Defining risk factors associated with renal and cognitive dysfunction
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CHAPTER 1

Introduction and aims of this thesis
Introduction

The growing epidemic of the global cardiovascular disease (CVD) epidemic has been a major health care concern. This epidemic has been attributed to the increased prevalence of CVD risk factors worldwide, including obesity, hypertension and diabetes mellitus (DM).\(^1\) Despite the fact that much has been learned about their epidemiology, implementation of meaningful strategies for the prevention of these risk factors remains a huge challenge.\(^1,2\) Some CVD risk factors cannot be influenced, such as age, sex and genetics. However, others are modifiable or can be prevented through a combination of individual-level and population-level interventions. Well-known modifiable risk factors include overweight, hypertension, dyslipidemia, smoking and DM.

Cardiovascular burden in individuals

The prevalence of CVD risk factors rises in the general population and they often cluster within subjects.\(^3,4\) Notably, overall cardiovascular burden is often underestimated, especially in young persons, since at young age individual cardiovascular risk factors remain undetected or do not exceed threshold values. However, by accounting for the conjoint effects of risk factors, they can indicate a significant increase in cardiovascular risk.\(^5\) This has led to the development of multicomponent cardiovascular risk scores that can be used to predict an individual's risk of a cardiovascular event within the next 5 to 10 years.\(^5-7\) Examples are the Framingham risk score for general cardiovascular disease (FRS) and the SCORE risk system, respectively developed in an American and an European population.\(^5,8\) These composite measures are based on age, gender, DM, smoking status, systolic blood pressure (SBP) and lipid levels. An increased cardiovascular risk profile is not only associated with coronary heart disease, stroke and chronic kidney disease (CKD), but also with cognitive dysfunction.\(^9\) Determining an individual's risk profile is an important cornerstone in the Dutch multidisciplinary Cardiovascular Risk Management guideline.\(^10\)

Cardiovascular risk profile and CKD

There is much overlap between risk factors for CVD and CKD.\(^11\) The presence of cardiovascular risk factors like DM, hypertension and obesity increases the risk of developing CKD in both younger and older adults.\(^12\) In the Netherlands, over one million people are considered to have CKD (due to disease as well as age-related decline), with a large proportion suffering from severe renal dysfunction.\(^13\) The risk of developing CKD increases concomitant with age, not only because age is a key predictor of CKD, but also because risk factors for CKD become more common as one ages.\(^12\) Therefore, it is not surprising that an adverse overall cardiovascular risk profile (as measured with the FRS) is associated with the presence of CKD.\(^14\) The impact of CKD is high as it associates with increased cardiovascular morbidity, mortality and with impairment in quality of life.\(^15\) Furthermore, CKD carries the risk of progression towards end-stage renal disease.\(^11\)
Cardiovascular risk profile and cognitive function
Several mid-life cardiovascular risk factors like hypercholesterolemia and hypertension have a negative effect on cognitive function in older age.\textsuperscript{16} Data also point towards a negative effect of modifiable risk factors like obesity, hypertension and smoking on cognitive performance in persons of younger age.\textsuperscript{17-19} However, the relationship of individual cardiovascular risk factors with cognitive function is less crystallized as compared to their relationship with renal function. Accordingly, even less evidence is available on the association of overall cardiovascular risk profile and cognitive function.\textsuperscript{20,21} Thus, there is some evidence pointing towards an adverse impact of cardiovascular risk factors on cognitive performance, but the relationship between overall cardiovascular burden and cognitive performance needs to be clarified yet.

The link between brain and kidney
Both the kidneys and the brain are highly vascularized end-organs, connected with each other through anatomic and vasoregulatory connections and similarities.\textsuperscript{22} Unlike most organs, the kidneys and brain are low resistance end-organs, each exposed to high blood flow throughout the cardiac cycle.\textsuperscript{23} Cardiovascular risk factors can cause similar (micro)vascular injury in both organs. Microvascular injury in the kidney may reflect the presence of (micro)vascular injury in the brain as injury takes place in similar vascular beds and endothelial structures.\textsuperscript{24}

Ito \textit{et al} suggested the ‘strain vessel hypothesis’ as a possible common pathogenic pathway.\textsuperscript{25} Based on the similarity of the juxtamedullary afferent arterioles in the kidney and the perforating arterioles in the brain, they are thought to be evolutionally developed to maintain optimal perfusion of vital structures like nephrons and the brainstem directly from large arteries. These ‘strain vessels’ are exposed to very high transmural pressures. Vascular damage induced by hypertension and DM occurs in these vessels. Therefore, increased albuminuria may be an indicator of vascular damage not only in the kidney but also in the brain.\textsuperscript{25} Besides the above mentioned mechanisms, in severe renal dysfunction (defined as an eGFR <60ml/min/1.73m\textsuperscript{2}) renal toxic effects of uremia, calcium-phosphate disturbances or other metabolic changes like anemia might also have an independent (negative) effect on cognitive function.\textsuperscript{23,24}

Several imaging studies showed diffuse cerebrovascular pathology in subjects with CKD, including white matter lesions, cerebral microhemorrhages and (silent) brain infarcts.\textsuperscript{26,27} This also suggests an association between another marker of cerebral function (cognition) and renal function (albuminuria and/or eGFR) (figure 1).
Several studies have demonstrated an independent and severity-dependent relationship between CKD and risk for cognitive decline, although this finding is not consistent throughout the whole literature.\textsuperscript{28} Notably, most studies have evaluated the relationship between renal and cognitive dysfunction based on one determinant of CKD only (eGFR). Only few have examined the association of another determinant of CKD (increased albuminuria) with cognitive function.\textsuperscript{28} So far, all studies omitted to investigate their mutual relationship on cognitive function.

Assessment of cognitive and renal dysfunction

_Cognitive dysfunction_ is a manifestation of damage to the brain tissue which causes loss of higher cerebral functions. Despite the fact that cognitive function is less easy to detect as compared to e.g. renal dysfunction (CKD), it has become increasingly clear that the onset of cognitive decline is earlier than previously realized. Recently, it was found that cognitive decline may be already evident at the age of 45 years.\textsuperscript{29} It is therefore hypothesized that poor cognitive function in old age is the result of a long term pathological and progressive process that spans at least two to three decades.

As the onset of cognitive decline already starts at younger age, it is important to have sensitive tools for detecting cognitive dysfunction in (young) adults. In clinical practice, cognitive assessment instruments are mainly used to screen for dementia, and therefore mainly designed for use in elderly subjects. Examples include the (Modified) MMSE, Digit
Symbol Substitution Test (DSST) or Trail Making Test (TMT). These tests are limited however limited by ceiling effects, especially in young subjects.

The Ruff Figural Fluency Test is a cognitive function test which measures nonverbal fluency.\textsuperscript{30} Due to its design, it overcomes the problem of a ceiling effect by providing a continuous parameter of cognition. Due to its wide score range, the RFFT reflects a broad spectrum of performance. It is therefore sensitive to subtle changes in cognitive performance in young and old persons.\textsuperscript{30} The RFFT is generally seen as a test for executive function and provides information regarding various cognitive abilities such as initiation, planning, divergent reasoning and the ability to switch between different tasks. Briefly, the RFFT requires participants to draw as many unique designs as possible within a set time limit by connecting dots in a different pattern in each part (1-5), while avoiding repetitions of designs (figure 2).

\textbf{Figure 2} The five parts of the Ruff Figural Fluency Test (RFFT).\textsuperscript{30}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{image}
\caption{The five parts of the Ruff Figural Fluency Test (RFFT).\textsuperscript{30}}
\end{figure}

\textit{Renal dysfunction} (or CKD) is a manifestation of damage to the renal tissue which causes loss of kidney function. CKD is an important health problem, not only because of the high prevalence, but also due to the related morbidity and mortality.\textsuperscript{11,31,32} In 2002 the term chronic kidney disease (CKD) was introduced and defined by the level of renal function expressed by (estimated) glomerular filtration rate (eGFR) and/or the presence of kidney damage like increased albuminuria.\textsuperscript{30} The current classification of CKD is based on the level (category) of eGFR and/or albuminuria (figure 3). Albuminuria is a marker of kidney damage and classified into normal to mildly increased, moderately increased and severely increased (defined as <30, 30-300 and $\geq$300 mg/g, respectively). Notably, a recent meta-analysis showed that not only albuminuria $\geq$30 mg/24h (moderately increased), but also a lower cut point of 10 mg/24h (mildly increased) is associated with increased mortality and cardiovascular disease.\textsuperscript{32} As is shown in figure 3 the prognosis of CKD worsens with increasing albuminuria and decreasing eGFR.
Risk factors associated with renal dysfunction influencing patient outcomes

Interventions for preservation of renal function beyond improving cardiovascular risk factors are also important to consider for patients with CKD. CKD is a well-known risk factor for injuries resulting from medication errors, also known as adverse drug events (ADEs). ADEs are a significant source of iatrogenic injury to patients. Various studies reported considerable dosing difficulties and subsequent medication errors in patients with CKD. However, renal function loss often remains unrecognized by physicians and pharmacists, even in high-risk patients such as elderly and those with DM. Therefore, intensified collaboration between health care workers (such as general practitioners (GPs), pharmacists, and nephrologists) is recommended with exchange of relevant patient information (medical history and co-morbidities) and more effective use of routinely collected data from electronic patient records such as laboratory results relating to renal function. These recommendations can be implemented in clinical practice in various ways. Thus, there is a need for evidence-based interventions.
Patients with CKD often experience a gradual decline in renal function which is initially asymptomatic.\textsuperscript{11} In patients with renal disease and a normal or mildly decreased renal function (eGFR >60 ml/min/1.73m\textsuperscript{2}), homeostatic renal mechanisms are able to keep the concentrations of electrolytes, acid-base balance and the volume of extracellular fluid within a normal range. The production of erythrocytes through the release of erythropoietin is still preserved in these stages of CKD. A further decline in renal function (eGFR \leq 60 ml/min/1.73m\textsuperscript{2}), is considered to be associated with a variety of hematological and biochemical abnormalities like anemia, hyperkalemia, hyperphosphatemia, hypocalcemia and uremia. These abnormalities are related to a decreased quality of life, increased morbidity and mortality.\textsuperscript{11,31} Anticipatory treatment during the earlier stages of CKD can significantly reduce the complications of these hematological and biochemical abnormalities. Therefore, the Kidney Disease Improving Global Outcomes (KDIGO) guidelines recommend that all patients with an eGFR \leq 60 ml/min/1.73m\textsuperscript{2} undergo evaluation for anemia and those with an eGFR \leq 45 ml/min/1.73 m\textsuperscript{2} for biochemical abnormalities and metabolic bone disease as well.\textsuperscript{11} The national Dutch guideline on CKD (Landelijke Transmurale Afspraak (LTA) chronische nierschade) makes a distinction between patients younger and older than 65 years. This guideline recommends evaluation of metabolic abnormalities in all patients aged <65 years with an eGFR between 45-60 ml/min/1.73 m\textsuperscript{2}, and from an eGFR 30-45 ml/min/1.73m\textsuperscript{2} in patients aged 65 years or older.\textsuperscript{37}

Notably, in current clinical practice several methods to assess renal function are applicable (including the Cockcroft-Gault formula, 24-hours urine creatinine clearance, the Modification of Diet in Renal Disease (MDRD) and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations). These separate renal function estimates are developed in different periods, in various populations with different laboratory assays. All estimates have been widely studied and they showed different strengths and limitations. Depending on the population in which they are used, their performance (precision and accuracy) differs. Therefore, it is unclear how the prevalence of biochemical abnormalities at different stages of renal function exactly changes when various measures of renal function are used.
Objectives and outline of the thesis

The general objective of this thesis is to describe risk factors for cognitive and/or renal dysfunction and to evaluate shared cardiovascular risk factors and patient outcomes. This general aim is explored in different observational studies. Part one of this thesis focuses on the kidney and contains two studies evaluating complications associated with renal dysfunction (like ADEs) which can have a negative impact on patient outcomes. Part two focuses on the brain and evaluates risk factors for cognitive dysfunction. The study in Part three of this thesis evaluates shared risk factors for both cognitive and renal dysfunction.

Chapter 2 describes the effectiveness of providing automatically generated eGFR ≤ 40-alerts towards community pharmacists to reduce medication errors in subjects with CKD. This study evaluates the number of subjects at risk for medication errors due to CKD and the number of potential ADEs. Chapter 3 was performed to evaluate the prevalence of biochemical abnormalities at different stages of CKD using two methods for the assessment of renal function, including the Modification of Diet in Renal Disease equation (MDRD-4 formula) and the 24-hour creatinine clearance. Chapter 4 provides reference data for a cognitive function test (RFFT) which needs to be sensitive to subtle changes in cognitive performance in both young and old persons. Specifically, we aimed to provide reference data stratified by age, gender and educational level. Chapter 5 addresses the association of an individual’s cardiovascular risk profile with cognitive function and explores this association in various age groups including both young and old adults. Chapter 6 further explores the association between cardiovascular risk profile and cognitive function. We evaluated whether improving cardiovascular risk (by statin treatment to improve dyslipidemia) is beneficial for cognitive performance in a large community-based population. Chapter 7 continues research into risk factors for cognitive dysfunction and explores overlapping risk factors with renal dysfunction. In this chapter we evaluate the cross-sectional association of both albuminuria and eGFR with cognitive function in a large community-based population cohort. Chapter 8 provides a summary and discussion of the findings in this thesis.
References


1 Introduction and aims of this thesis
PART 2
THE KIDNEY