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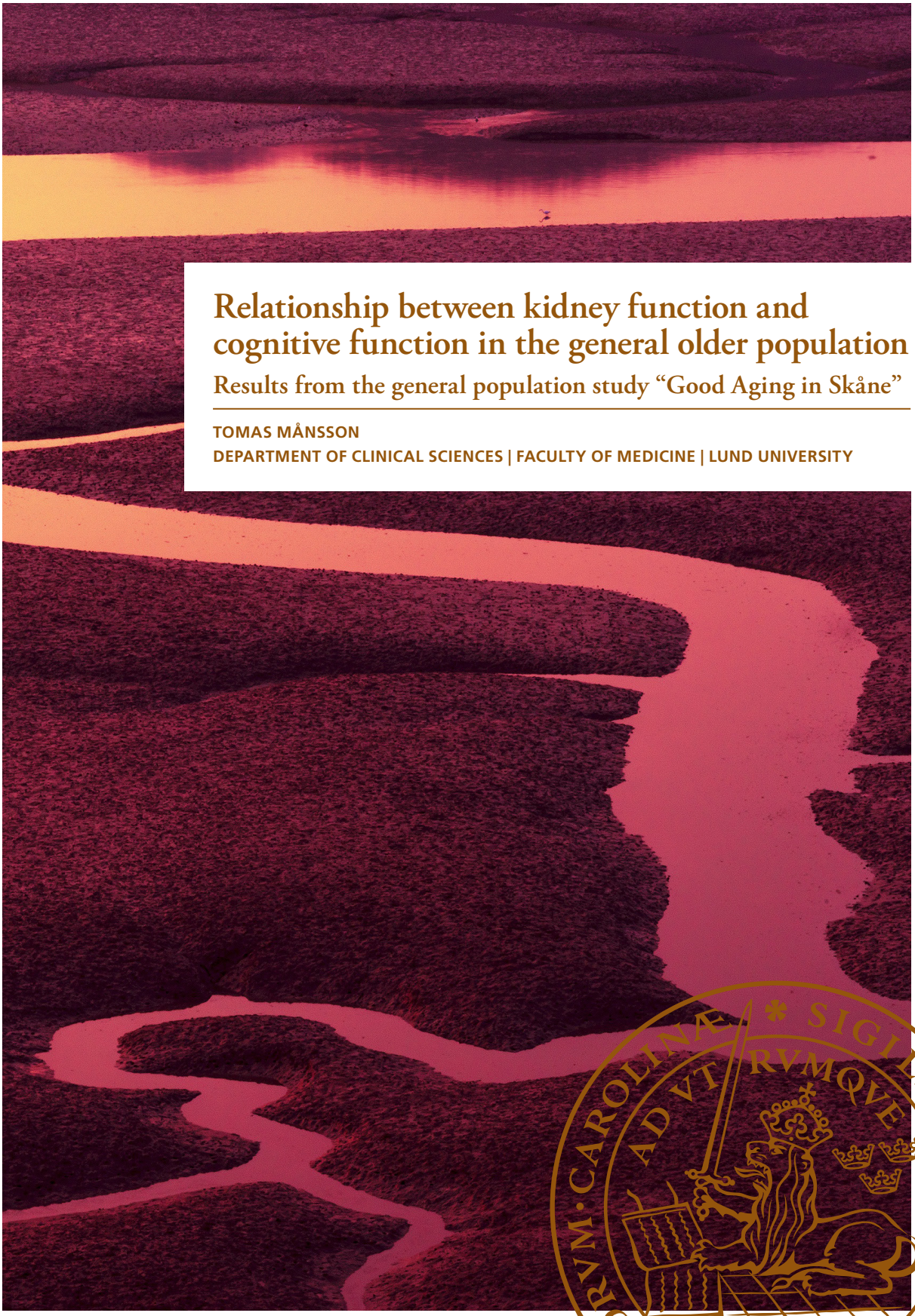

Relationship between kidney function and cognitive function in the general older population

Results from the general population study "Good Aging in Skåne"

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LUND
UNIVERSITY

DOCTORAL DISSERTATION

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Title and subtitle: Relationship between kidney function and cognitive function in the general older population. Results from the general population study “Good Aging in Skåne”

Abstract:

Impairment in both kidney function and cognitive function is common in the older population. The kidney and the brain share similar low vascular resistance properties, likely making both organs sensitive to arterial stiffness and hypertension. The main aim of this thesis was to investigate low kidney function, expressed by estimated glomerular filtration rate (eGFR), as a possible risk factor of future cognitive impairment.

Paper I

Cross-sectional study design. N = 2431. The relationship between eGFR and function in different cognitive domains was investigated using independent samples t-tests and multiple linear regression models. Low eGFR was associated with impaired function in various cognitive domains, but not meta-memory.

Paper II

Longitudinal study design. N = 882. In this paper we examined if chronic kidney disease (CKD) precedes dementia, minimal cognitive impairment (MCI), and/or worse function in different cognitive domains during the 6-year follow-up, using logistic regression models and linear regression models. Low eGFR was associated with decline in processing speed, but not with incident dementia or MCI.

Paper III

Cross-sectional study design. N = 390. Associations between CKD and markers of cerebral small vessel disease (CSVD) on magnetic resonance imaging (MRI) were explored using logistic regression models. We observed that CKD was associated with cerebral microbleeds (CMBs) and cortical atrophy only in the hypertensive sub-group.

Paper IV

Longitidinal study design. N = 2693 (CKD as outcome), 5253 (all-cause mortality as outcome). In this paper we examined if elevated pulse pressure (PP) precedes incident CKD (median survival time 15 years) and/or all-cause mortality (first quartile survival time 12 years), using Cox regression models. Elevated PP preceded both CKD and all-cause mortality.

In summary, we found that low eGFR increases the risk of future cognitive impairment. This association is likely to at least partly rest on a vascular basis. We also found that elevated PP increases the risk of future renal impairment.

Key words: Kidney function, glomerular filtration rate, cognition, cerebral small vessel disease, pulse pressure, elder, epidemiology

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Short summary

Introduction

Impaired kidney function and cognitive impairment become more prevalent with age and are very common in the older population [1-3] The kidney and the brain are high energy consuming organs dependent on a high and stable blood flow. The kidney and the brain have low vascular resistance mechanisms, presumably making both organs sensitive to arterial stiffness and hypertension [4, 5]. A possible connection between impaired kidney function and cognitive dysfunction on a vascular basis has been suggested [6, 7].

The most common method to assess kidney function is to measure the amount of blood filtered in the glomeruli of the kidneys per time unit, that is, the glomerular filtration rate. Chronic kidney disease is commonly defined as having a glomerular filtration rate < 60 ml/min/1.73m^2 for at least three months [8, 9].

Cerebral small vessel disease represents pathology of the small vessels of the brain and is strongly associated with cognitive impairment [10, 11]. The most reliable neuroimaging method to assess cerebral small vessel disease is magnetic resonance imaging [12, 13].

Pulse pressure is easily assessed by subtracting the diastolic blood pressure from the systolic blood pressure, taken in rest, and is used as a surrogate for arterial stiffness [14-16].

Aims

The main aim of this thesis was to evaluate impaired kidney function, expressed as low glomerular filtration rate, as a possible risk factor of future cognitive impairment.

Methods

The data for all studies in this thesis was collected from the ongoing cohort study Good Aging in Skåne "GÅS". In GÅS, subjects 60 years of age and older from the general population in the south part of Sweden have been invited regularly for clinical examination since 2001. The participants have been offered re-examinations every sixth year until 78 years of age, and every third year from 78 years of age, using the same study protocol. Each visit in GÅS include blood sampling, interview, medical history, anthropometrics, self-reported questionnaires, neuropsychological testing, and a physical examination.

A sub-group of 407 subjects from GÅS underwent magnetic resonance imaging of the brain in 2016 – 2018. The images were reviewed by an experienced neuroradiologist, and the following markers of cerebral small vessel disease were assessed: white matter hyperintensities, cerebral microbleeds, lacunar infarcts, and brain atrophy.

Kidney function was assessed by estimating glomerular filtration rate from creatinine and cystatin C, using the chronic kidney disease epidemiology collaboration equation [17].

A large test battery consisting of 12 neuropsychological tests was used to assess global cognitive function, as well as function in the cognitive domains learning and memory, language, complex attention, executive function, perceptual-motor, and meta-memory.

Paper I had a cross-sectional design. 2431 participants from the baseline visit in GÅS was included. An association between low glomerular filtration rate and impaired function in the cognitive domains mentioned above was examined using multiple linear regression models.

Paper II had a longitudinal design. Data was collected from baseline visit and the 6-year follow-up visit in GÅS and included 882 subjects. Linear regression models were used to examine if chronic kidney disease precedes worse performance on the cognitive tests included in GÅS. Logistic regression models were used to examine if chronic kidney disease precedes incident dementia and/or incident minimal cognitive impairment.

Paper III had a cross-sectional design. 390 subjects from the magnetic resonance sub-study in GÅS were included. Logistic regression models were used to examine potential associations between chronic kidney disease and markers of cerebral small vessel disease on magnetic resonance imaging of the brain.

Paper IV had a longitudinal design. Data was collected from participants who was included in GÅS at baseline and from the new participants who were randomly invited to the GÅS study six and twelve years later, using the same study protocol. Connections between elevated pulse pressure and incident chronic kidney disease (n = 2693), as well as all-cause mortality (n = 5253) were investigated using Cox regression models.

Main results

Paper I

Impaired kidney function, as well as the severity of impaired kidney function, was associated with impairment in global cognitive function, and in the cognitive domains learning and memory, language, complex attention, and executive function. An association between kidney function and meta-memory was not observed.

Paper II

Chronic kidney disease preceded decline in the cognitive function processing speed, which is part of the cognitive domain complex attention. Chronic kidney disease did not precede dementia or minimal cognitive impairment.

Paper III

Associations between chronic kidney disease and cerebral microbleeds, as well as cortical atrophy, were observed only in the hypertensive sub-group.

Paper IV

Elevated pulse pressure was associated with incident chronic kidney disease and all-cause mortality. When the event was incident chronic kidney disease, the median survival time was 15 years. When the event was all-cause mortality, the first quartile survival time was 12 years.

Discussion

The results of this thesis show that low glomerular filtration rate is associated with, and also can precede cognitive impairment. The results in paper II show that processing speed seems to be especially sensitive to impaired kidney function. Cerebral small vessel disease is highly associated with cognitive impairment. Processing speed seems to be linked to early manifestations of cerebral small vessel disease, whereas memory and language seem to be more robust and affected at more advanced stages of cerebral small vessel disease [10, 18, 19]. The group with chronic kidney disease in paper II had a mean glomerular filtration rate of 48 ml/min/1.73m^2, representing mildly to moderately chronic kidney disease [9], and therefore most likely an early stage of chronic kidney disease-related cognitive impairment. This rises the hypothesis that the association between low glomerular filtration rate and impaired cognitive function found, rests on early vascular implications.

The fact that we observed an association between chronic kidney disease and markers of cerebral small vessel disease only in the older hypertensive population is interesting and rises the following hypothesis: The connection between impairment in kidney function and cognitive function is due to a common vascular cause, that is, hypertension.

The kidney and the brain indeed are highly perfused organs sharing the same low vascular resistance mechanisms, presumably making both organs sensitive to hypertension [4, 5]. Hypertension is closely related to arterial stiffness, but if hypertension is the result of arterial stiffness or vice versa is not known [20, 21].

In paper IV, we found that arterial stiffness preceded incident chronic kidney disease. Since this was an observational study, it is hard to make any causal assumptions. A hypothesis, however, is that arterial stiffness could be a cause of low glomerular filtration rate.

In the future, to examine a possible connection between arterial stiffness and incident cerebral small vessel disease and cognitive impairment, we aim to investigate if arterial stiffness precedes incident cerebral small vessel disease and cognitive impairment.

Conclusion

The results in this thesis show that having a low glomerular filtration rate may increase the risk of future cognitive impairment. Further, the results show that elevated pulse pressure may increase the risk of future impairment in kidney function.

The finding of a glomerular filtration rate < 60 ml/min/1.73m^2 in an older individual should raise concern of cognitive function. The finding of a pulse pressure ≥ 60 mmHg in an older individual should raise concern of kidney function.

Suggestively, since a cardiovascular basis behind the association between low kidney function and cognitive impairment cannot be excluded, a finding of a glomerular filtration rate < 60 ml/min/1.73m^2 or a pulse pressure ≥ 60 mmHg in an older individual should raise concern of cardiovascular status, and overview of treatable cardiovascular risk factors, such as hypertension, diabetes, and smoking habits should be considered.

Populärvetenskaplig sammanfattning på svenska

Introduktion

Njursvikt och nedsatt kognitiv funktion (tankeförmåga) är vanligt förekommande i den äldre populationen. Radiologiska bildundersökningar av hjärnan hos äldre påvisar ofta olika former av förändringar och sjuklighet i hjärnans små blodkärl, så kallad cerebral småkärlssjuka. Dessa kärlförändringar är kopplade till nedsatt kognitiv funktion. Njurarna och hjärnan har liknande blodförsörjning med små blodkärl som är känsliga och sannolikt lätt skadas av högt blodtryck/hypertoni. Det är mot bakgrund av detta rimligt att misstänka att njursvikt kan vara kopplat till kognitiva problem, och att skador i de små blodkärlen i njurarna och hjärnan kan vara involverat i detta misstänkta samband. Tidigare studier har inte fullt ut kunna svara på vilka områden av kognitionen som kan vara nedsatta vid sänkt njurfunktion samt om nedsatt njurfunktion föregår nedsatt kognitiv funktion. Det viktigaste målet med avhandlingen var att utröna huruvida nedsatt njurfunktion kan förutspå framtida kognitiv nedsättning.

Kärlstyvhet är starkt kopplat till högt blodtryck/hypertension. Högt pulstryck tyder på nedsatt elasticitet/eftergivlighet i kroppens stora blodkärl och är ett etablerat sätt att mäta kärlstyvhet. Eftersom pulstryck är lätt att mäta i den kliniska vardagen, var en andra målsättning att utröna om ökat pulstryck kan förutspå insjuknande i framtida kronisk njursjukdom samt död. Huruvida förhöjt pulstryck föregår insjuknande i kronisk njursjukdom är inte fullständigt kartlagt tidigare.

Att på gruppnivå utröna om nedsatt njurfunktion föregår nedsatt kognitiv funktion, om ökat pulstryck föregår nedsatt njurfunktion, samt om dessa samband skulle kunna bero på vaskulär sjuklighet, är viktigt. Upptäckt av nedsatt njurfunktion och/eller ökat pulstryck i en individ skulle nämligen i så fall kunna indicera skärpt översyn och behandling av kardiovaskulära riskfaktorer hos denna individ.

Metoder

Njurfunktion mättes med hjälp av blodproverna kreatinin och cystatin C, vilka är ämnen som utsöndras via njurarna. Med hjälp av en matematisk formel kunde njurarnas filtreringsförmåga av blodet, och därigenom njurfunktionen, uppskattas med hjälp av dessa blodprover.

Kognitiv funktion mättes med hjälp av ett flertal kognitiva tester (12 stycken) som testar olika aspekter av den högre hjärnverksamheten (tänkandet).

Cerebral småkärlssjuka kunde påvisas med hjälp av magnetkameraundersökning som kan upptäcka tecken på cerebral småkärlssjuka i form av sjukliga förändringar i hjärnans vita substans, små infarkter (så kallade lakunära infarkter), minimala blödningar (så kallade mikroblödningar), och områden med reducerad hjärnvolym (så kallade atrofier).

Pulstrycket beräknas genom att subtrahera övertrycket (systoliska blodtrycket) med undertrycket (diastoliska blodtrycket).

I det första delarbetet undersöktes om det finns ett icke tidsangivet samband mellan nedsatt njurfunktion, inkluderande graden av nedsatt njurfunktion, och nedsatt kognitiv funktion.

I det andra delarbetet undersöktes om nedsatt njurfunktion tidsmässigt kan föregå försämring i kognitiv funktion eller insjuknande i kognitiv sjukdom.

I det tredje delarbetet undersöktes om det finns ett icke tidsangivet samband mellan nedsatt njurfunktion och cerebral småkärlssjuka.

I det fjärde delarbetet undersöktes om högt pulstryck tidsmässigt kan föregå insjuknande i kronisk njursjukdom och död.

Resultat

I det första delarbetet påvisades ett samband mellan såväl nedsatt njurfunktion som graden av nedsatt njurfunktion och nedsatt funktion i ett flertal kognitiva förmågor.

I det andra delarbetet påvisades att nedsatt njurfunktion kan föregå nedsättning i kognitiv funktion. Nedsatt njurfunktion föregick dock inte insjuknande i kognitiv sjukdom.

I det tredje delarbetet observerades att nedsatt njurfunktion var kopplat till förändringar i hjärnan som ses vid cerebral småkärlssjuka hos de som hade högt blodtryck/hypertoni, men inte hos övriga.

I det fjärde delarbetet sågs att förhöjt pulstryck som tecken på styva och åldrade kärl kan föregå både insjuknande i kronisk njursjukdom och död.

Slutsats

Nedsatt njurfunktion verkar vara kopplat till och även föregå nedsatt kognitiv funktion. Nedsatt njurfunktion föregick mönster av nedsatt kognitiv funktion som ses vid vaskulärt betingad kognitiv dysfunktion. Vi observerade att nedsatt njurfunktion var associerat till småkärlsskador i hjärnan, men bara hos de med hypertoni. Vi kunde vidare visa att förhöjt pulstryck kan föregå insjuknande i kronisk njursjukdom. En möjlig gemensam nämnare bakom sambanden vi hittade mellan njurfunktion och kognition kan vara skador i de små kärlen i njurarna och i hjärnan, vilka verkar vara känsliga för hypertoni och kärlstyvhet.

Sammantaget ger detta stöd för att nedsatt njurfunktion bör väcka uppmärksamhet på den kognitiva funktionen, och förhöjt pulstryck bör väcka uppmärksamhet på njurfunktionen. Vidare bör man vid nedsatt njurfunktion eller förhöjt pulstryck överväga att leta efter och hantera behandlingsbara kardiovaskulära riskfaktorer, såsom hypertoni, diabetes och rökning, i syfte att om möjligt undvika eller fördröja framtida försämring i den kognitiva funktionen.

För att djupare förstå kopplingen mellan njurfunktion, hjärnfunktion och vaskulär hälsa planerar vi i framtiden att undersöka om nedsatt njurfunktion föregår insjuknande i cerebral småkärlsjuka eller försämring i redan etablerad cerebral småkärlssjuka. Vi planerar också att undersöka om förhöjt pulstryck föregår insjuknande i cerebral småkärlssjuka eller försämring i redan etablerad cerebral småkärlssjuka, samt om förhöjt pulstryck föregår nedsättning i kognitiv funktion.

List of Papers

Paper I

Månsson T, Overton M, Pihlsgård M, Elmståhl S: Impaired kidney function is associated with lower cognitive function in the elder general population. Results from the Good Aging in Skåne (GÅS) cohort study. BMC Geriatr 2019, 19(1):360

Paper II

Månsson T, Elmståhl S: Impaired kidney function did not predict dementia or mild cognitive impairment in the elder general population. BMC nephrol 2021, 22:314

Paper III

Månsson T, Rosso A, Ellström K, Abul-Kasim A, Elmståhl S: Chronic kidney disease and its association with cerebral small vessel disease in the general older hypertensive population. *[Manuscript accepted for publication in BMC nephrol]* 2024

Paper IV

Månsson T, Rosso A, Ellström K, Elmståhl S: Elevated pulse pressure preceded incident chronic kidney disease and death. Results from the Good Aging in Skåne (GÅS) study. *[Manuscript submitted for publication]* 2023

Author's contribution to the papers

Paper I

TM and SE set up the study design. The manuscript was drafted by TM. TM performed the statistical analyses. MO provided valuable input regarding interpretation of the cognitive test results. All authors critically revised and approved the final manuscript.

Paper II

TM and SE set up the study design. The manuscript was drafted by TM. TM performed the statistical analyses. TM and SE both critically revised and approved the final manuscript.

Paper III

TM, AR and SE set up the study design. The manuscript was drafted by TM. TM performed the statistical analyses. KA-K examined and interpretated the MRI images. All authors critically revised and approved the final manuscript.

Paper IV

TM set up the study design. The manuscript was drafted by TM. TM performed most of the statistical analyses. AR performed part of the Kaplan-Meier estimates. All authors critically revised and approved the final manuscript.

Abbreviations

aMCIm	Amnestic MCI multiple domains
aMCIs	Amnestic MCI single domains
Ang II	Angiotensin II
AS	Arterial stiffness
ATC	Anatomical Therapeutic Chemical
BBB	Blood-brain barrier
BMI	Body mass index
BP	Blood pressure
CAA	Cerebral amyloid angiopathy
CADASIL	Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy
CARASIL	Cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy
CDR	Clinical dementia rating
CI	Confidence interval
CKD	Chronic kidney disease
CKD-EPI	Chronic kidney disease epidemiology collaboration
CMBs	Cerebral microbleeds
CPRS	Comprehensive psychopathological rating scale
CSF	Cerebrospinal fluid
CSVD	Cerebral small vessel disease
CT	Computed tomography
DBP	Diastolic blood pressure
DWI	Diffusion-weighted images
ED	Endothelial dysfunction
eGFR	Estimated glomerular filtration rate
ESC	European Association of Cardiology
GFR	Glomerular filtration rate

GÅS	Good aging in Skåne
HIV	Humane immunodeficiency viruses
HR	Hazard ratio
HT	Hypertension
ICD-10	International Classification of Diseases version 10
MCI	Minimal cognitive impairment
MDRD	Modification of Diet in Renal Disease
mGFR	Measured glomerular filtration rate
MMSE	Mini mental state examination
MRI	Magnetic resonance imaging
naMCIm	Non-amnestic MCI multiple domains
naMCIs	Non-amnestic MCI single domain
NSAID	Non-steroidal anti-inflammatory drugs
OR	Odds ratio
PP	Pulse pressure
RAS	Renin-angiotensin-system
SBP	Systolic blood pressure
SCB	Statistics Sweden
SD	Standard deviation
SEK	Swedish krona
SLE	Systemic lupus erythematosus
SNAC	Swedish national study on aging and care
STRIVE	Standards for reporting vascular changes on neuroimaging
SVD score	Cerebral small vessel disease score
SWAN	Susceptibility-weighted angiography
T1-MPRAGE	T1 magnetization-prepared rapid gradient echo
T2-FLAIR	T2-weighted fluid-attenuated inversion recovery
TMT	Trail making test
WMHs	White matter hyperintensities

Papers at a glance

Paper	I	II	III	IV
Aim	To investigate a possible connection between low eGFR and impaired function in different cognitive domains.	To examine if CKD precedes worsening in cognitive function and/or incident dementia and/or incident MCI.	To investigate a possible connection between CKD and markers of CSVD.	To examine if elevated PP is associated with incident CKD, and/or all-cause mortality.
Population and number of participants after exclusion	Participants from the baseline visit in GÅS (2001-2004) N = 2431	Subjects who visited the baseline visit in GÅS (2001-2004) and the 6-year follow-up visit from baseline N = 882	A sub-group of GÅS participants from Malmö who underwent MRI brain examination (2016-2018) N = 390	Participants from baseline in GÅS (2001-2004) and the new subjects recruited in wave 2 (2006-2012) and wave 3 (2012-2016) N = 2693 (outcome CKD) N = 5253 (outcome mortality)
Design	Cross-sectional	Longitudinal 6-year follow-up	Cross-sectional	Longitudinal Median survival time 15 y (event incident CKD) First quartile survival time 12 y (event all-cause mortality)
Explanatory variables	CKD (< 60 ml/min/1.73m^2) Level of eGFR impairment (< 30, 30 - < 45, 45 - < 60 ml/min/1.73m^2)	CKD (< 60 ml/min/1.73m^2)	CKD (< 60 ml/min/1.73m^2)	PP elevation (PP 60 - < 70 mmHg, 70 - < 80 mmHg, ≥ 80 mmHg)
Outcome	Function in complex attention, executive function, learning and memory, language, perceptual-motor, global, meta-memory	Incident dementia Incident MCI Worsened function in complex attention, executive function, learning and memory, language, perceptual-motor, global, meta-memory	Markers of CSVD (WMHs, lacunar infarcts, CMBs, cortical atrophy, composite CSVD, modified STRIVE)	Incident CKD All-cause mortality
Main statistical method	Independent samples t-tests Multiple linear regression models	Logistic regression models Linear logistic models	Logistic regression models	Cox regression models
Main results	CKD and level of eGFR impairment were associated with multiple cognitive domains, but not meta-memory.	CKD was associated with decline in processing speed, but not with dementia or MCI.	CKD was associated with CMBs and cortical atrophy only in the hypertensive sub-group.	Elevated PP was associated with incident CKD and all-cause mortality.

Introduction

The “Good Aging in Skåne” (GÅS) study is an ongoing cohort study of older adults in Skåne [22]. In GÅS, huge amount of data has been collected from a large study sample of older adults from the general population over a time period of more than two decades. Performing epidemiological studies on such data provides the opportunity to estimate the prevalence of various conditions and diseases in the general older population, as well as to identify associations and risk factors of such conditions and diseases. Comparatively, this is often not possible in selected clinical material, where more advanced stages of disease and comorbidity often interfere with correlation analyses.

Impairment in kidney function as well as impairment in cognitive function become more common with age and are very prevalent in the older population. The prevalence of chronic kidney disease (CKD) has been estimated to increase from 7 % in people 30 years and older to 23-36 % in people 65 years and older [1]. The prevalence of the most serious form of cognitive impairment, dementia, has been estimated to increase from 1 % in the age group 65-70 years to 45 % in people 95 years of age and older [3].

By definition, dementia includes loss of independence in the ability to perform the activities of daily living [23], and is a major cause of institutional care. Dementia has tremendous negative impact of the life of the affected individuals and their families [24-26].

Dementia is also associated with a great burden on the healthcare system and the municipalities care, as well as a great financial cost to society. The total financial cost of dementia in Sweden in 2019 has been estimated to approximately Swedish kronor (SEK) 80 billion [27]. Worldwide, the cost of dementia in 2019 has been estimated to astonishing 1,3 trillion US dollars [28].

To this date, no curable treatment of dementia is available. Due to the immense impact of the life of those affected and their relatives, as well as on society, it is of highest importance, if possible, to prevent dementia.

To prevent development of cognitive impairment including dementia, it is of essence to identify both risk factors of, and the pathophysiological pathways leading to, cognitive impairment.

The kidney and the brain share similar low vascular resistance properties, presumably making both organs sensitive to arterial stiffness (AS) and hypertension (HT) [4, 5]. This raises the hypothesis that kidney function and cognitive function could be related, and that this presumed connection could be based on vascular mechanisms.

Kidney function is often assessed in clinical practice by estimating the glomerular filtration rate (eGFR). To identify a potential important risk factor of cognitive impairment, we aimed to evaluate low eGFR as a risk factor of cognitive impairment. To evaluate a possible intervention strategy in the presence of low eGFR, we investigated a possible vascular mechanism behind the potential relationship between low eGFR and cognitive impairment.

A connection between low eGFR and cognitive dysfunction has been proposed previously. It is not clear which cognitive domains could be affected in this potential relationship [29-31]. In paper I and paper II, to increase knowledge of a potential relationship, as well as the strength in a possible relationship between eGFR and cognition, we investigated connections between low eGFR and various aspects of cognitive dysfunction, both cross-sectionally and longitudinally.

Cerebral small vessel disease (CSVD) is an important cause of cognitive decline and dementia [32, 33]. Low eGFR has been linked to CSVD in some previous studies, but which markers of CSVD that could be associated with low eGFR is not fully understood [34-37].

If low eGFR is indeed linked to CSVD, it could give support to the hypothesis that a possible connection between low eGFR and cognitive impairment is based on vascular mechanisms. In paper III, we investigated if CKD is associated with markers of CSVD on magnetic resonance imaging (MRI) examination of the brain.

Elevated pulse pressure (PP) is a surrogate for AS [14-16], and is associated with cardiovascular disease and mortality [38, 39]. PP elevation has been linked to CKD, but if elevated PP precedes CKD is not fully understood [40]. In paper IV, to further investigate the vascular role in renal dysfunction, we examined if elevated PP, as a surrogate for AS, preceded incident CKD.

Kidney function

The kidneys are paired internal organs with multiple important functions. Their main functions include [41]:

- Blood pressure (BP) regulation through the renin-angiotensin-system (RAS).
- Participation in the acid base homeostasis by regulating the concentration of bicarbonate in the blood.
- Conversion of vitamin D into its active form.
- Stimulation of the red bone marrow to produce erythrocytes via the hormone erythropoietin.
- Filtration of blood from water soluble toxins and metabolites.
- Maintaining electrolyte and water balance.

The filtration of blood takes place in the numerous small glomeruli situated in the cortex of the kidneys. The glomeruli represent distal sections of the arteries supplying the kidneys with blood. Primary urine is produced when fluid and small solutes and particles travel passively through the membrane of the glomerulus wall through hydrostatic pressure into the surrounding capsule of Bowman. The membrane of the glomerulus is fenestrated and negatively charged, impeding cells and bigger particles, like albumin, to filter through the wall. The primary urine is transferred from the capsule of Bowman through the proximal- and distal tubule and the collecting duct, in which active and passive uptake and secretion of solutes and fluid between the blood and the primary urine takes place. Urine is the outcome of the process. The urine is collected in the renal pelvis, and further transported into the ureters and the urine bladder [42].

Glomerular filtration rate (GFR) represents the volume of blood being filtered in the glomeruli per minute. GFR depends on the net filtration pressure, which is regulated both locally in the kidney and systemically. Locally, when the BP in the kidney is low or the concentration of sodium chloride in the tubules is low, the smooth muscles of the arterioles proximal to the glomeruli are relaxed, which increases the hydrostatic pressure in the glomeruli leading to increased GFR. The reverse takes place in the presence of high BP or high concentration of sodium chloride, which result in decreased GFR.

Kidney function can be assessed by measuring GFR (mGFR) or estimating GFR. Measurement of GFR can be done directly, by injecting an exogenous substance, known not to be altered in the body and 100 % excreted by the kidneys, into the blood stream. Clearance of the exogenous substance is then measured to assess GFR, that is, the concentration of the exogenous substance in the blood is measured at certain time intervals, and the diminishing concentration of foreign substance per time unit reflects the GFR. Examples of substances that can be used for this purpose are iohexol and inulin. The procedure of measuring GFR directly is however both invasive and time consuming [43].

Another method to assess GFR is to estimate GFR indirectly. This method is non-invasive and less time consuming and therefore commonly used to assess GFR in clinical practice. In this procedure, clearance of an endogenous substance eliminated by the kidneys is measured. The concentration of the endogenous substance in the blood or serum, reflects the GFR. Endogenous substances often used to estimate GFR indirectly are creatinine (crea) and cystatin C (cysC). The higher the concentration of the substance in the serum/blood, the lower the GFR, and vice versa. However, the concentration of any endogenous substance measured in the serum/blood is always dependent on other factors than GFR and varies between individuals. Other factors that often influence the concentration in the serum/blood of an endogenous substance are age, sex, and body constitution. To facilitate comparison between individuals of different weight and height, a standardized body surface area of $1.73m^2$ is commonly applied [43]. Different equations are used to estimate GFR from an endogenous substance. Beside body constitution, these equations often take consideration for age and sex, and sometimes also ethnicity. A reliable and commonly used equation to estimate GFR is the chronic kidney disease epidemiology collaboration (CKD-EPI) equation from 2012 [17], which also is recommended by the International Society of Nephrology [9]. In CKD-EPI, consideration is taken for age and sex.

A common definition of CKD is reduction in GFR below < 60 ml/min/$1.73m^2$ that lasts three months or more, irrespective of the aetiology. The level of impairment in GFR reflects the severity of CKD. GFR 45 –< 60 ml/min/$1.73m^2$ represents mild to moderate CKD, GFR 30 –< 45 ml/min/$1.73m^2$ represents moderate to severe CKD, and GFR < 30 represents severe CKD [9].

Since CKD itself is a known risk factor of the some of the main proposed causes of CKD, that is HT and cardiovascular disease [44, 45], determining the causes of CKD is not straightforward. It is, however, considered that the main causes of CKD in the western world are diabetes and HT, estimated to account for more than 50 % of cases. Other, less frequent, causes of CKD in the western world are considered autoimmune diseases, urological causes, urinary tract infections, systemic infections, hereditary conditions, and nephrotoxic pharmaceuticals [44, 46]. Potential causes of CKD are presented in table 1. Beside diabetes and HT, the traditional cardiovascular risk factors dyslipidemia and smoking are also established risk factors of CKD [9, 47].

Table 1. Considered causes of CKD [44, 46]

Main category	Subcategories/examples
Diabetes	Type 1 Type 2
Hypertension	Primary Secondary
Autoimmune diseases	Vasculitis SLE Sclerodermia
Urological causes	Prostatic diseases Kidney stones Maligniancy
Urinary tract infections	Pyelonephritis Bacterial prostatitis
Systemic infections	Hepatitis C HIV
Hereditary causes	Polycystic kidney disease Alport syndrome
Nephrotoxic pharmaceuticals	NSAID Lithium

Abbreviations: CKD = chronic kidney disease, HIV = humane immunodeficiency viruses, NSAID = non-steroidal anti-inflammatory drugs, SLE = systemic lupus erythematosus

The pathophysiology of HT-induced CKD is complex and not fully understood. The afferent arterioles of the glomeruli in the kidney dilate when blood pressure is low and constricts when blood pressure is high [42]. It is believed that the elevated pulsatile pressure that is related to HT, remodels and stiffens the afferent arterioles of the glomeruli, reducing the ability of the arterioles to constrict and dilate, leading to glomerular HT and fibrotization of the parenchyma of the kidney (hypertensive nephrosclerosis) [48, 49].

Again, since some of the considered complications of CKD also are known risk factors of CKD, that is HT and cardiovascular disease [44, 45], determining the effects of CKD is not straightforward. CKD is often asymptomatic until later stages of the condition (GFR < 30ml/min/1.73m^2) [50]. Symptoms of CKD include [46, 51]:

- Fatigue
- Anorexia
- Weight loss
- Nausea
- Pruritus
- Dyspnea
- Peripheral edema.

Complications of CKD include [45, 51]:

- HT
- Cardiovascular disease
- Anemia
- Osteoporosis
- Fluid retention
- Electrolytes abnormalities
- Acid-base abnormalities
- Coagulopathy
- Increased risk of infections
- Neuropathy.

The main complications of CKD are considered HT and cardiovascular disease. The mortality rate is elevated in CKD patients, mainly due to cardiovascular-related mortality [52, 53].

The pathophysiology behind CKD-related HT is complex and not fully understood. Sodium retention due to elevated levels of the hormones angiotensin II (Ang II) and aldosterone is considered to play an important role in CKD-related HT [48, 51]. In CKD, the RAS is up-regulated. Renin activates the hormone angiotensin I (produced by the liver) into active ang II. Ang II increases blood pressure through a number of activities, including sodium retention in the kidneys, peripheral vasoconstriction, increased sympathetic activity, increased antidiuretic hormone release from the posterior lobe of the pituitary gland, and the release of aldosterone from the cortex of the adrenal glands (which further increases sodium retention in the kidneys) [42].

The pathophysiology of cardiovascular disease induced by CKD is complex and not fully understood. Traditional cardiovascular risk factors, such as HT, diabetes, dyslipidemia, and smoking are strongly associated with CKD, but these traditional cardiovascular risk factors cannot explain all CKD-related cardiovascular disease. Non-traditional CKD-related risk factors of cardiovascular disease include [52, 54]:

- Hypercalcemia and hyperphosphatemia, which promote vascular calcification
- Chronic inflammation, which promotes vascular remodeling resulting in atherosclerosis and vascular calcification
- Salt and fluid retention, which leads to cardiomyopathy and heart failure.

CKD itself can induce the cardiovascular risk factors HT and dyslipidemia, resulting in a bilateral relationship, making the distinction between risk factors of CKD and the complications of CKD further complex [51, 54].

Cognitive function

Cognitive function refers to higher cerebral functions. Cognitive function as a collective concept of higher cerebral functions is referred to as global cognitive function. Cognitive function is, however, commonly categorized into different cognitive domains [55]. There are several definitions of such cognitive domains [56]. One of the most widely accepted definition is probably the one described in DSM-5, in which the following cognitive domains are described (sub-domains in parenthesis) [57]:

- Learning and memory (immediate memory, recent memory, very long-term memory)
- Language (expressive language, receptive language)
- Complex attention (sustained attention, divided attention, selective attention, processing speed)
- Executive function (planning, decision making, working memory, error correction, inhibition, mental flexibility)
- Perceptual-motor (visual perception, visuo-constructional, perceptual-motor, praxis, gnosis)
- Social cognition (recognition of emotions, theory of mind).

Meta-cognition is awareness of one's own cognitive functions. An important part of metacognition is meta-memory, that is, awareness of one's own ability to remember [58].

Dementia

Dementia represents a state of serious cognitive impairment, substantially affecting the function in daily life of the affected individual. The criteria of dementia according to DSM-IV are [23]:

A. Impairment of memory and at least one more cognitive domain.
B. Substantial impairment in social or occupational functioning, which represents a decline from a previous level of function.
C. The cognitive deficit is not entirely explained by delirium.

Dementia can have multiple causes, although the most common causes of dementia are Alzheimer´s disease, vascular dementia, and mixed forms of these pathologies. Examples of other causes of dementia are Lewy body dementia, frontotemporal dementia, and alcohol abuse [59, 60].

Minimal cognitive impairment

Minimal cognitive impairment (MCI) is a condition constituted of cognitive impairment that is not as severe as in the case of dementia, and functional abilities are essentially preserved [61]. The first definition of MCI was initially elaborated by the Mayo clinic in the late 1990s [62], and was by that time considered a precursor to Alzheimer´s disease. This meant that initially, memory was the only cognitive domain considered. At a symposium in 2003, the definition came to be challenged, and impairment in any cognitive domain replaced the mandatory memory impairment [63]. The definition of MCI has been elaborated by multiple workgroups since, but consensus seem to exist regarding the following four criteria [61]:

1. Self- or informant-reported cognitive complaint
2. Objective cognitive complaint
3. Preserved independence in functional abilities
4. Absence of dementia.

Cerebral small vessel disease

CSVD represents pathology of the small vessels in the brain, including small arteries, arterioles, venules, and capillaries. CSVD is often asymptomatic for many years in the early stages of the disease. The clinical aspects of CSVD include cognitive impairment that ranges from MCI to dementia, gait disorders, depression, urinary incontinence, and stroke [32, 64, 65]. CSVD has been estimated to contribute to about 50 % of all dementia [66], and is the cause behind approximately 25 % of all ischemic strokes [67, 68].

CSVD is assessed and diagnosed neuroradiologically. The most reliable neuroimaging method to assess markers of CSVD is MRI [10, 13, 65]. There are different views of how to define CSVD neuroradiologically. In 1996, Offenbacher and colleagues introduced the term microbleeds in their MRI study on small vessel-related abnormalities in the brain [69]. In the same article, they also defined white matter hyperintensities (WMHs) and lacunes. Two of the most influential work groups who have elaborated definitions of CSVD are Joanna Wardlaw et al, who presented the standards for reporting vascular changes on neuroimaging (STRIVE) in 2013 [70], and Julie Staals et al, who presented the cerebral small vessel disease score (SVD score) in 2014 [71].

The neuroimaging features according to STRIVE are recent small subcortical infarcts, lacunes, WMHs, perivascular spaces, cerebral microbleeds (CMBs), and brain atrophy [70].

The neuroimaging features according to the SVD score are lacunes, CMBs, perivascular spaces, and WMHs. The SVD score includes a points system, where presence of lacunes, WMHs, perivascular spaces, and CMBs each contribute with a point (total SVD score 0-4). Increasing total SVD score represents more pronounced occurrence of CSVD [71].

The neuroimaging features of CSVD according to STRIVE, and SVD score, as well as the neuroimaging features of microbleeds, WMHs, and lacunes according to Offenbacher et al are presented in table 2.

Table 2. Neuroimaging features of CSVD according to STRIVE [70], and the SVD score [71]. The neuroimaing features of lacunes, white matter hyperintensities, and microbleeds according to Offenbacher et al [69]

Neuroimaging feature	Definition according to STRIVE	Definition according to the SVD score	Definition according to Offenbacher and colleagues
Recent small subcortical infarcts	< 20 mm; ischemic lesions with respect to perforating arteries; radiologically and clinically indicate formation in recent weeks	-	-
Lacunes	3-15 mm; round or ovoid; subcortical; fluid-filled with CSF-like signal	> 3 - < 20 mm; round or ovoid; in basal ganglia, internal capsule, centrum semiovale, brainstem; with CSF-like signal	< 10 mm; with CSF-like signal
WMHs	Signal abnormality in the white matter; symmetric regardless of size; hyperintensity on T2	Periventricular and/or deep WMHs according to the Fazekas scale [72] on T2	Deep WMHs according to the Fazekas scale [72] on T2
Perivascular spaces	Usually < 3 mm; follow the course of penetrating vessels; often in basal gangliga; CSF-like signal on all MRI sequences	< 3 mm; punctate or linear (follow vessels); in basal ganglia, centrum semiovale; hyperintensities on T2	-
CMBs/microbleeds	2-5 mm (< 10 mm); round or ovoid; signal loss on T2*-weighted gradient echo; usually in deep gray or shite matter, brainstem, cerebellum, cortico-subcortical junction	< 5 mm; homogenous; round; low signal intensity on T2*-weighted gradient echo; in cerebellum, brain stem, basal ganglia, white matter, cortico-subcortical junction	2-5 mm; rounded; Signal loss on T2*-weighted gradient echo; within the brain parenchyma
Brain Atrophy	Atrophy not related to a macroscopic focal injury	-	-

Abbreviations: CMBs = Cerebral microbleeds, CSF = Cerebrospinal fluid, STRIVE = Standards for reporting vascular changes on neuroimaging, SVD score = Cerebral small vessel disease score, WMHs = White matter hyperintensities

Aetiology of CSVD

The by far most common types of CSVD are arteriosclerosis-related CSVD, and amyloid-related CSVD. Arteriosclerosis-related CSVD is sporadic and related to age and traditional vascular risk factors, such as HT, diabetes, and smoking habits. Amyloid-related CSVD, also known as cerebral amyloid angiopathy (CAA) can be both sporadic and hereditary. CAA is heavily related to Alzheimer´s disease [65, 73]. Other far less common causes of CSVD are genetic conditions, immune-mediated CSVD, and infectious-mediated CSVD. Genetic conditions causing CSVD most often affect younger people, examples include cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), and cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL). Immune-mediated CSVD include various forms of vasculitis. Examples of infectious-mediated CSVD are meningovascular neurosyphilis and cerebral malaria [65].

Prevalence of CSVD

Estimates of CSVD prevalence vary depending on which markers of CSVD are considered, but it is clear that the prevalence of CSVD increases with age, and that CSVD is highly common in the older population [74, 75]. For example, the prevalence of CMBs has been estimated to increase from 7 % in people 45-50 years of age to 36 % in people ≥ 80 years of age [76]. The prevalence of lacunar infarcts has been estimated to increase from 22 % at age 75 years to 32 % at age 80 years [77]. The prevalence of WMHs has been estimated to increase from 87 % in people 60-70 years of age to 100 % in people 80-90 years of age [78].

Arterial stiffness and pulse pressure

AS refers to loss of elasticity of the aorta and large arteries. Thanks to the protein elastin, the walls of the big arteries, especially the aorta, is stretched during systole, buffering blood. This buffering of blood reduces the systolic blood pressure (SBP). In diastole, the walls of the big arteries contract thanks to the elastic properties of elastin, pumping blood forward and maintaining BP during this phase of the cardiac cycle. In AS, the elastic properties of the arterial walls decrease (mainly the aorta and the large arteries), reducing the arterial compliance. This results in an increase of SBP and a drop in diastolic blood pressure (DBP) [79].

PP is calculated by subtracting the DBP from the SBP and is a surrogate for AS [14-16]. PP is dependent on the stroke volume of the heart and the arterial compliance, as demonstrated in the following equation [80]:

$$PP = SV/C$$

In this equation, SV = stroke volume and C = arterial compliance. The elastic properties of the aorta and large arteries are the main determinants of arterial compliance [81], that is, AS is the main determinant of arterial compliance. AS is associated with common cardiovascular risk factors, such as HT, diabetes, and smoking, as well as with cardiovascular events, such as coronary heart disease [82].

Possible connection between CKD, cognitive function, CSVD, and PP

CKD, impaired cognitive function, and CSVD are common in the older population. It has been estimated that 23-36 % of individuals ≥ 65 years of age have CKD [1]. This burden increases immensely with age and affects about 55-75% of individuals > 80 years [8]. Cognitive dysfunction also increases with age. The prevalence of the most severe form of cognitive dysfunction, dementia, has been estimated to increase from 1 % in the age group 65-70 years to 45 % in individuals ≥ 95 years of age [3]. The prevalence of CSVD also increases with age [71, 83]. The prevalence of CMBs has been estimated to increase from 7 % in people 45-50 years to 36 % in people ≥ 80 years [76], and the prevalence of lacunar infarcts has been estimated to increase from 22 % at age 75 years to 32 % at age 80 years [77].

The kidney and the brain are high energy consuming organs, dependent on healthy large and small blood vessels providing adequate blood supply [84]. In adults at rest, the kidney receives approximately 20 % of cardiac output and the brain receives approximately 15 % of cardiac output [84-86]. In order to achieve continues high volume blood flow, these organs share similar low vascular resistance systems, resulting in probable microvascular vulnerability to HT [4, 5]. Traditional cardiovascular risk factors, including HT, are strongly associated with CKD [9, 44], cognitive dysfunction [87, 88], and CSVD [5, 73]. Therefore, a connection between CKD and cognitive dysfunction on a vascular basis, is possible, which also has been proposed by others [6, 7]. Since the prevalence of HT is as high as 65 % in individuals ≥ 60 years of age [89], HT could represent the most common treatable risk factor of CKD, cognitive decline and CSVD.

HT is also strongly related to AS [90, 91]. Whether AS is a cause of HT or vice versa is debated [20, 21]. A common surrogate for AS is elevated PP [14-16]. PP is easily assessable in common medical practice. If PP precedes CKD is not known.

Aims

The main aim of this thesis was to evaluate the potential of eGFR as a risk factor of future cognitive dysfunction.

To reach this aim, the following sub-aims were set:

- To investigate if low eGFR/CKD, as well as level of impaired eGFR, is associated with dysfunction in different cognitive domains.
- To investigate if low eGFR/CKD can precede impaired function in different cognitive domains, as well as development of dementia and/or MCI.
- To investigate a potential vascular mechanism behind the possible association between low eGFR/CKD and cognitive dysfunction, we investigated if low eGFR/CKD is associated with markers of CSVD on MRI.
- To investigate a potential vascular mechanism behind low eGFR/CKD, an association between elevated PP, as a surrogate for AS, and incident CKD was examined.

Methods

Study population

The data included in all four studies of this thesis was obtained from the general population cohort study GÅS [22]. GÅS is an ongoing cohort study involving the general older population from the south part of Sweden, and is conducted at the Department of Geriatric Medicine, Skåne University Hospital, Sweden. The GÅS study is part of the "Swedish national study on aging and care" (SNAC) [92]. SNAC started as an initiative from the Swedish government, and is supported not only from the government, but also by the regions and municipalities involved. The aims of SNAC are to increase the knowledge of:

- Healthcare and social care of older people
- Normal ageing from a medical, social, and psychological perspective
- Describe the course of chronic disease in the older population
- Identify risk factors of disease in the older population.

Beside GÅS in Skåne, SNAC is constituted of three other cohort studies of the general older population in Sweden. The locations of these sister studies are:

- Blekinge (SNAC-Blekinge)
- Nordanstig (SNAC-Nordanstig), in Gälveborg
- Kungsholmen (SNAC-Kungsholmen), in Stockholm.

In GÅS, citizens aged sixty and above, have been randomly selected for invitation to the GÅS study using the population registry since 2001. Participants have been collected from five municipalities (Malmö, Eslöv, Hässleholm, Osby, and Ystad), representing both rural and urban parts of Skåne. Invitation is sent by letter. To increase the participation rate in fragile subjects, home visits are offered to those unable to attend the research center. The study visits include a comprehensive health examination conducted by a physician, a registered nurse, and a neuropsychological test administrator. Physical examination, medical history, collection of blood samples, interview, neuropsychological tests, anthropometrics, as well as self-reported questionnaires are being performed. Participants are invited to follow-up examinations every 6 years until age 78, thereafter every 3 years, until death.

At baseline in GÅS between 2001 and 2004, the aim was to recruit a total number of 2950-3000 participants of 60, 66, 72, 78, 81, 84, 87, 90, and 93 years of age. A total number of 2931 participants were recruited. To both maximize the number of individuals who were expected to be followed for a long period of time, and to maximize the number of individuals who were expected to have a high mortality rate, there was an oversampling of the youngest age groups (60 and 66 years) and the oldest age groups (90 and 93 years), respectively.

Every six years, new cohorts of subjects 60 and 81 years of age, have randomly been invited to the GÅS study using the Population Register. The identical study protocol as at the baseline visits have been used. The first additional cohort, named "Wave 2", was recruited in 2006 – 2012. The second, named "Wave 3", was recruited in 2012 – 2016. The third, named "Wave 3", was recruited in 2018 – 2022. A total number of 1523 new subjects were added in Wave 2, 1350 new subjects were recruited in Wave 3, and 1032 new subjects were recruited in Wave 4. The reason that relatively few new participants were recruited in Wave 4 were due to the national restrictions during the COVID-19 pandemic, where the reception at the GÅS research center were forced to close during a whole year.

A timeline of the GÅS study including recruitment of participants and follow up visits is presented in figure 1.

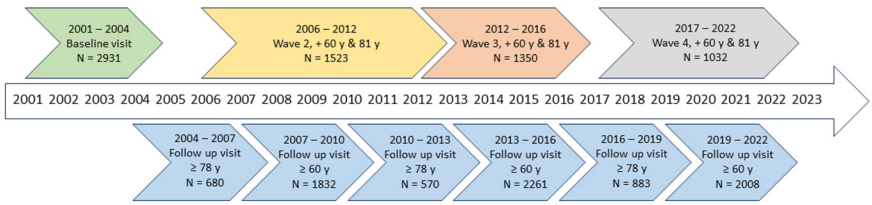

Figure 1. Timeline of the GÅS study

Between March 2016 to March 2018, a sub-group of 407 participants in Malmö were recruited for MRI brain examination as a sub-project of the GÅS study.

Study samples in paper I-IV

The study samples in all four papers consisted of participants in the GÅS study.

Paper I

Data from the baseline visit in GÅS was used. The participation rate at the baseline visit in GÅS was 59.9 %. Exclusion criteria were:

- Dementia
- Depression or missing data regarding depression
- Missing blood samples
- No participation in the cognitive tests
- Missing education data.

200 subjects had dementia, 282 were depressed or had missing data regarding depression, 116 had missing blood samples, 174 did not participate in any of the cognitive tests, and 119 had missing education data. Some participants fulfilled multiple exclusion criteria. Out of the 2931 subjects who attended the baseline visit in GÅS, a total number of 2431 subjects were included in the study. A flow chart of the participation selection in paper I is shown in figure 2.

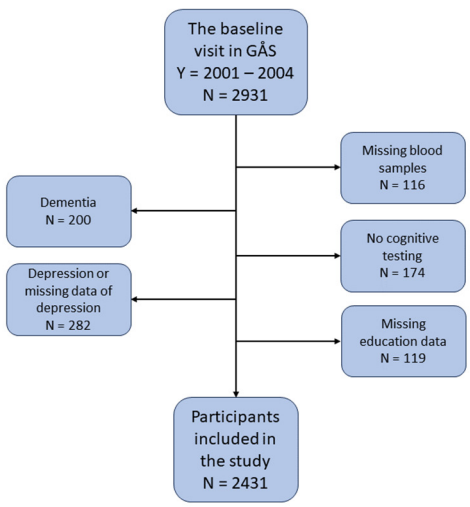

Figure 2. Flow chart of the participation selection in paper I

Paper II

Data from the baseline visit and the 6-year follow-up visit from baseline in GÅS was used. The participation rate of eligible subjects from the baseline visit to the 6-year follow up visit was 83.5 %. The inclusion criterion was attendance at both the baseline visit and the 6-year follow-up visit in GÅS. Out of the 2931 participants who attended the baseline visit, 656 participants had died, and another 82 participants were non-eligible due to that they died after the invitation was sent, they had moved, or were lost to follow-up for another reason. 361 participants were invited but declined participation. A flow chart of the participation rate from the baseline visit to the 6-year follow-up is demonstrated in figure 3.

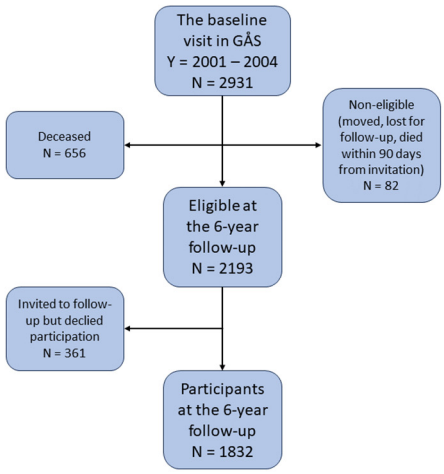

Figure 3. Flow chart of the participation rate from the baseline visit in GÅS to the 6-year follow-up

Exclusion criteria in paper II were:

- Dementia or MCI at the baseline visit
- Depression or missing data of depression at the baseline visit or at the follow-up visit
- No participation in the cognitive tests at the baseline visit or at the follow-up visit
- Change in CKD status from the baseline visit to the follow-up visit
- Missing blood samples and/or missing data regarding education, clinical dementia rating (CDR), smoking habits, and/or HT at the baseline visit or at the follow-up visit.

67 subjects fulfilled the criteria of dementia, and 307 subjects fulfilled the criteria of MCI at the baseline visit. 495 were depressed or had missing data regarding depression at the baseline visit or at the follow-up visit. 210 did not participate in any of the cognitive tests at the baseline visit or at the follow-up visit. 128 changed their CKD status from the baseline visit to the follow-up visit. 234 had missing blood samples, and 360 had missing data regarding education, CDR, smoking habits, and/or HT at baseline or at follow-up. In paper II, a total number of 905 subjects were included in the study, as shown in figure 4.

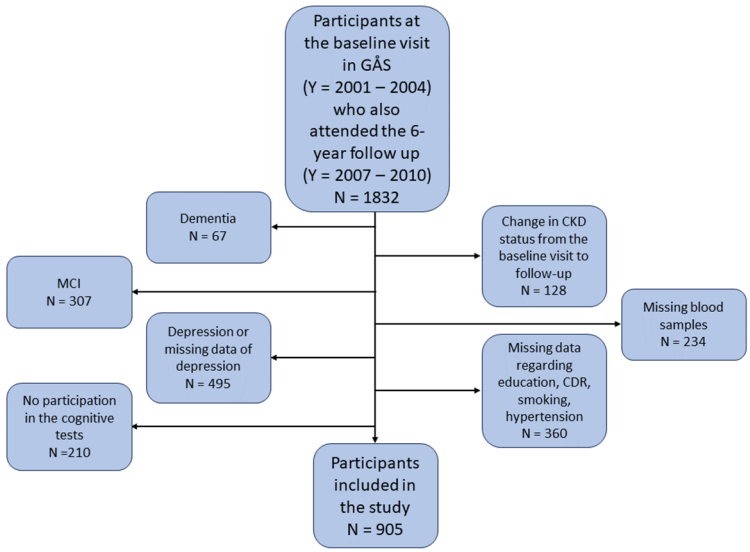

Figure 4. Flow chart of the participation selection in paper II
Exclusion due to dementia or MCI were only applied at the baseline visit. The other exclusion criteria were applied at both the baseline visit and the follow-up visit.

Paper III

Data from the sub-group of 407 subjects in GÅS, who underwent MRI investigation in March 2016 – March 2018, was used. The participation rate for the MRI study was 62.9 %. 17 of these subjects had missing blood samples and were therefore excluded, leaving a total number of 390 subjects included in the study. A flow chart of the participation selection in paper III is shown in figure 5.

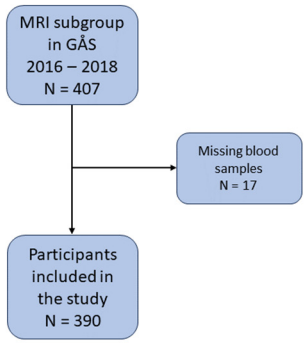

Figure 5. Flow chart of the participation selection in paper III
The only exclusion criterion was missing blood samples.

Paper IV

Data was collected from all the GÅS visits of the included participants, from the first visit and forward until December 20, 2022. Participants included in the fourth study were the subjects recruited at the baseline visit in GÅS back in 2001 – 2004 (participation rate 59.9 %), and the new participants recruited at Wave 2 in 2006 – 2012 (participation rate 72.6 %), and at Wave 3 in 2012 – 2016 (participation rate 70.3 %). The total number of eligible participants was 5804.

When CKD was the outcome, the inclusion criteria were:

- No CKD at the first visit
- Attending at least one visit after the first visit.

When CKD was the outcome, the exclusion criteria were:

- Missing blood samples at the first visit
- Missing PP at the first visit
- Missing body mass index (BMI) at the first visit
- Missing data regarding diabetes and/or smoking habits at the first visit.

951 participants had CKD at the first visit. 1451 attended no further visits in GÅS following the first visit. 485 participants had missing blood samples, PP, BMI, and/or missing data regarding diabetes and/or smoking habits at the first visit. Another 224 participants had missing blood samples and/or BMI at all visits following the inclusion visit and were therefore also excluded. When CKD was the outcome, a total number of 2693 subjects were included in the study. This is demonstrated in figure 6.

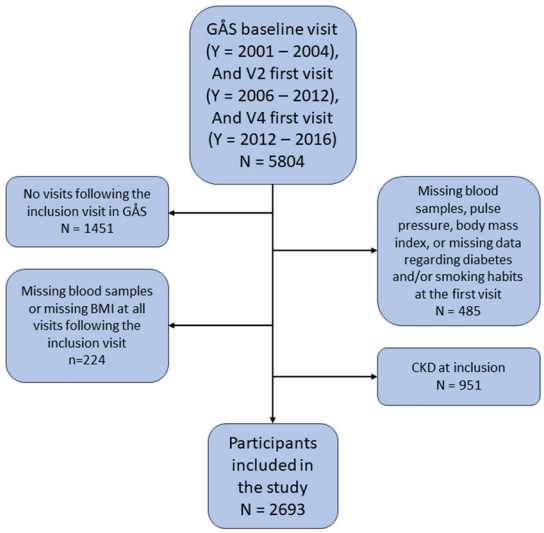

Figure 6. Flow chart of the participation selection in paper IV when the outcome was CKD

When the outcome was all-cause mortality, the only inclusion criteria were assessable data regarding PP, diabetes, and smoking habits at the first visit. 550 subjects had missing data at the first visit. One subject had missing data regarding the date of mortality, leaving a total number of 5253 subjects included in the study. A flow chart of the participation selection when the outcome was all-cause mortality is presented in figure 7.

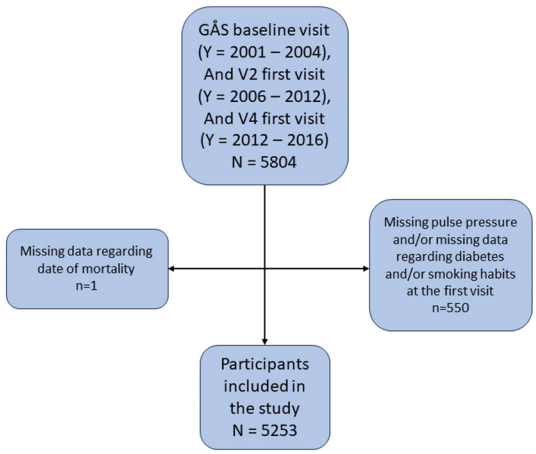

Figure 7. Flow chart of the participation selection in paper IV when the outcome was all-cause mortality

Kidney function

Blood sampling

Blood samples were taken non-fasted by a nurse and was cryopreserved at both baseline in 2001 – 2004, and at the 6-year follow-up visit in 2007 – 2010. Crea was analysed later by the hospital laboratory in Malmö using a modified Jaffe method with a Beckman Coulter LX 20 traceable to isotope-dilution mass spectrometry. CysC was analysed later by the same laboratory using Gentians reagent with a Beckman Coulter LX 20 [93].

Estimating glomerular filtration rate

GFR is commonly estimated indirectly by measuring the levels of different proteins in the blood known to be excreted by the kidneys. The most common proteins used to estimate GFR are crea and/or cysC. GFR is estimated from the protein concentration in the blood using a mathematical equation [9]. One of the most used equations to estimate GFR is the reliable and well-established chronic kidney disease epidemiology collaboration (CKD-EPI) equation [94]. In the first version of the equation from 2009, GFR was estimated from crea alone. In an updated version of the CKD-EPI from 2012, eGFR could be estimated based on crea, cysC or both crea and cysC (crea/cysC) [17].

The 2012 version of the CKD-EPI equation based on crea/cysC to estimate GFR is displayed in table 3. The 2012 version of the CKD-EPI equation based on cysC to estimate GFR is displayed in table 4.

Table 3. The 2012 version of the CKD-EPI equation based on crea/cysC to estimate GFR [17]

Sex	Crea mg/dl	CysC Mg/L	Equation for estimating GFR
Female	≤ 0,7	≤ 0,8	$130 \times (crea/0.7)^{-0.248} \times (cysC/0.8)^{-0.375} \times 0.995^{age}$
		> 0,8	$130 \times (crea/0.7)^{-0.248} \times (cysC/0.8)^{-0.711} \times 0.995^{age}$
Female	> 0,7	≤ 0,8	$130 \times (crea/0.7)^{-0.601} \times (cysC/0.8)^{-0.375} \times 0.995^{age}$
		> 0,8	$130 \times (crea/0.7)^{-0.601} \times (cysC/0.8)^{-0.711} \times 0.995^{age}$
Male	≤ 0,9	≤ 0,8	$135 \times (crea/0.9)^{-0.207} \times (cysC/0.8)^{-0.375} \times 0.995^{age}$
		> 0,8	$135 \times (crea/0.9)^{-0.207} \times (cysC/0.8)^{-0.711} \times 0.995^{age}$
Male	>0,9	≤ 0,8	$135 \times (crea/0.9)^{-0.601} \times (cysC/0.8)^{-0.375} \times 0.995^{age}$
		> 0,8	$135 \times (crea/0.9)^{-0.601} \times (cysC/0.8)^{-0.711} \times 0.995^{age}$

Table 4. The 2012 version of the CKD-EPI equation based on cysC to estimate GFR [17]

Sex	CysC Mg/L	Equation for estimating GFR
Female	≤ 0,8	$133 \times (cysC/0.8)^{-0,499} \times 0.996^{age} \times 0,932$
	> 0,8	$133 \times (cysC/0.8)^{-1,328} \times 0.996^{age} \times 0.932$
Male	≤ 0,8	$133 \times (cysC/0.8)^{-0,499} \times 0.996^{age}$
	> 0,8	$133 \times (cysC/0.8)^{-1,328} \times 0.996^{age}$

CKD was defined as having an eGFR of < 60 ml/min/1.73m^2 [9]. This definition of CKD was used in all papers of the thesis. In addition, in paper I, the level of eGFR impairment also was assessed. GFR was estimated from crea/cysC using the CKD-EPI equation from 2012 in paper I and paper II, since the use of both crea and cysC in this equation had proven to more accurately reflect GFR compared to estimating GFR from either crea or cysC alone [17].

However, in a large meta-analysis published in 2020 (n=23 667), comparing the use of crea, cysC and crea/cysC in the CKD-EPI equation, Zou et al [95] found that the use of crea/cysC indeed provided the highest accuracy, whereas the use of cysC alone provided the least amount of bias. A previous study of the GÅS material found a significant amount of variation between eGFR based on cysC compared to eGFR based on crea using the CKD-EPI equation (≥ 10 % variation was found in 65 %, and > 30 % variation was found in 19 % of the participants), indicating occurrence of bias in eGFR calculated from crea and/or cysC in the material [93]. The use of crea for estimating GFR can be problematic since crea is directly related to muscle mass. In the older population, where loss of muscle mass and sarcopenia is common, crea often overestimates GFR [96]. Low body weight is associated to sarcopenia in older people [97]. In paper III, the proportion of subjects who had eGFR close to the cut-off for CKD (50-70 ml/min/1.73m^2) was more than 50 %. To decrease bias and increase accuracy in paper III, GFR was estimated from crea/cysC in non-underweight participants, and from cysC alone in underweight participants. Underweight in older people is commonly defined as having a BMI of < 23 [98], and this definition was used to define underweight. The same procedure to assess eGFR was also used in paper IV.

Cognitive function

The cognitive tests and the cognitive domains

A cognitive test battery including 12 tests was used to assess the cognitive domains learning and memory, language, complex attention, executive function, perceptual-motor, as well as meta-memory, and global cognitive function.

Learning and memory

Immediate memory and *recent memory* are sub-domains of learning and memory [57]. Immediate memory was assessed using the *digit span forward test* [99]. In this test, the task was to orally repeat a series of numbers ranging from 1-9. The longest correct recalled digit span was used for assessment. Recent memory was assessed using the tests *free recall* and *recognition* [100]. In free recall, sixteen words were presented to the participant. The task was then to recall as many of these words as possible. The number of correctly recalled words were used for assessment. In recognition, the sixteen words from the test free recall was presented along with 16 new words. The task was to identify the words from the test free recall. The number of correctly recalled words minus the number of incorrect words were used for assessment.

Language

Expressive language is a sub-domain of language [57], and was assessed using the tests *word fluency F and A* [99]. In this test, the task was to name as many words as possible that start with the letter F and then A. One minute was given for each letter. The mean of the number of words from each letter was used for assessment.

Complex attention

The speed of processing is a sub-domain to complex attention [57], and was assessed using the tests *digit cancellation* [101], and *pattern comparison* [102]. In paper II, the *trail making test (TMT) A* was also used for assessment of processing speed [99]. In digit cancellation, rows of random numbers were presented to the participant. The task was to draw a line over as many fours as possible for 30 seconds. The number of correctly drawn lines were used for assessment. In pattern comparison, figures in pairs were presented. The task was to determine whether the figures in each pair were identical or not, during 2 x 30 seconds. The number of correct answers was used for assessment. In TMT A, the task was to draw lines between preprinted numbers, in ascending order (1-2-3 and so on). The time it took in seconds to complete the task was used for assessment. Participants who had one error or more were excluded. There was no time limit, but participants who finished the test ≤ 7 seconds (> 2 standard deviations (SD) from mean) were excluded due to suspicion of misprint in documentation.

Executive function

Mental flexibility and *working memory* are sub-domains to executive function [57]. Mental flexibility was assessed using the test *TMT B* [56, 99] in paper II, and *TMT B-A* [103] in paper I. In TMT B, the task was to draw lines between ascending numbers and letters alternating (1-A-2-B and so on). Participants who had one error or more were excluded. There was no time limit, but participants who finished the test ≤ 12 s (> 2 SD from mean) were excluded due to suspicion of misprint in documentation. In paper I, TMT B-A was used for assessment of mental flexibility, in order to avoid measuring the speed of perception [103]. In paper II, TMT B was used for assessment of mental flexibility.

Perceptual-motor

Visual perception is a sub-domain to perceptual-motor [57], and was assessed using the *mental rotations test*. The mental rotations test was a simplified version of the Shepard-Metzler test [104], including 10 assignments. The assignments consisted of comparing rotated three-dimensional figures in order to determine which were identical and not. The participant was given 45 s per assignment. The ratio of correctly answered assignments through the total number of answered assignments were used for assessment.

Meta-memory

Meta-memory was assessed using a *confidence judgement test* [105]. In this test, the participant answered questions of general knowledge, of the type "from which country does the word alcohol originate"? The participant had two answer options for each question. The total number of questions was 10. The participant was also assigned to declare, in percent (50, 60, 70, 80, 90, 100), how certain he/she had been of answering each of the 10 questions correctly. 50 % represented total uncertainty, and 100 % represented total certainty of having answered a question correctly. The following calibration formula was used to estimate the confidence:

$$\frac{1}{n}\sum_{t=1}^{T} nt(rt - ct)2$$

In this formula, *n* represented the total number of answered questions. *T* represented the number of confidence levels (6 levels). *rt* represented the confidence level. *nt* represented the number of times the confidence level *rt* was reported. *ct* represented the ratio of correct answers through the total number of answers where confidence level *rt* was reported. If the answer from the formula was zero, there was perfect calibration. That is, the participant´s judgement of his/her own ability to answer the questions correctly, corresponds perfectly with his/her actual performance. The higher the value from the formula, the more the participant was misjudging his/her ability of answering the questions correctly.

Global cognitive function

Global cognitive function was assessed using the test *mini mental state examination (MMSE)*. This commonly used screening test of cognitive impairment consisted of 11 assignments designed to assess multiple cognitive domains, together representing global cognitive function [106].

Dementia

Dementia was assessed by a physician from the participant´s medical history, or as a clinical assessment according to the DSM-IV criteria [23], that is:

- Impairment in memory and at least one more cognitive domain
- Significantly impaired social or professional function due to the cognitive impairment, which represent a significant impairment compared to earlier in life
- The cognitive impairment is not to be exclusively related to confusion.

MCI

MCI was defined as fulfilling the following four criteria [61]:

- Self-reported memory complaint
- Objective cognitive complaint
- Preserved functional independence
- No dementia.

Self-reported memory complaint was assessed in the questionnaire by the following question: “Do you think your memory has deteriorated”? The possible answers were “no”, “somewhat”, and “a lot”. The answers “somewhat” and “a lot” were regarded to represent self-reported memory complaint.

Objective cognitive complaint was assessed by comparing the participant´s performance on the different cognitive tests with a reference population. The reference population consisted of 3363 older participants from the sister study SNAC-Kungsholmen [92]. After exclusion due to dementia, depression, or missing data, 2730 individuals remained. Performing > 1.5 SD worse from the reference population mean on any of the cognitive tests was considered representative of objective cognitive complaint. Since the seventh percentile ≈ 1.5 SD, the best score of the worst seventh percentile on each of the cognitive tests performed by the reference population was used as cut-off value. Age, sex, and educational level can affect cognitive function. Therefore, cut-off values were calculated for different combinations of these variables.

Functional independence was assessed by a physician, using the CDR scale [107]. In CDR, function due to cognitive status, were evaluated in the following six items:

- Memory
- Orientation
- Judgement and problem solving
- Community affairs
- Home and hobbies
- Personal care.

In each of these items, the points 0, 0.5, 1, 2, and 3 could be scored, where 0 and 0.5 points represented no dependence, and questionable dependence, respectively. 1-3 points represented ascending degree of dependence. Functional independence was defined as ≤ 0.5 points in each of the six items.

The CDR scale is presented in table 5.

Table 5. Clinical Dementia Rating (CDR) [107]

	None 0	Questionable 0.5	Mild 1	Moderate 2	Severe 3
Memory	No memory loss or slight inconsistent forgetfulness	Consistent slight forgetfulness; partial recollection of events	Moderate memory loss; more marked for recent events; defect interferes with everyday activity	Severe memory loss; only highly learned material retained; new material rapidly lost	Severe memory loss; only fragments remain
Orientation	Fully oriented	Fully oriented but with slight difficulty with time relationships	Moderate difficulty with time relationships; oriented for place at examination; may have geographic disorientation elsewhere	Severe difficulty with time relationships; usually disoriented to time, often to place	Oriented to person only
Judgment and problem solving	Solves everyday problems and handles business and financial affairs well; judgment good in relation to past performance	Slight impairment in solving problems, similarities and differences	Moderate difficulty in handling problems, similarities and differences; social judgment usually maintained	Severely impaired in handling problems, similarities and differences; social judgment usually impaired	Unable to make judgments or solve problems
Community affairs	Independent function as usual in job, shopping, volunteer, and social groups	Slight impairment in these activities	Unable to function independently at these activities though may still be engaged in some; appears normal to casual inspection	No pretense of independent function outside the home; appears well enough to be taken to functions outside the family home	Appears too ill to be taken to functions outside the family home
Home and hobbies	Life at home, hobbies and intellectual interests well maintained	Life at home, hobbies and intellectual interests slightly impaired	Mild but definite impairment of functions at home; more difficult chores, and complicated hobbies and interests abandoned	Only simple chores preserved; very restricted interests, poorly maintained	No significant function in the home
Personal care	Fully capable of self-care	Fully capable of self-care	Needs prompting	Requires assistance in dressing, hygiene and keeping of personal effects	Requires much help with personal care; frequent incontinence

Score only as decline from previous usual level due to cognitive loss, not impairment due to other factors.

Dementia was assessed using the DSM-IV criteria of dementia (see above).

MCI can be divided into the following sub-groups [61]:

- amnestic MCI single domain (aMCIs)
- amnestic MCI multiple domains (aMCIm)
- non-amnestic MCI single domain (naMCIs)
- non-amnestic MCI multiple domains (naMCIm).

The definition of these MCI sub-groups are as follows [61]:

- aMCIs: impaired memory, but intact function in all other cognitive domains
- aMCIm: impaired memory and impaired function in at least one other cognitive domain
- naMCIs: impaired function in one cognitive domain other than memory
- naMCIm: impaired function in at least two cognitive domains other than memory.

The subjective memory complaint criterion, as well as the criteria for preserved functional independence and dementia, did not differ from the MCI criteria (see above).

The objective complaint in aMCIs was defined as performing > 1.5 SD worse from the reference population mean in ≥ 1 cognitive test representing the domain learning and memory, but no other domains.

The objective complaint in aMCIm was defined as performing > 1.5 SD worse than the reference population mean in cognitive tests representing ≥ 2 cognitive domains, including the domain learning and memory.

The objective complaint in naMCIs was defined as performing > 1.5 SD worse than the reference population mean in ≥ 1 cognitive test representing only one cognitive domain, but not the domain learning and memory.

The objective complaint in naMCIm was defined as performing > 1.5 SD from the reference population mean in cognitive tests representing ≥ 2 cognitive domains, but not the domain learning and memory.

Cerebral small vessel disease

Magnetic resonance imaging

A sub-group of 407 individuals underwent MRI examination of the brain. MRI was performed in the Radiology Department at Skåne University Hospital in Malmö, using a 3 Tesla MRI (General Electric discovery MR 750w). The MRI examination included:

- T1 magnetization-prepared rapid gradient echo (T1-MPRAGE)
- Diffusion-weighted images (DWI)
- T2-weighted fluid-attenuated inversion recovery (T2-FLAIR)
- Susceptibility-weighted angiography (SWAN).

An experienced neuroradiologist reviewed the MRI images for identification and quantification of WMHs, lacunar infarcts, CMBs, and brain atrophy. A comparison between the definition of these markers of CSVD in paper III compared to the definition in STRIVE [70], the SVD score [71], and Offenbacher et al [69] is presented in table 6.

White matter hyperintensities

WMHs were assessed using the Fazekas scale for WMHs [72], where a score of ≥ 2 was considered pathological and representative of pathological presence of WMHs. The T2-FLAIR sequence was used to assess WMHs.

Lacunar infarcts

Lacunar infarcts were defined as having ≥ 1 small infarction (<1.0 cm) in the deep white matter, the basal ganglia or pons [69]. The T2-FLAIR sequence was used to assess lacunar infarcts.

Cerebral microbleeds

CMBs were defined as having ≥ 1 small (0,2-0,5 cm) hypointense lesion [69], using the SWAN sequence.

Cortical atrophy

Cortical atrophy was defined as presence of at least one of the following entities: Global cortical atrophy (GCA) ≥ 1 according to the Pasquier scale [108], Koedam score ≥ 1 [109], and/or presence of frontal/frontotemporal/temporal atrophy (visually assessed by an experienced neuroradiologist). The T1-MPRAGE sequence was used for assessment.

The composite CSVD variable

The composite CSVD variable was constituted of a modified version of the SVD score, presented by Staals et al in 2014 [71]. Presence of CSVD according to the composite CSVD variable was defined as presence of at least one of the following: Fazekas scale ≥ 2, ≥ 1 lacunar infarct, and/or ≥ 1 CMB.

The modified STRIVE variable

The modified STRIVE variable was constituted of a modified version of STRIVE, presented by Wardlaw et al in 2013 [70]. Presence of CSVD according to the modified STRIVE variable was defined as presence of at least one of the following: Fazekas scale ≥ 2, ≥ 1 lacunar infarct, ≥ 1 CMB, cortical atrophy, and/or central atrophy. Presence of central atrophy was visually assessed by an experienced neuroradiologist using the T1-MPRAGE sequence.

Table 6. Definition of markers of CSVD in paper III compared to the same definition according to STRIVE [70], the SVD score [71], and by Offenbacher et al [69].

CSVD marker	Paper III	STRIVE	The SVD score	Offenbacher et al
WMHs	Periventricular and/or deep WMHs according to the Fazekas scale [72] on T2-FLAIR; a score of ≥ 2 was considered representative of WMHs	Signal abnormality in the white matter; symmetric regardless of size; hyperintensity on T2	Periventricular and/or deep white matter hyperintensities according to the Fazekas scale [72] on T2	Deep WMHs according to the Fazekas scale [72] on T2
Lacunar infarcts/lacunes	< 1.0 cm; with CSF-like signal on T2-FLAIR; located in the deep white matter, the basal ganglia or pons; ≥ 1 lacunar infarct was considered representative of presence of lacunar infarcts	3-15 mm; round or ovoid; subcortical; fluid-filled with CSF-like signal	> 3 - < 20 mm; round or ovoid; in basal ganglia, internal capsule, centrum semiovale, brainstem; with CSF-like signal	< 10 mm; with CSF-like signal
CMBs	2-5 mm; hypointense lesion on SWAN; ≥ 1 CMB was considered representative of presence of CMBs	2-5 mm (< 10 mm); round or ovoid; signal loss on T2*-weighted gradient echo; usually in deep gray or shite matter, brainstem, cerebellum, cortico-subcortical junction	< 5 mm; homogenous; round; low signal intensity on T2*-weighted gradient echo; in cerebellum, brain stem, basal ganglia, white matter, cortico-subcortical junction	2-5 mm; rounded; Signal loss on T2*-weighted gradient echo; within the brain parenchyma
Brain atrophy/cortical atrophy	Global cortical atrophy (GCA) ≥ 1 according to the Pasquier scale [108] and/or Koedam [109] score ≥ 1 and/or presence of frontal/frontotemporal/temporal atrophy on T1-MPRAGE	Atrophy not related to a macroscopic focal injury	-	-

Abbreviations: CMBs = Cerebral microbleeds, CSF = Cerebrospinal fluid, GCA = Global cortical atrophy, STRIVE = Standards for reporting vascular changes on neuroimaging, SVD score = Cerebral small vessel disease score, SWAN = Susceptibility-weighted angiography, T2-FLAIR = T2-weighted fluid-attenuated inversion recovery, WMHs = White matter hyperintensities

Hypertension

At each GÅS visits, a physician assessed a history of HT from the medical history as well as from the medical record. The medical record was reviewed for a diagnosis of primary or secondary HT according to the International Classification of Diseases version 10 (ICD-10). Current use of antihypertensive pharmaceuticals was documented using the following Anatomical Therapeutic Chemical (ATC) codes:

- Antihypertensive agents ATC02
- Diuretics TC03
- Beta-blockers ATC07
- Calcium antagonists ATC08
- RAS inhibitors ATC09.

Medical records were also reviewed in retrospect by the authors for an ICD-10 diagnosis of primary or secondary HT diagnosed any time before baseline in paper II and before the MRI examination in paper III.

Pulse pressure

BP was assessed by a physician using a sphygmomanometer. The BP was measured in the left arm in a sitting position after 5 minutes of rest using an appropriately sized cuff (standard 12 cm, smaller 9 cm, or a wider 15 cm). PP was assessed by subtracting the DBP from the SBP. The European Association of Cardiology (ESC) defines elevation of PP as PP $\geq$ 60 mmHg in older people [110]. As part of the Framingham study, Franklin et al [111] also found that a PP elevation around this level was associated with future cardiovascular events. Hence, the cut-off level for PP elevation was set at $\geq$ 60 mmHg.

Other cardiovascular variables

Diabetes

Diabetes was assessed by asking of a previous diagnosis of diabetes type 1 or 2 in the questionnaire, or a previous diagnosis of diabetes type 1 or 2 documented in the participant's medical record.

Smoking habits

Smoking habits was assessed by questionnaire. In paper I and II, smoking habits were defined as active smoker, former smoker, or never smoked. In paper IV, smoking habits were defined as active or former smoker, or never smoked.

Body mass index

BMI was assessed by the following formula: BMI = weight (in kilograms)/length (in meter)^2. Weith and length was measured by a nurse. Weight was measured with light clothes and no shoes after voiding bowels and bladder in non-fasting conditions (Tanita Cort, Japan) [112].

Demographic variables

Age

The number of lived years (integer) was used.

Sex

Sex was defined as male or female.

Level of education

Level of education was assessed by questionnaire and was defined as elementary school not completed or fulfilled elementary school, fulfilled secondary school, and one year or more of higher education or university degree.

Country of origin

Country of origin was assessed by questionnaire and was defined as born in Sweden or born in another country than Sweden.

Other variables

Depression

The comprehensive psychopathological rating scale (CPRS) was used to assess depression [113]. The scale included 10 items designed to assess depression, of which 9 consisted of questions, and one consisted of observation of the participant. The maximum possible score was 60. The CPRS has been shown to have high validity and high inter-rater reliability [114]. A translation of the CPRS score into clinical practice was conducted by Snaith et al in 1986 and has been widely accepted [115]. According to the work by Snaith et al, a CPRS score of 7 – 19 represents mild depression, a score of 20 – 34 represents moderate depression, and a score of 35 – 60 represents severe depression. Depression was assessed in paper I and paper II. A CPRS score of > 20 was regarded representative of depression [116].

Paper I

The first study had a cross-sectional design. 2931 participants recruited from the GÅS baseline in 2001 – 2004 constituted the study sample. The participation rate at baseline was 59.9 %.

Since depression is linked to cognitive impairment [117-119], individuals who were suspected of being depressed were excluded. Assessment of depression was based on CPRS. Individuals with dementia were excluded. Individuals who had missing blood samples, missing CPRS data (participants with ≤ 2 missing CPRS answers had these answers imputed based on the mean of the other CPRS answers), missing education data, and/or did not participate in any of the cognitive tests, were also excluded. The total number of participants left in the study was 2431. The mean age of the participants included in the study was 71.4 years (SD 10.3).

Participants were divided into groups based on kidney function. Analyses were made with the study sample divided into two groups based on kidney function: Impaired kidney function/CKD (GFR < 60 ml/min/1.73m^2), and normal kidney function (GFR ≥ 60 ml/min/1.73m^2), as well as four groups: < 30, 30 - < 45, 45 - < 60, and ≥ 60 ml/min/1.73m^2.

Analyses were made investigating associations between GFR divided into two and four groups, respectively, and performance on the different cognitive tests, representing the cognitive domains complex attention, executive function, learning and memory, language, and perceptual-motor, as well as global cognitive function and meta-memory. The same analyses were also made with stratification made of the study sample into the following four age groups: 60-69 y, 70-79 y, 80-89 y, and ≥ 90 y.

Paper II

The second study had a longitudinal design. Of the 2931 individuals who was recruited at the GÅS baseline visit in 2001 – 2004, 2193 were eligible at the 6-year follow-up. Of these 2193 individuals, 1832 also attended the 6-year follow-up in 2007 – 2010.

To avoid uncertainty of whether impaired kidney function preceded cognitive impairment, individuals who did not remain in their GFR group from baseline to follow-up were excluded. That is, only subjects who had a remaining eGFR of either < 60 ml/min/1.73m^2 or ≥ 60 ml/min/1.73m^2 from the baseline visit to the 6-year follow-up visit were included. Individuals with dementia or MCI at baseline were excluded. Since depression is linked to cognitive impairment [117-119], individuals who were suspected of being depressed at baseline or at follow-up were excluded. Individuals who had missing blood samples, missing CPRS data (participants with ≤ 2 missing CPRS answers had these answers imputed based on the mean of the other CPRS answers), missing education data, and/or did not participate in any of the cognitive tests, were also excluded. The total number of participants left in the study was 882. The mean age of the participants included in the study was 67.6 years (SD 8.53).

Participants were divided into two groups based on kidney function at baseline: Impaired kidney function/CKD (GFR < 60 ml/min/1.73m^2), and normal kidney function (GFR ≥ 60 ml/min/1.73m^2). The cumulative incidence of dementia and MCI, as well as the MCI sub-groups (aMCIs, aMCIm, naMCIs, and naMCIm), were compared at follow-up between the two groups.

To assess the impact of GFR status on different cognitive domains, the change in performance on the different cognitive tests from the baseline visit to the 6-year follow up visit were compared between the two groups. Function in the following cognitive domains were tested: Complex attention, executive function, learning and memory, language, and perceptual-motor. Function in global cognitive function and meta-memory was also tested.

Paper III

The third study had a cross-sectional design. A sub-group of 407 individuals from the GÅS study underwent MRI brain examination in March 2016 to March 2018. 17 of these were excluded due to missing blood samples, leaving 390 participants in the study. The mean age of the remaining participants was 75.4 (SD 3.6) years.

Associations between CKD, defined as eGFR < 60 ml/kg/1.73m^2, and markers of CSVD on MRI were investigated. Normal kidney function (≥ 60 ml/kg/1.73m^2) was set as reference. The following MRI findings were assessed: WMHs, lacunar infarcts, CMBs, cortical atrophy, composite CSVD, and modified STRIVE.

In a secondary analysis the same analyses as above were performed after stratification of the study sample based on HT status, that is HT or no HT.

Paper IV

The fourth study had a longitudinal design. The impact of elevated PP, as a surrogate for AS, on incident CKD (eGFR < 60 ml/kg/1.73m^2) and all-cause mortality was investigated. Elevated PP was set at three levels: 60 - < 70 mmHg, 70 - < 80 mmHg, and ≥ 80 mmHg. Normal PP was defined as < 60 mmHg and used as reference for all levels of elevated PP.

5804 subjects were recruited at three intervals in GÅS, that is, between 2001 – 2004, 2006 – 2012, and 2012 – 2016. These first GÅS visits represent the baseline visit of this study.

The number of included participants differed depending on outcome due to different inclusion and exclusion criteria. When the outcome was CKD, the inclusion criteria were absence of CKD at the baseline visit, and that the subjects attended at least one visit after the baseline visit. Exclusion criteria were missing blood samples, PP, BMI, and/or data regarding diabetes or smoking habits at the baseline visit. When the outcome was CKD, a total number of 2693 subjects were included in the study. The mean age of these subjects was 65.0 (SD 7.3) years.

When the outcome was all-cause mortality, the only inclusion criterion was assessable data regarding age, sex, PP, diabetes, and smoking habits at the baseline visit. When the outcome was all-cause mortality, 5253 subjects were included in the study. The mean age of these subjects was 69.4 (SD 10.3) years.

Subjects under the age of 78 in GÅS have been re-examined every 6 years, and subjects 78 years and older every 3 years, until death. Data was collected from all GÅS visits from the baseline visit and December 20, 2022.

Statistical methods

All statistical analyses in all four papers were performed using the IBM SPSS software. The statistical significance level was set to 0.05 in all papers.

Paper I

The study sample was divided into two groups based on eGFR (< 60, and ≥ 60 ml/min/1.73m^2), and into four groups based on eGFR (< 30, 30 - < 45, 45 - <60, ≥ 60 ml/min/1.73m^2). Normal kidney function (eGFR ≥ 60 ml/min/1.73m^2) was used as reference in both cases.

Individual samples t-tests were used to compare the results of the different cognitive tests between two (eGFR < 60, and ≥ 60 ml/min/1.73m^2), and four groups (eGFR < 30, 30 - < 45, 45 - <60, ≥ 60 ml/min/1.73m^2) based on kidney function, with no consideration taken to any potential confounders. Although the result from every single cognitive test was not normally distributed, the sample size was big enough to allow use of independent sample t-tests [120].

Multiple linear regression models were used to compare the results of the different cognitive tests between the two and the four groups based on kidney function, with adjustments made for the demographic variables age, sex, level of education, and country of origin. The same analyzes were also made after stratification of the study sample into four age groups (60-69 y, 70-79 y, 80-89 y, and ≥ 90 y).

Paper II

The odds for subjects with impaired kidney function/CKD (eGFR < 60 ml/min/1.73m^2) of developing dementia or MCI compared to those with normal kidney function (eGFR ≥ 60 ml/min/1.73m^2) were calculated using logistic regression models. The odds for subjects with impaired kidney function/CKD of developing aMCIs, aMCIm, naMCIs, or naMCIm compared to those with normal kidney function were calculated using a multinomial logistic regression model.

Change in function in different cognitive domains was assessed by calculating the difference in performance on each of the cognitive tests from baseline to follow-up. Linear regression models were used to analyse if the difference in performance on the tests from baseline to follow-up differed between those with impaired kidney function/CKD compared to those with normal kidney function, with adjustment made for age, sex, level of education, HT, diabetes, and smoking habits.

Paper III

Binary logistic regression models were used to investigate the association between CKD (< 60 ml/min/1.73m^2) and the presence of WMHs, lacunar infarcts, CMBs, cortical atrophy, composite CSVD, and modified STRIVE. Normal kidney function (≥ 60 ml/min/1.73m^2) was set as reference.

First, the logistic models were examined without covariates. We also estimated the logistic models including age and sex, since these covariates can affect both renal function and CSVD.

In a secondary analysis, the same logistic models were examined after stratification had been made by HT status, with adjustments made for age and sex.

Paper IV

Proportional hazard models were performed using Cox regression models. First, the association between the explanatory variable elevated PP (set at three levels: 60 - < 70 mmHg, 70 - < 80 mmHg, and ≥ 80 mmHg) at the inclusion visit and the event incident CKD (eGFR < 60 ml/kg/1.73m^2) during the follow-up period was examined. Normal PP (< 60 mmHg) was set as reference for all levels of elevated PP.

Second, using the same statistical model, the association between elevated PP at the inclusion visit and all-cause mortality during follow-up was examined. PP was set at the same three levels as above, with normal PP (< 60 mmHg) as reference for all levels of elevated PP.

The models above were set up both unadjusted, and adjusted for the covariates age, sex, diabetes, and smoking habits. HT is closely related to AS and elevated PP [90, 91, 121]. To avoid collinearity, HT was not included as a covariate in the statistical models.

Ethical considerations

The GÅS study is conducted in accordance with the Declaration of The Code of Ethics of the World Medical Association (Declaration of Helsinki) [122]. All participants in the GÅS study received written information. Written consent for participation in the GÅS study was obtained from either the participants or, when necessary, from relatives. To perform the studies of this thesis, approvals were obtained from the Ethics Committee of Lund University, Sweden (reference number: LU 744-20 and LU 744-00), and from the Regional Ethics Review Board, Lund University, Sweden (2015/859).

This project includes participants with cognitive impairment. These participants are to be regarded as extra vulnerable, and therefore in need of extra consideration in a research setting. The tests performed during the GÅS visits are non-invasive and considered safe and non-stressful. An exception is the potential discomfort and small risk of infection or thrombophlebitis from the needle during blood sampling. It is possible that the cognitive testing in subjects with cognitive impairment can induce stress or a feeling of inadequacy. To mitigate these issues, the cognitive tests were performed in a dedicated room with a trained professional, and the participants had an option to interrupt the testing at any time.

Another ethical aspect to consider is that the waiting time to see a general practitioner in primary care in Sweden has become longer in recent years. Since the GÅS study offers subjects a relatively extensive free health examination, it is possible that this health examination may have attracted some participants to take part in GÅS.

Overall, the negative aspects of participation in the GÅS study are considered mild and minor, both regarding subjects with and without cognitive impairment.

Results

Paper I

Participants with impaired kidney function/CKD (eGFR < 60 ml/min/1.73m^2) performed worse on all the cognitive tests, except the test "confidence judgement", compared to participants with normal kidney function (eGFR ≥ 60 ml/min/1.73m^2).

All the presented associations below represent results adjusted for the demographic covariates age, sex, level of education, and country of origin.

Associations between impaired kidney function/CKD and impairment in the cognitive domains learning and memory, language, complex attention, and executive function, as well as for global cognitive function, were observed.

Associations were seen between eGFR 45 - < 60 ml/min/1.73m^2 and the cognitive domains learning and memory, language, and executive function.

Associations were observed between eGFR 30 - < 45 ml/min/1.73m^2 and the cognitive domains learning and memory, language, complex attention, and executive function, as well as for global cognitive function.

Associations were seen between eGFR < 30 ml/min/1.73m^2 and the cognitive domain learning and memory, as well as for global cognitive function.

After stratification of the study sample into four age groups, associations were seen between impaired kidney function/CKD (eGFR < 60 ml/min/1.73m^2) and the cognitive domains learning and memory, complex attention, executive function, perceptual-motor, as well as for global cognitive function in the youngest age group (60-69 years).

In the age group 70-79 years, associations were seen between impaired kidney function/CKD and the cognitive domains learning and memory, language, complex attention, as well as for global cognitive function.

In the age group 80-89 years, no associations were seen between impaired kidney function/CKD and any of the tested cognitive domains.

In the age group ≥ 90 years, an association was seen between impaired kidney function/CKD and the cognitive domain learning and memory.

The results of the cognitive tests related to kidney function are presented in table 7 and table 8.

Table 7. Results of the cognitive tests in relation to two groups based on eGFR

Cognitive test	Cognitive domain	Number of participants	Mean test results	B-coefficient	95% CI for B	p-value
MMSE	Global	2402	26.86	0.411	0.140, 0.682	0.003
Digit span forward	Learning and memory	2379	6.28	0.037	-0.158, 0.232	0.708
Free recall	Learning and memory	2329	6.64	0.239	-0.005, 0.482	0.054
Recognition	Learning and memory	2299	11.56	0.562	0.224, 0.900	0.001
Word fluency	Language	2376	11.94	0.663	0.179, 1.148	0.007
Digit cancellation	Complex attention	2319	16.77	0.45	0.031, 0.869	0.035
Pattern comparison	Complex attention	2290	26.14	0.988	0.279, 1.697	0.006
TMT B-A	Executive function	1836	18.08	-3.707	-5.874, -1.539	0.001
Digit span backwards	Executive function	2373	5.33	0.159	-0.047, 0.365	0.131
Mental rotations	Perceptual-motor	2262	0.6	0.001	-0.019, 0.021	0.91
Confidence judgement	Meta-memory	2343	0.11	-0.003	-0.012, 0.006	0.546

Kidney function divided into two groups, impaired kidney function (eGFR <60 mL/min/1.73 m²) and normal kidney function (eGFR ≥60 mL/min/1.73 m²). Statistical method: Multiple linear regression models of cognitive tests in relation to kidney function. eGFR ≥60 mL/min/1.73 m² as reference in all calculations. All analyses adjusted for age, sex, education and country of origin. Significance level: 5 %. Abbreviations: eGFR = estimated glomerular filtration rate, CI = confidence interval, MMSE = mini mental state examination, TMT = trail making test

Table 8. Results of the cognitive tests in relation to four groups based on eGFR

Cognitive test	Cognitive domain	Number of participants	eGFR level	B-coefficient	95 % CI for B	p-value
MMSE	Global	2402	<30	-0.788	-1.412, -0.164	0.013
			30-<45	-0.776	-1.173, -0.379	<0.001
			45-<60	-0.246	-0.538, 0.046	0.099
Digit span forward	Learning and memory	2379	<30	-0.119	-0.569, 0.331	0.603
			30-<45	-0.112	-0.400, 0.175	0.444
			45-<60	-0.003	-0.214, 0.207	0.976
Free recall	Learning and memory	2329	<30	-0.341	-0.925, 0.243	0.252
			30-<45	-0.436	-0.798, -0.075	0.018
			45-<60	-0.162	-0.425, 0.101	0.226
Recognition	Learning and memory	2299	<30	-0.985	-1.790, -0.179	0.017
			30-<45	-0.809	-1.312, -0.306	0.002
			45-<60	-0.433	-0.799, -0.066	0.021
Word fluency	Language	2376	<30	-0.533	-1.675, 0.610	0.361
			30-<45	-0.832	-1.542, -0.121	0.022
			45-<60	-0.620	-1.143, -0.097	0.020
Digit cancellation	Complex attention	2319	<30	-0.307	-1.321, 0.706	0.553
			30-<45	-0.744	-1.375, -0.112	0.021
			45-<60	-0.371	-0.823, 0.081	0.108
Pattern comparison	Complex attention	2290	<30	-0.577	-2.303, 1.148	0.512
			30-<45	-2.121	-3.194, -1.048	<0.001
			45-<60	-0.672	-1.435, 0.091	0.084
TMT B-A	Executive function	1836	<30	2.479	-3.202, 8.161	0.392
			30-<45	4.993	1.612, 8.373	0.004
			45-<60	3.423	1.081, 5.765	0.004
Digit span backwards	Executive function	2373	<30	-0.303	-0.777, 0.172	0.211
			30-<45	-0.309	-0.614, -0.004	0.047
			45-<60	-0.094	-0.317, 0.128	0.404
Mental rotations	Perceptual-motor	2262	<30	0.016	-0.033, 0.065	0.530
			30-<45	-0.003	-0.033, 0.027	0.840
			45-<60	-0.002	-0.024, 0.019	0.845
Confidence judgement	Meta-memory	2343	<30	0.003	-0.019, 0.024	0.796
			30-<45	0.004	-0.010, 0.017	0.572
			45-<60	0.002	-0.007, 0.012	0.628

Kidney function divided into four groups, severely impaired (eGFR <30 mL/min/1.73 m²), moderately impaired (eGFR 30-<45 mL/min/1.73 m²), mildly impaired (eGFR 45-<60 mL/min/1.73 m²), and normal kidney function (eGFR ≥60 mL/min/1.73 m²). Statistical method: Multiple linear regression models of cognitive tests in relation to kidney function. eGFR ≥60 mL/min/1.73 m² as reference in all calculations. All analyses adjusted for age, sex, education and country of origin. Significance level: 5 %. Abbreviations: eGFR = estimated glomerular filtration rate, CI = confidence interval, MMSE = mini mental state examination, TMT = trail making test

Paper II

189 participants had unchanged status of impaired kidney function/CKD (remaining eGFR of < 60 mL/min/1.73m^2) and 693 had remaining normal kidney function (eGFR of ≥ 60 mL/min/1.73m^2) from the baseline visit in GÅS in 2001 – 2004 to the follow up visit six years later (2007 – 2010).

Unchanged impaired kidney function/CKD from the baseline visit to the follow-up visit, was not associated with development of dementia or MCI at the 6-year follow-up, after adjustments made for the demographic and cardiovascular covariates age, sex, level of education, HT, diabetes, and smoking habits.

Unchanged impaired kidney function/CKD from the baseline visit to the follow-up visit, was inversely associated with development of naMCIs at follow-up, with adjustments made for the same variables as above.

Unchanged impaired kidney function/CKD from the baseline visit to the follow-up visit, was associated with worse performance on the pattern comparison test and the TMT A test, after adjustments made for the same variables as above.

The incidences of dementia, MCI, and the MCI subtypes based on kidney function are presented in table 9. The differences in performance of the cognitive tests from the baseline visit to the 6-year follow-up visit are presented in table 10.

Table 9. Incidence of dementia, MCI and MCI subtypes at follow up based on kidney function at baseline

Outcome	Number of incidents from baseline to follow up (cumulative incidence in % in parenthesis)			OR* (95 % CI for OR) p-value
	All participants (n=882)	Participants with eGFR < 60 mL/min/1.73 m2 from baseline to follow up (n=189)	Participants with eGFR ≥ 60 mL/min/1.73 m2 from baseline to follow up (n=693)	All participants (n=882)
Dementia	13 (1.5 %)	9 (4.8 %)	4 (0.6 %)	1.93 (0.38-9.78) 0.43
MCI	150 (17.0 %)	23 (12.2 %)	127 (18.3 %)	0.56 (0.29-1.05) 0.07
aMCIs	35 (4.0 %)	6 (3.2 %)	29 (4.2 %)	0.80 (0.24-2.69) 0.72
aMCIm	22 (2.5 %)	6 (3.2 %)	16 (2.3 %)	1.28 (0.33-4.95) 0.72
naMCIs	80 (9.1 %)	9 (4.8 %)	71 (10.2 %)	0.38 (0.15-0.94) 0.04
naMCIm	13 (1.5 %)	2 (1.1 %)	11 (1.6 %)	0.33 (0.05-2.35) 0.27

Binary logistic regression models were used to calculate OR for dementia and MCI. A multinomial logistic model was used to calculate OR for the MCI subtypes. All calculations were adjusted for the following covariates: age, sex, level of education, hypertension, diabetes, and smoking habits. *Reference level for OR = Participants with eGFR ≥ 60 mL/min/1.73 m2 from baseline to follow up. Abbreviations: eGFR = estimated glomerular filtration rate, aMCIm = amnestic MCI multiple domains, aMCIs = amnestic MCI single domain, CI = confidence interval, MCI = minimal cognitive impairment, naMCIm = non-amnestic MCI multiple domains, naMCIs = non-amnestic MCI single domain, OR = odds ratio

Table 10. Performance on the cognitive tests at follow up based on kidney function at baseline

Cognitive test	Cognitive domain	Mean result baseline		Mean result 6-year follow-up		Mean change in test result from baseline to 6-year follow-up		Mean difference in test result change between baseline and follow-up (95 % CI) p-value
		eGFR in mL/min/1.73 m^2 from baseline to the 6-year follow-up visit						
		< 60 (n)	≥ 60 (n)	< 60 (n)	≥ 60 (n)	< 60 (n)	≥ 60 (n)	
MMSE	Global	26.81 (185)	27.86 (692)	25.71 (178)	27.45 (685)	-1.10	-0.41	-0.02 (-0.53, 0.49) 0.95
Digit span forwards	Learning and memory	5.63 (188)	5.80 (692)	5.27 (188)	5.62 (692)	-0.36	-0.18	-0.06 (-0.30, 0.19) 0.65
Free recall	Learning and memory	6.52 (183)	7.66 (683)	5.67 (187)	7.30 (691)	-0.85	-0.36	0.22 (-0.30, 0.73) 0.41
Recognition	Learning and memory	11.70 (181)	12.43 (679)	10.80 (187)	12.16 (687)	-0.90	-0.27	-0.02 (-0.74, 0.70) 0.95
Word fluency	Language	11.40 (189)	13.54 (690)	10.96 (186)	13.43 (689)	-0.44	-0.11	0.15 (-0.60, 0.91) 0.69
Digit cancellation	Complex attention	15.84 (182)	18.71 (688)	15.02 (164)	18.88 (682)	-0.82	0.17	-0.39 (-1.06, 0.28) 0.25
Pattern comparison	Complex attention	23.69 (182)	30.49 (687)	21.52 (164)	30.13 (682)	-2.17	-0.36	-1.27 (-2.39, -0.16) 0.03
TMT A*	Complex attention	16.15 s (176)	12.60 s (668)	18.77 s (160)	11.93 s (660)	2.62 s	-0.67 s	1.62 (0.20, 3.05) 0.03
TMT B*	Executive function	35.59 s (138)	25.13 s (617)	47.06 s (125)	25.68 s (610)	9.91 s	0.55 s	2.16 (-3.00, 7.28) 0.41
Digit span backwards	Executive function	4.05 (188)	4.40 (691)	3.84 (187)	4.28 (692)	-0.19	-0.12	-0.10 (-0.35, 0.16) 0.45
Mental rotations**	Perceptual motor	0.58 (174)	0.65 (680)	0.56 (170)	0.61 (686)	-0.02	-0.04	0.00 (-0.05, 0.05) 0.86
Confidence judgement***	Meta-memory	0.09 (184)	0.11 (681)	0.09 (187)	0.10 (692)	0.00	-0.01	0.01 (-0.02, 0.03) 0.67

Linear regression models were used to calculate the delta result for each cognitive test from baseline to follow up between the two eGFR groups. All analyses were adjusted for age, sex, level of education, hypertension, diabetes, and smoking habits at baseline. *The time (in seconds) to complete the TMT A and the TMT B test was measured. **In mental rotations, the proportion of correct answers divided with the total number of answered questions was calculated. *** A calibration formula was used to calculate confidence. 0 means perfect confidence judgement. The bigger the value, the worse confidence judgement. Abbreviations: eGFR = estimated glomerular filtration rate, CI = confidence interval, MMSE = mini mental state examination, n = number, s = seconds, TMT = trail making test

Paper III

All subtypes of CSVD (WMHs, lacunar infarcts, CMBs, and cortical atrophy) were more common in the group with CKD (eGFR < 60 ml/min/1.73m^2) compared to the group with normal kidney function. Participants with CKD also more often met the criteria for CSVD according to the composite CSVD variable and the modified STRIVE variable.

CKD was associated with WMHs, CMBs, cortical atrophy, and composite CSVD in an unadjusted model. After adjustments had been made for the demographic covariates age and sex, we observed an association between CKD and CMBs as well as cortical atrophy only in the hypertensive group, as shown in table 11. In the non-hypertensive group, no associations were seen between CKD and CSVD.

Table 11. Association between CKD (eGFR < 60 ml/min/1.73m^2) and CSVD, stratified by hypertension, adjusted for age and sex

Participants with hypertension (n=207)				Participants with no hypertension (n=185)			
	OR	CI	p-value		OR	CI	p-value
WMHs[1]	1.15	0.64-2.08	0.633	**WMHs[1]**	1.28	0.45-3.70	0.643
Lacunar infarcts[2]	1.11	0.44-2.82	0.825	**Lacunar infarcts[2]**	1.93	0.36-10.47	0.447
CMBs[3]	1.93	1.04-3.59	0.037	**CMBs[3]**	0.54	0.14-2.03	0.359
Cortical atrophy [4]	2.45	1.34-4.48	0.004	**Cortical atrophy [4]**	0.63	0.24-1.69	0.360
Composite CSVD [5]	1.50	0.82-2.73	0.186	**Composite CSVD [5]**	0.97	0.36-2.63	0.951
Modified STRIVE [6]	1.56	0.67-3.60	0.301	**Modified STRIVE [6]**	1.05	0.33-3.39	0.935

[1] WMHs defined as Fazekas scale ≥ 2. [2] Lacunar infarcts defined as presence of ≥ 1 lacunar infarct. [3] CMBs defined as presence of ≥ 1 CMB. [4] Cortical atrophy defined as GCA ≥ 1 and/or Koedam score ≥ 1 and/or ≥ 1 frontal/frontotemporal/temporal atrophy. [5] Presence of CSVD according to the composite CSVD variable was defined as Fazekas scale ≥ 2 and/or presence of ≥ 1 lacunar infarct and/or ≥ 1 CMB. [6] Presence of CSVD according to the modified STRIVE was defined as Fazekas scale ≥ 2 and/or presence of ≥ 1 lacunar infarct and/or presence of ≥ 1 CMB and/or presence of cortical atrophy and/or presence of central atrophy. eGFR calculated from creatinine and cystatin C in non-underweight participants and on cystatin C in underweight participants (BMI < 23) using the CKD-EPI equation. eGFR ≥ 60 ml/min/1.73m^2 as reference. Covariates: Age, sex. Binary logistic regression models were used to examine the association between CKD (eGFR < 60 ml/min/1.73m^2) and WMHs, lacunar infarcts, CMBs, cortical atrophy, CSVD composite, and modified STRIVE. Abbreviations: BMI = Body mass index, CKD = Chronic kidney disease, CKD-EPI = chronic kidney disease epidemiology collaboration, CMBs = Cerebral microbleeds, CSVD = Cerebral small vessel disease, eGFR = estimated glomerular filtration rate, GCA = Global cortical atrophy, MRI = Magnetic resonance imaging, OR = Odds ratio, SD = Standard deviation, STRIVE = Standards for reporting vascular changes on neuroimaging, WMHs = White matter hyperintensities

Paper IV

Unadjusted, all levels of PP elevation at the baseline visit were associated with incident CKD during the follow-up period. After adjustments for the covariates age, sex, diabetes, and smoking habits, the association between PP 60 - < 70 mmHg and ≥ 80 mmHg at baseline and incident CKD during the follow-up period remained, as demonstrated in table 12.

Table 12. Risk of developing CKD during follow-up according to level of pulse pressure elevation at the baseline visit

Baseline characteristic	Event	HR	95 % CI	p-value
PP 60 - ≤ 70 mmHg*	CKD	1.23	1.01-1.49	0.041
PP 70 - ≤ 80 mmHg*	CKD	0.96	0.76-1.22	0.751
PP ≥ 80 mmHg*	CKD	1.55	1.25-1.91	<0.001
Age	CKD	1.14	1.13-1.16	<0.001
Sex	CKD	1.18	1.02-1.38	0.031
Diabetes**	CKD	1.87	1.42-2.45	<0.001
Smoking***	CKD	1.29	1.11-1.51	0.001

*PP < 60 mmHg as reference. **Diabetes defined as diabetes mellitus type 1/type 2 or no diabetes (dichotome). ***Smoking defined as active/former smoker or never smoked (dichotome). CKD defined as eGFR < 60 ml/min/1.73m^2. Statistical method: Multivariate Cox proportional hazard regression model. Covariates: age, sex, diabetes, smoking. Significance level: 5 %. Abbreviations: CI = Confidence interval, CKD = Chronic kidney disease, HR = Hazard ratio, PP = pulse pressure

Unadjusted, all levels of PP elevation at the baseline visit were associated with all-cause mortality during the follow-up period. After adjustments for the covariates age, sex, diabetes, and smoking habits, only the correlation between the highest level of PP elevation (≥ 80 mmHg) at the baseline visit and all-cause mortality during follow-up remained. This is demonstrated in table 13.

Table 13. Risk of mortality during follow-up according to level of pulse pressure elevation at the baseline visit

Baseline characteristic	Event	HR	95 % CI	p-value
PP 60 - ≤ 70 mmHg*	Mortality	0.99	0.86-1.14	0.923
PP 70 - ≤ 80 mmHg*	Mortality	0.91	0.78-1.06	0.210
PP ≥ 80 mmHg*	Mortality	1.21	1.06-1.38	0.005
Age	Mortality	1.15	1.14-1.15	<0.001
Sex	Mortality	0.77	0.69-0.86	<0.001
Diabetes**	Mortality	1.30	1.09-1.54	0.003
Smoking***	Mortality	1.25	1.12-1.39	<0.001

*PP < 60 mmHg as reference. **Diabetes defined as diabetes mellitus type 1/type 2 or no diabetes (dichotome). ***Smoking defined as active/former smoker or never smoked (dichotome). Statistical method: Multivariate Cox proportional hazard regression models.Covariates: age, sex, diabetes, smoking. Significance level: 5 %. Abbreviations: CI = Confidence interval, CKD = Chronic kidney disease, HR = Hazard ratio, PP = pulse pressure

Discussion

Main findings and interpretation of results

An association between kidney function and cognitive function

In paper I, associations were observed between CKD, defined as eGFR < 60 ml/min/1.73m^2, as well as the severity of eGFR impairment, and impaired function in the cognitive domains learning and memory, language, complex attention, and executive function, as well as global cognitive function. As this was a cross-sectional designed study, nothing can be said about causality regarding these associations. For comparison, previous studies investigating which cognitive domains could be impaired in the presence of low eGFR have shown impairment in various cognitive domains, although processing speed, (which is a sub-domain to complex attention), and executive function seem to be more associated with low eGFR than other cognitive domains [31, 123]. Hence, the associations observed in paper I are in line with previous studies.

No associations were observed between low eGFR and meta-memory in paper I or paper II. This was new information, since no one, to our knowledge, previously had investigated such a relationship. Meta-memory is somewhat different from the other tested cognitive domains. The other cognitive domains reflect the ability to perform different cognitive tasks, while meta-memory represents the understanding and awareness of one´s own ability to perform tasks involving memory [124]. A theory of the reason that meta-memory was intact in older individuals with impaired kidney function, unlike most other tested cognitive domains, is that older people, in general, have reached a high degree of maturity and self-understanding that remains intact in earlier stages of cognitive impairment. All participants with dementia were excluded in paper I. In paper II, subjects with dementia were excluded at baseline but not at the 6-year follow-up visit. More advanced stages of dementia were likely underrepresented due to the relatively short follow-up period. Also, it is possible that subjects with more advanced stages of dementia were underrepresented due to selection bias and/or attrition bias (see the section “Internal validity” of this chapter). One can speculate that the understanding and awareness of one´s own cognitive abilities could become compromised in the presence of more advanced forms of cognitive impairment.

No associations with cognitive dysfunction were seen in the group with severely impaired kidney function (< 30 ml/min/1.73m^2) in paper I. This can probably be explained by a limited sample size, since only 70 participants had severely impaired kidney function. A stronger association between eGFR and cognitive function was seen in the younger age groups compared to the oldest. This can probably, at least partly, be explained by a limited sample size, since only 92-131 participants in the oldest age group (≥ 90 y) performed the different cognitive tests, compared to 1229-1255 in the youngest age group. Difference in sample size can however not explain the difference in association between eGFR and performance on the cognitive tests between the two middle age groups, whereas 445-464 participants performed the cognitive tests in the age group 70-79 years, compared to 489-552 participants in the age group 80-89 years.

Low eGFR preceded cognitive impairment

In paper II, which had a longitudinal design, we found that CKD preceded worse performance in processing speed, (which represents the cognitive domain complex attention), but not worse performance in any other cognitive domains. CKD also did not precede dementia or MCI. Due to differences in the psychometric properties between the cognitive tests, no comparison of effect sizes between results of the different tests were made. Since this was an observational study, it is hard to make any causal assumptions. The association found between CKD and worse processing speed over time, however, supports that CKD, based on low eGFR, could be a risk factor of future cognitive impairment.

An association was seen between CKD and the development of naMCIs in paper II. The association was however reversed, that is, having normal kidney function was associated with a higher risk of developing naMCIs from baseline to follow-up. This finding is less clinically plausible, and since multiple statistical analyses were done with significance level of 0.05, this finding was regarded as a false positive finding. An alternative explanation could be that the dropout rate was higher in the group with CKD that developed naMCIs compared to the group with normal kidney function that developed naMCIs. To confirm this observed association, it needs to be replicated in other study populations.

A possible vascular mechanism behind the association between impaired kidney function and cognitive dysfunction

Previous studies have found associations between low eGFR and various cognitive domains, although processing speed and executive function seem to be more associated with low eGFR than other cognitive domains [31, 123]. Hence, the associations observed between low eGFR and various cognitive domains/sub-domains in paper I, including processing speed and executive function, do not contradict an association between low eGFR and cognitive dysfunction on a vascular basis.

CKD was associated with worse processing speed over time in paper II. For comparison, a recent longitudinal review study found that in older people with vascular burden, only severely impaired kidney function (< 30 ml/min/1.73m^2) was associated with cognitive decline over time [125]. The study sample in paper II was relatively young and healthy. The mean age was 67.6 years (SD 8.53), and mean eGFR was 74 ml/min/1.73m^2 (SD 17.36). In the group with CKD, the mean eGFR was 48 ml/min/1.73m^2 (SD 9.18), representing mildly to moderately impaired kidney function [9]. Therefore, the cognitive implications in paper II, most likely represent an early stage of CKD-related cognitive impairment. Processing speed has previously been found to be highly sensitive to cerebrovascular disease [126, 127], and has been associated with early manifestations of CSVD, whereas memory and language seem to be more robust and affected at more advanced stages of CSVD [10, 18, 19]. The associations observed in paper II could therefore represent early vascular implications on cognition.

In paper III, we observed that CKD was associated with markers of CSVD in the form of CMBs and cortical atrophy, but only in the hypertensive sub-group. In the non-hypertensive sub-group, no associations between CKD and any markers of CSVD on MRI were observed. That an association was observed between CKD and CSVD only in the hypertensive sub-group might indicate a connection between CKD and CSVD on a vascular basis. HT is associated with CSVD [46, 65], and HT can probably be both a cause of, and an effect of, CKD [44-46]. It is likely that there is a complex interplay between HT, CKD, and CSVD, which is difficult to describe using statistical models. For example, in paper III, we cannot rule out that HT was a confounder in the relationship between CKD and CSVD. Nevertheless, the results in paper III imply that HT plays an important role in a relationship between HT, CKD, and CSVD. As mentioned in the introduction, CSVD is highly associated with cognitive impairment [32, 33]. This indicates a possible vascular basis behind the association found between low eGFR/CKD and cognitive impairment in paper I and paper II.

Since paper III had a cross-sectional design, nothing can be said about causality. As mentioned in the previous paragraph, the role of HT in the association observed between CKD and CSVD in the hypertensive sub-group in paper III also remains unclear. It is known that HT is associated with damage in the microvasculature of the kidneys (hypertensive nephrosclerosis) [9, 44], as well as with CSVD [12, 73], including both CMBs [128] and brain atrophy [129]. These previously known associations, along with the findings in paper III, indicate that HT, CKD, and CSVD are related. Even though we cannot determine any causal relationships, the associations give rise to the following hypotheses that are discussed in the paragraphs below.

There are studies indicating that HT not only is associated with, but likely is a cause of CSVD. A recent longitudinal study found that diastolic HT preceded CVSD progression [130]. Another recent longitudinal trial from the Framingham Heart Study, found that HT in mid to late life preceded development of CMBs later in life [131]. The causal relationship between HT and CKD is more complex since it is likely that the causality is bilateral. HT could be responsible for impaired kidney function due to hypertensive nephrosclerosis (as described in the introduction) [48, 49], but more advanced stages of CKD are also believed to be a cause of HT [45, 132].

AS is associated with CKD [133, 134], and CSVD [135, 136]. AS is associated with HT, elevated pulse wave velocity, and elevated PP [90, 91, 121]. Both the kidney and the brain have short end arterioles with auto-regulation properties, where smooth muscles of the arteriolar wall contract when the blood pressure is high and dilate when the blood pressure is low in order to maintain adequate organ perfusion. These short vessels branch from much larger arteries and are highly exposed to changes in blood pressure [137]. Arteriolar hyalinosis (subendothelial and medial wall accumulation of various serum proteins leading to loss of smooth muscle cell function and fibrosis) is common in aging and is associated with traditional vascular risk factors, including HT [138]. Loss of smooth muscle cells and fibrosis of the wall of the end arterioles of the kidney and the brain are believed to result in impaired auto-regulation and increased vulnerability to the elevated pulse wave velocity and elevated pulsatile pressure associated with AS [4, 5].

The endothelium of the end arterioles in the kidney and the brain is believed to play a crucial role in the auto-regulation properties of these vessels. The endothelium can induce relaxation of the smooth muscle cells of the arteriolar wall through the release of vasodilating substances, such as nitric oxide. Endothelial dysfunction (ED) is compatible with impaired function of these muscle relaxing properties [139]. ED is associated with HT [139], CKD [140], and CSVD [141].

A hypothesis regarding the pathophysiology behind that an association between CKD and markers of CSVD was observed only in the hypertensive group in paper III, is that HT-related damage to the microvasculature of the kidney and the brain is responsible for both CKD and CSVD. This HT-related damage could derive from hyalinosis and/or ED of the end arterioles of both organs.

Another hypothesis behind the relationship between HT, CKD, and CSVD include the function of the blood-brain barrier (BBB). The BBB regulate the transposition of various molecules, cells, and ions between the systemic circulation and the brain and plays a crucial role in maintaining an optimal milieu for the neurons. The BBB also protects the neurons from toxins [142]. HT is related to reduction in function of the BBB [143]. A history of HT, with a following reduction in the function of the BBB, could leave the brain more susceptible to damage from fluid and electrolyte imbalances linked to CKD [144].

In a recent longitudinal mouse study, Lau et al [145] found that CKD leads to dysfunction of the BBB independently of HT. Another hypothesis is that the combination of CKD and HT, both capable of impairing the function of the BBB, resulted in brain damage in paper III, but that CKD alone did not.

CKD has been associated with both AS and ED independently of HT [133, 146]. This raises the hypothesis that CKD could be indirectly involved in the development of HT and CSVD, through the development of AS and/or ED.

In paper IV, elevated PP, as a surrogate for AS, preceded incident CKD and all-cause mortality. Again, since this was an observational study, a causal relationship is hard to establish. However, these findings support that PP elevation is a risk factor of incident CKD, which supports the hypothesis that the associations between low eGFR/CKD found in paper I and paper II could have a vascular basis.

In summary, the associations described above in this sub-chapter give rise to the following main hypothesis regarding a possible mechanism behind the association between low eGFR and cognitive impairment: AS and HT can inflict damage to the abundant small end vessels of the kidney and the brain due to their low resistance mechanisms. This organ damage is represented as impairment in eGFR in the kidney and as markers of CSVD and cognitive impairment in the brain.

It is important to remember that the mechanisms behind the causes of CKD and CSVD, as well as the effects of CKD are complex (as mentioned in the introduction). In a possible connection between CKD and CSVD, common traditional risk factors of cardiovascular disease, including HT, diabetes, dyslipidemia, and smoking habits, are most likely involved. There are, however, previous studies that have found an association between CKD and stroke independent of traditional cardiovascular risk factors [147, 148]. CSVD is estimated to be responsible for 25 % of all ischemic stroke [67, 68]. This suggests that CKD itself could be a risk factor of CSVD. Considered effects of CKD include salt and fluid retention, chronic inflammation, and mineral bone disorder, which are likely to contribute to the development/worsening of CSVD [5, 45]. The mechanisms of how salt and fluid retention, chronic inflammation, and mineral bone disorder could promote CSVD are not fully understood. Salt and fluid retention is a well-known complication in more advanced stages of CKD. Salt and fluid retention increases the blood pressure, and HT likely worsen the renal function in an unfortunate cycle [44, 46, 54]. CKD is associated with a state of chronic inflammation [52, 54]. The aetiology of this systemic inflammation is not understood. One possible mechanism behind this systemic inflammatory state could be leakage of bacterial toxins from the gut into the systemic circulation [149, 150]. Possibly can also salt itself be toxic and promote systemic inflammation [151, 152]. In more advanced stages of CKD, excretion of phosphate is decreased, contributing to hyperphosphatemia. Parathyroid disorders are common in later stages of CKD, further promoting hyperphosphatemia and also hypercalcemia. Hyperphosphatemia and hypercalcemia lead to calcification at various locations including vascular calcification [52, 54], which could promote the development of CSVD.

Methodological considerations

An important and fundamental question in all epidemiological research is the question of validity.

Internal validity

As always regarding large epidemiological studies including the general population, the results from the data in GÅS could be biased due to selection bias in the recruitment of subjects to the study. The participation rates were 59.9 % at the GÅS baseline visit in 2001 – 2004, 72.6 % at the first visit for new participants in Wave 2 in 2006 – 2012, and 70.3 % at the first visit for new participants in Wave 3 in 2012 – 2016. The participation rates were higher in the younger age groups compared to the older age groups, which increases the risk for selection bias in the older age groups. Naturally, we cannot say much about the people who chose not to participate in GÅS, but one can speculate that a potential reason for some of these individuals, was that they were too frail and/or unhealthy to participate, even though home visits were offered those who were unable to attend the reception in GÅS. Indeed, research has shown that people who participate in population cohort studies tend to be healthier than those who do not [153, 154].

The participation rate of eligible subjects to the follow-up visits in GÅS have ranged from 65.1 % to 80.6 %. Again, research have shown that subjects with low compliance to follow-up in longitudinal studies are more likely to be unhealthy compared to those with high compliance [155, 156]. The result of such attrition bias could be that the study sample in GÅS over time becomes increasingly healthier compared to the population it was supposed to represent.

When studying a sample that is healthier than the population the sample aim to represent, there is a risk of underestimating or even completely miss an actual association between two factors or the impact of a potential risk factor on an event. For example, even though we found an association between CKD and worse processing speed in paper II, it is possible we could have missed a true association between CKD and incident dementia or MCI due to selection bias and/or attrition bias, where too many healthy subjects mask the true association. Another example applies to the results in paper IV. It is possible that the association between elevated PP and all-cause mortality in paper IV was underestimated due to selection bias and/or attrition bias of the healthiest subjects. For the same reason, it is even possible that the true association between PP and all-cause mortality exists at lower levels of elevated PP than observed in this study.

The famous philosopher and science theorist Sir Karl Popper claimed that one of the criteria of a scientific hypothesis is that the hypothesis must be falsifiable to be regarded as scientific. However, when performing epidemiological research with huge amount of data and with many possible sources of bias, it is not easy to falsify a hypothesis with certainty. It is important not to totally dismiss a potential association even though no association is observed. That no association is observed can always depend on a type II error due to random variation. The level of statistical significance was set at 5 % in all statistical models of all four studies of this thesis. This means (assuming that the statistical models are correct) that there in each calculation is a 5 % chance of receiving the result we did (or more extreme) just by chance.

Another source of uncertainty regarding the results, are the uncertainty that comes with potential bias. Examples of bias are selection bias and attrition bias, which are mentioned above.

Observations in epidemiological studies are always associated with some degree of uncertainty. To determine a hypothesis to be true or false with 100 % certainty is very hard. However, with increasing number of well-made studies involving different populations observing the same association (or absence of association), this association (or absence of association) is increasingly likely to be true.

External validity

The study sample in GÅS represents the general older population in the county of Skåne, Sweden. The fact that the participants in GÅS were recruited randomly from both urban and rural parts of the area increases the comparison to other older populations. The Swedish population is part of the so-called western culture and is, in general, a socioeconomically prosperous population. The GÅS study sample is therefore likely most comparable to other older populations of the western world, that is, the countries of the European union, Norway, Iceland, Switzerland, United Kingdom, USA, Australia, and New Zeeland. Even though a large proportion of the population of the city of Malmö is of non-European origin, this applies to the younger population in Malmö, not included in the GÅS study. Even if the population of non-European origin in Malmö was eligible, studies have shown that the participation rate of ethnic minorities tends to be low in clinical studies [157, 158].

New cohorts have been recruited to the GÅS study in 2006 – 2012 (Wave 2), 2012 – 2016 (Wave 3), and 2017 – 2022 (Wave 4) since the baseline visits in 2001 – 2004. The inclusion of different cohorts often come with birth cohort effects, that is, a variation in the characteristics between groups born in different years or decades. For example, Overton et al [159], found birth cohort effects on processing speed in two age groups in GÅS. The age groups were 60 year old subjects born in 1942 – 1943, 1948 – 1949, and 1954 – 1955, and 81 year old subjects born in 1920 – 1921, 1926 – 1927, and 1932 – 1933. The effects were seen independent of education. In paper IV, the cohorts from baseline, Wave 2, and Wave 3 were included in the analyses, and it is likely that birth cohort effects have induced differences between the cohorts. For example, since treatment of HT have become increasingly more efficient and strict from the late 50s and forward [160, 161], it is likely that the Wave 2 and Wave 3 cohorts have received more intense treatment of HT compared to the baseline cohort, which could be more exposed to HT. Therefore, in subjects from Wave 2 and Wave 3, there is a risk of underestimation of the impact of PP elevation, (which is heavily associated with HT [90, 121]), on CKD and all-cause mortality.

Reliability and variability

When performing longitudinal studies and re-examining subjects, the question of reliability is always an issue. For example, using the same neuropsychological tests at different occasions on the same individuals comes with a risk of practice effects. That is, that the participants perform better at the retests without any intervention [162, 163]. To deal with this issue, different versions of some of the neuropsychological tests were used at different GÅS visits. For example, three different versions of the mental rotations test, and three different versions of the TMT were used. The procedure of applying different versions of the same test, however, induces another risk of compromised reliability. It is hard to make different versions of a neuropsychological test exactly equally hard. There is always a risk that a different version of a neuropsychological test is harder or easier to perform, which could influence the result of the test [164].

Another factor that could influence the performance of the neuropsychological tests is the time of day the test is being performed [165, 166]. The neuropsychological testing in GÅS took place at different times of the day, which could have increased both the intra-individual variation and the inter-individual variation of the test results. An increase in variability can make observations of significant associations harder.

All blood samples were taken non-fasting and were examined at the same laboratory using the same techniques, which enhances reliability. However, the blood samples were taken at different times of the day, and previous studies have shown some diurnal variation for both crea and cysC [167, 168], which could have increased the variability.

Even though all MRI examinations were performed at the same Radiology Department, using the same 3 Tesla MRI, identification of markers of CSVD on MRI is associated with some issues of reproducibility between different raters [169-171]. To eliminate the inter-rater variability, all 407 MRI examinations were reviewed by the same experienced neuroradiologist. However, it should be mentioned that the use of a single rater comes with a price. If the rater has issues when assessing certain markers of CSVD on MRI, it will result in a systemic bias. Inter-rater variability can be improved with a larger sample size. The systemic bias that might come with the use of a single rater has no solution.

As with cognitive function, blood pressure is known to vary throughout the day [172, 173]. The blood pressure was taken at different times of the day between subjects and between different GÅS visits, which could have increased the variability.

Misclassification

GFR was estimated to evaluate kidney function in all studies covered by this thesis. CKD is defined as GFR < 60 ml/min/1.73m^2 for at least three months [9]. Our estimation of GFR was based on a single measurement of crea/cysC or cysC, and the duration criterion of at least three months was not considered. This means that we risk a misclassification into CKD. That is, subjects could have been classified as having CKD, when they in reality only temporarily had eGFR < 60 ml/min/1.73m^2 that lasted less than three months, and therefore should have been classified as having normal kidney function. This could have resulted in an unnecessary exclusion of healthy subjects at the baseline visits in paper IV. This could also have resulted in a dilution effect in the group with CKD in paper III. This dilution effect with healthy subjects misclassified as having CKD could have resulted in a risk of a weakened association or even a missed association (type II error) in paper III. For the same reason, the association between PP elevation and incident CKD could have been weakened in paper IV.

Measurement of albuminuria is another approach to evaluate presence of CKD. Measurement of albuminuria is not included in GÅS and was therefore not included in any of the four studies of this thesis. If presence of CKD had been based on both eGFR and albuminuria, the prevalence of CKD had most likely been greater in the study sample. However, the main aim of this thesis was to evaluate eGFR, not albuminuria, as a risk factor of cognitive impairment.

Even though the CKD-EPI equation is well-established and considered a reliant equation to estimate GFR from crea and/or cysC, no equation is 100 % accurate in doing so. A recent large review study found that estimating GFR using the CKD-EPI equation based on crea/cysC was superior in accuracy compared to estimating GFR based on crea or cysC alone [95]. Still crea/cysC had a p30 of only 73 %. This means that, when using the CKD-EPI equation based on crea/cysC to estimate GFR, 73 % of the results will be within +/- 30 % of mGFR, and 27 % will be above or below +/- 30 % from mGFR. Pottel et al [174] found a p30 of 85.6 % using the CKD-EPI equation based on crea/cysC in older adults (≥ 70 years) when mGFR was 58.5 ml/min/1.73m^2 (n = 1469). These findings obviously raise an amount of uncertainty regarding eGFR representing mGFR. This uncertainty is of most relevance when GFR is estimated to be around 60 ml/min/1.73m^2, since this is the limit for CKD [9].

To divide participants into groups with low eGFR/CKD and normal kidney function with high accuracy, we estimated GFR from crea/cysC in paper I and paper II [95]. To avoid misclassification due to falsely low crea in subjects with sarcopenia and sharpen the classification into CKD and normal kidney function further, GFR was estimated from crea/cysC in non-underweight subjects, but only from cysC in underweight subjects in paper III and paper IV [96-98]. Even though consideration was taken to misclassification due to sarcopenia in paper III and paper IV, the risk of misclassification due to factors other than GFR that can influence the level of cysC, was not taken into consideration. For example, the use of corticosteroids is associated with elevated cysC levels [175, 176].

Moreover, as described in a recent review article by Xiao et al [34], there are previous studies that have found cysC to be a risk factor of CSVD independent of eGFR based on creatinine. The cause of the relationship between cysC and CSVD independent of eGFR based on creatinine is not clear, but if other unknown factors than GFR (and known factors such as the use of corticosteroids) can influence serum level of cysC, we risk misclassification regarding level of eGFR/CKD status when we estimate GFR based on cysC. There have been theories proposed to explain why cysC could be a risk factor of CSVD independent of eGFR based on creatinine. These theories include CSVD-related release of microvesicles containing cysC [177] and selective filtering of particles of different sizes in the glomeruli, a phenomenon called "The shrunken pore syndrome" (SPS) [178]. In SPS, small molecules (including crea), are assumed to be more easily excreted in the glomeruli compared to larger particles (such as cysC). SPS is associated with elevated proteins associated with atherosclerosis [179]. To determine cysC as a risk factor of CSVD independent of GFR, GFR should be measured directly by assessing GFR based on excretion of an exogenous substance, such as iohexol or inulin. To the knowledge of the author, this has not yet been performed.

In paper III, to handle the issue of a possible misclassification due to the issue above, a sensitivity analysis was made. All statistical models were re-run with GFR estimated using the CKD-EPI equation based on crea/cysC in all participants. The number of subjects with CKD status decreased from 94 to 87. All estimates and CIs in the statistical models remained similar, and all associations remained, except for an association that was lost between CKD and CMBs in the hypertensive group adjusted for age and sex (p-value 0.063). An association was likely harder to observe due to a smaller CKD group and due to dilution of the group with normal kidney function.

As mentioned above, in paper I and paper II, no consideration was taken for low BMI as a proxy for sarcopenia. Hence, no consideration was taken for potential misclassification regarding level of eGFR due to overestimation of eGFR when based on crea/cysC instead of cysC only.

The DSM-IV criteria for dementia from 1994 were used to assess dementia in paper I and paper II [23]. Since then, new criteria for dementia have been published by the American Psychiatric Association in DSM-5 [57]. The term dementia has in DSM-5 been replaced by the term "major neurocognitive disorder". A major change in the criteria for dementia/major neurocognitive disorder in DSM-5 is that the mandatory impairment in memory (and one more cognitive domain) has been replaced by impairment in any single cognitive domain. Since the criterion of cognitive impairment was narrower in DSM-IV compared to DSM-5, there is a risk that subjects in paper II were misclassified as not having dementia at the follow-up visit. This could have made the group with the outcome incident dementia (n = 13) smaller than it in reality was, with the accompanying risk that we lost a true association between low eGFR/CKD and incident dementia.

The term MCI originates from investigators at the Mayo clinic in the late 1990s and was initially regarded as a precursor to Alzheimer´s disease [62]. Therefore, decline in memory was initially the only cognitive domain considered. The idea of MCI as a precursor to AD has since come to be challenged, and the definition of MCI has been revised to include decline in any cognitive domain [63]. Multiple workgroups have worked on a definition of MCI over the years. Consensus seems to exist on the following four criteria: self- or informant-reported cognitive complaint, objective cognitive complaint, preserved independence in functional abilities, and the absence of dementia [61]. In paper II, we used the initial Mayo criteria of self-reported memory complaint. This may have affected the incidence of MCI in our sample, and also contributed to a higher proportion of individuals with a precursor state to AD in the MCI group.

The CDR scale was used to assess the criteria informant cognitive complaint, as well as functional abilities, when assessing MCI. CDR is ideally assessed by interview of an informant and the subject [107]. In GÅS, CDR was by default assessed by a physician by interview and cognitive testing of the subject only. According to the GÅS protocol, if the subject had scored less than 27 points on the MMSE, an interview was performed with an informant after approval from the subject. Since information from an informant in most cases was missing, there is a risk of misclassification of MCI in paper II due to over/underestimation of the CDR score. In paper I and paper II, the same issue existed when assessing the criteria of dementia according to DSM-IV [23]. All criteria for dementia in DSM-IV were assessed by a physician through interview and cognitive testing of the subject, but by default according to the GÅS protocol, no informant interview was conducted (unless the subject had performed < 27 points on the MMSE, and the subject had approved the informant interview).

The definition of WMHs in paper III were similar to the definition of WMHs according to STRIVE [70], the SVD score [71], and Offenbacher et al [69], as presented in table 6. Since some degree of WMHs is present in almost all people over the age of 80 years [78], we considered Fazekas ≥ 2 as representative of presence of WMHs. This was also similar to the procedure used in the SVD score, where Fazekas ≥ 2 regarding deep WMHs and Fazekas 3 regarding Periventricular WMHs was compatible with score for presence of WMHs.

The definition of lacunar infarcts in our material included infarct size < 10 mm compared to up to 3 – 15 mm according to STRIVE [70], and > 3 - < 20 mm according to the SVD score [71]. This could have resulted in less infarcts defined as lacunar infarcts in our material compared to if we had used the definitions by STRIVE or the SVD score. The definition of CMBs in our material included microbleeds between 2-5 mm in size, similar to the size defined according to the SVD score, but smaller compared to CMBs according to STRIVE, where CMBs are sized from 2 mm up to 10 mm. If we make misclassifications in the dependent variable (in this case misclassify subjects as healthy, when they in fact have lacunar infarcts or CMBs), we risk weaken or even miss a true association.

Causality

Since all sub-studies of this thesis were observational studies, it is difficult to establish any causal relationships regarding any of the found associations. There is always risk that confounders either simulate a non-existing effect or obscure a true effect.

Strengths

A major strength using the GÅS dataset is that the GÅS study includes a great number of subjects who have been followed for many years, yielding power to the analyses. The GÅS study sample represents a general older population from both rural and urban parts of the county of Skåne, and includes a large age span, which facilitates comparison to other older populations.

The participants in GÅS have been randomly selected, which decreases (but does not eliminate) selection bias. To further minimize selection bias and also attrition, home visits have been offered to participants too unhealthy to visit the GÅS study centre.

The medical examinations in GÅS have been performed by physicians using a standardized medical protocol. The cognitive tests cover multiple cognitive domains and have been administered by trained test administrators using a standardized test protocol. Identical medical examinations and the same standardized test protocol were performed at all re-examinations.

The large number of subjects included in paper I, II, and IV allow to explore associations between different conditions and outcomes.

To estimate GFR, the well-established and reliable CKD-EPI equation was used [94]. The CKD-EPI equation has been shown to be superior in accuracy to the previously commonly used Modification of Diet in Renal Disease (MDRD) equation [180-182]. The CKD-EPI equation was based on crea/cysC in all subjects in paper I and paper II [17]. In the GÅS study sample, the CKD-EPI equation based on crea/cysC has previously been found to be highly accurate, and equal in accuracy compared to other equations based on crea/cysC, with a p30 of 100 % for subjects with eGFR $\geq$ 45 ml/min/1.73m^2 and 92.7 % for subjects with eGFR < 45 ml/min/1.73m^2 [183]. (See the section "Misclassification" of this chapter for a description of p30). Even though a recent large review study by Zou et al found that the CKD-EPI equation based on crea/cysC provided higher accuracy than estimating GFR from crea or cysC alone, the CKD-EPI equation based on cysC provided less bias [95]. The variation between eGFR based on crea compared to cysC in the GÅS material has previously been found to be relatively high (65 % had a variation $\geq$ 10 %, and 19 % had a variation > 30 %) [93]. Estimating GFR based on crea/cysC in a whole study sample of a general population, most likely provides the highest accuracy. However, estimating GFR based on crea can be problematic since crea is directly related to muscle mass. Loss of muscle mass and sarcopenia is especially common in the older population, where crea often overestimates GFR [96]. Underweight is commonly defined as BMI < 23 in the older population [98] and underweight in older people is associated with sarcopenia [97]. In paper III and paper IV, to prevent overestimation and increase accuracy, eGFR was based on cysC alone in participants with BMI < 23.

The great number of cognitive tests included in GÅS represents another strength. This enables the opportunity to assess almost all aspects of cognition. The reliability of the cognitive tests has also been found to be high. Overton et al showed that the test administrator effects on variability of the cognitive tests in GÅS is as low as 1,4 – 3,5 % [184].

The reliability of the MRI examinations of the brain is also likely to be high since the same image techniques and the same MRI laboratory were used in all examinations. Also, the same experienced neuroradiologist examined all MRI images in all subjects, (which also is entangled with limitations, see the section "Reliability and variability" of this chapter). The inter-rater reliability regarding WMHs, CMBs, and cortical atrophy according to the Pasquier scale and the Koedam score have found to be high in previous studies [170, 185-187], and moderate to high regarding lacunar infarcts [188].

Limitations

Many of the limitations are described under the sub-chapter "Methodological considerations" in this chapter. In addition to the limitations mentioned above, the following weaknesses need to be addressed.

In paper I, the cardiovascular risk factors HT, smoking habits, and diabetes type 2 were not proportionally distributed between the group with impaired kidney function and normal kidney function. Adjustments for cardiovascular risk factors were not done in the statistical analyses. Therefore, their potential as possible confounders were not investigated.

In paper II, subjects who were considered depressed (and therefore potentially cognitively impaired due to depression) both at the baseline visit and at the follow-up visit were excluded. Dementia and MCI are associated with depression [189-191]. There is a possibility that subjects who were not depressed at the baseline visit but were depressed at the follow-up visit and therefore excluded, in fact had developed dementia or MCI with depressive symptoms from the baseline visit to the follow-up visit. Since the exclusion of subjects who potentially had developed dementia or MCI could have resulted in lost true associations between CKD and dementia and/or MCI, the same calculations were performed including these subjects. No relevant differences in the results were found.

The cognitive tests in GÅS did not cover the cognitive domain "social cognition", which meant that a possible relationship between eGFR and social cognition could not be investigated.

Some of the investigated dependent variables in paper III were relatively uncommon. For example, only 10 cases with lacunar infarcts were observed in the group with CKD. We cannot exclude that true associations between CKD and some markers of CSVD on MRI were lost due to too small sample size. Also, since the groups were small, we had to limit the number of potential confounders included in the statistical models, which increases the risk of both type I and type II errors.

In paper III, the blood samples were taken at the most previous GÅS visit prior to the MRI examination. A sensitivity analysis was performed to identify the CKD status at the next study visit after the MRI examination. 52,1 % of the participants who underwent MRI continued attending visits in the GÅS study after the MRI examination. Of these participants, 13.2 % had missing eGFR status at the following GÅS visit. 69.3 % remained stable in their group based on eGFR. 3.3 % went from CKD to normal kidney function, and 14.2 % went from normal kidney function to CKD. We do not know if CKD in these cases appeared before or after the MRI examination. Presumably, some of the participants who had been classified as having normal kidney function, could have developed CKD before the MRI examination. Therefore, the observed associations between CKD and CSVD in paper III could be underestimated.

Even though PP elevation is an established surrogate for AS [14-16], as mentioned in the introduction, PP is determined not only of arterial compliance, but also of stroke volume [80]. Examples of conditions that can influence stroke volume and thereby PP are aortic valve disease and heart failure [192]. Also, the anatomy of the proximal aorta seems to influence PP [193, 194]. Therefore, PP elevation is probably not as accurate as measuring carotid-femoral PWV to assess AS [14, 90].

In paper IV, almost all subjects with elevated PP also had HT (89.2 %). We could therefore not make any stratification based on HT status, and this study could not determine if elevated PP is associated with incident CKD or all-cause mortality independent of HT.

In paper IV, we had no data regarding the cause of mortality of the subjects who died during follow-up. Therefore, we could not determine if elevated PP is associated with cardiovascular mortality.

Even though the GÅS study is an observational study, some findings during the collection of data cause the staff in GÅS to inform both the participant and the general practitioner of the participant (with permission from the participant of course), in accordance with the GÅS protocol. Examples of when this happens include the finding of severely impaired kidney function (< 30 ml/min/1.73m^2), and the finding of HT (SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg). These procedures are obviously ethically unquestionable and can help identify and lead to management of risk factors of the participants in GÅS, which most likely is beneficial to the participants. There is, however, a potential risk that the management of risk factors from shared information can lead to underestimation of the impact of these risk factors when examining outcomes connected to these risk factors in future follow-up visits.

Since there is always some degree of bias in observational studies (see the section "Methodological considerations" of this chapter), any associations found must be observed in other studies. The new findings in all of the papers of this thesis therefore need to be replicated in other studies.

Conclusion and clinical implications

This thesis supports that low eGFR (< 60 ml/min/1.73m^2), as a measure of renal impairment, is a risk factor of cognitive impairment in the general older population. To improve the classification into CKD and normal kidney function, GFR was estimated from cysC only in the underweight participants in paper III and paper IV. The procedure of estimating GFR from cysC only in underweight subjects based on BMI has not been validated and can therefore not yet be recommended in clinical practice.

We found an association between CKD (eGFR < 60 ml/min/1.73m^2) and markers of CSVD on MRI in the older hypertensive population, enhancing the theory that the association between kidney function and cognitive function, at least partly, rests on a vascular basis. It is likely that there is a complex interplay between HT, CKD, and CSVD. In the presence of CKD, it is probably important to assess and manage HT to prevent CSVD, cognitive impairment, and progress of CKD.

Furthermore, we found that PP elevation, as a surrogate for AS, was associated with incident CKD and all-cause mortality. This thesis also suggests a cut-off limit of ≥ 60 mmHg for when PP should be considered elevated, that is, relevant as a risk factor of future morbidity.

The associations observed in paper I – IV suggest that a finding of PP ≥ 60 mmHg should raise concern of kidney function, and that a finding of eGFR < 60 ml/min/1.73m^2 should raise concern of cognitive function in an older individual. Suggestively, these findings should also raise concern regarding the cardiovascular status in an older subject, and that evaluation and management of treatable cardiovascular risk factors, such as HT, diabetes, and smoking habits should be considered.

Future perspectives

Demographic surveys predict an increase in both the number of older people and the proportion of older people in western Europe, Sweden included [195, 196]. Statistics Sweden (SCB) predicts that the number of people aged 80 years and older in Sweden will increase from 559 600 in 2021 (representing 5 % of the population to more than 1.3 million in 2070 (representing 10 % of the population) [196].

To this date there is no known cure for cognitive impairment and dementia caused by vascular damage in the brain, and since the changes in the brain seen in vascular cognitive impairment and vascular dementia indeed consist of damaged vessels which have led to irreversible apoptosis of nervous tissue, a cure is not likely to be seen in the nearest future.

Dementia is associated with significant burden both to the affected individuals and to their family members [24-26]. The economic cost to society of dementia is immense. The National Board of Health and Welfare in Sweden estimated the total economic cost to society in Sweden in 2014 (including the cost of healthcare, nursing care, informal care, and loss of production) to SEK 62.9 billion [197]. In 2019, the total cost of dementia in Sweden had increased to approximately SEK 80 billion [27].

Dementia is common in older age groups. The prevalence of dementia in Europe has been estimated to 6.9 % – 9.1 % in people 65 years of age and older [198]. In Sweden, the prevalence of dementia has been estimated to 6.5 % – 8.0 % in people 60 years and older [199]. Along with the demographic changes predicted in the future with both a larger proportion and total number of older people, the prevalence of dementia is expected to increase. It has been estimated that the total number of adults living with dementia will increase with 62 % in Sweden, 74 % in western Europe, and astonishing 268 % worldwide, from 2019 to 2050 [200].

The prevalence of CKD is estimated to be about 10 % of the adult population [201]. The prevalence, however, increases with age [1], and along with the predicted changes in demographics in the future, both the proportion and total number of individuals with CKD can be expected to increase.

CKD is also associated with a high economic cost for society, as well as with a high burden of morbidity of the affected individuals in the advanced stages of the disease [201, 202]. The mean annual cost of health care per patient with severe CKD (< 30 ml/min/1.73m^2) has been estimated to be four times higher (9600 euros), and 45 times higher (87600 euros) for patients on haemodialysis, compared to the general population, in Sweden [203].

To reduce morbidity, and the risk of an overwhelming amount of older people suffering from vascular cognitive impairment including vascular dementia, as well as CKD, in the future, which the welfare system may not be able to handle, the best approach is most likely prevention. To prevent a future massive incidence of vascular cognitive impairment including vascular dementia, and CKD, it is crucial to identify individuals at risk of developing cerebral vascular damage, as well as CKD, at an early stage. If individuals at risk are identified early, potential treatable cardiovascular risk factors, such as HT, diabetes, and smoking habits can be identified and managed, thereby postponing both cognitive disorders and CKD.

In GÅS, follow-up MRI brain examinations as well as interpretation of these MRI images have been performed in 2022 – 2023 regarding 242 subjects out of the 407 subjects who underwent MRI brain examination in 2016 – 2018.

In future longitudinal studies, to further penetrate and better understand the connection between renal function, brain function, and vascular health, we aim to investigate if low GFR/CKD precedes incident CSVD and/or worsening of CSVD status.

In future longitudinal studies, we intend to investigate if PP elevation precedes incident CSVD and/or worsening of CSVD status, as well as cognitive impairment.

We also aim to validate the procedure of estimating GFR from crea/cysC in the non-underweight and from cysC in the underweight when underweight is based on BMI.

Since all sub-studies of this paper were observational, the new observed associations need to be replicated in other observational studies including different populations. Interventional studies, where the effects of identification and management of treatable cardiovascular risk factors in subjects with CKD on the outcome cognitive impairment, and in subjects with elevated PP on the outcome CKD, are also warranted.

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