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Blood coagulation factors as possible risk factors for cardiovascular diseases in a population-based cross-sectional study

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Zusammenfassung

Hintergrund und Ziel: Obwohl viele Risikofaktoren für kardiovaskuläre Erkrankungen (CVD), insbesondere Myokardinfarkt (MI) und ischämischer Schlaganfall (IS), bereits gut erforscht sind, gibt es weiterhin wenige populationsbasierte Studien im Bereich der primären Prävention, die sich mit tiefen Beinvenenthrombosen (DVT) und Lungenarterienembolie (PE) befassen. Insbesondere Untersuchungen zum Einfluss von Blutgerinnungsfaktoren als mögliche Risikofaktoren für venöse Thrombosen (VT) in der Bevölkerung sind wenig untersucht.

Methoden: Die Prävalenzen von Begleitfaktoren von CVD wurden in der bevölkerungs-basierten KORA-Fit-Studie (n = 3059) beschrieben. In einer Teilgruppe (KORA-Fit (S4), n = 805) wurden Parameter der Blutgerinnung gemessen und deren Assoziation mit dem Risiko für das Auftreten von CVD analysiert. Zur statistischen Auswertung wurden multivariable logistische Regressionsmodelle verwendet.

Ergebnisse: In KORA-Fit hatten insgesamt 9,7 % der TeilnehmerInnen eine Diagnose für einen MI, IS oder VT erhalten. Bei 4,6% der TeilnehmerInnen (3,7% der Männer und 5,3 % der Frauen) lag eine Diagnose für VT vor. Personen mit einer VT-Diagnose waren älter, hatten ein höheres relatives Körpergewicht, hatten häufiger die Diagnose Diabetes mellitus (14,5 % versus 7,8 % bei Personen ohne VT) und nahmen häufiger Antikoagulanzien (17,9 %) und andere Medikamente (30,7%) ein. Hinsichtlich klinischer Parameter wurden bei Personen mit einer VT-Diagnose eine geringere glomeruläre Filtrationsrate, höhere Leberenzymwerte (GGT, AST, ALT) und höhere Inflammationswerte (hsCRP) beobachtet.

Die Regressionsanalysen zeigten, dass erhöhte Plasma-Fibrinogen-Werte signifikant mit einem erhöhten Risiko für VT und MI assoziiert sind. Faktor VIII-Konzentrationen waren ebenfalls signifikant mit dem Risiko für VT verbunden. Plasma-Protein C war dagegen invers mit dem Risiko für VT assoziiert. Es bestand kein Zusammenhang zwischen den analysierten Blutgerinnungsfaktoren und der Prävalenz von Schlaganfall.

Schlussfolgerungen: In dieser populationsbasierten Studie zeigten sich signifikante Zusammenhänge zwischen Gerinnungsfaktoren und kardiovaskulären Erkrankungen. Die routinemäßige Bestimmung von Gerinnungsfaktoren wie Fibrinogen, Faktor VIII oder Protein C in der Bevölkerung könnte helfen, den Bereich der Primärprävention von CVD weiterzuentwickeln und soll daher in zukünftigen Studien weiter untersucht werden.

Abstract

Background and purpose: Even though many risk factors for cardiovascular diseases (CVD), especially for myocardial infarction (MI) and ischemic stroke (IS), are already well known and researched, there are still not enough representative population-based studies in the field of primary prevention, which investigated deep vein thrombosis (DVT) and pulmonary embolism (PE). Particularly, there is little research on blood coagulation factors and their impact as possible risk factors on venous thrombosis (VT) in the adult population.

Methods: The prevalence of common risk factors of CVD were described in the population-based KORA-Fit study (n = 3,059). In a subsample (KORA-Fit (S4), n = 805) also the blood concentrations of hemostatic factors were determined and their association with the CVD risk was analyzed. For statistical analysis multivariable logistic regression models were used.

Results: In KORA-Fit study overall 9.7% of the participants had been diagnosed with MI, IS or VT. 4.6% of all participants suffered from VT (3.7% men and 5.3% women). Participants with a VT diagnosis were older, had higher Body Mass Index, suffered from diabetes mellitus more often (14.5% versus 7.8% in participants without VT) and took more anticoagulants (17.9%) and other medication (30.7%). Regarding clinical laboratory parameters lower glomerular filtration rate, higher liver enzymes (GGT, AST, ALT) and higher levels of inflammatory markers (hsCRP) in participants with VT were observed.

The regression analysis indicated, that higher levels of fibrinogen are associated with higher risk of VT and MI. Factor VIII showed positive correlation only to VT. Plasma protein C had, however, an inverse association with VT. There was no correlation between analyzed blood coagulation factors and the prevalence of ischemic stroke.

Conclusions: In this population-based study a significant correlation between blood coagulation factors and cardiovascular diseases was observed. The evaluation of hemostatic factors in the adult population, such as fibrinogen, factor VIII, or protein C

may help to develop the field of primary prevention of CVD and should be a subject of further research.

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List of abbreviations

CVD	cardiovascular disease
DVT	deep vein thrombosis
PE	pulmonary embolism
VT	venous thrombosis
VTE	venous thromboembolism
MI	myocardial infarction
IS	ischemic stroke
DOACs	direct oral anticoagulants
PT	prothrombin time
INR	International Normalized Ratio
aPTT	activated partial thromboplastin time
BMI	Body Mass Index
vWF	von Willebrand Factor

1. Introduction

1.1. Epidemiology of cardiovascular diseases

Cardiovascular disease has been the most common cause of death worldwide for over two decades, and the number of people dying every year is constantly growing. The costs for diagnosis, prevention, therapy and rehabilitation are playing a big role in each country's health budget. In 2019 cardiovascular diseases were responsible for almost 17.9 million deaths (32% of all deaths worldwide). 85% of all registered deaths were due to the myocardial infarction and stroke [1]–[3]. Global direct and indirect costs for cardiovascular diseases are predicted to increase from US$ 950 billion up to US$ 1,044 billion by the year 2030. The prevalence of cardiovascular diseases in 2018 in the USA was estimated with 49.2% (126.9 million) in adults ≥ 20 years old. Excluding the arterial hypertension, which is the most common cardiovascular disease, the prevalence for CVD lied at 9.3% (26.1 million) in the same population group [4], [5].

This dissertation is focusing on cardiovascular diseases (CVD), including myocardial infarction (MI), ischemic stroke (IS), but also deep vein thrombosis (DVT) and especially pulmonary embolism (PE). DVT and PE are two main manifestation forms of venous thromboembolism (VTE) or venous thrombosis (VT). Depending on the source, the incidence of first-time VTE varies between 0.71 and 1.43 per 1,000 person-years and is responsible for 60,000 to 100,000 deaths worldwide annually. The incidence rate increased with higher age. The data were collected from retrospective studies and study reviews performed in adult Caucasian population in Canada, the USA, Norway and Switzerland [6]–[11].

Moreover, all of the above-mentioned endpoints have a negative impact on the quality of life of the affected patients. 1% of the adult population in EU with a diagnosed cardiovascular disease feel heavily impaired in their everyday life according to the epidemiological and healthcare data, gathered by the department of public health in Oxford University [12]. The Bonn Vein Study questioned and examined more than 3,000 adults in the normal population (between 18 and 79 years old). Thereby 79.2% of all participants reported to have had a phlebological disease in the past (this included DVT but also common complications of DVT, such as

varicosis, phlebitis, ulcus cruris, swelling etc.); 6.2% of the participants claimed to have difficulties performing their daily routine, due to their vein disease [13].

1.2. Clinical role of venous thromboembolism

Virchow's triad is the concept describing most important pathophysiological causes, leading to a thromboembolism. It includes factors such as stasis, endothelium changes and hypercoagulability. The concurrence of one or more of these factors increases drastically the risk of VTE. Stasis is normally conditioned by varicosis, any kind of immobility, local heat treatment or applied pressure from the outside. Endothelium alteration can happen due to inflammatory or traumatic reasons. Hypercoagulability is usually described in patients with changes in the blood composition. It can be due to acquired thrombophilia (e.g., use of contraceptives, antiphospholipid syndrome, antibodies against cardiolipin) or congenital (e.g., Protein C or S deficiency, deficiency of antithrombin III, heparin cofactor II deficiency, dysfibrinogenemia, factor XII deficiency) [8], [14], [15].

Deep vein thrombosis is the clinical consequence of a clot formation inside a blood vessel. The most common conditions that increase the risk of DVT are surgery or trauma, any kind of immobilization, oncological disease, pregnancy, heart failure, chronic venous insufficiency or a DVT in the past [8]. Also, lifestyle factors such as obesity (BMI > 30 kg/m^2) and smoking or use of estrogen or contraceptives are risk factors for DVT [14]. The most widespread hereditary factors, which increase the risk of a DVT are APC-Resistance/Factor V-Leiden mutation, prothrombin mutation, or protein C, protein S or antithrombin deficiency [8], [15], [16].

Pulmonary embolism is a heavy and underdiagnosed complication, which occurs in 50% of DVT patients. Thereby one of the pulmonal arteries is occluded by an embolus, which in more than 90% of the cases originated from the venous system of lower extremities or in pelvic veins [14], [16]. Acting physicians often do not run the necessary diagnostic tests, which in turn does not lead to the correct diagnosis at the start of the treatment. In only 45% of the cases, the diagnosis of PE is made ante mortem [17]. Despite preventive measures taken routinely during hospital stays, PE is still the leading morbidity and cause of death in postsurgical and pregnant patients in hospitals, as well as shortly after discharge [16].

One further complication of DVT is a post-thrombotic syndrome. It occurs in 50% of the patients within two years after DVT [8]. The range of clinical symptoms varies from leg pain and swelling to ulceration. According to patient's reports the symptoms and impaired life quality last for years [8], [16].

Moreover, after suffering from DVT, there is a 30% increased risk of a recurrent thrombosis event within the next 10 years [14]. Such relapses contribute to the high morbidity and can worsen the already existing post-thrombotic syndrome [8], [14], [16]. Anticoagulation, which is one of the essential components of DVT therapy, can prevent approximately 4 recurrences per 100 patient-years. New treatment possibilities, such as anticoagulation with DOACs offer more therapeutic options for treating physicians. However, their side effects and limitations should be taken into account, when prescribed [8].

1.3. Clinical role of myocardial infarction and ischemic stroke

Ischemic necrosis of myocardial area often occurs due to the atherosclerosis of coronary arteries – so called coronary heart disease. Clinically, myocardial infarction is differentiated in ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation myocardial infarction (NSTEMI), and others. While NSTEMI is caused by a sustained ischemia of subendocardial layer, STEMI is mostly caused by an occlusion of a coronary artery [15]. The affected myocardial area, which can no longer be sufficiently perfused is seen as an akinetic or dyskinetic myocardial tissue during the echocardiography [15], [16].

The damage of vital myocardial areas often results in a reduced ejection fraction, which increases the risk of post-infarction complications on the long term. A window of 24 hours after MI is clinically the most relevant, as more than 40% of MI patients do not survive the first 24 hours after the acute event [16], [18]. The most common early complications include different types of atrial or ventricular arrhythmia, acute heart failure or cardiogenic shock. Long term complications, such as myocardial aneurysms, are registered in 20% MI patients [15], [16]. Further relevant complications are chronical heart failure, Dressler syndrome, persistent angina pectoris or a relapse [16].

Due to the developing approach in diagnostics and treatment, such as advanced troponin measurements, pharmacological and invasive therapy, myocardial infarction can be better prevented, diagnosed and treated [19]–[21]. However, there is still a significant share of underdiagnosed MI patients. Depending on the source, 20 – 50% of all MI are inapparent or silent [16], [22], [23]. They do not cause classical symptoms and therefore often stay unrecognized and therefore untreated. Often elder patients and patients with diabetes mellitus are affected. In the meanwhile, silent myocardial infarctions often represent the first manifestation of coronary heart disease and can lead to a sudden cardiac death. Silent MI is also associated with an increased risk of heart failure [16], [22], [23].

There are many risk factors, that contribute to the development of the coronary heart disease, which develops due to progressing arteriosclerosis of the coronary arteries. These include increased plasma concentrations of LDL cholesterol, high blood pressure, a diagnosis of diabetes mellitus, smoking, older age and positive family history. Further important risk factors are e.g., obesity, low physical activity, obstructive sleep apnea syndrome or hyperfibrinogenemia [15], [16], [24], [25]. MONICA/KORA register of myocardial infarction in the Augsburg region reported the following prevalence of pre-existing diseases in patients with MI from 2009 till 2020 (25 – 84 years old): hypertension (72 – 82%), dyslipidemia (50 – 52%), diabetes mellitus (27 – 37%), current smoking (27 – 31%) [18].

Arteriosclerosis leads to the formation of a stable plaque, which due to the progression of the disease becomes unstable or so called “vulnerable”. In case of a plaque rupture, it occludes one of the coronary arteries. Most myocardial infarctions, that are consequently treated with percutaneous coronary intervention, show coronary stenosis of at least 50% [16], [26]–[29].

Ischemic stroke is still the second leading cause of mortality worldwide [16], [30]. The prognosis in IS patients strictly depends on the extent of the brain damage. The lethality of first IS is approximately 20-25%. After the second stroke the lethality is estimated with 40% within one month after the acute event [15], [16]. Stroke is a worldwide leader in disability and is also responsible for most cases of dementia and

depression [16], [30]–[32]. Approximately 50% of all IS patients are physically or mentally handicapped in their everyday life within 3 to 20 months after diagnosis [30], [33], [34]. According to the World Stroke Organization (WSO) 51.9 million years of healthy life are lost because of invalidity and death caused by IS [35].

In contrast to MI, the differentiation between ischemic and hemorrhagic stroke can only be made in the clinic which precludes prehospital treatment. Due to the small time window, where the neurological damage can still be reversed and therefore damaged brain cells can be saved, special clinic departments were established for fast and optimal treatment of IS, the so-called Stroke Units [16], [36].

50% of IS is caused by macroangiopathy of extracranial or intracranial arteries. Thereby the main risk factor is considered to be arterial hypertension. Patients with untreated high blood pressure are 4 times more likely to experience an IS as compared to patients with controlled hypertension. Other risk factors include older age, existing coronary heart disease, diabetes mellitus, and smoking [15], [16], [37].

Microangiopathy is responsible for approximately 25% of all IS. Here, small arterial branches in the brain obliterate and cause damaged perfusion. Arterial embolism as a consequence of atrial fibrillation provokes 20% of IS, which is also clinically important and requires certain preventive measure, such as administration of anticoagulants [15], [16], [37].

After acute treatment in the hospital, patients are offered participation in rehabilitating programs, where the main attention is paid to restoration of mobilization and socialization of the patients. However, there are many (52.2% of IS patients) severely handicapped patients who cannot actively participate in such a program. Thus, ischemic stroke is still a big challenge for the health care system and demands further research and investments to develop guidelines for prevention, therapy and aftercare [30], [38].

1.4. The blood coagulation system

Hemostasis is responsible for the bleeding control in the organism. The combined work of vascular walls, blood cells and plasma factors in the circulation enables the balance between two extreme conditions – thromboembolism and bleeding [14].

The primary hemostasis results in the formation of the so called “white thrombus” and vasoconstriction. It is initiated by an endothelial lesion or a vessel damage and can be divided into following steps – adherence, activation and aggregation. When endothelium is damaged, von Willebrand Factor (vWF), which circulates in blood, binds itself to collagen fibers of endothelium and glycoprotein receptors, which are located on the surface of thrombocytes. Subsequently, blood platelets adhere to the vascular wall. Through the connection between vWF and thrombocytes but also through small quantities of thrombin, which is being produced already at this stage, thrombocytes are activated. After this activation phase, thrombocytes are able to change their physical form and produce mediators which boost further platelet activation. The aggregation phase leads to a formation of a “white thrombus”, consisting of intertwined thrombocytes and fibrin molecules [14], [39], [40].

The secondary hemostasis aims at fibrin formation, which is the end product of the coagulation cascade. Different proenzymes (e.g., prothrombin or factor II) are converted into their active form (e.g., thrombin, also known as factor IIa). These processes are modulated by multiple inhibitors and cofactors. There are two options, how to activate the coagulation cascade – extrinsic and intrinsic pathway. Both of them lead to the activation of the factor II and boost the transformation of fibrinogen into fibrin. With sufficient amounts of thrombin in plasma it comes to the formation of insoluble fibrin polymer, which contributes to the bleeding control [14], [39], [40].

In vivo, Factor VIII (FVIII) is bound to the carrier protein von Willebrand-Factor (vWF). The latter preserves Factor VIII from a degradation in the plasma and extends its’ half-life time. Factor VIII and vWF connect the processes of thrombocyte adherence and plasmatic coagulation. In its’ active state, FVIII can boost the transformation of the Factor X to Xa [14].

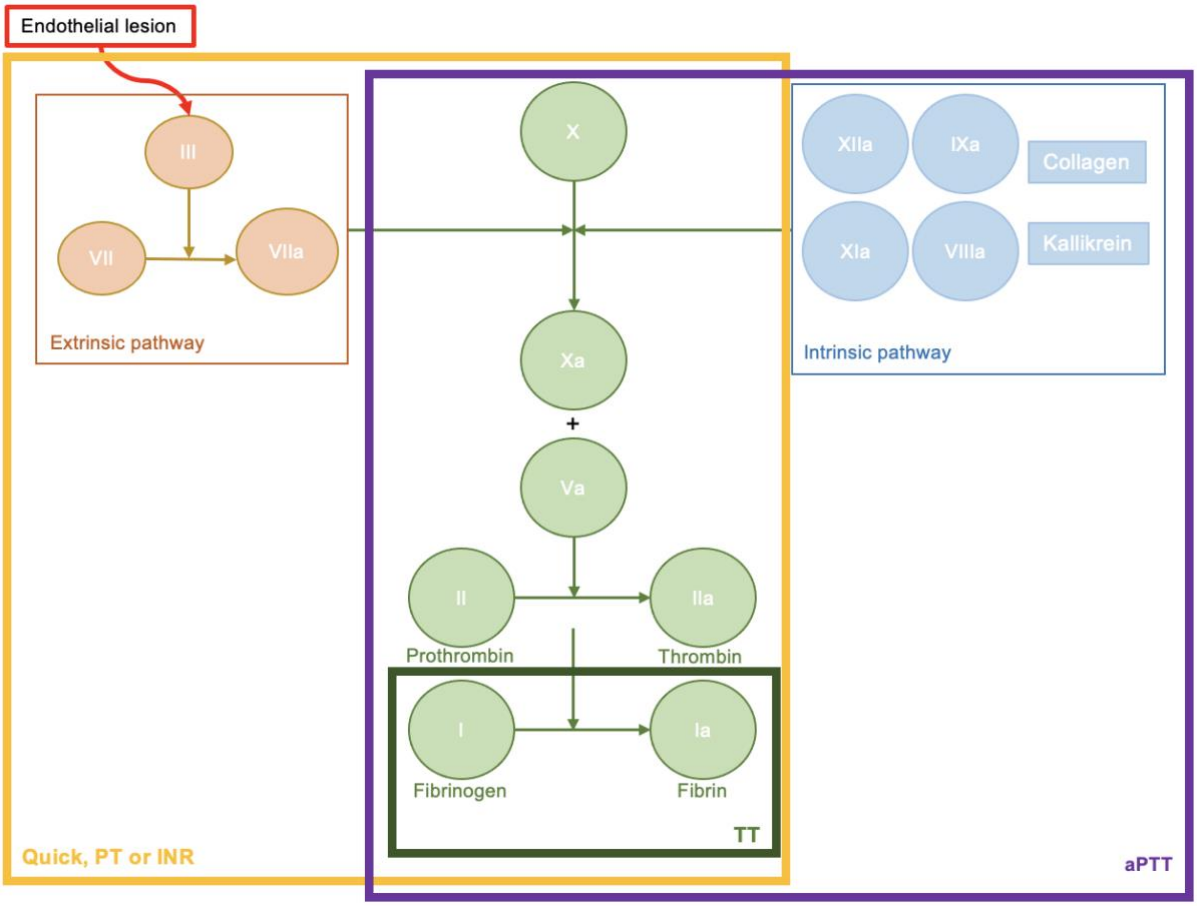


Figure 1: Plasmatic coagulation cascade
aPTT = activated partial thromboplastin time; TT = thrombin time; PT = prothrombin time, also called as Quick or INR.

As mentioned above the formation of thrombin is regulated by inhibitors. Protein S acts as a cofactor of protein C to inactivate factors Va (FVa) and VIIIa. When the plasma level of proteins C and S is too low, it can provoke thromboembolism and disseminated intravascular coagulation [14], [39], [40].

Coagulation reactions are always followed by fibrinolysis. It inducts plasmin formation from plasminogen and results not only in the dissolution of the existing blood clot but also stops further coagulation mechanisms. The breakdown of fibrin molecules leads to the release of d-dimers, which are clinically relevant for the diagnosis or therapy control in case of thromboembolism, as increased d-dimer concentrations indicate active fibrinolysis [14], [39], [40].

In the clinic routine such parameters as prothrombin time (PT) (also known as Quick), international normalized ratio (INR) and activated partial thromboplastin time

(aPTT) are commonly used as screening tests for pathological blood coagulation situation. aPTT assesses the intrinsic and common coagulation pathways, including FXII, FXI, FIX, FVIII, FX, FV, FII, and FI, and can be helpful during therapy control in patients taking unfractionated heparin. PT and INR are clinically relevant to measure the extrinsic and common coagulation pathways. Moreover, they are often necessary to monitor the treatment effect of vitamin-K antagonists. [14], [39], [40]

1.5. Current state of research

Due to the importance of the topic, possible associations between coagulation factors and cardiovascular diseases have been studied since long. Both patients and normal population groups underwent different research programs in order to clarify, if blood coagulation factors play a significant role in prevention, diagnosis or therapy. One of the most well-researched coagulation factors is fibrinogen. According to the results of epidemiological studies, increased plasma fibrinogen concentration is considered to be one of the major risk factors for cardiovascular disease [41]–[43].

Many patient-based studies have demonstrated that measuring the levels of some coagulation factors can predict a DVT or other CVD. In a Chinese Study from 2017, patients with a stable coronary artery disease and type-2 diabetes mellitus showed higher levels of fibrinogen [42]. Other patient-based studies indicate possible significance of other coagulation factors such as D-Dimer, antithrombin, factor VIII, von Willebrand Factor, protein C or protein S for the incidence and mortality of cardiovascular diseases [41], [44]–[48]. Imon et al. conducted a study among patients with a stable angina pectoris, where fibrinogen was shown to be “an independent predictor of subsequent acute coronary syndrome” [49].

In case of ischemic stroke, measuring the levels of plasma fibrinogen as a part of the secondary prevention program was suggested. After analyzing several TIA (transitory ischemic attack) trials, the risk of a relapse increased “linearly with fibrinogen levels” [50]

Much research was conducted focusing on different genetic mutations in coagulation factors, that suggested positive or inverse associations with the risk of cardiovascular diseases. Abhinand et al. conducted a meta-analysis of 72 published studies to

evaluate the association between MTFHR C677T mutation and risk of an ischemic stroke. The results suggest 30% increased risk of IS in people, who carry the mutation [51]. Another systematic review was performed by Zhang et al. in 2020, where 287 families of different ethnic groups were analyzed regarding possible mutations, which increase the risk of VTE. The results described 21 genes with a positive association to VTE [52].

Over the last 20 years more than 40 cardiovascular diseases were linked to certain single-gene defects. The most researched CVD is considered to be hypertrophic cardiomyopathy, which makes it the most widespread genetic CVD worldwide. Kelly and Semsarian [53] conducted a review, confirming, that CVD can also be caused by multiple genetic mutations, which can show an additive effect and cause a more severe progression of the CVD.

So far, however, much less research was conducted in the area of primary prevention, using population-based studies. Higher plasma fibrinogen concentrations were identified as cardiovascular risk factor in the population. There is also an indication that fibrinogen may carry “an inheritable risk for coronary artery disease in subjects with strong family anamnesis for myocardial infarction” [43], [54]. The Framingham study showed a significant positive association between fibrinogen levels in the normal population and the risk of CVD occurrence [54]. Wilhelmsen et al. conducted a population-based study, including 792 men. During the 13 years follow up cardiovascular accidents were diagnosed, as well as the common CVD risk factors were registered. The study implies a significant correlation between fibrinogen and myocardial infarction, as well as between fibrinogen and stroke [55]. Another population-based research, including almost 15.000 adult men showed a twofold increase in MI risk in subjects with increased fibrinogen levels [56].

In the literature review by Jenkins et al. several representative studies are described, which suggest a positive correlation between FVIII and VTE in normal population [57]. The study performed by Payne et al. suggests also racial differences, where black population has a higher VTE risk, when both FVIII and vWF are increased; and white population with high FVIII has a higher VTE risk [45].

A prospective study by Folsom et al. analyzed the levels of Protein C in more than 16.000 adults and reported a 3-fold increased VTE risk in people with low Protein C [58]. Bucciarelli et al. discovered in his case-control study a twofold VTE risk in subjects with low borderline plasma levels of Protein C [44].

1.6. Objectives and goals of the study

It is important to provide further research on risk factors of CVD, especially in view of few published population-based studies. The better understanding of cardiovascular risk factors can be a significant investment to primary CVD prevention programs. The focus in this study is on blood coagulation parameters as risk factors of CVD, especially, VT.

First, this study will provide a descriptive analysis of the prevalence of CVD (myocardial infarction, ischemic stroke, venous thrombosis) in a population-based study. Moreover, a descriptive analysis of blood coagulation factors as measured in blood samples of the study participants will be conducted.

Second, we will investigate, which blood coagulation factors are associated with CVD, and can be considered as possible risk factors to prevent cardiovascular diseases; the focus will be on venous thrombosis.

We will investigate these aims by using data from the population-based KORA-Fit study.

2. Methods

2.1. The KORA Fit study

In 1978 at the conference of National Heart, Lung and Blood Institute in Bethesda, Washington, it was established that there was not sufficient data, why the mortality of the myocardial infarction decreases. It was not clear at the time, whether the reason for that was declining of incidence, lower lethality or both. It was then decided that the WHO-MONICA Project (monitoring trends and determinants in cardiovascular disease) should take it under control and research the trends of cardiovascular mortality and morbidity worldwide. In 1996, as a continuation of the MONICA Project the KORA platform was established [59], [60]. KORA stands for Cooperative Health Research in the Region of Augsburg, Germany. It is a research platform for population-based studies. Altogether 4 cross-sectional baseline surveys (S1 1984/85, S2 1989/90, S3 1994/95 und S4 1999/2001) were conducted. In the years 2018 and 2019 the follow-up study KORA-Fit followed, to which all KORA participants born between 1945 – 1964 were invited for a re-examination; Finally, 3.059 eligible subjects participated, i.e., 64.4 % of all eligible persons [61], [62].

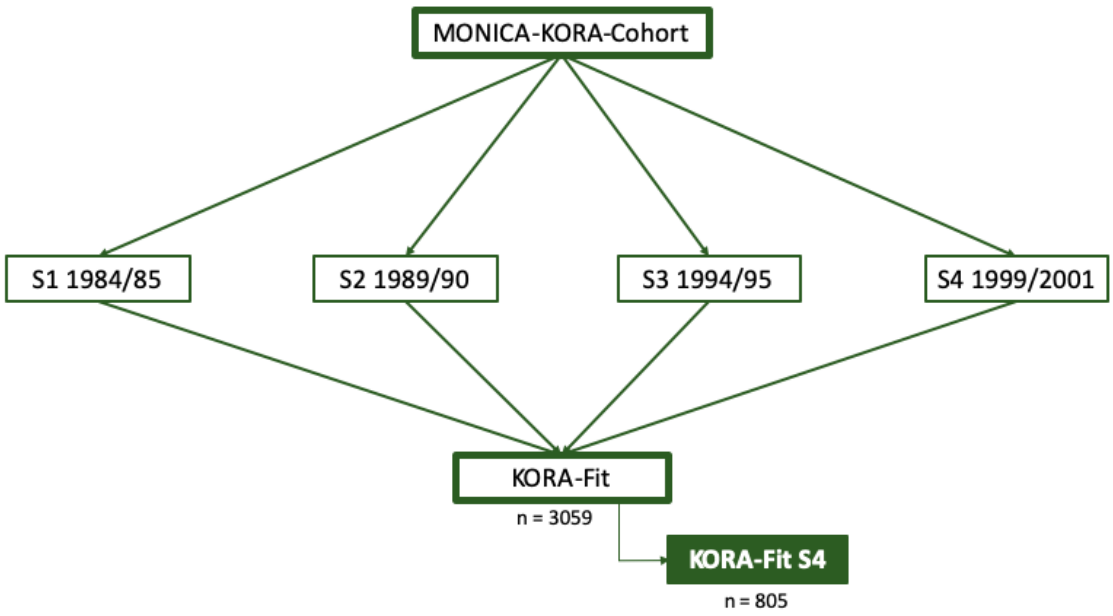


Figure 2: The KORA-Fit study

KORA-Fit Study is a follow-up study embedded in the MONICA/KORA cohort study, aiming at S1-S4 participants born 1945-1964. In KORA-Fit S4, hemostatic factors were analyzed.

2.2. Data collection

Sociodemographic data (e.g., education level) were collected by trained medical staff during a standardized interview with each participant. During the interview, also information about common risk factors for cardiovascular endpoints (e.g., Body Mass Index, smoking habits, physical activity, cancer in the anamnesis,) was collected. It was also registered, if a participant already had received a diagnosis of deep vein thrombosis, pulmonary embolism, myocardial infarction or ischemic stroke and whether the disease was treated in the hospital. During the physical examination, anthropometric data and blood pressure were measured in accordance with the MONICA protocol from the World Health Organization [63]. The level of education was assessed in school years. Subjects were considered physically active, if they declared doing sport for at least one hour per week.

2.3. Blood collection and laboratory measurements

In addition to the interview and physical examinations, blood testing took place. It included parameters of kidney and liver function but also analysis of known CVD risk factors such as serum cholesterol concentrations. Hs-CRP was measured as a marker of inflammation. In 805 participants originating from the S4 survey (KORA-Fit S4) citrate plasma samples were collected and coagulation factors were analyzed. The levels of the most common screening parameters were determined, which display the state of the coagulation system, such as aPPT, Quick and INR. Also, some clinically relevant coagulation factors and proteins were tested, namely antithrombin, fibrinogen, factor VIII, D-Dimer, protein C, and protein S (Table 1). Blood coagulation factors were analyzed in the laboratory at the University Clinic in Augsburg. Additional clinical laboratory parameters were analyzed according to standard laboratory methods in the Hospital of Ludwig-Maximilian University in Munich.

Table 1: Methods used for the analysis of blood coagulation factors in KORA-Fit S4 participants

BLOOD COAGULATION FACTOR	REFERENCE VALUE	MEASUREMENT TECHNIQUE	ASSAY OR REAGENTS	MEASURING DEVICE
Quick	82 - 125 %	photometric assay	Thromborel S Siemens Eschborn	BCS-XP, Siemens Eschborn
INR	0.9 - 1.15	derived from prothrombin ratio	Thromborel S Siemens Eschborn	BCS-XP, Siemens Eschborn
aPTT	26 - 36 sec.	photometric assay	Pathromtin SL, CaCl2 solution, Actin FS, Siemens Eschborn	BCS-XP, Siemens Eschborn
Antithrombin	83 - 118 %	chromogenic assay	Innovance Antithrombin, SCS Cleaner, Siemens Eschborn	BCS-XP, Siemens Eschborn
Fibrinogen	210 - 400 mg/dl	photometric and turbidimetric assay	Multifibren U, Siemens Eschborn	BCS-XP, Siemens Eschborn
D-Dimer	< 500 µg/L	turbidimetric assay	Innovance D-Dimer Kit, Siemens Eschborn	BCS-XP, Siemens Eschborn
Protein C	70-140 %	photometric assay	Berichrom Protein C, Siemens Eschborn	BCS-XP, Siemens Eschborn
Protein S	women: 52 - 126 % men: 73 - 130 %	photometric assay	Hemoclot Protein S, OVB-Puffer, CaCl2, SCS-Cleaner	CaoChrom, Wien
Factor VIII	70 - 150 %	photometric assay	Factor VIII deficient plasma, Pathromtin SL, CACL2, Siemens Eschborn	BCS-XP, Siemens Eschborn

Participants who acknowledged to take anticoagulants, were excluded from the analytic sample.

2.4. Statistical analysis

The study data were analyzed with the statistic software SPSS, Version 27.0.1.0. for MacOS. The descriptive data were given as absolute and relative frequency, mean and standard deviation, or in case of not normally distributed parameters, as median and 25th and 75th percentiles. Some of these results were also graphically represented. The Shapiro-Wilk test was used to test for normally distributed data. We used Mann-Whitney-U test as a non-parametric alternative of the t-Test for

continuous variables to compare differences between independent samples. For categorical data Fisher’s exact test was performed. As endpoints venous thrombosis (including deep vein thrombosis and pulmonary embolism), myocardial infarction and ischemic stroke were taken. To describe the relationship between independent variables and endpoints, odds ratios and 95% confidence intervals (binary logistic regression) were calculated. To ensure that our logistic model fits well, the data was tested for multicollinearity and linearity assumptions.

3. Results

3.1. Prevalence and determinants of cardiovascular diseases and venous thromboembolism in the KORA-Fit Study

Among all KORA Fit participants (n = 3,059), there were 46.4% male (n = 1,418) and 53.6% female (n = 1,641) with the mean age of 63.2 (SD = 5.52) years (Table 2).

Among all participants, 296 (9.7%) had received at least one diagnosis of the cardiovascular endpoints; significantly more men (n = 167) than women (n = 129, $p < 0.01$) suffered from CVD (Table 3). This was true for myocardial infarction and for stroke but not for the venous thromboembolism. For VT a female predominance (87 female versus 53 male) was observed.

The results of clinical laboratory testing in all participants showed a significant reduction of glomerular filtration rate in women (mean = 80.7 ml/min; SD 13.1), in comparison to men (82.1 ml/min; SD = 12.9; $p < 0.01$). Analysis of the liver function, measured through transaminases, showed significantly higher values in men in all three parameters (GGT, GOT and GPT). Total-cholesterol level was significantly higher in female participants, as well as non-HDL-cholesterol and HDL-cholesterol (see Table 16 in the Appendix).

More women than men used NSAID on a regular basis (3.2% female versus 1.7% male; $p = 0.010$). However, male participants took significantly more anti-diabetic medication, anti-hypertensive medication, anticoagulants, ASS, statins, and gout medication. The prevalence in multi-medication was higher in men as compared to women (16.6% male versus 12.6% female, $p < 0.01$) (see Table 17 in the Appendix).

Overall, the prevalence of VT was 4.6% (n = 140). The mean age of VT cases was 64.6 years (SD = 5.4), and the mean BMI was 30.3 kg/m^2 (SD = 6.9), which is significantly higher than in the group with no VT (mean BMI = 28.1 kg/m^2, SD = 5.2, $p < 0.01$) (Table 4). There was no statistically significant difference in physical activity, smoking pattern or prevalence of oncological diagnosis. However, the share of participants with diagnosed VT and diabetes mellitus was almost twice as high as to those without the diabetes ($p < 0.01$). Furthermore, subjects with VT (versus no VT) proved to have a lower level of education (mean = 11.6 years, SD = 2.6, $p = 0.02$).

Table 2: Characteristics of KORA-Fit participants stratified by sex

CATEGORY		n	OVERALL				MALE				FEMALE				p-Value
			%	100.0	n	3,059	%	46.4	n	1,418	%	53.6	n	1,641	
Age		3,059	Mean	63.2	SD	5.5	Mean	63	SD	5.6	Mean	63.4	SD	5.5	0.05
			Median	63			Median	63			Median	64			
			25 P	59	75 P	68	25 P	58	75 P	68	25 P	59	75 P	68	
Years of education (years)		3,059	Mean	12	SD	2.6	Mean	12.4	SD	2.7	Mean	11.6	SD	2.5	<0.01
			Median	11			Median	11			Median	11			
			25 P	10	75 P	13	25 P	10	75 P	13	25 P	10	75 P	13	
Body Mass Index (kg/m^2)		3,059	Mean	28.2	SD	5.3	Mean	28.6	SD	4.6	Mean	27.8	SD	5.9	<0.01
			Median	27.4			Median	28			Median	26.6			
			25 P	24.5	75 P	30.9	25 P	25.5	75 P	31	25 P	23.6	75 P	30.8	
Waist circumference (cm)		3,057	Mean	94.6	SD	14.3	Mean	100.7	SD	12.4	Mean	89.3	SD	13.8	<0.01
			Median	94.2			Median	99.4			Median	87.6			
			25 P	84	75 P	103.9	25 P	92.2	75 P	108.2	25 P	78.6	75 P	98	
Hip circumference (cm)		3,057	Mean	104.7	SD	10.4	Mean	104	SD	8.2	Mean	105.3	SD	12	0.68
			Median	103.1			Median	103			Median	103.1			
			25 P	97.8	75 P	109.3	25 P	98.7	75 P	107.9	25 P	96.7	75 P	111.4	
Waist-Hip-Ratio		3,057	Mean	0.9	SD	0.1	Mean	1	SD	0.1	Mean	0.8	SD	0.1	<0.01
			Median	0.9			Median	1			Median	0.8			
			25 P	0.8	75 P	1	25 P	0.9	75 P	1	25 P	0.8	75 P	0.9	
Physical activity	active	3,058	%	71.8	n	2,195	%	69.5	n	985	%	73.8	n	1,210	0.009
	not active		%	28.2	n	863	%	30.5	n	433	%	26.2	n	430	
Smoking	Smoker	3,056	%	14.2	n	434	%	13.9	n	197	%	14.5	n	237	<0.01
	Non-smoker		%	41.5	n	1,267	%	47.8	n	677	%	36	n	590	
	Never smoked		%	44.3	n	1,355	%	38.3	n	543	%	49.5	n	812	

Table 2 continued:

CATEGORY		n	OVERALL				MALE				FEMALE				p-Value
			%	100.0	n	3,059	%	46.4	n	1,418	%	53.6	n	1,641	
Systolic blood pressure (mmHg)		3,050	Mean	125.5	SD	16.8	Mean	129.7	SD	15.9	Mean	121.9	SD	16.8	<0.01
			Median	124			Median	128.5			Median	119			
			25 P	114	75 P	135.5	25 P	119	75 P	139.5	25 P	110.5	75 P	131.5	
Diastolic blood pressure (mmHg)		3,050	Mean	74.3	SD	9.9	Mean	76.5	SD	9.8	Mean	72.5	SD	9.6	<0.01
			Median	73.5			Median	76			Median	71.5			
			25 P	67.5	75 P	81	25 P	70	75 P	83	25 P	65.5	75 P	78.5	
Isolated Hypertension	yes	3,050	%	13.4	n	408	%	16.8	n	238	%	10.4	n	170	<0.01
	no		%	86.6	n	2,642	%	83.2	n	1,175	%	89.6	n	1,467	
Diabetes Mellitus	Yes	3,054	%	8.1	n	246	%	9.2	n	130	%	7.1	n	116	0.04
	No		%	91.9	n	2,808	%	90.8	n	1,287	%	92.9	n	1,521	
Cancer	Yes	3,058	%	12.9	n	396	%	11.1	n	158	%	14.5	n	238	<0.01
	No		%	87.1	n	2,662	%	88.9	n	1,260	%	85.5	n	1,402	

Table 3: Prevalence of cardiovascular diseases in KORA-Fit participants

CATEGORY		n	OVERALL				MALE				FEMALE				p-Value
			%	100.0	n	3,059	%	46.4	n	1,418	%	53.6	n	1,641	
Deep vein thrombosis in the anamnesis	Yes	3,056	%	4.2	n	127	%	3.4	n	48	%	4.8	n	79	0.08
	No		%	95.5	n	2,918	%	96.1	n	1,362	%	94.9	n	1,556	
	I don't know		%	0.4	n	11	%	0.5	n	7	%	0.2	n	4	
Pulmonary embolism in the anamnesis	Yes	3,056	%	1.1	n	35	%	1.3	n	19	%	1	n	16	0.16
	No		%	98.6	n	3,014	%	98.6	n	1,397	%	98.7	n	1,617	
	I don't know		%	0.2	n	7	%	0.1	n	1	%	0.4	n	6	
Myocardial infarction	Yes	3,058	%	3	n	92	%	4.9	n	70	%	1.3	n	22	<0.01
	No		%	97	n	2,966	%	95.1	n	1,348	%	98.7	n	1,618	
Ischemic stroke	Yes	3,058	%	2.7	n	82	%	3.6	n	51	%	1.9	n	31	<0.01
	No		%	97.3	n	2,976	%	96.4	n	1,367	%	98.1	n	1,609	
CVD	Yes	3,056	%	9.7	n	296	%	11.8	n	167	%	7.9	n	129	<0.01
	No		%	90.3	n	2,760	%	88.2	n	1,250	%	92.1	n	1,510	
Cardiovascular incident (MI or IS)	Yes	3,058	%	5.6	n	170	%	8.4	n	119	%	3.1	n	51	<0.01
	No		%	94.4	n	2,888	%	91.6	n	1,299	%	96.9	n	1,589	
VT	Yes	3,056	%	4.6	n	140	%	3.7	n	53	%	5.3	n	87	0.05
	No		%	95.4	n	2,916	%	96.3	n	1,364	%	94.7	n	1,552	

CVD = cardiovascular disease, VT = venous thrombosis, MI = myocardial infarction, IS = ischemic stroke

Table 4: Characteristics of KORA-Fit participants with a diagnosis of venous thrombosis

CATEGORY		n	VENOUS THROMBOSIS												p-Value
			OVERALL				YES				NO				
			%	100	n	3,056	%	4.6	n	140	%	95.3	n	2,916	
Sex	male	3,056	%	46.4	n	1,417	%	37.9	n	53	%	46.8	n	1,364	0.05
	female		%	53.6	n	1,639	%	62.1	n	87	%	53.2	n	1,552	
Age		3,059	Mean	63.2	SD	5.5	Mean	64.6	SD	5.4	Mean	63.1	SD	5.5	<0.01
			Median	63			Median	66			Median	63			
			25 P	59	75 P	68	25 P	61	75 P	69	25 P	59	75 P	68	
Years of education (years)		3,059	Mean	12	SD	2.6	Mean	11.6	SD	2.6	Mean	12	SD	2.6	0.02
			Median	11			Median	10			Median	11			
			25 P	10	75 P	13	25 P	10	75 P	13	25 P	10	75 P	13	
Body Mass Index (kg/m^2)		3,059	Mean	28.2	SD	5.3	Mean	30.3	SD	6.9	Mean	28.1	SD	5.2	<0.01
			Median	27.4			Median	28.2			Median	27.4			
			25 P	24.5	75 P	30.9	25 P	25.7	75 P	33.7	25 P	24.4	75 P	30.8	
Waist circumference (cm)		3,057	Mean	94.6	SD	14.3	Mean	98.2	SD	16.4	Mean	94.4	SD	14.2	0.02
			Median	94.2			Median	96.1			Median	94			
			25 P	84	75 P	103.9	25 P	86.2	75 P	107.7	25 P	83.8	75 P	103.8	
Hip circumference (cm)		3,057	Mean	104.7	SD	10.4	Mean	108.7	SD	14.1	Mean	104.5	SD	10.2	<0.01
			Median	103.1			Median	104.8			Median	103			
			25 P	97.8	75 P	109.3	25 P	98.9	75 P	113	25 P	97.7	75 P	109.2	
Waist-Hip-Ratio		3,057	Mean	0.9	SD	0.1	Mean	0.9	SD	0.1	Mean	0.9	SD	0.1	0.83
			Median	0.9			Median	0.9			Median	0.9			
			25 P	0.8	75 P	1	25 P	0.8	75 P	1	25 P	0.8	75 P	1	
Physical activity	active	3,058	%	71.8	n	2,195	%	72.1	n	101	%	71.8	n	2,093	1.00
	not active		%	28.2	n	863	%	27.9	n	39	%	28.2	n	823	
Smoking	Smoker	3,056	%	14.2	n	434	%	12.9	n	18	%	14.2	n	415	0.70
	Non-smoker		%	41.5	n	1,267	%	45	n	63	%	41.3	n	1,204	
	Never smoked		%	44.3	n	1,355	%	42.1	n	59	%	44.5	n	1,296	

Table 4 continued:

CATEGORY		n	VENOUS THROMBOSIS												p-Value
			OVERALL				YES				NO				
			%	100	n	3,056	%	4.6	n	140	%	95.3	n	2,916	
Systolic blood pressure (mmHg)		3,050	Mean	125.5	SD	16.8	Mean	124.9	SD	17	Mean	125.5	SD	16.8	0.89
			Median	124			Median	125			Median	123.5			
			25 P	114	75 P	135.5	25 P	115.5	75 P	134.5	25 P	113.5	75 P	135.5	
Diastolic blood pressure (mmHg)		3,050	Mean	74.3	SD	9.9	Mean	75	SD	10	Mean	74.3	SD	9.9	0.29
			Median	73.5			Median	78.6			Median	73.5			
			25 P	67.5	75 P	81	25 P	66.9	75 P	88.4	25 P	67.5	75 P	80.5	
Isolated Hypertension	yes	3,050	%	13.4	n	408	%	9.4	n	13	%	13.6	n	395	0.20
	no		%	86.6	n	2,642	%	90.6	n	126	%	86.4	n	2,515	
Diabetes Mellitus	Yes	3,054	%	8.1	n	246	%	14.5	n	20	%	7.8	n	226	<0.01
	No		%	91.9	n	2,808	%	91.9	n	118	%	92.2	n	2,688	
Cancer	Yes	3,058	%	12.9	n	396	%	14.3	n	20	%	12.9	n	376	0.61
	No		%	87.1	n	2,662	%	85.7	n	120	%	87.1	n	2,540	

Table 5: Medication use in KORA-Fit participants with a diagnosis of venous thrombosis

CATEGORY		n	VENOUS THROMBOSIS												p-Value
			OVERALL				YES				NO				
			%	100	n	3,056	%	4.6	n	140	%	95.3	n	2,916	
Anti-diabetic medication	Yes	3,056	%	7.7	n	236	%	13.6	n	19	%	7.4	n	217	0.014
	No		%	92.3	n	2,820	%	86.4	n	121	%	92.6	n	2,698	
Antihypertensive medication	Yes	3,056	%	42.7	n	1,304	%	55	n	77	%	42.1	n	1,227	<0.01
	No		%	57.3	n	1,752	%	45	n	63	%	57.9	n	1,688	
Beta blocker	Yes	3,056	%	20.8	n	636	%	25	n	35	%	20.6	n	601	0.24
	No		%	79.2	n	2,420	%	75	n	105	%	79.4	n	2,314	
ACE inhibitor	Yes	3,056	%	14.5	n	444	%	21.4	n	30	%	14.2	n	414	0.03
	No		%	85.5	n	2,612	%	78.6	n	110	%	85.8	n	2,501	
AT II inhibitor	Yes	3,056	%	19.3	n	590	%	20.7	n	29	%	19.2	n	561	0.66
	No		%	80.7	n	2,466	%	79.3	n	111	%	80.8	n	2,354	
Calcium channel blocker	Yes	3,056	%	12.3	n	377	%	13.6	n	19	%	12.3	n	358	0.60
	No		%	87.7	n	2,679	%	86.4	n	121	%	87.7	n	2,557	
Diuretic	Yes	3,056	%	17.6	n	538	%	31.4	n	44	%	16.9	n	494	<0.01
	No		%	82.4	n	2,518	%	68.6	n	96	%	83.1	n	2,421	
ASS	Yes	3,056	%	11.1	n	340	%	20.7	n	29	%	10.7	n	311	<0.01
	No		%	88.9	n	2,716	%	79.3	n	111	%	89.3	n	2,604	

Table 5 continued:

CATEGORY		n	VENOUS THROMBOSIS												p-Value
			OVERALL				YES				NO				
			%	100	n	3,056	%	4.6	n	140	%	95.3	n	2,916	
Anticoagulants	Yes	3,056	%	3.5	n	106	%	17.9	n	25	%	2.8	n	81	<0.01
	No		%	96.5	n	2,950	%	82.1	n	115	%	97.2	n	2,834	
Glycoside	Yes	3,056	%	0.1	n	4	%	0	n	0	%	0.1	n	4	1.00
	No		%	99.9	n	3,052	%	100	n	140	%	99.9	n	2,911	
Antiarrhythmic	Yes	3,056	%	0.5	n	14	%	0	n	0	%	0.5	n	14	1.00
	No		%	99.5	n	3,042	%	100	n	140	%	99.5	n	2,901	
Statine	Yes	3,056	%	17.5	n	534	%	28.6	n	40	%	16.9	n	494	<0.01
	No		%	82.5	n	2,522	%	71.4	n	100	%	83.1	n	2,421	
Fibrates	Yes	3,056	%	0.2	n	7	%	1.4	n	2	%	0.2	n	5	0.04
	No		%	99.8	n	3,049	%	98.6	n	138	%	99.8	n	2,910	
NSAID regularly	Yes	3,055	%	2.5	n	76	%	4.3	n	6	%	2.4	n	70	0.16
	No		%	97.5	n	2,979	%	95.7	n	134	%	97.6	n	2,844	
Gout medication	Yes	3,056	%	4.6	n	141	%	10	n	14	%	4.4	n	127	<0.01
	No		%	95.4	n	2,915	%	90	n	126	%	95.6	n	2,788	
Multimedication	Yes	3,049	%	14.5	n	442	%	30.7	n	43	%	13.7	n	399	<0.01
	No		%	85.5	n	2,607	%	69.3	n	97	%	86.3	n	2,509	

Participants with a VT diagnosis took significantly more often anticoagulants and more medicine overall than those without such a diagnosis ($p < 0.01$) (Table 5).

The results of the clinical laboratory testing showed no significant difference in serum total cholesterol concentrations between VT and no-VT groups (Table 6). However, a significant reduction of glomerular filtration rate (mean = 77.2 ml/min; SD = 13.4 for VT group versus mean = 81.5 ml/min; SD = 13 for no-VT group; $p < 0.01$) was registered. The overall inflammation level, measured with hs CRP, was slightly higher in VT group ($p < 0.01$).

Table 6: Results of clinical laboratory parameters in participants of the KORA-Fit study, overall and stratified by diagnosis of venous thrombosis

CATEGORY	n	VENOUS THROMBOSIS												p-Value
		OVERALL				YES				NO				
		%	100	n	3,056	%	4.6	n	140	%	95.3	n	2,916	
GFR (ml/min)	3,047	Mean	81.3	SD	13	Mean	77.2	SD	13.4	Mean	81.5	SD	13	<0.01
		Median	82.7			Median	78.6			Median	83.1			
		25 P	73	75 P	91.3	25 P	66.9	75 P	88.4	25 P	73.2	75 P	91.5	
Creatinine (mg/dl)	3,047	Mean	0.9	SD	0.2	Mean	0.9	SD	0.2	Mean	0.9	SD	0.2	0.23
		Median	0.9			Median	0.9			Median	0.9			
		25 P	0.8	75 P	1	25 P	0.8	75 P	1	25 P	0.8	75 P	1	
Total-cholesterole (mg/dl)	3,048	Mean	212.9	SD	41.7	Mean	207.8	SD	43.9	Mean	213.1	SD	41.6	0.08
		Median	212.4			Median	206.1			Median	212.9			
		25 P	184.7	75 P	239.1	25 P	176	75 P	239.4	25 P	185.2	75 P	239.1	
Non-HDL-cholesterole (mg/dl)	3,047	Mean	148.5	SD	40.6	Mean	145	SD	43.8	Mean	148.7	SD	40.4	0.19
		Median	146.5			Median	140.7			Median	146.8			
		25 P	120.8	75 P	174.1	25 P	115.3	75 P	171.9	25 P	120.9	75 P	174.1	
HDL-cholesterole (mg/dl)	3,047	Mean	64.3	SD	18.5	Mean	62.8	SD	18.7	Mean	64.4	SD	18.5	0.28
		Median	62			Median	60.6			Median	62			
		25 P	50.8	75 P	75.5	25 P	48.3	75 P	75	25 P	50.9	75 P	75.5	
LDL-cholesterole (mg/dl)	2,994	Mean	124.1	SD	37	Mean	119.2	SD	40.6	Mean	124.4	SD	36.9	0.06
		Median	123.1			Median	115.2			Median	123.5			
		25 P	98.6	75 P	146.8	25 P	93	75 P	144.8	25 P	98.9	75 P	146.9	
Triglycerides (mg/dl)	3,048	Mean	124.6	SD	78.7	Mean	133.3	SD	75.9	Mean	124.2	SD	78.9	0.07
		Median	106.9			Median	115.4			Median	106.7			
		25 P	78.2	75 P	147.8	25 P	83	75 P	165	25 P	78	75 P	147.4	

Table 6 continued:

CATEGORY	n	VENOUS THROMBOSIS												p-Value
		OVERALL				YES				NO				
		%	100	n	3,056	%	4.6	n	140	%	95.3	n	2,916	
GGT (U/l)	3,047	Mean	35.7	SD	43.6	Mean	38.1	SD	68	Mean	35.6	SD	42.1	0.58
		Median	24			Median	23.5			Median	24			
		25 P	17	75 P	38	25 P	15.3	75 P	37	25 P	17	75 P	39	
GOT, AST (U/l)	3,047	Mean	25.4	SD	10.3	Mean	26.2	SD	18	Mean	25.3	SD	9.8	0.79
		Median	23.4			Median	23			Median	23.4			
		25 P	20	75 P	27.9	25 P	19.8	75 P	28.6	25 P	20	75 P	27.9	
GPT, ALT (U/l)	3,048	Mean	27.4	SD	14.9	Mean	28.1	SD	21.7	Mean	27.3	SD	14.5	0.60
		Median	24			Median	23.9			Median	24			
		25 P	18.8	75 P	31.2	25 P	17.4	75 P	30.7	25 P	18.8	75 P	31.3	
hs CRP (mg/l)	3,047	Mean	2.7	SD	4.5	Mean	3.3	SD	4	Mean	2.7	SD	4.5	<0.01
		Median	1			Median	2			Median	1			
		25 P	1	75 P	3	25 P	1	75 P	4	25 P	1	75 P	3	

3% of all KORA-Fit participants were prevalent with MI (n = 92). The share of men, who suffered from MI, was significantly higher (76.1% male versus 23.9% female). The mean age of MI participants was 65.1 years (SD = 5). Participants with MI had a significantly higher BMI (mean = 29.2 kg/m^2; SD = 4.9) in comparison to the no-MI group (mean = 28.1 kg/m^2; SD = 5.3; p = 0.014). Subjects with an MI diagnosis also more often suffered from diabetes mellitus (0.2% in MI group versus 0.1% in no-MI group; p < 0.01) (see Table 18 in the Appendix). The analysis of clinical laboratory parameters showed, that participants prevalent with MI had significantly lower glomerular filtration rate and higher levels of transaminases. Total-cholesterol levels were, however, higher in no-MI group (see Table 19 in the Appendix). MI participants reported to take more medication, as opposed to no-MI group. Thereby the share of MI participants, taking ASS, statins and anti-hypertensive medication, was expectedly higher, as in no-MI participants (see Table 20 in the Appendix).

2.7% of all KORA-Fit participants suffered from IS (n = 82). Sex distribution showed male predominance (62.2% male versus 37.8% female). The mean age was 66 years old (SD = 4.8). Participants, prevalent with IS, also had diabetes mellitus more often (15.9% in IS group versus 7.8% in no-IS group) (see Table 21 in the Appendix). The analysis of clinical laboratory parameters showed no significant differences in glomerular filtration rate. IS participants showed higher levels of hs CRP (mean = 3.2 mg/L; SD = 4.5 in IS group versus mean = 2.7; SD = 4.5 in no-IS group; p = 0.02). Total-cholesterol level was significantly lower in IS participants (mean = 187.9 mg/dl; SD = 37.4 in IS group versus mean = 213.5 mg/dl; SD = 41.6 in no-IS group; p < 0.01) (see Table 22 in the Appendix). IS participants reported to take more medication, as opposed to no-IS group. Thereby the share of anti-hypertensive medication, ASS and statins was significantly higher, as in no-IS participants. The share of participants, who took anticoagulants was more than 6-fold higher, compared to no-IS group (19.5% in IS group vs 3% in no-IS group; p = 0.01) (see Table 23 in the Appendix).

3.2. Description and CVD prevalence in S4 participants of KORA-Fit

In the S4 participants of the KORA-Fit study, the association between blood coagulation markers and the prevalence of CVD was explored. The statistical

evaluation was performed among the KORA-Fit S4 participants with available citrate plasma. The proportion of 47% male (n = 378) and 53% female (n = 427) participants was similar to the whole KORA-Fit survey. Mean age was registered with 62,4 years (SD = 5,7), and there was no significant difference between male and female participants (Table 7).

Out of 805 participants, 8.6% (n = 69) have got a diagnosis of one of the cardiovascular endpoints. Thereby the share of men regarding all of the analyzed endpoints was significantly higher than the share of women, as reported for the entire KORA-Fit group. The exception was registered in the VT group, where there was no statistical difference in the sex distribution (Table 8).

The analysis of clinical laboratory parameters in KORA-Fit S4 participants showed no significant difference in glomerular filtration rate in males and females, in comparison to overall KORA-Fit group. S4 male participants showed increased levels of transaminases, as opposed to female participants (see Table 24 in the Appendix). The medication analysis indicated, that male S4 participants took more frequently ASS, anticoagulants, statins and gout medication (see Table 25 in the Appendix) than females.

Table 7: Characteristics of KORA-Fit S4 participants, stratified by sex

CATEGORY		n	OVERALL				MALE				FEMALE				p-Value
			%	100	n	805	%	47.0	n	378	%	53.0	n	427	
Age		805	Mean	62.4	SD	5.7	Mean	62.4	SD	5.8	Mean	62.4	SD	5.5	0.99
			Median	63			Median	62			Median	63			
			25 P	58	75 P	67	25 P	57	75 P	67	25 P	58	75 P	67	
Years of education (years)		805	Mean	12.3	SD	2.6	Mean	12.7	SD	2.7	Mean	11.9	SD	2.6	<0.01
			Median	11			Median	12			Median	11			
			25 P	10	75 P	13	25 P	10	75 P	13.5	25 P	10	75 P	13	
Body Mass Index (kg/m^2)		805	Mean	28.1	SD	5.2	Mean	28.7	SD	5	Mean	27.5	SD	5.4	<0.01
			Median	27.6			Median	28.2			Median	26.8			
			25 P	24.4	75 P	31.1	25 P	25.5	75 P	31.3	25 P	23.5	75 P	30.5	
Waist circumference (cm)		804	Mean	94.6	SD	14.5	Mean	101.3	SD	13.4	Mean	88.6	SD	12.8	<0.01
			Median	94.3			Median	100.6			Median	87.4			
			25 P	83.7	75 P	104.3	25 P	92.6	75 P	109.5	25 P	78.2	75 P	97.6	
Hip circumference (cm)		804	Mean	104.9	SD	10.2	Mean	104.6	SD	9.3	Mean	105.2	SD	10.9	0.84
			Median	103.4			Median	103.4			Median	103.4			
			25 P	98.5	75 P	109.5	25 P	99.1	75 P	108.2	25 P	97.6	75 P	111.2	
Waist-Hip-Ratio		804	Mean	0.9	SD	0.1	Mean	1	SD	0.1	Mean	0.8	SD	0.1	<0.01
			Median	0.9			Median	1			Median	0.8			
			25 P	0.8	75 P	1	25 P	0.9	75 P	1	25 P	0.8	75 P	0.9	
Physical activity	active	805	%	70.2	n	565	%	69	n	261	%	71.2	n	304.0	0.54
	not active		%	29.8	n	240	%	31	n	117	%	28.8	n	123.0	
Smoking	Smoker	805	%	13.7	n	110	%	14.8	n	56	%	12.6	n	54	<0.01
	Non-smoker		%	44.1	n	355	%	50.8	n	192	%	38.2	n	163	
	Never smoked		%	42.2	n	340	%	34.4	n	130	%	49.2	n	210	

Table 7 continued:

CATEGORY		n	OVERALL				MALE				FEMALE				p-Value
			%	100	n	805	%	47.0	n	378	%	53.0	n	427	
Systolic blood pressure (mmHg)		803	Mean	124.9	SD	16.7	Mean	130.2	SD	15.3	Mean	120.2	SD	16.5	<0.01
			Median	123			Median	128			Median	117.5			
			25 P	113.5	75 P	134.5	25 P	120	75 P	140	25 P	109.5	75 P	129.5	
Diastolic blood pressure (mmHg)		803	Mean	74.2	SD	9.6	Mean	76.7	SD	9.4	Mean	72.1	SD	9.3	<0.01
			Median	73.5			Median	75.5			Median	71			
			25 P	67.5	75 P	80.5	25 P	70.5	75 P	84	25 P	65.5	75 P	78	
Isolated Hypertension	yes	803	%	13.2	n	106	%	18.9	n	71	%	8.2	n	35	<0.01
	no		%	86.8	n	697	%	81.1	n	305	%	91.8	n	392	
Diabetes Mellitus	Yes	803	%	8.6	n	69	%	9.5	n	36	%	7.8	n	33	0.38
	No		%	91.4	n	734	%	90.5	n	342	%	92.2	n	392	
Cancer	Yes	805	%	11.4	n	92	%	10.6	n	40	%	12.2	n	52	0.51
	No		%	88.6	n	713	%	89.4	n	338	%	87.8	n	375	

Table 8: Prevalence of cardiovascular diseases in KORA-Fit S4 participants.

CATEGORY		n	OVERALL				MALE				FEMALE				p-Value
			%	100	n	805	%	47.0	n	378	%	53.0	n	427	
Deep vein thrombosis in the anamnesis	Yes	805	%	3	n	24	%	2.9	n	11	%	3	n	13	1.0
	No		%	96.9	n	780	%	97.1	n	367	%	96.7	n	413	
	I don't know		%	0.1	n	1	%	0	n	0	%	0.2	n	1	
Pulmonary embolism in the anamnesis	Yes	805	%	1	n	8	%	2.1	n	8	%	0	n	0	<0.01
	No		%	98.6	n	794	%	97.9	n	370	%	99.3	n	424	
	I don't know		%	0.4	n	3	%	0	n	0	%	0.7	n	3	
Myocardial infarction	Yes	805	%	3	n	24	%	5.3	n	20	%	0.9	n	4	<0.01
	No		%	97	n	781	%	94.7	n	358	%	99.1	n	423	
Ischemic stroke	Yes	805	%	2.7	n	22	%	4.2	n	16	%	1.4	n	6	0.02
	No		%	97.3	n	783	%	95.8	n	362	%	98.6	n	421	
CVD	Yes	805	%	8.6	n	69	%	12.7	n	48	%	4.9	n	21	<0.01
	No		%	91.4	n	736	%	87.3	n	330	%	95.1	n	406	
Cardiovascular inci dent (MI or IS)	Yes	805	%	5.5	n	44	%	9.3	n	35	%	2.1	n	9	<0.01
	No		%	94.5	n	761	%	90.7	n	343	%	97.9	n	418	
VT	Yes	805	%	3.2	n	26	%	3.4	n	13	%	3	n	13	0.84
	No		%	96.8	n	779	%	96.6	n	365	%	97	n	414	

CVD = cardiovascular disease, VT = venous thrombosis, MI = myocardial infarction, IS = ischemic stroke

The overall prevalence of participants with VT in the anamnesis was 3.2% (n = 26). The VT group was significantly older than the no-VT group, with a mean age of 64.6 years (SD = 5.4, p = 0.04) (Table 9).

Similar to the results in the entire KORA-Fit study, participants with prevalent VT showed a lower education level, with the mean of 11.3 years of education (SD = 2.5; p = 0.04), whereas the no-VT group had in average 12,3 years of education (SD = 2.6, p = 0.04). Participants with prevalent VT also had a higher mean BMI (mean = 31.1 kg/m^2; SD = 7.5; p = 0.04).

There was no significant difference between the groups regarding their physical activity, smoking pattern and cancer (Table 9).

The medication analysis of the S4 survey showed in comparison to the entire KORA-Fit group no significant difference regarding multimedication (p = 0.13). Participants with prevalent VT, similar to the results in the KORA-Fit survey, took significantly more anticoagulants as no-VT group (30.8% (n = 8) versus 2.6% (n = 20) respectively, p < 0.01) (Table 10).

The results of the clinical laboratory testing in KORA-Fit S4 participants showed lower levels of glomerular filtration rate in VT group, as opposed to no-VT group (mean = 74.2 ml/min; SD = 13.8 versus mean = 83.8 ml/min; SD = 12.8; p < 0.01). Creatinine levels were significantly higher in the participants with prevalent VT (mean = 1.0 mg/dl; SD = 0.2 versus mean = 0.9 mg/dl; SD = 0.2; p < 0.01). Such clinical biomarkers as cholesterol levels (including total cholesterol, non-HDL-cholesterol, HDL-cholesterol, and triglycerides), and transaminases (GGT, GOT, and GPT), as well as hs-CRP showed no significant difference between VT and no-VT groups (Table 11).

Table 9: Characteristics of KORA-Fit S4 participants with a diagnosis of venous thrombosis

CATEGORY		n	VENOUS THROMBOSIS												p-Value
			OVERALL				YES				NO				
			%	100	n	805	%	3.2	n	26	%	96.8	n	779	
Sex	male	805	%	47	n	378	%	50	n	13	%	46.9	n	365	0.84
	female		%	53	n	427	%	50	n	13	%	53.1	n	414	
Age		805	Mean	62.4	SD	5.7	Mean	64.6	SD	5.4	Mean	62.3	SD	5.7	0.04
			Median	63			Median	66			Median	63			
			25 P	58	75 P	67	25 P	61	75 P	68.3	25 P	57	75 P	67	
Years of education (years)		805	Mean	12.3	SD	2.6	Mean	11.3	SD	2.5	Mean	12.3	SD	2.6	0.04
			Median	11			Median	10			Median	11			
			25 P	10	75 P	13	25 P	10	75 P	13	25 P	10	75 P	13	
Body Mass Index (kg/m^2)		805	Mean	28.1	SD	5.2	Mean	31.1	SD	7.5	Mean	28	SD	5.1	0.04
			Median	27.6			Median	28.5			Median	27.4			
			25 P	24.4	75 P	31.1	25 P	26.3	75 P	34.1	25 P	24.3	75 P	31.1	
Waist circumference (cm)		804	Mean	94.6	SD	14.5	Mean	100.9	SD	19.1	Mean	94.4	SD	14.3	0.08
			Median	94.3			Median	97.4			Median	94.1			
			25 P	83.7	75 P	104.3	25 P	86.4	75 P	110.3	25 P	83.6	75 P	104	
Hip circumference (cm)		804	Mean	104.9	SD	10.2	Mean	110.4	SD	16.7	Mean	104.7	SD	9.8	0.10
			Median	103.4			Median	105.3			Median	103.3			
			25 P	98.5	75 P	109.5	25 P	99.5	75 P	113.2	25 P	98.4	75 P	109.5	
Waist-Hip-Ratio		804	Mean	0.9	SD	0.1	Mean	0.9	SD	0.1	Mean	0.9	SD	0.1	0.35
			Median	0.9			Median	0.9			Median	0.9			
			25 P	0.8	75 P	1	25 P	0.8	75 P	1	25 P	0.8	75 P	1	
Physical activity	active	805	%	70.2	n	565	%	80.8	n	21	%	69.8	n	544	0.28
	not active		%	29.8	n	240	%	19.2	n	5	%	30.2	n	235	
Smoking	Smoker	805	%	13.7	n	110	%	3.8	n	1	%	14	n	109	0.39
	Non-smoker		%	44.1	n	355	%	50	n	13	%	43.9	n	342	
	Never smoked		%	42.2	n	340	%	46.2	n	12	%	42.1	n	328	

Table 9 continued:

CATEGORY		n	VENOUS THROMBOSIS												p-Value
			OVERALL				YES				NO				
			%	100	n	805	%	3.2	n	26	%	96.8	n	779	
Systolic blood pressure (mmHg)		803	Mean	124.9	SD	16.7	Mean	131.8	SD	22.6	Mean	124.7	SD	16.5	0.03
			Median	123			Median	130			Median	122.8			
			25 P	113.5	75 P	134.5	25 P	123.5	75 P	142	25 P	113	75 P	134	
Diastolic blood pressure (mmHg)		803	Mean	74.2	SD	9.6	Mean	77.3	SD	12.4	Mean	74.1	SD	9.5	0.20
			Median	73.5			Median	76			Median	73.5			
			25 P	67.5	75 P	80.5	25 P	69.5	75 P	86	25 P	67.5	75 P	80.5	
Isolated Hypertension	Yes	803	%	13.2	n	106	%	16	n	4	%	13.1	n	102	0.56
	No		%	86.8	n	697	%	84	n	21	%	86.9	n	676	
Diabetes Mellitus	Yes	803	%	8.6	n	69	%	16	n	4	%	8.4	n	65	0.26
	No		%	91.4	n	734	%	84	n	21	%	91.6	n	713	
Cancer	Yes	805	%	11.4	n	92	%	7.7	n	2	%	11.6	n	90	0.76
	No		%	88.6	n	713	%	92.3	n	24	%	88.4	n	689	

Table 10: Medication use in KORA-Fit S4 participants with a diagnosis of venous thrombosis

CATEGORY		n	VENOUS THROMBOSIS												p-Value
			OVERALL				YES				NO				
			%	100	n	805	%	3.2	n	26	%	96.8	n	779	
Anti-diabetic medication	Yes	804	%	8.1	n	65	%	11.5	n	3	%	8	n	62	0.46
	No		%	91.9	n	739	%	88.5	n	23	%	92	n	716	
Antihypertensive medication	Yes	804	%	41.5	n	334	%	69.2	n	18	%	40.6	n	316	<0.01
	No		%	58.5	n	470	%	30.8	n	8	%	59.4	n	462	
Beta blocker	Yes	804	%	20.5	n	165	%	34.6	n	9	%	20.1	n	156	0.08
	No		%	79.5	n	639	%	65.4	n	17	%	79.9	n	622	
ACE inhibitor	Yes	804	%	13.1	n	105	%	42.3	n	11	%	12.1	n	94	<0.01
	No		%	86.9	n	699	%	57.7	n	15	%	87.9	n	684	
AT II inhibitor	Yes	804	%	19.7	n	158	%	15.4	n	4	%	19.8	n	154	0.80
	No		%	80.3	n	646	%	84.6	n	22	%	80.2	n	624	
Calcium channel blocker	Yes	804	%	12.9	n	104	%	15.4	n	4	%	12.9	n	100	0.76
	No		%	87.1	n	700	%	84.6	n	22	%	87.1	n	678	
Diuretic	Yes	804	%	16.3	n	131	%	19.2	n	5	%	16.2	n	126	0.60
	No		%	83.7	n	673	%	80.8	n	21	%	83.8	n	652	
ASS	Yes	804	%	10.3	n	83	%	11.5	n	3	%	10.3	n	80	0.74
	No		%	89.7	n	721	%	88.5	n	23	%	89.7	n	698	

Table 10 continued:

CATEGORY		n	VENOUS THROMBOSIS												p-Value
			OVERALL				YES				NO				
			%	100	n	805	%	3.2	n	26	%	96.8	n	779	
Anticoagulants	Yes	804	%	3.5	n	28	%	30.8	n	8	%	2.6	n	20	<0.01
	No		%	96.5	n	776	%	69.2	n	18	%	97.4	n	758	
Glycoside	Yes	804	%	0.1	n	1	%	0	n	0	%	0.1	n	1	1.00
	No		%	99.9	n	803	%	100	n	26	%	99.9	n	777	
Antiarrhythmic	Yes	804	%	0.4	n	3	%	0	n	0	%	0.4	n	3	1.00
	No		%	99.6	n	801	%	100	n	26	%	99.6	n	801	
Statine	Yes	804	%	16	n	129	%	34.6	n	9	%	15.4	n	120	0.02
	No		%	84	n	675	%	65.4	n	17	%	84.6	n	658	
Fibrats	Yes	804	%	0.4	n	3	%	3.8	n	1	%	0.3	n	2	0.09
	No		%	99.6	n	801	%	96.2	n	25	%	99.7	n	776	
NSAID regularly	Yes	804	%	2.4	n	19	%	7.7	n	2	%	2.2	n	17	0.12
	No		%	97.6	n	785	%	92.3	n	24	%	97.8	n	761	
Gout medication	Yes	804	%	4.7	n	38	%	7.7	n	2	%	4.6	n	36	0.35
	No		%	95.3	n	766	%	92.3	n	24	%	95.4	n	742	
Multimedication	Yes	804	%	12.7	n	102	%	23.1	n	6	%	12.3	n	96	0.13
	No		%	87.3	n	702	%	76.9	n	20	%	87.7	n	682	

Table 11: Results of clinical laboratory parameters in the participants of the KORA-Fit S4 study, overall and stratified by diagnosis of venous thrombosis

CATEGORY	n	VENOUS THROMBOSIS												p-Value
		OVERALL				YES				NO				
		%	100	n	805	%	3.2	n	26	%	96.8	n	779	
GFR (ml/min)	805	Mean	83.5	SD	13	Mean	74.2	SD	13.8	Mean	83.8	SD	12.8	<0.01
		Median	85			Median	75.7			Median	85.4			
		25 P	75.4	75 P	93.3	25 P	64.1	75 P	86.9	25 P	75.7	75 P	93.6	
Creatinine (mg/dl)	805	Mean	0.9	SD	0.2	Mean	1.0	SD	0.2	Mean	0.9	SD	0.2	<0.01
		Median	0.8			Median	0.9			Median	0.8			
		25 P	0.7	75 P	1	25 P	0.8	75 P	1.1	25 P	0.7	75 P	1	
Total-cholesterole (mg/dl)	805	Mean	211.2	SD	40.9	Mean	209.6	SD	42.2	Mean	211.2	SD	40.9	0.84
		Median	210			Median	197.0			Median	210.7			
		25 P	183	75 P	237	25 P	180.7	75 P	243.7	25 P	183	75 P	237	
Non-HDL-cholesterole (mg/dl)	805	Mean	147.3	SD	39.7	Mean	150.8	SD	42	Mean	147.1	SD	39.6	0.87
		Median	146			Median	142.5			Median	146			
		25 P	118.2	75 P	173	25 P	120.3	75 P	184	25 P	118.1	75 P	173	
HDL-cholesterole (mg/dl)	805	Mean	63.9	SD	19.1	Mean	58.8	SD	16.9	Mean	64.1	SD	19.1	0.15
		Median	61			Median	56.0			Median	62			
		25 P	49	75 P	75.2	25 P	44.1	75 P	70.3	25 P	49	75 P	75.3	
LDL-cholesterole (mg/dl)	789	Mean	123.1	SD	36.4	Mean	124.8	SD	38.3	Mean	123	SD	36.4	0.97
		Median	121.8			Median	115.5			Median	122.2			
		25 P	96.1	75 P	145.2	25 P	95.4	75 P	148.8	25 P	96.2	75 P	145.2	
Triglycerides (mg/dl)	805	Mean	124.4	SD	77.5	Mean	129.8	SD	55.9	Mean	124.3	SD	78.1	0.32
		Median	106			Median	114.5			Median	106			
		25 P	77	75 P	148.4	25 P	86.3	75 P	184.7	25 P	77	75 P	148	

Table 11 continued:

CATEGORY	n	VENOUS THROMBOSIS												p-Value
		OVERALL				YES				NO				
		%	100	n	805	%	3.2	n	26	%	96.8	n	779	
GGT (U/l)	805	Mean	35.7	SD	40.2	Mean	28.2	SD	16.6	Mean	36	SD	40.8	0.54
		Median	25			Median	24.0			Median	25			
		25 P	17	75 P	39	25 P	15.8	75 P	34.3	25 P	17	75 P	40	
GOT, AST (U/l)	805	Mean	26.2	SD	12.7	Mean	31.1	SD	38.4	Mean	26	SD	10.8	0.79
		Median	24			Median	25.0			Median	24			
		25 P	20.3	75 P	28.3	25 P	19.0	75 P	28.7	25 P	20.5	75 P	28.3	
GPT, ALT (U/l)	805	Mean	28.3	SD	16	Mean	33.0	SD	39.4	Mean	28.1	SD	14.6	0.60
		Median	25			Median	27.2			Median	25			
		25 P	19.1	75 P	32	25 P	21.2	75 P	30	25 P	19	75 P	32.2	
hs CRP (mg/l)	805	Mean	2.5	SD	3.8	Mean	2.3	SD	2.4	Mean	2.5	SD	3.8	1.00
		Median	1			Median	1.5			Median	1			
		25 P	1	75 P	3	25 P	1.0	75 P	3	25 P	1	75 P	3	

3.3. Association between blood coagulation factors and CVD

The results of blood coagulation factor analysis in blood samples of KORA-Fit S4 participants are presented in table 12, stratified by diagnosis of venous thrombosis. In participants with prevalent VT, significantly higher levels of factor VIII were observed as compared to the no-VT group (mean = 142.5%, SD = 40, versus mean = 123.1%, SD = 35.3, $p < 0.01$) (Table 12). Overall, the mean values of all blood coagulation factors were registered within the physiological range, except for d-dimers, which showed higher mean levels in both sexes (mean = 601.8 µg/L; SD = 389.3 for male versus mean = 514.8 µg/L; SD = 419.2 for female; $p = 0.20$).

The results of blood coagulation factors in participants of the KORA-Fit S4 survey, stratified by other cardiovascular endpoints showed significantly higher levels of fibrinogen in the participants with prevalent myocardial infarction and ischemic stroke. For participants with MI, the mean level of fibrinogen lied at 352.1 mg/dl (SD 109.3, $p = 0.04$), as compared to the no-MI group (mean = 303.8 mg/dl, SD = 63.0). For participants prevalent with IS, the mean level of fibrinogen lied at 313 mg/dl (SD = 79.6, $p = 0.04$) in comparison to the no-IS group (mean = 305.0 mg/dl, SD = 64.7) (see Tables 30 and 34 in the appendix).

Table 12: Results of blood coagulation factors in participants of KORA-Fit S4 study with or without a diagnosis of venous thrombosis

COAGULATION FACTOR	n	VENOUS THROMBOSIS												p-Value
		OVERALL				YES				NO				
		%	100	n	805	%	3.2	n	26	%	96.8	n	779	
Quick (%)	771	Mean	107.9	SD	9.6	Mean	108.2	SD	10.5	Mean	107.9	SD	9.6	0.78*
		Median	108.8			Median	106.8			Median	108.8			
		25 P	102.2	75 P	114.5	25 P	102.9	75 P	117.5	25 P	102.2	75 P	114.5	
INR	771	Mean	1	SD	0.1	Mean	1	SD	0.1	Mean	1	SD	0.1	0.85*
		Median	1			Median	1			Median	1			
		25 P	0.9	75 P	1	25 P	0.9	75 P	1	25 P	0.9	75 P	1	
aPTT (sec.)	774	Mean	31	SD	3.3	Mean	29.6	SD	4.7	Mean	31	SD	3.3	0.08*
		Median	30.7			Median	29.9			Median	30.7			
		25 P	28.7	75 P	32.9	25 P	26.4	75 P	32	25 P	28.7	75 P	32.9	
Antithrombin (%)	804	Mean	102.6	SD	10.9	Mean	102.5	SD	11	Mean	102.6	SD	10.9	0.65
		Median	102.5			Median	99.8			Median	102.7			
		25 P	95.5	75 P	109.2	25 P	94.5	75 P	108	25 P	95.5	75 P	109.2	
Fibrinogen (mg/dl)	758	Mean	305.2	SD	65.1	Mean	331.8	SD	93	Mean	304.3	SD	63.8	0.25
		Median	296.1			Median	308.2			Median	295.8			
		25 P	261.5	75 P	336.7	25 P	253.9	75 P	379.7	25 P	261.6	75 P	336	
D-Dimer (µg/l)	805	Mean	517.6	SD	418.3	Mean	601.8	SD	389.3	Mean	514.8	SD	419.2	0.20
		Median	405			Median	488.5			Median	405			
		25 P	306	75 P	556	25 P	290.3	75 P	821.5	25 P	306.0	75 P	554	
Protein C (%)	805	Mean	123.3	SD	19.3	Mean	111.8	SD	31.4	Mean	123.7	SD	18.7	0.17
		Median	123.4			Median	119.3			Median	123.5			
		25 P	111.4	75 P	138.4	25 P	85.9	75 P	137.4	25 P	111.5	75 P	138.6	
Protein S (%)	789	Mean	128.5	SD	36.8	Mean	115.2	SD	57.7	Mean	128.9	SD	35.8	0.11
		Median	126			Median	109.2			Median	126.1			
		25 P	105.1	75 P	146.6	25 P	86.8	75 P	144.4	25 P	105.4	75 P	146.8	
Factor VIII (%)	804	Mean	123.7	SD	35.6	Mean	142.5	SD	40	Mean	123.1	SD	35.3	<0.01
		Median	120.7			Median	140.7			Median	120.3			
		25 P	97.5	75 P	142.9	25 P	117.5	75 P	171.7	25 P	97.2	75 P	142.8	

** = participants taking anticoagulants were excluded*

Subsequently, the regression analysis for cardiovascular endpoints and blood coagulation factors was performed. The results indicated a positive correlation between fibrinogen level and venous thromboembolism (p = 0.03; OR = 1.01; 95% CI) 1.001 – 1.016) (Table 13), as well as between fibrinogen level and myocardial infarction (p = 0.04; OR = 1.01; 95% CI 1.00 – 1.01) (Table 14). Factor VIII also showed a significant positive correlation with venous thromboembolism (p = 0.02; OR = 1.01; 95% CI 1.002 – 1.024). Protein C was negatively correlated with venous thrombosis (p < 0.01; OR = 0.97; 95% CI 0.95 – 0.99) (Table 13). Regarding participants prevalent with ischemic stroke, no statistically significant association with blood coagulation factors was revealed (Table 15).

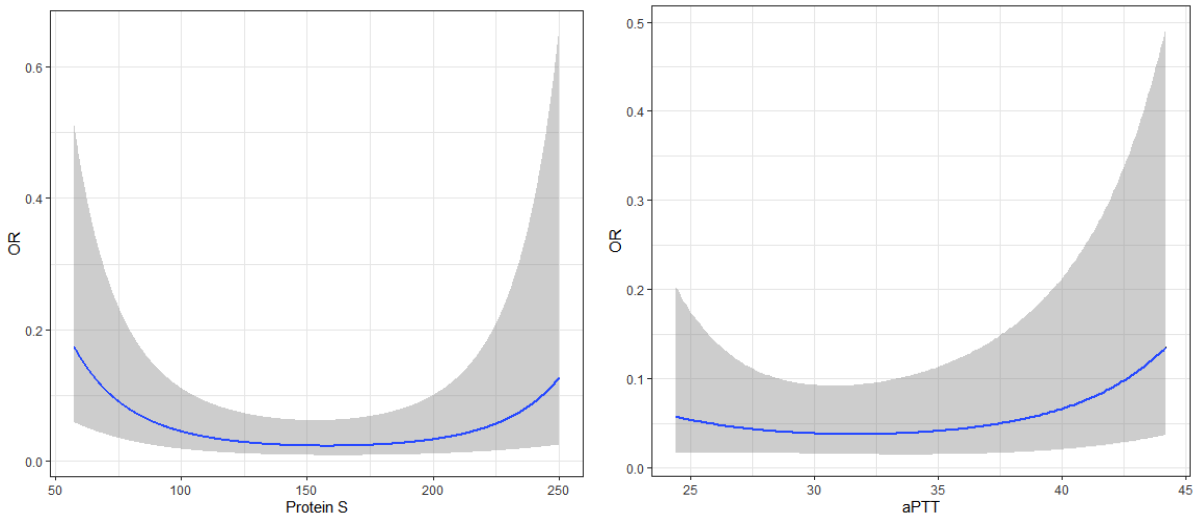
The linearity testing for VT indicated a nonlinear correlation for Protein S level and aPTT. The plots for a nonlinear correlation are represented in the Figure 3. However, the likelihood ratio test showed, that the p-value for overall association was statistically insignificant (p-value for overall association for protein S = 0.068 and for aPTT = 0.065).

Table 13: Odds ratio (OR) and 95% confidence interval (CI) for the risk of venous thrombosis by blood coagulation factors in KORA-Fit S4 participants

VARIABLE	n	p-Value	OR	95% CI	
				Lower	Upper
Quick	769	0.89	1.00	0.95	1.06
INR	769	1	1.01	0.00	8,892.9
aPPT	772	0.06	0.85	0.72	1.01
Antithrombin	802	0.4	1.02	0.98	1.05
Fibrinogen	**756**	**0.03**	**1.01**	**1.00**	**1.02**
D-Dimer	803	0.41	1.00	1.00	1.00
Protein C	**803**	**<0.01**	**0.97**	**0.95**	**0.99**
Protein S	787	0.08	0.99	0.98	1.00
Factor VIII	**802**	**0.02**	**1.01**	**1.00**	**1.02**

Logistic regression models, adjusted for age, sex, Body Mass Index, physical activity, smoking pattern, Diabetes mellitus, cancer and hs-CRP.

Figure 3: Plots for the non-linear association (Odds ratio, OR) between plasma protein S and aPTT and venous thrombosis



p-value for overall association for protein S = 0.0679; p-value for overall association for aPTT = 0.06467

Table 14: Odds ratio (OR) and 95% confidence interval (CI) for the risk of myocardial infarction by blood coagulation factors in KORA-Fit S4 participants

VARIABLE	n	p-Value	OR	95%CI	
				Lower	Upper
Quick	768	0.44	1.02	0.97	1.08
INR	768	0.38	0.02	<0.01	152.3
aPPT	771	0.78	0.98	0.84	1.14
Antithrombin	800	0.09	1.03	1.00	1.07
Fibrinogen	**754**	**0.04**	**1.01**	**1.00**	**1.01**
D-Dimer	801	0.99	1.00	1.00	1.00
Protein C	801	0.18	1.02	0.99	1.04
Protein S	785	0.52	1.00	0.98	1.01
Factor VIII	800	0.44	1.00	0.99	1.02

Adjusted for age, sex, Body Mass Index, smoking pattern, systolic blood pressure, Diabetes mellitus, cancer, glomerular Filtration Rate, Non-HDL-Cholesterole, Triglycerides

Table 15: Odds ratio (OR) and 95% confidence interval (CI) for the risk of ischemic stroke by blood coagulation factors in KORA-Fit S4 participants

VARIABLE	n	p-Value	OR	95% CI	
				Lower	Upper
Quick	768	0.83	0.99	0.94	1.05
INR	768	0.81	2.88	<0.01	17,216.3
aPPT	771	0.31	0.92	0.77	1.09
Antithrombin	800	0.58	0.99	0.95	1.03
Fibrinogen	754	0.43	1.00	0.99	1.01
D-Dimer	801	0.96	1.00	1.00	1.00
Protein C	801	0.75	1.00	0.98	1.03
Protein S	785	0.45	1.00	0.98	1.01
Factor VIII	800	0.21	1.01	1.00	1.02

Adjusted for age, sex, Body Mass Index, smoking pattern, systolic blood pressure, Diabetes mellitus, cancer, glomerular filtration rate, Non-HDL-Cholesterole, Triglycerides, hs-CRP, physical activity.

4. Discussion

4.1. Summary of the results

In this population cross-section study, the KORA-Fit study with 3.000 participants, we investigated the prevalence and possible determinants of myocardial infarction, ischemic stroke, and venous thromboembolism. In blood samples of 805 participants, we also analyzed blood coagulation factors.

Overall, 9.7 % of the participants had received a diagnosis of MI, IS or VT. 4.6% of the participants (3.7% of males and 5.3 % of females) had a diagnosis of VT. Subjects with a VT diagnosis were older, had a higher BMI, were more often suffering from diabetes mellitus (14.5 % versus 7.8 % non-VT), and took more often medications (30.7%), including anticoagulants (17.9 %). They showed a lower glomerular filtration rate, higher values of liver enzymes (GGT, AST, ALT) and higher inflammatory values (hsCRP).
The results of the regression analyses revealed a significant association between plasma fibrinogen and myocardial infarction. Regarding venous thrombosis significant positive associations were obtained for plasma fibrinogen and factor VIII. Protein C was the only blood coagulation factor showing a significant inverse association with venous thromboembolism. No significant findings were noted between coagulation factors and IS.

4.2. Discussion of the methods

The selected participants took part in a standardized interview, which was based on standard operation procedures and was conducted by a trained staff. However, self-reported data may be biased due to lack of precise knowledge of medical diagnosis or impaired memory, which could represent a possible limitation of the study. Blood sample collection was done after an overnight fast in the study center, ensuring high standardization.
KORA-Fit is a cross-sectional study thus no causal conclusions can be drawn from the results. A longitudinal study would overcome this limitation.
This is a study in a German population and transferability of the results to other ethnicities may not be possible.

4.3. Discussion of the results

4.3.1. Venous thromboembolism

The distribution of the participants regarding sex was the same in KORA-Fit survey, as well as in the KORA- Fit S4 study (46% male and 53% female). Further parameters, such as age, BMI, physical activity, smoking behavior, diabetes mellitus and cancer showed also no distinct differences between both study samples. This could indicate that S4 study group is a valid subsample of the adult population in the Augsburg region in Germany of the given age range.

The prevalence of the venous thrombosis in both KORA-Fit and KORA-Fit S4 was calculated with 4.6% and 3.2% respectively. According to the health reporting system in Germany the prevalence of VT lies between 2.9% and 5.1% among adult population [64].

In all determined endpoints in our study the share of men was always bigger. The only exception was venous thrombosis, where significantly more women were prevalent with VT (Table 3). Further studies, e.g. Tagalakis et al. [6], Diehm et al. [65] and Næss et al. [7] confirmed the female predominance regarding venous thrombosis. These are population-based studies, which are located in Canada, the USA and Norway [6], [7], [65]. According to the health reporting system in Germany, the share of women prevalent with VT is almost double as high in comparison to men (6.7% versus 3.5%) [64]. The Bonn Vein Study, based on the German adult population (18 – 79 years old), also reported female predominance regarding DVT (3.8% female versus 1.9% male) and PE (1.0% female versus 0.9% male)[13]. Silverstein et al. also noticed female predominance regarding VT (56%) in a study mostly in young women [10]. There are also studies reporting different findings. Heit et al. [66] reported in their review of retrospective population-based studies, that the incidence of venous thromboembolism is higher in the male population, if it is adjusted by age. He notices, that women are more prone to venous thromboembolism when they are young, as the incidence of VT can be connected to pregnancy, postpartum period and use of oral contraceptives. Richard H. White wrote in his review for Circulation that there were no representative studies, proving the significant difference between sex distribution, regarding the incidence of the venous

thromboembolism, as most of the researches showed similar incidence of VTE in both sexes [9].

Participants of KORA-Fit study and its S4 substudy, prevalent with VT, had a significantly higher Body Mass Index (Table 4 and 9). This result is similar to other population-based studies from different countries in Europe and North America, which indicated that the risk of VTE is positively associated with increasing BMI [67]–[70]. The analysis of ERFC (Emerging Risk Factors Collaboration) and UK Biobank, including over 1 million adults (mean age = 51.9 ± 9 years in ERFC; 56.4 ± 8.1 years, in UK Biobank) showed positive association between increasing BMI and the incidence of VT (HR per 1-SD higher BMI were 1.43 (CI 95%: 1.35 – 1.50) in ERFC; 1.37 (1.32 – 1.41) in UK Biobank) [67]. Two population-based studies from Italy and Denmark, including overall > 88,000 adults also showed that higher BMI significantly increased the risk DVT and PE [69], [70].

The analysis of KORA-Fit study showed a significantly higher prevalence of diabetes mellitus in the VT group (Table 4). This corresponds well with the results of some other researches and meta-analysis, e.g., Tsai et al. [68], Bai et al. [71], reporting a positive association between VT and diabetes mellitus in American and European adult populations. However, Gregson et al. [67] claimed in his analysis of population-based studies from UK Biobank and ERFC (Emerging Risk Factors Collaboration), that there is no consistent evidence proving the positive association between diabetes mellitus and VT. Thus, diabetes mellitus cannot be considered as an independent risk factor for VT [67] across all populations. Bell et al. suggested in his review of epidemiological studies, performed in adult populations in the USA and Europe, that there is either a small statistical association or no association between diabetes mellitus and VT. The differences in the results were explained by the use of different diagnostic criteria of diabetes mellitus, but also due to the lack of adjustment for age and BMI in most of the studies [72].

Participants prevalent with VT, in both KORA-Fit and in S4 survey, had a significantly lower level of education (Table 4 and 9). In our study the education level was measured in full years of completed education. Not many studies have been conducted, evaluating the significance of education level regarding the incidence of

VT. We found a few population-based studies in Sweden, where the education level was assessed in categories (under 9 years, 10 – 12 years and more than 13 years). Thereby, higher risk of VT was associated with an education level of less than 12 years [73], [74]. Till now there is no clear explanation for which mechanisms help to explain the influence of education level on the incidence or prevalence of VT. Rosengren et al. suggested in his population-based study that high levels of stress and manual labor contribute to the development of pulmonary embolism. However, he only included men in his study and there was no significant result regarding VT [75].

4.3.2. Myocardial infarction

The prevalence of myocardial infarction in KORA-Fit study as well in S4 substudy was estimated with 3% (mean age 65.1 ± 5 years) with significant domination of men with 76.1% over women with 23,9% (or male domination with 83.3% over 16.7% in KORA-Fit S4) (Tables 3 and 8; Tables 18 and 27 in the Appendix). This figure is slightly lower than the overall prevalence of myocardial infarction in adult population in Germany (4.7%). The source of data is DEGS (Studie zur Gesundheit Erwachsener in Deutschland), which is part of health monitoring program of Robert Koch Institute. The predominance of male adults was proven here as well (7% male versus 2.5% female) [76]. Over 8,000 adults from the average German population participated in this nationwide study (40 – 79 years old) [30], [76], whereas our KORA-Fit study included 3,059 adults from the Augsburg region. Differences in the study design help to explain the differences in the results. Our data are not age-standardized but self-reported MI was validated against medical records.

Our study showed that subjects with prevalent MI have a significantly higher Body Mass Index, as compared to the non-MI group (Table 18 in the Appendix). This corresponds well with other population-based and patient-based studies, conducted in Scandinavia, Germany, and in the USA, which reported BMI to be an independent risk factor for MI [77]–[82]. Population-based study in Scandinavia evaluated common risk factors and their impact on MI and atrial fibrillation in more than 120,000 adults (median age = 46.0 years, 25^{th} percentile = 36,1, 75^{th} percentile = 56,4). Per 5 kg/m^2 increase of BMI increased the risk of MI by 18% (HR 1.18, CI 95%, 1.11 – 1.24) [77]. Willich et al. conducted a study with MI patients treated in rehabilitation

centers in Germany (n = 2,441, mean age = 62.5 ± 10 years). The presence of the most common risk factors for MI was evaluated, and a BMI > 30 kg/m^2 was registered in 18% of all participants [78]. The results of a meta-analysis of five large studies underpinned the role of obesity as a risk factor of cardiovascular diseases. Framingham Heart Study, Nurses' Health Study, Buffalo Health Study, Charleston Heart Study and Düsseldorf Study showed positive association between increasing BMI and incidence of CVD and also proved higher mortality risk in obese people [82]–[87].

MI participants in KORA-Fit study also suffered from diabetes mellitus more often than participants without a diagnosis of MI (Tables 21a and 21b in the appendix). Diabetes mellitus was repeatedly described as an independent risk factor for MI in other studies [77], [80], [81], [88]. According to the MONICA-KORA register of myocardial infarction in the Augsburg region, 27 – 37% of all acute MI patients (25 – 84 years old) already have diabetes mellitus diagnosis [80]. A population-based study in Scandinavian population (n > 120,000 adults) reported a positive association between the diagnosis of diabetes mellitus and MI incidence (HR 2.18, CI 95%, 1.95 – 2.45) [77]. Another population-based study (n = 3,031, 35 – 64 years old) conducted in a Swedish MONICA region indicated that the risk of developing MI is three to five times higher for people with diabetes mellitus [88].

Another common risk factor for MI is considered to be smoking. In our study participants were divided into three groups, while assessing the smoking behavior (smoker, ex-smoker, never smoker). Thereby the share of MI participants was smaller in the "smoker" category and bigger in the non-smoker category which indicates that subjects with MI stopped smoking due to the health situation. Smoking was proven to be an independent risk factor for MI. For example, the INTERHEART case-control study evaluated most common risk factors for MI in 52 countries all over the world, including almost 3,000 participants (median age = 58 years, IQR 49 – 67). Statistically significant association between certain risk factors, e.g., hypertension, diabetes mellitus, current smoking, obesity was found [81].

Participants of KORA-Fit with prevalent MI showed significantly lower values of systolic blood pressure in comparison to the non-MI group (Tables 21a and 21b in

the appendix). One explanation for this unexpected finding can be the frequent use of antihypertensive medication, which is an essential part of treatment of coronary heart disease. Arterial hypertension was proven in many studies to be an independent risk factor for MI [77], [78], [81], [89]. Camen et al., for example, in their community-based study showed a positive association between rising blood pressure (10 mmHg increase) and MI incidence (HR 1.12, CI 95%, 1.10 – 1.13) [77]. The INTERHEART Study also revealed a positive correlation between arterial hypertension and MI (HR 2.48, CI 99%, 2.30 – 2.68) [81].

4.3.3. Ischemic stroke

The prevalence of ischemic stroke in KORA-Fit and S4 cohort was estimated with 2.7% and 3.0%, respectively (Table 21 and 31 in the Appendix). These findings correspond with the data from GEDA study (Gesundheit in Deutschland aktuell) [30], which calculated the prevalence of IS among adult German population with 2.5%. However, there was no big difference between sexes (2.4% in females versus 2.6% in males), whereas in KORA-Fit the difference between males and females was much more distinct (37.8% female cases versus 62.2% male cases).

In our study the participants with IS showed significant differences in smoking behavior. In the IS group the share of “smokers” and “non-smokers” was significantly higher as compared to the non-IS group (Table 21 in the Appendix). The reason why the share of “non-smokers” is bigger (57% non-smokers in the IS group) can be explained through cessation of smoking after being diagnosed with IS. Further studies also showed a positive association between smoking and the diagnosis of IS [90]–[94]. A meta-analysis of 25 population cohorts, including data from 24 countries in Europe and Northern America, divided the smoking pattern of the participants into three categories (“current smokers”, “former smokers” and “never smokers”). The Hazard Ratio of 2.07 (CI 95%, 1.82 – 2.36) for “current smokers” compared to “never smokers” was calculated. The HR for “former smokers” compared to “never smokers” was 1.37 (1.25 – 1.49) [92].

IS participants in our study more often had a diagnosis of diabetes mellitus than reported for the non-IS group (Tables 24a and 24b in the Appendix). The World Stroke Organization considers diabetes mellitus as a risk factor for IS [35]. Further

studies confirmed the importance of diagnosing and treating diabetes mellitus as a risk factor for IS [94]–[96]. A meta-analysis including data from over 100 prospective studies (1.27 million people, mean age = 52 ± 13 years) showed that the diagnosis of diabetes mellitus significantly increased the risk of IS (HR 2.27; CI 95%, 1.95 – 2.65) [96].

One of the most common risk factors for IS is considered to be arterial hypertension. Plenty of studies prove its' independence and relevance in the development of different cardiovascular diseases [35], [93], [94]. However, in our study there was no significant difference between systolic blood pressure in IS-group versus non IS-group (Tables 21 and 31 in the Appendix). As suggested above, treatment with antihypertensive drugs is effective and broadly used and may explain this lack of association.

4.3.4. Blood coagulation factors as risk factors for cardiovascular diseases

In the descriptive analysis of blood coagulation factors, conducted among S4 participants, all parameters were within the reference range, except for d-dimers and protein S (Table 26 in the Appendix). Higher levels of d-dimers in men (mean = 531.2 ± 467.3 µg/L) versus women (mean = 505.6 ± 370.0 µg/L (p = 0.95) were not statistically relevant; whereas the mean protein S plasma concentration is significantly higher in males compared to females. Higher levels of protein S in patients with VT, MI and IS groups were not statistically significant different from subjects without a CVD (Table 12 and Tables 30 and 34 in the Appendix). One possible explanation for higher levels of Protein S in S4 participants may be the increasing prevalence of obesity in the adult population. Iglesias et al. [97] indicated in his study, based on KORA-Fit database, that higher BMI levels were positively associated with blood coagulation factors, including protein S.

The results of the regression analyses demonstrated that the plasma levels of fibrinogen were significantly associated with both venous thrombosis and myocardial infarction. A possible connection between cardiovascular diseases and plasma fibrinogen, as well as the predictive role of fibrinogen for certain cardiovascular events (including myocardial infarction, stroke, coronary heart disease, venous

thrombosis) among the population was described in many studies [54]–[56], [98]. Kannel et al. performed a population-based study based on the Framingham Study, including 1,499 participants (47 – 79 years old) in which fibrinogen levels were measured. After 10 years of follow-up the risk of developing a cardiovascular disease was positively associated with rising fibrinogen levels [54]. In the Physicians' Health Study, over 22,000 male American physicians (40 – 84 years old) were included. The participants were initially free of coronary heart disease or IS. After 5 years of follow-up 199 participants, who suffered MI, and 199 controls were selected, and their fibrinogen levels were evaluated one more time. The study concluded that MI cases had significantly higher levels of fibrinogen at baseline, and claimed fibrinogen to be an independent risk factor for predicting MI. However, this study was only conducted among males and the findings were adjusted only by age and smoking [56]. Some authors assert that high levels of fibrinogen can even be an inheritable risk factor for myocardial infarction and for coronary artery disease [43]. A cross-sectional population-based study, including participants (n = 7,008, 20 – 79 years old) from West Pomerania (Germany) matched cases with family history of MI with controls. Participants with positive family anamnesis regarding MI had significantly higher levels of fibrinogen. Regression analysis showed a positive correlation between fibrinogen levels and positive family history [43].

In our study, plasma concentrations of factor VIII also showed a significant positive association with venous thromboembolism (p = 0.015; OR = 1,01; 95% CI 1.002 to 1,024) (Table 13). In the KORA-Fit S4 study, factor VIII was assessed in %[99]. In several publications, factor VIII, analyzed together with von Willebrand factor, confirmed that elevated levels of factor VIII should be considered as a risk factor for venous thromboembolism [45], [46], [57], [99]–[102]. The Leiden-Thrombophilia Study was the first to report the association between factor VIII and VTE (OR = 4.8, 95% CI = 2.3 – 10.0). It was a case-control study, including 474 patients and 474 controls. Factor VIII was, however, measured as FVIII:C (IU/dL) [99]. The GATE Study included 2,454 black and white adults and collected blood samples for the analysis of blood coagulation factors. The study showed that factor VIII increases the risk of VTE in whites only (OR: 2.35, 95% CI: 1.16 – 4.75) [45]. In another study, including VT patients and their relatives, FVIII:C was measured. The findings

showed, that high levels of FVIII:C increased the risk of VTE. Also, in this study the concentration of factor VIII (FVIII:C) was analyzed (IU/dL) [46].

The discovered association between protein C and venous thrombosis (OR = 0.971; 95% CI = 0.953 to 0.990) (Table 13) suggests a protective effect of increasing levels of protein C on VTE. The inherited prothrombotic mutations (e.g., factor V Leiden) are well described [103]–[105]. There is a lot of evidence, that the deficiency of the protein C significantly increases the risk of venous thrombosis [44], [58], [106], [107].

In our study no significant associations between IS and blood coagulation factors were identified. This is in contrast to literature reports showing that factor VIII, factor XI, as well as fibrinogen can be considered as possible risk factors for IS [50], [108], [109]. Most likely the cross-sectional nature of our study precludes the identification of less strong associations established in prospective studies.

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6. Appendix

Table 16: Results of clinical laboratory parameters in participants of the KORA-Fit study

CATEGORY	n	OVERALL				MALE				FEMALE				p-Value
		%	100.0	n	3,059	%	46.4	n	1,418	%	53.6	n	1,641	
GFR (ml/min)	3,047	Mean	81.3	SD	13	Mean	82.1	SD	12.9	Mean	80.7	SD	13.1	<0.01
		Median	82.7			Median	84.3			Median	81.6			
		25 P	73	75 P	91.3	25 P	73.9	75 P	91.7	25 P	72.1	75 P	91.2	
Creatinine (mg/dl)	3,047	Mean	0.9	SD	0.2	Mean	1	SD	0.3	Mean	0.8	SD	0.1	<0.01
		Median	0.9			Median	1			Median	0.8			
		25 P	0.8	75 P	1	25 P	0.9	75 P	1.1	25 P	0.7	75 P	0.9	
Total-cholesterole (mg/dl)	3,048	Mean	212.9	SD	41.7	Mean	200.7	SD	40	Mean	223.4	SD	40.4	<0.01
		Median	212.4			Median	200.5			Median	221			
		25 P	184.7	75 P	239.1	25 P	173.8	75 P	226.2	25 P	197	75 P	247	
Non-HDL-cholesterole (mg/dl)	3,047	Mean	148.5	SD	40.6	Mean	144.9	SD	39.7	Mean	151.7	SD	41	<0.01
		Median	146.5			Median	144			Median	148.5			
		25 P	120.8	75 P	174.1	25 P	115.9	75 P	171.3	25 P	124	75 P	176.7	
HDL-cholesterole (mg/dl)	3,047	Mean	64.3	SD	18.5	Mean	55.8	SD	14.6	Mean	71.7	SD	18.3	<0.01
		Median	62			Median	54.4			Median	70.4			
		25 P	50.8	75 P	75.5	25 P	45.3	75 P	64.3	25 P	58	75 P	83.4	
LDL-cholesterole (mg/dl)	2,994	Mean	124.1	SD	37	Mean	118.8	SD	36.0	Mean	128.6	SD	37.3	<0,01
		Median	123.1			Median	119.4			Median	126.5			
		25 P	98.6	75 P	146.8	25 P	92.7	75 P	143.2	25 P	103.6	75 P	150	
Triglycerides (mg/dl)	3,048	Mean	124.6	SD	78.7	Mean	134.2	SD	94.7	Mean	116.4	SD	60.5	<0.01
		Median	106.9			Median	113			Median	102.6			
		25 P	78.2	75 P	147.8	25 P	80.7	75 P	157.6	25 P	76.4	75 P	138.5	

Table 16 continued:

CATEGORY	n	OVERALL				MALE				FEMALE				p-Value
		%	100.0	n	3,059	%	46.4	n	1,418	%	53.6	n	1,641	
GGT (U/l)	3,047	Mean	35.7	SD	43.6	Mean	43.4	SD	44.3	Mean	29.2	SD	41.9	<0.01
		Median	24			Median	31			Median	19			
		25 P	17	75 P	38	25 P	22	75 P	50	25 P	14	75 P	29	
GOT, AST (U/l)	3,047	Mean	25.4	SD	10.3	Mean	26.9	SD	9.7	Mean	24.1	SD	10.6	<0.01
		Median	23.4			Median	25			Median	22.4			
		25 P	20	75 P	27.9	25 P	21.2	75 P	30	25 P	19.4	75 P	26	
GPT, ALT (U/l)	3,048	Mean	27.4	SD	14.9	Mean	31	SD	14.9	Mean	24.2	SD	14.1	<0.01
		Median	24			Median	27.6			Median	21.4			
		25 P	18.8	75 P	31.2	25 P	22	75 P	35.4	25 P	17.1	75 P	27	
hs CRP (mg/l)	3,047	Mean	2.7	SD	4.5	Mean	2.6	SD	5	Mean	2.8	SD	3.9	<0.01
		Median	1			Median	1			Median	2			
		25 P	1	75 P	3	25 P	1	75 P	3	25 P	1	75 P	3	

Table 17: Characteristics of KORA-Fit participants, stratified by medication

CATEGORY		n	OVERALL				MALE				FEMALE				p-Value
			%	100.0	n	3,059	%	46.4	n	1,418	%	53.6	n	1,641	
Anti-diabetic medication	Yes	3,056	%	7.7	n	236	%	9.2	n	130	%	6.5	n	106	<0.01
	No		%	92.3	n	2,820	%	90.8	n	1,287	%	93.5	n	1,533	
Antihypertensive medication	Yes	3,056	%	42.7	n	1,304	%	46.6	n	660	%	39.3	n	644	<0.01
	No		%	57.3	n	1,752	%	53.4	n	757	%	60.7	n	995	
Beta blocker	Yes	3,056	%	20.8	n	636	%	21.8	n	309	%	20	n	327	0.21
	No		%	79.2	n	2,420	%	78.2	n	1,108	%	80	n	1,312	
ACE inhibitor	Yes	3,056	%	14.5	n	444	%	17.1	n	243	%	12.3	n	201	<0.01
	No		%	85.5	n	2,612	%	82.9	n	1,174	%	87.7	n	1,438	
AT II inhibitor	Yes	3,056	%	19.3	n	590	%	22	n	312	%	17	n	278	<0.01
	No		%	80.7	n	2,466	%	78	n	1,105	%	83	n	1,361	
Calcium channel blocker	Yes	3,056	%	12.3	n	377	%	14.7	n	208	%	10.3	n	169	<0.01
	No		%	87.7	n	2,679	%	85.3	n	1,209	%	89.7	n	1,470	
Diuretic	Yes	3,056	%	17.6	n	538	%	19	n	269	%	16.4	n	269	0.06
	No		%	82.4	n	2,518	%	81	n	1,148	%	83.6	n	1,370	
ASS	Yes	3,056	%	11.1	n	340	%	14.7	n	208	%	8.1	n	132	<0.01
	No		%	88.9	n	2,716	%	85.3	n	1,209	%	91.9	n	1,507	

Table 17 continued:

CATEGORY		n	OVERALL				MALE				FEMALE				p-Value
			%	100.0	n	3,059	%	46.4	n	1,418	%	53.6	n	1,641	
Anticoagulants	Yes	3,056	%	3.5	n	106	%	5.2	n	73	%	2	n	33	<0.01
	No		%	96.5	n	2,950	%	94.8	n	1,344	%	98	n	1,606	
Glycoside	Yes	3,056	%	0.1	n	4	%	0.3	n	4	%	0	n	0	0.05
	No		%	99.9	n	3,052	%	99.7	n	1,413	%	100	n	1,639	
Antiarrhythmic	Yes	3,056	%	0.5	n	14	%	0.7	n	10	%	0.2	n	4	0.07
	No		%	99.5	n	3,042	%	99.3	n	1,407	%	99.8	n	1,635	
Statine	Yes	3,056	%	17.5	n	534	%	21.2	n	301	%	14.2	n	233	<0.01
	No		%	82.5	n	2,522	%	78.8	n	1,116	%	85.8	n	1,406	
Fibrats	Yes	3,056	%	0.2	n	7	%	0.2	n	3	%	0.2	n	4	1.00
	No		%	99.8	n	3,049	%	99.8	n	1,414	%	99.8	n	1,635	
NSAID regularly	Yes	3,055	%	2.5	n	76	%	1.7	n	24	%	3.2	n	52	0.010
	No		%	97.5	n	2,979	%	98.3	n	1,393	%	96.8	n	1,586	
Gout medication	Yes	3,056	%	4.6	n	141	%	8.5	n	120	%	1.3	n	21	<0.01
	No		%	95.4	n	2,915	%	91.5	n	1,297	%	98.7	n	1,618	
Multimedication	Yes	3,049	%	14.5	n	442	%	16.6	n	235	%	12.6	n	207	<0.01
	No		%	85.5	n	2,607	%	83.4	n	1,177	%	87.4	n	1,430	

Table 18: Characteristics of KORA-Fit participants with a diagnosis of myocardial infarction

CATEGORY		n	MYOCARDIAL INFARCTION												p-Value
			OVERALL				YES				NO				
			%	100	n	3,058	%	3.0	n	92	%	97.0	n	2,966	
Sex	male	3,056	%	46.4	n	1,417	%	76.1	n	70	%	45.4	n	1,348	<0.01
	female		%	53.6	n	1,639	%	23.9	n	22	%	54.6	n	1,618	
Age		3,059	Mean	63.2	SD	5.5	Mean	65.1	SD	5.1	Mean	63.2	SD	5.5	<0.01
			Median	63			Median	66			Median	63			
			25 P	59	75 P	68	25 P	61	75 P	69.8	25 P	59	75 P	68	
Years of education (years)		3,059	Mean	12	SD	2.6	Mean	11.6	SD	2.5	Mean	12	SD	2.6	0.07
			Median	11			Median	10			Median	11			
			25 P	10	75 P	13	25 P	10	75 P	12.8	25 P	10	75 P	13	
Body Mass Index (kg/m^2)		3,059	Mean	28.2	SD	5.3	Mean	29.2	SD	4.9	Mean	28.1	SD	5.3	0.014
			Median	27.4			Median	29			Median	27.4			
			25 P	24.5	75 P	30.9	25 P	25.9	75 P	32.1	25 P	24.4	75 P	30.9	
Waist circumference (cm)		3,057	Mean	94.6	SD	14.3	Mean	100.2	SD	12.5	Mean	94.4	SD	14.3	<0.01
			Median	94.2			Median	98.7			Median	93.9			
			25 P	84	75 P	103.9	25 P	92.6	75 P	108.3	25 P	83.8	75 P	103.7	
Hip circumference (cm)		3,057	Mean	104.7	SD	10.4	Mean	105	SD	9.3	Mean	104.7	SD	10.5	0.56
			Median	103.1			Median	103.2			Median	103.1			
			25 P	97.8	75 P	109.3	25 P	98.5	75 P	109.5	25 P	97.7	75 P	109.3	
Waist-Hip-Ratio		3,057	Mean	0.9	SD	0.1	Mean	1	SD	0.1	Mean	0.9	SD	0.1	<0.01
			Median	0.9			Median	0.9			Median	0.9			
			25 P	0.8	75 P	1	25 P	0.9	75 P	1	25 P	0.8	75 P	1	
Physical activity	active	3,058	%	71.8	n	2,195	%	79.3	n	73	%	71.5	n	2,122	0.13
	not active		%	28.2	n	863	%	20.7	n	19	%	28.5	n	844	
Smoking	Smoker	3,056	%	14.2	n	434	%	13	n	12	%	14.2	n	422	0.02
	Non-smoker		%	41.5	n	1,267	%	55.4	n	51	%	41	n	1,216	
	Never smoked		%	44.3	n	1,355	%	31.5	n	29	%	44.7	n	1,326	

Table 18 continued:

CATEGORY		n	MYOCARDIAL INFARCTION												p-Value
			OVERALL				YES				NO				
			%	100	n	3,058	%	3.0	n	92	%	97.0	n	2,966	
Systolic blood pressure (mmHg)		3,050	Mean	125.5	SD	16.8	Mean	123.7	SD	16.5	Mean	125.6	SD	16.9	0.40
			Median	124			Median	123			Median	124			
			25 P	114	75 P	135.5	25 P	113	75 P	133.5	25 P	114	75 P	135.5	
Diastolic blood pressure (mmHg)		3,050	Mean	74.3	SD	9.9	Mean	72.4	SD	9.9	Mean	74.4	SD	9.9	0.19
			Median	73.5			Median	73			Median	73.5			
			25 P	67.5	75 P	81	25 P	67	75 P	79.5	25 P	67.5	75 P	81	
Isolated Hypertension	yes	3,050	%	13.4	n	408	%	0.1	n	8	%	0.1	n	400	0.21
	no		%	86.6	n	2,642	%	0.9	n	83	%	0.9	n	2,559	
Diabetes Mellitus	Yes	3,054	%	8.1	n	246	%	0.2	n	18	%	0.1	n	228	<0.01
	No		%	91.9	n	2,808	%	0.8	n	74	%	0.9	n	2,734	
Cancer	Yes	3,058	%	12.9	n	396	%	0.1	n	13	%	0.1	n	383	0.75
	No		%	87.1	n	2,662	%	0.9	n	79	%	0.9	n	2,583	

Table 19: Results of clinical laboratory parameters in participants of the KORA-Fit study, overall and stratified by the diagnosis of myocardial infarction

CATEGORY	n	MYOCARDIAL INFARCTION												p-Value
		OVERALL				YES				NO				
		%	100	n	3,058	%	3.0	n	92	%	97.0	n	2,966	
GFR (ml/min)	3,047	Mean	81.3	SD	13	Mean	76.8	SD	66.4	Mean	81.5	SD	12.8	0.02
		Median	82.7			Median	79.5			Median	82.9			
		25 P	73	75 P	91.3	25 P	66.4	75 P	90.2	25 P	73.2	75 P	91.3	
Creatinine (mg/dl)	3,047	Mean	0.9	SD	0.2	Mean	1.1	SD	0.9	Mean	0.9	SD	0.2	<0.01
		Median	0.9			Median	1			Median	0.9			
		25 P	0.8	75 P	1	25 P	0.9	75 P	1.1	25 P	0.8	75 P	1	
Total-cholesterole (mg/dl)	3,048	Mean	212.9	SD	41.7	Mean	166.1	SD	43.4	Mean	214.3	SD	40.8	<0.01
		Median	212.4			Median	156.7			Median	213.3			
		25 P	184.7	75 P	239.1	25 P	134.2	75 P	185.8	25 P	186.8	75 P	240	
Non-HDL-cholesterole (mg/dl)	3,047	Mean	148.5	SD	40.6	Mean	112.6	SD	43.5	Mean	149.6	SD	40	<0.01
		Median	146.5			Median	100.8			Median	147.5			
		25 P	120.8	75 P	174.1	25 P	84.4	75 P	128.1	25 P	122.0	75 P	174.5	
HDL-cholesterole (mg/dl)	3,047	Mean	64.3	SD	18.5	Mean	53.6	SD	15.5	Mean	64.7	SD	18.5	<0.01
		Median	62			Median	52.6			Median	62.2			
		25 P	50.8	75 P	75.5	25 P	43.3	75 P	61.9	25 P	51.1	75 P	76	
LDL-cholesterole (mg/dl)	2,994	Mean	124.1	SD	37	Mean	85.2	SD	36.5	Mean	125.3	SD	36.4	<0.01
		Median	123.1			Median	75.9			Median	124			
		25 P	98.6	75 P	146.8	25 P	59.6	75 P	95.3	25 P	100.6	75 P	147.3	
Triglycerides (mg/dl)	3,048	Mean	124.6	SD	78.7	Mean	137.7	SD	115	Mean	124.2	SD	77.3	0.64
		Median	106.9			Median	106.9			Median	106.9			
		25 P	78.2	75 P	147.8	25 P	85	75 P	149.2	25 P	78	75 P	147.6	

Table 19 continued:

CATEGORY	n	MYOCARDIAL INFARCTION												p-Value
		OVERALL				YES				NO				
		%	100	n	3,058	%	3.0	n	92	%	97.0	n	2,966	
GGT (U/l)	3,047	Mean	35.7	SD	43.6	Mean	40.1	SD	31.7	Mean	35.6	SD	43.9	<0.01
		Median	24			Median	29			Median	24			
		25 P	17	75 P	38	25 P	21	75 P	49	25 P	17	75 P	38	
GOT, AST (U/l)	3,047	Mean	25.4	SD	10.3	Mean	26.8	SD	7.1	Mean	25.3	SD	10.4	<0.01
		Median	23.4			Median	26.6			Median	23.3			
		25 P	20	75 P	27.9	25 P	21.8	75 P	29.7	25 P	20	75 P	27.8	
GPT, ALT (U/l)	3,048	Mean	27.4	SD	14.9	Mean	30.5	SD	12.4	Mean	27.3	SD	15	<0.01
		Median	24			Median	29			Median	24			
		25 P	18.8	75 P	31.2	25 P	21.9	75 P	38	25 P	18.8	75 P	31	
hs CRP (mg/l)	3,047	Mean	2.7	SD	4.5	Mean	2.7	SD	3.6	Mean	2.7	SD	4.5	0.43
		Median	1			Median	1			Median	1			
		25 P	1	75 P	3	25 P	1	75 P	3	25 P	1	75 P	3	

Table 20: Medication use in KORA-Fit participants with a diagnosis of myocardial infarction

CATEGORY		n	MYOCARDIAL INFARCTION												p-Value
			OVERALL				YES				NO				
			%	100	n	3,058	%	3.0	n	92	%	97.0	n	2,966	
Anti-diabetic medication	Yes	3,056	%	7.7	n	236	%	18.5	n	17	%	7.4	n	219	<0.01
	No		%	92.3	n	2,820	%	81.5	n	75	%	92.6	n	2,745	
Antihypertensive medication	Yes	3,056	%	42.7	n	1,304	%	87	n	80	%	41.3	n	1,224	<0.01
	No		%	57.3	n	1,752	%	13	n	12	%	58.7	n	1,740	
Beta blocker	Yes	3,056	%	20.8	n	636	%	75	n	69	%	19.1	n	567	<0.01
	No		%	79.2	n	2,420	%	25	n	23	%	80.9	n	2,397	
ACE inhibitor	Yes	3,056	%	14.5	n	444	%	39.1	n	36	%	13.8	n	408	<0.01
	No		%	85.5	n	2,612	%	60.9	n	56	%	86.2	n	2,556	
AT II inhibitor	Yes	3,056	%	19.3	n	590	%	32.6	n	30	%	18.9	n	560	<0.01
	No		%	80.7	n	2,466	%	67.4	n	62	%	81.1	n	2,404	
Calcium channel blocker	Yes	3,056	%	12.3	n	377	%	27.2	n	25	%	11.9	n	352	<0.01
	No		%	87.7	n	2,679	%	72.8	n	67	%	88.1	n	2,612	
Diuretic	Yes	3,056	%	17.6	n	538	%	33.7	n	31	%	17.1	n	507	<0.01
	No		%	82.4	n	2,518	%	66.3	n	61	%	82.9	n	2,457	
ASS	Yes	3,056	%	11.1	n	340	%	80.4	n	74	%	9	n	266	<0.01
	No		%	88.9	n	2,716	%	19.6	n	18	%	91	n	2,698	

Table 20 continued:

CATEGORY		n	MYOCARDIAL INFARCTION												p-Value
			OVERALL				YES				NO				
			%	100	n	3,058	%	3.0	n	92	%	97.0	n	2,966	
Anticoagulants	Yes	3,056	%	3.5	n	106	%	10.9	n	10	%	3.2	n	96	<0.01
	No		%	96.5	n	2,950	%	89.1	n	82	%	96.8	n	2,868	
Glycoside	Yes	3,056	%	0.1	n	4	%	3.3	n	3	%	0	n	1	<0.01
	No		%	99.9	n	3,052	%	96.7	n	89	%	100	n	2,963	
Antiarrhythmic	Yes	3,056	%	0.5	n	14	%	0	n	0	%	0.5	n	14	1.00
	No		%	99.5	n	3,042	%	100	n	92	%	99.5	n	2,950	
Statine	Yes	3,056	%	17.5	n	534	%	76.1	n	70	%	15.7	n	464	<0.01
	No		%	82.5	n	2,522	%	23.9	n	22	%	84.3	n	2,500	
Fibrates	Yes	3,056	%	0.2	n	7	%	0	n	0	%	0.2	n	7	1.00
	No		%	99.8	n	3,049	%	100	n	92	%	99.8	n	2,957	
NSAID regularly	Yes	3,055	%	2.5	n	76	%	2.2	n	2	%	2.5	n	74	1.00
	No		%	97.5	n	2,979	%	97.8	n	90	%	97.5	n	2,889	
Gout medication	Yes	3,056	%	4.6	n	141	%	12	n	11	%	4.4	n	130	<0.01
	No		%	95.4	n	2,915	%	88	n	81	%	95.6	n	2,834	
Multimedication	Yes	3,049	%	14.5	n	442	%	59.8	n	55	%	13.1	n	387	<0.01
	No		%	85.5	n	2,607	%	40.2	n	37	%	86.9	n	2,570	

Table 21: Characteristics of KORA-Fit participants with a diagnosis of ischemic stroke

CATEGORY		n	ISCHEMIC STROKE												p-Value
			OVERALL				YES				NO				
			%	100	n	3,058	%	2.7	n	82	%	97.3	n	2,976	
Sex	male	3,056	%	46.4	n	1,417	%	62.2	n	51	%	45.9	n	1,367	<0.01
	female		%	53.6	n	1,639	%	37.8	n	31	%	54.1	n	1,609	
Age		3,059	Mean	63.2	SD	5.5	Mean	66	SD	4.8	Mean	63.1	SD	5.5	<0.01
			Median	63			Median	66.5			Median	63			
			25 P	59	75 P	68	25 P	62	75 P	71	25 P	59	75 P	68	
Years of education (years)		3,059	Mean	12	SD	2.6	Mean	11.7	SD	2.5	Mean	12	SD	2.6	0.24
			Median	11			Median	11			Median	11			
			25 P	10	75 P	13	25 P	10	75 P	13	25 P	10	75 P	13	
Body Mass Index (kg/m^2)		3,059	Mean	28.2	SD	5.3	Mean	29.5	SD	6.3	Mean	28.1	SD	5.3	0.02
			Median	27.4			Median	28.3			Median	27.4			
			25 P	24.5	75 P	30.9	25 P	25.6	75 P	32.5	25 P	24.5	75 P	30.8	
Waist circumference (cm)		3,057	Mean	94.6	SD	14.3	Mean	100.4	SD	16.6	Mean	94.4	SD	14.2	<0.01
			Median	94.2			Median	99.5			Median	94			
			25 P	84	75 P	103.9	25 P	90.3	75 P	110.7	25 P	83.8	75 P	103.7	
Hip circumference (cm)		3,057	Mean	104.7	SD	10.4	Mean	104.6	SD	12.1	Mean	104.7	SD	10.4	0.80
			Median	103.1			Median	102.7			Median	103.1			
			25 P	97.8	75 P	109.3	25 P	97.6	75 P	108.5	25 P	97.8	75 P	109.3	
Waist-Hip-Ratio		3,057	Mean	0.9	SD	0.1	Mean	1	SD	0.1	Mean	0.9	SD	0.1	<0.01
			Median	0.9			Median	1			Median	0.9			
			25 P	0.8	75 P	1	25 P	0.9	75 P	1	25 P	0.8	75 P	1	
Physical activity	active	3,058	%	71.8	n	2,195	%	65.9	n	54	%	71.9	n	2,141	0.26
	not active		%	28.2	n	863	%	34.1	n	28	%	28.1	n	835	
Smoking	Smoker	3,056	%	14.2	n	434	%	18.3	n	15	%	14.1	n	419	<0.01
	Non-smoker		%	41.5	n	1,267	%	57.3	n	47	%	41	n	1,220	
	Never smoked		%	44.3	n	1,355	%	24.4	n	20	%	44.9	n	1,335	

Table 21 continued:

CATEGORY		n	ISCHEMIC STROKE												p-Value
			OVERALL				YES				NO				
			%	100	n	3,058	%	2.7	n	82	%	97.3	n	2,976	
Systolic blood pressure (mmHg)		3,050	Mean	125.5	SD	16.8	Mean	126	SD	14.2	Mean	125.5	SD	16.9	0.29
			Median	124			Median	126.5			Median	123.5			
			25 P	114	75 P	135.5	25 P	117	75 P	137	25 P	113.5	75 P	135.5	
Diastolic blood pressure (mmHg)		3,050	Mean	74.3	SD	9.9	Mean	73.1	SD	9.5	Mean	74.4	SD	9.9	0.42
			Median	73.5			Median	73			Median	73.5			
			25 P	67.5	75 P	81	25 P	67	75 P	80	25 P	67.5	75 P	81	
Isolated Hypertension	yes	3,050	%	13.4	n	408	%	11.1	n	9	%	13.4	n	399	0.62
	no		%	86.6	n	2,642	%	88.9	n	72	%	86.6	n	2,570	
Diabetes Mellitus	Yes	3,054	%	8.1	n	246	%	15.9	n	13	%	7.8	n	233	0.02
	No		%	91.9	n	2,808	%	84.1	n	69	%	92.2	n	2,739	
Cancer	Yes	3,058	%	12.9	n	396	%	14.6	n	12	%	12.9	n	384	0.62
	No		%	87.1	n	2,662	%	85.4	n	70	%	87.1	n	2,592	

Table 22: Results of clinical laboratory parameters in participants of the KORA-Fit study, overall and stratified by diagnosis of ischemic stroke

CATEGORY	n	ISCHEMIC STROKE												p-Value
		OVERALL				YES				NO				
		%	100	n	3,058	%	2.7	n	82	%	97.3	n	2,976	
GFR (ml/min)	3,047	Mean	81.3	SD	13	Mean	78.1	SD	15.9	Mean	81.4	SD	12.9	0.10
		Median	82.7			Median	79.2			Median	82.8			
		25 P	73	75 P	91.3	25 P	70.8	75 P	88.3	25 P	73.1	75 P	91.3	
Creatinine (mg/dl)	3,047	Mean	0.9	SD	0.2	Mean	0.9	SD	0.3	Mean	0.9	SD	0.2	0.02
		Median	0.9			Median	0.9			Median	0.9			
		25 P	0.8	75 P	1	25 P	0.8	75 P	1.1	25 P	0.8	75 P	1	
Total-cholesterole (mg/dl)	3,048	Mean	212.9	SD	41.7	Mean	187.9	SD	37.4	Mean	213.5	SD	41.6	<0.01
		Median	212.4			Median	182.7			Median	213			
		25 P	184.7	75 P	239.1	25 P	156.9	75 P	220.3	25 P	185.8	75 P	239.7	
Non-HDL-cholesterole (mg/dl)	3,047	Mean	148.5	SD	40.6	Mean	130.3	SD	34.6	Mean	149	SD	40.6	<0.01
		Median	146.5			Median	123.3			Median	147			
		25 P	120.8	75 P	174.1	25 P	100.3	75 P	156.7	25 P	121	75 P	174.5	
HDL-cholesterole (mg/dl)	3,047	Mean	64.3	SD	18.5	Mean	57.6	SD	16.9	Mean	64.5	SD	18.5	<0.01
		Median	62			Median	54			Median	62			
		25 P	50.8	75 P	75.5	25 P	45.8	75 P	68.4	25 P	51	75 P	75.8	
LDL-cholesterole (mg/dl)	2,994	Mean	124.1	SD	37	Mean	105	SD	34.6	Mean	124.7	SD	37	<0.01
		Median	123.1			Median	103.2			Median	123.6			
		25 P	98.6	75 P	146.8	25 P	76.9	75 P	128.4	25 P	99.4	75 P	147	
Triglycerides (mg/dl)	3,048	Mean	124.6	SD	78.7	Mean	127.9	SD	59.4	Mean	124.6	SD	79.2	0.22
		Median	106.9			Median	115.6			Median	106.7			
		25 P	78.2	75 P	147.8	25 P	85.1	75 P	157.6	25 P	78	75 P	147.5	

Table 22 continued:

CATEGORY	n	ISCHEMIC STROKE												p-Value
		OVERALL				YES				NO				
		%	100	n	3,058	%	2.7	n	82	%	97.3	n	2,976	
GGT (U/l)	3,047	Mean	35.7	SD	43.6	Mean	40.3	SD	34.7	Mean	35.6	SD	43.8	0.05
		Median	24			Median	28.5			Median	24			
		25 P	17	75 P	38	25 P	18	75 P	48.0	25 P	17	75 P	38	
GOT, AST (U/l)	3,047	Mean	25.4	SD	10.3	Mean	25.9	SD	8.6	Mean	25.4	SD	10.3	0.44
		Median	23.4			Median	24.6			Median	23.4			
		25 P	20	75 P	27.9	25 P	19.3	75 P	30.9	25 P	20	75 P	27.8	
GPT, ALT (U/l)	3,048	Mean	27.4	SD	14.9	Mean	29.2	SD	15.3	Mean	27.3	SD	14.9	0.29
		Median	24			Median	25.2			Median	24			
		25 P	18.8	75 P	31.2	25 P	19.2	75 P	35.1	25 P	18.8	75 P	31.2	
hs CRP (mg/l)	3,047	Mean	2.7	SD	4.5	Mean	3.2	SD	4.5	Mean	2.7	SD	4.5	0.02
		Median	1			Median	2			Median	1			
		25 P	1	75 P	3	25 P	1	75 P	3.0	25 P	1	75 P	3	

Table 23: Medication use in KORA-Fit participants with a diagnosis of ischemic stroke

CATEGORY		n	ISCHEMIC STROKE												p-Value
			OVERALL				YES				NO				
			%	100	n	3,058	%	2.7	n	82	%	97.3	n	2,976	
Anti-diabetic medication	Yes	3,056	%	7.7	n	236	%	15.9	n	13	%	7.5	n	223	0.010
	No		%	92.3	n	2,820	%	84.1	n	69	%	92.5	n	2,751	
Antihypertensive medication	Yes	3,056	%	42.7	n	1,304	%	79.3	n	65	%	41.7	n	1,239	<0.01
	No		%	57.3	n	1,752	%	20.7	n	17	%	58.3	n	1,735	
Beta blocker	Yes	3,056	%	20.8	n	636	%	46.3	n	38	%	20.1	n	598	<0.01
	No		%	79.2	n	2,420	%	53.7	n	44	%	79.9	n	2,376	
ACE inhibitor	Yes	3,056	%	14.5	n	444	%	30.5	n	25	%	14.1	n	419	<0.01
	No		%	85.5	n	2,612	%	69.5	n	57	%	85.9	n	2,555	
AT II inhibitor	Yes	3,056	%	19.3	n	590	%	35.4	n	29	%	18.9	n	561	<0.01
	No		%	80.7	n	2,466	%	64.6	n	53	%	81.1	n	2,413	
Calcium channel blocker	Yes	3,056	%	12.3	n	377	%	26.8	n	22	%	11.9	n	355	<0.01
	No		%	87.7	n	2,679	%	73.2	n	60	%	88.1	n	2,619	
Diuretic	Yes	3,056	%	17.6	n	538	%	45.1	n	37	%	16.8	n	501	<0.01
	No		%	82.4	n	2,518	%	54.9	n	45	%	83.2	n	2,473	
ASS	Yes	3,056	%	11.1	n	340	%	58.5	n	48	%	9.8	n	292	<0.01
	No		%	88.9	n	2,716	%	41.5	n	34	%	90.2	n	2,974	

Table 23 continued:

CATEGORY		n	ISCHEMIC STROKE												p-Value
			OVERALL				YES				NO				
			%	100	n	3,058	%	2.7	n	82	%	97.3	n	2,976	
Anticoagulants	Yes	3,056	%	3.5	n	106	%	19.5	n	16	%	3.0	n	90	<0.01
	No		%	96.5	n	2,950	%	80.5	n	66	%	97.0	n	2,884	
Glycoside	Yes	3,056	%	0.1	n	4	%	1.2	n	1	%	0.1	n	3	0.10
	No		%	99.9	n	3,052	%	98.8	n	81	%	99.9	n	2,971	
Antiarrhythmic	Yes	3,056	%	0.5	n	14	%	1.2	n	1	%	0.4	n	13	0.32
	No		%	99.5	n	3,042	%	98.8	n	81	%	99.6	n	2,961	
Statine	Yes	3,056	%	17.5	n	534	%	56.1	n	46	%	16.4	n	488	<0.01
	No		%	82.5	n	2,522	%	43.9	n	36	%	83.6	n	2,486	
Fibrates	Yes	3,056	%	0.2	n	7	%	0.0	n	0	%	0.2	n	7	1.00
	No		%	99.8	n	3,049	%	100.0	n	82	%	99.8	n	2,967	
NSAID regularly	Yes	3,055	%	2.5	n	76	%	3.7	n	3	%	2.5	n	73	0.46
	No		%	97.5	n	2,979	%	96.3	n	79	%	97.5	n	2,900	
Gout medication	Yes	3,056	%	4.6	n	141	%	7.3	n	6	%	4.5	n	135	0.28
	No		%	95.4	n	2,915	%	92.7	n	76	%	95.5	n	2,839	
Multimedication	Yes	3,049	%	14.5	n	442	%	46.3	n	38	%	13.6	n	404	<0.01
	No		%	85.5	n	2,607	%	53.7	n	44	%	86.4	n	2,563	

Table 24: Results of clinical laboratory parameters in participants of the KORA-Fit S4 study

CATEGORY	n	OVERALL				MALE				FEMALE				p-Value
		%	100	n	805	%	47.0	n	378	%	53.0	n	427	
GFR (ml/min)	805	Mean	83.5	SD	13	Mean	84.3	SD	13	Mean	82.8	SD	12.9	0.05
		Median	85			Median	86.5			Median	83.4			
		25 P	75.4	75 P	93.3	25 P	75.4	75 P	94.5	25 P	74.9	75 P	92.9	
Creatinine (mg/dl)	805	Mean	0.9	SD	0.2	Mean	1	SD	0.2	Mean	0.8	SD	0.1	<0.01
		Median	0.8			Median	0.9			Median	0.8			
		25 P	0.7	75 P	1	25 P	0.8	75 P	1	25 P	0.7	75 P	0.8	
Total-cholesterole (mg/dl)	805	Mean	211.2	SD	40.9	Mean	200.1	SD	40.8	Mean	221	SD	38.5	<0.01
		Median	210			Median	199			Median	218.1			
		25 P	183	75 P	237	25 P	173.1	75 P	226.1	25 P	195	75 P	243	
Non-HDL-cholesterole (mg/dl)	805	Mean	147.3	SD	39.7	Mean	145	SD	40.4	Mean	149.3	SD	39	0.21
		Median	106			Median	144			Median	147			
		25 P	118.2	75 P	173	25 P	114.9	75 P	173.3	25 P	121.1	75 P	173	
HDL-cholesterole (mg/dl)	805	Mean	63.9	SD	19.1	Mean	55.2	SD	15.6	Mean	71.7	SD	18.5	<0.01
		Median	61			Median	54			Median	71			
		25 P	49	75 P	75.2	25 P	43.4	75 P	64.2	25 P	57	75 P	83.3	
LDL-cholesterole (mg/dl)	789	Mean	123.1	SD	36.4	Mean	118.8	SD	37.3	Mean	126.8	SD	35.3	<0.01
		Median	121.8			Median	118.2			Median	127			
		25 P	96.1	75 P	145.2	25 P	90.8	75 P	143.8	25 P	100.8	75 P	147.1	
Triglycerides (mg/dl)	805	Mean	124.4	SD	77.5	Mean	136.6	SD	94.1	Mean	113.7	SD	57	<0.01
		Median	106			Median	114			Median	100			
		25 P	77	75 P	148.4	25 P	80.6	75 P	164.3	25 P	73.1	75 P	136.0	

Table 24 continued:

CATEGORY	n	OVERALL				MALE				FEMALE				p-Value
		%	100	n	805	%	47.0	n	378	%	53.0	n	427	
GGT (U/l)	805	Mean	35.7	SD	40.2	Mean	42.7	SD	35.5	Mean	29.6	SD	43.1	<0.01
		Median	25			Median	32			Median	20			
		25 P	17	75 P	39	25 P	22	75 P	48	25 P	14	75 P	31	
GOT, AST (U/l)	805	Mean	26.2	SD	12.7	Mean	27.6	SD	10	Mean	24.9	SD	14.5	<0.01
		Median	24			Median	26			Median	22.5			
		25 P	20.3	75 P	28.3	25 P	22	75 P	30.4	25 P	19.1	75 P	26.9	
GPT, ALT (U/l)	805	Mean	28.3	SD	16	Mean	32.2	SD	14.6	Mean	24.8	SD	16.3	<0.01
		Median	25			Median	29			Median	22			
		25 P	19.1	75 P	32	25 P	23	75 P	36.2	25 P	17	75 P	27	
hs CRP (mg/l)	805	Mean	2.5	SD	3.8	Mean	2.3	SD	3.1	Mean	2.7	SD	4.3	0.06
		Median	1			Median	1			Median	2			
		25 P	1	75 P	3	25 P	1	75 P	3	25 P	1	75 P	3	

Table 25: Medication use in KORA-Fit S4 participants

MEDICATION		n	OVERALL				MALE				FEMALE				p-Value
			%	100	n	805	%	47.0	n	378	%	53.0	n	427	
Anti-diabetic medication	Yes	804	%	8.1	n	65	%	9.3	n	35	%	7	n	30	0.30
	No		%	91.9	n	739	%	90.7	n	343	%	93	n	396	
Antihypertensive medication	Yes	804	%	41.5	n	334	%	45	n	170	%	38.5	n	164	0.07
	No		%	58.5	n	470	%	55	n	208	%	61.5	n	262	
Beta blocker	Yes	804	%	20.5	n	165	%	21.4	n	81	%	19.7	n	84	0.60
	No		%	79.5	n	639	%	78.6	n	297	%	80.3	n	342	
ACE inhibitor	Yes	804	%	13.1	n	105	%	15.3	n	58	%	11	n	47	0.08
	No		%	86.9	n	699	%	84.7	n	320	%	89	n	379	
AT II inhibitor	Yes	804	%	19.7	n	158	%	22	n	83	%	17.6	n	75	0.13
	No		%	80.3	n	646	%	78	n	295	%	82.4	n	351	
Calcium channel blocker	Yes	804	%	12.9	n	104	%	13.5	n	51	%	12.4	n	53	0.67
	No		%	87.1	n	700	%	86.5	n	327	%	87.6	n	373	
Diuretic	Yes	804	%	16.3	n	131	%	19.8	n	75	%	13.1	n	56	0.013
	No		%	83.7	n	673	%	80.2	n	303	%	86.9	n	370	
ASS	Yes	804	%	10.3	n	83	%	14.3	n	54	%	6.8	n	29	<0.01
	No		%	89.7	n	721	%	85.7	n	324	%	93.2	n	397	

Table 25 continued:

MEDICATION		n	OVERALL				MALE				FEMALE				p-Value
			%	100	n	805	%	47.0	n	378	%	53.0	n	427	
Anticoagulants	Yes	804	%	3.5	n	28	%	5.8	n	22	%	1.4	n	6	<0.01
	No		%	96.5	n	776	%	94.2	n	356	%	98.6	n	420	
Glycoside	Yes	804	%	0.1	n	1	%	0.3	n	1	%	0	n	0	0.47
	No		%	99.9	n	803	%	99.7	n	377	%	100	n	426	
Antiarrhythmic	Yes	804	%	0.4	n	3	%	0.3	n	1	%	0.5	n	2	1.0
	No		%	99.6	n	801	%	99.7	n	377	%	99.5	n	424	
Statine	Yes	804	%	16	n	129	%	20.4	n	77	%	12.2	n	52	<0.01
	No		%	84	n	675	%	79.6	n	301	%	87.8	n	374	
Fibrats	Yes	804	%	0.4	n	3	%	0.5	n	2	%	0.2	n	1	0.60
	No		%	99.6	n	801	%	99.5	n	376	%	99.8	n	425	
NSAID regularly	Yes	804	%	2.4	n	19	%	1.9	n	7	%	2.8	n	12	0.49
	No		%	97.6	n	785	%	98.1	n	371	%	97.2	n	414	
Gout medication	Yes	804	%	4.7	n	38	%	9.5	n	36	%	0.5	n	2	<0.01
	No		%	95.3	n	766	%	90.5	n	342	%	99.5	n	424	
Multimedication	Yes	804	%	12.7	n	102	%	14	n	53	%	11.5	n	49	0.29
	No		%	87.3	n	702	%	86	n	325	%	88.5	n	377	

Table 26: Results of blood coagulation factors in participants of the KORA-Fit S4 study

COAGULATION FACTOR	n	OVERALL				MALE				FEMALE				p-Value
		%	100.0	n	805.0	%	47.0	n	378.0	%	53.0	n	427.0	
Quick (%)	771	Mean	107.9	SD	9.6	Mean	106.1	SD	9.8	Mean	109.5	SD	9.1	<0.01*
		Median	108.8			Median	106.7			Median	110.4			
		25 P	102.2	75 P	114.5	25 P	100.1	75 P	112.6	25 P	104.5	75 P	115.7	
INR	771	Mean	1	SD	0.1	Mean	1	SD	0.1	Mean	1	SD	0.1	<0.01*
		Median	1			Median	1			Median	0.9			
		25 P	0.9	75 P	1	25 P	0.9	75 P	1	25 P	0.9	75 P	1	
aPTT (sec.)	774	Mean	31	SD	3.3	Mean	31.5	SD	3.4	Mean	30.6	SD	3.2	<0.01*
		Median	30.7			Median	31.2			Median	30.3			
		25 P	28.7	75 P	32.9	25 P	29.3	75 P	33.5	25 P	28.4	75 P	32.6	
Antithrombin (%)	804	Mean	102.6	SD	10.9	Mean	100	SD	10.9	Mean	104.9	SD	10.4	<0.01
		Median	99.2			Median	99.2			Median	104.7			
		25 P	95.5	75 P	109.2	25 P	93.3	75 P	106.2	25 P	98.3	75 P	110.8	
Fibrinogen (mg/dl)	758	Mean	305.2	SD	65.1	Mean	303.9	SD	69.4	Mean	306.3	SD	61.1	0.13
		Median	296.1			Median	290.4			Median	300.3			
		25 P	261.5	75 P	336.7	25 P	258.3	75 P	330.4	25 P	263.5	75 P	341	
D-Dimer (µg/l)	805	Mean	517.6	SD	418.3	Mean	531.2	SD	467.3	Mean	505.6	SD	369.8	0.95
		Median	405			Median	404			Median	406			
		25 P	306	75 P	556	25 P	303.8	75 P	563	25 P	306	75 P	554	
Protein C (%)	805	Mean	123.3	SD	19.3	Mean	118.1	SD	19.8	Mean	127.8	SD	17.7	<0.01
		Median	123.4			Median	116.7			Median	129			
		25 P	111.4	75 P	138.4	25 P	107.3	75 P	131.3	25 P	116.2	75 P	142.1	
Protein S (%)	789	Mean	128.5	SD	36.8	Mean	136.4	SD	42.4	Mean	121.4	SD	29.2	<0.01
		Median	126			Median	131.9			Median	120.1			
		25 P	105.1	75 P	146.6	25 P	109.3	75 P	157.2	25 P	101.3	75 P	138.9	
Factor VIII (%)	804	Mean	123.7	SD	35.6	Mean	122.8	SD	37	Mean	124.6	SD	34.2	0.23
		Median	120.7			Median	119.1			Median	123.2			
		25 P	97.5	75 P	142.9	25 P	95.4	75 P	141.7	25 P	101.1	75 P	143.4	

** = participants taking anticoagulants were excluded*

Table 27: Characteristics of KORA-Fit S4 participants with a diagnosis of myocardial infarction

CATEGORY		n	MYOCARDIAL INFARCTION												p-Value
			OVERALL				YES				NO				
			%	100	n	805	%	3.0	n	24	%	97.0	n	781	
Sex	male	805	%	47	n	378	%	83.3	n	20	%	45.8	n	358	<0.01
	female		%	53	n	427	%	16.7	n	4	%	54.2	n	423	
Age		805	Mean	62.4	SD	5.7	Mean	62.5	SD	5.2	Mean	62.4	SD	5.7	0.95
			Median	63			Median	62.5			Median	63			
			25 P	58	75 P	67	25 P	59	75 P	67	25 P	57.5	75 P	67	
Years of education (years)		805	Mean	12.3	SD	2.6	Mean	12.1	SD	2.4	Mean	12.3	SD	2.6	0.88
			Median	11			Median	12			Median	12			
			25 P	10	75 P	13	25 P	10	75 P	12.8	25 P	10	75 P	13	
Body Mass Index (kg/m^2)		805	Mean	28.1	SD	5.2	Mean	29.5	SD	4	Mean	28	SD	5.2	0.06
			Median	27.6			Median	29.3			Median	27.4			
			25 P	24.4	75 P	31.1	25 P	26.7	75 P	32.5	25 P	24.3	75 P	31.1	
Waist circumference (cm)		804	Mean	94.6	SD	14.5	Mean	100.7	SD	10.9	Mean	94.4	SD	14.6	0.02
			Median	94.3			Median	102.8			Median	94.2			
			25 P	83.7	75 P	104.3	25 P	92.6	75 P	109.4	25 P	83.5	75 P	104	
Hip circumference (cm)		804	Mean	104.9	SD	10.2	Mean	104	SD	5.8	Mean	104.9	SD	10.3	0.96
			Median	103.4			Median	104			Median	103.4			
			25 P	98.5	75 P	109.5	25 P	99	75 P	108.6	25 P	98.4	75 P	109.6	
Waist-Hip-Ratio		804	Mean	0.9	SD	0.1	Mean	1	SD	0.1	Mean	0.9	SD	0.1	<0.01
			Median	0.9			Median	1			Median	0.9			
			25 P	0.8	75 P	1	25 P	0.9	75 P	1	25 P	0.8	75 P	1	
Physical activity	active	805	%	70.2	n	565	%	79.2	n	19	%	69.9	n	546	0.38
	not active		%	29.8	n	240	%	20.8	n	5	%	30.1	n	235	
Smoking	Smoker	805	%	13.7	n	110	%	16.7	n	4	%	13.6	n	106	0.71
	Non-smoker		%	44.1	n	355	%	37.5	n	9	%	44.3	n	346	
	Never smoked		%	42.2	n	340	%	45.8	n	11	%	42.1	n	329	

Table 27 continued:

CATEGORY		n	MYOCARDIAL INFARCTION												p-Value
			OVERALL				YES				NO				
			%	100	n	805	%	3.0	n	24	%	97.0	n	781	
Systolic blood pressure (mmHg)		803	Mean	124.9	SD	16.7	Mean	123.8	SD	18.5	Mean	124.9	SD	16.7	0.80
			Median	123			Median	121.3			Median	123			
			25 P	113.5	75 P	134.5	25 P	114.6	75 P	134.3	25 P	113.5	75 P	134.5	
Diastolic blood pressure (mmHg)		803	Mean	74.2	SD	9.6	Mean	76.1	SD	10.3	Mean	74.2	SD	9.6	0.15
			Median	73.5			Median	76.5			Median	73.5			
			25 P	67.5	75 P	80.5	25 P	73.1	75 P	84.3	25 P	67.5	75 P	80.5	
Isolated Hypertension	Yes	803	%	13.2	n	106	%	4.2	n	1	%	13.5	n	105	0.35
	No		%	86.8	n	697	%	95.8	n	23	%	86.5	n	674	
Diabetes Mellitus	Yes	803	%	8.6	n	69	%	8.3	n	2	%	8.6	n	67	1.00
	No		%	91.4	n	734	%	91.7	n	22	%	91.4	n	712	
Cancer	Yes	805	%	11.4	n	92	%	16.7	n	4	%	11.3	n	88	0.34
	No		%	88.6	n	713	%	83.3	n	20	%	88.7	n	693	

Table 28: Results of clinical laboratory parameters in participants of the KORA-Fit S4 study, overall and stratified by diagnosis of myocardial infarction

CATEGORY	n	MYOCARDIAL INFARCTION												p-Value
		OVERALL				YES				NO				
		%	100	n	805	%	3.0	n	24	%	97.0	n	781	
GFR (ml/min)	805	Mean	83.5	SD	13	Mean	79.6	SD	17	Mean	83.6	SD	12.8	0.26
		Median	85			Median	86.2			Median	85			
		25 P	75.4	75 P	93.3	25 P	68.6	75 P	94.2	25 P	75.4	75 P	93.3	
Creatinine (mg/dl)	805	Mean	0.9	SD	0.2	Mean	1	SD	0.2	Mean	0.9	SD	0.2	<0.01
		Median	0.8			Median	0.9			Median	0.8			
		25 P	0.7	75 P	1	25 P	0.8	75 P	1.1	25 P	0.7	75 P	1	
Total-cholesterole (mg/dl)	805	Mean	211.2	SD	40.9	Mean	164.5	SD	38.9	Mean	212.6	SD	40.2	<0.01
		Median	210			Median	152			Median	212			
		25 P	183	75 P	237	25 P	140.5	75 P	180.5	25 P	184.1	75 P	238	
Non-HDL-cholesterole (mg/dl)	805	Mean	147.3	SD	39.7	Mean	113.2	SD	39.7	Mean	148.3	SD	39.2	<0.01
		Median	146			Median	101			Median	146.4			
		25 P	118.2	75 P	173	25 P	87	75 P	138.2	25 P	121	75 P	173.9	
HDL-cholesterole (mg/dl)	805	Mean	63.9	SD	19.1	Mean	51.4	SD	13.3	Mean	64.3	SD	19.1	<0.01
		Median	61			Median	47.7			Median	62			
		25 P	49	75 P	75.2	25 P	40.3	75 P	58.8	25 P	49.4	75 P	75.4	
LDL-cholesterole (mg/dl)	789	Mean	123.1	SD	36.4	Mean	89.2	SD	32.8	Mean	124.1	SD	36.1	<0.01
		Median	121.8			Median	82.3			Median	122.6			
		25 P	96.1	75 P	145.2	25 P	66.6	75 P	111.7	25 P	98	75 P	146.1	
Triglycerides (mg/dl)	805	Mean	124.4	SD	77.5	Mean	119.9	SD	64	Mean	124.6	SD	77.9	0.77
		Median	106			Median	105.7			Median	106			
		25 P	77	75 P	148.4	25 P	85.3	75 P	122.9	25 P	76.7	75 P	149.4	

Table 28 continued:

CATEGORY	n	MYOCARDIAL INFARCTION												p-Value
		OVERALL				YES				NO				
		%	100	n	805	%	3.0	n	24	%	97.0	n	781	
GGT (U/l)	805	Mean	35.7	SD	40.2	Mean	36.1	SD	29	Mean	35.7	SD	40.5	0.96
		Median	25			Median	28			Median	25			
		25 P	17	75 P	39	25 P	21.3	75 P	38.8	25 P	17	75 P	39	
GOT, AST (U/l)	805	Mean	26.2	SD	12.7	Mean	27	SD	8.1	Mean	26.2	SD	12.8	0.75
		Median	24			Median	25.7			Median	24			
		25 P	20.3	75 P	28.3	25 P	21.1	75 P	30.5	25 P	20.1	75 P	28.3	
GPT, ALT (U/l)	805	Mean	28.3	SD	16	Mean	31.1	SD	12.2	Mean	28.2	SD	16.1	0.39
		Median	25			Median	30.5			Median	25			
		25 P	19.1	75 P	32	25 P	24.6	75 P	35.6	25 P	19	75 P	32	
hs CRP (mg/l)	805	Mean	2.5	SD	3.8	Mean	3.3	SD	4.7	Mean	2.5	SD	3.7	0.27
		Median	1			Median	1			Median	1			
		25 P	1	75 P	3	25 P	1	75 P	3	25 P	1	75 P	3	

Table 29: Medication use in KORA-Fit S4 participants with a diagnosis of myocardial infarction

CATEGORY		n	MYOCARDIAL INFARCTION												p-Value
			OVERALL				YES				NO				
			%	100	n	805	%	3.0	n	24	%	97.0	n	781	
Anti-diabetic medication	Yes	804	%	8.1	n	65	%	4.2	n	1	%	8.2	n	64	0.71
	No		%	91.9	n	739	%	95.8	n	23	%	91.8	n	716	
Antihypertensive medication	Yes	804	%	41.5	n	334	%	79.2	n	19	%	40.4	n	315	<0.01
	No		%	58.5	n	470	%	20.8	n	5	%	59.6	n	465	
Beta blocker	Yes	804	%	20.5	n	165	%	62.5	n	15	%	19.2	n	150	<0.01
	No		%	79.5	n	639	%	37.5	n	9	%	80.8	n	630	
ACE inhibitor	Yes	804	%	13.1	n	105	%	33.3	n	8	%	12.4	n	97	<0.01
	No		%	86.9	n	699	%	66.7	n	16	%	87.6	n	683	
AT II inhibitor	Yes	804	%	19.7	n	158	%	29.2	n	7	%	19.4	n	151	0.29
	No		%	80.3	n	646	%	70.8	n	17	%	80.6	n	629	
Calcium channel blocker	Yes	804	%	12.9	n	104	%	33.3	n	8	%	12.3	n	96	<0.01
	No		%	87.1	n	700	%	66.7	n	16	%	87.7	n	684	
Diuretic	Yes	804	%	16.3	n	131	%	20.8	n	5	%	16.2	n	126	0.57
	No		%	83.7	n	673	%	79.2	n	19	%	83.8	n	654	
ASS	Yes	804	%	10.3	n	83	%	79.2	n	19	%	8.2	n	64	<0.01
	No		%	89.7	n	721	%	20.8	n	5	%	91.8	n	716	

Table 29 continued:

CATEGORY		n	MYOCARDIAL INFARCTION												p-Value
			OVERALL				YES				NO				
			%	100	n	805	%	3.0	n	24	%	97.0	n	781	
Anticoagulants	Yes	804	%	3.5	n	28	%	8.3	n	2	%	3.3	n	26	0.20
	No		%	96.5	n	776	%	91.7	n	22	%	96.7	n	754	
Glycoside	Yes	804	%	0.1	n	1	%	0	n	0	%	0.1	n	1	1.00
	No		%	99.9	n	803	%	100	n	24	%	99.9	n	803	
Antiarrhythmic	Yes	804	%	0.4	n	3	%	0	n	0	%	0.4	n	3	1.00
	No		%	99.6	n	801	%	100	n	24	%	99.6	n	777	
Statine	Yes	804	%	16	n	129	%	70.8	n	17	%	14.4	n	112	<0.01
	No		%	84	n	675	%	29.2	n	7	%	85.6	n	668	
Fibrats	Yes	804	%	0.4	n	3	%	0	n	0	%	0.4	n	3	1.00
	No		%	99.6	n	801	%	100	n	24	%	99.6	n	777	
NSAID regularly	Yes	804	%	2.4	n	19	%	0	n	0	%	2.4	n	19	1.00
	No		%	97.6	n	785	%	100	n	24	%	97.6	n	761	
Gout medication	Yes	804	%	4.7	n	38	%	16.7	n	4	%	4.4	n	34	0.02
	No		%	95.3	n	766	%	83.3	n	20	%	95.6	n	746	
Multimedication	Yes	804	%	12.7	n	102	%	37.5	n	9	%	11.9	n	93	<0.01
	No		%	87.3	n	702	%	62.5	n	15	%	88.1	n	687	

Table 30: Results of blood coagulation factors in participants of KORA-Fit S4 study with or without a diagnosis of myocardial infarction

COAGULATION FACTOR	n	MYOCARDIAL INFARCTION												p-Value
		OVERALL				YES				NO				
		%	100	n	805	%	3.0	n	24	%	97.0	n	781	
Quick (%)	771	Mean	107.9	SD	9.6	Mean	107.5	SD	8	Mean	107.9	SD	9.7	0.69*
		Median	108.8			Median	106.5			Median	108.8			
		25 P	102.2	75 P	114.5	25 P	102.7	75 P	114.8	25 P	102.2	75 P	114.6	
INR	771	Mean	1	SD	0.1	Mean	1	SD	0	Mean	1	SD	0.1	0.77*
		Median	1			Median	1			Median	108.8			
		25 P	0.9	75 P	1	25 P	0.9	75 P	1	25 P	0.9	75 P	1	
aPTT (sec.)	774	Mean	31	SD	3.3	Mean	30.9	SD	3.4	Mean	31	SD	3.3	0.90*
		Median	30.7			Median	31.3			Median	30.7			
		25 P	28.7	75 P	32.9	25 P	28	75 P	33.3	25 P	28.7	75 P	32.9	
Antithrombin (%)	804	Mean	102.6	SD	10.9	Mean	104.9	SD	11.5	Mean	102.5	SD	10.9	0.55
		Median	102.5			Median	103.2			Median	102.4			
		25 P	95.5	75 P	109.2	25 P	95.9	75 P	111.4	25 P	95.5	75 P	109.1	
Fibrinogen (mg/dl)	758	Mean	305.2	SD	65.1	Mean	352.1	SD	109.3	Mean	303.8	SD	63	0.04
		Median	296.1			Median	314.8			Median	295.8			
		25 P	261.5	75 P	336.7	25 P	278.3	75 P	402.2	25 P	260.5	75 P	336	
D-Dimer (µg/l)	805	Mean	517.6	SD	418.3	Mean	522.7	SD	241.4	Mean	517.4	SD	422.7	0.19
		Median	405			Median	443			Median	404			
		25 P	306	75 P	556	25 P	348.3	75 P	690	25 P	304.5	75 P	554.5	
Protein C (%)	805	Mean	123.3	SD	19.3	Mean	120.8	SD	16.6	Mean	123.4	SD	19.4	0.32
		Median	123.4			Median	118.3			Median	123.5			
		25 P	111.4	75 P	138.4	25 P	106.4	75 P	135.1	25 P	111.4	75 P	138.7	
Protein S (%)	789	Mean	128.5	SD	36.8	Mean	123.7	SD	27.1	Mean	128.6	SD	37	0.68
		Median	126			Median	119.4			Median	126.1			
		25 P	105.1	75 P	146.6	25 P	104.9	75 P	142.6	25 P	105.1	75 P	146.8	
Factor VIII (%)	804	Mean	123.7	SD	35.6	Mean	133.1	SD	48.7	Mean	123.4	SD	35.1	0.40
		Median	120.7			Median	125.8			Median	120.7			
		25 P	97.5	75 P	142.9	25 P	103.4	75 P	155.6	25 P	97.4	75 P	142.8	

** = participants taking anticoagulants were excluded*

Table 31: Characteristics of KORA-Fit S4 participants with a diagnosis of ischemic stroke

CATEGORY		n	ISCHEMIC STROKE												p-Value
			OVERALL				YES				NO				
			%	100	n	805	%	3.0	n	24	%	97.0	n	781	
Sex	male	805	%	47	n	378	%	72.7	n	16	%	46.2	n	362	0.02
	female		%	53	n	427	%	27.3	n	6	%	53.8	n	421	
Age		805	Mean	62.4	SD	5.7	Mean	64.9	SD	4.4	Mean	62.3	SD	5.7	0.04
			Median	63			Median	65.5			Median	63			
			25 P	58	75 P	67	25 P	62.8	75 P	67.3	25 P	57	75 P	67	
Years of education (years)		805	Mean	12.3	SD	2.6	Mean	12.8	SD	2.6	Mean	12.3	SD	2.6	0.27
			Median	11			Median	12			Median	11			
			25 P	10	75 P	13	25 P	62.8	75 P	14	25 P	10	75 P	13	
Body Mass Index (kg/m^2)		805	Mean	28.1	SD	5.2	Mean	31.5	SD	9.4	Mean	28	SD	5	0.02
			Median	27.6			Median	31.7			Median	27.4			
			25 P	24.4	75 P	31.1	25 P	26.1	75 P	33.5	25 P	24.4	75 P	30.9	
Waist circumference (cm)		804	Mean	94.6	SD	14.5	Mean	103.8	SD	23	Mean	94.3	SD	14.2	0.02
			Median	94.3			Median	105.6			Median	94.2			
			25 P	83.7	75 P	104.3	25 P	88.5	75 P	116.2	25 P	83.6	75 P	104	
Hip circumference (cm)		804	Mean	104.9	SD	10.2	Mean	107.9	SD	18.5	Mean	104.8	SD	0.1	0.40
			Median	103.4			Median	105.6			Median	103.3			
			25 P	98.5	75 P	109.5	25 P	101.4	75 P	108.5	25 P	98.4	75 P	109.6	
Waist-Hip-Ratio		804	Mean	0.9	SD	0.1	Mean	1	SD	0.1	Mean	0.9	SD	0.1	<0.01
			Median	0.9			Median	1			Median	0.9			
			25 P	0.8	75 P	1	25 P	0.9	75 P	1.1	25 P	0.8	75 P	1	
Physical activity	active	805	%	70.2	n	565	%	68.2	n	15	%	70.2	n	550	0.82
	not active		%	29.8	n	240	%	31.8	n	7	%	29.8	n	233	
Smoking	Smoker	805	%	13.7	n	110	%	4.5	n	1	%	13.9	n	109	0.08
	Non-smoker		%	44.1	n	355	%	68.2	n	15	%	43.4	n	340	
	Never smoked		%	42.2	n	340	%	27.3	n	6	%	42.7	n	334	

Table 31 continued:

CATEGORY		n	ISCHEMIC STROKE												p-Value
			OVERALL				YES				NO				
			%	100	n	805	%	3.0	n	24	%	97.0	n	781	
Systolic blood pressure (mmHg)		803	Mean	124.9	SD	16.7	Mean	126.4	SD	16.7	Mean	124.9	SD	16.7	0.40
			Median	123			Median	126			Median	123			
			25 P	113.5	75 P	134.5	25 P	118.8	75 P	138.8	25 P	113	75 P	134.5	
Diastolic blood pressure (mmHg)		803	Mean	74.2	SD	9.6	Mean	76.3	SD	9.6	Mean	74.2	SD	9.7	0.22
			Median	73.5			Median	75.5			Median	73.5			
			25 P	67.5	75 P	80.5	25 P	71.5	75 P	80.3	25 P	67.5	75 P	80.5	
Isolated Hypertension	Yes	803	%	13.2	n	106	%	9.5	n	2	%	13.3	n	104	1.00
	No		%	86.8	n	697	%	90.5	n	19	%	86.7	n	678	
Diabetes Mellitus	Yes	803	%	8.6	n	69	%	18.2	n	4	%	8.3	n	65	0.11
	No		%	91.4	n	734	%	81.8	n	18	%	91.7	n	716	
Cancer	Yes	805	%	11.4	n	92	%	18.2	n	4	%	11.2	n	88	0.30
	No		%	88.6	n	713	%	81.8	n	18	%	88.8	n	695	

Table 32: Results of clinical laboratory parameters in participants of the KORA-Fit S4 study, overall and stratified by diagnosis of ischemic stroke

CATEGORY	n	ISCHEMIC STROKE												p-Value
		OVERALL				YES				NO				
		%	100	n	805	%	3.0	n	24	%	97.0	n	781	
GFR (ml/min)	805	Mean	83.5	SD	13	Mean	80.4	SD	18.7	Mean	83.6	SD	12.8	0.73
		Median	85			Median	86.4			Median	85			
		25 P	75.4	75 P	93.3	25 P	71.8	75 P	90.8	25 P	75.4	75 P	93.4	
Creatinine (mg/dl)	805	Mean	0.9	SD	0.2	Mean	1	SD	0.3	Mean	0.9	SD	0.2	0.31
		Median	0.8			Median	0.8			Median	0.8			
		25 P	0.7	75 P	1	25 P	0.8	75 P	1.1	25 P	0.7	75 P	1.0	
Total-cholesterole (mg/dl)	805	Mean	211.2	SD	40.9	Mean	182	SD	34.4	Mean	212	SD	40.8	<0.01
		Median	210			Median	178.5			Median	211.6			
		25 P	183	75 P	237	25 P	149.4	75 P	211	25 P	183.5	75 P	238	
Non-HDL-cholesterole (mg/dl)	805	Mean	147.3	SD	39.7	Mean	121.3	SD	32.5	Mean	148	SD	39.6	<0.01
		Median	146			Median	110.8			Median	146			
		25 P	118.2	75 P	173	25 P	98.4	75 P	153	25 P	120.1	75 P	174	
HDL-cholesterole (mg/dl)	805	Mean	63.9	SD	19.1	Mean	60.6	SD	22.6	Mean	64	SD	19	0.20
		Median	61			Median	51.5			Median	61.8			
		25 P	49	75 P	75.2	25 P	44.5	75 P	78.6	25 P	49	75 P	75.2	
LDL-cholesterole (mg/dl)	789	Mean	123.1	SD	36.4	Mean	97.5	SD	29.7	Mean	123.8	SD	36.4	<0.01
		Median	121.8			Median	88			Median	122.5			
		25 P	96.1	75 P	145.2	25 P	76.6	75 P	122.3	25 P	97.6	75 P	145.9	
Triglycerides (mg/dl)	805	Mean	124.4	SD	77.5	Mean	119.4	SD	67	Mean	124.6	SD	77.8	0.61
		Median	106			Median	96.6			Median	106			
		25 P	77	75 P	148.4	25 P	71.4	75 P	150.1	25 P	77	75 P	148.7	

Table 32 continued:

CATEGORY	n	ISCHEMIC STROKE												p-Value
		OVERALL				YES				NO				
		%	100	n	805	%	3.0	n	24	%	97.0	n	781	
GGT (U/l)	805	Mean	35.7	SD	40.2	Mean	34.5	SD	20.1	Mean	35.8	SD	40.6	0.33
		Median	25			Median	29.5			Median	25			
		25 P	17	75 P	39	25 P	17.8	75 P	44.8	25 P	17	75 P	39	
GOT, AST (U/l)	805	Mean	26.2	SD	12.7	Mean	30.1	SD	10.9	Mean	26.1	SD	12.7	0.02
		Median	24			Median	28			Median	24			
		25 P	20.3	75 P	28.3	25 P	22.5	75 P	36	25 P	20.3	75 P	28.1	
GPT, ALT (U/l)	805	Mean	28.3	SD	16	Mean	33.9	SD	16.2	Mean	28.1	SD	15.9	0.02
		Median	25			Median	29			Median	25			
		25 P	19.1	75 P	32	25 P	25.4	75 P	43.4	25 P	19	75 P	32	
hs CRP (mg/l)	805	Mean	2.5	SD	3.8	Mean	2.2	SD	2.4	Mean	2.5	SD	3.8	0.81
		Median	1			Median	2			Median	1			
		25 P	1	75 P	3	25 P	1	75 P	2.3	25 P	1	75 P	3	

Table 33: Medication us in KORA-Fit S4 participants with a diagnosis of ischemic stroke

CATEGORY		n	ISCHEMIC STROKE												p-Value
			OVERALL				YES				NO				
			%	100	n	805	%	3.0	n	24	%	97.0	n	781	
Anti-diabetic medication	Yes	804	%	8.1	n	65	%	18.2	n	4	%	7.8	n	61	0.09
	No		%	91.9	n	739	%	81.8	n	18	%	92.2	n	721	
Antihypertensive medication	Yes	804	%	41.5	n	334	%	72.7	n	16	%	40.7	n	318	<0.01
	No		%	58.5	n	470	%	27.3	n	6	%	59.3	n	464	
Beta blocker	Yes	804	%	20.5	n	165	%	50	n	11	%	19.7	n	154	<0.01
	No		%	79.5	n	639	%	50	n	11	%	80.3	n	628	
ACE inhibitor	Yes	804	%	13.1	n	105	%	18.2	n	4	%	12.9	n	101	0.52
	No		%	86.9	n	699	%	81.8	n	18	%	87.1	n	681	
AT II inhibitor	Yes	804	%	19.7	n	158	%	36.4	n	8	%	19.2	n	150	0.06
	No		%	80.3	n	646	%	63.6	n	14	%	80.8	n	632	
Calcium channel blocker	Yes	804	%	12.9	n	104	%	36.4	n	8	%	12.3	n	96	<0.01
	No		%	87.1	n	700	%	63.6	n	14	%	87.7	n	686	
Diuretic	Yes	804	%	16.3	n	131	%	45.5	n	10	%	15.5	n	121	<0.01
	No		%	83.7	n	673	%	54.5	n	12	%	84.5	n	661	
ASS	Yes	804	%	10.3	n	83	%	59.1	n	13	%	9	n	70	<0.01
	No		%	89.7	n	721	%	40.9	n	9	%	91	n	712	

Table 33 continued:

CATEGORY		n	ISCHEMIC STROKE												p-Value
			OVERALL				YES				NO				
			%	100	n	805	%	3.0	n	24	%	97.0	n	781	
Anticoagulants	Yes	804	%	3.5	n	28	%	18.2	n	4	%	3.1	n	24	<0.01
	No		%	96.5	n	776	%	81.8	n	18	%	96.9	n	758	
Glycoside	Yes	804	%	0.1	n	1	%	4.5	n	1	%	0	n	0	0.03
	No		%	99.9	n	803	%	95.5	n	21	%	100	n	782	
Antiarrhythmic	Yes	804	%	0.4	n	3	%	0	n	0	%	0.4	n	3	1.00
	No		%	99.6	n	801	%	100	n	22	%	99.6	n	779	
Statine	Yes	804	%	16	n	129	%	68.2	n	15	%	14.6	n	114	<0.01
	No		%	84	n	675	%	31.8	n	7	%	85.4	n	668	
Fibrats	Yes	804	%	0.4	n	3	%	0	n	0	%	0.4	n	3	1.00
	No		%	99.6	n	801	%	100	n	22	%	99.6	n	779	
NSAID regularly	Yes	804	%	2.4	n	19	%	9.1	n	2	%	2.2	n	17	0.09
	No		%	97.6	n	785	%	90.9	n	20	%	97.8	n	765	
Gout medication	Yes	804	%	4.7	n	38	%	9.1	n	2	%	4.6	n	36	0.28
	No		%	95.3	n	766	%	90.9	n	20	%	95.4	n	746	
Multimedication	Yes	804	%	12.7	n	102	%	50	n	11	%	11.6	n	91	<0.01
	No		%	87.3	n	702	%	50	n	11	%	88.4	n	691	

Table 34: Results of blood coagulation factors in participants of the KORA-Fit S4 study with or without a diagnosis of ischemic stroke

COAGULATION FACTOR	n	ISCHEMIC STROKE												p-Value
		OVERALL				YES				NO				
		%	100.0	n	805.0	%	3.0	n	24.0	%	97.0	n	781.0	
Quick (%)	771	Mean	107.9	SD	9.6	Mean	106.6	SD	7.5	Mean	107.9	SD	9.7	0.69*
		Median	108.8			Median	107.7			Median	108.8			
		25 P	102.2	75 P	114.5	25 P	99.5	75 P	113.3	25 P	102.3	75 P	114.7	
INR	771	Mean	1	SD	0.1	Mean	1	SD	0.04	Mean	1	SD	0.1	0.77*
		Median	1			Median	1			Median	1			
		25 P	0.9	75 P	1	25 P	0.9	75 P	1	25 P	0.9	75 P	1	
aPTT (sec.)	774	Mean	31	SD	3.3	Mean	30.1	SD	3.2	Mean	31	SD	3.3	0.90*
		Median	30.7			Median	30.2			Median	30.7			
		25 P	28.7	75 P	32.9	25 P	27	75 P	31.4	25 P	28.7	75 P	32.9	
Antithrombin (%)	804	Mean	102.6	SD	10.9	Mean	99.9	SD	8.4	Mean	102.7	SD	11	0.55
		Median	102.5			Median	101.2			Median	102.5			
		25 P	95.5	75 P	109.2	25 P	94.1	75 P	104.6	25 P	95.6	75 P	109.2	
Fibrinogen (mg/dl)	758	Mean	305.2	SD	65.1	Mean	313	SD	79.6	Mean	305	SD	64.7	0.04
		Median	296.1			Median	311.6			Median	296			
		25 P	261.5	75 P	336.7	25 P	258.3	75 P	389.5	25 P	261.4	75 P	336.4	
D-Dimer (µg/l)	805	Mean	517.6	SD	418.3	Mean	509.3	SD	287.3	Mean	517.8	SD	421.6	0.19
		Median	405			Median	456.5			Median	405			
		25 P	306	75 P	556	25 P	349.3	75 P	585.8	25 P	261.4	75 P	555	
Protein C (%)	805	Mean	123.3	SD	19.3	Mean	118.3	SD	21.3	Mean	123.4	SD	19.2	0.32
		Median	123.4			Median	119.8			Median	123.5			
		25 P	111.4	75 P	138.4	25 P	107.5	75 P	132.2	25 P	111.4	75 P	138.6	
Protein S (%)	789	Mean	128.5	SD	36.8	Mean	123.9	SD	41.6	Mean	128.6	SD	36.7	0.68
		Median	126			Median	113.9			Median	126.1			
		25 P	105.1	75 P	146.6	25 P	94.3	75 P	145.9	25 P	105.1	75 P	146.6	
Factor VIII (%)	804	Mean	123.7	SD	35.6	Mean	135.1	SD	51	Mean	123.4	SD	35	0.40
		Median	120.7			Median	122.7			Median	120.7			
		25 P	97.5	75 P	142.9	25 P	99.8	75 P	161.4	25 P	97.5	75 P	142.8	

** = participants taking anticoagulants were excluded*

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Affidavit

LMU LUDWIG-MAXIMILIANS-UNIVERSITÄT MÜNCHEN | Promotionsbüro Medizinische Fakultät | MMRS

Eidesstattliche Versicherung

Erhard, Anna

Name, Vorname

Ich erkläre hiermit an Eides statt, dass ich die vorliegende Dissertation mit dem Titel:

“Blood coagulation factors as possible risk factors for cardiovascular diseases in a population based cross-sectional study”

selbständig verfasst, mich außer der angegebenen keiner weiteren Hilfsmittel bedient und alle Erkenntnisse, die aus dem Schrifttum ganz oder annähernd übernommen sind, als solche kenntlich gemacht und nach ihrer Herkunft unter Bezeichnung der Fundstelle einzeln nachgewiesen habe.

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Apfeldorf, 21.07.2024

Ort, Datum

Erhard Anna

Unterschrift Doktorandin bzw. Doktorand