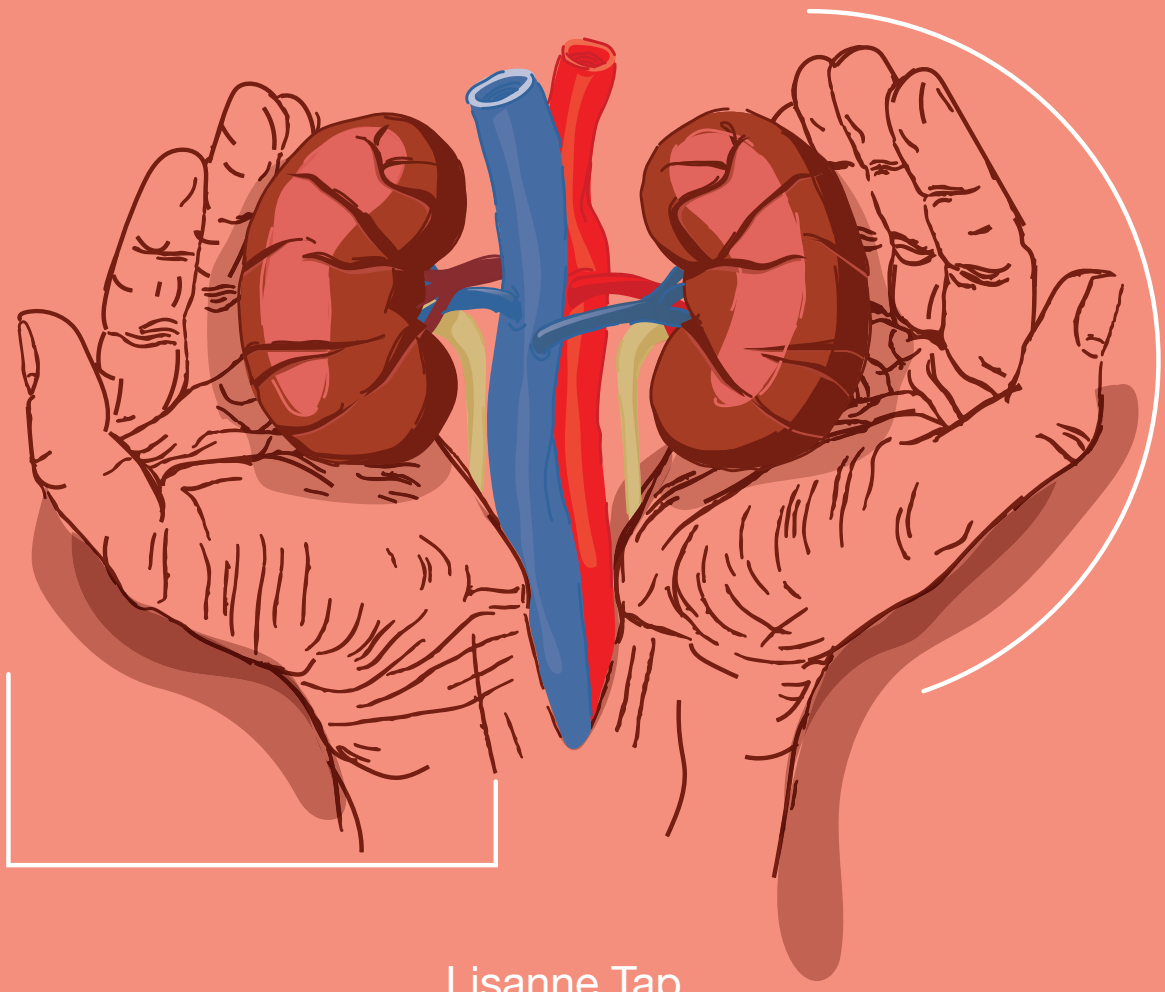
AGE-RELATED RENOVASCULAR CHANGES

consequences in late life



Lisanne Tap

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Age-related Renovascular Changes
consequences in late life

Leeftijds-gerelateerde veranderingen van nieren en bloedvaten
gevolgen op oudere leeftijd

Proefschrift

ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam
op gezag van de
rector magnificus

Prof. dr. R.C.M.E. Engels

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	Prof. dr. N. van der Velde

This thesis is dedicated to Gerrit and Gré.
May their memory forever be an inspiration.

Table of contents

Chapter 1.	**General introduction**	**09**
Part I.	**Renal aging**	**16**
Chapter 2.	**Screening for Chronic Kidney Disease**	**19**
2.1	Design and methodology of the Screening for CKD among Older People across Europe (SCOPE) study	21
Chapter 3.	**Estimating kidney function**	**41**
3.1	Clinical implications of estimating glomerular filtration rate in older adults	43
3.2	Estimated glomerular filtration rate and muscles in older adults	69
Chapter 4.	**Kidney function and mental health**	**83**
4.1	Kidney function, cognition and mood in late life	85
Part II.	**Vascular aging**	**100**
Chapter 5.	**Arterial stiffness, physical and mental health**	**103**
5.1	Links between vascular, bone and muscle aging	105
5.2	Aortic stiffness and quality of late life	133
5.3	Aortic stiffness and brain integrity in older adults	147
Chapter 6.	**Blood pressure (dys)regulation and falls**	**163**
6.1	Orthostatic hypotension, fear of falling and physical performance in older adults	165
Chapter 7.	**General discussion**	**181**
Chapter 8.	**English summary**	**201**
Chapter 9.	**Nederlandse samenvatting**	**207**
Appendices		**213**
About the author		214
PhD portfolio		215
List of publications		219
Affiliations		222
Dankwoord		226

Chapter 1

General introduction

The kidneys and the arteries are subject to age-related alterations and can be affected by shared risk factors. In this thesis, consequences of age-related and risk factor related renovascular changes in late life are investigated.

The kidneys are involved in many different essential processes in the human body. The kidneys work to maintain a constant extracellular environment that is required for adequate functioning of the cells. The nephrons, the functional unit of the kidneys, excrete waste products of metabolism and adjust urinary excretion of water and electrolytes in order to maintain homeostasis and regulate blood pressure. The glomerulus, the first part of the nephron, is the filtering unit with a three-layered structure that facilitates the flow of plasma water and small solutes and restricts the flow of large plasma proteins such as albumin. Kidney function is usually expressed as the glomerular filtration rate (GFR) and describes the total amount of fluid filtered per time unit. The second part of the nephron, the tubule, contains the fluid filtered through the glomerulus. By changes in tubular secretion and reabsorption, the kidneys are able to regulate the excretion of water and solutes such as electrolytes, organic acids, medications and toxins. The kidneys also have endocrine and metabolic functions; the kidneys produce hormones such as renin to help regulate blood pressure; erythropoietin, needed for the production of red blood cells, and activate vitamin D, which helps to maintain strong bones. During the aging process, all functions of the kidneys can be affected. In particular the number of nephrons decreases with 7.3% per age decade as result of sclerosis, atrophy and reabsorption.[1,2] Age-related loss of kidney function can be accelerated by several risk factors such as diabetes mellitus, hypertension and metabolic syndrome leading to chronic kidney disease (CKD).[3]

Measuring GFR is complex and time consuming in clinical practice and therefore GFR is estimated from serum markers.[4] Most often, serum creatinine levels are used to estimate kidney function, a product from the metabolism of creatine in skeletal muscle.[5] Creatinine production is therefore partly dependent on sex, age and body composition. Because of the lower muscle mass in women and older adults and the large variation in it,[6] the accuracy of currently used kidney function estimations, especially at older age, should be seriously questioned. Several equations can be found in the literature, which all have in common that these are corrected for factors influencing muscle mass.[5,7] However, the estimations show large variations in GFR, depending on which equation we use, with all consequences that this might entail.[5] It is of paramount importance to accurately assess kidney function, since misclassification can have implications on treatment strategies, such as failing to redose renally cleared drugs which might result in under- or overdosing and risk of adverse drug reactions.[8,9]

CKD, defined as a GFR below 60 mL per minute for more than 3 months,[4] is becoming more prevalent as result of the aging population and an increase in the number of risk factors of kidney function decline.[3] The severity of CKD can be classified based on eGFR in 5 stages using the Kidney Disease Improving Global Outcomes (KDIGO) guidelines[4]: eGFR ≥ 90, stage 1; eGFR 60 - 89.9 stage 2; eGFR 45 - 59.9, stage 3a; eGFR 30 - 44.9, stage 3b; eGFR 15 - 29.9, stage 4 and eGFR <15 ml/min/1.73m², stage 5. It should be noted that persons with an eGFR <60 ml/min/1.73m² should not be classified as having CKD unless they have other markers of kidney disease such as albuminuria.[4] Both early and advanced stages of CKD are associated with an increased risk of end-stage renal disease, comorbidity and higher mortality.[10,11] CKD also affects other outcomes relevant to older adults; decreased GFR is associated with lower physical function, joint problems and cognitive impairment and moreover, when kidney function declines, many drugs may accumulate which increases the risk of adverse drug reactions.[9,12,13] This is especially relevant in older adults, a population with high prevalences of multimorbidity and therefore polypharmacy.[14] Altogether, CKD has become a relevant public health care burden, which makes early detection of CKD relevant in order to identify and treat older adults with increased risk of adverse outcomes. However, an accurate method to screen for CKD, especially at older age, is still needed since data from younger populations cannot be extrapolated one on one to older adults.

Closely linked to the age-related changes of the kidney is the process of age-related changes of the vascular system. The main function of the arteries is to adequately deliver oxygen and nutrients to every cell in the human body. For this purpose, the arteries transform the pulsatile flow that the heart rhythmically generates into a steady blood flow. This function depends on the viscoelastic properties of the central arteries, of which essential elements are collagen, elastin and smooth muscle cells. Vascular aging is characterized by breaks in elastin fibers, the stretchable element of the arterial wall, and an accumulation of collagen, the stress resistant element of the arterial wall, resulting in a decline of the elastic properties and thus an increase in arterial stiffness.[15] The main determinant of arterial stiffness is age,[16] however this process can, just as kidney function decline, be accelerated by several cardiovascular risk factors.[17]

Increased arterial stiffness influences and modifies blood pressure profiles; arterial stiffness can cause an impaired cardiovagal baroreflex sensitivity, which plays an important role in short term blood pressure regulation.[18] Failure of this mechanism may lead to orthostatic hypotension, a common condition in older adults.[19,20] Stiff arteries also result in higher

systolic pressure because of a reduced capacitance and a lower diastolic pressure because of a less elastic recoil to support the diastolic pressure.[21] In addition, arterial stiffness increases the pulsatile pressure,[21] which represents the variations of the pressure curve around the steady component; this increased pressure can affect the microcirculation of high-flow organs such as the brain, the heart, and the kidneys.[22] As result of these hemodynamic changes, elevated arterial stiffness increases the risk of clinical and subclinical cardiovascular morbidity, such as the risk of stroke and myocardial infarction, and also the risk of mortality.[22-24] There seems to be increasing evidence that link arterial stiffness to other (non-cardiovascular) age-related degenerative processes, such as bone demineralization, muscle loss and consequent decreased quality of life.[25-27] However, it is not clear whether these processes share common pathways or even directly influence one another.

Identifying adults with elevated arterial stiffness could help to monitor and treat modifiable risk factors which might help to prevent the development of adverse outcome. Therefore, it is very relevant to investigate the role of arterial stiffness in terms of physical and mental health in late life to better understand clinical implications and to be able to implement arterial stiffness in current guidelines of treating older adults.

Part I of this thesis focusses on renal aging. The aim of this part of the thesis is to study clinical implications of using GFR equations at older age and to investigate the association of kidney function and geriatric outcome measures in late life. In **chapter 2.1**, we present the design of the SCOPE study, a multicenter cohort observational study on Screening for CKD among Older People across Europe. In **chapter 3.1,** the clinical implications of using GFR equations at older age are presented, based on preliminary results of the SCOPE study. In **chapter 3.2**, we investigate the possible relationship of estimated GFR and muscle mass and function in older adults of the IMPROveFALL study. **Chapter 4** focusses on associations between kidney function, cognition and mood in late life, also based on results of the SCOPE study. **Part II** of the thesis focuses on vascular aging and the role of blood pressure. The aim of this part of the thesis is to study the link between vascular aging and physical and mental health in diverse study populations of older adults. In **chapter 5.1**, we outline possible hypotheses regarding associations between arterial stiffness, bone demineralization and muscle loss by reviewing previous literature. **Chapter 5.2** investigates the possible impact of aortic stiffness on quality of late life, based on the Dutch study population of the SCOPE study. In **chapter 5.3**, we describe associations

between aortic stiffness and brain integrity in older adults with functional and cognitive complaints. In **chapter 6.1**, the role of orthostatic hypotension, as part of the process of vascular aging, is investigated in older fallers in order the examine the impact of blood pressure dysregulation on physical performance and fear of falling. Finally, in the general discussion in **chapter 7**, the main findings of this thesis are discussed including clinical implications and future directions. In **chapter 8** and **9** an English and Dutch summary are provided. The overall aim of the thesis is to better understand the role of renovascular aging in late life.

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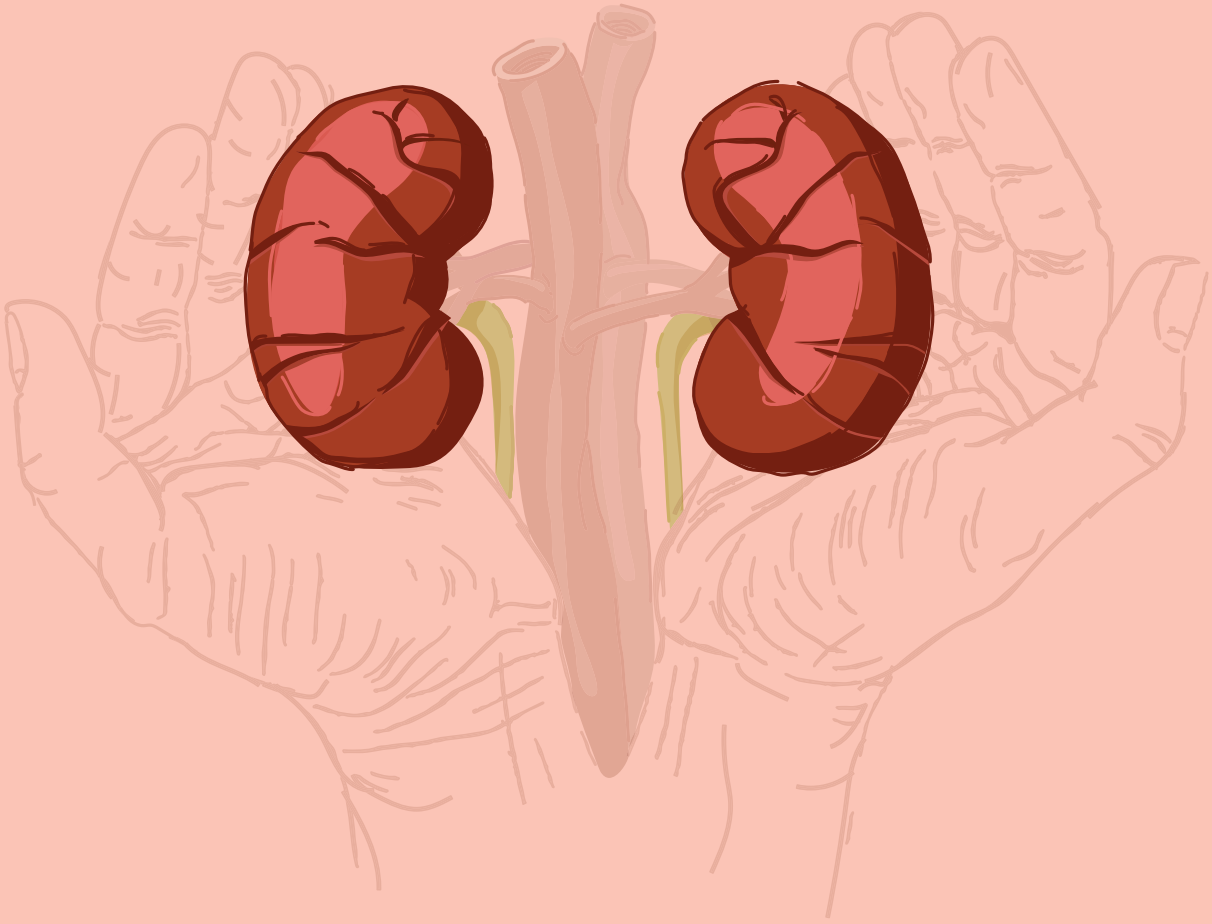
Part I. Renal aging



Chapter 2

Screening for Chronic Kidney Disease

2.1

Design and methodology of the Screening for CKD among Older People across Europe (SCOPE) study

A. Corsonello, **L. Tap**, R. Roller-Wirnsberger, G. Wirnsberger, C. Zoccali, T. Kostka, A. Guligowska, F. Mattace-Raso, P. Gil, L. Guardado Fuentes, I. Melzer, I. Yehoshua, F. Formiga, R. Moreno-Gonzalez, C. Weingart, E. Freiberger, J. Ärnlöv, A. Carlsson, S. Bustacchini, F. Lattanzio
on behalf of SCOPE investigators

Design and methodology of the screening for CKD among older patients across Europe (SCOPE) study: a multicenter cohort observational study
BMC Nephrology, Oct. 2018

Abstract

Background: Decline of renal function is common in older persons and the prevalence of chronic kidney disease (CKD) is rising with ageing. CKD affects different outcomes relevant to older persons, additionally to morbidity and mortality which makes CKD a relevant health burden in this population. Still, accurate laboratory measurement of kidney function is under debate, since current creatinine-based equations have a certain degree of inaccuracy when used in the older population. The aims of the study are as follows: to assess kidney function in a cohort of 75+ older persons using existing methodologies for CKD screening; to investigate existing and innovative biomarkers of CKD in this cohort, and to align laboratory and biomarker results with medical and functional data obtained from this cohort. The study was registered at ClinicalTrials.gov, identifier NCT02691546, February 25th 2016.

Methods/design: An observational, multinational, multicenter, prospective cohort study in community dwelling persons aged 75 years and over, visiting the outpatient clinics of participating institutions. The study will enroll 2450 participants and is carried out in Austria, Germany, Israel, Italy, the Netherlands, Poland and Spain. Participants will undergo clinical and laboratory evaluations at baseline and after 12 and 24 months- follow-up. Clinical evaluation also includes a comprehensive geriatric assessment (CGA). Local laboratory will be used for 'basic' parameters (including serum creatinine and albumin-to-creatinine ratio), whereas biomarker assessment will be conducted centrally. An intermediate telephone follow-up will be carried out at 6 and 18 months.

Discussion: Combining the use of CGA and the investigation of novel and existing independent biomarkers within the SCOPE study will help to provide evidence in the development of European guidelines and recommendations in the screening and management of CKD in older people.

Background

Evidence from epidemiological and clinical literature suggests that ageing contributes to the incidence of reduced renal filtration capacity.[1] In the presence of risk factors during ageing, such as diabetes, hypertension and others, filtration capacity further declines. This concept is underlined by many epidemiological studies showing a decline of measured estimated glomerular filtration rate (eGFR) with advancing age.[2] Kidney function is usually assessed by creatinine-based estimated glomerular filtration rate (eGFR) equations. However, those formulae have a certain degree of inaccuracy when used in older people due to changes in anthropometry and renal physiology during ageing.[3] Alternative filtration markers yielded different eGFR values for different cohorts of people tested.[4] This inaccuracy of laboratory measurements of kidney function suggests a risk of underdetection or overdetection of CKD, especially with advancing age.[5] Indeed, the eGFR threshold at which the risk of negative outcomes increases among older patients is hotly debated,[6] and current evidence suggests that such a threshold may be lower among older people compared to adult ones.[7-9] Additionally, the eGFR cut-offs at which the risk of death starts to increase may change as a function of the equation used among older people.[10] Thus, improving accuracy of CKD screening measures for older populations would be of help in reducing the risk of underdiagnosis to maximize prevention of CKD and its consequences while minimising the risks and cost of overdiagnosis.[6]

Diminished kidney function has become a relevant public health burden for all age groups, as CKD frequently results in an increased risk of end stage renal disease (ESRD), corbidity and mortality.[11] Besides "traditional" endpoints, CKD has been shown to impact nutritional status, inflammatory processes and anemia, [12] thereby affecting different outcomes especially relevant to older people. These include impaired physical function, frailty and disability,[13-16] cognitive impairment and dementia,[17-19] depression,[20-22] sensory impairment,[23] undernutrition and sarcopenia, [24-26] and adverse drug reactions (ADRs).[27,28] Therefore, early and sensitive detection of diminished renal function is essential to individually address care needs of older people with CKD and to address one of the major health burden in public health for the incoming decades.[29]

Incorporating scoring risk models for care planning of older people at risk for CKD has come into focus recently.[30] Risk prediction models are generally based on equations designed on the basis of prognostic factors and clinical outcomes, available at the time the prediction is made, and collected in specific and representative cohorts of individuals followed up for a given

period of time.[31] Built on evidence of such models, screening programmes for CKD can take into account the characteristics of the target population in addition to simple laboratory measures, biomarkers and disease-based investigations. Multi- and co-morbidity, polypharmacy, frailty, functional and cognitive impairment and disability should be considered as part of a patient centered approach in CKD management especially in older adults.[13,15,23-26,32-34]

So far, no CKD screening program has included all those variables also including data from comprehensive geriatric assessment (CGA), the only assessment technology able to capture the numerous domains of health status and their complex interactions in older people. Accordingly, the need for laboratory measurements able to identify accurately older people with CKD is a demand to address the public health challenges arising from the current demographic shifts. Indeed, this view is widely shared by the geriatric and nephrology communities, both in EU and USA.[35,36]

The aims of this multicenter study in Europe are to assess existing methodologies for CKD screening and investigate existing and innovative biomarkers of CKD in older persons. Furthermore, the Screening for CKD among Older People across Europe (SCOPE) study will provide evidence for including physical and functional health parameters of older people across Europe and help design a tailored risk prediction model for CKD in old age.

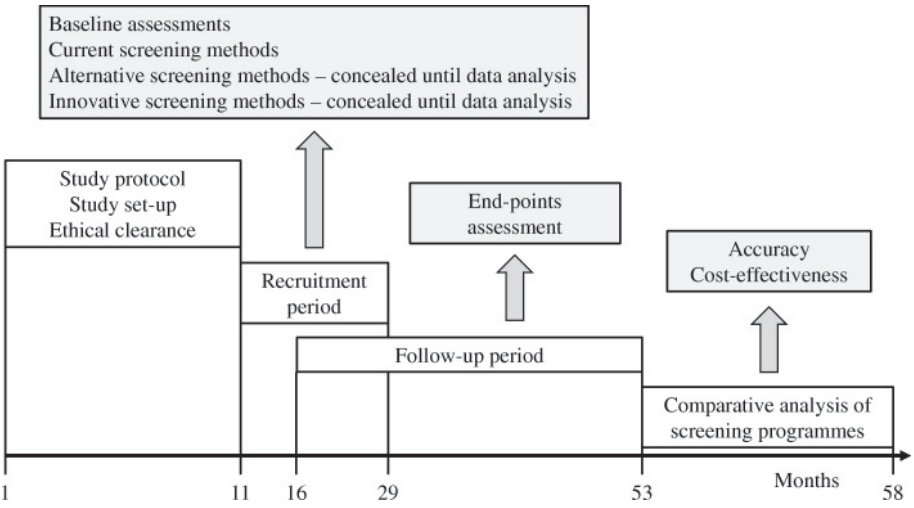
Methods

Study design

The SCOPE study is designed as an observational, multinational, multicenter, prospective cohort study in persons older than 75 years across Europe. This study is carried out in seven countries, including Austria, Germany, Israel, Italy, the Netherlands, Poland and Spain. Participants will undergo clinical and laboratory evaluations at the baseline (recruitment), and will be followed up at face to face visits at months 12 and 24 following enrollment. An intermediate telephone follow-up will be carried out at 6 and 18 months following recruitment. **Figure 1** shows the schematic flow of the observational clinical study.

The study design complies with the Declaration of Helsinki and Good Clinical Practice Guidelines. The enrollment has started in August 2016 and is ongoing.

Figure 1. Study design of the SCOPE project



Ethical approval/ monitoring

The study protocol was approved by ethics committees at all participating institutions. Patients are requested to sign a written informed consent before entering the study. Patients are also asked to sign a separate informed consent to the collection of DNA samples to be used for genetic testing, while those not giving their consent will be retained in the main cohort study.

In order to ensure high ethical and scientific standards of the project and to monitor the progress of the clinical study a Scientific Advisory Board (SAB) and a Data and Ethics Management Board (DEMB) was implemented within the Governance Structure. The SAB ensures a high standard of research, monitors the progress of the project by taking part in the project meetings, and provides final approval to any required study amendments. The DEMB supports the preparation of the relevant end-points for ethical review, advises on local research Ethical Committee applications, and reviews the relevant safety, morbidity and mortality end-points during the course of the study. The DEMB maintains an overview of the work throughout the whole course of the project and helps to foresee possible problems that might arise and how they can be addressed.

Study population

Persons aged 75 years and older, visiting the outpatient clinics of participating institutions are eligible for inclusion. The study design aims at minimizing self-

selection bias and enrolling real-world patients without stringent inclusion/ exclusion criteria. The few exclusion criteria are outlined in **Table 1**. Therefore, no other inclusion criteria will be considered. The SCOPE study aims to finally enroll 2450 participants.

Table 1. Exclusion criteria for participants enrollment into the SCOPE project

• Age < 75 years
• End stage renal disease (< 15 mL/min/1.73 m^2) or dialysis at time of enrollment
• History of solid organ or bone marrow transplantation
• Active malignancy within 24 months prior to screening or metastatic cancer
• Life expectancy less than 6 months
• Severe cognitive impairment (Mini Mental State Examination < 10)
• Any medical or other reason (e.g. known or suspected inability of the patient to comply with the protocol procedure) in the judgement of the investigators, that the patient is unsuitable for the study
• Unwilling to provide consent and those who cannot be followed-up

Study visits

Following enrollment, participants will be seen by the study teams at 12 and 24 months at a face to face meeting. Demographic data and socioeconomic status (occupation before retiring, economic status, formal and informal care) will be documented and followed up at each visit. Physical examination will be performed by medical doctors due to standardized procedure given in the visit protocol. Medical history and use of medication and adverse drug reactions classified according to the World Health Organization (WHO) definition[37] will be collected during follow-up visits. During all face to face visits a comprehensive geriatric assessment (CGA) will be performed. **Table 2** shows all domains checked during study visits.[38-51]

Healthcare resource consumption will be evaluated using a resource use questionnaire within a 6-month recall time-frame.[49] Following information will be retrieved: previous physician visits (GPs, specialists, or physician at the Emergency Room), use of diagnostic tests and specialist clinic procedures, use of care services (e.g. Nurse home visit, Physiotherapy, Home help, Social transport, Day care center) and hospital admissions (number and duration of hospitalization, type of reimbursement). Furthermore, caregiver burden will be measured using the Zarit Burden Interview (ZBI).[52]

During enrollment and at the two face to face follow up visits blood and urine samples will be collected and analysed for serum creatinine, urinary albumin and albumin-to-creatinine ratio.

Table 2. Comprehensive Geriatric Assessment domains tested during the SCOPE project

- Basic (ADL) and Instrumental Activities of Daily Living (IADL)/selfreported disability [38,39]
- Mini Mental State Examination (MMSE)/cognitive status [40]
- 15-items Geriatric Depression Scale (GDS)/mood [41]
- Cumulative Illness Rating Scale (CIRS)/overall comorbidity [42]
- History of falls and incident falls
- Vision and hearing impairment will be coded on a scale from 0 (adequate) to 4 (no vision/hearing present) [43]
- Lower urinary tract symptoms (LUTS): The presence of LUTS will be ascertained by asking the patient to rate on a 5-point (0–4) Likert scale how big a problem, if any, has each of the following items been during the last 4 weeks: 1. Dripping or leaking urine, 2. Pain or burning in urination, 3. Bleeding with urination, 4. Weak urine stream or incomplete emptying, 5. Waking up to urinate, 6. Need to urinate frequently during the day [44]
- Nutritional status: anthropometric parameters (calf circumference, arm circumference, Body mass index (kg/m^2), waist-hip ratio, waist-toheight ratio), Mini Nutritional Assessment (MNA) [45] and 24-h dietary recall[a] [46]
- Short Physical Performance Battery (SPPB) [47]
- Grip strength [48] measured by using JAMAR hydraulic dynamometer
- Bioelectrical impedance analysis (BIA)[b] [49] Muscle mass will be calculated using the Janssen et al. equation [50], using the instrument Akern BIA101
- Health related quality of life will be rated by the Euro-QoL 5D

[a]Data obtained from the 24-h dietary recall will be analyzed using nutritional databases suitable for the patient's country. Following the analysis, a detailed report (containing levels of consumption of various nutrients and energy) will be available. This level will be compared with recommended levels of intake [b]BIA will not be performed in patients with pacemaker or implantable cardioverter defibrillator.

Telephone follow-up

At 6- and 18-month participants and/or caregivers will be interviewed by phone to collect information on vital and functional status and healthcare resource consumption. Changes in medical history and adverse drug reactions will also be collected.

Laboratory parameters and biomarkers

Serum creatinine measurement will be standardised to Isotope-Dilution Mass Spectrometry at local level, when the method is available. Creatinine-based eGFR will be calculated using the Berlin Initiative Study 1 (BIS1) equation, which is the only method specifically developed in a population older than 70 years.[53] ESRD will be defined as GFR < 15 mL/min/1.73 m^2 or dialysis.[54] In case of unavailability of standardized creatinine methodology at local level, this measurement will be made by INRCA laboratories afterwards. The panel of laboratory parameters to be measured at baseline, 12-month and 24 months by local laboratories will also include: complete blood cells count, lipids profile, electrolytes, nutritional status, and urine analysis.

The project will also include the collection of blood and urine samples to investigate existing and innovative biomarkers of kidney function. Existing biomarkers of CKD like Cystatin C (CysC), [55] β-Trace protein (BTP), also known as lipocalin prostaglandin D2 synthase [56,57] Beta2-microglobulin [58] will be measured using published and established methods. Potential and new biomarkers will be also evaluated. Furthermore, the evaluation of experimental kidney damage biomarkers as well as untargeted analysis of metabolomics in serum and urine is currently be performed in ULSAM [59] and PIVUS [60] studies, in order to identify additional kidney damage biomarkers that may be validated in the SCOPE project. **Table 3** shows an overview on current, alternative and innovative biomarkers for CKD whose applicability in old age will be investigated within the SCOPE project.

The assessment of selected genetic and epigenetic parameters involved in hallmarks of aging will be also carried out to investigate their relationship with kidney function. This latter assessment will be limited to participants who signed a separate informed consent (patients not giving informed consent for genetic and epigenetic analysis will be retained in the main cohort study), and will include: DNA methylation, polymorphisms of mitochondrial DNA, polymorphisms of genes coding for proand anti-inflammatory cytokines (IL-6, IL-1, TNF-alpha, IL-10, IL-2, IL-17, IL-8) and chemokines (MCP-1 and RANTES), polymorphisms associated with molecules involved in the pathogenesis of metabolic and neurodegenerative diseases such as insulin and IGF-1 signaling pathway and APOE, Klotho, mTOR, and whole genome analysis by Affymetrix Chip Array 6.0.

Table 3. Biomarkers research in the SCOPE project

Current screening methods[a]	Alternative screening methods[b]	Innovative screening methods[b]
Serum creatinine	Serum cystatin C	Serum fibroblast growth factor 23
Creatinine-based eGFR	Serum ß-trace protein	Serum and urinary soluble TNF receptor 1
Urinary albumin	Serum ß2-microglobulin	Serum and urinary soluble TNF receptor 2
Albumin-to-creatinine ratio		Serum and urinary osteopontin
		Serum penthraxin 3
		Serum and urinary endostatin
		Serum and urinary TIM-1 (KIM-1)
		Serum TRAIL R2
		Serum and urinary endostatin

[a]current screening measures will be assessed at local laboratories and are immediately available after enrollment and follow-up visits; [b]alternative and innovative screening measures

Measured glomerular filtration rate

The assessment of measured glomerular filtration rate (mGFR) will be performed by single-dose inulin clearance.[61,62] Participants will be asked to sign a separate informed consent to participate in this sub-study, while those not giving their consent will be retained in the main cohort study. The objective of this sub-study will be the derivation of new eGFR equation(s) based on already known and/or novel biomarkers. The accuracy of new equation(s) in predicting mGFR will represent the primary study endpoint. Accuracy will be assessed by P30 (percentage of estimates within 30% of the mGFR). A sample of 400 participants will enable us to detect a difference of 2% in P30 between the new equations (based on the innovative and novel biomarkers) and the BIS equations, with significance level 0.05 and power 0.8 (considering a 1-sample and 1-sided test). In addition, we have evaluated that the sample will be sufficient to detect a statistically significant difference in 4,3 points in the Area under the ROC curve using the new equation(s) for discriminating participants below the critical threshold of 60 ml/min/ 1.73 m^2. Finally, the availability of mGFR in a subgroup of participants enrolled in the study will be used to investigate the relationship between innovative biomarkers and objectively measured kidney function.

Study endpoints

The primary study endpoints will be the rate of eGFR decline and the incidence of ESRD.

The secondary endpoints will include measures of conventional and geriatric outcome measures, such as: rate of CKD complications (anemia, hyperphosphatemia, acidosis, hypoalbuminemia, hyperparathyroidism, hyperkaliemia); rate of major comorbidities (e.g. hypertension and CV diseases);[42] overall and CV mortality; adverse drug reactions (ADRs); self-reported disability and objectively measured physical performance decline;[38,39,47] cognitive impairment;[40] depression;[41] malnutrition/undernutrition;[45,46] health-related quality of life;[51] healthcare resource consumption, including the estimation of caregiver burden.[52]

Information on vital status during follow-up will be obtained by interviewing the patients and/or their formal and/ or informal caregivers. For mortality during the follow-up period, date, place and cause of death will be retrieved by certificates of death exhibited by relatives or caregivers.

Data management and statistics

The SCOPE project will enroll a total of 2450 participants. On the basis of the primary end-points, a sample of 1900 patients will be able to differentiate between two equally sized subgroups according to a standardized difference in yearly rate of GFR decline of 0.13 mL/min/1.73 m^2 with a power of 80%. The same sample size allows to detect a hazard ratio of 1.2 in time-to-event analyses with 80% power for incidence of ESRD. Thus, even a 20% drop out rate will not affect statistical power of the study.

Every effort will be made to collect all data at the specified time points. In the case of missing (and not recoverable) data on primary endpoints, we will make the assumption that data are missing completely at random. Analyses will be carried out applying the list-wise deletion of cases with missing values in order to obtain unbiased estimations. Multiple imputation of missing data will be applied only for secondary endpoints and co-variates when found appropriate.

For continuous outcomes, generalized mixed models will be used while for dichotomous outcomes, random effect logistic or Cox regression will be applied. Effect modification by age and gender will be investigated using multiplicative interaction analyses.

Relevant exposure and co-variates will be selected based on plausible underlying hypothesis. Directed acyclic graphs may be used in order to create parsimonious multivariable models with minimized confounding.

If appropriate, repeated measurements of exposure and co-variates will be included in the models.

Economic monitoring

The economic analysis of the SCOPE project will include: i) cost of screening/diagnosis; ii) cost of follow-up (e.g. pharmacological treatment, specialist visits, laboratory visits over the 2-year follow-up); iii) cost of CKD complications (e.g. emergency room access, hospital admission, haemodialysis, etc.); iv) other health-related costs (e.g. hospital out-patient care referrals, nursing home placements, use of home care services). With this analysis, it will be possible to determine main predictors of costs in CKD using multivariate regression and to establish cost-effective ratio of the intervention (overall healthcare costs, divided by efficacy, expressed as survival or quality-adjusted survival).

In order to assess the cost-benefit profile of the screening program on a longer time horizon, clinical and economic results of the SCOPE project will be used to run a projection (10–15 years) using Markov modelling. The analysis consists in evaluating a hypothetical cohort of CKD patients, whose healthcare status is categorized into different initial Markov states, based on CKD biomarkers. Patients can move from one state to another, according to certain probabilities that will be derived from the SCOPE project, and can develop complications, such as cardiovascular morbidity, renal failure and need of dialysis, CKD related and non-related death.

Discussion

The SCOPE study is one of the largest prospective observational cohort studies aimed at screening for CKD among older persons across Europe. The current paper outlines the study protocol including statistical analysis of data, risk prediction modeling and economic evaluation of costs arising from CKD during the advanced ageing process.

The strength of the protocol outlined in this paper is the real life setting for recruitment of participants. All persons with age ≥ 75 years attending the outpatient services at participating institutions will be requested to participate in the study. No other inclusion criteria will be considered. This seems the primary strength of the SCOPE study. The collection of real life data in a longitudinal fashion over a two- years period of time will allow insight on the impact of renal function on the management and advanced care planning of older subjects prone to renal impairment.

It is expected that many of the participants enrolled will be affected by

multimorbidity.[63] The impact of disease clusters and management strategies from experts in the field of nephrology and geriatrics will open access to comparative effectiveness analysis of data and interventions.[64] People older than 75 years or people with impaired renal function have so far been rarely included into clinical trials. Aging population heralds a new geriatric "reality", namely an increase in older adults with CKD. Conversely, many older adults are living healthy and active, even with several chronic conditions. In this context longitudinal epidemiological studies are extremely valuable tools in observational research and have many uses and strengths.[65]

Multimorbidity, and in this context CKD have been shown to impact functional status, especially of older patients.[65] The systematic use of a CGA makes possible the investigation of multiple domains of health status in older persons. CGA is part of clinical practice of Geriatric Medicine[66] and is also useful in research investigating consequences of CKD[67,68] since it has been shown to affect different kind of outcomes relevant to older people. The inclusion of functional domains, as recently postulated by the World Health Organization (WHO)[69] in the design of screening models for CKD in older persons aligns the SCOPE projects with future demands for all Health Care systems around the globe.[70,71] Health care is currently provided and funded on a disease-centered approach in many health care systems. The inclusion of CGA in the longitudinal evaluation of study participants of the SCOPE project will allow a more patient-centered and individualized approach for screening and advanced care planning for older subjects prone to kidney function decline.[31,68] Furthermore, the search for biomarkers which are less influenced by muscle mass and more accurate in predicting outcomes compared to circulating creatinine is of special interest and will be further investigated. Thus, combining the use of CGA and the investigation of novel and existing independent biomarkers in within the SCOPE project, could help in building new evidence in the development of recommendations and guidelines for a patient-centered approach in the screening and management of older people at risk for CKD.

The alignment of an economic evaluation of care pathways and histories of study participants during the study period will give new input for care providers and planners in different health care and funding systems. Inclusion of costs of screening to achieve accurate diagnosis of CKD and related follow-up costs (e.g. pharmacological treatment, specialist visits, laboratory visits over the 2-year follow-up) will answer current call for actions coming from different bodies.[72] The focus on CKD related consumption of healthcare resources (e.g. emergency room access, hospital admission, hospital out-patient care referrals, nursing home placements, use of home

care services and others) using Markov modelling will provide key information for developments in public health.

Major drawback or limitation of the project is the lack of standardized management and care plans for older people currently available for all participating centres. Centres enrolling participants in the SCOPE projects are highly experienced in the management of older multimorbidity subjects at risk for renal impairment and related clinical complications, including changes in functional status. Guidelines on CKD management are mainly disease-centred and put a focus on morbidities and mortality. It is to be foreseen that the care pathways for participants will therefore still be tailored individually and according to needs, driven by expertise of staff in the participating centres. However, important information may be expected though, as the implementation of the CGA per se into care pathways has already been proven effective.[66] It seems noteworthy that the individualized care approach during complex care management of older subjects is part of daily routine in geriatric medicine. Alignment of care processes along CGA results seems feasible in the context of current scientific evidence.

In conclusion, the SCOPE project will close essential gaps in the care of older people with declining kidney function. Due to the extremely comprehensive study setting and data analysis it is to be expected that evidence arising from the SCOPE project will impact the management of older people suffering from CKD, as well as the quality of care delivered for older subjects at risk for CKD in daily routine. The high quality of data retrieved will however, also open doors for new research and innovation in the field of nephrology and geriatrics. Building on solid evidence arising from the current project, SCOPE will support the development of European recommendations and guidelines, as well as a European education program in the field of screening and management of CKD in older adults across Europe.

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Chapter 3

Estimating kidney function

3.1

Clinical implications of estimating glomerular filtration rate in older adults

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Clinical implications of estimating glomerular filtration rate with three different equations among older people. Preliminary results of the project "Screening for Chronic Kidney Disease among Older People across Europe (SCOPE)"

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Abstract

We aimed at investigating to what extent CKD may be staged interchangeably by three different eGFR equations in older people, and evaluating the source of discrepancies among equations in a population of 2257 patients older than 75 years enrolled in a multicenter observational study. eGFR was calculated by CKD-EPI, BIS and FAS equations.

Statistical analysis was carried out by Bland–Altman analysis. κ statistic was used to quantify the agreement between equations in classifying CKD stages. The impact of selected variables on the difference among equations was graphically explored.

The average difference between BIS and FAS was -0.24 (95% limits of agreement (95%LA = -4.64–4.14) mL/min/1.73 m^2. The difference between CKD-EPI and BIS and between CKD-EPI and FAS was 8.97 (95%LA = -2.90–20.84) and 8.72 (95%LA = -2.11–19.56) mL/min/1.73 m^2, respectively. As regards CKD stage classification, κ value was 0.47 for both CKD-EPI vs. FAS and CKD-EPI vs. BIS, while BIS and FAS had similar classificatory properties (κ = 0.90). Muscle mass was found related to the difference between CKD-EPI and BIS (R^2 = 0.11) or FAS (R^2 = 0.14), but not to the difference between BIS and FAS.

In conclusion, CKD-EPI and BIS/FAS equations are not interchangeable to assess eGFR among older people. Muscle mass may represent a relevant source of discrepancy among eGFR equations.

Introduction

Estimated glomerular filtration rate (eGFR) equations are routinely used for clinical assessment of kidney function, despite their accuracy among older patients still being a matter of debate. Identifying appropriate filtration markers and estimating equations for older and especially frail older people has come into focus and is of clinical as well as public interest as the prevalence of chronic kidney disease (CKD) is known to increase with age and to impact health status and survival in several different populations.[1,2] Timely detection of CKD allows to contrast some pathogenetic mechanisms such as uncontrolled hypertension or, in diabetic nephropathy, glomerular hyperfiltration in order to slow kidney function decline.[3] Importantly, it also allows to tailor the dosage of kidney-cleared medications, as well as CKD stage-specific interventions.[4]

To address current inconsistencies across recently published studies on determination of kidney function in older patients, it seems necessary to consider different statistical approaches, laboratory assays used to measure creatinine and specimen collection, handling, and storage. Furthermore, the impact of parameters like muscle mass, may impact internal consistency of measurement of kidney function, especially in this cohort of older subjects.[5] Indeed, sarcopenia, which is commonly observed among frail older people, may reduce creatine production leading to low serum creatinine levels even despite a significantly reduced glomerular filtration rate (GFR).[6] To this aim, several different eGFR equations have been developed and tested for these cohorts of patients.[7-11] Since 2012, KDIGO has adopted The Chronic Kidney Disease Epidemiological Collaborative (CKD-EPI) equation, but it cannot be considered universal in clinical practice yet.[4] This equation was developed from a population consisting of 8254 subjects pooled from 10 studies, including 13% of people aged >65 years and 28% diabetics, and externally validated in a population of 3896 subjects pooled from 16 other studies.[8] The Berlin Initiative Study (BIS)[9] has been developed to be used in elderly people, and Full Age Spectrum (FAS) equations for the whole life span adapting also for age and both equations have been externally validated against gold-standard measured GFR.[12,13] Several studies tried to compare the sensitivity of the different creatinine-based equations (CKD-EPI, BIS, FAS) in cohorts of older subjects[14] with striking differences in results. Nevertheless, creatinine-based eGFR is still the most widely used measure for clinical assessment of kidney function. Other biomarkers of kidney function, especially cystatin C, were investigated in an attempt to improve the accuracy of kidney function estimates. While the accuracy of equations including both creatinine and cystatin C in predicting measured GFR was found to be better than that observed with creatinine-based ones among older patients,[15] the agreement

between equations was found to be only marginally improved[16] and prognostic accuracy unchanged when adding cystatin C.[17] Thus, the additional costs generated by cystatin C assessment may not be associated with a true improvement in clinical assessment of kidney function. Indeed, it has been suggested that cystatin C may be cost-effective in young adults where it can help to reduce the number of false positives, but not in individuals aged ≥ 75 years.[18]

Additionally, even the accuracy of cystatin C-based eGFR in predicting measured GFR was found to improve when including fat-free mass in kidney function assessment among older CKD patients.[19]

It is therefore evident that a knowledge gap still exists and ongoing studies will likely help to bridge it.[20] Meanwhile, creatinine-based eGFR remains the less expensive and most widely available screening measure of kidney function.

Considering albumin-to-creatinine ratio (ACR) for staging of chronic kidney disease, the picture in ageing patients in daily clinical practice becomes even more complex.[21] Albuminuria and GFR are both relevant measures of the functionality of glomeruli. Albuminuria is mainly a measure of the glomerular capillary wall permeability to macro-molecules and increased albuminuria occurs earlier in the course of many kidney diseases compared to GFR decline.[22] Both parameters play an important role in detection and staging of CKD. The current evidence for the validity of these two surrogate markers for prediction and progression of CKD is stronger for GFR than for change of albuminuria over time.[21] However, during ageing the sensitivity of GFR determination and mathematical models applied to measure creatinine in the available test systems are strongly impacted by muscle mass. As early detection of a decline in kidney function is a key element in clinical complex care management for many doctors, the aim of the present study was to test how the mathematical models for eGFR calculation are affected by muscle mass and function as measured with bio-impedance analysis (BIA) and short physical performance battery (SPPB),[23] two simple tests applicable in daily clinical practice in a cohort of multi-morbid 75 years+ patients in different stages of CKD at time of inclusion. We also aimed at investigating how difference in eGFR between CKD-EPI, BIS and FAS formula may affect the predictive staging of patients when introducing ACR according to KDIGO guidelines.[4]

Materials and Methods

The SCOPE study (grant agreement number 436849), is a multicenter 2-year prospective cohort study involving patients older than 75 years attending

geriatric and nephrology outpatient services in participating institutions in Austria, Germany, Israel, Italy, the Netherlands, Poland and Spain.

Methods of the SCOPE study have been extensively described elsewhere.[20] Patients were requested to sign a written informed consent before entering the study. The study protocol was approved by ethics committees at all participating institutions, and complies with the Declaration of Helsinki and Good Clinical Practice Guidelines. Only baseline data are used in the present study.

Overall, 2461 patients were initially enrolled in the study. Of them, 204 patients were excluded from this study because of incomplete baseline data, thus leaving a final sample of 2257 patients to be included in the analysis. For testing the hypothesis of impact of muscle mass on detection of glomerular filtration rate, a sub-cohort of 1462/2257 participants was recruited for muscle mass measurements as outlined below.

2.1. Study Variables

Serum creatinine was measured at local level by standard methods. Creatinine-based eGFR was calculated using the equations described in **Table 1**.

Table 1. Estimated glomerular filtration rate equations used in the present study

Reference Study		Equation
CKD-EPI[8]	Women (Scr≤0.7)	$eGFR = 144 \times (Scr/0.7)^{-0.329} \times (0.993)^{Age}$
	(Scr>0.7)	$eGFR = 144 \times (Scr/0.7)^{-1.209} \times (0.993)^{Age}$
	Men (Scr≤0.9)	$eGFR = 141 \times (Scr/0.9)^{-0.411} \times (0.993)^{Age}$
	(Scr>0.9)	$eGFR = 141 \times (Scr/0.9)^{-1.209} \times (0.993)^{Age}$
BIS[9]	$3736 \times creatinine^{-0.87} \times age^{-0.95} \times 0.82$(if women)	
FAS[11]	$[107.3/(creatinine/Q)] \times 0.988^{(Age-40)}$ for age>40 years Q=median Scr value for age-/sex-specific healthy populations	

Abbreviations: Scr, serum creatinine in mg/dL; CKD-EPI, Chronic Kidney Disease–Epidemiologic Collaboration; BIS, Berlin Initiative Study; FAS, Full Age Spectrum.

Albumin in urine was detected by urine spot analysis and expressed as mg albumin per gram urine (mg/g); ACR was calculated according to KDIGO guidelines.[4]

Variables included in further analysis were age, sex and Body Mass Index (BMI) using the formula recommended in the guidelines of the European Society of Clinical Nutrition (ESPEN).[24]

Physical performance was included in the analysis for consideration of sarcopenia. Physical performance was measured by SPPB.[25] The SPPB includes gait speed (usual time to walk 4 m), five chair-stands test (time to rise from a chair and return to the seated position five times without using arms), and balance test (ability to stand with the feet together in the side-by-side, semi-tandem, and tandem positions). A score from 0 to 4 was assigned to performance on each task. Individuals received a score of 0 for each task they were unable to complete. Summing the three individual categorical scores, a summary performance score was created for each participant (range, 0–12), with higher scores indicating better lower body function.

To further validate muscle mass measures in comparison to SPPB values in a sub-cohort of 1462 participants in the SCOPE study, BIA was carried out by Akern BIA101 with BodyGram PLUS software (Akern srl, Pontassieve (FI), Italy), and muscle mass was calculated using the Janssen et al. equation.[26] BIA was not performed in patients with pacemaker or implantable cardioverter defibrillator.

2.2. Analytic Approach

Statistical analysis was performed by SPSS Statistical Software Package for Win V21.0 (SPSS Inc, Chicago, IL, USA) and MedCalc (MedCalc software bv, Ostend, Belgium). To investigate the impact of selected study variables on differences among equations, we used a graphic approach by GraphPad Prism 8 (GraphPad, San Diego, CA, USA).

Demographic and clinical characteristics of participants were expressed by descriptive statistics and the prevalence of selected disease was counted and expressed in percent of people affected in the cohort. Non-parametric tests were applied to calculate differences between groups.

Crude correlation among glomerular filtration rate calculated by CKD-EPI, BIS and FAS equation was investigated graphically. Bland–Altman plots were generated to plot the difference CKD-EPI-BIS, CKD-EPI-FAS and BIS-FAS against the mean of the two estimates, respectively, or the whole cohort of participants.

Furthermore, the prevalence of CKD stages obtained with different equations was investigated adding ACR and creatinine based glomerular filtration rates according to KDIGO guidelines.[4]

Cohen's kappa (κ) was calculated to quantify the agreement between equations in identifying people with different degrees of kidney dysfunction (eGFR > 90, stage 1; 90–60, stage 2; 60–45, stage 3a; 45–30, stage 3b; and <30 mL/min/1.73 m^2, stage 4–5). Finally, we also calculated the prevalence of each individual KDIGO stage of CKD based on eGFR and ACR. Analyses were further stratified by sex.

Finally, to investigate the impact of sarcopenia on the observed difference among study equations, we used a graphic approach plotting the difference of the values obtained by two equations on the value of the variable of interest (BMI, SPPB or muscle mass) and using local regression techniques to fit a parametric or non-parametric curve smoothing the relationship between the two variables. We adapted our choice on the basis of the regression curve best fitting the given distribution to calculate regression analysis.

2.3. Ethical Statement

The study protocol was approved by ethics committees at all participating institutions, and complies with the Declaration of Helsinki and Good Clinical Practice Guidelines. Only baseline data are used in the present study. Ethics approvals have been obtained by Ethics Committees in participating institutions as follows:

- Italian National Research Center on Aging (INRCA), Italy, #2015 0522 IN, 27 January 2016.
- University of Lodz, Poland, #RNN/314/15/KE, 17 November 2015.
- Medizinische Universität Graz, Austria, #28–314 ex 15/16, 5 August 2016
- Erasmus Medical Center Rotterdam, The Netherland, #MEC-2016-036 - #NL56039.078.15, v.4, 7 March 2016.
- Hospital Clínico San Carlos, Madrid, Spain, # 15/532-E_BC, 16 September 2016
- Bellvitge University Hospital Barcellona, Spain, #PR204/15, 29 January 2016.
- Friedrich-Alexander University Erlangen-Nürnberg, Germany, #340_15B, 21 January 2016.
- Helsinki committee in Maccabi Healthcare services, Bait Ba-lev, Bat Yam, Israel, #45/2016, 24 July 2016.

Results

General characteristics of the study population are reported in **Table 2**. As may be seen from the Table, men and women were equally distributed in the SCOPE cohort at baseline (1256 women/1001 men) with a median age of 80.3 ± 4.1 years for women and 80.4 ± 4.1 years for men. Men differed from women with a significantly lower eGFR as determined by CKD-EPI, BIS and FAS equation (data see **Table 2**, significance for all equations applied $p < 0.001$), had a higher amount of muscle mass in average and performed significantly better in the SPPB (women SPPB 8.3 ± 3.1, men SPPB 9.3 ± 2.7, $p < 0.001$). Diabetes ($p < 0.001$), heart failure ($p = 0.004$), atrial fibrillation ($p = 0.002$) and myocardial infarction ($p < 0.001$) were more frequent in men than in women, arterial hypertension and stroke should a similar tendency without reaching the level of statistical significance. When comparing levels of GFR calculated by CKD-EPI, BIS and FAS formula for the whole cohort of participants the average eGFR value was higher with CKD-EPI compared to BIS ($p < 0.001$) and FAS ($p < 0.001$) equations for the whole cohort (see **Table 2** and **Figure 1**).

The three eGFR equations were strongly correlated each other, even if the correlations between CKD-EPI and BIS or FAS were less linear compared to that observed between BIS and FAS (**Figure 1**, panels A–C).

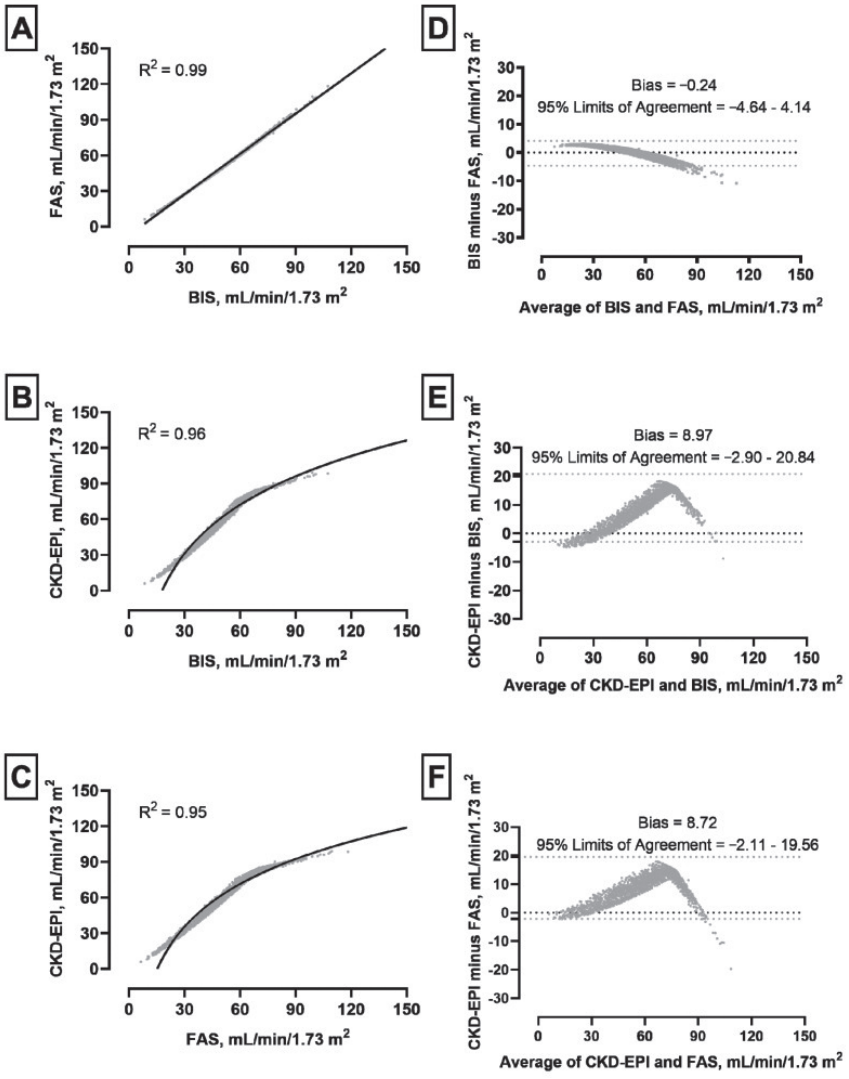
The Bland–Altman analysis showed that the bias between BIS and FAS was very small(–0.24 mL/min/1.73 m^2); greater difference was observed only for patients with high eGFR values (**Figure 1**, panel D). In contrast, there was a significant difference in calculated GFR values between CKD-EPI and BIS and also between CKD-EPI and FAS (8.97 mL/min/1.73 m^2 and 8.72 mL/min/1.73 m^2, respectively), peaking around 60 mL/min/1.73 m^2 for both equations (CKD-EPI compared to BIS, CKD-EPI compared to FAS). Additionally, the 95% upper limits of agreement were 20.84 and 19.56 mL/min/1.73 m^2, respectively (**Figure 1**, panels E and F).

Table 2. General characteristics of the study population in the SCOPE project

	All patients N=2257	Women N=1256	Men N=1001	p-value
Age, years	80.3±4.1	80.3±4.1	80.4±4.1	0.671
Sex, women, n (%)	1256 (55.6)	-	-	-
Body mass index, kg/m^2	27.8±4.7	27.9±4.9	27.6±4.5	0.153
Serum creatinine, mg/dL	1.11±0.56	0.93±0.41	1.33±0.64	<0.001
CKD-EPI eGFR, mL/min/1.73 m^2	63.8±19.4	65.4±18.1	58.9±20.5	<0.001
90 or more, n (%)	43 (1.9)	32 (2.5)	11 (1.1)	
60-89.9, n (%)	1335 (59.1)	807 (64.3)	528 (52.7)	
45-59.9, n (%)	433 (19.2)	240 (19.1)	193 (19.3)	
30-44.9, n (%)	271 (12.0)	112 (8.9)	159 (15.9)	
<30, n (%)	175 (7.8)	65 (5.2)	110 (11.0)	
BIS eGFR, mL/min/1.73 m^2	54.6±15.2	55.5±14.8	51.1±14.9	<0.001
90 or more, n (%)	9 (0.4)	7 (0.6)	2 (0.2)	
60-89.9, n (%)	759 (33.6)	471 (37.5)	288 (28.8)	
45-59.9, n (%)	877 (38.9)	499 (39.7)	378 (37.8)	
30-44.9, n (%)	451 (20.0)	213 (17.0)	238 (23.8)	
<30, n (%)	161 (7.1)	66 (5.3)	95 (9.5)	
FAS eGFR, mL/min/1.73 m^2	55.0±17.3	55.4±16.9	51.7±17.0	<0.001
90 or more, n (%)	29 (1.3)	18 (1.4)	11 (1.1)	
60-89.9, n (%)	775 (34.3)	467 (37.2)	308 (30.8)	
45-59.9, n (%)	791 (35.0)	454 (36.1)	337 (33.7)	
30-44.9, n (%)	450 (19.9)	227 (18.1)	223 (22.3)	
<30, n (%)	212 (9.4)	90 (7.2)	122 (12.2)	
ACR, mg/g	100±480	77.1±390	177±599	<0.001
<30, n (%)	1648 (73.0)	992 (79.0)	656 (65.5)	
30-300, n (%)	458 (20.3)	216 (17.2)	242 (24.2)	
>300, n (%)	151 (6.7)	48 (3.8)	103 (10.3)	
Muscle mass, kg (N=1,462)	22.7±6.8	18.0±3.8	29.0±4.4	<0.001
SPPB, score	8.7±2.9	8.3±3.1	9.3±2.7	<0.001
Hypertension, n (%)	1734 (76.8)	972 (76.6)	772 (77.1)	0.767
Diabetes Mellitus, n (%)	569 (25.2)	264 (21.0)	305 (30.5)	<0.001
Heart Failure, n (%)	373 (16.5)	182 (14.5)	191 (19.1)	0.004
Atrial fibrillation, n (%)	344 (15.2)	165 (1.1)	179 (17.9)	0.002
Myocardial infarction, n (%)	217 (9.6)	75 (6.0)	142 (14.2)	<0.001
Stroke, n (%)	131 (5.8)	61 (4.9)	70 (7.0)	0.031

Notes: continuous variables are expressed as mean±SD. Continuous values were compared between men and women using the independent t-test, categorical values were compared between men and women using the chi-square test. **Abbreviations**: CKD-EPI, Chronic Kidney Disease-Epidemiology collaboration ; eGFR, estimated Glomerular Filtration Rate; BIS, Berlin Initiative Study; FAS, Full Age Spectrum; ACR, Albumin-to-Creatinine Ratio; SPPB, Short Physical Performance Battery.

Figure 1. Crude correlations among eGFR equations (A,B,C) and Bland-Altman analysis (D,E,F)



Notes: In panel A-C, R^2 represents the square of the crude correlation coefficient of x and y. In panel D-F, the bland-altman method was used to calculate the mean difference between two equations (bias) and the corresponding 95% limits of agreement. **Abbreviations:** eGFR, estimated Glomerular Filtration Rate; FAS, Full Age Spectrum; BIS, Berlin Initiative Study; CKD-EPI, Chronic Kidney Disease-Epidemiology collaboration.

Properties of eGFR equations to classify and stage CKD were significantly different (**Tables 3–5**). The prevalence of stage 2 was 59.1% according to CKD-EPI, 33.6% according to BIS and 34.3% according to FAS, while the corresponding figures for stage 3a and 3b were 19.2%, 38.9%, and 35.0%, and 12.0%, 20.0% and 19.9%, respectively (**Table 2**). Overall, κ value was 0.47 for both CKD-EPI vs. FAS and CKD-EPI vs. BIS, while the classificatory properties of BIS and FAS were found to be very similar (κ = 0.90) (**Table 3**). When applying the KDIGO stratification system to our study population, the prevalence of stage 2 was much more prevalent with CKD-EPI compared to FAS or BIS among patients without proteinuria or with moderate proteinuria, while differences among equations were smaller in patients with severe proteinuria (**Table 3**).

Table 3. Prevalence of KDIGO stages with three different equations stratified by sex

eGFR values	**All patients, N=2257 ACR (mg/g)**			**Men, N=1001 ACR (mg/g)**			**Women, N=1256 ACR (mg/g)**		
CKD-EPI	<30	30-300	>300	<30	30-300	>300	<30	30-300	>300
>90	35 2.1%	7 1.5%	1 0.7%	8 1.2%	3 1.3%	0	27 2.7%	4 1.8%	1 2.1%
60-89.9	1133 68.8%	188 41.3%	13 8.6%	433 65.9%	86 36.1%	9 8.7%	700 70.7%	102 47.0%	4 8.3%
45-59.9	311 18.9%	98 21.5%	24 15.8%	128 19.5%	50 21.0%	15 14.4%	183 18.5%	48 22.1%	9 18.8%
30-44.9	133 8.1%	84 18.5%	51 33.6%	69 10.5%	52 21.8%	36 34.6%	64 6.5%	32 14.7%	15 31.3%
<30	35 2.1%	78 17.1%	63 41.4%	19 2.9%	47 19.7%	44 42.3%	19 2.9%	31 14.3%	19 39.6%
BIS									
>90	6 0.3%	3 0.8%	0	1 0.2%	1 0.4%	0	5 0.5%	2 0.9%	0
60-89.9	655 39.8%	97 21.3%	7 4.6%	247 37.6%	37 15.5%	5 4.8%	408 41.3%	60 27.6%	2 4.2%
45-59.9	710 43.1%	143 31.4%	23 15.1%	285 43.4%	80 33.6%	12 11.5%	425 42.9%	63 29.0%	11 22.9%
30-44.9	244 14.8%	140 30.8%	64 42.1%	109 16.6%	79 33.2%	48 46.2%	135 13.6%	61 28.1%	16 33.3%
<30	32 1.9%	72 15.8%	58 38.2%	15 2.3%	41 17.2%	39 37.5%	17 1.7%	31 14.3%	19 39.6%
FAS									
>90	22 1.3%	6 1.3%	1 0.7%	8 1.2%	3 1.3%	0	14 1.4%	3 1.4%	1 2.1%
60-89.9	669 40.7%	101 22.2%	6 3.9%	263 40.0%	42 17.6%	5 4.8%	406 41.1%	59 27.2%	1 2.1%
45-59.9	641 38.9%	131 28.8%	17 11.2%	254 38.7%	72 30.3%	9 8.7%	387 39.1%	59 27.2%	8 16.7%
30-44.9	267 16.2%	127 27.9%	53 34.9%	109 16.6%	72 30.3%	40 30.5%	158 16.0%	55 25.3%	13 27.1%
<30	48 2.9%	90 19.8%	75 49.3%	23 3.5%	49 20.6	50 48.1%	25 2.5%	41 18.9%	25 52.1%

Notes: eGFR values are expressed as mL/min/1.73m^2 and categorized according to KDIGO stages[4]: eGFR >90, stage 1; 60-89.9, stage 2; 45-59.9, stage 3a; 30-44.9, stage 3b; and <30, stage 4–5). Colour coding was used according to KDIGO[4]: Green = low risk, Yellow = moderately

increased risk, Orange = high risk, Red = very high risk. Prevalence is expressed as number and percentages. **Abbreviations**: eGFR, estimated Glomerular Filtration Rate; ACR, Albumin-to-Creatinine Ratio; CKD-EPI, Chronic Kidney Disease-Epidemiology collaboration; BIS, Berlin Initiative Study; FAS, Full Age Spectrum.

It is worth noting that 574 (43%) out of 1335 patients classified in stage 2 by CKD-EPI were classified in stage 3a by FAS equation, and 216 out of 433 (50%) patients classified in stage 3a by CKD-EPI were classified in stage 3b by FAS equation. Similar findings were obtained when comparing CKD-EPI and BIS equation, while such a difference was negligible when comparing BIS and FAS equations (**Table 4**). Finally, disagreement between CKD-EPI and FAS or BIS was more evident among women (**Table 5**) than men (**Table 6**).

BMI and SPPB score were not significantly correlated with difference among equations (**Figure 2,** panels A-F). The analysis regarding muscle mass was limited to 1462 patients undergoing BIA during the enrolment visit. The relationship between muscle mass and BIS minus FAS was not significant. Conversely, CKD-EPI minus FAS and CKD-EPI minus BIS increased together with decreasing muscle mass (**Figure 2**, panels G-I).

Table 4. Agreement among eGFR equations in all participants (n=2257)

		CKD-EPI						
		>90 (N=43)	**60-89.9 (N=1335)**	**45-59.9 (N=433)**	**30-44.9 (N=271)**	**<30 (N=175)**	κ	p
FAS	**>90**	29 (67.4%)					0.47	0.001
	60-89.9	14 (32.6%)	761 (57.0%)					
	45-59.9		574 (43.0%)	217 (50.1%)				
	30-44.9			216 (49.9%)	234 (86.3%)			
	<30				37 (13.7%)	175 (100%)		
BIS							0.47	0.001
	>90	9 (20.9%)						
	60-89.9	34 (79.1%)	725 (54.3%)					
	45-59.9		610 (45.7%)	267 (61.7%)				
	30-44.9			166 (38.3%)	267 (98.5%)	18 (10.3%)		
	<30				4 (1.5%)	157 (89.7%)		
					BIS			
		>90 (N=9)	**60-89.9 (N=759)**	**45-59.9 (N=877)**	**30-44.9 (N=451)**	**<30 (N=161)**	κ	*p*
FAS							0.90	0.001
	>90	9 (100%)	20 (2.6%)					
	60-89.9		738 (97.2%)	37 (4.2%)				
	45-59.9		1 (0.1%)	790 (90.1%)				
	30-44.9			50 (5.7%)	400 (88.7%)			
	<30				51 (11.3%)	161 (100%)		

Notes: eGFR values are expressed as mL/min/1.73m^2 and categorized according to KDIGO stages[4]: eGFR >90, stage 1; 60-89.9, stage 2; 45-59.9, stage 3a; 30-44.9, stage 3b; and <30, stage 4–5). Prevalence is expressed as number and percentages. Cohen's kappa (κ) was calculated to quantify the agreement between equations with corresponding p-value. **Abbreviations**: eGFR, estimated Glomerular Filtration Rate; CKD-EPI, Chronic Kidney Disease-Epidemiology collaboration; BIS, Berlin Initiative Study; FAS, Full Age Spectrum.

Table 5. Agreement among eGFR equations in women (n=1256)

		CKD-EPI						
		>90 (N=32)	**60-89.9 (N=807)**	**45-59.9 (N=240)**	**30-44.9 (N=112)**	**<30 (N=65)**	κ	*p*
FAS	**>90**	18 (56.3%)					0.36	0.001
	60-89.9	14 (43.8%)	453 (56.1%)					
	45-59.9		354 (43.9%)	100 (41.7%)				
	30-44.9			140 (58.3%)	87 (77.7%)			
	<30				25 (22.3%)	65 (100%)		
							0.41	0.001
BIS	**>90**	7 (21.9%)						
	60-89.9	25 (78.1%)	446 (55.3%)					
	45-59.9		361 (44.7%)	138 (57.5%)				
	30-44.9			102 (42.5%)	109 (97.3%)	2 (3.1%)		
	<30				3 (2.7%)	63 (96.9%)		
		BIS						
		>90 (N=7)	**60-89.9 (N=471)**	**45-59.9 (N=499)**	**30-44.9 (N=213)**	**<30 (N=66)**	κ	*p*
							0.90	0.001
FAS	**>90**	7 (100%)	11 (2.3%)					
	60-89.9		459 (97.5%)	8 (1.6%)				
	45-59.9		1 (0.2%)	453 (90.8%)				
	30-44.9			38 (7.6%)	188 (88.7%)			
	<30				24 (11.3%)	66 (100%)		

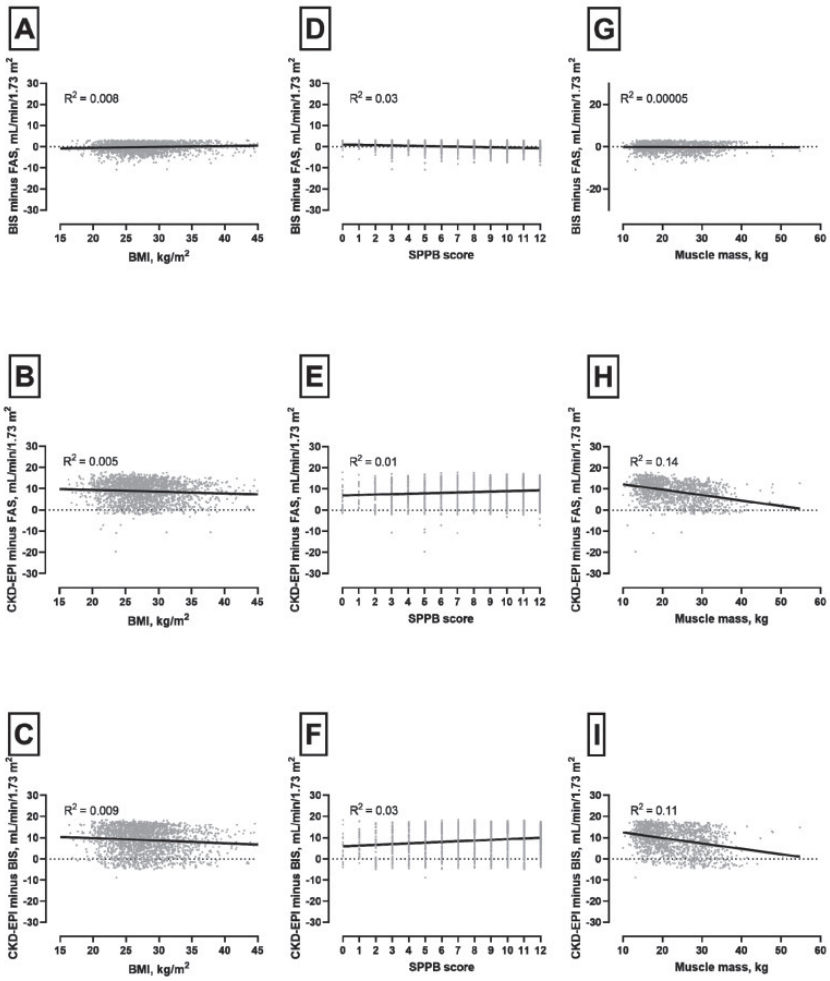
Notes: eGFR values are expressed as mL/min/1.73m^2 and categorized according to KDIGO stages[4]: eGFR >90, stage 1; 60-89.9, stage 2; 45-59.9, stage 3a; 30-44.9, stage 3b; and <30, stage 4–5). Prevalence is expressed as number and percentages. Cohen's kappa (κ) was calculated to quantify the agreement between equations with corresponding p-value. **Abbreviations**: eGFR, estimated Glomerular Filtration Rate; CKD-EPI, Chronic Kidney Disease-Epidemiology collaboration; BIS, Berlin Initiative Study; FAS, Full Age Spectrum

Table 6. Agreement among eGFR equations in men (n=1001)

		CKD-EPI						
		>90 (N=11)	**60-89.9 (N=528)**	**45-59.9 (N=193)**	**30-44.9 (N=159)**	**<30 (N=110)**	κ	*p*
FAS	**>90**	11 (100%)					0.57	0.001
	60-89.9		308 (58.3%)					
	45-59.9		220 (41.7%)	117 (60.6%)				
	30-44.9			76 (39.4%)	147 (92.5%)			
	<30				12 (7.5%)	110 (100%)		
							0.53	0.001
BIS	**>90**	2 (18.2%)						
	60-89.9	9 (81.8%)	279 (52.8%)					
	45-59.9		249 (47.2%)	129 (66.8%)				
	30-44.9			64 (33.2%)	158 (99.4%)	16 (14.5%)		
	<30				1 (0.6%)	94 (85.5%)		
		BIS						
		>90 (N=2)	**60-89.9 (N=288)**	**45-59.9 (N=378)**	**30-44.9 (N=238)**	**<30 (N=95)**	κ	*p*
FAS							0.89	0.001
	>90	2 (100%)	9 (3.1%)					
	60-89.9		279 (96.9%)	29 (7.7%)				
	45-59.9			337 (89.2%)				
	30-44.9			12 (3.2%)	211 (88.7%)			
	<30				27 (11.3%)	95 (100%)		

Notes: eGFR values are expressed as mL/min/1.73m² and categorized according to KDIGO stages[4]: eGFR >90, stage 1; 60-89.9, stage 2; 45-59.9, stage 3a; 30-44.9, stage 3b; and <30, stage 4–5). Prevalence is expressed as number and percentages. Cohen's kappa (κ) was calculated to quantify the agreement between equations with corresponding p-value. **Abbreviations**: eGFR, estimated Glomerular Filtration Rate; CKD-EPI, Chronic Kidney Disease-Epidemiology collaboration; BIS, Berlin Initiative Study; FAS, Full Age Spectrum

Figure 2. Graphical analysis of the impact of body mass index (panels **A**–**C**), physical performance (Panels **D**–**F**) and muscle mass* (Panels **G**–**I**) on the difference among eGFR equations



Notes: *n=1462. R^2 represents the square of the crude correlation coefficient of x and y. **Abbreviations**: eGFR, estimated glomerular filtration rate; BIS, Berlin Initiative Study; FAS, Full Age Spectrum, CKD-EPI, Chronic Kidney Disease-Epidemiology collaboration; BMI, body mass index; SPPB, short physical performance battery.

4. Discussion

Overall, our findings clearly show that BIS and FAS equations may provide different estimates of GFR compared to CKD-EPI equation in a population of older outpatients. It is important to notice that the greatest difference is observed for eGFR values around 60 mL/min/1.73 m^2. The fact that this range of GFR is of potential interest in daily clinical practice management of older subjects puts our results in the focus of experts as well as clinicians.

Determination of kidney function has been a topic of discussion among experts and may impact clinical management of patients as well as setting endpoints in future clinical studies.[21] Over the past decade, several attempts have been made to test creatinine-based mathematical models for determination of kidney function in different cohorts of patients and healthy subjects.[14] Furthermore, parameters like age, sex, muscle mass, may impact internal consistency of measurements of kidney function, especially in this cohort of older subjects.[5] It has been speculated that loss of muscle mass, which is common in the frail older persons, may impact production of creatine and ensuing low levels of serum creatinine even despite a depressed glomerular filtration rate (GFR).[6]

To date, only few studies including multimorbid older subjects, also including those with physical functional deficits, have focused on this burning issue for clinical practice, but also research. The older people participating in the SCOPE study represent a rich source and wealth in several dimensions: people older than 75 years and living in a community were recruited and followed up for two years on a voluntary basis in this observational study with a wide recruitment frame and only few exclusion criteria.[20] Not surprisingly, women are outnumbering men participants as it is a fact that women account for a higher percentage of older community dwelling persons in many EU countries nowadays.[27] The very open inclusion criteria concerning kidney function (only excluding people with an initial eGFR < 15 mL/min^{-1} during recruitment phase) furthermore contributed to a real-life picture when treating older people in clinical practice in the EU.

Given the fact that recent data on prevalence of CKD clearly demonstrated a sex bias for CKD, men being at higher risk for development of CKD,[28] it was the major interest of the study team to also address sex differences when looking at the impact of the method used to calculate eGFR on staging of CKD based on creatinine- and albuminuria-based guidelines.[4] The access to data from a cohort older than 75 years, many of them multimorbid and prone to loss of muscle mass, made it possible for the consortium to further test the hypothesis that impaired physical performance

and loss of muscle mass may impact the degree of agreement among eGFR equations in this cohort of older European citizens.[20]

Several studies reported on discrepancies between eGFR values obtained with different equations, but only a few of them included the most recently published BIS and FAS equations at the same time.A former study showed that the average difference between creatinine-based CKD-EPI and BIS was 9.5 mL/min/1.73m^2 in a population of 828 community-dwelling older people,[16] which is very close to the 8.97 mL/min/1.73 m^2 difference observed in the present study. The average 8.72 mL/min/1.73 m^2 difference between CKD-EPI and FAS, as well as the negligible average difference between BIS and FAS are not surprising given the fact that FAS has been designed to match the BIS equation for ages >70 years.[11] Additionally, FAS was recently reported to predict eGFR calculated by the creatinine/cystatin C-based CKD-EPI equation with a median bias 10.2 mL/min/1.73 m^2 (95%CI = 9.2–10.9) in a population of 1913 Chinese CKD patients aged 50.3±18.2 years.[29] Interestingly, the above differences were observed despite the good average diagnostic performance of CKD-EPI, BIS and FAS equations in predicting measured GFR. Indeed, da Silva Selistre recently reported that the median difference between CKD-EPI and FAS in predicting measured GFR was –2.0 (95%CI = –3.5; –2.5) mL/min/1.73 m^2, and the corresponding figure for the difference between CKD-EPI and BIS was 0.0 (95%CI = –1.5; 0.5). Thus, if we consider such a small difference between equations with respect to gold-standard measured GFR, the average differences between CKD-EPI and BIS or FAS equations observed in our study would be unexpected.

Nevertheless, eGFR equations are known to work well in populations for which they had been developed.[30] The FAS equation was originally developed in a life-span perspective to allow eGFR calculation from childhood to older age,[11] while the BIS equation was specifically developed in a population of people aged 70 years or more.[9] At variance, CKD-EPI was developed in a pooled population with a wide age range (50±15 years), but only 13.0% of the development and validation population was aged 65 years or more.[8] On the other hand, our study confirms the good agreement between BIS and FAS equations, which, given their history and intention of development, is less surprising.

As regards potential sources of discrepancy among eGFR equations, serum creatinine, and muscle mass are main correlates also impacting known sex differences of the CKD-EPI and BIS or FAS equations. Finally, differences among eGFR equations are much more evident among women and significantly impact the KDIGO staging of CKD. It is therefore evident that

choosing older people to undergo CKD-related diagnostic procedures and/or treatments will change depending on which equation is used to assess eGFR.

In our analysis, we tried to estimate the agreement in terms of CKD staging between equations, i.e., from the practitioner's perspective. Indeed, "misclassification" has important clinical implications in terms of staging and management of CKD, especially between stage 2 and 3 CKD. Given the high prevalence of stage 3 CKD and the highly variable risk of mortality as well as other negative outcomes in this group, current guidelines include a distinction between CKD stage 3a and 3b.[4] The risk associated with stage 3a CKD in older patients is still under discussion,[31] and GFR level at which the risk of mortality starts to increase may be lower among older patients compared to younger ones.[32] Additionally, older people with eGFR<60 mL/min/1.73 m^2 exhibit a slow progression of CKD.[33] However, current guidelines do not calibrate the definition of CKD for age and suggest many stage-specific therapeutic measures.[4] Relative "misclassification" is also more common in women in our study. Sex represents a relevant non-GFR determinant of serum creatinine,[34] and clinically relevant discrepancies between eGFR equations were found to be more frequent among women aged 75 or more.[35]

Failure to correctly classify older CKD patients also poses significant challenges in managing kidney cleared medications, especially among older patients with multiple chronic diseases treated with polypharmacy regimens. As an example, guideline recommendations suggest careful dosing of several hypoglycemic agents in patients with eGFR <60 mL/min/1.73 m^2.[36] Finally, disagreement between equations may have important implications when prescribing or dosing several other drugs,[37] including direct oral anticoagulants,[38] in terms of missing contraindication or dose reduction recommendation on one side, and underuse or underdosing on the other side.

Additionally, the difference between CKD-EPI and BIS or FAS equations increased together with reducing ACR and muscle mass in our study. The greatest difference between CKD-EPI and BIS or FAS equations was observed for lower ACR and muscle mass values. Creatinine is a metabolic product of creatine and phosphocreatine arising from the muscle compartment which is directly related to muscle mass,[39] and albuminuria also is known to be associated with muscle mass. Sarcopenia is a common occurrence among older adults and its prevalence increases dramatically with decreasing kidney function. In CKD patients, the prevalence of sarcopenia was found to be approximately 40% for eGFR = 60–89 mL/min/1.73 m^2, and approximately

60% for eGFR < 60 mL/min/1.73 m^2.[40] Thus, the above findings together with the observation that the difference between BIS and FAS was only marginally affected by serum creatinine, ACR and muscle mass in the present study, suggest that the population of the SCOPE study may be on one side very similar to that used for the development of the BIS and FAS equations (i.e., an older population aged 75 or more that includes sarcopenic patients), and on the other side very di_erent from that used for the development of the CKD-EPI equation (i.e., a younger population including only 13% of people aged 65 or more). Finally, part of the sex differences observed in our study for the different GFR equations may be attributed to the lower muscle mass of women participating in the SCOPE study (**Table 1**).[41]

Limitations and Strengths

Some limitations of the present study deserve consideration. Our study did not include a direct measurement of GFR. Thus, we cannot draw any definitive conclusion about the diagnostic accuracy of the study equations against a gold standard assessment. Indeed, experimental evidence suggests that intravenous inulin and iohexol may partially undergo extrarenal clearance,[42,43] which may represent a not negligible potential source of error when measuring GFR for developing or validating eGFR equations. Nevertheless, the amount of extrarenal clearance of GFR markers in humans is unknown and is worthy of future investigations. Additionally, patients with eGFR < 15 mL/min/1.73 m^2 were excluded. Nevertheless, this limitation is likely to have a minor role in the present study given the good agreement observed among equations in patients with severe CKD.

This study also has important strengths, including the enrollment of a real-world population of older outpatients and the opportunity to investigate the impact of objectively measured physical performance and body composition on the observed difference among equations.

Conclusions

Our results show that CKD-EPI and BIS or FAS equations cannot be considered interchangeable to assess eGFR in a population of older outpatients. Indeed, despite a fair overall concordance, the respective eGFRs differ significantly in the range of GFR corresponding to CKD stages 2–3b, and this could have a dramatic impact on our diagnostic and therapeutic approach. While our study does not allow to draw a definitive conclusion on diagnostic accuracy of each individual equation, BIS and FAS equations provided very similar eGFR

values and the difference between BIS and FAS seems to be unaffected by muscle mass. At variance, muscle mass seems to represent a major source of discrepancy between CKD-EPI and BIS or FAS. Thus, our findings suggest that the two most recent BIS and FAS equations specifically developed in older patients may be very useful for clinical assessment of eGFR in a population of older outpatients aged >75 years. Additionally, their substantial overlap would minimize discrepancy issues when monitoring progression of CKD. Finally, the impact of muscle mass on CKD staging and its predictivity, as well as the clinical usefulness of muscle mass assessment to decide which equation to use in clinical practice deserve to be further investigated.

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3.2
Estimated glomerular filtration rate and muscles in older adults

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Association of estimated glomerular filtration rate with muscle function in older persons who have fallen

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Abstract

Background: studies suggest that estimated glomerular filtration rate (eGFR) is less reliable in older persons and that a low serum-creatinine might reflect reduced muscle mass rather than high kidney function. This study investigates the possible relationship between eGFR and multiple elements of physical performance in older fallers.

Methods: baseline data of the IMPROveFALL-study were examined in participants ≥65 years. Serum-creatinine based eGFR was classified as normal (≥90 ml/min), mildly reduced (60–89 ml/min) or moderately–severely reduced (<60 ml/ min). Timed-Up-and-Go-test and Five-Times-Sit-to-Stand-test were used to assess mobility; calf circumference and handgrip strength to assess muscle status. Ancova models adjusted for age, sex, Charlson comorbidity index and body mass index were performed.

Results: a total of 578 participants were included. Participants with a normal eGFR had lower handgrip strength than those with a mildly reduced eGFR (–9.5%, $P < 0.001$) and those with a moderately–severely reduced eGFR (–6.3%, $P = 0.033$) with mean strengths of 23.4, 25.8 and 24.9 kg, respectively. Participants with a normal eGFR had a smaller calf circumference than those with a mildly reduced eGFR (35.5 versus 36.5 cm, $P = 0.006$). Mean time to complete the mobility tests did not differ.

Conclusions: in this study we found that older fallers with an eGFR ≥ 90 ml/min had smaller calf circumference and up to 10% lower handgrip strength than those with a reduced eGFR. This lower muscle mass is likely to lead to an overestimation of kidney function. This outcome therefore supports the search for biomarkers independent of muscle mass to estimate kidney function in older persons.

Introduction

The prevalence of chronic kidney disease (CKD) is rising, due to increased ageing of the population and an increase in the number of risk factors, such as obesity, diabetes and hypertension.[1] The prevalence of CKD, defined as a glomerular filtration rate (GFR) <60 ml/min/1.73 m^2,[2] rises in older persons with a prevalence from <1% in persons under 35 years to more than 33% in persons aged 75 years and over.[1,3,4] Additionally, CKD increases the risk of morbidity and mortality[5,6] and negatively affects multiple aspects of functionality and daily performance.[7-9]

In clinical practice, estimation of GFR (eGFR) is commonly used as a quick evaluation of kidney function.[10,11] For estimating GFR, serum-creatinine (s-creatinine) is used as marker, despite the fact that it may be misleading in older persons due to a reduction in muscle mass with ageing.[12] Recent studies have focussed on evaluation of new and independent filtration markers, such as serum cystatin C, ß-trace protein and $ß_2$-microglobuline, to assess renal function and to improve risk prediction related to decreased GFR.[13] However, in clinical practice s-creatinine based eGFR is still daily used. Therefore, it seems relevant to take a closer look at the accuracy of the s-creatinine based eGFR in older persons, since this estimation of renal function may be greatly influenced by muscle mass. Previous studies showed that low s-creatinine, resulting in higher eGFR values, partly reflects muscle atrophy and 'frailty' in older persons.[14,15] In the oldest old community-dwelling persons ≥90 years, where the prevalence of sarcopenia is higher,[12] a U-shaped relationship was found between eGFR and handgrip strength and mortality.[14] These findings generate the hypothesis that sarcopenic persons, having low s-creatinine, might group in categories with high eGFR values.

In this study we investigated whether s-creatinine based eGFR is associated with physical performance in persons aged 65 years and over who have fallen

Methods

Data collection

Baseline data from the Improving Medication Prescribing to reduce Risk Of FALLs (IMPROveFALL) study were analysed. The IMPROveFALL-study is a randomised multicentre trial investigating the effect of withdrawal of fall-risk increasing drugs versus 'care as usual' on reducing falls in community-dwelling persons. A detailed description of the methods can be found elsewhere.[16] In summary, individuals aged ≥65 years who visited the Emergency Department

(ED) because of a fall were asked to participate. Individuals had a Mini-Mental State Examination (MMSE) score of at least 21 out of 30 points.[17] The baseline visit took place within 2 months after ED attendance. The ethical committee of the Erasmus MC approved the study and all participants signed informed consent.

Covariates

Demographic data were collected from ED records. Medical history, use of medications, lifestyle factors and number of comorbidities were documented and Charlson comorbidity index (CCI) was determined. Height and weight were measured and body mass index (BMI) was calculated.

Biochemistry

S-creatinine, sex and age were used to calculate the eGFR in ml/min/1.73 m^2 with the Modification of Diet in Renal Disease (MDRD) Study formula widely used: $175 \times (\text{s-creatinine } (\mu\text{mol/l}) \times 0.0113)^{-1.154} \times \text{age}^{-0.203}$ (years) × 0.742 (if female). GFR was also estimated with the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula, because of the increasing use of this formula in general practice.[18] Kidney function was classified as proposed by the National Kidney Foundation[2] and slightly merged into the following three categories: normal (eGFR ≥ 90 ml/min/1.73 m^2), mildly reduced (eGFR 60–89 ml/min/1.73 m^2), moderately–severely reduced (eGFR 15–59 ml/min/1.73 m^2).

Physical performance

The Timed-Up-and-Go test (TUG) and the Five-Time-Sit-to-Stand test (FTSS) were used to assess mobility.[19,20] Handgrip strength was measured to reflect muscle strength and calf circumference to reflect muscle mass. Handgrip strength is reported as a validated indicator for global muscle strength[21] and was measured with a hand-held dynamometer (Takei TKK 540, Takei Scientific Instruments Co., Ltd., Tokyo, Japan) in standing position with arms beside the body, using the maximum strength from four alternating (right–left) attempts. For measuring calf circumference participants sat with a knee angle of 90° and the sole on the ground. The thickest part of both calves was measured with a measuring tape and the mean value was documented.

Statistical analyses

Statistical analyses were performed using SPSS statistical package 21.0 for Windows. Descriptive data for continues variables were presented as median and interquartile range (IQR). Numbers and percent prevalences were presented for dichotomous variables. Spearman's correlation analyses were used to investigate the relation of age with s-creatinine, eGFR (MDRD and CKD-EPI formula) and physical performance. Missing performance test measures, mostly due to injuries following fall, were excluded from all related analyses. Because of a right-skewed distribution, outcomes of physical performance were log transformed using the natural log. In analyses of covariance we compared mean (natural log transformed) scores of physical performance tests across three categories of eGFR (eGFR ≥ 90 ml/min, eGFR 60–89, eGFR < 60 ml/min). All models were adjusted for sex, age and CCI. Models investigating muscle mass and strength were also adjusted for BMI. We back transformed the results to the original scale. A two-tailed $p < 0.05$ was defined as statistically significant.

Results

Overall, 616 participants were enroled in the IMPROveFALL-study; information on s-creatinine was obtained from 578 participants. Median age was 76.3 years (IQR: 70.2–81.6), 39% were men, 50% lived with a partner, 72% were ADL independent and 58% were iADL independent. The 20% of the participants had diabetes mellitus, 21% had a history of coronary heart disease and 18% had a history of cancer. Using the MDRD-formula 115 participants (19.9%) had a normal eGFR, 314 participants (54.3%) had a mildly reduced eGFR and 149 participants (25.8%) had a moderately–severely reduced eGFR. Participants in the lowest category had a median eGFR of 50 ml/min (IQR: 41–55). When GFR was estimated with the CKD-EPI formula, the categories were different with 11.4, 62.5 and 26.1% from highest to lowest eGFR, respectively. Median s-creatinine was 75.0 µmol/l (IQR: 65.0–93.0), median eGFR was 72.0 ml/min (IQR: 59.0–85.0) using the MDRD-formula and 73.7 ml/min (IQR: 59.2–84.9) using the CKD-EPI formula. Median time to complete the TUG was 10.0 s (IQR: 8.0–14.0) and 15.0 s (IQR: 12.0–20.0) for the FTSS. Median handgrip strength was 24.7 kg (IQR: 19.9–32.3) and median calf circumference was 36.3 cm (IQR: 34.0–38.8). Characteristics of the participants are shown in **Table 1**.

Table 1. Characteristics of the participants (n = 578)

Age in years	76.3 (70.2–81.6)
Men, n (%)	226 (39.1)
Education	
≤ 6 years, n (%)	162 (27.9)
6 – 10 years, n (%)	214 (37.0)
>10 years, n (%)	203 (35.1)
Living with partner, n (%)	288 (49.8)
Widow(er), n (%)	194 (33.6)
Current smoker, n (%)	64 (11.1)
Former smoker, n (%)	201 (34.8)
ADL independent, n (%)	414 (72.0)
iADL independent, n (%)	331 (57.6)
BMI in kg/m² (n = 564)	27.1 (24.4–30.1)
MMSE in points	27.0 (25.0–29.0)
CCI score	2.0 (1.0–3.0)
CCI 0, n (%)	113 (19.6)
CCI 1-2, n (%)	291 (50.3)
CCI ≥3, n (%)	174 (30.1)
CHD, n (%)	120 (20.8)
Diabetes Mellitus, n (%)	118 (20.4)
Cancer, n (%)	106 (18.3)
Use of NSAIDs, n (%)	13 (2.2)
Use of diuretics, n (%)	56 (9.7)
Use of inhibitors of RAS, n (%)	73 (12.6)
S-Creatinine in µmol/L	75.0 (65.0–93.0)
eGFR, MDRD in ml/min	72.0 (59.0–85.0)
eGFR, CKD-EPI in ml/min	73.7 (59.2–84.9)
eGFR ≥ 90 ml/min, n (%)	115 (19.9) / 66 (11.4)*
eGFR 60 – 89 ml/min, n (%)	314 (54.3) / 361 (62.5)*
eGFR < 60 ml/min, n (%)	149 (25.8) / 151 (26.1)*
TUG in seconds (n = 520)	10.0 (8.0–14.0)
FTSS in seconds (n = 479)	15.0 (12.0–20.0)
Handgrip strength in kg (n = 570)	24.7 (19.9–32.3)
Calf circumference in cm (n = 566)	36.3 (34.0–38.8)

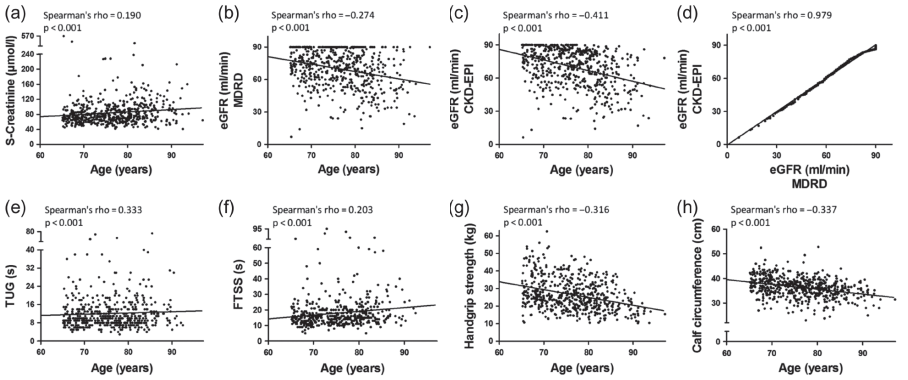
Notes: continuous values are expressed as median and interquartile range**.** *Data on eGFR categories are expressed as number and percentage using the MDRD-formula and CKD-EPI formula, respectively. **Abbreviations:** ADL, Activities of Daily Living; iADL, Instrumental Activities of Daily Living; BMI, Body Mass Index; MMSE, Mini Mental State Examination; CCI, Charlson Comorbidity Index; CHD, Coronary Heart Disease; NSAIDs, Non-Steroidal Anti-Inflammatory Drugs; RAS, Renin-Angiotensin System; S-Creatinine, serum-Creatinine; eGFR, estimated Glomerular Filtration Rate; MDRD, Modification of Diet in Renal Disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; TUG, Timed Up and Go test; FTSS, Five-Times-Sit-to-Stand test.

Age was associated with s-creatinine level (Spearman's r = 0.190, P < 0.001), whereas an inverse association was found between age and eGFR using both MDRD and CKD-EPI formula (Spearman's r = –0.274, P < 0.001 and Spearman's r = –0.411, P < 0.001, respectively). MDRD eGFR and CKD-EPI eGFR were strongly correlated (Spearman's r = 0.979, P < 0.001). Age was also associated with reduced physical performance. An association was found between age and both mobility tests (TUG Spearman's r = 0.333, P < 0.001; FTSS Spearman's r = 0.203, P < 0.001). An inverse association was found between age and handgrip strength (Spearman's r = –0.316, P < 0.001) and calf circumference (Spearman's r = –0.337, P < 0.001). Results are shown in **Figure 1**.

Mean time to complete the mobility tests did not differ between categories. Mean time in seconds for the TUG, from lowest to highest category, was 11.4 (95% CI: 10.5–12.3), 10.4 (95% CI: 9.9–10.9) and 11.0 (95% CI: 10.1–11.9), respectively. Mean time in seconds for the FTSS was 16.2 (95% CI: 15.0–17.5), 16.0 (95% CI: 15.3–16.8) and 16.8 (95% CI: 15.5–18.2), respectively.

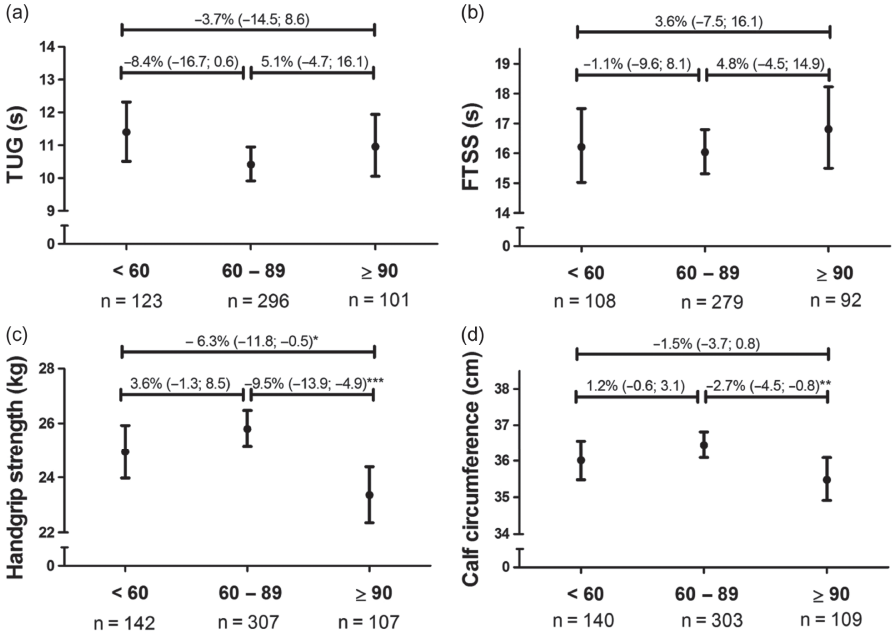
Mean handgrip strength was 9.5% lower in participants with a normal eGFR (23.4 kg, 95% CI: 22.4–24.4) than those with a mildly reduced eGFR (25.8 kg, 95% CI: 25.2–26.5) and 6.3% lower than those with a moderately–severely reduced eGFR (24.9 kg, 95% CI: 24.0–25.9). Mean calf circumference was 1.0 cm smaller in participants with a normal eGFR (35.5 cm, 95% CI: 34.9–36.1) than those with a mildly reduced eGFR (36.5 cm, 95% CI: 36.1–36.8). Mean calf circumference of participants with a moderately–severely reduced eGFR did not differ from those in other categories (36.0 cm, 95% CI: 35.5–36.6). Results of physical measures across categories of eGFR are shown in **Figure 2**.

Figure 1. Correlations of age with renal function (A-D) and physical performance (E-H)



Abbreviations: S-Creatinine, serum-Creatinine; eGFR, estimated Glomerular Filtration Rate; MDRD, Modification of Diet in Renal Disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; TUG, Timed Up and Go test; FTSS, Five-Times-Sit-to-Stand test.

Figure 2. Mean values of physical performance across categories of eGFR using the MDRD-formula



Notes: (a) Timed-Up-and-Go test (TUG), (b) Five-Times-Sit-to-Stand test (FTTS), (c) Handgrip strength, d. Calf circumference. eGFR values are expressed in mL/min. Dots represent mean values of back-transformed data, bars represent 95% confidence intervals. Reported estimates are the mean differences of the higher category compared to the lower category expressed in percentage (with 95% confidence interval of the difference). All analyses are adjusted for age, sex and Charlson comorbidity index. Analyses in (c, d) are also adjusted for body mass index. **P*-value < 0.05; ***P*-value < 0.01; ****P*-value < 0.001.

Estimates in models where the CKD-EPI formula was used, were slightly different. However, the shape of the results remained unchanged. Mean handgrip strength in participants with an eGFR ≥ 90 ml/min was 8.7% lower (23.2 kg, 95% CI: 21.9–24.7) than those with a mildly reduced eGFR (25.5 kg, 95% CI: 24.9–26.1). A mean difference of 7.2% and a tendency towards significance was found when compared to those with a moderately–severely reduced eGFR (25.0 kg, 95% CI: 24.1–26.1). No differences were found in mean calf circumference, whereas the shape of the results were the same as in models where the MDRD-formula was used (data not shown).

Discussion

In this study we showed that older fallers with an eGFR ≥ 90 ml/min had less muscle mass and strength than older fallers with a reduced eGFR. Handgrip strength was found to be 10% lower in participants with a normal eGFR than those with a reduced eGFR. No association was found between eGFR and mobility.

The consequences of kidney disease in older persons are frequently reported in studies.[5-9] However, few studies focussed on the significance of low s-creatinine and associated high eGFR. The implications of different eGFR values were investigated in a large study population of community-dwelling persons over the age of 50 in England.[22] Cox et al. found both low and high eGFR, assessed by the MDRD-formula, to predict mortality. Cardiovascular diseases were the leading causes of mortality in persons with reduced eGFR. Interestingly, persons in high eGFR groups died of respiratory and neoplastic causes. The hypothesis was that respiratory and neoplastic diseases cause cachexia and sarcopenia and the associated low s-creatinine values resulting in a high eGFR. These outcomes support our findings that high eGFR is associated with reduced muscle strength and mass. In a large study population of community-dwelling persons in Italy, a U-shaped relation was found between eGFR and physical performance in the oldest old group of persons ≥90 years.[14] Subjects in the highest eGFR band had the lowest handgrip strength and ADL values comparable with subjects with the

lowest eGFR. In our study, a similar trend was found across a wider and also younger age range. However, due to the fact that slightly different methods were used in our study, the results cannot be fully compared to the study of Montesanto et al.

There are several possible explanations for our results. In participants with higher eGFR, the observed smaller calf circumference and lesser handgrip strength, are likely manifestations of sarcopenia. Therefore, low s-creatinine resulting in high eGFR values might represent participants with less lean muscle mass and not necessarily with good filtration of s-creatinine in the kidney. Comparable results were also found using the CKD-EPI formula, although with less power most likely due to small shifts in numbers within eGFR categories. It should be noted that the MDRD-formula,[23] like most other eGFR formulae,[24] is validated in persons until the age of 70 years. Therefore, the MDRD-formula could be less reliable in older persons. This loss of reliability is the effect of changes in body composition with ageing, where, in general, muscle mass decreases.[25] We did not find any relation between eGFR and mobility; this might be due to the fact that mobility, although dependent on muscle mass, is determined by many factors such as balance, reaction time, eyesight and pain,[26,27] whereas handgrip strength and calf circumference are largely determined by muscle mass only.[21,28] Since the highest eGFR values, i.e. low s-creatinine values, are associated with the lowest muscle mass and strength, the accuracy of estimating kidney function in older persons with formulae based on s-creatinine should be seriously questioned.

The present study has several limitations. First, the cross-sectional design of the study limits the ability to draw conclusions about causality. Second, around 25 formulae are used for estimating GFR. We chose to use the MDRD and CKD-EPI-formula, the most used formulae nowadays.[18,29] It cannot be excluded that the use of another formula would have yielded (slightly) different results. Third, all participants attended the ED because of an accidental fall. Therefore, considering this characteristic, extrapolation to the general population is not possible. Our study also has strengths. First, we used data from a multicentre study, representing a heterogeneous group of older fallers throughout The Netherlands. Second, more than 500 participants in a relatively wide range of age were included in analyses. Third, since s-creatinine based eGFR is the most common way to evaluate kidney function in clinical practice, showing the implications of using this eGFR in older fallers, makes our outcomes clinically relevant.

In conclusion, we found that older fallers with a normal eGFR had

smaller calf circumference and up to 10% less handgrip strength than those with a reduced eGFR. This lower muscle mass is likely to lead to an overestimation of kidney function in such subjects. The findings of this study therefore support the current search for biomarkers independent of muscle mass to estimate kidney function in older persons. In clinical practice awareness of functional consequences of low s-creatinine and high eGFR values might be appropriate.

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Chapter 4

Kidney function and mental health

4.1

Kidney function, cognition and mood in late life

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Is kidney function associated with cognition and mood in late life? The Screening for CKD among Older People across Europe (SCOPE) study

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Abstract

Background: Chronic kidney disease (CKD), cognitive impairment and depression share common risk factors. Previous studies did not investigate the possible association between kidney function and cognitive and mood disorders in older persons in a broad range of kidney function. The present study explored associations between kidney function, cognition and mood in outpatients of 75 years and over.

Methods: Baseline data of 2252 participants of the SCOPE study, an international multicenter cohort observational study, were used in which community-dwelling persons of 75 years and over were enrolled to screen for CKD. Kidney function was estimated with the BIS1-eGFR equation, cognition was assessed with the Mini-Mental State Examination (MMSE) and mood with the Geriatric Depression Scale 15 items (GDS-15). Characteristics were compared across stages of CKD. Mean eGFR values were also compared across categories of MMSE (<24, 24-26, ≥27) and between groups with high and low score on the GDS-15 (>5/≤5).

Results: In total, 63% of the population had an eGFR <60mL/min. In advanced stages of CKD, participants were older and more often men than in earlier stages ($p<0.001$). Cardiovascular diseases and diabetes mellitus were more often found in those in advanced stages of CKD ($p<0.001$), and also cumulative comorbidity scores were higher than in those in earlier stages ($p<0.001$). Median MMSE was 29 in CKD stage 1-2 and 3, and 30 in CKD stage 4, whereas median GDS-15 score was 2 in all stages of CKD. Mean values of eGFR did not differ across categories of MMSE or between groups with high and low score on the GDS-15. Stratification for albuminuria did not change these results.

Conclusions: Older persons in more advanced stages of CKD did not have lower cognitive scores or higher rates of depressive symptoms than older persons in earlier stages. Future longitudinal studies might give information on the possible effect of kidney function on cognition and mood in late life.

Introduction

The prevalence of chronic kidney disease (CKD), cognitive impairment and cardiovascular conditions is growing as result of the aging population.[1-3] CKD, cognitive impairment and mood disorders can share common risk factors, such as hypertension and diabetes mellitus.[1,2,4,5] However, whether a decreased kidney function is associated with cognitive and mood disorders in the oldest old is not completely clear.

One of the potential mechanisms underlying the interaction between the kidney and the brain may include the presence of small vessel disease.[6] Persons with CKD have a higher burden of traditional vascular risk factors such as hypertension, diabetes mellitus and dyslipidaemia which are related to small vessel disease in the kidney.[6,7] The same risk factors are also associated with cerebral white matter lesions, microbleeds, lacunar infarcts and subcortical atrophy which are markers of cerebral small vessel disease increasing the risk of stroke, cognitive decline and dementia.[6,8-11] Moreover, the presence of small vessel disease may also underlie the association between CKD and depressive symptoms as result of a disruption of brain structures and connecting pathways in mood regulation.[12] Both cognition and mood may also be influenced by metabolic dysregulation and direct effects of lower glomerular filtration rate (GFR).[13-15]

Previous studies suggest that CKD and cognitive impairment might be correlated.[16] However, most studies did not focus on older patients in a broad range of GFR. In addition, in people in all stages of CKD, it was found that the prevalence of depressive symptoms ranged from 7 to 50 percent and depressive symptoms were more frequent in people in advanced stages of CKD than in people in earlier stages.[17] Nonetheless, most study populations were relatively small and studies did not focus on older persons. Therefore, the relationship between kidney function, cognition and mood in late life remains undetermined.

Since the identification of modifiable risk factors of cognitive and functional decline such as CKD is relevant, this study aimed to investigate the possible association between kidney function, cognition and mood in outpatients aged 75 years and over. We hypothesized that cognitive impairment and depressive symptoms would be more prevalent in advanced stages of CKD than in earlier stages and that persons with cognitive impairment and depressive symptoms would have lower levels of estimated GFR (eGFR) than persons without. Results of this study might provide important information in addition to known risk factors of adverse outcomes in persons with poor kidney function, cognitive impairment and depression.

These older persons might then benefit from improved therapeutic strategies when visiting their nephrologist, geriatrician or psychologist.

Methods

The present study was performed within the framework of the Screening for Chronic Kidney Disease among Older People across Europe (SCOPE) study. The SCOPE study (European Grant Agreement no. 436849), is a multicenter 2-year prospective cohort study involving patients older than 75 years attending outpatient services in participating institutions in Austria, Germany, Israel, Italy, The Netherlands, Poland and Spain. Methods of the SCOPE study have been extensively described elsewhere.[18] The primary objective of the SCOPE study was to investigate the currently available screening methods to identify community-dwelling older patients at risk of kidney disease. Patients with end-stage renal disease or dialysis, a history of solid organ or bone marrow transplantation, an active malignancy or metastatic cancer within 24 months prior to the visit, a life expectancy of less than 6 months, a severe cognitive impairment or patients unwilling to provide consent were ineligible for the SCOPE study. Participants were requested to sign a written informed consent before entering the study. The study protocol was approved by ethics committees at all participating institutions, and complies with the Declaration of Helsinki and Good Clinical Practice Guidelines. Only baseline data are used in the present study. Overall, 2,461 participants were initially enrolled in the study.

Kidney function

Serum creatinine (Isotope-Dilution Mass Spectrometry traceable) and albumin-to-creatinine ratio (ACR) were measured at local level by standard methods. Creatinine-based eGFR was calculated in mL/min/1.73m^2 using the Berlin Initiative Study 1 (BIS1) equation[19]: $3736 \times \text{creatinine}^{-0.87} \times \text{age}^{-0.95} \times 0.82$ (if woman).

The prevalence of stages of CKD was obtained using the Kidney Disease Improving Global Outcomes (KDIGO) guidelines[20]: eGFR ≥60, stage 1-2; 59.9-45, stage 3a; 44.9-30, stage 3b; and 15-30 mL/min/1.73 m^2, stage 4. Albuminuria was defined as a urine ACR ≥30 mg/g (≥3mg/mmol).[20]

Cognition

The cognitive functions were measured by the Mini-Mental State Examination (MMSE).[21] The MMSE is the most commonly administered psychometric screening tool of cognitive functioning and available and validated in all languages of participating countries. The score ranges from 0 to 30 points, whereas a score < 24 is frequently implemented as the cut-off value for abnormal and indicative

of cognitive impairment.[22] A meta-analysis of the accuracy of the MMSE in the detection of dementia and mild cognitive impairment showed a pooled sensitivity and specificity of 71.1% and 95.6% respectively in mixed specialist hospital settings.[23] A MMSE score of < 27 might identify those with a greater risk of cognitive dysfunction, especially in highly educated persons.[24] Therefore, in this study, we defined 3 categories based on the MMSE score: ≥ 27, 24-26 and <24.

Mood

The 15-item Geriatric Depression Scale-Short Form (GDS), available and validated in all languages of participating countries, was used to investigate depressive symptoms.[25] It focusses on functional and mood symptoms of depression. The score ranges from 0 to 15 points, with higher scores indicating more depressive symptomatology. The cut-off score most often used for this GDS version is 5 or 6.[26] A recent systematic review and meta-analysis showed a pooled sensitivity and specificity of 86% and 79%, respectively to detect depression in older persons.[27] In this study, a score > 5 was seen as suggestive of depressive symptoms.[25]

Other variables

Demographic data and socioeconomic status were documented. Information on alcohol use, smoking status, medical history and use of medication was collected and the cumulative illness rating scale for geriatrics (CIRS-G) was calculated in order to score the comorbidity burden by rating the severity of medical problems affecting various organ systems.[28] During the study visit, a comprehensive geriatric assessment (CGA) was performed including also information on basic activities of daily living (ADL) and instrumental ADL (IADL).[29,30]

Statistical analysis

Descriptive statistics were expressed as percentage for categorical variables and median and interquartile ranges (IQR) for continuous non-normally distributed variables. First, characteristics were compared across stages of CKD using the Chi square test and Kruskal Wallis test. Second, the correlation between age, MMSE and GDS was explored using the Spearman's correlation test. Third, mean eGFR values were compared across categories of cognition (MMSE<24, MMSE 24-26, MMSE≥27) using analysis of variance (ANOVA) in the total population and stratified for the presence of albuminuria. Then, mean eGFR values were also compared between participants with low and high score and GDS (score ≤5 and > 5) in the total population and stratified for the presence of albuminuria. A p-value of <0.05 was considered statistically significant.

Results

Overall, 2461 participants were initially enrolled in the SCOPE study. Of them, 209 participants had missing data on serum creatinine, MMSE and/or GDS leaving a final sample of 2252 participants to be included in the present study. Baseline characteristics are shown in **table 1**. Median age was 79.5 years (IQR 77.1-82.9), 55.7% were women and 24.5% were living alone. The majority of the population had hypertension (76.8%), 25.1% had diabetes mellitus, 17.2% had a history of malignancy and 16.6% had congestive heart failure. About 9% had a history of transient ischemic attack and 5.8% have had a stroke. The median total score on the CIRS-G was 8 (IQR 5-11). Only 0.6% of the participants had an eGFR ≥90mL/min/1.73m², 36.2% were classified as CKD stage 2, 38.3% had CKD stage 3A, 18.6% had CKD stage 3B and 6.3% had CKD stage 4. In 26.7% of the study population, albuminuria was present. Median score on the MMSE was 29 (IQR 27-30), 7.1% of the participants had a MMSE score < 24. Median score on the GDS was 2 (IQR 1-4), 14% of the participants had a GDS score > 5.

Characteristics stratified for stages of CKD (stage 1-2 merged) are presented in **table 2**. In advanced stages of CKD, participants were older, more often men and former smokers and had fewer years of education than in earlier stages. Comorbidities such as cardiovascular diseases (hypertension, atrial fibrillation, heart failure), diabetes mellitus and history of malignancy were more often found in those in advanced stages of CKD and the CIRS-G total score and severity index were higher than in those in earlier stages. In participants with CKD stage 1-2, 3a and 3b, median MMSE score was 29 (IQR 27-30), whereas median MMSE score in participants with CKD stage 4 was slightly higher with a median value of 30 (IQR 28-30). The proportion of participants with an MMSE score < 24 did not differ across stages of CKD, with a prevalence of 6.4% (stage 1-2), 7.7% (stage 3A), 9.3% (stage 3B) and 5% (stage 4). Median score on the GDS was the same in all stages of CKD, namely 2 (IQR 1-4). A GDS score > 5 was found in 13%, 15%, 14.1% and 14.2% of the participants in each stage of CKD, respectively.

A correlation was found between age and MMSE score (Spearman's rho -0.229, $p<0.001$) and age and GDS score (Spearman's rho 0.076, $p<0.001$).

Table 1. Baseline characteristics (n=2252)

Age, years	79.5 (77.1-82.9)
Women, %	55.7
Living alone, %	24.5
Education, years	11 (8-15)
Smoking status,	
Current smoker, %	4.4
Former smoker, %	39.5
Alcohol ≥ 1 unit a day, %	25.8
BMI, kg/m^2	27.3 (24.7-30.4)
ADL-independent, %	95.2
iADL-independent, n %	56
MMSE, score	29 (27-30)
MMSE < 24, %	7.1
GDS, score	2 (1-4)
GDS > 5, %	14
Hypertension, %	76.8
Diabetes mellitus, %	25.1
TIA, %	8.7
Stroke, %	5.8
Atrial fibrillation, %	15.3
COPD, %	11.8
Cancer, %	17.2
CHF, %	16.6
Vascular disease, %	12.6
CIRS-G, total score	8 (5-11)
CIRS-G, severity index	1.5 (1.2-1.8)
eGFR-BIS, mL/min/1.73 m^2	55.6 (45.1-64.4)
90 or more, %	0.6
60-89.9, %	36.2
45-59.9, %	38.3
30-44.9, %	18.6
30 or less, %	6.3
ACR, mg/g	11.2 (33.1-3.4)
Albuminuria, %	26.7

Notes: values are expressed as percentage or median (IQR) **Abbreviations**: BMI, Body Mass Index; (i)ADL, (instrumental) Activities of Daily Living; MMSE, Mini–Mental State Examination; GDS, Geriatric Depression Scale; TIA, Transient Ischemic Attack; COPD, Chronic Obstructive Pulmonary Disease; CHF, Congestive Heart Failure; CIRS-G, Cumulative Illness Rating Scale for Geriatrics; eGFR-BIS, Estimated Glomerular Filtration Rate; ACR, Albumin-to-Creatinine Ratio

Table 2. Baseline characteristics across stages of CKD

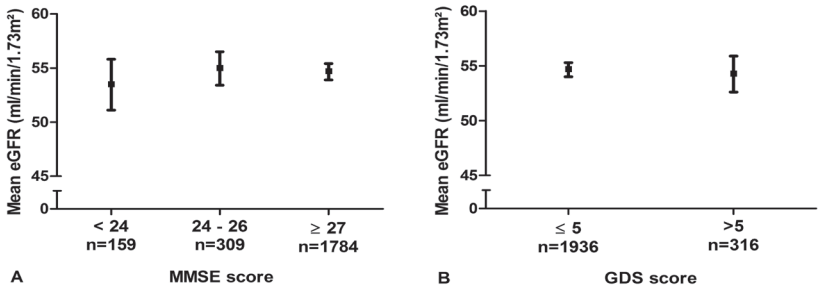
	Stages of CKD				
	Stage 1-2 (n=830)	**Stage 3A (n=862)**	**Stage 3B (n=419)**	**Stage 4 (n=141)**	**p-value**
Age, years	78.6 (76.5-81.1)	79.6 (77.3-83.1)	81 (78.2-85.1)	81 (77.7-84.8)	<0.001
Women, %	61.1	56.8	47.7	40.4	<0.001
Living alone, %	23.1	23.7	26	32.6	ns
Education, years	12 (8-16)	11.5 (8-15)	10 (8-13)	8 (8-12)	<0.001
Smoking status,					
Current smoker, %	5.5	3.6	4.1	3.5	ns
Former smoker, %	35.7	40	44.3	44.9	0.017
Alcohol ≥ 1 unit a day, %	26.6	24.2	27.2	24.8	ns
BMI, kg/m²	26.7 (24.2-29.6)	27.4 (24.8-30.6)	27.7 (25.3-31.0)	27.7 (24.9-31.4)	<0.001
ADL-independent, %	97.1	95.7	92.1	90.1	<0.001
iADL-independent, %	66	79.5	72.3	70.2	<0.001
MMSE, score	29 (27-30)	29 (27-30)	29 (27-30)	30 (28-30)	0.001
MMSE < 24, %	6.4	7.7	9.3	5	ns*
GDS, score	2 (1-4)	2 (1-4)	2 (1-4)	2 (1-4)	ns
GDS > 5, %	13	15	14.1	14.2	ns
Hypertension, %	66.3	77.6	89.3	96.5	<0.001
Diabetes mellitus, %	19.3	22.6	38.2	36.2	<0.001
TIA, %	8	8.4	11.2	7.8	ns
Stroke, %	4.3	5.7	7.9	9.2	0.023
Atrial fibrillation, %	9.3	16.6	22	22.7	<0.001
COPD, %	8.9	11.3	16.7	17.7	<0.001
Cancer, %	14.2	17.2	20.8	24.8	0.002
CHF, %	8.4	17.9	23.9	34.8	<0.001
Vascular disease, %	10.8	12.3	16.5	13.5	0.042
CIRS-G, total score	7 (4-10)	7 (5-10)	10 (7-14)	11.5 (8.3-15)	<0.001
CIRS-G, severity index	1.4 (1.2-1.7)	1.5 (1.2-1.8)	1.7 (1.3-1.9)	1.8 (1.5-2)	<0.001
eGFR-BIS, mL/min/1.73 m²	67.2 (63.6-73.1)	53.8 (50.2-56.9)	39.0 (34.9-42.3)	24 (20.5-27.1)	<0.001
ACR, mg/g	8.3 (1.9-18.7)	9.4 (3.3-24.3)	24.5 (7-121.8)	161 (53.7-1006)	<0.001
Albuminuria, %	14	20.8	45.6	81.6	<0.001

Notes: continuous variables are expressed as median (IQR). Continuous values were compared with the kruskal wallis test, categorical values were compared with the chi-quare test. *adjusted for age, sex and education **Abbreviations**: BMI, Body Mass Index; (i)ADL, (instrumental) Activities of Daily Living; MMSE, Mini–Mental State Examination; GDS, Geriatric Depression

Scale; TIA, Transient Ischemic Attack; COPD, Chronic Obstructive Pulmonary Disease; CHF, Congestive Heart Failure; CIRS-G, Cumulative Illness Rating Scale for Geriatrics; eGFR-BIS, Estimated Glomerular Filtration Rate; ACR, Albumin-to-Creatinine Ratio

Figure 1A shows mean values of eGFR across predefined categories of MMSE. One hundred and fifty nine participants had a MMSE score < 24, 309 had a MMSE score of 24-26 and 1784 participants had a MMSE score ≥ 27. Mean eGFR values did not differ across categories; mean values and 95% CI were 53.5 (51.1-55.8), 55 (53.4-56.5) and 54.7 (53.9-55.4) mL/min/1.73m^2, respectively. Mean values of eGFR did not differ between participants with a low (n=1936) and high score (n=316) on the GDS; mean values and 95% CI were 54.7 (54-55.3) and 54.3 (52.6-55.9) mL/min/1.73m^2, respectively. Results are shown in **figure 1B.**

Figure 1. Mean eGFR values across categories of MMSE (A) and in participants with low and high score on the GDS (B)

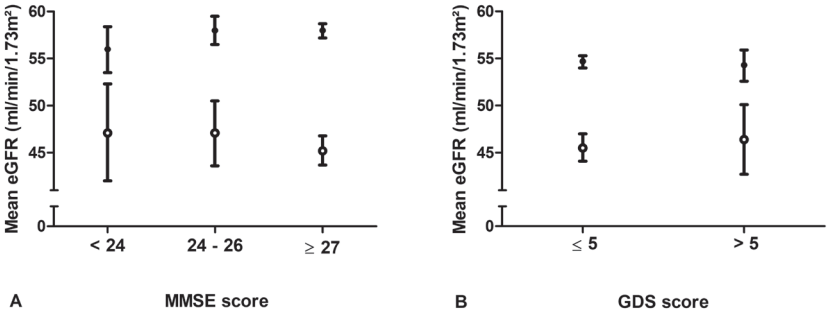


Notes: Squares represent mean values, bars represent 95% CI. **Abbreviations**: eGFR, estimated glomerular filtration rate; MMSE, mini-mental state examination; GDS, geriatric depression scale

In **figure 2A** mean values of eGFR in participants with and without albuminuria are shown across categories of MMSE. In participants *with* albuminuria, 45 participants had a MMSE score < 24, 86 had a MMSE score of 24-26 and 470 participants scored ≥ 27. Mean values of eGFR did not differ across categories; mean values and 95% CI were 47.1 (42-52.3), 47.1 (43.6-50.5) and 45.2 (43.7-46.8) mL/min/1.73m^2, respectively. In participants *without* albuminuria, the number of participants in the same categories were 114, 223 and 1314, respectively. Mean eGFR values did not differ across categories; mean values and 95% CI were 56 (53.5-58.4), 58 (56.5-59.5) and 58 (57.2-58.7) mL/min/1.73m^2, respectively. **Figure 2B** shows mean values of eGFR in participants with and without albuminuria in groups with a low and high

score on the GDS. In participants *with* albuminuria, mean values of eGFR did not differ between participants with a low (n=517) and high score (n=84); mean values and 95% CI were 45.5 (44.1-47) and 46.4 (42.7-50.1) mL/min/1.73m^2. In participants *without* albuminuria, mean values of eGFR did also not differ between groups. Mean eGFR was 58 mL/min/1.73m^2 (95 %CI 57.3-58.7) in participants with a low score (n=1419) and 57.1 mL/min/1.73m^2 (95% CI 55.4-58.8) in participants with a high score on the GDS (n=232).

Figure 2. Mean eGFR values across categories of MMSE (A) and in participants with low and high score on the GDS (B) stratified for albuminuria



Notes: Open dots represent mean values in participants *with* albuminuria, closed dots represent mean values in participants *without* albuminuria, bars represent corresponding 95% CI. *Albuminuria*: n=45, n=86, n=470 from lowest to highest category of MMSE score; participants per category GDS, n=517 (low), n=84 (high). *No albuminuria*: n=114, n=223, n=1314 from lowest to highest category of MMSE score; participants per category GDS, n=1419 (low), n=232 (high). **Abbreviations**: eGFR, estimated glomerular filtration rate; MMSE, mini-mental state examination; GDS, geriatric depression scale

Discussion

Within the framework of the SCOPE study, a large observational cohort including persons aged 75 years and older, we found that early or advanced kidney disease seemed to have no negative influence on cognition or mood in late life. Also, no differences in kidney function were observed in participants with and without cognitive impairment and in those with and without depressive symptoms. The presence of albuminuria did not influence our results.

We found that participants in progressively later stages of CKD were more likely to have risk factors for (cerebral) small vessel disease, such as hypertension and diabetes mellitus, than participants in earlier stages.[6] Also other conditions closely linked to (cerebral) small vessel disease were more

prevalent in those in advanced stages of CKD than in those in early stages, such as atrial fibrillation, congestive heart failure and history of stroke.[31-33] The presence of these risk factors is suggested to mediate associations between the kidney and the brain,[6] however, we were not able to confirm our prior hypothesis. Previous cross-sectional studies investigated the association between CKD and cognitive impairment in older persons. Most studies investigated this topic in specific populations, such as women with coronary artery disease [34] or only men.[35] In a large sample in the United States of America, it was found that lower levels of kidney function were associated with an increased prevalence of cognitive impairment, assessed with a six-item cognitive screening.[36] In this study, kidney function was assessed by the Modification of Diet in Renal Disease Study (MDRD) equation, an equation that is less reliable than the BIS1 equation in older persons,[19] therefore, it is possible that the method used to assess eGFR might have induced bias.

To the best of our knowledge, this is the first cross-sectional study investigating the possible association between kidney function and depressive symptoms in a large study population of community dwelling persons in late life within a broad range of eGFR. In a recent meta-analysis, lower kidney function was associated with higher prevalence of depression.[17] However, only two studies investigated persons with a mean age above 70 years.[37,38] In a Korean population-based cohort study including almost 1000 participants aged 65 years and older, it was found that an eGFR <45 mL/min was associated with poor physical quality of life but not with mental health.[37] In older patients admitted with congestive heart failure,[38] depression was more prevalent among those with than those without severe CKD (<30 vs ≥ 30mL/min). However, since this is a very specific study population, these results cannot be completely compared to our results. Both previous studies used different tools to investigate depressive symptoms:[37,38] the Short Form 36 (SF-36) health survey and the Beck Depression Inventory (BDI), respectively. Therefore it cannot be excluded that the different methods used might have affected the reported results.

A possible explanation for our findings could lie in the selection of our study population. Eligible persons were community-dwelling, 75 years and older and referred to the outpatient clinics of participating institutions, which might have resulted in a ceiling effect. Almost all participants were under regular medical monitoring at outpatient services, which might have resulted in a better control of cardiovascular risk factors. Therefore, the kidney function and its mediators might no longer be related on the outcomes of interest. One might argue whether kidney function is relevant for the brain (cognition and mood) in the outpatient with multimorbidity in late life or whether all

comorbidities in the older outpatient equally contribute to (disturbances in) cognition and mood.

Some limitations of the study need to be discussed. First, the cross sectional design does not allow to investigate causal inferences. Second, persons with relatively good cognition and mood are more likely to volunteer to participate in this study with an extensive protocol, which might have affected our results. Third, persons with end stage renal disease were not included in this study. It might be speculated that mood and cognition are not yet affected in stages 1-4 of CKD due to the asymptomatic nature of the disease. Fourth, there might be a survival bias in which individuals with CKD in advanced stages and possibly cognitive impairment and/or depressive symptoms already died and therefore were not included. Fifth, our study did not include a direct measurement of GFR, however, we used the eGFR-BIS1 equation which is one of the most reliable creatinine-based equations at older age.[19] Eventually, we used the MMSE to assess cognition and the GDS-15 to assess depressive symptoms. We cannot exclude that performing a complete neuropsychological evaluation or using other screening tools might have given different results and might be able to confirm our hypotheses. Ideally, such a complete neuropsychological evaluation can be used in future studies.

This study also has strengths. We have studied a large real-world population of older outpatients in 7 different countries across Europe, therefore our findings can be extrapolated to a large population of European citizens. Second, information on kidney function, cognition and mood were obtained systematically in all participating centers, which makes the results highly reliable.

Conclusion

In community-dwelling older persons in more advanced stages of CKD, cognitive impairment and depressive symptoms were not more prevalent than in older persons without or in earlier stages of CKD. Kidney function was comparable in those with and without any signs of cognitive or mood disorders. The identification of CKD as modifiable risk factor for cognitive impairment and depressive symptoms in late life might be relevant in order to optimize therapeutic strategies. Longitudinal studies might give additional information on the possible effect of kidney function on mental health in late life. An ongoing prospective SCOPE study is now conducted to investigate effects of CKD progression on these variables.

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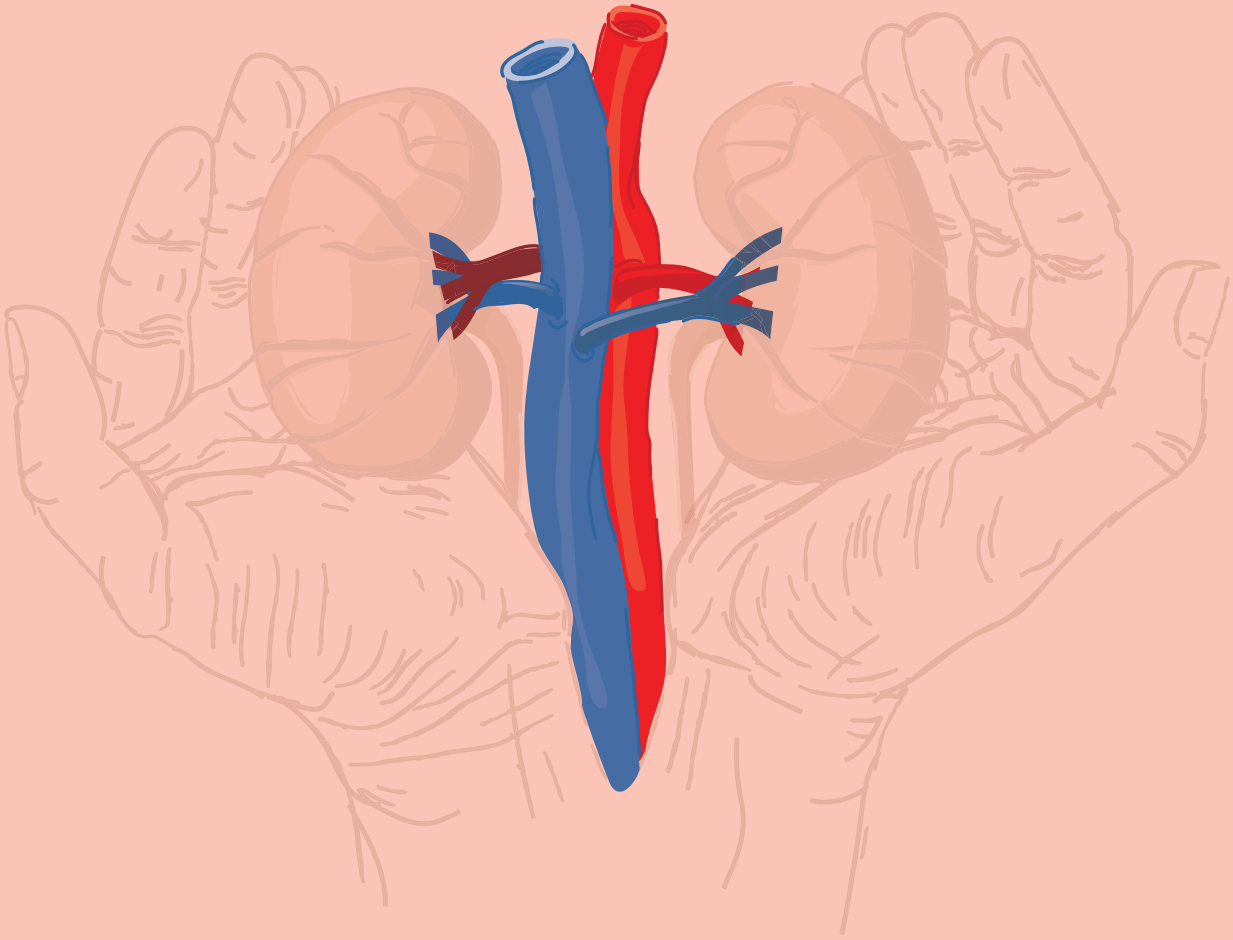
Part II. Vascular aging



Chapter 5

Arterial stiffness, physical and mental health

5.1
Links between vascular, bone and muscle aging

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Unraveling the links underlying arterial stiffness, bone demineralization and muscle loss

Hypertension, Sept. 2020

Abstract

The effects of elevated arterial stiffness on cardiovascular outcomes are widely studied, whereas the relation to non-cardiovascular outcomes relevant to older persons, such as the effect on bones and muscles, is less well established. Arterial stiffness, bone demineralization and muscle loss are all age-related processes with common risk factors, however, whether these are just parallel age-related alterations or whether these processes share common pathways is not yet understood.

In this review, we outline previous literature using different assessments of arterial stiffness in various populations across the world in order to produce a comprehensive overview. While there are many studies showing an association between arterial stiffness and loss of bone and muscle, the majority are cross-sectional and there is limited longitudinal evidence to justify causal conclusions. We also give an in-depth review of hypotheses and possible mechanisms which may underlie these associations including hormone dysregulation, impaired glucose metabolism and inflammation. This narrative review highlights the associations between vessels, bones and muscles with aging, offering insights into possible shared pathways.

Introduction

Aging brings a variety of molecular, physiological and organ-level changes. At the cellular level genomic instability, cell senescence and mitochondrial dysfunction are amongst its hallmarks,[1] while alterations in hormone levels and increased levels of cytokines have led to the concept of aging as a low grade inflammatory state.[2] Arterial stiffness is an age-related process which can be accelerated by several conditions such as hypertension, diabetes mellitus, the metabolic syndrome and chronic inflammation.[3-8] Elevated arterial stiffness leads to changes of the blood pressure profile and an increased pulsatile pressure and flow load, which can affect target organs, such as the heart, brain and kidneys[9-11] and therefore, increases the risk of cardiovascular morbidity and mortality.[12] Bones and muscles also deteriorate with age;[13, 14] In the aging bone, the balance between bone resorption and bone formation has changed as result of an increase in bone-resorbing osteoclasts and pro-osteoclastogenic interleukins, subsequently leading to loss of bone tissue and reduced mineral content with aging.[15] The loss of skeletal muscle occurs universally with age and is characterized by decreased quantity and quality of muscle leading to functional impairment. Animal models have shown changes in protein synthesis and breakdown, mitochondrial dysfunction and elevated reactive oxidant species (ROS) with fatty and fibrotic changes.[16] These age-related changes in the bones and muscles appear to share common risk factors with the process of vascular aging.[17-20] We have shown in a cohort of older men that the combination of high lean mass and low fat mass was associated with the best arterial and bone profiles i.e. the lowest arterial stiffness and the highest bone mineral density (BMD).[19] Hitherto, there is a paucity of studies investigating whether arterial stiffness and both bone and muscle deterioration are just parallel age-related processes or whether these processes share common pathways and directly influence one another.

In this narrative review, we give an overview of the literature in order to clarify the possible relationship between arterial stiffness and age-related non-cardiovascular outcomes, namely bone demineralization and muscle loss. We mainly focus on the clinical and epidemiological studies exploring the associations of arterial stiffness with manifestations of bone and muscle aging before concluding with a more in-depth overview of hypotheses underlying these associations including pre-clinical studies to describe potential mechanisms.

Methodological approaches

Arterial stiffness

In most of the clinical studies, arterial stiffness has been assessed using pulse wave velocity (PWV) either the brachial-ankle PWV (baPWV), an indicator of global arterial stiffness, or the carotid-femoral PWV (cfPWV) which assesses stiffness of the central arteries.[21] In some studies, arterial stiffness was assessed with other validated methods, such as central or peripheral pulse pressure (cPP or pPP) and cardio-ankle vascular index (CAVI).[22]

Bone Mineral Density (BMD)

BMD has been assessed with Dual-energy X-ray absorptiometry (DEXA) scans in most studies, the gold standard for BMD quantification.[23] Some studies have used computed tomography (CT) scans to assess BMD, whereas other studies have used the Achilles quantitative ultrasound system (QUS) which measures the speed of sound and the frequency-dependent broadband ultrasound attenuation (BUA). Levels of bone alkaline phosphatase (BAP), a sensitive and reliable indicator of bone metabolism,[24] were also used to assess bone (de)mineralization.

Muscle mass and function

Muscle mass was assessed in most studies using CT/DEXA imaging or Bioimpedance Analysis (BIA). These modalities for determining muscle quantity are frequently combined with measures of function such as grip strength.[25]

Results of the clinical and epidemiological studies

A. Arterial stiffness and BMD

Table 1 gives an overview on studies included in this study investigating associations between arterial stiffness and BMD. The baPWV has been used as marker of arterial stiffness in predominately Asian populations for studying the relationship between arterial stiffness and BMD. In hypertensive men in China (mean age 67.7±9.6 years),[26] baPWV was inversely correlated with femoral neck (FN) BMD in univariate and multivariate analyses, whereas no association was found in age-matched non-hypertensive men. The authors describe that this difference between groups may lie in excessive urinary calcium excretion in persons with hypertension which could decrease serum calcium, lead to secondary hyperparathyroidism and thus increase the calcium release from the bone into the blood. In Japanese women,

lumbar spine (LS) BMD and baPWV were negatively correlated, whereas a positive correlation was found between BAP levels and baPWV.[27] Although correlations were the strongest in subjects with normal body mass index and blood pressure, no correlations were found in adjusted analysis. Within the framework of the JPOS-study, one of the few longitudinal studies, it was investigated whether BMD had a role in the development of increased baPWV in Japanese middle-aged and elderly women during 10-years of follow-up.[28] Participants with increased arterial stiffness after 10 years showed lower BMD values at baseline than participants with a less pronounced increase in arterial stiffness. Low BMD at the level of the total hip (TH) remained different between groups after additional adjustments, suggesting an independent role of BMD in determining elevated arterial stiffness.

cfPWV has been shown to be predictive for morbidity, progression of end-organ diseases and even mortality.[29, 30] The possible association between cfPWV and BMD has also been previously investigated. Within the framework of the Baltimore longitudinal study of aging, a prospective study of normative aging in healthy volunteers,[31] no correlation was found between BMD and cfPWV in men, whereas, in women, an inverse correlation was found between BMD and cfPWV. This sex-specific relationship suggests that mediators of this association are probably differentially regulated between men and women. Several studies have investigated the possible relationship between cfPWV and BMD in patients with CKD or on dialysis,[32-34] populations that are known to have increased vascular calcification and arterial stiffness.[35, 36] In patients with CKD, a negative correlation was found between vascular calcification and BMD scores in the femoral region, whereas no association was found between cfPWV and BMD.[32] However, the small sample size might have affected the results. In a study of hemodialysis patients, using quantitative CT scan (QCT) to assess BMD, participants with progressively lower BMD were more likely to have a PWV≥9 m/s, even after adjustments, which supports the concept of a close interaction of vascular and bone disease in dialysis patients.[34] The authors suggest that mineral metabolism and alterations in bone remodeling might be factors influencing vascular properties in this specific patient group, however since this was a cross-sectional analysis, no conclusion can be drawn about causality.

To the best of our knowledge, only one study investigated the effect of arterial stiffness on bone metabolism during follow-up;[37] in a hyperhomocysteinemic population, arterial stiffness measured as cfPWV and cPP did not have an effect on changes in BMD within 2 years. The authors hypothesized that hyperhomocysteinemia, which is associated with both cardiovascular disease and osteoporosis, could be part of a common pathway

in the association between arterial stiffness and bone demineralization, however, they were not able to confirm this hypothesis.

In a large population-based cohort study in Canada, individuals between 40-70 years old were included in which it was observed that levels of cPP and pPP were inversely associated with BMD values.[38] Associations remained significant in multivariate analysis, implying an independent association between these parameters which further suggests that arterial stiffness and low BMD are both part of an accelerated aging process.

Only one study explored the possible association between BMD and CAVI, a blood pressure-independent parameter of overall vascular stiffness;[39] in middle-aged and older Chinese inpatients, FN BMD and TH BMD were negatively correlated with CAVI values. After adjusting for several confounders, this correlation was still present between TH BMD and CAVI values. The authors state that there might be an interaction between bone and vascular metabolic mechanisms, such as changes in hormone levels and an increase in proinflammatory cytokines with aging.

There seems to be increasing evidence linking arterial stiffness to bone demineralization, however, results are controversial. Associations may be strongly dependent on the tools which were used to assess arterial stiffness and BMD and on the study population in which associations were studied. Most studies have limited sample size, which limits the possibility of adjustment for potential confounders and therefore of investigating a potential independent association. Also, only a few longitudinal studies were conducted to establish causality. Therefore, the question whether these processes share common pathways or whether the same risk factors contribute to these age-related alterations still remains.

B. Arterial stiffness and muscle mass and function

The baPWV has been the most commonly used tool in studies of muscle function and arterial stiffness, with large cross-sectional studies finding significant associations across predominately Asian populations.[40-42] In **table 2**, an overview is presented on previous studies investigating associations between arterial stiffness and muscle mass and function. The J-SHIPP study explored the relationship of arterial stiffness with sarcopenia, finding the strongest association with baPWV compared to central pulse pressure[43] and suggesting that sarcopenic obesity poses the biggest risk[44], although neither study presents a postulated mechanism. Similarly, using baPWV in community-dwelling Chinese older adults, Zhang found an association between arterial stiffness and sarcopenia according to the Asian Working Group on Sarcopenia

definition, with an increase of 11% in the odds of being sarcopenic per 1 standard deviation increase in baPWV.[45] In this study, the relationship was only significant in men after adjustment, but not in women, suggesting that testosterone may be an important factor in the underlying mechanism, as sex discrepancies have been a common theme in the investigation of sarcopenia.

There have been relatively few studies using the gold standard tool for assessing arterial stiffness, cfPWV. The Health ABC study demonstrated an independent negative association of cfPWV with muscle parameters in men and white women based on CT and DEXA assessments.[46] The authors proposed that reduction in blood flow to limbs due to stiff arteries led to muscle decline, suggesting an additional role for microvascular dysfunction. Meanwhile, a small study of 54 patients in Portugal found significant inverse correlations between aortic PWV with both quantity (total lean mass) and quality of muscle (handgrip strength and sit-to-stand test).[47] However, the full results have yet to be published, and it is unclear if these correlations remain significant after adjustment for confounders such as age and blood pressure. A meta-analysis of cross-sectional studies found a pooled negative correlation of muscle mass and PWV, although this included studies from varying geographical locations, age ranges (from mean age 23 in one study to 74 in another) and using different methods of assessing both muscle mass and arterial stiffness (baPWV, cfPWV and carotid-ankle PWV).[48] They offer a variety of possible mechanisms including oxidative stress and insulin dysregulation as common pathways in muscle loss and arterial stiffening.

Our UK study in older adults found a much stronger association of sarcopenia with the CAVI compared to cfPWV, showing significant correlations for CAVI with all criteria for defining sarcopenia, which were stronger in women than in men, again suggesting a role for sex hormones in mediating these changes.[49] Similar findings were seen in a smaller Japanese study, showing a negative correlation of CAVI with skeletal muscle index (SMI) in both men and women.[50] A Korean study of middle aged men found that higher grade muscle mass deficit on BIA was associated with increased odds ratio (OR) for being in a high CAVI group.[51] However, the OR became non-significant after full adjustment for confounders, and the binary assessment of CAVI as low or high coupled with low age range of the sample (40-64 years) limits its comparability. In a Japanese study, CAVI was found to be associated with hand-grip strength in non-hypertensive women, but not in hypertensive women or men.[42] Finally, Xue found a significant association between CAVI and frailty as defined by Fried's frailty index in geriatric inpatients on multivariate regression, stating that arterial stiffness contributes to frailty on multiple levels.[52]

A study of post-menopausal women showed higher baPWV in women with reduced muscle indices compared to normal.[53] This study also suggested an exaggerated BP response to post-exercise muscle ischaemia in the sarcopenic group with menopause triggering an enhanced level of metaboreflex activation. Ochi found a significant negative association between carotid intimal thickness and sarcopenia in men, and showed baPWV as a modest predictor of sarcopenia in addition to age, height, low physical activity, free testosterone level, again suggesting sex differences which may result from different hormonal constitutions.[54]

Thus, while the evidence linking sarcopenia with arterial stiffness is irrefutable, the best method for assessing this relationship is, as yet, unclear. Both baPWV and CAVI include muscular and elastic arteries, rather than solely central aortic stiffness, thus may be better tools to evaluate the universal loss of muscle tissue in sarcopenia and highlight its cardiovascular repercussions.

Table 1. Literature investigating associations between arterial stiffness and bone mineral density (BMD)

Authors	Design	Population	Country	Size	Age, years (SD)	Arterial stiffness	BMD1	Associations in multivariate analyses	Covariates (if applicable)
Li XS 2016[26]	Cross-sectional	Hypertensive men (HTN) and control (no-HTN)	China	708	68.1 (9.5)	baPWV	*DEXA: LS,FN	*HTN:* baPWV-FN **+++**	Age, BMI, smoking, alcohol use, physical activity, SBP, DBP, DM, glucose, eGFR, cholesterol, triglycerides, antihypertensive medications, statins
Mikumo M 2009[27]	Cross-sectional	Postmenopausal women	Japan	143	57.9 (8.3)	*baPWV	DEXA: LS Blood: BAP levels	No associations	Age, height, SBP
Jaalkhorol M 2019[28]	Longitudinal (10 years)	Population-based	Japan	446	62.6 (7.9)	*baPWV	DEXA: LS, FN, TH	TH – baPWV **+**	baseline baPWV, Age, SBP
Giallauria F 2011[31]	Cross-sectional	Healthy adults	USA	633	66.5 (12.6)	*cfPWV	CT: cCSA	*Women:* cCSA-cfPWV **+**	Age, obesity, alcohol use, physical activity, MAP, menopause status, total estradiol, eGFR, calcium, antihypertensive medications, diuretics, HRT
Toussaint ND 2008[32]	Cross-sectional	Patients with CKD	Australia	47	64.5 (range 26-80)	cfPWV	*DEXA: LS,FN	No associations	Not described

Raggi P 2008[34]	Cross-sectional	Hemodialysis patients	USA	110	56.1 (14.5)	*cfPWV	DEXA: LS CT: TS	TS – cfPWV +	Age, sex, race, BMI, smoking, DM, duration of dialysis
van Dijk SC 2016[37]	Cross-sectional Longitudinal (2 years)	Patients with hyper-homocysteinemia	The Netherlands	519	72.3 (5.4)	cfPWV, cPP	*DEXA: LS, FN QUS: BUA calcaneus	No associations	Baseline BMD, Age, sex, BMI, smoking, alcohol use, hypertension, DM, cholesterol, eGFR, study center, treatment
El-Bikai R 2015[38]	Cross-sectional	Population-based	Canada	20.007	Range 40-70	cPP, pPP	*QUS: BUA calcaneus	cPP – BUA + pPP – BUA +	Age, sex, BMI, anti-osteoporotic and hypertensive medications
Zhang M 2019[39]	Cross-sectional	Geriatric inpatients	China	580	64.9 (11.4)	*CAVI	DEXA: LS,FN,TH	TH – CAVI ++	Age, sex, BMI, smoking, SBP, DM, CVD, HDL, uric acid, fibrinogen, eGFR

Abbreviations: BAP, bone alkaline phosphatase; baPWV, brachial-ankle pulse wave velocity; BMI, body mass index; BUA, broadband ultrasound attenuation; CAVI, cardio-ankle vascular index; cCSA, cross-sectional cortical bone area; cfPWV, carotic-femoral pulse wave velocity; cPP, central pulse pressure; CVD, cardiovascular diseases; DEXA, dual energy x-ray absorptiometry; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; FN, femoral neck; HDL, high density lipoprotein, HRT, hormone replacement therapy; LS, lumbar spine; MAP, mean arterial pressure, pPP, peripheral pulse pressure; SBP, systolic blood pressure; TH, total hip; TS, thoracic spine; QUS, quantative ultrasound **Notes**: * marks dependent variable, **+++** = p values < 0.001, **++** = p value < 0.01, **+** = p-value < 0.05

Table 2. Literature investigating associations between arterial stiffness and muscle loss

Authors	Design	Sample	Country	Size	Age, years (SD)	Arterial Stiffness	Muscle index	Associations in multivariate analyses	Covariates (if applicable)
Kim TN 2011[40]	Cross-sectional	Apparently healthy adults	Korea	510	53.6 (15.6)	*baPWV	CT+DEXA: MFR	MFR – baPWV +++	Age, sex, BMI, WC, smoking, alcohol use, physical activity, SBP, DBP, glucose, TG, HDL, cholesterol, ASM/height^2
Kohara K 2017[41]	Cross-sectional	Healthy adults	Japan	1518	67.9 (6.8)	baPWV	*CT: thigh CSA BIA: SMM	*Analysis of variance:* baPWV – CSA +++ baPWV – SMM +++ *No multivariate analysis*	-
Yamanashi H 2018 [42]	Cross-sectional	Community-dwelling adults	India (I) Japan (J)	I: 1501 J: 3136	I: 50.0 (6.8) J: 70.0 (9.7)	I: baPWV J: CAVI	*HGS	*Men:* I: baPWV – HGS + *Non-hypertensive women:* I: baPWV – HGS + J: CAVI – HGS +	I: Age, height, BMI, SBP, albumin, ischemic heart disease, smoking, daily energy intake, alcohol use, antihypertensive medication J: Age, height, BMI, DBP, cholesterol, HDL, eGFR, stroke, alcohol use, antihypertensive medication

Kohara K 2012[43]	Cross-sectional	Healthy adults	Japan	1024	66.2 (8.7)	*baPWV	CT: thigh CSA, VFA	VFA – baPWV **+++** *Men:* CSA – baPWV **+**	Age, height, weight, BP, cholesterol, HDL, TG, glucose, CRP, smoking, physical activity, antihypertensive medication, leptin
Zhang L 2019[45]	Cross-sectional	Community-dwelling adults	China	1002	72.3 (5.2)	baPWV	*BIA: ASMI HGS	baPWV – ASMI **++** baPWV – HGS **+**	Age, sex, BMI, smoking, alcohol use, BP, HR, cholesterol/HDL, HbA1C, CIMT, hypertension, DM, stroke
Abbatecola AM 2012[46]	Cross-sectional Longitudinal (6 years)	Community-based	USA	2272	73.7 (3)	cfPWV	*CT: thigh CSA DEXA: ALM to calculate sarcopenic index	*Men:* cfPWV – sarcopenic index **++** *White women:* cfPWV – sarcopenic index **+**	Age, BMI, SBP, PAD, CHD, IL-6, physical activity, fat mass, site, time, time^2, race, PWV-race interaction
Rodriguez AJ 2017[48]	Meta-analysis	Various	Various	8558	*Mean age ranges:* 23-73.6	Various: cfPWV, baPWV	Various: CT, DEXA, BIA	*Pooled results:* PWV – muscle tissue **+++**	Various (meta-analysis)
Kirkham FA 2018[49]	Cross-sectional	Healthy adults and adults with cardiovascular risk factors	UK	366	70.8 (7.9)	CAVI, crPWV, cfPWV	*BIA: SMI HGS	*Women*: CAVI – SMI **+++**	Age, sex, DM, dyslipidemia, hypertension, ischemic heart disease, BP, smoking
Sampaio RA 2014[50]	Cross-sectional	Healthy adults	Japan	175	> 65	CAVI	*BIA: SMI	CAVI – SMI **+**	Age, sex, BMI, MNA, grip strength, walking speed

Im IJ 2017[51]	Cross-sectional	Community dwelling men	Korea	3356	48.9 (6.1)	*CAVI	BIA: MMD	MMD – CAVI +	Age, BMI, MAP, HR, TG, GGT, leucocytes, HOMA-IR, alcohol use, smoking, regular exercise, medication
Xue Q 2019[52]	Cross-sectional	Geriatric inpatients	China	171	78.5 (9.2)	CAVI	*HGS and gait speed to determine frailty	CAVI – Frailty +++	Age, BMI, ADL, ABI, Hb, Albumin, eGFR, CRP, LDL
Figueroa A 2016[53]	Cross-sectional	Post-menopausal women	USA	36	58 (4)	*baPWV	DEXA: ASMI	*T test:* ASMI – baPWV ++ *No multivariate analysis*	-
Ochi M 2010[54]	Cross-sectional	Apparently healthy adults	Japan	496	Middle aged	baPWV	*CT: thigh CSA	*Men:* baPWV – CSA ++	Age, height, SBP, cholesterol, HDL, TG, glucose, insulin, CRP, testosterone, antihypertensive medication, smoking, physical activity, alcohol, CIMT

Abbreviations: ABI, ankle brachial index; ADL, activities of daily living; ALM, appendicular lean mass; ASM(I), appendicular skeletal muscle mass (index); baPWV, brachial-ankle pulse wave velocity; BIA, bioelectrical impendence analysis; BMI, body mass index; BP, blood pressure, CAVI, cardio-ankle vascular index; cfPWV, carotid-femoral pulse wave velocity; CHD, cardiac heart disease; CIMT, carotid intima-media thickness, CRP, c-reactive protein; crPWV, carotid-radial pulse wave velocity; CSA, cross-sectional area; CT, computerized tomography; DEXA, dual energy x-ray absorptiometry; DBP, diastolic blood pressure; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; GGT, gamma-glutamyl transferase; Hb(A1c), hemoglobin(A1c); HDL, high density lipoprotein; HGS, handgrip strength; HOMA-IR, homeostatic model assessment for insulin resistance; HR, heart rate; IL-6, interleukin-6; LDL, low density lipoprotein; MAP, mean arterial pressure; MFR, muscle-fat ratio; MMD, muscle mass deficit; MNA, mini-nutritional assessment; PAD, peripheral artery disease; SMI, skeletal mass index; SMM, skeletal muscle mass; SPB, systolic blood pressure; T2DM, type 2 diabetes mellitus; TG, triglycerides; VFA, visceral fat area; WC, waist circumference; **Notes**: *marks dependent variable, **+++** = p values < 0.001, **++** = p value < 0.01, **+** = p-value < 0.05

Possible mechanisms

A. Arterial stiffness and BMD

There is no clear consensus on how the processes of arterial stiffness and bone demineralization interact, however there are several hypotheses that link both processes. Large population-based studies have found that arterial calcifications changes arterial structural and functional properties and that those with the greatest bone loss have the most severe progression of aortic calcification.[55, 56] Non-collagenous proteins are important in the process of bone mineralization and have also been found in calcification of the arteries,[57] suggesting that vascular mineralization and bone demineralization might have a common etiology. We outline the commonly described hypotheses in **figure 1** and below, including inflammation, hormonal dysregulation and impaired glucose metabolism.

Inflammation

The immunosenescence in aging results in remodeling of specific cell types and more importantly seems to induce a permanent state of chronic inflammation.[58] Chronic inflammation and oxidative stress increase with age and might underlie both changes in blood vessel structure and bone mineralization.[59] Levels of C-reactive protein and pro-inflammatory cytokines, such as interleukins and TNF-alpha are associated with elevated arterial stiffness,[60, 61] possibly due to their role in endothelial dysfunction by inhibiting endothelium-dependent vasodilatation. The same cytokines have been shown to increase osteoclast activity and thus bone resportion.[62] Inflammatory cytokines increase the level of RANKL, which activates osteoclasts, and cause bone resorption and calcium to transfer from bone to the vessels wall.[63] RANKL is usually undetectable in normal vasculature, whereas significant amounts of RANKL have been detected in atherosclerotic tissue inducing angiogenesis and stimulating osteogenic differentiation and calcification in vascular smooth muscle cells.

Hormonal dysregulation

Parathyroid hormone (PTH) has an important role in regulating calcium-phosphate metabolism by stimulating osteoclastogenesis through activation of the osteoblastic cell, resulting in resorption of the bone matrix and secondary increase of serum calcium.[64] PTH has also been linked to vascular calcification, which might be a direct effect of PTH or a more indirect result of hyperphosphatemia or hypercalciemia.[65] Directly, PTH

induces an acute vasodilatory response of the vasculature by binding on the PTH receptors on the vascular smooth muscle cells (VSMCs).[66] Moreover, PTH is found to be a significant prosclerotic factor in these VSMCs, since it has a direct effect on production and reorganization of collagen. More indirectly, hyperphosphatemia increases activity of sodium-dependent cotransporters, which upregulates genes involved in matrix mineralization.[67] Both hyperphosphatemia and hypercalcemia can increase the release of matrix vesicles resulting in deposition of calcium phosphate mineral in the extracellular matrix, increasing vascular calcification and arterial stiffnening.[68] Estrogen also has an important role in vascular health and bone metabolism. Estrogen has protective effects on the cardiovascular system by altering serum lipid concentrations;[69] estrogen can lower phosphorus levels and reduce the production of inflammatory cytokines.[70, 71] Moreover, estrogen receptors are found on both vascular endothelial and smooth muscle cells, osteoblasts and osteoclasts,[72-74] which suggests a direct effect of estrogen on vascular structures and bone cells as well. Therefore, estrogen might be a mediator in the sex-specific association between arterial stiffness and bone demineralization.[31]

Impaired glucose metabolism

Changes in insulin regulation and glucose metabolism may be another underlying factor in both processes. Diabetes mellitus, impaired glucose regulation and metabolic syndrome are associated with elevated stiffness as result of accumulation of glycation end-products (AGEs) in the vessel wall.[75] Insulin resistance is found to be associated with lower bone strength independent of body weight or other potential confounders, suggesting that hyperinsulinemia (and not hyperglycemia) negatively affects bone structure.[76] It has been suggested that osteoblasts are insulin target cells and that bone resorption is stimulated by insulin signaling in osteoblasts.[77] Also, adipocytes and osteoblasts have a common progenitor and the differentiation is modulated by various shared pathways in which hormones and inflammatory mediators stimulate and inhibit both type of cells.[78] Therefore, impaired glucose metabolism including metabolic syndrome seems to concurrently influences both arterial stiffness and bone demineralization.

Other hypotheses

An optimal blood flow is essential in the formation of capillaries and angiogenic growth of the bone vasculature, in which Notch signaling in the endothelium of the bone plays a key role;[79] Notch promotes blood vessel

growth and couples angiogenesis and osteogenesis.[80] Since a non-optimal blood flow downregulates Notch signaling, this can result in defective angiogenesis and negatively affect bone homeostasis and repair. The renin-angiotensin-aldosterone system (RAAS), a critical regulator of blood volume and a determinant of arterial stiffness,[81] might also play a role in bone homeostasis, where angiotensin II increases the osteoclastogenesis and inhibits osteoblastic activity resulting in a decrease in bone mineral density.[82] There may also be a role for transcription factors involved in cell differentiation, such as peroxisome proliferator-activated receptor gamma (PPAR- γ), which is a positive promotor of adipogenesis and a negative regulator of osteoblastogenesis. [83] It is shown that PPAR- γ agonists reduce inflammation, adhesion moleculs and arterial stiffness by improving insulin sensitivity,[84] which makes it a relevant factor for future research.

B. Arterial stiffness and muscle mass and function

In terms of the potential mechanism whereby sarcopenia and vascular stiffness interact, there is no clear consensus, with manifold theories and likely multiple highly interrelated factors. While some studies have suggested chronic ischaemia from stiff vessels as the cause of muscle breakdown, others have highlighted the impact of atrophic myocytes on the body's oxidative state, resulting in chronic inflammation and augmenting vascular stiffening. The most commonly hypothesized mechanisms are outlined in **figure 1** and below.

Inflammation

Chronic inflammation and oxidative stress are frequently postulated to underlie changes in muscle and blood vessels with age. Aging cells show mitochondrial dysfunction, for example changes in peroxisome proliferator-activated receptor-γ coactivator-1α pathways,[85] leading to increased production of reactive oxidant species, further mitochondrial damage and reduced proliferative capacity, particularly in high oxygen consumption tissues such as skeletal muscle.[86] Deficient autophagy in muscle stem cells can exacerbate inflammation and impaired antioxidant molecules such as Sestrin have been implicated in skeletal muscle decline with age in animal models.[87-89] Increased CRP has been shown to predict loss of muscle,[18] while imbalanced production of reactive oxygen species can impair muscle cell maintenance.[90] Inflammatory mediators can act directly on muscle receptors to increase breakdown or indirectly by impairing production of anabolic proteins such as growth hormone. In arteries, an inflammatory state can reduce elastin and

increase stiffness, and these changes result in further release of inflammatory mediators. Whether low level inflammation is the cause or effect of muscle breakdown and arterial stiffening is yet to be determined.

Hormonal dysregulation

Testosterone has also been proposed as a link between cardiovascular risk and sarcopenia, with androgen-deprivation therapy resulting in increased fat and loss of muscle.[91] Ochi found an association of free testosterone with both loss of muscle mass and increased arterial stiffness, suggesting this may underlie the association in men.[54] However, this study used thigh muscle CT to define sarcopenia, showing a higher reduction in this parameter with age in men compared to women and thus possibly explaining the lack of association with arterial stiffness in women. Using whole body measures of muscle mass may be more useful in assessing the relationship in both sexes. Testosterone may increase the levels of type 1 and type 2 muscle fibers, possibly through increasing IGF-1 levels,[92] and its effect on arterial stiffness may also relate to changes in the muscular wall, although other theories include a vasodilatory effect or increase in inflammatory mediators.[93] Although there is some evidence to suggest testosterone therapy improves body composition,[94, 95] concerns over cardiovascular and prostate disease mean it is not currently recommended.

Impaired glucose metabolism

Other studies have suggested that changes in insulin regulation as the common underlying factor in these processes. Indeed, the association of sarcopenia and coronary artery calcification was reduced by adjustment for insulin resistance.[96] The exact mechanism for muscles is unidentified, as dysfunctional insulin signalling can cause muscle breakdown via resistance to insulin's anabolic activation of MAPK pathways, while muscle loss and change in proportion of type 1 to type 2 muscle fibers can act to reduce insulin sensitivity, with both elements likely exerting an amplifying effect.[97] Insulin may induce its anabolic effect on skeletal muscle by increasing endothelial-derived nitric oxide to increase amino acid delivery via vasodilation. Aging may lead to impaired endothelial responsiveness to insulin (due to increased endothelin1, reduced nitric oxide and systemic inflammation),[98] thereby mediating one element of insulin resistance on muscle. S6K1 has also been implicated as a possible causal pathway linking impaired skeletal muscle responses to insulin signalling,[99] which may be involved in vascular stiffening in diabetes.[100] A recent meta-analysis found increased prevalence of

sarcopenia in diabetics with higher risk of developing diabetic complications, concluding there is likely a bi-directional interaction between muscle wasting and insulin dysregulation.[101]

Other hypotheses

A study comparing the impact of sarcopenia on vascular function in Indian and Japanese patients suggested that baPWV in the Indian cohort and CAVI in the Japanese cohort was found to be only associated with loss of muscle in non-hypertensive individuals, postulating that differential activity of CD34 cells and platelets induced by hypertension may enhance angiogenesis and enable the maintenance of grip-strength despite underlying endothelial dysfunction.[42] One small study of neural tracts using diffusion tensor tractography found a deterioration of associated neural tracts for motor function in sarcopenic women compared to non-sarcopenic, proposing elevated arterial stiffness as the underlying mechanism for microscopic changes in neural structures leading to subsequent muscle atrophy.[102] The ability of ACE inhibitors to increase anabolism and reduce arterial stiffness has led some to consider the role of the renin-angiotensin-aldosterone system in the development of sarcopenia,[103] with sarcopenic patients showing higher rates of urinary angiotensinogen excretion.[104] Cardiovascular medications have shown some benefits in reducing sarcopenia, including espindolol (thought to reduce catabolic and increase anabolic sympathetic signalling) and ACE inhibitors (thought to have an as yet unspecified direct effect on skeletal muscle as well as their effect on insulin sensitivity and inflammation).[105] The RAS system may influence anabolic signalling cascades, thus offering a potential treatment option in the future to reduce both sarcopenia and cardiovascular risk. Sarcopenia also seems to be linked to atherosclerosis, with BIA-derived sarcopenia associated with an increased trend in coronary artery calcification scores.[96]

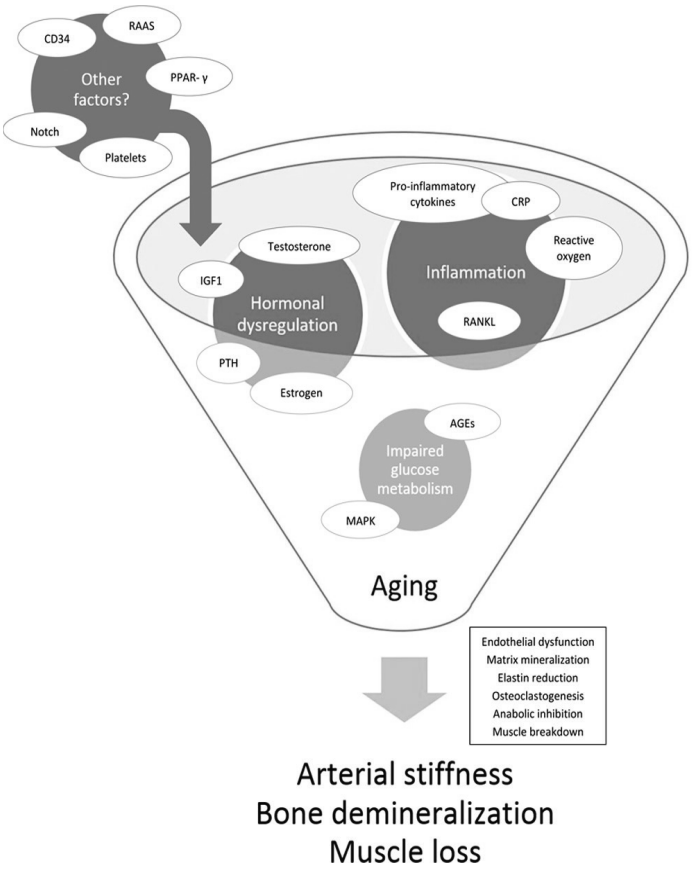
It could be argued that genetic and lifestyle factors such as diet, exercise and smoking underlie increases in adipose tissue in the development of all these conditions, yet Campos found that lack of muscle rather than addition of fatty tissue, was the key driver in the atherosclerotic process in sarcopenic patients.[106]

Conclusions

A large number of clinical studies report associations between arterial stiffness and bone and muscle loss. We have used pre-clinical studies to explore the common potential mechanisms linking the aging process in arteries, bones

and muscle. However, considerable research is needed to establish the mechanisms that connect arterial stiffness with muscle and bone deterioration during the aging process. Experimental, longitudinal, long-term, large-scale studies with sequential simultaneous measurements of artery, muscle and bone clinical phenotypes are presently missing. Chronic inflammation, hormonal changes and metabolic disorders could be common mechanisms for increasing the pace of arterial, bone and muscle aging. Dysregulation of blood flow and tissue hypoperfusion due to arterial stiffness could also be an accelerator of bone demineralization, whereas no such data exists on the possible effect of arterial stiffness on muscle mass and function. Regular exercise increases muscle and bone mass, and decreases arterial stiffness. It is possible that these actions are mediated through direct mechanical effects on muscle and bones but also through an effect of physical exercise on chronic inflammation and insulin resistance. Biomarkers of aging and of chronic inflammation will hopefully elucidate the mechanisms by which these complex processes of arterial stiffness, bone deterioration and muscle loss interact. The answer to these questions could determine new preventive and therapeutic targets in order to slow down these age-related degenerative processes and their multiple complications in older adults. A future meta-analysis on this topic would be of interest to establish the evidence from previous studies and could also confirm our conclusions.

Figure 1. Shared mechanisms underlying arterial stiffness, bone demineralization and muscle loss



Abbreviations: AGEs, Advanced glycation end products; CRP, C-reactive protein; IGF1, insulin-like growth factor 1; MAPK, mitogen-activated protein kinase; PPAR-γ, peroxisome proliferator-activated receptor gamma; PTH, parathyroid hormone; RAAS, renin-angiotensin-aldosteron system; RANKL, Receptor activator of nuclear factor kappa-B ligand

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5.2
Aortic stiffness and quality of late life

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The possible impact of aortic stiffness on quality of late life: an exploratory study

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Abstract

Purpose: Aortic stiffness (AS) is associated with cardiovascular events and all-cause mortality in the older population. AS might also influence the health-related quality of life (HRQOL) as a result of the negative effects of AS on cognitive and physical morbidity. We aimed to investigate the possible association between AS and HRQOL in people aged 75 years and over.

Patients and Methods: This cross-sectional study was part of the SCOPE study, an international multicenter cohort observational study. The indicators for AS were aortic pulse wave velocity (aPWV) and central pulse pressure (cPP). HRQOL was assessed using the EQ-5D index and the EQ-5D visual analog scale (VAS). ANCOVA and multivariate regression models were used to investigate possible associations.

Results: We included 280 Dutch participants of the SCOPE study. Median age was 79 years (IQR 76–83) and 42.1% were women. Participants reporting any problem on the EQ-5D index (n=214) had higher values of aPWV (12.6 vs 12.2 m/s, p = 0.024) than participants not experiencing any problem (n=66) and comparable values of cPP (44.4 vs 42.0 mmHg, p = 0.119). Estimates only slightly changed after adjustments. No association was found between indicators of AS and EQ-5D VAS.

Conclusion: Aortic stiffness was associated with impaired quality of late life. This association could be mediated by subclinical vascular pathology affecting mental and physical health.

Introduction

Aortic stiffness is a part of vascular aging,[1-3] a phenomenon which can be accelerated by risk factors such as hypertension and diabetes mellitus.[4-9] Aortic stiffness is a powerful predictor of cardiovascular events and all-cause mortality in several clinical populations as well as in community-dwelling older people.[10-12] Aortic stiffness is also associated with microvascular brain disease,[13,14] which can lead to decreased mental health in terms of cognition, mood, and daily functioning.[15,16] As a result of these effects, aortic stiffness might also have a negative impact on quality of life. The negative impact of aortic stiffness on quality of life could be a subclinical result of vascular pathology or a result of the presence of comorbidities.[17-20]

Previous studies have investigated the possible association between aortic stiffness and quality of life in several study populations.[21-27] These studies show conflicting results. Moreover, to the best of our knowledge, no previous study has investigated the possible association between aortic stiffness and the quality of late life.

Studying quality of life is relevant, since quality of life is a more powerful predictor of morbidity and mortality than many objective measures of health.[28] Health-related quality of life (HRQOL) can be seen as a broad measure of health status and a supplement to traditional parameters as morbidity and mortality.

The objective of this study was to determine whether there is an association between aortic stiffness and quality of life in older persons aged 75 years and over.

Materials and Methods

Study Population

The Screening for Chronic kidney disease among Older People across Europe (SCOPE) study is a multicenter observational study with a prospective design in seven European countries.[29] The primary objective of the study is to investigate the currently available screening methods to identify community-dwelling older patients at risk of kidney disease. A detailed description of the study protocol can be found elsewhere.[29] Patients with end-stage renal disease or dialysis, a history of solid organ or bone marrow transplantation, an active malignancy or metastatic cancer within 24 months prior to the visit, a life expectancy of less than 6 months, a severe cognitive impairment or patients unwilling to provide consent were ineligible for the SCOPE study. The current study population was a subset of the SCOPE study population

including only the Dutch participants (n=301). Data on aortic stiffness were only collected at participating centers in the Netherlands. The SCOPE study has been reviewed and approved by the Medical Ethics Committee of the Erasmus MC University Medical Center. This trial was conducted in accordance with the Declaration of Helsinki. This study was registered on the 25th February 2016 at clinicaltrials.gov, identifier NCT02691546. All participants provided written informed consent.

Study Visit

Baseline visit was scheduled at the Erasmus Medical Center Rotterdam or at the Havenziekenhuis Rotterdam. A comprehensive geriatric assessment was performed according to the SCOPE study protocol.[29] The assessment included questionnaires, physical examination, and functional tests. Also, non-fastened blood and urine samples were taken.

Aortic Stiffness

Aortic stiffness was determined measuring aortic Pulse Wave Velocity (aPWV) with the Mobil-O-Graph (IEM, Rheinland, Germany), a previously validated oscillometric method.[30] aPWV measurements were performed by a single measurement in resting sitting position using a brachial cuff. Other hemodynamic parameters that were obtained during the same measurement using inbuilt algorithms included blood pressure (both peripheral and central), mean arterial pressure (MAP), and heart rate (HR). In addition to aPWV, central pulse pressure (cPP) was also used as indicator of aortic stiffness.[31,32] cPP was defined as the difference between central systolic blood pressure (SBP) and central diastolic blood pressure (DBP). The measurement was carried out in every participant. However, we excluded participants in which the device was not able to conduct a proper wave analysis due to technical issues.

Health-Related Quality of Life

The Euro QoL-5-dimensions (EQ-5D) questionnaire was used to measure HRQOL.[33] The 5-level EQ-5D questionnaire has been validated in a variety of patient groups in six different countries, including the Netherlands.[34] The questionnaire consists of two parts: a descriptive profile and a visual analogue scale (VAS). The descriptive part of the questionnaire provides information on the following five dimensions: mobility, self-care, daily activities, pain and discomfort, and anxiety and depression. A five-level Likert scale from no problems to being unable to function on the specific domain was used to

gather information about the specific domains. This information was then converted into a single index value that informs on the overall HRQOL.[35] To calculate the EQ-5D index, a formula is used that weighs each dimension value with a tariff specific for the country at stake. The Dutch tariff was used in this study.[36] The index value is depicted on a scale with 0 indicating death and 1 indicating full health. The EQ-5D VAS is a 20 cm scale from 0 to 100 in which respondents can fill out their current state of health. Zero equals the worst imaginable health status and 100 the best imaginable health status.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics version 24 for Windows. Participants with missing values for the aortic stiffness parameters were excluded. Descriptive statistics were expressed as percentage for categorical variables, mean and standard deviation (±SD) for continuous normally distributed variables, and median and interquartile ranges [IQR] for continuous non-normally distributed variables. Participants with an EQ-5D index value of 1 were classified as "no problem on any dimension" (group 1), participants with an EQ-5D index value lower than 1 were classified as "any problem on the five dimensions" (group 2). First, characteristics were compared between these groups using the Mann–Whitney U-test and t-test for continuous variables. The Chi-square test was used to compare percentages. An analysis of covariance (ANCOVA) was used to investigate the possible association between aortic stiffness and the dichotomized version of EQ-5D index. Mean levels of aPWV and cPP were compared between these groups using two different models. Mean levels of pDBP and cDBP were also compared between these groups. We have identified potential covariates and included covariates with a p-value < 0.1 in the adjusted models when appropriate. Model 1 was adjusted for age, sex, mean arterial pressure and heart rate. Model 2 was additionally adjusted for Cumulative Illness Rating Scale (total score). A multivariable linear regression model was built to investigate the possible association between aortic stiffness (aPWV and cPP) and the EQ-5D VAS using the same models. A p-value of <0.05 was considered statistically significant.

Results

Table 1. Participants' characteristics

Characteristics	Total	No problem EQ-5D index (n=66)	Any problem EQ-5D index (n=214)	*p*-value
Age, years	79 [76-83]	78 [76-81]	79 [76-84]	0.047
Women, %	42.1	28.8	46.3	0.012
Education, years	12.1 (±4.5)	12.7 (±4.9)	11.9 (±4.4)	0.179
Packyears of smoking, years	5 [0-20]	3.9 [0-20]	6 [0-20.4]	0.528
Current smoker, %	5.0	3.0	5.6	0.824
Alcohol ≥1 unit a day, %	34.3	39.4	32.7	0.317
BMI, kg/m²	26.3 (±4.3)	26.1 (±3.3)	26.3 (±4.5)	0.760
ADL dependent, %	15.4	9.1	17.3	0.106
iADL dependent, %	48.6	25.8	55.6	<0.001
MMSE, score	29 [27-30]	28 [27-30]	29 [27-30]	0.988
GDS, score	2 [1-3]	0 [0-1]	2 [1-4]	<0.001
eGFR-BIS, mL/min	47.2 (±13.6)	46.6 (±13.1)	47.3 (±13.8)	0.701
Hypertension, %	70.7	62.1	73.4	0.079
Diabetes Mellitus, %	26.4	27.3	26.2	0.859
History of TIA/CVA, %	20.4	15.2	22.0	0.230
Atrial fibrillation, %	17.1	10.6	19.2	0.107
COPD, %	21.1	10.6	24.3	0.017
History of malignancy, %	23.6	15.2	26.2	0.065
CIRS, total score	12.8 (±4.9)	10.9 (±4.4)	13.4 (±4.9)	<0.001
CIRS, severity index	1.8 (±0.3)	1.8 (±0.3)	1.9 (±0.3)	0.271
Vascular parameters				
pSBP, mmHg	146.1 (±20.2)	148.2 (±20.3)	145.4 (±20.1)	0.337
pDBP, mmHg	85.1 (±11.2)	88.4 (±11.8)	84.1 (±10.9)	0.006
MAP, mmHg	113.0 (±14.0)	115.8 (±14.8)	112.2 (±13.6)	0.068
pPP, mmHg	60.9 (±15.5)	59.7 (±13.8)	61.2 (±16.0)	0.509
Heart rate, bpm	69.8 (±12.2)	70.5 (±12.9)	69.5 (±11.9)	0.579
cSBP, mmHg	130.6 (±17.4)	132.2 (±16.6)	130.1 (±17.6)	0.395
cDBP, mmHg	86.7 (±11.3)	90.3 (±11.8)	85.7 (±11.0)	0.004
cPP, mmHg	43.8 (±12.8)	42.0 (±10.1)	44.4 (±13.5)	0.119
aPWV, m/s	12.5 (±1.2)	12.2 (±0.9)	12.6 (±1.3)	0.024

Notes: Continuous variables are presented as mean (±SD) or median [IQR]. P-values are based on T-test and Mann–Whitney U-Test for continuous variables and Chi-square test for categorical variables. **Abbreviations:** BMI, Body Mass Index; (i)ADL, (instrumental) Activities of Daily Living; MMSE, Mini–Mental State Examination; GDS, Geriatric Depression Scale; eGFR-BIS, estimated Glomerular Filtration Rate; TIA/CVA, transient ischemic attack/cerebrovascular accident; COPD, chronic obstructive pulmonary disease; CIRS, Cumulative Illness Rating Scale; pSBP, peripheral

systolic blood pressure; pDBP, peripheral diastolic blood pressure; MAP, mean arterial pressure; pPP, peripheral pulse pressure; cSBP, central systolic blood pressure; cDBP, central diastolic blood pressure; aPWV, aortic Pulse Wave Velocity; cPP, central Pulse Pressure.

In total, 280 of the 301 Dutch participants were included in the study, 21 participants were not included due to missing values of aortic stiffness. Characteristics are shown in **Table 1**. Median age was 79 years [IQR 76–83] and 42.1% were women. Few participants were ADL dependent (15.4%) and 48.6% of the participants were iADL dependent. Over 70% of the 280 participants had hypertension, 26.4% diabetes mellitus, 23.6% a history of malignancy, 21.1% COPD, 20.4% a history of stroke and 17.1% atrial fibrillation. The mean score on the cumulative illness rating scale (CIRS) was 12.8±4.9 and the mean severity index of the CIRS was 1.8±0.3. The maximum value of 1 on the EQ-5D index (no problems) was scored by 66 participants (23.6%). Participants reporting any problem on the EQ-5D index (76.4%) were older, more often women, more often iADL dependent, had higher scores on the geriatric depression scale and also higher comorbidity rates than those without problems on the EQ-5D index, which resulted in a higher CIRS total score (mean values 13.4±4.9 vs 10.9±4.4, $p < 0.001$). Characteristics stratified for problems on the EQ-5D index are also presented in **Table 1**.

Participants with any problem on the EQ-5D index had lower peripheral (pDBP) and central DBP (cDBP) than participants without problems on the EQ-5D index. Mean values were 84.1±10.9 vs 88.4±11.8 mmHg (p=0.006) and 85.7±11.0 vs 90.3±11.8 mmHg (p=0.004), respectively. Also, participants with any problem on the EQ-5D index had higher values of aPWV than participants without problems on the EQ-5D index (p=0.024). Mean values were 12.6±1.3 and 12.2±0.9 m/s, respectively.

Table 2 shows the characteristics of the EQ-5D outcome measures. Median EQ-5D index was 0.86 [IQR 0.81–0.91] and the mean EQ-5D VAS was 74.9±14.8. No problems were reported by 42.5% of participants on mobility, 92.5% on self-care, 78.9% on daily activities, 44.6% on pain and discomfort, and 83.6% on anxiety and depression.

Table 2. Characteristics of health-related quality of life (n=280)

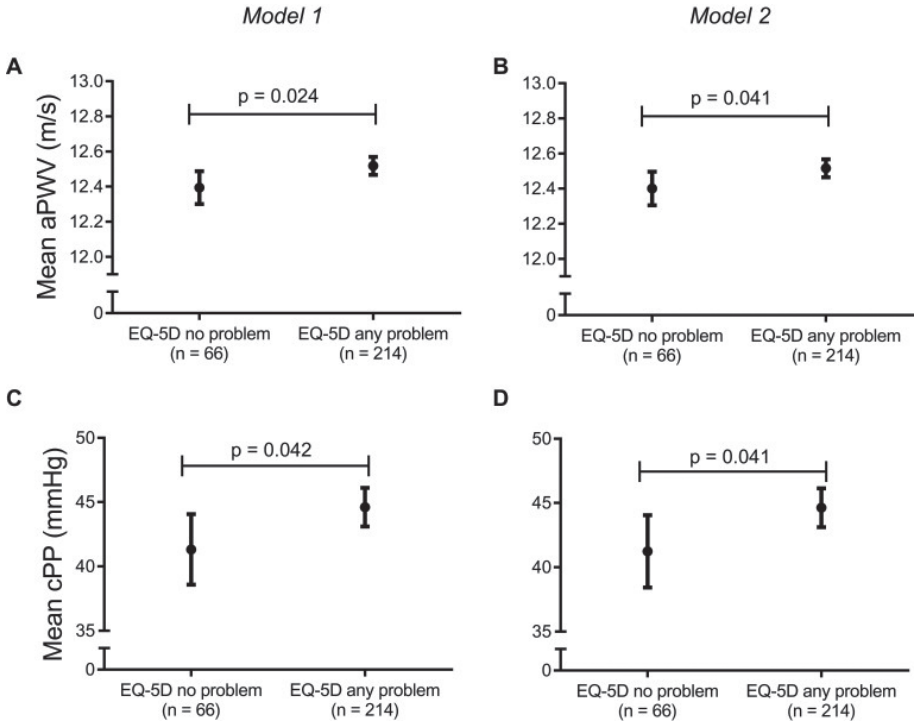
Characteristics	
EQ-5D index, score	0.86 [0.81-0.91]
EQ-5D VAS, score	74.9 (±14.8)
No problems per dimension	
Mobility, %	42.5
Self-care, %	92.5
Daily activities, %	78.9
Pain/discomfort, %	44.6
Anxiety/depression, %	83.6

Notes: Continuous variables are presented as mean (±SD) or median [IQR]. **Abbreviations**: EQ-5D VAS, EQ-5D Visual Analogue Scale

Figure 1 shows the mean levels of aortic stiffness according to EQ-5D index status (no problem vs any problem). The mean values of aPWV were higher in the any problem group than in the no problem group (12.52 m/s vs 12.39 m/s, p = 0.024). In model 2, the mean aPWV values remained unchanged with a 0.12 m/s higher mean aPWV in the group with any problem (p = 0.041). The mean values of cPP were 3.3 mmHg higher in the any problem group than in the no problem group (44.6 mmHg vs 41.3 mmHg, p = 0.042). This difference persisted in model 2 (44.6 mm Hg vs 41.2 mmHg, p = 0.041).

Mean levels of pDBP and cDBP were also compared between the two groups (no problem vs any problem). However, in multivariate analysis in both model 1 and model 2, mean values did not differ between groups (data not shown). A trend was observed between aPWV and EQ-5D VAS in model 1. Per m/s increase in aPWV, the EQ-5D VAS score changed with −4.15 (95% CI −8.71–0.42), whereas no association was found in model 2. No association was found between cPP and the EQ-5D VAS. In model 1, B coefficient and 95% CI for cPP were −0.05 (−0.21–0.11); Estimates in model 2 were only slightly changed.

Figure 1. Mean values of aortic stiffness according to EQ-5D index status (n=280)



Notes: Figure 1A and 1B: aortic Pulse Wave Velocity (aPWV) in m/s; Figure 1C and 1D: central Pulse Pressure (cPP) in mmHg. Model 1: adjusted for age, sex, mean arterial pressure and heart rate; Model 2: additionally adjusted for Cumulative Illness Rating Scale total score. Dots represent mean values, bars represent 95% confidence intervals.

Discussion

In this exploratory study, we found that aortic stiffness, assessed as aortic pulse wave velocity and central pulse pressure, was associated with an impaired quality of life in people of 75 years and over. This association in late life was independent of age, blood pressure levels, and comorbidities.

Several mechanisms might explain our results. First, the association between aortic stiffness and quality of late life could be mediated by impaired physical health. Aortic stiffness is known to play an important role in the development and progression of diseases in end-organs and the presence of these diseases could affect the quality of life.[37] However, the association between aortic stiffness and quality of life persisted even

after adjustment for cumulative comorbidities suggesting an independent role of aortic stiffness. Second, impaired mental health could also mediate the association between aortic stiffness and quality of life. Elevated aortic stiffness can lead to cerebral small vessel disease, which is associated with cognitive decline as well as mood disturbances.[15,38-40] It is very well possible that quality of life questionnaires might be able to detect vascular pathology already in a subclinical stage. Subclinical vascular damage could be already revealed in measures of quality of life before it results in multiple physical and mental comorbidities. An increase in aPWV of 1 m/s amplifies the risk of cardiovascular morbidity and mortality as well as all-cause mortality by 15%.[10] In this study, we found 0.12 m/s higher aPWV and 3.4 mmHg higher cPP in participants with poorer quality of life indexes. Although an increase in aPWV of 0.12 m/s or 3.4 mmHg higher cPP may seem relatively modest and the effect size is small, these differences could already have an impact on daily functioning, both physically and mentally. Therefore, aortic stiffness might be a tissue biomarker reflecting the vitality status of the single individual. In addition, aortic stiffness determines high mean SBP levels and low DBP levels, and consequently a wide pulse pressure.[41] It can be speculated that aortic stiffness together with consequent aberrant hemodynamic changes can affect quality of life by determining cardiovascular morbidity. It cannot be excluded that lower quality of life may also have an effect on aortic stiffness. It has been suggested that lower quality of life also represents people with lower social support or more depressive symptoms.[42,43] As result of this, it could be hypothesized that lower quality of life might also affect (hypertension) treatment compliance and therefore deterioration of health which negatively affects the function of the arteries. In addition, lower mobility and the presence of depressive symptoms and pain may also perpetuate a physically inactive lifestyle, which is associated with a change in vascular function and increase in stiffness.[44]

We found a discrepancy in the results of the EQ-5D index and the EQ-VAS. This discrepancy could be explained by the nature of the questionnaires. Noticing and reporting actual disabilities in daily life in the EQ-5D index does not necessarily mean that the self-perceived health on the EQ-VAS is scored as worse. Namely since in the EQ-VAS, an individual values his or her health position in life in the context of cultural and social aspects. In other words, these two questionnaires score different aspects of quality of life. Another well-known problem with the EQ-VAS is the end-of-scale bias which results in small numbers of extreme values, which could make the EQ-VAS less reliable than the EQ-5D index.

Some aspects of this study need further consideration. First, the

cross-sectional study design does not allow to draw causal inferences. Second, the sample size was relatively small and the population consisted of outpatient older persons. This could affect the power to investigate possible associations between aortic stiffness and quality of life. However, despite the limited number of participants and the possible selection bias, we were able to detect significant differences with a small effect size between those with and without problems in quality of life. The difference in cPP reached statistical significance in adjusted models, which might suggest that this result is due to chance or that the sample size for this specific analysis is underpowered. In a larger and more heterogeneous population, these differences might be amplified. Third, we measured aortic stiffness with an oscillometric method. This method is validated and gives reliable results when compared to invasive measurements,[30] however, the predictive value of this measurement to cardiovascular outcomes has not been investigated. One of the strengths of this study is the fact that we categorized EQ-5D index into no problem and any problem. The splitting partly resolved the problem of skewed values, but this made the results also more relevant in clinical practice. Another strength is the use of several markers of aortic stiffness such as aPWV and cPP. These central measures play a fundamental role in end organ disease and are therefore accurate and clinically relevant markers.[32,37]

The association between aortic stiffness and quality of life has been investigated before. Nevertheless, most previous studies did not observe an effect on overall HRQOL but only on the physical component of the HRQOL.[21,23,24,27] Only one study has described an effect on overall HRQOL.[25] However, this study was performed in a very small sample of 56 patients undergoing surgical aortic valve replacement. Our study sample differed from previous studies, since we have focussed on a specific population of older patients in late life, whereas the previous studies have focussed on younger patients or specific patient categories.

Conclusion

In conclusion, aortic stiffness was associated with impaired quality of life in people of 75 years and over. This association in late life was independent of age and other cardiovascular risk factors and might be mediated by subclinical vascular pathology affecting mental and physical health. Future research is required to establish whether aortic stiffness has a predictive value for a deterioration in quality of life.

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5.3

Aortic stiffness and brain integrity in older adults

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Aortic stiffness and brain integrity in elderly patients with cognitive and functional complaints

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Abstract

Purpose: Cerebral white matter lesions (WML) and brain atrophy are frequent in older persons and are associated with adverse outcomes. It has been suggested that aortic stiffness plays a role in the pathogenesis of WML and gray matter (GM) loss. There is, however, little evidence on the association between aortic stiffness and brain integrity in older patients. In this study, we investigated whether aortic stiffness is associated with WML and GM volume in older patients with cognitive and functional complaints.

Patients and methods: Fazekas score was used to analyze WML on brain imaging data of 84 persons; in a subanalysis on 42 MRI scans, the exact volume of white matter hyperintensities (WMH) and GM was determined using a brain-tissue and WMH tool. Aortic stiffness, measured as aortic pulse wave velocity (aPWV) and central pulse pressure (cPP), and blood pressure levels were non-invasively measured by the Mobil-O-Graph.

Results: Mean age was 76.6 (±6.8) years. Age was correlated with cPP (Spearman's ρ =0.296, P=0.008), aPWV (r^2=0.785, P<0.001) and WMH volume (r^2=0.297, P<0.001). cPP did not differ between categories of Fazekas, whereas aPWV increased with increasing Fazekas score (P for trend <0.001). After additional adjustment for age, levels of aPWV did not differ between categories. Both cPP and aPWV were associated with WMH volumes (lnB 0.025, P=0.055 and lnB 0.405, P<0.001, respectively); after additional adjustment for age, estimates were less consistent. Both cPP and aPWV were negatively associated with GM volumes in multivariate analysis (B=2.805, P=0.094 and B=111.052, P=0.032).

Conclusion: Higher aortic stiffness was partly associated with increased volume of WMH and decreased volume of GM and slightly influenced by blood pressure. Age also plays a role in this association in older patients.

Introduction

Cerebral white matter lesions (WML) and gray matter (GM) volume loss are frequently seen in older persons.[1,2] These age-related processes can be associated not only with gait disturbances and mood disorder but also with cognitive and functional decline and mortality.[3-8] Known risk factors for brain abnormalities are hypertension, diabetes mellitus, and inflammation.[9-12] Also genetic predisposition, such as Anderson–Fabry disease, can result in WML.[13,14] It has been suggested that arterial stiffness also plays a role in the pathogenesis of WML.[15]

Increased arterial stiffness leads to an increased pulsatile pressure, which can affect the microcirculation in high-flow organs leading to cerebral small vessel disease (CSVD).[15,16] A recent systematic review and meta-analysis was conducted on the association between arterial stiffness and CSVD.[17] Most studies included in the systematic review found an independent association between arterial stiffness and different markers of CSVD.[18-27] However, most of these studies investigated the effect of arterial stiffness on cerebral infarcts or cerebral microbleeds and not on WML.[20-22,24,25,27] Several studies used brachial-ankle pulse wave velocity (PWV) instead of more reliable central measurements (ie, aortic stiffness) or included specific categories of patients at risk for cardiovascular disease.[18,20-23,25,26] There is, however, little evidence on the possible association between aortic stiffness and WML in the older patient. Also, little is known on the association between arterial stiffness and GM volume, which has only been investigated in young adults and selected groups of patients.[28-31] No previous study has investigated the possible association between aortic stiffness and GM volume in older persons.

The aim of this study was to investigate the relationship between measures of aortic stiffness and both GM volume and the severity of cerebral WML load in a population of elderly patients with cognitive and functional complaints.

Materials and methods

From April 2015 to June 2016, all patients entering the outpatient clinic of geriatrics of the Erasmus MC, University Medical Center Rotterdam, were asked to participate in the study. Patients with (reliable) measurements of aortic stiffness and brain imaging were included. MRI and computed tomography (CT) scans were used for analysis when brain imaging was performed within 6 months before or after the study visit. The ethical committee of the hospital approved this study and all participants signed informed consent. During

the study visit, biographical information was collected and measurements of aortic stiffness were obtained. Medical history, medication, and lifestyle factors were documented. Height and weight were measured, and body mass index was calculated as kg/m^2. Global cognitive function was assessed with the Mini Mental State Examination score.[32] Katz index and Lawton and Brody index were used for scoring activities of daily living (ADL) and instrumental ADL, respectively.[33,34] Instrumental ADL dependency was defined as ≥1 limited activity.

Vascular measurements

Aortic stiffness was non-invasively measured with a validated method by the Mobil-O-Graph (Mobil-O-Graph 24 hours PWA Monitor; I.E.M. GmbH, Stolberg, Germany).[35,36] Central and peripheral systolic blood pressure (SBP), diastolic blood pressure (DBP), and pulse pressure (PP) were also measured. Aortic pulse wave velocity (aPWV) and central pulse pressure (cPP) were used to reflect aortic stiffness.[35,37] Mean arterial pressure (MAP) was calculated as DBP +1/3 (SBP–DBP).

Brain imaging

Brain imaging was performed as part of clinical work-up of patients with cognitive and/or functional complaints. The Fazekas scale was used by one experienced radiologist to score the severity of WML on MRI and CT scans.[38] The Fazekas scale represents the sum of deep white matter corps and periventricular corps divided into three categories of increasing severity (0= absent, 1= punctuate foci, 2= beginning confluence of foci, and 3= large confluent area). For more quantitative estimates, the brain tissue and white matter hyperintensity (WMH) segmentation tool, as developed by Quantib B.V. (www.quantib.com), was applied to T1-weighted and FLAIR scans. This tool generates automatic segmentations of GM, white matter (WM), cerebrospinal fluid and WMH in the cerebrum.[39] The algorithm used is available for clinical use in the Quantib Brain product (v1.2) and an improved version is available in Quantib ND (v1.5). From these segmentations, we computed volumes in milliliters of total GM and WMH.

Statistical analyses

All analyses were performed using SPSS statistics 24. Descriptive data for continuous variables were presented as mean ± SD or median and IQR. Number and percent prevalences were presented for dichotomous variables.

Data of variables with a skewed distribution (WMH in mm^3 and cPP) were log-transformed using the natural logarithm. Spearman's correlation analysis was used to investigate the relationship between age and cPP. Pearson's correlation analysis was performed to investigate the relationship between age (independent variable) and aPWV, the natural logarithm of WMH volume, and GM volume (dependent variables). In analysis of covariance (ANCOVA), mean cPP and aPWV were investigated across categories of Fazekas score in three different models: model A was unadjusted; model B was adjusted for MAP; model C was adjusted for MAP and age. Mean values of cPP were back transformed to original scale. The significant associations in ANCOVA analysis were reevaluated using the Bonferroni method for multiple testing ($P<0.0083$). Linear regression analysis was performed to assess whether cPP and aPWV (determinant) were associated with WMH and GM volume, as a continuous variable (outcome). The same models as in the ANCOVA analyses were used. All tests were two-sided and a P-value <0.05 was considered as statistically significant.

Results

In total, 250 patients signed informed consent. A total of 166 patients had no reliable measurements of aPWV and/or brain imaging available. Therefore, the study population consisted of 84 patients. The characteristics of the population are shown in **Table 1**. Mean age was 76.6±6.8 years, 65.5% were men, and 65.5% lived with a partner. Most of the patients were ADL independent (65.5%) and 26.2% were iADL independent.

Median peripheral SBP was 138.0 mmHg [IQR 124.0–148.0] and DBP was 83.5 mmHg [IQR 77.0–93.0]. Median central SBP was 125.5 mmHg [IQR 114.3–136.0] and DBP was 85.0 mmHg [IQR 78.0–94.5]. Median cPP was 37.5 mmHg [IQR 31.0–45.8]. Mean aPWV was 11.6±1.65 m/s. Fourteen percent of the patients were classified as Fazekas 0, 23.8% as Fazekas 1, 17.9% as Fazekas 2, and 44.0% as Fazekas 3. Median volume of WMH was 3.1 mL [IQR 0.8–6.4]. Mean GM volume was 679.5±130.7 mL.

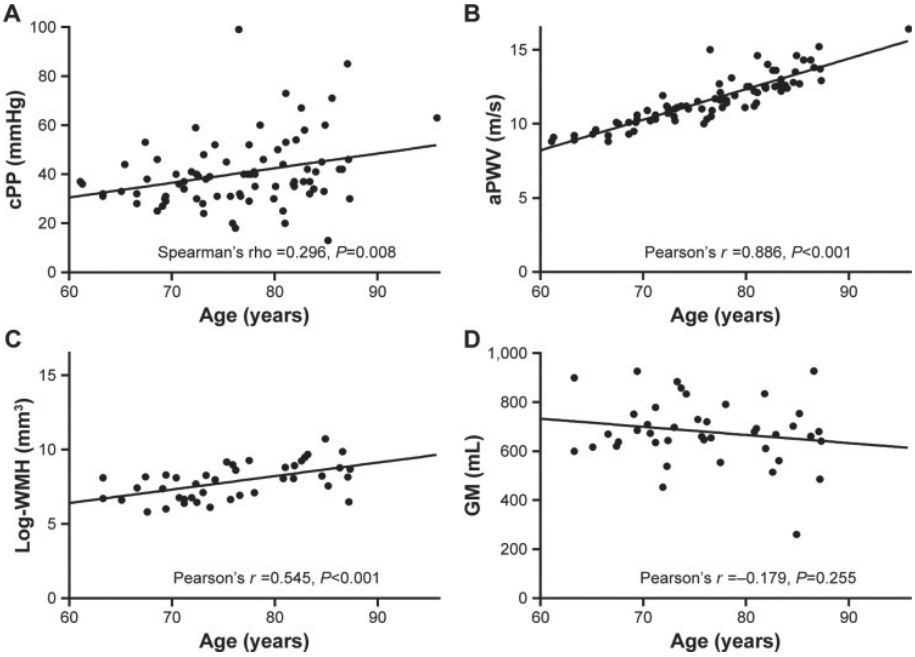
Age was associated with cPP (Spearman's r=0.296, P=0.008), aPWV (Pearson's r=0.886, P,0.001), and WMH volume (Pearson's r=0.545, P,0.001), but not with GM volume (Pearson's r=-0.179, P=0.255). Results are shown in **Figure 1**.

Table 1. Characteristics of the study population (n=84)

Age in years, mean (± SD)	76.4 (± 7.0)
Men, n (%)	55 (65.5)
Living alone, n (%)	29 (34.5)
Living with partner, n (%)	55 (65.5)
Current smoker, n (%)	11 (13.1)
Ex-smoker, n (%)	44 (52.4)
ADL independent, n (%)	55 (65.5)
iADL independent, n (%)	22 (26.2)
MMSE score, median [IQR]	25.5 [23 – 28]
Hypertension, n (%)	37 (44.0)
Diabetes mellitus, n (%)	24 (28.6)
Peripheral hemodynamics	
pSBP in mmHg, median [IQR]	138.0 [124.0 – 148.0]
pDBP in mmHg, median [IQR]	83.5 [77.0 – 93.0]
pPP in mmHg, median [IQR]	50.0 [42.5 – 63.8]
Central hemodynamics	
cSBP in mmHg, median [IQR]	125.5 [114.3 – 136.0]
cDBP in mmHg, median [IQR]	85.0 [78.0 – 94.5]
cPP in mmHg, median [IQR]	37.5 [31.0 – 45.8]
aPWV in m/s, mean (± SD)	11.6 (± 1.65)
Brain integrity	
Fazekas category 0, n (%)	12 (14.3)
Fazekas category 1, n (%)	20 (23.8)
Fazekas category 2, n (%)	15 (17.9)
Fazekas category 3, n (%)	37 (44.0)
WMH in ml, median [IQR][a]	3.1 [0.8 – 6.4]
Gray matter in ml, mean (± SD)[a]	679.5 (± 130.7)

Note: [a]Data on WMHand gray matter were available for 42 patients. **Abbreviations:** ADL, activities of daily living; iADL, instrumental activities of daily living; pSBP, peripheral systolic blood pressure; pDBP, peripheral diastolic blood pressure; pPP, peripheral pulse pressure; cSBP, central systolic blood pressure; cDBP, central diastolic blood pressure; cPP, central pulse pressure; aPWV, aortic pulse wave velocity; WMH, white matter hyperintensity.

Figure 1. Association between age and measures of aortic stiffness and brain integrity



Notes: (**A**) Central pulse pressure (cPP); (**B**) aortic pulse wave velocity (aPWV); (**C**) natural logarithm of white matter hyperintensities (log-WMH); and (**D**) gray matter (GM).

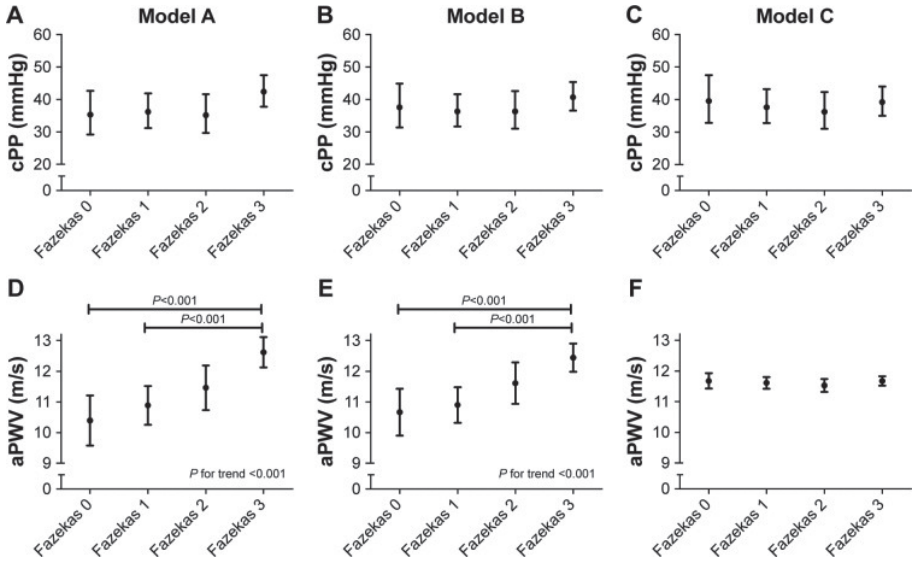
Figure 2 shows the mean values and 95% CI of cPP and aPWV across Fazekas categories. No differences were found in mean cPP values across categories of Fazekas in unadjusted analysis (**Figure 2A**). Mean values and 95% CI were 35.3 (29.2–42.7) mmHg, 36.2 (31.2–41.9) mmHg, 35.2 (29.7–41.7) mmHg, and 42.4 (37.8–47.5) mmHg from lowest to highest Fazekas categories, respectively. Mean values of cPP in model B slightly differed from univariate analysis (**Figure 2B**). Mean values and 95% CI were 37.6 (31.4–44.9) mmHg, 36.3 (31.7–41.6) mmHg, 36.3 (31.0–42.6) mmHg, and 40.7 (36.6–45.4) mmHg from lowest to highest Fazekas categories, respectively. In model C, no differences were found in mean values of cPP across categories of Fazekas (**Figure 2C**). Mean values and 95% CI were 39.5 (32.8–47.5) mmHg, 37.6 (32.7–43.2) mmHg, 36.2 (31.0–42.3) mmHg, and 39.2 (35.0–44.0) mmHg from lowest to highest Fazekas categories, respectively.

Mean values of aPWV increased from lowest to highest categories of Fazekas (test for trend P,0.001) in unadjusted analysis (**Figure 2D**). Mean values

and 95% CI were 10.4 (9.6–11.2) m/s, 10.9 (10.3–11.5) m/s, 11.5 (10.7–12.2) m/s, and 12.6 (12.1–13.1) m/s, respectively. A significant difference in aPWV was found between categories 0 and 3 (mean difference 2.2 m/s, P,0.001) and 1 and 3 (mean difference 1.7 m/s, P,0.001). In model B, aPWV was higher in those in Fazekas 3 than those in Fazekas 0 (mean difference 1.8 m/s, P,0.001) and in Fazekas 1 (mean difference 1.5 m/s, P,0.001). Furthermore, aPWV increased from lowest to highest categories of Fazekas (test for trend P,0.001) comparable with unadjusted analysis (**Figure 2E**). Mean values and 95% CI of aPWV from lowest to highest categories were 10.7 (9.9–11.4) m/s, 10.9 (10.3–11.5) m/s, 11.6 (10.9–12.3) m/s, and 12.4 (12.0–12.9) m/s, respectively. In model C, aPWV did no longer differ between categories of Fazekas. Mean values and 95% CI of aPWV were 11.7 (11.4–11.9) m/s, 11.6 (11.4–11.8) m/s, 11.5 (11.3–11.7) m/s, and 11.7 (11.5–11.8) m/s from lowest to highest Fazekas categories, respectively (**Figure 2F**).

Levels of cPP showed a trend toward linear association with (natural logarithm of) WMH (lnB =0.025, 95% CI –0.001; 0.052) and this trend only slightly changed in model B (lnB =0.027, 95% CI –0.001; 0.056). Nonetheless, in model C, no association was found between cPP and WMH (lnB =0.014, 95% CI –0.013; 0.040) (**Table 2**). Levels of aPWV were linearly associated with (natural logarithm of) WMH (lnB =0.405, 95% CI 0.204; 0.606) and remained significant in model B (lnB =0.449, 95% CI 0.233; 0.664). In model C, however, no association was found between aPWV and WMH (lnB =0.382, 95% CI -0.436; 1.201). Levels of cPP were negatively associated with GM volume in univariate analysis (B=-2.952, 95% CI -5.818; -0.086). In models B and C, a negative trend toward association was found between cPP and WMH (B=-3.080, 95% CI -6.207; 0.046; B=-2.805, 95% CI -6.111; 0.501, respectively). A negative trend was also found between aPWV and GM volume in univariate analysis (B=-22.235, 95% CI -47.653; 3.183). In model B, estimates were slightly less consistent (B=-22.766, 95% CI -50.495; 4.963). In model C, a negative association was found between aPWV and GM volume (B=-111.052, 95% CI -211.840; -10.265).

Figure 2. Mean values of aortic stiffness across categories of Fazekas scores



Notes: (A–C) Central pulse pressure (cPP); (D–F) aortic pulse wave velocity (aPWV). Model A, unadjusted; model B, adjusted for mean arterial pressure; model C, adjusted for mean arterial pressure and age. P-value <0.05/6 is statistically significant (Bonferroni correction). Dots represent mean values and bars represent 95% CI.

Table 2. Linear regression coefficients describing the associations between measures of aortic stiffness and brain integrity (n=42)

	WMH volume in mm³ lnB (95% CI)	GM volume in mL B (95% CI)
cPP (mmHg)		
Model A	0.025 (–0.001; 0.052)	–2.952 (–5.818; –0.086)
Model B	0.027 (–0.001; 0.056)	–3.080 (–6.207; 0.046)
Model C	0.014 (–0.013; 0.040)	–2.805 (–6.111; 0.501)
aPWV (m/s)		
Model A	0.405 (0.204; 0.606)	–22.235 (–47.653; 3.183)
Model B	0.449 (0.233; 0.664)	–22.766 (–50.495; 4.963)
Model C	0.382 (–0.436; 1.201)	–111.052 (–211.840; –10.265)

Notes: Model A, unadjusted; model B, adjusted for mean arterial pressure; model C, adjusted for mean arterial pressure and age.**Abbreviations:** WMH, white matter hyperintensity; GM, gray matter; cPP, central pulse pressure; aPWV, aortic pulse wave velocity

Discussion

In this study, we found that higher aortic stiffness was partly associated with a higher load of cerebral WML and lower GM volume in patients with cognitive and functional complaints. This association was slightly influenced by blood pressure. Higher aortic stiffness was found to be associated with a higher Fazekas score. The association was strongly mediated by age.

In a community-based cohort of 668 participants who were between the age of 69 and 93, higher levels of carotid-femoral pulse wave velocity were associated with diffuse microvascular brain lesions, which included subcortical infarcts and higher volumes of WMH.[24] Carotid pulse pressure was associated with increased risk of silent subcortical infarcts. However, this study was performed in an apparently healthy population of older individuals, and those with a history of stroke, transient ischemic attack, or dementia were excluded. Considering these differences in the inclusion, the results of the two studies are not completely comparable. Also, previous studies were most often performed in specific categories of patients such as young hypertensives and diabetics.[18,23] In these populations, higher aortic stiffness was associated with a greater volume of WMH. In addition, Saji et al found that increased brachial-ankle PWV was associated with WML in healthy adults in Japan.[40] Since brachial-ankle PWV is not a measure of aortic stiffness, these results could not be compared with our findings. A recent systematic review made an overview of all studies investigating the association between arterial stiffness and CSVD, summing up the results in diverse study populations using diverse methods of defining arterial stiffness and CSVD.[17] Out of the 15 cross-sectional studies included, 73% showed an association between greater arterial stiffness and CSVD.[17]

A few studies found an inverse relation between aortic stiffness and GM volume.[28-30] However, these studies were conducted in young and healthy adults, in type 2 diabetics, and in patients with manifest arterial disease. No previous study has investigated the potential role of aortic stiffness in determining brain integrity in older persons with cognitive and functional complaints.

The mechanisms underlying the association between aortic stiffness and CSVD have previously been described as when aortic stiffness increases the pulsatile pressure.[15,16] High pulsatile pressure increases the flow load and can cause damage in high-flow organs. This damage can be seen as WML, but also as cerebral microbleeds and lacunar infarcts, which are all markers of CSVD. The high pressure can affect the brain directly resulting in microvascular damage. Besides the direct damage that increased flow load

can cause, it may also induce an indirect remodeling response by elevating the vascular resistance to protect the microvascular system from high pressures. This response might lead to ischemia in the long term.[17] Moreover, GM atrophy may be the result of damages to the small cerebral arteries caused by vascular disease in advanced stage.[28] The role of age in vascular processes is attributed to degenerative changes. At a molecular level, vascular aging is characterized by breaks in elastin fibers, accumulation of collagen, fibrosis, inflammation, and calcifications. All these processes result in a decline of the elastic properties of the central large arteries.[41] Also cardiovascular diseases contribute to the decline of these elastic properties due to vascular remodeling.[9] Interestingly, in this study population, the majority have had or still had cardiovascular diseases. However, the role of age still seems to be very important. We cannot exclude that associations between aortic stiffness and brain integrity would be different in a study population with a wider range of age and therefore a different time of exposure to risk factors. Moreover, we are aware that participants of the present study have an elevated load of degenerative vascular alterations due to age and comorbidities and possibly patients with elevated vascular stiffness might not be included in the study due to morbidity or mortality.

This study has some limitations. First, the cross-sectional study design did not allow us to draw conclusions about causality. Second, the low number of available MRI scans can limit the possibility to add further adjustments in analysis on WMH and GM. Third, we included older patients within a relatively small range of age and with an elevated load of degenerative vascular alterations. These “ceiling effects” in a relatively small sample of elderly could limit the ability to assess the role of aortic stiffness in brain integrity.

This study also has strengths. First, we used both graded scores (Fazekas) and more quantitative and automatic methods for assessing the cerebral WML load in order to investigate the association between aortic stiffness and WML. Moreover, the Fazekas score was scored by one experienced radiologist, which makes the results less susceptible to variability as a result of different raters. Second, we used two parameters of central arterial stiffness. cPP and aPWV both reflect aortic stiffness.[35,37] Aortic stiffness is known to play a fundamental role in the development and progression of disease in end organs.[42] Thus, the use of aortic stiffness as a parameter to assess brain integrity makes the outcomes of this study clinically relevant.

Conclusion

We found that higher levels of aortic stiffness were partly associated with increased cerebral WML load and decreased GM volume in elderly patients with cognitive and functional complaints. This association seems to be slightly influenced by blood pressure and strongly driven by age. In this population of older patients, majority of whom were exposed to cardiovascular disease, age is still an important factor, most likely due to a cumulative exposure to risk factors and age-related degenerative processes. Prospective investigations in a larger geriatric population are recommended to investigate the independent role of aortic stiffness in the development and progression of WML and loss of GM over time.

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Chapter 6

Blood pressure dysregulation and falls

6.1

Orthostatic hypotension, fear of falling and physical performance in older adults

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Orthostatic drop in diastolic but not systolic blood pressure is associated with fear of falling in older fallers

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Abstract

Objectives: Orthostatic hypotension (OH) is frequent in older persons and associated with adverse outcomes. We investigated associations between OH, fear of falling and physical performance in older fallers.

Design: Cross-sectional study.

Setting and Participants: 523 participants of the IMPROveFALL study, aged ≥ 65 years who had visited the emergency department due to a fall.

Methods: OH was defined as a decline of ≥20mmHg systolic (SBP) or ≥10mmHg diastolic blood pressure (DBP) within 5 minutes of standing. Mobility was tested with the Timed-Up-and-Go-test (TUG) and Five-Times-Sit-to-Stand-test (FTSS), balance with the tandem test. ADL and iADL dependency and use of a walking aid were scored. Participants were classified as having fear/no fear of falling. Associations were investigated using ANCOVA and logistic regression models.

Results: In total, 49.7% had OH and median age was 76.2 years. Mean time to complete the TUG did not differ between fallers with and without OH, mean time was 10.6 seconds (95% CI 9.9-11.2) and 10.8 (95% CI 10.2-11.5), respectively. Mean time to complete the FTSS in both groups was 16.2 seconds (95% CI 15.4-17.1). No association was found between OH and balance, (i)ADL dependency or use of a walking aid. OR for fear of falling was 1.45 (95% CI 1.01-2.09) for older fallers with OH. Highest ORs were found in the groups with the greatest drop of DBP up to 4.22 (95% CI 1.89-9.45).

Conclusions and implications: Fear of falling is more frequent in older fallers with OH and especially in those with a greater drop in DBP. Low DBP is associated with low coronary supply and possibly an impaired organ perfusion. The present findings can help to understand the mechanisms underlying a multifactorial problem: falls.

Introduction

Orthostatic hypotension (OH) is very common in older persons and associated with several adverse outcomes,[1] such as syncope, cardiovascular morbidity and mortality.[2-4] Moreover, since OH can cause symptoms of dizziness and instability, it can also lead to falls and bone fractures[5]. Consequences of falls are known to contribute to physical impairment and decreased quality of life.[6,7] It is estimated that up to 10% of falls occur secondary to abnormal blood pressure responses such as OH.[5] However, it is not completely clear whether older fallers with OH differ from older fallers without OH in terms of their physical performance.

A recent systematic review and meta-analysis in older adults showed that OH was associated with objective or self-reported impaired balance and lower ADL performance.[8] No association was found with other physical functioning categories such as gait characteristics and mobility. All analyses in this study were stratified for different populations of older adults, such as community dwelling older persons, outpatients, inpatients, nursing home residents or patients with parkinsonism. However, no previous study has investigated the possible association between OH and physical performance in older fallers. The aim of this study was to investigate the possible association between OH and objective and self-reported physical performance in older persons who have fallen.

Methods

Baseline data from the Improving Medication Prescribing to reduce Risk Of FALLs (IMPROveFALL) study were analyzed. The IMPROveFALL-study is a randomized multicenter trial investigating the effect of withdrawal of fall-risk increasing drugs *versus* 'care as usual' on reducing falls in community-dwelling persons. A detailed description of the methods can be found elsewhere.[9] In summary, individuals aged ≥65 years who visited the Emergency Department (ED) because of a fall were asked to participate. Individuals had a Mini-Mental State Examination (MMSE) score of at least 21 out of 30 points.[10] The baseline visit took place within two months after ED attendance. The ethical committee of the Erasmus MC University Medical Center Rotterdam approved the study and all participants signed informed consent.

Orthostatic hypotension

OH was measured with a calibrated sphygmomanometer, in supine position followed by five minutes standing. Blood pressure was measured in supine position and after one, two, three, four, and five minutes standing. Systolic

(SBP) and diastolic blood pressure (DBP) was registered in millimeters of mercury (mmHg), heart rate in beats per minute (bpm). OH was defined as a drop in SBP of at least 20 mmHg or DBP of at least 10 mmHg within the 5 minutes in standing position.[11] Participants not completing the orthostatic challenge without the occurrence of OH were excluded from analyses, since no conclusion can be drawn about the presence of OH within those five minutes.

Physical performance

In order to assess physical performance, multiple performance tests were conducted.

Dynamic physical performance: mobility tests

In the Timed-Up-and-Go test (TUG), the participant has to stand up from sitting position and walk three meters along a line, perform a 180 degree turn and walk back to the chair and sit down.[12] The Five-Time-Sit-to-Stand test (FTSS) is a standardized test in which the participant stands up and sits down five consecutive times.[13] Both mobility tests were conducted twice, and the best time was used. If participants were not able to perform the TUG and/or FTSS, participants were only excluded from related analysis.

Static physical performance: balance test

A tandem stand test was used in order to assess balance.[13] The test is performed in standing position, in which the participant has to stand fully independently for 10 seconds with both feet in front of each other. The test is scored as correct or failed.

Functional (in)dependency

Katz index and Lawton and Brody index were used for scoring activities of daily living (ADL) and instrumental ADL, respectively.[14,15] The ADL scale assesses six functions: bathing, dressing, toileting, transferring, continence and eating.[14] The iADL scale assesses seven functions: use of telephone, transportation, preparation of a meal, household, shopping for groceries, taking medications and managing money.[15] Fully independent was defined as a score of zero, whereas (i)ADL-dependency was defined as having ≥1 limited activity. To determine functional dependency, it was documented whether or not a walking aid was used in daily activities.

Fear of falling

The Falls Efficacy Scale (FES) was used to assess fear of falling.[16] Each participant was asked to report how concerned about falling he/she felt while carrying out each of ten activities of daily living. Answers on each item were rated on a 4-point scale (0 = not concerned, 3 = very concerned). Fear of falling was present when the FES score was ≥1. Fear of falling can be seen as an indicator of physical performance, since fear of falling is associated with limitations in mobility.[17,18]

Statistical analysis

All analyses were performed using SPSS statistics 24. Descriptive data for continuous variables were presented as median and interquartile range (IQR). Percent prevalences were presented for dichotomous variables. Descriptive statistics were compared between participants with and without OH. A Mann Witney U test was performed for continuous variables, a Chi-square test was used to compare categorical data. Associations between OH and mobility were analyzed using analysis of variance (ANOVA). Mean (log transformed) time to complete the TUG and FTSS were compared between fallers with and without OH. Model A was unadjusted; Model B was adjusted for age, sex and additionally identified covariates ($p<0.01$). Mean values were back transformed to original scale. Associations between OH and balance, functional dependency (ADL, iADL and use of walking aid) and fear of falling were analyzed using logistic regression analysis. Odds ratios (ORs) and corresponding 95% confidence intervals (95%CI) were computed using the same two models (A and B) as previously described. If any association was found between OH and physical performance, physical performance scores were compared across categories of blood pressure changes during orthostatic challenge using ANCOVA and/or multivariate logistic regression analyses with model A and B. A p-value <0.05 was considered statistically significant.

Results

In total, 616 patients participated in the IMPROveFALL study. We excluded 93 patients with no completed orthostatic challenge. Therefore, the study population consisted of 523 participants.

Two hundred and sixty participants (49.7%) had OH. Characteristics of the study population are shown in **table 1** stratified for the presence of OH. Participants with OH were older than participants without OH (p=0.006). Median age was 77.4 years [IQR 71.2–82.6] in those with OH and 75.4 years

[IQR 69.5–80.5] in those without OH. No differences were found in medical history, such as diabetes mellitus, cerebrovascular diseases and pulmonary diseases between participants with and without OH. Participants with OH tended to have cardiovascular disease more often (35.0% vs 27.8%, p=0.072). The MMSE score was higher in those with OH than those without OH. Median MMSE was 28 [IQR 26–29] in participants with OH and 27 [IQR 25–29] in participants without OH (p=0.015).

Table 1. Baseline characteristics (n=523)

Variable	No OH (n=263)	OH (n=260)	p-value
Age, years	75.4 [69.5-80.5]	77.4 [71.2-82.6]	p=0.006
Men, %	38.8	39.6	p=0.85
BMI*, kg/m2	27.1 [24.4-30.5]	27.0 [24.2-29.4]	p=0.16
Smoking status			
never, %	54.0	52.7	p=0.93
former, %	34.6	36.2	
current, %	11.4	11.2	
Alcohol use			
<1 unit/day, %	62.7	63.5	p=0.06
1-2 units/day, %	23.5	28.5	
>2 units/day, %	14.1	8.1	
Medical history			
Diabetes Mellitus, %	21.7	19.6	p=0.56
Heart failure, %	3.0	4.2	p=0.47
Cardiovascular disease, %	27.8	35.0	p=0.07
TIA/CVA, %	18.6	14.6	p=0.22
Pulmonary disease, %	13.3	13.1	p=0.94
MMSE, score	27 [25-29]	28 [26-29]	p=0.015
Physical performance			
TUG†, seconds	10.0 [8.0– 14.0]	10.0 [8.0– 13.0]	p=0.55
FTSS‡, seconds	16.0 [12.0– 20.0]	15.0 [12.0– 20.0]	p=0.70
Tandem test failed, %	35.1	37.7	p=0.54
ADL dependency§, %	24.3	31.1	p=0.08
iADL dependency§, %	41.2	44.0	p=0.50
Use of walking aid‖, %	25.4	28.3	p=0.47
Fear of falling, %	30.4	38.8	p=0.043

Notes: Continuous variables are expressed as median and interquartile range. *BMI is available in 258 and 252 participants, respectively (n=510) † 239 and 234 participants were able to perform TUG, respectively (n=473) ‡ 226 and 212 participants were able to perform FTSS, respectively (n=438) § Information on (i)ADL dependency is available in 263 and 257 participants, respectively (n= 520) || Information on the use of a walking aid is available in 256 and 237 participants, respectively (n=493) **Abbreviations**: OH = orthostatic hypotension, BMI = Body mass index,

TIA = transient ischemic attack, CVA = cerebrovascular accident, MMSE = mini-mental-state-examination, TUG = Timed-Up-and-Go, FTSS = Five-Times-Sit-to-Stand, ADL = activities of daily living, iADL = instrumental activities of daily living

Time needed to complete the TUG (n=473) did not differ between participants with and without OH (10.0 vs 10.0 seconds). Also, mean time to complete the FTSS (n=438) did not differ between participants with and without OH (15.0 vs 16.0 seconds, respectively). In total, 37.7% of the participants with OH and 35.1% of the participants without OH failed to complete the tandem test (p=0.54). Participants with OH, were more often ADL-dependent with a borderline significance (31.1% vs 24.3%, p=0.08). No difference was found in iADL-dependency (44.0% vs 41.2%, respectively). Also the use of a walking aid did not differ between groups (28.3% vs 25.4%, respectively). Fear of falling was more frequent in participants with OH than participants without OH (38.8% vs 30.4%, p=0.043).

Vascular characteristics are presented in **Table 2**. Participants with OH had higher SBP and DBP at rest than participants without OH. Median SBP was 151 mmHg [IQR 140–170] and 145 mmHg [IQR 135–160], respectively (p<0.001). Median DBP was 80 mmHg [IQR 75–90] and 80 mmHg [IQR 74–85], respectively (p=0.033).

Table 2. Hemodynamic characteristics (n=523)

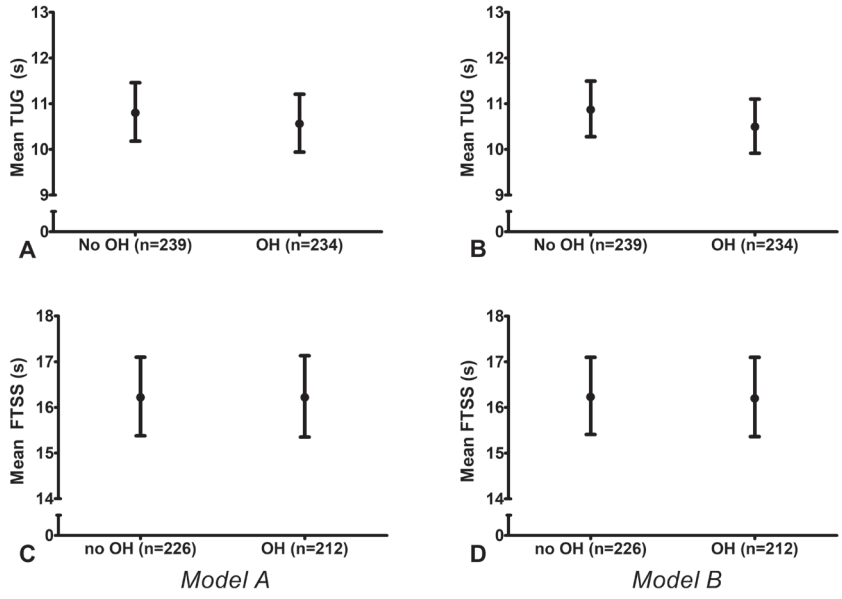
Variable	No OH (n=263)	OH (n=260)	p-value
SBP at rest, mmHg	145 [135– 160]	151 [140– 170]	p<0.001
DBP at rest, mmHg	80 [74– 85]	80 [75– 90]	p=0.033
Heart rate at rest, bpm*	68 [60– 76]	70 [60– 76]	p=0.23
Orthostatic test			
Delta SBP, mmHg	-5.0 [-10.0– 0.0]	-20.0 [-28.0– -15.0]	p<0.001
Delta DBP, mmHg	0.0 [-5.0– 5.0]	-10.0 [-11.0– -5.0]	p<0.001

Notes: Continuous variables are expressed as median and interquartile range *Heart rate is available in 262 and 251 participants, respectively (n=513) **Abbreviations:** OH = orthostatic hypotension, SBP = systolic blood pressure, DBP = diastolic blood pressure

Figure 1 shows mean time to complete the TUG and FTSS in participants with and without OH. In model A (**figure 1A**), mean time to complete the TUG did not differ between participants with and without OH with mean values of 10.6 (95%CI 9.9–11.2) and 10.8 (95%CI 10.2–11.5) seconds, respectively. After adjustments for age, sex, use of alcohol, SBP in rest, MMSE score and history of cardiovascular disease in model B (**figure 1B**), estimates were only

slightly changed. Mean time to complete the FTSS did also not differ between participants with and without OH, using model A (**figure 1C**). In both groups, mean values were 16.2 (95%CI 15.4–17.1) seconds. In model B (**figure 1D**), also no differences were found between those with and without OH.

Figure 1. Mean mobility scores in older fallers with and without orthostatic hypotension



Notes: Dots represent mean values, bars represent 95% confidence interval. Model A was unadjusted; Model B was adjusted for age, sex, alcohol use, systolic blood pressure in rest, Mini-Mental-State-Examination score and Cardiovascular disease. **Abbreviations**: OH = orthostatic hypotension, TUG = Timed-Up-and-Go, FTSS = Five-Times-Sit-to-Stand.

Table 3 presents ORs for low physical performance. In model A, the OR for failing the tandem test was 1.12 (95%CI 0.78–1.60) for participants with OH compared with participants without OH. For ADL- and iADL-dependence, ORs were 1.41 (95%CI 0.96–2.07) and 1.13 (95%CI 0.80–1.60), respectively. Also, the OR for the use of walking aid reached no statistical significance (OR 1.16, 95%CI 0.78–1.73). After adjustments using model B, estimates only slightly changed for these categories of physical performance. On the contrary, the OR for fear of falling was 1.45 (95%CI 1.01–2.09) for participants with OH compared with participants without OH using model

A (p-value=0.043). In model B, corresponding estimates were 1.48 (95%CI 1.00–2.18) with a p-value of 0.049.

Table 3. Odds ratios for low physical performance in older fallers with orthostatic hypotension

	Failed tandem test	**ADL dependency**	**iADL dependency**	**Use of walking aid**	**Fear of falling**
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
			Model A		
No OH (n=263)	1.00	1.00	1.00	1.00	1.00
OH (n=260)	1.12 (0.78-1.60)	1.41 (0.96-2.07)	1.13 (0.80-1.60)	1.16 (0.78-1.73)	1.45 (1.01-2.09)
			Model B		
No OH (n=263)	1.00	1.00	1.00	1.00	1.00
OH (n=260)	0.99 (0.67-1.50)	1.40 (0.92-2.12)	1.09 (0.73-1.61)	1.07 (0.68-1.68)	1.48 (1.00-2.18)

Notes: Model A was unadjusted; Model B was adjusted for age, sex, alcohol use, systolic blood pressure in rest, Mini-Mental-State-Examination score and Cardiovascular disease. **Abbreviations:** ADL= activities of daily living, iADL = instrumental activities of daily living, OH = orthostatic hypotension.

ORs for fear of falling were the highest in categories of a greater drop in DBP, whereas no association was found between drop in SBP and fear of falling (**Table 4**). There was no drop in DBP in 222 participants; in 141 participants, the drop was 1-9 mmHg; in 131 participants, the drop was 10-19 mmHg and in 29 participants, the drop was ≥20mmHg. In model A, corresponding ORs were 1.00, 1.13 (95%CI 0.71–1.80), 2.05 (95%CI 1.30–3.22) and 4.22 (95%CI 1.89–9.45), respectively. In model B, estimates were only slightly changed.

Table 4. OR for fear of falling in older fallers within categories of postural changes of blood pressure

	Fear of falling OR (95% CI)	
	Model A	Model B*
Systolic blood pressure (SBP)		
No drop SBP (n=113)	1.00	1.00
1-9 mmHg (n=71)	0.82 (0.44-1.54)	0.86 (0.45-1.66)
10-19 mmHg (n=151)	0.90 (0.54-1.51)	0.97 (0.57-1.65)
≥20 mmHg (n=188)	1.06 (0.65-1.72)	1.08 (0.64-1.82)
Diastolic blood pressure (DBP)		
No drop DBP (n=222)	1.00	1.00
1-9 mmHg (n=141)	1.13 (0.71-1.80)	1.19 (0.74-1.92)
10-19 mmHg (n=131)	2.05 (1.30-3.22)	2.09 (1.29-3.38)
≥20 mmHg (n=29)	4.22 (1.89-9.45)	4.67 (1.93-11.33)

Notes: Model A was unadjusted; Model B was adjusted for age, sex, alcohol use, systolic or diastolic blood pressure in rest*, Mini-Mental-State-Examination score and Cardiovascular disease. *Model B investigating drop in SBP is adjusted for SBP in rest, whereas model B investigating drop in DBP is adjusted for DBP in rest.

Discussion

In the present study, we found that older fallers with OH are more likely to have fear of falling than older fallers without OH. The higher the drop in DBP, the higher the chances of having fear of falling up to circa 400%. No association was found between OH and physical performance evaluated as mobility, balance and functional (in)dependency.

The prevalence of OH of 50% in these older fallers was comparable with previous literature. The prevalence of OH differs in different study populations of older persons and varies between 13 and 70% in geriatric outpatients.[19] Previous studies have investigated the possible association between OH and physical performance in older persons. Those studies did not focus on older fallers specifically. However, results of our study are in line with these earlier findings. A recent systematic review and meta-analysis has made an overview of these studies.[8] In the systematic review, less than half of the included studies showed an association between OH and physical functioning. In the meta-analysis, associations were found between OH and impaired balance and OH and ADL dependence, associations with other functional categories were less consistent. It needs to be pointed out that all included studies were conducted within community dwelling populations, nursing home residents or specific categories of patients such as geriatric

outpatients or inpatients and patients with parkinsonism. Older fallers might have been included in these studies, however, the results cannot be completely compared with our specific population of older fallers alone. Since it is expected that falls and related consequences are a growing health issue in the growing aging population,[20-22] it might be relevant to focus on this specific population.

Only few studies have investigated the possible association between OH and the fear of falling in older adults. In a relatively small study including 91 community dwelling adults, OH was present in 12% and fear of falling in 46% of the participants. No association was found between these variables.[23] In another relatively small study of older patients with uncontrolled hypertension, 21% of the patients were diagnosed with OH and circa 36% had fear of falling both in the OH group as in the non-OH group.[24] In contrast to these two studies, the present study found an association between OH and fear of falling in older persons. This difference may be explained by the different study populations and also by the fact that the current sample size is circa three times larger.

A possible hypothesis regarding the association between the presence of OH and fear of falling may lie in the mechanisms of cerebral hypoperfusion. OH can cause symptoms of dizziness, postural lightheadedness and blurred vision as result of cerebral hypoperfusion.[25] Also, chronic brain pathology, such as brain atrophy and white matter lesions, both more often present in those with OH,[26] might influence the perception of verticality, resulting in subjective dizziness.[27] In the present study, the drop of DBP seems to be the main factor driving this association. This association may be due to the role of DBP. During diastole, the coronary arteries are perfused.[28] Low DBP may reflect poorer cardiac condition and also higher arterial stiffening.[29,30] Noteworthy, DBP is a steady component of blood pressure, determining strongly the mean arterial pressure (MAP), which maintain organs perfusion. When DBP is low, or drops during postural change, the lower MAP may result in comparable symptoms of hypoperfusion leading to fear of falling. It is not completely clear why we did not find an association between OH and other physical performances scores. It can be speculated that participants in the present study without OH, but with a serious fall, already have low physical performance scores, comparable with those with OH. It might be challenging to investigate the role of OH in physical performance in this selected group of (frail) older fallers.

This study has several limitations. First, the study design was cross-sectional. Therefore, no conclusion can be drawn about causality. Second,

OH was measured with a calibrated sphygmomanometer and 1,2,3,4 and 5 minute blood pressure values were documented. We did not include continuous blood pressure measurements, which are ideally recommended in guidelines.[31] Therefore, this measurement may have underestimated the prevalence of OH. Third, differences in physical performances scores between the groups were small which might have limited the statistical power. The present study also has strengths. Different domains of physical performance were investigated giving an overview on different aspects of physical status. Both dynamic and static functionality tests were performed, functional dependency was scored and also a subjective measurement of physical performance, namely fear of falling, was investigated.[18,32] No previous study has focused on the possible association between OH and physical performance test scores in older fallers.

Conclusions and implications

Older fallers with OH are more likely to have fear of falling, especially those with a greater drop of DBP, whereas other measures of physical performance did not differ in older fallers with and without OH; Low DBP is associated with low coronary supply and possibly an impaired organ perfusion. Investigating this topic in this specific group of patients could help in understanding the mechanisms and consequences of such a multifactorial problem, namely falling, among older persons. Future studies including different categories of patients in larger study populations are needed to investigate these associations.

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Chapter 7

General discussion

The kidneys and the arteries undergo age-related structural and functional changes which can be accelerated by traditional and non-traditional cardiovascular risk factors. [1,2] Therefore, aging is an extremely heterogeneous process involving various domains of physical and mental health. Traditional risk factors such as hypertension, hypercholesterolemia and diabetes mellitus are widely used by health care professionals to stratify the risk of cardiovascular diseases.[3] Non-traditional risk factors on the other hand may be recognized as risk factors in the general population, such as inflammation and malnutrition, or be unique to patients with underlying diseases. As result, renal and vascular aging can have divergent impact in late life.

A decrease in kidney function and an increase of arterial stiffness are considered part of accelerated aging and are both associated with an increased risk of cardiovascular morbidity and mortality,[4-6] but might also affect other highly relevant outcomes in older adults. The general aim of this thesis was to investigate consequences of renovascular changes in late life. The findings can contribute to a better estimation of kidney function in late life and to a better understanding of the possible impact of chronic kidney disease (CKD), arterial stiffness and blood pressure dysregulation on physical and mental health in older adults.

The findings described in this thesis are based on three cohorts. The Improving Medication Prescribing to reduce Risk Of FALLs (IMPROveFALL) study is a randomized, multicenter trial conducted in The Netherlands between October 2008 and October 2011 assessing the effect of fall-risk-increasing-drugs withdrawal versus 'care as usual' as a method for falls reduction. Participants were 65 years or older and visited the emergency department because of a fall. Baseline data of this study including 616 participants was used to investigate specific questions on renal and vascular aging in older adults who have fallen. The second study was conducted at the outpatient clinic of geriatric medicine of the Erasmus MC, University Medical Center in Rotterdam between April 2015 and June 2016 and included participants referring with functional and/or cognitive complaints. In this study, data on arterial stiffness and physical and cognitive functioning was collected in order to make a comprehensive overview on multiple health domains in late life. The Screening for CKD among Older People across Europe (SCOPE) study is a multicenter 2-year prospective cohort study involving 2461 community-dwelling persons aged 75 years and over, visiting the outpatient clinics of participating institutions in 7 countries across Europe. Participants were included between August 2016 and February 2018 and underwent multiple clinical and laboratory evaluations. The design and rationale of this study is presented in this thesis. Findings presented in this thesis are based on

preliminary analyses of the baseline data of the European SCOPE database and of the baseline data of the Dutch subsample of the SCOPE study.

In this chapter, the main findings and clinical implications of these findings are discussed. Suggestions on directions for further research are also presented. Part one of this chapter will focus on renal aging and part two of this chapter will focus on vascular aging.

Part I Renal aging

With advancing age and as consequence of chronic diseases, the kidneys undergo structural and functional changes, such as sclerosis of the glomeruli and tubular atrophy.[7] These changes affect the kidney function and result in a decline in glomerular filtration rate (GFR). The direct measurement of GFR (mGFR) involves infusion of ideal filtration markers such as inulin or iohexol.[8] Measuring the urinary or plasma clearance of these exogenous substances is complex, expensive and time-consuming. Therefore, equations have been developed to estimate GFR (eGFR) from endogenous blood serum markers that are filtered by the glomerulus;[9] this method is easier, less expensive and quicker to execute in routine clinical practice. Most equations are based on serum creatinine as endogenous serum marker, a molecule that is freely filtered by the glomerulus. The production of creatinine depends on muscle mass and life style factors,[8] which also results in variations in serum creatinine levels in different populations or even within persons over time (**table 1**).

Table 1. Variations in production of serum creatinine

Variable	Serum creatinine levels
Aging	Lowered
Sex	
Men	Reference
Women	Lowered
Race	
Caucasian	Reference
African American	Raised
Body composition	
Normal	Reference
Muscular	Raised
Sarcopenic	Lowered
Obese	No effect
Sarcopenic-obese	Lowered
Chronic conditions	
Malnutrition	Lowered
Inflammation	Lowered
Life style factors	
Low physical exercise	Lowered
Vegetarian diet	Lowered

To overcome some of these limitations that the use of serum creatinine entails, equations also include variables such as age, sex, race or body size as surrogates for muscle mass. Still, since aging is a very heterogeneous process, the currently used GFR equations are not completely generalizable and have to deal with inaccuracy especially in late life.

The SCOPE study, presented in **chapter 2.1**, hopes to close essential gaps of knowledge on how to accurately assess kidney function in late life. Some evidence suggests that muscle mass independent markers, such as cystatin C, ß-trace protein and ß-2-microglobuline could better estimate GFR and predict negative outcomes.[10] However, the usefulness and cost-effectiveness of these filtration markers in screening older adults for CKD has not been investigated. Therefore, one of the specific objectives of the project is to assess these existing methodologies for CKD screening among older adults using real-life data from a European cohort of persons aged 75 years and over. Another specific objective of the SCOPE study is to investigate novel and potentially useful application of existing and innovative biomarkers of CKD in late life. This study focusses on untargeted metabolomics and proteomics analyses in serum and urine. Longitudinal analyses, not yet presented in this thesis, will likely provide a panel of completely novel

and strong kidney damage biomarkers that may substantially improve the identification of older adults at particular risk of CKD progression and cardiovascular events. Eventually, the systematic use of a comprehensive geriatric assessment (CGA) makes it possible to investigate consequences of CKD on multiple domains of health status.

Main findings and clinical implications

In **chapter 3.1** preliminary results of the SCOPE study are presented, which focused on to what extent CKD may be staged interchangeably by different currently used eGFR equations. Creatinine-based eGFR was calculated with three equations that are also used in daily practice: the CKD-EPI-, the BIS1- and the FAS-equation. The Bland-Altman analysis showed a small bias between the BIS1- and the FAS-equation, however, the bias between the CKD-EPI and the other two equations was very significant and peaking around 60mL/min. Since this is also the threshold for diagnosing CKD, these findings have highly interesting implications in daily clinical practice. Most interestingly, the difference between the CKD-EPI and the other two equations increased with decreasing levels of muscle mass.

In daily practice, clinical laboratories all over the world use the CKD-EPI-equation as recommended by the 2012 KDIGO Guidelines for the Evaluation and Management of CKD.[9] This recommendation is based on a systematic review that was published in 2012 that concluded that the use of the CKD-EPI equation was favored above the Modification of Diet in Renal Disease (MDRD) study-equation, despite the fact that neither the CKD-EPI- nor the MDRD-equation is optimal for all populations and GFR ranges.[11] A meta-analyses of data from 1.1 million adults endorses this recommendation.[12] The study of Matsushita et al found that the CKD-EPI-equation gave a more accurate GFR estimation then the, up till then, world-wide most commonly used MDRD-equation. A mildly reduced kidney function decline was more accurately categorized and in contrast to the MDRD-equation, the CKD-EPI-equation was also validated for persons above 70 years. However, one aspect of the validation of the CKD-EPI might not have received sufficient attention when it comes to the use of this equation in older adults: during the development of the CKD-EPI, only 4% of the study population was aged above 70 years and information on comorbidities (except for diabetes mellitus) was not known.[13] Therefore, the question raises: are we currently ready to estimate kidney function in late life?

Factors like age, sex and body mass index are already implemented in existing equations, but there still seems to be a large variation between

equations and subsequent eGFR values in older adults. Loss of muscle mass, which is common in frail older adults, results in low levels of serum creatinine even despite a depressed GFR. Current equations do not seem capable to account for this. eGFR equations are working well in the populations in which they have been developed; the BIS1-equation was specifically developed in a population of people aged 70 year and older,[14,15] whereas the FAS-equation was developed in a Full Age Spectrum (FAS).[16] Still, our findings suggest to be careful with interpretation of creatinine based eGFR values in late life. Most of the time, only data for creatinine-based eGFR equations is provided and in that case health care professionals treating older adults should be encouraged to use the BIS1- or FAS-equation to assess the kidney function.

In **chapter 3.2** multiple elements of physical performance were compared across different stages of CKD in older persons. It was investigated whether creatinine-based eGFR values were associated with handgrip strength, mobility scores and calf circumference, as markers of muscle strength and muscle mass. A smaller calf circumference and up to 10% lower grip strength was found in older adults with an eGFR value ≥90 mL/min when compared to older adults with an eGFR value of 60-90 mL/min and <60mL/min. Findings were the most striking while using the MDRD-equation to estimate GFR, but similar results were also found with the CKD-EPI-equation.

It is widely known that decreased kidney function is associated with negative outcomes such as an increased risk of morbidity and mortality,[4] but also with chronic inflammation, malnutrition and progressive loss of muscle mass and strength,[17,18] whereas higher GFR values are less associated with these negative outcomes. However, in the study in chapter 3.2, older persons with the best estimated kidney function, had the worst physical performances scores. These findings suggest that low serum creatinine and high eGFR values might represent older persons with less lean muscle mass and not necessarily older persons with good filtration rates.

In this study, persons aged 65 years and over were included and the mean age was 76 years; it is expected that in higher age ranges, results might be amplified. Previous literature supports this hypothesis. A large study population of community-dwelling persons in Italy investigated the relationship between eGFR, using the BIS1-equation, physical performance and mortality in the very oldest old of 90 years and over.[19] Still, even when using the BIS1-eGFR, a more reliable eGFR-equation in older adults, an U-shaped relationship was found between eGFR and mortality, suggesting that sarcopenic persons might cluster in the group with higher eGFR values. Mortality in this group was mainly a result of respiratory and neoplastic

diseases, which are both associated with cachexia and sarcopenia. Indeed, they also demonstrated that the oldest old adults with an eGFR >60 mL/min and <30 mL/min had the lowest muscle strength.

It once more suggests that lower muscle mass is likely to overestimate kidney function using eGFR-equations in (frail) older adults and the use of any creatinine-based eGFR equation at older age should be seriously questioned.

With the start of **chapter 4.1**, the focus was shifted from kidney function and physical health to kidney function and mental health, another important outcome related to late life well-being. There is increasing evidence linking CKD, cognitive impairment and mood disorders in older adults;[20,21] the kidneys and the brain can be affected by shared risk factors, such as hypertension and diabetes mellitus, and the aging process also profoundly affects both.[22] Early identification of modifiable risk factors of cognitive and functional decline such as CKD is of interest in order to be able to screen for mediators in this association. As follows, therapeutic strategies in patients with CKD but also in patients with (an increased risk of) dementia or depression can be optimized.

The link between kidney function decline, cognitive impairment and depressive symptoms seems to be mediated through vascular mechanisms including small vessel disease.[22] Consequences of CKD such as metabolic dysregulation, anemia and inflammation might also affect the brain.[23] The hypothesis in this European study in outpatients aged 75 years and over was that cognitive impairment and depressive symptoms would be more prevalent in those in advanced stages of CKD than in those in earlier stages. It was also hypothesized that older adults with cognitive impairment and depressive symptoms would have lower levels of eGFR than those without. Surprisingly, within the framework of the SCOPE study, these hypotheses could not be confirmed. As one would expect, the prevalence of conditions closely linked to (cerebral) small vessel disease such as atrial fibrillation, congestive heart failure and history of stroke, increased with the severity of CKD. Despite this fact, these conditions did not mediate an association between kidney function, cognitive impairment and depressive symptoms.

Most previous cross-sectional studies that found associations between kidney function and mental health did not focus on older persons specifically and this might explain the differences in results; when focusing on persons in late life only, a bias might be introduced in which individuals with CKD in more advanced stages and possibly cognitive impairment and/or depressive symptoms already died or were more likely to decline participation. Subsequently, those adults were not included in the SCOPE

study, a study with an extensive study protocol, which made it more difficult to find significant associations.

It must be emphasized that there are numerous challenges when investigating the possible impact of kidney function in late life. The optimal method for estimating GFR is not yet present and therefore it is important to interpret results with caution. In addition, there is a large selection of methods that can be used for assessing cognitive function or depressive symptoms, which might also explain divergent results in previous studies. In this study, the Mini-Mental-State-Examination (MMSE) and the Geriatric Depression Scale (GDS) were used to assess cognition and the presence of depressive symptoms, respectively. It cannot be excluded that the use of other tools to evaluate cognition and mood might also have given different results. Ideally, a complete neuropsychological evaluation should be used to assess all cognitive domains. With such complete data we might be able to confirm the link between the kidney and the brain at older age.

Future directions

The studies in this thesis demonstrated that creatinine-based eGFR equations have to deal with inaccuracy when used in older adults, mainly as consequence of progressive loss of muscle mass in older adults and the heterogeneity of the aging process. A given patient needs to be classified into the true stage of CKD to provide the best therapeutic strategies, considering that misclassification has highly relevant clinical implications. Therefore, it is of paramount importance to find new muscle mass independent markers to accurately assess kidney function in late life.

The last two decades the interest and research in other biomarkers of kidney function is growing, especially cystatin C has been investigated,[24,25] in an attempt to improve the accuracy of equations. Equations with both creatinine and cystatin C improved the prediction of mGFR when compared to equations that were only creatinine-based, also among older adults.[26] However, when adding cystatin C to the equation, the concordance between equations only marginally improves and the prognostic accuracy remained unchanged.[27,28] There is still a gap of knowledge on how to estimate kidney function accurately in older adults; a gap that the SCOPE study is aiming to fill. This study is likely to provide novel and strong kidney damage biomarkers to substantially improve the equations for older adults. Existing biomarkers of CKD will be explored like cystatin C, ß-trace protein and ß2-microglobuline.[24,29] Potential new biomarkers in serum and urine based on metabolomic and proteomic determinations or other techniques will also be

evaluated following the indications arising from two major studies that are currently performed: PIVUS and ULSAM.[30,31] Investigation of new biomarkers in various populations in both the community and hospital setting would be interesting in order to be able to make an ideal equation to estimate GFR. The ideal equation should be accurate, easy to use, low-cost and preferably generalizable.

Studies in this thesis also focused on associations between kidney function, functional and cognitive decline. We were not able to confirm our hypothesis that persons in advanced stages with CKD were more likely to have cognitive impairment and/or depressive symptoms. However, it is still likely that these conditions share common mechanisms, also in late life. Longitudinal studies are needed to establish causal inference, in which kidney function should be measured or accurately estimated. In order to do so, longitudinal analysis with data of the SCOPE study will hopefully contribute; within the data of the SCOPE study it is possible to investigate the effect of kidney function, assessed with mGFR or newly developed eGFR equations, on mental health. It might be of interest to investigate effects of CKD progression on cognitive impairment and depressive symptoms. Ideally, studies with a long follow-up might help to gain additional knowledge on these links in late life.

Part II Vascular aging

The aging process induces multiple physiological changes in the arterial wall, which is most evident in the large central arteries: a decreased distensibility (by breaks in elastin) and an increased wall thickness (by accumulation of collagen) result in an increase of arterial stiffness.[32] Cardiovascular risk factors such as hypertension and diabetes mellitus have additional impact on the arterial wall structure and act as an age-accelerator on the progression of arterial stiffness.[33,34]

The effect of arterial stiffness has been widely studied, demonstrating that hemodynamic changes as consequence of elevated arterial stiffness increases the risk of clinical and subclinical cardiovascular morbidity and mortality.[6,35-37] An overview on determinants of arterial stiffness, characteristics of the arterial wall and related consequences of these changes are presented in **table 2**. However, the potential impact of arterial stiffness and blood pressure dysregulation on physical and mental health in late life deserves additional attention and needs to be elucidated.

Table 2. Determinants, characteristics and consequences of aging of the arteries

Determinants	Characteristics	Consequences
Age[38]	Arterial wall[33]	Orthostatic hypotension[48]
Genetic background[39]	Endothelial dysfunction	Change of BP profile[49]
Life style factors	Elastin breakdown	Increase SBP
Low physical exercise[40]	Collagen accumulation	Decrease DBP
Smoking[41]	Smooth muscle cell	Increase PP
Hypertension[42]	dysfunction	Long-term effect on target organs
Diabetes Mellitus[43]	Calcification	Myocardial infarction[50]
Hypercholesterolemia[44]	Fibrosis	Heart failure[51]
Metabolic syndrome[45]	Arterial lumen[33]	Stroke[50]
Chronic kidney disease[46]	Increase diameter	Dementia[52]
Inflammation[47]		Chronic kidney disease[53]
		Mortality[6]

Abbreviations: BP, blood pressure; DBP, diastolic blood pressure; PP, pulse pressure; SBP, systolic blood pressure

Main findings and clinical implications

Whereas the effects of elevated arterial stiffness on cardiovascular outcomes are extensively studied, less is known about the effect of arterial stiffness on other organs. In **chapter 5.1** an in-depth review provided an overview on possible shared mechanism underlying the association between arterial stiffness, bone demineralization and muscle loss. This narritive review showed that there is no clear consensus on how these processes interact, but several hypotheses are described, such as the impact of immunosenescence, hormonal dysregulation and impaired glucose metabolism on all three processes.

So far, mainly cross-sectional studies have investigated these associations, which makes it not clear whether bone and muscle loss are just age-related processes parallel to vascular aging or whether these processes share common pathways or even directly influence one another.

Our review demonstrated that most cross-sectional studies have adjusted for multiple potential confounders, including age, in which an independent association remained. This suggests that there might be a link between arterial stiffness, bone demineralization and muscle loss aside from aging. Information from longitudinal studies is scarce, which it makes it difficult to draw conclusions about causality.

One longitudinal study was conducted in The Netherlands and

investigated the impact of aortic stiffness on change in bone mineral density (BMD) within 2 years.[54] In this study no associations were found, whereas in Japan, women with increased arterial stiffness after 10 years of follow-up had lower BMD levels at baseline in multivariate analysis.[55] These findings suggest an independent role of bone demineralization in determining arterial stiffness. Hypotheses on how bones would affect the vessels is, unfortunately, not presented, but the findings still have relevant implications; women with low bone mineral density should be examined for cardiovascular disease, since they seem to have a higher risk of development of arterial stiffness and (secondary) cardiovascular diseases.

To the best of our knowledge, only one study investigated the role of arterial stiffening on muscle loss.[56] This study demonstrated that arterial stiffness is associated with a higher risk of sarcopenia within 6 years of follow-up, independently of age and cardiovascular risk factors, but a significant role was played by chronic inflammation, as seen by high levels of pro-inflammatory cytokines on muscle mass decline over time.

All in all, common pathways are probable and considerable research is needed to further investigate this topic. Interventions acting on common pathways can be helpful to prevent further decline of arterial elastic properties, bone density and muscle mass and related frailty. It is possible that interventions such as physical exercise and optimizing nutritional status could have a positive direct mechanical effect on muscles and bones but also through an effect on common pathways as inflammation and insulin resistance.

In **chapter 5.2**, health-related quality of life was investigated in the Dutch subsample of the SCOPE study. Indicators of aortic stiffness, aortic pulse wave velocity and central pulse pressure were compared between adults who did not report any problems in quality of life and adults with an impaired quality of life. Both indicators of aortic stiffness were associated with an impaired quality of late life, independent of age, blood pressure levels and comorbidities. Quality of life is often used as an overarching term to qualify diverse domains in life such as physical, emotional, mental and functional well-being and an important endpoint in medical care.[57] It is likely that aortic stiffness plays a role in multiple domains and could therefore be seen as an independent tissue biomarker of vitality status in late life.

It can be hypothesized that subclinical vascular changes could be revealed in measures of quality of life before resulting in clinical cardiovascular comorbidities. Aortic stiffness can negatively impact *physical* health; aortic stiffness and consequent hemodynamic changes play a role in the

development and progression of end-organ diseases and have an impact on the heart, the kidneys and the brain.[49,58] A relatively small increase in aortic stiffness and consequent hemodynamic changes could result in a subclinical stage of cardiovascular morbidity affecting the physical part of quality of life. These same changes can also lead to cerebral small vessel disease which is associated with depressive symptoms and cognitive impairment;[52,59] if this is the case, clinical or subclinical, aortic stiffness might have a negative impact on *mental* health and consequent quality of life.

It cannot be excluded that impaired quality of life could also affect vascular properties and increase arterial stiffness. Lower quality of life might result in a lower treatment compliance due to lower social support of more depressive symptoms,[60,61] which could deteriorate (vascular) health. In addition, a physically inactive lifestyle,[62] often seen in persons with a lower quality of life, also has a negative impact on the arteries.

The findings presented in this chapter suggest that aortic stiffness measurements could be added as a routine non-invasive tool for clinical assessment of older adults to identify those in a subclinical stage of cardiovascular diseases. Then, targeted therapeutic strategies might avert further deterioration in late life.

In **chapter 5.3**, a study in older adults with cognitive and functional complaints is presented in which associations between indicators of aortic stiffness and brain integrity was investigated. Both gray matter volume (GM) and the severity of cerebral white matter lesions (WML) were areas of interest; no previous studies investigated these outcomes in older adults simultaneously with advanced techniques computing GM and WML volumes. Higher aortic stiffness, assessed as aortic pulse wave velocity and central pulse pressure, was partly associated with a higher load of cerebral WML and lower GM volumes independent of blood pressure levels. The association was strongly mediated by age.

Age plays an important role in functional and structural changes of the brain throughout life. Loss of gray matter appears to be constant in adult life, whereas white matter increases in the first four decades of life, but then rapidly decreases after the age of 60 years.[63,64] Lesions in the white matter can be seen on magnetic resonance imaging (MRI) even in the healthy aging brain, but it is likely that aged gray and white matter are more susceptible to age-related vascular changes such as aortic stiffness. Elevated aortic stiffness increases the pulsatile pressure and flow load leading to cerebral microvascular damage which contributes to the pathogenesis of cerebral small vessel disease.[37,65] More indirectly, high pressure induces an increase in

vascular resistance which might lead to ischemia in the long term.[66] Atrophy of gray matter might be the result of damage to small arteries in the brain caused by advanced vascular disease.[67] Age is an important factor as result of a cumulative exposure to risk factors and probably acts in a common pathway leading to a deterioration of vascular properties and brain integrity. A better understanding of risk factors contributing to gray matter and white matter changes during the aging process could help to focus on specific pathways and to inhibit the progression of various neurodegenerative or behavioral disorders. With this knowledge, targeted strategies, which for example focus on decreasing aortic stiffness, could be deployed to prevent an accelerated functional decline or to even preserve functional independence in late life. This in turn can be closely linked to a satisfying quality of life and a reduced risk of adverse events.

In the study presented in **chapter 6.1**, the role of orthostatic hypotension was investigated in older adults who were referred to the emergency department as a consequence of an accidental fall. The hypothesis in this study was that the age-related blood pressure postural dysregulation might influence physical performance and fear of falling in older persons who have fallen. Older adults with orthostatic hypotension were more likely to have fear of falling than adults without orthostatic hypotension. During postural changes, the magnitude of the drop in diastolic blood pressure increased the risk of having fear of falling up to 400%, whereas the role of the drop in systolic blood pressure seemed to be less relevant. These findings suggest that vascular aging leading to diastolic blood pressure dysregulation during postural changes has relevant implications in late life.

Low diastolic blood pressure is more often found in late life and associated with a poorer cardiac condition and higher arterial stiffening.[68-70] Diastolic blood pressure also strongly determines mean arterial pressure, which function is to maintain organs perfusion and function.[71] A low diastolic blood pressure or a greater drop in diastolic blood pressure during postural changes negatively influences organs perfusion which might result in cerebral hypoperfusion or related symptoms of orthostatic intolerance, such as lightheadedness, blurred vision and vertigo.[72,73] Cerebral hypoperfusion and/or orthostatic intolerance might be the underlying mechanism in the association between the diastolic blood pressure dysregulation during postural changes and fear of falling as these symptoms might trigger the sensation of fear of falling.

A recent review showed that fear of falling should not only be considered as a by-product of falls.[74] Fear of falling has an independent

effect on quality of life and thus on perceived well-being of older adults. Our findings contribute to a better understanding of mechanisms underlying fear of falling and thus suggest that the measurement of blood pressure profiles during postural change could have an important place in comprehensive assessments of the vitality status of older adults. Fear of falling and underlying factors are likely modifiable risk factors of an impaired quality of life and could therefore be targeted in interventions to improve or maintain quality of life.

Future directions

The studies in this thesis demonstrated that vascular aging plays a role in multiple health domains of physical and mental health in late life. Arterial stiffness modifies blood pressure profiles and can be accompanied by diastolic blood pressure dysregulation during postural changes which may result in an impaired quality of late life. Immunosenescence, hormonal dysregulation and impaired glucose metabolism are underlying shared mechanisms linking vascular aging and deterioration of physical and mental health and could be of interest in new preventive and therapeutic targets in order to slow down these processes and prevent frailty.

Future studies are needed in diverse study populations of older adults in clinical setting and in the general older population to confirm and further explore our cross-sectional results. Experimental studies and long-term longitudinal studies are needed to clarify causal inference and underlying shared pathways with aging. Studies should focus on the reduction of arterial stiffness and the effect on mental and physical health. It is possible that associations are mediated through direct mechanical effects of arterial stiffness on the bones, muscles and other organs, however experimental studies should also focus on targeting underlying pathways such as of chronic inflammation and insulin resistance; the effect of medication targeting signaling pathways could be evaluated, but it is also necessary to involve life style improvement such as promoting physical exercise and a good nutritional status in future studies on consequences of vascular aging in late life. Aging itself is a process with cumulative exposure to risk factors in which age cannot be targeted to improve outcomes. However, by identifying which underlying pathways are involved in accelerated aging, we might be able to maintain a good physical and mental health in late life.

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Chapter 8

English summary

Both the kidneys and the arteries undergo age-related alterations.

The deterioration of kidney function, determined as the glomerular filtration rate (GFR), can be accelerated by risk factors such as diabetes and hypertension, which can lead to chronic kidney disease (CKD). Measuring GFR is complex, therefore various equations based on serum creatinine are used in clinical practice to estimate kidney function. Creatinine is produced at a constant rate and continuously filtered by the kidneys and is therefore considered the most important surrogate marker for kidney function. However, the production of serum creatinine depends on sex, age and body composition and most equations have not been validated above the age of 70 years. The use of creatinine-based equations to estimate kidney function at older age should be seriously questioned since body composition changes significantly with age. Part of this thesis aims to investigate the implications of the use of these equations in late life.

Stiffening of the arteries is also an age-related process, in which the same risk factors as in kidney function decline are involved. As result, structural and functional vascular changes can occur at an accelerated rate, causing arterial stiffness to increase even further. Increased arterial stiffness modifies blood pressure profiles with an increase in systolic blood pressure and a decrease in diastolic blood pressure as result. Many studies have been conducted showing that these hemodynamic changes can lead to cardiovascular morbidity and mortality. However, less is known about consequences of arterial stiffness and hemodynamic alterations in late life, especially on non-cardiovascular outcome measures. Part of this thesis therefore focuses specifically on the consequences for physical and mental health at older age, outcome measures that are important for older adults.

After a general introduction on both renal and vascular aging in **chapter 1**, **part I** of this thesis, consisting of chapters 2, 3 and 4, starts with the focus on renal aging.

In **chapter 2.1** the protocol of the SCOPE study is described, a multicenter observational study in seven countries across Europe focusing on screening for CKD in adults over 75 years of age. The aim of this study is to investigate both existing methods and new biomarkers to screen for CKD. In addition, the laboratory and biomarker results will be compared with medical and functional data collected during a comprehensive geriatric assessment. This study, in which 2461 older adults were included and followed-up for two years, hopes to provide evidence for a better European guideline with recommendations on how to screen for CKD in late life and how to deal with CKD and its consequences at older age.

Chapter 3 describes two studies that both address the clinical implications of estimating GFR based on creatinine in older adults. In **chapter 3.1** the first and preliminary results of the SCOPE study are presented. In this study it was investigated to what extent CKD may be staged interchangeably by three different equations. Our results showed that the CKD-EPI equation was significantly different from the BIS1 and FAS equation. The biggest difference was found around the estimated GFR value of 60 mL/min, the threshold used to diagnose CKD. About 40% of the participants above this threshold with the CKD-EPI equation were below this threshold with the BIS1 and FAS equation. Furthermore, this study showed that the differences between equations increased even further in older adults with low muscle mass. These results demonstrate that creatinine-based equations to estimate kidney function at older age are not easily interchangeable and the main source of discrepancy between equations is muscle mass. In **chapter 3.2**, muscle strength and muscle mass were compared in older adults who had fallen. In this study, it was investigated whether hand grip strength, mobility scores and calf circumference differed across older adults in different categories of estimated GFR. Our results showed that older adults with the highest kidney function had up to 10% less strength and one centimeter smaller calf circumference than the older adults in lower categories. These findings were the most striking while using the MDRD-equation, but similar results were also found with the use of the CKD-EPI equation. These results suggest that lower muscle strength and mass in older patients is likely to lead to an overestimation of kidney function. This study once again underlines the need to search for muscle mass independent biomarkers to accurately reflect kidney function in the older population.

In **chapter 4.1**, the focus was shifted from kidney function and physical health to kidney function and mental health, another relevant outcome at older age. Baseline data of the SCOPE study was used to investigate associations between kidney function, cognition and mood. Deterioration of all these functions may be mediated through vascular mechanisms affecting the microcirculation of high-flow organs such as the kidneys and the brain. Surprisingly, our results do not confirm this hypothesis; cognitive impairment and depressive symptoms were not more prevalent in older adults in advanced stages of CKD and, vice versa, older adults with cognitive impairment and depressive symptoms had the same values of estimated GFR as older adults without problems with cognition and mood. However, since this study also used creatinine-based equations to estimate GFR, the hypothesis should ideally be retested with another method that more accurately reflects kidney function.

Part II of this thesis, covering chapters 5 and 6, focuses on vascular aging.

Chapter 5 consists of three parts in which the possible impact of arterial stiffness is described with particular regard to various (organ)systems and overall quality of late life.

Chapter 5.1 describes possible links between arterial stiffness on the one hand and bone demineralization and muscle loss on the other hand in a narrative review. A large number of clinical studies reported associations and these found associations were mostly independent of age and other (potential) risk factors. However, based on previous literature, it emerged that it is not completely understood how these processes, all age-related, interact. Possible hypotheses we describe include the role of the immune system, hormonal changes and impaired glucose metabolism. These factors may accelerate the processes of vascular aging and bone- and muscle loss. Only limited longitudinal studies have been performed which makes it hardly possible to investigate causal relationships. However, the in-depth overview of possible hypotheses underlying these associations, suggests that interventions targeting the underlying factors could help to slow down these processes and thereby prevent consequent complications.

In the study in **chapter 5.2** we investigated the association between indicators of aortic stiffness and quality of life. We found that older adults with an impaired quality of life had higher values of aortic stiffness than older adults with an optimal quality of life independent of age and comorbidity. These results suggest that aortic stiffness can be seen as a subclinical biomarker of late life vitality probably due to its negative impact on physical and mental health.

The study in **chapter 5.3** describes possible associations between aortic stiffness, cerebral gray matter volume and white matter lesions. Higher aortic stiffness was associated with lower gray matter volumes and a higher load of white matter lesions. This association was independent of blood pressure, but strongly mediated by age. Age can probably be seen as the key player in stiffening of the arteries which also negatively influences brain integrity.

Whether altered blood pressure profiles also (negatively) impact late life is described in **chapter 6.1**. We found that a drop in diastolic blood pressure during postural changes was associated with an increased risk of have fear of falling: the higher the drop of diastolic blood pressure, the greater the risk of having fear of falling. This association was not found between systolic blood pressure changes and fear of falling. These results suggest that diastolic blood pressure dysregulation most likely has relevant implications

in late life and thus a better regulation of diastolic blood pressure could be a relevant target in trying to maintain quality of life at older age.

To conclude, **chapter 7** contains a general discussion of the studies described in this thesis. This thesis provides new insights in underlying patterns that may be involved in the (accelerated) aging process in an attempt to unravel new targets for better diagnostic and therapeutic strategies to maintain or even improve quality of late life.

Chapter 9

Nederlandse samenvatting

Zowel de nieren als de bloedvaten ondergaan veranderingen gedurende het verouderingsproces.

De verslechtering van de nierfunctie, uitgedrukt als de glomerulaire filtratie snelheid (GFR), kan versneld worden door risicofactoren als diabetes en hypertensie wat kan leiden tot chronische nierziekte met alle mogelijke gevolgen van dien. Het meten van de GFR is complex, daarom wordt er in de klinische praktijk gebruik gemaakt van diverse formules gebaseerd op serum kreatinine om de nierfunctie te schatten. Kreatinine wordt met een vrij constante snelheid geproduceerd en continue door de nieren uit het bloed gefilterd en wordt om die reden gezien als de belangrijkste surrogaat marker voor de nierfunctie. Echter, de productie van kreatinine is afhankelijk van geslacht, leeftijd en lichaamssamenstelling en de meeste formules zijn niet gevalideerd boven de 70 jaar. Het gebruik van formules gebaseerd op kreatinine om de nierfunctie te schatten op oudere leeftijd dient in twijfel te worden getrokken omdat het lichaam sterk veranderd met het ouder worden. Een deel van dit proefschrift richt zich dan ook op het onderzoeken van de gevolgen van het gebruik van deze formules in het late leven.

Verstijving van de slagaders is een ander aan de veroudering gerelateerd proces, waarbij dezelfde risicofactoren als bij nierfunctieverslechtering een rol spelen. Hierdoor kunnen structurele en functionele vasculaire veranderingen versneld optreden waardoor de verstijving van de vaten (nog) verder toeneemt. Als gevolg van verstijving van de slagaders veranderen ook de bloeddruk profielen met een verhoging van de systolische bloeddruk en verlaging van de diastolische bloeddruk als resultaat. Er zijn veel onderzoeken verricht die aantonen dat deze hemodynamische veranderingen kunnen leiden tot cardiovasculaire aandoeningen en mortaliteit. Echter, er is minder bekend over gevolgen van verstijving van de slagaders en hemodynamische veranderingen in het laten leven, met name op het gebied van niet-cardiovasculaire uitkomstmaten. Een deel van dit proefschrift richt zich dan ook specifiek op de gevolgen voor fysieke en mentale gezondheid op oudere leeftijd, uitkomstmaten die belangrijk zijn voor de oudere mens.

Na een algemene inleiding over zowel renale als vasculaire veroudering in **hoofdstuk 1**, start **deel I** van het proefschrift bestaande uit de hoofdstukken 2, 3 en 4 dat zich focust op renale veroudering.

In **hoofdstuk 2.1** wordt het protocol van de SCOPE studie beschreven, een multicenter observationeel onderzoek in zeven landen in Europa dat zich richt op het screenen op chronische nierziekte bij 75-plussers. Deze studie heeft als doel om zowel bestaande methoden als nieuwe biomarkers

te onderzoeken voor het screenen op chronische nierziekte. Daarbij wordt het laboratorium- en biomarker onderzoek vergeleken met medische en functionele data die middels een structureel geriatrisch onderzoek worden verzameld. Deze studie, waarin 2461 ouderen werden geïncludeerd en gedurende 2 jaar opgevolgd werden, hoopt bewijs te kunnen leveren voor een betere Europese handleiding met aanbevelingen over hoe het beste te screenen op chronische nierziekte in het latere leven en hoe het beste om te gaan met chronische nierziekte en de gevolgen voor de oudere mens.

Hoofdstuk 3 beschrijft twee studies die ingaan op de klinische implicaties van het schatten van de GFR op basis van kreatinine op oudere leeftijd. In **hoofdstuk 3.1** werden de eerste voorlopige resultaten van de SCOPE studie gepresenteerd. Hier werd onderzocht in welke mate drie verschillende formules uitwisselbaar zijn om chronische nierziekte te categoriseren. Onze resultaten lieten zien dat de CKD-EPI formule significant verschilde van de BIS1 en de FAS formule. Het grootste verschil werd gevonden rondom de geschatte GFR waarde van 60 mL/min, de grens die gebruikt wordt voor het vaststellen van chronische nierziekte. Circa 40% van de deelnemers die boven deze grens zaten met de CKD-EPI formule werden wel onder de grens bevonden met de BIS1 en de FAS formule. Bovendien liet dit onderzoek zien dat de verschillen tussen formules nog verder toenamen bij hen met lage spiermassa. Deze resultaten tonen aan dat op kreatinine-gebaseerde formules om de nierfunctie te schatten op oudere leeftijd niet goed uitwisselbaar zijn en de grootste bron van discrepantie tussen formules door spiermassa komt. In **hoofdstuk 3.2** werden spierkracht en spiermassa vergeleken in ouderen die waren gevallen. In dit onderzoek werd gekeken of handknijpkracht, mobiliteit en kuitomvang verschilden tussen ouderen in verschillende categorieën van geschatte GFR. Onze resultaten lieten zien dat ouderen met de allerbeste nierfunctie wel tot 10% minder kracht hadden en één centimeter smallere kuitomvang dan de ouderen in een lagere categorie. Deze bevindingen waren het meest uitgesproken met de MDRD-formule, vergelijkbare resultaten werden ook gevonden met de CKD-EPI formule. Deze resultaten suggereren dat lagere spierkracht- en massa bij oudere patiënten waarschijnlijk leidt tot een overschatting van de nierfunctie. Dit onderzoek onderstreept nogmaals de noodzaak tot een zoektocht naar biomarkers die niet afhankelijk zijn van spiermassa om de nierfunctie accuraat te weerspiegelen in de oudere populatie.

In **hoofdstuk 4.1** werd de aandacht verschoven van nierfunctie en fysieke gezondheid naar nierfunctie en mentale gezondheid, een andere belangrijke uitkomt op oudere leeftijd. De baseline data van de SCOPE studie werd onderzocht op mogelijke verbanden tussen nierfunctie, geheugen en

stemming. Achteruitgang van al deze functies kan worden veroorzaakt door vasculaire mechanismen zoals aantasting van de microcirculatie van goed gevasculariseerde organen waaronder de nieren en het brein. Onze resultaten bevestigen die hypothese verassend genoeg niet; cognitieve stoornissen en depressieve symptomen kwamen niet vaker voor bij ouderen met nierfunctiestoornissen en, vice versa, ouderen met cognitieve stoornissen en depressieve symptomen hadden vergelijkbare geschatte nierfuncties met ouderen zonder problemen met de cognitie en stemming. Echter, omdat ook hier gebruik werd gemaakt van een geschatte nierfunctie gebaseerd op kreatinine, zou de hypothese idealiter nogmaals getoetst moeten worden met een methode die accurater de nierfunctie weerspiegelt.

Deel II van het proefschrift dat de hoofdstukken 5 en 6 beslaat, richt zich op vasculaire veroudering.

Hoofdstuk 5 bestaat uit drie delen waarin de mogelijke gevolgen van vaatverstijving worden beschreven met aandacht voor diverse (orgaan) systemen en algehele kwaliteit van het late leven.

Hoofdstuk 5.1 beschrijft mogelijke links tussen enerzijds vaatstijfheid en anderzijds botontkalking en spierverlies in een narratieve review. Een groot aantal klinische studies vonden een verband en deze verbanden bleken grotendeels onafhankelijk van leeftijd en andere (potentiële) risicofactoren. Echter, op basis van bekende literatuur kwam naar voren dat het niet geheel duidelijk is hoe deze processen, die leeftijdsgerelateerd zijn, op elkaar inwerken. Mogelijke hypothesen die wij beschrijven zijn onder andere de rol van het immuunsysteem, hormonale veranderingen en een veranderd glucose metabolisme. Deze factoren versnellen mogelijk het proces van vasculaire veroudering en botmassa- en spierverlies. Omdat er slechts beperkte longitudinale studies verricht zijn, kan er niet tot nauwelijks een causaal verband worden onderzocht. Het diepgaande overzicht van de mogelijke hypotheses die aan deze associaties ten grondslag liggen, suggereert echter dat interventies gericht op de onderliggende factoren zouden kunnen helpen om deze processen te vertragen en bijkomende complicaties te voorkomen.

In het onderzoek in **hoofdstuk 5.2** bestudeerden wij de associatie tussen indicatoren van vaatstijfheid en kwaliteit van leven. Wij vonden dat ouderen met een sub-optimale kwaliteit van leven hogere vaatstijfheid hadden dan ouderen met een optimale kwaliteit van leven onafhankelijk van leeftijd en comorbiditeit. Deze resultaten suggereren dat vaatstijfheid gezien kan worden als een subklinische biomarker van vitaliteit in het late leven waarschijnlijk als gevolg van een negatieve invloed op fysiek en geestelijk functioneren.

Het onderzoek in **hoofdstuk 5.3** beschrijft mogelijke associaties tussen vaatstijfheid, grijze stof volume en volume van witte stof schade in het brein. Een hogere vaatstijfheid was geassocieerd met een lager grijze stof volume en een hogere mate aan witte stof schade. Deze associatie was onafhankelijk van bloeddruk, maar werd sterk gemedieerd door leeftijd. Leeftijd kan waarschijnlijk worden gezien als de belangrijkste speler in vaatverstijving die tevens negatieve veranderingen teweegbrengt in de integriteit van het brein.

Of ook de veranderde bloeddruk profielen een effect hebben op het late leven wordt beschreven in **hoofdstuk 6.1**. Wij vonden dat diastolische bloeddruk veranderingen bij het opstaan een hoger risico gaven op het hebben van angst om te vallen: hoe groter de daling in diastolische bloeddruk, hoe groter het risico op angst om te vallen. Deze associatie werd niet gevonden tussen systolische bloeddruk veranderingen en angst om te vallen. Dit suggereert dat de verstoring van diastolische bloeddruk regulatie hoogst waarschijnlijk belangrijke implicaties heeft in het late leven en het beter reguleren van de diastolische bloeddruk zou dus een belangrijk doel kunnen zijn voor behoud van kwaliteit van leven op oudere leeftijd.

Tot slot bevat **hoofdstuk 7** een algemene discussie over de onderzoeken die in dit proefschift zijn beschreven. Dit proefschrift geeft inzicht in onderliggende patronen die mogelijk betrokken zijn bij het (versnelde) verouderingsproces in een poging nieuwe doelwitten aan het licht te kunnen brengen voor betere diagnostische en therapeutische strategieën en daarmee kwaliteit in het late leven te behouden of zelfs te verbeteren.

Appendices

About the author
PhD portfolio
List of publications
Affiliations
Dankwoord

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