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Magnetic resonance imaging measures of vascular structure and adipose tissue: relations to cardiovascular risk factors in the general population

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List of Abbreviations

AWT	Aortic wall thickness
AUC	Area under the curve
BMI	Body mass index
BP	Blood pressure
BSA	Body surface area
CI	Confidence interval
CVD	Cardiovascular disease
FLD	Fatty liver disease
GFR	Glomerular filtration rate
HbA1c	Hemoglobin A1c
HDL-C	High-density lipoprotein cholesterol
HFF	Hepatic fat fraction
IMT	Intima media thickness
KORA	Cooperative Health Research in the Region of Augsburg
LDL-C	Low-density lipoprotein cholesterol
MRA	Magnetic resonance angiography
MRI	Magnetic resonance imaging
OR	Odds ratio
PAD	Peripheral arterial diseases
PAT	Pericardial adipose tissue
PFF	Pancreatic fat fraction
ROI	Region of interest
SCAT	Subcutaneous adipose tissue
SD	Standard deviation
SHIP	Study of Health in Pomerania
TAT	Total adipose tissue
TG	Triglycerides
VAT	Visceral adipose tissue
WC	Waist circumference
WHR	Waist–hip ratio
WHtR	Waist–height ratio

ABSTRACT

Background: Individualized cardiovascular medicine aims at a better prevention and treatment of cardiovascular diseases in different subgroups of the population and patients compared to more universal diagnostic and therapeutic approaches. Biomarkers might allow people to be assigned to these different groups with different risks for the onset and course of cardiovascular diseases and the efficacy of therapies and side effects. To better predict the onset of diseases, subclinical cardiovascular changes are increasingly being investigated, and MRI has developed as an emerging tool to visualize subclinical changes in the cardiovascular system.

Aim: The aim of this work was to determine reference ranges for various MRI traits in the general population and to estimate associations of these MRI traits with established cardiovascular risk factors. Particular focus was placed on MRI parameters for vascular structure (thoracic and abdominal aorta, lower limb arteries) and for adipose tissue (e.g. hepatic, visceral, subcutaneous).

Methods: Data for this work was provided by the population-based epidemiological cohort studies "Study of Health in Pomerania" (SHIP) from Northeast Germany and "Cooperative Health Research in the Region of Augsburg" (KORA) from Southern Germany. In SHIP, various samples (SHIP-2, N=2333; SHIP-TREND, N=4420) with MRI examinations of the thoracic, abdominal and leg arteries in about half of the sample were used. KORA provided the FF4 sample of 2279 subjects, of whom 400 subjects participated in an MRI scan of the head and upper body. Established cardiovascular risk factors included e.g. overweight, elevated BP, triglycerides, and glucose levels, as well as high LDL and low HDL cholesterol levels. MRI-based parameters of thoracic and abdominal aortic diameters, thoracic aortic wall thickness, and leg arterial diameters as well as measures of body and organ fat levels were obtained using a 1.5 Tesla and a 3.0 Tesla scanner, respectively, in the two samples, SHIP and KORA. MRI-based measures of body and organ fat levels were evaluated in relation to the hypertension prevalence as a cardiovascular outcome measurement.

Results: Reference values were obtained for thoracic and abdominal aortic segment diameters (ascending, arch, descending, subphrenic, suprarenal, infrarenal), thoracic aortic segment wall thickness (ascending, descending) in women and men and vessel diameters of nine different segments of the lower limb arteries in men only. Then, associations of aortic diameters, aortic wall thickness and leg artery stenosis with cardiovascular risk factors were assessed and the following results were obtained: the median aortic diameter showed a positive association with male sex and age. Some cardiovascular risk factors such as systolic and diastolic BP, smoking, and HDL cholesterol were also associated with thoracic and abdominal aortic diameters. Male sex, older age, smoking, high levels of BMI and triglycerides were positively associated with MRI determined thoracic aortic wall thickness of the ascending and descending aorta. Furthermore, high HDL and low LDL cholesterol levels were correlated with aortic wall thickness. The reference diameters of pelvic and leg arteries decreased from proximal to distal and increased with age. Stenoses were relatively scarce overall, but more prevalent in lower leg arteries as compared to upper leg and pelvic arteries and associated with older age and diabetes.

In terms of the association of MRI-determined adiposity measures with BP traits, the following results were observed: higher MRI-derived hepatic fat fraction was associated with higher systolic and diastolic BP as well as with hypertension. In addition, MRI markers of total, visceral and pericardial adipose tissue were also highly correlated with prevalent hypertension, as were established anthropometric markers such as waist circumference and waist-height ratio. Overall, MRI-derived adipose tissue measurements performed similarly as anthropometric markers in identifying patients with hypertension.

Conclusions: This study demonstrated that subclinical imaging parameters of the vascular system and adipose tissue derived from MRI are variable in the population and are associated with several established cardiovascular risk factors, e.g. blood pressure and anthropometric measures.

This work contributes to the understanding of the relationship between established risk factors and emerging imaging biomarkers of vascular structure and adipose tissue. Future studies need to evaluate the use of these imaging biomarkers in individualized cardiovascular risk prediction. The use of standardized high-quality imaging techniques in the population can form the basis for the development of new prevention approaches.

This work is a summary of the following recently published original articles (attached in the **Appendix)**, and therefore contains original content from these publications, in terms of text, paragraphs, tables and figures.

1) Mensel B, Hesselbarth L, Wenzel M, Kuhn JP, Dorr M, Volzke H, Lieb W, Hegenscheid K, **Lorbeer R**. Thoracic and abdominal aortic diameters in a general population: MRI-based reference values and association with age and cardiovascular risk factors. Eur Radiol 2016;26:969-78.

2) Mensel B, Quadrat A, Schneider T, Kuhn JP, Dorr M, Volzke H, Lieb W, Hegenscheid K, **Lorbeer R**. MRI-based determination of reference values of thoracic aortic wall thickness in a general population. Eur Radiol 2014;24:2038-44.

3) **Lorbeer R**, Schneider T, Quadrat A, Kuhn JP, Dorr M, Volzke H, Lieb W, Hegenscheid K, Mensel B. Cardiovascular risk factors and thoracic aortic wall thickness in a general population. J Vasc Interv Radiol 2015;26:635-41.

4) **Lorbeer R**, Grotz A, Dorr M, Volzke H, Lieb W, Kuhn JP, Mensel B. Reference values of vessel diameters, stenosis prevalence, and arterial variations of the lower limb arteries in a male population sample using contrast-enhanced MR angiography. PLoS One 2018;13:e0197559.

5) **Lorbeer R**, Bayerl C, Auweter S, Rospleszcz S, Lieb W, Meisinger C, Heier M, Peters A, Bamberg F, Hetterich H. Association between MRI Derived Hepatic Fat Fraction and Blood Pressure in Subjects without History of Cardiovascular Disease. J Hypertens 2017; 35:737-744.

6) **Lorbeer R**, Rospleszcz S, Schlett CL, Heber SD, Machann J, Thorand B, Meisinger C, Heier M, Peters A, Bamberg F, Lieb W. Correlation of MRI-derived adipose tissue measurements and anthropometric markers with prevalent hypertension in the community. J Hypertens 2018; 36:1555-1562.

1. INTRODUCTION

Cardiovascular diseases (CVD) were the leading cause of non-communicable disease deaths in 2016 and responsible for 17.9 million deaths or 44% of non-communicable disease deaths (31% of total deaths). CVD is the leading cause of death worldwide (1). CVD are defined as diseases of the heart and/or circulatory system with coronary heart disease and stroke as major forms (2, 3). Myocardial infarction and stroke are acute cardiovascular events with high mortality (4, 5). In 2012 cardiovascular deaths were estimated to be 7.4 million due to heart attacks (ischemic heart disease) and 6.7 million due to strokes (6). More than 40% of cardiovascular deaths were premature deaths up to the age of 70 years. The majority of premature deaths from CVD are preventable. Deaths from CVD have been reduced in many Western countries by politically promoting a healthier lifestyle and providing equitable health care (7). These favourable changes must be maintained and transferred to developing countries.

Subclinical cardiovascular status is defined as a structural or functional change in the cardiovascular system without obvious clinical symptoms. Examples of subclinical cardiovascular abnormalities include impaired structure and function of the left or right ventricle and structural changes in arteries. Subclinical diseases demonstrate an increased risk of clinical diseases and events (8, 9). Early detection of subclinical cardiovascular alterations and a deeper understanding of the underlying risk factors that contribute to subclinical changes may facilitate early identification of patients at high cardiovascular risk and finally help to prevent manifest CVD and cardiovascular events. Therefore, it is also necessary to determine reference values for subclinical cardiovascular traits in the general population in order to identify impaired subclinical characteristics and to understand its association with CVD. Magnetic resonance imaging (MRI) has developed as an emerging tool to visualize subclinical cardiovascular changes in the general population (10).

Behavioural risk factors are responsible for about 80% of CVD and include unhealthy diet, physical inactivity and tobacco use (3). By identifying risk factors and new individual characteristics (biomarkers) that can indicate a different cardiovascular risk, cardiovascular medicine gain the potential to become more individualized. By means of a more appropriate prevention, treatment and assessment of the risks of onset and course of CVD as well as the effectiveness of therapies and side effects in different high-risk subgroups of the population, further prospects of cardiovascular mortality reduction are to be exploited (11).

In this work, population-based reference values for thoracic and abdominal aortic segment diameters, thoracic aortic segment wall thickness and vessel diameters of different segments of the lower limb were reported. Furthermore, population-based associations of established cardiovascular risk factors and selected new biomarker candidates of adipose tissue with measurements of subclinical vascular changes and hypertension were assessed. In particular, clinical MRI parameters of vascular structure and body and organ fat were investigated. This work was arranged in the following two parts: A) reference values of MRI-derived artery structure and their associations with established risk factors and B) MRI-derived adipose tissue as biomarkers for risk of hypertension and the comparison to anthropometric markers.

1.1. REFERENCE VALUES AND RISK FACTORS OF ARTERY STRUCTURE

The first work package (A) aimed to investigate 1) reference values for thoracic and abdominal aortic segment diameters, thoracic aortic segment wall thickness, vessel diameters of different segments of the lower limbs and 2) the role of established cardiovascular risk factors for artery structure remodelling in the general population.

1.1.1. THORACIC AND ABDOMINAL AORTIC DIAMETERS

The aorta connects the heart with the peripheral organs and plays a central role in the cardiovascular system. Aortic disease conditions such as thoracic or abdominal aneurysm and dissection are common and progress over time, often becoming life-threatening with a need for elective or emergency therapy (12, 13). Because these conditions are often associated with an increase in aortic diameter, the latter is an important parameter in deciding when and how to treat these patients (12). Moreover, there is evidence that an increased baseline diameter of the infrarenal aorta is a strong and independent risk factor for the development of abdominal aortic aneurysm (14). Therefore, it is crucial to know reference values for the different aortic segments. While a positive correlation of aortic diameter and age is well established, the association of other risk factors for CVD with aortic diameters and the cumulative and interactive effects of multiple risk factors on different aortic segments are not fully understood (15-17). In addition, further evidence is also needed with regard to how these factors affect different aortic segments.

1.1.2. THORACIC AORTIC WALL THICKNESS

Atherosclerotic CVD play a major role for morbidity and mortality in developed countries. An increased wall thickness of the common carotid artery can be regarded as a surrogate parameter of atherosclerosis and predicts cardiovascular events including myocardial infarction, stroke and cardiovascular mortality (18, 19). Studies investigating the thoracic aortic wall thickness (AWT) are rare. This is mainly due to the more difficult determination of the aortic wall by ultrasound. MRI is a non-invasive and feasible alternative method to measure the AWT (20).

Several cardiovascular risk factors are known to be associated with MRI determined AWT (20, 21). Significant associations of greater abdominal AWT with higher age, male gender, smoking status, higher systolic blood pressure (BP), higher low-density-lipoprotein cholesterol (LDL-C) and lower high-density-lipoprotein cholesterol (HDL-C) levels, and with higher blood glucose levels were demonstrated in the Dallas Heart Study (21). The results regarding age, sex and systolic BP confirm the results of the Multi-ethnic Study of Atherosclerosis investigating the thoracic AWT (20). Cardiovascular risk factors of the thoracic AWT in a general population have only been assessed for the descending aorta for selected parameters but not for the ascending aorta.

1.1.3. VESSEL DIAMETERS OF THE LOWER LIMB ARTERIES

Asymptomatic and symptomatic peripheral arterial diseases (PAD) represent common manifestations of the atherosclerotic disease process and are associated with an increased risk for other manifestations of CVD and mortality (22). To detect vascular remodelling triggered by atherosclerotic changes in the leg arteries at the subclinical status of PAD, the morphological characterization of leg arteries is of significant importance (23). Imaging diagnostic methods for the evaluation of leg arteries and PAD include digital subtraction angiography, duplex sonography and computed tomography angiography. So far reference values of leg arteries are not available and several studies have only investigated single segments of leg arteries by these different methods in patients but not in populations-based samples of relatively healthy subjects (24, 25).

Magnetic resonance angiography (MRA) is an alternative method to evaluate leg artery morphology non-radiation-based and is more sensitive and specific to detect stenosis compared to duplex sonography and computed tomography angiography (26). Until now only few studies have used MRA for investigations of leg arteries in patients (27) (but not in the general population) to establish important reference values for arterial morphology, to assess the subclinical status of PAD and obtain information on artery variants as vascular surgery conditions in the general community.

1.2. MRI-DERIVED ADIPOSE TISSUE MEASUREMENTS AND HYPERTENSION AS CARDIOVASCULAR RISK FACTOR

The second work package (B) analysed the interrelation of MRI parameters of adipose tissue with blood pressure and hypertension and the comparison with anthropometric markers.

Elevated BP is a major cardiovascular risk factor that is considered a CVD equivalent (28). On a parallel note, adiposity predisposes to cardio-metabolic disease conditions (29), and hypertension is an important link between increased body fat distribution and cardiovascular outcomes (30). However, it is not well established which is the best adiposity measurement for cardiovascular risk assessment and which most strongly correlates with hypertension. Since they are easy and cost-effective to measure, anthropometric markers have been investigated in a large number of studies, and are part of non-laboratory-based prediction algorithms for CVD in primary care (31).

Since anthropometry provides only indirect measurements of body fat distribution, it is of major interest to identify more accurate and direct measures of body fat and to explore their relation to CVD risk factors, including BP. MRI measures of body and organ fat obtained in this work include total adipose tissue (TAT), visceral adipose tissue (VAT), subcutaneous adipose tissue (SCAT), hepatic fat fraction (HFF), pancreatic fat fraction (PFF) as well as pericardial adipose tissue (PAT).

1.3. HYPOTHESES

The following hypotheses form the basis for the present habilitation consisting of the two work packages (A, B) that are graphically displayed in **Figure 1**.

A) Reference values and risk factors for MRI-derived traits of arterial structure

Hypothesis 1: Thoracic and abdominal aortic diameters vary by age and sex and are associated with established cardiovascular risk factors. (*Article 1* (32))
Hypothesis 2: Wall-thickness of the thoracic aorta varies by age and sex and depending on the levels of established cardiovascular risk factors. (*Article 2* (33) / *Article 3* (34))
Hypothesis 3: Leg arterial diameters in men have age-related reference values and leg artery stenoses are associated with established cardiovascular risk factors. (*Article 4* (35))

B) Association of MRI measurements of body and organ fat with blood pressure and hypertension

Hypothesis 4: MRI-derived hepatic fat levels are associated with systolic and diastolic BP and with prevalent hypertension. (*Article 5* (36))
Hypothesis 5: Body and organ fat values determined by MRI are more strongly associated with hypertension than established body measures of anthropometry such as body mass index (BMI), WC, or waist-hip ratio (WHR). (*Article 6* (37))

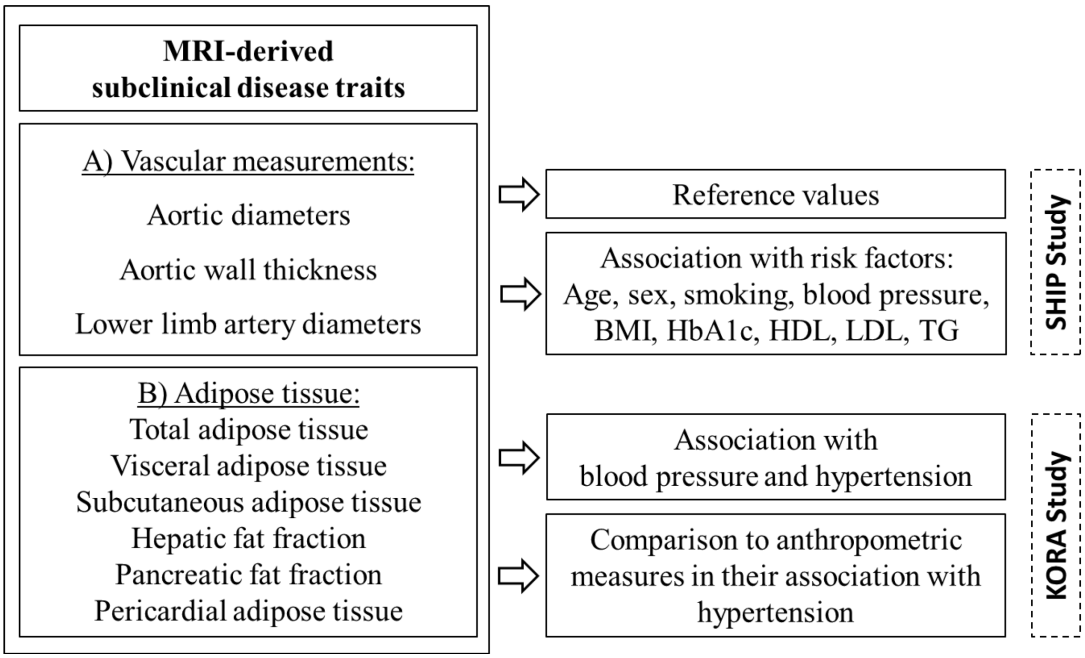

Figure 1 Field of study of "Magnetic resonance imaging measures of vascular structure and adipose tissue: relations to cardiovascular risk factors in the general population".

2. METHODS

2.1. STUDY SAMPLE

The data records for the individual analyses included two community-based samples, the "Study of Health in Pomerania" (SHIP), conducted in northeast Germany and the "Cooperative Health Research in the Region of Augsburg" (KORA), conducted in the south Germany (Bavaria).

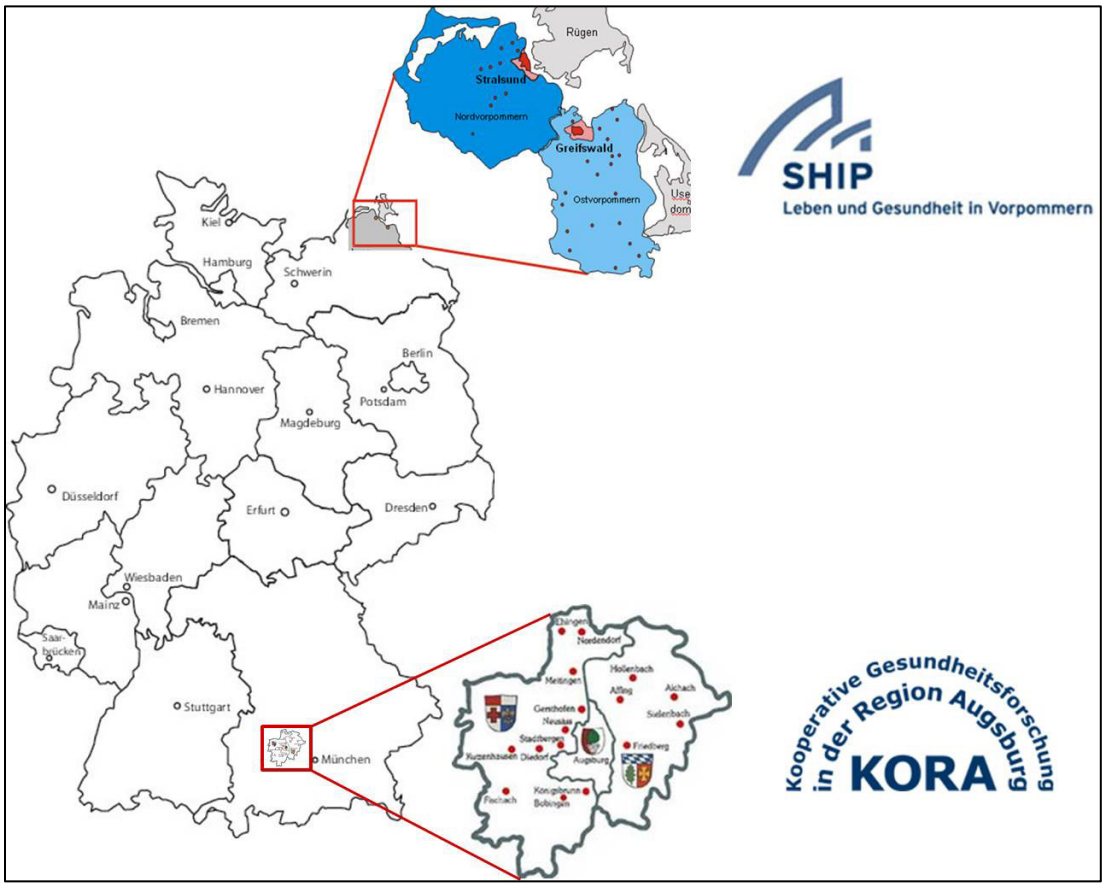

Figure 2 Study regions of "Study of Health in Pomerania" (SHIP) in northeast Germany and „Cooperative Health Research in the Region of Augsburg" (KORA) in south Germany.

2.1.1. STUDY OF HEALTH IN POMERANIA (SHIP)

SHIP is a population-based health study in Western Pomerania in northeast Germany **(Figure 2)** consisting of two cohorts. The aim of SHIP was to estimate the prevalence and incidence of risk factors, subclinical disorders and clinical diseases and to investigate the complex relationships between risk factors, subclinical disorders and clinical diseases. Thus, SHIP did not focus on a specific disease, but rather on several different highly prevalent diseases, such as CVD and the comprehensive analysis of health-related conditions (38). Basic recruitment of the first cohort (SHIP-0) was performed between 1997 and 2001 and included 4,308 subjects aged 20 to 79 years (39). After five years between 2003 and 2006, 3300 participants of the first cohort were re-examined (SHIP-1). SHIP-2 is the second follow-up of the first cohort and was conducted

between 2008 and 2012 with 2,333 subjects. In parallel, a second independent cohort (SHIP-TREND) was established between 2008 and 2012 with 4,420 subjects aged 20 to 79 years (38). In this period from 2008 to 2012, a subsample from the two cohorts were screened by cardiovascular MRI and MRA. For the assessment of vessel structure reference values, vascular healthy reference samples were used by excluding symptomatic subjects with vascular diseases including history of myocardial infarction, stroke, heart surgery, percutaneous transluminal, coronary angioplasty, thoracic or abdominal aneurysm, aortic dissection, claudication, lower extremity amputation and lower leg arteries stenosis yielding subsamples between 636 and 1759 participants for the different analyses.

2.1.2. COOPERATIVE HEALTH RESEARCH IN THE REGION OF AUGSBURG (KORA)

The KORA study is a population-based cohort health survey in the city of Augsburg and its surroundings in south Germany (**Figure 2**). The aim of the KORA study was also to investigate the links between risk factors, subclinical disorders and clinical diseases with special emphasis on diabetes, cardiovascular and pulmonary diseases and environmental conditions.

The basic study of the fourth cohort was conducted between 1999 and 2001 (KORA-S4) (40). A total of 4261 participants aged 25-74 years were examined during this period. The KORA-FF4 study is the second follow-up of the S4 baseline study and was conducted between 2013 and 2014 with 2279 participants.

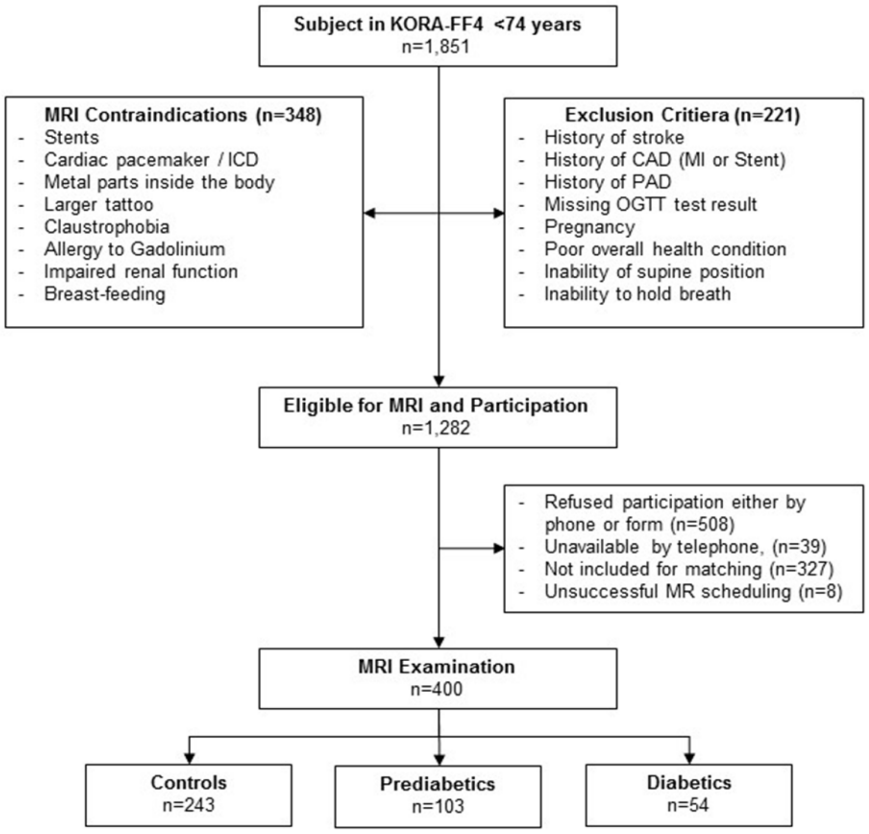

Figure 3 Participant flow diagram of the KORA-MRI Study**.**

The KORA-FF4 study included an MRI sub-study investigating subclinical cardiovascular disorders in 400 participants with prediabetes, diabetes and normal glucose metabolism. Exclusion criteria for this MRI sub-study were an age over 73 years, CVD defined as validated stroke, myocardial infarction or arterial occlusion, and contraindications for MRI scans (41) (**Figure 3).**

2.2. MEASUREMENT OF CARDIOVASCULAR RISK FACTORS

Information on age and sex was provided by the population registries in SHIP and KORA. Standardized personal interviews were used to collect smoking status that was categorized as never, former, or current smoker. Other factors considered to potentially affect cardiovascular remodelling included BP, BMI, haemoglobin A1c (HbA1c), LDL-C, HDL-C and TG. BMI was calculated as weight (kg) divided by the square of height (m^2).

Systolic and diastolic BP were measured at the right arm of seated subjects after a 5-minute rest period during the core examination. The mean of the second and third measurement was used for the present analysis. Hypertension was defined as systolic BP ≥140 mmHg or diastolic BP ≥90 mmHg or use of antihypertensive medication under the awareness of having hypertension. Medication intake within the last seven days was assessed during a medical interview by computer-based software, and participants were also asked to bring their medication packages with them. Antihypertensive medication was defined according to the German Hypertension Association and included antihypertensives, diuretics, beta blocking agents, calcium channel blockers or agents acting on the renin-angiotensin system. If participants reported that they had ever been told by a physician to have high or elevated BP they were characterized as being aware of hypertension.

Blood samples were taken from each participant's median antecubital vein in the supine position between 07.00 a.m. and 04.00 p.m. and were analysed immediately. Serum HbA1c levels were measured by high-performance liquid chromatography (SHIP: Bio-Rad DiamatTM Analyzer, ClinRep® kit, RECIPE Chemicals+ Instruments GmbH, Munich, Germany). LDL-C and HDL-C as well as triglyceride levels were determined enzymatically using reagents from Dade Behring (SHIP: Dimension VistaTM System, Flex® reagent cartridge, Dade Behring, Milton Keynes, UK).

2.3. MEASUREMENT OF MRI PARAMETERS

In SHIP, measurements of vascular structure were conducted by standardized whole-body MRI examination performed on a 1.5 Tesla MRI scanner (Magnetom Avanto; Siemens Healthcare, Erlangen, Germany). Imaging was performed using integrated coil elements and phased-array surface coils during free breathing with retrospective gating.

In KORA, all MRI examinations of the upper part of the body were performed on a 3 Tesla Magnetom Skyra (Siemens AG, Healthcare Sector, Erlangen Germany) using an 18 channel body coil in combination with the table-mounted spine matrix coil.

2.3.1. VESSEL PARAMETERS

Thoracic and abdominal aortic diameters

In SHIP, MRI-derived aortic diameters were measured on plain axial 3D T1-weighted volumetric interpolated breath-hold examination (VIBE) images. Outer diameters of six predefined aortic segments were measured: the ascending and descending aorta (level of the pulmonary trunk), the aortic arch (proximal to the origin of the left subclavian artery), the subdiaphragmic aorta (level of the aortic hiatus), and the supra- and infrarenal aorta (1 cm above/below the right renal artery origin; **Figure 4**). Diameters were measured on axial slices in coronal orientation from outer wall to outer wall. For analyses, vessel diameters were indexed by body surface area (BSA) calculated according to the Du Bois formula: $BSA=0.007184\times(\text{height in cm})^{0.725}\times(\text{weight in kg})^{0.425}$.

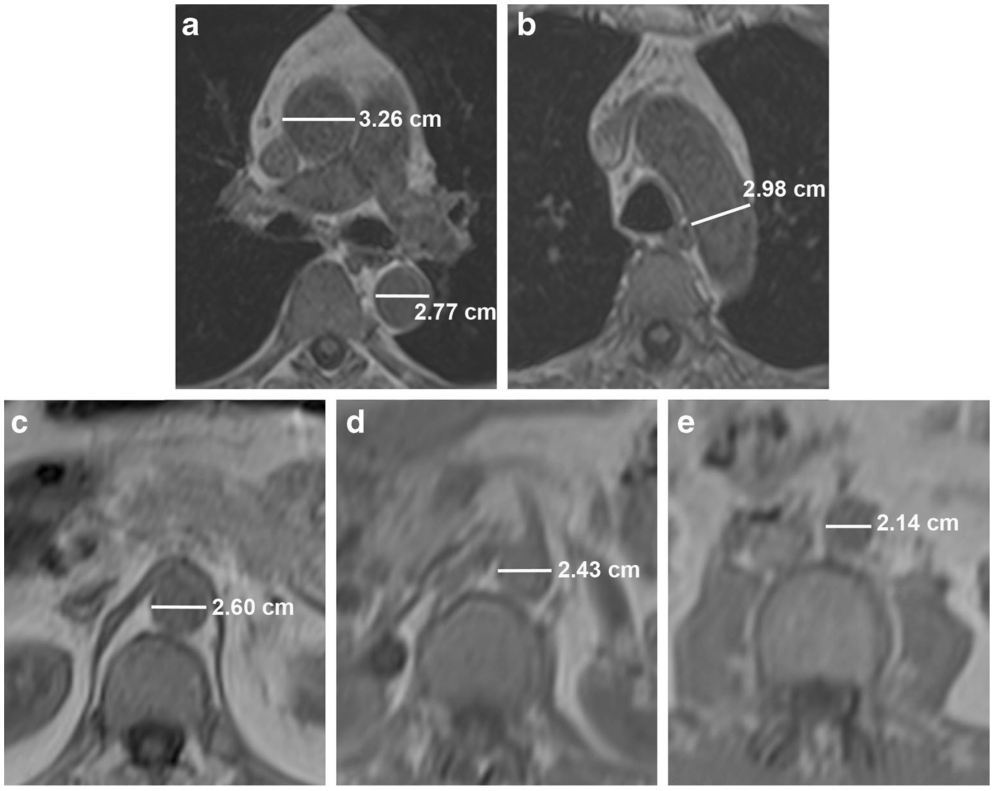

Figure 4 T1-weighted VIBE images illustrating diameter measurement in a 73-year-old male volunteer: **a** ascending and descending aorta, **b** aortic arch, **c** subphrenic aorta, **d** suprarenal aorta, **e** infrarenal aorta.

Aortic wall thickness

AWT was calculated from a two-dimensional cine steady-state free precession sequence acquired as part of a standard cardiac MRI protocol. The quality of all images selected for AWT measurements was rated as sufficient or insufficient before measurements were performed. Sufficient quality was defined as clear depiction of the inner and outer boundaries of the ascending and descending aortic wall without significant artifacts. Insufficient quality was defined as incomplete depiction of the wall of the descending or ascending aorta. Subjects with insufficient image quality were excluded.

Multiple slices covering the ascending and descending aorta were acquired. AWT was measured in a single sequence at the level of the right pulmonary artery, choosing the sequence most clearly depicting the wall of the ascending or descending aorta. First, the image with a trigger time closest to 600 ms was chosen to ensure better comparability and to minimize motion artifacts of the aorta. Subjects with a cardiac cycle < 520 ms were excluded. The image was magnified to 200-300% and contrast as well as brightness settings were adjusted for optimal aortic wall depiction. Then, two regions of interest (ROIs) were placed manually including the internal and external aortic wall of the ascending aorta (**Figure 5**). Next, the radius of each area was calculated, assuming that all areas are circular. AWT was calculated as the difference in the radii of external and internal aortic area. The ROIs were removed. And the procedure was repeated for the descending aorta.

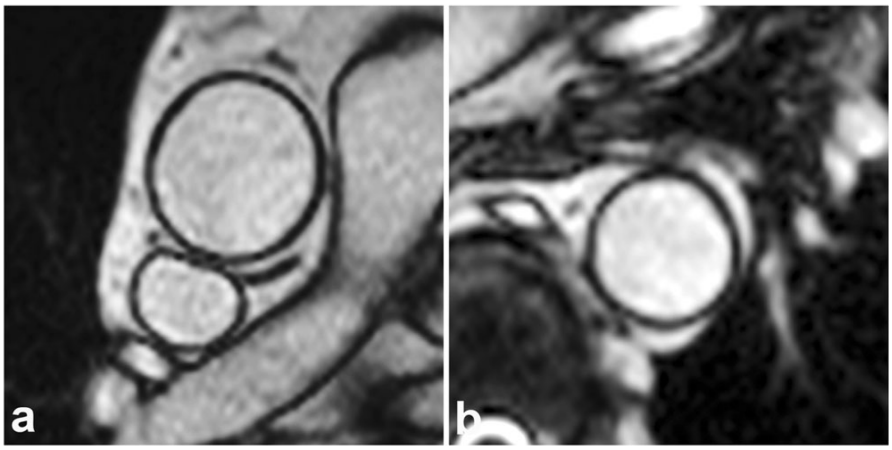

Figure 5 Cine images of a 51-year-old male volunteer displaying the ascending (a) and descending aorta (b) for measuring of AWT.

Lower limb artery diameters

MRA was done after a previous whole-body MRI in men only. Before the contrast medium Gadobutrol was applied, renal function had been assessed by estimating the glomerular filtration rate (GFR). Participants with an estimated GFR < 60 ml/min/1.73m^2 and known contrast allergy were excluded. The vessel measurements were done at 9 predefined artery segments at each side: 1) common iliac, 2) internal iliac, 3) external iliac, 4) femoral (proximal), 5) femoral (distal), 6) popliteal, 7) anterior tibial, 8) posterior tibial, and 9) fibular (**Figure 6**). Vessel diameter measurements were taken in T1-weighted contrast

enhanced flash sequences in the coronary layer. For overview purposes maximum intensity projection images were used additionally. For each predefined segment the image layer with the maximum vessel diameter was explored and the inner diameter perpendicular to the vessel wall was measured. All images used for the present analysis were evaluated visually for stenosis in the pelvic and leg arteries by one trained observer. Stenoses were graded compared to the assumed normal vascular diameter in the particular segment. The degree of stenosis (narrowing of the diameter) in each of the segments was categorized as grade 1 (30-49%), grade 2, (50-99%) and grade 3 (100%, thrombosis).

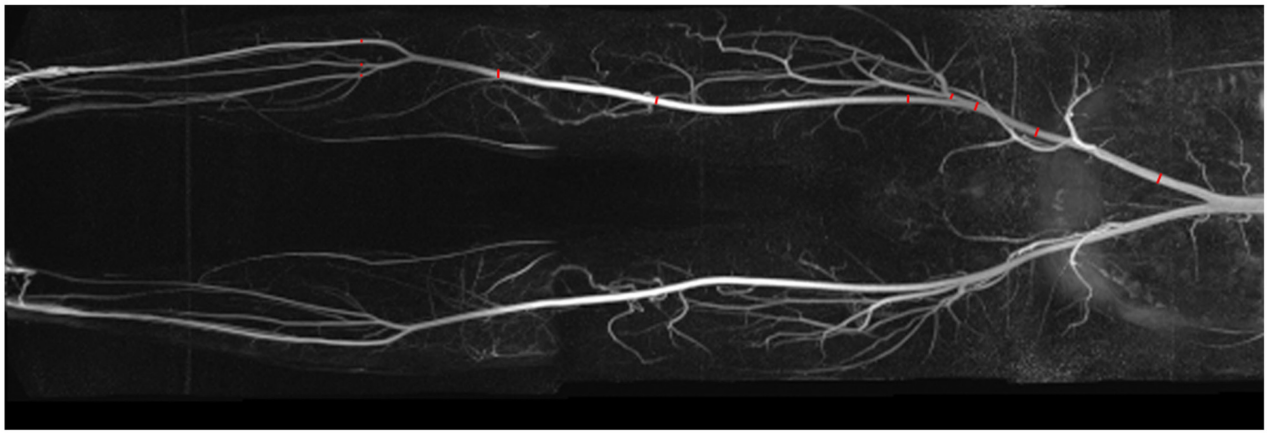

Figure 6 Example of male pelvic and leg arteries. Derived from contrast-enhanced MR angiography in the Study of Health in Pomerania. Red lines correspond to vessel measurements.

2.3.2. ADIPOSE TISSUE PARAMETERS

In KORA MRI-derived adipose tissue measurements TAT, VAT, SCAT as well as HFF, PFF and PAD were assessed as follows:

TAT, VAT, SCAT: Based on the volume-interpolated 3D in/opposed-phase VIBE-Dixon sequence a fat selective tomogram was calculated (slice thickness 5mm at 5mm increment). An in-house algorithm based on Matlab R2013a was used to automatically quantify the TAT from the femoral head to the cardiac apex, VAT from the femoral head to the diaphragm, and SCAT from the femoral head to the cardiac apex. All segmentations were manually adjusted if necessary. TAT, VAT and SCAT were indexed by squared height (m^2) (**Figure 7**).

HFF: The multi-echo Dixon was based on a VIBE sequence. For the estimation of liver proton density fat fraction, confounding effects of T2* decay and the spectral complexity of fat were taken into account. Acquisition time was approximately 15 seconds. A region of interest was manually drawn on one slice at the height of the portal vein including the whole liver parenchyma avoiding large vessels and surrounding extrahepatic tissue to measure HFF at the level of the portal vein. Data were given in per cent (%).

PFF: For quantitative assessment of pancreatic fat tissue content, one or two circular ROIs covering an area of approximately 100 mm^2 were drawn into the pancreatic head (caput), the pancreatic body (corpus) and

the pancreatic tail (cauda) on different MRI-layers, using a dedicated off-line workstation (Syngo Via, Siemens Healthcare, Erlangen, Germany). Images with severe image artefacts (e.g. phase swaps) were excluded from the analysis. Data were indexed in per cent (%).

PAT: was defined as any mediastinal fat between the pulmonary artery bifurcation and the diaphragm, this includes fat inside the visceral layer of the pericardial sac in close proximity to the myocardium as well as outside of the pericardial sac. Applying an automated procedure based on cluster analysis, PAT was quantified between thoracic diaphragm and vascular bifurcation of the pulmonary artery and carefully avoiding inclusion of mediastinal adipose tissue.

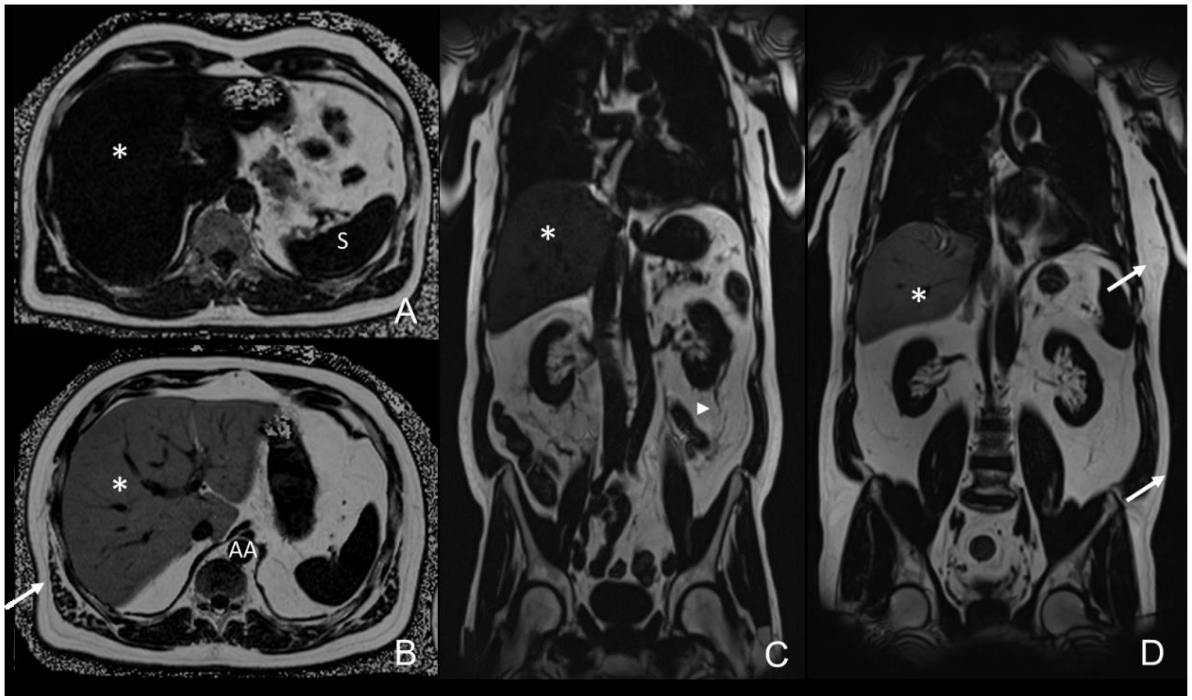

Figure 7 Examples of metabolic findings. Differences in hepatic adipose content based on a multi-echo DIXON sequence demonstrating normal signal (A) and attenuated signal due to steatosis (33% HFF, B) and subcutaneous (arrow) and visceral (arrowhead) adipose tissue between healthy control subject (C) and a subject with prediabetes (D).

2.4. STATISTICAL ANALYSES

Different methods of descriptive and analytical statistics were applied for the different study work packages. Reference values for the distribution of vascular imaging parameters in the population were defined as 5th and/or 95th percentiles and were determined separately for men and women and for different age groups in a healthy reference sample as described above.

Multivariable analyses of the relationship between risk factors and MRI traits included linear, logistic, negative binomial, censored and quantile regression analyses, as appropriate, to adjust for potential

confounders. Effect sizes were estimated together with 95% confidence intervals (CI). Nonlinearity of relationships was tested by residual analysis, polynomial regression, and by cubic splines.

Model performance and cut-off values of adipose tissue measurements for the prediction of hypertension were evaluated and compared to established prediction models by sensitivity, specificity, Youden Index, ROC curves and area under the curve (AUC) values. A p-value <0.05 was used to determine statistical significance. All statistical analyses were performed using the statistic package "Stata" (Stata Corporation, College Station, TX, USA).

3. RESULTS

3.1. REFERENCE VALUES OF ARTERY STRUCTURE

Thoracic and abdominal aortic diameters (Hypothesis 1 (32))

The unadjusted median diameters of the different aortic segments were as follows: ascending aorta (3.20 cm for women, 3.49 cm for men), aortic arch (2.73 cm, 2.93 cm), descending aorta (2.34 cm, 2.63 cm), subphrenic aorta (2.22 cm, 2.46 cm), suprarenal aorta (2.07 cm, 2.34 cm) and infrarenal aorta (1.75 cm, 1.97 cm) with a relative reduction of 45% for women and 44% for men (from ascending to infrarenal aorta). Each median aortic diameter was lower in women compared to men ($p<0.001$ for all aortic segments) with the relative reduction ranging between 7 % (aortic arch) and 12 % (suprarenal). Values for 5th percentile, median and 95th percentile increased with the 10-year age group.

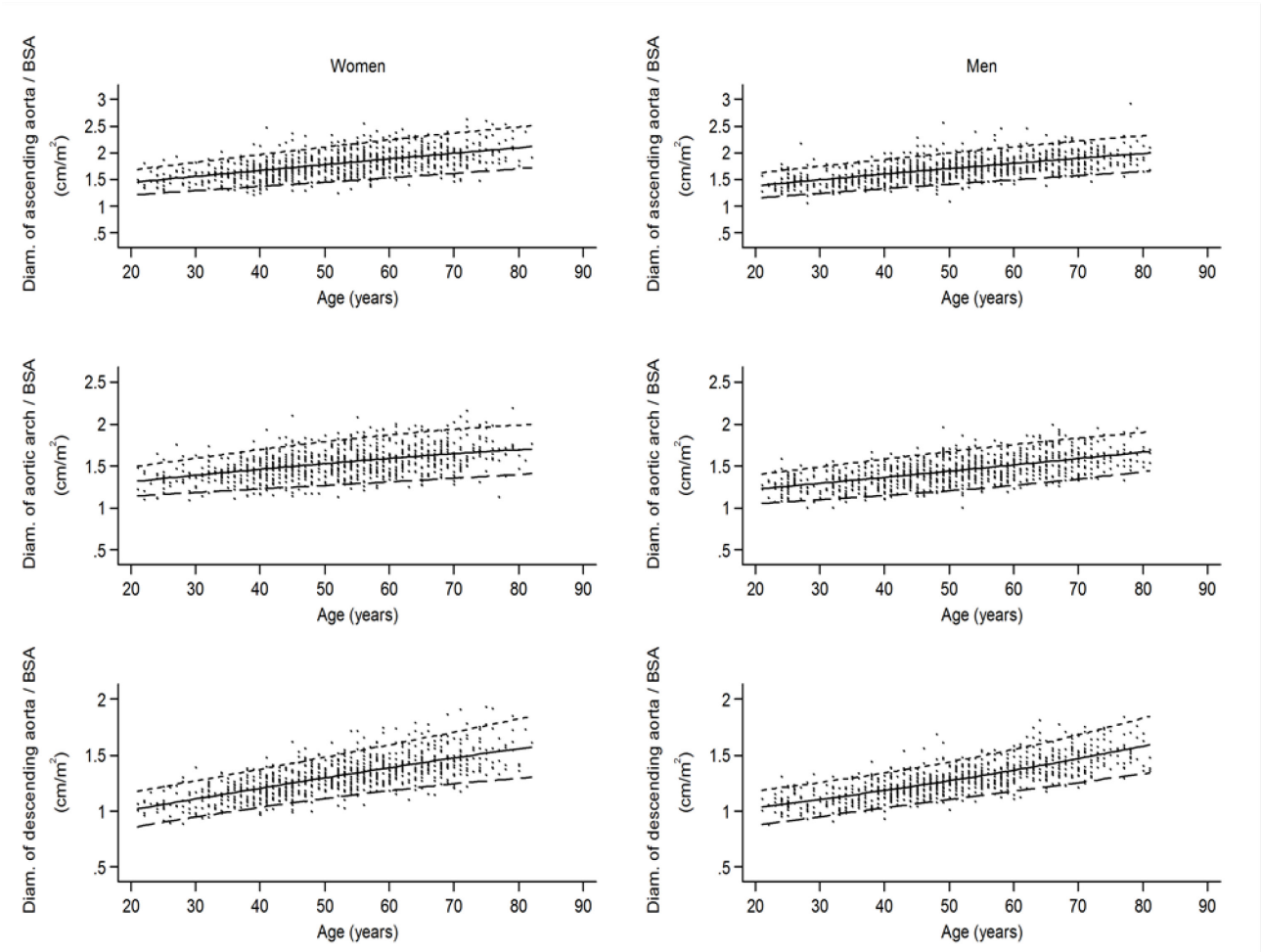

Figure 8 Age-specific distributions of BSA-indexed diameters of the thoracic ascending, the aortic arch and the descending aorta. The diameters are given as median values with 5th and 95th percentiles for women and men. The values were calculated using fractional polynomial regression models (N=1759). (32)

The significant increase in BSA-indexed diameters with each single year of age (all $p<0.001$) was similar for women and men for the median, 5th percentile and 95th percentile. BSA-indexed diameters varied between the lowest diameter for the female infrarenal aorta ($\beta_{p50}=0.005$, $\beta_{p5}=0.004$, $\beta_{p95}=0.006$) and the highest diameter for the female ascending aorta ($\beta_{p50}=0.011$, $\beta_{p5}=0.008$, $\beta_{p95}=0.014$), whereas the increase over age at the 95th percentile was always higher than at the 5th percentile (**Figure 8**).

Thoracic aortic wall thickness (Hypothesis 2 (33))

Median wall thickness of the ascending aorta was 1.46 mm (5th-95th range: 1.15-1.88 mm) for women and 1.56 mm (1.22-1.99 mm) for men. Median wall thickness of the descending aorta was 1.26 mm (0.97-1.58 mm) for women and 1.36 mm (1.04-1.75 mm) for men (**Table 1**). Thus, in both sexes, the wall of the ascending aorta was thicker than the wall of the descending aorta ($p<0.001$), and both walls were thicker in men compared to women ($p<0.001$). Median values as well as 5th and 95th percentiles increased with age for both the ascending and descending aorta and for women and men.

Table 1 Age- and sex-specific percentiles of AWT (mm) in the study sample. (33)

		Women						Men					
	Age		Percentiles						Percentiles				
Aorta	(years)	N	5th	25th	50th	75th	95th	N	5th	25th	50th	75th	95th
ascending		303	1.15	1.32	1.46	1.63	1.88	434	1.22	1.40	1.56	1.73	1.99
	20-29	16	1.09	1.18	1.28	1.37	1.57	31	1.18	1.27	1.41	1.56	1.70
	30-39	38	1.15	1.29	1.43	1.55	1.71	63	1.08	1.32	1.40	1.54	1.86
	40-49	75	1.15	1.30	1.41	1.61	1.94	111	1.20	1.38	1.53	1.71	1.91
	50-59	98	1.13	1.33	1.44	1.65	1.85	105	1.32	1.49	1.61	1.77	2.05
	60-69	57	1.31	1.48	1.57	1.70	1.93	80	1.28	1.50	1.67	1.81	2.10
	70+	19	1.22	1.40	1.48	1.71	2.26	44	1.34	1.55	1.66	1.82	2.11
descending		311	0.97	1.13	1.26	1.38	1.58	442	1.04	1.23	1.36	1.50	1.75
	20-29	17	0.84	0.99	1.04	1.18	1.26	29	0.91	1.05	1.18	1.32	1.42
	30-39	44	0.95	1.09	1.18	1.31	1.47	62	0.98	1.11	1.24	1.36	1.51
	40-49	74	0.94	1.09	1.22	1.32	1.48	114	1.03	1.21	1.33	1.42	1.57
	50-59	99	1.04	1.15	1.27	1.39	1.60	109	1.12	1.28	1.40	1.55	1.76
	60-69	59	1.11	1.25	1.38	1.49	1.68	85	1.18	1.32	1.45	1.61	1.84
	70+	18	1.09	1.16	1.28	1.43	1.60	43	1.24	1.35	1.46	1.68	1.83

Lower limb artery diameters (Hypothesis 3 (35))

BSA-indexed reference values of leg artery diameters increased with age in all segments, specifically in the upper leg arteries (**Table 2**). E.g., older age was associated with larger left reference diameter of common iliac artery (β=0.00229, p<0.001), internal iliac artery (β=0.00290, p<0.001) and external iliac artery (β=0.00248, p<0.001).

Table 2 Parameters for calculation of reference values (95th percentile) for BSA-indexed leg artery diameters according to age. (35)

N=636	BSA-indexed leg artery diameter (95th percentile) cm/m^2		
	Intercept	β_{age}	p*
Artery (left)			
common iliac	0.44444	0.00229	<0.001
internal iliac	0.21815	0.00290	<0.001
external iliac	0.37285	0.00248	<0.001
femoral (prox.)	0.40957	0.00167	0.017
femoral (dist.)	0.28461	0.00160	<0.001
popliteal	0.26946	0.00159	<0.001
anterior tibial	0.18772	0.00043	0.039
posterior tibial	0.14702	0.00077	<0.001
fibular	0.17649	0.00031	0.277
Artery (right)			
common iliac	0.46045	0.00228	<0.001
internal iliac	0.21419	0.00249	<0.001
external iliac	0.40033	0.00180	0.001
femoral (prox.)	0.39878	0.00172	0.003
femoral (dist.)	0.27089	0.00181	<0.001
popliteal	0.25155	0.00170	0.003
anterior tibial	0.18823	0.00039	0.175
posterior tibial	0.15903	0.00055	0.010
fibular	0.17224	0.00044	0.093

*Parameters are from weighted quantile regression; BSA, body surface area

3.2. ASSOCIATION BETWEEN CARDIOVASCULAR RISK FACTORS AND ARTERY STRUCTURE

Thoracic and abdominal aortic diameters (Hypothesis 1 (32))

For the ascending aorta (β=-0.049, p<0.001), the aortic arch (β=-0.061, p<0.001), and the subphrenic aorta (β=-0.018, p=0.004), the body surface area (BSA)-indexed diameters were lower in men than in women. There were no sex differences for the descending and the suprarenal aorta, while for the infrarenal aorta the diameter was higher in men than in women (β=0.013, p=0.013; **Table 3**).

As with unadjusted association, multivariable-adjusted association revealed significant increases in BSA-adjusted diameters of all six investigated aortic segments with age (p<0.001 for each aortic segment). Current smoking was positively associated with the diameter of the descending, subphrenic, suprarenal, and infrarenal aorta but not with the diameter of the ascending aorta and the aortic arch (**Table 3**). Consistent results for all aortic segments were observed for the positive associations of diastolic BP and HDL-C with BSA-adjusted aortic diameters and for the inverse association of systolic BP with aortic diameters. HbA1c and LDL-C were not associated with aortic diameters except for the subphrenic aorta (HbA1c: β=-0.008, p=0.041) and the infrarenal aorta (LDL-C: β=-0.005, p=0.042) with borderline significance. Furthermore, a higher triglyceride level was identified to be a potential risk factor for smaller aortic diameter, for example of the descending aorta (β=-0.011, p<0.001, **Table 3**).

The diameters of the descending aorta (adjusted R^2=0.56) and the subphrenic aorta (R^2=0.59) were most strongly affected by the cardiovascular risk factors investigated, while the aortic arch (R^2=0.35) and infrarenal aorta (R^2=0.38) were least affected by these factors.

Wall thickness of the ascending aorta (Hypothesis 2 (34))

Men had a higher wall thickness of the ascending aorta than women (β=0.086, p<0.001), and a higher age was associated with a higher AWT (β=0.006, p<0.001) in the SHIP-TREND sample. In addition, BMI showed a positive association with AWT values (β=0.013, p<0.001, **Table 4**).

In an age-adjusted model HDL-C was inversely associated with the wall thickness of the ascending aorta (β=-0.082, p<0.001). However, this relation became statistically non-significant in the multivariable model. LDL-C showed an inverse association with AWT (β=-0.024, p=0.009, **Table 4**).

Data of the SHIP-2 sample could confirm the results regarding sex, age and BMI. The values for the adjusted R^2 for each model were 0.2403 and 0.1461 for the SHIP-TREND and SHIP-2 sample, respectively.

Table 3 Cardiovascular risk factor model for BSA-indexed thoracic and abdominal aortic diameters. (32)

	Thoracic aorta diameter / BSA			Abdominal aorta diameter / BSA		
N=1759	ascending	arch	descending	subphrenic	suprarenal	infrarenal
Risk factors	β (95%CI)	β (95%CI)	β (95%CI)	β (95%CI)	β (95%CI)	β (95%CI)
Men	-0.049 (-0.070; -0.027)***	-0.061 (-0.078; -0.045)***	-0.005 (-0.018; 0.007)	-0.018 (-0.031; -0.006)**	-0.001 (-0.012; 0.010)	0.013 (0.003; 0.023)*
Age	0.011 (0.010; 0.012)***	0.007 (0.007; 0.008)***	0.010 (0.009; 0.010)***	0.010 (0.010; 0.011)***	0.008 (0.007; 0.008)***	0.006 (0.005; 0.006)***
Former smoker	-0.008 (-0.029; 0.013)	-0.003 (-0.019; 0.013)	0.011 (-0.002; 0.023)	0.014 (0.002; 0.026)*	0.005 (-0.006; 0.016)	0.001 (-0.009; 0.011)
Current smoker	0.006 (-0.018; 0.030)	0.007 (-0.012; 0.025)	0.031 (0.017; 0.046)***	0.039 (0.025; 0.053)***	0.030 (0.017; 0.043)***	0.026 (0.015; 0.038)***
Systolic BP	-0.001 (-0.002; -0.001)**	-0.001 (-0.001; 0.000)*	-0.001 (-0.001; 0.000)*	-0.001 (-0.001; -0.001)***	-0.001 (-0.002; -0.001)***	-0.001 (-0.001; 0.000)***
Diastolic BP	0.004 (0.003; 0.005)***	0.002 (0.001; 0.003)***	0.002 (0.001; 0.002)***	0.002 (0.001; 0.003)***	0.002 (0.002; 0.003)***	0.001 (0.000; 0.002)**
HbA1c	-0.005 (-0.018; 0.008)	0.000 (-0.010; 0.010)	-0.001 (-0.008; 0.007)	-0.008 (-0.016; 0.000)*	-0.004 (-0.011; 0.003)	-0.005 (-0.011; 0.002)
HDL-C	0.087 (0.057; 0.116)***	0.053 (0.031; 0.076)***	0.035 (0.017; 0.052)***	0.053 (0.036; 0.070)***	0.052 (0.036; 0.068)***	0.044 (0.030; 0.058)***
LDL-C	-0.004 (-0.014; 0.007)	0.002 (-0.006; 0.010)	-0.002 (-0.008; 0.004)	-0.005 (-0.011; 0.001)	-0.005 (-0.010; 0.001)	-0.005 (-0.010; 0.000)*
Triglycerides	-0.007 (-0.017; 0.003)	-0.012 (-0.020; -0.005)**	-0.011 (-0.017; -0.005)***	-0.011 (-0.017; -0.005)***	-0.010 (-0.015; -0.004)**	-0.008 (-0.013; -0.003)**
Adj. R^2	0.3983	0.3511	0.5607	0.5864	0.4908	0.3828

β-parameters are from linear regression; CI, confidence interval
* p<0.05, **p<0.01, ***p<0.001
HbA1c, hemoglobin A1c; HDL-C, high-density-lipoprotein cholesterol; LDL-C, low-density-lipoprotein cholesterol

Table 4 Cardiovascular risk factor model for wall thickness of the ascending aorta. (34)

	SHIP-TREND (N=747)				SHIP-2 (N=429)			
Risk factors	Partial R^2	β	(95%CI)	p	Partial R^2	β	(95%CI)	p
Men	0.0260	0.086	(0.046; 0.127)	<0.001	0.0734	0.111	(0.070; 0.151)	<0.001
Age	0.1109	0.006	(0.005; 0.008)	<0.001	0.0111	0.002	(0.000; 0.004)	0.044
Ex-smoker	0.0006	0.011	(-0.025; 0.048)	0.542	0.0054	0.029	(-0.012; 0.070)	0.162
Current smoker	0.0026	0.029	(-0.014; 0.072)	0.187	0.0003	0.008	(-0.044; 0.061)	0.753
BMI	0.0505	0.013	(0.009; 0.018)	<0.001	0.0127	0.005	(0.001; 0.010)	0.031
Systolic BP	0.0005	-0.0004	(-0.0019; 0.0011)	0.572	0.0000	-0.0001	(-0.0017; 0.0015)	0.920
Diastolic BP	0.0018	0.0013	(-0.0010; 0.0036)	0.274	0.0006	0.0006	(-0.0021; 0.0033)	0.654
HbA1c	0.0032	0.018	(-0.006; 0.042)	0.141	0.0030	-0.016	(-0.045; 0.014)	0.295
HDL-C	0.0035	0.043	(-0.012; 0.099)	0.126	0.0036	-0.032	(-0.086; 0.023)	0.253
LDL-C	0.0102	-0.024	(-0.043; -0.006)	0.009	0.0008	-0.006	(-0.026; 0.015)	0.587
Triglycerides	0.0031	0.013	(-0.005; 0.032)	0.153	0.0000	-0.001	(-0.0138; 0.0126)	0.928
	Adj. R^2				Adj. R^2			
Model	0.2403			<0.001	0.1461			<0.001

β-parameters are from linear regression; CI, confidence interval
HbA1c, hemoglobin A1c; HDL-C, high-density-lipoprotein cholesterol; LDL-C, low-density-lipoprotein cholesterol

Wall thickness of the descending aorta (Hypothesis 2 (34))

Multivariable adjusted analyses revealed a higher wall thickness of the descending aorta for men compared to women (β=0.105, p<0.001) in the SHIP-TREND sample. Higher age showed a positive association with higher AWT (β=0.006, p<0.001). Furthermore, an increasing BMI was associated with increasing AWT values (β=0.013, p<0.001) and current smoker had a higher AWT compared to never smoker (β=0.044, p=0.010).

HDL-C showed an inverse association with the wall thickness of the descending aorta (β=-0.071, p<0.001) in an age-adjusted model. However, this association turned into a positive association after multivariable adjustment (β=0.057, p=0.008). LDL-C was inversely associated with AWT in the multivariable adjusted model (β=-0.018, p=0.010). In sensitivity analyses, multivariable models with further adjustment for lipid

lowering medication, physical activity and alcohol consumption did not detect substantially changed results.

The results regarding sex, age and BMI could be confirmed by the data of the SHIP-2 sample. The adjusted R^2 were 0.3273 and 0.3418 for the SHIP-TREND and SHIP-2 sample, respectively.

The positive association of BMI with AWT of the ascending aorta increased with age (BMI*age interaction effect with p=0.048; **Figure 9**) and the increase of the AWT of the descending aorta by BMI is borderline stronger in current smokers compared to never smokers (BMI*smoking status interaction effect with p=0.056; **Figure 10**).

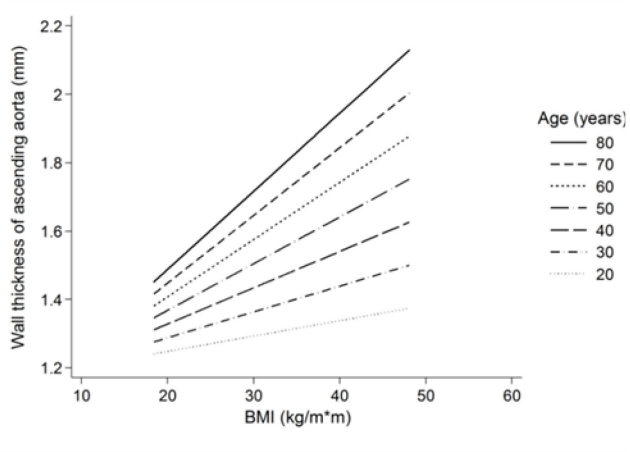

Figure 9 Association of BMI with wall thickness of the ascending aorta at different ages adjusted for sex, smoking, systolic and diastolic BP, HbA1c, HDL-C, LDL-C, and triglycerides (p-value for BMI x age interaction effect =0.048) in SHIP-TREND (N=747). (34)

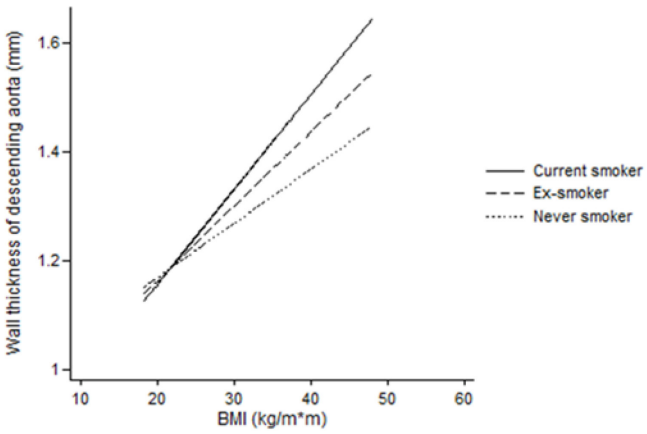

Figure 10 Association of BMI with wall thickness of the descending aorta for never smokers, ex-smokers, and current smokers adjusted for sex, age, systolic and diastolic BP, HbA1c, HDL-C, LDL-C, and triglycerides (p-value for BMI x smoking status interaction effect =0.056) in SHIP-TREND (N=747). (34)

Leg artery stenosis (Hypothesis 3 (35))

A number of 53 subjects (7.0% of 756) had at least one stenosis (1: n=19, 2: n=19, 3: n=9, 4: n=4, 5: n=1, 6: n=1), mainly in the lower leg arteries anterior tibial (n=28, 3.7%), posterior tibial (n=18, 2.4%) and fibular (n=20, 2.6%). Of all stenosis, 24% were of low severity (grade 1), 34% were grade 2 and 42% were severe (grade 3). The stenosis prevalence did not differ significantly between left and right vessel of each artery. The prevalence of stenosis increased considerably with age (odds ratio (OR)=1.07; p<0.001), diabetes (OR=3.58; p=0.001) and antithrombotic medication (OR=2.59; p=0.015).

3.3. ASSOCIATION OF MRI-DERIVED ADIPOSE TISSUE WITH HYPERTENSION (Hypotheses 4 (36) and 5 (37))

Among the MRT-derived adipose tissue measures, VAT and PAT had the highest AUC values for identifying individuals with prevalent hypertension (AUC: 0.75; 0.73, respectively), whereas waist–height ratio (WHtR) and WC were the best performing anthropometric markers (0.72; 0.70, respectively, **Table 5**). PFF and HC had lowest AUC values for hypertension (0.65; 0.63, respectively).

In multivariable-adjusted models, AUC values were highest for TAT and SCAT (AUC: 0.80, respectively, **Table 5)**, even though all adiposity traits improved the AUC beyond the basic model (AUC: 0.767) which included only the traditional risk factors (all $p \leq 0.016$ for improvement in AUC when added to a model with only traditional RF). Only AUC values of single adiposity traits differed among each other ($p<0.001$) whereas AUC values upon age- and sex as well as multivariable adjustment did not ($p=0.871$ for MRI-derived adipose tissue measurements; $p=0.219$ for anthropometric markers). Furthermore, formal statistical comparisons revealed that there were no statistically significant differences between any of the MRI-derived adipose tissue measurements and any of the anthropometric adiposity measures (comparing the respective AUCs) in identifying prevalent hypertension.

Table 5 AUC values for different statistical models investigating the presence of prevalent hypertension. Either models included only traditional risk factors (AUC_{basic}), only individual adiposity traits of interest, only individual adiposity traits of interest combined with age and sex, or each adiposity trait of interest combined with traditional risk factors. (37)

N=345	Hypertension AUC (95%CI) of single factor	Hypertension AUC (95%CI) of single factor + age and sex	Hypertension AUC (95%CI) single factor + basic model*	p**
			AUC_{basic}=0.7665	
TAT	0.72 (0.67;0.78)	0.79 (0.73;0.84)	0.80 (0.75;0.85)	<0.001
VAT	0.75 (0.70;0.81)	0.78 (0.73;0.83)	0.79 (0.75;0.84)	<0.001
SCAT	0.66 (0.60;0.72)	0.77 (0.72;0.83)	0.80 (0.75;0.84)	<0.001
HFF	0.72 (0.67;0.78)	0.76 (0.71;0.82)	0.79 (0.74;0.84)	0.002
PFF	0.65 (0.59;0.72)	0.74 (0.68;0.79)	0.78 (0.73;0.83)	0.016
PAT	0.73 (0.67;0.78)	0.76 (0.70;0.81)	0.79 (0.74;0.84)	0.001
	p<0.001	p=0.152	p=0.871	
BMI	0.68 (0.62;0.74)	0.77 (0.72;0.82)	0.79 (0.74;0.84)	<0.001
WC	0.70 (0.65;0.76)	0.78 (0.72;0.83)	0.79 (0.75;0.84)	<0.001
HC	0.63 (0.57;0.69)	0.75 (0.70;0.81)	0.79 (0.74;0.84)	<0.001
WHR	0.70 (0.64;0.76)	0.76 (0.71;0.82)	0.78 (0.73;0.83)	0.003
WHtR	0.72 (0.66;0.78)	0.78 (0.72;0.83)	0.79 (0.75;0.84)	<0.001
	p<0.001	p=0.110	p=0.219	

* Basic risk factor model for hypertension includes: age, sex, diabetes, physical activity, smoking status, alcohol consumption, total cholesterol, HDL-C

** Likelihood-ratio test (comparison: basic model vs. basic risk factor model + adiposity risk factor)

A 1-SD increment of TAT was associated with the highest odd for hypertension in the age- and sex-adjusted model (OR=2.20, p<0.001) and in the fully adjusted model (OR=1.97, p<0.001; **Figure 11**). Also SCAT and VAT were highly associated with hypertension in both models (all p<0.001). Among the different anthropometric marker, WC displayed the highest odd for hypertension in the age- and sex-adjusted model (OR=2.19, p<0.001) and in the fully adjusted model (OR=1.92, p<0.001). Similarly, TAT and WC were the most strongly associated marker of their respective groups (MRI markers and anthropometric markers, respectively) in relation to continuously modeled systolic BP. In a secondary analysis, when the best performing anthropometric marker WC was added to the multivariable-adjusted model with the different MRI-derived adiposity measures, only TAT was associated independently with prevalent hypertension (OR=1.93, p=0.049). To further explore the association between total adipose tissue and hypertension, different multivariable-adjusted models with an increasing number of potential confounders were provided. In essence, the strength of association decreased slightly from the unadjusted model to the fully adjusted model.

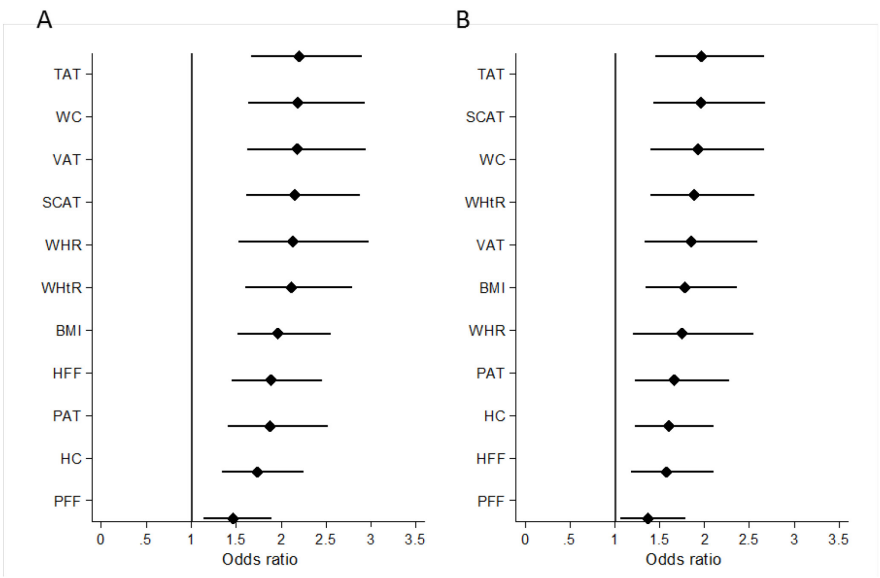

Figure 11 Association of MRI and anthropometric markers (SD increment) with presence of hypertension in the overall sample adjusted for age and sex only (A) and adjusted for age, sex, diabetes, physical activity, smoking status, alcohol consumption, total cholesterol and HDL-cholesterol (B) expressed by ORs and 95% confidence intervals (N=345). (37)

Comparing the 10th (reference) vs. 90th percentile, high levels of right lobe HFF and HFF at the portal vein were linearly associated with higher odds for hypertension (OR=2.15, p=0.029, OR=2.16, p=0.025, respectively, **Table 6**). The association between high levels of left lobe HFF and hypertension was less strong and borderline non-significant (OR=1.80, p=0.085).

The evaluation of the optimal HFF cut-off value for dividing the study sample into groups with low and high hypertension risk revealed different cut-off points for left lobe HFF (3.57%; sensitivity: 86%,

specificity: 50%), right lobe HFF (6.8%; sensitivity: 72%, specificity: 66%) and HFF at the portal vein (5.13%; sensitivity: 70%, specificity: 66%). The best prediction for hypertension of all HFF variables was observed for the left lobe HFF cut-off value (OR=2.62, p=0.003; right lobe HFF: OR=2.17, p=0.008, HFF at the portal vein: OR=2.00, p=0.015, **Table 6**).

Table 6 Association of hepatic fat fraction with hypertension. (36)

N=384	Hypertension, N=132 (34%)				
HFF, left liver lobe (%) Percentiles	OR (95%CI)	HFF, right liver lobe (%)	OR (95%CI)	HFF, portal vein (%)	OR (95%CI)
10th (1.4)	1	(2.0)	1	(1.7)	1
30th (2.9)	1.05 (0.99-1.11)	(3.9)	1.07 (1.01-1.14)	(3.0)	1.05 (1.01-1.09)
50th (5.1)	1.12 (0.97-1.28)	(6.3)	1.17 (1.01-1.34)	(4.6)	1.12 (1.01-1.22)
70th (8.9)	1.27 (0.92-1.62)	(11.2)	1.40 (0.98-1.83)	(9.6)	1.35 (1.00-1.71)
90th (19.8)	1.80 (0.60-3.01)	(22.8)	2.15 (0.68-3.63)	(21.8)	2.16 (0.71-3.61)
p	*0.085*		*0.029*		*0.025*
Optimal cut-off values*					
≤38th (3.57)	1	≤53th (6.8)	1	≤ 54th (5.13)	1
>38th (3.57)	2.62 (1.39-4.94)	>53th (6.8)	2.17 (1.22-3.87)	>54th (5.13)	2.00 (1.14-3.51)
p	*0.003*		*0.008*		*0.015*

Odds ratios (OR) from multivariable logistic regression, adjusted for age, sex, BMI and diabetes mellitus for different levels of HFF (percentiles, (%)), *Optimal HFF cut-off for the prediction of hypertension was calculated by maximal Youden Index (sensitivity + specificity – 1); HFF, hepatic fat fraction

4. DISCUSSION

This study was undertaken A) to describe reference values and risk factors for MRI traits of different arteries in the general population, and B) to assess associations of MRI-derived body and organ fat with BP and hypertension and to evaluate whether the MRI body composition traits explain prevalent hypertension more accurately than anthropometric measures.

Reference values were obtained for thoracic and abdominal aortic segment diameters (ascending, arch, descending, subphrenic, suprarenal, infrarenal), thoracic aortic segment wall thickness (ascending, descending) and vessel diameters of nine different segments of the lower limb arteries. The median aortic diameter showed a positive association with male sex and age. Some cardiovascular risk factors such as systolic and diastolic BP, smoking, and HDL cholesterol were associated with thoracic and abdominal aortic diameters. Male sex, older age, smoking, high levels of BMI and triglycerides were positively associated with MRI determined thoracic aortic wall thickness of the ascending and descending aorta. Furthermore, high HDL and low LDL cholesterol levels were correlated with aortic wall thickness. Leg artery stenoses were relatively scarce overall, but more prevalent in lower leg arteries as compared to upper leg and pelvic arteries and associated with older age and diabetes.

In terms of the association of MRI-determined adiposity measures with BP traits, the following results were observed. Higher MRI-derived hepatic fat fraction was associated with higher systolic and diastolic BP as well as with hypertension. In addition, MRI markers of total, visceral and pericardial adipose tissue were also highly correlated with prevalent hypertension, as were established anthropometric markers such as waist circumference and waist-height ratio. Overall, MRI-derived adipose tissue measurements performed similarly as anthropometric markers in identifying patients with hypertension.

4.1. REFERENCE VALUES OF ARTERY STRUCTURE

Thoracic and abdominal aortic diameters (Hypothesis 1 (32))

This is the first study presenting MRI-based age- and sex-specific reference diameters for the thoracic and abdominal aorta derived in an unselected European population. Additionally, the BSA-indexed aortic diameters of women and men were compared and their associations with cardiovascular risk factors were evaluated. The present results suggest that the median aortic diameter decreases from ascending to infrarenal aorta for women and men and that the median diameters of all aortic segments are lower in women than men, supporting the findings of earlier studies (15-17).

The present study analysed the association of age with median aortic diameter for both the thoracic and abdominal aorta after adjustment for BSA. The significant increase in aortic diameter with each single year of age was similar for women and men for the median, 5th percentile and 95th percentile. The associations between age and unadjusted diameters varied between different aortic segments. The association between age and diameter was stronger for the ascending aorta for women and men, while the association between

age and the diameter of the infrarenal aorta was the same for both sexes. This result is plausible in view of the different functions of the aortic segments. The ascending aorta is a conduit but also has a cushion function, ensuring continuous blood perfusion of the peripheral organs (42). The mechanical stress with rapidly alternating wall tension during the cardiac cycle, which contributes significantly to the aortic enlargement, is therefore much higher for the ascending aorta compared to the infrarenal segment.

Thoracic aortic wall thickness (Hypothesis 2 (33))

Reference values of AWT of the ascending and descending aorta were also derived from MRI-based measurements in a vascular healthy general population sample. The results show that the wall of the ascending aorta is thicker than the wall of the descending aorta and both walls are thicker in men compared to women. The wall thickness of the ascending and descending aorta increases with age in both sexes.

In an additional analysis, equations for calculating reference values based on a healthier subsample without the established cardiovascular risk factors hypertension, diabetes, and high total cholesterol levels were determined. Reference ranges for AWT in this subsample did not differ from those of the whole study population for female ascending aorta and male descending aorta and only slightly for female descending aorta and male ascending aorta. These observations suggest that more investigations of AWT risk factors are needed.

Measurement of AWT in different vascular territories is of growing interest as it may correlate with cardiovascular risk and predict future cardiovascular events. A recent study analysed the atherosclerotic disease burden in the abdominal aorta by quantifying the mean AWT and plaque burden using MRI. The authors observed a positive association of mean AWT with future cardiovascular events such as cardiovascular death, nonfatal cardiac and extracardiac events (43). A further study found a significantly higher wall thickness of the descending aorta in patients with a prior major cardiovascular event compared to patients without such events (44).

Lower limb artery diameters (Hypothesis 3 (35))

So far, artery diameters of the leg have been investigated by imaging methods only for few segments in smaller clinical samples. One study calculated mean aortic diameters in ten years age groups of male patients without vascular complaints and revealed diameters of 1.17 cm, 1.17 cm; 1.05 cm, 1.04 cm for the common iliac arteries (right and left) and the common femoral arteries (right and left), respectively in the age group of 50-60 years using computed tomography (24). In another study, the common femoral artery of a chosen site was characterized in healthy male subjects aged 8 to 81 years by mean and median diameters of 9.8 mm and 9.7 mm using an ultrasound examination (25). In the same sample of the latter study, mean diameter of the popliteal artery revealed 8.4 mm in the oldest male age group (mean age: 66.8 years) (45). The reported mean values of artery diameters are larger compared to the present study and are very close

to or even higher than the presented estimated upper reference values. Reference values were not reported in the smaller studies.

An increasing artery diameter with age is well established in the literature (25, 45). In the present study, all 9 analysed artery segments showed positive associations between BSA-indexed artery diameter reference values and age. A dilation of the upper leg arteries with older age was also demonstrated for the femoral and the popliteal artery by other studies (25, 45). The latter study could also demonstrate a positive association between the diameter of the posterior tibial artery and age. Strong evidence is also available for the dilation of thoracic and abdominal aortic diameters with increasing age (16, 17).

4.2. CARDIOVASCULAR RISK FACTORS AND ARTERY STRUCTURE

Thoracic and abdominal aortic diameters (Hypothesis 1 (32))

The present multivariable models for the assessment of cardiovascular risk factors and BSA-adjusted aortic diameters identified an inverse association with male sex for the ascending aorta, the aortic arch, and the subphrenic aorta, whereas only the infrarenal aorta revealed a positive association with male sex. In line with the present results, another study found a significantly greater diameter for the ascending and descending thoracic aorta after BSA adjustment for women (16). Furthermore, diastolic BP was positively and systolic BP was slightly inversely associated with diameters for all aortic segments investigated in the present study. The latter study found a greater positive association for diastolic BP compared to systolic BP with the thoracic aortic diameter (16). A further study showed a slightly weaker positive correlation for abdominal aortic diameter with systolic BP compared to diastolic BP (17). However, the studied populations were probably older and both results refer to absolute diameter measurements in contrast to the present BSA-adjusted results. In addition, the present study revealed current smoking status to be positively associated with thoracic and abdominal aortic diameters that could be confirmed only in women by the latter study.

The positive association of HDL-C with the diameters of all aortic segments in our study appeared paradoxical. Another study showed a predominantly inverse correlation of thoracic and abdominal aortic diameters with HDL-C (17). When considering that an increase in aortic diameter is part of a vascular aging process with consecutive atherosclerosis and vascular dilatation and that HDL-C protects against this sequel, it would be more reasonable to find an inverse association (46). However, recent data suggest that not only the amount of HDL-C in blood is critical but also its function (47).

Thoracic aortic wall thickness (Hypothesis 2 (34))

Previous studies identified several factors influencing aortic AWT, including positive associations with age, male sex, black ethnicity, smoking, higher systolic BP, higher low-density lipoprotein levels, and higher fasting glucose levels (21).

In the present population-based study, the associations of several cardiovascular risk factors with MRI determined thoracic AWT of the ascending and descending aorta were evaluated. Age, gender, BMI and LDL-C were associated with the AWT of the ascending and descending aorta. The AWT of the descending aorta was additionally associated with smoking status and HDL-C.

Regarding the risk factors of the AWT of the descending aorta, higher age, male gender, higher BMI, current smoking, higher HDL-C level and lower LDL-C level were associated with increasing AWT. There were no associations of systolic and diastolic BP, HbA1c and triglycerides levels with AWT. Consistent with these results, the likewise population-based Multiethnic Study of Atherosclerosis study also revealed increasing thoracic AWT with advancing age and for men as compared to women. However, the analyses in the latter study were obtained in a much smaller sample (n=196) and adjusted for height and weight only (20). In a subsequent analysis including 1053 participants, systolic BP was also positively associated with thoracic AWT but not current smoking or HDL-C (8). The present analyses were adjusted for a larger number of potential confounding variables.

A study with 2466 subjects investigating the abdominal aorta (21) and a study with 3711 subjects investigating the common carotid artery (48) reported positive associations of wall thickness with higher age, male gender and current smoking status. In contrast to the present results, both studies revealed an inverse association between HDL-C and wall thickness that seems to be plausible since HDL-C is regarded as a protective cardiovascular risk factor (49). However, both studies either did not adjust (48) or did not reveal a significant result (21) for BMI that is correlated with HDL-C (50). In both present study samples (SHIP-TREND, SHIP-2), a higher BMI was associated with higher AWT of the descending aorta. This is biologically plausible even though other studies did not find an association between BMI and AWT (21, 48). In the present study, beside age and gender, BMI contributes the most to the variance of AWT, suggesting that BMI is a relevant risk factor for thoracic AWT. Furthermore, the present study could observe a higher increase of AWT by BMI in current smokers compared to non-smokers.

One pathophysiological explanation of the result of a strong association between age and AWT is that the increase of the thoracic AWT with age consists mainly of intimal thickening and degeneration and sclerosis of the tunica media (51). The process is initiated by the focal retention of apoB lipoproteins on sub-endothelial extracellular matrix molecules. The intima thickens over a complex cascade including an inflammatory response, the entering of monocytes differentiating into macrophages and finally becoming cholesterol-laden foam cells, the migration of smooth muscle cells, a scar-like response and focal necrosis (52). The earliest stages occur in the childhood and progress over time. Several factors including male gender, hypertension, dyslipidemia, diabetes mellitus and genetic factors further promote the intimal thickening (53). However, not all mechanisms and interactions are fully understood.

Lower limb artery stenosis (Hypothesis 3 (35))

This present study is the first study investigating stenosis prevalence in single pelvic and leg arteries by using MRA. In this relatively healthy sample from the general population, the overall stenosis prevalence was 7.0% with the highest prevalence in the lower leg arteries anterior tibial, posterior tibial and fibular. As expected, it was observed that stenosis was significantly commonly present in older ages. This finding is in line with studies demonstrating an increasing PAD prevalence measured by ABI of the anterior and posterior tibial arteries for older ages (54). Additionally, this present study revealed diabetes mellitus as risk factors for lower limb artery stenosis.

For the first time, a wide range of segments of left and right pelvic and leg arteries could be investigated simultaneously by MRA examination in a large male sample. The MRA examination was part of a whole-body MRI examination within two cohorts of a population-based study that has established high quality standards (38). Therefore, the present findings represent preliminary results for further potential association studies with either correlates of the large basic examination program or other whole-body MRI parameters.

4.3. MRI-DERIVED ADIPOSE TISSUE MEASUREMENTS AND HYPERTENSION

Hepatic fat fraction and hypertension (Hypothesis 4 (36))

This present study could also demonstrate consistent associations of continuous MRI-derived hepatic fat levels and other MRI-derived body and organ fat measurement levels with systolic and diastolic BP as well as with prevalent hypertension. HFF values were obtained at three different locations in the liver: in the left liver lobe, in the right liver lobe and at the level of the portal vein based on either multi-echo 1H MRS or multi-echo Dixon sequences with consistent results for all three measurements.

Most evidence for the association between hepatic fat and BP is available for non-alcoholic fatty liver disease (FLD) measured by ultrasound (55, 56), in which FLD is inconsistently considered either as an outcome (55) or as a risk factor for BP (56). The results of the present study are in good agreement with the results of another cross-sectional study, revealing FLD, defined as a hyperechogenic pattern of the liver and increased serum alanine transferase levels, as a risk factor for hypertension (57).

Furthermore, a longitudinal study supports the finding of a higher hypertension risk for a group with moderate to severe degree of non-alcoholic FLD compared to a normal group (58). In most prior studies, FLD was modelled as a binary (present vs. absent) or categorical trait so that evidence for the association between a continuous measure of hepatic fat and BP is rare (59, 60). In a cross-sectional study of 156 adults, gender- and age-adjusted correlation coefficient for HFF and systolic BP was low and further adjustment for visceral adipose tissue rendered the association non-significant (60).

FLD has been linked to hypertension by several pathways: It is associated with the development of insulin resistance and diabetes mellitus (61). Furthermore, FLD leads to increased systemic inflammation (62). Both have relevant impact on the endothelium leading to vascular dysfunction and atherosclerosis with decreased vascular elasticity.

Other MRI-derived adipose tissue measurements and hypertension (Hypothesis 5 (37))

The present study also evaluated the associations of other direct measurements of body and organ fat distribution with blood pressure and revealed that TAT, VAT and PAT were strongly associated with prevalent hypertension. The associations of different CT-based fat measurements, including pericardial fat, intrathoracic fat and VAT with CVD risk factors were already evaluated in a subsample of the Framingham Offspring cohort (n=1155 participants). One main result was, that VAT was more strongly associated with systolic BP, diastolic BP and hypertension than pericardial (defined as adipose tissue located within the pericardium) and intrathoracic fat (63); and that intrathoracic fat was more strongly associated with BP and hypertension than pericardial fat. Similarly, in the present MRI study, VAT was more strongly associated with prevalent hypertension than PAT (as the sum of epicardial and paracardial fat). However, MRI-derived measurements of TAT and SCAT displayed even higher ORs for hypertension as compared to VAT and PAT.

Comparison to anthropometric markers (Hypothesis 5 (37))

Anthropometric markers are commonly used as surrogate markers of body fat distribution and obesity in prediction models for CVD and hypertension, because they are relatively easy to measure (64). In the present study, WC and WHtR displayed the strongest associations with hypertension of all anthropometric markers in the multivariable-adjusted model. This observation is supported by the published literature, where several studies reported that markers of central adiposity including WC, WHtR and WHR predict CVD risk and hypertension better than BMI (65-67).

A comprehensive comparison of anthropometric markers and more direct fat measures determined by bioelectrical impedance analysis, including total body fat, percentage body fat, trunk fat mass and percentage trunk fat, with respect to their association with hypertension was conducted in a sample from the Chinese general population and revealed female WHtR and male BMI as the strongest correlates for hypertension. While in the present study AUC values (for differentiating between individuals with vs. without hypertension) differed for individual fat measures, these differences disappeared after adding traditional risk factors (age, sex, diabetes mellitus, physical activity, smoking status, alcohol consumption, total cholesterol and HDL-C) to the statistical model.

Another study investigated whether intrathoracic or pericardial fat were associated with BP and hypertension, independent of BMI and WC or of VAT and observed that a) only intrathoracic fat displayed a borderline significant association with hypertension when added to a model including BMI and WC in women b) VAT, but not intrathoracic or pericardial fat, was independently and statistically significantly associated with systolic BP and hypertension only in women in multivariable models including both measurements (VAT and intrathoracic or pericardial fat, respectively) (63). The present analyses detected that only TAT was associated with hypertension independently of basic cardiovascular risk factors in a statistical model that included the most strongly associated anthropometric marker, WC.

4.4. STRENGTH AND LIMITATIONS

Strengths of the present studies include large sample sizes, the population-based design, a comprehensive and high-quality measurement of cardiovascular risk factors, covariates and multiple traits of vascular structure and adipose tissue.

Both studies, SHIP and KORA offered a wide range of imaging measurements of subclinical vascular and adiposity phenotypes. A comprehensive advanced MRI examination program was conducted in SHIP (vascular structure) and KORA (body and organ fat content).

Some limitations merit also consideration. All samples were middle-aged and of European descent. The applicability of the findings to other age groups or ethnicities remains to be established. Another limitation arises from the mostly applied cross-sectional design that does not allow detecting possible cause-effect relationships. Currently follow-up information to assess associations of risk factors with change in imaging parameters of subclinical CVD was not available in these samples.

Furthermore, some studies are limited by the fact that only a subgroup of the whole study sample could be examined by MRI because of eligibility, contraindications, and willingness (due to a long examination time or due to the need for applying contrast agents). So, the representativeness of the study samples for their initial cohort samples and the population of the study regions are also limited. However, additional analyses revealed only slight differences between the subsamples with MRI examination and the overall sample. As expected, participants of the MRI subsamples were a bit younger and healthier regarding hypertension and diabetes mellitus with lower proportion of current smokers and with lower BMI compared to non-participants of the MRI subsample in SHIP and they were slightly younger, more often men and less often hypertensive in KORA. In sensitivity analyses, calculated inverse observation probability weighted estimates did not change the results substantially so that they allowed a generalization of the main findings on the initial study samples.

4.5. PERSPECTIVE

In this habilitation, imaging measurements of MRI played a major role in characterizing subclinical vascular status and adipose tissue status of participants of two large population-based cohorts. On the one hand, imaging measurements of subclinical CVD were modelled as outcome phenotypes and were strongly associated with established cardiovascular risk factors. On the other hand, imaging measurements of adipose tissue status were related as biomarker candidates to hypertension. These results demonstrate a high potential of clinical imaging parameters for the description and understanding of the pathway from risk factors to CVD with specific focus on the subclinical status and therefore their potential use for new clinical and population-based prevention programs and individualized medicine approaches. However, some challenges still have to be coped with.

Although the association between subclinical and clinical CVD is well established, the predictive values of MRI measurements of subclinical CVD as emerging biomarker candidates for clinical CVD were not extensively studied so far. A final evaluation of a reasonable application of MRI measurements during routine vascular MRI to identify subjects with high cardiovascular risk is, therefore, not yet possible. Thus, more longitudinal studies need to address whether subclinical MRI measurements provide additional predictive information for future cardiovascular events or death beyond established risk factors. Specifically, prospective studies are warranted that investigate the longitudinal predictive performance of individual MRI measurements of structure of thoracic, abdominal and leg arteries for cardiovascular events including incident heart failure, myocardial infarction, stroke and cardiovascular death independently of established cardiovascular risk factors. Furthermore, the predictive values of MRI-derived measurements of adipose tissue with respect to changes in BP over time and incident hypertension needs to be compared among themselves and with anthropometric markers.

An important issue in imaging examinations is the standardization of imaging methods, measurement definitions and reading procedures that further needs to be developed continuously. Since imaging examination methods still depend strongly on examiner and image reader, MRI readers of the present study were trained before certification procedures. They had to yield a mean bias for intra- and inter-observer variability lower than 5%, and a double SD of the bias lower than 25% for selected outcomes in order to qualify as observer for the examinations. Exemplarily, intra- and inter-reader analysis for measuring thoracic AWT using cine MRI was performed. The intra-reader analysis revealed a mean bias for the ascending and descending aorta below 1% with limits of agreement below 10%. The inter-reader analysis revealed a mean bias below 2% with limits of agreement below 12%. Some other examinations (e.g. evaluation of pancreatic fat) or single parameters displayed higher inter-and intra-reader variability of measurements that necessitate the interpretation and conclusion of results to be done more cautiously.

Image reading methods cover a wide range from manual reading methods to semi-automatic and full-automatic reading methods. To avoid potential bias from inter- and intra-reader differences, manual reading methods should be reduced and more full-automatic reading methods should be developed and used in large population-based samples.

MRI-derived measurements depend strongly on the applied methods including different sequences, technical parameters, and the focus of investigation. This study used e.g. cine MRI for measuring AWT with highly valid and reliable results, while the dark blood imaging method is also widely used for the AWT investigation. Another example is the use of 3D fluid-attenuated inversion recovery images instead of established 3D T1-based segmentation to measure total gray and white matter volume in the KORA study. Therefore, measurement differences between different MRI methods need to be evaluated and results of inter-device or inter-method studies should be published to better combine the evidence of MRI biomarker candidates from different studies.

Population-based studies aim to investigate a large number of imaging related risk factor and phenotype parameters with a standard examination protocol. It follows that for a wide range of organs and body

regions, technical parameters are adjusted adequately. However, the specific sequences are often able to measure additional parameters of organs and body regions that were not within the focus of investigation but provide further significant information of subclinical change of function and structure that needs to be studied. A KORA study determined e.g. the clinical utility of lung volumes derives from non-dedicated MRI sequences during chest imaging by comparing with pulmonary function tests and revealed independent association with several pulmonary function parameters. In a next step, these lung volume parameters will be correlated with cardiac function and structure parameters in KORA.

The challenge of using cardiovascular imaging biomarkers for individualized medicine requires further research and clinical translation concepts. After evaluating predictive values of imaging biomarker candidates for clinical CVD or death, clinical studies need to investigate how individualized interventions in groups with different cardiovascular risk according to the biomarker candidate can improve clinical outcomes. Therefore, it is necessary to define cut-off values for higher risk groups and to study if the potential reduction of incident cardiovascular events by an additional therapy is larger in the high-risk group compared to the low-risk group. Especially in the case of limited clinical resources, this additional therapy can be offered to a smaller group with a larger effect. This additional therapy can range from a longer motivation talk about health behaviour within the doctor-patient conversation to offering a secondary prevention program. In a first step, the patients with a routine indicated MRI would benefit from the additional image analysis and data.

4.6. CONCLUSIONS

The presented studies demonstrated that subclinical imaging parameters of the vascular system and adipose tissue derived from MRI are variable in the population and are associated with established risk factors.

Specifically it is concluded that:

a) Reference values of thoracic and abdominal aortic diameters as well as thoracic AWT vary by age and sex. The median aortic diameter shows a positive association with male sex and age, though the association with sex disappears after BSA adjustment. In addition, the presented results demonstrate that some cardiovascular risk factors such as systolic and diastolic BP, smoking, and HDL-C were associated with thoracic and abdominal aortic diameters. Cardiovascular risk factors including male sex, older age, current smoking, high levels of BMI and triglycerides were positively associated with MRI determined thoracic AWT of the ascending and descending aorta. Furthermore, high HDL-C and low LDL-C levels were correlated with AWT. The ascending AWT was greater than the descending AWT and both were higher in men than in women. The increase in wall thickness with age is slightly stronger in men compared to women. The reference diameters of pelvic and leg arteries decreased from proximal to distal and increased with age. Stenoses were relatively scarce overall, but more prevalent in lower leg arteries as compared to upper leg and pelvic arteries and associated with older age and diabetes mellitus.

b) Higher MRI-derived hepatic fat levels was associated with higher systolic and diastolic BP as well as with hypertension independently of other risk factors in a healthy sample from the general population without prior cardiovascular events. This finding suggests that HFF as assessed by MRI is a potential biomarker candidate for a more accurate cardiovascular risk assessment. Overall, MRI-derived adipose tissue measurements perform similarly in identifying patients with hypertension compared to anthropometric markers. Especially, also the MRI markers TAT, VAT and PAT were highly correlated with prevalent hypertension. Furthermore, the established anthropometric markers WC and WHtR were also confirmed to be significantly and independently associated with hypertension.

This work contributes to the understanding of the relationships between selected established cardiovascular risk factors and new biomarker candidates of adipose tissue with subclinical vascular changes and hypertension as precursors to clinical CVD, events and mortality, thus demonstrating the potential of these biomarkers for use in individualized cardiovascular risk prediction. The use of standardized high-quality imaging techniques in the population can form the basis for the development of new prevention approaches.

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6. APPENDIX

ORIGINAL ARTICLES

Overview

1) Mensel B, Hesselbarth L, Wenzel M, Kuhn JP, Dorr M, Volzke H, Lieb W, Hegenscheid K, **Lorbeer R**. Thoracic and abdominal aortic diameters in a general population: MRI-based reference values and association with age and cardiovascular risk factors. Eur Radiol 2016;26:969-78. doi: 10.1007/s00330-015-3926-6
2) Mensel B, Quadrat A, Schneider T, Kuhn JP, Dorr M, Volzke H, Lieb W, Hegenscheid K, **Lorbeer R**. MRI-based determination of reference values of thoracic aortic wall thickness in a general population. Eur Radiol 2014;24:2038-44. doi: 10.1007/s00330-014-3188-8
3) **Lorbeer R**, Schneider T, Quadrat A, Kuhn JP, Dorr M, Volzke H, Lieb W, Hegenscheid K, Mensel B. Cardiovascular risk factors and thoracic aortic wall thickness in a general population. J Vasc Interv Radiol 2015;26:635-41. doi: 10.1016/j.jvir.2014.12.022
4) **Lorbeer R**, Grotz A, Dorr M, Volzke H, Lieb W, Kuhn JP, Mensel B. Reference values of vessel diameters, stenosis prevalence, and arterial variations of the lower limb arteries in a male population sample using contrast-enhanced MR angiography. PLoS One 2018;13:e0197559. doi: 10.1371/journal.pone.0197559
5) **Lorbeer R**, Bayerl C, Auweter S, Rospleszcz S, Lieb W, Meisinger C, Heier M, Peters A, Bamberg F, Hetterich H. Association between MRI Derived Hepatic Fat Fraction and Blood Pressure in Subjects without History of Cardiovascular Disease. J Hypertens 2017; 35:737-744. doi: 10.1097/HJH.0000000000001245
6) **Lorbeer R**, Rospleszcz S, Schlett CL, Heber SD, Machann J, Thorand B, Meisinger C, Heier M, Peters A, Bamberg F, Lieb W. Correlation of MRI-derived adipose tissue measurements and anthropometric markers with prevalent hypertension in the community. J Hypertens 2018; 36:1555-1562. doi: 10.1097/HJH.0000000000001741

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