 0.088)	8.27E-01	8.92E-01
EN-RAGE	P80511	-0.077 (-0.160, 0.005)	6.63E-02	1.26E-01		-0.015 (-0.101, 0.071)	7.28E-01	8.32E-01
Ep-CAM	P16422	-0.040 (-0.118, 0.037)	3.08E-01	3.99E-01		-0.051 (-0.128, 0.027)	2.00E-01	3.76E-01
EPHB4	P54760	**-0.239 (-0.320, -0.158)**	**8.42E-09**	**2.45E-07**		**-0.233 (-0.313, -0.153)**	**1.46E-08**	**1.62E-06**
FABP2	P12104	-0.059 (-0.137, 0.019)	1.39E-01	2.18E-01		-0.089 (-0.169, -0.009)	2.84E-02	8.95E-02
FABP4	P15090	**-0.238 (-0.334, -0.143)**	**1.20E-06**	**1.47E-05**		**-0.195 (-0.308, -0.082)**	**7.19E-04**	**4.65E-03**
FAS	P25445	**-0.099 (-0.179, -0.018)**	**1.61E-02**	**4.20E-02**		-0.076 (-0.157, 0.004)	6.24E-02	1.57E-01
FGF19	O95750	-0.048 (-0.127, 0.030)	2.30E-01	3.18E-01		-0.018 (-0.099, 0.063)	6.68E-01	7.86E-01
FGF21	Q9NSA1	**-0.110 (-0.188, -0.032)**	**5.94E-03**	**1.93E-02**		-0.078 (-0.163, 0.007)	7.36E-02	1.71E-01
FGF-23	Q9GZV9	**-0.196 (-0.284, -0.109)**	**1.14E-05**	**9.82E-05**		**-0.166 (-0.254, -0.079)**	**1.99E-04**	**1.60E-03**
FLT3L	P49771	-0.027 (-0.107, 0.052)	5.00E-01	5.82E-01		-0.003 (-0.083, 0.077)	9.42E-01	9.62E-01
FS	P19883	**-0.122 (-0.199, -0.044)**	**2.11E-03**	**8.47E-03**		**-0.099 (-0.177, -0.021)**	**1.34E-02**	**4.80E-02**
Gal-4	P56470	**-0.191 (-0.269, -0.114)**	**1.32E-06**	**1.54E-05**		**-0.144 (-0.224, -0.064)**	**4.17E-04**	**3.14E-03**
Gal-9	O00182	**-0.167 (-0.246, -0.087)**	**4.31E-05**	**3.24E-04**		**-0.112 (-0.195, -0.030)**	**7.43E-03**	**2.88E-02**
GDF-15	Q99988	**-0.301 (-0.392, -0.209)**	**1.54E-10**	**1.80E-08**		**-0.224 (-0.321, -0.127)**	**6.82E-06**	**1.14E-04**
GDF-2	Q9UK05	0.005 (-0.078, 0.089)	9.03E-01	9.19E-01		-0.026 (-0.111, 0.059)	5.52E-01	7.09E-01
GH	P01241	0.081 (-0.006, 0.167)	6.82E-02	1.28E-01		0.030 (-0.061, 0.120)	5.21E-01	6.94E-01
GIF	P27352	-0.068 (-0.151, 0.014)	1.04E-01	1.73E-01		-0.037 (-0.120, 0.045)	3.74E-01	5.62E-01
GLO1	Q04760	-0.011 (-0.088, 0.066)	7.76E-01	8.33E-01		0.004 (-0.073, 0.081)	9.21E-01	9.58E-01
GPVI	Q9HCN6	-0.033 (-0.110, 0.044)	4.01E-01	4.92E-01		-0.023 (-0.100, 0.053)	5.53E-01	7.09E-01
GRN	P28799	**-0.132 (-0.212, -0.052)**	**1.22E-03**	**5.18E-03**		-0.099 (-0.180, -0.019)	1.54E-02	5.26E-02
GT	P51161	0.018 (-0.060, 0.096)	6.49E-01	7.17E-01		-0.012 (-0.092, 0.068)	7.68E-01	8.59E-01
HAOX1	Q9UJM8	-0.068 (-0.147, 0.011)	9.19E-02	1.65E-01		-0.027 (-0.108, 0.054)	5.19E-01	6.94E-01
HB-EGF	Q99075	-0.055 (-0.132, 0.022)	1.59E-01	2.43E-01		-0.034 (-0.111, 0.043)	3.92E-01	5.71E-01
HGF	P14210	**-0.117 (-0.198, -0.036)**	**4.61E-03**	**1.60E-02**		-0.019 (-0.108, 0.069)	6.66E-01	7.86E-01
HO-1	P09601	-0.066 (-0.145, 0.014)	1.05E-01	1.73E-01		-0.066 (-0.147, 0.015)	1.11E-01	2.42E-01

Table S6. Longitudinal associations between 233 proteomic biomarkers and the annual rate of change in eGFRcr (N=1140) [a]

Biomarker	**UniProt_ID**	**Model 1**				**Model 2**		
		β (95%CI)	**P**	**FDR**		**β (95%CI)**	**P**	**FDR**
hOSCAR	Q8IYS5	**-0.138 (-0.215, -0.062)**	**3.75E-04**	**1.90E-03**		**-0.116 (-0.192, -0.040)**	**2.70E-03**	**1.39E-02**
HSP 27	P04792	0.081 (0.007, 0.156)	3.28E-02	7.23E-02		0.073 (-0.001, 0.147)	5.37E-02	1.41E-01
ICAM-2	P13598	**-0.121 (-0.198, -0.043)**	**2.32E-03**	**9.17E-03**		**-0.110 (-0.188, -0.033)**	**5.42E-03**	**2.22E-02**
IDUA	P35475	-0.049 (-0.126, 0.029)	2.20E-01	3.13E-01		-0.006 (-0.085, 0.073)	8.80E-01	9.32E-01
IFNG	P01579	-0.072 (-0.148, 0.004)	6.41E-02	1.22E-01		-0.058 (-0.134, 0.018)	1.35E-01	2.79E-01
IGFBP-1	P08833	0.002 (-0.077, 0.081)	9.63E-01	9.63E-01		**-0.140 (-0.234, -0.046)**	**3.51E-03**	**1.60E-02**
IGFBP-2	P18065	**-0.120 (-0.200, -0.039)**	**3.59E-03**	**1.35E-02**		**-0.226 (-0.318, -0.135)**	**1.36E-06**	**3.65E-05**
IGFBP-7	Q16270	**-0.170 (-0.252, -0.088)**	**4.99E-05**	**3.56E-04**		**-0.135 (-0.217, -0.053)**	**1.30E-03**	**7.39E-03**
IgG Fc receptor II-b	P31994	-0.028 (-0.105, 0.050)	4.86E-01	5.72E-01		-0.020 (-0.097, 0.057)	6.08E-01	7.53E-01
IL-10	P22301	-0.043 (-0.123, 0.037)	2.94E-01	3.87E-01		-0.036 (-0.116, 0.044)	3.84E-01	5.69E-01
IL-10RB	Q08334	**-0.190 (-0.273, -0.106)**	**9.41E-06**	**8.43E-05**		**-0.160 (-0.245, -0.076)**	**1.99E-04**	**1.60E-03**
IL-12B	P29460	**-0.135 (-0.218, -0.051)**	**1.52E-03**	**6.22E-03**		**-0.132 (-0.220, -0.045)**	**3.02E-03**	**1.41E-02**
IL-15RA	Q13261	**-0.200 (-0.284, -0.115)**	**3.61E-06**	**3.82E-05**		**-0.181 (-0.266, -0.097)**	**2.59E-05**	**3.42E-04**
IL-16	Q14005	-0.083 (-0.160, -0.006)	3.49E-02	7.32E-02		-0.048 (-0.125, 0.030)	2.28E-01	4.05E-01
IL-17D	Q8TAD2	-0.007 (-0.083, 0.068)	8.49E-01	8.83E-01		-0.017 (-0.092, 0.058)	6.56E-01	7.86E-01
IL-17RA	Q96F46	-0.040 (-0.120, 0.041)	3.35E-01	4.22E-01		-0.026 (-0.105, 0.054)	5.29E-01	7.00E-01
IL-18	Q14116	**-0.113 (-0.194, -0.032)**	**6.36E-03**	**2.00E-02**		-0.050 (-0.135, 0.034)	2.41E-01	4.23E-01
IL-18BP	O95998	**-0.260 (-0.342, -0.178)**	**6.37E-10**	**3.71E-08**		**-0.235 (-0.317, -0.152)**	**2.70E-08**	**1.62E-06**
IL-18R1	Q13478	**-0.116 (-0.195, -0.038)**	**3.77E-03**	**1.39E-02**		-0.030 (-0.114, 0.055)	4.93E-01	6.68E-01
IL-1RA	P18510	**-0.113 (-0.192, -0.034)**	**5.09E-03**	**1.72E-02**		-0.009 (-0.097, 0.079)	8.49E-01	9.11E-01
IL1-RL2	Q9HB29	-0.073 (-0.155, 0.009)	8.13E-02	1.50E-01		-0.055 (-0.139, 0.030)	2.04E-01	3.76E-01
IL-1RT1	P14778	**-0.109 (-0.187, -0.030)**	**6.84E-03**	**2.10E-02**		-0.097 (-0.176, -0.017)	1.69E-02	5.62E-02
IL-1RT2	P27930	-0.031 (-0.108, 0.047)	4.40E-01	5.28E-01		-0.013 (-0.093, 0.067)	7.55E-01	8.54E-01
IL-27	Q8NEV9	-0.048 (-0.127, 0.030)	2.25E-01	3.16E-01		-0.038 (-0.116, 0.041)	3.47E-01	5.39E-01
IL2-RA	P01589	**-0.228 (-0.306, -0.149)**	**1.69E-08**	**3.94E-07**		**-0.194 (-0.273, -0.115)**	**1.66E-06**	**3.87E-05**
IL-4RA	P24394	**-0.148 (-0.230, -0.066)**	**4.08E-04**	**2.02E-03**		**-0.151 (-0.232, -0.070)**	**2.54E-04**	**1.97E-03**
IL-6	P05231	-0.092 (-0.171, -0.012)	2.35E-02	5.53E-02		-0.041 (-0.123, 0.040)	3.18E-01	5.18E-01
IL-6RA	P08887	**-0.102 (-0.180, -0.025)**	**9.85E-03**	**2.87E-02**		-0.083 (-0.160, -0.005)	3.59E-02	1.07E-01
IL-7	P13232	-0.030 (-0.104, 0.044)	4.29E-01	5.20E-01		-0.030 (-0.104, 0.044)	4.27E-01	6.10E-01
IL-8	P10145	**-0.104 (-0.183, -0.025)**	**1.01E-02**	**2.91E-02**		-0.052 (-0.133, 0.029)	2.05E-01	3.76E-01
ITGB1BP2	Q9UKP3	0.003 (-0.074, 0.079)	9.48E-01	9.52E-01		0.009 (-0.067, 0.085)	8.15E-01	8.92E-01
ITGB2	P05107	-0.012 (-0.093, 0.069)	7.73E-01	8.33E-01		0.012 (-0.069, 0.093)	7.67E-01	8.59E-01
JAM-A	Q9Y624	-0.025 (-0.102, 0.053)	5.30E-01	6.08E-01		-0.015 (-0.092, 0.062)	6.98E-01	8.09E-01
KIM1	Q96D42	**-0.323 (-0.402, -0.244)**	**3.54E-15**	**8.24E-13**		**-0.292 (-0.377, -0.206)**	**4.08E-11**	**9.51E-09**
KLK6	Q92876	-0.088 (-0.169, -0.007)	3.32E-02	7.23E-02		**-0.124 (-0.206, -0.042)**	**2.97E-03**	**1.41E-02**
LDL receptor	P01130	**-0.096 (-0.171, -0.020)**	**1.34E-02**	**3.63E-02**		-0.090 (-0.190, 0.011)	8.12E-02	1.87E-01
LEP	P41159	-0.079 (-0.176, 0.017)	1.08E-01	1.77E-01		0.040 (-0.088, 0.169)	5.38E-01	7.04E-01
LIFR	P42702	**-0.095 (-0.174, -0.016)**	**1.83E-02**	**4.57E-02**		-0.053 (-0.135, 0.028)	1.99E-01	3.76E-01
LIGHT	O43557	-0.029 (-0.106, 0.048)	4.59E-01	5.42E-01		0.009 (-0.068, 0.086)	8.17E-01	8.92E-01
LOX-1	P78380	-0.038 (-0.117, 0.042)	3.56E-01	4.41E-01		0.055 (-0.032, 0.141)	2.15E-01	3.92E-01
LPL	P06858	0.044 (-0.050, 0.139)	3.60E-01	4.43E-01		-0.023 (-0.121, 0.075)	6.42E-01	7.83E-01
LTBR	P36941	**-0.163 (-0.250, -0.075)**	**2.69E-04**	**1.46E-03**		**-0.154 (-0.240, -0.067)**	**5.10E-04**	**3.72E-03**
MARCO	Q9UEW3	-0.051 (-0.128, 0.026)	1.92E-01	2.83E-01		-0.019 (-0.097, 0.059)	6.35E-01	7.79E-01
MB	P02144	0.013 (-0.080, 0.106)	7.83E-01	8.33E-01		0.020 (-0.073, 0.114)	6.66E-01	7.86E-01
MCP-2	P80075	-0.045 (-0.121, 0.030)	2.40E-01	3.31E-01		-0.028 (-0.103, 0.048)	4.73E-01	6.48E-01
MEPE	Q9NQ76	-0.089 (-0.171, -0.007)	3.24E-02	7.23E-02		**-0.118 (-0.199, -0.037)**	**4.28E-03**	**1.81E-02**
MERTK	Q12866	-0.013 (-0.092, 0.067)	7.52E-01	8.19E-01		-0.012 (-0.091, 0.068)	7.73E-01	8.59E-01
MMP-1	P03956	-0.057 (-0.135, 0.021)	1.54E-01	2.36E-01		-0.042 (-0.120, 0.035)	2.86E-01	4.83E-01

Table S6. Longitudinal associations between 233 proteomic biomarkers and the annual rate of change in eGFRcr (N=1140) [a]

Biomarker	**UniProt_ID**	**Model 1**				**Model 2**		
		β (95%CI)	**P**	**FDR**		**β (95%CI)**	**P**	**FDR**
MMP-12	P39900	**-0.260 (-0.341, -0.179)**	**5.13E-10**	**3.71E-08**		**-0.215 (-0.300, -0.131)**	**6.98E-07**	**2.32E-05**
MMP-2	P08253	-0.072 (-0.151, 0.006)	7.16E-02	1.34E-01		-0.073 (-0.151, 0.005)	6.79E-02	1.65E-01
MMP-3	P08254	-0.024 (-0.117, 0.068)	6.05E-01	6.81E-01		-0.027 (-0.119, 0.065)	5.67E-01	7.19E-01
MMP-7	P09237	**-0.163 (-0.244, -0.082)**	**7.61E-05**	**4.93E-04**		**-0.157 (-0.238, -0.076)**	**1.64E-04**	**1.47E-03**
MMP-9	P14780	0.007 (-0.071, 0.086)	8.52E-01	8.83E-01		0.082 (0.001, 0.163)	4.85E-02	1.31E-01
MPO	P05164	-0.058 (-0.136, 0.020)	1.47E-01	2.28E-01		-0.017 (-0.095, 0.062)	6.73E-01	7.88E-01
NEMO	Q9Y6K9	0.027 (-0.050, 0.104)	4.89E-01	5.73E-01		0.034 (-0.043, 0.110)	3.86E-01	5.69E-01
Notch 3	Q9UM47	-0.095 (-0.177, -0.014)	2.17E-02	5.22E-02		**-0.111 (-0.193, -0.029)**	**7.86E-03**	**3.00E-02**
NT3	P20783	-0.049 (-0.134, 0.036)	2.62E-01	3.55E-01		-0.026 (-0.111, 0.060)	5.54E-01	7.09E-01
NT-proBNP	P16860	**-0.264 (-0.350, -0.179)**	**1.65E-09**	**7.69E-08**		**-0.249 (-0.336, -0.162)**	**2.77E-08**	**1.62E-06**
OPG	O00300	**-0.118 (-0.202, -0.033)**	**6.55E-03**	**2.04E-02**		-0.068 (-0.154, 0.018)	1.20E-01	2.55E-01
OPN	P10451	**-0.145 (-0.226, -0.064)**	**4.65E-04**	**2.21E-03**		**-0.156 (-0.236, -0.076)**	**1.37E-04**	**1.28E-03**
OSM	P13725	-0.004 (-0.082, 0.074)	9.26E-01	9.34E-01		0.085 (0.003, 0.167)	4.25E-02	1.22E-01
PAI	P05121	-0.067 (-0.145, 0.011)	9.43E-02	1.66E-01		-0.031 (-0.113, 0.050)	4.49E-01	6.33E-01
PAR-1	P25116	-0.067 (-0.144, 0.009)	8.32E-02	1.53E-01		-0.044 (-0.120, 0.032)	2.55E-01	4.41E-01
PARP-1	P09874	-0.046 (-0.124, 0.032)	2.45E-01	3.34E-01		-0.014 (-0.091, 0.064)	7.33E-01	8.33E-01
PCSK9	Q8NBP7	**-0.111 (-0.189, -0.033)**	**5.60E-03**	**1.86E-02**		**-0.104 (-0.185, -0.023)**	**1.22E-02**	**4.51E-02**
PDGF subunit A	P04085	-0.031 (-0.109, 0.047)	4.35E-01	5.25E-01		-0.022 (-0.099, 0.056)	5.87E-01	7.35E-01
PDGF subunit B	P01127	0.011 (-0.066, 0.088)	7.82E-01	8.33E-01		0.019 (-0.057, 0.095)	6.28E-01	7.75E-01
PD-L1	Q9NZQ7	**-0.138 (-0.218, -0.057)**	**8.55E-04**	**3.76E-03**		**-0.107 (-0.187, -0.026)**	**9.24E-03**	**3.47E-02**
PD-L2	Q9BQ51	-0.066 (-0.144, 0.013)	9.98E-02	1.70E-01		-0.047 (-0.125, 0.031)	2.41E-01	4.23E-01
PECAM-1	P16284	-0.041 (-0.119, 0.038)	3.07E-01	3.99E-01		-0.029 (-0.107, 0.048)	4.57E-01	6.34E-01
PGF	P49763	**-0.239 (-0.329, -0.148)**	**2.66E-07**	**4.43E-06**		**-0.206 (-0.296, -0.115)**	**9.25E-06**	**1.44E-04**
PGLYRP1	O75594	**-0.126 (-0.208, -0.045)**	**2.50E-03**	**9.61E-03**		-0.078 (-0.161, 0.005)	6.52E-02	1.62E-01
PIgR	P01833	**-0.159 (-0.239, -0.079)**	**1.01E-04**	**6.22E-04**		**-0.143 (-0.224, -0.062)**	**5.77E-04**	**4.07E-03**
PLC	P98160	**-0.222 (-0.310, -0.134)**	**7.94E-07**	**1.09E-05**		**-0.217 (-0.306, -0.128)**	**2.07E-06**	**4.38E-05**
PON3	Q15166	0.066 (-0.012, 0.145)	9.54E-02	1.67E-01		-0.040 (-0.130, 0.049)	3.79E-01	5.66E-01
PRELP	P51888	**-0.114 (-0.200, -0.029)**	**8.45E-03**	**2.52E-02**		-0.089 (-0.174, -0.005)	3.87E-02	1.14E-01
PRSS27	Q9BQR3	-0.093 (-0.172, -0.014)	2.11E-02	5.13E-02		-0.098 (-0.177, -0.020)	1.45E-02	5.03E-02
PRSS8	Q16651	**-0.201 (-0.282, -0.120)**	**1.19E-06**	**1.47E-05**		**-0.173 (-0.260, -0.085)**	**1.16E-04**	**1.13E-03**
PSGL-1	Q14242	-0.089 (-0.170, -0.008)	3.06E-02	6.93E-02		-0.024 (-0.110, 0.062)	5.86E-01	7.35E-01
PSP-D	P35247	**-0.094 (-0.172, -0.016)**	**1.83E-02**	**4.57E-02**		**-0.098 (-0.176, -0.020)**	**1.39E-02**	**4.91E-02**
PTX3	P26022	-0.077 (-0.156, 0.002)	5.50E-02	1.10E-01		-0.037 (-0.117, 0.043)	3.68E-01	5.57E-01
RAGE	Q15109	**-0.122 (-0.204, -0.039)**	**4.07E-03**	**1.48E-02**		**-0.166 (-0.249, -0.084)**	**8.50E-05**	**8.61E-04**
RARRES2	Q99969	**-0.168 (-0.250, -0.087)**	**5.19E-05**	**3.56E-04**		**-0.117 (-0.202, -0.033)**	**6.53E-03**	**2.62E-02**
REN	P00797	**-0.151 (-0.234, -0.068)**	**3.73E-04**	**1.90E-03**		-0.085 (-0.175, 0.004)	6.26E-02	1.57E-01
RETN	Q9HD89	**-0.149 (-0.232, -0.066)**	**4.56E-04**	**2.21E-03**		-0.104 (-0.187, -0.020)	1.57E-02	5.30E-02
SCF	P21583	0.017 (-0.067, 0.102)	6.84E-01	7.48E-01		-0.047 (-0.138, 0.045)	3.17E-01	5.18E-01
SCGB3A2	Q96PL1	-0.090 (-0.169, -0.010)	2.76E-02	6.30E-02		**-0.124 (-0.214, -0.034)**	**7.04E-03**	**2.78E-02**
SELE	P16581	**-0.100 (-0.177, -0.024)**	**1.04E-02**	**2.91E-02**		-0.056 (-0.134, 0.023)	1.66E-01	3.27E-01
SELP	P16109	-0.048 (-0.126, 0.030)	2.26E-01	3.16E-01		-0.032 (-0.110, 0.045)	4.11E-01	5.95E-01
SERPINA12	Q8IW75	0.033 (-0.045, 0.111)	4.05E-01	4.94E-01		0.039 (-0.039, 0.117)	3.23E-01	5.19E-01
SHPS-1	P78324	**-0.100 (-0.181, -0.019)**	**1.60E-02**	**4.20E-02**		-0.085 (-0.166, -0.004)	3.95E-02	1.15E-01
SIRT2	Q8IXJ6	-0.020 (-0.096, 0.057)	6.13E-01	6.84E-01		-0.005 (-0.081, 0.071)	9.00E-01	9.45E-01
SL-2	P09238	**-0.147 (-0.225, -0.069)**	**2.20E-04**	**1.22E-03**		**-0.132 (-0.210, -0.055)**	**8.46E-04**	**5.31E-03**
SOD2	P04179	-0.043 (-0.120, 0.034)	2.70E-01	3.62E-01		-0.022 (-0.099, 0.054)	5.68E-01	7.19E-01
SORT1	Q99523	-0.084 (-0.161, -0.006)	3.40E-02	7.32E-02		-0.057 (-0.136, 0.023)	1.61E-01	3.23E-01
SPON2	Q9BUD6	**-0.170 (-0.253, -0.088)**	**5.20E-05**	**3.56E-04**		**-0.175 (-0.259, -0.092)**	**4.24E-05**	**4.94E-04**

Table S6. Longitudinal associations between 233 proteomic biomarkers and the annual rate of change in eGFRcr (N=1140) [a]

Biomarker	UniProt_ID	Model 1				Model 2		
		β (95%CI)	P	FDR		β (95%CI)	P	FDR
SRC	P12931	0.076 (0.002, 0.151)	4.45E-02	9.17E-02		0.072 (-0.002, 0.146)	5.62E-02	1.45E-01
ST1A1	P50225	-0.010 (-0.087, 0.067)	8.07E-01	8.51E-01		0.000 (-0.076, 0.077)	9.94E-01	9.94E-01
ST2	Q01638	-0.093 (-0.176, -0.011)	2.69E-02	6.20E-02		-0.041 (-0.125, 0.043)	3.40E-01	5.31E-01
STAMBP	O95630	-0.011 (-0.088, 0.066)	7.76E-01	8.33E-01		0.001 (-0.076, 0.077)	9.87E-01	9.94E-01
STK4	Q13043	0.045 (-0.031, 0.120)	2.44E-01	3.34E-01		0.049 (-0.026, 0.123)	2.02E-01	3.76E-01
TF	P13726	-0.067 (-0.148, 0.015)	1.09E-01	1.78E-01		-0.090 (-0.172, -0.007)	3.29E-02	1.01E-01
TFPI	P10646	-0.038 (-0.115, 0.039)	3.32E-01	4.20E-01		-0.047 (-0.124, 0.030)	2.28E-01	4.05E-01
TGF-α	P01135	**-0.098 (-0.180, -0.017)**	**1.84E-02**	**4.57E-02**		-0.020 (-0.108, 0.068)	6.56E-01	7.86E-01
TGF-β1	P01137	-0.061 (-0.138, 0.016)	1.23E-01	1.99E-01		-0.032 (-0.110, 0.046)	4.16E-01	5.99E-01
TGM2	P21980	-0.020 (-0.099, 0.059)	6.23E-01	6.91E-01		0.040 (-0.041, 0.121)	3.29E-01	5.22E-01
THBS2	P35442	-0.094 (-0.175, -0.013)	2.25E-02	5.35E-02		-0.032 (-0.117, 0.052)	4.54E-01	6.33E-01
THPO	P40225	-0.045 (-0.124, 0.035)	2.72E-01	3.62E-01		-0.063 (-0.143, 0.016)	1.18E-01	2.52E-01
TIE2	Q02763	-0.049 (-0.126, 0.028)	2.14E-01	3.06E-01		-0.027 (-0.105, 0.050)	4.85E-01	6.61E-01
TIMP4	Q99727	-0.082 (-0.165, 0.001)	5.22E-02	1.06E-01		-0.062 (-0.146, 0.023)	1.55E-01	3.14E-01
TLT-2	Q5T2D2	-0.091 (-0.170, -0.012)	2.44E-02	5.69E-02		-0.090 (-0.170, -0.011)	2.54E-02	8.12E-02
TM	P07204	**-0.162 (-0.247, -0.078)**	**1.69E-04**	**9.61E-04**		**-0.146 (-0.230, -0.061)**	**7.13E-04**	**4.65E-03**
TNF-R1	P19438	**-0.276 (-0.367, -0.184)**	**4.88E-09**	**1.73E-07**		**-0.221 (-0.315, -0.127)**	**4.57E-06**	**8.88E-05**
TNF-R2	P20333	**-0.256 (-0.342, -0.171)**	**5.20E-09**	**1.73E-07**		**-0.214 (-0.300, -0.127)**	**1.41E-06**	**3.65E-05**
TNFRSF10A	O00220	**-0.137 (-0.220, -0.054)**	**1.19E-03**	**5.15E-03**		-0.075 (-0.161, 0.011)	8.78E-02	2.00E-01
TNFRSF10C	O14798	-0.060 (-0.138, 0.019)	1.35E-01	2.12E-01		-0.037 (-0.115, 0.042)	3.58E-01	5.52E-01
TNFRSF11A	Q9Y6Q6	**-0.266 (-0.356, -0.175)**	**9.99E-09**	**2.59E-07**		**-0.214 (-0.306, -0.121)**	**6.37E-06**	**1.14E-04**
TNFRSF13B	O14836	**-0.201 (-0.286, -0.116)**	**4.11E-06**	**4.17E-05**		**-0.164 (-0.250, -0.079)**	**1.74E-04**	**1.50E-03**
TNFRSF14	Q92956	**-0.146 (-0.230, -0.062)**	**6.62E-04**	**2.97E-03**		**-0.123 (-0.207, -0.039)**	**3.97E-03**	**1.76E-02**
TNFRSF9	Q07011	**-0.249 (-0.336, -0.161)**	**3.45E-08**	**7.30E-07**		**-0.234 (-0.322, -0.145)**	**2.36E-07**	**9.18E-06**
TNFSF10	P50591	-0.038 (-0.116, 0.041)	3.49E-01	4.35E-01		-0.029 (-0.109, 0.050)	4.68E-01	6.46E-01
TNFSF13B	Q9Y275	-0.063 (-0.143, 0.018)	1.26E-01	2.03E-01		-0.038 (-0.118, 0.043)	3.60E-01	5.52E-01
TNF-α	P01375	**-0.092 (-0.167, -0.017)**	**1.66E-02**	**4.30E-02**		-0.076 (-0.150, -0.001)	4.64E-02	1.30E-01
TNF-β	P01374	-0.061 (-0.140, 0.019)	1.34E-01	2.12E-01		-0.050 (-0.130, 0.030)	2.17E-01	3.92E-01
t-PA	P00750	-0.039 (-0.117, 0.038)	3.24E-01	4.14E-01		-0.004 (-0.083, 0.076)	9.30E-01	9.60E-01
TR	P02786	-0.066 (-0.144, 0.012)	9.78E-02	1.70E-01		-0.005 (-0.086, 0.075)	8.95E-01	9.44E-01
TRAIL-R2	O14763	**-0.226 (-0.311, -0.142)**	**1.71E-07**	**3.32E-06**		**-0.180 (-0.267, -0.094)**	**4.24E-05**	**4.94E-04**
TRANCE	O14788	-0.008 (-0.086, 0.070)	8.41E-01	8.79E-01		-0.017 (-0.095, 0.062)	6.76E-01	7.88E-01
TR-AP	P13686	-0.088 (-0.168, -0.007)	3.31E-02	7.23E-02		-0.089 (-0.169, -0.008)	3.11E-02	9.67E-02
TWEAK	O43508	0.050 (-0.028, 0.129)	2.09E-01	3.01E-01		0.009 (-0.071, 0.089)	8.23E-01	8.92E-01
uPA	P00749	-0.069 (-0.152, 0.013)	9.98E-02	1.70E-01		-0.063 (-0.145, 0.019)	1.30E-01	2.73E-01
U-PAR	Q03405	-0.071 (-0.155, 0.012)	9.31E-02	1.66E-01		-0.027 (-0.111, 0.057)	5.32E-01	7.00E-01
VEGF-A	P15692	**-0.179 (-0.261, -0.098)**	**1.75E-05**	**1.46E-04**		**-0.127 (-0.211, -0.043)**	**2.96E-03**	**1.41E-02**
VEGFD	O43915	**-0.112 (-0.189, -0.035)**	**4.49E-03**	**1.58E-02**		**-0.119 (-0.197, -0.041)**	**2.74E-03**	**1.39E-02**
VSIG2	Q96IQ7	**-0.207 (-0.292, -0.122)**	**1.87E-06**	**2.07E-05**		**-0.173 (-0.259, -0.088)**	**7.60E-05**	**8.05E-04**
vWF	P04275	-0.051 (-0.129, 0.027)	2.01E-01	2.91E-01		-0.011 (-0.090, 0.067)	7.74E-01	8.59E-01
XCL1	P47992	**-0.149 (-0.225, -0.073)**	**1.28E-04**	**7.63E-04**		**-0.120 (-0.196, -0.043)**	**2.23E-03**	**1.21E-02**

[a] Linear regressions were used to estimate β (95% CI) of the annual rate of change in eGFRcr (per year) per 1 standard deviation increase in biomarkers. The biomarkers are sorted alphabetically. **In bold are biomarkers significantly associated with the annual rate of change in eGFRcr (FDR <0.05)**.

Model 1: Adjusted for age, sex, and eGFRcr at baseline;

Model 2: Model 1 plus body mass index, physical activity, smoking status, alcohol consumption, systolic blood pressure, use of antihypertensive medication, triglycerides (naturally log-transformed), high-density lipoprotein cholesterol, use of lipid-lowering medication, prevalent diabetes, prevalent cardiovascular diseases, and fasting status at baseline.

Abbreviations: CI, confidence interval; eGFRcr, creatinine-based estimated glomerular filtration rate; FDR, Benjamini–Hochberg false-discovery rate. Full names of the biomarkers can be found in Additional file 1: Table S1.

Table S7. Longitudinal associations between 233 proteomic biomarkers and the annual rate of change in CKD-EPI Equation 2009-based and CKD-EPI Equation 2021-based eGFRcr (N=1140) [a]

Biomarker	UniProt_ID	CKD-EPI Equation 2009-based eGFRcr				CKD-EPI Equation 2021-based eGFRcr		
		β (95%CI)	P	FDR		β (95%CI)	P	FDR
4E-BP1	Q13541	-0.009 (-0.087, 0.069)	8.19E-01	8.92E-01		-0.012 (-0.093, 0.069)	7.70E-01	8.71E-01
ACE2	Q9BYF1	-0.072 (-0.159, 0.016)	1.09E-01	2.41E-01		-0.069 (-0.160, 0.022)	1.38E-01	2.89E-01
ADA	P00813	-0.046 (-0.125, 0.034)	2.62E-01	4.46E-01		-0.050 (-0.133, 0.033)	2.34E-01	4.13E-01
ADAM-TS13	Q76LX8	0.015 (-0.062, 0.092)	7.06E-01	8.14E-01		0.016 (-0.064, 0.096)	6.94E-01	8.12E-01
ADM	P35318	**-0.157 (-0.249, -0.065)**	**8.67E-04**	**5.31E-03**		**-0.163 (-0.259, -0.067)**	**8.78E-04**	**5.25E-03**
AGRP	O00253	**-0.147 (-0.239, -0.055)**	**1.76E-03**	**9.75E-03**		**-0.150 (-0.246, -0.055)**	**2.02E-03**	**1.09E-02**
ALCAM	Q13740	-0.088 (-0.170, -0.006)	3.55E-02	1.07E-01		-0.089 (-0.175, -0.004)	4.02E-02	1.19E-01
AMBP	P02760	**-0.154 (-0.242, -0.065)**	**6.72E-04**	**4.61E-03**		**-0.162 (-0.254, -0.070)**	**5.44E-04**	**3.78E-03**
ANG-1	Q15389	0.000 (-0.076, 0.077)	9.94E-01	9.94E-01		-0.004 (-0.083, 0.075)	9.22E-01	9.59E-01
AP-N	P15144	-0.041 (-0.120, 0.038)	3.04E-01	5.07E-01		-0.039 (-0.121, 0.043)	3.50E-01	5.45E-01
Axin-1	O15169	0.026 (-0.050, 0.103)	4.97E-01	6.69E-01		0.025 (-0.054, 0.104)	5.39E-01	7.09E-01
AXL	P30530	-0.073 (-0.153, 0.006)	6.88E-02	1.65E-01		-0.076 (-0.158, 0.006)	6.91E-02	1.67E-01
BMP-6	P22004	-0.031 (-0.108, 0.047)	4.38E-01	6.22E-01		-0.034 (-0.115, 0.046)	4.03E-01	5.83E-01
BOC	Q9BWV1	-0.056 (-0.134, 0.023)	1.63E-01	3.26E-01		-0.055 (-0.137, 0.026)	1.82E-01	3.56E-01
CA5A	P35218	-0.079 (-0.162, 0.003)	5.93E-02	1.52E-01		-0.082 (-0.167, 0.004)	6.12E-02	1.53E-01
CASP-3	P42574	0.002 (-0.075, 0.078)	9.64E-01	9.81E-01		-0.002 (-0.081, 0.077)	9.63E-01	9.80E-01
CASP8	Q14790	-0.018 (-0.100, 0.064)	6.67E-01	7.86E-01		-0.022 (-0.107, 0.063)	6.08E-01	7.54E-01
CCL11	P51671	-0.074 (-0.153, 0.006)	7.01E-02	1.67E-01		-0.077 (-0.159, 0.006)	6.95E-02	1.67E-01
CCL13	Q99616	-0.029 (-0.106, 0.047)	4.53E-01	6.33E-01		-0.034 (-0.114, 0.046)	4.01E-01	5.83E-01
CCL15	Q16663	**-0.135 (-0.214, -0.055)**	**8.93E-04**	**5.34E-03**		**-0.139 (-0.221, -0.057)**	**9.72E-04**	**5.66E-03**
CCL16	O15467	**-0.116 (-0.194, -0.037)**	**4.00E-03**	**1.76E-02**		**-0.120 (-0.202, -0.039)**	**3.92E-03**	**1.69E-02**
CCL17	Q92583	-0.071 (-0.148, 0.006)	7.21E-02	1.70E-01		-0.076 (-0.156, 0.004)	6.16E-02	1.53E-01
CCL19	Q99731	-0.010 (-0.091, 0.071)	8.06E-01	8.90E-01		-0.011 (-0.095, 0.073)	7.94E-01	8.89E-01
CCL2	P13500	-0.064 (-0.142, 0.014)	1.05E-01	2.36E-01		-0.067 (-0.148, 0.014)	1.07E-01	2.35E-01
CCL20	P78556	-0.003 (-0.081, 0.074)	9.32E-01	9.60E-01		-0.001 (-0.082, 0.080)	9.83E-01	9.87E-01
CCL23	P55773	**-0.122 (-0.202, -0.041)**	**2.97E-03**	**1.41E-02**		**-0.128 (-0.211, -0.045)**	**2.59E-03**	**1.28E-02**
CCL24	O00175	-0.038 (-0.114, 0.038)	3.31E-01	5.22E-01		-0.040 (-0.119, 0.039)	3.24E-01	5.23E-01
CCL25	O15444	-0.072 (-0.150, 0.005)	6.68E-02	1.64E-01		-0.074 (-0.154, 0.007)	7.33E-02	1.74E-01
CCL28	Q9NRJ3	-0.077 (-0.154, 0.000)	5.00E-02	1.34E-01		-0.077 (-0.157, 0.002)	5.68E-02	1.49E-01
CCL3	P10147	**-0.116 (-0.197, -0.036)**	**4.77E-03**	**1.98E-02**		**-0.121 (-0.205, -0.038)**	**4.55E-03**	**1.93E-02**
CCL4	P13236	-0.079 (-0.159, 0.001)	5.15E-02	1.36E-01		-0.086 (-0.169, -0.003)	4.34E-02	1.25E-01
CCL7	P80098	**-0.135 (-0.216, -0.053)**	**1.19E-03**	**6.91E-03**		**-0.144 (-0.229, -0.060)**	**8.15E-04**	**5.13E-03**
CD163	Q86VB7	-0.025 (-0.107, 0.056)	5.47E-01	7.09E-01		-0.025 (-0.110, 0.060)	5.63E-01	7.24E-01
CD244	Q9BZW8	-0.035 (-0.112, 0.041)	3.66E-01	5.57E-01		-0.040 (-0.120, 0.039)	3.22E-01	5.23E-01
CD4	P01730	-0.019 (-0.101, 0.062)	6.46E-01	7.84E-01		-0.023 (-0.108, 0.062)	5.97E-01	7.53E-01
CD40	P25942	-0.050 (-0.127, 0.027)	2.05E-01	3.76E-01		-0.053 (-0.133, 0.027)	1.96E-01	3.81E-01
CD40-L	P29965	0.003 (-0.074, 0.080)	9.36E-01	9.60E-01		0.001 (-0.079, 0.081)	9.80E-01	9.87E-01
CD5	P06127	-0.035 (-0.113, 0.044)	3.88E-01	5.69E-01		-0.038 (-0.119, 0.044)	3.62E-01	5.58E-01
CD6	P30203	0.006 (-0.072, 0.084)	8.79E-01	9.32E-01		0.005 (-0.076, 0.086)	9.05E-01	9.50E-01
CD84	Q9UIB8	-0.001 (-0.078, 0.076)	9.88E-01	9.94E-01		-0.004 (-0.084, 0.076)	9.18E-01	9.59E-01
CD8A	P01732	-0.080 (-0.159, -0.001)	4.76E-02	1.31E-01		-0.085 (-0.167, -0.003)	4.13E-02	1.20E-01
CD93	Q9NPY3	**-0.211 (-0.290, -0.132)**	**1.69E-07**	**7.88E-06**		**-0.219 (-0.301, -0.137)**	**1.72E-07**	**8.03E-06**
CDCP1	Q9H5V8	-0.085 (-0.168, -0.002)	4.41E-02	1.25E-01		-0.084 (-0.170, 0.002)	5.44E-02	1.44E-01
CDH5	P33151	-0.087 (-0.163, -0.012)	2.34E-02	7.57E-02		-0.089 (-0.168, -0.011)	2.57E-02	8.21E-02
CEACAM8	P31997	0.060 (-0.028, 0.148)	1.83E-01	3.57E-01		0.058 (-0.034, 0.149)	2.17E-01	3.95E-01
CHI3L1	P36222	**-0.188 (-0.275, -0.100)**	**2.65E-05**	**3.42E-04**		**-0.191 (-0.282, -0.101)**	**3.71E-05**	**4.80E-04**
CHIT1	Q13231	**-0.112 (-0.189, -0.035)**	**4.20E-03**	**1.81E-02**		**-0.115 (-0.194, -0.035)**	**4.75E-03**	**1.98E-02**
CNTN1	Q12860	-0.054 (-0.135, 0.027)	1.91E-01	3.68E-01		-0.055 (-0.139, 0.029)	1.99E-01	3.84E-01

Table S7. Longitudinal associations between 233 proteomic biomarkers and the annual rate of change in CKD-EPI Equation 2009-based and CKD-EPI Equation 2021-based eGFRcr (N=1140) ^{a}

Biomarker	**UniProt_ID**	**CKD-EPI Equation 2009-based eGFRcr**				**CKD-EPI Equation 2021-based eGFRcr**		
		β (95%CI)	**P**	**FDR**		**β (95%CI)**	**P**	**FDR**
COL1A1	P02452	-0.056 (-0.133, 0.021)	1.52E-01	3.11E-01		-0.058 (-0.138, 0.022)	1.57E-01	3.16E-01
CPA1	P15085	-0.040 (-0.121, 0.041)	3.32E-01	5.22E-01		-0.042 (-0.127, 0.042)	3.26E-01	5.24E-01
CPB1	P15086	-0.067 (-0.149, 0.015)	1.11E-01	2.42E-01		-0.070 (-0.155, 0.016)	1.09E-01	2.35E-01
CSF1	P09603	**-0.107 (-0.191, -0.022)**	**1.34E-02**	**4.80E-02**		**-0.110 (-0.198, -0.022)**	**1.41E-02**	**4.89E-02**
CST5	P28325	-0.067 (-0.151, 0.016)	1.13E-01	2.44E-01		-0.071 (-0.158, 0.015)	1.07E-01	2.35E-01
CSTB	P04080	-0.063 (-0.146, 0.019)	1.31E-01	2.73E-01		-0.069 (-0.154, 0.016)	1.12E-01	2.40E-01
CTRC	Q99895	0.043 (-0.038, 0.125)	2.98E-01	4.99E-01		0.045 (-0.040, 0.130)	3.01E-01	5.02E-01
CTSL1	P07711	**-0.167 (-0.248, -0.086)**	**5.16E-05**	**5.73E-04**		**-0.170 (-0.254, -0.087)**	**6.99E-05**	**7.75E-04**
CTSZ	Q9UBR2	**-0.129 (-0.213, -0.046)**	**2.36E-03**	**1.25E-02**		**-0.136 (-0.223, -0.050)**	**2.00E-03**	**1.09E-02**
CX3CL1	P78423	**-0.183 (-0.268, -0.099)**	**2.10E-05**	**3.06E-04**		**-0.189 (-0.276, -0.101)**	**2.56E-05**	**3.73E-04**
CXCL1	P09341	-0.044 (-0.119, 0.032)	2.56E-01	4.41E-01		-0.047 (-0.126, 0.031)	2.35E-01	4.13E-01
CXCL10	P02778	-0.040 (-0.118, 0.038)	3.14E-01	5.18E-01		-0.041 (-0.122, 0.040)	3.20E-01	5.23E-01
CXCL11	O14625	-0.052 (-0.129, 0.025)	1.84E-01	3.57E-01		-0.056 (-0.136, 0.024)	1.68E-01	3.35E-01
CXCL16	Q9H2A7	-0.081 (-0.161, -0.001)	4.76E-02	1.31E-01		-0.082 (-0.166, 0.001)	5.34E-02	1.44E-01
CXCL5	P42830	0.013 (-0.062, 0.089)	7.27E-01	8.32E-01		0.011 (-0.067, 0.089)	7.86E-01	8.84E-01
CXCL6	P80162	-0.044 (-0.119, 0.032)	2.57E-01	4.41E-01		-0.047 (-0.125, 0.032)	2.43E-01	4.15E-01
CXCL9	Q07325	-0.069 (-0.150, 0.012)	9.35E-02	2.12E-01		-0.072 (-0.156, 0.011)	9.04E-02	2.04E-01
DCN	P07585	-0.022 (-0.106, 0.061)	6.02E-01	7.50E-01		-0.019 (-0.106, 0.067)	6.60E-01	7.93E-01
DECR1	Q16698	0.039 (-0.038, 0.116)	3.20E-01	5.18E-01		0.038 (-0.042, 0.118)	3.51E-01	5.45E-01
Dkk-1	O94907	-0.007 (-0.085, 0.071)	8.63E-01	9.23E-01		-0.011 (-0.092, 0.070)	7.97E-01	8.89E-01
DLK-1	P80370	-0.095 (-0.175, -0.014)	2.10E-02	6.89E-02		-0.100 (-0.183, -0.016)	1.93E-02	6.25E-02
DNER	Q8NFT8	0.005 (-0.076, 0.085)	9.12E-01	9.52E-01		0.006 (-0.078, 0.090)	8.85E-01	9.33E-01
EGFR	P00533	0.009 (-0.071, 0.088)	8.27E-01	8.92E-01		0.009 (-0.073, 0.092)	8.24E-01	9.01E-01
EN-RAGE	P80511	-0.015 (-0.101, 0.071)	7.28E-01	8.32E-01		-0.018 (-0.107, 0.071)	6.97E-01	8.12E-01
Ep-CAM	P16422	-0.051 (-0.128, 0.027)	2.00E-01	3.76E-01		-0.051 (-0.132, 0.029)	2.10E-01	3.89E-01
EPHB4	P54760	**-0.233 (-0.313, -0.153)**	**1.46E-08**	**1.62E-06**		**-0.243 (-0.327, -0.160)**	**1.24E-08**	**1.45E-06**
FABP2	P12104	-0.089 (-0.169, -0.009)	2.84E-02	8.95E-02		-0.093 (-0.176, -0.010)	2.76E-02	8.70E-02
FABP4	P15090	**-0.195 (-0.308, -0.082)**	**7.19E-04**	**4.65E-03**		**-0.202 (-0.319, -0.085)**	**7.51E-04**	**4.86E-03**
FAS	P25445	-0.076 (-0.157, 0.004)	6.24E-02	1.57E-01		-0.083 (-0.167, 0.000)	5.02E-02	1.39E-01
FGF19	O95750	-0.018 (-0.099, 0.063)	6.68E-01	7.86E-01		-0.018 (-0.102, 0.066)	6.75E-01	8.03E-01
FGF21	Q9NSA1	-0.078 (-0.163, 0.007)	7.36E-02	1.71E-01		-0.078 (-0.166, 0.011)	8.66E-02	1.98E-01
FGF-23	Q9GZV9	**-0.166 (-0.254, -0.079)**	**1.99E-04**	**1.60E-03**		**-0.169 (-0.259, -0.078)**	**2.89E-04**	**2.32E-03**
FLT3L	P49771	-0.003 (-0.083, 0.077)	9.42E-01	9.62E-01		0.000 (-0.083, 0.083)	1.00E+00	1.00E+00
FS	P19883	**-0.099 (-0.177, -0.021)**	**1.34E-02**	**4.80E-02**		**-0.104 (-0.185, -0.023)**	**1.19E-02**	**4.34E-02**
Gal-4	P56470	**-0.144 (-0.224, -0.064)**	**4.17E-04**	**3.14E-03**		**-0.148 (-0.231, -0.065)**	**4.65E-04**	**3.38E-03**
Gal-9	O00182	**-0.112 (-0.195, -0.030)**	**7.43E-03**	**2.88E-02**		**-0.116 (-0.202, -0.031)**	**7.70E-03**	**2.94E-02**
GDF-15	Q99988	**-0.224 (-0.321, -0.127)**	**6.82E-06**	**1.14E-04**		**-0.231 (-0.332, -0.130)**	**7.77E-06**	**1.29E-04**
GDF-2	Q9UK05	-0.026 (-0.111, 0.059)	5.52E-01	7.09E-01		-0.022 (-0.111, 0.066)	6.19E-01	7.60E-01
GH	P01241	0.030 (-0.061, 0.120)	5.21E-01	6.94E-01		0.034 (-0.060, 0.128)	4.82E-01	6.61E-01
GIF	P27352	-0.037 (-0.120, 0.045)	3.74E-01	5.62E-01		-0.036 (-0.122, 0.050)	4.14E-01	5.87E-01
GLO1	Q04760	0.004 (-0.073, 0.081)	9.21E-01	9.58E-01		0.002 (-0.078, 0.082)	9.66E-01	9.80E-01
GPVI	Q9HCN6	-0.023 (-0.100, 0.053)	5.53E-01	7.09E-01		-0.028 (-0.107, 0.052)	4.92E-01	6.63E-01
GRN	P28799	-0.099 (-0.180, -0.019)	1.54E-02	5.26E-02		-0.101 (-0.184, -0.017)	1.80E-02	6.08E-02
GT	P51161	-0.012 (-0.092, 0.068)	7.68E-01	8.59E-01		-0.014 (-0.097, 0.069)	7.46E-01	8.47E-01
HAOX1	Q9UJM8	-0.027 (-0.108, 0.054)	5.19E-01	6.94E-01		-0.024 (-0.108, 0.060)	5.80E-01	7.43E-01
HB-EGF	Q99075	-0.034 (-0.111, 0.043)	3.92E-01	5.71E-01		-0.038 (-0.118, 0.042)	3.49E-01	5.45E-01
HGF	P14210	-0.019 (-0.108, 0.069)	6.66E-01	7.86E-01		-0.018 (-0.110, 0.073)	6.93E-01	8.12E-01
HO-1	P09601	-0.066 (-0.147, 0.015)	1.11E-01	2.42E-01		-0.069 (-0.153, 0.015)	1.08E-01	2.35E-01

Table S7. Longitudinal associations between 233 proteomic biomarkers and the annual rate of change in CKD-EPI Equation 2009-based and CKD-EPI Equation 2021-based eGFRcr (N=1140) [a]

Biomarker	UniProt_ID	CKD-EPI Equation 2009-based eGFRcr				CKD-EPI Equation 2021-based eGFRcr		
		β (95%CI)	P	FDR		β (95%CI)	P	FDR
hOSCAR	Q8IYS5	**-0.116 (-0.192, -0.040)**	**2.70E-03**	**1.39E-02**		**-0.121 (-0.200, -0.042)**	**2.57E-03**	**1.28E-02**
HSP 27	P04792	0.073 (-0.001, 0.147)	5.37E-02	1.41E-01		0.074 (-0.003, 0.151)	5.89E-02	1.51E-01
ICAM-2	P13598	**-0.110 (-0.188, -0.033)**	**5.42E-03**	**2.22E-02**		**-0.114 (-0.195, -0.033)**	**5.66E-03**	**2.28E-02**
IDUA	P35475	-0.006 (-0.085, 0.073)	8.80E-01	9.32E-01		-0.007 (-0.090, 0.075)	8.63E-01	9.19E-01
IFNG	P01579	-0.058 (-0.134, 0.018)	1.35E-01	2.79E-01		-0.058 (-0.137, 0.021)	1.48E-01	3.02E-01
IGFBP-1	P08833	**-0.140 (-0.234, -0.046)**	**3.51E-03**	**1.60E-02**		**-0.145 (-0.242, -0.047)**	**3.71E-03**	**1.63E-02**
IGFBP-2	P18065	**-0.226 (-0.318, -0.135)**	**1.36E-06**	**3.65E-05**		**-0.234 (-0.329, -0.139)**	**1.46E-06**	**3.79E-05**
IGFBP-7	Q16270	**-0.135 (-0.217, -0.053)**	**1.30E-03**	**7.39E-03**		**-0.136 (-0.221, -0.050)**	**1.86E-03**	**1.06E-02**
IgG Fc receptor II-b	P31994	-0.020 (-0.097, 0.057)	6.08E-01	7.53E-01		-0.021 (-0.101, 0.058)	5.98E-01	7.53E-01
IL-10	P22301	-0.036 (-0.116, 0.044)	3.84E-01	5.69E-01		-0.034 (-0.117, 0.049)	4.17E-01	5.87E-01
IL-10RB	Q08334	**-0.160 (-0.245, -0.076)**	**1.99E-04**	**1.60E-03**		**-0.166 (-0.254, -0.078)**	**2.09E-04**	**1.80E-03**
IL-12B	P29460	**-0.132 (-0.220, -0.045)**	**3.02E-03**	**1.41E-02**		**-0.139 (-0.230, -0.048)**	**2.70E-03**	**1.28E-02**
IL-15RA	Q13261	**-0.181 (-0.266, -0.097)**	**2.59E-05**	**3.42E-04**		**-0.188 (-0.276, -0.100)**	**2.73E-05**	**3.74E-04**
IL-16	Q14005	-0.048 (-0.125, 0.030)	2.28E-01	4.05E-01		-0.051 (-0.131, 0.029)	2.13E-01	3.91E-01
IL-17D	Q8TAD2	-0.017 (-0.092, 0.058)	6.56E-01	7.86E-01		-0.015 (-0.092, 0.063)	7.13E-01	8.22E-01
IL-17RA	Q96F46	-0.026 (-0.105, 0.054)	5.29E-01	7.00E-01		-0.027 (-0.109, 0.056)	5.28E-01	7.00E-01
IL-18	Q14116	-0.050 (-0.135, 0.034)	2.41E-01	4.23E-01		-0.055 (-0.142, 0.033)	2.20E-01	3.97E-01
IL-18BP	O95998	**-0.235 (-0.317, -0.152)**	**2.70E-08**	**1.62E-06**		**-0.244 (-0.330, -0.159)**	**2.51E-08**	**1.95E-06**
IL-18R1	Q13478	-0.030 (-0.114, 0.055)	4.93E-01	6.68E-01		-0.027 (-0.115, 0.061)	5.43E-01	7.09E-01
IL-1RA	P18510	-0.009 (-0.097, 0.079)	8.49E-01	9.11E-01		-0.011 (-0.102, 0.081)	8.17E-01	8.98E-01
IL1-RL2	Q9HB29	-0.055 (-0.139, 0.030)	2.04E-01	3.76E-01		-0.056 (-0.144, 0.032)	2.10E-01	3.89E-01
IL-1RT1	P14778	-0.097 (-0.176, -0.017)	1.69E-02	5.62E-02		-0.099 (-0.181, -0.016)	1.88E-02	6.23E-02
IL-1RT2	P27930	-0.013 (-0.093, 0.067)	7.55E-01	8.54E-01		-0.011 (-0.094, 0.073)	8.02E-01	8.90E-01
IL-27	Q8NEV9	-0.038 (-0.116, 0.041)	3.47E-01	5.39E-01		-0.037 (-0.119, 0.044)	3.69E-01	5.61E-01
IL2-RA	P01589	**-0.194 (-0.273, -0.115)**	**1.66E-06**	**3.87E-05**		**-0.199 (-0.281, -0.117)**	**2.15E-06**	**4.56E-05**
IL-4RA	P24394	**-0.151 (-0.232, -0.070)**	**2.54E-04**	**1.97E-03**		**-0.153 (-0.237, -0.069)**	**3.62E-04**	**2.81E-03**
IL-6	P05231	-0.041 (-0.123, 0.040)	3.18E-01	5.18E-01		-0.041 (-0.126, 0.043)	3.40E-01	5.42E-01
IL-6RA	P08887	-0.083 (-0.160, -0.005)	3.59E-02	1.07E-01		-0.085 (-0.165, -0.005)	3.80E-02	1.13E-01
IL-7	P13232	-0.030 (-0.104, 0.044)	4.27E-01	6.10E-01		-0.035 (-0.112, 0.043)	3.79E-01	5.66E-01
IL-8	P10145	-0.052 (-0.133, 0.029)	2.05E-01	3.76E-01		-0.055 (-0.139, 0.029)	2.03E-01	3.87E-01
ITGB1BP2	Q9UKP3	0.009 (-0.067, 0.085)	8.15E-01	8.92E-01		0.006 (-0.073, 0.085)	8.80E-01	9.32E-01
ITGB2	P05107	0.012 (-0.069, 0.093)	7.67E-01	8.59E-01		0.010 (-0.074, 0.095)	8.07E-01	8.91E-01
JAM-A	Q9Y624	-0.015 (-0.092, 0.062)	6.98E-01	8.09E-01		-0.020 (-0.100, 0.060)	6.27E-01	7.65E-01
KIM1	Q96D42	**-0.292 (-0.377, -0.206)**	**4.08E-11**	**9.51E-09**		**-0.301 (-0.390, -0.212)**	**5.09E-11**	**1.18E-08**
KLK6	Q92876	**-0.124 (-0.206, -0.042)**	**2.97E-03**	**1.41E-02**		**-0.132 (-0.217, -0.047)**	**2.29E-03**	**1.21E-02**
LDL receptor	P01130	-0.090 (-0.190, 0.011)	8.12E-02	1.87E-01		-0.091 (-0.196, 0.013)	8.62E-02	1.98E-01
LEP	P41159	0.040 (-0.088, 0.169)	5.38E-01	7.04E-01		0.037 (-0.096, 0.170)	5.87E-01	7.48E-01
LIFR	P42702	-0.053 (-0.135, 0.028)	1.99E-01	3.76E-01		-0.050 (-0.135, 0.034)	2.41E-01	4.15E-01
LIGHT	O43557	0.009 (-0.068, 0.086)	8.17E-01	8.92E-01		0.007 (-0.073, 0.088)	8.56E-01	9.19E-01
LOX-1	P78380	0.055 (-0.032, 0.141)	2.15E-01	3.92E-01		0.054 (-0.036, 0.143)	2.39E-01	4.15E-01
LPL	P06858	-0.023 (-0.121, 0.075)	6.42E-01	7.83E-01		-0.022 (-0.124, 0.079)	6.66E-01	7.96E-01
LTBR	P36941	**-0.154 (-0.240, -0.067)**	**5.10E-04**	**3.72E-03**		**-0.161 (-0.251, -0.071)**	**4.49E-04**	**3.38E-03**
MARCO	Q9UEW3	-0.019 (-0.097, 0.059)	6.35E-01	7.79E-01		-0.017 (-0.098, 0.064)	6.82E-01	8.07E-01
MB	P02144	0.020 (-0.073, 0.114)	6.66E-01	7.86E-01		0.017 (-0.080, 0.113)	7.36E-01	8.40E-01
MCP-2	P80075	-0.028 (-0.103, 0.048)	4.73E-01	6.48E-01		-0.031 (-0.109, 0.048)	4.43E-01	6.14E-01
MEPE	Q9NQ76	**-0.118 (-0.199, -0.037)**	**4.28E-03**	**1.81E-02**		**-0.125 (-0.209, -0.041)**	**3.43E-03**	**1.54E-02**
MERTK	Q12866	-0.012 (-0.091, 0.068)	7.73E-01	8.59E-01		-0.007 (-0.090, 0.075)	8.61E-01	9.19E-01
MMP-1	P03956	-0.042 (-0.120, 0.035)	2.86E-01	4.83E-01		-0.047 (-0.127, 0.034)	2.53E-01	4.31E-01

Table S7. Longitudinal associations between 233 proteomic biomarkers and the annual rate of change in CKD-EPI Equation 2009-based and CKD-EPI Equation 2021-based eGFRcr (N=1140) [a]

Biomarker	UniProt_ID	CKD-EPI Equation 2009-based eGFRcr				CKD-EPI Equation 2021-based eGFRcr		
		β (95%CI)	P	FDR		β (95%CI)	P	FDR
MMP-12	P39900	**-0.215 (-0.300, -0.131)**	**6.98E-07**	**2.32E-05**		**-0.226 (-0.314, -0.138)**	**5.18E-07**	**1.72E-05**
MMP-2	P08253	-0.073 (-0.151, 0.005)	6.79E-02	1.65E-01		-0.073 (-0.155, 0.008)	7.79E-02	1.83E-01
MMP-3	P08254	-0.027 (-0.119, 0.065)	5.67E-01	7.19E-01		-0.029 (-0.125, 0.066)	5.46E-01	7.09E-01
MMP-7	P09237	**-0.157 (-0.238, -0.076)**	**1.64E-04**	**1.47E-03**		**-0.159 (-0.243, -0.074)**	**2.42E-04**	**2.01E-03**
MMP-9	P14780	0.082 (0.001, 0.163)	4.85E-02	1.31E-01		0.083 (-0.001, 0.167)	5.41E-02	1.44E-01
MPO	P05164	-0.017 (-0.095, 0.062)	6.73E-01	7.88E-01		-0.022 (-0.103, 0.060)	6.03E-01	7.54E-01
NEMO	Q9Y6K9	0.034 (-0.043, 0.110)	3.86E-01	5.69E-01		0.032 (-0.047, 0.111)	4.31E-01	6.01E-01
Notch 3	Q9UM47	**-0.111 (-0.193, -0.029)**	**7.86E-03**	**3.00E-02**		**-0.112 (-0.197, -0.027)**	**1.01E-02**	**3.78E-02**
NT3	P20783	-0.026 (-0.111, 0.060)	5.54E-01	7.09E-01		-0.021 (-0.110, 0.067)	6.39E-01	7.76E-01
NT-proBNP	P16860	**-0.249 (-0.336, -0.162)**	**2.77E-08**	**1.62E-06**		**-0.256 (-0.346, -0.165)**	**4.03E-08**	**2.35E-06**
OPG	O00300	-0.068 (-0.154, 0.018)	1.20E-01	2.55E-01		-0.069 (-0.158, 0.020)	1.29E-01	2.74E-01
OPN	P10451	**-0.156 (-0.236, -0.076)**	**1.37E-04**	**1.28E-03**		**-0.163 (-0.246, -0.080)**	**1.23E-04**	**1.20E-03**
OSM	P13725	0.085 (0.003, 0.167)	4.25E-02	1.22E-01		0.086 (0.001, 0.171)	4.85E-02	1.37E-01
PAI	P05121	-0.031 (-0.113, 0.050)	4.49E-01	6.33E-01		-0.035 (-0.119, 0.050)	4.18E-01	5.87E-01
PAR-1	P25116	-0.044 (-0.120, 0.032)	2.55E-01	4.41E-01		-0.049 (-0.127, 0.030)	2.25E-01	4.04E-01
PARP-1	P09874	-0.014 (-0.091, 0.064)	7.33E-01	8.33E-01		-0.014 (-0.095, 0.067)	7.31E-01	8.39E-01
PCSK9	Q8NBP7	**-0.104 (-0.185, -0.023)**	**1.22E-02**	**4.51E-02**		**-0.107 (-0.191, -0.022)**	**1.31E-02**	**4.64E-02**
PDGF subunit A	P04085	-0.022 (-0.099, 0.056)	5.87E-01	7.35E-01		-0.027 (-0.107, 0.054)	5.13E-01	6.83E-01
PDGF subunit B	P01127	0.019 (-0.057, 0.095)	6.28E-01	7.75E-01		0.015 (-0.064, 0.095)	7.03E-01	8.15E-01
PD-L1	Q9NZQ7	**-0.107 (-0.187, -0.026)**	**9.24E-03**	**3.47E-02**		**-0.114 (-0.198, -0.031)**	**7.39E-03**	**2.87E-02**
PD-L2	Q9BQ51	-0.047 (-0.125, 0.031)	2.41E-01	4.23E-01		-0.047 (-0.128, 0.034)	2.58E-01	4.36E-01
PECAM-1	P16284	-0.029 (-0.107, 0.048)	4.57E-01	6.34E-01		-0.034 (-0.115, 0.047)	4.12E-01	5.87E-01
PGF	P49763	**-0.206 (-0.296, -0.115)**	**9.25E-06**	**1.44E-04**		**-0.212 (-0.306, -0.118)**	**1.07E-05**	**1.66E-04**
PGLYRP1	O75594	-0.078 (-0.161, 0.005)	6.52E-02	1.62E-01		-0.083 (-0.169, 0.003)	5.80E-02	1.50E-01
PIgR	P01833	**-0.143 (-0.224, -0.062)**	**5.77E-04**	**4.07E-03**		**-0.148 (-0.232, -0.064)**	**5.67E-04**	**3.78E-03**
PLC	P98160	**-0.217 (-0.306, -0.128)**	**2.07E-06**	**4.38E-05**		**-0.225 (-0.318, -0.133)**	**2.03E-06**	**4.56E-05**
PON3	Q15166	-0.040 (-0.130, 0.049)	3.79E-01	5.66E-01		-0.042 (-0.135, 0.051)	3.72E-01	5.63E-01
PRELP	P51888	-0.089 (-0.174, -0.005)	3.87E-02	1.14E-01		-0.089 (-0.177, 0.000)	4.89E-02	1.37E-01
PRSS27	Q9BQR3	-0.098 (-0.177, -0.020)	1.45E-02	5.03E-02		**-0.106 (-0.188, -0.024)**	**1.09E-02**	**4.03E-02**
PRSS8	Q16651	**-0.173 (-0.260, -0.085)**	**1.16E-04**	**1.13E-03**		**-0.178 (-0.269, -0.087)**	**1.30E-04**	**1.21E-03**
PSGL-1	Q14242	-0.024 (-0.110, 0.062)	5.86E-01	7.35E-01		-0.023 (-0.112, 0.066)	6.07E-01	7.54E-01
PSP-D	P35247	**-0.098 (-0.176, -0.020)**	**1.39E-02**	**4.91E-02**		-0.098 (-0.179, -0.017)	1.74E-02	5.95E-02
PTX3	P26022	-0.037 (-0.117, 0.043)	3.68E-01	5.57E-01		-0.037 (-0.120, 0.046)	3.86E-01	5.72E-01
RAGE	Q15109	**-0.166 (-0.249, -0.084)**	**8.50E-05**	**8.61E-04**		**-0.174 (-0.260, -0.088)**	**7.62E-05**	**8.07E-04**
RARRES2	Q99969	**-0.117 (-0.202, -0.033)**	**6.53E-03**	**2.62E-02**		**-0.126 (-0.214, -0.038)**	**4.83E-03**	**1.98E-02**
REN	P00797	-0.085 (-0.175, 0.004)	6.26E-02	1.57E-01		-0.089 (-0.182, 0.004)	6.04E-02	1.53E-01
RETN	Q9HD89	-0.104 (-0.187, -0.020)	1.57E-02	5.30E-02		**-0.111 (-0.199, -0.024)**	**1.22E-02**	**4.38E-02**
SCF	P21583	-0.047 (-0.138, 0.045)	3.17E-01	5.18E-01		-0.052 (-0.147, 0.042)	2.77E-01	4.64E-01
SCGB3A2	Q96PL1	**-0.124 (-0.214, -0.034)**	**7.04E-03**	**2.78E-02**		**-0.130 (-0.223, -0.036)**	**6.61E-03**	**2.61E-02**
SELE	P16581	-0.056 (-0.134, 0.023)	1.66E-01	3.27E-01		-0.057 (-0.139, 0.025)	1.73E-01	3.42E-01
SELP	P16109	-0.032 (-0.110, 0.045)	4.11E-01	5.95E-01		-0.037 (-0.117, 0.043)	3.69E-01	5.61E-01
SERPINA12	Q8IW75	0.039 (-0.039, 0.117)	3.23E-01	5.19E-01		0.042 (-0.039, 0.122)	3.10E-01	5.13E-01
SHPS-1	P78324	-0.085 (-0.166, -0.004)	3.95E-02	1.15E-01		-0.090 (-0.174, -0.006)	3.48E-02	1.05E-01
SIRT2	Q8IXJ6	-0.005 (-0.081, 0.071)	9.00E-01	9.45E-01		-0.008 (-0.087, 0.071)	8.41E-01	9.12E-01
SL-2	P09238	**-0.132 (-0.210, -0.055)**	**8.46E-04**	**5.31E-03**		**-0.138 (-0.218, -0.057)**	**8.44E-04**	**5.17E-03**
SOD2	P04179	-0.022 (-0.099, 0.054)	5.68E-01	7.19E-01		-0.024 (-0.104, 0.055)	5.48E-01	7.09E-01
SORT1	Q99523	-0.057 (-0.136, 0.023)	1.61E-01	3.23E-01		-0.061 (-0.144, 0.021)	1.44E-01	3.00E-01
SPON2	Q9BUD6	**-0.175 (-0.259, -0.092)**	**4.24E-05**	**4.94E-04**		**-0.179 (-0.266, -0.092)**	**5.95E-05**	**6.93E-04**

Table S7. Longitudinal associations between 233 proteomic biomarkers and the annual rate of change in CKD-EPI Equation 2009-based and CKD-EPI Equation 2021-based eGFRcr (N=1140) [a]

Biomarker	UniProt_ID	CKD-EPI Equation 2009-based eGFRcr				CKD-EPI Equation 2021-based eGFRcr		
		β (95%CI)	P	FDR		β (95%CI)	P	FDR
SRC	P12931	0.072 (-0.002, 0.146)	5.62E-02	1.45E-01		0.072 (-0.005, 0.149)	6.52E-02	1.60E-01
ST1A1	P50225	0.000 (-0.076, 0.077)	9.94E-01	9.94E-01		-0.002 (-0.081, 0.078)	9.67E-01	9.80E-01
ST2	Q01638	-0.041 (-0.125, 0.043)	3.40E-01	5.31E-01		-0.039 (-0.127, 0.048)	3.78E-01	5.66E-01
STAMBP	O95630	0.001 (-0.076, 0.077)	9.87E-01	9.94E-01		-0.003 (-0.082, 0.077)	9.47E-01	9.77E-01
STK4	Q13043	0.049 (-0.026, 0.123)	2.02E-01	3.76E-01		0.047 (-0.031, 0.124)	2.35E-01	4.13E-01
TF	P13726	-0.090 (-0.172, -0.007)	3.29E-02	1.01E-01		-0.093 (-0.179, -0.007)	3.34E-02	1.04E-01
TFPI	P10646	-0.047 (-0.124, 0.030)	2.28E-01	4.05E-01		-0.051 (-0.131, 0.028)	2.06E-01	3.89E-01
TGF-α	P01135	-0.020 (-0.108, 0.068)	6.56E-01	7.86E-01		-0.023 (-0.115, 0.068)	6.20E-01	7.60E-01
TGF-β1	P01137	-0.032 (-0.110, 0.046)	4.16E-01	5.99E-01		-0.036 (-0.117, 0.045)	3.88E-01	5.72E-01
TGM2	P21980	0.040 (-0.041, 0.121)	3.29E-01	5.22E-01		0.040 (-0.044, 0.125)	3.47E-01	5.45E-01
THBS2	P35442	-0.032 (-0.117, 0.052)	4.54E-01	6.33E-01		-0.031 (-0.119, 0.057)	4.85E-01	6.61E-01
THPO	P40225	-0.063 (-0.143, 0.016)	1.18E-01	2.52E-01		-0.068 (-0.151, 0.014)	1.04E-01	2.34E-01
TIE2	Q02763	-0.027 (-0.105, 0.050)	4.85E-01	6.61E-01		-0.028 (-0.108, 0.052)	4.89E-01	6.62E-01
TIMP4	Q99727	-0.062 (-0.146, 0.023)	1.55E-01	3.14E-01		-0.065 (-0.153, 0.023)	1.48E-01	3.02E-01
TLT-2	Q5T2D2	-0.090 (-0.170, -0.011)	2.54E-02	8.12E-02		-0.098 (-0.181, -0.016)	1.90E-02	6.23E-02
TM	P07204	**-0.146 (-0.230, -0.061)**	**7.13E-04**	**4.65E-03**		**-0.154 (-0.242, -0.067)**	**5.52E-04**	**3.78E-03**
TNF-R1	P19438	**-0.221 (-0.315, -0.127)**	**4.57E-06**	**8.88E-05**		**-0.231 (-0.329, -0.133)**	**3.95E-06**	**7.66E-05**
TNF-R2	P20333	**-0.214 (-0.300, -0.127)**	**1.41E-06**	**3.65E-05**		**-0.223 (-0.313, -0.133)**	**1.22E-06**	**3.55E-05**
TNFRSF10A	O00220	-0.075 (-0.161, 0.011)	8.78E-02	2.00E-01		-0.078 (-0.167, 0.011)	8.67E-02	1.98E-01
TNFRSF10C	O14798	-0.037 (-0.115, 0.042)	3.58E-01	5.52E-01		-0.035 (-0.117, 0.046)	3.98E-01	5.83E-01
TNFRSF11A	Q9Y6Q6	**-0.214 (-0.306, -0.121)**	**6.37E-06**	**1.14E-04**		**-0.221 (-0.317, -0.125)**	**7.36E-06**	**1.29E-04**
TNFRSF13B	O14836	**-0.164 (-0.250, -0.079)**	**1.74E-04**	**1.50E-03**		**-0.170 (-0.259, -0.081)**	**1.85E-04**	**1.66E-03**
TNFRSF14	Q92956	**-0.123 (-0.207, -0.039)**	**3.97E-03**	**1.76E-02**		**-0.132 (-0.219, -0.045)**	**2.94E-03**	**1.37E-02**
TNFRSF9	Q07011	**-0.234 (-0.322, -0.145)**	**2.36E-07**	**9.18E-06**		**-0.243 (-0.335, -0.151)**	**2.27E-07**	**8.83E-06**
TNFSF10	P50591	-0.029 (-0.109, 0.050)	4.68E-01	6.46E-01		-0.030 (-0.112, 0.053)	4.83E-01	6.61E-01
TNFSF13B	Q9Y275	-0.038 (-0.118, 0.043)	3.60E-01	5.52E-01		-0.035 (-0.118, 0.049)	4.16E-01	5.87E-01
TNF-α	P01375	-0.076 (-0.150, -0.001)	4.64E-02	1.30E-01		-0.077 (-0.154, 0.000)	5.14E-02	1.41E-01
TNF-β	P01374	-0.050 (-0.130, 0.030)	2.17E-01	3.92E-01		-0.053 (-0.136, 0.029)	2.07E-01	3.89E-01
t-PA	P00750	-0.004 (-0.083, 0.076)	9.30E-01	9.60E-01		-0.002 (-0.085, 0.080)	9.58E-01	9.80E-01
TR	P02786	-0.005 (-0.086, 0.075)	8.95E-01	9.44E-01		-0.008 (-0.092, 0.076)	8.49E-01	9.16E-01
TRAIL-R2	O14763	**-0.180 (-0.267, -0.094)**	**4.24E-05**	**4.94E-04**		**-0.187 (-0.276, -0.097)**	**4.49E-05**	**5.51E-04**
TRANCE	O14788	-0.017 (-0.095, 0.062)	6.76E-01	7.88E-01		-0.018 (-0.100, 0.063)	6.57E-01	7.93E-01
TR-AP	P13686	-0.089 (-0.169, -0.008)	3.11E-02	9.67E-02		-0.090 (-0.174, -0.007)	3.45E-02	1.05E-01
TWEAK	O43508	0.009 (-0.071, 0.089)	8.23E-01	8.92E-01		0.003 (-0.080, 0.086)	9.41E-01	9.74E-01
uPA	P00749	-0.063 (-0.145, 0.019)	1.30E-01	2.73E-01		-0.062 (-0.147, 0.022)	1.49E-01	3.02E-01
U-PAR	Q03405	-0.027 (-0.111, 0.057)	5.32E-01	7.00E-01		-0.030 (-0.117, 0.057)	4.97E-01	6.66E-01
VEGF-A	P15692	**-0.127 (-0.211, -0.043)**	**2.96E-03**	**1.41E-02**		**-0.135 (-0.222, -0.048)**	**2.36E-03**	**1.22E-02**
VEGFD	O43915	**-0.119 (-0.197, -0.041)**	**2.74E-03**	**1.39E-02**		**-0.122 (-0.203, -0.041)**	**3.09E-03**	**1.41E-02**
VSIG2	Q96IQ7	**-0.173 (-0.259, -0.088)**	**7.60E-05**	**8.05E-04**		**-0.179 (-0.268, -0.090)**	**8.10E-05**	**8.20E-04**
vWF	P04275	-0.011 (-0.090, 0.067)	7.74E-01	8.59E-01		-0.008 (-0.090, 0.073)	8.41E-01	9.12E-01
XCL1	P47992	**-0.120 (-0.196, -0.043)**	**2.23E-03**	**1.21E-02**		**-0.122 (-0.201, -0.042)**	**2.66E-03**	**1.28E-02**

[a] eGFRcr were calculated based on both the CKD-EPI Equation 2009 and CKD-EPI Equation 2021, and linear regressions were used to estimate β (95% CI) of the annual rate of change in eGFRcr (per year) per 1 standard deviation increase in biomarkers, adjusted for age, sex, body mass index, physical activity, smoking status, alcohol consumption, systolic blood pressure, use of antihypertensive medication, triglycerides (naturally log-transformed), high-density lipoprotein cholesterol, use of lipid-lowering medication, prevalent diabetes, prevalent cardiovascular diseases, fasting status, and baseline eGFRcr (i.e., Model 2 in Additional file 1: Table S6). The biomarkers are sorted alphabetically. **In bold are biomarkers significantly associated with the annual rate of change in eGFRcr (FDR <0.05), and cells with green background are 65 biomarkers significant in both outcomes**.

Abbreviations: CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CI, confidence interval; eGFRcr, creatinine-based estimated glomerular filtration rate; FDR, Benjamini–Hochberg false-discovery rate. Full names of the biomarkers can be found in Additional file 1: Table S1.

Table S8. Sensitivity analyses of longitudinal associations between 66 proteomic biomarkers and the annual rate of change in eGFRcr [a]

Biomarker	**UniProt_ID**	**Model 2a (N = 1027)**				**Model 2b (N = 1086)**				**Model 2c (N = 989)**				**Model 2d (N = 1113)**				**Model 2e (N = 1140)**		
		β (95%CI)	**P**	**FDR**		**β (95%CI)**	**P**	**FDR**		**β (95%CI)**	**P**	**FDR**		**β (95%CI)**	**P**	**FDR**		**β (95%CI)**	**P**	**FDR**
ADM	P35318	**-0.118 (-0.213, -0.023)**	**1.52E-02**	**1.97E-02**		**-0.148 (-0.242, -0.054)**	**2.00E-03**	**4.30E-03**		**-0.162 (-0.246, -0.077)**	**1.86E-04**	**4.92E-04**		**-0.139 (-0.231, -0.047)**	**3.13E-03**	**5.53E-03**		**-0.158 (-0.253, -0.062)**	**1.22E-03**	**1.74E-03**
AGRP	O00253	**-0.141 (-0.236, -0.046)**	**3.54E-03**	**7.43E-03**		**-0.135 (-0.228, -0.042)**	**4.64E-03**	**8.50E-03**		**-0.130 (-0.216, -0.044)**	**3.20E-03**	**4.92E-03**		**-0.118 (-0.211, -0.025)**	**1.28E-02**	**1.51E-02**		**-0.153 (-0.248, -0.058)**	**1.56E-03**	**2.15E-03**
AMBP	P02760	**-0.135 (-0.226, -0.044)**	**3.60E-03**	**7.43E-03**		**-0.123 (-0.214, -0.032)**	**8.00E-03**	**1.20E-02**		**-0.131 (-0.211, -0.051)**	**1.34E-03**	**2.46E-03**		**-0.137 (-0.226, -0.049)**	**2.37E-03**	**4.76E-03**		**-0.145 (-0.235, -0.054)**	**1.78E-03**	**2.30E-03**
CCL15	Q16663	**-0.116 (-0.197, -0.035)**	**5.25E-03**	**9.91E-03**		**-0.120 (-0.199, -0.040)**	**3.24E-03**	**6.48E-03**		**-0.101 (-0.175, -0.027)**	**7.31E-03**	**1.00E-02**		**-0.122 (-0.201, -0.043)**	**2.59E-03**	**4.79E-03**		**-0.158 (-0.241, -0.075)**	**1.98E-04**	**3.99E-04**
CCL16	O15467	-0.066 (-0.147, 0.016)	1.15E-01	1.17E-01		**-0.084 (-0.166, -0.002)**	**4.55E-02**	**4.85E-02**		**-0.082 (-0.155, -0.009)**	**2.71E-02**	**3.07E-02**		**-0.100 (-0.179, -0.021)**	**1.28E-02**	**1.51E-02**		**-0.138 (-0.219, -0.057)**	**8.75E-04**	**1.37E-03**
CCL23	P55773	**-0.103 (-0.185, -0.021)**	**1.40E-02**	**1.85E-02**		**-0.109 (-0.190, -0.029)**	**7.96E-03**	**1.20E-02**		**-0.115 (-0.188, -0.042)**	**1.96E-03**	**3.32E-03**		**-0.095 (-0.176, -0.014)**	**2.12E-02**	**2.29E-02**		**-0.130 (-0.213, -0.046)**	**2.30E-03**	**2.76E-03**
CCL3	P10147	**-0.098 (-0.180, -0.017)**	**1.79E-02**	**2.14E-02**		**-0.114 (-0.195, -0.033)**	**6.10E-03**	**1.01E-02**		**-0.101 (-0.174, -0.027)**	**7.47E-03**	**1.01E-02**		**-0.095 (-0.176, -0.015)**	**2.07E-02**	**2.27E-02**		**-0.135 (-0.220, -0.051)**	**1.64E-03**	**2.22E-03**
CCL7	P80098	**-0.095 (-0.182, -0.008)**	**3.31E-02**	**3.64E-02**		**-0.117 (-0.201, -0.034)**	**5.95E-03**	**1.01E-02**		**-0.139 (-0.215, -0.064)**	**3.17E-04**	**7.75E-04**		**-0.108 (-0.190, -0.027)**	**9.27E-03**	**1.22E-02**		**-0.161 (-0.245, -0.077)**	**1.66E-04**	**3.67E-04**
CD93	Q9NPY3	**-0.188 (-0.268, -0.109)**	**3.60E-06**	**5.94E-05**		**-0.172 (-0.252, -0.091)**	**3.37E-05**	**2.47E-04**		**-0.178 (-0.251, -0.105)**	**2.09E-06**	**1.72E-05**		**-0.200 (-0.279, -0.122)**	**6.52E-07**	**8.61E-06**		**-0.218 (-0.299, -0.137)**	**1.47E-07**	**1.77E-06**
CHI3L1	P36222	**-0.195 (-0.283, -0.106)**	**1.63E-05**	**1.80E-04**		**-0.180 (-0.268, -0.092)**	**6.17E-05**	**4.07E-04**		**-0.167 (-0.247, -0.086)**	**5.19E-05**	**1.76E-04**		**-0.190 (-0.278, -0.102)**	**2.22E-05**	**1.13E-04**		**-0.209 (-0.299, -0.119)**	**6.04E-06**	**2.66E-05**
CHIT1	Q13231	**-0.087 (-0.166, -0.009)**	**2.95E-02**	**3.30E-02**		**-0.106 (-0.184, -0.029)**	**7.34E-03**	**1.15E-02**		**-0.092 (-0.163, -0.021)**	**1.16E-02**	**1.50E-02**		**-0.100 (-0.177, -0.023)**	**1.11E-02**	**1.38E-02**		**-0.123 (-0.202, -0.044)**	**2.23E-03**	**2.73E-03**
CSF1	P09603	-0.084 (-0.171, 0.004)	6.02E-02	6.41E-02		**-0.088 (-0.173, -0.002)**	**4.43E-02**	**4.80E-02**		**-0.108 (-0.186, -0.030)**	**6.94E-03**	**9.96E-03**		**-0.088 (-0.173, -0.004)**	**4.09E-02**	**4.15E-02**		**-0.126 (-0.214, -0.039)**	**4.65E-03**	**5.20E-03**
CTSL1	P07711	**-0.137 (-0.221, -0.054)**	**1.23E-03**	**4.06E-03**		**-0.160 (-0.242, -0.078)**	**1.42E-04**	**7.79E-04**		**-0.174 (-0.247, -0.100)**	**3.98E-06**	**2.63E-05**		**-0.142 (-0.223, -0.061)**	**6.29E-04**	**1.66E-03**		**-0.181 (-0.264, -0.097)**	**2.22E-05**	**7.61E-05**
CTSZ	Q9UBR2	**-0.109 (-0.194, -0.025)**	**1.10E-02**	**1.52E-02**		**-0.102 (-0.187, -0.017)**	**1.93E-02**	**2.60E-02**		**-0.106 (-0.184, -0.029)**	**7.14E-03**	**1.00E-02**		**-0.123 (-0.206, -0.040)**	**3.69E-03**	**6.08E-03**		**-0.147 (-0.233, -0.062)**	**7.51E-04**	**1.27E-03**
CX3CL1	P78423	**-0.154 (-0.239, -0.068)**	**4.43E-04**	**1.95E-03**		**-0.150 (-0.237, -0.064)**	**6.78E-04**	**2.24E-03**		**-0.124 (-0.202, -0.047)**	**1.69E-03**	**2.94E-03**		**-0.180 (-0.265, -0.096)**	**2.84E-05**	**1.25E-04**		**-0.190 (-0.277, -0.103)**	**1.91E-05**	**7.00E-05**
EPHB4	P54760	**-0.188 (-0.269, -0.107)**	**6.07E-06**	**8.01E-05**		**-0.190 (-0.273, -0.107)**	**7.85E-06**	**1.30E-04**		**-0.187 (-0.261, -0.114)**	**7.21E-07**	**8.92E-06**		**-0.224 (-0.305, -0.143)**	**6.03E-08**	**3.21E-06**		**-0.240 (-0.322, -0.158)**	**1.31E-08**	**2.87E-07**
FABP4	P15090	**-0.162 (-0.278, -0.046)**	**6.13E-03**	**1.09E-02**		**-0.182 (-0.297, -0.067)**	**1.97E-03**	**4.30E-03**		**-0.123 (-0.229, -0.017)**	**2.26E-02**	**2.72E-02**		**-0.194 (-0.307, -0.081)**	**7.79E-04**	**1.90E-03**		**-0.203 (-0.319, -0.086)**	**6.48E-04**	**1.13E-03**
FGF-23	Q9GZV9	**-0.136 (-0.226, -0.046)**	**2.96E-03**	**6.73E-03**		**-0.143 (-0.232, -0.054)**	**1.67E-03**	**4.08E-03**		**-0.133 (-0.213, -0.053)**	**1.21E-03**	**2.34E-03**		**-0.136 (-0.224, -0.047)**	**2.61E-03**	**4.79E-03**		**-0.174 (-0.265, -0.084)**	**1.67E-04**	**3.67E-04**
FS	P19883	-0.067 (-0.148, 0.013)	1.01E-01	1.04E-01		**-0.084 (-0.164, -0.005)**	**3.82E-02**	**4.27E-02**		**-0.127 (-0.199, -0.055)**	**5.40E-04**	**1.27E-03**		**-0.083 (-0.161, -0.005)**	**3.78E-02**	**3.90E-02**		**-0.117 (-0.198, -0.037)**	**4.42E-03**	**5.03E-03**
Gal-4	P56470	**-0.125 (-0.206, -0.044)**	**2.60E-03**	**6.36E-03**		**-0.115 (-0.196, -0.034)**	**5.51E-03**	**9.67E-03**		**-0.128 (-0.203, -0.054)**	**7.46E-04**	**1.64E-03**		**-0.129 (-0.210, -0.049)**	**1.58E-03**	**3.49E-03**		**-0.162 (-0.244, -0.079)**	**1.24E-04**	**3.03E-04**
Gal-9	O00182	**-0.122 (-0.207, -0.038)**	**4.62E-03**	**9.24E-03**		**-0.105 (-0.187, -0.022)**	**1.29E-02**	**1.80E-02**		**-0.087 (-0.164, -0.010)**	**2.74E-02**	**3.07E-02**		**-0.105 (-0.187, -0.022)**	**1.30E-02**	**1.51E-02**		**-0.117 (-0.203, -0.031)**	**7.53E-03**	**7.76E-03**
GDF-15	Q99988	**-0.193 (-0.296, -0.090)**	**2.55E-04**	**1.30E-03**		**-0.195 (-0.293, -0.096)**	**1.05E-04**	**6.28E-04**		**-0.189 (-0.278, -0.101)**	**3.04E-05**	**1.43E-04**		**-0.213 (-0.311, -0.116)**	**2.00E-05**	**1.10E-04**		**-0.245 (-0.345, -0.146)**	**1.50E-06**	**8.23E-06**
hOSCAR	Q8IYS5	**-0.093 (-0.171, -0.014)**	**2.03E-02**	**2.36E-02**		**-0.102 (-0.178, -0.026)**	**8.54E-03**	**1.22E-02**		**-0.111 (-0.182, -0.041)**	**2.06E-03**	**3.34E-03**		**-0.104 (-0.180, -0.028)**	**7.03E-03**	**9.67E-03**		**-0.130 (-0.208, -0.052)**	**1.13E-03**	**1.70E-03**
ICAM-2	P13598	**-0.129 (-0.207, -0.051)**	**1.29E-03**	**4.06E-03**		**-0.088 (-0.167, -0.010)**	**2.79E-02**	**3.44E-02**		**-0.107 (-0.179, -0.034)**	**3.83E-03**	**5.74E-03**		**-0.103 (-0.181, -0.025)**	**9.69E-03**	**1.25E-02**		**-0.107 (-0.187, -0.026)**	**9.18E-03**	**9.32E-03**
IGFBP-1	P08833	-0.077 (-0.179, 0.024)	1.36E-01	1.36E-01		-0.082 (-0.178, 0.014)	9.54E-02	9.54E-02		**-0.095 (-0.181, -0.010)**	**2.89E-02**	**3.18E-02**		**-0.131 (-0.226, -0.037)**	**6.24E-03**	**8.76E-03**		**-0.149 (-0.246, -0.053)**	**2.48E-03**	**2.92E-03**
IGFBP-2	P18065	**-0.175 (-0.267, -0.082)**	**2.28E-04**	**1.26E-03**		**-0.208 (-0.302, -0.115)**	**1.30E-05**	**1.72E-04**		**-0.213 (-0.298, -0.128)**	**9.46E-07**	**8.92E-06**		**-0.215 (-0.306, -0.123)**	**4.39E-06**	**3.22E-05**		**-0.243 (-0.339, -0.148)**	**6.07E-07**	**4.00E-06**
IGFBP-7	Q16270	**-0.118 (-0.201, -0.035)**	**5.41E-03**	**9.92E-03**		**-0.106 (-0.191, -0.022)**	**1.35E-02**	**1.85E-02**		**-0.099 (-0.175, -0.023)**	**1.06E-02**	**1.39E-02**		**-0.117 (-0.200, -0.034)**	**5.92E-03**	**8.68E-03**		**-0.141 (-0.225, -0.056)**	**1.09E-03**	**1.68E-03**
IL-10RB	Q08334	**-0.117 (-0.206, -0.029)**	**8.97E-03**	**1.38E-02**		**-0.127 (-0.213, -0.041)**	**3.82E-03**	**7.21E-03**		**-0.159 (-0.236, -0.082)**	**5.23E-05**	**1.76E-04**		**-0.128 (-0.212, -0.043)**	**3.19E-03**	**5.53E-03**		**-0.172 (-0.259, -0.086)**	**1.01E-04**	**2.77E-04**
IL-12B	P29460	**-0.114 (-0.203, -0.025)**	**1.19E-02**	**1.60E-02**		**-0.099 (-0.188, -0.011)**	**2.80E-02**	**3.44E-02**		**-0.138 (-0.218, -0.057)**	**8.29E-04**	**1.71E-03**		**-0.129 (-0.217, -0.041)**	**4.01E-03**	**6.31E-03**		**-0.155 (-0.245, -0.064)**	**8.24E-04**	**1.33E-03**
IL-15RA	Q13261	**-0.158 (-0.244, -0.072)**	**3.42E-04**	**1.61E-03**		**-0.156 (-0.242, -0.070)**	**3.70E-04**	**1.44E-03**		**-0.156 (-0.234, -0.078)**	**9.56E-05**	**2.96E-04**		**-0.167 (-0.252, -0.083)**	**1.08E-04**	**4.21E-04**		**-0.199 (-0.286, -0.112)**	**8.37E-06**	**3.25E-05**
IL-18BP	O95998	**-0.204 (-0.287, -0.121)**	**1.72E-06**	**3.79E-05**		**-0.193 (-0.277, -0.109)**	**6.93E-06**	**1.30E-04**		**-0.193 (-0.269, -0.116)**	**8.90E-07**	**8.92E-06**		**-0.223 (-0.305, -0.140)**	**1.46E-07**	**3.21E-06**		**-0.248 (-0.333, -0.164)**	**1.04E-08**	**2.87E-07**
IL2-RA	P01589	**-0.174 (-0.253, -0.094)**	**1.99E-05**	**1.88E-04**		**-0.155 (-0.235, -0.074)**	**1.83E-04**	**8.62E-04**		**-0.164 (-0.237, -0.092)**	**8.97E-06**	**5.38E-05**		**-0.193 (-0.273, -0.114)**	**1.89E-06**	**1.78E-05**		**-0.215 (-0.297, -0.134)**	**2.44E-07**	**2.30E-06**
IL-4RA	P24394	**-0.116 (-0.200, -0.032)**	**7.10E-03**	**1.17E-02**		**-0.142 (-0.225, -0.060)**	**7.25E-04**	**2.28E-03**		**-0.127 (-0.201, -0.053)**	**8.21E-04**	**1.71E-03**		**-0.126 (-0.207, -0.044)**	**2.45E-03**	**4.76E-03**		**-0.159 (-0.242, -0.075)**	**2.04E-04**	**3.99E-04**
KIM1	Q96D42	**-0.237 (-0.327, -0.148)**	**2.50E-07**	**8.26E-06**		**-0.263 (-0.353, -0.173)**	**1.46E-08**	**9.65E-07**		**-0.271 (-0.349, -0.193)**	**1.42E-11**	**9.35E-10**		**-0.241 (-0.330, -0.152)**	**1.22E-07**	**3.21E-06**		**-0.313 (-0.401, -0.225)**	**4.16E-12**	**2.74E-10**
KLK6	Q92876	**-0.111 (-0.194, -0.029)**	**8.40E-03**	**1.32E-02**		**-0.094 (-0.178, -0.010)**	**2.81E-02**	**3.44E-02**		**-0.084 (-0.161, -0.008)**	**3.03E-02**	**3.22E-02**		**-0.120 (-0.202, -0.037)**	**4.37E-03**	**6.71E-03**		**-0.137 (-0.221, -0.053)**	**1.39E-03**	**1.95E-03**
LTBR	P36941	**-0.114 (-0.202, -0.026)**	**1.11E-02**	**1.52E-02**		**-0.101 (-0.190, -0.012)**	**2.56E-02**	**3.31E-02**		**-0.126 (-0.205, -0.046)**	**2.08E-03**	**3.34E-03**		**-0.143 (-0.229, -0.056)**	**1.29E-03**	**3.05E-03**		**-0.169 (-0.258, -0.080)**	**2.05E-04**	**3.99E-04**
MEPE	Q9NQ76	**-0.100 (-0.182, -0.018)**	**1.74E-02**	**2.12E-02**		**-0.096 (-0.178, -0.014)**	**2.22E-02**	**2.93E-02**		-0.068 (-0.143, 0.008)	7.76E-02	8.00E-02		**-0.120 (-0.200, -0.039)**	**3.57E-03**	**6.04E-03**		**-0.124 (-0.207, -0.040)**	**3.72E-03**	**4.31E-03**
MMP-12	P39900	**-0.184 (-0.270, -0.097)**	**3.48E-05**	**2.87E-04**		**-0.187 (-0.273, -0.102)**	**1.98E-05**	**1.97E-04**		**-0.227 (-0.304, -0.150)**	**1.05E-08**	**3.46E-07**		**-0.195 (-0.280, -0.109)**	**8.45E-06**	**5.58E-05**		**-0.227 (-0.314, -0.140)**	**3.74E-07**	**2.94E-06**

Table S8. Sensitivity analyses of longitudinal associations between 66 proteomic biomarkers and the annual rate of change in eGFRcr [a]

Biomarker	**UniProt_ID**	**Model 2a (N = 1027)**			**Model 2b (N = 1086)**			**Model 2c (N = 989)**			**Model 2d (N = 1113)**			**Model 2e (N = 1140)**		
		β (95%CI)	**P**	**FDR**	**β (95%CI)**	**P**	**FDR**	**β (95%CI)**	**P**	**FDR**	**β (95%CI)**	**P**	**FDR**	**β (95%CI)**	**P**	**FDR**
MMP-7	P09237	**-0.119 (-0.206, -0.031)**	**8.22E-03**	**1.32E-02**	**-0.135 (-0.219, -0.052)**	**1.46E-03**	**3.93E-03**	**-0.138 (-0.212, -0.064)**	**2.79E-04**	**7.09E-04**	**-0.134 (-0.217, -0.052)**	**1.37E-03**	**3.13E-03**	**-0.160 (-0.243, -0.076)**	**1.83E-04**	**3.90E-04**
Notch 3	Q9UM47	**-0.109 (-0.191, -0.026)**	**1.00E-02**	**1.44E-02**	**-0.092 (-0.175, -0.009)**	**2.97E-02**	**3.56E-02**	**-0.087 (-0.163, -0.011)**	**2.56E-02**	**3.02E-02**	**-0.106 (-0.188, -0.024)**	**1.09E-02**	**1.38E-02**	**-0.116 (-0.200, -0.031)**	**7.26E-03**	**7.61E-03**
NT-proBNP	P16860	**-0.243 (-0.332, -0.155)**	**8.55E-08**	**5.64E-06**	**-0.253 (-0.343, -0.162)**	**5.21E-08**	**1.72E-06**	**-0.224 (-0.304, -0.143)**	**6.33E-08**	**1.39E-06**	**-0.230 (-0.318, -0.142)**	**3.71E-07**	**6.13E-06**	**-0.258 (-0.348, -0.167)**	**2.80E-08**	**4.63E-07**
OPN	P10451	**-0.128 (-0.210, -0.046)**	**2.28E-03**	**5.80E-03**	**-0.127 (-0.209, -0.045)**	**2.44E-03**	**5.03E-03**	**-0.156 (-0.231, -0.082)**	**4.24E-05**	**1.76E-04**	**-0.146 (-0.226, -0.065)**	**3.79E-04**	**1.16E-03**	**-0.169 (-0.252, -0.086)**	**6.40E-05**	**1.92E-04**
PCSK9	Q8NBP7	**-0.094 (-0.175, -0.013)**	**2.24E-02**	**2.55E-02**	-0.078 (-0.160, 0.004)	6.38E-02	6.58E-02	**-0.079 (-0.154, -0.003)**	**4.13E-02**	**4.32E-02**	**-0.092 (-0.173, -0.010)**	**2.73E-02**	**2.86E-02**	**-0.120 (-0.204, -0.036)**	**5.01E-03**	**5.42E-03**
PD-L1	Q9NZQ7	**-0.121 (-0.201, -0.041)**	**3.17E-03**	**6.97E-03**	**-0.085 (-0.168, -0.003)**	**4.15E-02**	**4.56E-02**	**-0.083 (-0.157, -0.008)**	**2.97E-02**	**3.21E-02**	**-0.084 (-0.164, -0.003)**	**4.25E-02**	**4.25E-02**	**-0.133 (-0.216, -0.050)**	**1.75E-03**	**2.30E-03**
PGF	P49763	**-0.157 (-0.252, -0.061)**	**1.33E-03**	**4.06E-03**	**-0.161 (-0.255, -0.067)**	**8.13E-04**	**2.44E-03**	**-0.182 (-0.265, -0.099)**	**1.93E-05**	**9.79E-05**	**-0.182 (-0.273, -0.091)**	**9.39E-05**	**3.87E-04**	**-0.213 (-0.306, -0.120)**	**7.96E-06**	**3.25E-05**
PIgR	P01833	**-0.114 (-0.196, -0.032)**	**6.50E-03**	**1.13E-02**	**-0.133 (-0.215, -0.050)**	**1.62E-03**	**4.08E-03**	**-0.144 (-0.218, -0.069)**	**1.73E-04**	**4.75E-04**	**-0.126 (-0.207, -0.045)**	**2.31E-03**	**4.76E-03**	**-0.147 (-0.231, -0.063)**	**6.14E-04**	**1.09E-03**
PLC	P98160	**-0.182 (-0.273, -0.091)**	**9.57E-05**	**5.74E-04**	**-0.176 (-0.268, -0.084)**	**1.83E-04**	**8.62E-04**	**-0.172 (-0.254, -0.090)**	**4.54E-05**	**1.76E-04**	**-0.201 (-0.290, -0.111)**	**1.12E-05**	**6.71E-05**	**-0.223 (-0.315, -0.131)**	**2.07E-06**	**1.05E-05**
PRSS8	Q16651	**-0.159 (-0.250, -0.069)**	**5.71E-04**	**2.21E-03**	**-0.147 (-0.236, -0.057)**	**1.31E-03**	**3.77E-03**	**-0.162 (-0.244, -0.080)**	**1.16E-04**	**3.32E-04**	**-0.161 (-0.249, -0.073)**	**3.56E-04**	**1.16E-03**	**-0.175 (-0.265, -0.085)**	**1.45E-04**	**3.41E-04**
PSP-D	P35247	-0.073 (-0.152, 0.006)	6.90E-02	7.23E-02	-0.071 (-0.151, 0.009)	8.11E-02	8.23E-02	-0.064 (-0.135, 0.008)	8.18E-02	8.31E-02	**-0.094 (-0.172, -0.016)**	**1.87E-02**	**2.13E-02**	**-0.105 (-0.185, -0.024)**	**1.09E-02**	**1.09E-02**
RAGE	Q15109	**-0.134 (-0.218, -0.050)**	**1.88E-03**	**4.96E-03**	**-0.156 (-0.241, -0.071)**	**3.06E-04**	**1.26E-03**	**-0.126 (-0.202, -0.049)**	**1.33E-03**	**2.46E-03**	**-0.149 (-0.232, -0.066)**	**4.52E-04**	**1.30E-03**	**-0.174 (-0.260, -0.089)**	**6.69E-05**	**1.92E-04**
RARRES2	Q99969	**-0.101 (-0.185, -0.017)**	**1.82E-02**	**2.14E-02**	**-0.092 (-0.177, -0.007)**	**3.37E-02**	**3.83E-02**	**-0.087 (-0.165, -0.010)**	**2.63E-02**	**3.04E-02**	**-0.097 (-0.182, -0.012)**	**2.46E-02**	**2.62E-02**	**-0.138 (-0.225, -0.050)**	**2.07E-03**	**2.58E-03**
SCGB3A2	Q96PL1	-0.092 (-0.186, 0.001)	5.21E-02	5.64E-02	**-0.100 (-0.191, -0.008)**	**3.28E-02**	**3.83E-02**	-0.039 (-0.122, 0.044)	3.57E-01	3.57E-01	**-0.132 (-0.222, -0.042)**	**4.00E-03**	**6.31E-03**	**-0.133 (-0.227, -0.040)**	**5.25E-03**	**5.59E-03**
SL-2	P09238	**-0.097 (-0.176, -0.018)**	**1.65E-02**	**2.06E-02**	**-0.117 (-0.195, -0.039)**	**3.43E-03**	**6.67E-03**	**-0.144 (-0.217, -0.072)**	**9.86E-05**	**2.96E-04**	**-0.120 (-0.197, -0.042)**	**2.45E-03**	**4.76E-03**	**-0.147 (-0.227, -0.067)**	**3.35E-04**	**6.33E-04**
SPON2	Q9BUD6	**-0.121 (-0.209, -0.034)**	**6.85E-03**	**1.16E-02**	**-0.151 (-0.237, -0.066)**	**5.49E-04**	**1.91E-03**	**-0.133 (-0.210, -0.057)**	**6.83E-04**	**1.55E-03**	**-0.155 (-0.238, -0.071)**	**2.96E-04**	**1.03E-03**	**-0.177 (-0.263, -0.090)**	**6.51E-05**	**1.92E-04**
TM	P07204	**-0.126 (-0.213, -0.038)**	**4.85E-03**	**9.42E-03**	**-0.094 (-0.180, -0.007)**	**3.34E-02**	**3.83E-02**	**-0.131 (-0.209, -0.053)**	**1.03E-03**	**2.06E-03**	**-0.118 (-0.203, -0.034)**	**6.12E-03**	**8.76E-03**	**-0.143 (-0.229, -0.056)**	**1.20E-03**	**1.74E-03**
TNF-R1	P19438	**-0.172 (-0.269, -0.075)**	**5.29E-04**	**2.18E-03**	**-0.155 (-0.253, -0.057)**	**2.02E-03**	**4.30E-03**	**-0.179 (-0.265, -0.093)**	**5.06E-05**	**1.76E-04**	**-0.204 (-0.298, -0.109)**	**2.58E-05**	**1.21E-04**	**-0.239 (-0.335, -0.143)**	**1.28E-06**	**7.70E-06**
TNF-R2	P20333	**-0.178 (-0.267, -0.089)**	**8.54E-05**	**5.64E-04**	**-0.158 (-0.247, -0.069)**	**4.93E-04**	**1.81E-03**	**-0.175 (-0.255, -0.095)**	**1.80E-05**	**9.79E-05**	**-0.205 (-0.292, -0.118)**	**3.92E-06**	**3.22E-05**	**-0.230 (-0.319, -0.142)**	**4.01E-07**	**2.94E-06**
TNFRSF11A	Q9Y6Q6	**-0.146 (-0.242, -0.050)**	**2.88E-03**	**6.73E-03**	**-0.177 (-0.272, -0.082)**	**2.67E-04**	**1.17E-03**	**-0.199 (-0.284, -0.115)**	**3.94E-06**	**2.63E-05**	**-0.182 (-0.276, -0.089)**	**1.36E-04**	**4.98E-04**	**-0.224 (-0.319, -0.128)**	**4.50E-06**	**2.12E-05**
TNFRSF13B	O14836	**-0.109 (-0.197, -0.020)**	**1.60E-02**	**2.03E-02**	**-0.139 (-0.226, -0.052)**	**1.76E-03**	**4.16E-03**	**-0.122 (-0.202, -0.043)**	**2.60E-03**	**4.09E-03**	**-0.149 (-0.235, -0.063)**	**6.73E-04**	**1.71E-03**	**-0.174 (-0.262, -0.086)**	**1.10E-04**	**2.89E-04**
TNFRSF14	Q92956	**-0.112 (-0.197, -0.028)**	**9.44E-03**	**1.42E-02**	-0.083 (-0.168, 0.002)	5.51E-02	5.77E-02	**-0.090 (-0.167, -0.013)**	**2.27E-02**	**2.72E-02**	**-0.108 (-0.192, -0.024)**	**1.16E-02**	**1.42E-02**	**-0.137 (-0.224, -0.050)**	**2.07E-03**	**2.58E-03**
TNFRSF9	Q07011	**-0.183 (-0.273, -0.093)**	**7.48E-05**	**5.49E-04**	**-0.198 (-0.289, -0.107)**	**2.09E-05**	**1.97E-04**	**-0.211 (-0.292, -0.131)**	**3.23E-07**	**5.33E-06**	**-0.217 (-0.306, -0.128)**	**1.78E-06**	**1.78E-05**	**-0.246 (-0.337, -0.154)**	**1.61E-07**	**1.77E-06**
TRAIL-R2	O14763	**-0.145 (-0.233, -0.056)**	**1.35E-03**	**4.06E-03**	**-0.227 (-0.334, -0.120)**	**3.22E-05**	**2.47E-04**	**-0.127 (-0.204, -0.049)**	**1.42E-03**	**2.53E-03**	**-0.157 (-0.243, -0.070)**	**3.85E-04**	**1.16E-03**	**-0.188 (-0.275, -0.101)**	**2.31E-05**	**7.61E-05**
VEGF-A	P15692	**-0.139 (-0.225, -0.054)**	**1.47E-03**	**4.21E-03**	**-0.115 (-0.200, -0.030)**	**8.36E-03**	**1.22E-02**	**-0.161 (-0.238, -0.083)**	**5.35E-05**	**1.76E-04**	**-0.100 (-0.185, -0.016)**	**1.92E-02**	**2.15E-02**	**-0.149 (-0.235, -0.062)**	**7.80E-04**	**1.29E-03**
VEGFD	O43915	**-0.104 (-0.183, -0.025)**	**9.98E-03**	**1.44E-02**	**-0.107 (-0.186, -0.029)**	**7.17E-03**	**1.15E-02**	**-0.090 (-0.167, -0.013)**	**2.14E-02**	**2.66E-02**	**-0.105 (-0.183, -0.027)**	**8.20E-03**	**1.10E-02**	**-0.116 (-0.197, -0.036)**	**4.80E-03**	**5.28E-03**
VSIG2	Q96IQ7	**-0.146 (-0.233, -0.060)**	**9.25E-04**	**3.39E-03**	**-0.143 (-0.231, -0.055)**	**1.49E-03**	**3.93E-03**	**-0.115 (-0.194, -0.036)**	**4.51E-03**	**6.61E-03**	**-0.154 (-0.241, -0.067)**	**5.08E-04**	**1.40E-03**	**-0.174 (-0.262, -0.085)**	**1.21E-04**	**3.03E-04**
XCL1	P47992	**-0.128 (-0.207, -0.049)**	**1.54E-03**	**4.25E-03**	**-0.109 (-0.185, -0.032)**	**5.57E-03**	**9.67E-03**	**-0.084 (-0.154, -0.014)**	**1.84E-02**	**2.34E-02**	**-0.108 (-0.184, -0.032)**	**5.41E-03**	**8.11E-03**	**-0.140 (-0.219, -0.062)**	**4.46E-04**	**8.18E-04**

[a] Several sensitivity analyses were performed based on model 2 in Additional file 1: Table S6, and only the 66 biomarkers significantly associated with the annual rate of change in eGFRcr were included. Linear regressions were used to estimate β (95% CI) of the annual rate of change in eGFRcr (per year) per 1 standard deviation increase in biomarkers. The biomarkers are sorted alphabetically. **In bold are biomarkers significantly associated with the annual rate of change in eGFRcr (FDR <0.05), and cells with green background are 57 biomarkers significant across Model 2a, 2b, and 2c.**

Model 2a: repeated analyses of model 2 after excluding participants who were non-fasting before at the time of blood sampling (n = 113);

Model 2b: repeated analyses of model 2 after excluding participants who had chronic kidney disease at baseline (n = 54);

Model 2c: repeated analyses of model 2 after excluding participants who had an increase in eGFRcr during follow up (n = 151);

Model 2d: repeated analyses of model 2 further adjusting for UACR at F4 in linear regression models;

Model 2e: repeated analyses of model 2 applying inverse probability weighting-weight in linear regression models.

Abbreviations: CI, confidence interval; eGFRcr, creatinine-based estimated glomerular filtration rate; FDR, Benjamini–Hochberg false-discovery rate; UACR, urine albumin-creatinine ratio. Full names of the biomarkers can be found in Additional file 1: Table S1.

Table S9. Sensitivity analyses of association of 66 proteomic biomarkers with rapid decline in eGFRcr and CKD incidence [a]

Biomarker	**UniProt_ID**	**Associations with change in eGFRcr (N = 1140)**				**Associations with rapid eGFRcr decline[b] (N = 1140; cases = 83, controls = 1057)**				**Associations with CKD incidence [c] (N = 1086; cases = 262, controls = 824)**				**Associations with CKD incidence [d] (N = 990; cases = 166, controls = 824)**		
		β (95%CI)	**P**	**FDR**		**OR (95%CI)**	**P**	**FDR**		**HR (95%CI)**	**P**	**FDR**		**HR (95%CI)**	**P**	**FDR**
KIM1	Q96D42	-0.292 (-0.377, -0.206)	4.08E-11	9.51E-09		**2.09 (1.60, 2.74)**	**8.05E-08**	**5.31E-06**		**1.45 (1.23, 1.71)**	**9.94E-06**	**3.01E-04**		**1.55 (1.26, 1.92)**	**3.54E-05**	**5.85E-04**
NT-proBNP	P16860	-0.249 (-0.336, -0.162)	2.77E-08	1.62E-06		**1.86 (1.44, 2.42)**	**2.51E-06**	**2.77E-05**		**1.30 (1.10, 1.54)**	**1.87E-03**	**1.12E-02**		**1.38 (1.13, 1.68)**	**1.83E-03**	**1.10E-02**
EPHB4	P54760	-0.233 (-0.313, -0.153)	1.46E-08	1.62E-06		**1.83 (1.41, 2.41)**	**9.56E-06**	**6.72E-05**		**1.29 (1.10, 1.52)**	**2.25E-03**	**1.14E-02**		**1.32 (1.08, 1.62)**	**7.11E-03**	**2.47E-02**
IL-18BP	O95998	-0.235 (-0.317, -0.152)	2.70E-08	1.62E-06		**1.99 (1.52, 2.61)**	**5.49E-07**	**9.06E-06**		**1.24 (1.05, 1.47)**	**1.08E-02**	**2.98E-02**		**1.30 (1.07, 1.57)**	**7.06E-03**	**2.47E-02**
CD93	Q9NPY3	-0.211 (-0.290, -0.132)	1.69E-07	7.88E-06		**1.85 (1.44, 2.40)**	**1.96E-06**	**2.58E-05**		1.20 (1.02, 1.40)	2.78E-02	6.11E-02		1.23 (1.00, 1.52)	5.29E-02	9.19E-02
TNFRSF9	Q07011	-0.234 (-0.322, -0.145)	2.36E-07	9.18E-06		**1.99 (1.53, 2.61)**	**3.97E-07**	**8.74E-06**		**1.51 (1.30, 1.75)**	**4.12E-08**	**2.72E-06**		**1.67 (1.33, 2.09)**	**8.68E-06**	**3.44E-04**
MMP-12	P39900	-0.215 (-0.300, -0.131)	6.98E-07	2.32E-05		**1.96 (1.52, 2.55)**	**2.67E-07**	**8.74E-06**		**1.25 (1.06, 1.47)**	**8.93E-03**	**2.68E-02**		**1.47 (1.19, 1.81)**	**4.10E-04**	**3.86E-03**
TNF-R2	P20333	-0.214 (-0.300, -0.127)	1.41E-06	3.65E-05		**1.72 (1.33, 2.23)**	**4.00E-05**	**1.55E-04**		**1.31 (1.12, 1.54)**	**7.94E-04**	**5.82E-03**		**1.36 (1.11, 1.68)**	**3.53E-03**	**1.46E-02**
IGFBP-2	P18065	-0.226 (-0.318, -0.135)	1.36E-06	3.65E-05		**1.81 (1.35, 2.45)**	**8.54E-05**	**2.45E-04**		**1.29 (1.08, 1.54)**	**5.37E-03**	**2.07E-02**		**1.43 (1.13, 1.82)**	**2.76E-03**	**1.22E-02**
IL2-RA	P01589	-0.194 (-0.273, -0.115)	1.66E-06	3.87E-05		**1.69 (1.33, 2.16)**	**1.76E-05**	**8.30E-05**		**1.21 (1.04, 1.40)**	**1.26E-02**	**3.32E-02**		**1.29 (1.06, 1.56)**	**1.02E-02**	**2.71E-02**
PLC	P98160	-0.217 (-0.306, -0.128)	2.07E-06	4.38E-05		**1.91 (1.43, 2.59)**	**1.73E-05**	**8.30E-05**		**1.31 (1.10, 1.57)**	**2.82E-03**	**1.33E-02**		**1.35 (1.07, 1.70)**	**1.03E-02**	**2.71E-02**
TNF-R1	P19438	-0.221 (-0.315, -0.127)	4.57E-06	8.88E-05		**1.79 (1.35, 2.38)**	**5.63E-05**	**1.99E-04**		**1.24 (1.05, 1.47)**	**1.31E-02**	**3.33E-02**		**1.29 (1.04, 1.60)**	**2.06E-02**	**4.53E-02**
TNFRSF11A	Q9Y6Q6	-0.214 (-0.306, -0.121)	6.37E-06	1.14E-04		**1.67 (1.26, 2.20)**	**3.03E-04**	**7.40E-04**		**1.49 (1.23, 1.79)**	**2.95E-05**	**3.44E-04**		**1.55 (1.25, 1.94)**	**8.72E-05**	**9.59E-04**
GDF-15	Q99988	-0.224 (-0.321, -0.127)	6.82E-06	1.14E-04		**1.95 (1.47, 2.61)**	**5.18E-06**	**4.89E-05**		**1.27 (1.06, 1.52)**	**8.44E-03**	**2.65E-02**		**1.42 (1.13, 1.79)**	**2.73E-03**	**1.22E-02**
PGF	P49763	-0.206 (-0.296, -0.115)	9.25E-06	1.44E-04		**1.92 (1.45, 2.59)**	**1.02E-05**	**6.72E-05**		1.17 (0.97, 1.41)	1.08E-01	1.55E-01		1.22 (0.97, 1.55)	8.95E-02	1.31E-01
CX3CL1	P78423	-0.183 (-0.268, -0.099)	2.10E-05	3.06E-04		**1.53 (1.18, 1.99)**	**1.45E-03**	**2.52E-03**		**1.23 (1.05, 1.44)**	**1.08E-02**	**2.98E-02**		1.22 (0.99, 1.49)	5.71E-02	9.67E-02
IL-15RA	Q13261	-0.181 (-0.266, -0.097)	2.59E-05	3.42E-04		**1.80 (1.38, 2.35)**	**1.39E-05**	**7.80E-05**		**1.41 (1.20, 1.65)**	**3.13E-05**	**3.44E-04**		**1.58 (1.29, 1.95)**	**1.14E-05**	**3.44E-04**
CHI3L1	P36222	-0.188 (-0.275, -0.100)	2.65E-05	3.42E-04		**1.71 (1.33, 2.21)**	**3.32E-05**	**1.46E-04**		**1.34 (1.15, 1.57)**	**2.32E-04**	**2.18E-03**		**1.51 (1.25, 1.82)**	**1.56E-05**	**3.44E-04**
TRAIL-R2	O14763	-0.180 (-0.267, -0.094)	4.24E-05	4.94E-04		**1.35 (1.10, 1.77)**	**1.19E-02**	**1.51E-02**		**1.52 (1.26, 1.84)**	**1.45E-05**	**3.01E-04**		**1.59 (1.26, 2.01)**	**8.68E-05**	**9.59E-04**
SPON2	Q9BUD6	-0.175 (-0.259, -0.092)	4.24E-05	4.94E-04		**1.68 (1.29, 2.22)**	**1.91E-04**	**5.05E-04**		1.17 (0.98, 1.40)	8.84E-02	1.33E-01		1.24 (1.00, 1.54)	5.09E-02	9.19E-02
CTSL1	P07711	-0.167 (-0.248, -0.086)	5.16E-05	5.73E-04		**1.74 (1.36, 2.24)**	**1.42E-05**	**7.80E-05**		1.16 (1.00, 1.35)	5.26E-02	8.91E-02		**1.28 (1.06, 1.54)**	**1.02E-02**	**2.71E-02**
VSIG2	Q96IQ7	-0.173 (-0.259, -0.088)	7.60E-05	8.05E-04		**1.48 (1.14, 1.92)**	**3.02E-03**	**4.86E-03**		**1.26 (1.08, 1.49)**	**4.38E-03**	**1.81E-02**		**1.39 (1.14, 1.69)**	**1.22E-03**	**1.00E-02**
RAGE	Q15109	-0.166 (-0.249, -0.084)	8.50E-05	8.61E-04		**1.53 (1.17, 2.00)**	**1.82E-03**	**3.08E-03**		1.12 (0.95, 1.32)	1.83E-01	2.28E-01		1.13 (0.92, 1.39)	2.38E-01	2.71E-01
PRSS8	Q16651	-0.173 (-0.260, -0.085)	1.16E-04	1.13E-03		**1.80 (1.35, 2.43)**	**7.40E-05**	**2.33E-04**		1.14 (0.96, 1.35)	1.33E-01	1.82E-01		1.25 (1.00, 1.55)	5.02E-02	9.19E-02
OPN	P10451	-0.156 (-0.236, -0.076)	1.37E-04	1.28E-03		**1.65 (1.29, 2.13)**	**8.24E-05**	**2.45E-04**		**1.23 (1.06, 1.42)**	**6.15E-03**	**2.13E-02**		**1.26 (1.04, 1.53)**	**1.64E-02**	**3.73E-02**
MMP-7	P09237	-0.157 (-0.238, -0.076)	1.64E-04	1.47E-03		**1.56 (1.21, 2.01)**	**6.21E-04**	**1.32E-03**		**1.22 (1.03, 1.44)**	**1.80E-02**	**4.25E-02**		**1.33 (1.09, 1.63)**	**5.81E-03**	**2.25E-02**
TNFRSF13B	O14836	-0.164 (-0.250, -0.079)	1.74E-04	1.50E-03		**1.39 (1.07, 1.80)**	**1.47E-02**	**1.84E-02**		1.18 (0.99, 1.41)	5.94E-02	9.34E-02		1.23 (0.98, 1.54)	6.92E-02	1.13E-01

Table S9. Sensitivity analyses of association of 66 proteomic biomarkers with rapid decline in eGFRcr and CKD incidence [a]

Biomarker	**UniProt_ID**	**Associations with change in eGFRcr (N = 1140)**			**Associations with rapid eGFRcr decline[b] (N = 1140; cases = 83, controls = 1057)**			**Associations with CKD incidence [c] (N = 1086; cases = 262, controls = 824)**			**Associations with CKD incidence [d] (N = 990; cases = 166, controls = 824)**		
		β (95%CI)	**P**	**FDR**	**OR (95%CI)**	**P**	**FDR**	**HR (95%CI)**	**P**	**FDR**	**HR (95%CI)**	**P**	**FDR**
IL-10RB	Q08334	-0.160 (-0.245, -0.076)	1.99E-04	1.60E-03	**1.90 (1.44, 2.53)**	**6.65E-06**	**5.49E-05**	1.13 (0.96, 1.32)	1.32E-01	1.82E-01	1.19 (0.96, 1.48)	1.05E-01	1.44E-01
FGF-23	Q9GZV9	-0.166 (-0.254, -0.079)	1.99E-04	1.60E-03	**1.38 (1.10, 1.71)**	**3.88E-03**	**5.96E-03**	1.09 (0.93, 1.28)	3.01E-01	3.36E-01	1.16 (0.98, 1.38)	8.46E-02	1.27E-01
IL-4RA	P24394	-0.151 (-0.232, -0.070)	2.54E-04	1.97E-03	**1.59 (1.27, 1.98)**	**3.87E-05**	**1.55E-04**	1.06 (0.91, 1.23)	4.64E-01	4.86E-01	1.12 (0.93, 1.34)	2.23E-01	2.59E-01
Gal-4	P56470	-0.144 (-0.224, -0.064)	4.17E-04	3.14E-03	**1.49 (1.17, 1.90)**	**1.06E-03**	**1.94E-03**	1.15 (1.00, 1.33)	5.11E-02	8.91E-02	1.23 (1.03, 1.48)	2.56E-02	5.27E-02
LTBR	P36941	-0.154 (-0.240, -0.067)	5.10E-04	3.72E-03	**1.61 (1.27, 2.03)**	**5.73E-05**	**1.99E-04**	1.10 (0.93, 1.29)	2.57E-01	3.03E-01	1.09 (0.90, 1.33)	3.78E-01	3.90E-01
PIgR	P01833	-0.143 (-0.224, -0.062)	5.77E-04	4.07E-03	**1.58 (1.23, 2.06)**	**4.66E-04**	**1.06E-03**	1.00 (0.85, 1.18)	9.98E-01	9.98E-01	1.11 (0.89, 1.38)	3.46E-01	3.63E-01
AMBP	P02760	-0.154 (-0.242, -0.065)	6.72E-04	4.61E-03	**1.67 (1.25, 2.24)**	**5.83E-04**	**1.28E-03**	1.19 (0.99, 1.43)	5.84E-02	9.34E-02	1.19 (0.96, 1.47)	1.12E-01	1.47E-01
TM	P07204	-0.146 (-0.230, -0.061)	7.13E-04	4.65E-03	**1.44 (1.11, 1.88)**	**7.09E-03**	**9.55E-03**	**1.26 (1.07, 1.49)**	**5.65E-03**	**2.07E-02**	**1.29 (1.05, 1.59)**	**1.51E-02**	**3.56E-02**
FABP4	P15090	-0.195 (-0.308, -0.082)	7.19E-04	4.65E-03	**1.65 (1.16, 2.34)**	**5.47E-03**	**7.69E-03**	1.27 (1.03, 1.55)	2.22E-02	5.05E-02	**1.37 (1.08, 1.75)**	**1.04E-02**	**2.71E-02**
ADM	P35318	-0.157 (-0.249, -0.065)	8.67E-04	5.31E-03	**1.37 (1.03, 1.85)**	**3.38E-02**	**3.72E-02**	**1.29 (1.07, 1.55)**	**6.92E-03**	**2.28E-02**	**1.38 (1.09, 1.75)**	**8.09E-03**	**2.54E-02**
SL-2	P09238	-0.132 (-0.210, -0.055)	8.46E-04	5.31E-03	**1.49 (1.18, 1.89)**	**8.42E-04**	**1.59E-03**	1.15 (1.00, 1.32)	5.05E-02	8.91E-02	1.22 (1.01, 1.46)	4.15E-02	8.05E-02
CCL15	Q16663	-0.135 (-0.214, -0.055)	8.93E-04	5.34E-03	**1.49 (1.18, 1.88)**	**6.70E-04**	**1.34E-03**	1.15 (1.00, 1.33)	5.73E-02	9.34E-02	1.21 (1.01, 1.45)	3.63E-02	7.26E-02
CCL7	P80098	-0.135 (-0.216, -0.053)	1.19E-03	6.91E-03	**1.37 (1.09, 1.71)**	**5.58E-03**	**7.69E-03**	**1.25 (1.09, 1.44)**	**1.78E-03**	**1.12E-02**	**1.31 (1.11, 1.56)**	**1.70E-03**	**1.10E-02**
IGFBP-7	Q16270	-0.135 (-0.217, -0.053)	1.30E-03	7.39E-03	**1.54 (1.20, 1.98)**	**6.55E-04**	**1.34E-03**	1.12 (0.96, 1.31)	1.60E-01	2.11E-01	1.16 (0.97, 1.39)	1.04E-01	1.44E-01
AGRP	O00253	-0.147 (-0.239, -0.055)	1.76E-03	9.75E-03	**1.38 (1.03, 1.86)**	**3.25E-02**	**3.64E-02**	1.24 (1.02, 1.50)	3.03E-02	6.25E-02	1.25 (0.97, 1.61)	8.13E-02	1.25E-01
XCL1	P47992	-0.120 (-0.196, -0.043)	2.23E-03	1.21E-02	**1.28 (1.04, 1.57)**	**1.84E-02**	**2.21E-02**	**1.16 (1.03, 1.31)**	**1.54E-02**	**3.75E-02**	**1.21 (1.04, 1.40)**	**1.24E-02**	**3.02E-02**
CTSZ	Q9UBR2	-0.129 (-0.213, -0.046)	2.36E-03	1.25E-02	**1.67 (1.28, 2.18)**	**1.62E-04**	**4.45E-04**	1.16 (1.00, 1.35)	5.09E-02	8.91E-02	1.18 (0.96, 1.44)	1.16E-01	1.47E-01
hOSCAR	Q8IYS5	-0.116 (-0.192, -0.040)	2.70E-03	1.39E-02	**1.56 (1.20, 2.05)**	**1.11E-03**	**1.97E-03**	1.16 (1.00, 1.34)	5.16E-02	8.91E-02	1.22 (1.00, 1.49)	5.18E-02	9.19E-02
VEGFD	O43915	-0.119 (-0.197, -0.041)	2.74E-03	1.39E-02	**1.35 (1.04, 1.75)**	**2.39E-02**	**2.77E-02**	0.96 (0.84, 1.11)	6.08E-01	6.27E-01	1.00 (0.84, 1.19)	9.99E-01	9.99E-01
VEGF-A	P15692	-0.127 (-0.211, -0.043)	2.96E-03	1.41E-02	**1.64 (1.28, 2.09)**	**7.33E-05**	**2.33E-04**	**1.27 (1.08, 1.50)**	**3.21E-03**	**1.41E-02**	**1.33 (1.11, 1.61)**	**2.60E-03**	**1.22E-02**
IL-12B	P29460	-0.132 (-0.220, -0.045)	3.02E-03	1.41E-02	**1.69 (1.27, 2.25)**	**3.20E-04**	**7.55E-04**	1.16 (0.99, 1.36)	7.38E-02	1.13E-01	1.25 (1.03, 1.51)	2.50E-02	5.27E-02
CCL23	P55773	-0.122 (-0.202, -0.041)	2.97E-03	1.41E-02	**1.34 (1.03, 1.74)**	**2.94E-02**	**3.35E-02**	1.12 (0.96, 1.30)	1.46E-01	1.96E-01	1.12 (0.93, 1.35)	2.23E-01	2.59E-01
KLK6	Q92876	-0.124 (-0.206, -0.042)	2.97E-03	1.41E-02	**1.40 (1.08, 1.82)**	**1.03E-02**	**1.37E-02**	1.03 (0.88, 1.20)	7.42E-01	7.54E-01	1.07 (0.89, 1.28)	4.87E-01	4.94E-01
IGFBP-1	P08833	-0.140 (-0.234, -0.046)	3.51E-03	1.60E-02	**1.48 (1.12, 1.95)**	**5.59E-03**	**7.69E-03**	1.23 (1.02, 1.47)	3.00E-02	6.25E-02	**1.32 (1.07, 1.63)**	**1.07E-02**	**2.71E-02**
TNFRSF14	Q92956	-0.123 (-0.207, -0.039)	3.97E-03	1.76E-02	1.26 (0.98, 1.59)	6.36E-02	6.77E-02	1.17 (1.01, 1.36)	3.31E-02	6.61E-02	1.13 (0.95, 1.36)	1.65E-01	2.02E-01
CCL16	O15467	-0.116 (-0.194, -0.037)	4.00E-03	1.76E-02	**1.40 (1.07, 1.86)**	**1.80E-02**	**2.20E-02**	1.14 (0.97, 1.35)	1.02E-01	1.49E-01	1.13 (0.94, 1.37)	2.04E-01	2.44E-01
CHIT1	Q13231	-0.112 (-0.189, -0.035)	4.20E-03	1.81E-02	**1.36 (1.03, 1.87)**	**4.37E-02**	**4.73E-02**	1.12 (0.94, 1.34)	2.07E-01	2.48E-01	1.15 (0.91, 1.45)	2.47E-01	2.76E-01

Table S9. Sensitivity analyses of association of 66 proteomic biomarkers with rapid decline in eGFRcr and CKD incidence [a]

Biomarker	UniProt_ID	Associations with change in eGFRcr (N = 1140)				Associations with rapid eGFRcr decline[b] (N = 1140; cases = 83, controls = 1057)				Associations with CKD incidence [c] (N = 1086; cases = 262, controls = 824)				Associations with CKD incidence [d] (N = 990; cases = 166, controls = 824)		
		β (95%CI)	P	FDR		OR (95%CI)	P	FDR		HR (95%CI)	P	FDR		HR (95%CI)	P	FDR
MEPE	Q9NQ76	-0.118 (-0.199, -0.037)	4.28E-03	1.81E-02		1.26 (0.99, 1.63)	6.63E-02	6.95E-02		1.06 (0.91, 1.23)	4.60E-01	4.86E-01		1.11 (0.92, 1.34)	2.90E-01	3.14E-01
CCL3	P10147	-0.116 (-0.197, -0.036)	4.77E-03	1.98E-02		**1.37 (1.09, 1.69)**	**4.39E-03**	**6.59E-03**		**1.24 (1.08, 1.42)**	**2.05E-03**	**1.13E-02**		**1.26 (1.06, 1.49)**	**7.77E-03**	**2.54E-02**
ICAM-2	P13598	-0.110 (-0.188, -0.033)	5.42E-03	2.22E-02		**1.45 (1.13, 1.86)**	**3.72E-03**	**5.85E-03**		1.07 (0.93, 1.24)	3.53E-01	3.88E-01		1.11 (0.92, 1.32)	2.71E-01	2.98E-01
RARRES2	Q99969	-0.117 (-0.202, -0.033)	6.53E-03	2.62E-02		**1.40 (1.06, 1.89)**	**2.06E-02**	**2.43E-02**		1.20 (1.01, 1.42)	3.63E-02	7.04E-02		1.19 (0.96, 1.47)	1.09E-01	1.46E-01
SCGB3A2	Q96PL1	-0.124 (-0.214, -0.034)	7.04E-03	2.78E-02		1.16 (0.89, 1.49)	2.50E-01	2.50E-01		1.10 (0.96, 1.26)	1.87E-01	2.29E-01		1.16 (0.96, 1.39)	1.16E-01	1.47E-01
Gal-9	O00182	-0.112 (-0.195, -0.030)	7.43E-03	2.88E-02		1.24 (0.96, 1.60)	1.02E-01	1.03E-01		**1.37 (1.19, 1.58)**	**1.82E-05**	**3.01E-04**		**1.32 (1.11, 1.57)**	**1.37E-03**	**1.00E-02**
Notch 3	Q9UM47	-0.111 (-0.193, -0.029)	7.86E-03	3.00E-02		**1.53 (1.20, 1.97)**	**7.98E-04**	**1.55E-03**		1.08 (0.94, 1.24)	2.66E-01	3.07E-01		1.16 (0.97, 1.38)	9.58E-02	1.37E-01
PD-L1	Q9NZQ7	-0.107 (-0.187, -0.026)	9.24E-03	3.47E-02		1.25 (0.98, 1.58)	7.17E-02	7.39E-02		**1.30 (1.13, 1.51)**	**3.44E-04**	**2.84E-03**		**1.30 (1.10, 1.55)**	**2.76E-03**	**1.22E-02**
PCSK9	Q8NBP7	-0.104 (-0.185, -0.023)	1.22E-02	4.51E-02		**1.46 (1.12, 1.89)**	**4.82E-03**	**7.07E-03**		1.06 (0.92, 1.23)	3.88E-01	4.19E-01		1.10 (0.91, 1.32)	3.17E-01	3.38E-01
FS	P19883	-0.099 (-0.177, -0.021)	1.34E-02	4.80E-02		**1.58 (1.24, 2.02)**	**2.43E-04**	**6.16E-04**		1.11 (0.96, 1.28)	1.68E-01	2.13E-01		1.20 (0.98, 1.47)	7.03E-02	1.13E-01
CSF1	P09603	-0.107 (-0.191, -0.022)	1.34E-02	4.80E-02		**1.54 (1.18, 2.04)**	**2.13E-03**	**3.52E-03**		1.09 (0.93, 1.29)	2.73E-01	3.11E-01		1.18 (0.96, 1.46)	1.21E-01	1.51E-01
PSP-D	P35247	-0.098 (-0.176, -0.020)	1.39E-02	4.91E-02		**1.36 (1.07, 1.72)**	**1.18E-02**	**1.51E-02**		1.11 (0.96, 1.29)	1.66E-01	2.13E-01		1.18 (0.98, 1.41)	7.79E-02	1.22E-01

[a] The 66 biomarkers significantly associated with the annual rate of change in eGFRcr (model 2 in Additional file 1: Table S6) were used to investigate their associations with rapid eGFRcr decline and incident CKD.

[b] Rapid eGFRcr decline case (yes/no) was defined as the annual rate of change in eGFRcr < -3 ml/min/1.73 m^2/year, and was used to investigate their associations with the 66 eGFRcr-associated biomarkers in logistic regressions. Association estimates refer to a 1 standard deviation increase in biomarker concentrations, adjusting for age, sex, body mass index, physical activity, smoking status, alcohol consumption, systolic blood pressure, use of antihypertensive medication, triglycerides (naturally log-transformed), high-density lipoprotein cholesterol, use of lipid-lowering medication, prevalent diabetes, prevalent cardiovascular diseases, fasting status, and baseline eGFRcr.

[c] A CKD case was defined as eGFRcr < 60 ml/min per 1.73m^2. An incident eGFRcr-based CKD case was defined as participants free of CKD at S4 and identified as CKD at F4 or FF4. Interval-censored Cox regressions (500 bootstrap samples were used to construct confidence intervals) was used to estimate HRs, adjusting for the same covariates above. The results presented here is the same to the related results in Table S10. Detailed description can be found in the footnote of Table S10.

[d] Incident eGFRcr-based CKD cases were redefined as follows: Participants free of CKD at S4 or F4, respectively, had to have more than 25% decline in eGFRcr together with eGFRcr < 60 ml/min per 1.73m^2 at the following follow-up (i.e., F4 or FF4), or participants free of CKD at S4 had to have more than 50% decline in eGFRcr together with eGFRcr < 60 ml/min per 1.73m^2 at FF4. The controls were defined as eGFRcr ≥ 60 ml/min per 1.73m^2 at S4, F4, and FF4.

In bold are biomarkers significantly associated with the rapid eGFRcys decline or incident CKD (FDR <0.05), and cells with green background are 27 biomarkers significantly associated with both incident CKD outcomes.

Abbreviations: CI, confidence interval; CKD, chronic kidney disease; eGFRcr, creatinine-based estimated glomerular filtration rate; FDR, Benjamini–Hochberg false-discovery rate; HR, hazard ratio; OR, odds ratio. Full names of the biomarkers can be found in Additional file 1: Table S1.

Table S10. Association of 66 proteomic biomarkers with the annual rate of change in eGFRcys and CKD incidence [a]

Biomarker	UniProt_ID	Associations with change in eGFRcr (N = 1140)				Associations with change in eGFRcys (N = 1140)				Associations with CKD incidence (N = 1086; cases = 262, controls = 824)		
		β (95%CI)	**P**	**FDR**		**β (95%CI)**	**P**	**FDR**		**HR (95%CI)**	**P**	**FDR**
KIM1	Q96D42	-0.292 (-0.377, -0.206)	4.08E-11	9.51E-09		**-0.138 (-0.229, -0.047)**	**3.08E-03**	**1.32E-02**		**1.45 (1.23, 1.71)**	**9.94E-06**	**3.01E-04**
NT-proBNP	P16860	-0.249 (-0.336, -0.162)	2.77E-08	1.62E-06		**-0.238 (-0.331, -0.145)**	**5.66E-07**	**3.74E-05**		**1.30 (1.10, 1.54)**	**1.87E-03**	**1.12E-02**
EPHB4	P54760	-0.233 (-0.313, -0.153)	1.46E-08	1.62E-06		**-0.184 (-0.273, -0.095)**	**5.18E-05**	**8.57E-04**		**1.29 (1.10, 1.52)**	**2.25E-03**	**1.14E-02**
IL-18BP	O95998	-0.235 (-0.317, -0.152)	2.70E-08	1.62E-06		**-0.161 (-0.252, -0.069)**	**6.13E-04**	**5.06E-03**		**1.24 (1.05, 1.47)**	**1.08E-02**	**2.98E-02**
CD93	Q9NPY3	-0.211 (-0.290, -0.132)	1.69E-07	7.88E-06		**-0.137 (-0.223, -0.051)**	**1.76E-03**	**8.94E-03**		1.20 (1.02, 1.40)	2.78E-02	6.11E-02
TNFRSF9	Q07011	-0.234 (-0.322, -0.145)	2.36E-07	9.18E-06		**-0.170 (-0.269, -0.070)**	**8.59E-04**	**6.30E-03**		**1.51 (1.30, 1.75)**	**4.12E-08**	**2.72E-06**
MMP-12	P39900	-0.215 (-0.300, -0.131)	6.98E-07	2.32E-05		-0.089 (-0.179, 0.001)	5.23E-02	7.85E-02		**1.25 (1.06, 1.47)**	**8.93E-03**	**2.68E-02**
TNF-R2	P20333	-0.214 (-0.300, -0.127)	1.41E-06	3.65E-05		**-0.197 (-0.294, -0.101)**	**6.49E-05**	**8.57E-04**		**1.31 (1.12, 1.54)**	**7.94E-04**	**5.82E-03**
IGFBP-2	P18065	-0.226 (-0.318, -0.135)	1.36E-06	3.65E-05		**-0.168 (-0.268, -0.068)**	**1.01E-03**	**6.56E-03**		**1.29 (1.08, 1.54)**	**5.37E-03**	**2.07E-02**
IL2-RA	P01589	-0.194 (-0.273, -0.115)	1.66E-06	3.87E-05		**-0.108 (-0.193, -0.022)**	**1.40E-02**	**3.18E-02**		**1.21 (1.04, 1.40)**	**1.26E-02**	**3.32E-02**
PLC	P98160	-0.217 (-0.306, -0.128)	2.07E-06	4.38E-05		**-0.142 (-0.240, -0.044)**	**4.58E-03**	**1.59E-02**		**1.31 (1.10, 1.57)**	**2.82E-03**	**1.33E-02**
TNF-R1	P19438	-0.221 (-0.315, -0.127)	4.57E-06	8.88E-05		**-0.174 (-0.279, -0.070)**	**1.09E-03**	**6.56E-03**		**1.24 (1.05, 1.47)**	**1.31E-02**	**3.33E-02**
TNFRSF11A	Q9Y6Q6	-0.214 (-0.306, -0.121)	6.37E-06	1.14E-04		**-0.208 (-0.308, -0.109)**	**4.37E-05**	**8.57E-04**		**1.49 (1.23, 1.79)**	**2.95E-05**	**3.44E-04**
GDF-15	Q99988	-0.224 (-0.321, -0.127)	6.82E-06	1.14E-04		-0.063 (-0.168, 0.042)	2.36E-01	2.78E-01		**1.27 (1.06, 1.52)**	**8.44E-03**	**2.65E-02**
PGF	P49763	-0.206 (-0.296, -0.115)	9.25E-06	1.44E-04		-0.073 (-0.171, 0.026)	1.47E-01	1.79E-01		1.17 (0.97, 1.41)	1.08E-01	1.55E-01
CX3CL1	P78423	-0.183 (-0.268, -0.099)	2.10E-05	3.06E-04		-0.086 (-0.177, 0.006)	6.72E-02	9.30E-02		**1.23 (1.05, 1.44)**	**1.08E-02**	**2.98E-02**
IL-15RA	Q13261	-0.181 (-0.266, -0.097)	2.59E-05	3.42E-04		**-0.138 (-0.231, -0.044)**	**4.03E-03**	**1.48E-02**		**1.41 (1.20, 1.65)**	**3.13E-05**	**3.44E-04**
CHI3L1	P36222	-0.188 (-0.275, -0.100)	2.65E-05	3.42E-04		-0.037 (-0.130, 0.055)	4.27E-01	4.48E-01		**1.34 (1.15, 1.57)**	**2.32E-04**	**2.18E-03**
TRAIL-R2	O14763	-0.180 (-0.267, -0.094)	4.24E-05	4.94E-04		**-0.105 (-0.198, -0.013)**	**2.61E-02**	**4.78E-02**		**1.52 (1.26, 1.84)**	**1.45E-05**	**3.01E-04**
SPON2	Q9BUD6	-0.175 (-0.259, -0.092)	4.24E-05	4.94E-04		**-0.122 (-0.213, -0.031)**	**8.98E-03**	**2.47E-02**		1.17 (0.98, 1.40)	8.84E-02	1.33E-01
CTSL1	P07711	-0.167 (-0.248, -0.086)	5.16E-05	5.73E-04		-0.016 (-0.103, 0.070)	7.15E-01	7.26E-01		1.16 (1.00, 1.35)	5.26E-02	8.91E-02
VSIG2	Q96IQ7	-0.173 (-0.259, -0.088)	7.60E-05	8.05E-04		-0.077 (-0.168, 0.013)	9.37E-02	1.19E-01		**1.26 (1.08, 1.49)**	**4.38E-03**	**1.81E-02**
RAGE	Q15109	-0.166 (-0.249, -0.084)	8.50E-05	8.61E-04		**-0.101 (-0.189, -0.013)**	**2.46E-02**	**4.63E-02**		1.12 (0.95, 1.32)	1.83E-01	2.28E-01
PRSS8	Q16651	-0.173 (-0.260, -0.085)	1.16E-04	1.13E-03		**-0.104 (-0.197, -0.012)**	**2.72E-02**	**4.86E-02**		1.14 (0.96, 1.35)	1.33E-01	1.82E-01
OPN	P10451	-0.156 (-0.236, -0.076)	1.37E-04	1.28E-03		**-0.101 (-0.188, -0.014)**	**2.36E-02**	**4.59E-02**		**1.23 (1.06, 1.42)**	**6.15E-03**	**2.13E-02**
MMP-7	P09237	-0.157 (-0.238, -0.076)	1.64E-04	1.47E-03		-0.093 (-0.179, -0.007)	3.32E-02	5.63E-02		**1.22 (1.03, 1.44)**	**1.80E-02**	**4.25E-02**
TNFRSF13B	O14836	-0.164 (-0.250, -0.079)	1.74E-04	1.50E-03		**-0.139 (-0.230, -0.047)**	**3.07E-03**	**1.32E-02**		1.18 (0.99, 1.41)	5.94E-02	9.34E-02
IL-10RB	Q08334	-0.160 (-0.245, -0.076)	1.99E-04	1.60E-03		-0.093 (-0.184, -0.002)	4.62E-02	7.43E-02		1.13 (0.96, 1.32)	1.32E-01	1.82E-01
FGF-23	Q9GZV9	-0.166 (-0.254, -0.079)	1.99E-04	1.60E-03		-0.051 (-0.145, 0.043)	2.86E-01	3.20E-01		1.09 (0.93, 1.28)	3.01E-01	3.36E-01
IL-4RA	P24394	-0.151 (-0.232, -0.070)	2.54E-04	1.97E-03		-0.063 (-0.150, 0.024)	1.54E-01	1.85E-01		1.06 (0.91, 1.23)	4.64E-01	4.86E-01
Gal-4	P56470	-0.144 (-0.224, -0.064)	4.17E-04	3.14E-03		-0.081 (-0.165, 0.003)	5.99E-02	8.78E-02		1.15 (1.00, 1.33)	5.11E-02	8.91E-02
LTBR	P36941	-0.154 (-0.240, -0.067)	5.10E-04	3.72E-03		**-0.124 (-0.216, -0.031)**	**8.70E-03**	**2.47E-02**		1.10 (0.93, 1.29)	2.57E-01	3.03E-01
PIgR	P01833	-0.143 (-0.224, -0.062)	5.77E-04	4.07E-03		**-0.120 (-0.206, -0.035)**	**6.00E-03**	**1.98E-02**		1.00 (0.85, 1.18)	9.98E-01	9.98E-01
AMBP	P02760	-0.154 (-0.242, -0.065)	6.72E-04	4.61E-03		**-0.190 (-0.283, -0.097)**	**6.24E-05**	**8.57E-04**		1.19 (0.99, 1.43)	5.84E-02	9.34E-02
TM	P07204	-0.146 (-0.230, -0.061)	7.13E-04	4.65E-03		**-0.105 (-0.195, -0.015)**	**2.24E-02**	**4.49E-02**		**1.26 (1.07, 1.49)**	**5.65E-03**	**2.07E-02**
FABP4	P15090	-0.195 (-0.308, -0.082)	7.19E-04	4.65E-03		**-0.165 (-0.285, -0.044)**	**7.39E-03**	**2.22E-02**		1.27 (1.03, 1.55)	2.22E-02	5.05E-02
ADM	P35318	-0.157 (-0.249, -0.065)	8.67E-04	5.31E-03		**-0.138 (-0.238, -0.038)**	**6.78E-03**	**2.13E-02**		**1.29 (1.07, 1.55)**	**6.92E-03**	**2.28E-02**
SL-2	P09238	-0.132 (-0.210, -0.055)	8.46E-04	5.31E-03		**-0.120 (-0.201, -0.039)**	**3.79E-03**	**1.47E-02**		1.15 (1.00, 1.32)	5.05E-02	8.91E-02
CCL15	Q16663	-0.135 (-0.214, -0.055)	8.93E-04	5.34E-03		-0.042 (-0.126, 0.042)	3.31E-01	3.60E-01		1.15 (1.00, 1.33)	5.73E-02	9.34E-02
CCL7	P80098	-0.135 (-0.216, -0.053)	1.19E-03	6.91E-03		**-0.095 (-0.181, -0.010)**	**2.88E-02**	**4.99E-02**		**1.25 (1.09, 1.44)**	**1.78E-03**	**1.12E-02**
IGFBP-7	Q16270	-0.135 (-0.217, -0.053)	1.30E-03	7.39E-03		-0.049 (-0.137, 0.038)	2.69E-01	3.12E-01		1.12 (0.96, 1.31)	1.60E-01	2.11E-01
AGRP	O00253	-0.147 (-0.239, -0.055)	1.76E-03	9.75E-03		-0.054 (-0.151, 0.044)	2.82E-01	3.20E-01		1.24 (1.02, 1.50)	3.03E-02	6.25E-02
XCL1	P47992	-0.120 (-0.196, -0.043)	2.23E-03	1.21E-02		**-0.103 (-0.183, -0.022)**	**1.27E-02**	**3.11E-02**		**1.16 (1.03, 1.31)**	**1.54E-02**	**3.75E-02**
CTSZ	Q9UBR2	-0.129 (-0.213, -0.046)	2.36E-03	1.25E-02		-0.089 (-0.178, -0.000)	4.93E-02	7.57E-02		1.16 (1.00, 1.35)	5.09E-02	8.91E-02
hOSCAR	Q8IYS5	-0.116 (-0.192, -0.040)	2.70E-03	1.39E-02		-0.032 (-0.114, 0.049)	4.36E-01	4.49E-01		1.16 (1.00, 1.34)	5.16E-02	8.91E-02
VEGFD	O43915	-0.119 (-0.197, -0.041)	2.74E-03	1.39E-02		-0.075 (-0.156, 0.007)	7.27E-02	9.80E-02		0.96 (0.84, 1.11)	6.08E-01	6.27E-01
VEGF-A	P15692	-0.127 (-0.211, -0.043)	2.96E-03	1.41E-02		**-0.142 (-0.230, -0.054)**	**1.56E-03**	**8.55E-03**		**1.27 (1.08, 1.50)**	**3.21E-03**	**1.41E-02**
IL-12B	P29460	-0.132 (-0.220, -0.045)	3.02E-03	1.41E-02		-0.088 (-0.182, 0.005)	6.37E-02	9.13E-02		1.16 (0.99, 1.36)	7.38E-02	1.13E-01
CCL23	P55773	-0.122 (-0.202, -0.041)	2.97E-03	1.41E-02		**-0.111 (-0.197, -0.026)**	**1.06E-02**	**2.69E-02**		1.12 (0.96, 1.30)	1.46E-01	1.96E-01
KLK6	Q92876	-0.124 (-0.206, -0.042)	2.97E-03	1.41E-02		**-0.174 (-0.260, -0.088)**	**7.97E-05**	**8.77E-04**		1.03 (0.88, 1.20)	7.42E-01	7.54E-01
IGFBP-1	P08833	-0.140 (-0.234, -0.046)	3.51E-03	1.60E-02		**-0.122 (-0.222, -0.022)**	**1.65E-02**	**3.63E-02**		1.23 (1.02, 1.47)	3.00E-02	6.25E-02
TNFRSF14	Q92956	-0.123 (-0.207, -0.039)	3.97E-03	1.76E-02		**-0.116 (-0.204, -0.028)**	**1.00E-02**	**2.64E-02**		1.17 (1.01, 1.36)	3.31E-02	6.61E-02
CCL16	O15467	-0.116 (-0.194, -0.037)	4.00E-03	1.76E-02		-0.078 (-0.161, 0.006)	6.76E-02	9.30E-02		1.14 (0.97, 1.35)	1.02E-01	1.49E-01
CHIT1	Q13231	-0.112 (-0.189, -0.035)	4.20E-03	1.81E-02		-0.011 (-0.091, 0.070)	7.97E-01	7.97E-01		1.12 (0.94, 1.34)	2.07E-01	2.48E-01

Table S10. Association of 66 proteomic biomarkers with the annual rate of change in eGFRcys and CKD incidence [a]

Biomarker	UniProt_ID	Associations with change in eGFRcr (N = 1140)				Associations with change in eGFRcys (N = 1140)				Associations with CKD incidence (N = 1086; cases = 262, controls = 824)		
		β (95%CI)	P	FDR		β (95%CI)	P	FDR		HR (95%CI)	P	FDR
MEPE	Q9NQ76	-0.118 (-0.199, -0.037)	4.28E-03	1.81E-02		-0.091 (-0.176, -0.006)	3.69E-02	6.08E-02		1.06 (0.91, 1.23)	4.60E-01	4.86E-01
CCL3	P10147	-0.116 (-0.197, -0.036)	4.77E-03	1.98E-02		**-0.101 (-0.186, -0.016)**	**1.98E-02**	**4.21E-02**		**1.24 (1.08, 1.42)**	**2.05E-03**	**1.13E-02**
ICAM-2	P13598	-0.110 (-0.188, -0.033)	5.42E-03	2.22E-02		-0.040 (-0.122, 0.042)	3.38E-01	3.60E-01		1.07 (0.93, 1.24)	3.53E-01	3.88E-01
RARRES2	Q99969	-0.117 (-0.202, -0.033)	6.53E-03	2.62E-02		**-0.134 (-0.224, -0.045)**	**3.21E-03**	**1.32E-02**		1.20 (1.01, 1.42)	3.63E-02	7.04E-02
SCGB3A2	Q96PL1	-0.124 (-0.214, -0.034)	7.04E-03	2.78E-02		**-0.110 (-0.204, -0.016)**	**2.19E-02**	**4.49E-02**		1.10 (0.96, 1.26)	1.87E-01	2.29E-01
Gal-9	O00182	-0.112 (-0.195, -0.030)	7.43E-03	2.88E-02		-0.044 (-0.132, 0.045)	3.33E-01	3.60E-01		**1.37 (1.19, 1.58)**	**1.82E-05**	**3.01E-04**
Notch 3	Q9UM47	-0.111 (-0.193, -0.029)	7.86E-03	3.00E-02		-0.087 (-0.173, -0.001)	4.85E-02	7.57E-02		1.08 (0.94, 1.24)	2.66E-01	3.07E-01
PD-L1	Q9NZQ7	-0.107 (-0.187, -0.026)	9.24E-03	3.47E-02		**-0.106 (-0.191, -0.022)**	**1.36E-02**	**3.18E-02**		**1.30 (1.13, 1.51)**	**3.44E-04**	**2.84E-03**
PCSK9	Q8NBP7	-0.104 (-0.185, -0.023)	1.22E-02	4.51E-02		**-0.149 (-0.234, -0.065)**	**5.65E-04**	**5.06E-03**		1.06 (0.92, 1.23)	3.88E-01	4.19E-01
FS	P19883	-0.099 (-0.177, -0.021)	1.34E-02	4.80E-02		-0.072 (-0.154, 0.010)	8.39E-02	1.11E-01		1.11 (0.96, 1.28)	1.68E-01	2.13E-01
CSF1	P09603	-0.107 (-0.191, -0.022)	1.34E-02	4.80E-02		-0.079 (-0.169, 0.012)	8.76E-02	1.13E-01		1.09 (0.93, 1.29)	2.73E-01	3.11E-01
PSP-D	P35247	-0.098 (-0.176, -0.020)	1.39E-02	4.91E-02		-0.063 (-0.145, 0.018)	1.29E-01	1.60E-01		1.11 (0.96, 1.29)	1.66E-01	2.13E-01

[a] The 66 biomarkers significantly associated with the annual rate of change in eGFRcr (model 2 in Additional file 1: Table S6) were used to investigate their associations with the annual rate of change in eGFRcys using linear regressions and eGFRcr-based incident CKD using interval-censored Cox regressions (500 bootstrap samples were used to construct confidence intervals). Association estimates refer to a 1 standard deviation increase in biomarker concentrations, adjusted for age, sex, body mass index, physical activity, smoking status, alcohol consumption, systolic blood pressure, use of antihypertensive medication, triglycerides (naturally log-transformed), high-density lipoprotein cholesterol, use of lipid-lowering medication, prevalent diabetes, prevalent cardiovascular diseases, fasting status, and baseline eGFRcr/eGFRcys. The biomarkers are sorted by FDR in the eGFRcr results.

In bold are biomarkers significantly associated with the annual rate of change in eGFRcys or incident CKD (FDR <0.05), and cells with green background are 21 biomarkers significantly associated with both the annual rate of change in eGFRcys and incident CKD.

Abbreviations: CI, confidence interval; CKD, chronic kidney disease; eGFRcr, creatinine-based estimated glomerular filtration rate; eGFRcys, cystatin C-based estimated glomerular filtration rate; FDR, Benjamini–Hochberg false-discovery rate; HR, hazard ratio. Full names of the biomarkers can be found in Additional file 1: Table S1.

Table S11. Longitudinal associations between 233 proteomic biomarkers and the annual rate of change in eGFRcys (N=1140) [a]

Biomarker	UniProt_ID	Model 1				Model 2		
		β (95%CI)	P	FDR		β (95%CI)	P	FDR
4E-BP1	Q13541	-0.048 (-0.129, 0.033)	2.43E-01	4.07E-01		-0.004 (-0.086, 0.077)	9.14E-01	9.72E-01
ACE2	Q9BYF1	-0.040 (-0.126, 0.046)	3.57E-01	5.10E-01		0.022 (-0.069, 0.113)	6.41E-01	8.50E-01
ADA	P00813	-0.051 (-0.135, 0.032)	2.27E-01	3.88E-01		-0.011 (-0.094, 0.073)	8.04E-01	9.22E-01
ADAM-TS13	Q76LX8	-0.044 (-0.125, 0.037)	2.91E-01	4.62E-01		-0.019 (-0.099, 0.061)	6.38E-01	8.50E-01
ADM	P35318	**-0.161 (-0.259, -0.064)**	**1.21E-03**	**1.38E-02**		-0.138 (-0.238, -0.038)	6.78E-03	6.58E-02
AGRP	O00253	-0.089 (-0.180, 0.001)	5.34E-02	1.64E-01		-0.054 (-0.151, 0.044)	2.82E-01	6.08E-01
ALCAM	Q13740	-0.066 (-0.154, 0.021)	1.38E-01	2.70E-01		-0.049 (-0.136, 0.037)	2.64E-01	5.79E-01
AMBP	P02760	**-0.217 (-0.308, -0.125)**	**3.59E-06**	**2.09E-04**		**-0.190 (-0.283, -0.097)**	**6.24E-05**	**3.03E-03**
ANG-1	Q15389	-0.057 (-0.138, 0.024)	1.67E-01	3.06E-01		-0.047 (-0.126, 0.033)	2.54E-01	5.73E-01
AP-N	P15144	0.000 (-0.082, 0.083)	9.95E-01	9.95E-01		0.023 (-0.060, 0.105)	5.89E-01	8.09E-01
Axin-1	O15169	-0.023 (-0.103, 0.058)	5.82E-01	6.92E-01		-0.014 (-0.093, 0.066)	7.38E-01	8.95E-01
AXL	P30530	-0.096 (-0.180, -0.012)	2.49E-02	9.67E-02		-0.071 (-0.155, 0.014)	1.01E-01	3.26E-01
BMP-6	P22004	-0.031 (-0.112, 0.051)	4.60E-01	6.06E-01		-0.004 (-0.085, 0.077)	9.29E-01	9.80E-01
BOC	Q9BWV1	-0.048 (-0.130, 0.035)	2.60E-01	4.20E-01		-0.024 (-0.106, 0.058)	5.68E-01	8.02E-01
CA5A	P35218	-0.093 (-0.176, -0.009)	2.91E-02	1.06E-01		-0.034 (-0.120, 0.053)	4.46E-01	7.20E-01
CASP-3	P42574	-0.036 (-0.117, 0.045)	3.79E-01	5.29E-01		-0.023 (-0.103, 0.056)	5.64E-01	8.01E-01
CASP8	Q14790	-0.091 (-0.175, -0.007)	3.37E-02	1.14E-01		-0.024 (-0.109, 0.061)	5.84E-01	8.09E-01
CCL11	P51671	**-0.131 (-0.213, -0.048)**	**1.92E-03**	**1.60E-02**		-0.092 (-0.175, -0.009)	2.97E-02	1.54E-01
CCL13	Q99616	-0.089 (-0.170, -0.008)	3.13E-02	1.09E-01		-0.075 (-0.156, 0.005)	6.56E-02	2.50E-01
CCL15	Q16663	-0.075 (-0.160, 0.010)	8.27E-02	2.12E-01		-0.042 (-0.126, 0.042)	3.31E-01	6.42E-01
CCL16	O15467	-0.081 (-0.165, 0.003)	5.83E-02	1.70E-01		-0.078 (-0.161, 0.006)	6.76E-02	2.50E-01
CCL17	Q92583	-0.052 (-0.133, 0.030)	2.13E-01	3.74E-01		-0.037 (-0.118, 0.043)	3.62E-01	6.56E-01
CCL19	Q99731	0.005 (-0.080, 0.091)	9.01E-01	9.37E-01		0.027 (-0.058, 0.111)	5.39E-01	7.80E-01
CCL2	P13500	-0.085 (-0.167, -0.003)	4.12E-02	1.33E-01		-0.064 (-0.146, 0.017)	1.22E-01	3.86E-01
CCL20	P78556	-0.028 (-0.109, 0.053)	5.02E-01	6.43E-01		0.010 (-0.072, 0.091)	8.15E-01	9.22E-01
CCL23	P55773	-0.087 (-0.173, -0.001)	4.77E-02	1.50E-01		-0.111 (-0.197, -0.026)	1.06E-02	8.52E-02
CCL24	O00175	-0.016 (-0.097, 0.066)	7.05E-01	8.01E-01		-0.026 (-0.105, 0.054)	5.28E-01	7.71E-01
CCL25	O15444	0.001 (-0.082, 0.083)	9.88E-01	9.95E-01		0.001 (-0.081, 0.082)	9.87E-01	9.91E-01
CCL28	Q9NRJ3	-0.040 (-0.122, 0.041)	3.29E-01	4.92E-01		-0.049 (-0.130, 0.031)	2.28E-01	5.48E-01
CCL3	P10147	**-0.120 (-0.206, -0.035)**	**5.66E-03**	**2.93E-02**		-0.101 (-0.186, -0.016)	1.98E-02	1.32E-01
CCL4	P13236	-0.076 (-0.160, 0.008)	7.47E-02	2.02E-01		-0.060 (-0.144, 0.023)	1.57E-01	4.31E-01
CCL7	P80098	**-0.154 (-0.240, -0.069)**	**4.14E-04**	**6.43E-03**		-0.095 (-0.181, -0.010)	2.88E-02	1.52E-01
CD163	Q86VB7	-0.001 (-0.084, 0.082)	9.86E-01	9.95E-01		0.053 (-0.032, 0.138)	2.24E-01	5.46E-01
CD244	Q9BZW8	-0.084 (-0.165, -0.004)	3.95E-02	1.30E-01		-0.064 (-0.144, 0.016)	1.17E-01	3.75E-01
CD4	P01730	**-0.140 (-0.225, -0.055)**	**1.24E-03**	**1.38E-02**		-0.096 (-0.182, -0.010)	2.81E-02	1.52E-01
CD40	P25942	-0.036 (-0.118, 0.046)	3.86E-01	5.29E-01		-0.019 (-0.099, 0.062)	6.50E-01	8.50E-01
CD40-L	P29965	-0.035 (-0.116, 0.047)	4.02E-01	5.41E-01		-0.018 (-0.099, 0.063)	6.62E-01	8.57E-01
CD5	P06127	**-0.124 (-0.205, -0.042)**	**2.89E-03**	**1.89E-02**		-0.083 (-0.165, -0.002)	4.59E-02	2.07E-01
CD6	P30203	-0.066 (-0.147, 0.015)	1.12E-01	2.49E-01		-0.031 (-0.113, 0.050)	4.48E-01	7.20E-01
CD84	Q9UIB8	-0.026 (-0.107, 0.055)	5.22E-01	6.48E-01		-0.011 (-0.091, 0.069)	7.90E-01	9.22E-01
CD8A	P01732	**-0.117 (-0.201, -0.033)**	**6.49E-03**	**3.29E-02**		-0.082 (-0.166, 0.002)	5.55E-02	2.23E-01
CD93	Q9NPY3	**-0.130 (-0.216, -0.043)**	**3.47E-03**	**1.97E-02**		**-0.137 (-0.223, -0.051)**	**1.76E-03**	**2.78E-02**
CDCP1	Q9H5V8	-0.025 (-0.112, 0.063)	5.80E-01	6.92E-01		0.014 (-0.073, 0.101)	7.55E-01	9.07E-01
CDH5	P33151	-0.035 (-0.115, 0.045)	3.89E-01	5.30E-01		-0.028 (-0.107, 0.052)	4.97E-01	7.56E-01
CEACAM8	P31997	**-0.126 (-0.213, -0.039)**	**4.62E-03**	**2.56E-02**		-0.019 (-0.111, 0.073)	6.84E-01	8.68E-01
CHI3L1	P36222	-0.074 (-0.163, 0.015)	1.03E-01	2.35E-01		-0.037 (-0.130, 0.055)	4.27E-01	7.20E-01
CHIT1	Q13231	0.001 (-0.080, 0.083)	9.76E-01	9.95E-01		-0.011 (-0.091, 0.070)	7.97E-01	9.22E-01
CNTN1	Q12860	-0.007 (-0.092, 0.078)	8.79E-01	9.27E-01		0.009 (-0.075, 0.094)	8.31E-01	9.22E-01

Table S11. Longitudinal associations between 233 proteomic biomarkers and the annual rate of change in eGFRcys (N=1140) [a]

Biomarker	UniProt_ID	Model 1				Model 2		
		β (95%CI)	**P**	**FDR**		**β (95%CI)**	**P**	**FDR**
COL1A1	P02452	0.060 (-0.021, 0.142)	1.48E-01	2.81E-01		0.026 (-0.055, 0.108)	5.29E-01	7.71E-01
CPA1	P15085	-0.002 (-0.087, 0.083)	9.63E-01	9.93E-01		0.002 (-0.083, 0.087)	9.55E-01	9.80E-01
CPB1	P15086	-0.013 (-0.099, 0.072)	7.58E-01	8.29E-01		0.012 (-0.074, 0.098)	7.88E-01	9.22E-01
CSF1	P09603	-0.118 (-0.209, -0.026)	1.16E-02	5.18E-02		-0.079 (-0.169, 0.012)	8.76E-02	2.92E-01
CST5	P28325	-0.065 (-0.152, 0.021)	1.40E-01	2.70E-01		-0.064 (-0.151, 0.022)	1.43E-01	4.29E-01
CSTB	P04080	-0.093 (-0.178, -0.007)	3.36E-02	1.14E-01		-0.037 (-0.123, 0.049)	3.95E-01	6.81E-01
CTRC	Q99895	0.030 (-0.055, 0.116)	4.87E-01	6.30E-01		0.041 (-0.044, 0.126)	3.46E-01	6.50E-01
CTSL1	P07711	-0.055 (-0.142, 0.032)	2.13E-01	3.74E-01		-0.016 (-0.103, 0.070)	7.15E-01	8.81E-01
CTSZ	Q9UBR2	**-0.134 (-0.223, -0.045)**	**3.12E-03**	**1.91E-02**		-0.089 (-0.178, -0.000)	4.93E-02	2.09E-01
CX3CL1	P78423	-0.062 (-0.154, 0.030)	1.88E-01	3.37E-01		-0.086 (-0.177, 0.006)	6.72E-02	2.50E-01
CXCL1	P09341	-0.037 (-0.117, 0.043)	3.65E-01	5.19E-01		-0.030 (-0.108, 0.049)	4.57E-01	7.20E-01
CXCL10	P02778	0.012 (-0.071, 0.095)	7.70E-01	8.31E-01		0.018 (-0.065, 0.100)	6.74E-01	8.63E-01
CXCL11	O14625	-0.072 (-0.153, 0.009)	8.25E-02	2.12E-01		-0.048 (-0.129, 0.032)	2.40E-01	5.59E-01
CXCL16	Q9H2A7	-0.096 (-0.180, -0.011)	2.61E-02	9.81E-02		-0.061 (-0.146, 0.023)	1.54E-01	4.31E-01
CXCL5	P42830	-0.024 (-0.104, 0.056)	5.56E-01	6.78E-01		-0.018 (-0.097, 0.061)	6.49E-01	8.50E-01
CXCL6	P80162	-0.079 (-0.158, 0.000)	5.09E-02	1.58E-01		-0.057 (-0.135, 0.022)	1.59E-01	4.31E-01
CXCL9	Q07325	-0.040 (-0.127, 0.048)	3.71E-01	5.21E-01		-0.047 (-0.133, 0.040)	2.90E-01	6.14E-01
DCN	P07585	0.033 (-0.056, 0.121)	4.69E-01	6.14E-01		0.034 (-0.053, 0.122)	4.43E-01	7.20E-01
DECR1	Q16698	0.026 (-0.055, 0.108)	5.23E-01	6.48E-01		0.037 (-0.044, 0.117)	3.69E-01	6.60E-01
Dkk-1	O94907	-0.079 (-0.162, 0.003)	5.85E-02	1.70E-01		-0.060 (-0.141, 0.021)	1.47E-01	4.29E-01
DLK-1	P80370	-0.095 (-0.179, -0.010)	2.86E-02	1.06E-01		-0.084 (-0.168, 0.001)	5.18E-02	2.14E-01
DNER	Q8NFT8	0.099 (0.015, 0.183)	2.05E-02	8.09E-02		0.076 (-0.008, 0.160)	7.64E-02	2.66E-01
EGFR	P00533	0.007 (-0.076, 0.090)	8.68E-01	9.19E-01		0.016 (-0.068, 0.099)	7.14E-01	8.81E-01
EN-RAGE	P80511	-0.085 (-0.172, 0.002)	5.45E-02	1.65E-01		0.013 (-0.077, 0.103)	7.77E-01	9.22E-01
Ep-CAM	P16422	-0.035 (-0.117, 0.047)	3.99E-01	5.40E-01		-0.052 (-0.133, 0.029)	2.10E-01	5.26E-01
EPHB4	P54760	**-0.177 (-0.267, -0.087)**	**1.21E-04**	**2.34E-03**		**-0.184 (-0.273, -0.095)**	**5.18E-05**	**3.03E-03**
FABP2	P12104	-0.039 (-0.122, 0.043)	3.52E-01	5.07E-01		-0.104 (-0.187, -0.020)	1.50E-02	1.06E-01
FABP4	P15090	**-0.208 (-0.314, -0.103)**	**1.17E-04**	**2.34E-03**		-0.165 (-0.285, -0.044)	7.39E-03	6.89E-02
FAS	P25445	-0.068 (-0.154, 0.017)	1.17E-01	2.51E-01		-0.050 (-0.135, 0.034)	2.42E-01	5.59E-01
FGF19	O95750	-0.063 (-0.146, 0.019)	1.31E-01	2.68E-01		-0.009 (-0.094, 0.075)	8.26E-01	9.22E-01
FGF21	Q9NSA1	-0.040 (-0.123, 0.043)	3.49E-01	5.07E-01		-0.018 (-0.107, 0.072)	6.97E-01	8.73E-01
FGF-23	Q9GZV9	-0.076 (-0.171, 0.019)	1.17E-01	2.51E-01		-0.051 (-0.145, 0.043)	2.86E-01	6.11E-01
FLT3L	P49771	-0.024 (-0.108, 0.060)	5.72E-01	6.91E-01		0.007 (-0.076, 0.091)	8.65E-01	9.33E-01
FS	P19883	-0.080 (-0.162, 0.002)	5.52E-02	1.65E-01		-0.072 (-0.154, 0.010)	8.39E-02	2.88E-01
Gal-4	P56470	**-0.132 (-0.214, -0.049)**	**1.73E-03**	**1.59E-02**		-0.081 (-0.165, 0.003)	5.99E-02	2.36E-01
Gal-9	O00182	-0.097 (-0.184, -0.009)	2.99E-02	1.07E-01		-0.044 (-0.132, 0.045)	3.33E-01	6.42E-01
GDF-15	Q99988	**-0.176 (-0.277, -0.075)**	**6.42E-04**	**8.63E-03**		-0.063 (-0.168, 0.042)	2.36E-01	5.55E-01
GDF-2	Q9UK05	0.078 (-0.010, 0.166)	8.21E-02	2.12E-01		0.062 (-0.027, 0.151)	1.70E-01	4.55E-01
GH	P01241	0.070 (-0.021, 0.161)	1.31E-01	2.68E-01		-0.002 (-0.096, 0.093)	9.72E-01	9.80E-01
GIF	P27352	-0.042 (-0.128, 0.045)	3.42E-01	5.01E-01		0.002 (-0.084, 0.088)	9.59E-01	9.80E-01
GLO1	Q04760	-0.050 (-0.131, 0.031)	2.24E-01	3.87E-01		-0.030 (-0.111, 0.051)	4.66E-01	7.20E-01
GPVI	Q9HCN6	-0.059 (-0.140, 0.022)	1.56E-01	2.90E-01		-0.042 (-0.122, 0.038)	3.00E-01	6.21E-01
GRN	P28799	-0.047 (-0.132, 0.038)	2.78E-01	4.47E-01		-0.008 (-0.092, 0.077)	8.61E-01	9.33E-01
GT	P51161	-0.006 (-0.088, 0.076)	8.87E-01	9.31E-01		-0.065 (-0.149, 0.018)	1.25E-01	3.89E-01
HAOX1	Q9UJM8	-0.015 (-0.098, 0.068)	7.31E-01	8.15E-01		0.038 (-0.046, 0.123)	3.74E-01	6.60E-01
HB-EGF	Q99075	-0.072 (-0.152, 0.009)	8.23E-02	2.12E-01		-0.042 (-0.122, 0.039)	3.07E-01	6.21E-01
HGF	P14210	**-0.129 (-0.215, -0.043)**	**3.20E-03**	**1.91E-02**		-0.021 (-0.114, 0.071)	6.48E-01	8.50E-01
HO-1	P09601	-0.029 (-0.112, 0.055)	5.02E-01	6.43E-01		-0.031 (-0.117, 0.054)	4.69E-01	7.20E-01

Table S11. Longitudinal associations between 233 proteomic biomarkers and the annual rate of change in eGFRcys (N=1140) [a]

Biomarker	UniProt_ID	Model 1				Model 2		
		β (95%CI)	**P**	**FDR**		**β (95%CI)**	**P**	**FDR**
hOSCAR	Q8IYS5	-0.043 (-0.126, 0.040)	3.09E-01	4.78E-01		-0.032 (-0.114, 0.049)	4.36E-01	7.20E-01
HSP 27	P04792	0.031 (-0.048, 0.109)	4.46E-01	5.91E-01		0.016 (-0.061, 0.093)	6.86E-01	8.68E-01
ICAM-2	P13598	-0.057 (-0.139, 0.025)	1.71E-01	3.11E-01		-0.040 (-0.122, 0.042)	3.38E-01	6.46E-01
IDUA	P35475	-0.032 (-0.114, 0.049)	4.40E-01	5.89E-01		0.009 (-0.073, 0.092)	8.26E-01	9.22E-01
IFNG	P01579	0.040 (-0.040, 0.121)	3.28E-01	4.92E-01		0.051 (-0.029, 0.131)	2.08E-01	5.26E-01
IGFBP-1	P08833	0.060 (-0.024, 0.143)	1.60E-01	2.96E-01		-0.122 (-0.222, -0.022)	1.65E-02	1.13E-01
IGFBP-2	P18065	-0.068 (-0.154, 0.018)	1.20E-01	2.53E-01		**-0.168 (-0.268, -0.068)**	**1.01E-03**	**2.12E-02**
IGFBP-7	Q16270	-0.077 (-0.166, 0.012)	8.83E-02	2.15E-01		-0.049 (-0.137, 0.038)	2.69E-01	5.86E-01
IgG Fc receptor II-b	P31994	0.020 (-0.061, 0.101)	6.30E-01	7.27E-01		0.023 (-0.057, 0.103)	5.74E-01	8.06E-01
IL-10	P22301	0.000 (-0.085, 0.086)	9.94E-01	9.95E-01		-0.010 (-0.094, 0.075)	8.23E-01	9.22E-01
IL-10RB	Q08334	-0.117 (-0.208, -0.025)	1.24E-02	5.46E-02		-0.093 (-0.184, -0.002)	4.62E-02	2.07E-01
IL-12B	P29460	-0.085 (-0.175, 0.004)	6.10E-02	1.72E-01		-0.088 (-0.182, 0.005)	6.37E-02	2.47E-01
IL-15RA	Q13261	**-0.144 (-0.239, -0.049)**	**2.92E-03**	**1.89E-02**		**-0.138 (-0.231, -0.044)**	**4.03E-03**	**4.47E-02**
IL-16	Q14005	-0.065 (-0.146, 0.016)	1.17E-01	2.51E-01		-0.022 (-0.103, 0.059)	5.91E-01	8.09E-01
IL-17D	Q8TAD2	0.060 (-0.019, 0.139)	1.37E-01	2.70E-01		0.042 (-0.036, 0.120)	2.93E-01	6.14E-01
IL-17RA	Q96F46	-0.072 (-0.157, 0.012)	9.39E-02	2.21E-01		-0.049 (-0.132, 0.034)	2.45E-01	5.59E-01
IL-18	Q14116	**-0.118 (-0.203, -0.033)**	**6.82E-03**	**3.38E-02**		-0.029 (-0.117, 0.059)	5.19E-01	7.71E-01
IL-18BP	O95998	**-0.180 (-0.273, -0.088)**	**1.32E-04**	**2.36E-03**		**-0.161 (-0.252, -0.069)**	**6.13E-04**	**1.59E-02**
IL-18R1	Q13478	-0.044 (-0.127, 0.040)	3.04E-01	4.73E-01		0.066 (-0.023, 0.155)	1.44E-01	4.29E-01
IL-1RA	P18510	-0.101 (-0.184, -0.017)	1.80E-02	7.25E-02		0.034 (-0.057, 0.126)	4.62E-01	7.20E-01
IL1-RL2	Q9HB29	-0.042 (-0.129, 0.044)	3.39E-01	5.01E-01		-0.003 (-0.091, 0.086)	9.53E-01	9.80E-01
IL-1RT1	P14778	**-0.111 (-0.194, -0.028)**	**9.05E-03**	**4.39E-02**		-0.092 (-0.175, -0.009)	3.06E-02	1.55E-01
IL-1RT2	P27930	-0.027 (-0.109, 0.054)	5.10E-01	6.48E-01		0.003 (-0.080, 0.087)	9.41E-01	9.80E-01
IL-27	Q8NEV9	-0.003 (-0.086, 0.081)	9.50E-01	9.84E-01		-0.002 (-0.085, 0.081)	9.62E-01	9.80E-01
IL2-RA	P01589	**-0.130 (-0.217, -0.043)**	**3.41E-03**	**1.97E-02**		-0.108 (-0.193, -0.022)	1.40E-02	1.02E-01
IL-4RA	P24394	-0.051 (-0.139, 0.037)	2.54E-01	4.13E-01		-0.063 (-0.150, 0.024)	1.54E-01	4.31E-01
IL-6	P05231	-0.039 (-0.124, 0.046)	3.68E-01	5.20E-01		-0.008 (-0.094, 0.078)	8.58E-01	9.33E-01
IL-6RA	P08887	-0.063 (-0.144, 0.019)	1.35E-01	2.69E-01		-0.042 (-0.123, 0.039)	3.13E-01	6.21E-01
IL-7	P13232	-0.068 (-0.146, 0.010)	8.79E-02	2.15E-01		-0.071 (-0.149, 0.006)	7.23E-02	2.61E-01
IL-8	P10145	-0.105 (-0.189, -0.022)	1.32E-02	5.57E-02		-0.035 (-0.119, 0.050)	4.18E-01	7.11E-01
ITGB1BP2	Q9UKP3	-0.013 (-0.094, 0.067)	7.44E-01	8.18E-01		-0.006 (-0.085, 0.074)	8.91E-01	9.53E-01
ITGB2	P05107	-0.038 (-0.123, 0.048)	3.84E-01	5.29E-01		0.002 (-0.083, 0.087)	9.64E-01	9.80E-01
JAM-A	Q9Y624	-0.043 (-0.124, 0.039)	3.04E-01	4.73E-01		-0.024 (-0.105, 0.056)	5.52E-01	7.89E-01
KIM1	Q96D42	**-0.198 (-0.283, -0.113)**	**5.80E-06**	**2.70E-04**		**-0.138 (-0.229, -0.047)**	**3.08E-03**	**4.12E-02**
KLK6	Q92876	**-0.122 (-0.208, -0.037)**	**4.89E-03**	**2.65E-02**		**-0.174 (-0.260, -0.088)**	**7.97E-05**	**3.10E-03**
LDL receptor	P01130	-0.076 (-0.156, 0.004)	6.11E-02	1.72E-01		-0.046 (-0.151, 0.060)	3.94E-01	6.81E-01
LEP	P41159	-0.113 (-0.216, -0.011)	3.07E-02	1.08E-01		-0.046 (-0.179, 0.087)	5.00E-01	7.56E-01
LIFR	P42702	-0.014 (-0.098, 0.069)	7.35E-01	8.15E-01		0.052 (-0.033, 0.137)	2.31E-01	5.50E-01
LIGHT	O43557	-0.049 (-0.129, 0.032)	2.34E-01	3.96E-01		-0.002 (-0.082, 0.079)	9.69E-01	9.80E-01
LOX-1	P78380	**-0.118 (-0.202, -0.035)**	**5.54E-03**	**2.93E-02**		0.002 (-0.088, 0.092)	9.61E-01	9.80E-01
LPL	P06858	-0.019 (-0.118, 0.081)	7.13E-01	8.07E-01		-0.103 (-0.205, -0.001)	4.79E-02	2.09E-01
LTBR	P36941	-0.123 (-0.217, -0.029)	1.06E-02	5.04E-02		-0.124 (-0.216, -0.031)	8.70E-03	7.75E-02
MARCO	Q9UEW3	-0.015 (-0.096, 0.067)	7.24E-01	8.11E-01		0.011 (-0.070, 0.093)	7.84E-01	9.22E-01
MB	P02144	-0.037 (-0.134, 0.059)	4.46E-01	5.91E-01		-0.045 (-0.141, 0.050)	3.51E-01	6.55E-01
MCP-2	P80075	-0.020 (-0.100, 0.059)	6.15E-01	7.21E-01		-0.000 (-0.079, 0.079)	1.00E+00	1.00E+00
MEPE	Q9NQ76	-0.055 (-0.141, 0.032)	2.15E-01	3.74E-01		-0.091 (-0.176, -0.006)	3.69E-02	1.75E-01
MERTK	Q12866	0.023 (-0.060, 0.107)	5.82E-01	6.92E-01		0.030 (-0.052, 0.113)	4.70E-01	7.20E-01
MMP-1	P03956	-0.067 (-0.149, 0.015)	1.11E-01	2.49E-01		-0.050 (-0.131, 0.031)	2.24E-01	5.46E-01

Table S11. Longitudinal associations between 233 proteomic biomarkers and the annual rate of change in eGFRcys (N=1140) [a]

Biomarker	UniProt_ID	Model 1				Model 2		
		β (95%CI)	P	FDR		β (95%CI)	P	FDR
MMP-12	P39900	**-0.141 (-0.229, -0.053)**	**1.74E-03**	**1.59E-02**		-0.089 (-0.179, 0.001)	5.23E-02	2.14E-01
MMP-2	P08253	-0.063 (-0.146, 0.019)	1.33E-01	2.69E-01		-0.059 (-0.141, 0.023)	1.58E-01	4.31E-01
MMP-3	P08254	-0.034 (-0.132, 0.063)	4.87E-01	6.30E-01		-0.036 (-0.132, 0.060)	4.60E-01	7.20E-01
MMP-7	P09237	-0.080 (-0.166, 0.006)	6.79E-02	1.86E-01		-0.093 (-0.179, -0.007)	3.32E-02	1.65E-01
MMP-9	P14780	-0.073 (-0.155, 0.009)	8.27E-02	2.12E-01		0.022 (-0.063, 0.106)	6.19E-01	8.38E-01
MPO	P05164	-0.041 (-0.123, 0.041)	3.27E-01	4.92E-01		0.012 (-0.070, 0.094)	7.66E-01	9.16E-01
NEMO	Q9Y6K9	-0.005 (-0.086, 0.075)	8.98E-01	9.37E-01		0.003 (-0.077, 0.082)	9.48E-01	9.80E-01
Notch 3	Q9UM47	-0.068 (-0.154, 0.018)	1.21E-01	2.55E-01		-0.087 (-0.173, -0.001)	4.85E-02	2.09E-01
NT3	P20783	0.012 (-0.077, 0.102)	7.85E-01	8.43E-01		0.047 (-0.042, 0.136)	3.04E-01	6.21E-01
NT-proBNP	P16860	**-0.245 (-0.336, -0.153)**	**1.97E-07**	**4.19E-05**		**-0.238 (-0.331, -0.145)**	**5.66E-07**	**1.32E-04**
OPG	O00300	-0.013 (-0.103, 0.077)	7.71E-01	8.31E-01		0.045 (-0.045, 0.135)	3.31E-01	6.42E-01
OPN	P10451	-0.076 (-0.165, 0.012)	8.97E-02	2.15E-01		-0.101 (-0.188, -0.014)	2.36E-02	1.41E-01
OSM	P13725	-0.093 (-0.175, -0.011)	2.59E-02	9.81E-02		0.010 (-0.075, 0.096)	8.14E-01	9.22E-01
PAI	P05121	-0.071 (-0.154, 0.011)	8.95E-02	2.15E-01		-0.044 (-0.129, 0.041)	3.11E-01	6.21E-01
PAR-1	P25116	-0.065 (-0.146, 0.015)	1.11E-01	2.49E-01		-0.037 (-0.116, 0.042)	3.63E-01	6.56E-01
PARP-1	P09874	-0.001 (-0.083, 0.081)	9.82E-01	9.95E-01		0.039 (-0.042, 0.120)	3.45E-01	6.50E-01
PCSK9	Q8NBP7	**-0.152 (-0.234, -0.069)**	**3.17E-04**	**5.27E-03**		**-0.149 (-0.234, -0.065)**	**5.65E-04**	**1.59E-02**
PDGF subunit A	P04085	-0.069 (-0.151, 0.013)	9.71E-02	2.26E-01		-0.053 (-0.134, 0.028)	2.02E-01	5.20E-01
PDGF subunit B	P01127	-0.026 (-0.107, 0.054)	5.21E-01	6.48E-01		-0.015 (-0.094, 0.065)	7.19E-01	8.81E-01
PD-L1	Q9NZQ7	**-0.133 (-0.219, -0.048)**	**2.30E-03**	**1.69E-02**		-0.106 (-0.191, -0.022)	1.36E-02	1.02E-01
PD-L2	Q9BQ51	-0.044 (-0.127, 0.039)	3.03E-01	4.73E-01		-0.018 (-0.100, 0.064)	6.71E-01	8.63E-01
PECAM-1	P16284	-0.050 (-0.133, 0.032)	2.30E-01	3.90E-01		-0.031 (-0.112, 0.050)	4.50E-01	7.20E-01
PGF	P49763	-0.096 (-0.195, 0.004)	6.00E-02	1.72E-01		-0.073 (-0.171, 0.026)	1.47E-01	4.29E-01
PGLYRP1	O75594	**-0.140 (-0.227, -0.052)**	**1.73E-03**	**1.59E-02**		-0.080 (-0.167, 0.008)	7.39E-02	2.61E-01
PIgR	P01833	**-0.134 (-0.219, -0.048)**	**2.19E-03**	**1.69E-02**		-0.120 (-0.206, -0.035)	6.00E-03	6.08E-02
PLC	P98160	-0.127 (-0.225, -0.028)	1.15E-02	5.18E-02		**-0.142 (-0.240, -0.044)**	**4.58E-03**	**4.85E-02**
PON3	Q15166	0.061 (-0.022, 0.143)	1.48E-01	2.81E-01		-0.043 (-0.137, 0.050)	3.62E-01	6.56E-01
PRELP	P51888	0.012 (-0.078, 0.102)	7.96E-01	8.51E-01		0.034 (-0.055, 0.124)	4.48E-01	7.20E-01
PRSS27	Q9BQR3	**-0.144 (-0.227, -0.061)**	**6.67E-04**	**8.63E-03**		**-0.149 (-0.230, -0.067)**	**3.79E-04**	**1.26E-02**
PRSS8	Q16651	**-0.131 (-0.218, -0.044)**	**3.08E-03**	**1.91E-02**		-0.104 (-0.197, -0.012)	2.72E-02	1.51E-01
PSGL-1	Q14242	-0.065 (-0.150, 0.020)	1.35E-01	2.69E-01		0.024 (-0.066, 0.114)	5.99E-01	8.17E-01
PSP-D	P35247	-0.049 (-0.131, 0.034)	2.45E-01	4.08E-01		-0.063 (-0.145, 0.018)	1.29E-01	3.95E-01
PTX3	P26022	-0.108 (-0.190, -0.025)	1.10E-02	5.11E-02		-0.054 (-0.138, 0.029)	2.03E-01	5.20E-01
RAGE	Q15109	-0.043 (-0.131, 0.045)	3.38E-01	5.01E-01		-0.101 (-0.189, -0.013)	2.46E-02	1.43E-01
RARRES2	Q99969	**-0.184 (-0.271, -0.097)**	**3.72E-05**	**1.08E-03**		**-0.134 (-0.224, -0.045)**	**3.21E-03**	**4.12E-02**
REN	P00797	-0.082 (-0.170, 0.006)	6.69E-02	1.86E-01		0.010 (-0.084, 0.104)	8.31E-01	9.22E-01
RETN	Q9HD89	**-0.151 (-0.239, -0.063)**	**7.73E-04**	**9.47E-03**		-0.095 (-0.183, -0.007)	3.41E-02	1.66E-01
SCF	P21583	0.022 (-0.066, 0.110)	6.26E-01	7.25E-01		-0.031 (-0.127, 0.065)	5.25E-01	7.71E-01
SCGB3A2	Q96PL1	-0.073 (-0.157, 0.011)	9.03E-02	2.15E-01		-0.110 (-0.204, -0.016)	2.19E-02	1.38E-01
SELE	P16581	-0.010 (-0.091, 0.071)	8.07E-01	8.59E-01		0.037 (-0.045, 0.119)	3.77E-01	6.61E-01
SELP	P16109	-0.062 (-0.143, 0.020)	1.39E-01	2.70E-01		-0.038 (-0.119, 0.043)	3.55E-01	6.56E-01
SERPINA12	Q8IW75	0.024 (-0.057, 0.106)	5.59E-01	6.78E-01		0.025 (-0.056, 0.106)	5.45E-01	7.83E-01
SHPS-1	P78324	-0.108 (-0.194, -0.022)	1.38E-02	5.74E-02		-0.088 (-0.172, -0.003)	4.27E-02	1.99E-01
SIRT2	Q8IXJ6	-0.016 (-0.096, 0.064)	6.96E-01	7.95E-01		0.006 (-0.073, 0.086)	8.76E-01	9.41E-01
SL-2	P09238	**-0.130 (-0.212, -0.048)**	**1.89E-03**	**1.60E-02**		**-0.120 (-0.201, -0.039)**	**3.79E-03**	**4.41E-02**
SOD2	P04179	-0.036 (-0.117, 0.045)	3.83E-01	5.29E-01		-0.014 (-0.094, 0.066)	7.26E-01	8.86E-01
SORT1	Q99523	-0.072 (-0.153, 0.010)	8.50E-02	2.15E-01		-0.038 (-0.120, 0.045)	3.71E-01	6.60E-01
SPON2	Q9BUD6	-0.080 (-0.171, 0.012)	8.76E-02	2.15E-01		-0.122 (-0.213, -0.031)	8.98E-03	7.75E-02

Table S11. Longitudinal associations between 233 proteomic biomarkers and the annual rate of change in eGFRcys (N=1140) [a]

Biomarker	**UniProt_ID**	**Model 1**				**Model 2**		
		β (95%CI)	**P**	**FDR**		**β (95%CI)**	**P**	**FDR**
SRC	P12931	0.037 (-0.041, 0.116)	3.52E-01	5.07E-01		0.033 (-0.044, 0.110)	4.03E-01	6.90E-01
ST1A1	P50225	-0.027 (-0.108, 0.054)	5.19E-01	6.48E-01		-0.008 (-0.088, 0.072)	8.42E-01	9.30E-01
ST2	Q01638	0.001 (-0.086, 0.088)	9.78E-01	9.95E-01		0.077 (-0.011, 0.164)	8.71E-02	2.92E-01
STAMBP	O95630	-0.021 (-0.102, 0.060)	6.05E-01	7.15E-01		-0.003 (-0.083, 0.077)	9.45E-01	9.80E-01
STK4	Q13043	0.016 (-0.063, 0.096)	6.83E-01	7.84E-01		0.025 (-0.053, 0.103)	5.29E-01	7.71E-01
TF	P13726	-0.022 (-0.108, 0.064)	6.16E-01	7.21E-01		-0.044 (-0.131, 0.042)	3.14E-01	6.21E-01
TFPI	P10646	-0.027 (-0.108, 0.055)	5.21E-01	6.48E-01		-0.030 (-0.110, 0.050)	4.65E-01	7.20E-01
TGF-α	P01135	**-0.175 (-0.260, -0.089)**	**6.63E-05**	**1.54E-03**		-0.067 (-0.159, 0.026)	1.58E-01	4.31E-01
TGF-β1	P01137	-0.085 (-0.167, -0.004)	3.95E-02	1.30E-01		-0.050 (-0.132, 0.031)	2.25E-01	5.46E-01
TGM2	P21980	-0.026 (-0.109, 0.057)	5.40E-01	6.63E-01		0.049 (-0.036, 0.134)	2.56E-01	5.73E-01
THBS2	P35442	-0.069 (-0.155, 0.016)	1.13E-01	2.49E-01		-0.020 (-0.108, 0.068)	6.59E-01	8.57E-01
THPO	P40225	-0.085 (-0.169, -0.001)	4.68E-02	1.49E-01		-0.098 (-0.181, -0.015)	2.03E-02	1.32E-01
TIE2	Q02763	0.026 (-0.055, 0.107)	5.29E-01	6.52E-01		0.056 (-0.025, 0.136)	1.75E-01	4.59E-01
TIMP4	Q99727	-0.052 (-0.141, 0.037)	2.51E-01	4.13E-01		-0.034 (-0.124, 0.056)	4.56E-01	7.20E-01
TLT-2	Q5T2D2	**-0.131 (-0.215, -0.047)**	**2.32E-03**	**1.69E-02**		**-0.133 (-0.216, -0.050)**	**1.79E-03**	**2.78E-02**
TM	P07204	-0.115 (-0.206, -0.024)	1.30E-02	5.57E-02		-0.105 (-0.195, -0.015)	2.24E-02	1.38E-01
TNF-R1	P19438	**-0.237 (-0.341, -0.133)**	**9.09E-06**	**3.02E-04**		**-0.174 (-0.279, -0.070)**	**1.09E-03**	**2.12E-02**
TNF-R2	P20333	**-0.237 (-0.334, -0.140)**	**1.97E-06**	**1.53E-04**		**-0.197 (-0.294, -0.101)**	**6.49E-05**	**3.03E-03**
TNFRSF10A	O00220	**-0.183 (-0.272, -0.095)**	**5.24E-05**	**1.36E-03**		**-0.135 (-0.225, -0.045)**	**3.36E-03**	**4.12E-02**
TNFRSF10C	O14798	-0.057 (-0.140, 0.026)	1.79E-01	3.24E-01		-0.019 (-0.102, 0.063)	6.44E-01	8.50E-01
TNFRSF11A	Q9Y6Q6	**-0.258 (-0.357, -0.159)**	**3.59E-07**	**4.19E-05**		**-0.208 (-0.308, -0.109)**	**4.37E-05**	**3.03E-03**
TNFRSF13B	O14836	**-0.166 (-0.258, -0.073)**	**4.84E-04**	**7.04E-03**		**-0.139 (-0.230, -0.047)**	**3.07E-03**	**4.12E-02**
TNFRSF14	Q92956	**-0.142 (-0.232, -0.053)**	**1.78E-03**	**1.59E-02**		-0.116 (-0.204, -0.028)	1.00E-02	8.33E-02
TNFRSF9	Q07011	**-0.159 (-0.260, -0.058)**	**2.10E-03**	**1.69E-02**		**-0.170 (-0.269, -0.070)**	**8.59E-04**	**2.00E-02**
TNFSF10	P50591	0.014 (-0.070, 0.098)	7.43E-01	8.18E-01		0.007 (-0.077, 0.092)	8.65E-01	9.33E-01
TNFSF13B	Q9Y275	-0.043 (-0.128, 0.042)	3.16E-01	4.84E-01		-0.024 (-0.108, 0.060)	5.79E-01	8.07E-01
TNF-α	P01375	-0.047 (-0.128, 0.034)	2.53E-01	4.13E-01		-0.041 (-0.120, 0.039)	3.15E-01	6.21E-01
TNF-β	P01374	0.015 (-0.069, 0.099)	7.22E-01	8.11E-01		0.016 (-0.068, 0.099)	7.12E-01	8.81E-01
t-PA	P00750	-0.042 (-0.123, 0.040)	3.18E-01	4.85E-01		-0.014 (-0.096, 0.069)	7.48E-01	9.03E-01
TR	P02786	**-0.126 (-0.208, -0.044)**	**2.51E-03**	**1.78E-02**		-0.048 (-0.132, 0.036)	2.61E-01	5.78E-01
TRAIL-R2	O14763	**-0.149 (-0.241, -0.056)**	**1.66E-03**	**1.59E-02**		-0.105 (-0.198, -0.013)	2.61E-02	1.48E-01
TRANCE	O14788	0.021 (-0.062, 0.103)	6.22E-01	7.24E-01		-0.010 (-0.092, 0.072)	8.08E-01	9.22E-01
TR-AP	P13686	0.013 (-0.072, 0.098)	7.64E-01	8.31E-01		0.011 (-0.074, 0.096)	7.98E-01	9.22E-01
TWEAK	O43508	0.045 (-0.038, 0.127)	2.86E-01	4.57E-01		0.017 (-0.067, 0.100)	6.94E-01	8.73E-01
uPA	P00749	0.059 (-0.029, 0.146)	1.89E-01	3.37E-01		0.060 (-0.026, 0.146)	1.74E-01	4.59E-01
U-PAR	Q03405	-0.064 (-0.152, 0.024)	1.51E-01	2.84E-01		-0.009 (-0.096, 0.079)	8.48E-01	9.32E-01
VEGF-A	P15692	**-0.197 (-0.283, -0.111)**	**8.53E-06**	**3.02E-04**		**-0.142 (-0.230, -0.054)**	**1.56E-03**	**2.78E-02**
VEGFD	O43915	-0.068 (-0.149, 0.013)	1.02E-01	2.35E-01		-0.075 (-0.156, 0.007)	7.27E-02	2.61E-01
VSIG2	Q96IQ7	-0.111 (-0.201, -0.020)	1.66E-02	6.77E-02		-0.077 (-0.168, 0.013)	9.37E-02	3.08E-01
vWF	P04275	-0.065 (-0.147, 0.018)	1.23E-01	2.56E-01		-0.027 (-0.109, 0.055)	5.12E-01	7.70E-01
XCL1	P47992	**-0.125 (-0.206, -0.044)**	**2.60E-03**	**1.78E-02**		-0.103 (-0.183, -0.022)	1.27E-02	9.87E-02

[a] Linear regressions were used to estimate β (95% CI) of the annual rate of change in eGFRcys (per year) per 1 standard deviation increase in biomarkers. The biomarkers are sorted alphabetically. **In bold are biomarkers significantly associated with the annual rate of change in eGFRcys (FDR <0.05)**.

Model 1: Adjusted for age, sex, and eGFRcys at baseline;

Model 2: Model 1 plus body mass index, physical activity, smoking status, alcohol consumption, systolic blood pressure, use of antihypertensive medication, triglycerides (naturally log-transformed), high-density lipoprotein cholesterol, use of lipid-lowering medication, prevalent diabetes, prevalent cardiovascular diseases, and fasting status at baseline.

Abbreviations: CI, confidence interval; eGFRcys, cystatin C-based estimated glomerular filtration rate; FDR, Benjamini–Hochberg false-discovery rate. Full names of the biomarkers can be found in Additional file 1: Table S1.

Table S12. Longitudinal associations between baseline characteristics and the annual rate of change in eGFRcr and eGFRcys (N=1140) [a]

	Change in eGFRcr			**Change in eGFRcys**	
	β (95%CI)	**P**		**β (95%CI)**	**P**
Age, per SD	-0.236 (-0.319, -0.153)	<0.001		-0.188 (-0.279, -0.096)	<0.001
Sex (reference: male)	-0.034 (-0.229, 0.162)	0.734		0.080 (-0.123, 0.284)	0.439
Body mass index, per SD	-0.048 (-0.130, 0.035)	0.258		-0.040 (-0.127, 0.046)	0.362
Smoking status					
Never smoker	Reference			Reference	
Former smoker	-0.138 (-0.312, 0.036)	0.120		-0.061 (-0.243, 0.121)	0.513
Current smoker	-0.317 (-0.567, -0.066)	0.013		-0.246 (-0.509, 0.017)	0.066
Alcohol consumption					
No alcohol consumption	Reference			Reference	
>0 and <20 g/day	0.169 (-0.022, 0.361)	0.083		0.128 (-0.072, 0.328)	0.211
≥ 20 g/day	0.114 (-0.103, 0.330)	0.303		0.191 (-0.036, 0.418)	0.099
Physically active (reference: no)	0.047 (-0.107, 0.202)	0.548		-0.011 (-0.172, 0.150)	0.896
Systolic blood pressure, per SD	-0.055 (-0.136, 0.027)	0.188		-0.043 (-0.128, 0.042)	0.321
Use of antihypertensive medication (reference: no)	-0.284 (-0.458, -0.109)	0.001		-0.221 (-0.404, -0.038)	0.018
Triglycerides (mmol/L), per IQR	-0.021 (-0.103, 0.060)	0.605		-0.031 (-0.115, 0.054)	0.480
High-density lipoprotein cholesterol, per SD	0.047 (-0.045, 0.140)	0.314		0.028 (-0.069, 0.124)	0.574
Use of lipid-lowering medication (reference: no)	-0.005 (-0.255, 0.246)	0.971		-0.095 (-0.357, 0.166)	0.475
Type 2 diabetes (reference: no) [b]	-0.188 (-0.529, 0.153)	0.279		-0.194 (-0.551, 0.163)	0.286
Cardiovascular diseases (reference: no)	0.119 (-0.122, 0.361)	0.333		0.033 (-0.219, 0.285)	0.797
Fasting status (reference: no) [b]	0.310 (0.005, 0.615)	0.046		0.705 (0.388, 1.023)	<0.001
eGFR [c] (ml/min/1.73 m^2), per SD	-0.355 (-0.436, -0.274)	<0.001		-0.344 (-0.437, -0.252)	<0.001

[a] Multivariate linear regression was used to estimate β (95% CI) of associations between baseline characteristics and the annual rate of change in eGFR for per 1 SD/IQR increase in continuous variables. For categorical variables, β (95% CI) were estimated from categories compared with the reference.

[b] Participants who were non-fasting before blood was taken were predominantly participants with diabetes. Among 1140 participants included in longitudinal analysis, 60 out of 94 participants with diabetes were non-fasting, which explains the non-significant results of diabetes with change in eGFR in the multivariate linear regression model. When fasting status was excluded from the multivariate linear regression model, participants with diabetes had significantly faster declines in both eGFRcr and eGFRcys compared with participants without diabetes.

[c] Baseline eGFRcr or eGFRcys were used depending on the outcome.

Abbreviations: CI, confidence interval; eGFRcr, creatinine-based estimated glomerular filtration rate; eGFRcys, cystatin C-based estimated glomerular filtration rate; IQR, interquartile range; SD, standard deviation.

Table S13. Association of 21 proteomic biomarkers with UACR [a]

Biomarker	UniProt_ID	Associations with change in eGFRcr (N = 1140)				Associations with log (UACR) (N = 1113)		
		β (95%CI)	P	FDR		β (95%CI)	P	FDR
KIM1	Q96D42	-0.292 (-0.377, -0.206)	4.08E-11	9.51E-09		**0.129 (0.096, 0.161)**	**1.30E-14**	**2.73E-13**
EPHB4	P54760	-0.233 (-0.313, -0.153)	1.46E-08	1.62E-06		0.029 (-0.002, 0.059)	6.87E-02	7.60E-02
IL-18BP	O95998	-0.235 (-0.317, -0.152)	2.70E-08	1.62E-06		**0.036 (0.004, 0.067)**	**2.57E-02**	**3.60E-02**
NT-proBNP	P16860	-0.249 (-0.336, -0.162)	2.77E-08	1.62E-06		**0.073 (0.040, 0.106)**	**1.76E-05**	**1.85E-04**
TNFRSF9	Q07011	-0.234 (-0.322, -0.145)	2.36E-07	9.18E-06		**0.052 (0.019, 0.086)**	**2.41E-03**	**7.22E-03**
IGFBP-2	P18065	-0.226 (-0.318, -0.135)	1.36E-06	3.65E-05		**0.048 (0.013, 0.083)**	**6.54E-03**	**1.37E-02**
TNF-R2	P20333	-0.214 (-0.300, -0.127)	1.41E-06	3.65E-05		**0.036 (0.003, 0.069)**	**3.39E-02**	**4.19E-02**
IL2-RA	P01589	-0.194 (-0.273, -0.115)	1.66E-06	3.87E-05		**0.034 (0.004, 0.064)**	**2.83E-02**	**3.72E-02**
PLC	P98160	-0.217 (-0.306, -0.128)	2.07E-06	4.38E-05		**0.041 (0.007, 0.075)**	**1.80E-02**	**2.92E-02**
TNF-R1	P19438	-0.221 (-0.315, -0.127)	4.57E-06	8.88E-05		**0.055 (0.019, 0.090)**	**2.77E-03**	**7.28E-03**
TNFRSF11A	Q9Y6Q6	-0.214 (-0.306, -0.121)	6.37E-06	1.14E-04		**0.067 (0.032, 0.102)**	**1.86E-04**	**1.30E-03**
IL-15RA	Q13261	-0.181 (-0.266, -0.097)	2.59E-05	3.42E-04		0.028 (-0.004, 0.060)	9.06E-02	9.52E-02
TRAIL-R2	O14763	-0.180 (-0.267, -0.094)	4.24E-05	4.94E-04		**0.054 (0.021, 0.087)**	**1.17E-03**	**4.92E-03**
OPN	P10451	-0.156 (-0.236, -0.076)	1.37E-04	1.28E-03		**0.036 (0.006, 0.067)**	**1.95E-02**	**2.92E-02**
TM	P07204	-0.146 (-0.230, -0.061)	7.13E-04	4.65E-03		0.033 (0.001, 0.065)	4.59E-02	5.36E-02
ADM	P35318	-0.157 (-0.249, -0.065)	8.67E-04	5.31E-03		**0.042 (0.007, 0.076)**	**1.93E-02**	**2.92E-02**
CCL7	P80098	-0.135 (-0.216, -0.053)	1.19E-03	6.91E-03		**0.055 (0.024, 0.086)**	**4.45E-04**	**2.33E-03**
XCL1	P47992	-0.120 (-0.196, -0.043)	2.23E-03	1.21E-02		0.018 (-0.011, 0.046)	2.35E-01	2.35E-01
VEGF-A	P15692	-0.127 (-0.211, -0.043)	2.96E-03	1.41E-02		**0.047 (0.015, 0.078)**	**3.93E-03**	**9.17E-03**
CCL3	P10147	-0.116 (-0.197, -0.036)	4.77E-03	1.98E-02		**0.039 (0.008, 0.069)**	**1.27E-02**	**2.42E-02**
PD-L1	Q9NZQ7	-0.107 (-0.187, -0.026)	9.24E-03	3.47E-02		**0.049 (0.019, 0.079)**	**1.61E-03**	**5.64E-03**

[a] Linear regressions were used to estimate β (95% CI) of naturally log-transformed UACR (measured at the first follow-up F4) with per 1 standard deviation increase in the 21 biomarkers significantly associated with kidney function decline and incident CKD (Figure 3), adjusted for age, sex, body mass index, physical activity, smoking status, alcohol consumption, systolic blood pressure, use of antihypertensive medication, triglycerides (naturally log-transformed), high-density lipoprotein cholesterol, use of lipid-lowering medication, prevalent diabetes, prevalent cardiovascular diseases, fasting status, and eGFRcr at baseline S4. The biomarkers are sorted by FDR in the eGFRcr results. **In bold are 17 biomarkers significantly associated with UACR (FDR <0.05)**.

Abbreviations: CI, confidence interval; eGFRcr, creatinine-based estimated glomerular filtration rate; FDR, Benjamini–Hochberg false-discovery rate; UACR, urine albumin-creatinine ratio. Full names of the biomarkers can be found in Additional file 1: Table S1.

Table S14. Summary of druggable targets and their corresponding disease of the 21 identified proteins [a]

Biomarker	UniProt_ID	Drug information					Disease information		Clinical trials
		Drug ID	**Drug Name**	**Type**	**Mechanism of Action**	**Action Type**	**Disease ID**	**Disease Name**	**Status [b]**
ADM	P35318	CHEMBL4650434	ENIBARCIMAB	Antibody	ADM stabiliser	Stabiliser	EFO_0006834	septic shock	Completed
ADM	P35318	CHEMBL4650434	ENIBARCIMAB	Antibody	ADM stabiliser	Stabiliser	EFO_0003144	heart failure	Recruiting
ADM	P35318	CHEMBL4650434	ENIBARCIMAB	Antibody	ADM stabiliser	Stabiliser	MONDO_0100096	COVID-19	Not yet recruiting
EPHB4	P54760	CHEMBL24828	VANDETANIB	Small molecule	Ephrin receptor inhibitor	Inhibitor	MONDO_0002108	thyroid cancer	Active, not recruiting
EPHB4	P54760	CHEMBL24828	VANDETANIB	Small molecule	Ephrin receptor inhibitor	Inhibitor	MONDO_0015277	medullary thyroid gland carcinoma	Active, not recruiting
EPHB4	P54760	CHEMBL24828	VANDETANIB	Small molecule	Ephrin receptor inhibitor	Inhibitor	MONDO_0002108	thyroid cancer	Active, not recruiting
EPHB4	P54760	CHEMBL24828	VANDETANIB	Small molecule	Ephrin receptor inhibitor	Inhibitor	EFO_0003060	non-small cell lung carcinoma	Active, not recruiting
EPHB4	P54760	CHEMBL24828	VANDETANIB	Small molecule	Ephrin receptor inhibitor	Inhibitor	MONDO_0015277	medullary thyroid gland carcinoma	Not yet recruiting
EPHB4	P54760	CHEMBL24828	VANDETANIB	Small molecule	Ephrin receptor inhibitor	Inhibitor	EFO_0003060	non-small cell lung carcinoma	Completed
EPHB4	P54760	CHEMBL24828	VANDETANIB	Small molecule	Ephrin receptor inhibitor	Inhibitor	MONDO_0015277	medullary thyroid gland carcinoma	Recruiting
EPHB4	P54760	CHEMBL24828	VANDETANIB	Small molecule	Ephrin receptor inhibitor	Inhibitor	EFO_0001378	multiple myeloma	Completed
EPHB4	P54760	CHEMBL24828	VANDETANIB	Small molecule	Ephrin receptor inhibitor	Inhibitor	MONDO_0002367	kidney cancer	Completed
EPHB4	P54760	CHEMBL24828	VANDETANIB	Small molecule	Ephrin receptor inhibitor	Inhibitor	MONDO_0007254	breast cancer	Completed
EPHB4	P54760	CHEMBL24828	VANDETANIB	Small molecule	Ephrin receptor inhibitor	Inhibitor	EFO_0003841	thyroid neoplasm	Active, not recruiting
EPHB4	P54760	CHEMBL24828	VANDETANIB	Small molecule	Ephrin receptor inhibitor	Inhibitor	EFO_1001951	colorectal carcinoma	Completed
EPHB4	P54760	CHEMBL24828	VANDETANIB	Small molecule	Ephrin receptor inhibitor	Inhibitor	EFO_0003060	non-small cell lung carcinoma	Completed
EPHB4	P54760	CHEMBL24828	VANDETANIB	Small molecule	Ephrin receptor inhibitor	Inhibitor	MONDO_0004192	urethra cancer	Completed
EPHB4	P54760	CHEMBL24828	VANDETANIB	Small molecule	Ephrin receptor inhibitor	Inhibitor	EFO_0003060	non-small cell lung carcinoma	Active, not recruiting
EPHB4	P54760	CHEMBL24828	VANDETANIB	Small molecule	Ephrin receptor inhibitor	Inhibitor	MONDO_0002108	thyroid cancer	Completed
EPHB4	P54760	CHEMBL24828	VANDETANIB	Small molecule	Ephrin receptor inhibitor	Inhibitor	EFO_0000182	hepatocellular carcinoma	Completed
EPHB4	P54760	CHEMBL24828	VANDETANIB	Small molecule	Ephrin receptor inhibitor	Inhibitor	EFO_0000630	oligoastrocytoma	Completed
EPHB4	P54760	CHEMBL24828	VANDETANIB	Small molecule	Ephrin receptor inhibitor	Inhibitor	EFO_1001465	gliosarcoma	Completed
EPHB4	P54760	CHEMBL24828	VANDETANIB	Small molecule	Ephrin receptor inhibitor	Inhibitor	EFO_0007535	verrucous carcinoma	Completed
EPHB4	P54760	CHEMBL24828	VANDETANIB	Small molecule	Ephrin receptor inhibitor	Inhibitor	MONDO_0004992	cancer	Completed

Only part of rows in Table S14 are presented in the thesis, due to its extensive length. Full content of Table S14 is available on:
https://bmcmedicine.biomedcentral.com/articles/10.1186/s12916-023-02962-z#Sec21

[a] To annotate druggable targets of the 21 proteins significantly associated with kidney function decline and incident chronic kidney disease (Figure 3), related information was gathered from Open Targets Platform (https://platform.opentargets.org/) based on their UniProt_IDs on February 17, 2023.

[b] **/:** No information on known drug are available; **Active**, not recruiting: The study is ongoing, and participants are receiving an intervention or being examined, but potential participants are not currently being recruited or enrolled; **Completed**: The study has ended normally, and participants are no longer being examined or treated (that is, the last participant's last visit has occurred); **Enrolling by invitation**: The study is selecting its participants from a population, or group of people, decided on by the researchers in advance. These studies are not open to everyone who meets the eligibility criteria but only to people in that particular population, who are specifically invited to participate; **Not yet recruiting**: The study has not started recruiting participants; **Recruiting**: The study is currently recruiting participants. (https://beta.clinicaltrials.gov/glossary)

Table S15. Proteomic biomarkers [a] associated with kidney function and/or chronic kidney disease in previous cross-sectional or longitudinal proteomic studies [b]

Full name	**Biomarker**	**UniProt_ID**	**Panel**	**PMID**
Adrenomedullin	ADM	P35318	CVD II	35544531, 34872085, 32638487, 34759008
Macrophage inflammatory protein-1alpha	CCL3	P10147	Inflammation	34612501, 30802263, 28784837, 32879938
Monocyte chemotactic protein 3	CCL7	P80098	Inflammation	34612501, 32879938
Ephrin type-B receptor 4	EPHB4	P54760	CVD III	34465608
Insulin-like growth factor-binding 2	IGFBP-2	P18065	CVD III	35544531, 21165148
Interleukin-15 receptor subunit alpha	IL-15RA	Q13261	Inflammation	34612501, 31011203, 32879938, 21165148, 34465608, 34759008
Interleukin-18-binding	IL-18BP	O95998	CVD III	21165148
Interleukin-2 receptor subunit alpha	IL2-RA	P01589	CVD III	30802263
Kidney Injury Molecule	KIM1	Q96D42	CVD II	34465608, 30802263, 34872085, 34759008
N-terminal prohormone brain natriuretic peptide	NT-proBNP	P16860	CVD III	35544531, 34872085
Osteopontin	OPN	P10451	CVD III	34465608
Programmed cell death 1 ligand 1	PD-L1	Q9NZQ7	Inflammation	34612501, 34759008, 32879938
Perlecan	PLC	P98160	CVD III	25578432
Thrombomodulin	TM	P07204	CVD II	30802263, 34759008, 28784837, 34872085
Tumor necrosis factor receptor 1	TNF-R1	P19438	CVD III	30802263, 28784837, 32717193, 21165148, 31011203, 34465608, 32638487, 34135082
Tumor necrosis factor receptor 2	TNF-R2	P20333	CVD III	30802263, 28784837, 31011203, 34465608, 34135082, 32717193, 32638487
Tumor necrosis factor receptor superfamily member 11A	TNFRSF11A	Q9Y6Q6	CVD II	34872085, 34759008, 32717193
Tumor necrosis factor receptor superfamily member 9	TNFRSF9	Q07011	Inflammation	34612501, 32879938, 34759008
TNF-related apoptosis-inducing ligand receptor 2	TRAIL-R2	O14763	CVD II	30802263, 28784837, 32638487, 34759008, 34872085, 32717193
Vascular endothelial growth factor A	VEGF-A	P15692	Inflammation	34759008, 30802263, 34612501
Lymphotactin	XCL1	P47992	CVD II	34872085

[a] The 21 biomarkers significantly associated with kidney function decline and incident CKD (Figure 3).

[b] To identify relevant publications on proteomics and kidney disease, we searched electronic databases including PubMed and Web of Science. Our search strategy consisted of a combination of search terms and keywords related to proteomics and kidney disease. Here are the search terms (“Proteomics” OR “Proteomic” OR “Proteome” OR “Protein biomarker” OR “Protein profiling” OR “Protein signature”) AND (“Kidney function” OR “Kidney dysfunction” OR “glomerular filtration rate” OR “GFR” OR “kidney disease” OR “kidney failure” OR “CKD” OR “Renal function” OR “Renal dysfunction” OR “Renal insufficiency” OR “Renal disease” OR “Renal failure” OR “end stage of kidney disease” OR “ESKD” OR “end stage of renal disease” OR “ESRD” OR “Nephrology” OR “Albuminuria” OR “Proteinuria” OR “Hemodialysis”). We limited the search to title and abstract fields. Additionally, we manually searched the reference lists of the retrieved articles to identify additional studies. Proteins significantly associated with kidney outcomes after multiple testing correction in each study were extracted.

Abbreviations: CKD, chronic kidney disease; CVD II, Cardiovascular II Olink panel; CVD III, Cardiovascular III Olink panel.

Table S16. Evaluation of bias due to participant overlap in two-sample Mendelian randomization analysis [a]

Exposure	No. IVs	***psi* = 0 [b]**						***psi* = 0.1**						***psi* = 0.3**					***psi* = 0.5**			
		MR_Method	**β (95%CI)**	**SE**	**P-value**	**FDR**		**MR_Method**	**β (95%CI)**	**SE**	**P-value**	**FDR**		**β (95%CI)**	**SE**	**P-value**	**FDR**		**β (95%CI)**	**SE**	**P-value**	**FDR**
ADM	1	Wald ratio	0.033 (-0.026, 0.092)	0.030	0.279	0.653		Maximum likelihood	0.033 (-0.026, 0.091)	0.030	0.277	0.693		0.033 (-0.026, 0.091)	0.030	0.272	0.691		0.033 (-0.025, 0.090)	0.029	0.268	0.688
CCL7	1	Wald ratio	-0.022 (-0.105, 0.061)	0.042	0.610	0.831		Maximum likelihood	-0.022 (-0.105, 0.062)	0.043	0.611	0.846		-0.022 (-0.106, 0.062)	0.043	0.613	0.846		-0.022 (-0.106, 0.063)	0.043	0.616	0.847
EPHB4	1	Wald ratio	-0.015 (-0.070, 0.041)	0.028	0.609	0.831		Maximum likelihood	-0.015 (-0.070, 0.041)	0.028	0.610	0.846		-0.015 (-0.071, 0.042)	0.029	0.612	0.846		-0.015 (-0.071, 0.042)	0.029	0.613	0.847
IGFBP-2	1	Wald ratio	0.008 (-0.133, 0.150)	0.072	0.908	0.962		Maximum likelihood	0.008 (-0.133, 0.150)	0.072	0.908	0.965		0.008 (-0.133, 0.150)	0.072	0.908	0.965		0.008 (-0.132, 0.149)	0.072	0.908	0.964
IL-15RA	1	Wald ratio	-0.028 (-0.065, 0.010)	0.019	0.147	0.530		Maximum likelihood	-0.028 (-0.065, 0.010)	0.019	0.150	0.636		-0.028 (-0.065, 0.010)	0.019	0.153	0.648		-0.028 (-0.066, 0.011)	0.019	0.157	0.615
IL2-RA	1	Wald ratio	-0.004 (-0.022, 0.013)	0.009	0.646	0.831		Maximum likelihood	-0.004 (-0.022, 0.014)	0.009	0.647	0.846		-0.004 (-0.022, 0.014)	0.009	0.647	0.846		-0.004 (-0.022, 0.014)	0.009	0.647	0.847
OPN	1	Wald ratio	0.065 (-0.035, 0.165)	0.051	0.202	0.606		Maximum likelihood	0.065 (-0.034, 0.165)	0.051	0.200	0.679		0.065 (-0.032, 0.163)	0.050	0.190	0.648		0.065 (-0.030, 0.161)	0.049	0.181	0.615
PD-L1	1	Wald ratio	0.010 (-0.018, 0.038)	0.014	0.488	0.798		Maximum likelihood	0.010 (-0.018, 0.038)	0.014	0.487	0.828		0.010 (-0.018, 0.038)	0.014	0.486	0.825		0.010 (-0.018, 0.038)	0.014	0.484	0.823
PLC	1	Wald ratio	-0.054 (-0.110, 0.002)	0.029	0.058	0.346		Maximum likelihood	-0.054 (-0.111, 0.002)	0.029	0.061	0.455		-0.054 (-0.112, 0.003)	0.029	0.065	0.426		-0.054 (-0.113, 0.004)	0.030	0.070	0.398
TM	1	Wald ratio	-0.008 (-0.062, 0.046)	0.028	0.767	0.878		Maximum likelihood	-0.008 (-0.063, 0.046)	0.028	0.767	0.883		-0.008 (-0.063, 0.046)	0.028	0.768	0.882		-0.008 (-0.063, 0.046)	0.028	0.769	0.881
TNF-R1	1	Wald ratio	0.020 (-0.122, 0.162)	0.072	0.780	0.878		Maximum likelihood	0.020 (-0.121, 0.162)	0.072	0.780	0.883		0.020 (-0.121, 0.161)	0.072	0.778	0.882		0.020 (-0.120, 0.160)	0.071	0.777	0.881
TNF-R2	1	Wald ratio	0.022 (-0.029, 0.073)	0.026	0.394	0.709		Maximum likelihood	0.022 (-0.029, 0.073)	0.026	0.392	0.741		0.022 (-0.028, 0.073)	0.026	0.388	0.733		0.022 (-0.028, 0.072)	0.026	0.384	0.726
TNFRSF11A	1	Wald ratio	0.024 (0.002, 0.046)	0.011	**0.030**	0.272		Maximum likelihood	0.024 (0.002, 0.046)	0.011	**0.030**	0.455		0.024 (0.003, 0.046)	0.011	**0.029**	0.426		0.024 (0.003, 0.046)	0.011	**0.028**	0.398
TNFRSF9	1	Wald ratio	0.048 (-0.006, 0.103)	0.028	0.082	0.368		Maximum likelihood	0.048 (-0.006, 0.102)	0.028	0.080	0.455		0.048 (-0.005, 0.101)	0.027	0.075	0.426		0.048 (-0.004, 0.101)	0.027	0.070	0.398
TRAIL-R2	1	Wald ratio	-0.001 (-0.028, 0.027)	0.014	0.968	0.968		Maximum likelihood	-0.001 (-0.028, 0.027)	0.014	0.968	0.968		-0.001 (-0.028, 0.027)	0.014	0.968	0.968		-0.001 (-0.028, 0.027)	0.014	0.968	0.968
VEGF-A	1	Wald ratio	0.006 (-0.006, 0.019)	0.006	0.317	0.653		Maximum likelihood	0.006 (-0.006, 0.019)	0.006	0.317	0.693		0.006 (-0.006, 0.019)	0.006	0.316	0.691		0.006 (-0.006, 0.019)	0.006	0.315	0.688
XCL1	1	Wald ratio	0.006 (-0.006, 0.019)	0.006	0.327	0.653		Maximum likelihood	0.006 (-0.006, 0.019)	0.006	0.326	0.693		0.006 (-0.006, 0.019)	0.006	0.325	0.691		0.006 (-0.006, 0.019)	0.006	0.324	0.688

[a] The function “MendelianRandomization::mr_maxlik” was used toevaluate bias due to the participant overlap in two-sample Mendelian randomization analysis. The parameter psi is set to zero when there is no participant overlap, and arises if the samples for the associations with the exposure and the outcome overlap. Several values for *psi* (0.1, 0.3, and 0.5) were set to evaluate the bias due to participant overlap.

[b] MR results in Table 3.

Abbreviations: CI, confidence interval; eGFR, glomerular filtration rate; IVs, instrumental variables; FDR, Benjamini–Hochberg false-discovery rate; MR, Mendelian randomization; psi: Indicator of the correlation between the association with the exposure and the association with the outcome for each variant resulting from sample overlap; SE, standard error; SNP, single nucleotide polymorphism. Full names of the biomarkers can be found in Additional file 1: Table S1.

Table S17. STROBE Statement—checklist of items in reports of observational studies

	Item No.	Recommendation	Page No.
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5-6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-6
Participants	6	(*a*) *Cohort study* —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5-6
		Case-control study —Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	
		Cross-sectional study —Give the eligibility criteria, and the sources and methods of selection of participants	
		(*b*) *Cohort study* —For matched studies, give matching criteria and number of exposed and unexposed	5-6
		Case-control study —For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-8
Bias	9	Describe any efforts to address potential sources of bias	
Study size	10	Explain how the study size was arrived at	5-6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	19-20
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8-11
		(*b*) Describe any methods used to examine subgroups and interactions	NA
		(*c*) Explain how missing data were addressed	7 & Additional file 2: Text S1
		(*d*) *Cohort study* —If applicable, explain how loss to follow-up was addressed	9 & Additional file 2: Text S2
		Case-control study —If applicable, explain how matching of cases and controls was addressed	
		Cross-sectional study —If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	9
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Figure 1
		(b) Give reasons for non-participation at each stage	Figure 1
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	11-12
		(b) Indicate number of participants with missing data for each variable of interest	NA
		(c) *Cohort study* —Summarise follow-up time (eg, average and total amount)	5-6
Outcome data	15*	*Cohort study* —Report numbers of outcome events or summary measures over time	13
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	12-15
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	13-14
Discussion			
Key results	18	Summarise key results with reference to study objectives	15
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	19-20
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	15-20
Generalisability	21	Discuss the generalisability (external validity) of the study results	20
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	22

Table S18. STROBE-MR checklist of recommended items in reports of Mendelian randomization studies

Item No.	Section	Checklist item	Page No.
1	**TITLE and ABSTRACT**	Indicate Mendelian randomization (MR) as the study's design in the title and/or the abstract if that is a main purpose of the study	3
	INTRODUCTION		
2	**Background**	Explain the scientific background and rationale for the reported study. What is the exposure? Is a potential causal relationship between exposure and outcome plausible? Justify why MR is a helpful method to address the study question	4-5
3	**Objectives**	State specific objectives clearly, including pre-specified causal hypotheses (if any). State that MR is a method that, under specific assumptions, intends to estimate causal effects	5
	METHODS		
4	**Study design and data sources**	Present key elements of the study design early in the article. Consider including a table listing sources of data for all phases of the study. For each data source contributing to the analysis, describe the following:	
	a)	Setting: Describe the study design and the underlying population, if possible. Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection, when available.	5-6
	b)	Participants: Give the eligibility criteria, and the sources and methods of selection of participants. Report the sample size, and whether any power or sample size calculations were carried out prior to the main analysis	5-6
	c)	Describe measurement, quality control and selection of genetic variants	11 & Additional file 2: Text S3
	d)	For each exposure, outcome, and other relevant variables, describe methods of assessment and diagnostic criteria for diseases	6-8
	e)	Provide details of ethics committee approval and participant informed consent, if relevant	6
5	**Assumptions**	Explicitly state the three core IV assumptions for the main analysis (relevance, independence and exclusion restriction) as well assumptions for any additional or sensitivity analysis	11, 19 & Additional file 2: Text S3
6	**Statistical methods: main analysis**	Describe statistical methods and statistics used	
	a)	Describe how quantitative variables were handled in the analyses (i.e., scale, units, model)	NA
	b)	Describe how genetic variants were handled in the analyses and, if applicable, how their weights were selected	11 & Additional file 2: Text S3
	c)	Describe the MR estimator (e.g. two-stage least squares, Wald ratio) and related statistics. Detail the included covariates and, in case of two-sample MR, whether the same covariate set was used for adjustment in the two samples	11 & Additional file 2: Text S3
	d)	Explain how missing data were addressed	NA
	e)	If applicable, indicate how multiple testing was addressed	14
7	**Assessment of assumptions**	Describe any methods or prior knowledge used to assess the assumptions or justify their validity	11
8	**Sensitivity analyses and additional analyses**	Describe any sensitivity analyses or additional analyses performed (e.g. comparison of effect estimates from different approaches, independent replication, bias analytic techniques, validation of instruments, simulations)	NA
9	**Software and pre-registration**		
	a)	Name statistical software and package(s), including version and settings used	11
	b)	State whether the study protocol and details were pre-registered (as well as when and where)	NA
	RESULTS		
10	**Descriptive data**		
	a)	Report the numbers of individuals at each stage of included studies and reasons for exclusion. Consider use of a flow diagram	Figure 1
	b)	Report summary statistics for phenotypic exposure(s), outcome(s), and other relevant variables (e.g. means, SDs, proportions)	12
	c)	If the data sources include meta-analyses of previous studies, provide the assessments of heterogeneity across these studies	NA
	d)	For two-sample MR: i. Provide justification of the similarity of the genetic variant-exposure associations between the exposure and outcome samples ii. Provide information on the number of individuals who overlap between the exposure and outcome studies	19 & Additional file 2: Text S3
11	**Main results**		
	a)	Report the associations between genetic variant and exposure, and between genetic variant and outcome, preferably on an interpretable scale	14
	d)	Consider plots to visualize results (e.g. forest plot, scatterplot of associations between genetic variants and outcome versus between genetic variants and exposure)	NA
	b)	Report any additional statistics (e.g., assessments of heterogeneity across genetic variants, such as I^2, Q statistic or E-value)	NA
13	**Sensitivity analyses and additional analyses**		
	a)	Report any sensitivity analyses to assess the robustness of the main results to violations of the assumptions	NA
	b)	Report results from other sensitivity analyses or additional analyses	NA
	c)	Report any assessment of direction of causal relationship (e.g., bidirectional MR)	NA

Table S18. STROBE-MR checklist of recommended items in reports of Mendelian randomization studies

Item No.	Section	Checklist item	Page No.
	d)	When relevant, report and compare with estimates from non-MR analyses	NA
	e)	Consider additional plots to visualize results (e.g., leave-one-out analyses)	NA
	DISCUSSION		
14	**Key results**	Summarize key results with reference to study objectives	14
15	**Limitations**	Discuss limitations of the study, taking into account the validity of the IV assumptions, other sources of potential bias, and imprecision. Discuss both direction and magnitude of any potential bias and any efforts to address them	19
16	**Interpretation**		
	a)	Meaning: Give a cautious overall interpretation of results in the context of their limitations and in comparison with other studies	20
	b)	Mechanism: Discuss underlying biological mechanisms that could drive a potential causal relationship between the investigated exposure and the outcome, and whether the gene-environment equivalence assumption is reasonable. Use causal language carefully, clarifying that IV estimates may provide causal effects only under certain assumptions	19
	c)	Clinical relevance: Discuss whether the results have clinical or public policy relevance, and to what extent they inform effect sizes of possible interventions	NA
17	**Generalizability**	Discuss the generalizability of the study results (a) to other populations, (b) across other exposure periods/timings, and (c) across other levels of exposure	19
	OTHER INFORMATION		
18	**Funding**	Describe sources of funding and the role of funders in the present study and, if applicable, sources of funding for the databases and original study or studies on which the present study is based	22
19	**Data and data sharing**	Provide the data used to perform all analyses or report where and how the data can be accessed, and reference these sources in the article. Provide the statistical code needed to reproduce the results in the article, or report whether the code is publicly accessible and if so, where	22
20	**Conflicts of Interest**	All authors should declare all potential conflicts of interest	22

Additional file 2: Supplementary Text and Figure

Proteomic profiling of longitudinal changes in kidney function among middle-aged and older men and women: the KORA S4/F4/FF4 Study

Jie-sheng Lin, Jana Nano, Agnese Petrera, Stefanie M. Hauck, Tanja Zeller, Wolfgang Koenig, Christian L. Müller, Annette Peters, Barbara Thorand

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Text S1. Assessment of kidney outcomes

Cystatin C was measured using the ARCHITECT MULTIGENT Cystatin C assay (Abbott, Wiesbaden, Germany) using immunoturbidimetry at S4 (baseline) and N Latex Cystatin C assay (Siemens Healthcare Diagnostics Products GmbH) using particle-enhanced immunonephelometry at F4/FF4 (first and second follow-up). Cystatin C at F4 was measured during July-October 2008, so the values were calibrated to the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) standard by multiplying by a factor of 1.174 as suggested by Siemens. S4 and FF4 values were measured in 2015 and 2017, respectively, and corresponded to the IFCC standard. Cystatin C-based estimated glomerular filtration rate (eGFRcys) was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation 2012 [23].

In comparison to creatinine-based estimated glomerular filtration rate (eGFRcr), there were 278, 5, and 17 missing values on eGFRcys at S4, F4, and FF4, respectively. Regression imputation was used to impute the missing values of eGFRcys. A linear mixed-effects model with random intercepts for each participant was constructed as eGFRcys (dependent variable) against eGFRcr (independent variable), and included age at the time of eGFR measurement, sex, and follow-up wave as covariates, using R package “lme4”. The predicted values were used to replace the missing values on eGFRcys.

Additionally, at KORA F4, urinary albumin and urinary creatinine were determined from frozen urine (sampled by a random spot urine specimen) with a modified kinetic rate Jaffe method (CREATININ-JK, Greiner, Bahlingen, Germany) on a Cobas Mira analyzer (Roche Diagnostics, Mannheim, Germany) and by nephelometry on a BN II analyzer (Siemens, Erlangen, Germany). Urinary albumin to creatinine ratio was calculated as urinary albumin/urinary creatinine (mg/g).

Text S2. Inverse probability weighting

To partially address bias caused by loss to follow-up (due to death or other reasons, e.g., refusal or inability to contact, Figure 1B), the inverse probability weighting method [27] was used to examine the impact of loss to follow-up in the present study. Each participant's probability of loss to follow-up (P1) was estimated by logistic regression model with loss to follow-up (yes/no) as outcomes, including baseline age, sex, body mass index, physical activity, smoking status, alcohol consumption, systolic blood pressure, use of antihypertensive medication, triglycerides (naturally log-transformed), high-density lipoprotein cholesterol, use of lipid-lowering medication, prevalent diabetes, prevalent cardiovascular diseases, fasting status, and creatinine-based estimated glomerular filtration rate (eGFRcr) as predictors. Inverse probability weighting-weight was calculated as 1/(1-P1). Then the weight was applied in sensitivity analyses of associations between the 66 significant biomarkers and the annual rate of change in eGFRcr in linear regression models.

Text S3. Mendelian randomization analysis

Capitalizing on the fact that genotypes are assigned randomly when passed from parents to offspring, Mendelian randomization (MR) represents an effective approach to reducing the risk of reverse causation by employing single nucleotide polymorphisms (SNPs) as instrumental variables (IV) to assess unconfounded exposure-outcome associations. To maximize statistical power, we applied a two-sample MR design using the largest genome-wide association studies (GWAS) results to date for selecting instruments for our significant biomarkers and kidney function decline. Additional file 2: Figure S3 shows the process of MR analysis. Publicly available protein quantitative trait loci (pQTL) data for 1463 Olink Explore 1536-based proteins (also based on the Olink's proximity extension assay technology) in 35571 European-ancestry population from UK Biobank Pharma Proteomics Project [31] was used to identify SNPs associated with eGFR decline-associated proteins. We found pQTLs for all 21 top proteins. Selection of pQTL was based on cis-SNPs with a multiple-testing-corrected significance at the level $p < 3.4E-11$ (associations with a genome-wide significance, i.e., $p < 5.0E-8$, are unavailable). In the next step, linkage disequilibrium clumping with $r^2 < 0.001$ within 10000kb region was conducted to identify independent SNPs. Since only 1 SNP was available for each protein, none of the SNPs was excluded in this step. SNPs-eGFR decline associations were extracted from a Meta-analysis, including 62 European-ancestry GWAS in 343339 individuals, which aimed to identify genetic loci for eGFR decline, which was defined as "(eGFR at follow-up – eGFR at baseline)/ number of years of follow-up" [32]. Eighteen out of 21 proteins had SNPs-eGFR decline data available. Furthermore, we conducted data harmonization to make sure that the effects of SNPs on proteins and eGFR decline were corresponding to the same allele. In order to test the assumption of MR that IVs should not be associated with confounders, associations between selected SNPs and other traits were searched for in the PhenoScanner V2 [33]. One SNP (rs198389) was excluded given its associations with blood pressure (Additional file 1: Table S2), leaving 17 proteins for MR analysis (Additional file 1: Table S3). Wald ratio was calculated since only one SNP instrument was available for each protein. All the MR analyses were performed using R package “TwoSampleMR v.0.5.6” [34].

There may be participant overlap between the two GWAS studies, since the GWAS of proteins was conducted among 35571 participants from UK Biobank and the GWAS of eGFR decline was conducted among 343339 European-ancestry individuals, including 15442 participants from UK Biobank. Thus, there may be bias due to the participant overlap [35]. A maximum likelihood method was used to address this problem, using R package “MendelianRandomization v.0.6.0”. The function “MendelianRandomization::mr_maxlik” allows setting a correlation parameter *psi*, which indicates the correlation between the association with the exposure and the association with the outcome for each variant resulting from sample overlap [36], to adjust for bias due to the participant overlap in two-sample MR analysis. The parameter *psi* is set to zero when there is no participant overlap, and arises if the samples for the associations with the exposure and the outcome overlap. Because we were unable to estimate the exact correction parameter *psi* among overlapping samples, several values for *psi* (0.1, 0.3, and 0.5) were set to evaluate the bias due to participant overlap.

The STROBE (Strengthening the Reporting of Observational Studies in Epidemiology)-MR checklist of recommended items to address in reports of MR studies [37] is presented in Additional file 1: Table S18.

Figure S1. Example of the annual rate of change in eGFR for each participant

Abbreviations: eGFR, estimated glomerular filtration.

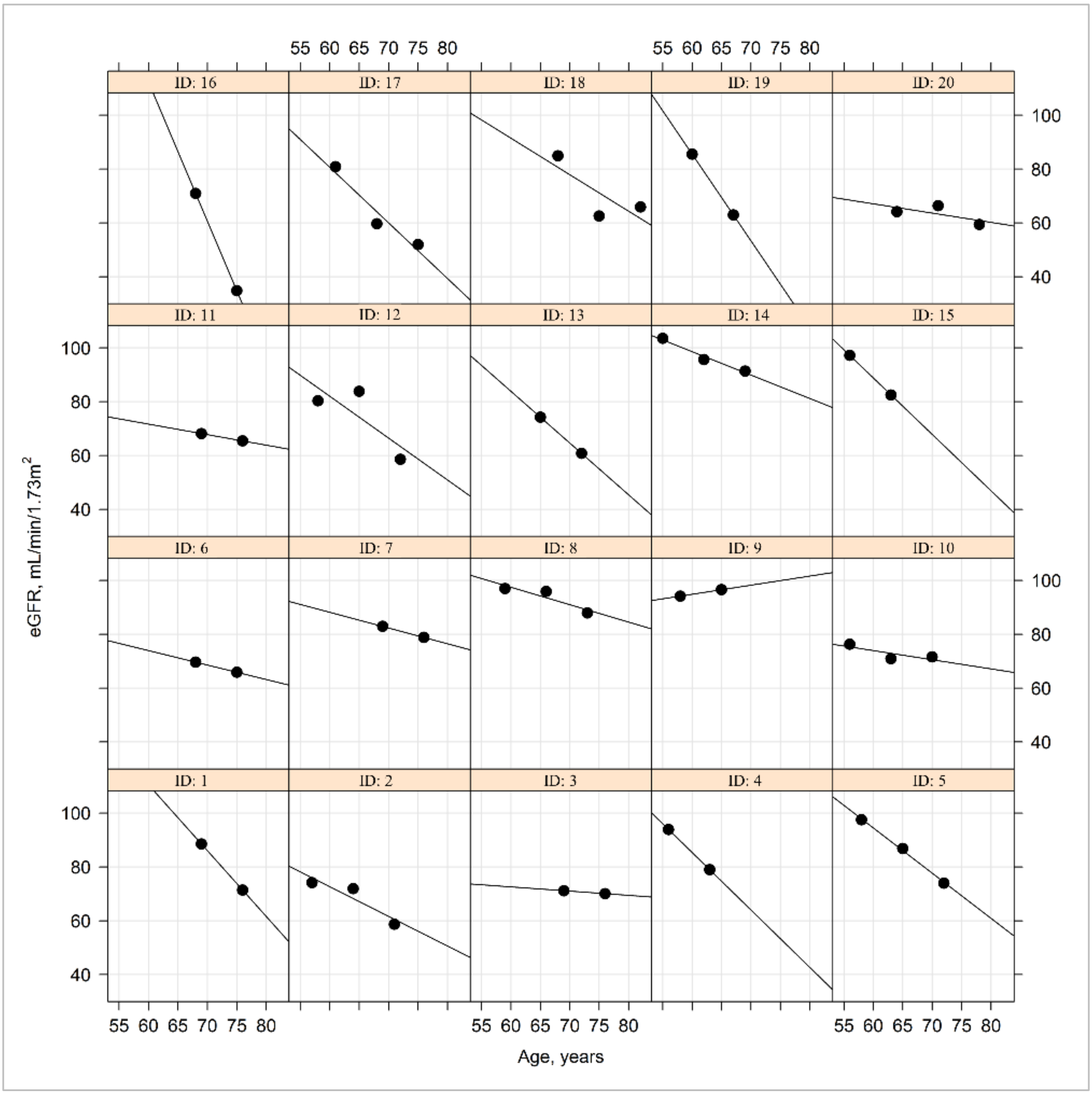


Figure S2. Flowchart of statistical analyses

Abbreviations: CKD, chronic kidney disease based on eGFRcr; eGFRcr, creatinine-based estimated glomerular filtration rate; eGFRcys, cystatin C-based estimated glomerular filtration rate; FDR, Benjamini–Hochberg false-discovery rate.

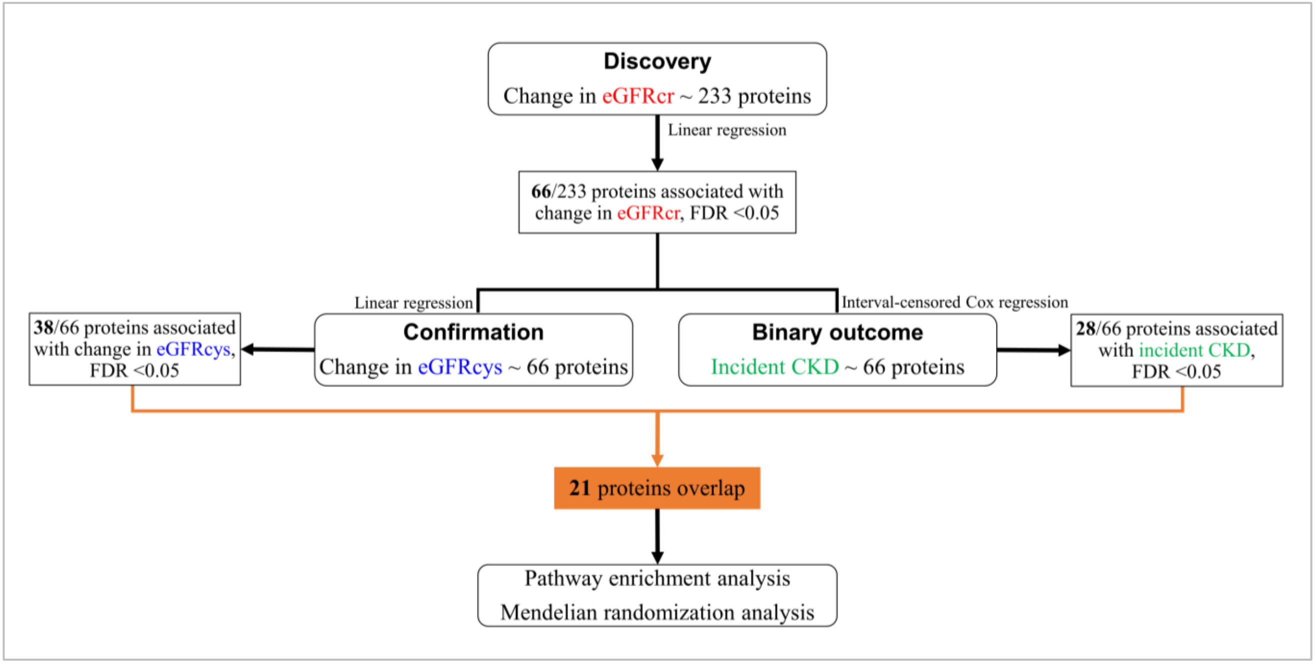


Figure S3. Genetic instrument selection and data harmonization for Mendelian randomization analysis

Abbreviations: eGFR, glomerular filtration rate; LD, linkage disequilibrium; MR, Mendelian randomization; SNP, single nucleotide polymorphism.

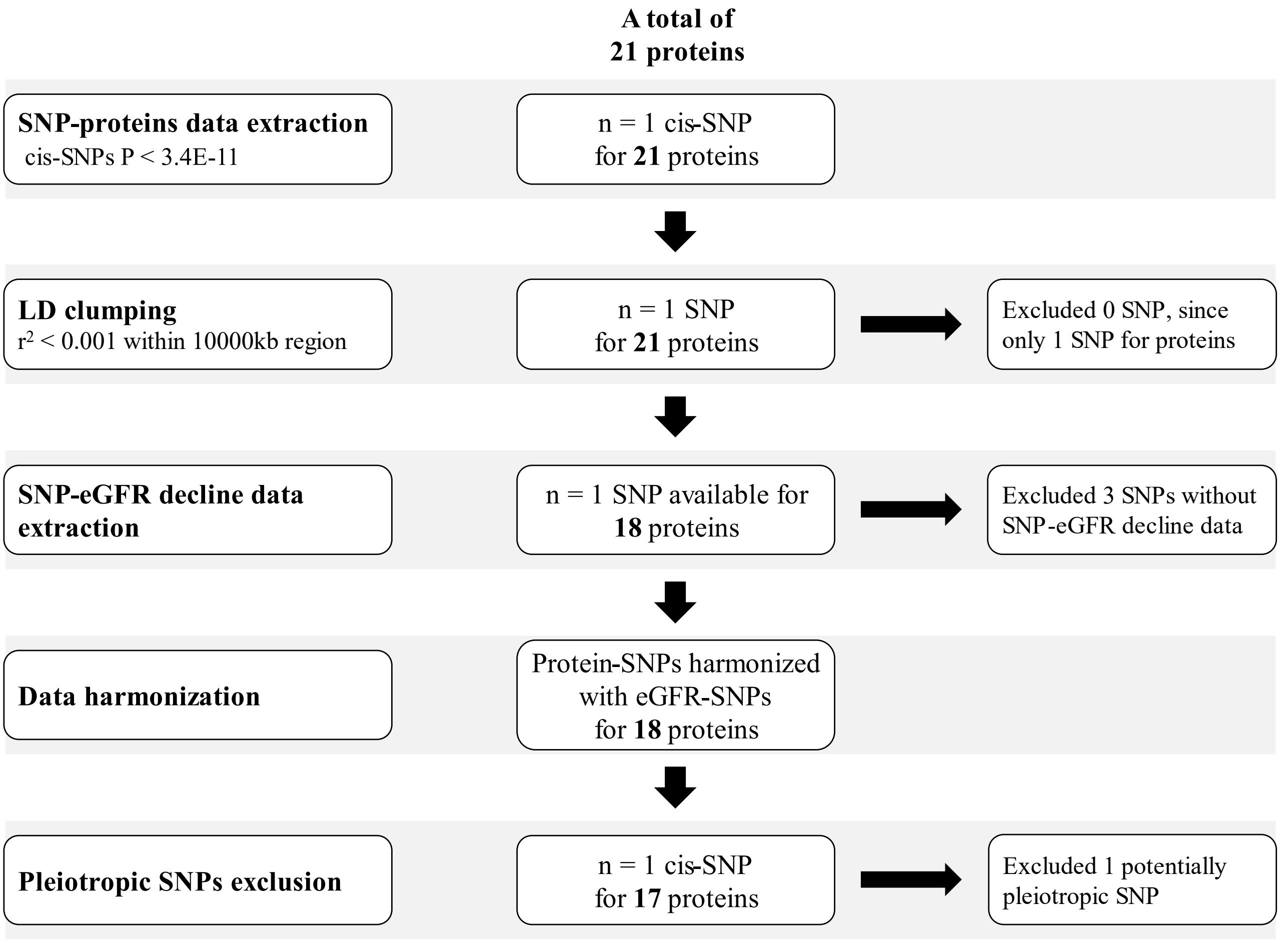


Figure S4. Distribution and correlation between the annual rate of change in eGFRcr and eGFRcys. A) Distribution of the annual rate of change in eGFRcr. **B)** Distribution of the annual rate of change in eGFRcys. **C)** Correlation between the annual rate of change in eGFRcr and eGFRcys. **D)** Correlation between the annual rate of change in eGFRcr and eGFRcr 2021.

Abbreviations: eGFRcr, creatinine-based estimated glomerular filtration rate; eGFRcr 2021, eGFRcr calculated by the Chronic Kidney Disease Epidemiology Collaboration equation 2021; eGFRcys, cystatin C-based estimated glomerular filtration rate; No.Measurement, the number of measurements on eGFR at baseline and follow-up.

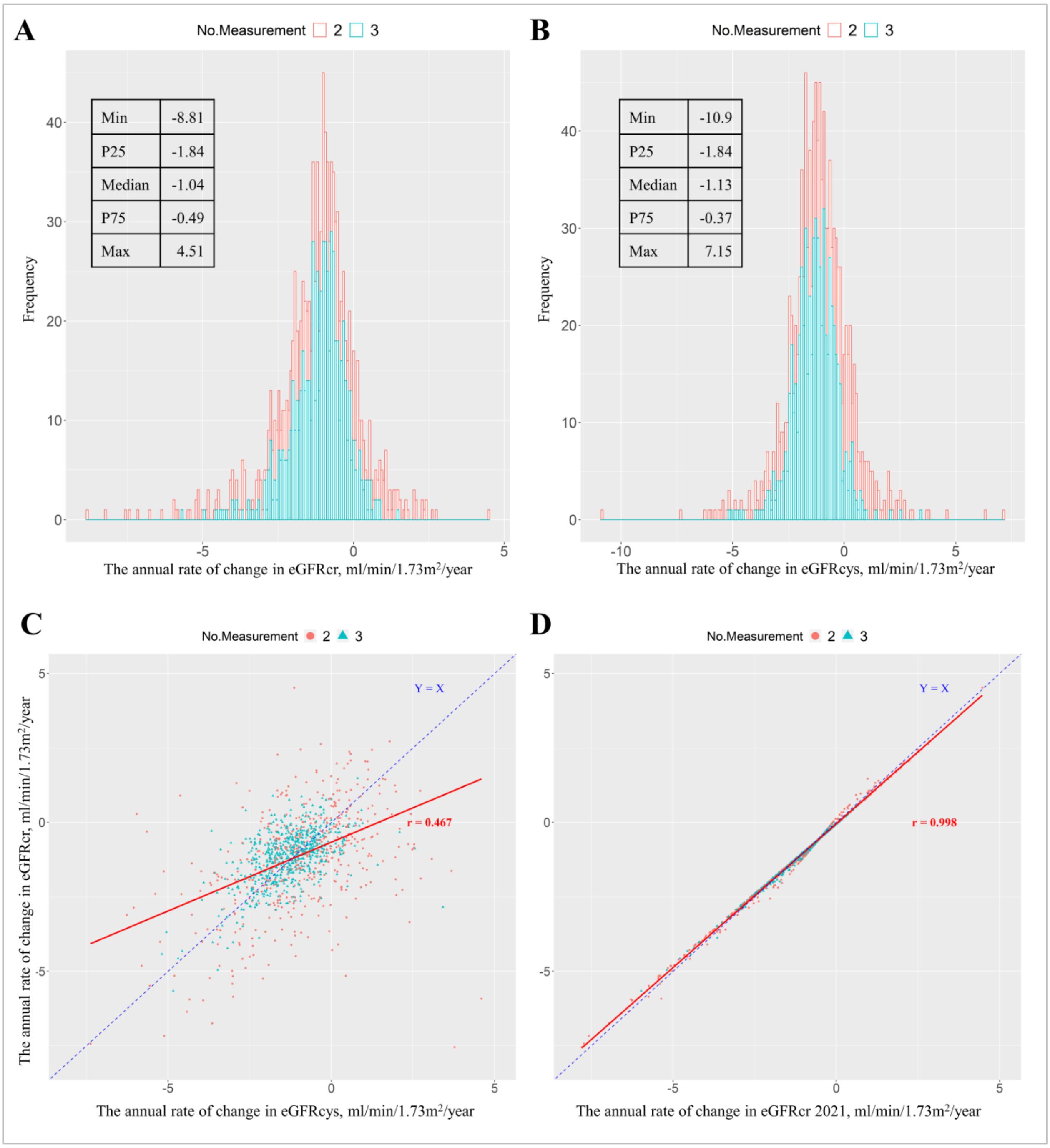


Figure S5. Overlap of proteomic biomarkers between biomarkers associated with the annual rate of change in eGFRcr in several sensitivity analyses. Several sensitivity analyses were performed based on model 2 in Additional file 1: Table S6, and only the 66 biomarkers significantly associated with the annual rate of change in eGFRcr were included. Detailed information is presented in Additional file 1: Table S8. Model 2a: repeated analyses of model 2 after excluding participants who were non-fasting before at the time of blood sampling (n = 113); Model 2b: repeated analyses of model 2 after excluding participants who had chronic kidney disease at baseline (n = 54); Model 2c: repeated analyses of model 2 after excluding participants who had an increase in eGFRcr during follow-up (n = 151).

Abbreviations: eGFRcr, creatinine-based estimated glomerular filtration rate.

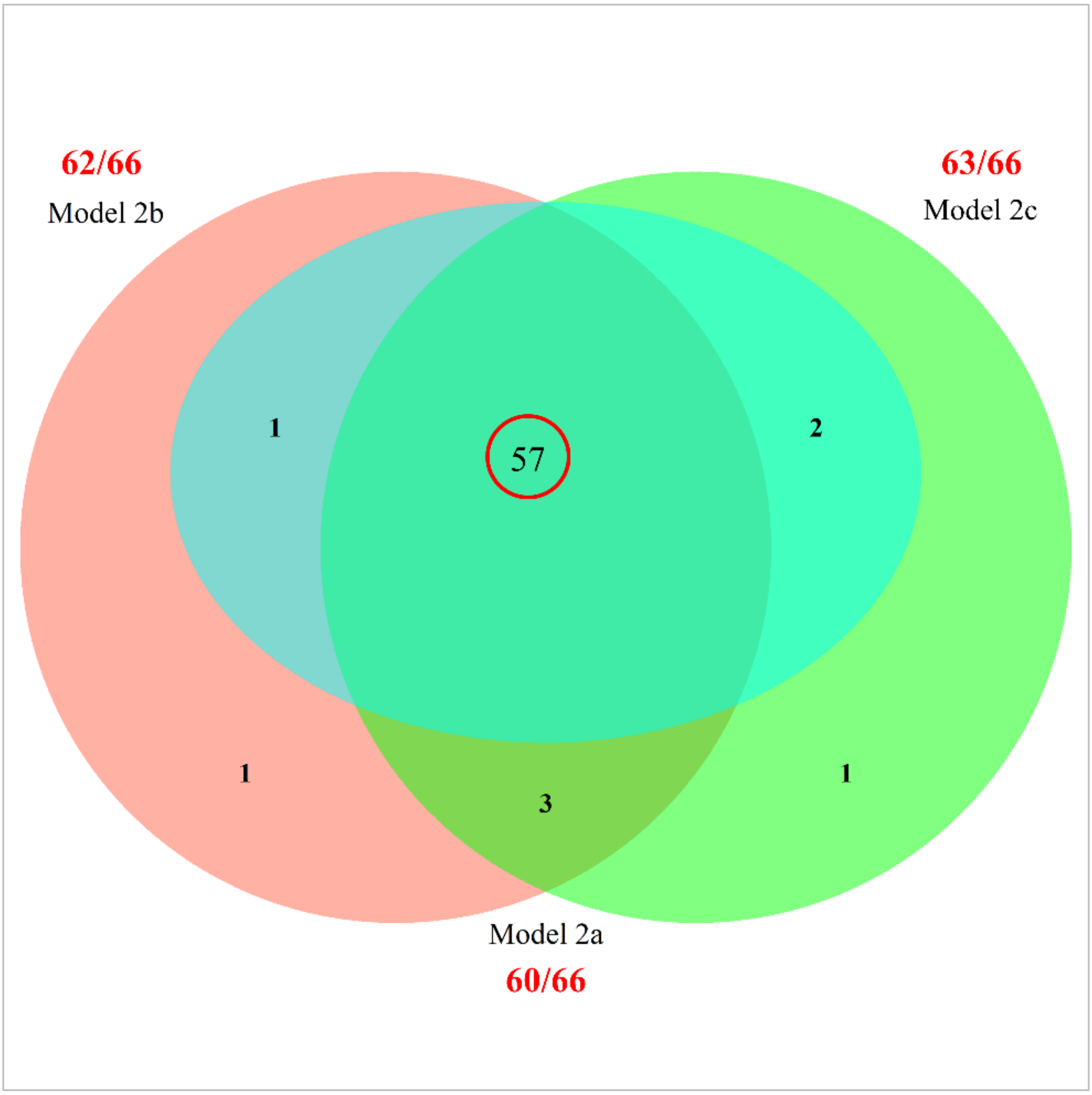


Figure S6. Longitudinal associations between 66 proteomic biomarkers and the annual rate of change in eGFRcys. The 66 biomarkers significantly associated with the annual rate of change in eGFRcr were taken to investigate their associations with the annual rate of change in eGFRcys. Detailed results of beta coefficients and FDR for the associations are presented in Additional file 1: Table S9.

Abbreviations: eGFRcr, creatinine-based estimated glomerular filtration rate; eGFRcys, cystatin C-based estimated glomerular filtration rate; FDR, Benjamini–Hochberg false-discovery rate. Full names of the biomarkers can be found in Additional file 1: Table S1.

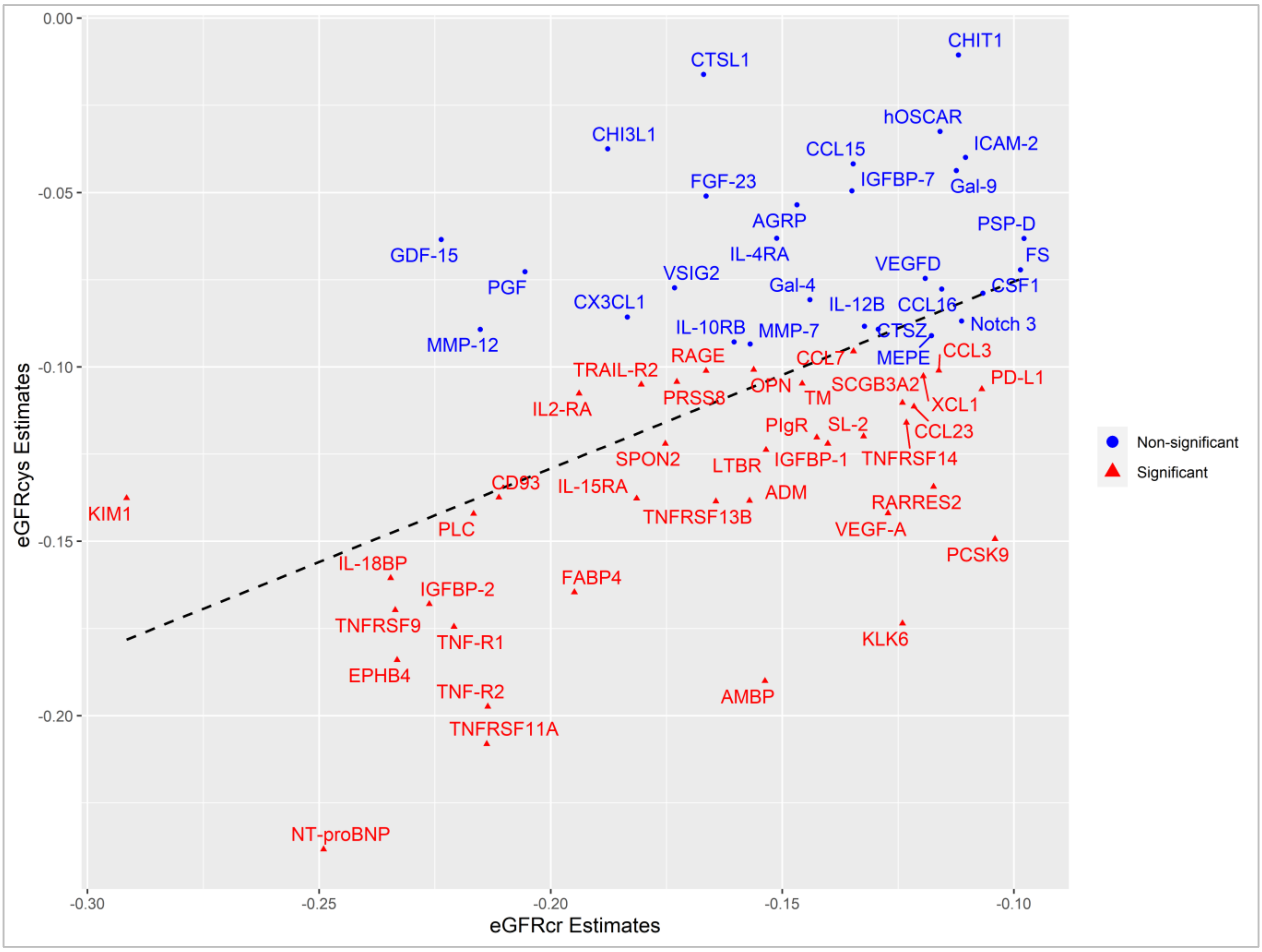


Figure S7. Association of 66 proteomic biomarkers with eGFRcr-based CKD incidence. Only 66 biomarkers significantly associated with the annual rate of change in eGFRcr were used to investigate their associations with incident CKD. The biomarkers are sorted by HRs.

Abbreviations: CI, confidence interval; CKD, chronic kidney disease; eGFRcr, creatinine-based estimated glomerular filtration rate; HR, hazard ratio; FDR, Benjamini–Hochberg false-discovery rate. Full names of the biomarkers can be found in Additional file 1: Table S1

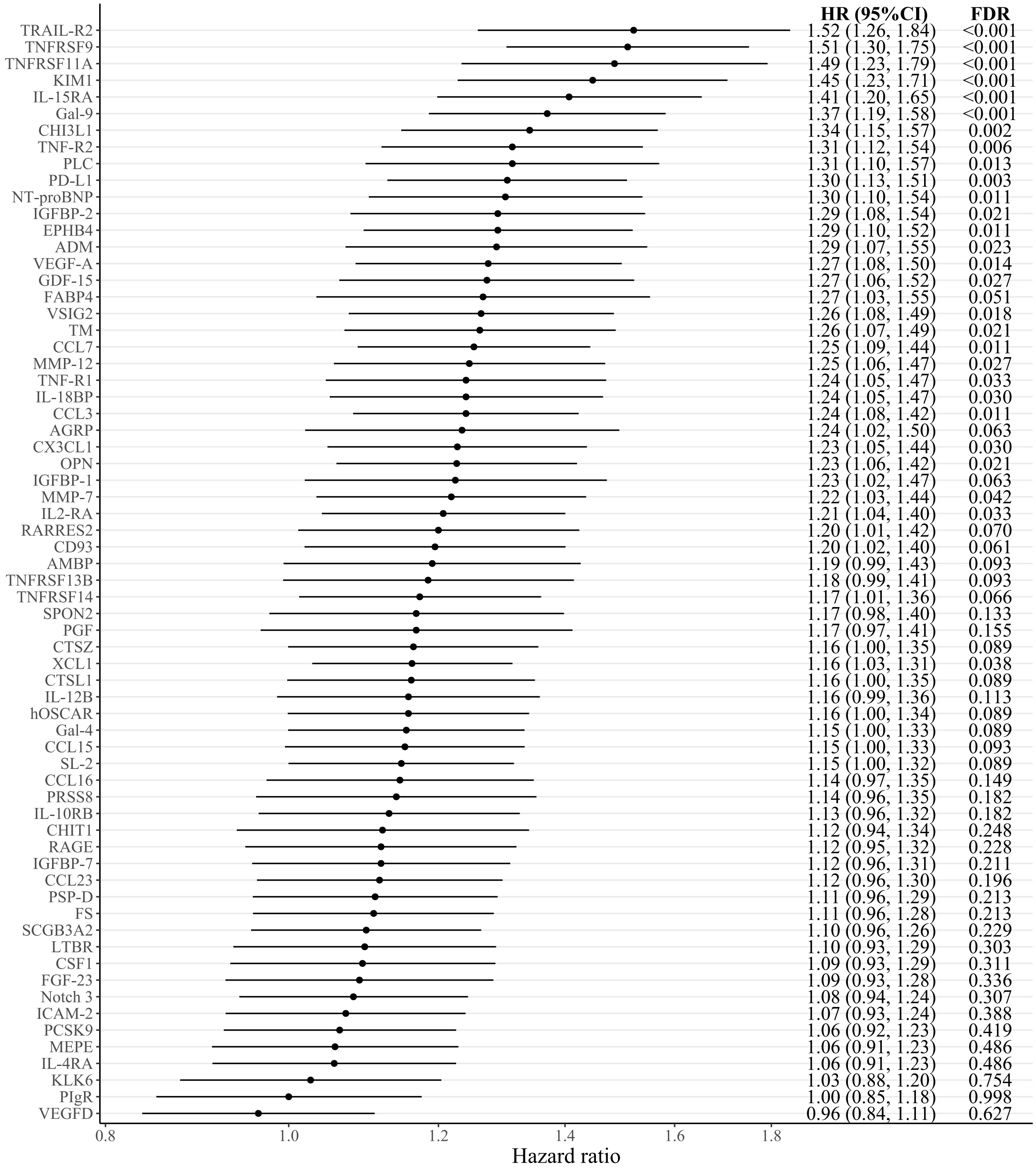
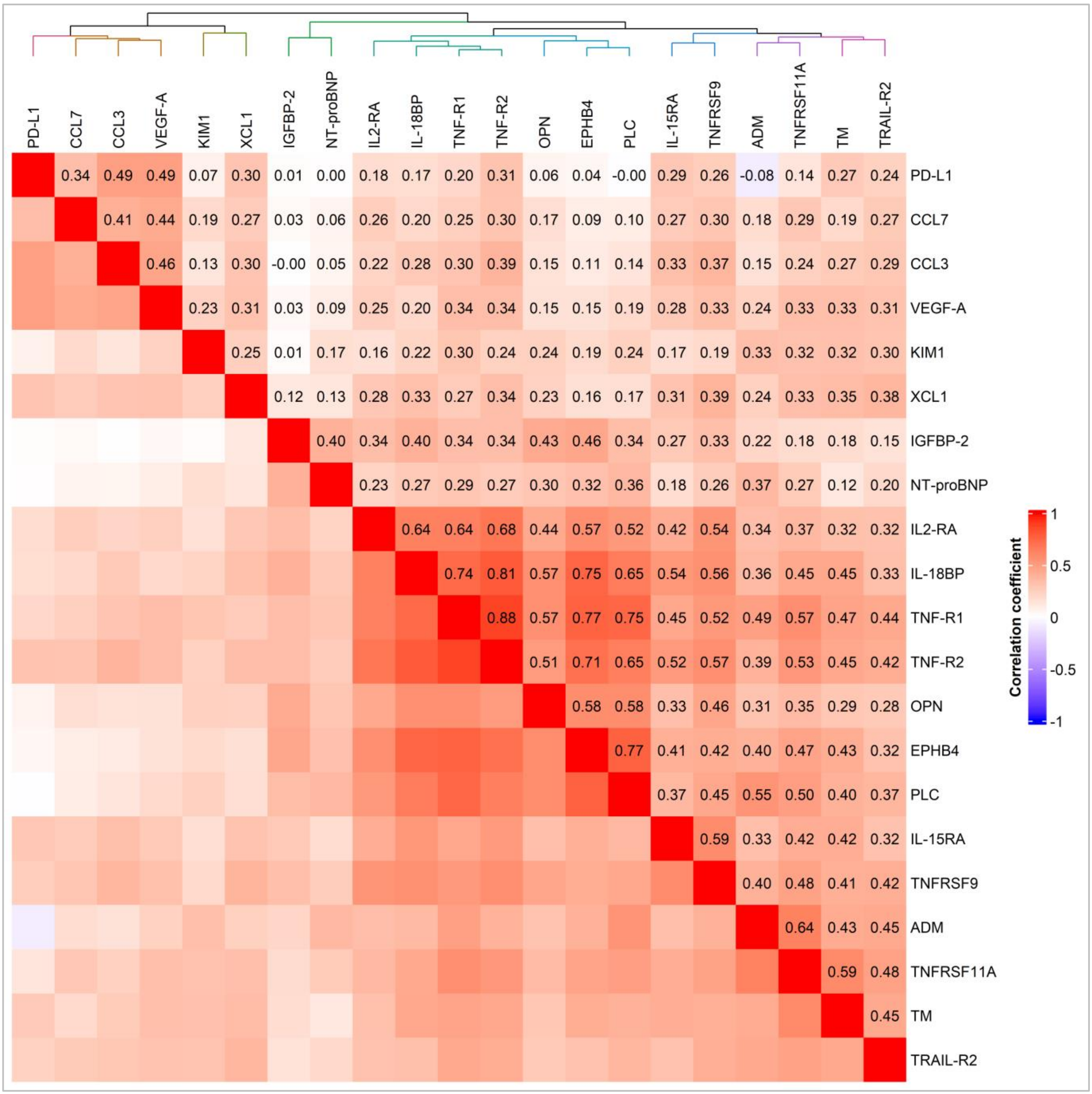


Figure S8. Pairwise correlation matrix between the 21 identified proteomic biomarkers. Correlation between the 21 biomarkers associated with the annual rate of change in eGFRcr, annual rate of change in eGFRcys, and incident CKD (Figure 3).

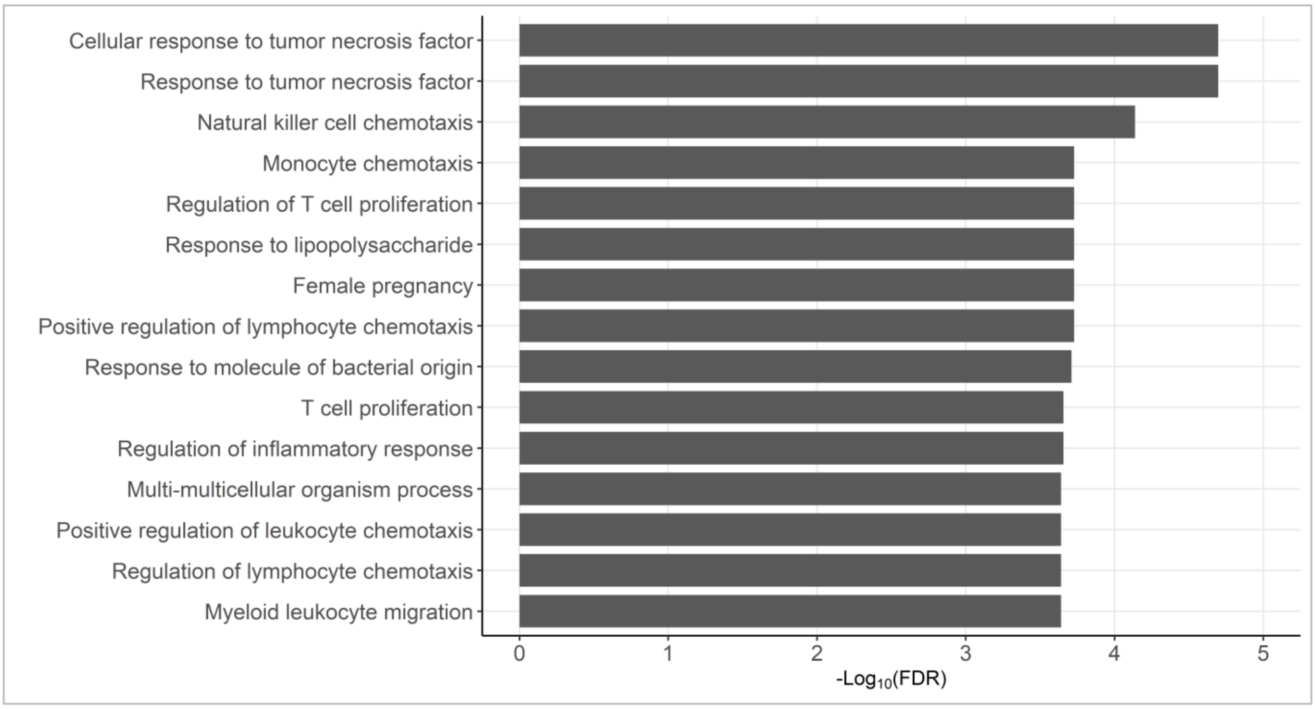
Abbreviations: CKD, chronic kidney disease; eGFRcr, creatinine-based estimated glomerular filtration rate; eGFRcys, cystatin C-based estimated glomerular filtration rate. Full names of the biomarkers can be found in Additional file 1: Table S1.



	PD-L1	CCL7	CCL3	VEGF-A	KIM1	XCL1	IGFBP-2	NT-proBNP	IL2-RA	IL-18BP	TNF-R1	TNF-R2	OPN	EPHB4	PLC	IL-15RA	TNFRSF9	ADM	TNFRSF11A	TM	TRAIL-R2
PD-L1		0.34	0.49	0.49	0.07	0.30	0.01	0.00	0.18	0.17	0.20	0.31	0.06	0.04	-0.00	0.29	0.26	-0.08	0.14	0.27	0.24
CCL7			0.41	0.44	0.19	0.27	0.03	0.06	0.26	0.20	0.25	0.30	0.17	0.09	0.10	0.27	0.30	0.18	0.29	0.19	0.27
CCL3				0.46	0.13	0.30	-0.00	0.05	0.22	0.28	0.30	0.39	0.15	0.11	0.14	0.33	0.37	0.15	0.24	0.27	0.29
VEGF-A					0.23	0.31	0.03	0.09	0.25	0.20	0.34	0.34	0.15	0.15	0.19	0.28	0.33	0.24	0.33	0.33	0.31
KIM1						0.25	0.01	0.17	0.16	0.22	0.30	0.24	0.24	0.19	0.24	0.17	0.19	0.33	0.32	0.32	0.30
XCL1							0.12	0.13	0.28	0.33	0.27	0.34	0.23	0.16	0.17	0.31	0.39	0.24	0.33	0.35	0.38
IGFBP-2								0.40	0.34	0.40	0.34	0.34	0.43	0.46	0.34	0.27	0.33	0.22	0.18	0.18	0.15
NT-proBNP									0.23	0.27	0.29	0.27	0.30	0.32	0.36	0.18	0.26	0.37	0.27	0.12	0.20
IL2-RA										0.64	0.64	0.68	0.44	0.57	0.52	0.42	0.54	0.34	0.37	0.32	0.32
IL-18BP											0.74	0.81	0.57	0.75	0.65	0.54	0.56	0.36	0.45	0.45	0.33
TNF-R1												0.88	0.57	0.77	0.75	0.45	0.52	0.49	0.57	0.47	0.44
TNF-R2													0.51	0.71	0.65	0.52	0.57	0.39	0.53	0.45	0.42
OPN														0.58	0.58	0.33	0.46	0.31	0.35	0.29	0.28
EPHB4															0.77	0.41	0.42	0.40	0.47	0.43	0.32
PLC																0.37	0.45	0.55	0.50	0.40	0.37
IL-15RA																	0.59	0.33	0.42	0.42	0.32
TNFRSF9																		0.40	0.48	0.41	0.42
ADM																			0.64	0.43	0.45
TNFRSF11A																				0.59	0.48
TM																					0.45
TRAIL-R2																					

Figure S9. Pathway enrichment analysis of the 21 identified biomarkers showing top biological processes related to kidney function. The 21 biomarkers significantly associated with the annual rate of change in eGFRcr, annual rate of change in eGFRcys, and incident CKD (Figure 3), were included in the pathway enrichment analysis. The y-axis signifies the top 15 biological processes in kidney function. The x-axis is the -log10 of the FDR.

Abbreviations: CKD, chronic kidney disease; eGFRcr, creatinine-based estimated glomerular filtration rate; eGFRcys, cystatin C-based estimated glomerular filtration rate; FDR, Benjamini–Hochberg false-discovery rate.



Paper II

Title:	Associations of Proteomics With Hypertension and Systolic Blood Pressure: KORA S4/F4/FF4 and KORA Age1/Age2 Cohort Studies
Authors:	Jie-sheng Lin, Agnese Petrera, Stefanie M. Hauck, Christian L. Müller, Annette Peters, Barbara Thorand
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Hypertension

ORIGINAL ARTICLE

Associations of Proteomics With Hypertension and Systolic Blood Pressure: KORA S4/F4/FF4 and KORA Age1/Age2 Cohort Studies

Jie-sheng Lin, Agnese Petrera, Stefanie M. Hauck, Christian L. Müller, Annette Peters, Barbara Thorand

BACKGROUND: Hypertension, a complex condition, is primarily defined based on blood pressure readings without involving its pathophysiological mechanisms. We aimed to identify biomarkers through a proteomic approach, thereby enhancing the future definition of hypertension with insights into its molecular mechanisms.

METHODS: The discovery analysis included 1560 participants, aged 55 to 74 years at baseline, from the KORA (Cooperative Health Research in the Region of Augsburg) S4/F4/FF4 cohort study, with 3332 observations over a median of 13.4 years of follow-up. Generalized estimating equations were used to estimate the associations of 233 plasma proteins with hypertension and systolic blood pressure (SBP). For validation, proteins significantly associated with hypertension or SBP in the discovery analysis were validated in the KORA Age1/Age2 cohort study (1024 participants, 1810 observations). A 2-sample Mendelian randomization analysis was conducted to infer causalities of validated proteins with SBP.

RESULTS: Discovery analysis identified 49 proteins associated with hypertension and 99 associated with SBP. Validation in the KORA Age1/Age2 study replicated 7 proteins associated with hypertension and 23 associated with SBP. Three proteins, NT-proBNP (N-terminal pro-B-type natriuretic peptide), KIM1 (kidney injury molecule 1), and OPG (osteoprotegerin), consistently showed positive associations with both outcomes. Five proteins demonstrated potential causal associations with SBP in Mendelian randomization analysis, including NT-proBNP and OPG.

CONCLUSIONS: We identified and validated 7 hypertension-associated and 23 SBP-associated proteins across 2 cohort studies. KIM1, NT-proBNP, and OPG demonstrated robust associations, and OPG was identified for the first time as associated with blood pressure. For NT-proBNP (protective) and OPG, causal associations with SBP were suggested. ***(Hypertension.* 2024;81:1156–1166. DOI: 10.1161/HYPERTENSIONAHA.123.22614.)** • **Supplement Material**.

Key Words: blood pressure ■ cohort studies ■ hypertension ■ Mendelian randomization analysis ■ proteomics

Hypertension, characterized by persistently high blood pressure (BP), is a complex condition involving multiple pathophysiological mechanisms and target organs such as the heart, brain, and kidney. BP is regulated by a complex interplay of multiple pathophysiological mechanisms, including the sympathetic nervous system, REN (renin)-angiotensin-aldosterone system, endothelium, and immune system.[1] High levels of BP are related to multiple adverse health outcomes, such as cardiovascular disease (CVD) and kidney disease.[2] An estimated 1.28 billion adults aged 30 to 79 years had hypertension globally in 2019 based on the World Health Organization definition of hypertension.[3,4] The cutoff value of BP to define hypertension is mainly based on continuous associations between a range of BP levels and CVD risks, and it has changed over time. In the American College of Cardiology/American Heart Association guidelines released in 2017, hypertension is

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Correspondence to: Barbara Thorand, Institute of Epidemiology, Helmholtz Zentrum München, German Research Center for Environmental Health, Ingolstädter Landstraße 1, D-85764 Neuherberg, Germany. Email barbara.thorand@helmholtz-munich.de

Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/HYPERTENSIONAHA.123.22614.

For Sources of Funding and Disclosures, see page 1165.

Hypertension is available at www.ahajournals.org/journal/hyp

NOVELTY AND RELEVANCE

What Is New?

Conducted both discovery and validation analyses based on 2 large prospective cohort studies.

Utilized state-of-the-art proteomic technology for the measurement of 233 inflammation and cardiovascular disease–related proteins.

What Is Relevant?

Discovery and validation of 7 hypertension-associated and 23 systolic blood pressure–associated proteins.

Reported robust positive associations of KIM1, NT-proBNP, and OPG with hypertension and systolic blood pressure.

Provided suggestive evidence for potential causal associations of NT-proBNP (inverse) and OPG (positive) on systolic blood pressure.

Clinical/Pathophysiological Implications?

Contributed valuable insights into the molecular mechanisms underlying hypertension.

Identified novel biomarkers, paving the way for a comprehensive definition and assessment of hypertension in the future.

Nonstandard Abbreviations and Acronyms

BP	blood pressure
CVD	cardiovascular disease
FDR	Benjamini-Hochberg false discovery rate
KORA	Cooperative Health Research in the Region of Augsburg
MONICA	Monitoring of Trends and Determinants in Cardiovascular Diseases
MR	Mendelian randomization
OR	odds ratio
SBP	systolic blood pressure
SNP	single-nucleotide polymorphism

Full names of the proteins can be found in Table S1

redefined as systolic BP (SBP) ≥130 mm Hg or diastolic BP ≥80 mm Hg.[5]

Notably, hypertension is primarily defined based on a readout of BP without involving its pathophysiological mechanisms. BP can naturally fluctuate throughout the day, rising in the morning and falling in the late afternoon and evening. Hypertension is a complex condition, making it challenging and insufficient to define solely on a readout of BP or a single marker, which may oversimplify the complexity of hypertension and potentially overlook key aspects of the condition. Therefore, there is a growing need for new biomarkers that supplement the definition of hypertension, further improve the prediction of hypertension progression, and provide information on patients' responses to treatment.

Proteomics allows for the identification of hundreds of proteins, making it a useful tool to discover new biomarkers and explore the underlying mechanisms of diseases. However, there are only a few proteomic studies about hypertension in humans. Gajjala et al[6] compared the expression of 403 plasma proteins between 118 patients with hypertension and 85 normotensive controls and identified 27 proteins differentially expressed. Similarly, Xu et al[7] identified 111 of 404 serum proteins differentially expressed between 20 patients with hypertension and 20 controls and found 4 proteins involved in the REN-angiotensin-aldosterone system. In a urinary proteomic study among 56 patients with hypertension and 19 controls, Matafora et al[8] found that patients with hypertension had higher levels of urinary uromodulin, which regulates water and salt balance and BP. The close relation between BP change and age is a challenge for longitudinal proteomic studies on hypertension,[9] and thus, previous proteomic studies in humans tend to be cross-sectional studies with small sample sizes. To date, there is only 1 longitudinal proteomic study on primary hypertension. Lin et al[10] investigated the associations of 79 plasma CVD-related proteins with BP progression over 5 years and found that REN was positively associated with BP progression in the discovery cohort (n=804) but not in the validation cohort (n=2659). Only 2 repeated measurements of BP were included in their longitudinal analysis, with a relatively short follow-up duration.

Therefore, we aimed to assess the association of 233 plasma proteins with hypertension and SBP in a community-based prospective cohort, with a median follow-up time of 13.4 years and 2 follow-up visits. Furthermore, we validated the results in another cohort study. Additionally, we explored the potential causality of the identified associations through a 2-sample Mendelian randomization (MR) approach.

METHODS

Data Availability

Because of the sensitive nature of the data collected for this study and because the informed consent given by study participants does not cover data posting in public databases, cooperation partners can obtain permission to use data under the terms of a project agreement (https://helmholtz-muenchen.managed-otrs.com/external).

A full description of the methods section is available in Text S1, with a summary provided below.

Study Population

The MONICA study (Monitoring of Trends and Determinants in Cardiovascular Diseases) conducted 3 health surveys S1 to S3 between 1984 and 1995 in Augsburg, Germany, and the KORA study (Cooperative Health Research in the Region of Augsburg) expanded on MONICA Augsburg by recruiting participants for a fourth survey (S4) based on the same criteria between 1999 and 2001 (Figure S1).[11] The MONICA/KORA study was approved by the local ethical committee, and all participants provided written informed consent. The present study was based on 1653 participants aged 55 to 74 years at KORA S4 and its 2 subsequent follow-up surveys, KORA F4/FF4 (Figure 1A). A total of 1560 participants were included at KORA S4 after the exclusion of 10 participants without measurement of BP and 83 with incomplete measurement of proteins. Participants without follow-up information on BP were excluded at F4 and FF4, respectively, leaving 1115 participants at F4 and 657 participants at FF4 (19 participants were only followed up at FF4, but not at F4). In summary, 1560 participants with 3332 observations from KORA S4/F4/FF4 were included for discovery analysis, with a median follow-up time of 13.4 (25th percentile, 7.1; 75th percentile, 13.5) years.

For validation, a subset of participants was drawn from the KORA Age1/Age2 study (Figure S1), which included participants at MONICA/KORA S1 to S4 born in the year 1943 or before (ie, age ≥65 years). In 2009 (KORA-Age1), a random subsample of 1079 participants underwent medical examinations and were invited to participate in the follow-up in 2012 (KORA-Age2). Figure 1B shows that 1024 participants with measurements on BP and proteins at KORA-Age1 and 786 participants with follow-up information at KORA-Age2 were included in the validation analysis, with a median follow-up time of 2.87 (25th percentile, 2.79; 75th percentile, 2.94) years. Since the KORA Age1/Age2 study also included participants at KORA S4, 142 of the 1024 participants overlapped with the 1560 participants from KORA S4/F4/FF4, but examinations were performed at different time points.

Assessment of Proteins, BP, and Covariates

Detailed assessment methods are available in Text S1. Olink proximity extension assay technology[12] was used to measure plasma proteins, including CVD II, CVD III, and inflammation panels. At KORA S4, 233 proteins were measured, and of these, 231 proteins were available at KORA-Age1 (Table S1). *Z*-score transformations were conducted for all proteins. BP and covariates such as age and smoking status were measured at baseline and follow-up. Hypertension was defined based on the World Health Organization definition.[3]

Statistical Analysis

Discovery Analysis in KORA S4/F4/FF4

To address bias from participant dropouts (Figure 1), we calculated inverse probability weights[13] and applied these in the following analyses. Generalized estimating equations were used to

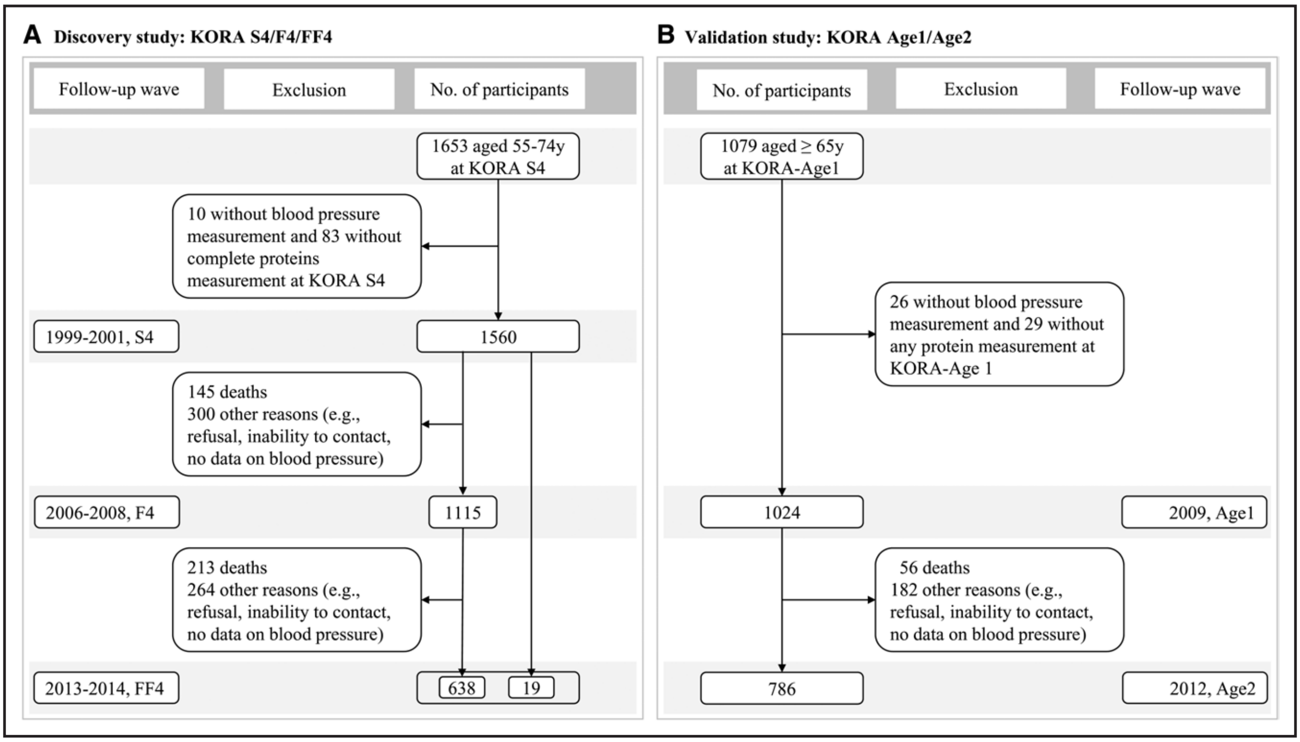

Figure 1. Flowchart of study participants.

A, Participants from KORA (Cooperative Health Research in the Region of Augsburg) S4/F4/FF4 study included in discovery analysis. **B**, Participants from KORA Age1/Age2 study included in validation analysis.

estimate the associations of proteins with repeated measurements of dichotomous hypertension (yes/no) and continuous SBP using the R package geepack. Any participant with protein measurement and BP data for at least 1 time point was included.

In the discovery analysis of the KORA S4/F4/FF4 study, the associations of 233 proteins with prevalent hypertension and levels of SBP were estimated by generalized estimating equations applying 2 models. Model 1, adjusted for age and sex; and model 2, model 1 plus body mass index, smoking status, alcohol consumption, physical activity, naturally log-transformed triglycerides, high-density lipoprotein cholesterol, use of lipid-lowering medication, prevalent diabetes, prevalent CVD, fasting status, and kidney function. For the associations with SBP, both models were further adjusted for the use of antihypertensive medication. Covariates in both models were treated as time-varying covariates, except sex. The Benjamini-Hochberg false discovery rate (FDR) was used to adjust for multiple testing, and FDR <0.05 was considered statistically significant.[14]

Validation Analysis in KORA Age1/Age2

The proteins significantly associated with hypertension or SBP (FDR <0.05) in the discovery analysis were taken to validate their associations with hypertension or SBP in the KORA Age1/Age2 study using generalized estimating equations, applying the same model 2 as described above, respectively. Proteins were considered validated if they demonstrated significant associations at a threshold of $P<0.05$.

Sensitivity Analysis

Sensitivity analyses were performed as follows: (1) in the validation analysis, a sensitivity analysis was conducted after excluding 142 participants who overlapped with KORA S4/F4/FF4; and (2) for associations with SBP, linear mixed-effects models were used in both discovery and validation analyses, applying the aforementioned model 2, using R package lme4.

MR Analysis on SBP

A 2-sample MR analysis was conducted to estimate the potential causal associations of proteins with SBP using publicly available genome-wide association studies. Single-nucleotide polymorphisms (SNPs), serving as instrumental variables for proteins, were selected from a genome-wide association study mapping protein quantitative trait loci in 35 571 European-ancestry people.[15] Of 27 validated proteins, 26 had available protein quantitative trait loci based on *cis*-SNPs with $P<5\times10^{-8}$. To refine SNPs, linkage disequilibrium clumping ($r^2<0.01$ within a 10 000-kb region) was applied based on a reference panel using 1000 Genomes data from 503 European samples.[16] The associations of SNPs with SBP were extracted from a genome-wide association study identifying loci associated with BP in >1 million European-ancestry people.[17] Finally, 26 proteins with 1 to 17 SNPs were used for MR analysis (Table S2) using the R package TwoSampleMR. The function MendelianRandomization::mr_mr_ivw was used to evaluate bias due to participant overlap.[18,19] Details are presented in Text S1.

RESULTS

Characteristics of the Study Population

The characteristics of participants at KORA S4 and KORA-Age1 (ie, baseline for each study) are presented in the Table. In KORA S4, participants had a significantly lower mean age of 63.9 (5.46) years compared with 75.9 (6.57) years in KORA-Age1. Unexpectedly, despite the age difference, the average SBP in KORA S4 was only slightly lower at 136.4 (20.5) mm Hg compared with 138.6 (21.0) mm Hg in KORA-Age1. The difference in the proportion of use of antihypertensive medication (36.7% in KORA S4 versus 70.1% in KORA-Age1) may partly explain this relatively small difference. Significant differences were also observed across various lifestyle- and health-related variables, as well as the prevalence of diseases. Table S3 provides detailed information on the characteristics of participants across KORA S4/F4/FF4 and KORA Age1/Age2, and characteristics for participants with and without follow-up information on BP are summarized in Table S4.

Table. **Baseline Characteristics of Participants**

Characteristics	KORA S4 1999–2001 n=1560	KORA-Age1 2009 n=1024	*P* value*
	Mean (SD) or No. (%)		
Age, y	63.9 (5.46)	75.9 (6.57)	<0.001
Sex, female, n (%)	759 (48.7)	507 (49.5)	0.699
Body mass index, kg/m^2	28.5 (4.36)	28.4 (4.36)	0.561
Smoking status, n (%)			<0.001
Never smoker	747 (47.9)	550 (53.7)	
Former smoker	594 (38.1)	427 (41.7)	
Current smoker	219 (14.0)	47 (4.60)	
Alcohol consumption			<0.001
No alcohol consumption	437 (28.0)	363 (35.4)	
>0 and <20 g/d	592 (37.9)	362 (35.4)	
≥20 g/d	531 (34.1)	299 (29.2)	
Physically active, n (%)	655 (42.0)	553 (54.0)	<0.001
Triglycerides, mmol/L; median (interquartile range)	1.37 (0.94)	1.41 (1.01)	0.473
High-density lipoprotein cholesterol, mmol/L	1.49 (0.42)	1.44 (0.37)	0.002
Use of lipid-lowering medication, n (%)	183 (11.7)	293 (28.6)	<0.001
Type 2 diabetes, n (%)	148 (9.50)	181 (17.7)	<0.001
Cardiovascular diseases, n (%)	191 (12.2)	316 (30.9)	<0.001
Fasting, n (%)	1375 (88.1)	56 (5.50)	<0.001
Estimated glomerular filtration rate, mL/(min·1.73 m^2)	82.5 (13.3)	67.3 (17.4)	<0.001
Hypertension, n (%)	882 (56.5)	770 (75.2)	<0.001
Use of antihypertensive medication, n (%)	572 (36.7)	718 (70.1)	<0.001
Systolic blood pressure, mm Hg	136.4 (20.5)	138.6 (21.0)	0.007
Diastolic blood pressure, mm Hg	80.6 (10.6)	75.6 (10.9)	<0.001

KORA indicates Cooperative Health Research in the Region of Augsburg.

**P* value was estimated by *t* test (continuous variables) or χ^2 test (categorical variables).

Discovery of Proteins Associated With Hypertension or SBP

In the discovery analyses of the associations of 233 proteins with hypertension conducted within the KORA S4/F4/FF4 study, 149 proteins were significant in model 1 (FDR <0.05), while 48 proteins remained significant after adjustment for additional covariates in model 2, and in addition, REN became significant in model 2 (Table S5; Figure 2A). Among the 49 significant proteins in model 2, 43 proteins were positively (odds ratios [ORs], 1.13–1.33) and 6 proteins were inversely (ORs, 0.82–0.87) associated with prevalent hypertension. When investigating the associations with SBP, 99 of 233 proteins were significant in model 2 (FDR <0.05), with 96 proteins positively associated (β-coefficients, 1.15–3.95 mm Hg) and 3 proteins inversely associated (β, −1.54 to −1.14) with SBP (Table S6; Figure 3A). In the sensitivity analysis for SBP using linear mixed-effects models, all 99 proteins remained significant (FDR <0.05), and an additional 18 proteins showed significance (Table S7).

There were 31 proteins significantly associated with both hypertension and SBP (Table S8; Figure 4A). Among these 31 proteins, the top 5 proteins with the highest ORs for the associations with hypertension were NT-proBNP (N-terminal pro-B-type natriuretic peptide; OR, 1.33 [95% CI, 1.20–1.49]), HGF (hepatocyte growth factor; OR, 1.27 [95% CI, 1.14–1.42]), CEACAM8 (carcinoembryonic antigen-related cell adhesion molecule 8; OR, 1.27 [95% CI, 1.13–1.41]), KIM1 (kidney injury molecule 1; OR, 1.26 [95% CI, 1.13–1.40]), and TGF-α (transforming growth factor alpha; OR, 1.24 [95% CI, 1.11–1.39]). The top 5 proteins with the highest β-coefficients for the associations with SBP were KIM1 (β, 3.95 [95% CI, 2.80–5.10]), OPG (osteoprotegerin; β, 3.34 [95% CI, 2.32–4.36]), NT-proBNP (β, 3.02 [95% CI, 1.96–4.24]), HGF (β, 2.93 [95% CI, 1.88–3.99]), and CHI3L1 (chitinase-3-like 1; β, 2.66 [95% CI, 1.63–3.69]).

Validation of Proteins Associated With Hypertension or SBP

When validating the 49 proteins significantly associated with hypertension in the discovery analysis, 7 proteins were associated with hypertension at a threshold of $P<0.05$ in the KORA Age1/Age2 study (Table S9; Figure 2B). Of the 99 SBP-associated proteins in the discovery study, 23 proteins were validated (Table S10; Figure 3B), and 3 validated proteins (ie, NT-proBNP, KIM1, and OPG) were associated with both hypertension and SBP (Figure 4B). Among these 27 validated proteins, 26 were positively associated with hypertension or SBP, while PON3 (paraoxonase) demonstrated

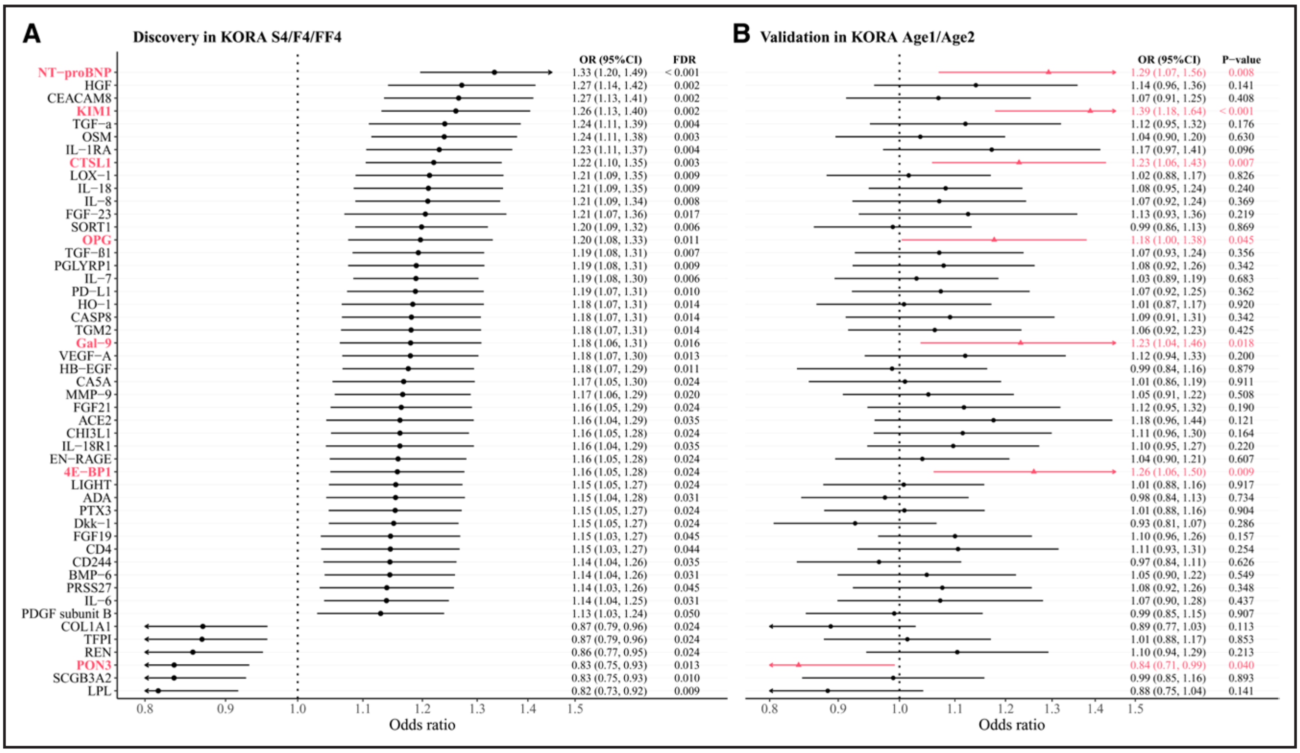

Figure 2. Associations of 49 proteins with hypertension in the discovery and validation studies.
A, Significant associations of 49 proteins with hypertension in the KORA (Cooperative Health Research in the Region of Augsburg) S4/F4/FF4 study (Benjamini-Hochberg false discovery rate [FDR] <0.05). **B**, Validation of the associations of 49 proteins with hypertension in the KORA Age1/Age2 study. Proteins were considered validated at a threshold of $P<0.05$. This figure illustrates the results of model 2, as detailed in Table S9. Proteins in bold and red are successfully validated. OR indicates odds ratio. Full names of the proteins can be found in Table S1.

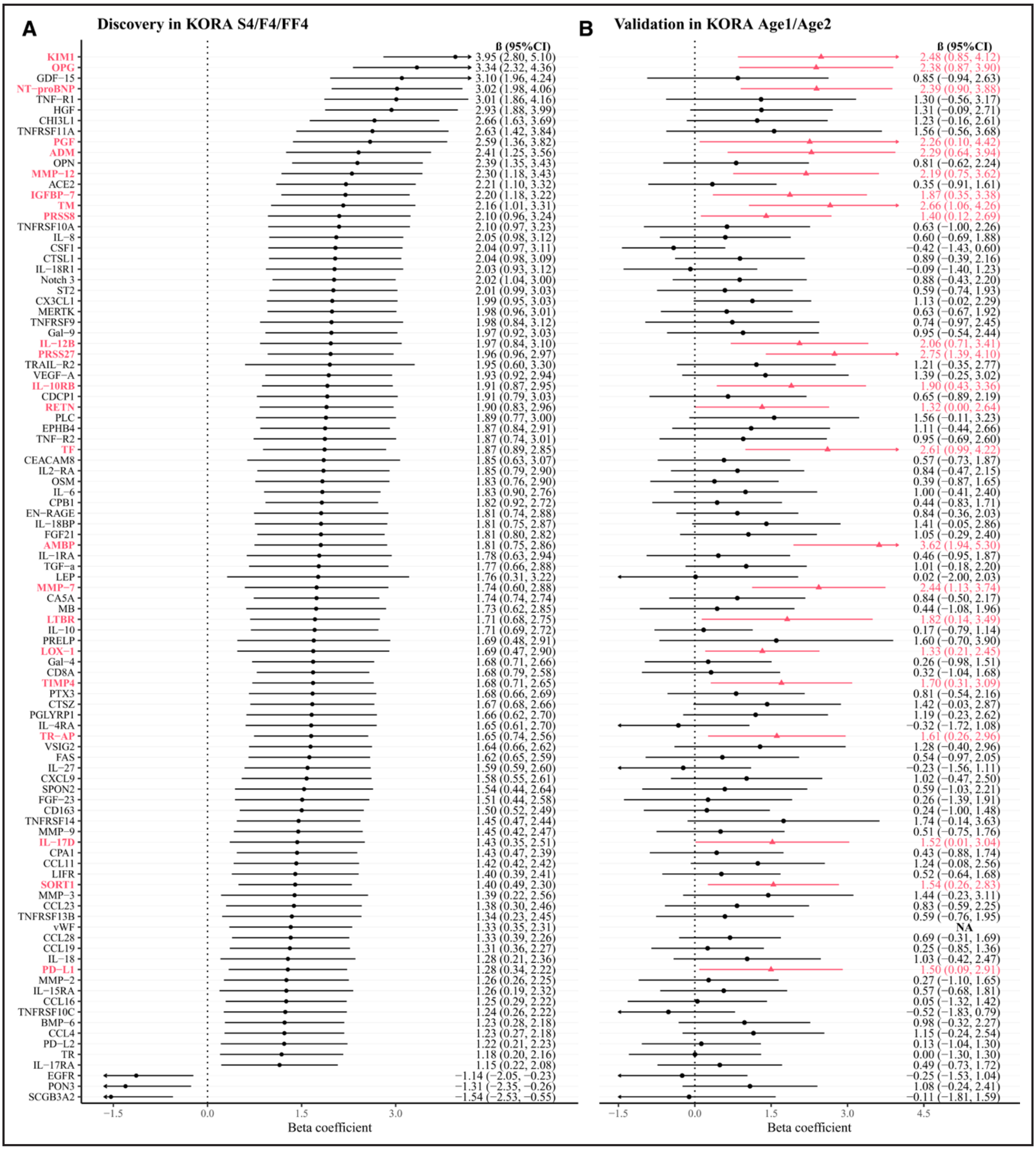

Figure 3. Associations of 99 proteins with systolic blood pressure (SBP) in the discovery and validation studies. **A**, Significant associations of 99 proteins with SBP in the KORA (Cooperative Health Research in the Region of Augsburg) S4/F4/FF4 study (Benjamini-Hochberg false discovery rate <0.05). **B**, Validation of the associations of 99 proteins with SBP in the KORA Age1/Age2 study. Proteins were considered validated at a threshold of *P*<0.05. This figure illustrates the results of model 2, as detailed in Table S10. Proteins in bold and red are successfully validated. NA indicates not available. Full names of the proteins can be found in Table S1.

an inverse association. The correlations between these 27 validated proteins are presented in Figures S2 and S3. In the sensitivity analysis (Tables S9 and S10) that excluded 142 overlapping participants, PON3 and OPG were not significantly associated with hypertension, but the direction of the associations remained consistent, indicating that the lack of significance could be due to reduced statistical power. OPG maintained its association with SBP. The sensitivity analysis using linear mixed-effects models identified 29 significant proteins

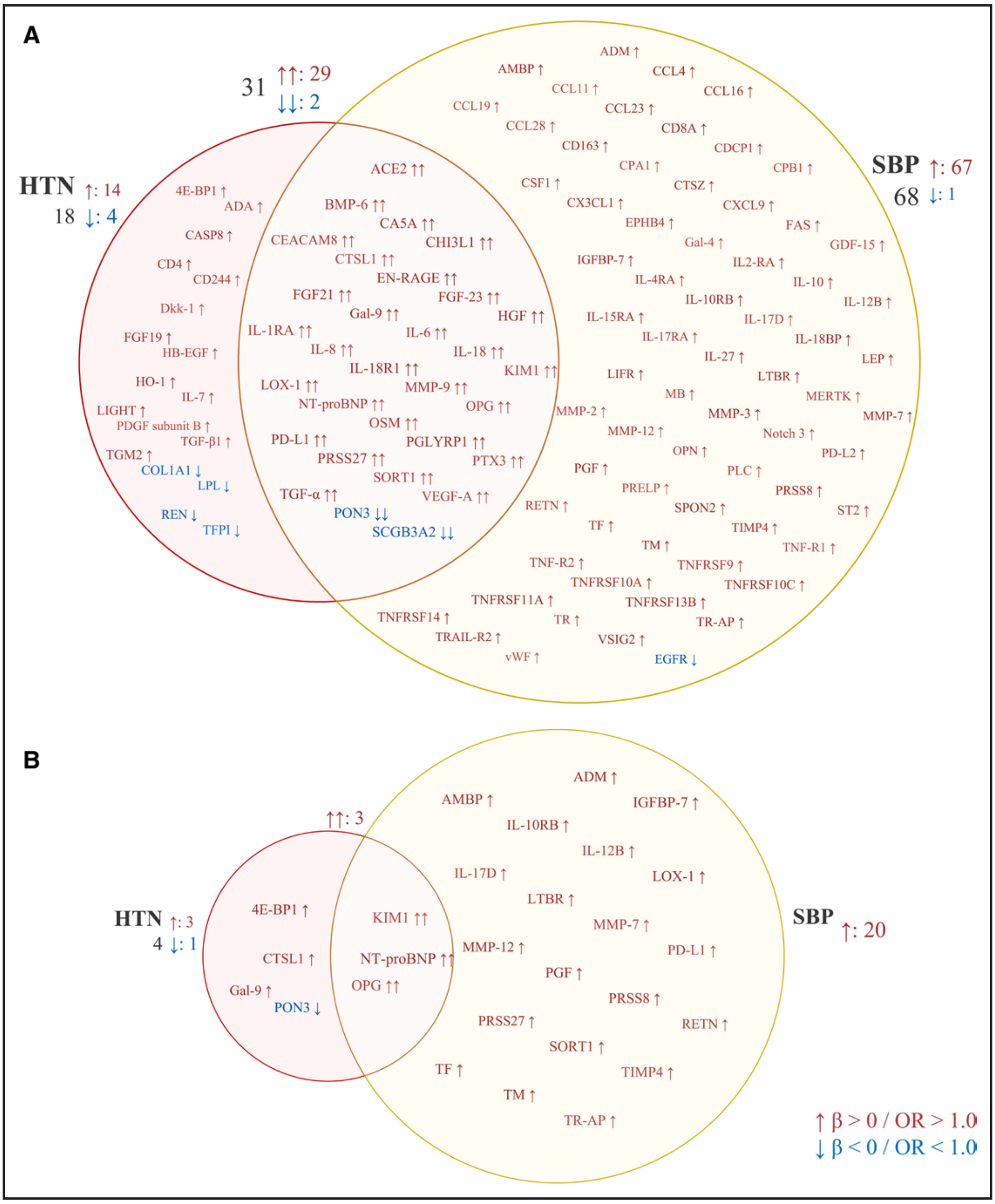

Figure 4. Overlap of proteins associated with hypertension (HTN) and systolic blood pressure (SBP).
A, Overlap of proteins associated with HTN and SBP in the discovery analysis in the KORA (Cooperative Health Research in the Region of Augsburg) S4/F4/FF4 study. Detailed results are presented in Table S8. **B**, Overlap of proteins associated with HTN and SBP in the validation analysis in the KORA Age1/Age2 study. Detailed results are presented in Tables S9 and S10. OR indicates odds ratio. Full names of the proteins can be found in Table S1.

($P<0.05$), of which 21 overlapped with the above 23 SBP-validated proteins (Table S11). The overall robustness of the results was maintained.

MR Analysis on SBP

Table S12 presents the main results of the MR analysis, including heterogeneity, pleiotropy, and Steiger directionality tests. Since no evidence of directional horizontal pleiotropy (Egger *P* value >0.05) was observed, for proteins with ≥2 SNPs, MR results from inverse variance weighted or weighted median (when heterogeneity test was significant with Q *P* value <0.05) are presented. There were 5 of 26 proteins that demonstrated potential causal associations with SBP ($P<0.05/26$). NT-proBNP (β, −2.46 [95% CI, −2.77 to −2.15) and IL-10RB (interleukin-10 receptor subunit beta; β, −0.19 [95% CI, −0.31 to −0.08]) showed inverse associations, while

TIMP4 (tissue inhibitor of metalloproteinase inhibitor 4; β, 0.56 [95% CI, 0.25–0.87]), PD-L1 (programmed cell death 1 ligand 1; β, 0.28 [95% CI, 0.12–0.44]), and OPG (β, 0.41 [95% CI, 0.16–0.66]) exhibited positive associations. The Steiger directionality tests indicate that the variance explained in proteins was significantly higher than in SBP, suggesting causal directions from proteins to SBP. When accounting for potential bias due to participant overlap in the 2 genome-wide association studies, the causal associations with SBP remained robust for 4 of the 5 identified proteins, that is, NT-proBNP, OPG, PD-L1, and TIMP4 (Table S13).

DISCUSSION

In this prospective study conducted on 2 cohorts, we identified 49 hypertension-associated and 99 SBP-associated proteins of a total of 233 CVD- and inflammation-related plasma proteins in the KORA S4/F4/FF4 study. Upon validating these proteins in the KORA Age1/Age2 study, 7 and 23 proteins were associated with hypertension and SBP, respectively. Three proteins, NT-proBNP, KIM1, and OPG, were consistently associated with both hypertension and SBP in the discovery and validation analyses. In MR analysis, 5 proteins showed potential causal associations with SBP, including IL-10RB, NT-proBNP, OPG, PD-L1, and TIMP4.

Studies about proteomics and BP in humans are limited. We only found 3 cross-sectional studies with small sample sizes[6–8] and 1 longitudinal study.[10] A few previously reported proteins in the 3 cross-sectional studies were replicated in our discovery analysis, including latency-associated peptide TGF-β1 (transforming growth factor beta-1),[7] TNFRSF14 (tumor necrosis factor receptor superfamily member 14), and PLC (perlecan).[8] Using the same protein measurement technology as in the present study, Lin et al[10] identified REN from 79 plasma CVD I–based proteins, showing a positive association with BP progression in the discovery cohort only. In contrast, we observed an inverse association of REN with hypertension in the discovery analysis.

REN is an enzyme produced by special cells in the kidneys in response to triggers such as low blood volume, decreased sodium levels, or reduced BP.[1,20] The release of REN initiates the REN-angiotensin-aldosterone system, which regulates blood volume and vascular resistance by controlling sodium and water retention, as well as vascular tone, ultimately leading to increases in BP.[1,20] Low-REN hypertension, a subtype of hypertension, is characterized by low levels of REN, and this subtype accounts for nearly one-third of all patients with hypertension, while medium- or high-REN hypertension represents more than one-third.[21] Interestingly, although Lin et al and our studies observed opposite significant REN-hypertension associations in discovery analysis, neither study was able to validate the association of REN. The different subtypes of hypertension with varying REN levels among the included participants may explain the discrepancy.

The successful replication of previously reported proteins supports the viability of the proteomic approach for identifying biomarkers for hypertension and BP. Furthermore, our discovery analysis identified several proteins associated with both hypertension and SBP that are established biomarkers for hypertension, such as IL-6 (interleukin-6), LOX-1 (lectin-like oxidized low-density lipoprotein receptor 1), NT-proBNP, TNF-α (tumor necrosis factor-alpha), and VEGF-A (vascular endothelial growth factor A).[22,23] Additionally, NT-proBNP was successfully validated for its associations with both hypertension and SBP in our validation analysis.

NT-proBNP is an inactive peptide released along with the active peptide BNP (B-type natriuretic peptide) in a 1:1 ratio from the heart upon myocardial stretching or pressure overload on the heart. Both NT-proBNP and BNP are strongly associated with various adverse CVD outcomes and are used for the diagnosis or exclusion of heart failure.[24] Since NT-proBNP is more stable, it forms a good marker of BNP output. BNP can regulate BP through its natriuretic, diuretic, and vasodilatory effects, which reduce sodium and water retention and ease blood vessels, resulting in decreasing blood volume and vascular resistance.[25] In our discovery analysis, NT-proBNP was the biomarker with the strongest association with hypertension and one of the top SBP-associated biomarkers. Our results were in line with results from an American cohort study, consisting of 3798 middle-aged participants, which reported a positive association of baseline NT-proBNP with incident hypertension.[26] However, a similar prospective study, comprising 1323 participants aged ≥45 years, failed to observe a significant association of baseline NT-proBNP with incident hypertension.[27] A European population-based study observed that higher levels of NT-proBNP were associated with prevalent hypertension (n=5307), whereas lower baseline NT-proBNP was associated with incident hypertension n=2389).[28] In a study using an MR approach to investigate the causal associations of 227 proteins with BP, NT-proBNP was inversely associated with both SBP and diastolic BP, but the epidemiological association analyses showed positive cross-sectional associations of NT-proBNP with BP.[29] This aligns with the results from the present study, where we observed a positive association of NT-proBNP with hypertension and SBP, while our MR analysis found evidence for an inverse causal association of NT-proBNP with SBP. A potential explanation for the opposite direction of association between observational studies and MR could be that compensatory mechanisms and environmental factors influence protein expression,[30] leading to elevated levels of NT-proBNP/BNP in individuals with hypertension to counteract increases in BP levels. Therefore, high

NT-proBNP/BNP levels might be a consequence of BP elevation, suggesting that NT-proBNP could serve as a marker for hypertension and elevated BP.

KIM1 is a protein expressed in response to kidney injury and is positively associated with impaired kidney function.[31] In our previous study investigating the association of proteomics with kidney function decline, we found KIM1 was the protein with the strongest positive association.[32] While KIM1 is recognized as a key biomarker for kidney function, its direct association with BP is not as well-documented. Two cohort studies have reported that urinary KIM1 was not associated with incident hypertension.[33,34] In contrast, our present study observed strong positive associations of plasma KIM1 with SBP and hypertension, which is consistent with several cross-sectional studies that have demonstrated positive associations of plasma/serum KIM1 with BP and hypertension.[35–37] The difference in biosamples used to measure KIM1 may partially explain these distinct findings. As KIM1 is mainly expressed in renal tubular epithelial cells, urinary KIM1 may more directly reflect kidney damage but may not directly relate to BP change, while plasma/serum KIM1 may represent a broader systemic influence, such as inflammatory response and endothelial dysfunction, which are related to BP regulation.[1,38] The kidneys play a key role in the regulation of BP through the REN-angiotensin-aldosterone system, and conversely, BP can also affect kidney function. Chronic high BP can damage kidney function, impacting the kidneys' ability to effectively regulate BP.[39] Given the evidence from observational studies and the bidirectional relationship between the kidneys and BP, KIM1 may serve as a potential marker for BP change and provide valuable insights into the complex interplay between kidney function and BP. Further studies are warranted to explore the clinical implications of KIM1 in the prediction of the development of hypertension.

OPG was another protein that demonstrated positive associations with SBP and hypertension, with the MR analysis also suggesting a positive causal association of OPG with SBP. OPG is a decoy receptor in the TNF-related activation-induced cytokine (RANKL)/TNF receptor superfamily member 11A (RANK)/OPG system, inhibiting bone resorption by obstructing the interaction between RANKL and RANK, thereby playing a key role in bone remodeling.[40] Moreover, increasing evidence confirms the relationship of OPG with various CVD, where OPG plays a role in regulating vascular endothelial cell function and the atherosclerotic process in the arteries,[40] which could potentially influence BP regulation. In addition to CVD, previous studies have also reported associations of OPG with kidney function.[41,42] However, despite the close relations of OPG with CVD and kidney function, as well as the above potential mechanisms, it is important to note that direct biological and epidemiological evidence linking OPG to BP is currently lacking. Thus, more comprehensive studies are needed to fully elucidate the role of OPG in BP regulation and hypertension.

In MR analysis, we also found suggestive evidence for potential causal associations of IL-10RB, PD-L1, and TIMP4 with SBP. IL-10RB, a key component in the IL-10 signaling pathway, and PD-L1, a pivotal regulator in immune checkpoint modulation, have crucial roles in immune system regulation.[43,44] While direct associations of IL-10RB and PD-L1 with BP are scarce, considering the known involvement of the immune system in BP regulation, it is plausible that IL-10RB and PD-L1 may influence BP. Similarly, TIMP4, a key regulator of matrix metalloproteinases, is involved in immune and inflammatory responses.[45] TIMP4 contributes to pathological changes in the blood vessels through processes such as tissue remodeling, angiogenesis, and inflammation,[45] suggesting that TIMP4 may also be associated with BP regulation.

Key strengths of our study include conducting both discovery and validation analyses based on 2 large prospective cohort studies and simultaneous measurement of numerous proteins. There are also several limitations to consider. First, we did not investigate the association with incident hypertension given that our participants were relatively old and exhibited a high prevalence of hypertension at baseline. Second, we were unable to account for the effect of changes in proteins during follow-up since we only measured proteins at baseline. Third, the validation study may not be perfect for validation due to differences in participant characteristics between the discovery and validation studies. Fourth, we only included 233 CVD- and inflammation-related proteins. Finally, an unexpected decline in average SBP across KORA S4/F4/FF4 was observed, probably because individuals who participated in the follow-up examinations tended to be healthier and the proportion of antihypertensive medication use increased. Although we applied inverse probability weighting, bias resulting from loss to follow-up may not be fully controlled.

In conclusion, our study identified and validated 7 hypertension-associated and 23 SBP-associated proteins across 2 cohort studies. Among these, 3 proteins—KIM1, NT-proBNP, and OPG—demonstrated robust positive associations with both hypertension and SBP. Notably, this is the first epidemiological study to report associations of OPG with hypertension and SBP. Additionally, results from the MR analysis provide evidence for a potential protective effect of NT-proBNP and a causal effect of OPG on SBP. These findings may contribute valuable insights into the molecular mechanisms underlying hypertension and provide evidence for a comprehensive definition and assessment of hypertension in the future.

PERSPECTIVES

Our study takes a significant step forward in hypertension research by using a proteomic approach to identify biomarkers associated with hypertension and SBP. The successful discovery and validation of 7 hypertension-associated and 23 SBP-associated proteins across 2 cohort studies supports the feasibility of this approach and shows its potential for identifying novel biomarkers. Among these proteins, KIM1, NT-proBNP, and OPG demonstrated robust positive associations with both hypertension and SBP. Notably, this is the first epidemiological study to report associations of OPG with hypertension and SBP. The potential protective effect of NT-proBNP and a causal effect of OPG on SBP, as evidenced by our MR analysis, further support the robustness and credibility of our findings. Our study may enhance the understanding of the molecular mechanisms underlying hypertension and pave the way for a more comprehensive assessment of hypertension that goes beyond mere BP readings. Future studies are expected to explore these proteins as potential therapeutic targets and monitoring tools for tracking treatment responses in patients.

ARTICLE INFORMATION

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Affiliations

Institute of Epidemiology (J.-s.L., A. Peters, B.T.), Metabolomics and Proteomics Core (A. Petrera, S.M.H.), and Institute of Computational Biology (C.L.M.), Helmholtz Zentrum München, German Research Center for Environmental Health (GmbH), Neuherberg, Germany. Institute for Medical Information Processing, Biometry, and Epidemiology (IBE), Faculty of Medicine, LMU Munich, Pettenkofer School of Public Health, Munich, Germany (J.-s.L., B.T.). Department of Statistics (C.L.M.) and Chair of Epidemiology, Institute for Medical Information Processing, Biometry and Epidemiology, Medical Faculty (A. Peters), Ludwig-Maximilians-Universität München, Munich, Germany. Center for Computational Mathematics, Flatiron Institute, New York, NY (C.L.M.). German Center for Diabetes Research, Partner München-Neuherberg, Germany (A. Peters, B.T.).

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Author Contributions

J.-s. Lin drafted the analysis plan, performed the statistical analysis, interpreted the data, and wrote the first draft of the manuscript. C.L. Müller and A. Peters contributed to the analysis plan and data interpretation. B. Thorand designed the study and contributed to the analysis plan and data interpretation. A. Petrera, S.M. Hauck, A. Peters, and B. Thorand contributed data. All authors read and approved the final manuscript. J.-s. Lin and B. Thorand had primary responsibility for the final content.

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Disclosures

None.

Supplemental Material

Text S1
Figures S1–S3
Tables S1–S13

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Supplemental Text S1 and Figure S1-S3

Associations of proteomics with hypertension and systolic blood pressure: KORA S4/F4/FF4 and KORA Age1/Age2 cohort studies

Jie-sheng Lin, MSc, Agnese Petrera, PhD, Stefanie M. Hauck, PhD, Christian L. Müller, PhD, Annette Peters, PhD, Barbara Thorand, PhD [1, 2, 3 *]

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Text S1. Full description of the methods section

Study population

The Monitoring of Trends and Determinants in Cardiovascular Diseases (MONICA) study conducted 3 health surveys S1 to S3 among the population aged 25-74 years between 1984 and 1995 in Augsburg, Germany, and the Cooperative Health Research in the Region of Augsburg (KORA) study expanded on MONICA Augsburg by recruiting participants for a fourth survey (S4) based on the same criteria between 1999 and 2001 (Figure S1) [1]. The MONICA/KORA study was approved by the local ethical committee and all participants provided written informed consent. The present study was based on 1653 participants aged 55-74 years at KORA S4 and its two subsequent follow-up surveys KORA F4/FF4 (Figure 1A). A total of 1560 participants were included at KORA S4 after exclusion of 10 participants without measurement of BP and 83 with incomplete measurement of proteins. Participants without follow-up information on BP were excluded at F4 and FF4, respectively, leaving 1115 participants at F4 and 657 participants at FF4 (19 participants were only followed up at FF4, but not at F4). In summary, 1560 participants with 3332 observations from KORA S4/F4/FF4 were included for discovery analysis, with a median follow-up time of 13.4 (25th percentile: 7.1, 75th percentile: 13.5) years.

For validation, a subset of participants was drawn from the KORA Age1/Age2 study (Figure S1), which included participants at MONICA/KORA S1-S4 born in the year 1943 or before (i.e., age $\geq$ 65 years). In 2009 (KORA-Age1), a random sub-sample of 1079 participants underwent medical examinations and participated in the follow-up in 2012 (KORA-Age2). Figure 1B shows that 1024 participants with measurements on BP and proteins at KORA-Age1 and 786 participants with follow-up information at KORA-Age2 were included in the validation analysis, with a median follow-up time of 2.87 (25th percentile: 2.79, 75th percentile: 2.94) years. Since the KORA Age1/Age2 study also included participants at KORA S4, 142 out of the 1024 participants overlapped with the 1560 participants from KORA S4/F4/FF4 but examinations were performed at different time points.

Measurement of proteins

Olink's proximity extension assay technology [2] was used to measure plasma proteins at both KORA S4 and KORA-Age1, including the Proseek Multiplex cardiovascular disease (CVD) II, CVD III, and Inflammation panels (Olink, Upsala, Sweden). Normalized protein expression values on a log2 scale were generated from the measurements, where higher values represent higher protein levels. Details of the measurement and selection of the proteins have been reported previously [3]. At KORA S4, 233 proteins were measured among 1560 participants, and out of these, 231 proteins were available at KORA-Age1 among 1024 participants (Supplemental Material 2: Table S1). Z-score transformations were conducted for all proteins in participants at KORA S4 and KORA-Age1, respectively.

Assessment of blood pressure and antihypertensive medication

Information on sociodemographic characteristics, lifestyle factors, medical history, medication use, blood pressure (BP), anthropometric indices, etc. were gathered by trained medical staff during a standardized face-to-face interview or medical examination [1]. For BP measurement, participants sat in a chair with back supported for at least 5 minutes before the 1st measurement, with right lower arm resting on table at heart level. BP was measured by an automatic digital oscillometer (HEM 705CP-II Omron Corporation Japan) 3 times in a 3-minute interval. The mean of the 2nd and 3rd measurements was used for the present study. Information on medications used within the past 7 days before the interview was provided by the participants and antihypertensive medications were classified by guidelines of the German Hypertension Society. Hypertension was defined as systolic BP (SBP) $\geq$ 140 mm Hg and/or diastolic BP (DBP) $\geq$ 90 mm Hg, or reported use of antihypertensive medications given that participants were aware of having hypertension [4].

Covariates

Covariates included age, sex, body mass index, smoking status, alcohol consumption, physical activity, triglycerides, high-density lipoprotein cholesterol, use of lipid-lowering medication, use of antihypertensive medication, prevalent diabetes, prevalent cardiovascular diseases, fasting status (whether fasting for at least 8 hours before blood draw), and kidney function (creatinine-based estimated glomerular filtration rate) at baseline and follow-up. Detailed categories of categorical variables are presented in Table 1 and details of covariates measurements have been reported previously [3].

Statistical analysis

Continues variables were reported as mean ± standard deviation for normally distributed data and as median (interquartile range) for skewed data. Categorical variables were presented as total numbers with the corresponding percentages.

Discovery of hypertension and SBP-associated proteins in KORA S4/F4/FF4

To address bias from participant dropouts (Figure 1), we utilized the inverse probability weighting method [5]. The probability of each participant's dropout (yes/no) was determined using logistic regression, considering baseline covariates from model 2 below as predictors. The weight was calculated as 1/ (1-dropout probability) and applied in the following analyses. To take into account repeated measurements of hypertension and SBP for each participant, generalized estimating equations (GEE) with exchangeable correlation structure were used to estimate the associations of proteins with dichotomous hypertension (yes/no) and continuous SBP, using R package "geepack". Given the well-documented phenomenon that DBP declines after the age of 50, and hypertension in adults over 50 years is predominantly characterized by elevations in SBP, we focus on SBP as a continuous BP outcome given the age range of our participants. Any participant with protein measurement and BP data for at least one time point was included.

In the discovery analysis among KORA S4/F4/FF4 study, the associations of 233 proteins with prevalent hypertension and levels of SBP were estimated by GEE. Two models were constructed to control potential confounders: model 1, adjusted for age and sex; model 2, model 1 plus body mass index, smoking status, alcohol consumption, physical activity, naturally log-transformed triglycerides, high-density lipoprotein cholesterol, use of lipid-lowering medication, prevalent diabetes, prevalent cardiovascular diseases, fasting status, and kidney function. For the associations with continuous SBP, both models were further adjusted for use of antihypertensive medication. Covariates in both models were treated as time-varying covariates, except sex. Benjamini–Hochberg False-discovery rate (FDR) was used to adjust for multiple testing and FDR < 0.05 was considered statistically significant [6].

Validation of hypertension and SBP-associated proteins in KORA Age1/Age2

The proteins significantly associated with dichotomous hypertension or continuous SBP (FDR < 0.05) in the discovery analysis among KORA S4/F4/FF4 study were taken to validate their associations with hypertension or SBP in KORA Age1/Age2 study using GEE, applying the same model 2 as described above, respectively. Proteins were considered validated if they demonstrated significant associations at a threshold of P-value < 0.05.

Sensitivity analyses were performed as follows: 1) In the validation analysis, sensitivity analysis was conducted after excluding 142 participants who overlapped with KORA S4/F4/FF4. 2) For associations with SBP, linear mixed-effects models were used in both discovery and validation analyses, applying the aforementioned model 2, using R package “lme4”.

Mendelian randomization analysis on SBP

Two-sample Mendelian randomization (MR) analysis was conducted to estimate the potential causal associations of proteins with SBP utilizing publicly available genome-wide association studies (GWAS). We focused the MR on SBP given its nature as a continuous variable, providing more statistical power, and benefitting from the larger scale of available GWAS compared to the dichotomous outcome of hypertension. Single nucleotide polymorphisms (SNPs), serving as instrumental variables (IVs) for proteins, were selected from a GWAS mapping protein quantitative trait loci (pQTL) of 2923 plasma proteins based on Olink’s proximity extension assay technology in 35571 participants from a European-ancestry population from the UK Biobank Pharma Proteomics Project [7]. Out of 27 validated proteins (Figure 4B), 26 had available pQTLs based on cis-SNPs with genome-wide significance (P-value < 5E-8). To refine SNPs, linkage disequilibrium clumping was applied based on a reference panel using 1000 genomes data from 503 European samples [8], excluding SNPs with $r^2 < 0.01$ within a 10000kb region, leading to the removal of 68 to 2701 SNPs per protein. The associations of SNPs with SBP were extracted from a GWAS identifying loci associated with BP in more than 1 million European-ancestry people [9]. After excluding 84 SNPs without SNPs-SBP associations, data harmonization was performed to ensure that the effects of SNPs on proteins and SBP were corresponding to the same allele, and 2 palindromic SNPs were further excluded (Table S2), leaving 26 proteins with 1 to 17 SNPs for MR analysis.

Inverse variance weighted MR was performed for proteins with 2 or more SNPs, while Wald ratio was calculated when only 1 SNP instrument was available. Cochran's Q test was performed to test for instrument heterogeneity for proteins with 2 or more SNPs, and MR-Egger regression was used to assess directional horizontal pleiotropy for proteins with 3 or more SNPs. Weighted median MR was performed to estimate the proteins-SBP associations when the heterogeneity test was significant but without horizontal pleiotropy, whereas MR-Egger regression was used when the horizontal pleiotropy test was significant. MR Steiger directionality test was conducted to compare the variance explained in proteins and SBP by SNPs and to test their causal direction. All MR analyses were performed using the R package "TwoSampleMR".

There may be bias due to the participant overlap between the two GWAS studies [10], as both GWAS included participants from the UK Biobank. To assess this potential bias, we re-performed MR analysis based on the above harmonized datasets using R package "MendelianRandomization". For proteins with only 1 SNP instrument, Wald ratio was calculated. For proteins with 2 or more SNPs, inverse variance weighted MR with fixed effects was performed and if the heterogeneity test was significant, inverse variance weighted MR with random effects was performed. All the analyses were carried out using the function "MendelianRandomization::mr_mr_ivw", allowing setting a correlation parameter psi, which indicates the correlation between the association with the exposure and the association with the outcome for each variant resulting from sample overlap [11]. The parameter psi is set to 0 when there is no participant overlap, and arises if the samples for the associations with the exposure and the outcome overlap. Since we were unable to estimate the exact correction parameter psi among overlapping samples, we set several values for psi (0.1, 0.3, 0.5, 0.7, and 0.9) to assess the bias due to participant overlap.

All analyses were conducted by R version 4.1.0 (R Development Core Team, Vienna, Austria) and RStudio version 1.4.1717 (RStudio, Boston, MA, USA).

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Figure S1. General study design of the MONICA/KORA study.
Abbreviations: KORA, Cooperative Health Research in the Region of Augsburg; MONICA, Monitoring of Trends and Determinants in Cardiovascular Diseases

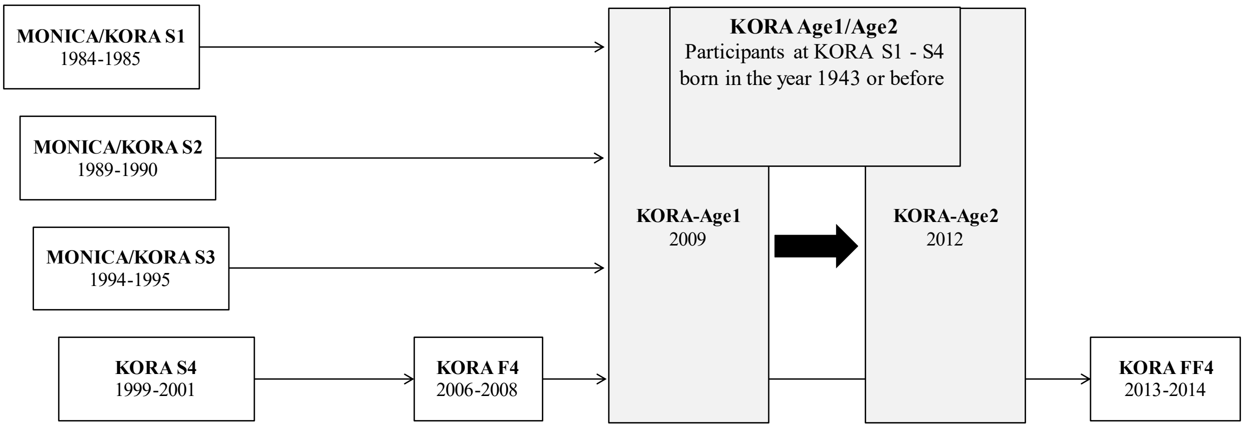
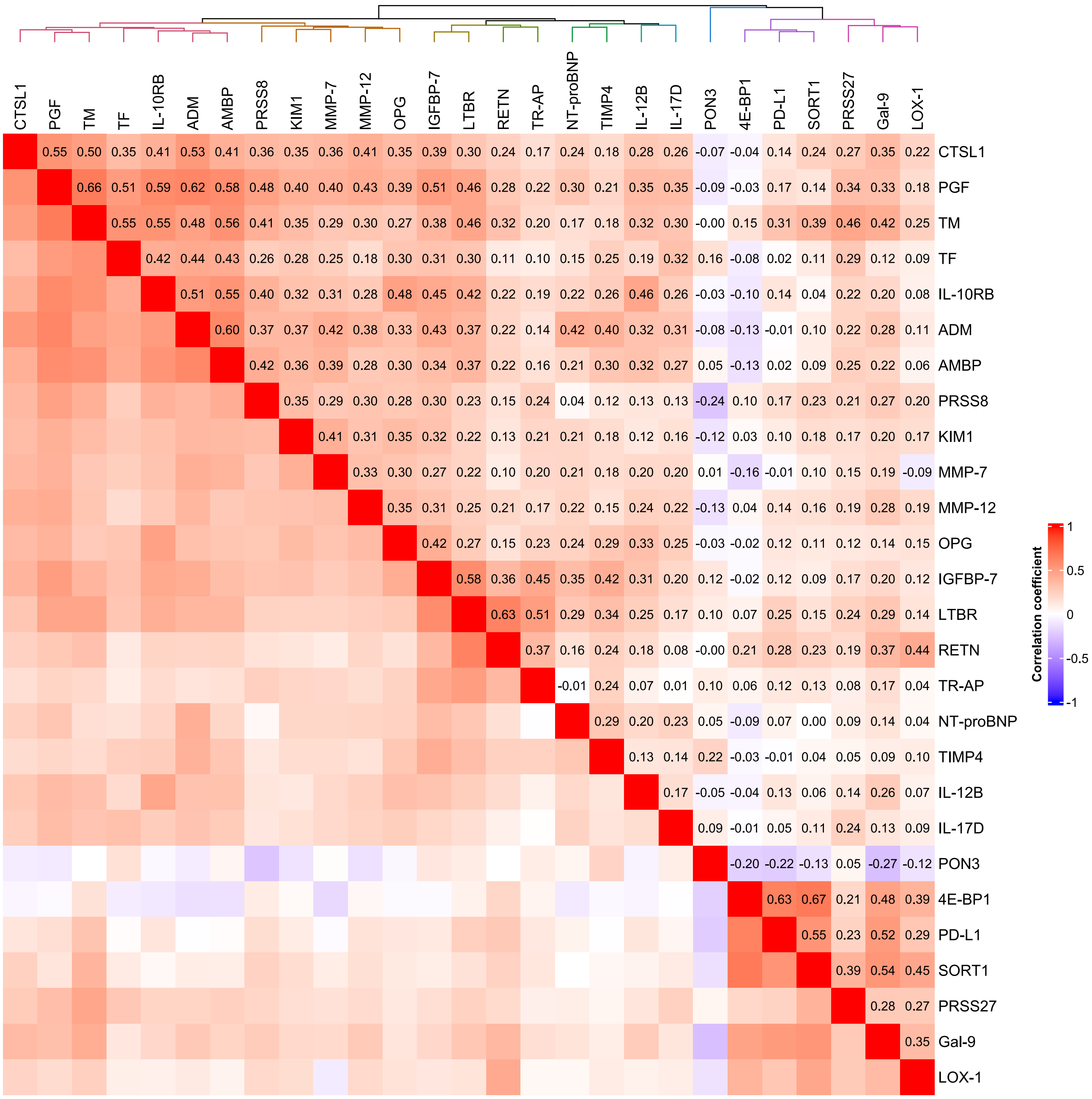


Figure S2. Pairwise correlation matrix between the 27 validated proteins associated with hypertension and systolic blood pressure (Figure 4B) among 1560 participants from the KORA S4 study.

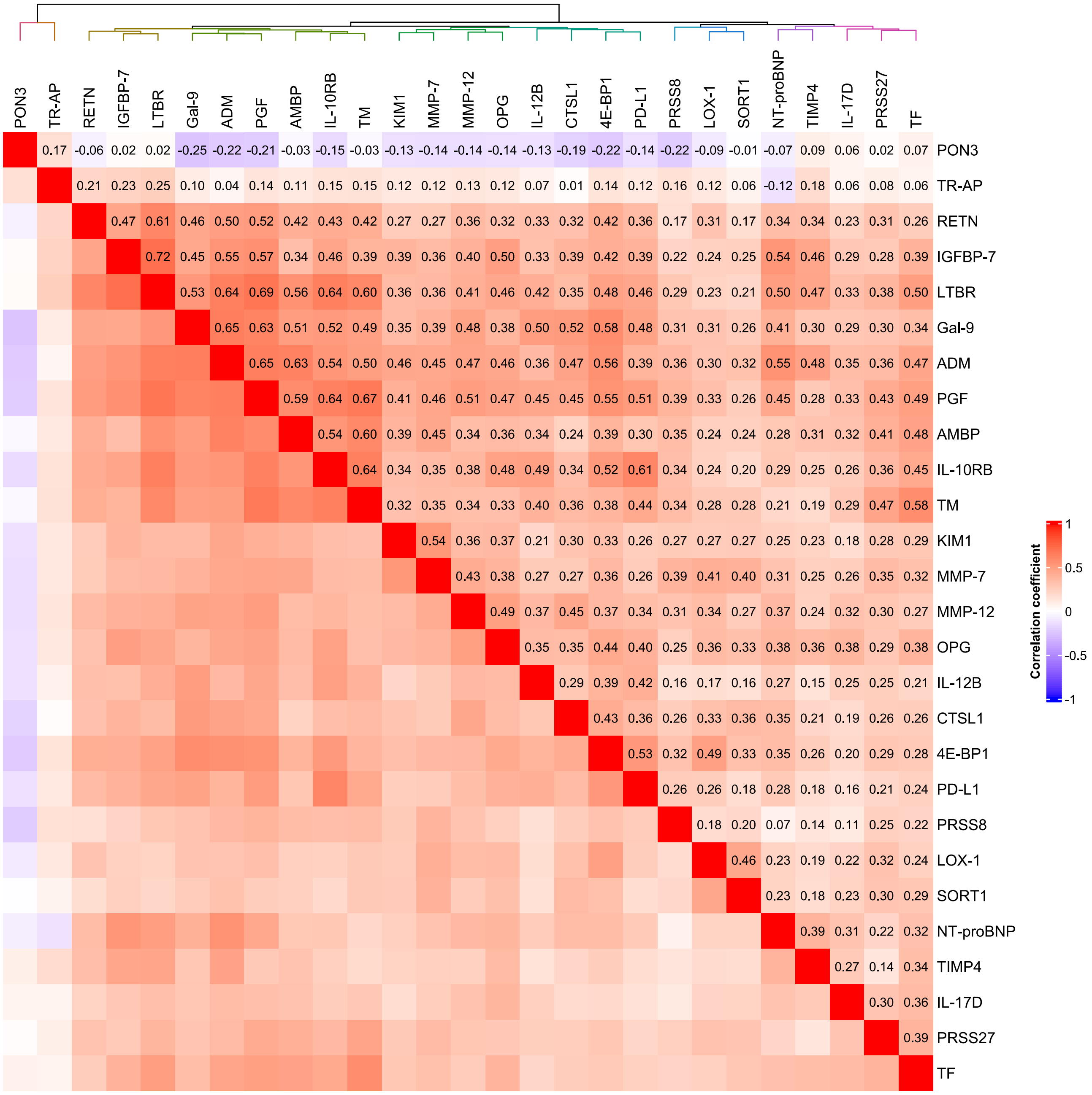
Abbreviations: KORA, Cooperative Health Research in the Region of Augsburg; Full names of the proteins can be found in Table S1.



CTSL1	PGF	TM	TF	IL-10RB	ADM	AMBP	PRSS8	KIM1	MMP-7	MMP-12	OPG	IGFBP-7	LTBR	RETN	TR-AP	NT-proBNP	TIMP4	IL-12B	IL-17D	PON3	4E-BP1	PD-L1	SORT1	PRSS27	Gal-9	LOX-1	
	0.55	0.50	0.35	0.41	0.53	0.41	0.36	0.35	0.36	0.41	0.35	0.39	0.30	0.24	0.17	0.24	0.18	0.28	0.26	-0.07	-0.04	0.14	0.24	0.27	0.35	0.22	CTSL1
		0.66	0.51	0.59	0.62	0.58	0.48	0.40	0.40	0.43	0.39	0.51	0.46	0.28	0.22	0.30	0.21	0.35	0.35	-0.09	-0.03	0.17	0.14	0.34	0.33	0.18	PGF
			0.55	0.55	0.48	0.56	0.41	0.35	0.29	0.30	0.27	0.38	0.46	0.32	0.20	0.17	0.18	0.32	0.30	-0.00	0.15	0.31	0.39	0.46	0.42	0.25	TM
				0.42	0.44	0.43	0.26	0.28	0.25	0.18	0.30	0.31	0.30	0.11	0.10	0.15	0.25	0.19	0.32	0.16	-0.08	0.02	0.11	0.29	0.12	0.09	TF
					0.51	0.55	0.40	0.32	0.31	0.28	0.48	0.45	0.42	0.22	0.19	0.22	0.26	0.46	0.26	-0.03	-0.10	0.14	0.04	0.22	0.20	0.08	IL-10RB
						0.60	0.37	0.37	0.42	0.38	0.33	0.43	0.37	0.22	0.14	0.42	0.40	0.32	0.31	-0.08	-0.13	-0.01	0.10	0.22	0.28	0.11	ADM
							0.42	0.36	0.39	0.28	0.30	0.34	0.37	0.22	0.16	0.21	0.30	0.32	0.27	0.05	-0.13	0.02	0.09	0.25	0.22	0.06	AMBP
								0.35	0.29	0.30	0.28	0.30	0.23	0.15	0.24	0.04	0.12	0.13	0.13	-0.24	0.10	0.17	0.23	0.21	0.27	0.20	PRSS8
									0.41	0.31	0.35	0.32	0.22	0.13	0.21	0.21	0.18	0.12	0.16	-0.12	0.03	0.10	0.18	0.17	0.20	0.17	KIM1
										0.33	0.30	0.27	0.22	0.10	0.20	0.21	0.18	0.20	0.20	0.01	-0.16	-0.01	0.10	0.15	0.19	-0.09	MMP-7
											0.35	0.31	0.25	0.21	0.17	0.22	0.15	0.24	0.22	-0.13	0.04	0.14	0.16	0.19	0.28	0.19	MMP-12
												0.42	0.27	0.15	0.23	0.24	0.29	0.33	0.25	-0.03	-0.02	0.12	0.11	0.12	0.14	0.15	OPG
													0.58	0.36	0.45	0.35	0.42	0.31	0.20	0.12	-0.02	0.12	0.09	0.17	0.20	0.12	IGFBP-7
														0.63	0.51	0.29	0.34	0.25	0.17	0.10	0.07	0.25	0.15	0.24	0.29	0.14	LTBR
															0.37	0.16	0.24	0.18	0.08	-0.00	0.21	0.28	0.23	0.19	0.37	0.44	RETN
																-0.01	0.24	0.07	0.01	0.10	0.06	0.12	0.13	0.08	0.17	0.04	TR-AP
																	0.29	0.20	0.23	0.05	-0.09	0.07	0.00	0.09	0.14	0.04	NT-proBNP
																		0.13	0.14	0.22	-0.03	-0.01	0.04	0.05	0.09	0.10	TIMP4
																			0.17	-0.05	-0.04	0.13	0.06	0.14	0.26	0.07	IL-12B
																				0.09	-0.01	0.05	0.11	0.24	0.13	0.09	IL-17D
																					-0.20	-0.22	-0.13	0.05	-0.27	-0.12	PON3
																						0.63	0.67	0.21	0.48	0.39	4E-BP1
																							0.55	0.23	0.52	0.29	PD-L1
																								0.39	0.54	0.45	SORT1
																									0.28	0.27	PRSS27
																										0.35	Gal-9
																											LOX-1

Figure S3. Pairwise correlation matrix between the 27 validated proteins associated with hypertension and systolic blood pressure (Figure 4B) among 1024 participants from the KORA-Age1 study.

Abbreviations: KORA, Cooperative Health Research in the Region of Augsburg; Full names of the proteins can be found in Table S1.



	PON3	TR-AP	RETN	IGFBP-7	LTBR	Gal-9	ADM	PGF	AMBP	IL-10RB	TM	KIM1	MMP-7	MMP-12	OPG	IL-12B	CTSL1	4E-BP1	PD-L1	PRSS8	LOX-1	SORT1	NT-proBNP	TIMP4	IL-17D	PRSS27	TF
PON3		0.17	-0.06	0.02	0.02	-0.25	-0.22	-0.21	-0.03	-0.15	-0.03	-0.13	-0.14	-0.14	-0.14	-0.13	-0.19	-0.22	-0.14	-0.22	-0.09	-0.01	-0.07	0.09	0.06	0.02	0.07
TR-AP			0.21	0.23	0.25	0.10	0.04	0.14	0.11	0.15	0.15	0.12	0.12	0.13	0.12	0.07	0.01	0.14	0.12	0.16	0.12	0.06	-0.12	0.18	0.06	0.08	0.06
RETN				0.47	0.61	0.46	0.50	0.52	0.42	0.43	0.42	0.27	0.27	0.36	0.32	0.33	0.32	0.42	0.36	0.17	0.31	0.17	0.34	0.34	0.23	0.31	0.26
IGFBP-7					0.72	0.45	0.55	0.57	0.34	0.46	0.39	0.39	0.36	0.40	0.50	0.33	0.39	0.42	0.39	0.22	0.24	0.25	0.54	0.46	0.29	0.28	0.39
LTBR						0.53	0.64	0.69	0.56	0.64	0.60	0.36	0.36	0.41	0.46	0.42	0.35	0.48	0.46	0.29	0.23	0.21	0.50	0.47	0.33	0.38	0.50
Gal-9							0.65	0.63	0.51	0.52	0.49	0.35	0.39	0.48	0.38	0.50	0.52	0.58	0.48	0.31	0.31	0.26	0.41	0.30	0.29	0.30	0.34
ADM								0.65	0.63	0.54	0.50	0.46	0.45	0.47	0.46	0.36	0.47	0.56	0.39	0.36	0.30	0.32	0.55	0.48	0.35	0.36	0.47
PGF									0.59	0.64	0.67	0.41	0.46	0.51	0.47	0.45	0.45	0.55	0.51	0.39	0.33	0.26	0.45	0.28	0.33	0.43	0.49
AMBP										0.54	0.60	0.39	0.45	0.34	0.36	0.34	0.24	0.39	0.30	0.35	0.24	0.24	0.28	0.31	0.32	0.41	0.48
IL-10RB											0.64	0.34	0.35	0.38	0.48	0.49	0.34	0.52	0.61	0.34	0.24	0.20	0.29	0.25	0.26	0.36	0.45
TM												0.32	0.35	0.34	0.33	0.40	0.36	0.38	0.44	0.34	0.28	0.28	0.21	0.19	0.29	0.47	0.58
KIM1													0.54	0.36	0.37	0.21	0.30	0.33	0.26	0.27	0.27	0.27	0.25	0.23	0.18	0.28	0.29
MMP-7														0.43	0.38	0.27	0.27	0.36	0.26	0.39	0.41	0.40	0.31	0.25	0.26	0.35	0.32
MMP-12															0.49	0.37	0.45	0.37	0.34	0.31	0.34	0.27	0.37	0.24	0.32	0.30	0.27
OPG																0.35	0.35	0.44	0.40	0.25	0.36	0.33	0.38	0.36	0.38	0.29	0.38
IL-12B																	0.29	0.39	0.42	0.16	0.17	0.16	0.27	0.15	0.25	0.25	0.21
CTSL1																		0.43	0.36	0.26	0.33	0.36	0.35	0.21	0.19	0.26	0.26
4E-BP1																			0.53	0.32	0.49	0.33	0.35	0.26	0.20	0.29	0.28
PD-L1																				0.26	0.26	0.18	0.28	0.18	0.16	0.21	0.24
PRSS8																					0.18	0.20	0.07	0.14	0.11	0.25	0.22
LOX-1																						0.46	0.23	0.19	0.22	0.32	0.24
SORT1																							0.23	0.18	0.23	0.30	0.29
NT-proBNP																								0.39	0.31	0.22	0.32
TIMP4																									0.27	0.14	0.34
IL-17D																										0.30	0.36
PRSS27																											0.39
TF																											

Supplemental Table S1-S13

Associations of proteomics with hypertension and systolic blood pressure: KORA S4/F4/FF4 and KORA Age1/Age2 cohort studies

Jie-sheng Lin, MSc, Agnese Petrera, PhD, Stefanie M. Hauck, PhD, Christian L. Müller, PhD, Annette Peters, PhD, Barbara Thorand, PhD

Excel file of Supplemental Table S1-S13 is available online

Table S1. Normalized expression values for proteomic biomarkers at KORA S4 and KORA-Age1

Full name	Protein	UniProt_ID	Panel	KORA S4, 1999-2001 (N = 1560)		KORA-Age1, 2009 (N = 1024)
				Mean (SD)		Mean (SD)
Eukaryotic translation initiation factor 4E-binding protein 1	4E-BP1	Q13541	Inflammation	9.25 (1.19)		5.08 (0.65)
Angiotensin-converting enzyme 2	ACE2	Q9BYF1	CVD II	4.21 (0.70)		4.04 (0.68)
Adenosine deaminase	ADA	P00813	Inflammation	6.35 (0.76)		5.29 (0.37)
A disintegrin and metalloase with thrombospondin motifs 13	ADAM-TS13	Q76LX8	CVD II	6.29 (0.13)		5.83 (0.18)
Adrenomedullin	ADM	P35318	CVD II	6.86 (0.48)		10.0 (0.41)
Agouti-related	AGRP	O00253	CVD II	5.05 (0.48)		4.90 (0.47)
CD166 antigen	ALCAM	Q13740	CVD III	7.10 (0.31)		7.53 (0.29)
Protein AMBP	AMBP	P02760	CVD II	8.11 (0.22)		8.35 (0.21)
Angiopoietin-1	ANG-1	Q15389	CVD II	9.66 (1.02)		8.64 (0.98)
Aminopeptidase N	AP-N	P15144	CVD III	4.81 (0.33)		6.12 (0.34)
Axin-1	Axin-1	O15169	Inflammation	6.27 (1.61)		2.50 (0.66)
Tyrosine-kinase receptor UFO	AXL	P30530	CVD III	8.78 (0.37)		8.70 (0.37)
Bone morphogenetic	BMP-6	P22004	CVD II	5.11 (0.58)		4.24 (0.42)
Brother of CDO	BOC	Q9BWV1	CVD II	4.27 (0.30)		4.12 (0.25)
Carbonic anhydrase 5A, mitochondrial	CA5A	P35218	CVD II	2.28 (0.96)		3.08 (1.01)
Caspase-3	CASP-3	P42574	CVD III	7.57 (1.44)		5.20 (0.86)
Caspase-8	CASP8	Q14790	Inflammation	2.73 (0.99)		1.52 (0.47)
Eotaxin	CCL11	P51671	Inflammation	6.51 (0.58)		6.55 (0.57)
Monocyte chemotactic protein 4	CCL13	Q99616	Inflammation	12.6 (1.06)		12.1 (0.88)
C-C motif chemokine 15	CCL15	Q16663	CVD III	6.64 (0.52)		7.89 (0.58)
C-C motif chemokine 16	CCL16	O15467	CVD III	6.16 (0.58)		7.08 (0.64)
C-C motif chemokine 17	CCL17	Q92583	CVD II	8.54 (1.13)		7.61 (0.90)
C-C motif chemokine 19	CCL19	Q99731	Inflammation	7.55 (1.25)		9.05 (1.19)
Monocyte chemotactic protein 1	CCL2	P13500	Inflammation	11.5 (0.51)		10.5 (0.48)
C-C motif chemokine 20	CCL20	P78556	Inflammation	4.39 (1.23)		5.86 (1.25)
C-C motif chemokine 23	CCL23	P55773	Inflammation	9.22 (0.55)		10.1 (0.62)
C-C motif chemokine 24	CCL24	O00175	CVD III	4.81 (0.93)		5.32 (0.96)
C-C motif chemokine 25	CCL25	O15444	Inflammation	5.94 (0.55)		5.73 (0.60)
C-C motif chemokine 28	CCL28	Q9NRJ3	Inflammation	2.14 (0.39)		1.74 (0.57)
Macrophage inflammatory protein-1alpha	CCL3	P10147	Inflammation	5.03 (0.62)		5.75 (0.61)
C-C motif chemokine 4	CCL4	P13236	Inflammation	6.16 (0.73)		5.52 (0.73)
Monocyte chemotactic protein 3	CCL7	P80098	Inflammation	1.91 (0.62)		1.31 (0.69)
Scavenger receptor cysteine-rich type 1 M130	CD163	Q86VB7	CVD III	7.94 (0.56)		8.31 (0.53)
Natural killer cell receptor 2B4	CD244	Q9BZW8	Inflammation	7.47 (0.59)		4.84 (0.36)
T-cell surface glycoCD4	CD4	P01730	CVD II	5.36 (0.51)		5.07 (0.35)
CD40L receptor	CD40	P25942	Inflammation	12.1 (0.63)		10.5 (0.53)
CD40 ligand	CD40-L	P29965	CVD II	6.55 (1.49)		2.78 (0.72)
T-cell surface glycoprotein CD5	CD5	P06127	Inflammation	5.73 (0.79)		5.25 (0.50)
T cell surface glycoprotein CD6 isoform	CD6	P30203	Inflammation	6.31 (0.96)		5.00 (0.55)
SLAM family member 5	CD84	Q9UIB8	CVD II	5.32 (0.55)		5.13 (0.38)
T-cell surface glycoprotein CD8 alpha chain	CD8A	P01732	Inflammation	9.92 (0.68)		8.93 (0.72)
Complement component C1q receptor	CD93	Q9NPY3	CVD III	10.6 (0.36)		10.8 (0.34)
CUB domain-containing protein 1	CDCP1	Q9H5V8	Inflammation	3.70 (0.67)		4.20 (0.65)
Cadherin-5	CDH5	P33151	CVD III	4.31 (0.39)		4.02 (0.39)
Carcinoembryonic antigen-related cell adhesion molecule 8	CEACAM8	P31997	CVD II	4.28 (0.76)		4.52 (0.63)
Chitinase-3-like 1	CHI3L1	P36222	CVD III	3.95 (0.96)		6.67 (1.04)
Chitotriosidase-1	CHIT1	Q13231	CVD III	5.19 (1.49)		NA

Table S1. Normalized expression values for proteomic biomarkers at KORA S4 and KORA-Age1

Full name	Protein	UniProt_ID	Panel	KORA S4, 1999-2001 (N = 1560)		KORA-Age1, 2009 (N = 1024)
				Mean (SD)		Mean (SD)
Contactin-1	CNTN1	Q12860	CVD III	4.42 (0.39)		3.35 (0.37)
Collagen alpha-1(I) chain	COL1A1	P02452	CVD III	2.80 (0.41)		2.12 (0.50)
Carboxypeptidase A1	CPA1	P15085	CVD III	5.62 (0.72)		6.07 (0.76)
Carboxypeptidase B	CPB1	P15086	CVD III	5.52 (0.69)		6.56 (0.71)
Macrophage colony-stimulating factor 1	CSF1	P09603	Inflammation	10.0 (0.23)		9.49 (0.38)
Cystatin D	CST5	P28325	Inflammation	5.43 (0.54)		7.67 (0.59)
Cystatin-B	CSTB	P04080	CVD III	4.43 (0.76)		4.07 (0.65)
Chymotrypsin C	CTRC	Q99895	CVD II	9.64 (0.79)		10.2 (0.84)
Cathepsin L1	CTSL1	P07711	CVD II	6.94 (0.32)		7.51 (0.37)
Cathepsin Z	CTSZ	Q9UBR2	CVD III	5.45 (0.45)		4.83 (0.38)
Fractalkine	CX3CL1	P78423	Inflammation	5.75 (0.42)		4.52 (0.62)
C-X-C motif chemokine 1	CXCL1	P09341	Inflammation	9.31 (1.18)		7.54 (0.96)
C-X-C motif chemokine 10	CXCL10	P02778	Inflammation	8.94 (0.95)		7.35 (1.03)
C-X-C motif chemokine 11	CXCL11	O14625	Inflammation	7.39 (1.23)		5.39 (0.95)
C-X-C motif chemokine 16	CXCL16	Q9H2A7	CVD III	4.86 (0.32)		5.95 (0.34)
C-X-C motif chemokine 5	CXCL5	P42830	Inflammation	11.1 (1.46)		9.48 (1.37)
C-X-C motif chemokine 6	CXCL6	P80162	Inflammation	8.26 (1.01)		5.78 (0.69)
C-X-C motif chemokine 9	CXCL9	Q07325	Inflammation	7.17 (0.77)		6.95 (1.00)
Decorin	DCN	P07585	CVD II	5.11 (0.28)		5.20 (0.32)
2,4-dienoyl-CoA reductase, mitochondrial	DECR1	Q16698	CVD II	8.76 (1.45)		4.59 (0.89)
Dickkopf-related 1	Dkk-1	O94907	CVD II	9.04 (0.79)		8.37 (0.60)
delta homolog 1	DLK-1	P80370	CVD III	5.88 (0.65)		7.01 (0.61)
Delta and Notch-like epidermal growth factor-related receptor	DNER	Q8NFT8	Inflammation	9.26 (0.25)		8.34 (0.44)
Epidermal growth factor receptor	EGFR	P00533	CVD III	2.97 (0.23)		3.19 (0.24)
Protein S100-A12	EN-RAGE	P80511	Inflammation	2.29 (0.92)		2.56 (1.06)
Epithelial cell adhesion molecule	Ep-CAM	P16422	CVD III	5.13 (1.05)		4.88 (1.05)
Ephrin type-B receptor 4	EPHB4	P54760	CVD III	5.44 (0.34)		4.97 (0.39)
Fatty acid-binding, intestinal	FABP2	P12104	CVD II	9.12 (0.75)		8.50 (0.83)
Fatty acid-binding, adipocyte	FABP4	P15090	CVD III	5.37 (0.78)		4.50 (0.93)
Tumor necrosis factor receptor superfamily member 6	FAS	P25445	CVD III	5.84 (0.49)		6.46 (0.42)
Fibroblast growth factor 19	FGF19	O95750	Inflammation	7.81 (0.95)		8.67 (1.01)
Fibroblast growth factor 21	FGF21	Q9NSA1	Inflammation	5.82 (1.15)		5.38 (1.26)
Fibroblast growth factor 23	FGF-23	Q9GZV9	CVD II	3.86 (0.58)		1.25 (0.69)
Fms-related tyrosine kinase 3 ligand	FLT3L	P49771	Inflammation	9.28 (0.41)		9.22 (0.48)
Follistatin	FS	P19883	CVD II	11.8 (0.42)		12.1 (0.41)
Galectin-4	Gal-4	P56470	CVD III	3.69 (0.51)		4.31 (0.56)
Galectin-9	Gal-9	O00182	CVD II	8.87 (0.37)		9.02 (0.35)
Growth/differentiation factor 15	GDF-15	Q99988	CVD III	5.25 (0.56)		5.11 (0.66)
Growth/differentiation factor 2	GDF-2	Q9UK05	CVD II	8.89 (0.56)		8.92 (0.55)
Growth hormone	GH	P01241	CVD II	8.03 (2.09)		9.47 (1.85)
Gastric intrinsic factor	GIF	P27352	CVD II	7.95 (1.03)		8.31 (1.21)
Lactoylglutathione lyase	GLO1	Q04760	CVD II	6.89 (1.14)		4.19 (0.58)
Human GPVI Antibody	GPVI	Q9HCN6	CVD III	3.01 (0.98)		1.46 (0.43)
Granulins	GRN	P28799	CVD III	5.23 (0.34)		5.40 (0.36)
Gastrotropin	GT	P51161	CVD II	1.74 (0.65)		2.07 (0.70)
Hydroxyacid oxidase 1	HAOX1	Q9UJM8	CVD II	5.35 (1.41)		6.13 (1.38)
Proheparin-binding EGF-like growth factor	HB-EGF	Q99075	CVD II	6.39 (0.68)		4.29 (0.50)

Table S1. Normalized expression values for proteomic biomarkers at KORA S4 and KORA-Age1

Full name	Protein	UniProt_ID	Panel	KORA S4, 1999-2001 (N = 1560)		KORA-Age1, 2009 (N = 1024)
				Mean (SD)		Mean (SD)
Hepatocyte growth factor	HGF	P14210	Inflammation	8.92 (0.46)		7.85 (0.47)
Heme oxygenase 1	HO-1	P09601	CVD II	11.5 (0.40)		12.5 (0.37)
Osteoclast-associated immunoglobulin-like receptor	hOSCAR	Q8IYS5	CVD II	10.7 (0.24)		10.8 (0.24)
Heat shock 27 kDa	HSP 27	P04792	CVD II	10.3 (0.34)		12.5 (0.52)
Intercellular adhesion molecule 2	ICAM-2	P13598	CVD III	4.94 (0.42)		5.28 (0.40)
Alpha-L-iduronidase	IDUA	P35475	CVD II	6.41 (0.47)		6.07 (0.50)
Interferon-gamma	IFNG	P01579	Inflammation	6.82 (0.95)		7.07 (1.11)
Insulin-like growth factor-binding 1	IGFBP-1	P08833	CVD III	5.22 (1.07)		5.68 (1.17)
Insulin-like growth factor-binding 2	IGFBP-2	P18065	CVD III	7.41 (0.72)		8.48 (0.76)
Insulin-like growth factor-binding 7	IGFBP-7	Q16270	CVD III	7.39 (0.40)		8.04 (0.49)
Low affinity immunoglobulin gamma Fc region receptor II-b	IgG Fc receptor II-b	P31994	CVD II	3.65 (0.91)		2.73 (0.82)
Interleukin-10	IL-10	P22301	Inflammation	3.38 (0.67)		2.48 (0.84)
Interleukin-10 receptor subunit beta	IL-10RB	Q08334	Inflammation	5.85 (0.33)		5.82 (0.34)
Interleukin-12 subunit beta	IL-12B	P29460	Inflammation	5.50 (0.68)		6.00 (0.73)
Interleukin-15 receptor subunit alpha	IL-15RA	Q13261	Inflammation	1.24 (0.34)		1.06 (0.51)
Pro-interleukin-16	IL-16	Q14005	CVD II	7.86 (1.20)		6.06 (0.51)
Interleukin-17D	IL-17D	Q8TAD2	CVD II	2.50 (0.39)		2.92 (0.36)
Interleukin-17 receptor A	IL-17RA	Q96F46	CVD III	4.15 (0.69)		3.70 (0.52)
Interleukin-18	IL-18	Q14116	CVD II	8.28 (0.76)		8.95 (0.59)
Interleukin-18-binding protein	IL-18BP	O95998	CVD III	6.16 (0.38)		6.81 (0.42)
Interleukin-18 receptor 1	IL-18R1	Q13478	Inflammation	8.44 (0.41)		6.73 (0.40)
Interleukin-1 receptor antagonist	IL-1RA	P18510	CVD II	5.14 (0.81)		4.77 (0.65)
Interleukin-1 receptor-like 2	IL1-RL2	Q9HB29	CVD II	5.07 (0.47)		4.87 (0.42)
Interleukin-1 receptor type 1	IL-1RT1	P14778	CVD III	6.33 (0.31)		5.54 (0.31)
Interleukin-1 receptor type 2	IL-1RT2	P27930	CVD III	5.55 (0.36)		6.00 (0.35)
Interleukin-27	IL-27	Q8NEV9	CVD II	6.15 (0.39)		6.25 (0.40)
Interleukin-2 receptor subunit alpha	IL2-RA	P01589	CVD III	3.37 (0.45)		4.31 (0.54)
Interleukin-4 receptor subunit alpha	IL-4RA	P24394	CVD II	2.29 (0.35)		2.67 (0.40)
Interleukin-6	IL-6	P05231	Inflammation	2.78 (0.89)		2.78 (1.04)
Interleukin-6 receptor subunit alpha	IL-6RA	P08887	CVD III	11.7 (0.40)		12.6 (0.38)
Interleukin-7	IL-7	P13232	Inflammation	3.38 (0.77)		0.75 (0.56)
Interleukin-8	IL-8	P10145	Inflammation	5.43 (0.80)		4.99 (0.73)
Melusin	ITGB1BP2	Q9UKP3	CVD II	7.42 (1.61)		2.19 (0.75)
Integrin beta-2	ITGB2	P05107	CVD III	6.17 (1.02)		6.12 (0.48)
Junctional adhesion molecule A	JAM-A	Q9Y624	CVD III	6.23 (1.22)		5.47 (0.75)
Kidney Injury Molecule 1	KIM1	Q96D42	CVD II	7.27 (0.81)		7.50 (0.86)
Kallikrein-6	KLK6	Q92876	CVD III	2.18 (0.37)		3.95 (0.42)
Low-density liporeceptor	LDL receptor	P01130	CVD III	4.32 (0.55)		4.62 (0.60)
Leptin	LEP	P41159	CVD II	7.56 (1.21)		7.44 (1.19)
Leukemia inhibitory factor receptor	LIFR	P42702	Inflammation	3.85 (0.31)		3.10 (0.33)
Tumor necrosis factor ligand superfamily member 14	LIGHT	O43557	Inflammation	5.07 (1.02)		3.44 (0.52)
Lectin-like oxidized LDL receptor 1	LOX-1	P78380	CVD II	6.65 (0.83)		6.64 (0.55)
Lipolipase	LPL	P06858	CVD II	9.52 (0.50)		9.49 (0.42)
Lymphotoxin-beta receptor	LTBR	P36941	CVD III	3.63 (0.43)		3.19 (0.43)
Macrophage receptor MARCO	MARCO	Q9UEW3	CVD II	6.07 (0.20)		7.00 (0.21)
Myoglobin	MB	P02144	CVD III	7.53 (0.58)		7.96 (0.69)
Monocyte chemotactic protein 2	MCP-2	P80075	Inflammation	8.57 (0.74)		7.40 (0.68)

Table S1. Normalized expression values for proteomic biomarkers at KORA S4 and KORA-Age1

Full name	Protein	UniProt_ID	Panel	KORA S4, 1999-2001 (N = 1560)		KORA-Age1, 2009 (N = 1024)
				Mean (SD)		Mean (SD)
Matrix extracellular phosphoglyco	MEPE	Q9NQ76	CVD III	5.34 (0.46)		4.48 (0.49)
Tyrosine-kinase Mer	MERTK	Q12866	CVD II	6.07 (0.42)		6.12 (0.37)
Matrix metalloproteinase-1	MMP-1	P03956	Inflammation	11.4 (1.25)		12.3 (1.06)
Matrix metalloase-12	MMP-12	P39900	CVD II	6.87 (0.71)		7.06 (0.79)
Matrix metalloase-2	MMP-2	P08253	CVD III	3.82 (0.38)		3.00 (0.37)
Matrix metalloase-3	MMP-3	P08254	CVD III	7.46 (0.72)		6.44 (0.75)
Matrix metalloase-7	MMP-7	P09237	CVD II	10.0 (0.72)		11.3 (0.50)
Matrix metalloase-9	MMP-9	P14780	CVD III	4.90 (0.86)		4.00 (0.85)
Myeloperoxidase	MPO	P05164	CVD III	3.75 (0.79)		3.29 (0.63)
NF-kappa-B essential modulator	NEMO	Q9Y6K9	CVD II	8.07 (1.28)		3.78 (0.65)
Neurogenic locus notch homolog 3	Notch 3	Q9UM47	CVD III	5.02 (0.42)		5.23 (0.45)
Neurotrophin-3	NT3	P20783	Inflammation	2.24 (0.42)		2.45 (0.59)
N-terminal pro-B-type natriuretic peptide	NT-proBNP	P16860	CVD III	3.46 (1.12)		3.91 (1.35)
Osteoprotegerin	OPG	O00300	Inflammation	10.0 (0.36)		9.47 (0.39)
Osteopontin	OPN	P10451	CVD III	7.18 (0.53)		7.64 (0.65)
Oncostatin-M	OSM	P13725	Inflammation	3.56 (0.89)		2.92 (0.79)
Plasminogen activator inhibitor 1	PAI	P05121	CVD III	6.46 (0.88)		5.13 (0.92)
ase-activated receptor 1	PAR-1	P25116	CVD II	9.43 (0.63)		8.56 (0.52)
Poly [ADP-ribose] polymerase 1	PARP-1	P09874	CVD II	5.71 (2.00)		4.16 (0.52)
Proconvertase subtilisin/kexin type 9	PCSK9	Q8NBP7	CVD III	3.38 (0.39)		2.84 (0.38)
Platelet-derived growth factor subunit A	PDGF subunit A	P04085	CVD III	4.08 (1.02)		2.02 (0.85)
Platelet-derived growth factor subunit B	PDGF subunit B	P01127	CVD II	10.6 (1.06)		7.77 (1.20)
Programmed cell death 1 ligand 1	PD-L1	Q9NZQ7	Inflammation	7.24 (0.48)		5.64 (0.48)
Programmed cell death 1 ligand 2	PD-L2	Q9BQ51	CVD II	2.92 (0.38)		3.26 (0.38)
Platelet endothelial cell adhesion molecule	PECAM-1	P16284	CVD III	5.63 (0.87)		4.58 (0.49)
Placenta growth factor	PGF	P49763	CVD II	7.68 (0.38)		8.09 (0.40)
Peptidoglycan recognition 1	PGLYRP1	O75594	CVD III	6.87 (0.50)		7.64 (0.57)
Polymeric immunoglobulin receptor	PIgR	P01833	CVD II	6.86 (0.15)		6.79 (0.15)
Perlecan	PLC	P98160	CVD III	7.88 (0.33)		8.14 (0.38)
Paraoxonase	PON3	Q15166	CVD III	6.07 (0.69)		6.04 (0.62)
Prolargin	PRELP	P51888	CVD II	8.58 (0.26)		8.70 (0.26)
Serine protease 27	PRSS27	Q9BQR3	CVD II	8.93 (0.45)		8.89 (0.45)
Prostasin	PRSS8	Q16651	CVD II	8.85 (0.39)		9.26 (0.43)
P-selectin glycoligand 1	PSGL-1	Q14242	CVD II	4.82 (0.36)		5.10 (0.30)
Pulmonary surfactant-associated D	PSP-D	P35247	CVD III	3.08 (0.73)		3.07 (0.75)
Pentraxin-related PTX3	PTX3	P26022	CVD II	4.69 (0.44)		4.22 (0.46)
Receptor for advanced glycosylation end products	RAGE	Q15109	CVD II	13.5 (0.44)		13.7 (0.43)
Retinoic acid receptor responder 2	RARRES2	Q99969	CVD III	11.2 (0.35)		11.4 (0.33)
Renin	REN	P00797	CVD II	6.84 (0.84)		6.70 (0.97)
Resistin	RETN	Q9HD89	CVD III	5.97 (0.58)		6.06 (0.58)
Stem cell factor	SCF	P21583	CVD II	8.87 (0.45)		9.00 (0.40)
Secretoglobin family 3A member 2	SCGB3A2	Q96PL1	CVD III	2.11 (0.87)		2.40 (0.85)
E-selectin	SELE	P16581	CVD III	11.8 (0.60)		11.4 (0.62)
P-selectin	SELP	P16109	CVD III	10.7 (0.94)		9.58 (0.55)
Serpin A12	SERPINA12	Q8IW75	CVD II	2.72 (1.07)		3.82 (1.10)
Tyrosine-phosphatase non-receptor type substrate 1	SHPS-1	P78324	CVD III	3.54 (0.52)		3.67 (0.44)
SIR2-like protein 2	SIRT2	Q8IXJ6	Inflammation	6.40 (1.70)		1.32 (0.65)

Table S1. Normalized expression values for proteomic biomarkers at KORA S4 and KORA-Age1

Full name	Protein	UniProt_ID	Panel	KORA S4, 1999-2001 (N = 1560)		KORA-Age1, 2009 (N = 1024)
				Mean (SD)		Mean (SD)
Matrix metalloproteinase-10	SL-2	P09238	Inflammation	8.45 (0.61)		8.05 (0.68)
Superoxide dismutase [Mn], mitochondrial	SOD2	P04179	CVD II	10.0 (0.10)		10.7 (0.10)
Sortilin	SORT1	Q99523	CVD II	9.14 (0.35)		7.86 (0.29)
Spondin-2	SPON2	Q9BUD6	CVD II	8.65 (0.26)		9.75 (0.19)
Proto-oncogene tyrosine-kinase Src	SRC	P12931	CVD II	8.25 (0.81)		5.95 (0.76)
Sulfotransferase 1A1	ST1A1	P50225	Inflammation	4.01 (1.13)		0.75 (0.66)
Protein ST2	ST2	Q01638	CVD III	4.14 (0.57)		4.38 (0.57)
STAM-binding protein	STAMBP	O95630	Inflammation	7.63 (1.54)		3.45 (0.43)
Serine/threonine-kinase 4	STK4	Q13043	CVD II	6.23 (0.98)		3.39 (0.82)
Tissue factor	TF	P13726	CVD II	5.53 (0.33)		6.07 (0.32)
Tissue factor pathway inhibitor	TFPI	P10646	CVD III	8.46 (0.40)		9.14 (0.38)
Transforming growth factor alpha	TGF-α	P01135	Inflammation	2.97 (0.46)		2.27 (0.46)
Latency-associated peptide transforming growth factor beta-1	TGF-β1	P01137	Inflammation	8.04 (0.58)		6.15 (0.44)
Protein-glutamine gamma-glutamyltransferase 2	TGM2	P21980	CVD II	8.92 (0.52)		8.04 (0.43)
Thrombospondin-2	THBS2	P35442	CVD II	6.36 (0.20)		6.24 (0.21)
Thrombopoietin	THPO	P40225	CVD II	3.43 (0.46)		3.92 (0.43)
Angiopoietin-1 receptor	TIE2	Q02763	CVD II	8.14 (0.25)		7.34 (0.22)
Tissue inhibitor of metalloproteinases 4	TIMP4	Q99727	CVD III	3.23 (0.53)		4.10 (0.57)
Trem-like transcript 2	TLT-2	Q5T2D2	CVD III	5.22 (0.47)		4.74 (0.52)
Thrombomodulin	TM	P07204	CVD II	10.6 (0.32)		9.76 (0.31)
Tumor necrosis factor receptor 1	TNF-R1	P19438	CVD III	6.46 (0.43)		7.09 (0.52)
Tumor necrosis factor receptor 2	TNF-R2	P20333	CVD III	5.92 (0.43)		5.75 (0.54)
Tumor necrosis factor receptor superfamily member 10A	TNFRSF10A	O00220	CVD II	3.77 (0.43)		3.32 (0.48)
Tumor necrosis factor receptor superfamily member 10C	TNFRSF10C	O14798	CVD III	6.52 (0.54)		5.72 (0.60)
Tumor necrosis factor receptor superfamily member 11A	TNFRSF11A	Q9Y6Q6	CVD II	5.90 (0.47)		5.43 (0.57)
Tumor necrosis factor receptor superfamily member 13B	TNFRSF13B	O14836	CVD II	10.1 (0.39)		10.2 (0.50)
Tumor necrosis factor receptor superfamily member 14	TNFRSF14	Q92956	CVD III	4.99 (0.56)		4.74 (0.50)
Tumor necrosis factor receptor superfamily member 9	TNFRSF9	Q07011	Inflammation	7.24 (0.47)		6.05 (0.62)
TNF-related apoptosis-inducing ligand	TNFSF10	P50591	Inflammation	8.08 (0.30)		8.35 (0.29)
Tumor necrosis factor ligand superfamily member 13B	TNFSF13B	Q9Y275	CVD III	6.93 (0.40)		6.63 (0.43)
Tumor necrosis factor-alpha	TNF-α	P01375	Inflammation	2.82 (0.53)		3.11 (0.61)
Tumor necrosis factor-beta	TNF-β	P01374	Inflammation	4.67 (0.47)		4.11 (0.49)
Tissue-type plasminogen activator	t-PA	P00750	CVD III	6.44 (0.90)		5.53 (0.56)
Transferrin receptor 1	TR	P02786	CVD III	5.75 (0.57)		5.83 (0.62)
TNF-related apoptosis-inducing ligand receptor 2	TRAIL-R2	O14763	CVD II	5.67 (0.44)		5.81 (0.59)
TNF-related activation-induced cytokine	TRANCE	O14788	Inflammation	4.56 (0.57)		4.46 (0.59)
Tartrate-resistant acid phosphatase type 5	TR-AP	P13686	CVD III	3.38 (0.41)		4.79 (0.37)
Tumor necrosis factor Ligand superfamily member 12	TWEAK	O43508	Inflammation	9.06 (0.33)		8.32 (0.33)
Urokinase-type plasminogen activator	uPA	P00749	Inflammation	9.96 (0.33)		9.48 (0.31)
Urokinase plasminogen activator surface receptor	U-PAR	Q03405	CVD III	5.40 (0.72)		5.59 (0.47)
Vascular endothelial growth factor A	VEGF-A	P15692	Inflammation	10.5 (0.45)		11.0 (0.41)
Vascular endothelial growth factor D	VEGFD	O43915	CVD II	8.15 (0.42)		8.36 (0.52)
V-set and immunoglobulin domain-containing 2	VSIG2	Q96IQ7	CVD II	4.85 (0.53)		3.94 (0.63)
von Willebrand factor	vWF	P04275	CVD III	7.51 (0.70)		NA
Lymphotactin	XCL1	P47992	CVD II	4.87 (0.58)		4.87 (0.66)

Abbreviations: CVD II, Cardiovascular II Olink panel; CVD III, Cardiovascular III Olink panel SD, standard deviation.

Table S2. Harmonized summary statistics used in two-sample Mendelian randomization analysis

SNP	exposure	UniProt_ID	effect_allele.E	other_allele.E	effect_allele.O	other_allele.O	beta.E	beta.O	eaf.E	eaf.O	chr.O	pos.O	se.O	N.O	pval.O	chr.E	pos.E	se.E	pval.E	N.E
rs10045568	IL-12B	P29460	T	C	T	C	0.058	0.072	0.575	0.569	5	158949047	0.034	595016	3.30E-02	5	159522039	0.008	1.74E-14	34049
rs10060059	IL-12B	P29460	G	A	G	A	0.176	-0.031	0.599	0.597	5	158860939	0.032	695955	3.20E-01	5	159433931	0.007	1.25E-123	34049
rs112042454	IL-12B	P29460	C	T	C	T	-0.372	0.128	0.020	0.020	5	158766570	0.111	704545	2.51E-01	5	159339562	0.025	1.80E-48	34049
rs114799616	IL-12B	P29460	C	A	C	A	-0.212	-0.008	0.041	0.037	5	158915823	0.086	647799	9.23E-01	5	159488815	0.018	1.21E-31	34049
rs115056992	IL-12B	P29460	A	T	A	T	0.187	0.151	0.060	0.056	5	158863744	0.070	663764	3.18E-02	5	159436736	0.015	1.15E-33	34049
rs116377621	IL-12B	P29460	G	A	G	A	-0.365	-0.101	0.025	0.025	5	158821370	0.099	716299	3.08E-01	5	159394362	0.023	5.61E-56	34049
rs116679244	IL-12B	P29460	C	T	C	T	0.126	0.297	0.029	0.029	5	158268315	0.097	647637	2.29E-03	5	158841307	0.022	7.76E-09	34049
rs141816421	IL-12B	P29460	A	T	A	T	-0.417	0.039	0.044	0.043	5	158705774	0.078	683287	6.20E-01	5	159278766	0.018	3.44E-121	34049
rs148653348	IL-12B	P29460	T	C	T	C	-0.326	0.462	0.017	0.017	5	158763058	0.131	623102	4.04E-04	5	159336050	0.028	1.28E-30	34049
rs2546892	IL-12B	P29460	A	G	A	G	0.245	-0.123	0.163	0.167	5	158755475	0.041	719432	2.58E-03	5	159328467	0.010	5.68E-136	34049
rs62385376	IL-12B	P29460	A	C	A	C	0.123	0.212	0.073	0.073	5	158319324	0.059	717349	2.95E-04	5	158892316	0.014	1.26E-18	34049
rs72804588	IL-12B	P29460	G	A	G	A	-0.172	0.240	0.024	0.024	5	157896533	0.108	636413	2.62E-02	5	158469525	0.024	1.17E-12	34049
rs73816544	IL-12B	P29460	C	T	C	T	0.130	0.001	0.037	0.040	5	158764938	0.079	703642	9.85E-01	5	159337930	0.019	8.92E-12	34049
rs7447732	IL-12B	P29460	T	C	T	C	0.261	0.052	0.690	0.691	5	158529135	0.033	720804	1.12E-01	5	159102127	0.008	1.00E-200	34049
rs889049	IL-12B	P29460	G	C	G	C	-0.056	0.031	0.597	0.591	5	159073887	0.031	723521	3.11E-01	5	159646880	0.007	4.16E-14	34049
rs10401670	RETN	Q9HD89	C	T	C	T	-0.186	-0.007	0.570	0.571	19	7742802	0.033	631841	8.32E-01	19	7677916	0.008	1.69E-132	33590
rs11260022	RETN	Q9HD89	A	G	A	G	0.061	-0.027	0.177	0.172	19	7765728	0.042	676633	5.27E-01	19	7700842	0.010	4.22E-10	33590
rs117029024	RETN	Q9HD89	A	G	A	G	-0.357	-0.192	0.018	0.017	19	7678488	0.130	607350	1.41E-01	19	7613602	0.029	1.66E-34	33590
rs12611038	RETN	Q9HD89	C	T	C	T	0.047	-0.034	0.653	0.659	19	7771742	0.034	658903	3.18E-01	19	7706856	0.008	5.89E-09	33590
rs3745367	RETN	Q9HD89	A	G	A	G	0.140	0.006	0.246	0.246	19	7734511	0.037	650707	8.68E-01	19	7669625	0.009	9.70E-54	33590
rs62113430	RETN	Q9HD89	T	C	T	C	0.083	0.104	0.142	0.143	19	7681910	0.043	730095	1.59E-02	19	7617024	0.011	1.02E-14	33590
rs1042579	TM	P07204	A	G	A	G	0.201	-0.081	0.192	0.196	20	23028724	0.038	736539	3.40E-02	20	23048087	0.009	4.30E-107	33693
rs13041010	TM	P07204	A	G	A	G	0.074	0.074	0.191	0.197	20	22876884	0.039	684506	6.16E-02	20	22896246	0.009	1.16E-15	33693
rs699799	TM	P07204	T	C	T	C	-0.139	0.012	0.027	0.040	20	23117887	0.093	701574	8.96E-01	20	23137250	0.022	3.27E-10	33693
rs73087653	TM	P07204	C	T	C	T	-0.147	-0.150	0.029	0.025	20	23115550	0.102	675668	1.42E-01	20	23134913	0.022	2.20E-11	33693
rs73096990	TM	P07204	G	A	G	A	-0.098	0.069	0.058	0.065	20	22905373	0.065	680878	2.86E-01	20	22924736	0.015	1.76E-10	33693
rs1047616	Gal-9	O00182	A	G	A	G	-0.075	-0.031	0.376	0.375	17	25642522	0.031	742962	3.20E-01	17	27315496	0.007	3.86E-24	33655
rs112807803	Gal-9	O00182	A	G	A	G	-0.152	-0.044	0.374	0.371	17	25875002	0.032	680289	1.78E-01	17	27547976	0.008	7.10E-88	33655
rs11653716	Gal-9	O00182	G	C	G	C	0.151	-0.171	0.031	0.037	17	26084532	0.085	714731	4.41E-02	17	27757506	0.021	4.82E-13	33655
rs11655061	Gal-9	O00182	A	G	A	G	0.287	0.008	0.440	0.440	17	25882115	0.031	709376	8.01E-01	17	27555089	0.007	1.00E-200	33655
rs117169825	Gal-9	O00182	A	G	A	G	-0.263	-0.019	0.012	0.013	17	26505946	0.148	607577	8.97E-01	17	28178920	0.035	9.81E-14	33655
rs117440679	Gal-9	O00182	T	A	T	A	-0.465	-0.010	0.016	0.017	17	25996670	0.132	621900	9.42E-01	17	27669644	0.030	1.31E-54	33655
rs118132064	Gal-9	O00182	C	G	C	G	0.245	0.053	0.012	0.012	17	26168052	0.150	660898	7.25E-01	17	27841026	0.034	5.85E-13	33655
rs141811751	Gal-9	O00182	C	A	C	A	-0.219	0.129	0.037	0.035	17	26310044	0.087	666041	1.39E-01	17	27983018	0.020	8.69E-29	33655
rs142481876	Gal-9	O00182	A	G	A	G	-0.443	-0.217	0.019	0.018	17	26007420	0.126	624417	8.51E-02	17	27680394	0.028	3.08E-58	33655
rs151166422	Gal-9	O00182	C	A	C	A	0.135	0.232	0.039	0.037	17	26138036	0.082	697265	4.86E-03	17	27811010	0.019	6.96E-13	33655
rs28943568	Gal-9	O00182	A	G	A	G	0.178	0.145	0.049	0.055	17	26082645	0.071	692197	4.21E-02	17	27755619	0.017	1.37E-26	33655

Table S2. Harmonized summary statistics used in two-sample Mendelian randomization analysis

SNP	exposure	UniProt_ID	effect_allele.E	other_allele.E	effect_allele.O	other_allele.O	beta.E	beta.O	eaf.E	eaf.O	chr.O	pos.O	se.O	N.O	pval.O	chr.E	pos.E	se.E	pval.E	N.E
rs28999370	Gal-9	O00182	C	G	C	G	0.193	-0.044	0.025	0.025	17	26108414	0.104	665992	6.72E-01	17	27781388	0.024	2.31E-16	33655
rs74637202	Gal-9	O00182	G	C	G	C	-0.231	0.073	0.023	0.021	17	26076386	0.110	687073	5.07E-01	17	27749360	0.024	8.55E-22	33655
rs76538025	Gal-9	O00182	C	G	C	G	-0.173	0.024	0.048	0.049	17	26598575	0.074	670459	7.44E-01	17	28271549	0.017	3.51E-24	33655
rs78581808	Gal-9	O00182	T	G	T	G	-0.386	-0.091	0.014	0.014	17	25972124	0.136	660200	5.04E-01	17	27645098	0.031	6.04E-35	33655
rs1053889	PD-L1	Q9NZQ7	A	G	A	G	0.050	0.020	0.567	0.565	9	4860980	0.030	739624	5.00E-01	9	4860980	0.008	2.26E-11	33436
rs10815201	PD-L1	Q9NZQ7	T	G	T	G	0.088	0.051	0.252	0.259	9	5385642	0.034	729779	1.42E-01	9	5385642	0.009	3.00E-24	33436
rs10815251	PD-L1	Q9NZQ7	A	T	A	T	-0.071	0.022	0.103	0.107	9	5599565	0.049	734214	6.47E-01	9	5599565	0.012	6.69E-09	33436
rs111229088	PD-L1	Q9NZQ7	T	G	T	G	0.203	0.085	0.033	0.031	9	5537761	0.096	644839	3.76E-01	9	5537761	0.021	2.72E-21	33436
rs117248841	PD-L1	Q9NZQ7	A	G	A	G	0.141	0.010	0.035	0.036	9	6169383	0.091	593313	9.15E-01	9	6169383	0.021	2.83E-11	33436
rs12684195	PD-L1	Q9NZQ7	C	A	C	A	0.048	-0.006	0.435	0.434	9	5274545	0.032	682324	8.40E-01	9	5274545	0.008	2.89E-10	33436
rs62557692	PD-L1	Q9NZQ7	T	G	T	G	0.118	0.005	0.046	0.044	9	5341118	0.074	722397	9.49E-01	9	5341118	0.018	4.25E-11	33436
rs72705410	PD-L1	Q9NZQ7	G	C	G	C	-0.238	-0.096	0.051	0.049	9	5426078	0.072	712305	1.84E-01	9	5426078	0.017	1.08E-44	33436
rs74791855	PD-L1	Q9NZQ7	C	T	C	T	-0.262	-0.080	0.042	0.042	9	5467256	0.080	668711	3.12E-01	9	5467256	0.019	7.87E-44	33436
rs76820622	PD-L1	Q9NZQ7	T	C	T	C	-0.143	-0.103	0.048	0.048	9	5421235	0.072	720123	1.52E-01	9	5421235	0.017	2.24E-16	33436
rs822335	PD-L1	Q9NZQ7	C	T	C	T	0.311	0.078	0.661	0.659	9	5448218	0.032	727521	1.41E-02	9	5448218	0.008	1.00E-200	33436
rs10845054	LOX-1	P78380	G	A	G	A	0.049	0.012	0.348	0.353	12	10303535	0.032	730145	7.14E-01	12	10150936	0.008	6.40E-10	33374
rs11165186	TF	P13726	C	A	C	A	0.143	-0.088	0.135	0.144	1	95088721	0.043	716660	4.18E-02	1	94623165	0.010	8.61E-45	33714
rs143287604	TF	P13726	A	G	A	G	-0.111	-0.037	0.036	0.040	1	95344994	0.081	675703	6.47E-01	1	94879438	0.019	4.48E-09	33714
rs143389615	TF	P13726	C	T	C	T	-0.155	0.121	0.022	0.021	1	95268140	0.116	613571	2.99E-01	1	94802584	0.025	2.58E-10	33714
rs2997380	TF	P13726	A	G	A	G	0.046	0.046	0.615	0.614	1	95189230	0.031	723914	1.42E-01	1	94723674	0.007	1.52E-10	33714
rs6666213	TF	P13726	G	A	G	A	0.185	-0.010	0.373	0.375	1	95274365	0.031	733251	7.38E-01	1	94808809	0.007	7.76E-145	33714
rs77251639	TF	P13726	T	G	T	G	-0.218	0.076	0.020	0.021	1	95207846	0.115	638606	5.08E-01	1	94742290	0.026	7.95E-17	33714
rs77287244	TF	P13726	T	C	T	C	0.131	0.013	0.035	0.036	1	95396698	0.084	695801	8.78E-01	1	94931142	0.019	5.07E-12	33714
rs841692	TF	P13726	T	C	T	C	-0.090	0.042	0.506	0.512	1	94995491	0.030	725898	1.70E-01	1	94529935	0.007	2.40E-38	33714
rs111782374	IL-10RB	Q08334	T	C	T	C	0.225	-0.023	0.034	0.036	21	35044489	0.089	633381	7.93E-01	21	33672183	0.020	3.31E-28	33848
rs112268545	IL-10RB	Q08334	C	T	C	T	0.114	0.052	0.037	0.034	21	34592463	0.092	638182	5.72E-01	21	33220158	0.020	8.76E-09	33848
rs11701698	IL-10RB	Q08334	G	T	G	T	0.065	-0.038	0.217	0.218	21	34393945	0.037	703855	3.06E-01	21	33021637	0.009	1.16E-12	33848
rs118022807	IL-10RB	Q08334	A	C	A	C	-0.096	-0.175	0.096	0.099	21	34847394	0.051	734239	6.19E-04	21	33475087	0.013	1.73E-14	33848
rs13052004	IL-10RB	Q08334	G	C	G	C	-0.116	0.109	0.045	0.040	21	34844455	0.085	618827	2.03E-01	21	33472148	0.018	3.73E-10	33848
rs141300348	IL-10RB	Q08334	T	C	T	C	0.207	0.015	0.025	0.027	21	35111072	0.099	679371	8.80E-01	21	33738767	0.024	4.53E-18	33848
rs148144975	IL-10RB	Q08334	A	G	A	G	0.235	0.271	0.015	0.014	21	35075297	0.143	635553	5.76E-02	21	33702992	0.031	2.84E-14	33848
rs2239573	IL-10RB	Q08334	A	G	A	G	0.279	-0.015	0.697	0.703	21	34638859	0.035	658194	6.64E-01	21	33266554	0.008	1.00E-200	33848
rs2834132	IL-10RB	Q08334	A	G	A	G	0.095	0.000	0.636	0.637	21	34555833	0.031	742529	9.95E-01	21	33183527	0.008	2.30E-35	33848
rs35704817	IL-10RB	Q08334	A	G	A	G	0.182	-0.078	0.036	0.035	21	34769729	0.086	686090	3.66E-01	21	33397423	0.020	7.19E-20	33848
rs75172755	IL-10RB	Q08334	C	T	C	T	-0.128	0.138	0.035	0.036	21	34454915	0.084	705145	9.95E-02	21	33082609	0.020	3.92E-10	33848
rs77556568	IL-10RB	Q08334	G	A	G	A	0.182	-0.060	0.025	0.027	21	35175256	0.098	719947	5.42E-01	21	33802952	0.024	1.01E-14	33848
rs8132901	IL-10RB	Q08334	T	G	T	G	0.053	-0.010	0.344	0.344	21	34525262	0.032	736373	7.49E-01	21	33152956	0.008	1.26E-11	33848

Table S2. Harmonized summary statistics used in two-sample Mendelian randomization analysis

SNP	exposure	UniProt_ID	effect_allele.E	other_allele.E	effect_allele.O	other_allele.O	beta.E	beta.O	eaf.E	eaf.O	chr.O	pos.O	se.O	N.O	pval.O	chr.E	pos.E	se.E	pval.E	N.E
rs8178484	IL-10RB	Q08334	C	T	C	T	0.500	-0.096	0.458	0.454	21	34651253	0.031	696623	2.01E-03	21	33278948	0.008	1.00E-200	33848
rs112227853	PON3	Q15166	G	A	G	A	0.258	-0.012	0.046	0.048	7	95070043	0.072	720393	8.68E-01	7	95440731	0.018	4.64E-49	33848
rs11982574	PON3	Q15166	C	T	C	T	0.114	0.109	0.055	0.060	7	95106429	0.066	701540	9.56E-02	7	95477117	0.016	1.78E-12	33848
rs2188477	PON3	Q15166	G	C	G	C	-0.061	-0.015	0.286	0.286	7	94671367	0.034	711900	6.59E-01	7	95042055	0.008	4.84E-14	33848
rs2706888	PON3	Q15166	T	C	T	C	-0.054	0.049	0.627	0.628	7	95424457	0.031	724275	1.18E-01	7	95795145	0.007	6.42E-13	33848
rs6465422	PON3	Q15166	A	G	A	G	0.075	0.063	0.251	0.251	7	94311300	0.035	714440	7.62E-02	7	94681988	0.008	5.62E-19	33848
rs705379	PON3	Q15166	A	G	A	G	0.239	0.020	0.477	0.476	7	94953895	0.031	715331	5.16E-01	7	95324583	0.007	1.00E-200	33848
rs77427869	PON3	Q15166	A	G	A	G	-0.224	-0.137	0.011	0.011	7	95648342	0.160	617431	3.92E-01	7	96019030	0.036	3.18E-10	33848
rs78641443	PON3	Q15166	A	G	A	G	0.205	-0.042	0.080	0.077	7	95124329	0.058	702526	4.66E-01	7	95495017	0.013	3.65E-53	33848
rs11225332	MMP-12	P39900	C	T	C	T	-0.065	0.047	0.403	0.404	11	102452231	0.032	690411	1.33E-01	11	102581500	0.007	1.07E-18	33658
rs11225446	MMP-12	P39900	T	G	T	G	0.131	0.021	0.145	0.140	11	102754637	0.044	726694	6.32E-01	11	102883907	0.010	1.62E-39	33658
rs117258300	MMP-12	P39900	G	A	G	A	-0.237	0.010	0.023	0.024	11	103307599	0.106	680049	9.27E-01	11	103436871	0.023	4.61E-24	33658
rs117261184	MMP-12	P39900	A	G	A	G	0.235	-0.041	0.019	0.023	11	102796794	0.112	712757	7.17E-01	11	102926065	0.026	7.83E-20	33658
rs118191062	MMP-12	P39900	C	T	C	T	-0.403	0.121	0.028	0.026	11	103026146	0.099	687884	2.19E-01	11	103155417	0.021	2.34E-81	33658
rs145242717	MMP-12	P39900	T	C	T	C	-0.448	0.126	0.060	0.067	11	102655808	0.063	699239	4.63E-02	11	102785077	0.015	1.00E-200	33658
rs17101053	MMP-12	P39900	C	G	C	G	0.105	-0.048	0.056	0.057	11	103402686	0.066	713977	4.64E-01	11	103531958	0.015	4.27E-12	33658
rs1892971	MMP-12	P39900	A	G	A	G	0.239	0.038	0.216	0.223	11	102795606	0.036	726033	2.96E-01	11	102924877	0.009	2.95E-172	33658
rs3758861	MMP-12	P39900	A	G	A	G	0.101	-0.009	0.125	0.134	11	102598600	0.044	732940	8.35E-01	11	102727869	0.011	1.20E-21	33658
rs504875	MMP-12	P39900	A	G	A	G	0.544	-0.011	0.950	0.943	11	102678441	0.068	691786	8.72E-01	11	102807710	0.016	1.00E-200	33658
rs539860	MMP-12	P39900	T	C	T	C	-0.113	0.088	0.588	0.593	11	102845816	0.031	707425	4.70E-03	11	102975087	0.007	6.27E-57	33658
rs72978276	MMP-12	P39900	G	A	G	A	-0.101	0.058	0.143	0.138	11	102293494	0.046	664111	2.08E-01	11	102422763	0.010	3.72E-24	33658
rs11225418	MMP-7	P09237	C	A	C	A	-0.062	-0.017	0.229	0.232	11	102640805	0.036	729442	6.45E-01	11	102770074	0.009	9.16E-13	32981
rs17881871	MMP-7	P09237	A	G	A	G	-0.219	-0.101	0.015	0.014	11	102391788	0.138	646950	4.63E-01	11	102521057	0.030	5.82E-13	32981
rs56857975	MMP-7	P09237	T	C	T	C	0.566	-0.002	0.061	0.063	11	102397005	0.064	700338	9.80E-01	11	102526274	0.015	1.00E-200	32981
rs74666402	MMP-7	P09237	G	C	G	C	-0.170	-0.153	0.021	0.019	11	102264678	0.121	627492	2.06E-01	11	102393947	0.026	8.98E-11	32981
rs7946641	MMP-7	P09237	A	G	A	G	0.151	0.084	0.449	0.432	11	102415001	0.031	705055	6.61E-03	11	102544270	0.007	1.10E-92	32981
rs112559027	IGFBP-7	Q16270	A	G	A	G	-0.183	-0.159	0.028	0.027	4	57889023	0.095	704930	9.43E-02	4	57022857	0.021	1.85E-17	34090
rs116686317	IGFBP-7	Q16270	G	A	G	A	-0.159	0.143	0.045	0.043	4	57903239	0.080	652629	7.24E-02	4	57037073	0.017	1.09E-20	34090
rs12505579	IGFBP-7	Q16270	T	C	T	C	-0.061	0.036	0.143	0.139	4	57692939	0.045	700749	4.25E-01	4	56826773	0.010	2.51E-09	34090
rs1277295	IGFBP-7	Q16270	G	A	G	A	0.118	-0.055	0.946	0.942	4	57928957	0.066	709658	4.06E-01	4	57062791	0.016	5.31E-14	34090
rs13135301	IGFBP-7	Q16270	T	C	T	C	0.193	0.013	0.015	0.015	4	58061796	0.143	578615	9.27E-01	4	57195630	0.031	3.90E-10	34090
rs2067626	IGFBP-7	Q16270	A	G	A	G	-0.222	-0.045	0.047	0.050	4	57955561	0.078	592283	5.64E-01	4	57089395	0.017	1.34E-37	34090
rs35297343	IGFBP-7	Q16270	C	T	C	T	-0.118	0.025	0.067	0.066	4	57963121	0.067	598920	7.11E-01	4	57096955	0.015	3.24E-15	34090
rs4131368	IGFBP-7	Q16270	T	A	T	A	0.057	-0.013	0.499	0.493	4	58026924	0.031	715505	6.81E-01	4	57160758	0.007	7.42E-16	34090
rs4865187	IGFBP-7	Q16270	C	T	C	T	0.140	-0.028	0.090	0.090	4	57975148	0.053	723130	5.93E-01	4	57108982	0.012	6.37E-30	34090
rs7663799	IGFBP-7	Q16270	G	A	G	A	-0.371	0.012	0.926	0.931	4	57961809	0.060	722197	8.37E-01	4	57095643	0.014	5.89E-165	34090
rs77531259	IGFBP-7	Q16270	G	A	G	A	-0.155	0.061	0.047	0.048	4	57938199	0.072	718984	3.94E-01	4	57072033	0.017	1.78E-20	34090

Table S2. Harmonized summary statistics used in two-sample Mendelian randomization analysis

SNP	exposure	UniProt_ID	effect_allele.E	other_allele.E	effect_allele.O	other_allele.O	beta.E	beta.O	eaf.E	eaf.O	chr.O	pos.O	se.O	N.O	pval.O	chr.E	pos.E	se.E	pval.E	N.E
rs917675	IGFBP-7	Q16270	G	A	G	A	0.060	-0.064	0.269	0.269	4	58140193	0.034	726381	6.06E-02	4	57274027	0.008	9.13E-14	34090
rs11466764	KIM1	Q96D42	C	G	C	G	0.120	-0.058	0.158	0.159	5	156945657	0.042	721170	1.65E-01	5	157518649	0.009	1.14E-37	33908
rs13190482	KIM1	Q96D42	C	T	C	T	-0.332	-0.100	0.029	0.032	5	156626716	0.091	680459	2.70E-01	5	157199705	0.020	9.04E-60	33908
rs140582515	KIM1	Q96D42	C	T	C	T	0.149	-0.012	0.021	0.022	5	156480843	0.108	696583	9.10E-01	5	157053832	0.023	2.10E-10	33908
rs148658998	KIM1	Q96D42	A	G	A	G	-0.172	-0.017	0.014	0.014	5	156544919	0.134	700007	9.00E-01	5	157117908	0.029	2.12E-09	33908
rs152119	KIM1	Q96D42	G	C	G	C	-0.201	0.012	0.719	0.720	5	156616410	0.034	726254	7.18E-01	5	157189399	0.008	6.78E-155	33908
rs182445378	KIM1	Q96D42	T	C	T	C	-0.276	0.086	0.012	0.012	5	155663618	0.147	660839	5.57E-01	5	156236608	0.032	1.59E-17	33908
rs182522294	KIM1	Q96D42	T	C	T	C	-0.489	0.033	0.015	0.016	5	156489289	0.131	654295	8.01E-01	5	157062278	0.028	4.09E-68	33908
rs183793800	KIM1	Q96D42	A	G	A	G	-0.392	-0.114	0.014	0.014	5	156485435	0.142	614426	4.23E-01	5	157058424	0.030	6.20E-40	33908
rs190584164	KIM1	Q96D42	A	G	A	G	0.294	-0.240	0.016	0.017	5	155845153	0.121	677773	4.77E-02	5	156418143	0.028	1.30E-26	33908
rs2434708	KIM1	Q96D42	A	C	A	C	-0.212	0.134	0.474	0.469	5	156230976	0.030	723017	1.04E-05	5	156803965	0.007	1.00E-200	33908
rs56084311	KIM1	Q96D42	G	C	G	C	-1.228	-0.003	0.012	0.012	5	156482296	0.147	692268	9.86E-01	5	157055285	0.031	1.00E-200	33908
rs72798933	KIM1	Q96D42	T	C	T	C	0.183	-0.010	0.052	0.055	5	155795123	0.072	629642	8.93E-01	5	156368113	0.016	3.21E-32	33908
rs76246936	KIM1	Q96D42	A	G	A	G	-0.179	0.046	0.068	0.068	5	156627753	0.066	610824	4.91E-01	5	157200742	0.014	3.22E-37	33908
rs76414090	KIM1	Q96D42	T	C	T	C	-0.178	-0.195	0.029	0.030	5	157284125	0.094	648882	3.83E-02	5	157857117	0.021	4.09E-18	33908
rs7720047	KIM1	Q96D42	A	G	A	G	0.049	0.354	0.265	0.260	5	157423813	0.035	727428	1.26E-24	5	157996805	0.008	2.25E-10	33908
rs77447213	KIM1	Q96D42	A	T	A	T	-0.070	-0.076	0.087	0.085	5	155643780	0.055	712422	1.70E-01	5	156216770	0.012	4.96E-09	33908
rs77692553	KIM1	Q96D42	G	A	G	A	-0.147	-0.047	0.072	0.077	5	155908055	0.059	677343	4.26E-01	5	156481045	0.013	6.55E-28	33908
rs116711172	TIMP4	Q99727	G	A	G	A	0.194	0.238	0.029	0.031	3	12259467	0.100	639753	1.69E-02	3	12217967	0.022	6.51E-19	33687
rs11712981	TIMP4	Q99727	A	G	A	G	-0.270	0.112	0.031	0.032	3	12862471	0.090	677022	2.14E-01	3	12820972	0.021	9.55E-39	33687
rs148260600	TIMP4	Q99727	G	A	G	A	0.285	0.199	0.013	0.013	3	12075098	0.142	678363	1.60E-01	3	12033598	0.032	9.07E-19	33687
rs71304101	TIMP4	Q99727	A	G	A	G	-0.274	-0.147	0.121	0.124	3	12396913	0.046	735045	1.38E-03	3	12355414	0.011	2.29E-137	33687
rs73025253	TIMP4	Q99727	C	A	C	A	0.254	0.228	0.039	0.037	3	12411089	0.083	695076	5.83E-03	3	12369590	0.019	7.77E-43	33687
rs76814907	TIMP4	Q99727	T	C	T	C	-0.089	-0.041	0.080	0.084	3	11948015	0.057	686999	4.73E-01	3	11906541	0.013	1.25E-11	33687
rs117622967	OPG	O00300	A	T	A	T	0.112	-0.072	0.040	0.039	8	120227642	0.083	660465	3.85E-01	8	119215402	0.018	1.95E-10	33649
rs140306080	OPG	O00300	T	C	T	C	0.339	0.078	0.018	0.019	8	119916415	0.119	652947	5.13E-01	8	118904176	0.026	2.25E-38	33649
rs3134095	OPG	O00300	C	T	C	T	-0.161	-0.101	0.947	0.945	8	119886101	0.067	726125	1.32E-01	8	118873862	0.015	4.31E-26	33649
rs4336638	OPG	O00300	G	A	G	A	-0.099	-0.019	0.924	0.925	8	120033524	0.062	637172	7.57E-01	8	119021285	0.013	6.62E-14	33649
rs4629902	OPG	O00300	C	A	C	A	0.080	0.021	0.672	0.667	8	119444843	0.032	730318	5.06E-01	8	118432604	0.007	6.17E-28	33649
rs6469812	OPG	O00300	C	T	C	T	0.187	0.093	0.546	0.547	8	120128070	0.030	734020	2.02E-03	8	119115831	0.007	1.04E-160	33649
rs73317303	OPG	O00300	T	C	T	C	0.065	-0.052	0.133	0.140	8	119498706	0.045	686612	2.55E-01	8	118486467	0.010	1.72E-10	33649
rs77038034	OPG	O00300	T	C	T	C	-0.086	-0.156	0.057	0.055	8	120023569	0.068	721692	2.14E-02	8	119011330	0.015	7.47E-09	33649
rs77914317	OPG	O00300	C	A	C	A	-0.169	-0.072	0.041	0.041	8	120060095	0.078	689393	3.57E-01	8	119047856	0.017	2.84E-22	33649
rs12871071	IL-17D	Q8TAD2	A	G	A	G	0.311	-0.158	0.020	0.020	13	21292061	0.113	686446	1.61E-01	13	20717922	0.025	1.28E-34	33084
rs17052265	IL-17D	Q8TAD2	G	A	G	A	0.258	-0.031	0.013	0.013	13	21057591	0.144	675441	8.30E-01	13	20483452	0.031	9.16E-17	33084
rs34670631	IL-17D	Q8TAD2	A	T	A	T	0.123	0.021	0.041	0.042	13	21667469	0.078	710861	7.85E-01	13	21093330	0.018	2.78E-12	33084
rs59560466	IL-17D	Q8TAD2	T	C	T	C	0.385	-0.047	0.097	0.095	13	21121844	0.053	692387	3.78E-01	13	20547705	0.012	1.00E-200	33084

Table S2. Harmonized summary statistics used in two-sample Mendelian randomization analysis

SNP	exposure	UniProt_ID	effect_allele.E	other_allele.E	effect_allele.O	other_allele.O	beta.E	beta.O	eaf.E	eaf.O	chr.O	pos.O	se.O	N.O	pval.O	chr.E	pos.E	se.E	pval.E	N.E
rs74036276	IL-17D	Q8TAD2	T	A	T	A	0.176	0.307	0.015	0.016	13	20955971	0.134	635154	2.16E-02	13	20381832	0.029	8.47E-10	33084
rs7989813	IL-17D	Q8TAD2	T	C	T	C	-0.053	0.018	0.738	0.737	13	21001070	0.035	707805	6.12E-01	13	20426931	0.008	4.93E-11	33084
rs9509387	IL-17D	Q8TAD2	T	C	T	C	-0.140	-0.004	0.030	0.034	13	21400939	0.089	655332	9.62E-01	13	20826800	0.021	1.12E-11	33084
rs9550679	IL-17D	Q8TAD2	A	G	A	G	-0.145	-0.027	0.082	0.083	13	21513621	0.055	728179	6.20E-01	13	20939482	0.013	1.93E-30	33084
rs9552244	IL-17D	Q8TAD2	G	A	G	A	-0.121	-0.072	0.080	0.078	13	21141822	0.058	704607	2.15E-01	13	20567683	0.013	5.96E-21	33084
rs141692260	NT-proBNP	P16860	G	A	G	A	0.180	-0.372	0.038	0.036	1	12058191	0.087	635339	2.05E-05	1	11998134	0.020	4.97E-19	33043
rs198389	NT-proBNP	P16860	G	A	G	A	0.183	-0.458	0.419	0.416	1	11919271	0.031	720701	4.02E-50	1	11859214	0.008	1.20E-127	33043
rs148253103	PGF	P49763	C	T	C	T	0.218	-0.027	0.014	0.016	14	75442203	0.130	647960	8.36E-01	14	74975500	0.029	7.23E-14	34049
rs58052725	PGF	P49763	C	T	C	T	0.090	-0.038	0.063	0.064	14	75066579	0.063	718091	5.40E-01	14	74599876	0.014	6.85E-11	34049
rs6574205	PGF	P49763	C	G	C	G	-0.153	0.158	0.525	0.528	14	75453039	0.030	735631	1.60E-07	14	74986336	0.007	2.84E-114	34049
rs149642807	TR-AP	P13686	A	G	A	G	-0.483	-0.018	0.119	0.120	19	11683849	0.048	684209	7.14E-01	19	11573034	0.011	1.00E-200	33896
rs34803265	TR-AP	P13686	A	G	A	G	-0.154	0.194	0.064	0.067	19	11618630	0.065	649177	2.98E-03	19	11507815	0.015	8.55E-26	33896
rs61149527	TR-AP	P13686	C	T	C	T	-0.090	0.092	0.076	0.078	19	11668916	0.058	705591	1.11E-01	19	11558101	0.014	2.22E-11	33896
rs72999181	TR-AP	P13686	A	G	A	G	0.169	0.113	0.046	0.043	19	11755767	0.082	650683	1.68E-01	19	11644952	0.017	6.05E-23	33896
rs74181610	TR-AP	P13686	G	T	G	T	0.261	-0.149	0.133	0.138	19	11839610	0.044	726374	7.30E-04	19	11728795	0.011	5.51E-135	33896
rs76151643	TR-AP	P13686	T	A	T	A	-0.247	0.184	0.012	0.011	19	12132535	0.151	664041	2.23E-01	19	12021720	0.033	5.73E-14	33896
rs2218793	ADM	P35318	A	C	A	C	-0.107	0.023	0.280	0.284	11	10380828	0.033	731822	4.85E-01	11	10359281	0.008	3.08E-42	33966
rs9332432	ADM	P35318	G	A	G	A	0.060	-0.051	0.586	0.586	11	9939485	0.031	721813	1.01E-01	11	9917938	0.007	3.05E-17	33966
rs34076655	PRSS27	Q9BQR3	T	C	T	C	0.070	-0.011	0.257	0.258	16	2920475	0.035	724606	7.54E-01	16	2870474	0.008	1.24E-18	33564
rs71386687	PRSS27	Q9BQR3	T	G	T	G	0.387	-0.099	0.082	0.078	16	2767894	0.063	598957	1.17E-01	16	2717893	0.013	5.16E-193	33564
rs530565	SORT1	Q99523	T	C	T	C	-0.164	0.085	0.981	0.981	1	110018148	0.118	660749	4.74E-01	1	109475526	0.028	2.92E-09	33628
rs61394658	SORT1	Q99523	A	G	A	G	-0.187	0.077	0.227	0.224	1	109873290	0.036	732557	3.30E-02	1	109330668	0.009	1.77E-97	33628
rs7528419	SORT1	Q99523	G	A	G	A	0.120	-0.023	0.222	0.222	1	109817192	0.037	723974	5.33E-01	1	109274570	0.009	2.19E-41	33628
rs71579330	LTBR	P36941	T	C	T	C	0.153	0.147	0.032	0.031	12	6640443	0.097	601419	1.32E-01	12	6531277	0.022	1.33E-12	33457
rs7309525	LTBR	P36941	T	C	T	C	-0.045	0.049	0.347	0.338	12	6831976	0.032	718889	1.29E-01	12	6722810	0.008	7.97E-09	33457
rs72759048	AMBP	P02760	A	G	A	G	-0.090	-0.009	0.202	0.201	9	116818660	0.039	684349	8.11E-01	9	114056380	0.009	1.99E-23	33908
rs72759050	AMBP	P02760	A	T	A	T	-0.214	-0.060	0.027	0.028	9	116820327	0.097	661699	5.38E-01	9	114058047	0.022	1.58E-22	33908
rs889555	PRSS8	Q16651	T	C	T	C	0.115	0.078	0.282	0.283	16	31122571	0.034	717278	2.22E-02	16	31111250	0.008	5.71E-49	33527
rs9410966	CTSL1	P07711	A	G	A	G	0.059	-0.012	0.200	0.204	9	90407826	0.037	740182	7.40E-01	9	87792911	0.009	1.22E-10	33693

Only part of columns in Table S2 are presented in the thesis. Full content of Table S2 is available on:
https://www.ahajournals.org/doi/suppl/10.1161/HYPERTENSIONAHA.123.22614

Abbreviations: E, exposure; O, outcome; SNPs, single nucleotide polymorphism.

Table S3. Characteristics of participants over the study period

	KORA S4/F4/FF4				**KORA Age1/Age2**		
	KORA S4, 1999-2001 (N = 1560)	**KORA F4, 2006-2008 (N = 1115)**	**KORA FF4, 2013-2014 (N = 657)**		**KORA-Age1, 2009 (N = 1024)**	**KORA-Age2, 2012 (N = 786)**	
	Mean (standard deviation) or number (%)						***P*-value [a]**
Age (years)	63.9 (5.46)	70.3 (5.39)	76.0 (4.92)		75.9 (6.57)	78.06 (6.32)	< 0.001
Sex, N (%) female	759 (48.7)	546 (49.0)	313 (47.6)		507 (49.5)	387 (49.2)	0.699
Body mass index (kg/m^2)	28.5 (4.36)	28.7 (4.51)	28.3 (4.49)		28.4 (4.36)	28.1 (4.27)	0.561
Smoking status, N (%)							< 0.001
Never smoker	747 (47.9)	549 (49.2)	330 (50.2)		550 (53.7)	441 (56.1)	
Former smoker	594 (38.1)	485 (43.5)	293 (44.6)		427 (41.7)	315 (40.1)	
Current smoker	219 (14.0)	81 (7.30)	34 (5.20)		47 (4.60)	30 (3.80)	
Alcohol consumption							< 0.001
No alcohol consumption	437 (28.0)	359 (32.2)	183 (27.9)		363 (35.4)	156 (19.8)	
>0 and <20 g/day	592 (37.9)	423 (37.9)	270 (41.1)		362 (35.4)	410 (52.2)	
≥ 20 g/day	531 (34.1)	333 (29.9)	204 (31.0)		299 (29.2)	220 (28.0)	
Physically active, N (%)	655 (42.0)	557 (50.0)	329 (50.1)		553 (54.0)	417 (53.1)	< 0.001
Triglycerides (mmol/L), median (interquartile range)	1.37 (0.94)	1.29 (0.87)	1.23 (0.67)		1.41 (1.01)	1.51 (1.04)	0.473
High-density lipoprotein cholesterol (mmol/L)	1.49 (0.42)	1.44 (0.36)	1.73 (0.47)		1.44 (0.37)	1.47 (0.42)	0.002
Use of lipid-lowering medication, N (%)	183 (11.7)	271 (24.3)	223 (33.9)		293 (28.6)	250 (31.8)	< 0.001
Type 2 diabetes, N (%)	148 (9.50)	179 (16.1)	140 (21.3)		181 (17.7)	132 (16.8)	< 0.001
Cardiovascular diseases, N (%)	191 (12.2)	180 (16.1)	124 (18.9)		316 (30.9)	227 (28.9)	< 0.001
Fasting, N (%)	1375 (88.1)	1105 (99.1)	654 (99.5)		56 (5.50)	35 (4.50)	< 0.001
Estimated glomerular filtration rate (ml/min/1.73 m^2)	82.5 (13.3)	75.9 (14.8)	67.5 (15.4)		67.3 (17.4)	62.7 (17.1)	< 0.001
Hypertension, N (%)	882 (56.5)	700 (62.8)	433 (65.9)		770 (75.2)	596 (75.8)	< 0.001
Use of antihypertensive medication, N (%)	572 (36.7)	639 (57.3)	429 (65.3)		718 (70.1)	559 (71.1)	< 0.001
Systolic blood pressure (mm Hg)	136.4 (20.5)	128.7 (19.7)	123.2 (19.0)		138.6 (21.0)	135.1 (19.0)	0.007
Diastolic blood pressure (mm Hg)	80.6 (10.6)	74.2 (10.0)	69.2 (9.52)		75.6 (10.9)	73.2 (10.4)	< 0.001

[a] P-value was estimated by t-Test (continuous variables) or chi-squared test (categorical variables) between KORA S4 and KORA-Age1

Table S4. Baseline characteristics for participants with and without follow-up information on blood pressure

	KORA S4/F4/FF4				**KORA Age1/Age2**		
	Follow-up (N = 1134)	**Lost to follow-up (N = 426)**			**Follow-up (N = 786)**	**Lost to follow-up (N = 238)**	
	Mean (SD) or number (%)		***P*-value** [a]		**Mean (SD) or number (%)**		***P*-value** [a]
Age (years)	63.3 (5.37)	65.7 (5.29)	< 0.001		75.1 (6.32)	78.7 (6.65)	<0.001
Sex, N (%) female	556 (49.0)	203 (47.7)	0.669		387 (49.2)	120 (50.4)	0.806
Body mass index (kg/m^2)	28.4 (4.26)	29.0 (4.62)	0.021		28.4 (4.37)	28.4 (4.35)	0.911
Smoking status, N (%)			0.001				0.008
Never smoker	559 (49.3)	188 (44.1)			441 (56.1)	109 (45.8)	
Former smoker	439 (38.7)	155 (36.4)			307 (39.1)	120 (50.4)	
Current smoker	136 (12.0)	83 (19.5)			38 (4.80)	9 (3.80)	
Alcohol consumption			0.001				0.032
No alcohol consumption	291 (25.7)	146 (34.3)			263 (33.4)	100 (42.0)	
>0 and <20 g/day	458 (40.3)	134 (31.4)			292 (37.2)	70 (29.4)	
≥ 20 g/day	385 (34.0)	146 (34.3)			231 (29.4)	68 (28.6)	
Physically active, N (%)	507 (44.7)	148 (34.7)	< 0.001		459 (58.4)	94 (39.5)	<0.001
Triglycerides (mmol/L), median (interquartile range)	1.35 (0.97)	1.42 (0.97)	0.118		1.41 (1.00)	1.42 (0.97)	0.407
High-density lipoprotein cholesterol (mmol/L)	1.50 (0.43)	1.46 (0.41)	0.098		1.45 (0.35)	1.40 (0.42)	0.069
Use of lipid-lowering medication, N (%)	127 (11.2)	56 (13.1)	0.329		220 (28.0)	73 (30.7)	0.471
Type 2 diabetes, N (%)	94 (8.30)	54 (12.7)	0.011		128 (16.3)	53 (22.3)	0.043
Cardiovascular diseases, N (%)	135 (11.9)	56 (13.1)	0.562		221 (28.1)	95 (39.9)	0.001
Fasting, N (%)	1021 (90.0)	354 (83.1)	< 0.001		40 (5.10)	16 (6.70)	0.419
Estimated glomerular filtration rate (ml/min/1.73 m^2)	82.9 (12.2)	81.3 (15.8)	0.031		69.3 (16.2)	60.8 (19.5)	<0.001
Hypertension, N (%)	613 (54.1)	269 (63.1)	0.002		579 (73.7)	191 (80.3)	0.048
Use of antihypertensive medication, N (%)	387 (34.1)	185 (43.4)	0.001		531 (67.6)	187 (78.6)	0.002
Systolic blood pressure (mm Hg)	135.1 (19.9)	139.7 (21.9)	< 0.001		138.2 (20.3)	139.9 (23.1)	0.295
Diastolic blood pressure (mm Hg)	80.6 (10.5)	80.5 (10.9)	0.898		76.1 (10.6)	73.9 (11.5)	0.007

[a] P-value was estimated by t-Test (continuous variables) or chi-squared test (categorical variables). SD, standard deviation

Table S5. Associations between 233 proteins and hypertension in KORA S4/F4/FF4 study
(participants = 1560; observation = 3332) [a]

Protein	**UniProt_ID**	**Model 1**				**Model 2**		
		OR (95%CI)	**P**	**FDR**		**OR (95%CI)**	**P**	**FDR**
4E-BP1	Q13541	**1.21 (1.10, 1.34)**	**7.64E-05**	**2.78E-04**		**1.16 (1.05, 1.28)**	**3.56E-03**	**2.44E-02**
ACE2	Q9BYF1	**1.34 (1.21, 1.48)**	**9.92E-09**	**1.36E-07**		**1.16 (1.04, 1.29)**	**6.51E-03**	**3.48E-02**
ADA	P00813	**1.21 (1.10, 1.34)**	**1.39E-04**	**4.56E-04**		**1.15 (1.04, 1.28)**	**5.66E-03**	**3.14E-02**
ADAM-TS13	Q76LX8	1.02 (0.93, 1.12)	7.10E-01	7.49E-01		0.96 (0.88, 1.05)	3.87E-01	5.50E-01
ADM	P35318	**1.39 (1.25, 1.54)**	**4.25E-10**	**8.25E-09**		1.15 (1.03, 1.29)	1.10E-02	5.11E-02
AGRP	O00253	**1.26 (1.14, 1.38)**	**2.92E-06**	**1.68E-05**		1.13 (1.01, 1.25)	2.54E-02	8.56E-02
ALCAM	Q13740	1.09 (0.98, 1.20)	9.74E-02	1.30E-01		1.00 (0.90, 1.11)	9.68E-01	9.90E-01
AMBP	P02760	**1.20 (1.09, 1.31)**	**2.41E-04**	**7.29E-04**		1.00 (0.91, 1.11)	9.47E-01	9.90E-01
ANG-1	Q15389	**1.11 (1.01, 1.22)**	**2.63E-02**	**4.17E-02**		1.12 (1.02, 1.23)	1.36E-02	5.78E-02
AP-N	P15144	1.07 (0.98, 1.17)	1.38E-01	1.78E-01		1.01 (0.92, 1.12)	7.62E-01	8.61E-01
Axin-1	O15169	1.08 (0.98, 1.19)	1.19E-01	1.56E-01		1.09 (0.99, 1.20)	8.80E-02	1.87E-01
AXL	P30530	**1.18 (1.08, 1.29)**	**3.87E-04**	**1.13E-03**		1.04 (0.95, 1.15)	3.98E-01	5.54E-01
BMP-6	P22004	**1.19 (1.08, 1.31)**	**3.15E-04**	**9.28E-04**		**1.14 (1.04, 1.26)**	**5.60E-03**	**3.14E-02**
BOC	Q9BWV1	1.02 (0.93, 1.12)	6.48E-01	6.98E-01		1.00 (0.91, 1.10)	9.84E-01	9.90E-01
CA5A	P35218	**1.42 (1.28, 1.57)**	**8.63E-12**	**2.87E-10**		**1.17 (1.05, 1.30)**	**3.52E-03**	**2.44E-02**
CASP-3	P42574	1.03 (0.94, 1.13)	5.24E-01	5.87E-01		1.04 (0.94, 1.14)	4.67E-01	6.15E-01
CASP8	Q14790	**1.25 (1.14, 1.38)**	**5.90E-06**	**2.80E-05**		**1.18 (1.07, 1.31)**	**1.35E-03**	**1.37E-02**
CCL11	P51671	1.09 (0.98, 1.20)	1.02E-01	1.36E-01		1.06 (0.96, 1.17)	2.59E-01	4.05E-01
CCL13	Q99616	1.09 (0.99, 1.19)	9.38E-02	1.28E-01		1.06 (0.96, 1.17)	2.47E-01	3.91E-01
CCL15	Q16663	**1.13 (1.02, 1.24)**	**1.46E-02**	**2.61E-02**		1.04 (0.94, 1.15)	4.47E-01	5.94E-01
CCL16	O15467	**1.17 (1.07, 1.29)**	**1.08E-03**	**2.71E-03**		1.04 (0.94, 1.14)	4.88E-01	6.28E-01
CCL17	Q92583	1.09 (0.99, 1.20)	6.76E-02	9.73E-02		1.10 (1.00, 1.21)	5.74E-02	1.38E-01
CCL19	Q99731	**1.21 (1.09, 1.34)**	**2.96E-04**	**8.84E-04**		1.09 (0.99, 1.21)	8.35E-02	1.81E-01
CCL2	P13500	**1.18 (1.07, 1.30)**	**7.72E-04**	**2.02E-03**		1.11 (1.01, 1.23)	3.26E-02	9.49E-02
CCL20	P78556	**1.12 (1.01, 1.23)**	**2.50E-02**	**4.00E-02**		1.02 (0.93, 1.13)	6.51E-01	7.65E-01
CCL23	P55773	**1.12 (1.02, 1.23)**	**1.58E-02**	**2.81E-02**		1.05 (0.95, 1.16)	3.28E-01	4.77E-01
CCL24	O00175	1.02 (0.93, 1.12)	7.26E-01	7.58E-01		1.00 (0.90, 1.10)	9.26E-01	9.85E-01
CCL25	O15444	1.00 (0.91, 1.10)	9.58E-01	9.70E-01		0.96 (0.87, 1.06)	4.07E-01	5.61E-01
CCL28	Q9NRJ3	1.02 (0.93, 1.13)	6.71E-01	7.14E-01		1.09 (0.98, 1.21)	1.07E-01	2.17E-01
CCL3	P10147	**1.24 (1.10, 1.40)**	**5.13E-04**	**1.46E-03**		1.08 (0.98, 1.20)	1.33E-01	2.46E-01
CCL4	P13236	**1.19 (1.07, 1.34)**	**2.26E-03**	**4.97E-03**		1.11 (1.00, 1.24)	5.02E-02	1.27E-01
CCL7	P80098	**1.21 (1.10, 1.34)**	**1.57E-04**	**5.00E-04**		1.09 (0.99, 1.21)	8.24E-02	1.81E-01
CD163	Q86VB7	**1.36 (1.24, 1.50)**	**2.42E-10**	**5.13E-09**		1.14 (1.03, 1.26)	1.27E-02	5.46E-02
CD244	Q9BZW8	**1.22 (1.10, 1.34)**	**7.91E-05**	**2.84E-04**		**1.14 (1.04, 1.26)**	**6.58E-03**	**3.48E-02**
CD4	P01730	**1.29 (1.16, 1.44)**	**2.39E-06**	**1.45E-05**		**1.15 (1.03, 1.27)**	**8.68E-03**	**4.40E-02**
CD40	P25942	**1.17 (1.06, 1.28)**	**1.69E-03**	**3.94E-03**		1.12 (1.02, 1.23)	2.11E-02	7.70E-02
CD40-L	P29965	**1.12 (1.02, 1.23)**	**2.04E-02**	**3.46E-02**		1.12 (1.01, 1.23)	2.56E-02	8.56E-02
CD5	P06127	**1.18 (1.07, 1.30)**	**1.21E-03**	**2.98E-03**		1.12 (1.01, 1.23)	3.25E-02	9.49E-02
CD6	P30203	**1.14 (1.04, 1.26)**	**6.31E-03**	**1.23E-02**		1.09 (0.99, 1.20)	8.40E-02	1.81E-01
CD84	Q9UIB8	**1.12 (1.02, 1.23)**	**1.95E-02**	**3.34E-02**		1.10 (1.00, 1.21)	4.03E-02	1.11E-01
CD8A	P01732	**1.28 (1.17, 1.41)**	**3.48E-07**	**2.61E-06**		1.13 (1.03, 1.25)	1.44E-02	5.97E-02
CD93	Q9NPY3	0.98 (0.89, 1.08)	7.09E-01	7.49E-01		0.94 (0.85, 1.04)	2.10E-01	3.45E-01
CDCP1	Q9H5V8	**1.16 (1.04, 1.29)**	**6.84E-03**	**1.32E-02**		1.08 (0.97, 1.19)	1.63E-01	2.82E-01
CDH5	P33151	1.04 (0.94, 1.14)	4.66E-01	5.32E-01		0.95 (0.87, 1.05)	3.32E-01	4.81E-01
CEACAM8	P31997	**1.37 (1.24, 1.53)**	**5.37E-09**	**7.82E-08**		**1.27 (1.13, 1.41)**	**2.41E-05**	**1.79E-03**
CHI3L1	P36222	**1.27 (1.15, 1.40)**	**1.59E-06**	**1.00E-05**		**1.16 (1.05, 1.28)**	**3.65E-03**	**2.44E-02**
CHIT1	Q13231	0.97 (0.88, 1.07)	5.22E-01	5.87E-01		0.97 (0.88, 1.07)	5.59E-01	6.93E-01
CNTN1	Q12860	0.99 (0.90, 1.09)	8.14E-01	8.43E-01		0.95 (0.86, 1.05)	3.02E-01	4.58E-01
COL1A1	P02452	**0.86 (0.78, 0.95)**	**1.89E-03**	**4.24E-03**		**0.87 (0.79, 0.96)**	**4.03E-03**	**2.44E-02**

Table S5. Associations between 233 proteins and hypertension in KORA S4/F4/FF4 study (participants = 1560; observation = 3332) [a]

Protein	UniProt_ID	Model 1				Model 2		
		OR (95%CI)	P	FDR		OR (95%CI)	P	FDR
CPA1	P15085	1.09 (0.99, 1.20)	7.65E-02	1.09E-01		1.08 (0.97, 1.19)	1.52E-01	2.73E-01
CPB1	P15086	**1.19 (1.07, 1.31)**	**1.00E-03**	**2.53E-03**		1.12 (1.01, 1.24)	2.71E-02	8.78E-02
CSF1	P09603	**1.24 (1.13, 1.37)**	**9.56E-06**	**4.37E-05**		1.08 (0.97, 1.20)	1.40E-01	2.54E-01
CST5	P28325	1.01 (0.92, 1.11)	8.42E-01	8.68E-01		0.95 (0.86, 1.05)	3.09E-01	4.59E-01
CSTB	P04080	**1.24 (1.12, 1.38)**	**5.72E-05**	**2.15E-04**		1.11 (1.00, 1.24)	4.59E-02	1.19E-01
CTRC	Q99895	**1.13 (1.03, 1.24)**	**1.30E-02**	**2.35E-02**		1.13 (1.02, 1.25)	1.56E-02	6.28E-02
CTSL1	P07711	**1.34 (1.22, 1.48)**	**4.24E-09**	**6.59E-08**		**1.22 (1.10, 1.35)**	**8.92E-05**	**3.46E-03**
CTSZ	Q9UBR2	**1.19 (1.08, 1.31)**	**6.30E-04**	**1.73E-03**		1.03 (0.93, 1.13)	6.21E-01	7.45E-01
CX3CL1	P78423	**1.13 (1.03, 1.24)**	**1.17E-02**	**2.17E-02**		1.11 (1.00, 1.23)	5.59E-02	1.36E-01
CXCL1	P09341	1.08 (0.99, 1.19)	8.84E-02	1.21E-01		1.08 (0.98, 1.19)	1.20E-01	2.27E-01
CXCL10	P02778	**1.18 (1.06, 1.31)**	**1.57E-03**	**3.70E-03**		1.05 (0.95, 1.16)	3.58E-01	5.15E-01
CXCL11	O14625	**1.19 (1.08, 1.31)**	**6.88E-04**	**1.84E-03**		1.13 (1.03, 1.25)	1.18E-02	5.18E-02
CXCL16	Q9H2A7	1.00 (0.91, 1.10)	9.72E-01	9.76E-01		0.91 (0.82, 1.00)	6.14E-02	1.45E-01
CXCL5	P42830	1.03 (0.94, 1.13)	5.63E-01	6.16E-01		1.05 (0.96, 1.15)	3.06E-01	4.59E-01
CXCL6	P80162	**1.20 (1.09, 1.32)**	**2.17E-04**	**6.75E-04**		1.13 (1.03, 1.25)	1.14E-02	5.11E-02
CXCL9	Q07325	**1.17 (1.06, 1.30)**	**2.79E-03**	**5.86E-03**		1.11 (1.00, 1.23)	5.13E-02	1.29E-01
DCN	P07585	**1.11 (1.01, 1.22)**	**3.10E-02**	**4.84E-02**		0.99 (0.90, 1.10)	9.07E-01	9.79E-01
DECR1	Q16698	1.07 (0.98, 1.18)	1.36E-01	1.76E-01		1.09 (0.99, 1.20)	9.04E-02	1.88E-01
Dkk-1	O94907	**1.16 (1.06, 1.28)**	**1.80E-03**	**4.10E-03**		**1.15 (1.05, 1.27)**	**3.70E-03**	**2.44E-02**
DLK-1	P80370	1.08 (0.99, 1.19)	8.66E-02	1.20E-01		0.93 (0.84, 1.03)	1.58E-01	2.77E-01
DNER	Q8NFT8	**0.83 (0.76, 0.92)**	**1.73E-04**	**5.45E-04**		0.89 (0.80, 0.98)	1.52E-02	6.23E-02
EGFR	P00533	0.94 (0.86, 1.03)	1.77E-01	2.20E-01		0.88 (0.80, 0.97)	1.14E-02	5.11E-02
EN-RAGE	P80511	**1.24 (1.12, 1.36)**	**1.97E-05**	**8.04E-05**		**1.16 (1.05, 1.28)**	**3.97E-03**	**2.44E-02**
Ep-CAM	P16422	1.04 (0.94, 1.14)	4.65E-01	5.32E-01		1.05 (0.95, 1.17)	2.95E-01	4.50E-01
EPHB4	P54760	1.09 (1.00, 1.19)	6.08E-02	8.97E-02		1.00 (0.90, 1.10)	9.65E-01	9.90E-01
FABP2	P12104	0.94 (0.85, 1.03)	1.62E-01	2.03E-01		0.95 (0.86, 1.05)	2.94E-01	4.50E-01
FABP4	P15090	**1.66 (1.47, 1.87)**	**5.55E-16**	**6.47E-14**		1.14 (1.00, 1.31)	5.52E-02	1.35E-01
FAS	P25445	**1.15 (1.04, 1.28)**	**6.10E-03**	**1.20E-02**		1.03 (0.93, 1.14)	5.65E-01	6.96E-01
FGF19	O95750	**1.16 (1.06, 1.27)**	**1.49E-03**	**3.54E-03**		**1.15 (1.03, 1.27)**	**9.08E-03**	**4.50E-02**
FGF21	Q9NSA1	**1.30 (1.18, 1.43)**	**2.50E-07**	**2.08E-06**		**1.16 (1.05, 1.29)**	**4.08E-03**	**2.44E-02**
FGF-23	Q9GZV9	**1.36 (1.20, 1.55)**	**2.96E-06**	**1.68E-05**		**1.21 (1.07, 1.36)**	**2.01E-03**	**1.74E-02**
FLT3L	P49771	1.05 (0.95, 1.15)	3.32E-01	3.92E-01		0.96 (0.88, 1.06)	4.74E-01	6.18E-01
FS	P19883	**1.18 (1.07, 1.30)**	**5.93E-04**	**1.66E-03**		1.11 (1.01, 1.22)	3.87E-02	1.07E-01
Gal-4	P56470	**1.25 (1.13, 1.38)**	**1.12E-05**	**4.93E-05**		1.10 (0.99, 1.22)	7.88E-02	1.76E-01
Gal-9	O00182	**1.39 (1.26, 1.54)**	**1.86E-10**	**4.82E-09**		**1.18 (1.06, 1.31)**	**1.77E-03**	**1.59E-02**
GDF-15	Q99988	**1.21 (1.09, 1.34)**	**2.39E-04**	**7.29E-04**		1.11 (0.99, 1.24)	7.61E-02	1.72E-01
GDF-2	Q9UK05	1.02 (0.92, 1.12)	7.63E-01	7.94E-01		1.07 (0.97, 1.19)	1.70E-01	2.90E-01
GH	P01241	**0.85 (0.76, 0.94)**	**2.50E-03**	**5.34E-03**		1.00 (0.89, 1.12)	9.82E-01	9.90E-01
GIF	P27352	1.02 (0.93, 1.12)	6.61E-01	7.06E-01		0.96 (0.87, 1.05)	3.65E-01	5.22E-01
GLO1	Q04760	1.10 (1.00, 1.21)	4.24E-02	6.33E-02		1.11 (1.01, 1.23)	2.98E-02	9.02E-02
GPVI	Q9HCN6	1.09 (0.99, 1.20)	8.85E-02	1.21E-01		1.09 (0.99, 1.20)	8.91E-02	1.87E-01
GRN	P28799	**1.18 (1.07, 1.29)**	**9.36E-04**	**2.40E-03**		1.05 (0.95, 1.16)	3.21E-01	4.71E-01
GT	P51161	1.02 (0.93, 1.12)	7.21E-01	7.57E-01		0.99 (0.90, 1.10)	9.02E-01	9.77E-01
HAOX1	Q9UJM8	**1.25 (1.13, 1.37)**	**1.43E-05**	**6.08E-05**		1.09 (0.99, 1.21)	8.83E-02	1.87E-01
HB-EGF	Q99075	**1.22 (1.11, 1.34)**	**6.46E-05**	**2.39E-04**		**1.18 (1.07, 1.29)**	**9.82E-04**	**1.14E-02**
HGF	P14210	**1.48 (1.33, 1.63)**	**6.54E-14**	**3.05E-12**		**1.27 (1.14, 1.42)**	**1.30E-05**	**1.51E-03**
HO-1	P09601	**1.21 (1.10, 1.34)**	**1.10E-04**	**3.67E-04**		**1.18 (1.07, 1.31)**	**1.51E-03**	**1.41E-02**
hOSCAR	Q8IYS5	**1.14 (1.04, 1.26)**	**7.53E-03**	**1.43E-02**		1.06 (0.96, 1.17)	2.44E-01	3.91E-01
HSP 27	P04792	0.92 (0.84, 1.01)	7.79E-02	1.10E-01		0.94 (0.85, 1.03)	1.97E-01	3.27E-01

Table S5. Associations between 233 proteins and hypertension in KORA S4/F4/FF4 study (participants = 1560; observation = 3332) [a]

Protein	**UniProt_ID**	**Model 1**				**Model 2**		
		OR (95%CI)	**P**	**FDR**		**OR (95%CI)**	**P**	**FDR**
ICAM-2	P13598	1.07 (0.98, 1.18)	1.30E-01	1.69E-01		1.01 (0.92, 1.11)	7.79E-01	8.64E-01
IDUA	P35475	**1.17 (1.06, 1.29)**	**1.26E-03**	**3.04E-03**		1.08 (0.98, 1.19)	1.14E-01	2.25E-01
IFNG	P01579	1.06 (0.97, 1.17)	2.19E-01	2.69E-01		1.00 (0.91, 1.10)	9.73E-01	9.90E-01
IGFBP-1	P08833	**0.74 (0.67, 0.81)**	**1.61E-09**	**2.89E-08**		0.93 (0.84, 1.04)	2.28E-01	3.69E-01
IGFBP-2	P18065	**0.80 (0.73, 0.88)**	**4.46E-06**	**2.21E-05**		0.96 (0.86, 1.07)	4.40E-01	5.93E-01
IGFBP-7	Q16270	**1.22 (1.10, 1.34)**	**8.38E-05**	**2.88E-04**		1.09 (0.99, 1.21)	8.36E-02	1.81E-01
IgG Fc receptor II-b	P31994	1.06 (0.97, 1.16)	2.24E-01	2.72E-01		1.01 (0.92, 1.12)	7.69E-01	8.61E-01
IL-10	P22301	**1.15 (1.05, 1.27)**	**3.92E-03**	**8.01E-03**		1.12 (1.01, 1.23)	2.57E-02	8.56E-02
IL-10RB	Q08334	**1.18 (1.07, 1.29)**	**6.59E-04**	**1.79E-03**		1.01 (0.91, 1.12)	8.47E-01	9.27E-01
IL-12B	P29460	**1.27 (1.15, 1.41)**	**3.67E-06**	**1.94E-05**		1.07 (0.97, 1.19)	1.84E-01	3.11E-01
IL-15RA	Q13261	**1.15 (1.05, 1.27)**	**3.38E-03**	**6.98E-03**		1.02 (0.92, 1.13)	6.48E-01	7.65E-01
IL-16	Q14005	**1.18 (1.07, 1.30)**	**7.20E-04**	**1.91E-03**		1.12 (1.01, 1.23)	2.83E-02	8.93E-02
IL-17D	Q8TAD2	1.00 (0.91, 1.10)	9.65E-01	9.74E-01		1.01 (0.92, 1.11)	7.65E-01	8.61E-01
IL-17RA	Q96F46	1.09 (0.99, 1.20)	9.69E-02	1.30E-01		1.09 (0.98, 1.20)	1.09E-01	2.19E-01
IL-18	Q14116	**1.33 (1.19, 1.47)**	**1.82E-07**	**1.63E-06**		**1.21 (1.09, 1.35)**	**5.98E-04**	**9.38E-03**
IL-18BP	O95998	**1.12 (1.02, 1.23)**	**1.89E-02**	**3.28E-02**		1.00 (0.91, 1.11)	9.51E-01	9.90E-01
IL-18R1	Q13478	**1.43 (1.29, 1.58)**	**2.24E-12**	**8.69E-11**		**1.16 (1.04, 1.29)**	**6.75E-03**	**3.50E-02**
IL-1RA	P18510	**1.50 (1.35, 1.65)**	**3.66E-15**	**2.85E-13**		**1.23 (1.11, 1.37)**	**1.44E-04**	**4.29E-03**
IL1-RL2	Q9HB29	1.08 (0.98, 1.19)	1.45E-01	1.83E-01		0.92 (0.83, 1.02)	1.21E-01	2.27E-01
IL-1RT1	P14778	1.03 (0.94, 1.12)	5.46E-01	6.03E-01		1.02 (0.92, 1.11)	7.54E-01	8.61E-01
IL-1RT2	P27930	1.11 (1.01, 1.21)	3.30E-02	5.13E-02		0.99 (0.90, 1.10)	9.01E-01	9.77E-01
IL-27	Q8NEV9	**1.15 (1.04, 1.26)**	**4.46E-03**	**8.96E-03**		1.08 (0.98, 1.19)	1.24E-01	2.32E-01
IL2-RA	P01589	**1.16 (1.05, 1.27)**	**2.30E-03**	**5.02E-03**		1.08 (0.98, 1.19)	1.41E-01	2.55E-01
IL-4RA	P24394	1.03 (0.94, 1.13)	4.99E-01	5.67E-01		1.00 (0.91, 1.10)	9.99E-01	9.99E-01
IL-6	P05231	**1.27 (1.14, 1.42)**	**1.03E-05**	**4.62E-05**		**1.14 (1.04, 1.25)**	**5.31E-03**	**3.09E-02**
IL-6RA	P08887	1.08 (0.99, 1.19)	9.48E-02	1.28E-01		1.00 (0.91, 1.11)	9.51E-01	9.90E-01
IL-7	P13232	**1.18 (1.07, 1.29)**	**6.07E-04**	**1.68E-03**		**1.19 (1.08, 1.30)**	**2.13E-04**	**5.52E-03**
IL-8	P10145	**1.27 (1.15, 1.41)**	**3.53E-06**	**1.91E-05**		**1.21 (1.09, 1.34)**	**4.31E-04**	**8.37E-03**
ITGB1BP2	Q9UKP3	1.09 (0.99, 1.20)	6.73E-02	9.73E-02		1.11 (1.01, 1.22)	3.37E-02	9.71E-02
ITGB2	P05107	1.05 (0.95, 1.17)	2.99E-01	3.57E-01		0.99 (0.90, 1.09)	8.39E-01	9.22E-01
JAM-A	Q9Y624	1.02 (0.93, 1.13)	6.16E-01	6.68E-01		1.02 (0.93, 1.13)	6.47E-01	7.65E-01
KIM1	Q96D42	**1.42 (1.28, 1.57)**	**1.29E-11**	**3.77E-10**		**1.26 (1.13, 1.40)**	**3.08E-05**	**1.79E-03**
KLK6	Q92876	0.91 (0.83, 0.99)	3.74E-02	5.69E-02		0.91 (0.82, 1.01)	6.97E-02	1.59E-01
LDL receptor	P01130	**1.21 (1.10, 1.34)**	**8.37E-05**	**2.88E-04**		0.94 (0.85, 1.06)	3.13E-01	4.62E-01
LEP	P41159	**1.79 (1.59, 2.03)**	**0.00E+00**	**0.00E+00**		1.20 (1.03, 1.39)	1.72E-02	6.68E-02
LIFR	P42702	**1.26 (1.15, 1.39)**	**1.44E-06**	**9.57E-06**		1.11 (1.00, 1.23)	4.23E-02	1.13E-01
LIGHT	O43557	**1.22 (1.11, 1.34)**	**4.71E-05**	**1.80E-04**		**1.15 (1.05, 1.27)**	**3.99E-03**	**2.44E-02**
LOX-1	P78380	**1.26 (1.14, 1.39)**	**4.99E-06**	**2.42E-05**		**1.21 (1.09, 1.35)**	**4.76E-04**	**8.54E-03**
LPL	P06858	**0.75 (0.67, 0.84)**	**3.80E-07**	**2.77E-06**		**0.82 (0.73, 0.92)**	**6.37E-04**	**9.38E-03**
LTBR	P36941	1.09 (0.99, 1.20)	8.27E-02	1.15E-01		1.01 (0.91, 1.12)	8.30E-01	9.17E-01
MARCO	Q9UEW3	**1.23 (1.12, 1.36)**	**2.50E-05**	**1.01E-04**		1.08 (0.98, 1.19)	1.19E-01	2.27E-01
MB	P02144	**1.19 (1.08, 1.30)**	**4.68E-04**	**1.35E-03**		1.04 (0.94, 1.15)	4.77E-01	6.18E-01
MCP-2	P80075	**1.17 (1.06, 1.29)**	**1.22E-03**	**2.98E-03**		1.12 (1.01, 1.23)	2.96E-02	9.02E-02
MEPE	Q9NQ76	0.98 (0.89, 1.07)	6.02E-01	6.55E-01		0.93 (0.84, 1.02)	1.35E-01	2.47E-01
MERTK	Q12866	**1.12 (1.02, 1.23)**	**2.31E-02**	**3.77E-02**		1.08 (0.98, 1.19)	1.21E-01	2.27E-01
MMP-1	P03956	1.10 (0.99, 1.21)	6.35E-02	9.31E-02		1.09 (0.98, 1.20)	1.03E-01	2.11E-01
MMP-12	P39900	**1.13 (1.03, 1.25)**	**1.29E-02**	**2.35E-02**		1.06 (0.95, 1.17)	2.95E-01	4.50E-01
MMP-2	P08253	1.03 (0.94, 1.13)	5.03E-01	5.68E-01		1.00 (0.91, 1.10)	9.72E-01	9.90E-01
MMP-3	P08254	0.99 (0.90, 1.10)	9.13E-01	9.29E-01		0.97 (0.87, 1.08)	6.10E-01	7.37E-01

Table S5. Associations between 233 proteins and hypertension in KORA S4/F4/FF4 study (participants = 1560; observation = 3332) [a]

Protein	UniProt_ID	Model 1				Model 2		
		OR (95%CI)	P	FDR		OR (95%CI)	P	FDR
MMP-7	P09237	**1.16 (1.06, 1.28)**	**2.11E-03**	**4.68E-03**		1.12 (1.01, 1.24)	3.78E-02	1.06E-01
MMP-9	P14780	**1.21 (1.10, 1.33)**	**8.70E-05**	**2.94E-04**		**1.17 (1.06, 1.29)**	**2.46E-03**	**2.04E-02**
MPO	P05164	1.06 (0.96, 1.17)	2.21E-01	2.70E-01		1.00 (0.91, 1.10)	9.60E-01	9.90E-01
NEMO	Q9Y6K9	1.07 (0.97, 1.17)	1.86E-01	2.30E-01		1.07 (0.97, 1.18)	1.54E-01	2.75E-01
Notch 3	Q9UM47	1.07 (0.97, 1.17)	1.58E-01	2.00E-01		1.03 (0.93, 1.14)	5.43E-01	6.77E-01
NT3	P20783	1.04 (0.94, 1.15)	4.04E-01	4.69E-01		1.04 (0.94, 1.15)	4.77E-01	6.18E-01
NT-proBNP	P16860	**1.30 (1.18, 1.44)**	**3.07E-07**	**2.38E-06**		**1.33 (1.20, 1.49)**	**2.05E-07**	**4.77E-05**
OPG	O00300	**1.28 (1.16, 1.41)**	**1.60E-06**	**1.00E-05**		**1.20 (1.08, 1.33)**	**8.73E-04**	**1.07E-02**
OPN	P10451	1.01 (0.92, 1.10)	8.88E-01	9.11E-01		0.98 (0.89, 1.08)	6.54E-01	7.65E-01
OSM	P13725	**1.32 (1.19, 1.46)**	**6.46E-08**	**6.85E-07**		**1.24 (1.11, 1.38)**	**8.10E-05**	**3.46E-03**
PAI	P05121	**1.24 (1.13, 1.36)**	**7.78E-06**	**3.62E-05**		1.13 (1.02, 1.24)	1.60E-02	6.34E-02
PAR-1	P25116	**1.15 (1.05, 1.26)**	**2.46E-03**	**5.31E-03**		1.12 (1.02, 1.22)	2.31E-02	8.14E-02
PARP-1	P09874	**1.14 (1.04, 1.26)**	**7.52E-03**	**1.43E-02**		1.11 (1.00, 1.22)	4.54E-02	1.19E-01
PCSK9	Q8NBP7	1.07 (0.98, 1.18)	1.44E-01	1.83E-01		0.95 (0.86, 1.05)	2.96E-01	4.50E-01
PDGF subunit A	P04085	**1.12 (1.02, 1.23)**	**1.91E-02**	**3.30E-02**		1.12 (1.02, 1.23)	2.01E-02	7.44E-02
PDGF subunit B	P01127	**1.12 (1.02, 1.23)**	**1.78E-02**	**3.12E-02**		**1.13 (1.03, 1.24)**	**1.04E-02**	**4.96E-02**
PD-L1	Q9NZQ7	**1.25 (1.12, 1.39)**	**3.52E-05**	**1.39E-04**		**1.19 (1.07, 1.31)**	**7.35E-04**	**1.00E-02**
PD-L2	Q9BQ51	1.07 (0.98, 1.18)	1.43E-01	1.83E-01		1.02 (0.92, 1.12)	7.43E-01	8.53E-01
PECAM-1	P16284	1.03 (0.93, 1.13)	5.63E-01	6.16E-01		1.03 (0.93, 1.13)	5.81E-01	7.09E-01
PGF	P49763	**1.28 (1.16, 1.41)**	**1.13E-06**	**7.73E-06**		1.12 (1.00, 1.25)	4.55E-02	1.19E-01
PGLYRP1	O75594	**1.30 (1.18, 1.43)**	**7.93E-08**	**8.03E-07**		**1.19 (1.08, 1.31)**	**6.44E-04**	**9.38E-03**
PIgR	P01833	1.00 (0.92, 1.09)	9.98E-01	9.98E-01		0.97 (0.88, 1.07)	5.43E-01	6.77E-01
PLC	P98160	**1.25 (1.14, 1.38)**	**4.38E-06**	**2.21E-05**		1.04 (0.94, 1.16)	4.15E-01	5.69E-01
PON3	Q15166	**0.67 (0.60, 0.74)**	**6.66E-15**	**3.88E-13**		**0.83 (0.75, 0.93)**	**1.27E-03**	**1.34E-02**
PRELP	P51888	**1.21 (1.05, 1.39)**	**9.66E-03**	**1.80E-02**		1.07 (0.95, 1.20)	2.46E-01	3.91E-01
PRSS27	Q9BQR3	**1.12 (1.02, 1.22)**	**2.09E-02**	**3.52E-02**		**1.14 (1.03, 1.26)**	**9.30E-03**	**4.51E-02**
PRSS8	Q16651	**1.32 (1.19, 1.46)**	**8.77E-08**	**8.51E-07**		1.13 (1.02, 1.26)	2.28E-02	8.14E-02
PSGL-1	Q14242	**1.23 (1.11, 1.37)**	**8.40E-05**	**2.88E-04**		1.11 (0.99, 1.23)	6.34E-02	1.48E-01
PSP-D	P35247	**0.90 (0.82, 0.99)**	**2.38E-02**	**3.85E-02**		0.89 (0.81, 0.98)	1.89E-02	7.20E-02
PTX3	P26022	**1.16 (1.06, 1.28)**	**1.27E-03**	**3.04E-03**		**1.15 (1.05, 1.27)**	**4.04E-03**	**2.44E-02**
RAGE	Q15109	0.90 (0.82, 0.99)	3.55E-02	5.45E-02		0.93 (0.84, 1.03)	1.61E-01	2.80E-01
RARRES2	Q99969	**1.29 (1.17, 1.42)**	**2.86E-07**	**2.30E-06**		1.06 (0.96, 1.18)	2.48E-01	3.91E-01
REN	P00797	1.04 (0.95, 1.14)	4.25E-01	4.90E-01		**0.86 (0.77, 0.95)**	**3.35E-03**	**2.44E-02**
RETN	Q9HD89	**1.22 (1.10, 1.35)**	**1.49E-04**	**4.83E-04**		1.12 (1.02, 1.25)	2.37E-02	8.24E-02
SCF	P21583	**0.90 (0.82, 0.99)**	**2.76E-02**	**4.35E-02**		0.93 (0.84, 1.03)	1.68E-01	2.87E-01
SCGB3A2	Q96PL1	**0.77 (0.69, 0.85)**	**2.23E-07**	**1.93E-06**		**0.83 (0.75, 0.93)**	**7.75E-04**	**1.00E-02**
SELE	P16581	**1.29 (1.17, 1.41)**	**6.18E-08**	**6.85E-07**		1.12 (1.01, 1.23)	2.79E-02	8.91E-02
SELP	P16109	1.06 (0.96, 1.16)	2.34E-01	2.82E-01		1.05 (0.95, 1.16)	3.09E-01	4.59E-01
SERPINA12	Q8IW75	**1.13 (1.03, 1.25)**	**1.26E-02**	**2.31E-02**		1.09 (0.99, 1.21)	6.78E-02	1.56E-01
SHPS-1	P78324	1.05 (0.96, 1.16)	3.04E-01	3.62E-01		0.98 (0.89, 1.07)	6.25E-01	7.47E-01
SIRT2	Q8IXJ6	**1.12 (1.02, 1.23)**	**2.23E-02**	**3.69E-02**		1.11 (1.01, 1.22)	3.64E-02	1.04E-01
SL-2	P09238	1.06 (0.97, 1.16)	2.01E-01	2.48E-01		1.03 (0.93, 1.13)	5.98E-01	7.25E-01
SOD2	P04179	1.10 (1.01, 1.21)	3.34E-02	5.16E-02		1.08 (0.98, 1.18)	1.19E-01	2.27E-01
SORT1	Q99523	**1.28 (1.16, 1.41)**	**5.02E-07**	**3.55E-06**		**1.20 (1.09, 1.32)**	**2.50E-04**	**5.82E-03**
SPON2	Q9BUD6	**1.12 (1.02, 1.24)**	**1.59E-02**	**2.81E-02**		1.02 (0.92, 1.13)	7.34E-01	8.48E-01
SRC	P12931	0.96 (0.88, 1.05)	3.86E-01	4.52E-01		0.99 (0.90, 1.08)	7.74E-01	8.63E-01
ST1A1	P50225	1.08 (0.98, 1.19)	1.17E-01	1.55E-01		1.08 (0.98, 1.19)	1.13E-01	2.24E-01
ST2	Q01638	**1.25 (1.13, 1.38)**	**1.30E-05**	**5.61E-05**		1.12 (1.01, 1.25)	2.98E-02	9.02E-02
STAMBP	O95630	1.11 (1.01, 1.22)	3.80E-02	5.75E-02		1.10 (1.00, 1.21)	5.24E-02	1.30E-01

Table S5. Associations between 233 proteins and hypertension in KORA S4/F4/FF4 study (participants = 1560; observation = 3332) [a]

Protein	UniProt_ID	Model 1				Model 2		
		OR (95%CI)	P	FDR		OR (95%CI)	P	FDR
STK4	Q13043	1.02 (0.93, 1.12)	6.50E-01	6.98E-01		1.04 (0.95, 1.14)	3.95E-01	5.54E-01
TF	P13726	1.03 (0.94, 1.13)	5.44E-01	6.03E-01		1.03 (0.94, 1.14)	5.42E-01	6.77E-01
TFPI	P10646	**0.88 (0.80, 0.96)**	**5.19E-03**	**1.03E-02**		**0.87 (0.79, 0.96)**	**4.09E-03**	**2.44E-02**
TGF-α	P01135	**1.36 (1.22, 1.52)**	**1.88E-08**	**2.31E-07**		**1.24 (1.11, 1.39)**	**1.47E-04**	**4.29E-03**
TGF-β1	P01137	**1.25 (1.14, 1.38)**	**4.46E-06**	**2.21E-05**		**1.19 (1.08, 1.31)**	**3.25E-04**	**6.88E-03**
TGM2	P21980	**1.34 (1.21, 1.48)**	**1.25E-08**	**1.62E-07**		**1.18 (1.07, 1.31)**	**1.51E-03**	**1.41E-02**
THBS2	P35442	**1.31 (1.18, 1.45)**	**1.55E-07**	**1.44E-06**		1.12 (1.01, 1.25)	3.04E-02	9.08E-02
THPO	P40225	0.97 (0.88, 1.07)	5.45E-01	6.03E-01		1.01 (0.92, 1.12)	7.69E-01	8.61E-01
TIE2	Q02763	**1.12 (1.02, 1.22)**	**2.31E-02**	**3.77E-02**		1.04 (0.94, 1.14)	4.46E-01	5.94E-01
TIMP4	Q99727	**1.16 (1.05, 1.28)**	**4.17E-03**	**8.46E-03**		1.09 (0.98, 1.21)	9.73E-02	2.01E-01
TLT-2	Q5T2D2	1.10 (1.01, 1.21)	3.89E-02	5.85E-02		1.02 (0.93, 1.12)	6.80E-01	7.92E-01
TM	P07204	**1.25 (1.14, 1.38)**	**3.19E-06**	**1.77E-05**		1.12 (1.01, 1.25)	2.68E-02	8.78E-02
TNF-R1	P19438	**1.32 (1.19, 1.46)**	**4.67E-08**	**5.44E-07**		1.09 (0.98, 1.21)	1.15E-01	2.25E-01
TNF-R2	P20333	**1.23 (1.11, 1.36)**	**4.34E-05**	**1.69E-04**		1.04 (0.94, 1.16)	4.25E-01	5.76E-01
TNFRSF10A	O00220	**1.26 (1.09, 1.45)**	**1.79E-03**	**4.10E-03**		1.08 (0.95, 1.23)	2.23E-01	3.63E-01
TNFRSF10C	O14798	**1.11 (1.02, 1.22)**	**2.14E-02**	**3.58E-02**		1.03 (0.94, 1.14)	4.94E-01	6.32E-01
TNFRSF11A	Q9Y6Q6	**1.39 (1.26, 1.54)**	**2.18E-10**	**5.08E-09**		1.14 (1.02, 1.26)	2.00E-02	7.44E-02
TNFRSF13B	O14836	**1.24 (1.12, 1.37)**	**1.83E-05**	**7.61E-05**		1.10 (1.00, 1.22)	5.95E-02	1.41E-01
TNFRSF14	Q92956	**1.16 (1.04, 1.28)**	**5.65E-03**	**1.12E-02**		1.08 (0.97, 1.19)	1.57E-01	2.77E-01
TNFRSF9	Q07011	**1.17 (1.06, 1.29)**	**1.81E-03**	**4.10E-03**		1.05 (0.94, 1.16)	3.96E-01	5.54E-01
TNFSF10	P50591	1.04 (0.95, 1.15)	3.74E-01	4.40E-01		0.98 (0.89, 1.09)	7.35E-01	8.48E-01
TNFSF13B	Q9Y275	0.96 (0.87, 1.06)	4.04E-01	4.69E-01		0.91 (0.82, 1.00)	4.66E-02	1.19E-01
TNF-α	P01375	**1.19 (1.05, 1.36)**	**8.70E-03**	**1.63E-02**		1.04 (0.94, 1.16)	4.49E-01	5.94E-01
TNF-β	P01374	1.10 (0.99, 1.21)	6.46E-02	9.41E-02		1.00 (0.90, 1.10)	9.59E-01	9.90E-01
t-PA	P00750	**1.15 (1.05, 1.27)**	**3.37E-03**	**6.98E-03**		1.03 (0.94, 1.14)	5.03E-01	6.40E-01
TR	P02786	**1.26 (1.15, 1.39)**	**2.43E-06**	**1.45E-05**		1.11 (1.00, 1.22)	4.22E-02	1.13E-01
TRAIL-R2	O14763	**1.23 (1.09, 1.39)**	**8.64E-04**	**2.24E-03**		1.03 (0.93, 1.15)	5.20E-01	6.59E-01
TRANCE	O14788	1.10 (1.00, 1.21)	4.78E-02	7.09E-02		1.00 (0.91, 1.11)	9.22E-01	9.85E-01
TR-AP	P13686	1.01 (0.92, 1.11)	8.96E-01	9.16E-01		0.96 (0.87, 1.06)	4.00E-01	5.54E-01
TWEAK	O43508	**0.90 (0.82, 0.98)**	**2.19E-02**	**3.65E-02**		0.94 (0.85, 1.04)	2.07E-01	3.42E-01
uPA	P00749	1.05 (0.96, 1.16)	2.57E-01	3.08E-01		1.00 (0.91, 1.10)	9.26E-01	9.85E-01
U-PAR	Q03405	1.09 (0.98, 1.21)	1.05E-01	1.39E-01		1.03 (0.93, 1.14)	5.72E-01	7.02E-01
VEGF-A	P15692	**1.35 (1.22, 1.50)**	**3.32E-09**	**5.53E-08**		**1.18 (1.07, 1.30)**	**1.17E-03**	**1.30E-02**
VEGFD	O43915	0.92 (0.83, 1.01)	7.43E-02	1.06E-01		1.00 (0.90, 1.11)	9.85E-01	9.90E-01
VSIG2	Q96IQ7	**1.11 (1.01, 1.21)**	**2.41E-02**	**3.87E-02**		1.04 (0.94, 1.15)	4.18E-01	5.70E-01
vWF	P04275	**1.15 (1.05, 1.27)**	**2.73E-03**	**5.79E-03**		1.07 (0.97, 1.18)	1.91E-01	3.21E-01
XCL1	P47992	1.09 (0.99, 1.21)	8.16E-02	1.15E-01		1.00 (0.91, 1.10)	9.69E-01	9.90E-01

[a] To take into account repeated measurements of outcome, generalized estimating equations with exchangeable correlation structure were used to estimate OR (95% CI) of dichotomous hypertension (yes/no) per 1 standard deviation increase in proteins concentration. The proteins are sorted alphabetically. **In bold are proteins significantly associated with prevalent hypertension at the threshold of FDR < 0.05.**

Model 1: Adjusted for age at each wave of survey (time-varying covariates), and sex;

Model 2: Model 1 plus body mass index, smoking status, alcohol consumption, physical activity, naturally log-transformed triglycerides, high-density lipoprotein cholesterol, use of lipid-lowering medication, prevalent diabetes, prevalent cardiovascular diseases, fasting status, and kidney function at each wave of survey.

Abbreviations: CI, confidence interval; FDR, Benjamini–Hochberg false-discovery rate; OR, odds ratio. Full names of the proteins can be found in Table S1.

Table S6. Associations between 233 proteins and SBP in KORA S4/F4/FF4 study (participants = 1560; observation = 3332) [a]

Protein	UniProt_ID	Model 1				Model 2		
		β (95%CI)	P	FDR		β (95%CI)	P	FDR
4E-BP1	Q13541	**1.52 (0.52, 2.52)**	**2.83E-03**	**6.23E-03**		0.92 (-0.02, 1.87)	5.59E-02	1.09E-01
ACE2	Q9BYF1	**3.24 (2.19, 4.30)**	**1.69E-09**	**7.86E-08**		**2.21 (1.10, 3.32)**	**1.00E-04**	**1.46E-03**
ADA	P00813	**1.70 (0.68, 2.71)**	**1.05E-03**	**2.78E-03**		1.08 (0.11, 2.05)	2.93E-02	6.37E-02
ADAM-TS13	Q76LX8	-0.25 (-1.16, 0.65)	5.83E-01	6.29E-01		-0.62 (-1.51, 0.26)	1.69E-01	2.68E-01
ADM	P35318	**2.82 (1.68, 3.97)**	**1.24E-06**	**1.33E-05**		**2.41 (1.25, 3.56)**	**4.38E-05**	**8.51E-04**
AGRP	O00253	**1.46 (0.39, 2.54)**	**7.41E-03**	**1.41E-02**		0.77 (-0.31, 1.85)	1.60E-01	2.56E-01
ALCAM	Q13740	**1.58 (0.54, 2.63)**	**3.03E-03**	**6.48E-03**		1.08 (0.06, 2.11)	3.86E-02	7.92E-02
AMBP	P02760	**2.21 (1.13, 3.29)**	**5.78E-05**	**2.75E-04**		**1.81 (0.75, 2.86)**	**8.04E-04**	**4.07E-03**
ANG-1	Q15389	0.48 (-0.49, 1.45)	3.33E-01	3.97E-01		0.13 (-0.80, 1.06)	7.81E-01	8.42E-01
AP-N	P15144	0.88 (-0.06, 1.82)	6.51E-02	9.48E-02		0.56 (-0.35, 1.47)	2.28E-01	3.30E-01
Axin-1	O15169	0.41 (-0.54, 1.37)	3.99E-01	4.49E-01		0.23 (-0.69, 1.15)	6.25E-01	7.33E-01
AXL	P30530	**1.77 (0.79, 2.75)**	**3.88E-04**	**1.33E-03**		1.06 (0.12, 2.00)	2.76E-02	6.06E-02
BMP-6	P22004	**1.75 (0.74, 2.75)**	**6.93E-04**	**2.13E-03**		**1.23 (0.28, 2.18)**	**1.13E-02**	**3.08E-02**
BOC	Q9BWV1	0.42 (-0.66, 1.50)	4.48E-01	4.99E-01		0.17 (-0.87, 1.21)	7.55E-01	8.26E-01
CA5A	P35218	**2.66 (1.66, 3.66)**	**1.74E-07**	**2.70E-06**		**1.74 (0.74, 2.74)**	**6.64E-04**	**3.77E-03**
CASP-3	P42574	0.27 (-0.71, 1.25)	5.93E-01	6.30E-01		0.03 (-0.91, 0.97)	9.58E-01	9.81E-01
CASP8	Q14790	**1.64 (0.59, 2.69)**	**2.19E-03**	**5.11E-03**		0.86 (-0.15, 1.88)	9.55E-02	1.70E-01
CCL11	P51671	**1.76 (0.75, 2.78)**	**6.87E-04**	**2.13E-03**		**1.42 (0.42, 2.42)**	**5.50E-03**	**1.76E-02**
CCL13	Q99616	0.86 (-0.07, 1.79)	6.85E-02	9.91E-02		0.41 (-0.47, 1.29)	3.64E-01	4.64E-01
CCL15	Q16663	0.48 (-0.56, 1.51)	3.65E-01	4.21E-01		0.43 (-0.56, 1.42)	3.97E-01	4.95E-01
CCL16	O15467	**1.74 (0.71, 2.78)**	**9.73E-04**	**2.66E-03**		**1.25 (0.29, 2.22)**	**1.08E-02**	**2.99E-02**
CCL17	Q92583	0.55 (-0.36, 1.47)	2.37E-01	2.97E-01		0.42 (-0.47, 1.30)	3.58E-01	4.61E-01
CCL19	Q99731	**1.78 (0.84, 2.72)**	**2.00E-04**	**7.66E-04**		**1.31 (0.36, 2.27)**	**7.15E-03**	**2.08E-02**
CCL2	P13500	**1.46 (0.50, 2.41)**	**2.81E-03**	**6.23E-03**		0.82 (-0.12, 1.75)	8.66E-02	1.55E-01
CCL20	P78556	**1.18 (0.23, 2.12)**	**1.50E-02**	**2.53E-02**		0.58 (-0.35, 1.52)	2.21E-01	3.24E-01
CCL23	P55773	**1.52 (0.41, 2.63)**	**7.38E-03**	**1.41E-02**		**1.38 (0.30, 2.46)**	**1.25E-02**	**3.35E-02**
CCL24	O00175	0.13 (-0.85, 1.10)	8.00E-01	8.21E-01		-0.00 (-0.94, 0.93)	9.93E-01	9.94E-01
CCL25	O15444	0.46 (-0.49, 1.42)	3.43E-01	4.05E-01		0.49 (-0.43, 1.41)	2.98E-01	3.99E-01
CCL28	Q9NRJ3	**1.40 (0.44, 2.37)**	**4.39E-03**	**8.97E-03**		**1.33 (0.39, 2.26)**	**5.39E-03**	**1.74E-02**
CCL3	P10147	**1.48 (0.36, 2.59)**	**9.29E-03**	**1.69E-02**		0.73 (-0.33, 1.79)	1.77E-01	2.75E-01
CCL4	P13236	**1.98 (0.96, 2.99)**	**1.29E-04**	**5.09E-04**		**1.23 (0.27, 2.18)**	**1.17E-02**	**3.18E-02**
CCL7	P80098	**1.69 (0.64, 2.74)**	**1.65E-03**	**4.08E-03**		1.16 (0.11, 2.21)	2.98E-02	6.43E-02
CD163	Q86VB7	**2.73 (1.77, 3.68)**	**2.13E-08**	**5.86E-07**		**1.50 (0.52, 2.49)**	**2.86E-03**	**9.84E-03**
CD244	Q9BZW8	**1.13 (0.20, 2.07)**	**1.72E-02**	**2.85E-02**		0.61 (-0.30, 1.52)	1.87E-01	2.84E-01
CD4	P01730	**1.55 (0.57, 2.54)**	**2.04E-03**	**4.86E-03**		0.87 (-0.08, 1.82)	7.25E-02	1.32E-01
CD40	P25942	0.97 (-0.02, 1.96)	5.48E-02	8.26E-02		0.73 (-0.21, 1.66)	1.27E-01	2.13E-01
CD40-L	P29965	0.86 (-0.07, 1.80)	7.02E-02	1.01E-01		0.45 (-0.45, 1.35)	3.24E-01	4.26E-01
CD5	P06127	0.50 (-0.50, 1.50)	3.28E-01	3.94E-01		0.19 (-0.76, 1.14)	6.96E-01	7.91E-01
CD6	P30203	0.74 (-0.22, 1.70)	1.32E-01	1.75E-01		0.19 (-0.72, 1.10)	6.80E-01	7.77E-01
CD84	Q9UIB8	**1.19 (0.24, 2.15)**	**1.38E-02**	**2.39E-02**		0.70 (-0.22, 1.62)	1.34E-01	2.18E-01
CD8A	P01732	**2.32 (1.43, 3.20)**	**3.36E-07**	**4.89E-06**		**1.68 (0.79, 2.58)**	**2.36E-04**	**1.90E-03**
CD93	Q9NPY3	0.87 (-0.22, 1.96)	1.18E-01	1.61E-01		1.05 (0.02, 2.08)	4.54E-02	9.04E-02
CDCP1	Q9H5V8	**2.65 (1.51, 3.80)**	**5.60E-06**	**3.73E-05**		**1.91 (0.79, 3.03)**	**8.61E-04**	**4.27E-03**
CDH5	P33151	0.50 (-0.44, 1.43)	2.96E-01	3.63E-01		0.02 (-0.87, 0.91)	9.60E-01	9.81E-01
CEACAM8	P31997	**2.54 (1.27, 3.80)**	**8.26E-05**	**3.70E-04**		**1.85 (0.63, 3.07)**	**2.87E-03**	**9.84E-03**
CHI3L1	P36222	**3.29 (2.24, 4.33)**	**7.18E-10**	**4.18E-08**		**2.66 (1.63, 3.69)**	**4.34E-07**	**1.44E-05**
CHIT1	Q13231	-0.07 (-1.07, 0.92)	8.84E-01	8.95E-01		0.08 (-0.87, 1.04)	8.61E-01	9.04E-01
CNTN1	Q12860	0.75 (-0.28, 1.79)	1.54E-01	2.02E-01		0.52 (-0.46, 1.50)	2.97E-01	3.99E-01
COL1A1	P02452	0.26 (-0.68, 1.19)	5.90E-01	6.30E-01		0.43 (-0.47, 1.33)	3.48E-01	4.51E-01

Table S6. Associations between 233 proteins and SBP in KORA S4/F4/FF4 study (participants = 1560; observation = 3332) [a]

Protein	UniProt_ID	Model 1				Model 2		
		β (95%CI)	P	FDR		β (95%CI)	P	FDR
CPA1	P15085	**1.24 (0.29, 2.19)**	**1.02E-02**	**1.83E-02**		**1.43 (0.47, 2.39)**	**3.55E-03**	**1.20E-02**
CPB1	P15086	**1.92 (1.03, 2.82)**	**2.42E-05**	**1.41E-04**		**1.82 (0.92, 2.72)**	**6.97E-05**	**1.08E-03**
CSF1	P09603	**2.43 (1.39, 3.48)**	**5.21E-06**	**3.68E-05**		**2.04 (0.97, 3.11)**	**1.86E-04**	**1.72E-03**
CST5	P28325	1.03 (0.00, 2.05)	4.90E-02	7.57E-02		0.70 (-0.30, 1.70)	1.72E-01	2.71E-01
CSTB	P04080	**1.67 (0.64, 2.70)**	**1.44E-03**	**3.69E-03**		1.04 (0.03, 2.04)	4.32E-02	8.67E-02
CTRC	Q99895	1.04 (0.06, 2.02)	3.79E-02	5.96E-02		1.11 (0.14, 2.07)	2.47E-02	5.59E-02
CTSL1	P07711	**2.33 (1.24, 3.42)**	**2.92E-05**	**1.54E-04**		**2.04 (0.98, 3.09)**	**1.55E-04**	**1.72E-03**
CTSZ	Q9UBR2	**2.34 (1.37, 3.32)**	**2.61E-06**	**2.15E-05**		**1.67 (0.68, 2.66)**	**9.19E-04**	**4.28E-03**
CX3CL1	P78423	**1.84 (0.83, 2.86)**	**3.67E-04**	**1.28E-03**		**1.99 (0.95, 3.03)**	**1.79E-04**	**1.72E-03**
CXCL1	P09341	0.44 (-0.51, 1.40)	3.63E-01	4.21E-01		0.18 (-0.74, 1.09)	7.03E-01	7.95E-01
CXCL10	P02778	**1.65 (0.60, 2.71)**	**2.09E-03**	**4.93E-03**		0.98 (-0.05, 2.00)	6.11E-02	1.18E-01
CXCL11	O14625	**1.09 (0.12, 2.05)**	**2.73E-02**	**4.38E-02**		0.60 (-0.33, 1.52)	2.05E-01	3.09E-01
CXCL16	Q9H2A7	0.30 (-0.78, 1.37)	5.87E-01	6.30E-01		0.08 (-0.94, 1.10)	8.78E-01	9.13E-01
CXCL5	P42830	-0.12 (-1.10, 0.86)	8.14E-01	8.32E-01		-0.31 (-1.25, 0.63)	5.16E-01	6.33E-01
CXCL6	P80162	**1.42 (0.51, 2.33)**	**2.25E-03**	**5.20E-03**		0.81 (-0.06, 1.67)	6.77E-02	1.27E-01
CXCL9	Q07325	**1.75 (0.73, 2.78)**	**8.17E-04**	**2.37E-03**		**1.58 (0.55, 2.61)**	**2.74E-03**	**9.81E-03**
DCN	P07585	**1.85 (0.74, 2.96)**	**1.09E-03**	**2.85E-03**		1.19 (0.10, 2.29)	3.25E-02	6.91E-02
DECR1	Q16698	0.44 (-0.59, 1.47)	3.99E-01	4.49E-01		0.29 (-0.70, 1.27)	5.71E-01	6.82E-01
Dkk-1	O94907	0.95 (-0.02, 1.93)	5.49E-02	8.26E-02		0.60 (-0.33, 1.53)	2.07E-01	3.09E-01
DLK-1	P80370	**1.21 (0.19, 2.23)**	**2.05E-02**	**3.37E-02**		0.78 (-0.23, 1.79)	1.31E-01	2.17E-01
DNER	Q8NFT8	-0.73 (-1.79, 0.33)	1.80E-01	2.33E-01		-0.50 (-1.50, 0.50)	3.28E-01	4.30E-01
EGFR	P00533	-0.88 (-1.84, 0.07)	7.05E-02	1.01E-01		**-1.14 (-2.05, -0.23)**	**1.43E-02**	**3.68E-02**
EN-RAGE	P80511	**2.52 (1.43, 3.61)**	**5.47E-06**	**3.73E-05**		**1.81 (0.74, 2.88)**	**9.04E-04**	**4.28E-03**
Ep-CAM	P16422	-0.47 (-1.54, 0.61)	3.95E-01	4.49E-01		-0.34 (-1.38, 0.70)	5.21E-01	6.35E-01
EPHB4	P54760	**1.86 (0.83, 2.88)**	**4.12E-04**	**1.39E-03**		**1.87 (0.84, 2.91)**	**3.75E-04**	**2.50E-03**
FABP2	P12104	-0.93 (-1.92, 0.05)	6.29E-02	9.22E-02		-0.12 (-1.10, 0.85)	8.06E-01	8.53E-01
FABP4	P15090	**3.11 (1.80, 4.42)**	**3.23E-06**	**2.51E-05**		1.62 (0.22, 3.03)	2.35E-02	5.38E-02
FAS	P25445	**2.13 (1.14, 3.13)**	**2.72E-05**	**1.48E-04**		**1.62 (0.65, 2.59)**	**1.02E-03**	**4.52E-03**
FGF19	O95750	**1.26 (0.18, 2.34)**	**2.21E-02**	**3.60E-02**		0.81 (-0.27, 1.90)	1.41E-01	2.28E-01
FGF21	Q9NSA1	**2.20 (1.19, 3.21)**	**1.98E-05**	**1.22E-04**		**1.81 (0.80, 2.82)**	**4.67E-04**	**3.02E-03**
FGF-23	Q9GZV9	**1.68 (0.58, 2.78)**	**2.66E-03**	**6.01E-03**		**1.51 (0.44, 2.58)**	**5.71E-03**	**1.78E-02**
FLT3L	P49771	0.84 (-0.23, 1.90)	1.23E-01	1.67E-01		0.26 (-0.78, 1.30)	6.26E-01	7.33E-01
FS	P19883	**1.35 (0.31, 2.39)**	**1.06E-02**	**1.89E-02**		1.06 (0.04, 2.09)	4.19E-02	8.49E-02
Gal-4	P56470	**2.09 (1.11, 3.06)**	**2.66E-05**	**1.47E-04**		**1.68 (0.71, 2.66)**	**6.98E-04**	**3.78E-03**
Gal-9	O00182	**2.66 (1.57, 3.74)**	**1.60E-06**	**1.55E-05**		**1.97 (0.92, 3.03)**	**2.33E-04**	**1.90E-03**
GDF-15	Q99988	**3.16 (2.03, 4.29)**	**4.41E-08**	**8.56E-07**		**3.10 (1.96, 4.24)**	**1.08E-07**	**5.03E-06**
GDF-2	Q9UK05	0.52 (-0.56, 1.59)	3.44E-01	4.05E-01		0.45 (-0.61, 1.51)	4.08E-01	5.05E-01
GH	P01241	-0.76 (-1.86, 0.33)	1.72E-01	2.24E-01		0.32 (-0.78, 1.42)	5.71E-01	6.82E-01
GIF	P27352	-0.47 (-1.47, 0.54)	3.63E-01	4.21E-01		-0.58 (-1.56, 0.41)	2.53E-01	3.57E-01
GLO1	Q04760	0.87 (-0.13, 1.88)	8.91E-02	1.24E-01		0.63 (-0.34, 1.61)	2.04E-01	3.09E-01
GPVI	Q9HCN6	0.70 (-0.26, 1.66)	1.51E-01	1.99E-01		0.48 (-0.43, 1.40)	3.01E-01	4.01E-01
GRN	P28799	**1.38 (0.32, 2.44)**	**1.11E-02**	**1.95E-02**		0.96 (-0.07, 2.00)	6.88E-02	1.28E-01
GT	P51161	-0.49 (-1.51, 0.53)	3.48E-01	4.08E-01		-0.28 (-1.30, 0.75)	5.99E-01	7.12E-01
HAOX1	Q9UJM8	**1.61 (0.55, 2.68)**	**3.01E-03**	**6.48E-03**		0.68 (-0.40, 1.76)	2.18E-01	3.22E-01
HB-EGF	Q99075	**1.23 (0.23, 2.24)**	**1.57E-02**	**2.64E-02**		0.78 (-0.18, 1.74)	1.10E-01	1.89E-01
HGF	P14210	**3.81 (2.79, 4.84)**	**3.81E-13**	**2.96E-11**		**2.93 (1.88, 3.99)**	**5.42E-08**	**3.16E-06**
HO-1	P09601	**1.70 (0.62, 2.77)**	**1.94E-03**	**4.65E-03**		1.12 (0.06, 2.17)	3.88E-02	7.92E-02
hOSCAR	Q8IYS5	1.01 (-0.05, 2.06)	6.08E-02	9.02E-02		0.79 (-0.24, 1.81)	1.31E-01	2.17E-01
HSP 27	P04792	-0.39 (-1.31, 0.54)	4.11E-01	4.60E-01		-0.22 (-1.13, 0.69)	6.32E-01	7.36E-01

Table S6. Associations between 233 proteins and SBP in KORA S4/F4/FF4 study (participants = 1560; observation = 3332) [a]

Protein	**UniProt_ID**	**Model 1**				**Model 2**		
		β (95%CI)	**P**	**FDR**		**β (95%CI)**	**P**	**FDR**
ICAM-2	P13598	0.68 (-0.28, 1.64)	1.67E-01	2.18E-01		0.20 (-0.73, 1.13)	6.72E-01	7.71E-01
IDUA	P35475	**1.68 (0.68, 2.68)**	**9.80E-04**	**2.66E-03**		0.85 (-0.16, 1.86)	9.81E-02	1.72E-01
IFNG	P01579	0.15 (-0.82, 1.12)	7.67E-01	7.94E-01		-0.17 (-1.12, 0.78)	7.28E-01	8.15E-01
IGFBP-1	P08833	**-2.08 (-3.14, -1.02)**	**1.26E-04**	**5.09E-04**		-0.16 (-1.38, 1.06)	8.00E-01	8.51E-01
IGFBP-2	P18065	-0.63 (-1.67, 0.41)	2.35E-01	2.96E-01		0.92 (-0.19, 2.02)	1.04E-01	1.79E-01
IGFBP-7	Q16270	**2.72 (1.66, 3.77)**	**4.44E-07**	**5.75E-06**		**2.20 (1.18, 3.22)**	**2.48E-05**	**5.79E-04**
IgG Fc receptor II-b	P31994	0.32 (-0.63, 1.27)	5.09E-01	5.59E-01		0.13 (-0.81, 1.06)	7.92E-01	8.50E-01
IL-10	P22301	**1.69 (0.65, 2.74)**	**1.53E-03**	**3.84E-03**		**1.71 (0.69, 2.72)**	**9.84E-04**	**4.50E-03**
IL-10RB	Q08334	**2.48 (1.44, 3.51)**	**2.67E-06**	**2.15E-05**		**1.91 (0.87, 2.95)**	**3.28E-04**	**2.31E-03**
IL-12B	P29460	**2.74 (1.61, 3.87)**	**2.02E-06**	**1.81E-05**		**1.97 (0.84, 3.10)**	**6.44E-04**	**3.77E-03**
IL-15RA	Q13261	**1.56 (0.48, 2.64)**	**4.52E-03**	**9.16E-03**		**1.26 (0.19, 2.32)**	**2.08E-02**	**4.89E-02**
IL-16	Q14005	**1.53 (0.44, 2.61)**	**5.71E-03**	**1.11E-02**		1.02 (-0.02, 2.06)	5.48E-02	1.08E-01
IL-17D	Q8TAD2	**1.36 (0.25, 2.47)**	**1.59E-02**	**2.65E-02**		**1.43 (0.35, 2.51)**	**9.16E-03**	**2.57E-02**
IL-17RA	Q96F46	**1.29 (0.34, 2.24)**	**7.71E-03**	**1.44E-02**		**1.15 (0.22, 2.08)**	**1.53E-02**	**3.88E-02**
IL-18	Q14116	**2.25 (1.20, 3.29)**	**2.57E-05**	**1.46E-04**		**1.28 (0.21, 2.36)**	**1.95E-02**	**4.68E-02**
IL-18BP	O95998	**2.13 (1.07, 3.19)**	**8.60E-05**	**3.71E-04**		**1.81 (0.75, 2.87)**	**7.76E-04**	**4.07E-03**
IL-18R1	Q13478	**3.22 (2.17, 4.28)**	**2.19E-09**	**8.50E-08**		**2.03 (0.93, 3.12)**	**2.87E-04**	**2.13E-03**
IL-1RA	P18510	**3.07 (1.98, 4.16)**	**3.43E-08**	**7.27E-07**		**1.78 (0.63, 2.94)**	**2.51E-03**	**9.12E-03**
IL1-RL2	Q9HB29	**1.74 (0.65, 2.82)**	**1.72E-03**	**4.22E-03**		0.67 (-0.40, 1.73)	2.19E-01	3.22E-01
IL-1RT1	P14778	**1.29 (0.34, 2.24)**	**7.66E-03**	**1.44E-02**		1.03 (0.08, 1.99)	3.45E-02	7.24E-02
IL-1RT2	P27930	**1.38 (0.37, 2.39)**	**7.61E-03**	**1.44E-02**		0.54 (-0.48, 1.56)	2.98E-01	3.99E-01
IL-27	Q8NEV9	**1.95 (0.92, 2.99)**	**2.14E-04**	**8.06E-04**		**1.59 (0.59, 2.60)**	**1.86E-03**	**7.33E-03**
IL2-RA	P01589	**1.94 (0.82, 3.06)**	**6.96E-04**	**2.13E-03**		**1.85 (0.79, 2.90)**	**5.87E-04**	**3.60E-03**
IL-4RA	P24394	**1.40 (0.34, 2.46)**	**9.85E-03**	**1.78E-02**		**1.65 (0.61, 2.70)**	**1.92E-03**	**7.44E-03**
IL-6	P05231	**1.98 (1.02, 2.94)**	**5.57E-05**	**2.70E-04**		**1.83 (0.90, 2.76)**	**1.11E-04**	**1.50E-03**
IL-6RA	P08887	0.54 (-0.52, 1.61)	3.18E-01	3.84E-01		0.16 (-0.86, 1.18)	7.56E-01	8.26E-01
IL-7	P13232	0.53 (-0.39, 1.44)	2.57E-01	3.18E-01		0.22 (-0.66, 1.10)	6.24E-01	7.33E-01
IL-8	P10145	**2.71 (1.60, 3.82)**	**1.75E-06**	**1.63E-05**		**2.05 (0.98, 3.12)**	**1.66E-04**	**1.72E-03**
ITGB1BP2	Q9UKP3	0.50 (-0.46, 1.45)	3.09E-01	3.77E-01		0.34 (-0.57, 1.25)	4.58E-01	5.65E-01
ITGB2	P05107	0.95 (0.01, 1.89)	4.80E-02	7.45E-02		0.41 (-0.50, 1.32)	3.74E-01	4.71E-01
JAM-A	Q9Y624	0.19 (-0.77, 1.16)	6.94E-01	7.28E-01		0.00 (-0.92, 0.93)	9.94E-01	9.94E-01
KIM1	Q96D42	**4.34 (3.22, 5.46)**	**3.09E-14**	**7.19E-12**		**3.95 (2.80, 5.10)**	**1.52E-11**	**3.54E-09**
KLK6	Q92876	-0.56 (-1.57, 0.46)	2.80E-01	3.46E-01		0.08 (-0.93, 1.10)	8.73E-01	9.12E-01
LDL receptor	P01130	**1.61 (0.57, 2.66)**	**2.47E-03**	**5.65E-03**		0.01 (-1.11, 1.13)	9.83E-01	9.93E-01
LEP	P41159	**3.66 (2.38, 4.93)**	**1.79E-08**	**5.86E-07**		**1.76 (0.31, 3.22)**	**1.71E-02**	**4.29E-02**
LIFR	P42702	**2.45 (1.48, 3.43)**	**7.23E-07**	**8.86E-06**		**1.40 (0.39, 2.41)**	**6.65E-03**	**1.96E-02**
LIGHT	O43557	**1.12 (0.12, 2.12)**	**2.75E-02**	**4.38E-02**		0.52 (-0.44, 1.49)	2.88E-01	3.94E-01
LOX-1	P78380	**2.32 (1.08, 3.57)**	**2.62E-04**	**9.41E-04**		**1.69 (0.47, 2.90)**	**6.39E-03**	**1.93E-02**
LPL	P06858	-1.16 (-2.34, 0.02)	5.37E-02	8.18E-02		-0.53 (-1.71, 0.64)	3.73E-01	4.71E-01
LTBR	P36941	**1.79 (0.75, 2.83)**	**7.29E-04**	**2.18E-03**		**1.71 (0.68, 2.75)**	**1.17E-03**	**5.04E-03**
MARCO	Q9UEW3	**1.38 (0.41, 2.35)**	**5.27E-03**	**1.04E-02**		0.56 (-0.41, 1.54)	2.54E-01	3.57E-01
MB	P02144	**1.84 (0.70, 2.98)**	**1.53E-03**	**3.84E-03**		**1.73 (0.62, 2.85)**	**2.33E-03**	**8.76E-03**
MCP-2	P80075	**1.42 (0.45, 2.39)**	**4.30E-03**	**8.86E-03**		0.86 (-0.07, 1.79)	7.15E-02	1.31E-01
MEPE	Q9NQ76	0.29 (-0.68, 1.26)	5.55E-01	6.05E-01		0.55 (-0.40, 1.51)	2.58E-01	3.59E-01
MERTK	Q12866	**2.09 (1.05, 3.13)**	**8.02E-05**	**3.67E-04**		**1.98 (0.96, 3.01)**	**1.53E-04**	**1.72E-03**
MMP-1	P03956	0.95 (-0.05, 1.94)	6.27E-02	9.22E-02		0.73 (-0.23, 1.69)	1.34E-01	2.18E-01
MMP-12	P39900	**2.03 (0.94, 3.12)**	**2.59E-04**	**9.41E-04**		**2.30 (1.18, 3.43)**	**5.91E-05**	**9.83E-04**
MMP-2	P08253	**1.61 (0.55, 2.67)**	**2.95E-03**	**6.42E-03**		**1.26 (0.26, 2.25)**	**1.33E-02**	**3.47E-02**
MMP-3	P08254	1.26 (0.05, 2.47)	4.06E-02	6.34E-02		**1.39 (0.22, 2.56)**	**2.01E-02**	**4.79E-02**

Table S6. Associations between 233 proteins and SBP in KORA S4/F4/FF4 study (participants = 1560; observation = 3332) [a]

Protein	UniProt_ID	Model 1				Model 2		
		β (95%CI)	P	FDR		β (95%CI)	P	FDR
MMP-7	P09237	**1.49 (0.32, 2.65)**	**1.25E-02**	**2.17E-02**		**1.74 (0.60, 2.88)**	**2.87E-03**	**9.84E-03**
MMP-9	P14780	**2.00 (0.92, 3.07)**	**2.60E-04**	**9.41E-04**		**1.45 (0.42, 2.47)**	**5.72E-03**	**1.78E-02**
MPO	P05164	1.02 (-0.00, 2.04)	5.04E-02	7.73E-02		0.60 (-0.38, 1.58)	2.27E-01	3.30E-01
NEMO	Q9Y6K9	0.34 (-0.64, 1.33)	4.95E-01	5.46E-01		0.17 (-0.79, 1.12)	7.34E-01	8.19E-01
Notch 3	Q9UM47	**2.46 (1.46, 3.45)**	**1.31E-06**	**1.33E-05**		**2.02 (1.04, 3.00)**	**5.65E-05**	**9.83E-04**
NT3	P20783	-0.04 (-1.15, 1.08)	9.50E-01	9.50E-01		0.14 (-0.91, 1.18)	8.00E-01	8.51E-01
NT-proBNP	P16860	**2.70 (1.63, 3.76)**	**7.78E-07**	**9.06E-06**		**3.02 (1.98, 4.06)**	**1.34E-08**	**1.04E-06**
OPG	O00300	**3.89 (2.85, 4.92)**	**1.76E-13**	**2.05E-11**		**3.34 (2.32, 4.36)**	**1.39E-10**	**1.62E-08**
OPN	P10451	**2.21 (1.15, 3.27)**	**4.42E-05**	**2.19E-04**		**2.39 (1.35, 3.43)**	**6.84E-06**	**1.99E-04**
OSM	P13725	**2.52 (1.41, 3.62)**	**8.06E-06**	**5.14E-05**		**1.83 (0.76, 2.90)**	**7.86E-04**	**4.07E-03**
PAI	P05121	**1.26 (0.25, 2.26)**	**1.45E-02**	**2.47E-02**		0.51 (-0.48, 1.49)	3.16E-01	4.18E-01
PAR-1	P25116	**1.07 (0.13, 2.00)**	**2.53E-02**	**4.10E-02**		0.82 (-0.07, 1.70)	7.12E-02	1.31E-01
PARP-1	P09874	1.00 (-0.08, 2.09)	7.08E-02	1.01E-01		0.60 (-0.44, 1.64)	2.59E-01	3.59E-01
PCSK9	Q8NBP7	0.95 (-0.10, 2.00)	7.54E-02	1.06E-01		0.50 (-0.51, 1.52)	3.31E-01	4.30E-01
PDGF subunit A	P04085	0.77 (-0.19, 1.73)	1.17E-01	1.61E-01		0.40 (-0.53, 1.33)	3.94E-01	4.94E-01
PDGF subunit B	P01127	0.56 (-0.41, 1.53)	2.57E-01	3.18E-01		0.22 (-0.71, 1.15)	6.43E-01	7.45E-01
PD-L1	Q9NZQ7	**1.61 (0.59, 2.62)**	**1.93E-03**	**4.65E-03**		**1.28 (0.34, 2.22)**	**7.81E-03**	**2.25E-02**
PD-L2	Q9BQ51	**1.47 (0.44, 2.50)**	**5.22E-03**	**1.04E-02**		**1.22 (0.21, 2.23)**	**1.76E-02**	**4.33E-02**
PECAM-1	P16284	0.29 (-0.68, 1.26)	5.62E-01	6.09E-01		0.06 (-0.87, 1.00)	8.98E-01	9.30E-01
PGF	P49763	**2.87 (1.63, 4.10)**	**5.13E-06**	**3.68E-05**		**2.59 (1.36, 3.82)**	**3.56E-05**	**7.54E-04**
PGLYRP1	O75594	**2.06 (0.98, 3.13)**	**1.80E-04**	**7.00E-04**		**1.66 (0.62, 2.70)**	**1.76E-03**	**7.06E-03**
PIgR	P01833	0.67 (-0.33, 1.68)	1.89E-01	2.43E-01		1.10 (0.09, 2.11)	3.26E-02	6.91E-02
PLC	P98160	**2.24 (1.11, 3.37)**	**1.00E-04**	**4.24E-04**		**1.89 (0.77, 3.00)**	**9.04E-04**	**4.28E-03**
PON3	Q15166	**-2.65 (-3.62, -1.68)**	**8.25E-08**	**1.48E-06**		**-1.31 (-2.35, -0.26)**	**1.44E-02**	**3.68E-02**
PRELP	P51888	**2.27 (0.94, 3.60)**	**8.35E-04**	**2.37E-03**		**1.69 (0.48, 2.91)**	**6.45E-03**	**1.93E-02**
PRSS27	Q9BQR3	**1.77 (0.74, 2.80)**	**7.20E-04**	**2.18E-03**		**1.96 (0.96, 2.97)**	**1.25E-04**	**1.54E-03**
PRSS8	Q16651	**2.68 (1.55, 3.81)**	**3.45E-06**	**2.60E-05**		**2.10 (0.96, 3.24)**	**2.92E-04**	**2.13E-03**
PSGL-1	Q14242	**1.50 (0.47, 2.53)**	**4.28E-03**	**8.86E-03**		0.69 (-0.33, 1.72)	1.85E-01	2.84E-01
PSP-D	P35247	0.18 (-0.75, 1.11)	7.10E-01	7.40E-01		0.14 (-0.76, 1.05)	7.55E-01	8.26E-01
PTX3	P26022	**1.79 (0.73, 2.84)**	**8.94E-04**	**2.48E-03**		**1.68 (0.66, 2.69)**	**1.22E-03**	**5.14E-03**
RAGE	Q15109	-0.57 (-1.70, 0.55)	3.17E-01	3.84E-01		0.11 (-1.02, 1.23)	8.53E-01	9.00E-01
RARRES2	Q99969	**1.87 (0.76, 2.98)**	**9.93E-04**	**2.66E-03**		1.25 (0.16, 2.34)	2.51E-02	5.61E-02
REN	P00797	-0.22 (-1.37, 0.94)	7.11E-01	7.40E-01		-1.22 (-2.29, -0.14)	2.66E-02	5.90E-02
RETN	Q9HD89	**2.11 (1.03, 3.19)**	**1.28E-04**	**5.09E-04**		**1.90 (0.83, 2.96)**	**4.91E-04**	**3.09E-03**
SCF	P21583	0.31 (-0.83, 1.45)	5.95E-01	6.30E-01		0.88 (-0.24, 2.00)	1.23E-01	2.07E-01
SCGB3A2	Q96PL1	**-2.72 (-3.68, -1.76)**	**2.51E-08**	**5.86E-07**		**-1.54 (-2.53, -0.55)**	**2.28E-03**	**8.71E-03**
SELE	P16581	**2.00 (0.92, 3.08)**	**2.82E-04**	**9.94E-04**		1.07 (-0.04, 2.18)	5.78E-02	1.12E-01
SELP	P16109	0.61 (-0.35, 1.56)	2.15E-01	2.73E-01		0.29 (-0.63, 1.21)	5.35E-01	6.49E-01
SERPINA12	Q8IW75	0.92 (-0.11, 1.95)	8.09E-02	1.14E-01		0.68 (-0.33, 1.68)	1.86E-01	2.84E-01
SHPS-1	P78324	**1.34 (0.30, 2.39)**	**1.18E-02**	**2.06E-02**		0.84 (-0.16, 1.84)	9.93E-02	1.73E-01
SIRT2	Q8IXJ6	0.76 (-0.21, 1.72)	1.24E-01	1.67E-01		0.43 (-0.50, 1.35)	3.65E-01	4.64E-01
SL-2	P09238	0.44 (-0.53, 1.42)	3.73E-01	4.28E-01		0.78 (-0.20, 1.75)	1.18E-01	2.01E-01
SOD2	P04179	0.35 (-0.63, 1.34)	4.82E-01	5.34E-01		0.15 (-0.79, 1.08)	7.58E-01	8.26E-01
SORT1	Q99523	**2.25 (1.34, 3.16)**	**1.31E-06**	**1.33E-05**		**1.40 (0.49, 2.30)**	**2.43E-03**	**9.00E-03**
SPON2	Q9BUD6	**1.56 (0.47, 2.65)**	**5.12E-03**	**1.03E-02**		**1.54 (0.44, 2.64)**	**6.09E-03**	**1.87E-02**
SRC	P12931	-0.65 (-1.63, 0.33)	1.96E-01	2.50E-01		-0.66 (-1.62, 0.30)	1.77E-01	2.75E-01
ST1A1	P50225	0.44 (-0.54, 1.43)	3.78E-01	4.32E-01		0.21 (-0.74, 1.16)	6.65E-01	7.67E-01
ST2	Q01638	**2.79 (1.75, 3.82)**	**1.29E-07**	**2.15E-06**		**2.01 (0.99, 3.03)**	**1.16E-04**	**1.50E-03**
STAMBP	O95630	0.85 (-0.13, 1.82)	8.92E-02	1.24E-01		0.52 (-0.40, 1.44)	2.70E-01	3.72E-01

Table S6. Associations between 233 proteins and SBP in KORA S4/F4/FF4 study (participants = 1560; observation = 3332) [a]

Protein	**UniProt_ID**	**Model 1**				**Model 2**		
		β (95%CI)	**P**	**FDR**		**β (95%CI)**	**P**	**FDR**
STK4	Q13043	-0.03 (-1.02, 0.96)	9.50E-01	9.50E-01		-0.16 (-1.12, 0.80)	7.46E-01	8.26E-01
TF	P13726	**1.73 (0.76, 2.70)**	**4.87E-04**	**1.60E-03**		**1.87 (0.89, 2.85)**	**1.92E-04**	**1.72E-03**
TFPI	P10646	-0.31 (-1.33, 0.71)	5.52E-01	6.04E-01		-0.30 (-1.31, 0.70)	5.53E-01	6.67E-01
TGF-α	P01135	**2.55 (1.43, 3.66)**	**8.16E-06**	**5.14E-05**		**1.77 (0.66, 2.88)**	**1.76E-03**	**7.06E-03**
TGF-β1	P01137	**1.73 (0.76, 2.69)**	**4.42E-04**	**1.47E-03**		1.07 (0.15, 2.00)	2.31E-02	5.34E-02
TGM2	P21980	**1.89 (0.81, 2.97)**	**6.04E-04**	**1.95E-03**		0.99 (-0.07, 2.05)	6.73E-02	1.27E-01
THBS2	P35442	**2.14 (1.05, 3.24)**	**1.21E-04**	**5.05E-04**		1.16 (0.08, 2.25)	3.54E-02	7.36E-02
THPO	P40225	-0.10 (-1.11, 0.90)	8.42E-01	8.57E-01		0.15 (-0.84, 1.14)	7.69E-01	8.33E-01
TIE2	Q02763	**1.22 (0.24, 2.19)**	**1.45E-02**	**2.47E-02**		0.58 (-0.39, 1.55)	2.43E-01	3.46E-01
TIMP4	Q99727	**2.02 (1.03, 3.01)**	**6.77E-05**	**3.16E-04**		**1.68 (0.71, 2.65)**	**6.57E-04**	**3.77E-03**
TLT-2	Q5T2D2	0.97 (-0.03, 1.97)	5.67E-02	8.47E-02		0.58 (-0.38, 1.55)	2.34E-01	3.37E-01
TM	P07204	**2.51 (1.35, 3.68)**	**2.27E-05**	**1.35E-04**		**2.16 (1.01, 3.31)**	**2.25E-04**	**1.90E-03**
TNF-R1	P19438	**3.29 (2.13, 4.44)**	**2.35E-08**	**5.86E-07**		**3.01 (1.86, 4.16)**	**2.74E-07**	**1.06E-05**
TNF-R2	P20333	**2.27 (1.14, 3.41)**	**8.51E-05**	**3.71E-04**		**1.87 (0.74, 3.01)**	**1.24E-03**	**5.14E-03**
TNFRSF10A	O00220	**2.53 (1.32, 3.73)**	**4.14E-05**	**2.10E-04**		**2.10 (0.97, 3.23)**	**2.69E-04**	**2.09E-03**
TNFRSF10C	O14798	**1.50 (0.50, 2.49)**	**3.17E-03**	**6.72E-03**		**1.24 (0.26, 2.22)**	**1.32E-02**	**3.47E-02**
TNFRSF11A	Q9Y6Q6	**3.15 (1.93, 4.36)**	**3.80E-07**	**5.21E-06**		**2.63 (1.42, 3.84)**	**2.16E-05**	**5.58E-04**
TNFRSF13B	O14836	**1.50 (0.38, 2.63)**	**8.88E-03**	**1.63E-02**		**1.34 (0.23, 2.45)**	**1.76E-02**	**4.33E-02**
TNFRSF14	Q92956	**1.72 (0.71, 2.74)**	**8.62E-04**	**2.42E-03**		**1.45 (0.47, 2.44)**	**3.83E-03**	**1.28E-02**
TNFRSF9	Q07011	**1.95 (0.83, 3.07)**	**6.47E-04**	**2.06E-03**		**1.98 (0.84, 3.12)**	**6.80E-04**	**3.77E-03**
TNFSF10	P50591	-0.07 (-1.14, 1.00)	8.98E-01	9.06E-01		0.02 (-1.03, 1.07)	9.69E-01	9.86E-01
TNFSF13B	Q9Y275	0.15 (-0.88, 1.19)	7.70E-01	7.94E-01		0.01 (-1.00, 1.02)	9.85E-01	9.93E-01
TNF-α	P01375	**1.56 (0.46, 2.65)**	**5.36E-03**	**1.05E-02**		0.97 (-0.05, 2.00)	6.32E-02	1.21E-01
TNF-β	P01374	0.66 (-0.38, 1.71)	2.14E-01	2.73E-01		0.05 (-1.01, 1.11)	9.25E-01	9.54E-01
t-PA	P00750	**1.38 (0.45, 2.32)**	**3.65E-03**	**7.66E-03**		0.80 (-0.14, 1.73)	9.63E-02	1.70E-01
TR	P02786	**1.78 (0.74, 2.82)**	**7.95E-04**	**2.34E-03**		**1.18 (0.20, 2.16)**	**1.84E-02**	**4.46E-02**
TRAIL-R2	O14763	**2.11 (0.84, 3.39)**	**1.18E-03**	**3.05E-03**		**1.95 (0.60, 3.30)**	**4.68E-03**	**1.54E-02**
TRANCE	O14788	-0.23 (-1.26, 0.79)	6.54E-01	6.89E-01		-0.61 (-1.62, 0.40)	2.38E-01	3.40E-01
TR-AP	P13686	**1.98 (1.05, 2.91)**	**3.22E-05**	**1.67E-04**		**1.65 (0.74, 2.56)**	**3.75E-04**	**2.50E-03**
TWEAK	O43508	-0.76 (-1.75, 0.22)	1.30E-01	1.74E-01		-0.85 (-1.80, 0.10)	7.98E-02	1.44E-01
uPA	P00749	0.81 (-0.14, 1.75)	9.57E-02	1.32E-01		0.49 (-0.43, 1.41)	2.98E-01	3.99E-01
U-PAR	Q03405	**1.29 (0.33, 2.25)**	**8.64E-03**	**1.60E-02**		1.12 (0.17, 2.08)	2.15E-02	5.01E-02
VEGF-A	P15692	**2.48 (1.45, 3.51)**	**2.50E-06**	**2.15E-05**		**1.93 (0.92, 2.94)**	**1.77E-04**	**1.72E-03**
VEGFD	O43915	-0.51 (-1.55, 0.54)	3.44E-01	4.05E-01		0.19 (-0.84, 1.23)	7.16E-01	8.06E-01
VSIG2	Q96IQ7	**1.49 (0.51, 2.46)**	**2.82E-03**	**6.23E-03**		**1.64 (0.66, 2.62)**	**1.03E-03**	**4.52E-03**
vWF	P04275	**1.69 (0.70, 2.68)**	**8.36E-04**	**2.37E-03**		**1.33 (0.35, 2.31)**	**7.91E-03**	**2.25E-02**
XCL1	P47992	1.09 (0.07, 2.10)	3.63E-02	5.75E-02		0.72 (-0.26, 1.69)	1.49E-01	2.39E-01

[a] To take into account repeated measurements of outcome, generalized estimating equations with exchangeable correlation structure were used to estimate β (95% CI) of levels of SBP per 1 standard deviation increase in proteins concentration. The proteins are sorted alphabetically. **In bold are proteins significantly associated with SBP at the threshold of FDR < 0.05.**

Model 1: Adjusted for age, use of antihypertensive medication at each wave of survey (time-varying covariates) and sex;

Model 2: Model 1 plus body mass index, smoking status, alcohol consumption, physical activity, naturally log-transformed triglycerides, high-density lipoprotein cholesterol, use of lipid-lowering medication, prevalent diabetes, prevalent cardiovascular diseases, fasting status, and kidney function at each wave of survey.

Abbreviations: CI, confidence interval; FDR, Benjamini–Hochberg false-discovery rate; SBP, systolic blood pressure. Full names of the proteins can be found in Table S1.

Table S7. Sensitivity analysis of associations between 233 proteins and SBP in KORA S4/F4/FF4 study (participants = 1560; observation = 3332) [a]

Protein	UniProt_ID	Generalized estimating equations				Linear mixed-effects models		
		β (95%CI)	P	FDR		β (95%CI)	P	FDR
ACE2	Q9BYF1	**2.21 (1.10, 3.32)**	**1.00E-04**	**1.46E-03**		**2.21 (1.23, 3.18)**	**9.61E-06**	**1.49E-04**
ADM	P35318	**2.41 (1.25, 3.56)**	**4.38E-05**	**8.51E-04**		**2.30 (1.32, 3.27)**	**3.91E-06**	**7.59E-05**
AMBP	P02760	**1.81 (0.75, 2.86)**	**8.04E-04**	**4.07E-03**		**1.83 (0.89, 2.76)**	**1.42E-04**	**7.86E-04**
BMP-6	P22004	**1.23 (0.28, 2.18)**	**1.13E-02**	**3.08E-02**		**1.33 (0.43, 2.23)**	**4.01E-03**	**1.07E-02**
CA5A	P35218	**1.74 (0.74, 2.74)**	**6.64E-04**	**3.77E-03**		**1.70 (0.76, 2.64)**	**4.14E-04**	**1.66E-03**
CEACAM8	P31997	**1.85 (0.63, 3.07)**	**2.87E-03**	**9.84E-03**		**1.70 (0.75, 2.64)**	**4.26E-04**	**1.68E-03**
CTSL1	P07711	**2.04 (0.98, 3.09)**	**1.55E-04**	**1.72E-03**		**1.95 (1.03, 2.86)**	**3.06E-05**	**2.97E-04**
FGF-23	Q9GZV9	**1.51 (0.44, 2.58)**	**5.71E-03**	**1.78E-02**		**1.46 (0.53, 2.39)**	**2.13E-03**	**6.54E-03**
Gal-9	O00182	**1.97 (0.92, 3.03)**	**2.33E-04**	**1.90E-03**		**1.95 (1.02, 2.89)**	**4.66E-05**	**3.87E-04**
IL-17D	Q8TAD2	**1.43 (0.35, 2.51)**	**9.16E-03**	**2.57E-02**		**1.23 (0.33, 2.13)**	**7.21E-03**	**1.79E-02**
IL-18	Q14116	**1.28 (0.21, 2.36)**	**1.95E-02**	**4.68E-02**		**1.44 (0.52, 2.37)**	**2.20E-03**	**6.67E-03**
IL-1RA	P18510	**1.78 (0.63, 2.94)**	**2.51E-03**	**9.12E-03**		**1.77 (0.80, 2.74)**	**3.50E-04**	**1.43E-03**
IL-27	Q8NEV9	**1.59 (0.59, 2.60)**	**1.86E-03**	**7.33E-03**		**1.55 (0.65, 2.45)**	**7.63E-04**	**2.82E-03**
IL-4RA	P24394	**1.65 (0.61, 2.70)**	**1.92E-03**	**7.44E-03**		**1.50 (0.60, 2.41)**	**1.16E-03**	**3.96E-03**
KIM1	Q96D42	**3.95 (2.80, 5.10)**	**1.52E-11**	**3.54E-09**		**3.85 (2.92, 4.77)**	**7.29E-16**	**1.70E-13**
LEP	P41159	**1.76 (0.31, 3.22)**	**1.71E-02**	**4.29E-02**		**1.67 (0.32, 3.01)**	**1.56E-02**	**3.42E-02**
LOX-1	P78380	**1.69 (0.47, 2.90)**	**6.39E-03**	**1.93E-02**		**1.51 (0.58, 2.43)**	**1.51E-03**	**4.77E-03**
MERTK	Q12866	**1.98 (0.96, 3.01)**	**1.53E-04**	**1.72E-03**		**1.87 (0.98, 2.77)**	**4.12E-05**	**3.56E-04**
MMP-12	P39900	**2.30 (1.18, 3.43)**	**5.91E-05**	**9.83E-04**		**2.12 (1.17, 3.06)**	**1.16E-05**	**1.59E-04**
MMP-7	P09237	**1.74 (0.60, 2.88)**	**2.87E-03**	**9.84E-03**		**1.79 (0.88, 2.69)**	**1.10E-04**	**6.58E-04**
PD-L2	Q9BQ51	**1.22 (0.21, 2.23)**	**1.76E-02**	**4.33E-02**		**1.16 (0.26, 2.06)**	**1.17E-02**	**2.71E-02**
PGF	P49763	**2.59 (1.36, 3.82)**	**3.56E-05**	**7.54E-04**		**2.46 (1.52, 3.40)**	**3.60E-07**	**9.32E-06**
PRELP	P51888	**1.69 (0.48, 2.91)**	**6.45E-03**	**1.93E-02**		**1.55 (0.61, 2.48)**	**1.17E-03**	**3.97E-03**
PRSS27	Q9BQR3	**1.96 (0.96, 2.97)**	**1.25E-04**	**1.54E-03**		**1.87 (0.97, 2.78)**	**5.13E-05**	**3.98E-04**
PRSS8	Q16651	**2.10 (0.96, 3.24)**	**2.92E-04**	**2.13E-03**		**2.25 (1.27, 3.23)**	**7.21E-06**	**1.29E-04**
PTX3	P26022	**1.68 (0.66, 2.69)**	**1.22E-03**	**5.14E-03**		**1.60 (0.70, 2.50)**	**5.24E-04**	**2.03E-03**
SORT1	Q99523	**1.40 (0.49, 2.30)**	**2.43E-03**	**9.00E-03**		**1.53 (0.63, 2.44)**	**9.42E-04**	**3.27E-03**
SPON2	Q9BUD6	**1.54 (0.44, 2.64)**	**6.09E-03**	**1.87E-02**		**1.52 (0.59, 2.45)**	**1.38E-03**	**4.46E-03**
TF	P13726	**1.87 (0.89, 2.85)**	**1.92E-04**	**1.72E-03**		**1.71 (0.80, 2.63)**	**2.52E-04**	**1.24E-03**
TM	P07204	**2.16 (1.01, 3.31)**	**2.25E-04**	**1.90E-03**		**2.26 (1.34, 3.18)**	**1.75E-06**	**3.71E-05**
TNFRSF10A	O00220	**2.10 (0.97, 3.23)**	**2.69E-04**	**2.09E-03**		**2.07 (1.14, 3.00)**	**1.40E-05**	**1.82E-04**
TNFRSF11A	Q9Y6Q6	**2.63 (1.42, 3.84)**	**2.16E-05**	**5.58E-04**		**2.59 (1.62, 3.55)**	**1.94E-07**	**5.65E-06**
TNFRSF13B	O14836	**1.34 (0.23, 2.45)**	**1.76E-02**	**4.33E-02**		**1.40 (0.47, 2.34)**	**3.37E-03**	**9.45E-03**
TRAIL-R2	O14763	**1.95 (0.60, 3.30)**	**4.68E-03**	**1.54E-02**		**1.95 (1.00, 2.90)**	**5.69E-05**	**4.09E-04**
VSIG2	Q96IQ7	**1.64 (0.66, 2.62)**	**1.03E-03**	**4.52E-03**		**1.60 (0.66, 2.53)**	**8.24E-04**	**2.95E-03**
CCL11	P51671	**1.42 (0.42, 2.42)**	**5.50E-03**	**1.76E-02**		**1.60 (0.69, 2.51)**	**5.82E-04**	**2.19E-03**
CCL19	Q99731	**1.31 (0.36, 2.27)**	**7.15E-03**	**2.08E-02**		**1.37 (0.46, 2.28)**	**3.13E-03**	**8.90E-03**
CCL23	P55773	**1.38 (0.30, 2.46)**	**1.25E-02**	**3.35E-02**		**1.49 (0.58, 2.41)**	**1.42E-03**	**4.55E-03**
CCL28	Q9NRJ3	**1.33 (0.39, 2.26)**	**5.39E-03**	**1.74E-02**		**1.32 (0.42, 2.22)**	**3.98E-03**	**1.07E-02**
CCL4	P13236	**1.23 (0.27, 2.18)**	**1.17E-02**	**3.18E-02**		**1.31 (0.40, 2.23)**	**4.98E-03**	**1.28E-02**
CD8A	P01732	**1.68 (0.79, 2.58)**	**2.36E-04**	**1.90E-03**		**1.70 (0.78, 2.61)**	**2.78E-04**	**1.27E-03**
CDCP1	Q9H5V8	**1.91 (0.79, 3.03)**	**8.61E-04**	**4.27E-03**		**2.02 (1.10, 2.94)**	**1.79E-05**	**2.09E-04**
CSF1	P09603	**2.04 (0.97, 3.11)**	**1.86E-04**	**1.72E-03**		**2.13 (1.19, 3.07)**	**1.02E-05**	**1.49E-04**
CX3CL1	P78423	**1.99 (0.95, 3.03)**	**1.79E-04**	**1.72E-03**		**1.99 (1.07, 2.92)**	**2.60E-05**	**2.64E-04**
CXCL9	Q07325	**1.58 (0.55, 2.61)**	**2.74E-03**	**9.81E-03**		**1.68 (0.77, 2.59)**	**2.86E-04**	**1.28E-03**
EN-RAGE	P80511	**1.81 (0.74, 2.88)**	**9.04E-04**	**4.28E-03**		**1.76 (0.83, 2.69)**	**2.19E-04**	**1.11E-03**
FGF21	Q9NSA1	**1.81 (0.80, 2.82)**	**4.67E-04**	**3.02E-03**		**1.85 (0.90, 2.79)**	**1.28E-04**	**7.47E-04**
HGF	P14210	**2.93 (1.88, 3.99)**	**5.42E-08**	**3.16E-06**		**2.86 (1.90, 3.83)**	**6.41E-09**	**2.49E-07**
IL-10	P22301	**1.71 (0.69, 2.72)**	**9.84E-04**	**4.50E-03**		**1.80 (0.91, 2.70)**	**8.25E-05**	**5.49E-04**

Table S7. Sensitivity analysis of associations between 233 proteins and SBP in KORA S4/F4/FF4 study (participants = 1560; observation = 3332) [a]

Protein	UniProt_ID	Generalized estimating equations				Linear mixed-effects models		
		β (95%CI)	**P**	**FDR**		**β (95%CI)**	**P**	**FDR**
IL-10RB	Q08334	**1.91 (0.87, 2.95)**	**3.28E-04**	**2.31E-03**		**1.95 (1.03, 2.88)**	**3.84E-05**	**3.44E-04**
IL-12B	P29460	**1.97 (0.84, 3.10)**	**6.44E-04**	**3.77E-03**		**1.99 (1.03, 2.96)**	**5.39E-05**	**4.05E-04**
IL-15RA	Q13261	**1.26 (0.19, 2.32)**	**2.08E-02**	**4.89E-02**		**1.34 (0.41, 2.26)**	**4.85E-03**	**1.26E-02**
IL-18R1	Q13478	**2.03 (0.93, 3.12)**	**2.87E-04**	**2.13E-03**		**2.03 (1.07, 2.98)**	**3.44E-05**	**3.21E-04**
IL-6	P05231	**1.83 (0.90, 2.76)**	**1.11E-04**	**1.50E-03**		**1.91 (0.99, 2.83)**	**4.90E-05**	**3.94E-04**
IL-8	P10145	**2.05 (0.98, 3.12)**	**1.66E-04**	**1.72E-03**		**1.99 (1.09, 2.90)**	**1.77E-05**	**2.09E-04**
LIFR	P42702	**1.40 (0.39, 2.41)**	**6.65E-03**	**1.96E-02**		**1.43 (0.51, 2.36)**	**2.44E-03**	**7.30E-03**
OPG	O00300	**3.34 (2.32, 4.36)**	**1.39E-10**	**1.62E-08**		**3.27 (2.36, 4.19)**	**3.59E-12**	**4.18E-10**
OSM	P13725	**1.83 (0.76, 2.90)**	**7.86E-04**	**4.07E-03**		**1.82 (0.91, 2.74)**	**1.01E-04**	**6.39E-04**
PD-L1	Q9NZQ7	**1.28 (0.34, 2.22)**	**7.81E-03**	**2.25E-02**		**1.37 (0.45, 2.30)**	**3.73E-03**	**1.03E-02**
TGF-α	P01135	**1.77 (0.66, 2.88)**	**1.76E-03**	**7.06E-03**		**1.82 (0.88, 2.75)**	**1.45E-04**	**7.87E-04**
TNFRSF9	Q07011	**1.98 (0.84, 3.12)**	**6.80E-04**	**3.77E-03**		**2.04 (1.09, 2.98)**	**2.38E-05**	**2.52E-04**
VEGF-A	P15692	**1.93 (0.92, 2.94)**	**1.77E-04**	**1.72E-03**		**2.02 (1.10, 2.95)**	**1.89E-05**	**2.10E-04**
CCL16	O15467	**1.25 (0.29, 2.22)**	**1.08E-02**	**2.99E-02**		**1.32 (0.40, 2.23)**	**4.81E-03**	**1.26E-02**
CD163	Q86VB7	**1.50 (0.52, 2.49)**	**2.86E-03**	**9.84E-03**		**1.59 (0.66, 2.53)**	**8.51E-04**	**3.00E-03**
CHI3L1	P36222	**2.66 (1.63, 3.69)**	**4.34E-07**	**1.44E-05**		**2.60 (1.66, 3.54)**	**6.91E-08**	**2.30E-06**
CPA1	P15085	**1.43 (0.47, 2.39)**	**3.55E-03**	**1.20E-02**		**1.35 (0.44, 2.26)**	**3.78E-03**	**1.03E-02**
CPB1	P15086	**1.82 (0.92, 2.72)**	**6.97E-05**	**1.08E-03**		**1.70 (0.79, 2.61)**	**2.72E-04**	**1.27E-03**
CTSZ	Q9UBR2	**1.67 (0.68, 2.66)**	**9.19E-04**	**4.28E-03**		**1.70 (0.77, 2.63)**	**3.34E-04**	**1.41E-03**
EGFR	P00533	**-1.14 (-2.05, -0.23)**	**1.43E-02**	**3.68E-02**		**-1.08 (-1.99, -0.17)**	**2.04E-02**	**4.21E-02**
EPHB4	P54760	**1.87 (0.84, 2.91)**	**3.75E-04**	**2.50E-03**		**1.79 (0.87, 2.71)**	**1.36E-04**	**7.72E-04**
FAS	P25445	**1.62 (0.65, 2.59)**	**1.02E-03**	**4.52E-03**		**1.59 (0.69, 2.50)**	**5.49E-04**	**2.10E-03**
Gal-4	P56470	**1.68 (0.71, 2.66)**	**6.98E-04**	**3.78E-03**		**1.77 (0.85, 2.69)**	**1.69E-04**	**8.95E-04**
GDF-15	Q99988	**3.10 (1.96, 4.24)**	**1.08E-07**	**5.03E-06**		**3.01 (2.04, 3.97)**	**1.22E-09**	**7.51E-08**
IGFBP-7	Q16270	**2.20 (1.18, 3.22)**	**2.48E-05**	**5.79E-04**		**2.08 (1.16, 2.99)**	**9.44E-06**	**1.49E-04**
IL-17RA	Q96F46	**1.15 (0.22, 2.08)**	**1.53E-02**	**3.88E-02**		**1.17 (0.27, 2.07)**	**1.05E-02**	**2.48E-02**
IL-18BP	O95998	**1.81 (0.75, 2.87)**	**7.76E-04**	**4.07E-03**		**1.84 (0.92, 2.76)**	**9.61E-05**	**6.22E-04**
IL2-RA	P01589	**1.85 (0.79, 2.90)**	**5.87E-04**	**3.60E-03**		**1.81 (0.90, 2.72)**	**1.06E-04**	**6.49E-04**
LTBR	P36941	**1.71 (0.68, 2.75)**	**1.17E-03**	**5.04E-03**		**1.72 (0.80, 2.64)**	**2.56E-04**	**1.24E-03**
MB	P02144	**1.73 (0.62, 2.85)**	**2.33E-03**	**8.76E-03**		**1.76 (0.80, 2.72)**	**3.28E-04**	**1.41E-03**
MMP-2	P08253	**1.26 (0.26, 2.25)**	**1.33E-02**	**3.47E-02**		**1.12 (0.23, 2.02)**	**1.41E-02**	**3.19E-02**
MMP-3	P08254	**1.39 (0.22, 2.56)**	**2.01E-02**	**4.79E-02**		**1.26 (0.22, 2.30)**	**1.79E-02**	**3.86E-02**
MMP-9	P14780	**1.45 (0.42, 2.47)**	**5.72E-03**	**1.78E-02**		**1.38 (0.46, 2.29)**	**3.13E-03**	**8.90E-03**
Notch 3	Q9UM47	**2.02 (1.04, 3.00)**	**5.65E-05**	**9.83E-04**		**1.88 (0.97, 2.80)**	**5.79E-05**	**4.09E-04**
NT-proBNP	P16860	**3.02 (1.98, 4.06)**	**1.34E-08**	**1.04E-06**		**2.90 (1.97, 3.84)**	**1.29E-09**	**7.51E-08**
OPN	P10451	**2.39 (1.35, 3.43)**	**6.84E-06**	**1.99E-04**		**2.23 (1.33, 3.14)**	**1.38E-06**	**3.20E-05**
PGLYRP1	O75594	**1.66 (0.62, 2.70)**	**1.76E-03**	**7.06E-03**		**1.58 (0.66, 2.50)**	**8.04E-04**	**2.93E-03**
PLC	P98160	**1.89 (0.77, 3.00)**	**9.04E-04**	**4.28E-03**		**1.76 (0.81, 2.71)**	**2.95E-04**	**1.29E-03**
PON3	Q15166	**-1.31 (-2.35, -0.26)**	**1.44E-02**	**3.68E-02**		**-1.32 (-2.33, -0.31)**	**1.03E-02**	**2.47E-02**
RETN	Q9HD89	**1.90 (0.83, 2.96)**	**4.91E-04**	**3.09E-03**		**1.75 (0.83, 2.68)**	**2.08E-04**	**1.08E-03**
SCGB3A2	Q96PL1	**-1.54 (-2.53, -0.55)**	**2.28E-03**	**8.71E-03**		**-1.44 (-2.42, -0.46)**	**4.10E-03**	**1.09E-02**
ST2	Q01638	**2.01 (0.99, 3.03)**	**1.16E-04**	**1.50E-03**		**1.75 (0.80, 2.71)**	**3.40E-04**	**1.41E-03**
TIMP4	Q99727	**1.68 (0.71, 2.65)**	**6.57E-04**	**3.77E-03**		**1.53 (0.60, 2.46)**	**1.33E-03**	**4.39E-03**
TNF-R1	P19438	**3.01 (1.86, 4.16)**	**2.74E-07**	**1.06E-05**		**2.97 (2.01, 3.93)**	**1.84E-09**	**8.57E-08**
TNF-R2	P20333	**1.87 (0.74, 3.01)**	**1.24E-03**	**5.14E-03**		**1.92 (0.97, 2.87)**	**7.22E-05**	**4.95E-04**
TNFRSF10C	O14798	**1.24 (0.26, 2.22)**	**1.32E-02**	**3.47E-02**		**1.41 (0.51, 2.31)**	**2.12E-03**	**6.54E-03**
TNFRSF14	Q92956	**1.45 (0.47, 2.44)**	**3.83E-03**	**1.28E-02**		**1.51 (0.59, 2.43)**	**1.34E-03**	**4.39E-03**
TR	P02786	**1.18 (0.20, 2.16)**	**1.84E-02**	**4.46E-02**		**1.22 (0.31, 2.13)**	**8.92E-03**	**2.16E-02**
TR-AP	P13686	**1.65 (0.74, 2.56)**	**3.75E-04**	**2.50E-03**		**1.70 (0.79, 2.61)**	**2.69E-04**	**1.27E-03**

Table S7. Sensitivity analysis of associations between 233 proteins and SBP in KORA S4/F4/FF4 study (participants = 1560; observation = 3332) [a]

Protein	UniProt_ID	Generalized estimating equations				Linear mixed-effects models		
		β (95%CI)	P	FDR		β (95%CI)	P	FDR
vWF	P04275	**1.33 (0.35, 2.31)**	**7.91E-03**	**2.25E-02**		**1.37 (0.47, 2.27)**	**3.00E-03**	**8.73E-03**
DCN	P07585	1.19 (0.10, 2.29)	3.25E-02	6.91E-02		**1.07 (0.16, 1.98)**	**2.20E-02**	**4.45E-02**
FS	P19883	1.06 (0.04, 2.09)	4.19E-02	8.49E-02		**1.18 (0.28, 2.08)**	**1.04E-02**	**2.47E-02**
PIgR	P01833	1.10 (0.09, 2.11)	3.26E-02	6.91E-02		**1.15 (0.23, 2.07)**	**1.49E-02**	**3.31E-02**
REN	P00797	-1.22 (-2.29, -0.14)	2.66E-02	5.90E-02		**-1.32 (-2.28, -0.36)**	**7.04E-03**	**1.76E-02**
THBS2	P35442	1.16 (0.08, 2.25)	3.54E-02	7.36E-02		**1.13 (0.19, 2.07)**	**1.89E-02**	**4.00E-02**
ADA	P00813	1.08 (0.11, 2.05)	2.93E-02	6.37E-02		**1.05 (0.14, 1.97)**	**2.45E-02**	**4.88E-02**
CXCL10	P02778	0.98 (-0.05, 2.00)	6.11E-02	1.18E-01		**1.07 (0.17, 1.98)**	**2.00E-02**	**4.17E-02**
TGF-β1	P01137	1.07 (0.15, 2.00)	2.31E-02	5.34E-02		**1.22 (0.32, 2.12)**	**8.23E-03**	**2.02E-02**
CCL7	P80098	1.16 (0.11, 2.21)	2.98E-02	6.43E-02		**1.42 (0.50, 2.34)**	**2.49E-03**	**7.35E-03**
TNF-α	P01375	0.97 (-0.05, 2.00)	6.32E-02	1.21E-01		**1.10 (0.20, 2.00)**	**1.70E-02**	**3.69E-02**
ALCAM	Q13740	1.08 (0.06, 2.11)	3.86E-02	7.92E-02		**1.13 (0.18, 2.08)**	**1.94E-02**	**4.08E-02**
AXL	P30530	1.06 (0.12, 2.00)	2.76E-02	6.06E-02		**1.10 (0.19, 2.02)**	**1.81E-02**	**3.88E-02**
CSTB	P04080	1.04 (0.03, 2.04)	4.32E-02	8.67E-02		**1.09 (0.17, 2.02)**	**2.10E-02**	**4.30E-02**
FABP4	P15090	1.62 (0.22, 3.03)	2.35E-02	5.38E-02		**1.51 (0.35, 2.68)**	**1.12E-02**	**2.60E-02**
IL-1RT1	P14778	1.03 (0.08, 1.99)	3.45E-02	7.24E-02		**1.04 (0.14, 1.94)**	**2.35E-02**	**4.73E-02**
RARRES2	Q99969	1.25 (0.16, 2.34)	2.51E-02	5.61E-02		**1.34 (0.39, 2.28)**	**5.81E-03**	**1.47E-02**
SELE	P16581	1.07 (-0.04, 2.18)	5.78E-02	1.12E-01		**1.18 (0.25, 2.10)**	**1.25E-02**	**2.85E-02**
U-PAR	Q03405	1.12 (0.17, 2.08)	2.15E-02	5.01E-02		**1.15 (0.23, 2.06)**	**1.44E-02**	**3.24E-02**
ADAM-TS13	Q76LX8	-0.62 (-1.51, 0.26)	1.69E-01	2.68E-01		-0.60 (-1.50, 0.30)	1.91E-01	2.76E-01
AGRP	O00253	0.77 (-0.31, 1.85)	1.60E-01	2.56E-01		0.77 (-0.19, 1.73)	1.15E-01	1.82E-01
ANG-1	Q15389	0.13 (-0.80, 1.06)	7.81E-01	8.42E-01		0.25 (-0.65, 1.14)	5.86E-01	6.86E-01
BOC	Q9BWV1	0.17 (-0.87, 1.21)	7.55E-01	8.26E-01		-0.01 (-0.90, 0.89)	9.88E-01	1.00E+00
CCL17	Q92583	0.42 (-0.47, 1.30)	3.58E-01	4.61E-01		0.50 (-0.40, 1.40)	2.77E-01	3.76E-01
CD4	P01730	0.87 (-0.08, 1.82)	7.25E-02	1.32E-01		0.92 (-0.01, 1.85)	5.39E-02	9.90E-02
CD40-L	P29965	0.45 (-0.45, 1.35)	3.24E-01	4.26E-01		0.48 (-0.41, 1.38)	2.92E-01	3.82E-01
CD84	Q9UIB8	0.70 (-0.22, 1.62)	1.34E-01	2.18E-01		0.73 (-0.16, 1.62)	1.10E-01	1.76E-01
CTRC	Q99895	1.11 (0.14, 2.07)	2.47E-02	5.59E-02		0.98 (0.07, 1.89)	3.42E-02	6.63E-02
DECR1	Q16698	0.29 (-0.70, 1.27)	5.71E-01	6.82E-01		0.24 (-0.66, 1.15)	5.96E-01	6.94E-01
Dkk-1	O94907	0.60 (-0.33, 1.53)	2.07E-01	3.09E-01		0.71 (-0.18, 1.61)	1.19E-01	1.86E-01
FABP2	P12104	-0.12 (-1.10, 0.85)	8.06E-01	8.53E-01		-0.01 (-0.91, 0.89)	9.84E-01	1.00E+00
GDF-2	Q9UK05	0.45 (-0.61, 1.51)	4.08E-01	5.05E-01		0.51 (-0.45, 1.48)	2.96E-01	3.85E-01
GH	P01241	0.32 (-0.78, 1.42)	5.71E-01	6.82E-01		0.32 (-0.70, 1.35)	5.36E-01	6.34E-01
GIF	P27352	-0.58 (-1.56, 0.41)	2.53E-01	3.57E-01		-0.55 (-1.45, 0.36)	2.38E-01	3.32E-01
GLO1	Q04760	0.63 (-0.34, 1.61)	2.04E-01	3.09E-01		0.58 (-0.33, 1.49)	2.10E-01	2.98E-01
GT	P51161	-0.28 (-1.30, 0.75)	5.99E-01	7.12E-01		-0.17 (-1.08, 0.74)	7.14E-01	7.89E-01
HAOX1	Q9UJM8	0.68 (-0.40, 1.76)	2.18E-01	3.22E-01		0.64 (-0.30, 1.57)	1.82E-01	2.65E-01
HB-EGF	Q99075	0.78 (-0.18, 1.74)	1.10E-01	1.89E-01		0.92 (0.03, 1.81)	4.41E-02	8.28E-02
HO-1	P09601	1.12 (0.06, 2.17)	3.88E-02	7.92E-02		1.06 (0.13, 1.99)	2.60E-02	5.13E-02
hOSCAR	Q8IYS5	0.79 (-0.24, 1.81)	1.31E-01	2.17E-01		0.85 (-0.05, 1.75)	6.59E-02	1.17E-01
HSP 27	P04792	-0.22 (-1.13, 0.69)	6.32E-01	7.36E-01		-0.35 (-1.24, 0.54)	4.39E-01	5.39E-01
IDUA	P35475	0.85 (-0.16, 1.86)	9.81E-02	1.72E-01		0.88 (-0.03, 1.79)	5.82E-02	1.06E-01
IgG Fc receptor II-b	P31994	0.13 (-0.81, 1.06)	7.92E-01	8.50E-01		0.13 (-0.76, 1.03)	7.69E-01	8.34E-01
IL-16	Q14005	1.02 (-0.02, 2.06)	5.48E-02	1.08E-01		0.92 (0.00, 1.83)	4.91E-02	9.08E-02
IL1-RL2	Q9HB29	0.67 (-0.40, 1.73)	2.19E-01	3.22E-01		0.43 (-0.54, 1.40)	3.85E-01	4.78E-01
ITGB1BP2	Q9UKP3	0.34 (-0.57, 1.25)	4.58E-01	5.65E-01		0.33 (-0.56, 1.22)	4.65E-01	5.65E-01
LPL	P06858	-0.53 (-1.71, 0.64)	3.73E-01	4.71E-01		-0.73 (-1.81, 0.34)	1.81E-01	2.65E-01
MARCO	Q9UEW3	0.56 (-0.41, 1.54)	2.54E-01	3.57E-01		0.60 (-0.31, 1.51)	1.94E-01	2.79E-01
NEMO	Q9Y6K9	0.17 (-0.79, 1.12)	7.34E-01	8.19E-01		0.13 (-0.77, 1.03)	7.73E-01	8.34E-01

Table S7. Sensitivity analysis of associations between 233 proteins and SBP in KORA S4/F4/FF4 study (participants = 1560; observation = 3332) [a]

Protein	UniProt_ID	Generalized estimating equations				Linear mixed-effects models		
		β (95%CI)	P	FDR		β (95%CI)	P	FDR
PAR-1	P25116	0.82 (-0.07, 1.70)	7.12E-02	1.31E-01		0.81 (-0.08, 1.70)	7.53E-02	1.30E-01
PARP-1	P09874	0.60 (-0.44, 1.64)	2.59E-01	3.59E-01		0.50 (-0.42, 1.41)	2.85E-01	3.77E-01
PDGF subunit B	P01127	0.22 (-0.71, 1.15)	6.43E-01	7.45E-01		0.29 (-0.60, 1.19)	5.23E-01	6.24E-01
PSGL-1	Q14242	0.69 (-0.33, 1.72)	1.85E-01	2.84E-01		0.60 (-0.35, 1.55)	2.15E-01	3.04E-01
RAGE	Q15109	0.11 (-1.02, 1.23)	8.53E-01	9.00E-01		-0.05 (-0.99, 0.89)	9.18E-01	9.50E-01
SCF	P21583	0.88 (-0.24, 2.00)	1.23E-01	2.07E-01		0.77 (-0.20, 1.74)	1.21E-01	1.89E-01
SERPINA12	Q8IW75	0.68 (-0.33, 1.68)	1.86E-01	2.84E-01		0.74 (-0.17, 1.66)	1.10E-01	1.76E-01
SOD2	P04179	0.15 (-0.79, 1.08)	7.58E-01	8.26E-01		0.19 (-0.71, 1.08)	6.80E-01	7.58E-01
SRC	P12931	-0.66 (-1.62, 0.30)	1.77E-01	2.75E-01		-0.71 (-1.60, 0.17)	1.16E-01	1.82E-01
STK4	Q13043	-0.16 (-1.12, 0.80)	7.46E-01	8.26E-01		-0.19 (-1.08, 0.70)	6.68E-01	7.49E-01
TGM2	P21980	0.99 (-0.07, 2.05)	6.73E-02	1.27E-01		0.81 (-0.11, 1.74)	8.43E-02	1.43E-01
THPO	P40225	0.15 (-0.84, 1.14)	7.69E-01	8.33E-01		0.24 (-0.67, 1.15)	5.99E-01	6.95E-01
TIE2	Q02763	0.58 (-0.39, 1.55)	2.43E-01	3.46E-01		0.56 (-0.34, 1.46)	2.21E-01	3.10E-01
VEGFD	O43915	0.19 (-0.84, 1.23)	7.16E-01	8.06E-01		-0.02 (-0.94, 0.90)	9.63E-01	9.89E-01
XCL1	P47992	0.72 (-0.26, 1.69)	1.49E-01	2.39E-01		0.76 (-0.14, 1.66)	9.81E-02	1.61E-01
4E-BP1	Q13541	0.92 (-0.02, 1.87)	5.59E-02	1.09E-01		0.86 (-0.06, 1.77)	6.64E-02	1.17E-01
Axin-1	O15169	0.23 (-0.69, 1.15)	6.25E-01	7.33E-01		0.24 (-0.66, 1.14)	6.02E-01	6.95E-01
CASP8	Q14790	0.86 (-0.15, 1.88)	9.55E-02	1.70E-01		0.86 (-0.07, 1.78)	7.04E-02	1.22E-01
CCL20	P78556	0.58 (-0.35, 1.52)	2.21E-01	3.24E-01		0.75 (-0.16, 1.65)	1.07E-01	1.73E-01
CCL25	O15444	0.49 (-0.43, 1.41)	2.98E-01	3.99E-01		0.50 (-0.41, 1.40)	2.83E-01	3.77E-01
CCL3	P10147	0.73 (-0.33, 1.79)	1.77E-01	2.75E-01		0.87 (-0.06, 1.80)	6.55E-02	1.17E-01
CD244	Q9BZW8	0.61 (-0.30, 1.52)	1.87E-01	2.84E-01		0.66 (-0.25, 1.56)	1.55E-01	2.30E-01
CD40	P25942	0.73 (-0.21, 1.66)	1.27E-01	2.13E-01		0.76 (-0.14, 1.66)	9.83E-02	1.61E-01
CD5	P06127	0.19 (-0.76, 1.14)	6.96E-01	7.91E-01		0.27 (-0.65, 1.18)	5.68E-01	6.68E-01
CD6	P30203	0.19 (-0.72, 1.10)	6.80E-01	7.77E-01		0.18 (-0.72, 1.09)	6.92E-01	7.68E-01
CST5	P28325	0.70 (-0.30, 1.70)	1.72E-01	2.71E-01		0.72 (-0.20, 1.64)	1.23E-01	1.89E-01
CXCL1	P09341	0.18 (-0.74, 1.09)	7.03E-01	7.95E-01		0.14 (-0.75, 1.03)	7.60E-01	8.31E-01
CXCL11	O14625	0.60 (-0.33, 1.52)	2.05E-01	3.09E-01		0.74 (-0.16, 1.64)	1.06E-01	1.73E-01
CXCL5	P42830	-0.31 (-1.25, 0.63)	5.16E-01	6.33E-01		-0.22 (-1.11, 0.67)	6.29E-01	7.18E-01
CXCL6	P80162	0.81 (-0.06, 1.67)	6.77E-02	1.27E-01		0.86 (-0.04, 1.76)	6.02E-02	1.09E-01
DNER	Q8NFT8	-0.50 (-1.50, 0.50)	3.28E-01	4.30E-01		-0.40 (-1.31, 0.50)	3.83E-01	4.78E-01
FGF19	O95750	0.81 (-0.27, 1.90)	1.41E-01	2.28E-01		0.79 (-0.12, 1.70)	8.78E-02	1.46E-01
FLT3L	P49771	0.26 (-0.78, 1.30)	6.26E-01	7.33E-01		0.21 (-0.69, 1.12)	6.47E-01	7.35E-01
IFNG	P01579	-0.17 (-1.12, 0.78)	7.28E-01	8.15E-01		-0.07 (-0.96, 0.82)	8.80E-01	9.19E-01
IL-7	P13232	0.22 (-0.66, 1.10)	6.24E-01	7.33E-01		0.44 (-0.45, 1.33)	3.38E-01	4.33E-01
CCL2	P13500	0.82 (-0.12, 1.75)	8.66E-02	1.55E-01		0.99 (0.09, 1.89)	3.05E-02	5.96E-02
MCP-2	P80075	0.86 (-0.07, 1.79)	7.15E-02	1.31E-01		0.94 (0.05, 1.83)	3.96E-02	7.49E-02
CCL13	Q99616	0.41 (-0.47, 1.29)	3.64E-01	4.64E-01		0.53 (-0.37, 1.43)	2.45E-01	3.37E-01
MMP-1	P03956	0.73 (-0.23, 1.69)	1.34E-01	2.18E-01		0.84 (-0.06, 1.73)	6.82E-02	1.20E-01
SL-2	P09238	0.78 (-0.20, 1.75)	1.18E-01	2.01E-01		0.92 (0.01, 1.82)	4.73E-02	8.81E-02
NT3	P20783	0.14 (-0.91, 1.18)	8.00E-01	8.51E-01		0.22 (-0.68, 1.13)	6.28E-01	7.18E-01
SIRT2	Q8IXJ6	0.43 (-0.50, 1.35)	3.65E-01	4.64E-01		0.40 (-0.50, 1.30)	3.81E-01	4.78E-01
ST1A1	P50225	0.21 (-0.74, 1.16)	6.65E-01	7.67E-01		0.14 (-0.77, 1.04)	7.66E-01	8.34E-01
STAMBP	O95630	0.52 (-0.40, 1.44)	2.70E-01	3.72E-01		0.48 (-0.42, 1.38)	3.00E-01	3.88E-01
TNF-β	P01374	0.05 (-1.01, 1.11)	9.25E-01	9.54E-01		0.00 (-0.92, 0.93)	9.95E-01	1.00E+00
LIGHT	O43557	0.52 (-0.44, 1.49)	2.88E-01	3.94E-01		0.59 (-0.32, 1.50)	2.01E-01	2.87E-01
TNFSF10	P50591	0.02 (-1.03, 1.07)	9.69E-01	9.86E-01		0.29 (-0.62, 1.20)	5.31E-01	6.31E-01
TRANCE	O14788	-0.61 (-1.62, 0.40)	2.38E-01	3.40E-01		-0.54 (-1.45, 0.36)	2.41E-01	3.35E-01
TWEAK	O43508	-0.85 (-1.80, 0.10)	7.98E-02	1.44E-01		-0.68 (-1.60, 0.24)	1.50E-01	2.24E-01

Table S7. Sensitivity analysis of associations between 233 proteins and SBP in KORA S4/F4/FF4 study (participants = 1560; observation = 3332) [a]

Protein	**UniProt_ID**	**Generalized estimating equations**				**Linear mixed-effects models**		
		β (95%CI)	**P**	**FDR**		**β (95%CI)**	**P**	**FDR**
uPA	P00749	0.49 (-0.43, 1.41)	2.98E-01	3.99E-01		0.65 (-0.26, 1.56)	1.60E-01	2.36E-01
AP-N	P15144	0.56 (-0.35, 1.47)	2.28E-01	3.30E-01		0.49 (-0.41, 1.39)	2.83E-01	3.77E-01
CASP-3	P42574	0.03 (-0.91, 0.97)	9.58E-01	9.81E-01		0.01 (-0.89, 0.91)	9.80E-01	1.00E+00
CCL15	Q16663	0.43 (-0.56, 1.42)	3.97E-01	4.95E-01		0.42 (-0.50, 1.33)	3.73E-01	4.74E-01
CCL24	O00175	-0.00 (-0.94, 0.93)	9.93E-01	9.94E-01		0.04 (-0.85, 0.94)	9.22E-01	9.50E-01
CD93	Q9NPY3	1.05 (0.02, 2.08)	4.54E-02	9.04E-02		0.97 (0.06, 1.87)	3.76E-02	7.18E-02
CDH5	P33151	0.02 (-0.87, 0.91)	9.60E-01	9.81E-01		0.08 (-0.81, 0.98)	8.56E-01	9.02E-01
CHIT1	Q13231	0.08 (-0.87, 1.04)	8.61E-01	9.04E-01		0.10 (-0.80, 0.99)	8.29E-01	8.82E-01
CNTN1	Q12860	0.52 (-0.46, 1.50)	2.97E-01	3.99E-01		0.52 (-0.43, 1.47)	2.81E-01	3.77E-01
COL1A1	P02452	0.43 (-0.47, 1.33)	3.48E-01	4.51E-01		0.36 (-0.54, 1.26)	4.29E-01	5.29E-01
CXCL16	Q9H2A7	0.08 (-0.94, 1.10)	8.78E-01	9.13E-01		0.12 (-0.80, 1.04)	7.98E-01	8.53E-01
DLK-1	P80370	0.78 (-0.23, 1.79)	1.31E-01	2.17E-01		0.71 (-0.20, 1.63)	1.28E-01	1.95E-01
Ep-CAM	P16422	-0.34 (-1.38, 0.70)	5.21E-01	6.35E-01		-0.33 (-1.24, 0.58)	4.73E-01	5.71E-01
GPVI	Q9HCN6	0.48 (-0.43, 1.40)	3.01E-01	4.01E-01		0.50 (-0.39, 1.40)	2.73E-01	3.72E-01
GRN	P28799	0.96 (-0.07, 2.00)	6.88E-02	1.28E-01		0.98 (0.07, 1.89)	3.44E-02	6.63E-02
ICAM-2	P13598	0.20 (-0.73, 1.13)	6.72E-01	7.71E-01		0.30 (-0.60, 1.19)	5.16E-01	6.20E-01
IGFBP-1	P08833	-0.16 (-1.38, 1.06)	8.00E-01	8.51E-01		-0.08 (-1.07, 0.91)	8.75E-01	9.18E-01
IGFBP-2	P18065	0.92 (-0.19, 2.02)	1.04E-01	1.79E-01		0.77 (-0.21, 1.75)	1.24E-01	1.90E-01
IL-1RT2	P27930	0.54 (-0.48, 1.56)	2.98E-01	3.99E-01		0.46 (-0.45, 1.38)	3.24E-01	4.17E-01
IL-6RA	P08887	0.16 (-0.86, 1.18)	7.56E-01	8.26E-01		0.20 (-0.69, 1.10)	6.55E-01	7.41E-01
ITGB2	P05107	0.41 (-0.50, 1.32)	3.74E-01	4.71E-01		0.41 (-0.49, 1.31)	3.76E-01	4.76E-01
JAM-A	Q9Y624	0.00 (-0.92, 0.93)	9.94E-01	9.94E-01		0.05 (-0.85, 0.94)	9.21E-01	9.50E-01
KLK6	Q92876	0.08 (-0.93, 1.10)	8.73E-01	9.12E-01		-0.00 (-0.92, 0.92)	1.00E+00	1.00E+00
LDL receptor	P01130	0.01 (-1.11, 1.13)	9.83E-01	9.93E-01		0.10 (-0.93, 1.13)	8.46E-01	8.96E-01
MEPE	Q9NQ76	0.55 (-0.40, 1.51)	2.58E-01	3.59E-01		0.41 (-0.51, 1.33)	3.85E-01	4.78E-01
MPO	P05164	0.60 (-0.38, 1.58)	2.27E-01	3.30E-01		0.49 (-0.41, 1.40)	2.87E-01	3.78E-01
PAI	P05121	0.51 (-0.48, 1.49)	3.16E-01	4.18E-01		0.70 (-0.22, 1.61)	1.36E-01	2.05E-01
PCSK9	Q8NBP7	0.50 (-0.51, 1.52)	3.31E-01	4.30E-01		0.71 (-0.21, 1.63)	1.31E-01	1.98E-01
PDGF subunit A	P04085	0.40 (-0.53, 1.33)	3.94E-01	4.94E-01		0.52 (-0.37, 1.42)	2.55E-01	3.49E-01
PECAM-1	P16284	0.06 (-0.87, 1.00)	8.98E-01	9.30E-01		0.12 (-0.78, 1.02)	7.98E-01	8.53E-01
PSP-D	P35247	0.14 (-0.76, 1.05)	7.55E-01	8.26E-01		0.20 (-0.70, 1.10)	6.59E-01	7.41E-01
SELP	P16109	0.29 (-0.63, 1.21)	5.35E-01	6.49E-01		0.35 (-0.55, 1.25)	4.49E-01	5.47E-01
SHPS-1	P78324	0.84 (-0.16, 1.84)	9.93E-02	1.73E-01		0.79 (-0.11, 1.70)	8.63E-02	1.46E-01
TFPI	P10646	-0.30 (-1.31, 0.70)	5.53E-01	6.67E-01		-0.14 (-1.04, 0.75)	7.56E-01	8.31E-01
TLT-2	Q5T2D2	0.58 (-0.38, 1.55)	2.34E-01	3.37E-01		0.79 (-0.12, 1.70)	8.76E-02	1.46E-01
TNFSF13B	Q9Y275	0.01 (-1.00, 1.02)	9.85E-01	9.93E-01		0.00 (-0.91, 0.92)	9.98E-01	1.00E+00
t-PA	P00750	0.80 (-0.14, 1.73)	9.63E-02	1.70E-01		0.82 (-0.11, 1.74)	8.32E-02	1.43E-01

[a] For associations with SBP, linear mixed-effects models were also used to estimate β (95% CI) of levels of SBP per 1 standard deviation increase in proteins concentration, applying the model 2 as described in Table S6, using R package “lme4”. Results of model 2 from generalized estimating equations, as detailed in Table S6, were also presented in this table. **In bold are proteins significantly associated with SBP at the threshold of FDR < 0.05. Cells with green background are 99 proteins significantly associated with SBP in both analysis, and cells with blue background are proteins only significant in one of the analyses.**

Abbreviations: CI, confidence interval; FDR, Benjamini–Hochberg false-discovery rate; SBP, systolic blood pressure. Full names of the proteins can be found in Table S1.

Table S8. Associations of 233 proteins with hypertension and SBP in KORA S4/F4/FF4 study (participants = 1560; observation = 3332) [a]

Protein	UniProt_ID	Hypertension				SBP		
		OR (95%CI)	P	FDR		β (95%CI)	P	FDR
ACE2	Q9BYF1	**1.16 (1.04, 1.29)**	**6.51E-03**	**3.48E-02**		**2.21 (1.10, 3.32)**	**1.00E-04**	**1.46E-03**
BMP-6	P22004	**1.14 (1.04, 1.26)**	**5.60E-03**	**3.14E-02**		**1.23 (0.28, 2.18)**	**1.13E-02**	**3.08E-02**
CA5A	P35218	**1.17 (1.05, 1.30)**	**3.52E-03**	**2.44E-02**		**1.74 (0.74, 2.74)**	**6.64E-04**	**3.77E-03**
CEACAM8	P31997	**1.27 (1.13, 1.41)**	**2.41E-05**	**1.79E-03**		**1.85 (0.63, 3.07)**	**2.87E-03**	**9.84E-03**
CHI3L1	P36222	**1.16 (1.05, 1.28)**	**3.65E-03**	**2.44E-02**		**2.66 (1.63, 3.69)**	**4.34E-07**	**1.44E-05**
CTSL1	P07711	**1.22 (1.10, 1.35)**	**8.92E-05**	**3.46E-03**		**2.04 (0.98, 3.09)**	**1.55E-04**	**1.72E-03**
EN-RAGE	P80511	**1.16 (1.05, 1.28)**	**3.97E-03**	**2.44E-02**		**1.81 (0.74, 2.88)**	**9.04E-04**	**4.28E-03**
FGF21	Q9NSA1	**1.16 (1.05, 1.29)**	**4.08E-03**	**2.44E-02**		**1.81 (0.80, 2.82)**	**4.67E-04**	**3.02E-03**
FGF-23	Q9GZV9	**1.21 (1.07, 1.36)**	**2.01E-03**	**1.74E-02**		**1.51 (0.44, 2.58)**	**5.71E-03**	**1.78E-02**
Gal-9	O00182	**1.18 (1.06, 1.31)**	**1.77E-03**	**1.59E-02**		**1.97 (0.92, 3.03)**	**2.33E-04**	**1.90E-03**
HGF	P14210	**1.27 (1.14, 1.42)**	**1.30E-05**	**1.51E-03**		**2.93 (1.88, 3.99)**	**5.42E-08**	**3.16E-06**
IL-18	Q14116	**1.21 (1.09, 1.35)**	**5.98E-04**	**9.38E-03**		**1.28 (0.21, 2.36)**	**1.95E-02**	**4.68E-02**
IL-18R1	Q13478	**1.16 (1.04, 1.29)**	**6.75E-03**	**3.50E-02**		**2.03 (0.93, 3.12)**	**2.87E-04**	**2.13E-03**
IL-1RA	P18510	**1.23 (1.11, 1.37)**	**1.44E-04**	**4.29E-03**		**1.78 (0.63, 2.94)**	**2.51E-03**	**9.12E-03**
IL-6	P05231	**1.14 (1.04, 1.25)**	**5.31E-03**	**3.09E-02**		**1.83 (0.90, 2.76)**	**1.11E-04**	**1.50E-03**
IL-8	P10145	**1.21 (1.09, 1.34)**	**4.31E-04**	**8.37E-03**		**2.05 (0.98, 3.12)**	**1.66E-04**	**1.72E-03**
KIM1	Q96D42	**1.26 (1.13, 1.40)**	**3.08E-05**	**1.79E-03**		**3.95 (2.80, 5.10)**	**1.52E-11**	**3.54E-09**
LOX-1	P78380	**1.21 (1.09, 1.35)**	**4.76E-04**	**8.54E-03**		**1.69 (0.47, 2.90)**	**6.39E-03**	**1.93E-02**
MMP-9	P14780	**1.17 (1.06, 1.29)**	**2.46E-03**	**2.04E-02**		**1.45 (0.42, 2.47)**	**5.72E-03**	**1.78E-02**
NT-proBNP	P16860	**1.33 (1.20, 1.49)**	**2.05E-07**	**4.77E-05**		**3.02 (1.98, 4.06)**	**1.34E-08**	**1.04E-06**
OPG	O00300	**1.20 (1.08, 1.33)**	**8.73E-04**	**1.07E-02**		**3.34 (2.32, 4.36)**	**1.39E-10**	**1.62E-08**
OSM	P13725	**1.24 (1.11, 1.38)**	**8.10E-05**	**3.46E-03**		**1.83 (0.76, 2.90)**	**7.86E-04**	**4.07E-03**
PD-L1	Q9NZQ7	**1.19 (1.07, 1.31)**	**7.35E-04**	**1.00E-02**		**1.28 (0.34, 2.22)**	**7.81E-03**	**2.25E-02**
PGLYRP1	O75594	**1.19 (1.08, 1.31)**	**6.44E-04**	**9.38E-03**		**1.66 (0.62, 2.70)**	**1.76E-03**	**7.06E-03**
PON3	Q15166	**0.83 (0.75, 0.93)**	**1.27E-03**	**1.34E-02**		**-1.31 (-2.35, -0.26)**	**1.44E-02**	**3.68E-02**
PRSS27	Q9BQR3	**1.14 (1.03, 1.26)**	**9.30E-03**	**4.51E-02**		**1.96 (0.96, 2.97)**	**1.25E-04**	**1.54E-03**
PTX3	P26022	**1.15 (1.05, 1.27)**	**4.04E-03**	**2.44E-02**		**1.68 (0.66, 2.69)**	**1.22E-03**	**5.14E-03**
SCGB3A2	Q96PL1	**0.83 (0.75, 0.93)**	**7.75E-04**	**1.00E-02**		**-1.54 (-2.53, -0.55)**	**2.28E-03**	**8.71E-03**
SORT1	Q99523	**1.20 (1.09, 1.32)**	**2.50E-04**	**5.82E-03**		**1.40 (0.49, 2.30)**	**2.43E-03**	**9.00E-03**
TGF-α	P01135	**1.24 (1.11, 1.39)**	**1.47E-04**	**4.29E-03**		**1.77 (0.66, 2.88)**	**1.76E-03**	**7.06E-03**
VEGF-A	P15692	**1.18 (1.07, 1.30)**	**1.17E-03**	**1.30E-02**		**1.93 (0.92, 2.94)**	**1.77E-04**	**1.72E-03**
4E-BP1	Q13541	**1.16 (1.05, 1.28)**	**3.56E-03**	**2.44E-02**		0.92 (-0.02, 1.87)	5.59E-02	1.09E-01
ADA	P00813	**1.15 (1.04, 1.28)**	**5.66E-03**	**3.14E-02**		1.08 (0.11, 2.05)	2.93E-02	6.37E-02
ADM	P35318	1.15 (1.03, 1.29)	1.10E-02	5.11E-02		**2.41 (1.25, 3.56)**	**4.38E-05**	**8.51E-04**
AMBP	P02760	1.00 (0.91, 1.11)	9.47E-01	9.90E-01		**1.81 (0.75, 2.86)**	**8.04E-04**	**4.07E-03**
CASP8	Q14790	**1.18 (1.07, 1.31)**	**1.35E-03**	**1.37E-02**		0.86 (-0.15, 1.88)	9.55E-02	1.70E-01
CCL11	P51671	1.06 (0.96, 1.17)	2.59E-01	4.05E-01		**1.42 (0.42, 2.42)**	**5.50E-03**	**1.76E-02**
CCL16	O15467	1.04 (0.94, 1.14)	4.88E-01	6.28E-01		**1.25 (0.29, 2.22)**	**1.08E-02**	**2.99E-02**
CCL19	Q99731	1.09 (0.99, 1.21)	8.35E-02	1.81E-01		**1.31 (0.36, 2.27)**	**7.15E-03**	**2.08E-02**
CCL23	P55773	1.05 (0.95, 1.16)	3.28E-01	4.77E-01		**1.38 (0.30, 2.46)**	**1.25E-02**	**3.35E-02**
CCL28	Q9NRJ3	1.09 (0.98, 1.21)	1.07E-01	2.17E-01		**1.33 (0.39, 2.26)**	**5.39E-03**	**1.74E-02**
CCL4	P13236	1.11 (1.00, 1.24)	5.02E-02	1.27E-01		**1.23 (0.27, 2.18)**	**1.17E-02**	**3.18E-02**
CD163	Q86VB7	1.14 (1.03, 1.26)	1.27E-02	5.46E-02		**1.50 (0.52, 2.49)**	**2.86E-03**	**9.84E-03**
CD244	Q9BZW8	**1.14 (1.04, 1.26)**	**6.58E-03**	**3.48E-02**		0.61 (-0.30, 1.52)	1.87E-01	2.84E-01
CD4	P01730	**1.15 (1.03, 1.27)**	**8.68E-03**	**4.40E-02**		0.87 (-0.08, 1.82)	7.25E-02	1.32E-01
CD8A	P01732	1.13 (1.03, 1.25)	1.44E-02	5.97E-02		**1.68 (0.79, 2.58)**	**2.36E-04**	**1.90E-03**
CDCP1	Q9H5V8	1.08 (0.97, 1.19)	1.63E-01	2.82E-01		**1.91 (0.79, 3.03)**	**8.61E-04**	**4.27E-03**
COL1A1	P02452	**0.87 (0.79, 0.96)**	**4.03E-03**	**2.44E-02**		0.43 (-0.47, 1.33)	3.48E-01	4.51E-01
CPA1	P15085	1.08 (0.97, 1.19)	1.52E-01	2.73E-01		**1.43 (0.47, 2.39)**	**3.55E-03**	**1.20E-02**

Table S8. Associations of 233 proteins with hypertension and SBP in KORA S4/F4/FF4 study (participants = 1560; observation = 3332) [a]

Protein	**UniProt_ID**	**Hypertension**				**SBP**		
		OR (95%CI)	**P**	**FDR**		**β (95%CI)**	**P**	**FDR**
CPB1	P15086	1.12 (1.01, 1.24)	2.71E-02	8.78E-02		**1.82 (0.92, 2.72)**	**6.97E-05**	**1.08E-03**
CSF1	P09603	1.08 (0.97, 1.20)	1.40E-01	2.54E-01		**2.04 (0.97, 3.11)**	**1.86E-04**	**1.72E-03**
CTSZ	Q9UBR2	1.03 (0.93, 1.13)	6.21E-01	7.45E-01		**1.67 (0.68, 2.66)**	**9.19E-04**	**4.28E-03**
CX3CL1	P78423	1.11 (1.00, 1.23)	5.59E-02	1.36E-01		**1.99 (0.95, 3.03)**	**1.79E-04**	**1.72E-03**
CXCL9	Q07325	1.11 (1.00, 1.23)	5.13E-02	1.29E-01		**1.58 (0.55, 2.61)**	**2.74E-03**	**9.81E-03**
Dkk-1	O94907	**1.15 (1.05, 1.27)**	**3.70E-03**	**2.44E-02**		0.60 (-0.33, 1.53)	2.07E-01	3.09E-01
EGFR	P00533	0.88 (0.80, 0.97)	1.14E-02	5.11E-02		**-1.14 (-2.05, -0.23)**	**1.43E-02**	**3.68E-02**
EPHB4	P54760	1.00 (0.90, 1.10)	9.65E-01	9.90E-01		**1.87 (0.84, 2.91)**	**3.75E-04**	**2.50E-03**
FAS	P25445	1.03 (0.93, 1.14)	5.65E-01	6.96E-01		**1.62 (0.65, 2.59)**	**1.02E-03**	**4.52E-03**
FGF19	O95750	**1.15 (1.03, 1.27)**	**9.08E-03**	**4.50E-02**		0.81 (-0.27, 1.90)	1.41E-01	2.28E-01
Gal-4	P56470	1.10 (0.99, 1.22)	7.88E-02	1.76E-01		**1.68 (0.71, 2.66)**	**6.98E-04**	**3.78E-03**
GDF-15	Q99988	1.11 (0.99, 1.24)	7.61E-02	1.72E-01		**3.10 (1.96, 4.24)**	**1.08E-07**	**5.03E-06**
HB-EGF	Q99075	**1.18 (1.07, 1.29)**	**9.82E-04**	**1.14E-02**		0.78 (-0.18, 1.74)	1.10E-01	1.89E-01
HO-1	P09601	**1.18 (1.07, 1.31)**	**1.51E-03**	**1.41E-02**		1.12 (0.06, 2.17)	3.88E-02	7.92E-02
IGFBP-7	Q16270	1.09 (0.99, 1.21)	8.36E-02	1.81E-01		**2.20 (1.18, 3.22)**	**2.48E-05**	**5.79E-04**
IL-10	P22301	1.12 (1.01, 1.23)	2.57E-02	8.56E-02		**1.71 (0.69, 2.72)**	**9.84E-04**	**4.50E-03**
IL-10RB	Q08334	1.01 (0.91, 1.12)	8.47E-01	9.27E-01		**1.91 (0.87, 2.95)**	**3.28E-04**	**2.31E-03**
IL-12B	P29460	1.07 (0.97, 1.19)	1.84E-01	3.11E-01		**1.97 (0.84, 3.10)**	**6.44E-04**	**3.77E-03**
IL-15RA	Q13261	1.02 (0.92, 1.13)	6.48E-01	7.65E-01		**1.26 (0.19, 2.32)**	**2.08E-02**	**4.89E-02**
IL-17D	Q8TAD2	1.01 (0.92, 1.11)	7.65E-01	8.61E-01		**1.43 (0.35, 2.51)**	**9.16E-03**	**2.57E-02**
IL-17RA	Q96F46	1.09 (0.98, 1.20)	1.09E-01	2.19E-01		**1.15 (0.22, 2.08)**	**1.53E-02**	**3.88E-02**
IL-18BP	O95998	1.00 (0.91, 1.11)	9.51E-01	9.90E-01		**1.81 (0.75, 2.87)**	**7.76E-04**	**4.07E-03**
IL-27	Q8NEV9	1.08 (0.98, 1.19)	1.24E-01	2.32E-01		**1.59 (0.59, 2.60)**	**1.86E-03**	**7.33E-03**
IL2-RA	P01589	1.08 (0.98, 1.19)	1.41E-01	2.55E-01		**1.85 (0.79, 2.90)**	**5.87E-04**	**3.60E-03**
IL-4RA	P24394	1.00 (0.91, 1.10)	9.99E-01	9.99E-01		**1.65 (0.61, 2.70)**	**1.92E-03**	**7.44E-03**
IL-7	P13232	**1.19 (1.08, 1.30)**	**2.13E-04**	**5.52E-03**		0.22 (-0.66, 1.10)	6.24E-01	7.33E-01
LEP	P41159	1.20 (1.03, 1.39)	1.72E-02	6.68E-02		**1.76 (0.31, 3.22)**	**1.71E-02**	**4.29E-02**
LIFR	P42702	1.11 (1.00, 1.23)	4.23E-02	1.13E-01		**1.40 (0.39, 2.41)**	**6.65E-03**	**1.96E-02**
LIGHT	O43557	**1.15 (1.05, 1.27)**	**3.99E-03**	**2.44E-02**		0.52 (-0.44, 1.49)	2.88E-01	3.94E-01
LPL	P06858	**0.82 (0.73, 0.92)**	**6.37E-04**	**9.38E-03**		-0.53 (-1.71, 0.64)	3.73E-01	4.71E-01
LTBR	P36941	1.01 (0.91, 1.12)	8.30E-01	9.17E-01		**1.71 (0.68, 2.75)**	**1.17E-03**	**5.04E-03**
MB	P02144	1.04 (0.94, 1.15)	4.77E-01	6.18E-01		**1.73 (0.62, 2.85)**	**2.33E-03**	**8.76E-03**
MERTK	Q12866	1.08 (0.98, 1.19)	1.21E-01	2.27E-01		**1.98 (0.96, 3.01)**	**1.53E-04**	**1.72E-03**
MMP-12	P39900	1.06 (0.95, 1.17)	2.95E-01	4.50E-01		**2.30 (1.18, 3.43)**	**5.91E-05**	**9.83E-04**
MMP-2	P08253	1.00 (0.91, 1.10)	9.72E-01	9.90E-01		**1.26 (0.26, 2.25)**	**1.33E-02**	**3.47E-02**
MMP-3	P08254	0.97 (0.87, 1.08)	6.10E-01	7.37E-01		**1.39 (0.22, 2.56)**	**2.01E-02**	**4.79E-02**
MMP-7	P09237	1.12 (1.01, 1.24)	3.78E-02	1.06E-01		**1.74 (0.60, 2.88)**	**2.87E-03**	**9.84E-03**
Notch 3	Q9UM47	1.03 (0.93, 1.14)	5.43E-01	6.77E-01		**2.02 (1.04, 3.00)**	**5.65E-05**	**9.83E-04**
OPN	P10451	0.98 (0.89, 1.08)	6.54E-01	7.65E-01		**2.39 (1.35, 3.43)**	**6.84E-06**	**1.99E-04**
PDGF subunit B	P01127	**1.13 (1.03, 1.24)**	**1.04E-02**	**4.96E-02**		0.22 (-0.71, 1.15)	6.43E-01	7.45E-01
PD-L2	Q9BQ51	1.02 (0.92, 1.12)	7.43E-01	8.53E-01		**1.22 (0.21, 2.23)**	**1.76E-02**	**4.33E-02**
PGF	P49763	1.12 (1.00, 1.25)	4.55E-02	1.19E-01		**2.59 (1.36, 3.82)**	**3.56E-05**	**7.54E-04**
PLC	P98160	1.04 (0.94, 1.16)	4.15E-01	5.69E-01		**1.89 (0.77, 3.00)**	**9.04E-04**	**4.28E-03**
PRELP	P51888	1.07 (0.95, 1.20)	2.46E-01	3.91E-01		**1.69 (0.48, 2.91)**	**6.45E-03**	**1.93E-02**
PRSS8	Q16651	1.13 (1.02, 1.26)	2.28E-02	8.14E-02		**2.10 (0.96, 3.24)**	**2.92E-04**	**2.13E-03**
REN	P00797	**0.86 (0.77, 0.95)**	**3.35E-03**	**2.44E-02**		-1.22 (-2.29, -0.14)	2.66E-02	5.90E-02
RETN	Q9HD89	1.12 (1.02, 1.25)	2.37E-02	8.24E-02		**1.90 (0.83, 2.96)**	**4.91E-04**	**3.09E-03**
SPON2	Q9BUD6	1.02 (0.92, 1.13)	7.34E-01	8.48E-01		**1.54 (0.44, 2.64)**	**6.09E-03**	**1.87E-02**
ST2	Q01638	1.12 (1.01, 1.25)	2.98E-02	9.02E-02		**2.01 (0.99, 3.03)**	**1.16E-04**	**1.50E-03**

Table S8. Associations of 233 proteins with hypertension and SBP in KORA S4/F4/FF4 study (participants = 1560; observation = 3332) [a]

Protein	UniProt_ID	Hypertension				SBP		
		OR (95%CI)	P	FDR		β (95%CI)	P	FDR
TF	P13726	1.03 (0.94, 1.14)	5.42E-01	6.77E-01		**1.87 (0.89, 2.85)**	**1.92E-04**	**1.72E-03**
TFPI	P10646	**0.87 (0.79, 0.96)**	**4.09E-03**	**2.44E-02**		-0.30 (-1.31, 0.70)	5.53E-01	6.67E-01
TGF-β1	P01137	**1.19 (1.08, 1.31)**	**3.25E-04**	**6.88E-03**		1.07 (0.15, 2.00)	2.31E-02	5.34E-02
TGM2	P21980	**1.18 (1.07, 1.31)**	**1.51E-03**	**1.41E-02**		0.99 (-0.07, 2.05)	6.73E-02	1.27E-01
TIMP4	Q99727	1.09 (0.98, 1.21)	9.73E-02	2.01E-01		**1.68 (0.71, 2.65)**	**6.57E-04**	**3.77E-03**
TM	P07204	1.12 (1.01, 1.25)	2.68E-02	8.78E-02		**2.16 (1.01, 3.31)**	**2.25E-04**	**1.90E-03**
TNF-R1	P19438	1.09 (0.98, 1.21)	1.15E-01	2.25E-01		**3.01 (1.86, 4.16)**	**2.74E-07**	**1.06E-05**
TNF-R2	P20333	1.04 (0.94, 1.16)	4.25E-01	5.76E-01		**1.87 (0.74, 3.01)**	**1.24E-03**	**5.14E-03**
TNFRSF10A	O00220	1.08 (0.95, 1.23)	2.23E-01	3.63E-01		**2.10 (0.97, 3.23)**	**2.69E-04**	**2.09E-03**
TNFRSF10C	O14798	1.03 (0.94, 1.14)	4.94E-01	6.32E-01		**1.24 (0.26, 2.22)**	**1.32E-02**	**3.47E-02**
TNFRSF11A	Q9Y6Q6	1.14 (1.02, 1.26)	2.00E-02	7.44E-02		**2.63 (1.42, 3.84)**	**2.16E-05**	**5.58E-04**
TNFRSF13B	O14836	1.10 (1.00, 1.22)	5.95E-02	1.41E-01		**1.34 (0.23, 2.45)**	**1.76E-02**	**4.33E-02**
TNFRSF14	Q92956	1.08 (0.97, 1.19)	1.57E-01	2.77E-01		**1.45 (0.47, 2.44)**	**3.83E-03**	**1.28E-02**
TNFRSF9	Q07011	1.05 (0.94, 1.16)	3.96E-01	5.54E-01		**1.98 (0.84, 3.12)**	**6.80E-04**	**3.77E-03**
TR	P02786	1.11 (1.00, 1.22)	4.22E-02	1.13E-01		**1.18 (0.20, 2.16)**	**1.84E-02**	**4.46E-02**
TRAIL-R2	O14763	1.03 (0.93, 1.15)	5.20E-01	6.59E-01		**1.95 (0.60, 3.30)**	**4.68E-03**	**1.54E-02**
TR-AP	P13686	0.96 (0.87, 1.06)	4.00E-01	5.54E-01		**1.65 (0.74, 2.56)**	**3.75E-04**	**2.50E-03**
VSIG2	Q96IQ7	1.04 (0.94, 1.15)	4.18E-01	5.70E-01		**1.64 (0.66, 2.62)**	**1.03E-03**	**4.52E-03**
vWF	P04275	1.07 (0.97, 1.18)	1.91E-01	3.21E-01		**1.33 (0.35, 2.31)**	**7.91E-03**	**2.25E-02**
ADAM-TS13	Q76LX8	0.96 (0.88, 1.05)	3.87E-01	5.50E-01		-0.62 (-1.51, 0.26)	1.69E-01	2.68E-01
AGRP	O00253	1.13 (1.01, 1.25)	2.54E-02	8.56E-02		0.77 (-0.31, 1.85)	1.60E-01	2.56E-01
ALCAM	Q13740	1.00 (0.90, 1.11)	9.68E-01	9.90E-01		1.08 (0.06, 2.11)	3.86E-02	7.92E-02
ANG-1	Q15389	1.12 (1.02, 1.23)	1.36E-02	5.78E-02		0.13 (-0.80, 1.06)	7.81E-01	8.42E-01
AP-N	P15144	1.01 (0.92, 1.12)	7.62E-01	8.61E-01		0.56 (-0.35, 1.47)	2.28E-01	3.30E-01
Axin-1	O15169	1.09 (0.99, 1.20)	8.80E-02	1.87E-01		0.23 (-0.69, 1.15)	6.25E-01	7.33E-01
AXL	P30530	1.04 (0.95, 1.15)	3.98E-01	5.54E-01		1.06 (0.12, 2.00)	2.76E-02	6.06E-02
BOC	Q9BWV1	1.00 (0.91, 1.10)	9.84E-01	9.90E-01		0.17 (-0.87, 1.21)	7.55E-01	8.26E-01
CASP-3	P42574	1.04 (0.94, 1.14)	4.67E-01	6.15E-01		0.03 (-0.91, 0.97)	9.58E-01	9.81E-01
CCL13	Q99616	1.06 (0.96, 1.17)	2.47E-01	3.91E-01		0.41 (-0.47, 1.29)	3.64E-01	4.64E-01
CCL15	Q16663	1.04 (0.94, 1.15)	4.47E-01	5.94E-01		0.43 (-0.56, 1.42)	3.97E-01	4.95E-01
CCL17	Q92583	1.10 (1.00, 1.21)	5.74E-02	1.38E-01		0.42 (-0.47, 1.30)	3.58E-01	4.61E-01
CCL2	P13500	1.11 (1.01, 1.23)	3.26E-02	9.49E-02		0.82 (-0.12, 1.75)	8.66E-02	1.55E-01
CCL20	P78556	1.02 (0.93, 1.13)	6.51E-01	7.65E-01		0.58 (-0.35, 1.52)	2.21E-01	3.24E-01
CCL24	O00175	1.00 (0.90, 1.10)	9.26E-01	9.85E-01		-0.00 (-0.94, 0.93)	9.93E-01	9.94E-01
CCL25	O15444	0.96 (0.87, 1.06)	4.07E-01	5.61E-01		0.49 (-0.43, 1.41)	2.98E-01	3.99E-01
CCL3	P10147	1.08 (0.98, 1.20)	1.33E-01	2.46E-01		0.73 (-0.33, 1.79)	1.77E-01	2.75E-01
CCL7	P80098	1.09 (0.99, 1.21)	8.24E-02	1.81E-01		1.16 (0.11, 2.21)	2.98E-02	6.43E-02
CD40	P25942	1.12 (1.02, 1.23)	2.11E-02	7.70E-02		0.73 (-0.21, 1.66)	1.27E-01	2.13E-01
CD40-L	P29965	1.12 (1.01, 1.23)	2.56E-02	8.56E-02		0.45 (-0.45, 1.35)	3.24E-01	4.26E-01
CD5	P06127	1.12 (1.01, 1.23)	3.25E-02	9.49E-02		0.19 (-0.76, 1.14)	6.96E-01	7.91E-01
CD6	P30203	1.09 (0.99, 1.20)	8.40E-02	1.81E-01		0.19 (-0.72, 1.10)	6.80E-01	7.77E-01
CD84	Q9UIB8	1.10 (1.00, 1.21)	4.03E-02	1.11E-01		0.70 (-0.22, 1.62)	1.34E-01	2.18E-01
CD93	Q9NPY3	0.94 (0.85, 1.04)	2.10E-01	3.45E-01		1.05 (0.02, 2.08)	4.54E-02	9.04E-02
CDH5	P33151	0.95 (0.87, 1.05)	3.32E-01	4.81E-01		0.02 (-0.87, 0.91)	9.60E-01	9.81E-01
CHIT1	Q13231	0.97 (0.88, 1.07)	5.59E-01	6.93E-01		0.08 (-0.87, 1.04)	8.61E-01	9.04E-01
CNTN1	Q12860	0.95 (0.86, 1.05)	3.02E-01	4.58E-01		0.52 (-0.46, 1.50)	2.97E-01	3.99E-01
CST5	P28325	0.95 (0.86, 1.05)	3.09E-01	4.59E-01		0.70 (-0.30, 1.70)	1.72E-01	2.71E-01
CSTB	P04080	1.11 (1.00, 1.24)	4.59E-02	1.19E-01		1.04 (0.03, 2.04)	4.32E-02	8.67E-02
CTRC	Q99895	1.13 (1.02, 1.25)	1.56E-02	6.28E-02		1.11 (0.14, 2.07)	2.47E-02	5.59E-02

Table S8. Associations of 233 proteins with hypertension and SBP in KORA S4/F4/FF4 study (participants = 1560; observation = 3332) [a]

Protein	UniProt_ID	Hypertension				SBP		
		OR (95%CI)	P	FDR		β (95%CI)	P	FDR
CXCL1	P09341	1.08 (0.98, 1.19)	1.20E-01	2.27E-01		0.18 (-0.74, 1.09)	7.03E-01	7.95E-01
CXCL10	P02778	1.05 (0.95, 1.16)	3.58E-01	5.15E-01		0.98 (-0.05, 2.00)	6.11E-02	1.18E-01
CXCL11	O14625	1.13 (1.03, 1.25)	1.18E-02	5.18E-02		0.60 (-0.33, 1.52)	2.05E-01	3.09E-01
CXCL16	Q9H2A7	0.91 (0.82, 1.00)	6.14E-02	1.45E-01		0.08 (-0.94, 1.10)	8.78E-01	9.13E-01
CXCL5	P42830	1.05 (0.96, 1.15)	3.06E-01	4.59E-01		-0.31 (-1.25, 0.63)	5.16E-01	6.33E-01
CXCL6	P80162	1.13 (1.03, 1.25)	1.14E-02	5.11E-02		0.81 (-0.06, 1.67)	6.77E-02	1.27E-01
DCN	P07585	0.99 (0.90, 1.10)	9.07E-01	9.79E-01		1.19 (0.10, 2.29)	3.25E-02	6.91E-02
DECR1	Q16698	1.09 (0.99, 1.20)	9.04E-02	1.88E-01		0.29 (-0.70, 1.27)	5.71E-01	6.82E-01
DLK-1	P80370	0.93 (0.84, 1.03)	1.58E-01	2.77E-01		0.78 (-0.23, 1.79)	1.31E-01	2.17E-01
DNER	Q8NFT8	0.89 (0.80, 0.98)	1.52E-02	6.23E-02		-0.50 (-1.50, 0.50)	3.28E-01	4.30E-01
Ep-CAM	P16422	1.05 (0.95, 1.17)	2.95E-01	4.50E-01		-0.34 (-1.38, 0.70)	5.21E-01	6.35E-01
FABP2	P12104	0.95 (0.86, 1.05)	2.94E-01	4.50E-01		-0.12 (-1.10, 0.85)	8.06E-01	8.53E-01
FABP4	P15090	1.14 (1.00, 1.31)	5.52E-02	1.35E-01		1.62 (0.22, 3.03)	2.35E-02	5.38E-02
FLT3L	P49771	0.96 (0.88, 1.06)	4.74E-01	6.18E-01		0.26 (-0.78, 1.30)	6.26E-01	7.33E-01
FS	P19883	1.11 (1.01, 1.22)	3.87E-02	1.07E-01		1.06 (0.04, 2.09)	4.19E-02	8.49E-02
GDF-2	Q9UK05	1.07 (0.97, 1.19)	1.70E-01	2.90E-01		0.45 (-0.61, 1.51)	4.08E-01	5.05E-01
GH	P01241	1.00 (0.89, 1.12)	9.82E-01	9.90E-01		0.32 (-0.78, 1.42)	5.71E-01	6.82E-01
GIF	P27352	0.96 (0.87, 1.05)	3.65E-01	5.22E-01		-0.58 (-1.56, 0.41)	2.53E-01	3.57E-01
GLO1	Q04760	1.11 (1.01, 1.23)	2.98E-02	9.02E-02		0.63 (-0.34, 1.61)	2.04E-01	3.09E-01
GPVI	Q9HCN6	1.09 (0.99, 1.20)	8.91E-02	1.87E-01		0.48 (-0.43, 1.40)	3.01E-01	4.01E-01
GRN	P28799	1.05 (0.95, 1.16)	3.21E-01	4.71E-01		0.96 (-0.07, 2.00)	6.88E-02	1.28E-01
GT	P51161	0.99 (0.90, 1.10)	9.02E-01	9.77E-01		-0.28 (-1.30, 0.75)	5.99E-01	7.12E-01
HAOX1	Q9UJM8	1.09 (0.99, 1.21)	8.83E-02	1.87E-01		0.68 (-0.40, 1.76)	2.18E-01	3.22E-01
hOSCAR	Q8IYS5	1.06 (0.96, 1.17)	2.44E-01	3.91E-01		0.79 (-0.24, 1.81)	1.31E-01	2.17E-01
HSP 27	P04792	0.94 (0.85, 1.03)	1.97E-01	3.27E-01		-0.22 (-1.13, 0.69)	6.32E-01	7.36E-01
ICAM-2	P13598	1.01 (0.92, 1.11)	7.79E-01	8.64E-01		0.20 (-0.73, 1.13)	6.72E-01	7.71E-01
IDUA	P35475	1.08 (0.98, 1.19)	1.14E-01	2.25E-01		0.85 (-0.16, 1.86)	9.81E-02	1.72E-01
IFNG	P01579	1.00 (0.91, 1.10)	9.73E-01	9.90E-01		-0.17 (-1.12, 0.78)	7.28E-01	8.15E-01
IGFBP-1	P08833	0.93 (0.84, 1.04)	2.28E-01	3.69E-01		-0.16 (-1.38, 1.06)	8.00E-01	8.51E-01
IGFBP-2	P18065	0.96 (0.86, 1.07)	4.40E-01	5.93E-01		0.92 (-0.19, 2.02)	1.04E-01	1.79E-01
IgG Fc receptor II-b	P31994	1.01 (0.92, 1.12)	7.69E-01	8.61E-01		0.13 (-0.81, 1.06)	7.92E-01	8.50E-01
IL-16	Q14005	1.12 (1.01, 1.23)	2.83E-02	8.93E-02		1.02 (-0.02, 2.06)	5.48E-02	1.08E-01
IL1-RL2	Q9HB29	0.92 (0.83, 1.02)	1.21E-01	2.27E-01		0.67 (-0.40, 1.73)	2.19E-01	3.22E-01
IL-1RT1	P14778	1.02 (0.92, 1.11)	7.54E-01	8.61E-01		1.03 (0.08, 1.99)	3.45E-02	7.24E-02
IL-1RT2	P27930	0.99 (0.90, 1.10)	9.01E-01	9.77E-01		0.54 (-0.48, 1.56)	2.98E-01	3.99E-01
IL-6RA	P08887	1.00 (0.91, 1.11)	9.51E-01	9.90E-01		0.16 (-0.86, 1.18)	7.56E-01	8.26E-01
ITGB1BP2	Q9UKP3	1.11 (1.01, 1.22)	3.37E-02	9.71E-02		0.34 (-0.57, 1.25)	4.58E-01	5.65E-01
ITGB2	P05107	0.99 (0.90, 1.09)	8.39E-01	9.22E-01		0.41 (-0.50, 1.32)	3.74E-01	4.71E-01
JAM-A	Q9Y624	1.02 (0.93, 1.13)	6.47E-01	7.65E-01		0.00 (-0.92, 0.93)	9.94E-01	9.94E-01
KLK6	Q92876	0.91 (0.82, 1.01)	6.97E-02	1.59E-01		0.08 (-0.93, 1.10)	8.73E-01	9.12E-01
LDL receptor	P01130	0.94 (0.85, 1.06)	3.13E-01	4.62E-01		0.01 (-1.11, 1.13)	9.83E-01	9.93E-01
MARCO	Q9UEW3	1.08 (0.98, 1.19)	1.19E-01	2.27E-01		0.56 (-0.41, 1.54)	2.54E-01	3.57E-01
MCP-2	P80075	1.12 (1.01, 1.23)	2.96E-02	9.02E-02		0.86 (-0.07, 1.79)	7.15E-02	1.31E-01
MEPE	Q9NQ76	0.93 (0.84, 1.02)	1.35E-01	2.47E-01		0.55 (-0.40, 1.51)	2.58E-01	3.59E-01
MMP-1	P03956	1.09 (0.98, 1.20)	1.03E-01	2.11E-01		0.73 (-0.23, 1.69)	1.34E-01	2.18E-01
MPO	P05164	1.00 (0.91, 1.10)	9.60E-01	9.90E-01		0.60 (-0.38, 1.58)	2.27E-01	3.30E-01
NEMO	Q9Y6K9	1.07 (0.97, 1.18)	1.54E-01	2.75E-01		0.17 (-0.79, 1.12)	7.34E-01	8.19E-01
NT3	P20783	1.04 (0.94, 1.15)	4.77E-01	6.18E-01		0.14 (-0.91, 1.18)	8.00E-01	8.51E-01
PAI	P05121	1.13 (1.02, 1.24)	1.60E-02	6.34E-02		0.51 (-0.48, 1.49)	3.16E-01	4.18E-01

Table S8. Associations of 233 proteins with hypertension and SBP in KORA S4/F4/FF4 study (participants = 1560; observation = 3332) [a]

Protein	**UniProt_ID**	**Hypertension**				**SBP**		
		OR (95%CI)	**P**	**FDR**		**β (95%CI)**	**P**	**FDR**
PAR-1	P25116	1.12 (1.02, 1.22)	2.31E-02	8.14E-02		0.82 (-0.07, 1.70)	7.12E-02	1.31E-01
PARP-1	P09874	1.11 (1.00, 1.22)	4.54E-02	1.19E-01		0.60 (-0.44, 1.64)	2.59E-01	3.59E-01
PCSK9	Q8NBP7	0.95 (0.86, 1.05)	2.96E-01	4.50E-01		0.50 (-0.51, 1.52)	3.31E-01	4.30E-01
PDGF subunit A	P04085	1.12 (1.02, 1.23)	2.01E-02	7.44E-02		0.40 (-0.53, 1.33)	3.94E-01	4.94E-01
PECAM-1	P16284	1.03 (0.93, 1.13)	5.81E-01	7.09E-01		0.06 (-0.87, 1.00)	8.98E-01	9.30E-01
PIgR	P01833	0.97 (0.88, 1.07)	5.43E-01	6.77E-01		1.10 (0.09, 2.11)	3.26E-02	6.91E-02
PSGL-1	Q14242	1.11 (0.99, 1.23)	6.34E-02	1.48E-01		0.69 (-0.33, 1.72)	1.85E-01	2.84E-01
PSP-D	P35247	0.89 (0.81, 0.98)	1.89E-02	7.20E-02		0.14 (-0.76, 1.05)	7.55E-01	8.26E-01
RAGE	Q15109	0.93 (0.84, 1.03)	1.61E-01	2.80E-01		0.11 (-1.02, 1.23)	8.53E-01	9.00E-01
RARRES2	Q99969	1.06 (0.96, 1.18)	2.48E-01	3.91E-01		1.25 (0.16, 2.34)	2.51E-02	5.61E-02
SCF	P21583	0.93 (0.84, 1.03)	1.68E-01	2.87E-01		0.88 (-0.24, 2.00)	1.23E-01	2.07E-01
SELE	P16581	1.12 (1.01, 1.23)	2.79E-02	8.91E-02		1.07 (-0.04, 2.18)	5.78E-02	1.12E-01
SELP	P16109	1.05 (0.95, 1.16)	3.09E-01	4.59E-01		0.29 (-0.63, 1.21)	5.35E-01	6.49E-01
SERPINA12	Q8IW75	1.09 (0.99, 1.21)	6.78E-02	1.56E-01		0.68 (-0.33, 1.68)	1.86E-01	2.84E-01
SHPS-1	P78324	0.98 (0.89, 1.07)	6.25E-01	7.47E-01		0.84 (-0.16, 1.84)	9.93E-02	1.73E-01
SIRT2	Q8IXJ6	1.11 (1.01, 1.22)	3.64E-02	1.04E-01		0.43 (-0.50, 1.35)	3.65E-01	4.64E-01
SL-2	P09238	1.03 (0.93, 1.13)	5.98E-01	7.25E-01		0.78 (-0.20, 1.75)	1.18E-01	2.01E-01
SOD2	P04179	1.08 (0.98, 1.18)	1.19E-01	2.27E-01		0.15 (-0.79, 1.08)	7.58E-01	8.26E-01
SRC	P12931	0.99 (0.90, 1.08)	7.74E-01	8.63E-01		-0.66 (-1.62, 0.30)	1.77E-01	2.75E-01
ST1A1	P50225	1.08 (0.98, 1.19)	1.13E-01	2.24E-01		0.21 (-0.74, 1.16)	6.65E-01	7.67E-01
STAMBP	O95630	1.10 (1.00, 1.21)	5.24E-02	1.30E-01		0.52 (-0.40, 1.44)	2.70E-01	3.72E-01
STK4	Q13043	1.04 (0.95, 1.14)	3.95E-01	5.54E-01		-0.16 (-1.12, 0.80)	7.46E-01	8.26E-01
THBS2	P35442	1.12 (1.01, 1.25)	3.04E-02	9.08E-02		1.16 (0.08, 2.25)	3.54E-02	7.36E-02
THPO	P40225	1.01 (0.92, 1.12)	7.69E-01	8.61E-01		0.15 (-0.84, 1.14)	7.69E-01	8.33E-01
TIE2	Q02763	1.04 (0.94, 1.14)	4.46E-01	5.94E-01		0.58 (-0.39, 1.55)	2.43E-01	3.46E-01
TLT-2	Q5T2D2	1.02 (0.93, 1.12)	6.80E-01	7.92E-01		0.58 (-0.38, 1.55)	2.34E-01	3.37E-01
TNFSF10	P50591	0.98 (0.89, 1.09)	7.35E-01	8.48E-01		0.02 (-1.03, 1.07)	9.69E-01	9.86E-01
TNFSF13B	Q9Y275	0.91 (0.82, 1.00)	4.66E-02	1.19E-01		0.01 (-1.00, 1.02)	9.85E-01	9.93E-01
TNF-α	P01375	1.04 (0.94, 1.16)	4.49E-01	5.94E-01		0.97 (-0.05, 2.00)	6.32E-02	1.21E-01
TNF-β	P01374	1.00 (0.90, 1.10)	9.59E-01	9.90E-01		0.05 (-1.01, 1.11)	9.25E-01	9.54E-01
t-PA	P00750	1.03 (0.94, 1.14)	5.03E-01	6.40E-01		0.80 (-0.14, 1.73)	9.63E-02	1.70E-01
TRANCE	O14788	1.00 (0.91, 1.11)	9.22E-01	9.85E-01		-0.61 (-1.62, 0.40)	2.38E-01	3.40E-01
TWEAK	O43508	0.94 (0.85, 1.04)	2.07E-01	3.42E-01		-0.85 (-1.80, 0.10)	7.98E-02	1.44E-01
uPA	P00749	1.00 (0.91, 1.10)	9.26E-01	9.85E-01		0.49 (-0.43, 1.41)	2.98E-01	3.99E-01
U-PAR	Q03405	1.03 (0.93, 1.14)	5.72E-01	7.02E-01		1.12 (0.17, 2.08)	2.15E-02	5.01E-02
VEGFD	O43915	1.00 (0.90, 1.11)	9.85E-01	9.90E-01		0.19 (-0.84, 1.23)	7.16E-01	8.06E-01
XCL1	P47992	1.00 (0.91, 1.10)	9.69E-01	9.90E-01		0.72 (-0.26, 1.69)	1.49E-01	2.39E-01

[a] To take into account repeated measurements of outcome, generalized estimating equations with exchangeable correlation structure were used to estimate OR (95% CI) and β (95% CI) of dichotomous hypertension (yes/no) and levels of SBP per 1 standard deviation increase in proteins concentration, applying the model 2 as described in Table S5 & S6. **In bold are proteins significantly associated with outcomes at the threshold of FDR < 0.05. Cells with green background are 31 proteins significantly associated with both SBP and hypertension, and cells with blue background are proteins only associated with either SBP or hypertension.**

Abbreviations: CI, confidence interval; FDR, Benjamini–Hochberg false-discovery rate; OR, odds ratio; SBP, systolic blood pressure. Full names of the proteins can be found in Table S1.

Table S9. Validation of the associations of 49 proteins with hypertension in KORA Age1/Age2 study [a]

Protein	UniProt_ID	Discovery in KORA S4/F4/FF4 (participants = 1560; observation = 3332)			Validation in KORA Age1/Age2 (participants = 1024; observation = 1810)		Sensitivity analysis for validation in KORA Age1/Age2 (participants = 882; observation = 1533) [b]	
		OR (95%CI)	P	FDR	OR (95%CI)	P	OR (95%CI)	P
KIM1	Q96D42	1.26 (1.13, 1.40)	3.08E-05	1.79E-03	**1.39 (1.18, 1.64)**	**8.63E-05**	**1.36 (1.15, 1.62)**	**5.02E-04**
NT-proBNP	P16860	1.33 (1.20, 1.49)	2.05E-07	4.77E-05	**1.29 (1.07, 1.56)**	**7.84E-03**	**1.28 (1.04, 1.57)**	**1.83E-02**
4E-BP1	Q13541	1.16 (1.05, 1.28)	3.56E-03	2.44E-02	**1.26 (1.06, 1.50)**	**8.63E-03**	**1.31 (1.08, 1.59)**	**5.24E-03**
Gal-9	O00182	1.18 (1.06, 1.31)	1.77E-03	1.59E-02	**1.23 (1.04, 1.46)**	**1.78E-02**	**1.22 (1.02, 1.47)**	**3.34E-02**
CTSL1	P07711	1.22 (1.10, 1.35)	8.92E-05	3.46E-03	**1.23 (1.06, 1.43)**	**7.10E-03**	**1.23 (1.04, 1.44)**	**1.33E-02**
OPG	O00300	1.20 (1.08, 1.33)	8.73E-04	1.07E-02	**1.18 (1.00, 1.38)**	**4.48E-02**	1.13 (0.95, 1.34)	1.58E-01
PON3	Q15166	0.83 (0.75, 0.93)	1.27E-03	1.34E-02	**0.84 (0.71, 0.99)**	**3.98E-02**	0.86 (0.73, 1.03)	9.40E-02
ACE2	Q9BYF1	1.16 (1.04, 1.29)	6.51E-03	3.48E-02	1.18 (0.96, 1.44)	1.21E-01	1.17 (0.93, 1.46)	1.81E-01
IL-1RA	P18510	1.23 (1.11, 1.37)	1.44E-04	4.29E-03	1.17 (0.97, 1.41)	9.61E-02	1.21 (0.98, 1.49)	7.16E-02
HGF	P14210	1.27 (1.14, 1.42)	1.30E-05	1.51E-03	1.14 (0.96, 1.36)	1.41E-01	1.07 (0.89, 1.28)	4.85E-01
FGF-23	Q9GZV9	1.21 (1.07, 1.36)	2.01E-03	1.74E-02	1.13 (0.93, 1.36)	2.19E-01	1.11 (0.91, 1.35)	3.01E-01
TGF-α	P01135	1.24 (1.11, 1.39)	1.47E-04	4.29E-03	1.12 (0.95, 1.32)	1.76E-01	1.13 (0.92, 1.38)	2.45E-01
VEGF-A	P15692	1.18 (1.07, 1.30)	1.17E-03	1.30E-02	1.12 (0.94, 1.33)	2.00E-01	1.09 (0.91, 1.31)	3.34E-01
FGF21	Q9NSA1	1.16 (1.05, 1.29)	4.08E-03	2.44E-02	1.12 (0.95, 1.32)	1.90E-01	1.05 (0.88, 1.25)	5.85E-01
CHI3L1	P36222	1.16 (1.05, 1.28)	3.65E-03	2.44E-02	1.11 (0.96, 1.30)	1.64E-01	1.10 (0.93, 1.29)	2.80E-01
CD4	P01730	1.15 (1.03, 1.27)	8.68E-03	4.40E-02	1.11 (0.93, 1.31)	2.54E-01	1.16 (0.96, 1.41)	1.31E-01
REN	P00797	0.86 (0.77, 0.95)	3.35E-03	2.44E-02	1.10 (0.94, 1.29)	2.13E-01	1.10 (0.93, 1.30)	2.90E-01
FGF19	O95750	1.15 (1.03, 1.27)	9.08E-03	4.50E-02	1.10 (0.96, 1.26)	1.57E-01	1.08 (0.94, 1.25)	2.54E-01
IL-18R1	Q13478	1.16 (1.04, 1.29)	6.75E-03	3.50E-02	1.10 (0.95, 1.27)	2.20E-01	1.12 (0.95, 1.32)	1.72E-01
CASP8	Q14790	1.18 (1.07, 1.31)	1.35E-03	1.37E-02	1.09 (0.91, 1.31)	3.42E-01	1.14 (0.95, 1.37)	1.53E-01
IL-18	Q14116	1.21 (1.09, 1.35)	5.98E-04	9.38E-03	1.08 (0.95, 1.24)	2.40E-01	1.09 (0.95, 1.26)	2.12E-01
PGLYRP1	O75594	1.19 (1.08, 1.31)	6.44E-04	9.38E-03	1.08 (0.92, 1.26)	3.42E-01	1.05 (0.89, 1.25)	5.68E-01
PRSS27	Q9BQR3	1.14 (1.03, 1.26)	9.30E-03	4.51E-02	1.08 (0.92, 1.26)	3.48E-01	1.08 (0.91, 1.27)	3.72E-01
PD-L1	Q9NZQ7	1.19 (1.07, 1.31)	7.35E-04	1.00E-02	1.07 (0.92, 1.25)	3.62E-01	1.11 (0.93, 1.33)	2.35E-01
IL-6	P05231	1.14 (1.04, 1.25)	5.31E-03	3.09E-02	1.07 (0.90, 1.28)	4.37E-01	1.09 (0.90, 1.33)	3.69E-01
IL-8	P10145	1.21 (1.09, 1.34)	4.31E-04	8.37E-03	1.07 (0.92, 1.24)	3.69E-01	1.06 (0.90, 1.24)	4.93E-01
TGF-β1	P01137	1.19 (1.08, 1.31)	3.25E-04	6.88E-03	1.07 (0.93, 1.24)	3.56E-01	1.09 (0.93, 1.28)	2.97E-01
CEACAM8	P31997	1.27 (1.13, 1.41)	2.41E-05	1.79E-03	1.07 (0.91, 1.25)	4.08E-01	1.05 (0.89, 1.24)	5.38E-01
TGM2	P21980	1.18 (1.07, 1.31)	1.51E-03	1.41E-02	1.06 (0.92, 1.23)	4.25E-01	1.09 (0.93, 1.28)	2.74E-01
MMP-9	P14780	1.17 (1.06, 1.29)	2.46E-03	2.04E-02	1.05 (0.91, 1.22)	5.08E-01	1.07 (0.91, 1.26)	4.06E-01
BMP-6	P22004	1.14 (1.04, 1.26)	5.60E-03	3.14E-02	1.05 (0.90, 1.22)	5.49E-01	1.09 (0.92, 1.29)	3.44E-01
EN-RAGE	P80511	1.16 (1.05, 1.28)	3.97E-03	2.44E-02	1.04 (0.90, 1.21)	6.07E-01	1.04 (0.88, 1.22)	6.68E-01
OSM	P13725	1.24 (1.11, 1.38)	8.10E-05	3.46E-03	1.04 (0.90, 1.20)	6.30E-01	1.05 (0.89, 1.23)	5.69E-01
IL-7	P13232	1.19 (1.08, 1.30)	2.13E-04	5.52E-03	1.03 (0.89, 1.19)	6.83E-01	1.05 (0.89, 1.23)	5.90E-01
LOX-1	P78380	1.21 (1.09, 1.35)	4.76E-04	8.54E-03	1.02 (0.88, 1.17)	8.26E-01	1.04 (0.89, 1.21)	6.32E-01
TFPI	P10646	0.87 (0.79, 0.96)	4.09E-03	2.44E-02	1.01 (0.88, 1.17)	8.53E-01	1.04 (0.89, 1.21)	6.53E-01
CA5A	P35218	1.17 (1.05, 1.30)	3.52E-03	2.44E-02	1.01 (0.86, 1.19)	9.11E-01	0.99 (0.83, 1.17)	8.77E-01
PTX3	P26022	1.15 (1.05, 1.27)	4.04E-03	2.44E-02	1.01 (0.88, 1.16)	9.04E-01	1.01 (0.87, 1.17)	9.09E-01
HO-1	P09601	1.18 (1.07, 1.31)	1.51E-03	1.41E-02	1.01 (0.87, 1.17)	9.20E-01	1.03 (0.88, 1.21)	7.05E-01
LIGHT	O43557	1.15 (1.05, 1.27)	3.99E-03	2.44E-02	1.01 (0.88, 1.16)	9.17E-01	0.99 (0.86, 1.15)	9.19E-01
PDGF subunit B	P01127	1.13 (1.03, 1.24)	1.04E-02	4.96E-02	0.99 (0.85, 1.15)	9.07E-01	1.02 (0.87, 1.20)	7.99E-01
SCGB3A2	Q96PL1	0.83 (0.75, 0.93)	7.75E-04	1.00E-02	0.99 (0.85, 1.16)	8.93E-01	0.96 (0.82, 1.13)	6.46E-01
SORT1	Q99523	1.20 (1.09, 1.32)	2.50E-04	5.82E-03	0.99 (0.86, 1.13)	8.69E-01	0.98 (0.85, 1.13)	7.81E-01
HB-EGF	Q99075	1.18 (1.07, 1.29)	9.82E-04	1.14E-02	0.99 (0.84, 1.16)	8.79E-01	0.99 (0.83, 1.19)	9.28E-01
ADA	P00813	1.15 (1.04, 1.28)	5.66E-03	3.14E-02	0.98 (0.84, 1.13)	7.34E-01	1.00 (0.86, 1.16)	9.97E-01
CD244	Q9BZW8	1.14 (1.04, 1.26)	6.58E-03	3.48E-02	0.97 (0.84, 1.11)	6.26E-01	0.96 (0.82, 1.13)	6.23E-01
Dkk-1	O94907	1.15 (1.05, 1.27)	3.70E-03	2.44E-02	0.93 (0.81, 1.07)	2.86E-01	0.94 (0.81, 1.09)	4.32E-01
COL1A1	P02452	0.87 (0.79, 0.96)	4.03E-03	2.44E-02	0.89 (0.77, 1.03)	1.13E-01	**0.85 (0.72, 0.99)**	**3.52E-02**
LPL	P06858	0.82 (0.73, 0.92)	6.37E-04	9.38E-03	0.88 (0.75, 1.04)	1.41E-01	0.94 (0.79, 1.12)	4.74E-01

[a] The 49 proteins significantly associated with hypertension (FDR < 0.05) in the discovery analysis among KORA S4/F4/FF4 study were taken to validate their associations with hypertension in KORA Age1/Age2 study using generalized estimating equations, applying the model 2 as described in Table S5. OR (95% CI) refer to per 1 standard deviation increase in proteins concentration. **In results of validation analysis, in bold are proteins significantly associated with prevalent hypertension at the threshold of P < 0.05**. The proteins are sorted by values of OR and whether P < 0.05 in validation analysis.

[b] Sensitivity analysis was performed in validation analysis after excluding 142 participants overlapped with KORA S4/F4/FF4 study.

Abbreviations: CI, confidence interval; FDR, Benjamini–Hochberg false-discovery rate; OR, odds ratio. Full names of the proteins can be found in Table S1.

Table S10. Validation of the associations of 99 proteins with SBP in KORA Age1/Age2 study [a]

Protein	**UniProt_ID**	**Discovery in KORA S4/F4/FF4 (participants = 1560; observation = 3332)**			**Validation in KORA Age1/Age2 (participants = 1024; observation = 1810)**		**Sensitivity analysis for validation in KORA Age1/Age2 (participants = 882; observation = 1533) [b]**	
		β (95%CI)	**P**	**FDR**	**β (95%CI)**	**P**	**β (95%CI)**	**P**
AMBP	P02760	1.81 (0.75, 2.86)	8.04E-04	4.07E-03	**3.62 (1.94, 5.30)**	**2.45E-05**	**4.06 (2.24, 5.89)**	**1.28E-05**
PRSS27	Q9BQR3	1.96 (0.96, 2.97)	1.25E-04	1.54E-03	**2.75 (1.39, 4.10)**	**6.77E-05**	**2.93 (1.47, 4.39)**	**8.56E-05**
TM	P07204	2.16 (1.01, 3.31)	2.25E-04	1.90E-03	**2.66 (1.06, 4.26)**	**1.09E-03**	**2.87 (1.12, 4.63)**	**1.33E-03**
TF	P13726	1.87 (0.89, 2.85)	1.92E-04	1.72E-03	**2.61 (0.99, 4.22)**	**1.54E-03**	**3.04 (1.29, 4.79)**	**6.56E-04**
KIM1	Q96D42	3.95 (2.80, 5.10)	1.52E-11	3.54E-09	**2.48 (0.85, 4.12)**	**2.93E-03**	**2.29 (0.52, 4.06)**	**1.13E-02**
MMP-7	P09237	1.74 (0.60, 2.88)	2.87E-03	9.84E-03	**2.44 (1.13, 3.74)**	**2.68E-04**	**2.28 (0.86, 3.69)**	**1.60E-03**
NT-proBNP	P16860	3.02 (1.98, 4.06)	1.34E-08	1.04E-06	**2.39 (0.90, 3.88)**	**1.64E-03**	**2.94 (1.33, 4.56)**	**3.46E-04**
OPG	O00300	3.34 (2.32, 4.36)	1.39E-10	1.62E-08	**2.38 (0.87, 3.90)**	**1.99E-03**	**2.44 (0.79, 4.09)**	**3.83E-03**
ADM	P35318	2.41 (1.25, 3.56)	4.38E-05	8.51E-04	**2.29 (0.64, 3.94)**	**6.40E-03**	**2.58 (0.80, 4.36)**	**4.48E-03**
PGF	P49763	2.59 (1.36, 3.82)	3.56E-05	7.54E-04	**2.26 (0.10, 4.42)**	**4.06E-02**	2.19 (-0.19, 4.56)	7.11E-02
MMP-12	P39900	2.30 (1.18, 3.43)	5.91E-05	9.83E-04	**2.19 (0.75, 3.62)**	**2.76E-03**	**2.09 (0.58, 3.60)**	**6.76E-03**
IL-12B	P29460	1.97 (0.84, 3.10)	6.44E-04	3.77E-03	**2.06 (0.71, 3.41)**	**2.85E-03**	**2.16 (0.69, 3.64)**	**3.98E-03**
IL-10RB	Q08334	1.91 (0.87, 2.95)	3.28E-04	2.31E-03	**1.90 (0.43, 3.36)**	**1.12E-02**	**2.03 (0.44, 3.62)**	**1.26E-02**
IGFBP-7	Q16270	2.20 (1.18, 3.22)	2.48E-05	5.79E-04	**1.87 (0.35, 3.38)**	**1.56E-02**	**1.79 (0.14, 3.43)**	**3.32E-02**
LTBR	P36941	1.71 (0.68, 2.75)	1.17E-03	5.04E-03	**1.82 (0.14, 3.49)**	**3.39E-02**	**2.05 (0.22, 3.89)**	**2.82E-02**
TIMP4	Q99727	1.68 (0.71, 2.65)	6.57E-04	3.77E-03	**1.70 (0.31, 3.09)**	**1.62E-02**	**1.50 (0.02, 2.98)**	**4.76E-02**
TR-AP	P13686	1.65 (0.74, 2.56)	3.75E-04	2.50E-03	**1.61 (0.26, 2.96)**	**1.94E-02**	1.48 (-0.02, 2.99)	5.35E-02
SORT1	Q99523	1.40 (0.49, 2.30)	2.43E-03	9.00E-03	**1.54 (0.26, 2.83)**	**1.87E-02**	**1.63 (0.24, 3.02)**	**2.14E-02**
IL-17D	Q8TAD2	1.43 (0.35, 2.51)	9.16E-03	2.57E-02	**1.52 (0.01, 3.04)**	**4.82E-02**	**2.00 (0.31, 3.69)**	**2.01E-02**
PD-L1	Q9NZQ7	1.28 (0.34, 2.22)	7.81E-03	2.25E-02	**1.50 (0.09, 2.91)**	**3.73E-02**	**1.90 (0.17, 3.62)**	**3.10E-02**
PRSS8	Q16651	2.10 (0.96, 3.24)	2.92E-04	2.13E-03	**1.40 (0.12, 2.69)**	**3.21E-02**	**1.39 (0.04, 2.73)**	**4.30E-02**
LOX-1	P78380	1.69 (0.47, 2.90)	6.39E-03	1.93E-02	**1.33 (0.21, 2.45)**	**2.04E-02**	**1.44 (0.22, 2.66)**	**2.11E-02**
RETN	Q9HD89	1.90 (0.83, 2.96)	4.91E-04	3.09E-03	**1.32 (0.00, 2.64)**	**4.92E-02**	1.20 (-0.21, 2.61)	9.42E-02
TNFRSF14	Q92956	1.45 (0.47, 2.44)	3.83E-03	1.28E-02	1.74 (-0.14, 3.63)	7.00E-02	1.67 (-0.38, 3.71)	1.10E-01
PRELP	P51888	1.69 (0.48, 2.91)	6.45E-03	1.93E-02	1.60 (-0.70, 3.90)	1.72E-01	1.58 (-0.82, 3.97)	1.98E-01
PLC	P98160	1.89 (0.77, 3.00)	9.04E-04	4.28E-03	1.56 (-0.11, 3.23)	6.69E-02	1.55 (-0.27, 3.37)	9.56E-02
TNFRSF11A	Q9Y6Q6	2.63 (1.42, 3.84)	2.16E-05	5.58E-04	1.56 (-0.56, 3.68)	1.49E-01	1.69 (-0.61, 3.99)	1.49E-01
MMP-3	P08254	1.39 (0.22, 2.56)	2.01E-02	4.79E-02	1.44 (-0.23, 3.11)	9.07E-02	1.19 (-0.68, 3.05)	2.12E-01
CTSZ	Q9UBR2	1.67 (0.68, 2.66)	9.19E-04	4.28E-03	1.42 (-0.03, 2.87)	5.44E-02	1.34 (-0.26, 2.95)	1.00E-01
IL-18BP	O95998	1.81 (0.75, 2.87)	7.76E-04	4.07E-03	1.41 (-0.05, 2.86)	5.86E-02	1.24 (-0.35, 2.83)	1.25E-01
VEGF-A	P15692	1.93 (0.92, 2.94)	1.77E-04	1.72E-03	1.39 (-0.25, 3.02)	9.60E-02	1.28 (-0.47, 3.03)	1.53E-01
HGF	P14210	2.93 (1.88, 3.99)	5.42E-08	3.16E-06	1.31 (-0.09, 2.71)	6.65E-02	1.05 (-0.50, 2.60)	1.85E-01
TNF-R1	P19438	3.01 (1.86, 4.16)	2.74E-07	1.06E-05	1.30 (-0.56, 3.17)	1.71E-01	1.07 (-0.95, 3.09)	2.98E-01
VSIG2	Q96IQ7	1.64 (0.66, 2.62)	1.03E-03	4.52E-03	1.28 (-0.40, 2.96)	1.35E-01	0.97 (-0.94, 2.87)	3.19E-01
CCL11	P51671	1.42 (0.42, 2.42)	5.50E-03	1.76E-02	1.24 (-0.08, 2.56)	6.53E-02	1.22 (-0.26, 2.69)	1.06E-01
CHI3L1	P36222	2.66 (1.63, 3.69)	4.34E-07	1.44E-05	1.23 (-0.16, 2.61)	8.28E-02	1.37 (-0.15, 2.88)	7.82E-02
TRAIL-R2	O14763	1.95 (0.60, 3.30)	4.68E-03	1.54E-02	1.21 (-0.35, 2.77)	1.28E-01	1.23 (-0.41, 2.87)	1.43E-01
PGLYRP1	O75594	1.66 (0.62, 2.70)	1.76E-03	7.06E-03	1.19 (-0.23, 2.62)	9.98E-02	1.13 (-0.43, 2.69)	1.56E-01
CCL4	P13236	1.23 (0.27, 2.18)	1.17E-02	3.18E-02	1.15 (-0.24, 2.54)	1.05E-01	1.26 (-0.28, 2.80)	1.09E-01
CX3CL1	P78423	1.99 (0.95, 3.03)	1.79E-04	1.72E-03	1.13 (-0.02, 2.29)	5.43E-02	**1.35 (0.06, 2.65)**	**4.10E-02**
EPHB4	P54760	1.87 (0.84, 2.91)	3.75E-04	2.50E-03	1.11 (-0.44, 2.66)	1.61E-01	0.95 (-0.75, 2.66)	2.72E-01
PON3	Q15166	-1.31 (-2.35, -0.26)	1.44E-02	3.68E-02	1.08 (-0.24, 2.41)	1.09E-01	1.15 (-0.27, 2.58)	1.12E-01
FGF21	Q9NSA1	1.81 (0.80, 2.82)	4.67E-04	3.02E-03	1.05 (-0.29, 2.40)	1.24E-01	0.93 (-0.51, 2.38)	2.05E-01
IL-18	Q14116	1.28 (0.21, 2.36)	1.95E-02	4.68E-02	1.03 (-0.42, 2.47)	1.63E-01	1.16 (-0.41, 2.73)	1.47E-01
CXCL9	Q07325	1.58 (0.55, 2.61)	2.74E-03	9.81E-03	1.02 (-0.47, 2.50)	1.80E-01	0.90 (-0.74, 2.53)	2.84E-01
TGF-α	P01135	1.77 (0.66, 2.88)	1.76E-03	7.06E-03	1.01 (-0.18, 2.20)	9.67E-02	1.40 (-0.26, 3.06)	9.85E-02
IL-6	P05231	1.83 (0.90, 2.76)	1.11E-04	1.50E-03	1.00 (-0.41, 2.40)	1.65E-01	0.64 (-0.89, 2.18)	4.11E-01
BMP-6	P22004	1.23 (0.28, 2.18)	1.13E-02	3.08E-02	0.98 (-0.32, 2.27)	1.39E-01	1.33 (-0.07, 2.74)	6.31E-02
TNF-R2	P20333	1.87 (0.74, 3.01)	1.24E-03	5.14E-03	0.95 (-0.69, 2.60)	2.57E-01	0.94 (-0.85, 2.72)	3.03E-01
Gal-9	O00182	1.97 (0.92, 3.03)	2.33E-04	1.90E-03	0.95 (-0.54, 2.44)	2.13E-01	0.96 (-0.63, 2.54)	2.38E-01
CTSL1	P07711	2.04 (0.98, 3.09)	1.55E-04	1.72E-03	0.89 (-0.39, 2.16)	1.72E-01	0.66 (-0.75, 2.06)	3.58E-01
Notch 3	Q9UM47	2.02 (1.04, 3.00)	5.65E-05	9.83E-04	0.88 (-0.43, 2.20)	1.89E-01	1.02 (-0.45, 2.49)	1.73E-01
GDF-15	Q99988	3.10 (1.96, 4.24)	1.08E-07	5.03E-06	0.85 (-0.94, 2.63)	3.52E-01	0.58 (-1.41, 2.57)	5.66E-01

Table S10. Validation of the associations of 99 proteins with SBP in KORA Age1/Age2 study [a]

Protein	UniProt_ID	Discovery in KORA S4/F4/FF4 (participants = 1560; observation = 3332)				Validation in KORA Age1/Age2 (participants = 1024; observation = 1810)			Sensitivity analysis for validation in KORA Age1/Age2 (participants = 882; observation = 1533) [b]	
		β (95%CI)	P	FDR		β (95%CI)	P		β (95%CI)	P
IL2-RA	P01589	1.85 (0.79, 2.90)	5.87E-04	3.60E-03		0.84 (-0.47, 2.15)	2.09E-01		0.77 (-0.63, 2.16)	2.80E-01
EN-RAGE	P80511	1.81 (0.74, 2.88)	9.04E-04	4.28E-03		0.84 (-0.36, 2.03)	1.71E-01		0.65 (-0.70, 2.00)	3.49E-01
CA5A	P35218	1.74 (0.74, 2.74)	6.64E-04	3.77E-03		0.84 (-0.50, 2.17)	2.21E-01		0.69 (-0.74, 2.13)	3.42E-01
CCL23	P55773	1.38 (0.30, 2.46)	1.25E-02	3.35E-02		0.83 (-0.59, 2.25)	2.51E-01		0.80 (-0.88, 2.48)	3.52E-01
OPN	P10451	2.39 (1.35, 3.43)	6.84E-06	1.99E-04		0.81 (-0.62, 2.24)	2.65E-01		0.82 (-0.70, 2.34)	2.91E-01
PTX3	P26022	1.68 (0.66, 2.69)	1.22E-03	5.14E-03		0.81 (-0.54, 2.16)	2.38E-01		0.64 (-0.82, 2.11)	3.90E-01
TNFRSF9	Q07011	1.98 (0.84, 3.12)	6.80E-04	3.77E-03		0.74 (-0.97, 2.45)	3.98E-01		0.55 (-1.28, 2.38)	5.56E-01
CCL28	Q9NRJ3	1.33 (0.39, 2.26)	5.39E-03	1.74E-02		0.69 (-0.31, 1.69)	1.75E-01		0.76 (-0.46, 1.97)	2.21E-01
CDCP1	Q9H5V8	1.91 (0.79, 3.03)	8.61E-04	4.27E-03		0.65 (-0.89, 2.19)	4.07E-01		0.54 (-1.22, 2.30)	5.49E-01
TNFRSF10A	O00220	2.10 (0.97, 3.23)	2.69E-04	2.09E-03		0.63 (-1.00, 2.26)	4.47E-01		0.66 (-1.06, 2.39)	4.51E-01
MERTK	Q12866	1.98 (0.96, 3.01)	1.53E-04	1.72E-03		0.63 (-0.67, 1.92)	3.43E-01		0.93 (-0.51, 2.38)	2.06E-01
IL-8	P10145	2.05 (0.98, 3.12)	1.66E-04	1.72E-03		0.60 (-0.69, 1.88)	3.60E-01		0.43 (-0.98, 1.83)	5.51E-01
TNFRSF13B	O14836	1.34 (0.23, 2.45)	1.76E-02	4.33E-02		0.59 (-0.76, 1.95)	3.91E-01		0.45 (-0.97, 1.86)	5.35E-01
ST2	Q01638	2.01 (0.99, 3.03)	1.16E-04	1.50E-03		0.59 (-0.74, 1.93)	3.85E-01		0.66 (-0.77, 2.09)	3.65E-01
SPON2	Q9BUD6	1.54 (0.44, 2.64)	6.09E-03	1.87E-02		0.59 (-1.03, 2.21)	4.76E-01		0.54 (-1.25, 2.33)	5.53E-01
CEACAM8	P31997	1.85 (0.63, 3.07)	2.87E-03	9.84E-03		0.57 (-0.73, 1.87)	3.88E-01		0.27 (-1.11, 1.65)	7.01E-01
IL-15RA	Q13261	1.26 (0.19, 2.32)	2.08E-02	4.89E-02		0.57 (-0.68, 1.81)	3.71E-01		0.78 (-1.02, 2.58)	3.98E-01
FAS	P25445	1.62 (0.65, 2.59)	1.02E-03	4.52E-03		0.54 (-0.97, 2.05)	4.81E-01		0.44 (-1.20, 2.08)	5.97E-01
LIFR	P42702	1.40 (0.39, 2.41)	6.65E-03	1.96E-02		0.52 (-0.64, 1.68)	3.78E-01		0.49 (-1.02, 2.00)	5.26E-01
TNFRSF10C	O14798	1.24 (0.26, 2.22)	1.32E-02	3.47E-02		-0.52 (-1.83, 0.79)	4.38E-01		-0.42 (-1.85, 1.01)	5.66E-01
MMP-9	P14780	1.45 (0.42, 2.47)	5.72E-03	1.78E-02		0.51 (-0.75, 1.76)	4.30E-01		0.37 (-1.02, 1.76)	6.00E-01
IL-17RA	Q96F46	1.15 (0.22, 2.08)	1.53E-02	3.88E-02		0.49 (-0.73, 1.72)	4.32E-01		0.12 (-1.24, 1.48)	8.63E-01
IL-1RA	P18510	1.78 (0.63, 2.94)	2.51E-03	9.12E-03		0.46 (-0.95, 1.87)	5.20E-01		0.51 (-1.00, 2.02)	5.08E-01
CPB1	P15086	1.82 (0.92, 2.72)	6.97E-05	1.08E-03		0.44 (-0.83, 1.71)	4.99E-01		0.38 (-0.99, 1.75)	5.86E-01
MB	P02144	1.73 (0.62, 2.85)	2.33E-03	8.76E-03		0.44 (-1.08, 1.96)	5.71E-01		0.29 (-1.40, 1.97)	7.40E-01
CPA1	P15085	1.43 (0.47, 2.39)	3.55E-03	1.20E-02		0.43 (-0.88, 1.74)	5.22E-01		0.38 (-1.03, 1.78)	6.01E-01
CSF1	P09603	2.04 (0.97, 3.11)	1.86E-04	1.72E-03		-0.42 (-1.43, 0.60)	4.22E-01		-0.62 (-1.68, 0.44)	2.53E-01
OSM	P13725	1.83 (0.76, 2.90)	7.86E-04	4.07E-03		0.39 (-0.87, 1.65)	5.48E-01		0.18 (-1.24, 1.61)	8.03E-01
ACE2	Q9BYF1	2.21 (1.10, 3.32)	1.00E-04	1.46E-03		0.35 (-0.91, 1.61)	5.91E-01		0.27 (-1.12, 1.67)	7.00E-01
IL-4RA	P24394	1.65 (0.61, 2.70)	1.92E-03	7.44E-03		-0.32 (-1.72, 1.08)	6.51E-01		-0.42 (-1.91, 1.08)	5.85E-01
CD8A	P01732	1.68 (0.79, 2.58)	2.36E-04	1.90E-03		0.32 (-1.04, 1.68)	6.45E-01		0.43 (-1.08, 1.94)	5.78E-01
MMP-2	P08253	1.26 (0.26, 2.25)	1.33E-02	3.47E-02		0.27 (-1.10, 1.65)	6.98E-01		0.09 (-1.41, 1.59)	9.07E-01
Gal-4	P56470	1.68 (0.71, 2.66)	6.98E-04	3.78E-03		0.26 (-0.98, 1.51)	6.79E-01		0.02 (-1.34, 1.38)	9.79E-01
FGF-23	Q9GZV9	1.51 (0.44, 2.58)	5.71E-03	1.78E-02		0.26 (-1.39, 1.91)	7.58E-01		0.34 (-1.40, 2.09)	7.01E-01
CCL19	Q99731	1.31 (0.36, 2.27)	7.15E-03	2.08E-02		0.25 (-0.85, 1.36)	6.54E-01		0.52 (-0.68, 1.72)	3.99E-01
EGFR	P00533	-1.14 (-2.05, -0.23)	1.43E-02	3.68E-02		-0.25 (-1.53, 1.04)	7.05E-01		-0.35 (-1.77, 1.07)	6.33E-01
CD163	Q86VB7	1.50 (0.52, 2.49)	2.86E-03	9.84E-03		0.24 (-1.00, 1.48)	7.08E-01		-0.13 (-1.55, 1.29)	8.58E-01
IL-27	Q8NEV9	1.59 (0.59, 2.60)	1.86E-03	7.33E-03		-0.23 (-1.56, 1.11)	7.38E-01		-0.29 (-1.72, 1.15)	6.96E-01
IL-10	P22301	1.71 (0.69, 2.72)	9.84E-04	4.50E-03		0.17 (-0.79, 1.14)	7.25E-01		0.14 (-1.05, 1.33)	8.18E-01
PD-L2	Q9BQ51	1.22 (0.21, 2.23)	1.76E-02	4.33E-02		0.13 (-1.04, 1.30)	8.30E-01		-0.06 (-1.26, 1.13)	9.16E-01
SCGB3A2	Q96PL1	-1.54 (-2.53, -0.55)	2.28E-03	8.71E-03		-0.11 (-1.81, 1.59)	8.97E-01		-0.15 (-1.96, 1.67)	8.74E-01
IL-18R1	Q13478	2.03 (0.93, 3.12)	2.87E-04	2.13E-03		-0.09 (-1.40, 1.23)	8.97E-01		-0.38 (-1.83, 1.07)	6.12E-01
CCL16	O15467	1.25 (0.29, 2.22)	1.08E-02	2.99E-02		0.05 (-1.32, 1.42)	9.42E-01		-0.20 (-1.71, 1.30)	7.92E-01
LEP	P41159	1.76 (0.31, 3.22)	1.71E-02	4.29E-02		0.02 (-2.00, 2.03)	9.88E-01		0.10 (-2.08, 2.28)	9.29E-01
TR	P02786	1.18 (0.20, 2.16)	1.84E-02	4.46E-02		0.00 (-1.30, 1.30)	9.95E-01		-0.08 (-1.47, 1.31)	9.10E-01
vWF	P04275	1.33 (0.35, 2.31)	7.91E-03	2.25E-02		NA	NA		NA	NA

[a] The 99 proteins significantly associated with SBP (FDR < 0.05) in the discovery analysis among KORA S4/F4/FF4 study were taken to validate their associations with SBP in KORA Age1/Age2 study using generalized estimating equations, applying the model 2 as described in Table S6. β (95% CI) for levels of SBP refer to per 1 standard deviation increase in proteins concentration. **In results of validation analysis, in bold are proteins significantly associated with SBP at the threshold of P < 0.05**. The proteins are sorted by values of β and whether P < 0.05 in validation analysis. vWF was unavailable in KORA Age1/Age2 study.

[b] Sensitivity analysis was performed in validation analysis after excluding 142 participants overlapped with KORA S4/F4/FF4 study.

Abbreviations: CI, confidence interval; FDR, Benjamini–Hochberg false-discovery rate; SBP, systolic blood pressure. Full names of the proteins can be found in Table S1.

Table S11. Sensitivity analysis of associations of 99 proteins with SBP in KORA Age1/Age2 study (participants = 1024; observation = 1810) [a]

Protein	**UniProt_ID**	**Generalized estimating equations**			**Linear mixed-effects models**	
		β (95%CI)	**P**		**β (95%CI)**	**P**
ADM	P35318	**2.29 (0.64, 3.94)**	**6.40E-03**		**2.12 (0.58, 3.66)**	**7.18E-03**
AMBP	P02760	**3.62 (1.94, 5.30)**	**2.45E-05**		**3.23 (1.89, 4.57)**	**2.57E-06**
IL-17D	Q8TAD2	**1.52 (0.01, 3.04)**	**4.82E-02**		**1.73 (0.46, 2.99)**	**7.79E-03**
KIM1	Q96D42	**2.48 (0.85, 4.12)**	**2.93E-03**		**2.43 (1.17, 3.70)**	**1.77E-04**
LOX-1	P78380	**1.33 (0.21, 2.45)**	**2.04E-02**		**1.28 (0.09, 2.47)**	**3.59E-02**
MMP-12	P39900	**2.19 (0.75, 3.62)**	**2.76E-03**		**2.24 (0.89, 3.59)**	**1.20E-03**
MMP-7	P09237	**2.44 (1.13, 3.74)**	**2.68E-04**		**2.29 (1.02, 3.56)**	**4.11E-04**
PGF	P49763	**2.26 (0.10, 4.42)**	**4.06E-02**		**2.02 (0.59, 3.44)**	**5.63E-03**
PRSS27	Q9BQR3	**2.75 (1.39, 4.10)**	**6.77E-05**		**2.53 (1.32, 3.74)**	**4.37E-05**
SORT1	Q99523	**1.54 (0.26, 2.83)**	**1.87E-02**		**1.45 (0.25, 2.66)**	**1.86E-02**
TF	P13726	**2.61 (0.99, 4.22)**	**1.54E-03**		**2.27 (0.98, 3.56)**	**5.65E-04**
TM	P07204	**2.66 (1.06, 4.26)**	**1.09E-03**		**2.40 (1.14, 3.66)**	**1.98E-04**
IL-10RB	Q08334	**1.90 (0.43, 3.36)**	**1.12E-02**		**1.73 (0.44, 3.02)**	**8.68E-03**
IL-12B	P29460	**2.06 (0.71, 3.41)**	**2.85E-03**		**2.03 (0.77, 3.28)**	**1.57E-03**
OPG	O00300	**2.38 (0.87, 3.90)**	**1.99E-03**		**2.36 (1.02, 3.69)**	**5.45E-04**
PD-L1	Q9NZQ7	**1.50 (0.09, 2.91)**	**3.73E-02**		**1.36 (0.11, 2.61)**	**3.39E-02**
IGFBP-7	Q16270	**1.87 (0.35, 3.38)**	**1.56E-02**		**1.77 (0.48, 3.07)**	**7.29E-03**
LTBR	P36941	**1.82 (0.14, 3.49)**	**3.39E-02**		**1.58 (0.23, 2.94)**	**2.22E-02**
NT-proBNP	P16860	**2.39 (0.90, 3.88)**	**1.64E-03**		**2.38 (1.00, 3.77)**	**7.83E-04**
TIMP4	Q99727	**1.70 (0.31, 3.09)**	**1.62E-02**		**1.75 (0.46, 3.04)**	**8.12E-03**
TR-AP	P13686	**1.61 (0.26, 2.96)**	**1.94E-02**		**1.45 (0.27, 2.63)**	**1.62E-02**
PRSS8	Q16651	**1.40 (0.12, 2.69)**	**3.21E-02**		1.23 (-0.03, 2.49)	5.69E-02
CCL11	P51671	1.24 (-0.08, 2.56)	6.53E-02		**1.34 (0.12, 2.56)**	**3.13E-02**
CCL4	P13236	1.15 (-0.24, 2.54)	1.05E-01		**1.18 (0.01, 2.35)**	**4.76E-02**
HGF	P14210	1.31 (-0.09, 2.71)	6.65E-02		**1.35 (0.00, 2.69)**	**4.96E-02**
CHI3L1	P36222	1.23 (-0.16, 2.61)	8.28E-02		**1.27 (0.00, 2.53)**	**4.95E-02**
CTSZ	Q9UBR2	1.42 (-0.03, 2.87)	5.44E-02		**1.33 (0.06, 2.60)**	**4.00E-02**
IL-18BP	O95998	1.41 (-0.05, 2.86)	5.86E-02		**1.35 (0.05, 2.65)**	**4.24E-02**
PLC	P98160	1.56 (-0.11, 3.23)	6.69E-02		**1.59 (0.10, 3.08)**	**3.62E-02**
RETN	Q9HD89	**1.32 (0.00, 2.64)**	**4.92E-02**		1.20 (-0.09, 2.50)	6.82E-02
TNFRSF14	Q92956	1.74 (-0.14, 3.63)	7.00E-02		**1.61 (0.17, 3.05)**	**2.90E-02**
ACE2	Q9BYF1	0.35 (-0.91, 1.61)	5.91E-01		0.55 (-0.69, 1.79)	3.88E-01
BMP-6	P22004	0.98 (-0.32, 2.27)	1.39E-01		0.95 (-0.24, 2.15)	1.17E-01
CA5A	P35218	0.84 (-0.50, 2.17)	2.21E-01		1.03 (-0.18, 2.25)	9.59E-02
CEACAM8	P31997	0.57 (-0.73, 1.87)	3.88E-01		0.40 (-0.84, 1.65)	5.27E-01
CTSL1	P07711	0.89 (-0.39, 2.16)	1.72E-01		0.86 (-0.39, 2.12)	1.77E-01
FGF-23	Q9GZV9	0.26 (-1.39, 1.91)	7.58E-01		0.18 (-1.10, 1.46)	7.79E-01
Gal-9	O00182	0.95 (-0.54, 2.44)	2.13E-01		1.05 (-0.35, 2.44)	1.42E-01
IL-18	Q14116	1.03 (-0.42, 2.47)	1.63E-01		1.11 (-0.08, 2.30)	6.84E-02
IL-1RA	P18510	0.46 (-0.95, 1.87)	5.20E-01		0.58 (-0.74, 1.90)	3.89E-01
IL-27	Q8NEV9	-0.23 (-1.56, 1.11)	7.38E-01		-0.24 (-1.47, 0.98)	7.00E-01
IL-4RA	P24394	-0.32 (-1.72, 1.08)	6.51E-01		-0.34 (-1.60, 0.92)	5.99E-01
LEP	P41159	0.02 (-2.00, 2.03)	9.88E-01		-0.03 (-1.86, 1.80)	9.73E-01
MERTK	Q12866	0.63 (-0.67, 1.92)	3.43E-01		0.63 (-0.59, 1.85)	3.13E-01
PD-L2	Q9BQ51	0.13 (-1.04, 1.30)	8.30E-01		0.18 (-1.02, 1.39)	7.67E-01
PRELP	P51888	1.60 (-0.70, 3.90)	1.72E-01		1.29 (-0.08, 2.66)	6.59E-02
PTX3	P26022	0.81 (-0.54, 2.16)	2.38E-01		0.76 (-0.44, 1.95)	2.14E-01
SPON2	Q9BUD6	0.59 (-1.03, 2.21)	4.76E-01		0.61 (-0.72, 1.95)	3.68E-01
TNFRSF10A	O00220	0.63 (-1.00, 2.26)	4.47E-01		0.43 (-0.86, 1.71)	5.16E-01
TNFRSF11A	Q9Y6Q6	1.56 (-0.56, 3.68)	1.49E-01		1.31 (-0.17, 2.79)	8.30E-02
TNFRSF13B	O14836	0.59 (-0.76, 1.95)	3.91E-01		0.47 (-0.80, 1.73)	4.71E-01
TRAIL-R2	O14763	1.21 (-0.35, 2.77)	1.28E-01		1.09 (-0.26, 2.43)	1.13E-01
VSIG2	Q96IQ7	1.28 (-0.40, 2.96)	1.35E-01		1.19 (-0.13, 2.51)	7.87E-02

Table S11. Sensitivity analysis of associations of 99 proteins with SBP in KORA Age1/Age2 study (participants = 1024; observation = 1810) [a]

Protein	UniProt_ID	Generalized estimating equations			Linear mixed-effects models	
		β (95%CI)	P		β (95%CI)	P
CCL19	Q99731	0.25 (-0.85, 1.36)	6.54E-01		0.47 (-0.72, 1.66)	4.37E-01
CCL23	P55773	0.83 (-0.59, 2.25)	2.51E-01		0.92 (-0.31, 2.15)	1.45E-01
CCL28	Q9NRJ3	0.69 (-0.31, 1.69)	1.75E-01		0.77 (-0.39, 1.93)	1.93E-01
CD8A	P01732	0.32 (-1.04, 1.68)	6.45E-01		0.32 (-0.90, 1.53)	6.09E-01
CDCP1	Q9H5V8	0.65 (-0.89, 2.19)	4.07E-01		0.75 (-0.47, 1.96)	2.30E-01
CSF1	P09603	-0.42 (-1.43, 0.60)	4.22E-01		-0.36 (-1.52, 0.80)	5.41E-01
CX3CL1	P78423	1.13 (-0.02, 2.29)	5.43E-02		1.01 (-0.20, 2.22)	1.02E-01
CXCL9	Q07325	1.02 (-0.47, 2.50)	1.80E-01		1.19 (-0.15, 2.53)	8.24E-02
EN-RAGE	P80511	0.84 (-0.36, 2.03)	1.71E-01		0.76 (-0.43, 1.95)	2.14E-01
FGF21	Q9NSA1	1.05 (-0.29, 2.40)	1.24E-01		1.04 (-0.20, 2.29)	1.01E-01
IL-10	P22301	0.17 (-0.79, 1.14)	7.25E-01		0.36 (-0.80, 1.52)	5.41E-01
IL-15RA	Q13261	0.57 (-0.68, 1.81)	3.71E-01		0.42 (-0.79, 1.63)	4.95E-01
IL-18R1	Q13478	-0.09 (-1.40, 1.23)	8.97E-01		-0.03 (-1.25, 1.19)	9.58E-01
IL-6	P05231	1.00 (-0.41, 2.40)	1.65E-01		0.98 (-0.25, 2.22)	1.20E-01
IL-8	P10145	0.60 (-0.69, 1.88)	3.60E-01		0.68 (-0.53, 1.88)	2.70E-01
LIFR	P42702	0.52 (-0.64, 1.68)	3.78E-01		0.60 (-0.59, 1.79)	3.22E-01
OSM	P13725	0.39 (-0.87, 1.65)	5.48E-01		0.55 (-0.63, 1.73)	3.62E-01
TGF-α	P01135	1.01 (-0.18, 2.20)	9.67E-02		1.04 (-0.22, 2.30)	1.07E-01
TNFRSF9	Q07011	0.74 (-0.97, 2.45)	3.98E-01		0.67 (-0.66, 2.00)	3.26E-01
VEGF-A	P15692	1.39 (-0.25, 3.02)	9.60E-02		1.29 (-0.09, 2.66)	6.79E-02
CCL16	O15467	0.05 (-1.32, 1.42)	9.42E-01		-0.01 (-1.23, 1.22)	9.93E-01
CD163	Q86VB7	0.24 (-1.00, 1.48)	7.08E-01		0.39 (-0.82, 1.60)	5.29E-01
CPA1	P15085	0.43 (-0.88, 1.74)	5.22E-01		0.40 (-0.79, 1.58)	5.12E-01
CPB1	P15086	0.44 (-0.83, 1.71)	4.99E-01		0.35 (-0.85, 1.55)	5.69E-01
EGFR	P00533	-0.25 (-1.53, 1.04)	7.05E-01		-0.20 (-1.42, 1.02)	7.47E-01
EPHB4	P54760	1.11 (-0.44, 2.66)	1.61E-01		1.06 (-0.28, 2.39)	1.22E-01
FAS	P25445	0.54 (-0.97, 2.05)	4.81E-01		0.47 (-0.77, 1.72)	4.55E-01
Gal-4	P56470	0.26 (-0.98, 1.51)	6.79E-01		0.43 (-0.85, 1.71)	5.11E-01
GDF-15	Q99988	0.85 (-0.94, 2.63)	3.52E-01		0.94 (-0.54, 2.42)	2.15E-01
IL-17RA	Q96F46	0.49 (-0.73, 1.72)	4.32E-01		0.51 (-0.65, 1.67)	3.90E-01
IL2-RA	P01589	0.84 (-0.47, 2.15)	2.09E-01		0.84 (-0.42, 2.10)	1.90E-01
MB	P02144	0.44 (-1.08, 1.96)	5.71E-01		0.51 (-0.85, 1.87)	4.64E-01
MMP-2	P08253	0.27 (-1.10, 1.65)	6.98E-01		0.39 (-0.82, 1.60)	5.29E-01
MMP-3	P08254	1.44 (-0.23, 3.11)	9.07E-02		1.26 (-0.12, 2.63)	7.39E-02
MMP-9	P14780	0.51 (-0.75, 1.76)	4.30E-01		0.59 (-0.57, 1.75)	3.19E-01
Notch 3	Q9UM47	0.88 (-0.43, 2.20)	1.89E-01		0.90 (-0.37, 2.17)	1.64E-01
OPN	P10451	0.81 (-0.62, 2.24)	2.65E-01		0.65 (-0.65, 1.95)	3.29E-01
PGLYRP1	O75594	1.19 (-0.23, 2.62)	9.98E-02		1.03 (-0.25, 2.30)	1.14E-01
PON3	Q15166	1.08 (-0.24, 2.41)	1.09E-01		0.82 (-0.48, 2.11)	2.18E-01
SCGB3A2	Q96PL1	-0.11 (-1.81, 1.59)	8.97E-01		-0.43 (-1.65, 0.78)	4.85E-01
ST2	Q01638	0.59 (-0.74, 1.93)	3.85E-01		0.59 (-0.64, 1.83)	3.46E-01
TNF-R1	P19438	1.30 (-0.56, 3.17)	1.71E-01		1.27 (-0.21, 2.75)	9.36E-02
TNF-R2	P20333	0.95 (-0.69, 2.60)	2.57E-01		0.87 (-0.52, 2.26)	2.21E-01
TNFRSF10C	O14798	-0.52 (-1.83, 0.79)	4.38E-01		-0.45 (-1.63, 0.73)	4.56E-01
TR	P02786	0.00 (-1.30, 1.30)	9.95E-01		-0.05 (-1.24, 1.14)	9.35E-01
vWF	P04275	NA	NA		NA	NA

[a] For associations with SBP, linear mixed-effects models were also used to estimate β (95% CI) of levels of SBP per 1 standard deviation increase in proteins concentration, applying the model 2 as described in Table S10, using R package "lme4". Results of model 2 from generalized estimating equations, as detailed in Table S10, were also presented in this table. **In bold are proteins significantly associated with SBP at the threshold of P < 0.05. Cells with green background are 21 proteins significantly associated with SBP in both analysis, and cells with blue background are proteins only significant in one of the analyses.** vWF was unavailable in KORA Age1/Age2 study.

Abbreviations: CI, confidence interval; FDR, Benjamini–Hochberg false-discovery rate; SBP, systolic blood pressure. Full names of the proteins can be found in Table S1.

Table S12. Results of the two-sample Mendelian randomization analysis between 26 proteins and SBP [a]

Protein	**UniProt_ID**	**MR_Method** [b]	**No. IVs**	**Results of MR**			**Heterogeneity tests**			**Pleiotropy tests**			**Steiger directionality test**			
				β (95%CI)	**SE**	**P-value**	**Q**	**Q df**	**Q P-value**	**Egger intercept**	**Egger SE**	**Egger P-value**	**% variance in exposure**	**% variance in outcome**	**Correct causal direction**	**Steiger P-value**
ADM	P35318	Inverse variance weighted	2	-0.39 (-0.93, 0.15)	0.28	1.61E-01	1.08	1	3.00E-01				0.754%	0.00044%	TRUE	**6.90E-53**
AMBP	P02760	Inverse variance weighted	2	0.19 (-0.43, 0.80)	0.31	5.48E-01	0.08	1	7.83E-01				0.574%	0.00007%	TRUE	**1.77E-41**
CTSL1	P07711	Wald ratio	1	-0.21 (-1.46, 1.04)	0.64	7.41E-01							0.123%	0.00001%	TRUE	**4.77E-10**
Gal-9	O00182	Inverse variance weighted	15	0.11 (-0.08, 0.29)	0.09	2.65E-01	23.4	14	5.45E-02	0.032	0.045	4.86E-01	8.195%	0.00371%	TRUE	**0.00E+00**
IGFBP-7	Q16270	Inverse variance weighted	11	-0.12 (-0.36, 0.11)	0.12	3.05E-01	11.2	10	3.41E-01	-0.064	0.032	7.63E-02	4.672%	0.00182%	TRUE	**0.00E+00**
IL-10RB	Q08334	Weighted median	14	-0.19 (-0.31, -0.08)	0.06	**9.57E-04**	24.6	13	**2.64E-02**	0.019	0.029	5.10E-01	7.742%	0.00461%	TRUE	**0.00E+00**
IL-12B	P29460	Weighted median	15	-0.06 (-0.28, 0.16)	0.11	6.15E-01	65.0	14	1.52E-08	0.050	0.057	3.93E-01	11.19%	0.00977%	TRUE	**0.00E+00**
IL-17D	Q8TAD2	Inverse variance weighted	9	-0.05 (-0.29, 0.19)	0.12	6.99E-01	10.0	8	2.65E-01	0.028	0.040	5.10E-01	4.581%	0.00154%	TRUE	**0.00E+00**
KIM1	Q96D42	Weighted median	17	-0.06 (-0.25, 0.14)	0.10	5.64E-01	138.7	16	**1.27E-21**	0.120	0.065	8.35E-02	12.50%	0.01942%	TRUE	**0.00E+00**
LOX-1	P78380	Wald ratio	1	0.24 (-1.03, 1.51)	0.65	7.14E-01							0.114%	0.00002%	TRUE	**2.41E-09**
LTBR	P36941	Inverse variance weighted	2	0.06 (-1.94, 2.06)	1.02	9.54E-01	4.56	1	**3.27E-02**				0.250%	0.00070%	TRUE	**2.87E-17**
MMP-12	P39900	Inverse variance weighted	12	-0.14 (-0.29, 0.01)	0.08	7.68E-02	15.1	11	1.79E-01	-0.038	0.026	1.68E-01	11.50%	0.00277%	TRUE	**0.00E+00**
MMP-7	P09237	Inverse variance weighted	5	0.15 (-0.10, 0.40)	0.13	2.31E-01	7.18	4	1.27E-01	0.063	0.035	1.68E-01	4.428%	0.00141%	TRUE	**2.93E-303**
NT-proBNP	P16860	Inverse variance weighted	2	-2.46 (-2.77, -2.15)	0.16	**7.61E-54**	0.76	1	3.84E-01				1.973%	0.03360%	TRUE	**8.49E-106**
OPG	O00300	Inverse variance weighted	9	0.41 (0.16, 0.66)	0.13	**1.48E-03**	9.28	8	3.19E-01	-0.035	0.044	4.61E-01	4.117%	0.00291%	TRUE	**3.95E-282**
PD-L1	Q9NZQ7	Inverse variance weighted	11	0.28 (0.12, 0.44)	0.08	**7.31E-04**	3.11	10	9.79E-01	-0.003	0.022	9.08E-01	5.251%	0.00203%	TRUE	**0.00E+00**
PGF	P49763	Inverse variance weighted	2	-0.25 (-1.14, 0.64)	0.45	5.78E-01	0.11	1	7.41E-01				1.794%	0.00379%	TRUE	**8.93E-119**
PON3	Q15166	Inverse variance weighted	8	0.08 (-0.15, 0.31)	0.12	5.05E-01	9.67	7	2.08E-01	0.005	0.035	8.90E-01	4.813%	0.00146%	TRUE	**0.00E+00**
PRSS27	Q9BQR3	Inverse variance weighted	2	-0.25 (-0.55, 0.06)	0.15	1.12E-01	0.04	1	8.51E-01				2.814%	0.00042%	TRUE	**2.05E-196**
PRSS8	Q16651	Wald ratio	1	0.67 (0.10, 1.25)	0.29	2.22E-02							0.643%	0.00073%	TRUE	**6.28E-44**
RETN	Q9HD89	Inverse variance weighted	6	0.13 (-0.19, 0.46)	0.17	4.19E-01	8.36	5	1.37E-01	-0.025	0.047	6.25E-01	3.318%	0.00138%	TRUE	**1.98E-228**
SORT1	Q99523	Inverse variance weighted	3	-0.36 (-0.67, -0.04)	0.16	2.50E-02	0.44	2	8.03E-01	0.076	0.122	6.44E-01	1.940%	0.00075%	TRUE	**6.32E-134**
TF	P13726	Inverse variance weighted	8	-0.18 (-0.44, 0.07)	0.13	1.50E-01	7.75	7	3.56E-01	0.034	0.039	4.22E-01	3.697%	0.00143%	TRUE	**8.50E-257**
TIMP4	Q99727	Weighted median	6	0.56 (0.25, 0.87)	0.16	**4.15E-04**	11.2	5	**4.81E-02**	0.027	0.141	8.59E-01	3.492%	0.00397%	TRUE	**2.83E-235**
TM	P07204	Weighted median	5	-0.34 (-0.71, 0.02)	0.19	6.37E-02	9.90	4	**4.22E-02**	0.129	0.082	2.12E-01	1.985%	0.00161%	TRUE	**9.21E-135**
TR-AP	P13686	Weighted median	6	-0.15 (-0.35, 0.06)	0.10	1.60E-01	22.1	5	**4.95E-04**	-0.159	0.091	1.57E-01	5.358%	0.00382%	TRUE	**0.00E+00**

[a] Two-sample MR analyses were conducted to estimate the potential causal associations of 26 validated proteins with SBP. Various MR methods were performed, considering the number of IVs and the presence of heterogeneity and directional horizontal pleiotropy. **For results of MR, in bold are significant P-value at a Bonferroni-corrected level of 0.05/26**.

[b] Since no evidence of directional horizontal pleiotropy (Egger_P-value > 0.05) was observed, for proteins with 2 or more SNPs, MR results from inverse variance weighted or weighted median (when heterogeneity test was significant with Q_P-value < 0.05) are presented. Wald ratio was calculated proteins with only 1 SNP.

Table S13. Assessment of bias due to participant overlap in two-sample Mendelian randomization analysis [a]

Exposure	**UniProt_ID**	**No. IVs**	***psi* = 0.1**				***psi* = 0.3**			***psi* = 0.5**			***psi* = 0.7**			***psi* = 0.9**		
			Method	**β (95%CI)**	**SE**	**P-value**	**β (95%CI)**	**SE**	**P-value**	**β (95%CI)**	**SE**	**P-value**	**β (95%CI)**	**SE**	**P-value**	**β (95%CI)**	**SE**	**P-value**
ADM	P35318	2	IVW	-0.38 (-0.91, 0.15)	0.27	1.60E-01	-0.37 (-0.91, 0.17)	0.28	1.74E-01	-0.37 (-0.92, 0.18)	0.28	1.87E-01	-0.36 (-0.92, 0.19)	0.28	1.99E-01	-0.36 (-0.92, 0.20)	0.29	2.11E-01
AMBP	P02760	2	IVW	0.19 (-0.42, 0.80)	0.31	5.47E-01	0.19 (-0.42, 0.80)	0.31	5.42E-01	0.19 (-0.41, 0.79)	0.31	5.36E-01	0.19 (-0.41, 0.79)	0.30	5.31E-01	0.19 (-0.40, 0.78)	0.30	5.25E-01
CTSL1	P07711	1	Wald ratio	-0.21 (-1.46, 1.04)	0.64	7.43E-01	-0.21 (-1.48, 1.06)	0.65	7.45E-01	-0.21 (-1.49, 1.07)	0.65	7.47E-01	-0.21 (-1.50, 1.08)	0.66	7.50E-01	-0.21 (-1.51, 1.09)	0.67	7.52E-01
Gal-9	O00182	15	IVW	0.11 (-0.04, 0.25)	0.07	1.40E-01	0.12 (-0.02, 0.26)	0.07	1.02E-01	0.13 (-0.01, 0.27)	0.07	6.91E-02	0.15 (0.01, 0.29)	0.07	4.14E-02	0.17 (0.03, 0.31)	0.07	1.92E-02
IGFBP-7	Q16270	11	IVW	-0.11 (-0.34, 0.11)	0.11	3.14E-01	-0.10 (-0.33, 0.12)	0.11	3.69E-01	-0.09 (-0.32, 0.13)	0.11	4.29E-01	-0.08 (-0.30, 0.15)	0.11	4.95E-01	-0.07 (-0.29, 0.16)	0.11	5.69E-01
IL-10RB	Q08334	14	IVW_RE	-0.14 (-0.28, -0.01)	0.07	3.86E-02	-0.14 (-0.28, 0.01)	0.07	6.24E-02	-0.13 (-0.29, 0.03)	0.08	1.04E-01	-0.12 (-0.29, 0.05)	0.09	1.80E-01	-0.10 (-0.30, 0.10)	0.10	3.30E-01
IL-12B	P29460	15	IVW_RE	-0.02 (-0.30, 0.25)	0.14	8.62E-01	0.00 (-0.28, 0.28)	0.14	9.99E-01	0.03 (-0.26, 0.32)	0.15	8.48E-01	0.07 (-0.24, 0.37)	0.16	6.78E-01	0.12 (-0.22, 0.46)	0.17	4.80E-01
IL-17D	Q8TAD2	9	IVW	-0.05 (-0.26, 0.17)	0.11	6.68E-01	-0.04 (-0.25, 0.18)	0.11	7.41E-01	-0.02 (-0.24, 0.19)	0.11	8.32E-01	-0.01 (-0.22, 0.21)	0.11	9.54E-01	0.02 (-0.20, 0.23)	0.11	8.68E-01
KIM1	Q96D42	17	IVW_RE	-0.11 (-0.36, 0.14)	0.13	3.98E-01	-0.09 (-0.37, 0.18)	0.14	4.98E-01	-0.07 (-0.37, 0.22)	0.15	6.23E-01	-0.05 (-0.39, 0.29)	0.17	7.86E-01	0.01 (-0.43, 0.45)	0.22	9.67E-01
LOX-1	P78380	1	Wald ratio	0.24 (-1.03, 1.50)	0.65	7.12E-01	0.24 (-1.01, 1.49)	0.64	7.09E-01	0.24 (-1.00, 1.47)	0.63	7.06E-01	0.24 (-0.98, 1.46)	0.62	7.02E-01	0.24 (-0.97, 1.44)	0.61	6.98E-01
LTBR	P36941	2	IVW	0.12 (-0.84, 1.07)	0.49	8.13E-01	0.20 (-0.75, 1.15)	0.48	6.76E-01	0.29 (-0.65, 1.22)	0.48	5.48E-01	0.37 (-0.54, 1.28)	0.46	4.30E-01	0.44 (-0.43, 1.32)	0.45	3.22E-01
MMP-12	P39900	12	IVW	-0.13 (-0.27, -0.00)	0.07	4.65E-02	-0.13 (-0.26, 0.00)	0.07	5.80E-02	-0.12 (-0.26, 0.01)	0.07	7.07E-02	-0.12 (-0.25, 0.02)	0.07	8.45E-02	-0.11 (-0.25, 0.02)	0.07	9.96E-02
MMP-7	P09237	5	IVW	0.15 (-0.03, 0.34)	0.10	1.06E-01	0.16 (-0.02, 0.35)	0.09	8.98E-02	0.17 (-0.02, 0.35)	0.09	7.41E-02	0.18 (-0.01, 0.36)	0.09	5.92E-02	0.18 (0.00, 0.36)	0.09	4.55E-02
NT-proBNP	P16860	2	IVW	-2.45 (-2.83, -2.07)	0.19	**1.13E-36**	-2.45 (-2.86, -2.04)	0.21	**8.84E-32**	-2.45 (-2.89, -2.01)	0.22	**4.37E-28**	-2.45 (-2.91, -1.99)	0.24	**3.39E-25**	-2.45 (-2.94, -1.96)	0.25	**7.11E-23**
OPG	O00300	9	IVW	0.41 (0.18, 0.64)	0.12	**5.78E-04**	0.42 (0.19, 0.65)	0.12	**3.16E-04**	0.43 (0.21, 0.65)	0.11	**1.55E-04**	0.44 (0.23, 0.66)	0.11	**6.30E-05**	0.46 (0.25, 0.67)	0.11	**1.79E-05**
PD-L1	Q9NZQ7	11	IVW	0.28 (0.12, 0.44)	0.08	**6.85E-04**	0.28 (0.12, 0.44)	0.08	**5.20E-04**	0.29 (0.13, 0.44)	0.08	**3.84E-04**	0.29 (0.13, 0.44)	0.08	**2.76E-04**	0.29 (0.14, 0.44)	0.08	**1.90E-04**
PGF	P49763	2	IVW	-0.25 (-1.14, 0.64)	0.46	5.83E-01	-0.25 (-1.15, 0.65)	0.46	5.90E-01	-0.25 (-1.16, 0.67)	0.47	5.96E-01	-0.25 (-1.17, 0.68)	0.47	6.02E-01	-0.24 (-1.17, 0.69)	0.47	6.08E-01
PON3	Q15166	8	IVW	0.08 (-0.11, 0.27)	0.10	4.17E-01	0.09 (-0.10, 0.28)	0.10	3.66E-01	0.10 (-0.09, 0.29)	0.10	3.13E-01	0.11 (-0.08, 0.30)	0.10	2.60E-01	0.12 (-0.07, 0.31)	0.10	2.06E-01
PRSS27	Q9BQR3	2	IVW	-0.25 (-0.55, 0.06)	0.16	1.15E-01	-0.25 (-0.55, 0.06)	0.16	1.19E-01	-0.25 (-0.56, 0.07)	0.16	1.22E-01	-0.25 (-0.56, 0.07)	0.16	1.26E-01	-0.25 (-0.56, 0.07)	0.16	1.30E-01
PRSS8	Q16651	1	Wald ratio	0.67 (0.10, 1.25)	0.29	2.18E-02	0.67 (0.12, 1.23)	0.28	1.78E-02	0.67 (0.14, 1.21)	0.27	1.42E-02	0.67 (0.16, 1.19)	0.26	1.09E-02	0.67 (0.18, 1.17)	0.25	8.06E-03
RETN	Q9HD89	6	IVW	0.13 (-0.12, 0.39)	0.13	2.95E-01	0.15 (-0.10, 0.40)	0.13	2.46E-01	0.16 (-0.08, 0.41)	0.13	1.96E-01	0.18 (-0.06, 0.43)	0.13	1.43E-01	0.21 (-0.03, 0.45)	0.12	9.09E-02
SORT1	Q99523	3	IVW	-0.36 (-0.67, -0.04)	0.16	2.73E-02	-0.35 (-0.67, -0.03)	0.16	3.04E-02	-0.35 (-0.68, -0.03)	0.17	3.36E-02	-0.35 (-0.68, -0.02)	0.17	3.70E-02	-0.35 (-0.69, -0.02)	0.17	4.03E-02
TF	P13726	8	IVW	-0.18 (-0.42, 0.06)	0.12	1.45E-01	-0.17 (-0.41, 0.07)	0.12	1.73E-01	-0.16 (-0.40, 0.09)	0.12	2.05E-01	-0.15 (-0.39, 0.10)	0.13	2.44E-01	-0.13 (-0.38, 0.11)	0.13	2.92E-01
TIMP4	Q99727	6	IVW_RE	0.51 (0.15, 0.87)	0.18	5.85E-03	0.52 (0.17, 0.88)	0.18	3.74E-03	0.54 (0.19, 0.88)	0.18	2.30E-03	0.55 (0.22, 0.89)	0.17	**1.36E-03**	0.57 (0.24, 0.90)	0.17	**7.57E-04**
TM	P07204	5	IVW_RE	-0.19 (-0.69, 0.31)	0.26	4.62E-01	-0.16 (-0.69, 0.36)	0.27	5.43E-01	-0.13 (-0.68, 0.41)	0.28	6.33E-01	-0.10 (-0.67, 0.47)	0.29	7.35E-01	-0.06 (-0.65, 0.54)	0.30	8.51E-01
TR-AP	P13686	6	IVW_RE	-0.16 (-0.49, 0.18)	0.17	3.57E-01	-0.14 (-0.47, 0.18)	0.17	3.87E-01	-0.13 (-0.45, 0.19)	0.16	4.18E-01	-0.12 (-0.44, 0.20)	0.16	4.50E-01	-0.11 (-0.43, 0.20)	0.16	4.83E-01

[a] The function "MendelianRandomization::mr_mr_ivw" was used to evaluate bias due to the participant overlap in two-sample Mendelian randomization analysis. The parameter psi is set to zero when there is no participant overlap, and arises if the samples for the associations with the exposure and the outcome overlap. Several values for *psi* (0.1, 0.3, 0.5, 0.7, and 0.9) were set to evaluate the bias due to participant overlap. For proteins with only 1 SNP instrument, Wald ratio was calculated. For proteins with 2 or more SNPs, IVW MR with fixed effects was performed and if the heterogeneity test was significant, IVW MR with random effects was performed. **P-value in bold are significant at a Bonferroni-corrected level of 0.05/26.**

Abbreviations: CI, confidence interval; IVs, instrumental variables; IVW, inverse variance weighted; IVW_RE, IVW with random effects; MR, Mendelian randomization; psi: Indicator of the correlation between the association with the exposure and the association with the outcome for each variant resulting from sample overlap; SE, standard error; SNP, single nucleotide polymorphism. Full names of the proteins can be found in Table S1.

Appendix: Paper III

Title:	Longitudinal and cross-sectional associations of myocardial stress markers with kidney function and chronic kidney disease: the BiomarCaRE project
Authors:	Jie-sheng Lin, Tanja Zeller, Wolfgang Koenig, Pekka Jousilahti, Frank Kee, Licia Iacoviello, Hugh Tunstall-Pedoe, Stefan Söderberg, Giancarlo Cesana, Luigi Palmieri, Veikko Salomaa, Julia de Man Lapidoth, Roberto De Ponti, Chiara Donfrancesco, Thiess Lorenz, Kari Kuulasmaa, Stefan Blankenberg, Annette Peters, Barbara Thorand; on behalf of the BiomarCaRE investigators
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Longitudinal and cross-sectional associations of myocardial stress markers with kidney function and chronic kidney disease: the BiomarCaRE project

Jie-sheng Lin[1, 2], Tanja Zeller[3, 4, 5], Wolfgang Koenig[6, 7, 8], Pekka Jousilahti[9], Frank Kee[10], Licia Iacoviello[11, 12], Hugh Tunstall-Pedoe[13], Stefan Söderberg[14], Giancarlo Cesana[15], Luigi Palmieri[16], Veikko Salomaa[9], Julia de Man Lapidoth[14], Roberto De Ponti[17],Chiara Donfrancesco[16], Thiess Lorenz[4, 5, 18], Kari Kuulasmaa[9], Stefan Blankenberg[4, 5, 18], Annette Peters[1, 2, 7, 19], Barbara Thorand[1, 2, 19 *]; on behalf of the BiomarCaRE investigators

[1] *Institute of Epidemiology, Helmholtz Zentrum München, German Research Center for Environmental Health (GmbH), Neuherberg, Germany*

[2] *Institute for Medical Information Processing, Biometry, and Epidemiology (IBE), Faculty of Medicine, LMU Munich, Pettenkofer School of Public Health, Munich, Germany*

[3] *University Center of Cardiovascular Science, University Heart and Vascular Center, University Medical Center Hamburg-Eppendorf, Hamburg, Germany*

[4] *German Center for Cardiovascular Research (DZHK), partner site Hamburg/Kiel/Luebeck, Hamburg, Germany*

[5] *Center for Population Health Innovation (POINT), University Heart and Vascular Center Hamburg, University Medical Center Hamburg-Eppendorf, Hamburg, Germany*

[6] *Deutsches Herzzentrum München, Technische Universität München, Munich, Germany*

[7] *German Center for Cardiovascular Research (DZHK), Partner site Munich Heart Alliance, Munich, Germany*

[8] *Institute of Epidemiology and Medical Biometry, University of Ulm, Ulm, Germany*

[9] *Department of Public Health and Welfare, Finnish Institute for Health and Welfare (THL), Helsinki, Finland*

[10] *Centre for Public Health, Queens University of Belfast, Belfast, Northern Ireland, UK*

[11] *Department of Epidemiology and Prevention, IRCCS Neuromed, Pozzilli, Italy*

[12] *Department of Medicine and Surgery, LUM University, Casamassima, Italy*

[13] *Cardiovascular Epidemiology Unit, Institute of Cardiovascular Research, University of Dundee, Dundee, Scotland*

[14] *Department of Public Health and Clinical Medicine, Umeå University, Umeå, Sweden*

[15] *Department of Medicine and Surgery, University of Milano-Bicocca, Milan, Italy*

[16] *Department of Cardiovascular, Endocrine-Metabolic Diseases and Aging, Istituto Superiore di Sanità-ISS, Rome, Italy*

[17] *Research Center in Epidemiology and Preventive Medicine (EPIMED), Department of Medicine and Surgery, University of Insubria, Varese, Italy*

[18] *Department of Cardiology, University Heart and Vascular Center Hamburg, University Medical Center Hamburg-Eppendorf, Hamburg, Germany*

[19] *German Center for Diabetes Research (DZD), Partner München-Neuherberg, Neuherberg, Germany*

[*] **Corresponding author**

Abstract

Aims: Given the complex physiological relationship between cardiovascular disease (CVD) and chronic kidney disease (CKD), CVD-related markers may also serve as CKD biomarkers. Therefore, we examined associations of three major CVD-markers [mid-regional pro-adrenomedullin (MR-proADM), MR-pro-atrial natriuretic peptide (MR-proANP), and N-terminal pro-B-type natriuretic peptide (NT-proBNP)] with kidney function and CKD.

Methods and Results: We included a maximum of 61830 participants for cross-sectional analysis and 4205 for longitudinal analysis (NT-proBNP only). Kidney function was assessed by estimated glomerular filtration rate (eGFR), calculated from either creatinine or cystatin C only or a combination of both indices (eGFRcr-cys). The three CVD markers were logarithmically transformed followed by Z-score standardization and also categorized into four groups (G1-4) individually. Cross-sectional analyses found that higher levels of all three markers were associated with lower eGFR and higher CKD prevalence across all eGFR assessments. For example, fully-adjusted β and 95% confidence intervals (CIs) for eGFRcr-cys were -2.35 (-2.49, -2.21) ml/min/1.73m^2 per 1 standard deviation (SD) increase in log-transformed NT-proBNP and -11.2 (-11.8, -10.5) for G4 compared with G1, respectively. Corresponding odds ratios for CKDcr-cys (eGFRcr-cys < 60 ml/min/1.73m^2) were 1.81 (1.72, 1.90) and 5.72 (4.82, 6.78). Associations with eGFR were more pronounced among participants with CVD and diabetes. In longitudinal analyses, participants with higher baseline NT-proBNP had faster declines in eGFR. β (95% CIs) for a 10-year decline in eGFRcr-cys were -1.37 (-1.77, -0.98) ml/min/1.73m^2/10-year per 1 SD increase in log-transformed NT-proBNP, and -7.28 (-9.92, -4.64) for G4 compared with G1. Corresponding hazard ratios for incident CKDcr-cys were 1.39 (1.20, 1.62) and 4.40 (2.63, 7.36).

Conclusions: Higher levels of MR-proADM, MR-proANP, and NT-proBNP were associated with lower eGFR and higher CKD prevalence, and NT-proBNP was also associated with faster eGFR decline and higher CKD incidence, indicating their potential as CKD biomarkers.

Keywords: MR-proADM; MR-proANP; NT-proBNP; Kidney function; Chronic kidney disease

Introduction

Chronic kidney disease (CKD) is characterized by a gradual kidney function decline, with a median prevalence of 9.5% among adults and children worldwide [1]. Given the asymptomatic onset, early CKD detection remains challenging. Heart and kidneys interact bidirectionally, and a spectrum of disorders involving both organs is termed cardiorenal syndrome [2]. CKD and cardiovascular disease (CVD) share common risk factors such as diabetes [3], and mechanisms of disease development such as overactivation of the renin-angiotensin-aldosterone system (RAAS) [4, 5]. Given their complex interactions, mid-regional pro-adrenomedullin (MR-proADM), MR-pro-atrial natriuretic peptide (MR-proANP), and N-terminal pro-B-type natriuretic peptide (NT-proBNP), some of the prominent CVD-related markers [6-9], may be useful as CKD biomarkers.

MR-proADM, MR-proANP, and NT-proBNP are stable surrogate markers for ADM, ANP, and BNP, respectively, because the latter three markers have shorter half-lives. ANP, BNP, and ADM are all vasodilators. The elevations of these markers in the circulation usually occur in response to ventricular/atrial wall stretch and volume overload [7, 8, 10], which in turn, are positively associated with impaired kidney function [3, 11]. On the other hand, these markers are partially dependent on kidney clearance for elimination, and thus, the elevations of these markers are related to kidney function decline [12-15]. The above evidence suggests that these markers could be biomarkers for kidney function decline.

Epidemiological studies have shown that MR-proADM/ADM [16-18], MR-proANP/ANP [16, 19], and NT-proBNP/BNP [20-31], are positively associated with kidney function decline as well as the development and progression of CKD. Our previous study, including 233 proteomic biomarkers, also found that higher levels of ADM and NT-proBNP were associated with a faster kidney function decline and higher CKD incidence [32]. However, there are only a few studies regarding MR-proADM/ADM and MR-proANP/ANP, which have mainly focused on end-stage kidney disease (ESKD), the last stage of CKD, among patients with diabetes and CKD [16-18, 33], while studies in the general population are scarce [19]. Given diabetes is a major cause of CKD, the associations may differ between patients with diabetes and the general population, limiting the generalizability of previous findings. To date, the largest study investigating NT-proBNP with incident ESKD comprised 10749 white and black participants, but they focused on ESKD and found the association differed by ethnicity [23]. Thus, large studies based on the general population with diverse genetic backgrounds are needed to further understand the associations of these markers with early stages of CKD, which is a more prevalent condition than ESKD.

We aimed to investigate the longitudinal (NT-proBNP only) and cross-sectional associations of MR-proADM, MR-proANP, and NT-proBNP with kidney function and CKD in a large general population from the Biomarkers for Cardiovascular Risk Assessment in Europe (BiomarCaRE) project [34]. Given they are CVD-related markers and both CVD and diabetes are major CKD causes, we further aimed to assess if the associations differed by CVD and diabetes.

Methods

Study design and population

BiomarCaRE has relied on the European population of the Monitoring of Trends and Determinants in Cardiovascular Diseases (MONICA), Risk, Genetics, Archiving and Monograph (MORGAM) project [35]. All studies included in BiomarCaRE adhered to the Declaration of Helsinki and were approved by their respective local ethical committees, and all participants gave written informed consent. We included seven studies from BiomarCaRE comprising 61830 participants with data on both NT-proBNP and kidney function: FINRISK Study, MONICA/Cooperative Health Research in the Region of Augsburg (MONICA/KORA), Moli-sani Study, MONICA Brianza Study, Northern Sweden MONICA Study, Prospective Epidemiological Study of Myocardial Infarction Belfast (PRIME/Belfast), and Scottish Heart Health Extended Cohort (SHHEC). Short descriptions of each study are presented in Table S1. Data on MR-proANP (N = 9499) and MR-proADM (N = 9327) were only available in the FINRISK and PRIME/Belfast studies. Harmonized data on age, sex, body mass index, smoking status (current smoker), alcohol consumption, systolic blood pressure, use of antihypertensive medication, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, history of diabetes, and history of CVD were included. Diabetes (any type of diabetes) and CVD (myocardial ischemia, stroke, and for some participants in the MONICA Brianza Study, angina pectoris) were assessed based on documented or self-reported history of these conditions. Used categories of categorical variables are presented in Table 1. Missing values of covariates, up to 5.7%, were imputed by multiple imputation. For longitudinal analysis, follow-up measurement of kidney function was available in the MONICA/KORA study. Figure S1 shows that a maximum of 4205 participants with 10208 observations were included in the longitudinal analysis, with a mean follow-up time of 11.1 years.

Laboratory measurements

Details are presented in Text S1. Briefly, plasma MR-proADM and MRproANP were measured using immunoluminometric assays. Serum NT-proBNP was measured using an electrochemiluminescence immunoassay. Plasma/serum creatinine was measured by the kinetic alkaline picrate Jaffe method or the enzymatic method. Serum cystatin C was measured using a Latex immunoassay. Table S2 presents intra- and inter-assay coefficients of variation.

Assessment of kidney function and CKD

Kidney function was assessed by estimated glomerular filtration rate (eGFR), with creatinine-based (eGFRcr), cystatin C-based eGFR (eGFRcys), and combined creatinine and cystatin C-based eGFR (eGFRcr-cys), calculated using the Chronic Kidney Disease Epidemiology Collaboration equations (equations are presented in Text S1) [36, 37]. CKD cases were defined as eGFR < 60 ml/min per 1.73m^2 [38]. Incident CKD cases were defined as participants free of CKD at baseline and identified as CKD cases at any stage of the follow-up.

Statistical analysis

All analyses were conducted by R v. 4.3.2 and RStudio v. 2023.12.1.

Transformation of markers

A log10 transformation was applied to each marker, followed by Z-score standardization for comparability across different markers. The standard deviations (SD) of log-transformed markers were 0.43 for NT-proBNP, 0.22 for MR-proANP, and 0.12 for MR-proADM, respectively. Original levels of NT-proBNP were also categorized into four groups (G1, G2, G3, and G4): < 48, 48-125 (including 48), 125-300 (including 125), and ≥ 300 pg/ml. The value of 48 is the median value of NT-proBNP among the 61830 participants. The values of 125 and 300 are used as thresholds to rule in heart failure (HF) and acute HF, respectively [6]. Categories of MR-proANP were: < 40, 40-80, 80-120, and ≥ 120 pmol/l. The value of 40 can be used as a threshold to rule out HF while 120 is used for ruling in acute HF [6]. These cut-off values of MR-proANP corresponded to the 37.3th, 84.5th (same as value 125 of NT-proBNP among 61830 participants), and 95.6th percentiles in the participants from the FINRISK and PRIME/Belfast studies. MR-proADM levels were categorized based on cut-off values corresponding to these percentiles: 0.425, 0.609, and 0.766 nmol/l.

Associations with kidney function and CKD

In cross-sectional analysis, linear regression was used to estimate β coefficients and 95% confidence intervals (CIs) of eGFR per 1 SD increase in log-transformed markers. Model 1: adjusted for age, sex, and study cohort. Model 2: model 1 plus body mass index, smoking status, alcohol consumption, systolic blood pressure, use of antihypertensive medication, high-density lipoprotein-cholesterol, log-transformed triglycerides, history of diabetes, and history of CVD. The same linear regression models were applied for grouped markers (G1-4), with G1 serving as the reference group. Logistic regression was used to estimate odds ratios (ORs) of prevalent CKD. In sensitivity analyses, CKD cases were redefined as all three eGFR < 60 ml/min per 1.73m^2 and non-cases as all three eGFR ≥ 60 ml/min per 1.73m^2.

In longitudinal analysis in the MONICA/KORA study, linear mixed-effects models were used to investigate the associations of NT-proBNP with change in eGFR, using "lme4" package. The follow-up duration was used as the timescale and divided by 10 to give a 10-year change. The fixed effects included standardized log-transformed NT-proBNP, follow-up duration, and their interaction terms, while random effects included random intercept and random slope (i.e., individual differences in eGFR change). The β coefficient of the interaction term is the impact of NT-proBNP on the 10-year change in eGFR. The same models were applied for grouped NT-proBNP (G1-4), with G1 serving as the reference group. Participants with at least one follow-up measurement on eGFR were included. For associations with incident CKD, interval-censored Cox regression models with 1000 bootstrap samples for 95% CIs estimation were performed, using "icenReg" package. The first two models in longitudinal analyses were similar to the cross-sectional analysis, with the exclusion of study cohort, and model 3 further adjusted for baseline eGFR. Since model 3 may be overcorrected [39], we used model 2 as our main model. Linear mixed-effects models included time-varying covariates, except for sex. To address bias due to participants lost to follow-up (Figure S1), inverse probability weighting-weights were applied in all longitudinal analyses (details in Text S2).

Stratified and sensitivity analyses

Interaction terms of standardized log-transformed markers with CVD or diabetes were included in the aforementioned final models in both cross-sectional and longitudinal analyses, and stratified analyses were performed if a significant interaction ($p < 0.05$) was found. Sensitivity analyses were conducted by further adjusting for low-density lipoprotein cholesterol, and E-values [40] were calculated to assess the robustness of observed associations to potential unmeasured or uncontrolled confounders.

Non-linear associations analysis

Restricted cubic spline functions with three knots were used to investigate the non-linear associations of original levels of three markers with prevalent CKDcr-cys in logistic regression models and non-linear associations of NT-proBNP with incident CKD in Cox proportional hazards models, adjusting for the covariates as in the aforementioned final models, using “rms” package. Participants with levels of markers < 2.5th percentile or > 97.5th percentile were excluded. P-values for nonlinearity were calculated using ANOVA tests.

Results

The 61830 participants included in the cross-sectional analysis had an average age of 51.8 ± 12.5 years (Table 1), and characteristics of participants across study cohorts are presented in Table S3 & S4. The baseline characteristics of participants from the MONICA/KORA study included in the longitudinal analysis are shown in Table S5.

Cross-sectional associations

Higher levels of three myocardial stress markers were associated with lower eGFR across all three eGFR assessments (Table S6 & Figure 1A). In model 2, the β (95% CIs) of eGFRcr-cys per 1 SD increase in log-transformed markers were -5.60 (-5.94, -5.26) ml/min/1.73m^2 for MR-proADM, -2.93 (-3.30, -2.57) for MR-proANP, and -2.35 (-2.49, -2.21) for NT-proBNP, respectively (Table 2). Figure S2 shows that compared with G1, G2-G4 with higher levels of markers had significantly lower eGFR. For instance, β (95% CIs) of eGFRcr-cys for G2-G4 compared with G1 of NT-proBNP in model 2 were -1.41 (-1.69, -1.14), -4.10 (-4.52, -3.68), and -11.2 (-11.8, -10.5), respectively (Table 2).

Results for CKD showed consistent associations, with higher levels of three markers associated with a higher prevalence of CKD across all three CKD assessments (Table S7 & Figure 1B). Fully-adjusted ORs (95% CIs) of CKDcr-cys per 1 SD increase in log-transformed markers were 3.04 (2.65, 3.48) for MR-proADM, 1.80 (1.58, 2.05) for MR-proANP, and 1.81 (1.72, 1.90) for NT-proBNP, respectively (Table 3). Associations with categories of markers also revealed significantly higher CKD prevalence in G2-G4 compared with G1, with G4 demonstrating the strongest associations (Figure S3). For example, Table 3 shows that fully-adjusted ORs (95%

CIs) of CKDcr-cys across G2-G4 compared with G1 of NT-proBNP were 1.37 (1.19, 1.58), 2.56 (2.19, 2.99), and 5.72 (4.82, 6.78). In sensitivity analyses using redefined CKD cases, the association with per 1 SD increase in log-transformed markers remained significant with higher ORs but wider 95% CIs (Table S8 & Figure S4).

Longitudinal associations

Participants with higher baseline NT-proBNP levels had faster eGFR declines during follow-up (Table 4 & Figure 2). In model 2, the β (95% CIs) of a 10-year decline in eGFRcr-cys per 1 SD increase in log-transformed NT-proBNP were -1.37 (-1.77, -0.98) ml/min/1.73m^2/10-year, and -1.04 (-1.88, -0.20), -3.37 (-4.66, -2.07), and -7.28 (-9.92, -4.64) for G2-4 compared with G1. Regarding incident CKD, we observed 179 incident CKDcr-cys cases / 30856 person-years during follow-up. Baseline NT-proBNP levels were positively associated with incident CKD across all three incident CKD assessments (Table S9 & Figure 3). In model 2, hazard ratio (95% CIs) was 1.39 (1.20, 1.62) per 1 SD increase in log-transformed NT-proBNP for incident CKDcr-cys. For categories of NT-proBNP, G4 shows significantly higher risks of incident CKD compared with G1 of NT-proBNP, with hazard ratio of 4.40 (2.63, 7.36) for incident CKDcr-cys. In model 3 further adjusting for baseline eGFR in longitudinal analyses, all significant associations of log-transformed NT-proBNP and G4 compared with G1 remained significant (Table 4 & Table S9).

Stratified by CVD/diabetes

Significant interactions with both CVD and diabetes were mainly found in the cross-sectional analyses with eGFR (P-interaction < 0.05, Figure 4). In stratified analyses, significant inverse associations of three markers with eGFR were observed in both participants with and without CVD or diabetes, while the associations were stronger among participants with diabetes or CVD (Table S10-S12). For example, the β (95% CIs) of eGFRcr-cys per 1 SD increase in log-transformed NT-proBNP were -2.13 (-2.27, -1.98) ml/min/1.73m^2 among participants without CVD and -4.76 (-5.32, -4.20) among participants with CVD, respectively. Similar results were observed for MR-proANP and MR-proADM. For interaction analysis for prevalent CKD, only a few significant interactions were observed (Figure S5). For instance, interaction with diabetes among associations of MR-proADM with CKDcr-cys, and the associations were stronger among participants with diabetes. In longitudinal analysis, although significant interactions of NT-proBNP with CVD were observed among associations with incident CKDcr-cys (P-interaction < 0.05, Figure S6), there was no significant difference in associations among participants with and without CVD, probably due to small sample size in participants with CVD.

Non-linear associations

A modest non-linear association of NT-proBNP with the prevalence of CKDcr-cys in cross-sectional analysis was observed (Figure S7, P-nonlinear = 0.012). The shape of the associations tended to be steeper after reaching an NT-proBNP level of around 200 pg/ml. For MR-proADM and MR-proANP, the shape of the associations also tended to be steeper for marker levels above G3, but with P-nonlinear > 0.05. Investigating NT-proBNP and incident CKD in the longitudinal analyses found no evidence of nonlinearity (Figure S8, P-nonlinear >0.05).

Discussion

In the present study, we investigated the associations of MR-proADM, MR-proANP, and NT-proBNP with kidney function and CKD in the general population based on pooled individual-level data from several large population-based studies. Cross-sectional analysis found that higher levels of these markers were associated with lower kidney function and a higher prevalence of CKD. Similarly, longitudinal analysis based on the MONICA/KORA study found that higher baseline NT-proBNP levels were associated with faster kidney function decline and a higher incidence of CKD. We observed significant interaction effects with CVD and diabetes mainly in the cross-sectional analyses of kidney function, with the associations being more pronounced among participants with CVD or diabetes. To the best of our knowledge, the present study has the largest sample size among cross-sectional studies in the field.

Our findings for NT-proBNP are consistent with most previous studies. A European general population-based study consisting of 8121 participants found an inverse cross-sectional association between serum NT-proBNP and kidney function [41]. Similar associations have also been observed in a cross-sectional study based on the Northern Sweden MONICA Study (N = 10185) [42], and two small cross-sectional studies among patients with hypertension (N = 207) [43] or acute HF (N = 138) [44]. Several community-based cohort studies, including two Japanese [20, 21] and one American studies [22], have also reported positive associations of serum/plasma NT-proBNP with faster kidney function decline and CKD incidence. Another cohort study reported a positive association of baseline plasma NT-proBNP with incident ESKD [23]. Various cohort studies among CKD patients have reported positive associations of circulating NT-proBNP with incident ESKD and other adverse CKD outcomes [24-30]. Collectively, circulating NT-proBNP exhibits strong associations with kidney function and kidney diseases.

Findings for MR-proANP and MR-proADM are also consistent with previous studies. A cohort study comprising 294 Japanese residents reported a positive association of plasma ANP with incident CKD [19]. Another cohort found that plasma MR-proANP and MR-proADM were positively associated with the progression of CKD among 177 CKD patients from three European countries [16]. Positive associations of MR-proADM with severe kidney outcomes such as incident ESKD have also been reported in cohort studies conducted among patients with diabetes [17, 18]. Two clinical trials have reported that starting human ANP infusion at the beginning of heart bypass surgery improves postoperative kidney function in patients, regardless of their CKD status [45, 46]. In another clinical trial, HF patients treated with the angiotensin-neprilysin inhibition LCZ696, a drug that suppresses the RAAS and increases natriuretic peptides levels, had a significantly lower mortality rate and a non-significantly lower kidney dysfunction incidence, compared to those treated with enalaprilin [47]. The above findings indicate the potential of MR-proANP and MR-proADM as biomarkers of kidney function decline.

In the present study, in extension to previous work, significant interactions of MR-proADM, MR-proANP, and NT-proBNP with CVD and diabetes on the cross-sectional associations with kidney function were observed, with the associations being more pronounced among participants with CVD and diabetes. This could be partially explained by the fact that both CVD and diabetes are important risk factors for the development of CKD, thus these individuals may be more susceptible to the impact of these markers on kidney function [38, 48]. Results of non-linear associations could also support CVD-stratified results. Although no convincing non-linear associations were confirmed, the shapes of associations tended to become steeper with increasing marker levels. Since higher levels of these markers are strongly associated with CVD, the observed steeper associations with higher marker levels were similar to CVD-stratified results. Our findings suggest the importance of monitoring these markers, particularly in individuals with CVD or diabetes.

The precise mechanisms remain elusive. The elevation of these markers, as well as their active forms ADM, ANP, and BNP in the circulation, can be attributed to conditions such as ventricular/atrial wall stretch and volume overload. ADM, ANP, and BNP counteract these conditions through multiple effects, including vasodilatory, natriuretic, and diuretic effects, partially by inhibiting the actions of RAAS [7, 8, 12]. Chronic and excessive presence of these conditions can result in impaired cardiac function such as cardiac output decrease, thereby contributing to an overactivation of RAAS, a key player in CKD development [11]. On the other hand, kidney function decline can lead to an accumulation of these markers in the circulation [12-15]. Nonetheless, compelling evidence has suggested that cardiac pathology remains the primary determinant for elevation of these markers [8, 49]. Given the intricate interplay between the heart and kidneys, these markers may serve as valuable biomarkers for disorders involving both organs, such as the cardiorenal syndrome.

Key strengths of our study include the largest sample size derived from the general population in the cross-sectional analysis, and the estimation of kidney function using creatinine and/or cystatin C. Several limitations should also be acknowledged. First, in longitudinal analysis, data were only available in a restricted dataset and only baseline NT-proBNP was considered, and thus, we were unable to explore the impact of dynamic changes in NT-proBNP over time. Second, the counterintuitively inverse associations between obesity and levels of natriuretic peptides (e.g., MR-proANP and NT-proBNP), as reported in previous studies [50], may have had impacts on our observed associations, despite our adjustment for body mass index. Third, the definition of CKD cases using a single creatinine and/or cystatin C measurement, and different assays across surveys, as well as the lack of follow-up confirmatory tests after a certain period such as three months, could potentially result in misclassification. However, sensitivity analysis of redefined CKD showed robust results. Fourth, analyses of MR-proADM and MR-proANP were only based on cross-sectional data, but our study contributes significantly to the existing literature due to its large general population-based sample size. Finally, unmeasured or uncontrolled confounders (e.g., medications that affect both the levels of these makers and kidney function) may have had impacts on the observed associations, but our sensitivity analyses and E-values suggested that our results were robust to potential unmeasured or uncontrolled confounders (Table S13-15).

In conclusion, our study found cross-sectional associations of higher levels of MR-proADM, MR-proANP, and NT-proBNP with lower kidney function and a higher prevalence of CKD, with the associations being more pronounced among individuals with CVD and diabetes. Moreover, higher NT-proBNP levels were also associated with faster kidney function decline and a higher incidence of CKD. Our findings indicate the potential utility of these myocardial stress markers as valuable biomarkers of kidney health, particularly in the context of comorbidities such as CVD and diabetes. Further research is warranted to understand the underlying mechanisms driving these associations.

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Authors' Contributions: JSL designed the study, drafted the analysis plan, performed the statistical analysis, interpreted the data, and wrote the first draft of the manuscript. TZ, WK, PJ, FK, LI, HTP, SS, GC, LP, VS, RDP, CD, KK, SB, AP, and BT contributed data. TL contributed to data curation. AP contributed to the analysis plan. BT designed the study and contributed to the analysis plan and data interpretation. All authors read and approved the final manuscript. JSL and BT had primary responsibility for the final content.

Data sharing statement: The MORGAM/BiomarCaRE data are not available in a public repository. Access to the data is restricted by the ethical approvals and the legislation of the European Union and the countries of each study. Approval by the Principal Investigator of each cohort study and the MORGAM/BiomarCaRE Steering Group will be required for release of the data. The MORGAM Manual at https://www.thl.fi/publications/morgam/manual/contents.htm gives more information on access to the data. The informed consent given by MONICA/KORA study participants does not cover data posting in public databases. Cooperation partners can obtain permission to use MONICA/KORA data under the terms of a project agreement (https://helmholtz-muenchen.managed-otrs.com/external).

Supplementary Materials: Text S1. Details of laboratory measurements and kidney function assessment; **Text S2.** Inverse probability weighting; **Table S1.** Overview and description of contributing studies/cohorts in BiomarCaRE; **Table S2.** Intra-assay and inter-assay coefficients of variation for laboratory measurements in included study cohorts; **Table S3.** Baseline characteristics of participants included in the cross-sectional analysis across study cohorts; **Table S4.** Characteristics of participants with data on MR-proADM and MR-proANP; **Table S5.** Baseline characteristics of participants from the MONICA/KORA study included in the longitudinal analysis; **Table S6.** Cross-sectional associations of 3 myocardial stress markers with kidney function; **Table S7.** Cross-sectional associations of 3 myocardial stress markers with CKD; **Table S8.** Sensitivity analysis of cross-sectional associations of 3 myocardial stress markers with CKD; **Table S9.** Longitudinal associations of NT-proBNP with incident CKD; **Table S10.** Cross-sectional associations of NT-proBNP with kidney function stratified by CVD and diabetes; **Table S11.** Cross-sectional associations of MR-proANP with kidney function stratified by CVD and diabetes; **Table S12.** Cross-sectional associations of MR-proADM with kidney function stratified by CVD and diabetes; **Table S13.** Sensitivity analysis of cross-sectional associations of 3 myocardial stress markers with eGFRcr-cys and CKDcr-cys; **Table S14.** Sensitivity analysis of longitudinal associations of NT-proBNP with change in eGFRcr-cys and incident CKDcr-cys; **Table S15.** E-values to assess the robustness of observed associations to potential unmeasured or uncontrolled confounders; **Figure S1.** Flowchart of study participants from the MONICA/KORA study included in the longitudinal analysis; **Figure S2.** Cross-sectional associations of 3 myocardial stress markers with kidney function; **Figure S3.** Cross-sectional associations of 3 myocardial stress markers with CKD; **Figure S4.** Sensitivity analysis of cross-sectional associations of 3 myocardial stress markers with CKD; **Figure S5.** Cross-sectional associations of 3 myocardial stress markers with CKD stratified by CVD and diabetes; **Figure S6.** Longitudinal associations of NT-proBNP with 10-year change in kidney function and incident CKD stratified by CVD and diabetes; **Figure S7.** Shapes of the associations between 3 myocardial stress markers and prevalent CKDcr-cys; **Figure S8.** Shapes of the associations between NT-proBNP and incident CKD

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Tables

Table 1. Baseline characteristics of participants included in the cross-sectional analysis across categories of NT-proBNP

Characteristics	Total (N = 61830)	G1 (N = 30939)	G2 (N = 21284)	G3 (N = 7109)	G4 (N = 2498)	*P*-value [a]
	Categories of NT-proBNP					
	Mean (standard deviation) or number (%)					
Study cohort, N (%)						<0.001
FINRISK	6858 (11.1)	3468 (11.2)	2359 (11.1)	775 (10.9)	256 (10.2)	
MONICA/KORA	5790 (9.4)	2834 (9.2)	2081 (9.8)	661 (9.3)	214 (8.6)	
Moli-sani	22243 (36.0)	10672 (34.5)	7764 (36.5)	2753 (38.7)	1054 (42.2)	
MONICA_Brianza	3623 (5.9)	2136 (6.9)	1143 (5.4)	281 (4.0)	63 (2.5)	
Northern Sweden MONICA	10414 (16.8)	5560 (18.0)	3435 (16.1)	1026 (14.4)	393 (15.7)	
PRIME/Belfast	1539 (2.5)	1010 (3.3)	403 (1.9)	82 (1.2)	44 (1.8)	
SHHEC	11363 (18.4)	5259 (17.0)	4099 (19.3)	1531 (21.5)	474 (19.0)	
Age (years)	51.8 (12.5)	47.7 (10.9)	53.1 (12.0)	60.2 (12.1)	66.3 (10.7)	<0.001
Sex, N (%) female	32209 (52.1)	12716 (41.1)	13755 (64.6)	4574 (64.3)	1164 (46.6)	<0.001
Body mass index (kg/m^2)	27.2 (6.07)	27.1 (5.74)	27.0 (6.24)	27.7 (6.29)	28.6 (7.46)	<0.001
Current smoker, N (%)	17229 (27.9)	9424 (30.5)	5631 (26.5)	1637 (23.0)	537 (21.5)	<0.001
Alcohol consumption, N (%)						<0.001
No alcohol consumption	20265 (32.8)	9160 (29.6)	7546 (35.5)	2670 (37.6)	889 (35.6)	
>0 and <20 g/day	27001 (43.7)	13646 (44.1)	9324 (43.8)	3014 (42.4)	1017 (40.7)	
≥ 20 g/day	14564 (23.6)	8133 (26.3)	4414 (20.7)	1425 (20.0)	592 (23.7)	
Systolic blood pressure (mm Hg)	135.8 (32.5)	132.3 (32.5)	136.0 (32.0)	144.3 (28.0)	152.1 (39.1)	<0.001
Use of antihypertensive medication, N (%)	11096 (17.9)	3420 (11.1)	4076 (19.2)	2354 (33.1)	1246 (49.9)	<0.001
Hypertension, N (%)	27574 (44.6)	11352 (36.7)	9804 (46.1)	4485 (63.1)	1933 (77.4)	<0.001
HDL-cholesterol (mmol/L)	1.46 (0.39)	1.41 (0.37)	1.51 (0.40)	1.51 (0.42)	1.41 (0.41)	<0.001
LDL-cholesterol (mmol/L)	3.37 (1.02)	3.39 (1.00)	3.37 (1.02)	3.35 (1.05)	3.31 (1.09)	<0.001
Triglycerides (mmol/L), median [IQR]	1.26 [0.91, 1.78]	1.28 [0.91, 1.83]	1.21 [0.89, 1.70]	1.29 [0.95, 1.80]	1.38 [1.03, 1.87]	<0.001

Characteristics	**Categories of NT-proBNP**					***P*-value** [a]
	Total (N = 61830)	**G1 (N = 30939)**	**G2 (N = 21284)**	**G3 (N = 7109)**	**G4 (N = 2498)**	
	Mean (standard deviation) or number (%)					
Diabetes, N (%)	2890 (4.7)	1040 (3.4)	955 (4.5)	538 (7.6)	357 (14.3)	<0.001
Cardiovascular diseases, N (%)	2563 (4.1)	528 (1.7)	730 (3.4)	708 (10.0)	597 (23.9)	<0.001
eGFRcr (ml/min/1.73 m^2)	97.3 (16.7)	100.8 (15.6)	96.4 (15.7)	90.3 (16.8)	80.7 (20.4)	<0.001
CKDcr, N (%)	1833 (3.0)	539 (1.7)	543 (2.6)	364 (5.1)	387 (15.5)	<0.001
eGFRcys (ml/min/1.73 m^2)	94.4 (22.5)	99.5 (20.1)	93.3 (21.6)	84.0 (24.4)	71.3 (26.4)	<0.001
CKDcys, N (%)	4663 (7.5)	878 (2.8)	1562 (7.3)	1310 (18.4)	913 (36.5)	<0.001
eGFRcr-cys (ml/min/1.73 m^2)	99.1 (19.4)	103.5 (17.4)	98.2 (18.4)	90.2 (20.6)	78.2 (23.6)	<0.001
CKDcr-cys, N (%)	1956 (3.2)	365 (1.2)	530 (2.5)	538 (7.6)	523 (20.9)	<0.001
MR-proADM, (nmol/l), median [IQR] [b]	0.47 [0.39, 0.56]	0.44 [0.37, 0.51]	0.48 [0.41, 0.58]	0.55 [0.47, 0.66]	0.65 [0.56, 0.78]	<0.001
MR-proANP, (pmol/l), median [IQR] [b]	48.1 [35.2, 67.6]	39.6 [30.5, 52.6]	53.9 [41.7, 70.8]	78.9 [59.3, 103.0]	127.5 [91.4, 183.5]	<0.001
NT-proBNP, (pg/ml), median [IQR]	48.0 [25.4, 89.6]	25.4 [15.9, 35.6]	72.5 [58.9, 92.1]	169.4 [142.6, 209.3]	501.2 [367.7, 837.2]	<0.001

[a] P-value was estimated by ANOVA test / Kruskal–Wallis test (continuous variables), or chi-squared test (categorical variables)

[b] MR-proADM and MR-proANP are only available in study FINRISK and PRIME/Belfast.

Abbreviations: CKD, chronic kidney disease; cr, creatinine-based; cys, cystatin C-based; cr-cys, combined creatinine and cystatin C-based; eGFR, estimated glomerular filtration rate; G, group; HDL, high-density lipoprotein; IQR, interquartile range; LDL, low-density lipoprotein; MR-proADM, mid-regional pro-adrenomedullin; MR-proANP, mid-regional pro-atrial natriuretic peptide; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

Table 2. Cross-sectional associations of 3 myocardial stress markers with kidney function assessed by eGFRcr-cys [a]

Markers	Items	Categories of markers				per 1 SD increase in log-transformed
		G1	G2	G3	G4	
NT-proBNP						
	Median, pg/ml	25.4	72.5	169.4	501.2	48.0
	N	30939	21284	7109	2498	61830
	Model 1	Ref.	-1.22 (-1.51, -0.94) ***	-4.23 (-4.66, -3.80) ***	-11.7 (-12.4, -11.0) ***	-2.32 (-2.47, -2.18) ***
	Model 2	Ref.	-1.41 (-1.69, -1.14) ***	-4.10 (-4.52, -3.68) ***	-11.2 (-11.8, -10.5) ***	-2.35 (-2.49, -2.21) ***
MR-proANP						
	Median, pmol/l	30.8	53.7	92.8	147.2	46.8
	N	3540	4493	1048	418	9499
	Model 1	Ref.	-2.16 (-2.88, -1.45) ***	-5.30 (-6.43, -4.17) ***	-12.4 (-13.9, -10.8) ***	-2.83 (-3.20, -2.47) ***
	Model 2	Ref.	-2.68 (-3.39, -1.98) ***	-5.74 (-6.86, -4.62) ***	-11.8 (-13.4, -10.2) ***	-2.93 (-3.30, -2.57) ***
MR-proADM						
	Median, nmol/l	0.37	0.50	0.66	0.86	0.46
	N	3492	4397	1029	409	9327
	Model 1	Ref.	-5.55 (-6.20, -4.89) ***	-12.4 (-13.5, -11.4) ***	-22.2 (-23.7, -20.7) ***	-5.84 (-6.17, -5.52) ***
	Model 2	Ref.	-5.24 (-5.90, -4.58) ***	-11.7 (-12.7, -10.6) ***	-21.0 (-22.6, -19.5) ***	-5.60 (-5.94, -5.26) ***

[a] Linear regression was used to estimate beta coefficients and 95% CI of eGFR for G2-4 compared with G1 of markers, as well as for per 1 SD increase in log-transformed markers. Only results for eGFRcr-cys are presented in this table, while results for all three eGFR assessments are presented in Table S6.

Model 1: adjusted for age, sex, and study cohort;

Model 2: model 1 plus body mass index, smoking status, alcohol consumption, systolic blood pressure, use of antihypertensive medication, high-density lipoprotein cholesterol, log-transformed triglycerides, diabetes, and cardiovascular diseases.

Abbreviations: CI, confidence interval; G, group; eGFR, estimated glomerular filtration rate; eGFRcr-cys, creatinine and cystatin C-based eGFR; MR-proADM, mid-regional pro-adrenomedullin; MR-proANP, mid-regional pro-atrial natriuretic peptide; NT-proBNP, N-terminal pro-B-type natriuretic peptide; Ref, reference; SD, standard deviation.

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Table 3. Cross-sectional associations of 3 myocardial stress markers with CKDcr-cys [a]

Markers	Items	Categories of markers				per 1 SD increase in log-transformed
		G1	G2	G3	G4	
NT-proBNP						
	Median, pg/ml	25.4	72.5	169.4	501.2	48.0
	Cases / controls	365 / 30574	530 / 20754	538 / 6571	523 / 1975	1956 / 59874
	Model 1	Ref.	1.35 (1.17, 1.55) ***	2.62 (2.25, 3.06) ***	6.14 (5.22, 7.24) ***	1.84 (1.75, 1.93) ***
	Model 2	Ref.	1.37 (1.19, 1.58) ***	2.56 (2.19, 2.99) ***	5.72 (4.82, 6.78) ***	1.81 (1.72, 1.90) ***
MR-proANP						
	Median, pmol/l	30.8	53.7	92.8	147.2	46.8
	Cases / controls	39 / 3501	124 / 4369	58 / 990	79 / 339	300 / 9199
	Model 1	Ref.	1.48 (1.00, 2.21)	2.22 (1.40, 3.57) ***	7.35 (4.63, 11.8) ***	1.92 (1.70, 2.18) ***
	Model 2	Ref.	1.54 (1.05, 2.31) *	2.17 (1.36, 3.50) **	6.39 (3.96, 10.5) ***	1.80 (1.58, 2.05) ***
MR-proADM						
	Median, nmol/l	0.37	0.50	0.66	0.86	0.46
	Cases / controls	32 / 3460	98 / 4299	58 / 971	108 / 301	296 / 9031
	Model 1	Ref.	1.86 (1.25, 2.84) **	4.52 (2.83, 7.35) ***	28.8 (18.1, 46.8) ***	2.93 (2.59, 3.32) ***
	Model 2	Ref.	2.02 (1.35, 3.12) ***	5.04 (3.08, 8.36) ***	34.6 (20.8, 58.6) ***	3.04 (2.65, 3.48) ***

[a] Logistic regression was used to estimate OR and 95% CI of prevalent CKD for G2-4 compared with G1 of markers, as well as for per 1 SD increase in log-transformed markers. Only results for CKDcr-cys are presented in this table, while results for all three CKD assessments are presented in Table S7.

Model 1: adjusted for age, sex, and study cohort;

Model 2: model 1 plus body mass index, smoking status, alcohol consumption, systolic blood pressure, use of antihypertensive medication, high-density lipoprotein cholesterol, log-transformed triglycerides, diabetes, and cardiovascular diseases.

Abbreviations: CI, confidence interval; CKD, chronic kidney disease; CKDcr-cys, creatinine and cystatin C-based CKD; G, group; MR-proADM, mid-regional pro-adrenomedullin; MR-proANP, mid-regional pro-atrial natriuretic peptide; NT-proBNP, N-terminal pro-B-type natriuretic peptide; OR, odds ratio; Ref, reference; SD, standard deviation.

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Table 4. Longitudinal associations of NT-proBNP with 10-year change in kidney function [a]

eGFR	Items	Categories of NT-proBNP				per 1 SD increase in log-transformed
		G1	G2	G3	G4	
eGFRcr						
	Median, pg/ml	25.7	72.2	166.2	477.6	46.0
	participants; observations	2178; 5330	1494; 3622	445; 1055	88; 201	4205; 10208
	Model 1	Ref.	-0.90 (-1.66, -0.14) *	-3.11 (-4.27, -1.94) ***	-8.41 (-10.8, -6.01) ***	-1.37 (-1.74, -1.01) ***
	Model 2	Ref.	-0.80 (-1.55, -0.05) *	-2.74 (-3.90, -1.58) ***	-8.17 (-10.6, -5.77) ***	-1.26 (-1.62, -0.89) ***
	Model 3	Ref.	-0.81 (-1.66, 0.04)	-3.19 (-4.51, -1.88) ***	-8.51 (-11.2, -5.77) ***	-1.39 (-1.80, -0.99) ***
eGFRcys						
	Median, pg/ml	25.3	72.7	161.8	518.0	47.2
	participants; observations	1345; 3643	948; 2520	295; 747	63; 151	2651; 7061
	Model 1	Ref.	-0.95 (-1.92, 0.02)	-2.82 (-4.31, -1.33) ***	-5.36 (-8.40, -2.33) ***	-1.12 (-1.58, -0.66) ***
	Model 2	Ref.	-0.73 (-1.68, 0.22)	-2.29 (-3.76, -0.83) **	-4.79 (-7.78, -1.80) **	-0.93 (-1.38, -0.48) ***
	Model 3	Ref.	-0.86 (-1.92, 0.19)	-2.48 (-4.10, -0.87) **	-5.71 (-8.97, -2.45) ***	-1.08 (-1.57, -0.58) ***
eGFRcr-cys						
	Median, pg/ml	25.3	72.7	161.8	518.0	47.2
	participants; observations	1345; 3643	948; 2520	295; 747	63; 151	2651; 7061
	Model 1	Ref.	-1.21 (-2.06, -0.35) **	-3.80 (-5.12, -2.48) ***	-7.78 (-10.5, -5.09) ***	-1.54 (-1.95, -1.14) ***
	Model 2	Ref.	-1.04 (-1.88, -0.20) *	-3.37 (-4.66, -2.07) ***	-7.28 (-9.92, -4.64) ***	-1.37 (-1.77, -0.98) ***
	Model 3	Ref.	-1.14 (-2.08, -0.20) *	-3.62 (-5.06, -2.18) ***	-8.10 (-11.0, -5.20) ***	-1.53 (-1.97, -1.09) ***

[a] Linear mixed-effects models were used to investigate the associations of NT-proBNP with change in eGFR, using “lme4” package. The follow-up duration was used as the timescale and divided by 10 to give a 10-year change. The fixed effects included standardized log-transformed NT-proBNP, follow-up duration, and their interaction terms, while random effects included random intercept and random slope (i.e., individual differences in eGFR change). The β coefficient of the interaction term is the impact of NT-proBNP on the 10-year change in eGFR. The same models were applied for grouped NT-proBNP (G1-4), with G1 serving as the reference group.

Model 1: adjusted for age and sex;

Model 2: model 1 plus body mass index, smoking status, alcohol consumption, systolic blood pressure, use of antihypertensive medication, high-density lipoprotein cholesterol, log-transformed triglycerides, diabetes, and cardiovascular diseases;

Model 3: model 2 plus baseline eGFR.

Abbreviations: CI, confidence interval; G, group; eGFR, estimated glomerular filtration rate; eGFRcr, creatinine-based eGFR; eGFRcys, cystatin C-based eGFR; eGFRcr-cys, creatinine and cystatin C-based eGFR; NT-proBNP, N-terminal pro-B-type natriuretic peptide; Ref, reference; SD, standard deviation.

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Figures and figure legends

Figure 1. Cross-sectional associations of 3 myocardial stress markers with kidney function and CKD. A). Linear regression was used to estimate beta coefficients and 95% CI of eGFR per 1 SD increase in log-transformed markers. **B).** Logistic regression was used to estimate odds ratios of CKD. Detailed information on adjusted models is described in Table 2 & 3. Data from 61830 participants for NT-proBNP, 9499 for MR-proANP, and 9327 for MR-proADM were included in these analyses.

Abbreviations: CI, confidence interval; CKD, chronic kidney disease; cr, creatinine-based; cys, cystatin C-based; cr-cys, combined creatinine and cystatin C-based; eGFR, estimated glomerular filtration rate; MR-proADM, mid-regional pro-adrenomedullin; MR-proANP, mid-regional pro-atrial natriuretic peptide; NT-proBNP, N-terminal pro-B-type natriuretic peptide; SD, standard deviation; * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

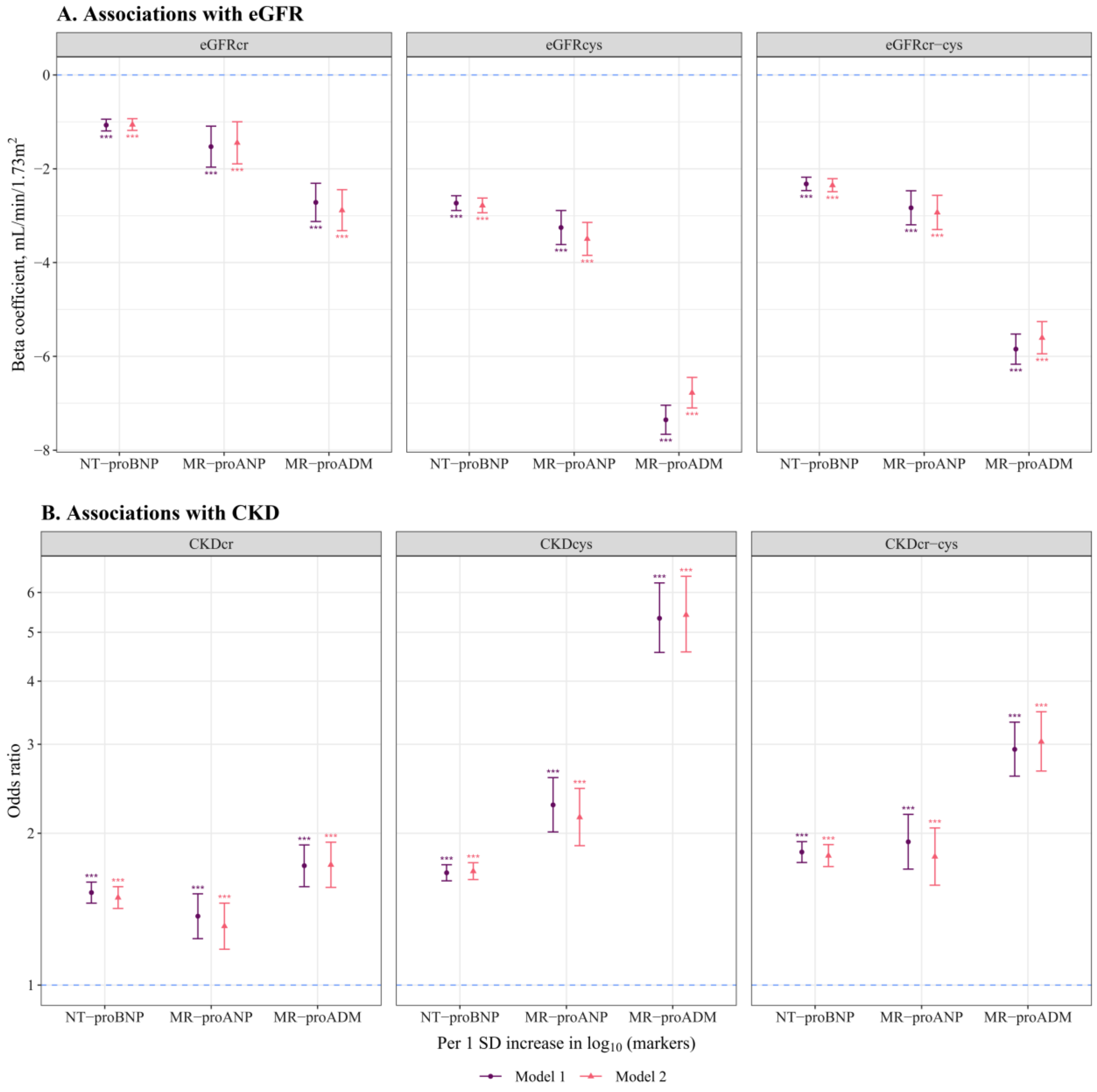


Figure 2. Longitudinal associations of NT-proBNP with 10-year change in kidney function. Linear mixed-effects model was used to estimate beta coefficients and 95% CI of the change in eGFR for G2-4 compared with G1 of NT-proBNP, as well as for per 1 SD increase in log-transformed NT-proBNP. The follow-up duration was used as a timescale and divided by 10 to give a 10-year change. Detailed information on adjusted models is described in Table 4. A maximum of 4205 participants with 10208 observations were included in these analyses.

Abbreviations: CI, confidence interval; G, group; eGFR, estimated glomerular filtration rate; eGFRcr, creatinine-based eGFR; eGFRcys, cystatin C-based eGFR; eGFRcr-cys, creatinine and cystatin C-based eGFR; NT-proBNP, N-terminal pro-B-type natriuretic peptide; SD, standard deviation; * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

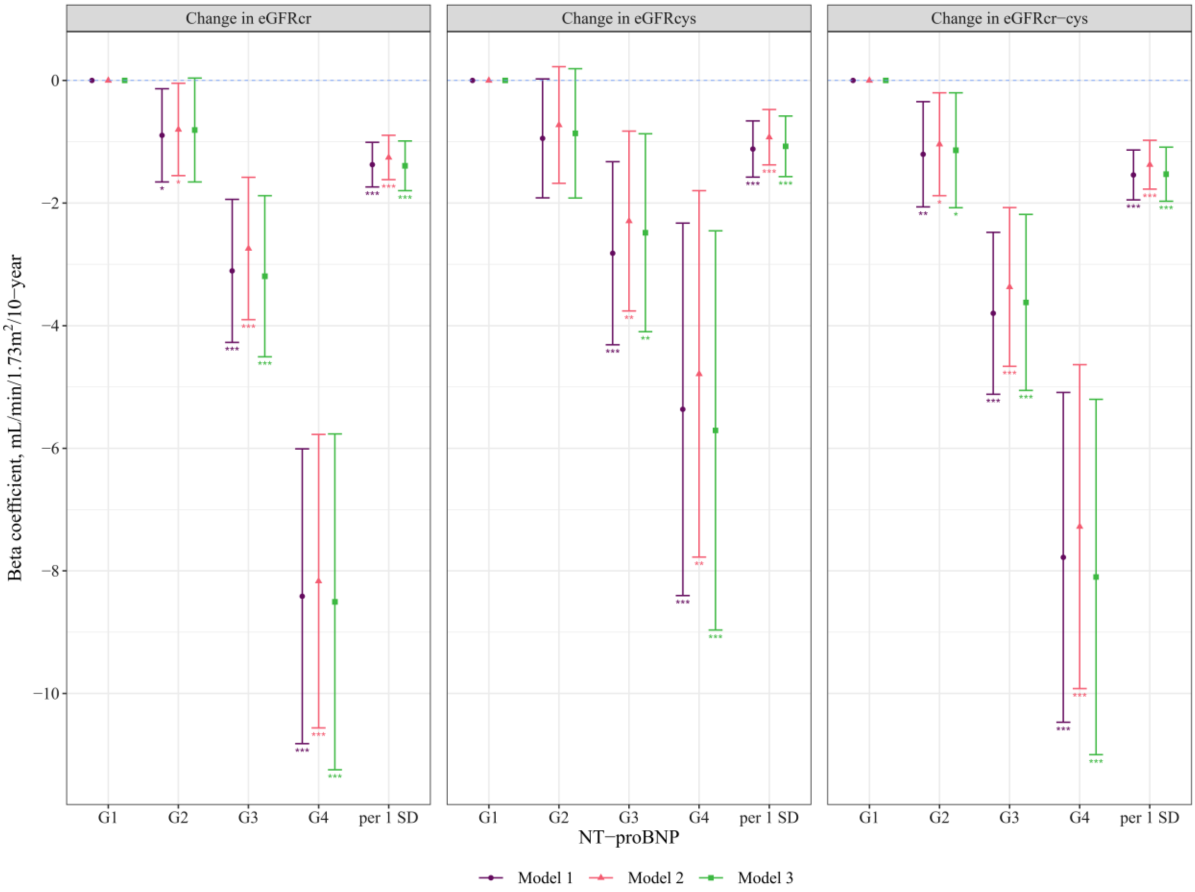


Figure 3. Longitudinal associations of NT-proBNP with incident CKD. Interval-censored Cox regression was used to estimate HR and 95% CI (1000 bootstrap samples for 95% CI estimation) of incident CKD for G2-4 compared with G1 of NT-proBNP, as well as for per 1 SD increase in log-transformed NT-proBNP. A total of 4167 participants free of CKDcr, 2557 free of CKDcys, and 2621 free of CKDcr-cys at baseline were included in these analyses. Detailed results are presented in Table S9.

Abbreviations: CI, confidence interval; CKD, chronic kidney disease; CKDcr, creatinine-based CKD; CKDcys, cystatin C-based CKD; CKDcr-cys, creatinine and cystatin C-based CKD; G, group; HR, hazard ratio; NT-proBNP, N-terminal pro-B-type natriuretic peptide; SD, standard deviation; * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

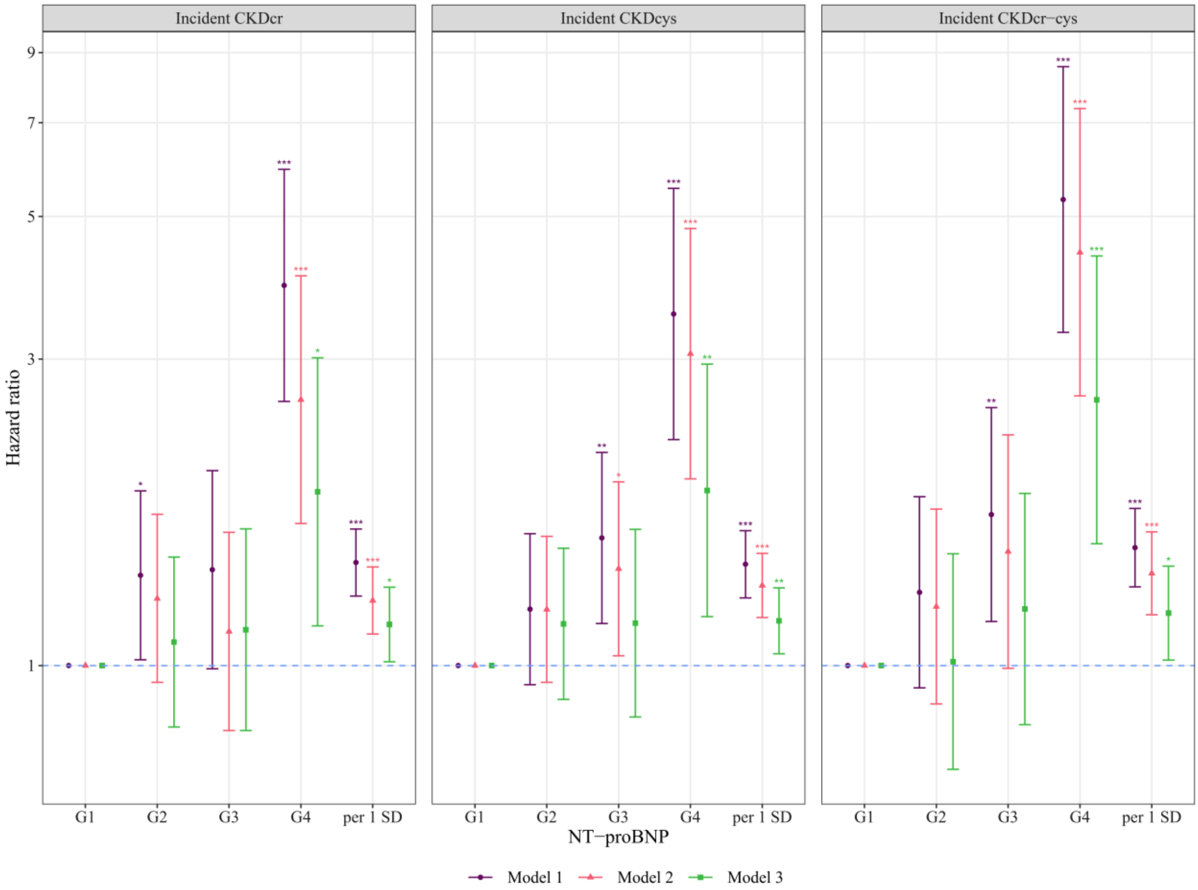
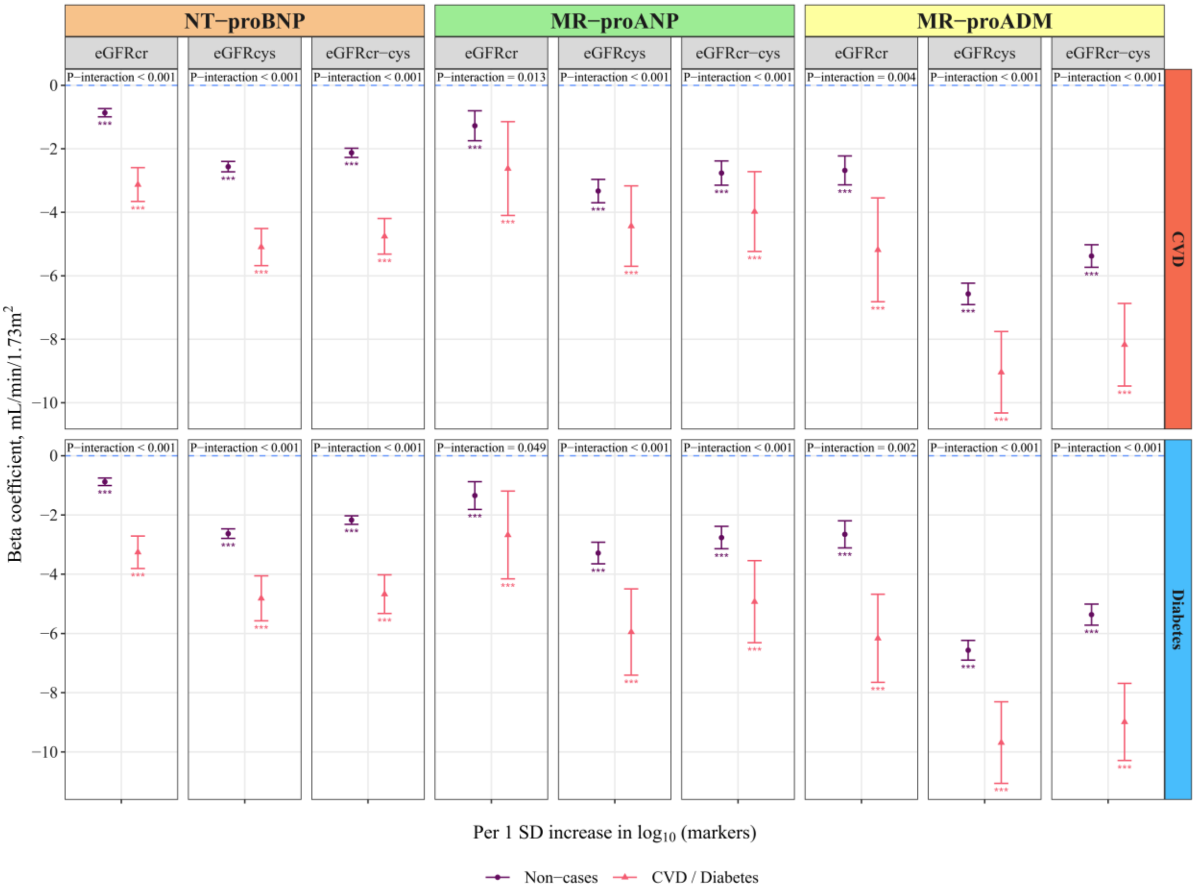


Figure 4. Cross-sectional associations of 3 myocardial stress markers with kidney function stratified by CVD and diabetes. Interaction terms of standardized log-transformed markers with CVD or diabetes were included in linear regression, applying model 2 described in Table 2, to test the significance of interaction. Data from 61830 participants for NT-proBNP, 9499 for MR-proANP, and 9327 for MR-proADM were included in these analyses. Please refer to Table S10-12 for detailed results.

Abbreviations: CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; eGFRcr, creatinine-based eGFR; eGFRcys, cystatin C-based eGFR; eGFRcr-cys, creatinine and cystatin C-based eGFR; MR-proADM, mid-regional pro-adrenomedullin; MR-proANP, mid-regional pro-atrial natriuretic peptide; NT-proBNP, N-terminal pro-B-type natriuretic peptide; SD, standard deviation; * p < 0.05, ** p < 0.01, *** p < 0.001.



Supplementary materials

Longitudinal and cross-sectional associations of myocardial stress markers with kidney function and chronic kidney disease: the BiomarCaRE project

Jie-sheng Lin, Tanja Zeller, Wolfgang Koenig, Pekka Jousilahti, Frank Kee, Licia Iacoviello, Hugh Tunstall-Pedoe, Stefan Söderberg, Giancarlo Cesana, Luigi Palmieri, Veikko Salomaa, Julia de Man Lapidoth, Roberto De Ponti, Chiara Donfrancesco, Thiess Lorenz, Kari Kuulasmaa, Stefan Blankenberg, Annette Peters, Barbara Thorand; on behalf of the BiomarCaRE investigators

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Supplementary texts

Text S1. Details of laboratory measurements and kidney function assessment

In BiomarCaRE/MORGAM, plasma/serum samples were used to measure the following markers and indices: Plasma MR-proADM and MRproANP (only available in study FINRISK and PRIME/Belfast) were measured on the BRAHMS KRYPTOR automated system with immunoluminometric assay (BRAHMS/Thermo Fisher Scientific, Hennigsdorf, Berlin, Germany). Serum NT-proBNP was measured on the ELECSYS 2010 or the Cobas e411 using an electrochemiluminescence immunoassay (ECLIA, Roche Diagnostics, Mannheim, Germany). Plasma/serum creatinine was measured by the kinetic alkaline picrate Jaffe method on the Abbott Architect c8000 with the isotope dilution mass spectrometry (IDMS) traceable (NIST SRM 967) Abbott Architect Assay CREATININE. Serum cystatin C was measured on the Abbott Architect c8000 with the Latex immunoassay. High-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and triglycerides were measured locally by routine methods.

In the baseline of MONICA/KORA study (S3 & S4), part of creatinine was measured by the enzymatic method (CREA plus, Boehringer, Mannheim, Germany). In follow-up surveys of MONICA/KORA study, creatinine was assessed in serum using a modified kinetic rate Jaffe method at MONICA/KORA F3 & F4 and the first part of FF4 (CREA Flex, Dade Behring / Siemens Healthcare Diagnostics Products GmbH), and a Jaffe method for the second part of FF4 (Cobas 8000 instrument, Roche Diagnostics, Mannheim, Germany). Serum creatinine at MONICA/KORA F3 &F4 and FF4 (part 1) were Isotope-Dilution Mass Spectrometry standardized. Serum cystatin C was measured using N Latex Cystatin C assay (Siemens Healthcare Diagnostics Products GmbH) using particle-enhanced immunonephelometry at MONICA/KORA F3/F4/FF4. Cystatin C at F3/F4 was calibrated to the International Federation of Clinical Chemistry and Laboratory Medicine standard by multiplying by a factor of 1.174 as suggested by Siemens.

Kidney function was assessed by estimated glomerular filtration rate (eGFR), with creatinine-based (eGFRcr), cystatin C-based eGFR (eGFRcys), and combined creatinine and cystatin C-based eGFR (eGFRcr-cys), calculated using the following Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations:

The CKD-EPI Creatinine Equation 2021 [1]:

$\text{eGFRcr} = 142 \times \min(\mathbf{cr}/k,1)^{\alpha} \times \max(\mathbf{cr}/k,1)^{-1.200} \times 0.9938^{\text{Age}} \times 1.012$ [if female], where **cr** is creatinine, k is 0.7 for females and 0.9 males, α is -0.241 for females and -0.302 for males, min indicates the minimum of cr/k or 1, max indicates the maximum of cr/k or 1.

The CKD-EPI Cystatin C Equation 2012 [2]:

$\text{eGFRcys} = 133 \times \min(\mathbf{cys}/0.8,1)^{-0.499} \times \max(\mathbf{cys}/0.8,1)^{-1.328} \times 0.9962^{\text{Age}} \times 0.932$ [if female], where **cys** is cystatin C, min indicates the minimum of cys/0.8 or 1, max indicates the maximum of cys/0.8 or 1.

The CKD-EPI Creatinine-Cystatin C Equation 2021 [1]:

$\text{eGFRcr-cys} = 135 \times \min(\mathbf{cr}/k,1)^{\alpha} \times \max(\mathbf{cr}/k,1)^{-0.544} \times \min(\mathbf{cys}/0.8,1)^{-0.323} \times \max(\mathbf{cys}/0.8,1)^{-0.778} \times 0.9961^{\text{Age}} \times 0.963$ [if female], where **cr** is creatinine, **cys** is cystatin C, k is 0.7 for females and 0.9 males, α is -0.219 for females and -0.144 for males, min indicates the minimum of cr/k or 1 and the minimum of cys/0.8 or 1, max indicates the maximum of cr/k or 1 and the maximum of cys/0.8 or 1.

Text S2. Inverse probability weighting

To partially address bias caused by loss to follow-up in the longitudinal analysis (due to death or other reasons, e.g., refusal or inability to contact, Figure S1), the inverse probability weighting-weights were applied in all longitudinal analyses in the present study. Each participant's probability of loss to follow-up (P1) was estimated by logistic regression model with loss to follow-up (yes/no) as outcomes, including baseline age, sex, body mass index, smoking status, alcohol consumption, systolic blood pressure, use of antihypertensive medication, log-transformed triglycerides, high-density lipoprotein-cholesterol, diabetes, cardiovascular diseases, creatinine-based estimated glomerular filtration rate, and standardized log-transformed NT-proBNP as predictors. Inverse probability weighting-weight was calculated as 1/(1-P1). Then the weight was applied in longitudinal analyses of associations of NT-proBNP with the change in kidney function and incident chronic kidney disease.

Supplementary tables

Table S1. Overview and description of contributing studies/cohorts in BiomarCaRE

Study cohort [Reference]	Country	Study/cohort full name and short description
FINRISK [3]	Finland	The FINRISK study is a series of population-based cardiovascular risk factor surveys carried out every five years in five (or six in 2002) districts of Finland, including North Karelia, Northern Savo (former Kuopio), Southwestern Finland, Oulu Province, Lapland Province (in 2002 only) and the region of Helsinki and Vantaa. A stratified random sample was drawn for each survey from the national population register; the age range was 25-74 years. All individuals enrolled in the study received a physical examination, a self-administered questionnaire, and a blood sample was drawn. For the current analysis, we used only the FINRISK 1997 survey. In 1997, altogether 11500 individuals were invited and 8444 (73%) participated in the clinical examination. The Coordinating Ethics Committee of the Helsinki and Uusimaa Hospital District approved the study, which followed the declaration of Helsinki. All subjects gave written informed consent. https://www.thl.fi/publications/morgam/cohorts/full/finland/fin-fina.htm
Cooperative Health Research in the Region of Augsburg (MONICA/KORA) [4, 5]	Germany	The WHO Multinational Monitoring of Trends and Determinants in Cardiovascular Diseases (MONICA)/Cooperative Health Research in the Region of Augsburg (KORA) cohorts comprise all respondents from representative sample surveys from the city of Augsburg and the less urban Landkreis Augsburg and Landkreis Aichach-Friedberg regions in Bavaria, Southern Germany. List of municipalities and population registers were used as sampling frames for the first and the second stage of two-stage sampling, respectively. The second stage of sampling was stratified by sex and ten-year age group. The Survey 3 (S3) baseline examination (1994-1995) was carried out as part of the WHO MONICA project and consisted of 4856 men and women aged 25-74 years with a response rate of 75%, and 3006 participants were followed up after 10 years (2004-2005, F3). The Survey 4 (S4) baseline examination was carried out in 1999-2001 and includes 4261 participants (response rate: 66%), and 3080 participants were followed up after 7 years (2006-2008, F4) and 2279 participants after 14 years (2013-2014, FF4). The BiomarCaRE project includes 4692 and 4221 participants from S3 and S4, respectively. https://www.thl.fi/publications/morgam/cohorts/full/germany/ger-auga.htm
Moli-sani Study [6]	Italy	The cohort of the Moli-sani Study was recruited in the Molise region from city hall registries by multistage sampling. First, townships were sampled in major areas by cluster sampling; then, within each township, participants aged 35 years or over were selected by simple random sampling. Exclusion criteria were pregnancy at the time of recruitment, lack of understanding, current multiple trauma or coma, or refusal to sign the informed consent. A total of 24325 men (47%) and women (53%) over the age of 35 were examined at baseline from 2005 to 2010. The participation rate was 70%. https://www.thl.fi/publications/morgam/cohorts/full/italy/ita-mola.htm
MONICA Brianza Study [7]	Italy	The MONICA-Brianza Cohort Study is a prospective study of three cohorts of 25-64 years old residents in Brianza, a highly-industrialized area located between Milan and the Swiss border, Northern Italy. Gender- and ten-year age-stratified samples were randomly drawn in 1986, 1990, and 1993, and cardiovascular risk factors were investigated at baseline following the procedures of the WHO MONICA Project. The overall participation rate was 69%. For all subjects' whole blood and serum samples were stored in a biobank. The protocol was approved by the Monza Hospital Ethical Committee. https://www.thl.fi/publications/morgam/cohorts/full/italy/ita-bria.htm

Study cohort [Reference]	Country	Study/cohort full name and short description
Northern Sweden MONICA Study [8]	Sweden	The Northern Sweden MONICA study covered the two northernmost counties of Sweden, i.e., Norrbotten and Västerbotten with altogether 510,000 inhabitants. Population surveys performed in 1986, 1990, 1994, 1999, 2004, and 2009, with altogether 10,517 unique participants, were included in the present study. On the first two occasions, 2,000 persons aged 25 to 64 years were randomly selected, and in the last three surveys, the upper age limit was extended to 74 years, and 2,500 individuals were invited. A stratified randomized selection procedure by age and sex (250 persons in each sex/10-year age stratum) has been used. The participation rate was 69-81%. https://www.thl.fi/publications/morgam/cohorts/full/sweden/swe-nswa.htm https://www.umu.se/forskning/projekt/monica-studien/
Prospective Epidemiological Study of Myocardial Infarction (PRIME) Belfast [9]	United Kingdom	The PRIME/Belfast study examined the classic and putative cardiovascular risk factors to explain the large difference in heart disease incidence in Ireland. The study includes men aged 50-59 from Belfast, Northern Ireland (N=2745). Baseline examinations took place in 1990-1993 and targeted cohorts which had broadly similar social class structures to the background population, initially sampling from industries and various employment groups, employment groups with more than 10% of their workforce of foreign origin were excluded. https://www.thl.fi/publications/morgam/cohorts/full/uk/unk-bela.htm
Scottish Heart Health Extended Cohort (SHHEC) [10]	United Kingdom	This consists of two overlapping studies which share a common protocol and methods: the Scottish Heart Health Study randomly recruited men and women aged 40-59 across 22 Scottish districts in 1984-1987; Scottish MONICA similarly recruited men and women aged 25-64 in Edinburgh and North Glasgow in 1986, and in North Glasgow again in 1989, 1992 (up to 74), and in 1995 as part of the WHO MONICA Project. They are now combined as one cohort. https://www.thl.fi/publications/morgam/cohorts/full/uk/unk-sco.htm

Table S2. Intra-assay and inter-assay coefficients of variation for laboratory measurements in included study cohorts

Study cohort	Creatinine (N = 61830)		Cystatin C (N = 61830)		NT-proBNP (N = 61830)		MR-proADM (N = 9327)[a]		MR-proANP (N = 9499)[a]	
	Intra-assay (%)	Inter-assay (%)	Intra-assay (%)	Inter-assay (%)	Intra-assay (%)	Inter-assay (%)	Intra-assay (%)	Inter-assay (%)	Intra-assay (%)	Inter-assay (%)
FINRISK	0-0.09	2.28-4.69	3.34	1.80-3.31	2.58	1.38	2.17	2.43	3.65	2.33
MONICA/KORA	0.97-2.74	4.22-6.44	1.03-1.17	6.82-7.79	1.17	5.52-9.18				
MATISS	1.20-2.53	4.10-5.4	0.80-2.46	4.60-5.00	3.23	6.30-8.80				
Moli-sani	0.76-1.55	4.56-6.96	4.10-6.2	1.09-1.75	2.30	5.44-6.50				
MONICA_Brianza	0.97	2.36-4.65	1.04	4.04-5.76	2.64	3.28-5.20				
Northern Sweden MONICA	0.67-5.2	5.78-8.07	0.78-2.78	4.10-12.47	1.48	5.88-8.70				
PRIME/Belfast	0-0.09	2.28-4.69	3.34	1.80-3.31	2.58	1.38	2.17	2.43	3.65	2.33
SHHEC[b]	1.25	4.68	NA	NA	1.13-1.17	6.63-6.73				

[a] MR-proADM and MR-proANP are only available in study FINRISK and PRIME/Belfast.

[b] Values of intra-assay and inter-assay of cystatin C are unavailable in SHHEC.

Abbreviations: MR-proADM, mid-regional pro-adrenomedullin; MR-proANP, mid-regional pro-atrial natriuretic peptide; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

Table S3. Baseline characteristics of participants included in the cross-sectional analysis across study cohorts

Characteristics	FINRISK (N = 6858)	MONICA/KORA (N = 5790)	Moli-sani (N = 22243)	MONICA_Brianza (N = 3623)	Northern Sweden MONICA (N = 10414)	PRIME/Belfast (N = 1539)	SHHEC (N = 11363)
	Mean (standard deviation) or number (%)						
Age (years)	48.8 (13.3)	48.0 (13.7)	56.2 (12.0)	46.8 (11.3)	50.0 (13.6)	54.7 (2.9)	49.6 (9.2)
Sex, N (%) female	3588 (52.3)	3071 (53.0)	11938 (53.7)	1939 (53.5)	5668 (54.4)	0 (0.0)	6005 (52.8)
Body mass index (kg/m^2)	26.7 (4.61)	27.2 (7.75)	28.1 (5.18)	26.1 (8.48)	27.4 (7.08)	26.2 (3.46)	26.0 (5.52)
Current Smoker, N (%)	1781 (26.0)	1562 (27.0)	4943 (22.2)	1147 (31.7)	2331 (22.4)	440 (28.6)	5025 (44.2)
Alcohol consumption, N (%)							
No alcohol consumption	2698 (39.3)	1789 (30.9)	6857 (30.8)	1420 (39.2)	3501 (33.6)	627 (40.7)	3373 (29.7)
>0 and <20 g/day	3335 (48.6)	2161 (37.3)	8869 (39.9)	0 (0.0)	6770 (65.0)	341 (22.2)	5525 (48.6)
≥ 20 g/day	825 (12.0)	1840 (31.8)	6517 (29.3)	2203 (60.8)	143 (1.4)	571 (37.1)	2465 (21.7)
Systolic blood pressure (mm Hg)	136.5 (25.0)	131.8 (48.3)	141.4 (24.6)	134.9 (65.9)	130.2 (32.6)	134.5 (30.5)	132.0 (20.4)
Use of antihypertensive medication, N (%)	983 (14.3)	743 (12.8)	6589 (29.6)	397 (11.0)	1352 (13.0)	155 (10.1)	877 (7.7)
Hypertension, N (%)	3132 (45.7)	2052 (35.4)	12613 (56.7)	1300 (35.9)	3616 (34.7)	618 (40.2)	4243 (37.3)
HDL-cholesterol (mmol/L)	1.45 (0.36)	1.49 (0.39)	1.45 (0.34)	1.42 (0.37)	1.47 (0.45)	1.18 (0.33)	1.49 (0.44)
LDL-cholesterol (mmol/L)	3.07 (0.85)	3.47 (0.99)	3.30 (0.86)	3.26 (0.98)	3.72 (1.29)	3.81 (0.87)	3.30 (1.05)
Triglycerides (mmol/L), median [IQR]	1.16 [0.87, 1.56]	1.37 [0.99, 1.90]	1.21 [0.89, 1.66]	1.10 [0.80, 1.54]	1.16 [0.82, 1.68]	1.63 [1.17, 2.36]	1.54 [1.10, 2.16]
Diabetes, N (%)	401 (5.8)	262 (4.5)	1466 (6.6)	94 (2.6)	438 (4.2)	37 (2.4)	192 (1.7)
Cardiovascular diseases, N (%)	433 (6.3)	235 (4.1)	682 (3.1)	64 (1.8)	574 (5.5)	103 (6.7)	472 (4.2)
eGFRcr (ml/min/1.73 m^2)	91.9 (19.4)	102.4 (15.2)	95.7 (14.8)	95.8 (17.6)	102.1 (16.9)	88.3 (19.2)	98.2 (16.3)
CKDcr, N (%)	322 (4.7)	76 (1.3)	583 (2.6)	165 (4.6)	217 (2.1)	122 (7.9)	348 (3.1)
eGFRcys (ml/min/1.73 m^2)	98.8 (19.5)	99.8 (19.7)	85.8 (22.3)	93.7 (20.2)	93.8 (23.8)	83.9 (15.9)	108.4 (17.2)
CKDcys, N (%)	227 (3.3)	218 (3.8)	2860 (12.9)	202 (5.6)	954 (9.2)	81 (5.3)	121 (1.1)
eGFRcr-cys (ml/min/1.73 m^2)	98.4 (18.0)	104.5 (17.0)	93.4 (18.4)	97.3 (18.5)	101.3 (21.9)	88.4 (15.6)	108.2 (16.6)
CKDcr-cys, N (%)	202 (2.9)	79 (1.4)	980 (4.4)	136 (3.8)	382 (3.7)	64 (4.2)	113 (1.0)
NT-proBNP, (pg/ml), median [IQR]	47.4 [24.8, 87.6]	49.2 [26.1, 90.4]	50.3 [26.5, 94.2]	39.4 [20.5, 71.9]	44.5 [23.4, 83.5]	34.5 [19.2, 62.3]	52.3 [28.0, 97.6]
MR-proANP, (pmol/l), median [IQR] [a]	44.2 [33.2, 61.0]	NA	NA	NA	NA	66.8 [52.5, 87.0]	NA
MR-proADM, (nmol/l), median [IQR] [a]	0.47 [0.39, 0.57]	NA	NA	NA	NA	0.45 [0.40, 0.51]	NA

[a] MR-proADM and MR-proANP are only available in study FINRISK and PRIME/Belfast.

Abbreviations: CKD, chronic kidney disease; cr, creatinine-based; cys, cystatin C-based; cr-cys, combined creatinine and cystatin C-based; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; IQR, interquartile range; LDL, low-density lipoprotein; MR-proADM, mid-regional pro-adrenomedullin; MR-proANP, mid-regional pro-atrial natriuretic peptide; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

Table S4. Characteristics of participants with data on MR-proADM and MR-proANP

Characteristics	Total (N = 9503)	FINRISK [a] (N = 7637)	PRIME/Belfast [a] (N = 1866)	*P*-value [b]
	Mean (standard deviation) or number (%)			
Age (years)	49.4 (12.3)	48.1 (13.3)	54.7 (2.9)	<0.001
Sex, N (%) female	3811 (40.1)	3811 (49.9)	0 (0.0)	<0.001
Body mass index (kg/m^2)	26.66 (4.50)	26.74 (4.71)	26.31 (3.49)	<0.001
Current smoker, N (%)	2554 (26.9)	2028 (26.6)	526 (28.2)	0.162
Alcohol consumption, N (%)				<0.001
No alcohol consumption	3711 (39.1)	2946 (38.6)	765 (41.0)	
>0 and <20 g/day	4143 (43.6)	3736 (48.9)	407 (21.8)	
≥ 20 g/day	1649 (17.4)	955 (12.5)	694 (37.2)	
Systolic blood pressure (mm Hg)	136.0 (26.8)	136.3 (24.3)	134.9 (35.0)	0.042
Use of antihypertensive medication, N (%)	1243 (13.1)	1062 (13.9)	181 (9.7)	<0.001
Hypertension, N (%)	4193 (44.1)	3456 (45.3)	737 (39.5)	<0.001
HDL-cholesterol (mmol/L)	1.39 (0.37)	1.44 (0.36)	1.19 (0.34)	<0.001
LDL-cholesterol (mmol/L)	3.23 (0.91)	3.08 (0.86)	3.83 (0.88)	<0.001
Triglycerides (mmol/L), median [IQR]	1.24 [0.91, 1.73]	1.17 [0.88, 1.58]	1.67 [1.19, 2.40]	<0.001
Diabetes, N (%)	484 (5.1)	435 (5.7)	49 (2.6)	<0.001
Cardiovascular diseases, N (%)	574 (6.0)	457 (6.0)	117 (6.3)	0.681
eGFRcr (ml/min/1.73 m^2)	91.3 (19.6)	92.3 (19.5)	87.0 (19.2)	<0.001
eGFRcys (ml/min/1.73 m^2)	96.2 (19.8)	99.2 (19.5)	84.1 (15.9)	<0.001
eGFRcr-cys (ml/min/1.73 m^2)	96.7 (18.1)	98.8 (18.1)	87.9 (15.5)	<0.001
NT-proBNP, (pg/ml), median [IQR]	44.5 [23.7, 82.9]	47.4 [24.8, 87.6]	34.5 [19.2, 62.4]	<0.001
MR-proANP, (pmol/l), median [IQR]	46.8 [33.9, 66.4]	42.8 [32.0, 59.6]	64.8 [50.9, 84.7]	<0.001
MR-proADM, (nmol/l), median [IQR]	0.46 [0.39, 0.55]	0.47 [0.39, 0.56]	0.45 [0.39, 0.51]	<0.001

[a] MR-proADM and MR-proANP are only available in study FINRISK and PRIME/Belfast.

[b] P-value was estimated by t-Test / Mann-Whitney U test (continuous variables) or chi-squared test (categorical variables).

Abbreviations: eGFRcr, creatinine-based estimated glomerular filtration rate; eGFRcys, cystatin C-based eGFR; eGFRcr-cys, combined creatinine and cystatin C-based eGFR; IQR, interquartile range; KORA, Cooperative Health Research in the Region of Augsburg; LDL, low-density lipoprotein; MR-proADM, mid-regional pro-adrenomedullin; MR-proANP, mid-regional pro-atrial natriuretic peptide; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

Table S5. Baseline characteristics of participants from the MONICA/KORA study included in the longitudinal analysis

Characteristics	Total (N = 4167)	Non-cases (N = 3931)	Incident CKDcr (N = 236)	*P*-value [a]
	Mean (standard deviation) or number (%)			
Age (years)	46.5 (12.8)	45.6 (12.4)	61.9 (8.8)	<0.001
Sex, N (%) female	2226 (53.4)	2109 (53.7)	117 (49.6)	0.250
Body mass index (kg/m^2)	26.6 (4.36)	26.4 (4.30)	28.9 (4.65)	<0.001
Current smoker, N (%)	1008 (24.2)	980 (24.9)	28 (11.9)	<0.001
Alcohol consumption, N (%)				0.081
No alcohol consumption	1177 (28.2)	1096 (27.9)	81 (34.3)	
>0 and <20 g/day	1646 (39.5)	1565 (39.8)	81 (34.3)	
≥ 20 g/day	1344 (32.3)	1270 (32.3)	74 (31.4)	
Systolic blood pressure (mm Hg)	126.7 (17.9)	126.1 (17.5)	137.9 (20.8)	<0.001
Use of antihypertensive medication, N (%)	527 (12.6)	412 (10.5)	115 (48.7)	<0.001
Hypertension, N (%)	1315 (31.6)	1159 (29.5)	156 (66.1)	<0.001
HDL-cholesterol (mmol/L)	1.48 (0.44)	1.49 (0.44)	1.43 (0.43)	0.047
LDL-cholesterol (mmol/L)	3.50 (1.06)	3.49 (1.06)	3.78 (1.06)	<0.001
Triglycerides (mmol/L), median [IQR]	1.37 [0.99, 1.92]	1.36 [0.98, 1.92]	1.54 [1.20, 2.09]	<0.001
Diabetes, N (%)	133 (3.2)	99 (2.5)	34 (14.4)	<0.001
Cardiovascular diseases, N (%)	268 (6.4)	219 (5.6)	49 (20.8)	<0.001
eGFRcr (ml/min/1.73 m^2)	102.0 (15.0)	103.1 (14.3)	82.6 (13.2)	<0.001
eGFRcys (ml/min/1.73 m^2)	97.5 (18.1)	98.9 (17.2)	73.9 (16.1)	<0.001
eGFRcr-cys (ml/min/1.73 m^2)	102.7 (15.4)	104.0 (14.5)	80.5 (14.0)	<0.001
NT-proBNP, (pg/ml), median [IQR]	45.9 [25.1, 81.8]	44.5 [24.5, 78.2]	90.6 [47.9, 160.1]	<0.001

[a] P-value was estimated by t-Test / Mann-Whitney U test (continuous variables) or chi-squared test (categorical variables).

Abbreviations: CKDcr, creatinine-based chronic kidney disease; eGFRcr, creatinine-based estimated glomerular filtration rate; eGFRcys, cystatin C-based eGFR; eGFRcr-cys, combined creatinine and cystatin C-based eGFR; IQR, interquartile range; KORA, Cooperative Health Research in the Region of Augsburg; LDL, low-density lipoprotein; MONICA, Monitoring of Trends and Determinants in Cardiovascular Diseases; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

Table S6. Cross-sectional associations of 3 myocardial stress markers with kidney function [a]

Markers	eGFR	Items	Categories of markers				per 1 SD increase in log-transformed
			G1	G2	G3	G4	
NT-proBNP							
		Median, pg/ml	25.4	72.5	169.4	501.2	48.0
		N	30939	21284	7109	2498	61830
	eGFRcr						
		Model 1	Ref.	-0.06 (-0.31, 0.19)	-1.28 (-1.65, -0.90) ***	-7.24 (-7.82, -6.65) ***	-1.07 (-1.19, -0.95) ***
		Model 2	Ref.	-0.10 (-0.35, 0.14)	-1.12 (-1.49, -0.74) ***	-6.92 (-7.51, -6.34) ***	-1.06 (-1.18, -0.93) ***
	eGFRcys						
		Model 1	Ref.	-1.77 (-2.09, -1.45) ***	-5.34 (-5.82, -4.86) ***	-12.5 (-13.2, -11.7) ***	-2.73 (-2.89, -2.57) ***
		Model 2	Ref.	-2.03 (-2.35, -1.72) ***	-5.26 (-5.73, -4.79) ***	-11.9 (-12.6, -11.1) ***	-2.78 (-2.94, -2.63) ***
	eGFRcr-cys						
		Model 1	Ref.	-1.22 (-1.51, -0.94) ***	-4.23 (-4.66, -3.80) ***	-11.7 (-12.4, -11.0) ***	-2.32 (-2.47, -2.18) ***
		Model 2	Ref.	-1.41 (-1.69, -1.14) ***	-4.10 (-4.52, -3.68) ***	-11.2 (-11.8, -10.5) ***	-2.35 (-2.49, -2.21) ***
MR-proANP							
		Median, pmol/l	30.8	53.7	92.8	147.2	46.8
		N	3540	4493	1048	418	9499
	eGFRcr						
		Model 1	Ref.	-1.88 (-2.75, -1.01) ***	-2.90 (-4.26, -1.53) ***	-7.13 (-9.04, -5.22) ***	-1.53 (-1.97, -1.09) ***
		Model 2	Ref.	-1.95 (-2.82, -1.08) ***	-2.78 (-4.16, -1.40) ***	-6.53 (-8.48, -4.57) ***	-1.45 (-1.90, -1.00) ***
	eGFRcys						
		Model 1	Ref.	-1.84 (-2.56, -1.13) ***	-5.94 (-7.06, -4.81) ***	-14.0 (-15.6, -12.4) ***	-3.25 (-3.61, -2.89) ***
		Model 2	Ref.	-2.65 (-3.33, -1.97) ***	-6.79 (-7.88, -5.71) ***	-13.7 (-15.2, -12.1) ***	-3.49 (-3.85, -3.14) ***
	eGFRcr-cys						
		Model 1	Ref.	-2.16 (-2.88, -1.45) ***	-5.30 (-6.43, -4.17) ***	-12.4 (-13.9, -10.8) ***	-2.83 (-3.20, -2.47) ***
		Model 2	Ref.	-2.68 (-3.39, -1.98) ***	-5.74 (-6.86, -4.62) ***	-11.8 (-13.4, -10.2) ***	-2.93 (-3.30, -2.57) ***

Markers	eGFR	Items	Categories of markers				per 1 SD increase in log-transformed
			G1	G2	G3	G4	
MR-proADM							
		Median, nmol/l	0.37	0.50	0.66	0.86	0.46
		N	3492	4397	1029	409	9327
	eGFRcr						
		Model 1	Ref.	-2.61 (-3.43, -1.79) ***	-4.68 (-6.01, -3.35) ***	-10.9 (-12.8, -9.00) ***	-2.72 (-3.12, -2.31) ***
		Model 2	Ref.	-2.85 (-3.69, -2.01) ***	-4.97 (-6.34, -3.60) ***	-11.2 (-13.2, -9.23) ***	-2.88 (-3.32, -2.45) ***
	eGFRcys						
		Model 1	Ref.	-6.98 (-7.61, -6.35) ***	-16.4 (-17.4, -15.4) ***	-27.5 (-29.0, -26.1) ***	-7.35 (-7.66, -7.04) ***
		Model 2	Ref.	-6.22 (-6.85, -5.60) ***	-14.8 (-15.8, -13.7) ***	-25.2 (-26.7, -23.7) ***	-6.77 (-7.10, -6.45) ***
	eGFRcr-cys						
		Model 1	Ref.	-5.55 (-6.20, -4.89) ***	-12.4 (-13.5, -11.4) ***	-22.2 (-23.7, -20.7) ***	-5.84 (-6.17, -5.52) ***
		Model 2	Ref.	-5.24 (-5.90, -4.58) ***	-11.7 (-12.7, -10.6) ***	-21.0 (-22.6, -19.5) ***	-5.60 (-5.94, -5.26) ***

[a] Linear regression was used to estimate beta coefficients and 95% CI of eGFR for G2-4 compared with G1 of makers, as well as for per 1 SD increase in log-transformed markers.
Model 1: adjusted for age, sex, and study cohort;
Model 2: model 1 plus body mass index, smoking status, alcohol consumption, systolic blood pressure, use of antihypertensive medication, high-density lipoprotein cholesterol, log-transformed triglycerides, diabetes, and cardiovascular diseases.
Abbreviations: CI, confidence interval; G, group; eGFR, estimated glomerular filtration rate; eGFRcr, creatinine-based eGFR; eGFRcys, cystatin C-based eGFR; eGFRcr-cys, creatinine and cystatin C-based eGFR; MR-proADM, mid-regional pro-adrenomedullin; MR-proANP, mid-regional pro-atrial natriuretic peptide; NT-proBNP, N-terminal pro-B-type natriuretic peptide; Ref, reference; SD, standard deviation.
* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Table S7. Cross-sectional associations of 3 myocardial stress markers with CKD [a]

Markers	CKD	Items	Categories of markers				per 1 SD increase in log-transformed
			G1	G2	G3	G4	
NT-proBNP		Median, pg/ml	25.4	72.5	169.4	501.2	48.0
	CKDcr	Cases / controls	539 / 30400	543 / 20741	364 / 6745	387 / 2111	1833 / 59997
		Model 1	Ref.	1.11 (0.98, 1.26)	1.60 (1.38, 1.86) ***	4.30 (3.67, 5.05) ***	1.53 (1.45, 1.60) ***
		Model 2	Ref.	1.10 (0.97, 1.25)	1.51 (1.30, 1.76) ***	3.93 (3.33, 4.64) ***	1.49 (1.42, 1.57) ***
	CKDcys	Cases / controls	878 / 30061	1562 / 19722	1310 / 5799	913 / 1585	4663 / 57167
		Model 1	Ref.	1.54 (1.40, 1.69) ***	2.59 (2.33, 2.87) ***	4.91 (4.33, 5.57) ***	1.67 (1.61, 1.73) ***
		Model 2	Ref.	1.63 (1.49, 1.79) ***	2.72 (2.44, 3.04) ***	4.88 (4.28, 5.57) ***	1.68 (1.62, 1.75) ***
	CKDcr-cys	Cases / controls	365 / 30574	530 / 20754	538 / 6571	523 / 1975	1956 / 59874
		Model 1	Ref.	1.35 (1.17, 1.55) ***	2.62 (2.25, 3.06) ***	6.14 (5.22, 7.24) ***	1.84 (1.75, 1.93) ***
		Model 2	Ref.	1.37 (1.19, 1.58) ***	2.56 (2.19, 2.99) ***	5.72 (4.82, 6.78) ***	1.81 (1.72, 1.90) ***
MR-proANP		Median, pmol/l	30.8	53.7	92.8	147.2	46.8
	CKDcr	Cases / controls	110 / 3430	250 / 4243	86 / 962	77 / 341	523 / 8976
		Model 1	Ref.	1.17 (0.91, 1.51)	1.39 (1.00, 1.95)	3.30 (2.30, 4.74) ***	1.37 (1.24, 1.52) ***
		Model 2	Ref.	1.18 (0.92, 1.53)	1.35 (0.96, 1.89)	2.93 (2.01, 4.26) ***	1.31 (1.18, 1.45) ***
	CKDcys	Cases / controls	19 / 3521	119 / 4374	97 / 951	108 / 310	343 / 9156
		Model 1	Ref.	1.83 (1.13, 3.14) *	4.11 (2.46, 7.20) ***	10.4 (6.15, 18.4) ***	2.28 (2.01, 2.58) ***
		Model 2	Ref.	2.05 (1.26, 3.53) **	4.29 (2.54, 7.57) ***	9.87 (5.73, 17.7) ***	2.15 (1.89, 2.45) ***
	CKDcr-cys	Cases / controls	39 / 3501	124 / 4369	58 / 990	79 / 339	300 / 9199
		Model 1	Ref.	1.48 (1.00, 2.21)	2.22 (1.40, 3.57) ***	7.35 (4.63, 11.8) ***	1.92 (1.70, 2.18) ***
		Model 2	Ref.	1.54 (1.05, 2.31) *	2.17 (1.36, 3.50) **	6.39 (3.96, 10.5) ***	1.80 (1.58, 2.05) ***

Markers	CKD	Items	Categories of markers				per 1 SD increase in log-transformed
			G1	G2	G3	G4	
MR-proADM		Median, nmol/l	0.37	0.50	0.66	0.86	0.46
	CKDcr	Cases / controls	123 / 3369	226 / 4171	72 / 957	98 / 311	519 / 8808
		Model 1	Ref.	1.21 (0.96, 1.53)	1.62 (1.16, 2.25) **	7.12 (5.09, 9.95) ***	1.72 (1.57, 1.90) ***
		Model 2	Ref.	1.25 (0.99, 1.60)	1.68 (1.19, 2.37) **	7.29 (5.05, 10.5) ***	1.73 (1.56, 1.92) ***
	CKDcys	Cases / controls	11 / 3481	85 / 4312	100 / 929	144 / 265	340 / 8987
		Model 1	Ref.	4.09 (2.26, 8.17) ***	20.8 (11.2, 42.5) ***	130.2 (68.3, 271.5) ***	5.33 (4.56, 6.27) ***
		Model 2	Ref.	3.96 (2.17, 7.96) ***	19.8 (10.4, 41.2) ***	130.4 (65.7, 280.9) ***	5.42 (4.57, 6.45) ***
	CKDcr-cys	Cases / controls	32 / 3460	98 / 4299	58 / 971	108 / 301	296 / 9031
		Model 1	Ref.	1.86 (1.25, 2.84) **	4.52 (2.83, 7.35) ***	28.8 (18.1, 46.8) ***	2.93 (2.59, 3.32) ***
		Model 2	Ref.	2.02 (1.35, 3.12) ***	5.04 (3.08, 8.36) ***	34.6 (20.8, 58.6) ***	3.04 (2.65, 3.48) ***

[a] Logistic regression was used to estimate OR and 95% CI of prevalent CKD for G2-4 compared with G1 of makers, as well as for per 1 SD increase in log-transformed markers.
Model 1: adjusted for age, sex, and study cohort;
Model 2: model 1 plus body mass index, smoking status, alcohol consumption, systolic blood pressure, use of antihypertensive medication, high-density lipoprotein cholesterol, log-transformed triglycerides, diabetes, and cardiovascular diseases.

Abbreviations: CI, confidence interval; CKD, chronic kidney disease; CKDcr, creatinine-based CKD; CKDcys, cystatin C-based CKD; CKDcr-cys, creatinine and cystatin C-based CKD; G, group; MR-proADM, mid-regional pro-adrenomedullin; MR-proANP, mid-regional pro-atrial natriuretic peptide; NT-proBNP, N-terminal pro-B-type natriuretic peptide; OR, odds ratio; Ref, reference; SD, standard deviation.

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Table S8. Sensitivity analysis of cross-sectional associations of 3 myocardial stress markers with CKD [a]

Markers	**Items**	**Categories of markers**				**per 1 SD increase in log-transformed**
		G1	**G2**	**G3**	**G4**	
NT-proBNP						
	Median, pg/ml	25.3	72.0	167.7	489.5	45.7
	Cases / controls	154 / 29680	219 / 19406	230 / 5669	294 / 1498	897 / 56253
	Model 2	Ref.	1.41 (1.14, 1.76) **	2.87 (2.27, 3.63) ***	9.22 (7.24, 11.8) ***	2.19 (2.04, 2.35) ***
MR-proANP						
	Median, pmol/l	30.8	53.5	92.8	146.3	45.9
	Cases / controls	6 / 3417	27 / 4152	29 / 895	50 / 286	112 / 8750
	Model 2	Ref.	1.41 (0.59, 3.91)	3.81 (1.55, 10.9) **	13.6 (5.53, 39.3) ***	2.75 (2.21, 3.44) ***
MR-proADM						
	Median, nmol/l	0.37	0.49	0.66	0.86	0.46
	Cases / controls	3 / 3361	17 / 4104	19 / 876	73 / 244	112 / 8585
	Model 2	Ref.	3.34 (1.10, 14.5)	17.6 (5.28, 80.6) ***	285.9 (85.7, 1331.4) ***	8.21 (6.17, 11.2) ***

[a] CKD cases were redefined as all 3 eGFR < 60 ml/min per $1.73m^2$ and non-cases were redefined as all 3 eGFR ≥ 60 ml/min per $1.73m^2$. Logistic regression was used to estimate OR and 95% CI of prevalent CKD for G2-4 compared with G1 of makers, as well as for per 1 SD increase in log-transformed markers.

Model 2: adjusted for age, sex, study cohort, body mass index, smoking status, alcohol consumption, systolic blood pressure, use of antihypertensive medication, high-density lipoprotein cholesterol, log-transformed triglycerides, diabetes, and cardiovascular diseases.

Abbreviations: CI, confidence interval; CKD, chronic kidney disease; CKDcr, creatinine-based CKD; CKDcys, cystatin C-based CKD; CKDcr-cys, creatinine and cystatin C-based CKD; eGFR, estimated glomerular filtration rate; G, group; MR-proADM, mid-regional pro-adrenomedullin; MR-proANP, mid-regional pro-atrial natriuretic peptide; NT-proBNP, N-terminal pro-B-type natriuretic peptide; OR, odds ratio; Ref, reference; SD, standard deviation.

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Table S9. Longitudinal associations of NT-proBNP with incident CKD [a]

Incident CKD	Items	Categories of NT-proBNP				per 1 SD increase in log-transformed
		G1	G2	G3	G4	
Incident CKDcr						
	Median, pg/ml	25.7	72.2	166.2	477.6	45.9
	Cases / person-year	59 / 24335	98 / 16289	54 / 4598	25 / 814	236 / 46036
	Model 1	Ref.	1.38 (1.02, 1.87) *	1.41 (0.99, 2.01)	3.91 (2.58, 5.92) ***	1.45 (1.28, 1.63) ***
	Model 2	Ref.	1.27 (0.94, 1.72)	1.13 (0.79, 1.61)	2.59 (1.66, 4.04) ***	1.26 (1.12, 1.42) ***
	Model 3	Ref.	1.09 (0.80, 1.48)	1.14 (0.79, 1.63)	1.86 (1.15, 3.01) *	1.16 (1.01, 1.32) *
Incident CKDcys						
	Median, pg/ml	25.2	72.4	162.5	503.1	45.9
	Cases / person-year	73 / 16118	109 / 10774	69 / 2933	22 / 456	273 / 30280
	Model 1	Ref.	1.22 (0.93, 1.60)	1.58 (1.16, 2.15) **	3.53 (2.25, 5.53) ***	1.44 (1.27, 1.62) ***
	Model 2	Ref.	1.22 (0.94, 1.59)	1.42 (1.04, 1.93) *	3.06 (1.95, 4.79) ***	1.33 (1.19, 1.49) ***
	Model 3	Ref.	1.16 (0.89, 1.52)	1.16 (0.83, 1.63)	1.87 (1.19, 2.95) **	1.17 (1.04, 1.32) **
Incident CKDcr-cys						
	Median, pg/ml	25.3	72.6	161.9	509.2	46.8
	Cases / person-year	40 / 16225	67 / 10954	50 / 3131	22 / 546	179 / 30856
	Model 1	Ref.	1.30 (0.92, 1.83)	1.72 (1.17, 2.52) **	5.31 (3.30, 8.55) ***	1.53 (1.33, 1.76) ***
	Model 2	Ref.	1.24 (0.87, 1.75)	1.50 (0.99, 2.29)	4.40 (2.63, 7.36) ***	1.39 (1.20, 1.62) ***
	Model 3	Ref.	1.01 (0.69, 1.49)	1.23 (0.81, 1.85)	2.59 (1.55, 4.34) ***	1.21 (1.02, 1.43) *

[a] Interval-censored Cox regression was used to estimate HR and 95% CI (1000 bootstrap samples for 95% CI estimation) of incident CKD for G2-4 compared with G1 of NT-proBNP, as well as for per 1 SD increase in log-transformed NT-proBNP. A total of 4167 participants free of CKDcr, 2557 free of CKDcys, and 2621 free of CKDcr-cys at baseline were included in these analyses.

Please refer to the footnote of Table 4 for detailed information on Model 1, Model 2, and Model 3.

Abbreviations: CI, confidence interval; CKD, chronic kidney disease; CKDcr, creatinine-based CKD; CKDcys, cystatin C-based CKD; CKDcr-cys, creatinine and cystatin C-based CKD; G, group; HR, hazard ratio; NT-proBNP, N-terminal pro-B-type natriuretic peptide; Ref, reference; SD, standard deviation.

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Table S10. Cross-sectional associations of NT-proBNP with kidney function stratified by CVD and diabetes

Stratified factors	Items	Categories of NT-proBNP				per 1 SD increase in log-transformed	P-interaction [a]
		G1	G2	G3	G4		
Non-CVD							
	Median, pg/ml	25.3	72.3	167.7	474.2	46.6	
	N	30411	20554	6401	1901	59267	
	eGFRcr	Ref.	-0.08 (-0.32, 0.17)	-0.97 (-1.35, -0.58) ***	-6.54 (-7.18, -5.90) ***	-0.87 (-0.99, -0.74) ***	< 0.001
	eGFRcys	Ref.	-2.02 (-2.33, -1.70) ***	-5.12 (-5.61, -4.63) ***	-11.0 (-11.8, -10.2) ***	-2.56 (-2.73, -2.40) ***	< 0.001
	eGFRcr-cys	Ref.	-1.40 (-1.68, -1.12) ***	-3.94 (-4.38, -3.51) ***	-10.5 (-11.2, -9.77) ***	-2.13 (-2.27, -1.98) ***	< 0.001
CVD							
	Median, pg/ml	27.4	81.0	187.9	579.7	128.7	
	N	528	730	708	597	2563	
	eGFRcr	Ref.	-1.09 (-2.88, 0.69)	-3.09 (-4.94, -1.23) **	-9.00 (-11.0, -7.02) ***	-3.13 (-3.66, -2.59) ***	
	eGFRcys	Ref.	-3.85 (-5.83, -1.88) ***	-7.76 (-9.81, -5.71) ***	-15.7 (-17.9, -13.5) ***	-5.09 (-5.68, -4.51) ***	
	eGFRcr-cys	Ref.	-2.93 (-4.82, -1.04) **	-6.53 (-8.50, -4.57) ***	-14.4 (-16.5, -12.3) ***	-4.76 (-5.32, -4.20) ***	
Non-diabetes							
	Median, pg/ml	25.3	72.4	168.9	486.4	47.2	
	N	29899	20329	6571	2141	58940	
	eGFRcr	Ref.	-0.06 (-0.31, 0.19)	-0.91 (-1.29, -0.53) ***	-6.37 (-6.99, -5.75) ***	-0.88 (-1.01, -0.75) ***	< 0.001
	eGFRcys	Ref.	-1.96 (-2.28, -1.65) ***	-5.00 (-5.48, -4.52) ***	-11.4 (-12.2, -10.6) ***	-2.63 (-2.79, -2.47) ***	< 0.001
	eGFRcr-cys	Ref.	-1.35 (-1.63, -1.07) ***	-3.83 (-4.26, -3.40) ***	-10.6 (-11.3, -9.93) ***	-2.17 (-2.31, -2.03) ***	< 0.001
Diabetes							
	Median, pg/ml	26.4	75.3	178.9	564.2	70.2	
	N	1040	955	538	357	2890	
	eGFRcr	Ref.	-0.94 (-2.34, 0.46)	-4.14 (-5.90, -2.39) ***	-11.1 (-13.2, -9.04) ***	-3.26 (-3.81, -2.71) ***	
	eGFRcys	Ref.	-3.97 (-5.91, -2.03) ***	-9.23 (-11.7, -6.80) ***	-16.3 (-19.1, -13.4) ***	-4.81 (-5.57, -4.05) ***	
	eGFRcr-cys	Ref.	-3.06 (-4.72, -1.39) ***	-8.11 (-10.2, -6.02) ***	-15.9 (-18.4, -13.5) ***	-4.67 (-5.33, -4.02) ***	

[a] Interaction terms of standardized log-transformed markers with CVD or diabetes were included in model 2 described in Table S6 to test the significance of interaction.

Abbreviations: CVD, cardiovascular disease; G, group; eGFR, estimated glomerular filtration rate; eGFRcr, creatinine-based eGFR; eGFRcys, cystatin C-based eGFR; eGFRcr-cys, creatinine and cystatin C-based eGFR; NT-proBNP, N-terminal pro-B-type natriuretic peptide; Ref, reference; SD, standard deviation; * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Table S11. Cross-sectional associations of MR-proANP with kidney function stratified by CVD and diabetes

Stratified factors	Items	Categories of MR-proANP				per 1 SD increase in log-transformed	P-interaction [a]
		G1	G2	G3	G4		
Non-CVD							
	Median, pmol/l	30.8	53.5	92.2	143.2	45.7	
	N	3469	4265	895	296	8925	
	eGFRcr	Ref.	-2.14 (-3.02, -1.26) ***	-2.36 (-3.81, -0.91) **	-6.04 (-8.24, -3.83) ***	-1.27 (-1.75, -0.80) ***	0.013
	eGFRcys	Ref.	-2.77 (-3.46, -2.09) ***	-6.68 (-7.81, -5.54) ***	-13.2 (-15.0, -11.5) ***	-3.33 (-3.70, -2.96) ***	< 0.001
	eGFRcr-cys	Ref.	-2.87 (-3.58, -2.15) ***	-5.46 (-6.64, -4.29) ***	-11.4 (-13.2, -9.65) ***	-2.76 (-3.15, -2.38) ***	< 0.001
CVD							
	Median, pmol/l	33.1	59.8	97.0	163.0	76.3	
	N	71	228	153	122	574	
	eGFRcr	Ref.	3.37 (-1.72, 8.47)	-2.36 (-7.93, 3.21)	-4.41 (-10.4, 1.57)	-2.62 (-4.10, -1.15) ***	
	eGFRcys	Ref.	0.66 (-3.73, 5.05)	-5.15 (-9.95, -0.35) *	-11.4 (-16.6, -6.25) ***	-4.43 (-5.70, -3.17) ***	
	eGFRcr-cys	Ref.	2.32 (-2.02, 6.66)	-4.36 (-9.10, 0.38)	-8.85 (-13.9, -3.75) ***	-3.98 (-5.23, -2.72) ***	
Non-diabetes							
	Median, pmol/l	30.8	53.6	92.7	147.0	46.5	
	N	3402	4278	966	369	9015	
	eGFRcr	Ref.	-2.07 (-2.96, -1.18) ***	-2.80 (-4.24, -1.37) ***	-5.87 (-7.94, -3.80) ***	-1.34 (-1.81, -0.87) ***	0.049
	eGFRcys	Ref.	-2.52 (-3.21, -1.82) ***	-6.41 (-7.53, -5.30) ***	-13.0 (-14.6, -11.4) ***	-3.29 (-3.65, -2.92) ***	< 0.001
	eGFRcr-cys	Ref.	-2.67 (-3.39, -1.95) ***	-5.54 (-6.70, -4.39) ***	-11.1 (-12.8, -9.47) ***	-2.76 (-3.14, -2.39) ***	< 0.001
Diabetes							
	Median, pmol/l	30.7	56.2	94.1	148.0	55.3	
	N	138	215	82	49	484	
	eGFRcr	Ref.	0.56 (-3.15, 4.26)	-1.68 (-6.71, 3.35)	-11.4 (-17.3, -5.39) ***	-2.67 (-4.16, -1.19) ***	
	eGFRcys	Ref.	-5.19 (-8.89, -1.49) **	-12.3 (-17.3, -7.27) ***	-21.1 (-27.1, -15.2) ***	-5.95 (-7.41, -4.49) ***	
	eGFRcr-cys	Ref.	-2.95 (-6.45, 0.56)	-8.27 (-13.0, -3.52) ***	-18.2 (-23.8, -12.5) ***	-4.92 (-6.31, -3.54) ***	

[a] Interaction terms of standardized log-transformed markers with CVD or diabetes were included in model 2 described in Table S6 to test the significance of interaction.

Abbreviations: CVD, cardiovascular disease; G, group; eGFR, estimated glomerular filtration rate; eGFRcr, creatinine-based eGFR; eGFRcys, cystatin C-based eGFR; eGFRcr-cys, creatinine and cystatin C-based eGFR; MR-proANP, mid-regional pro-atrial natriuretic peptide; Ref, reference; SD, standard deviation; * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Table S12. Cross-sectional associations of MR-proADM with kidney function stratified by CVD and diabetes

Stratified factors	Items	Categories of MR-proADM				per 1 SD increase in log-transformed	P-interaction [a]
		G1	G2	G3	G4		
Non-CVD	Median, nmol/l	0.37	0.49	0.66	0.86	0.46	
	N	3410	4130	892	326	8758	
	eGFRcr	Ref.	-2.74 (-3.59, -1.88) ***	-4.82 (-6.26, -3.37) ***	-10.1 (-12.3, -8.01) ***	-2.68 (-3.14, -2.23) ***	0.004
	eGFRcys	Ref.	-6.29 (-6.93, -5.66) ***	-14.4 (-15.5, -13.3) ***	-24.9 (-26.5, -23.3) ***	-6.57 (-6.91, -6.23) ***	< 0.001
	eGFRcr-cys	Ref.	-5.22 (-5.89, -4.55) ***	-11.4 (-12.5, -10.2) ***	-20.3 (-22.0, -18.6) ***	-5.38 (-5.74, -5.02) ***	< 0.001
CVD	Median, nmol/l	0.39	0.52	0.68	0.86	0.57	
	N	82	267	137	83	569	
	eGFRcr	Ref.	-5.93 (-10.4, -1.47) **	-8.50 (-13.7, -3.26) **	-18.4 (-24.5, -12.3) ***	-5.18 (-6.82, -3.55) ***	
	eGFRcys	Ref.	-5.62 (-9.21, -2.02) **	-17.5 (-21.7, -13.3) ***	-26.0 (-30.9, -21.1) ***	-9.04 (-10.3, -7.75) ***	
	eGFRcr-cys	Ref.	-6.58 (-10.2, -2.96) ***	-15.1 (-19.3, -10.8) ***	-25.4 (-30.4, -20.5) ***	-8.17 (-9.47, -6.87) ***	
Non-diabetes	Median, nmol/l	0.37	0.49	0.66	0.86	0.46	
	N	3386	4185	938	342	8851	
	eGFRcr	Ref.	-2.72 (-3.58, -1.87) ***	-4.85 (-6.28, -3.42) ***	-10.2 (-12.3, -8.08) ***	-2.65 (-3.11, -2.20) ***	0.002
	eGFRcys	Ref.	-6.16 (-6.79, -5.52) ***	-14.7 (-15.7, -13.6) ***	-24.6 (-26.1, -23.0) ***	-6.57 (-6.90, -6.23) ***	< 0.001
	eGFRcr-cys	Ref.	-5.13 (-5.80, -4.46) ***	-11.5 (-12.6, -10.4) ***	-20.2 (-21.8, -18.5) ***	-5.36 (-5.72, -5.01) ***	< 0.001
Diabetes	Median, nmol/l	0.36	0.51	0.68	0.87	0.53	
	N	106	212	91	67	476	
	eGFRcr	Ref.	-6.21 (-10.2, -2.17) **	-8.40 (-13.6, -3.23) **	-19.9 (-25.6, -14.1) ***	-6.16 (-7.65, -4.67) ***	
	eGFRcys	Ref.	-8.32 (-12.2, -4.50) ***	-17.8 (-22.7, -12.9) ***	-30.8 (-36.2, -25.3) ***	-9.68 (-11.1, -8.31) ***	
	eGFRcr-cys	Ref.	-8.35 (-12.0, -4.71) ***	-15.4 (-20.0, -10.7) ***	-28.7 (-33.8, -23.5) ***	-8.99 (-10.3, -7.68) ***	

[a] Interaction terms of standardized log-transformed markers with CVD or diabetes were included in model 2 described in Table S6 to test the significance of interaction.

Abbreviations: CVD, cardiovascular disease; G, group; eGFR, estimated glomerular filtration rate; eGFRcr, creatinine-based eGFR; eGFRcys, cystatin C-based eGFR; eGFRcr-cys, creatinine and cystatin C-based eGFR; MR-proADM, mid-regional pro-adrenomedullin; Ref, reference; SD, standard deviation; * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Table S13. Sensitivity analysis of cross-sectional associations of 3 myocardial stress markers with eGFRcr-cys and CKDcr-cys [a]

eGFR / CKD	**Markers**	**Categories of markers**				**per 1 SD increase in log-transformed**
		G1	**G2**	**G3**	**G4**	
eGFRcr-cys						
		Beta coefficient (95% CI)				
	NT-proBNP	Ref.	-1.51 (-1.79, -1.24) ***	-4.31 (-4.73, -3.89) ***	-11.5 (-12.1, -10.8) ***	-2.44 (-2.58, -2.30) ***
	MR-proANP	Ref.	-2.68 (-3.38, -1.97) ***	-5.72 (-6.85, -4.60) ***	-11.8 (-13.4, -10.2) ***	-2.93 (-3.29, -2.56) ***
	MR-proADM	Ref.	-5.24 (-5.90, -4.58) ***	-11.6 (-12.7, -10.6) ***	-21.0 (-22.6, -19.5) ***	-5.60 (-5.94, -5.25) ***
CKDcr-cys						
		Odds ratio (95% CI)				
	NT-proBNP	Ref.	1.38 (1.19, 1.59) ***	2.58 (2.21, 3.01) ***	5.77 (4.87, 6.85) ***	1.81 (1.72, 1.90) ***
	MR-proANP	Ref.	1.54 (1.05, 2.31) *	2.17 (1.36, 3.50) **	6.40 (3.96, 10.5) ***	1.80 (1.58, 2.05) ***
	MR-proADM	Ref.	2.02 (1.35, 3.11) ***	5.04 (3.08, 8.36) ***	34.6 (20.8, 58.7) ***	3.04 (2.66, 3.49) ***

[a] Sensitivity analyses were conducted to test the robustness of the results by further adjusting for low-density lipoprotein cholesterol in model 2, as described in Table 2 and Table 3. These sensitivity analyses were limited to eGFRcr-cys and CKDcr-cys. Data from 61830 participants for NT-proBNP, 9499 for MR-proANP, and 9327 for MR-proADM were included in these analyses.

Abbreviations: CI, confidence interval; CKDcr-cys, creatinine and cystatin C-based chronic kidney disease; G, group; eGFRcr-cys, creatinine and cystatin C-based estimated glomerular filtration rate; MR-proADM, mid-regional pro-adrenomedullin; MR-proANP, mid-regional pro-atrial natriuretic peptide; NT-proBNP, N-terminal pro-B-type natriuretic peptide; Ref, reference; SD, standard deviation.

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Table S14. Sensitivity analysis of longitudinal associations of NT-proBNP with change in eGFRcr-cys and incident CKDcr-cys [a]

eGFR / CKD	Items	Categories of NT-proBNP				per 1 SD increase in log-transformed
		G1	G2	G3	G4	
Change in eGFRcr-cys						
		Beta coefficient (95% CI)				
	Model 2 + LDL-C	Ref.	-1.05 (-1.88, -0.21) *	-3.24 (-4.53, -1.94) ***	-7.02 (-9.66, -4.39) ***	-1.33 (-1.73, -0.93) ***
	Model 3 + LDL-C	Ref.	-1.14 (-2.07, -0.20) *	-3.55 (-4.98, -2.12) ***	-7.97 (-10.9, -5.08) ***	-1.50 (-1.94, -1.06) ***
Incident CKDcr-cys						
		Hazard ratio (95% CI)				
	Model 2 + LDL-C	Ref.	1.18 (0.83, 1.68)	1.43 (0.93, 2.19)	4.40 (2.66, 7.29) ***	1.39 (1.20, 1.61) ***
	Model 3 + LDL-C	Ref.	0.98 (0.68, 1.42)	1.17 (0.75, 1.83)	2.60 (1.52, 4.47) ***	1.21 (1.03, 1.42) *

[a] Sensitivity analyses were conducted to test the robustness of the results by further adjusting for low-density lipoprotein cholesterol in model 2 and model 3, as described in Table 4 and Table S9. These sensitivity analyses were limited to the 10-year change in eGFRcr-cys and incident CKDcr-cys. A total of 2651 participants with 7061 observations were included for the analysis with change in eGFRcr-cys and 2621 free of CKDcr-cys at baseline were included for the analysis with incident CKDcr-cys.

Abbreviations: CI, confidence interval; CKDcr-cys, creatinine and cystatin C-based chronic kidney disease; G, group; eGFRcr-cys, creatinine and cystatin C-based estimated glomerular filtration rate; LDL-C, low-density lipoprotein cholesterol; NT-proBNP, N-terminal pro-B-type natriuretic peptide; Ref, reference; SD, standard deviation.

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Table S15. E-values to assess the robustness of observed associations to potential unmeasured or uncontrolled confounders [a]

eGFR / CKD	Markers	Cases / controls	per 1 SD increase in log-transformed	E-values [b]	
				Point estimate	Lower limit
Prevalent CKDcr-cys					
			OR (95% CI)	**OR**	
	NT-proBNP	1956 / 59874	1.81 (1.72, 1.90) ***	3.02	2.83
	MR-proANP	300 / 9199	1.80 (1.58, 2.05) ***	3.00	2.54
	MR-proADM	296 / 9031	3.04 (2.65, 3.48) ***	5.53	4.74
Incident CKDcr-cys					
			HR (95% CI)	**HR**	
	NT-proBNP	179 / 2621	1.39 (1.20, 1.62) ***	2.13	1.69

[a] To assess the robustness of associations observed in our analyses to potential unmeasured or uncontrolled confounding, E-values were calculated [11, 12]. The E-value is defined as the minimum strength of association on the risk ratio scale that an unmeasured confounder would need to have with both exposure and outcome to fully explain away a specific exposure-outcome association, conditional on the measured covariates. In simpler terms, the E-value indicates how strongly an unmeasured confounder would have to be to fully account for the observed association. A large E-value (e.g., > 2) implies that considerable unmeasured confounding would be needed to explain away an effect estimate. In contrast, a small E-value implies that little unmeasured confounding would be needed to explain away an effect estimate.

[b] Results of per 1 SD increase in log-transformed markers based on model 2 as described in Table 2 and Table S9 were used to calculate E-values. E-value (point estimate) was calculated using the estimated OR (e.g., 1.81 for NT-proBNP with prevalent CKDcr-cys) based on the formula: Point estimate = OR + sqrt (OR * (OR - 1)). Similarly, E-value (lower limit) was calculated based on the same formula using the lower limit of 95% CI. The E-value for HR was calculated in a similar way as for the OR. The minimum point estimate is 2.13 in these calculations, which means that an unmeasured confounder would need to be associated with both exposure and outcome by a risk ratio of more than 2.13-fold each, above and beyond the measured confounders, to explain away the observed association. These E-values suggest that our results were robust to potential unmeasured confounding.

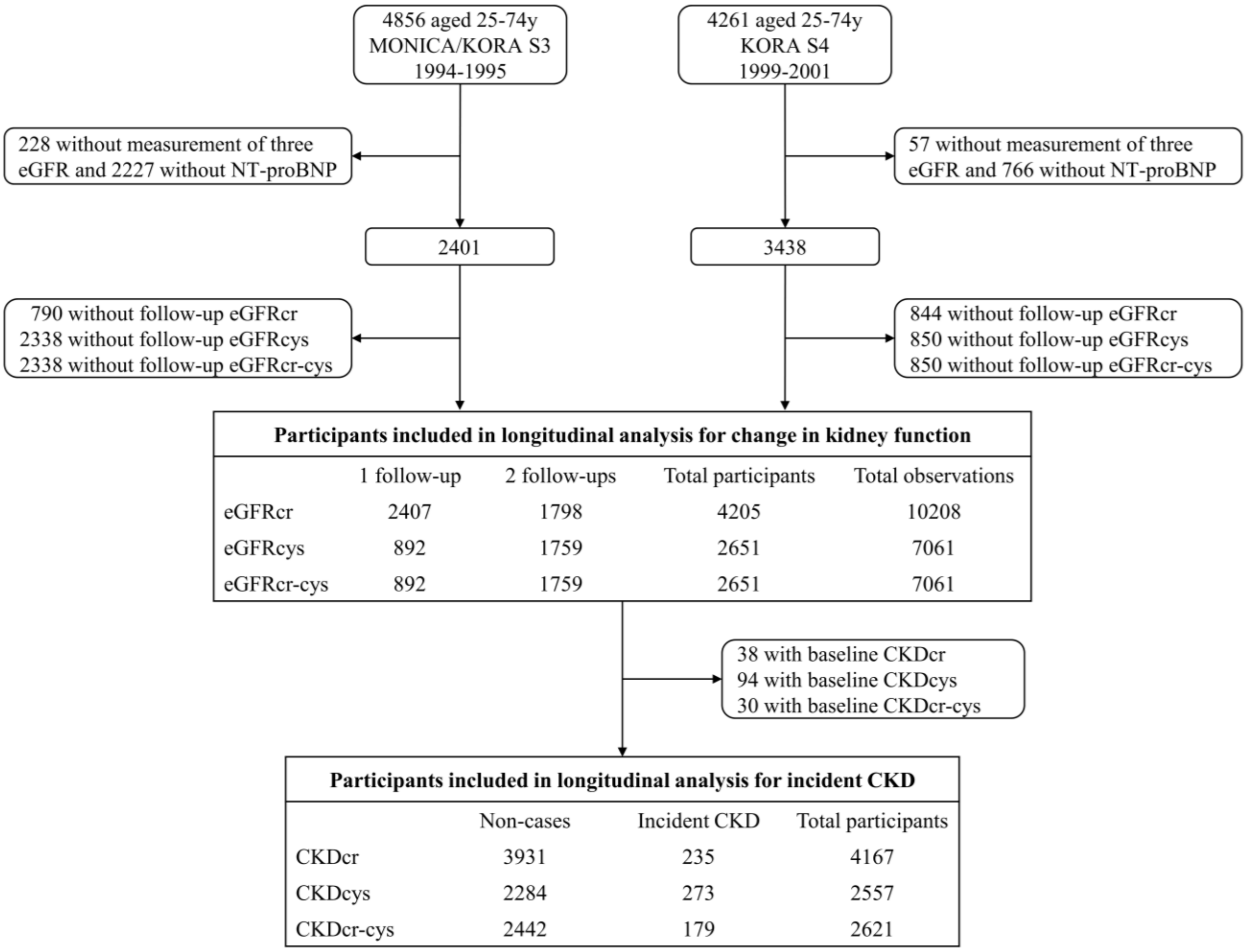
Abbreviations: CI, confidence interval; CKDcr-cys, creatinine and cystatin C-based chronic kidney disease; HR, hazard ratio; MR-proADM, mid-regional pro-adrenomedullin; MR-proANP, mid-regional pro-atrial natriuretic peptide; NT-proBNP, N-terminal pro-B-type natriuretic peptide; OR, odds ratio; Ref, reference; SD, standard deviation.

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Supplementary figures

Figure S1. Flowchart of study participants from the MONICA/KORA study included in the longitudinal analysis.

Abbreviations: CKD, chronic kidney disease; cr, creatinine-based; cys, cystatin C-based; cr-cys, combined creatinine and cystatin C-based; eGFR, estimated glomerular filtration rate; KORA, Cooperative Health Research in the Region of Augsburg; MONICA, Monitoring of Trends and Determinants in Cardiovascular Diseases; NT-proBNP, N-terminal pro-B-type natriuretic peptide.



Participants included in longitudinal analysis for change in kidney function

	1 follow-up	2 follow-ups	Total participants	Total observations
eGFRcr	2407	1798	4205	10208
eGFRcys	892	1759	2651	7061
eGFRcr-cys	892	1759	2651	7061

Participants included in longitudinal analysis for incident CKD

	Non-cases	Incident CKD	Total participants
CKDcr	3931	235	4167
CKDcys	2284	273	2557
CKDcr-cys	2442	179	2621

Figure S2. Cross-sectional associations of 3 myocardial stress markers with kidney function. Linear regression was used to estimate beta coefficients and 95% CI of eGFR across G2-4 compared with G1 of markers. Detailed information on adjusted models is described in Table 2. Data from 61830 participants for NT-proBNP, 9499 for MR-proANP, and 9327 for MR-proADM were included in these analyses.

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; eGFRcr, creatinine-based eGFR; eGFRcys, cystatin C-based eGFR; eGFRcr-cys, creatinine and cystatin C-based eGFR; G, group; MR-proADM, mid-regional pro-adrenomedullin; MR-proANP, mid-regional pro-atrial natriuretic peptide; NT-proBNP, N-terminal pro-B-type natriuretic peptide; * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

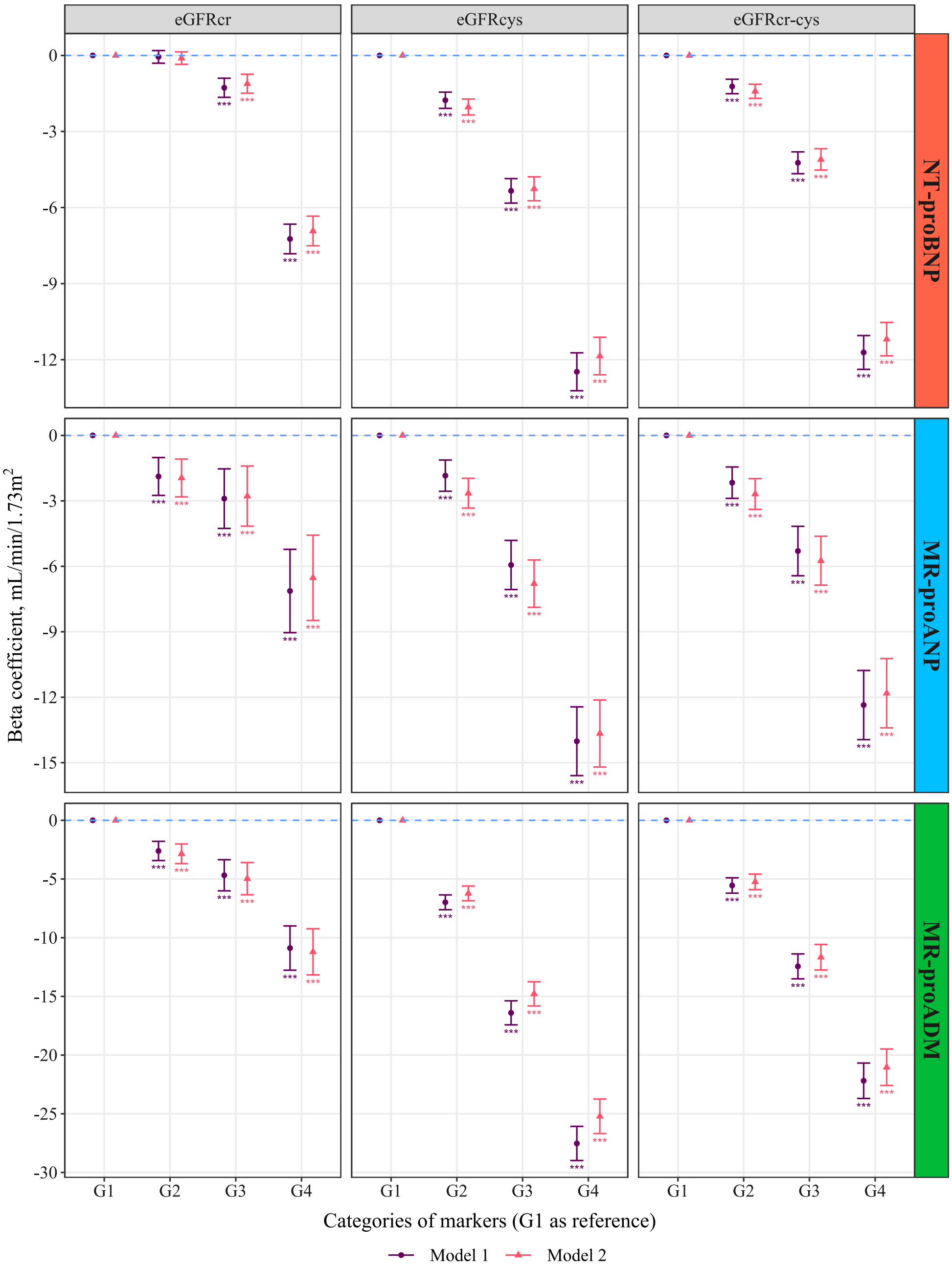


Figure S3. Cross-sectional associations of 3 myocardial stress markers with CKD. Logistic regression was used to estimate odds ratios and 95% CI of prevalent CKD across G2-4 compared with G1 of markers. Detailed information on adjusted models is described in Table 3. Data from 61830 participants for NT-proBNP, 9499 for MR-proANP, and 9327 for MR-proADM were included in these analyses.

Abbreviations: CI, confidence interval; CKD, chronic kidney disease; CKDcr, creatinine-based CKD; CKDcys, cystatin C-based CKD; CKDcr-cys, creatinine and cystatin C-based CKD; G, group; MR-proADM, mid-regional pro-adrenomedullin; MR-proANP, mid-regional pro-atrial natriuretic peptide; NT-proBNP, N-terminal pro-B-type natriuretic peptide; * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

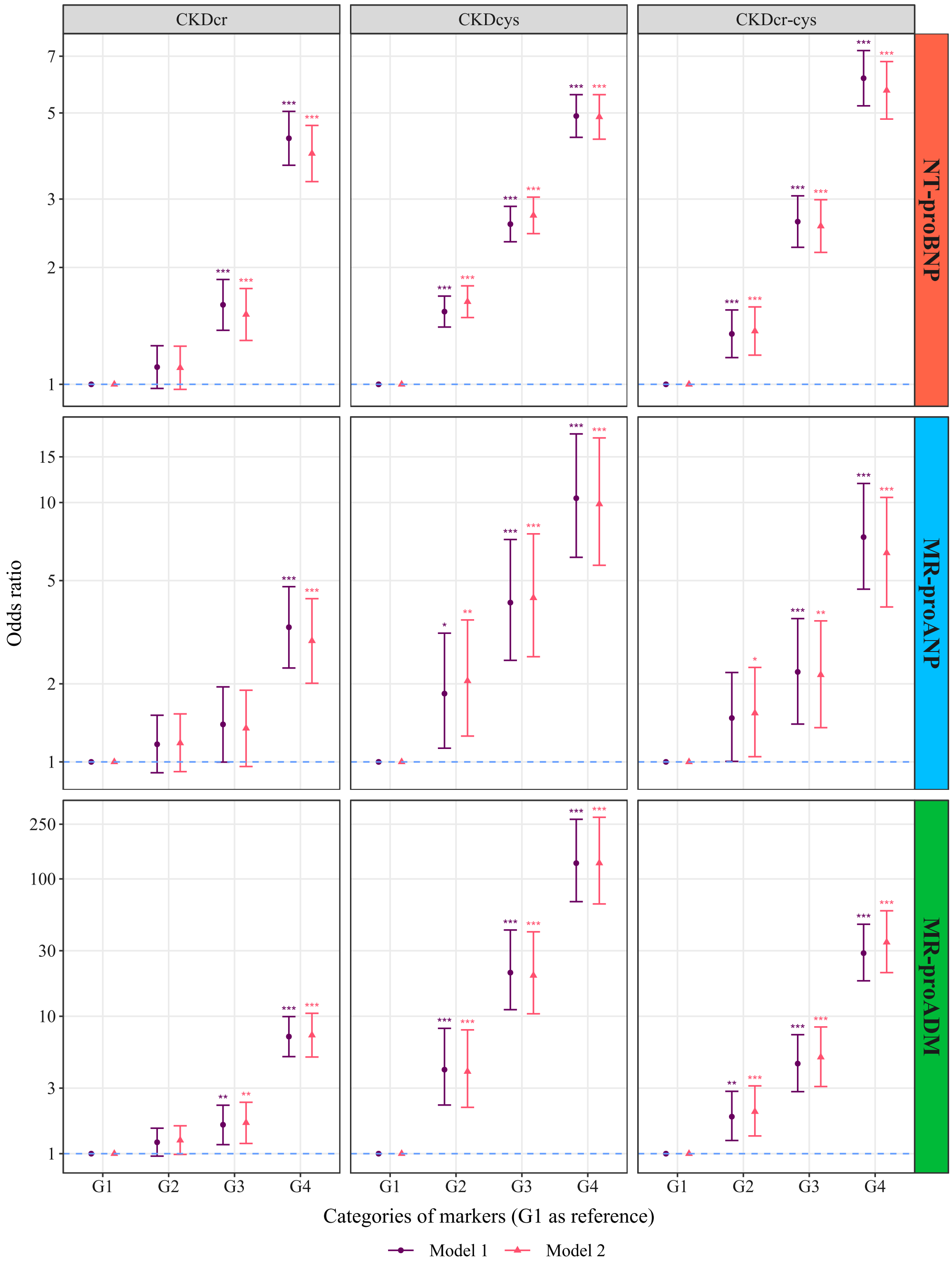


Figure S4. Sensitivity analysis of cross-sectional associations of 3 myocardial stress markers with CKD. CKD cases were redefined as all 3 eGFR < 60 ml/min per $1.73m^2$ and non-cases were redefined as all 3 eGFR ≥ 60 ml/min per $1.73m^2$. Logistic regression was used to estimate odds ratio and 95% CI of prevalent CKD per 1 SD increase in log-transformed markers. Detailed information on adjusted models is described in Table S8. Data from 57150 participants for NT-proBNP, 8862 for MR-proANP, and 8697 for MR-proADM were included in these analyses.

Abbreviations: CI, confidence interval; CKD, chronic kidney disease; CKDcr, creatinine-based CKD; CKDcys, cystatin C-based CKD; CKDcr-cys, creatinine and cystatin C-based CKD; eGFR, estimated glomerular filtration rate; MR-proADM, mid-regional pro-adrenomedullin; MR-proANP, mid-regional pro-atrial natriuretic peptide; NT-proBNP, N-terminal pro-B-type natriuretic peptide; SD, standard deviation; * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

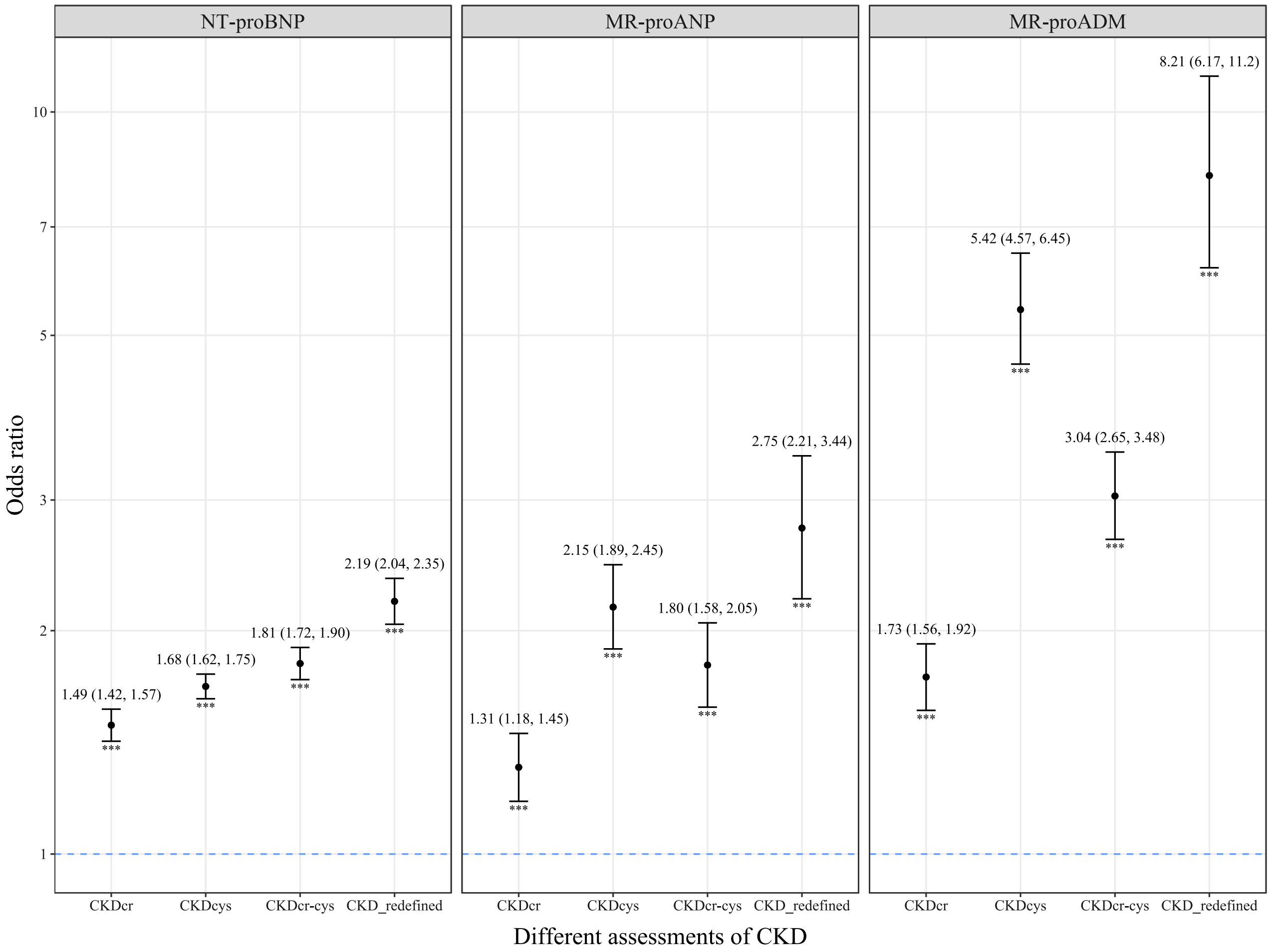


Figure S5. Cross-sectional associations of 3 myocardial stress markers with CKD stratified by CVD and diabetes. Interaction terms of standardized log-transformed markers with CVD or diabetes were included in logistic regression, applying model 2 described in Table 3, to test the significance of interaction. Data from 61830 participants for NT-proBNP, 9499 for MR-proANP, and 9327 for MR-proADM were included in these analyses.

Abbreviations: CVD, cardiovascular disease; CKD, chronic kidney disease; CKDcr, creatinine-based CKD; CKDcys, cystatin C-based CKD; CKDcr-cys, creatinine and cystatin C-based CKD; MR-proADM, mid-regional pro-adrenomedullin; MR-proANP, mid-regional pro-atrial natriuretic peptide; NT-proBNP, N-terminal pro-B-type natriuretic peptide; SD, standard deviation; * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

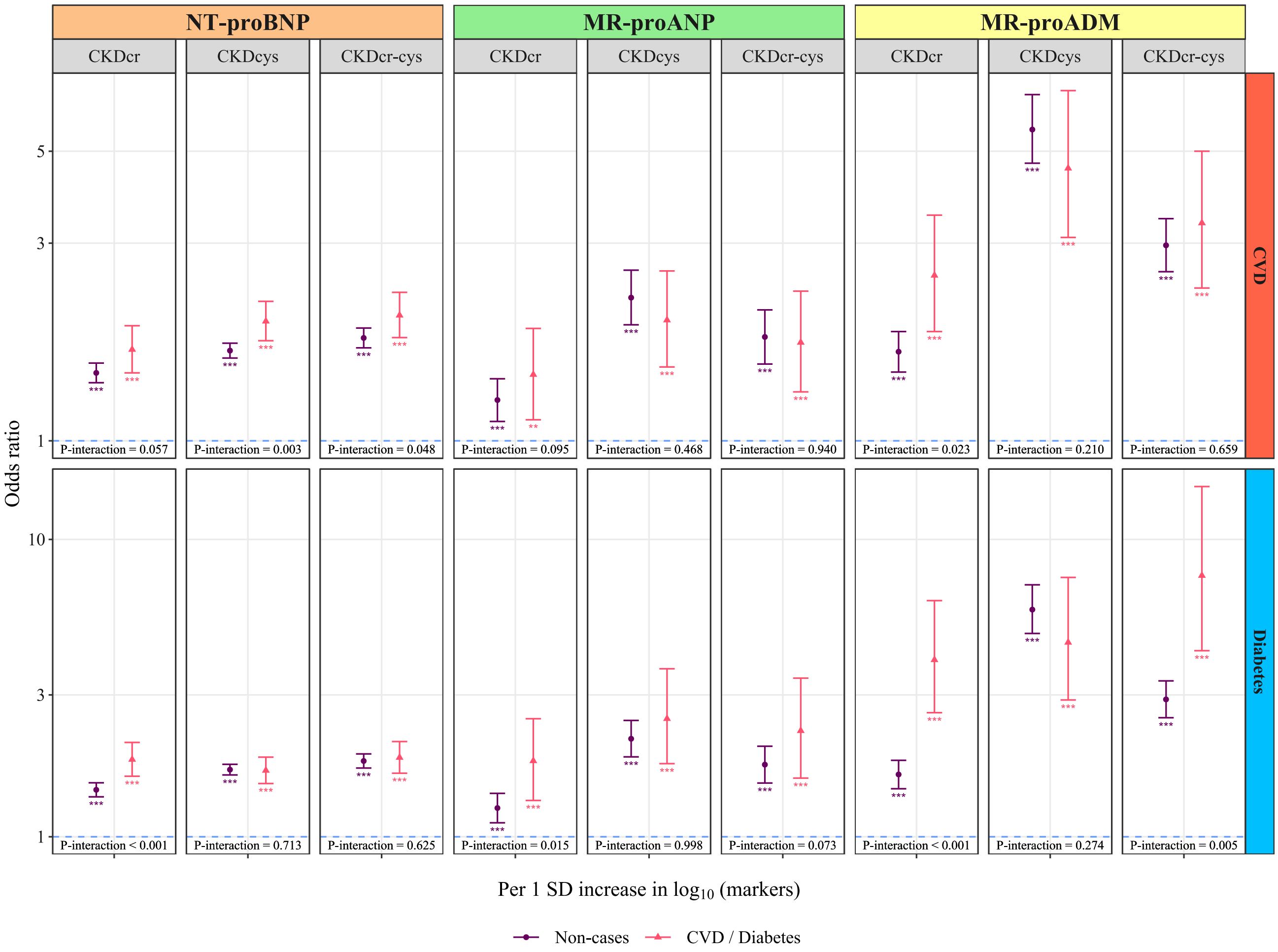


Figure S6. Longitudinal associations of NT-proBNP with 10-year change in kidney function and incident CKD stratified by CVD and diabetes. Interaction terms of standardized log-transformed markers with CVD or diabetes were included in model 3 described in Table 4 and Table S9 to test the significance of interaction. A maximum of 4205 participants with 10208 observations were included for analyses with change in kidney function and a maximum of 4167 participants free of CKDcr at baseline were included for analyses with incident CKD.

Abbreviations: CVD, cardiovascular disease; CKD, chronic kidney disease; cr, creatinine-based; cys, cystatin C-based; cr-cys, combined creatinine and cystatin C-based; eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal pro-B-type natriuretic peptide; SD, standard deviation; * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

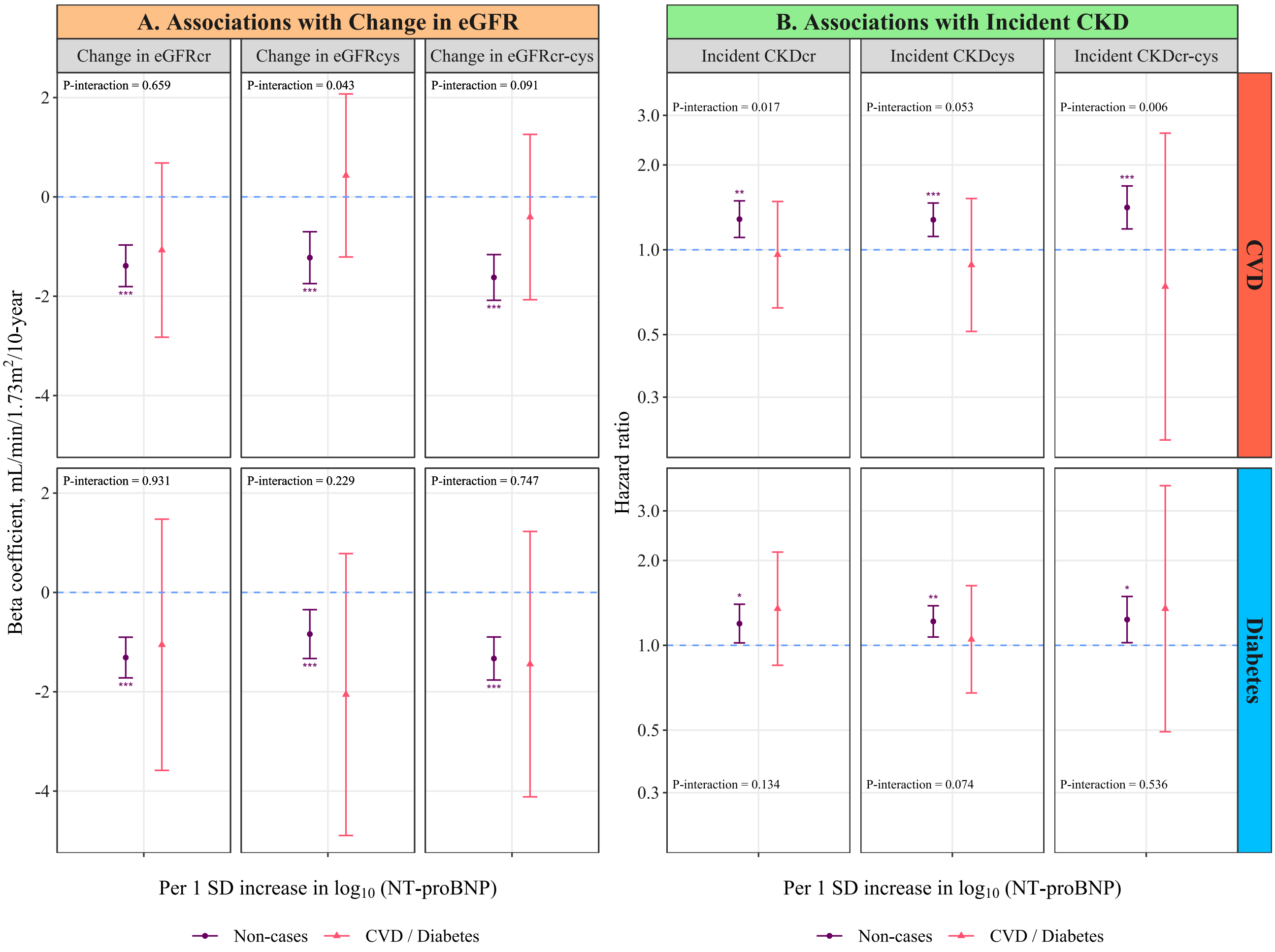


Figure S7. Shapes of the associations between 3 myocardial stress markers and prevalent CKDcr-cys. Restricted cubic spline functions were used to estimate the non-linear associations between original levels of markers and prevalent CKDcr-cys in logistic regression models, applying model 2 as described in Table 3. Participants with levels of markers < 2.5th percentile or > 97.5th percentile were not included in the non-linear association analysis. Finally, 58638 participants for NT-proBNP, 9030 for MR-proANP, and 8861 for MR-proADM were included in these analyses. ORs and 95% CI s of prevalent CKDcr-cys across G2-G4 compared with G1 of markers are plotted, using the minimum marker levels within each category as x-axis locations.

Abbreviations: CI, confidence interval; CKDcr-cys, creatinine and cystatin C-based CKD; G, group; MR-proADM, mid-regional pro-adrenomedullin; MR-proANP, mid-regional pro-atrial natriuretic peptide; NT-proBNP, N-terminal pro-B-type natriuretic peptide; OR, odds ratio.

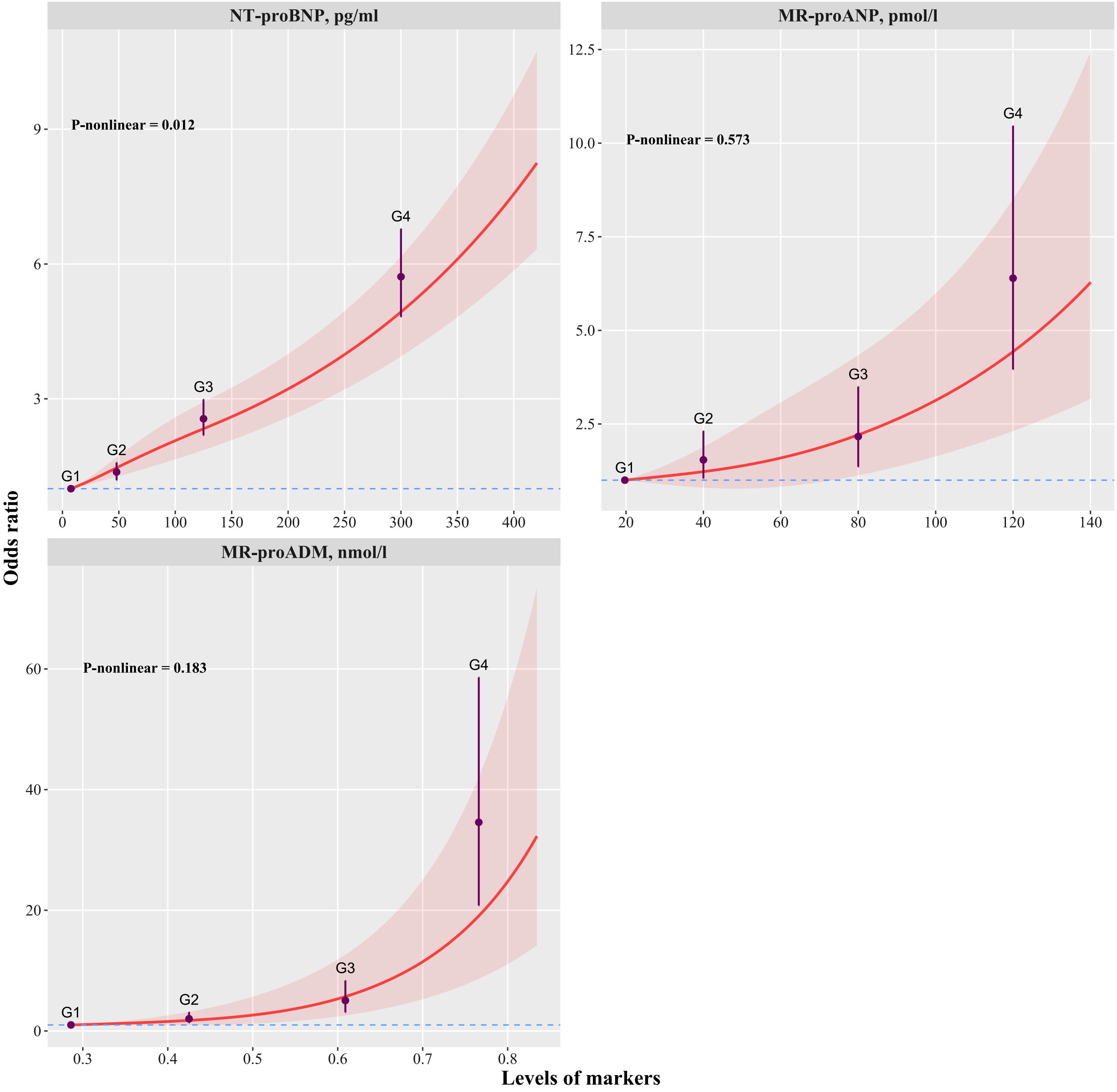
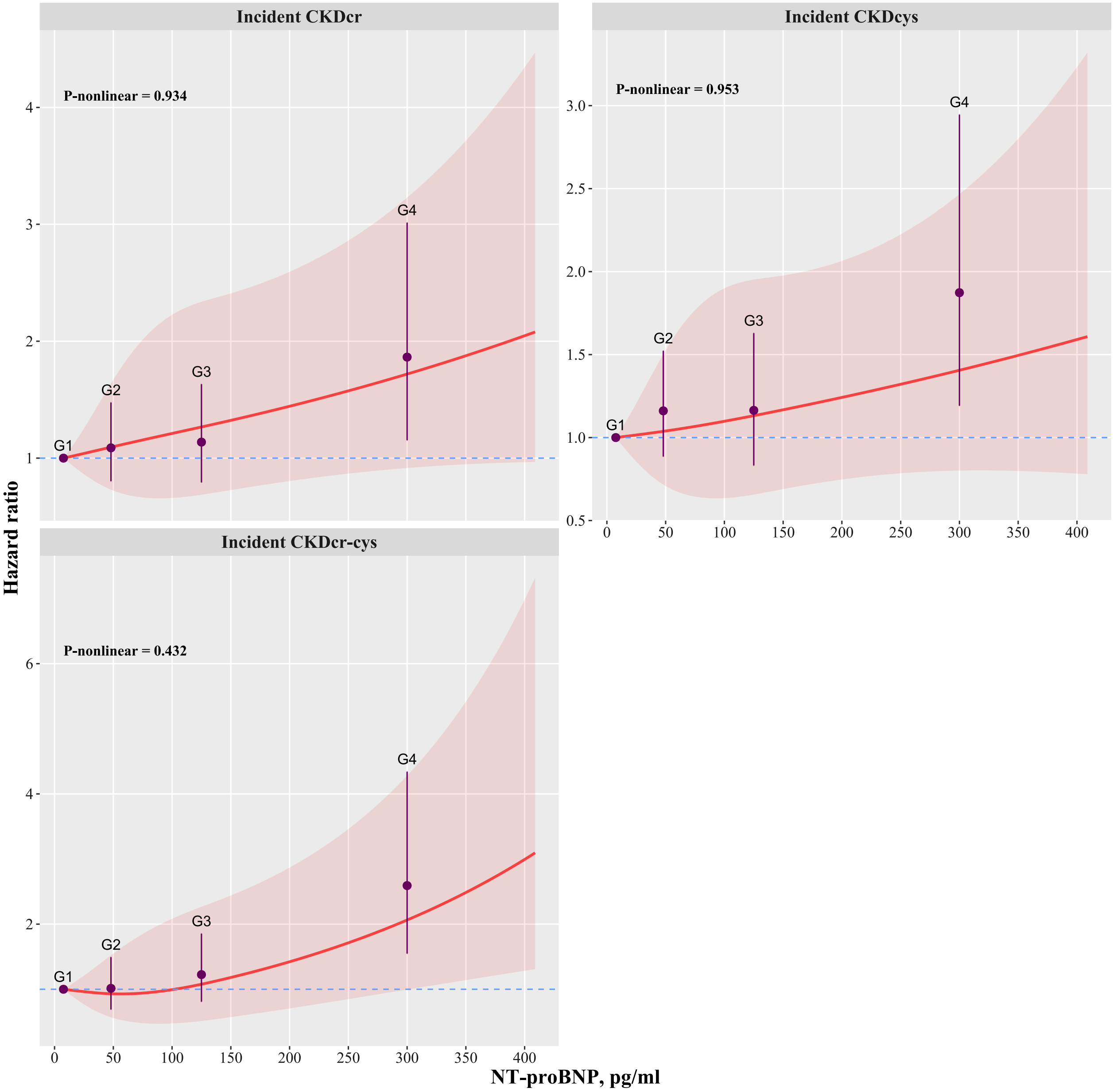


Figure S8. Shapes of the associations between NT-proBNP and incident CKD. Restricted cubic spline functions were used to estimate the non-linear associations between original levels of NT-proBNP and incident CKD in the Cox proportional hazards models, applying model 3 as described in Table 4. Participants with levels of NT-proBNP < 2.5th percentile or > 97.5th percentile were not included in the non-linear association analysis. Finally, 4013 participants free of CKDcr, 2465 free of CKDcys, and 2523 free of CKDcr-cys at baseline were included in these analyses. HRs and 95% CI s of incident CKD across G2-G4 compared with G1 of NT-proBNP are plotted, using the minimum NT-proBNP levels within each category as x-axis locations.

Abbreviations: CI, confidence interval; CKD, chronic kidney disease; CKDcr, creatinine-based CKD; CKDcys, cystatin C-based CKD; CKDcr-cys, creatinine and cystatin C-based CKD; G, group; HR, hazard ratio; NT-proBNP, N-terminal pro-B-type natriuretic peptide; SD, standard deviation.



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Jiesheng Lin
Munich, November 19, 2024

List of all scientific publications to date

Publications as first author or co-first authors, sorted by newest

1. **Lin JS**, Petrera A, Hauck SM, Muller CL, Peters A, Thorand B. Associations of Proteomics With Hypertension and Systolic Blood Pressure: KORA S4/F4/FF4 and KORA Age1/Age2 Cohort Studies. Hypertension, 2024, 81(5): 1156-1166.
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