The use of health claims data for epidemiology and costs of chronic kidney disease

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The use of health claims data for epidemiology and costs of chronic kidney disease

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There is freedom waiting for you,
On the breezes of the sky,
And you ask “What if I fall?”
Oh but my darling,
What if you fly?

Erin Hanson

Voor Daniël en Lotte

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General introduction

Chronic kidney disease

Chronic kidney disease (CKD) is characterized by a gradual and irreversible reduction in kidney function. The kidneys play a vital role in maintaining body homeostasis. Their life-sustaining activities include filtering of waste products and their excretion via the urine, reabsorption of nutrients, regulation of electrolytes and acid-base homeostasis, the control of fluid balance and blood pressure, and regulation of bone metabolism and red blood cell production. The glomerular filtration rate (GFR) is used as an index of kidney function and reflects the total amount of fluids filtered through the glomeruli per minute with normal values ranging from 90 to 120 mL/min/1.73 m^2.[1] In clinical practice, the GFR is most commonly estimated with serum creatinine levels using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) or the MDRD (Modification of Diet in Renal Disease) equation.[2]

According to international guidelines, CKD is defined as a decreased kidney function (GFR <60 mL/min/1.73 m^2) or the presence of markers of kidney damage (i.e. albuminuria or urinary sediment abnormalities) which have to be present for more than three months.[3,4] CKD is categorized into five stages based on thresholds of GFR and three stages based on thresholds of albuminuria, as an indication of the severity of kidney damage (Figure 1.1). The staging of CKD helps to more accurately define the risks of a CKD patient (regarding the risk of progression of kidney failure, morbidity, and mortality) and facilitates choices in clinical management strategies.

There are multiple causes of CKD, of which atherosclerosis, diabetes, and hypertension are most common.[5,6] Other risk factors for CKD development are old age, increased body-mass index, smoking and low socioeconomic status.[7,8] CKD itself is an independent risk factor for cardiovascular disease and accelerated atherosclerosis, cognitive dysfunction, hospitalization, and mortality.[5] Other complications of CKD that contribute to the high morbidity, mortality, and poor quality of life of patients include hypertension, anemia, mineral bone disorder and an increased risk of cancer.[9]

A person is considered to have end-stage kidney disease (ESKD) when the GFR is below 15 mL/min/1.73 m^2 for more than three months (GFR Stage G5). In this final stage of CKD, the remaining kidney function is no longer capable of sustaining life for an extended period of time in most patients. Therefore, many patients with ESKD are considered candidates for kidney replacement therapy (KRT), in the form of dialysis (hemodialysis or peritoneal dialysis) or kidney transplantation. An alternative for KRT is comprehensive conservative management which is a palliative approach to

the management of ESKD patients characterized by non-dialytic treatment with active supportive care and maximal conservative treatment.[6,10] Although KRT can be a life-saving option for ESKD patients, it is still associated with an increased risk of morbidity (such as cardiovascular events), and a significant reduction of quality of life. In addition, these patients often have a drastically decreased life expectancy compared with individuals of similar age and sex without ESKD.[6,11]

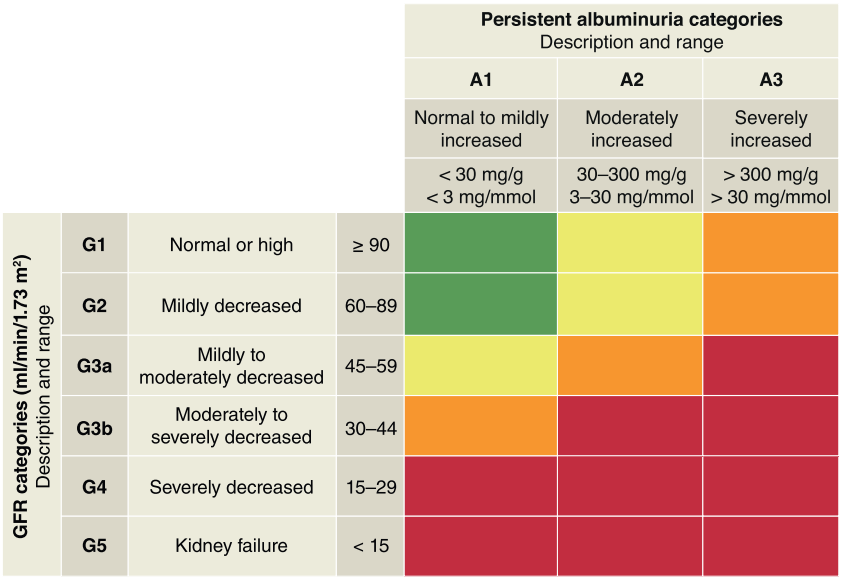


Figure 1.1: Classification and according prognosis of CKD by GFR and albuminuria categories.

Abbreviations: CKD, chronic kidney disease; GFR, glomerular filtration rate
Colors represent the risk for progression, morbidity, and mortality. Green: low risk (if no other markers of kidney disease, no CKD); yellow: moderately increased risk; orange: high risk; red: very high risk.
Figure adapted from Kidney Disease: Improving Global Outcome (KDIGO) CKD work group (2012).[3]

Early detection of CKD by primary care physicians is crucial to allow timely efforts and interventions to slow down the progression of kidney failure, to prevent or treat complications, and to arrange an optimal timing for the start of KRT.[5,7] Guidelines recommend the referral of CKD patients to a nephrologist when the estimated GFR falls below 30 mL/min/1.73 m^2.[3] Even then, for these patients the risk of early mortality is five to ten times higher than the risk of progressing to ESKD.[6,11,12] This increased mortality risk rises exponentially with age and with the level of kidney failure and is mainly attributable to death from cardiovascular disease.[13,14]

The global burden of CKD is substantial. A recent study estimated that in 2017 around 834.5 million individuals had CKD making it one of the most common chronic diseases in the world. Of these, 3.9 million individuals (0.47%) were treated with KRT worldwide.[15] Notwithstanding the improvements in the management of CKD patients and the implementation of international guidelines over the past decades, CKD remains one of the leading causes of mortality and morbidity worldwide.[6] CKD accounts for approximately 2.1% of deaths worldwide and ranked 13th in the list of causes of death by the World Health Organization in 2016.[16]

Using health claims data for kidney research

Health claims databases contain routinely collected data for reimbursement purposes.[17] Every healthcare provision leaves a trail of digital information describing a patient's care pathway through the healthcare system, from the first encounter with the general practitioner until the last treatment in the hospital, at least as long as the provided care is part of a reimbursement scheme.[18] Such databases include information like sociodemographic data (e.g. age, sex, postal code), medication prescription records, primary care data and hospital data, and other delivered healthcare. The first use of health claims data for clinical research dates back to the early '80s when researchers started to explore the use of the United States Medicare data.[19] Since then, health claims data became increasingly popular to use for research purposes as a result of their unique features. They are now being used to answer a wide variety of healthcare-related research questions in different medical disciplines.

The large size, comprehensiveness and longitudinal nature of many health claims databases provide unique opportunities for various study designs, such as cohort studies, cross-sectional studies, or case-control studies.[20,21] Besides, data collection is less costly and time-consuming as compared with traditional data sources, making it relatively easy to study large samples along with rare conditions.[22] Often, health claims databases have nationwide coverage, including individuals of all ages and socioeconomic backgrounds, and are thereby representative of large patient populations comprising the elderly, children, the very poor and the institutionalized.[23] In addition, since health claims data is routinely collected for reimbursement purposes, they hold detailed information on healthcare costs. Furthermore, health claims data has the potential of studying regional differences and trends in disease prevalence, outcomes and healthcare costs over longer periods of time.[24] All these unique characteristics and the non-experimental nature of health claims data, being

a reflection of real-life healthcare provisions, make them an important and relevant data source for both researchers and health policymakers.[17,25]

Despite the huge potential of this readily available information, some limitations should also be noted. Most health claims databases are a result of reimbursement and billing processes and, therefore, their data is not specifically collected to serve clinical research purposes.[18,26] The majority of claims databases will not contain clinical and laboratory data, like for example information on kidney function and diagnosis. In the Netherlands, using only the data available in the Dutch health claims database, the identification of kidney disease patients can only be based on diagnosis codes, which may result in an underestimation of the actual number of patients having CKD.[20,27,28]

Dutch health insurance claims database

Vektis manages and collects the health claims data of all health insurers in the Netherlands.[29] It aims to ease the administrative processes in healthcare by making these smarter and more efficient, as well as to provide data-driven insight into healthcare consumption in the Netherlands and to facilitate research with data from the Vektis database. The Vektis database is a nationwide population database covering 99% of all insured individuals in the Netherlands, thereby comprising approximately 17 million Dutch residents. The database contains all health claims for medical procedures covered by the Dutch Health Insurance Act from 2012 onwards.[30] Before registration in the database, all claims are subject to technical and content checks, as well as checks for plausibility on record or period level. For each health claim registered in the database, detailed information is available on the type of claim, the date of registration and timeline of the claim, a code identifying the healthcare provider registering the claim as well as information on the reimbursed costs of the claim available as a sum of intermediate products per calendar year. Claims can be traced back to individuals via encrypted personal identifiers and linked to basic demographic data, such as sex, year of birth, area of residence, and a proxy for date of death. Next, an individual's socioeconomic status (SES), as established by the Netherlands Institute for Social Research based on a person's postal code, is available.[31] The SES score is derived from the mean income in the residential area, the percentage of people with low education and low income as well as the fraction of unemployed people in the area.

The Vektis database contains among other things, claims data for pharmaceutical care, which includes information on the dispensed medications, the Anatomical

Therapeutic Chemical (ATC) code, and information on the annual supplied quantity of medication. The Defined Daily Dose (DDD) is a designed technical unit reflecting the presumed average maintenance dose per day for a medication used for its primary indication.[32] The annual quantity provided is a product of the DDD times the number of days a drug was prescribed. Besides pharmacy dispensing data, the Vektis database contains information about medical expenses.[33] This enables detailed evaluation of real-life healthcare costs and the assessment of the financial impact of diseases on society, including those of CKD.

To this end, the Vektis database provides opportunities for kidney research. For example, it enables comprehensive studies on healthcare expenditure and medication use in CKD patients who are cared for in the hospital. Moreover, the size and coverage of the database make it possible to compare results with a matched sample from the general population. Until now, the use of health claims data for kidney research in the Netherlands is still in its infancy. Box 1.1 describes the Dutch healthcare system as well as the Dutch health insurance system which forms the background of all studies included in this thesis.

Box 1.1: The Dutch healthcare and health insurance system

The Dutch healthcare system is one of the best-valued systems in the world, resulting in a high standard of care with a low number of avoidable hospitalizations, a relatively low avoidable mortality, and an increasing life expectancy.[34] However, the Dutch health system is also one of the most expensive in Europe.[34] One of the main characteristics of the Dutch healthcare system is the gatekeeping principle, which means that hospital care and specialist care (except for emergency care) require a referral from a general practitioner (GP) or another primary care provider. As a result, only 7% of the contacts with a GP end up in a referral to secondary care.

The payment and provision of Dutch healthcare through healthcare insurance are embedded in a social security system.[35] Since basic healthcare insurance is obligatory in the Netherlands, approximately 99.8% of the roughly 17 million Dutch citizens have healthcare insurance.[36,37] The benefit package of the basic health insurance defined under the Health Insurance Act comprises medical care (including care provided by GPs, hospitals and medical specialists), home nursing care, pharmaceutical care, medical aids and devices, medication, maternity care, transportation of sick people by ambulance or taxi, and mental care. Care not covered by the basic insurance can be insured via voluntary health insurance.[34]

GPs are paid through a fee-for-service and pay-for-performance system. Hospitals are paid by a physician-claims system named diagnosis treatment combinations (DBCs), a system adapted from the diagnosis-related group (DRG) system. This system was introduced in 2005 and reformed in 2012, drastically reducing the number of available DBCs from 30 000 to 4000 to simplify the system and make it less susceptible to errors and fraud. Within the new system the DBCs are named DOTs (DBCs On the way to Transparency), however, in this thesis we will call them DBCs for reasons of clarity. A DBC corresponds to a specific medical condition in a specific medical discipline. It contains information on a complete care episode, from establishing the diagnosis in an outpatient situation to the last check after treatment or after discharge from the hospital. Multiple DBCs can be active at the same time when a patient is being treated for various (chronic) conditions. Every DBC has a fixed price which can be assigned to the costs of all intermediate products, i.e. medical activities, which covers all direct (costs of medical specialists, nurses, use of medical equipment and diagnostic procedures) and indirect (e.g. education or research) costs of a care episode.[38] Hospital care of which the costs are disproportionately high (such as intensive care or very expensive medication) is generally not included in a DBC, but is payed for through additional reimbursements or supplements.[34]

Aims and objectives of this thesis

The first aim of this thesis is to examine the value and limitations of health claims data for kidney research. To achieve this aim we have formulated the following two research objectives:

1. to explore the opportunities and challenges of health claims databases and provide an overview of health claims databases in the world that have been used for research on kidney disease patients.
2. to validate Dutch health claims data for the identification of patients with CKD Stage G4-G5 not treated with KRT.

The second aim of this thesis is to study healthcare expenditure and use of healthcare resources (including medication use) of CKD patients (e.g. CKD Stage G4-G5 not treated with KRT and CKD Stage G5 treated with dialysis or kidney transplantation) using Dutch health claims data. To achieve our second aim we formulated the following two research objectives:

3. to estimate healthcare costs of patients with CKD Stage G4-G5 not treated with KRT and CKD Stage G5 treated with dialysis therapy or kidney transplantation using health claims data.
4. to examine the medication use of patients with CKD Stage G4-G5 not treated with KRT and CKD Stage G5 treated with dialysis or kidney transplantation using health claims data.

Furthermore, this thesis elaborated on the development of the Dutch Kidney Atlas. This is a website that describes the burden of CKD in the Netherlands, in terms of the number of patients, healthcare expenditures, treatment (besides KRT), medication, outcomes, and other conditions of CKD patients and the geographical variation per region in the Netherlands.

Outline of this thesis

Part 1 of this thesis provides insight into the value and use of health claims data for kidney research. **Chapter 2** reviews health claims databases used for kidney research around the world. It describes characteristics of the databases regarding coverage, content, and accessibility as well as their main publications. Furthermore, we introduce the Dutch Kidney Atlas based on data from the Dutch health claims database. Finally, the major strengths and limitations of health claims databases and the validity of health claims data to identify kidney disease patients are discussed.

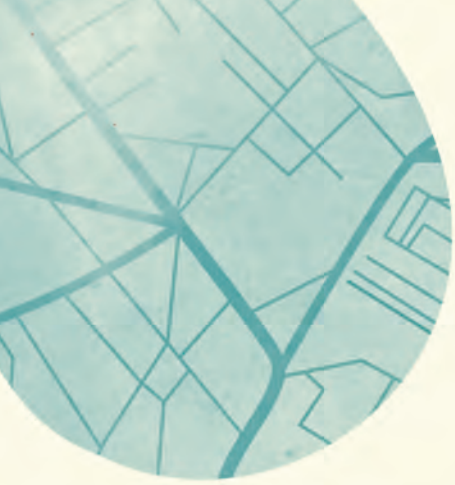
Part 2 focuses on the validity of Dutch health claims data. **Chapter 3** describes a validation study testing the validity of health claims data in identifying CKD Stages G3-G5 patients. It compares the identification of CKD Stages G3-G5 patients using health claims data from a regional hospital in Zwolle with patients identified based on eGFR data from a laboratory database, serving as a reference.

Part 3 examines healthcare cost and utilization in advanced CKD patients (with and without KRT) using Dutch health claims data. **Chapter 4** describes the healthcare costs of patients on different kidney replacement therapy modalities. **Chapter 5** studies age-related differences in healthcare costs and utilization of patients with CKD and compared these results with a matched control group from the general population.

Part 4 examines medication use in advanced CKD patients (with and without KRT) using Dutch health claims data. **Chapter 6** investigates the prevalence of polypharmacy and describes the most commonly prescribed medications in CKD patients with and without KRT compared with a matched sample from the general population.

Chapter 7 describes antidepressant prescription in the Dutch CKD population and their matched controls.

Chapter 8 provides a general discussion of the findings presented in this thesis and elaborates on the possibilities of Dutch health claims data for kidney research.



Part 1

Value and use of health claims data for kidney research

2

Health claims databases used for kidney research around the world

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Abstract

Health claims databases offer opportunities for studies on large populations of patients with kidney disease and health outcomes in a non-experimental setting. Among others, their unique features enable studies on healthcare costs or longitudinal, epidemiological data with nationwide coverage. However, health claims databases also have several limitations. Because clinical data and information on kidney function are often lacking, the identification of patients with kidney disease depends on the actual presence of diagnosis codes only. Investigating the validity of these data is, therefore, crucial to assess whether outcomes derived from health claims data are truly meaningful. Also, one should take into account the coverage and content of a health claims database, especially when making international comparisons. In this article, an overview is provided of international health claims databases and their main publications in the area of nephrology. The structure and contents of the Dutch health claims database will be described, as well as an initiative to use the outcomes for research and the development of the Dutch Kidney Atlas. Finally, we will discuss to what extent one might be able to identify patients with kidney disease using health claims databases, as well as their strengths and limitations.

Introduction

There are many registries and studies collecting information on patients with chronic kidney disease (CKD) and patients on kidney replacement therapy (KRT). In recent decades, these have been supplemented by administrative healthcare data, including health insurance claims data, thereby providing new research opportunities.

Health claims data are routinely collected for payment purposes, and for this purpose they usually are comprehensive and complete. These generally contain sociodemographic data and longitudinal data on medical diagnoses and procedures, pharmacological treatment, and costs. Most of these databases have nationwide coverage, include all age categories and offer data that reflect day-to-day clinical practice. However, when using administrative data for healthcare research, it is important to recognize their unique opportunities as well as their limitations. Furthermore, for international comparisons, one should take into consideration the differences in database characteristics when analyzing and interpreting these data.[25] Nowadays, several health claims databases of national and regional healthcare systems are available and are being used for kidney research.

In this article, we provide a worldwide overview of health claims databases and summarize their main publications in the area of nephrology. Next, we will introduce the Dutch health claims database and a new initiative to use it for research and the development of a Dutch Kidney Atlas. Finally, we will discuss to what extent they allow identification of patients with kidney disease as well as the strengths and limitations of such databases.

Worldwide health insurance claims databases in kidney research

We selected papers in which health claims data, whether or not combined with other administrative databases, were used for research on patients with kidney disease. A systematic literature search was not possible because the use of health claims data is often not clearly mentioned in the articles. We performed an Internet and PubMed search in August 2019 using different search terms (e.g. health claims data, health insurance claims data, healthcare claims data, administrative data in combination with terms to search for research on patients with kidney disease such as CKD, dialysis, or kidney transplantation). We selected suitable papers based on the abstract and methods section. In addition, we checked the references of selected papers and checked other published papers by the main authors.

We identified 13 health claims databases in 10 countries (Canada, China, the UK, France, India, Japan, South Korea, Taiwan, the Netherlands, and the USA) that were used for research on patients with kidney disease and resulted in at least one publication in English in a scientific journal (Table 2.1). Other countries, such as Austria and Germany, have a health claims database that is used for clinical research. However, we were unable to find papers published in scientific journals specifically focusing on kidney disease patients from these countries.[17] In some countries in Southeast Asia, health claims databases have been recently established and so far their use for research purposes has been rare.[39] The use of health claims databases for kidney research worldwide may therefore be expanded.

The organization of healthcare systems, healthcare financing, and socio-economic settings differ importantly between countries.[24] This results in differences in the coverage, the size and the content of the health claims databases. A recent study presented a comprehensive overview of existing systems and financing for kidney care and demonstrated significant heterogeneity.[40] In countries where health insurance is obligatory or universally accessible (such as Canada, France, Japan, South Korea, the Netherlands, and Taiwan), health claims databases have (almost) complete coverage of all country or province inhabitants (Table 2.1). The coverage of the Chinese claims databases, in contrast, is much less complete. Although they comprise a large number of individuals, the content of these is limited to the ones with access to healthcare insurance. The USA does not have universal healthcare coverage and the Medicare program only provides health insurance for American citizens ≥65 years of age as well as for people of all ages with severe diseases such as those with end-stage kidney disease. Therefore, the Medicare claims database covers a selection of the US population. Furthermore, the Rajiv Aarogyasri Community Health Insurance Scheme is an Indian state government program providing free hospital care to poor individuals. Noteworthy is the Hospital Episode Statistics (HES) database, which provides admission data for National Health Service (NHS) hospitals in the UK.

Within health claims data, kidney disease patients are generally identified with International Classification of Disease codes in combination with medical procedure codes. In Japan, patients are identified with Diagnosis Procedure Codes (DPC), whereas in the Netherlands patients are identified using diagnosis treatment combinations (DBC), a system similar to the DPC system.

When evaluating studies using health claims data, it is essential to consider the coverage (such as age distribution, health system characteristics, insurance coverage, and percentage of the population with healthcare insurance) and the specific procedure of patient selection to correctly interpret its results. This is of special importance when making international comparisons.

Table 2.1: Overview of health claims databases in the world used for kidney research.

Country or province	Number of inhabitants in 2018	Health claims database	Coverage	Linkage to other (administrative) databases
Canada - Alberta	4.3 million	Alberta Provincial Physician Claims database	>99% of inhabitants	Part of the Alberta Kidney Disease Network database; linkage to the Northern and Southern Alberta Renal Programs and clinical laboratory data
Canada - Manitoba	1.4 million	Manitoba Health Physician Claims database	>99% of inhabitants	Linkage to Manitoba Renal Program Dialysis Registry
Canada - Ontario	14.3 million	Ontario Health Insurance Plan database (OHIP)	>99% of inhabitants	Linkage to Ontario's central organ and tissue donation agency, Canadian Institute for Health Information Discharge Abstract Database (CIHI-DAD), National Ambulatory Care Reporting System (data on emergency room visits), Ontario Registered Persons Database Information (demographics and vital status), Ontario Drug Benefit Plan (outpatient prescription drug usage for individuals ≥65 years)
Canada - Quebec	8.4 million	Régie de l'assurance maladie du Québec (RAMQ)	>99% of inhabitants	Linkage to Canadian Organ Replacement Register (CORR)
China	1.4 billion	China Health Insurance Research Association database (CHIRA)	977 million insured people in 2015	
		Commercial Health Insurance database (CHI)	60 million customers in 2015	

Table 2.1 *(continued)*

Country or province	Number of inhabitants in 2018	Health claims database	Coverage	Linkage to other (administrative) databases
UK	55.3 million	Hospital Episode Statistics (HES)	All admissions to NHS hospitals in the UK	Linkage to the Office for National Statistics (ONS) for mortality data
France	66.9 million	Système national d'information interrégimes de l'Assurance Maladie (Sniiram)	96% of inhabitants	Linkage to French Renal Epidemiology and Information Network (REIN) registry, French national hospital computerized medical information system (PMSI)
India - Andhra Pradesh	1.3 billion	Rajiv Aarogyasri Community Health Insurance Scheme	81% of inhabitants	
Japan	127.2 million	National Database of Health Insurance Claims and Specific Health Checkups of Japan (NDB)	90% of inhabitants	
South Korea	51.1 million	Health Insurance and Review Assessment Service (HIRA)	98% of inhabitants	Linkage to a national health screening program (including 10 million Koreans) providing information on serum creatinine and urine albumin measurements
Taiwan	23.8 million	National Health Insurance Administration Research Database (NHIRD)	>99% of inhabitants	Linkage to e.g. death registry, cancer registry, reportable infectious disease registry
The Netherlands	17.1 million	Vektis database	98% of inhabitants	
USA	327.2 million	Medicare Services	Individuals aged ≥65 years and end-stage kidney disease patients	Linkage to the United States Renal Data System (USRDS), Scientific registry of transplant recipients (SRTS), National Health and Nutrition Examination Survey data (NHANES)

Accessibility of health claims databases

Several barriers to the secondary use of administrative data in general have been identified. The impact of these barriers differs considerably between countries and influences the availability and utility of health claims data for research per country.[41]

In general, the complexity and the enormous amount of unprocessed raw data make it difficult and laborious to work with health claims databases. The pre-processing of data is time-consuming and requires experience with working with big data. In addition, extensive application processes, as well as data processing fees, are usually needed to access the data.

Data accessibility differs across countries. For example, the National Health Insurance Research Database (NHIRD) of Taiwan is known for its high accessibility. The database is publicly available and any researcher may apply for data that are provided for a small processing fee.[42] In other countries (e.g. South Korea, Japan, France, the Netherlands, Canada, the UK, and the USA), researchers have to go through more extensive data request procedures.[43–49] Physical access to extracts of de-identified data is sometimes only possible in a designated secure environment (the Netherlands) or researchers are required to have a secured physical environment at their institution (Japan).[44,49] In France, data are supplied on a secure, electronic medium while in Canada access is provided via a secure, online research environment.[45,50] Information about the accessibility of the databases of China and India was not available on public websites or in publications.[43]

The processing fees are determined by fees for data extraction, the complexity of the data request, and possible extra delivered services such as professional assistance in working with the complex databases. The level of the fees is therefore difficult to determine, but they are often described as costly. The extra financing needed for the use of health claims databases as well as the expertise needed for a study on health claims data (e.g. data analyst specialized in big data, nephrologist, epidemiologist, and PhD student) may be challenging, especially for grant applications that use a fixed amount and usually mainly reimburse the salary costs of the researcher.

Studies using health claims data

Health claims data are being used to answer a wide variety of healthcare-related questions in different fields of research. Several countries have the ability to link their health claims database to other administrative databases such as national dialysis and transplantation registries, national vital statistics, or clinical laboratory data (Table 2.1). This linkage capacity greatly expands its research possibilities.[26]

In general, studies using health claims data mainly focus on the epidemiology of a disease, including patients' morbidity and survival, evaluating healthcare costs

and the delivery of healthcare services, describing prescription patterns and the effectiveness of pharmacological therapies, and exploring clinical outcomes.[48] Table 2.2 provides a selection of papers on patients with kidney disease based on health claims data (or a combination of health claims data and other linked administrative data) published in scientific journals. We divided these articles into three main fields of research, i.e. validation studies (see Table 2.3), cost studies, and descriptive and outcome studies, to provide insights into the variety of study questions.

Most papers reported on patients receiving dialysis treatment and significantly less on patients with kidney transplantation or CKD patients not treated with KRT. Interestingly, health claims data can also provide opportunities to report on specific kidney diseases such as polycystic kidney disease.[51] Several papers focused on the validity of health claims data to identify patients with chronic kidney disease[20,52–55], dialysis[56–58], and kidney transplantation.[59] The results of these validity studies are presented in Table 2.3 and will be discussed later.

As health claims databases include reimbursement data, it is possible to study healthcare costs. Several studies provided cost estimations for dialysis and kidney transplantation in different countries.[60–68] Estimations of healthcare costs of CKD patients not treated with KRT were less common and only provided in two studies.[69,70] Since health claims usually contain longitudinal data with nationwide coverage, studies frequently report epidemiological data such as incidence and prevalence of kidney diseases, the occurrence of kidney disease-related risk factors/comorbidities, mortality rates and their trends over time. A wide range of outcomes has been described using health claims data. Frequently studied outcomes include those that are cardiovascular-related, such as cardiovascular disease in transplant patients, stroke, atrial fibrillation, and major cardiovascular events. The comprehensive drug delivery data of pharmacies provide unique opportunities for pharmaco-epidemiological research to study the use and effects of medication in CKD patients. This results, for example, in studies reporting the use of warfarin, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers or β-blockers in dialysis patients or metformin use in CKD patients. With pharmacological data, it is important to realize that non-reimbursable drugs or over-the-counter drugs remain undetected in health claims data. Other less common outcomes reported include depressive disorder in kidney transplantation, fracture risk and associated mortality in kidney transplantation, the peptic ulcer rebleeding risk in dialysis patients, or the risk of end-stage kidney disease after hypertensive disorders in pregnancy (see Table 2.2).

Table 2.2: Selection of papers on kidney disease patients based on health claims data published in scientific journals.

Study types	Author	Journal	Year	Country/ region	Population	Title
Cost studies	Chang et al.[60]	*Nephrology*	2015	Taiwan	Dialysis	Trends of cost and mortality of patients on haemodialysis with end stage renal disease
	Chang et al.[61]	*Sci Rep*	2016	Taiwan	Dialysis	Cost-effectiveness of haemodialysis and peritoneal dialysis: a national cohort study with 14 years follow-up and matched for comorbidities and propensity score
	Couchoud et al.[62]	*Nephrol Dial Transplant*	2015	France	Dialysis, transplantation	Economic impact of a modification of the treatment trajectories of patients with end-stage renal disease
	Couillerot-Peyrondet et al.[63]	*Eur J Health Econ*	2017	France	Dialysis, transplantation	A comprehensive approach to assess the costs of renal replacement therapy for end-stage renal disease in France: the importance of age, diabetes status, and clinical events
	Helmuth et al.[64]	*Clin J Am Soc Nephrol*	2019	USA	Transplantation	Secular trends in the cost of immunosuppressants after solid organ transplantation in the United States
	Honeycutt et al.[70]	*J Am Soc Nephrol*	2013	USA	CKD	Medical costs of CKD in the Medicare population
	Kao et al.[65]	*Perit Dial Int*	2013	Taiwan	Dialysis	Lifetime costs for peritoneal dialysis and haemodialysis in patients in Taiwan
	Kitazawa et al.[66]	*Transplant Proc*	2017	Japan	Transplantation	Cost analysis of transplantation in Japan, performed with the use of the National Database
	Mohnen et al.[67]	*PLoS One*	2019	Netherlands	Dialysis, transplantation	Healthcare costs of patients on different renal replacement modalities – analysis of Dutch health insurance claims data
	van Oosten et al.[69]	*Nephrol Dial Transplant*	2019	Netherlands	CKD, dialysis, transplantation	Age-related difference in healthcare use and costs of patients with chronic kidney disease and matched controls: analysis of Dutch health claims data
	Shaikh et al.[68]	*Kidney Int*	2018	India	Dialysis	Utilization, costs, and outcomes for patients receiving publicly funded haemodialysis in India

Table 2.2 *(continued)*

Study types	Author	Journal	Year	Country/ region	Population	Title
Descriptive and outcome studies	Chettiar et al.[72]	*Clin J Am Soc Nephrol*	2018	USA	Dialysis, transplantation	Association of inpatient palliative care with health care utilization and postdischarge outcomes among Medicare beneficiaries with end stage kidney disease
	Choi et al.[73]	*Am J Nephrol*	2017	South Korea	Dialysis, transplantation	Disparities in kidney transplantation access among Korean patients initiating dialysis: a population-based cohort study using national health insurance data (2003-2013)
	Dobbels et al.[74]	*Am J Kidney Dis*	2008	USA	Transplantation	Depressive disorder in renal transplantation: an analysis of Medicare claims
	Farrugia et al.[75]	*Kidney Int*	2014	UK	Transplantation	Malignancy-related mortality following kidney transplantation is common
	Ferreira et al.[76]	*Nephrol Dial Transplant*	2019	France	Dialysis	Angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, β-blockers or both in incident end- stage renal disease patients without cardiovascular disease: a propensity-matched longitudinal cohort study
	Ferro et al.[77]	*Clinical Transplant*	2015	UK	Transplantation	Fracture risk and mortality post-kidney transplantation
	Han et al.[78]	*Clin J Am Soc Nephrol*	2015	South Korea	Dialysis	Dialysis modality and mortality in the elderly: a meta- analysis
	Hayer et al.[79]	*Diabetologia*	2014	UK	Transplantation	Infection-related mortality is higher for kidney allograft recipients with pretransplant diabetes mellitus
	Hung et al.[80]	*Lancet Diabetes Endocrinol*	2015	Taiwan	CKD	Metformin use and mortality in patients with advanced chronic kidney disease: national, retrospective, observational, cohort study
	Kim et al.[81]	*Int J Cardiol*	2015	South Korea	Dialysis	Risk of major cardiovascular events among incident dialysis patients: a Korean national population-based study
	Kitchlu et al.[82]	*Nephrol Dial Transplant*	2012	Canada, Ontario	Dialysis	Beta-blockers and cardiovascular outcomes in dialysis patients: a cohort study in Ontario, Canada

Table 2.2 *(continued)*

Study types	Author	Journal	Year	Country/ region	Population	Title
	Komenda et al.[83]	*CMAJ Open*	2015	Canada, Manitoba	Dialysis	Secular trends in end-stage renal disease requiring dialysis in Manitoba, Canada: a population-based study
	Kuo et al.[84]	*Am J Kidney Dis*	2007	Taiwan	CKD	Epidemiological features of CKD in Taiwan
	Lam et al.[85]	*Transplantation*	2017	Canada, Ontario	Transplantation	The risk of cardiovascular disease is not increasing over time despite aging and higher comorbidity burden of kidney transplant recipients
	Lenihan et al.[86]	*Transplantation*	2019	USA	Transplantation	Trends in the medical complexity and outcomes of Medicare-insured patients undergoing kidney transplant in the years 1998-2014
	Li et al.[87]	*Nephrol Dial Transplant*	2012	Taiwan	Transplantation	Malignancies after renal transplantation in Taiwan: a nationwide population-based study
	Liao et al.[88]	*Kidney Int*	2015	Taiwan	Dialysis	Incidence and risk factors for new-onset atrial fibrillation among patients with end-stage renal disease undergoing renal replacement therapy
	René et al.[89]	*Nephrol Dial Transplant*	2017	Canada, Quebec	Dialysis	Association of erythropoiesis-stimulating agents and the incidence risk of cancer diagnosis among chronic dialysis patients: a nested case-control study
	Tonelli et al.[90]	*Kidney Int*	2018	Canada, Alberta	CKD	A population-based cohort study defines prognoses in severe chronic kidney disease
	Wang et al.[91]	*Kidney Int*	2019	China	CKD, dialysis, transplantation	Executive summary for the 2015 Annual Data Report of the China Kidney Disease Network (CK-NET)
	Wang et al.[92]	*Am J Kidney Dis*	2014	Taiwan	Dialysis	Risk of stroke in long-term dialysis patients compared with the general population
	Wang et al.[93]	*Clin J Am Soc Nephrol*	2015	Taiwan	Dialysis	Comparison of subdural haematoma risk between haemodialysis and peritoneal dialysis patients with ESRD

Table 2.2 *(continued)*

Study types	Author	Journal	Year	Country/ region	Population	Title
	Wang et al.[94]	*Nephrol Dial Transplant*	2018	Taiwan	Dialysis	Risk of new-onset diabetes in end-stage renal disease patients undergoing dialysis: analysis from registry data of Taiwan
	Weinhandl et al.[95]	*Am J Nephrol*	2019	USA	Dialysis	Contemporary trends in clinical outcomes among dialysis patients with Medicare coverage
	Wu et al.[96]	*Gut*	2011	Taiwan	Dialysis	Long-term peptic ulcer rebleeding risk estimation in patients undergoing haemodialysis: a 10-year nationwide cohort study
	Wu et al.[97]	*Am J Obstet Gynecol*	2014	Taiwan	Dialysis	End-stage renal disease after hypertensive disorders in pregnancy
	Yoon et al.[98]	*Stroke*	2017	South Korea	Dialysis	Warfarin use in patients with atrial fibrillation undergoing haemodialysis
	Yu et al.[51]	*Lancet Oncol*	2016	Taiwan	Polycystic kidney disease	Risk of cancer in patients with polycystic kidney disease: a propensity-score matched analysis of a nationwide, population-based cohort study
Validation studies	For more details see Table 2.3					

The number of published papers on kidney disease patients differs widely by database, with Taiwan being the leading country in utilizing claims data for clinical research. Data from Taiwan's NHIRD is available for any researcher in Taiwan for a small processing fee, which has been shown to increase the publication rate dramatically. This emphasizes the importance of keeping the financial and technical barriers for the reuse of health claims data for research purposes as low as possible.[71]

The Dutch Kidney Atlas

Recently, Dutch health claims data have been processed to study patients with kidney disease in the Dutch Kidney Atlas project. Box 2.1 provides a detailed description of the Dutch health claims database (called Vektis) and the related healthcare system. The Dutch Kidney Atlas project provides information on the number of CKD patients {CKD Stage G4–G5 [estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2]} not treated with KRT, those on dialysis and kidney transplant patients, their healthcare costs, prescribed medication, outcomes (such as the number of hospital visits, intensive care unit admittance, and mortality) and comorbid disorders like diabetes mellitus, hypertension, and cardiovascular diseases. Data are published on a website (www.nieratlas.nl) and are reported by age group and sex and are compared with a reference group from the general population. Figure 2.1 shows several graphs presented in the Dutch Kidney Atlas. Data are presented on a national level as well as on a regional level to demonstrate potential geographic variation. Furthermore, the website includes data since 2012 and will be updated on an annual basis. The website was designed for public use by healthcare professionals, policymakers, researchers, and insurance companies, as well as patients with CKD.

The Dutch Kidney Atlas project also involves scientific research on patients with CKD using the Dutch health claims database. So far, two studies on the healthcare costs of patients with CKD with and without KRT have been published.[67,69]

Box 2.1. Dutch health claims database

In the Netherlands, healthcare provision and payment for healthcare and healthcare-related services through insurance is embedded within a social security system.[35] Because basic health insurance is obligatory for all Dutch residents, an estimated 99.8% [36] of the Dutch population of approximately 17 million people has healthcare insurance.[37] The Dutch healthcare system has a gatekeeping principle which means that patients can easily contact a primary care provider (e.g. general practitioner, dentist, midwife, and physiotherapist), but hospital care and specialist care require a referral from a primary care provider, with emergency care as an exception.

Basic health insurance covers the main aspects of healthcare, including primary care, hospital care, medication, mental healthcare, maternity care and home nursing care. Care not covered by the basic insurance can be insured through voluntary health insurance. Health insurance companies pay the hospital based on DBCs (Diagnose behandel combinatie); a system similar to the concept of diagnosis-related groups (DRGs). A DBC contains information characterizing the delivered hospital care for a specific medical condition or complaint by type of specialism. The DBC comprises all medical activities needed from establishing the diagnosis to the last check after treatment, and thereby describing a complete care episode. Every type of DBC has a fixed price, which is the sum of costs of all intermediate products, i.e., the activities, thereby covering all direct and indirect costs of a care episode.[38]

The health claims data of all Dutch health insurance companies are collected in the Vektis database which covers (almost) all inhabitants of the Netherlands. For each health claim in the Vektis database, data is available on patient characteristics (year of birth, sex, area of residence, socio-economic status, date of death), and the costs involved.[26] Vektis complies with the Dutch law and the European General Data Protection Regulation (GDPR). To ensure privacy whilst performing the present research, Vektis pseudonymised the persons' national identification number, and data access is only allowed in a physically secured environment designated by Vektis; only aggregated data are allowed to leave this secured environment. All contributing insurance companies provided permission for the use of this national data.

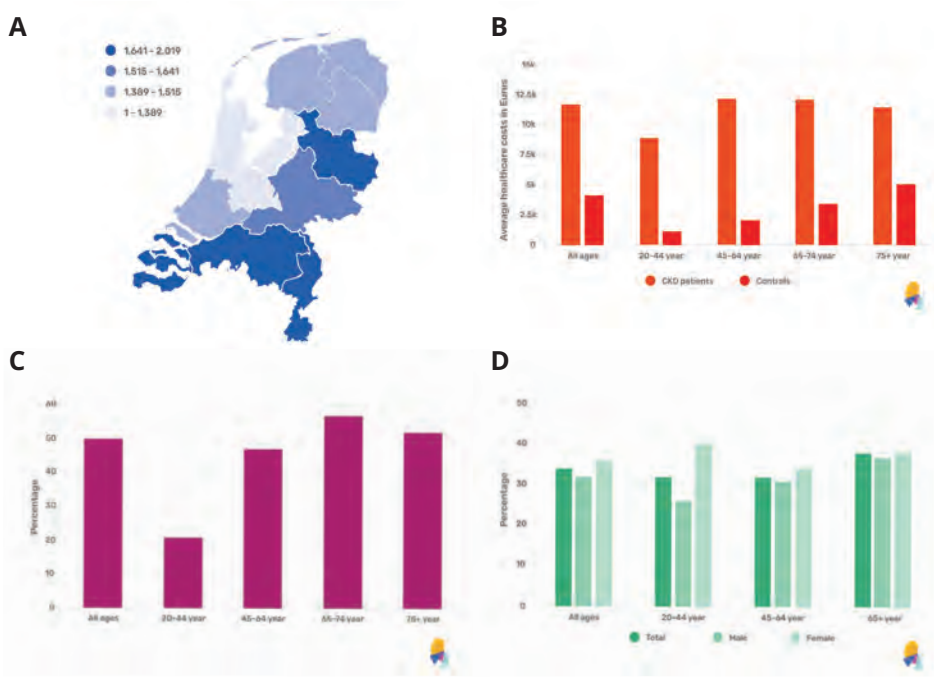


Figure 2.1: Examples of the Dutch Kidney Atlas.

A. Geographical variation of the number of patients with chronic kidney disease Stage G4-G5 (diagnosis code eGFR < 30 mL/min/1.73 m^2) not treated with kidney replacement therapy, per province of the Netherlands, 2017, numbers per million insured population.
B. Total healthcare costs (€) of patients with chronic kidney disease Stage G4-G5 (diagnosis code eGFR < 30 mL/min/1.73 m^2) not treated with kidney replacement therapy, compared with a matched control group, 2017, presented for the total group and different age groups.
C. Statin use in prevalent dialysis patients, 2017, percentage of the total population, presented for the total group and different age groups.
D. Percentage of kidney transplant patients visiting the emergency department per year, 2017, presented for the total group and subgroups based on age and gender.

Identification of persons with kidney disease

Administrative databases are the result of administrative processes, such as reimbursement in the case of health claims databases, and are therefore not designed for clinical research purposes.[26] Because clinical data and information on kidney function are lacking in health claims databases, the identification of patients with kidney disease depends on diagnosis codes only, which in turn depends on the proper registration of the codes by the involved healthcare professional or organization. Investigating the accuracy of this identification is, therefore, crucial to assess whether data derived from health claims data are truly representative and this information on the validity of the diagnosis codes should be provided in research articles using

health claims data.[20,27] Some studies assessed the validity of health claims data to identify patients with CKD, dialysis, or kidney transplantation (Table 2.3). Apart from one study using Dutch health claims data, all studies were performed in Canada or the USA. Of all available studies, five studied the validity of health claims data in the identification of CKD patients, three of dialysis patients and one of kidney transplant patients. However, the use of different case definitions and reference populations does impede the direct comparison between studies. In the following paragraphs, we will discuss the studies that have assessed the validity of health claims data to identify patients with CKD, dialysis, or kidney transplantation in more detail.

Chronic Kidney Disease

A study in Alberta, Canada, tested health claims data for the identification of CKD (defined as an eGFR <60 mL/min/1.73 m^2) against a gold standard derived from outpatient serum creatinine measurements. In this study, 19% of CKD patients were correctly identified as such with health claims data (sensitivity or true-positive rate) and 60% of the patients with CKD-related claims data did have an eGFR <60 mL/min/1.73 m^2 [positive predictive value (PPV) 60%].[52] Similar results were found in a study from Ontario, Canada, using patients with a serum creatinine laboratory test following a prescription of medication as the gold standard (sensitivity 18%, PPV 65%).[53] In both studies, sensitivity was markedly higher for CKD patients defined as an eGFR <30 mL/min/1.73 m^2 (65% and 59%, respectively). Two US studies tested the validity of Medicare data. One study used patients with hospitalization for myocardial infarction as the gold standard (sensitivity 27%, PPV 89%),[20] while the second study used research study measurements as a reference (sensitivity 16%, PPV 76%).[54] Recently we tested the validity of Dutch health claims data using a laboratory database as the gold standard. Sensitivity was markedly higher in patients with advanced CKD (eGFR <30 mL/min/1.73 m^2) than in patients with CKD (eGFR <60 mL/min/1.73 m^2), being 51% and 27%, respectively.[55] All studies had high specificity for CKD. The negative predictive value (NPV) varied in all studies and with a wide range (36%–98%).

Health claims data have low sensitivity for the estimation of the overall CKD prevalence in the general population since health claims data only detect CKD patients treated in a hospital and registered for the specific Diagnose Behandel Combinaties (DBCs) and not the ones treated by a general practitioner or those who are not treated at all. However, they do, to a large extent, reflect the population of CKD with an actual reference to a nephrologist.

Dialysis

All available studies indicate that identifying patients undergoing dialysis with health claims data is accurate. A study in Ontario, Canada, showed a reasonably good identification of dialysis patients with a sensitivity of 81% and a PPV of 78% when compared with a gold standard of registry data.[56] These results were confirmed in patients in Manitoba, Canada (sensitivity 77%, PPV 85%), also using registry data as the gold standard.[57] A US study accurately identified hemodialysis using health claims data compared with medical records data as the gold standard (PPV 91%) but was less precise for patients treated with peritoneal dialysis (PPV 67%).[58] In the Netherlands, the number of dialysis (hemodialysis and peritoneal dialysis) patients identified with Dutch health claims data was compared with the number of patients in the Dutch registry for end-stage kidney disease (Renine: Registratie Nierfunctievervanging Nederland). Since the analysis was only possible on aggregated data, sensitivity could not be calculated, but the correspondence between the databases was very high (99%).[67]

Kidney transplantation

Identification of performed kidney transplantations was shown to be very accurate using Canadian health claims data compared with data from three Canadian transplantation centers serving as the gold standard (sensitivity 98%, PPV 96%).[59] Also, Dutch health claims data were shown to very accurately identify the number of performed kidney transplantations per year when compared with the Dutch registry for end-stage kidney disease, with a correspondence of 99% between the databases.[67]

In KRT patients, who are generally all treated within the standard healthcare system, both the PPV and NPV are high. This makes it possible to compare outcomes between patients with and without KRT. In contrast, not all affected CKD patients (not treated with KRT) are known or treated within the (hospital) care system. Therefore, in CKD patients, the PPV is high, but the NPV generally is low. In CKD patients, it may therefore be more difficult to identify those without CKD using health claims data.[20] Please note that both the PPV and NPV depend on the prevalence of the disease in the population.[99]

Table 2.3: Overview of studies of the validity of health claims data in the identification of CKD, dialysis, and kidney transplant patients.

Author	Health claims database	Study Population	Reference population	Age	Case definition	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	PPV (95% CI)
CKD									
Fleet et al.[53]	Ontario Health Insurance Plan database (OHIP), Ontario (Canada)	Patients with ICD-10 and physician claims diagnostic codes for CKD, between 1 July 2007 and 31 December 2010	Patients with an outpatient prescription medication and a serum creatinine test the year prior to the prescription date from a laboratory in Southwestern Ontario	≥65 years	eGFR <60 mL/min/1.73 m^2	18.0 (17.7–18.4)	98.2 (98.1–98.3)	85.2 (84.5–85.9)	67.7 (67.4–68.0)
					eGFR <45 mL/min/1.73 m^2	32.7 (32.0–33.3)	96.9 (96.7–97.0)	65.4 (64.4–66.3)	88.8 (88.6–89.0)
					eGFR <30 mL/min/1.73 m^2	58.8 (57.4–60.1)	94.6 (94.5–94.7)	32.5 (31.6–33.5)	98.1 (98.0–98.2)
Muntner et al.[54]	Medicare claims data, USA	Patients with ICD-9 discharge codes associated with hospitalization or physician evaluation and claims associated with outpatient physician visits for CKD, between January 2003 and October 2007	Participants enrolled in the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study with data available on eGFR and albumin-creatinine ratio	≥65 years	eGFR <60 mLmin/1.73 m^2 or ACR >30 mg/g	15.5 (14.0–17.1)	97.7 (97.2–98.1)	75.6 (71.4–79.5)	71.5 (70.4–72.6)
					eGFR <60 mL/min/1.73 m^2	20.6 (18.5–22.8)	97.1 (96.6–97.5)	63.9 (59.2–68.3)	83.0 (82.1–83.9)
					eGFR <45 mL/min/1.73 m^2	37.1 (32.7–41.6)	95.8 (95.3–96.2)	39.0 (34.5–43.7)	95.4 (94.9–95.9)
					eGFR <30 mL/min/1.73 m^2	56.4 (45.8–66.6)	94.2 (93.6–94.8)	11.8 (8.9–15.1)	99.4 (99.1–99.5)

Table 2.3 *(continued)*

Author	Health claims database	Study Population	Reference population	Age	Case definition	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	PPV (95% CI)
Ronksley et al.[52]	Alberta Provincial Physician Claims database, Alberta (Canada)	Patients with ICD-9 and ICD-10 codes for CKD, between 1 January 2004 and 31 December 2004	Patients with at least two outpatient serum creatinine measurements within a 1-year time period	≥18 years	eGFR <60 mL/min/1.73 m^2				
					One claim or one hospitalization in one year	18.9 (–)	97.29 (–)	60.59 (–)	83.99 (–)
					Two claims or one hospitalization in 1 year	14.29 (–)	98.19 (–)	63.69 (–)	83.39 (–)
					Three claims or one hospitalization in 1 year	11.89 (–)	98.59 (–)	64.09 (–)	82.99 (–)
					eGFR <30 mL/min/1.73 m^2				
					One claim or one hospitalization in 1 year	64.79 (–)	96.59 (–)	24.09 (–)	99.49 (–)
					Two claims or one hospitalization in 1 year	56.59 (–)	97.79 (–)	29.39 (–)	99.29 (–)
					Three claims or one hospitalization in 1 year	49.99 (–)	98.19 (–)	31.49 (–)	99.19 (–)
Winkelmayer et al.[20]	Medicare claims data, USA	Patients with ICD-9 diagnosis codes for CKD, during 1999 and/or 2000	Patients with hospitalization for myocardial infarction with a serum creatinine measurement	≥65 years	eGFR <60 mL/min/1.73 m^2 for 6-months period	20.7 (18.5–22.9)	96.0 (94.4–97.5)	91.6 (88.5–94.8)	36.3 (34.0–38.7)
					eGFR <60 mL/min/1.73 m^2 for 12-month period	26.6 (24.2–28.9)	93.3 (91.3–95.2)	89.3 (86.3–92.4)	37.4 (35.0–39.8)

Table 2.3 *(continued)*

Author	Health claims database	Study Population	Reference population	Age	Case definition	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	PPV (95% CI)
Van Oosten et al.[55]	Vektis database, the Netherlands	Patients with DBC codes for CKD, between 1 January 2014 and 31 December 2014	Patients with an outpatient serum creatinine measurement in 2014	≥18 years	One eGFR <60 mL/min/1.73 m^2	20 (19–21)	100 (100–100)	96 (95–97)	84 (83–84)
					At least two eGFR <60 mL/min/1.73 m^2 at least 90 days apart	27 (25–28)	100 (100–100)	90 (88–91)	52 (51–52)
					One eGFR <30 mL min/1.73 m^2	42 (38–46)	100 (100–100)	83 (79–87)	98 (98–99)
					At least two eGFR <30 mL/min/1.73 m^2 at least 90 days apart	51 (47–56)	100 (99–100)	80 (76–84)	98 (98–99)
Dialysis									
Clement et al.[56]	Alberta Provincial Physician Claims database, Alberta (Canada)	Patients with physician claims for outpatient dialysis, between 1 January 2008 and 31 December 2008	ESRD registry [Northern Alberta (NARP) and Southern Alberta (SARP) registries]	≥18 years	1. At least one claim	81.1 (–)	NA	77.7 (–)	NA
					2. At least two claims	78.6 (–)	NA	80.7 (–)	NA
					3. At least two claims at least 90 days apart	63.1 (–)	NA	84.8 (–)	NA
					4. Continuous claims at least 90 days apart with no gap in claims >21 days	58.2 (–)	NA	85.9 (–)	NA

Table 2.3 *(continued)*

Author	Health claims database	Study Population	Reference population	Age	Case definition	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	PPV (95% CI)
Komenda et al.[57]	Manitoba Health Physician Claims database, Manitoba (Canada)	Patients with physician claims for outpatient dialysis, between 1 January 2004 to 31 December 2010	Manitoba Renal Program Dialysis Registry	>18 years	**1-year period (2010)**				
					1. At least one claim	77.0 (74.7–79.2)	93.8 (92.9–94.7)	85.2 (83.2–87.2)	89.8 (88.7–90.9)
					2. Any two claims	74.6 (72.3–76.9)	94.4 (93. 6–95.2)	86.0 (84.0–88.0)	88.9 (87.8–90.0)
					3. Any two claims at least 90 days apart	64.8 (62.2–67.3)	97.1 (96.5–97.7)	91.2 (89.5–93.0)	85.6 (84.4–86.8)
					4. Any two claims at least 90 days apart with no gaps in treatment >21 days	52.7 (50.1–55.4)	97.5 (96.9–98.1)	90.7 (88.7–92.7)	81.7 (80.4–83.0)
					5-year period (2004-2008)				
					1. At least one claim	87.6 (86.3–89.0)	91.3 (90.7–91.9)	74.4 (72.8–76.0)	96.2 (95.8–96.7)
					2. Any two claims	86.0 (84.7–87.4)	93.4 (92.9–93.9)	78.9 (77.4–80.4)	95.9 (95.4–96.3)
					3. Any two claims at least 90 days apart	72.0 (70.2–73.8)	99.6 (99.5–99.8)	98.3 (97.7–98.9)	92.5 (92.0–93.1)
					4. Any two claims at least 90 days apart with no gaps in treatment >21 days	47.6 (45.6–49.6)	99.8 (99.7–99.9)	98.3 (97.6–99.0)	86.9 (86.2–87.5)

Table 2.3 *(continued)*

Author	Health claims database	Study Population	Reference population	Age	Case definition	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	PPV (95% CI)
Taneja et al.[58]	Health Alliance Plan (HAP) database, USA	Patients with ESKD and dialysis-related billing codes for peritoneal dialysis or hemodialysis, between 1 January 2005 and 31 December 2008	Patient medical record	18–63 years	Any PD-related claim—in a 30-day window	NA	NA	34.9 (–)	NA
					Any PD-related claim—in a 90-day window	NA	NA	67.4 (–)	NA
					Any PD-related claim—in a 180-day window	NA	NA	67.4 (–)	NA
					Any HD-related claim—in a 30-day window	NA	NA	86.7 (–)	NA
					Any HD-related claim—in a 90-day window	NA	NA	90.8 (–)	NA
					Any HD-related claim—in a 180-day window	NA	NA	93.1 (–)	NA
Kidney transplantation									
Lam et al.[59]	Ontario Health Insurance Plan database (OHIP), Ontario (Canada)	Patients with kidney transplantation related claims, between 1 January 2008 and 31 December 2011	Three major transplant centers in Ontario (Toronto General Hospital, University Hospital – London and Ottawa Hospital)	All	A claim for a kidney-only transplant	98 (97–99)	NA	96 (95–97)	NA

Abbreviations: CI, confidence interval; ICD, International Classification of Diseases.

Opportunities and challenges of health claims data

Health claims databases have strengths and limitations, depending on the research question that investigators would like to address.[22]

Opportunities

Claims databases have several specific advantages over other types of research data, regarding scope, flexibility, costs, and statistical power.[22]

Regarding the scope of health claims databases, they are generally very comprehensive and complete and often cover the inhabitants of an entire country or region. These databases usually contain data on demographics (e.g. age, sex, and postal code), prescribed medication, diagnosis, hospital care, and other delivered healthcare, including a complete care pathway of a patient from the first contact with a nephrologist until the last treatment. Since health claims data are collected for payment purposes, they contain data on healthcare costs. Moreover, with health claims data, it is possible to study CKD patients treated with and without KRT in the same data set. Health claims databases often contain data over longer periods of time as well as geographic data, making it possible to study regional differences. Furthermore, since health claims data are collected on a routine basis, they provide information on a non-experimental setting.

The flexibility of health claims data provides opportunities to use different study designs (e.g. cohort studies and case-control design). In addition, for investigators, the data collection is relatively inexpensive and less time-consuming compared with other data collections such as randomized controlled trials or cohort studies. Considering this, with health claims data it is relatively easy to obtain a sufficient number of cases and provide adequate statistical power at relatively low cost.[22]

These unique features of health claims databases make it possible to monitor trends in disease prevalence, treatment or healthcare costs over time, providing insight into the effect of changes in policy or guidelines. Therefore health claims data could play a valuable role in guiding health policy and improving quality of care, with the Alberta Kidney Disease Network as an example of a unique collaboration between researchers and policymakers.[24] In addition, health claims data could potentially be used as a quality indicator without providing extra administrative burden for the caregiver, as outcomes can be traced back to individual healthcare providers. For instance, the number of cardiovascular complications in CKD patients, identified using health claims

data, can be used to comment on the quality of cardiovascular care on the condition that one can adjust for patient case-mix.

Challenges

Health claims data were not designed for clinical research and therefore the researcher cannot control the design, collection, and processing of data.[26] Studies have shown that administrative databases, including health claims databases, have limitations in scope (availability of relevant data), data quality, and the ability to adjust for patient case-mix.[100] Since the majority of health claims databases lack both clinical and laboratory data, the identification of patients is based on specific diagnosis or procedure codes. As a result, the identification of patient groups with health claims data may result in undercoding or overcoding of diagnoses or outcomes.[20,28] In a database designed for reimbursement purposes, this undercoding or overcoding can be related to coding optimization (i.e. a diagnosis or procedure with higher reimbursement fees is more likely to be coded than the one with lower reimbursement fees). In addition, as previously discussed in the CKD validation studies, usually health claims data are only able to identify CKD patients who are treated by nephrologists while patients who do not come to the attention of health services remain undetected with health claims data. This may be an important limitation in countries that do not have universal healthcare coverage.

Furthermore, the lack of clinical information like severity and progression of the disease, clinical parameters (e.g. smoking and bodyweight) or risk factors might lead, for some research questions, to an incomplete adjustment for potential confounders.[22] Next, in countries without universal healthcare coverage, such as the USA, elderly individuals or those with lower socioeconomic status, may be overrepresented in the population.[22]

There are several ways to deal with these challenges of health claims data. First, part of the lacking information with regard to the prevalence of chronic diseases or morbidity in CKD patients may be derived from specific medication use. Studies show that data on prescribed medication can be used as a proxy for the prevalence of several chronic diseases.[101] A proxy can be very valid, for example, in the case of identifying patients with diabetes mellitus using anti-diabetic drugs and insulin analogs, but less valid if drugs have overlapping indications (e.g. inhalation therapy prescribed for patients with asthma and those with chronic obstructive pulmonary disease).

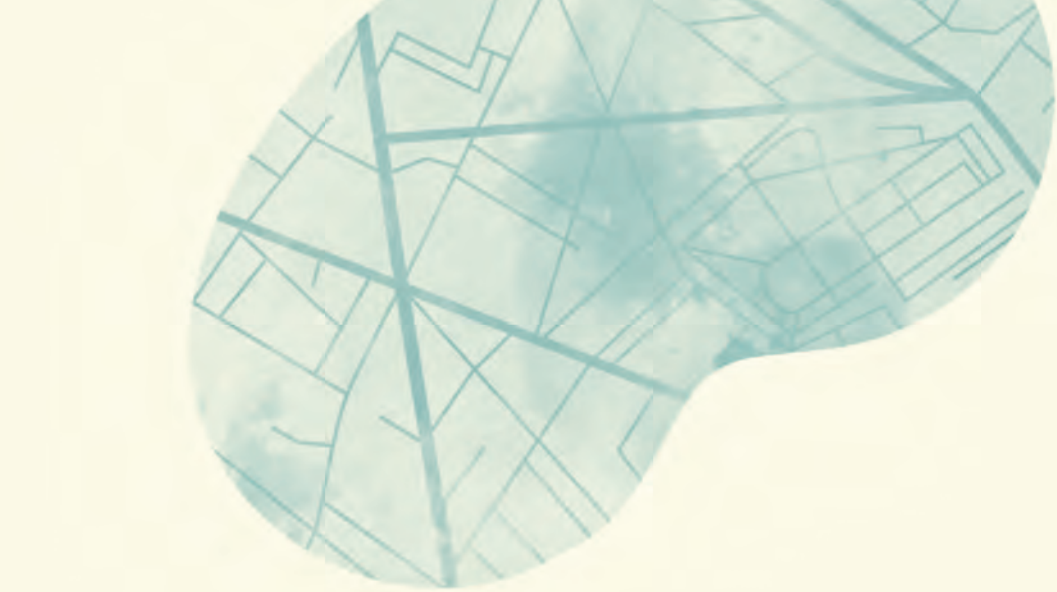
Second, record linkage of other unrelated administrative databases to health claims databases is a promising tool to add value to the data and it improves and broadens their usage for health research.[26] Record linkage, by means of a unique and direct identifier (i.e. social security number or NHS number), is increasingly used worldwide to combine administrative datasets (e.g. the Alberta kidney disease database).[24] In case this unique identifier is lacking, indirect linkage tools could be a valid option, although it may introduce less precise record matching.[102] In many countries, maintainers of administrative health databases, such as governmental agencies and health insurance companies, are often reluctant to share administrative databases. The general data protection rules, among others, underlie the restrictive sharing and linking of health data. Therefore the World Health Organization advocates the development of a metadata standard to improve data-sharing policies, thereby increasing the research potential of routinely collected health datasets.[103] We stress the importance of improving the utility of claims data while protecting confidentiality.

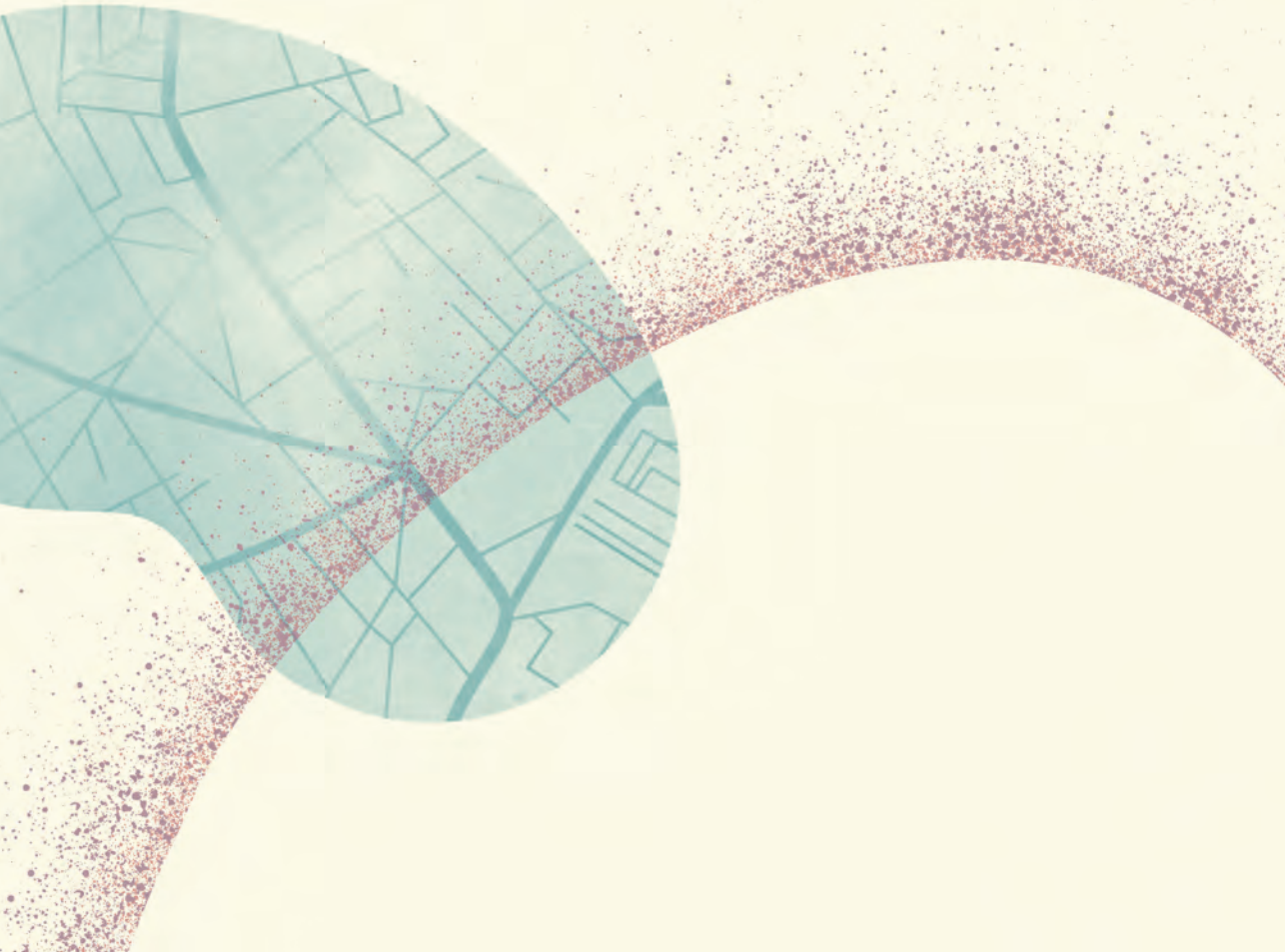
Nevertheless, when comparing the results of different health claims databases one must bear in mind the differences in characteristics of the study populations, the regional differences in insurance coverage, and the registration of diagnosis or healthcare use. This might limit the extrapolation of the results to other countries. Apart from important privacy issues this also limits the possibilities of merging international databases. In addition, coding and coverage of diagnoses, procedures, or treatments may change over time. One should be aware of these possible changes within a healthcare system when comparing health claims data over a longer period of time.

Conclusion

Health claims databases offer important opportunities for studies on large populations of patients with (kidney) disease and health outcomes in a non-experimental setting. However, one should take into account the limitations of health claims data and consider the characteristics of a health claims database, especially when making international comparisons. Since research with health claims data uses codes to identify kidney disease patients and to define other key study variables, information on the validity of these codes in measuring the association of the code with the real variable is indispensable. Available studies indicate that identifying patients undergoing dialysis and the number of performed kidney transplantations using health claims data is accurate, whereas health claims data have low sensitivity for the estimation of the overall CKD prevalence in the general population.

So far, health claims data in 10 countries have been used for studies on kidney disease patients. The unique features of health claims data provide specific research opportunities, such as studying healthcare costs or studying longitudinal, epidemiological data with nationwide coverage. For the optimal utility of health claims data, it is important to keep financial and technical barriers low, while protecting confidentiality. In addition, health claims data can be used to create a nationwide atlas (e.g. the Dutch Kidney Atlas) providing national and regional information on, for instance, the numbers, healthcare costs, prescribed medications, treatments, and outcomes of kidney patients.





Part 2

Validity of Dutch health claims data

3

The validity of Dutch health claims data for identifying patients with chronic kidney disease - a hospital-based study in the Netherlands

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Abstract

Background Health claims data may be an efficient and easily accessible source to study chronic kidney disease (CKD) prevalence in a nationwide population. Our aim was to study Dutch claims data for their ability to identify CKD patients in different subgroups.

Methods From a laboratory database we selected 24 895 adults with at least one creatinine measurement in 2014 ordered at an outpatient clinic. Of these, 15 805 had ≥2 creatinine measurements at least three months apart and could be assessed for the chronicity criterion. We estimated the validity of a claim-based diagnosis of CKD and advanced CKD. The estimated glomerular filtration rate (eGFR)-based definitions for CKD (eGFR <60 mL/min/1.73 m^2) and advanced CKD (eGFR <30 mL/min/1.73 m^2) satisfying and not satisfying the chronicity criterion served as the reference group. Analyses were stratified by age and sex.

Results In general, sensitivity of claims data was highest in the population with the chronicity criterion as reference group. Sensitivity was higher in advanced CKD patients than in CKD patients [51% (95% CI 47%-56%) versus 27% (95% CI 25%-28%)]. Furthermore, sensitivity was higher in young versus elderly patients. In patients with advanced CKD, sensitivity was 72% (95% CI 62%-83%) for patients aged 20-59 years and 43% (95% CI 38%-49%) in patients ≥75 years. The specificity of CKD and advanced CKD was 99% or higher. Positive predictive values ranged from 72% to 99% and negative predictive values ranged from 40% to 100%.

Conclusion When using health claims data for the estimation of CKD prevalence, it is important to take into account the characteristics of the population at hand. The younger the subjects and the more advanced the stage of CKD the higher the sensitivity of such data. Understanding which patients are selected using health claims data is crucial for a correct interpretation of study results.

Introduction

In recent decades, health insurance claims data have become available as a source of big data. Health claims databases often contain already well-defined data sets and hold information on patient demographics and healthcare resource use in a non-experimental setting over large populations. It has been suggested that health claims databases may have considerable advantages in calculating disease prevalence over large populations and observing trends over longer periods of time.[22,48]

Typically, health claims data lack both clinical and laboratory data and the identification of patients with specific diseases is solely based on specific diagnosis codes. This entails an inherent danger of inaccurate identification and possible undercoding or overcoding of diagnoses.[21] Validity studies are necessary to investigate whether health claims data can provide reliable estimates of the frequency of these diseases.

Only a few studies have assessed the accuracy of health claims data in identifying patients with chronic kidney disease (CKD) not treated with kidney replacement therapy.[20,28,52–54,104] These studies provided limited information on the validity in specific patient subgroups. Understanding the relationship between patient characteristics and the ability to identify them with health claims data may assist in assessing the value of health claims in estimating CKD prevalence in those subgroups.

Therefore, our study aims to determine the validity of Dutch health claims data in identifying CKD patients in various patient subgroups (defined by age and sex) and for different definitions of CKD, using a hospital-based database in the Netherlands.

Methods

Study population

Serum creatinine measurements from a regional medical laboratory serving general practitioners (GPs) and a hospital in the city of Zwolle, the Netherlands, served as a reference. There were no other large medical laboratories in this region. From this laboratory database, we selected adults (≥18 years) with at least one serum creatinine measurement between 1 January and 31 December 2014. Information in the laboratory database included the patient's date of birth and sex, the value and the measurement date of serum creatinine, the type of physician ordering the measurement (GP or medical specialist), and the care setting (primary care; secondary care divided in outpatients versus inpatients). Data on these individuals were linked

to the health claims database of the Zwolle hospital which includes claims data of all delivered hospital care for a specific medical condition or complaint. This medical care can be delivered during a hospital admittance or during (a) visit(s) at the outpatient clinic. Patients treated with dialysis or kidney transplantation were identified using health claims data and excluded from our study.[67]

For our main analyses, we selected an outpatient population in which the last serum creatinine measurement was ordered in the outpatient clinic. We consider this the best proxy for the general population, as during hospitalization kidney function can temporarily deteriorate without the patient having CKD and because CKD patients solely known to a GP cannot be detected with hospital claims. Secondary analyses were performed for a GP and inpatient population, in which the last serum creatinine measurement was ordered by a GP or in an inpatient setting.

Identification of CKD patients

In the Netherlands, hospital care is reimbursed via physician claims named diagnosis treatment combinations (DBC), a system similar to Diagnosis Procedure Codes. Every hospital DBC code corresponds to a specific medical condition in a specific medical discipline.[38] This DBC comprises all delivered hospital care for this condition, for example, care delivered during a hospital admittance or at an outpatient clinic as well as laboratory or radiology procedures. Table 3.1 provides an overview of the identification methods of CKD patients using the health claims and laboratory databases.

Hospital health claims database. Patients with a DBC code 0313.11.324 'chronic renal insufficiency eGFR 30-60 mL/min/1.73 m^2' and/or a DBC code 0313.11.325 'chronic renal insufficiency eGFR <30 mL/min/1.73 m^2' were defined as patients with a claim-based diagnosis of CKD or advanced CKD, respectively.

Laboratory database. Kidney function was estimated by calculating the estimated glomerular filtration rate (eGFR) for each creatinine measurement in 2014 using the Chronic Kidney Disease Epidemiology Collaboration formula. Ethnicity status was not included in the eGFR equation because this was not available. For the diagnosis of CKD (Stages G3–G5) and advanced CKD (Stage G4–G5), we used four different definitions based on a single creatinine measurement or ≥2 measurements at least three months apart, thereby satisfying the chronicity criterion according to international guidelines (Table 3.1).[105] In cases where different creatinine measurements of a patient resulted in different CKD classification (i.e. no CKD, CKD or advanced CKD), we classified this

person in the category with the highest eGFR to ensure that a temporary decrease in eGFR did not result in a premature diagnosis of chronic (advanced) CKD.

Table 3.1: Identification of CKD patients using a health claims database and a laboratory database.

Health claims database		Laboratory database	
Study population	**Claim-based diagnosis**	**Reference group**	**eGFR-based definition** [a]
CKD	DBC code 0313.11.324: eGFR 30–60 mL/min/1.73 m^2 or DBC code 0313.11.325: eGFR <30 mL/min/1.73 m^2	CKD_{single}	One eGFR calculation of <60 mL/min/1.73 m^2 (not satisfying chronicity criterion)
		CKD_{chron}	≥2 eGFR calculations of <60 mL/min/1.73 m^2 at least 3 months apart (satisfying chronicity criterion)
Advanced CKD	DBC code 0313.11.325: eGFR <30 mL/min/1.73 m^2	Advanced CKD_{single}	One eGFR calculation of <30 mL/min/1.73 m^2 (not satisfying chronicity criterion)
		Advanced CKD_{chron}	≥2 eGFR calculations of <30 mL/min/1.73 m^2 at least 3 months apart (satisfying chronicity criterion)

Abbreviations: CKD, chronic kidney disease; DBC, 'diagnosis treatment combination', in Dutch: 'diagnose behandeling combinatie; eGFR, estimated glomerular filtration rate.
a. For calculation of the eGFR the Chronic Kidney Disease Epidemiology Collaboration formula was used.

Statistical analysis

We estimated the validity of the claim-based diagnoses of CKD and advanced CKD using the four eGFR based CKD definitions applied to the laboratory database as the reference group (see Table 3.1). Stratified analyses were performed by sex and age groups (i.e. 20-59 years, 60-74 years, ≥75 years). Since the sensitivity of claims data was relatively low in patients >75 years of age we performed a subgroup analysis with patients under the age of 75 years. For our main analysis, we used eGFR calculations derived from creatinine measurements in an outpatient setting. Secondary analyses were performed for eGFR calculations conducted in GP and inpatient settings. We estimated the validity of health claims data by calculating the sensitivity (true-positive rate; the proportion of actual CKD patients correctly identified as such with health claims data), the specificity (true-negative rate; the proportion of actual negatives using the claim-based definition correctly identified as having no CKD using the eGFR-based definition), the positive predictive value (PPV - the probability

that CKD is actually present among those with a claim-based diagnosis of CKD), and the negative predictive value (NPV - the probability that CKD is actually absent among those without a claim-based diagnosis of CKD) by using the eGFR-based CKD study populations as the reference group (see online supplementary file). The CKD prevalence was calculated using the number of CKD patients identified using the eGFR-based definition of CKD divided by the total general population of Zwolle. In a separate analysis, CKD prevalence estimates were adjusted for age and sex using the Dutch general population of 2014 as a reference. Adjusted CKD prevalence was derived by applying the weights of the reference population to the observed variable specific prevalence (e.g. CKD prevalence per age group) in the Zwolle population. This weighted average provides a single summary of CKD prevalence that would be expected if the region of Zwolle had the age and sex distribution of the reference population. SPSS 24.0 and SAS 9.4 were used for all calculations.

Results

Baseline characteristics

We identified 67 773 individuals with at least one serum creatinine measurement in 2014 (Table 3.2). Their mean age was 60.5 (SD 16.9) years, 46% were male and the prevalence of CKD (eGFR <60 mL/min/1.73 m^2), based on a single creatinine measurement (CKD_{single}), was 19.1%, with 2.1% having an eGFR <30 mL/min/1.73 m^2. A subset of 36 504 individuals had ≥2 creatinine measurements in 2014 at least three months apart and could be assessed for satisfying the chronicity criterion. In this group, with a mean age of 63.8 (SD 15.6) years and 47% males, 20.8% of individuals had an eGFR <60 mL/min/1.73 m^2 and 2.2% had an eGFR <30 mL/min/1.73 m^2.

In 24 895 outpatient individuals, 19.8% [95% confidence interval (CI) 19.3–20.3%] had an eGFR <60 mL/min/1.73 m^2 and 2.9% (95% CI 2.7–3.1%) an eGFR <30 mL/min/1.73 m^2 (Table 3.2). Of this outpatient population, 15 805 individuals had ≥2 creatinine measurements at least three months apart. Using the chronicity criterion 21.5% (95% CI 20.9–22.1%) had an eGFR <60 mL/min/1.73 m^2 and 3.4% (95% CI 3.1–3.7%) an eGFR <30 mL/min/1.73 m^2. The CKD prevalence adjusted for age and sex was lower compared with the unadjusted CKD prevalence in the outpatient study group (Table 3.2). In the same group of outpatient individuals, the unadjusted prevalence of CKD based on health claims was 4.1% (95% CI 3.9–4.4%) and 6.1% (95% CI 5.7–6.5%) in the population where the chronicity criteria could be taken into account. After adjustment for age and sex the prevalence was lower with, respectively, 2.9% (95% CI 2.7–3.1%)

and 4.0% (95% CI 3.7–4.3%). The prevalence of advanced CKD (based on health claims data) was 1.5% (95% CI 1.3–1.6%) and 2.2% (95% CI 2.0–2.4%) in the population eligible to check for the chronicity criteria. After adjustment, the prevalence was lower with, respectively, 1.0% (95% CI 0.9–1.2%) and 1.5% (95% CI 1.3–1.7%).

Table 3.2: Baseline characteristics.

	Overall population[a]		**Outpatient population**[b]	
Characteristics	**Patients with ≥1 serum creatinine measurement**	**Patients allowing to test for chronicity**[c]	**Patients with ≥1 serum creatinine measurement**	**Patients allowing to test for chronicity**[c]
Total				
n	67 773	36 504	24 895	15 805
Age (years), mean (SD)	60.5 (16.9)	63.8 (15.6)	58.1 (16.6)	60.5 (15.8)
Gender				
Male, *n* (%)	31 438 (46.4)	17 030 (46.7)	11 976 (48.1)	7795 (49.3)
Age groups (years), *n* (%)				
20–59	28 911 (42.7)	12 571 (34.4)	12 056 (48.4)	6762 (42.8)
60–74	23 817 (35.1)	13 993 (38.3)	8622 (34.6)	5853 (37.0)
≥75	15 045 (22.2)	9940 (27.2)	4217 (16.9)	3190 (20.2)
CKD				
n	12 978	7587	4924	3405
Unadjusted prevalence (95% CI)[d]	19.1 (18.8–19.4)	20.8 (20.4–21.2)	19.8 (19.3–20.3)	21.5 (20.9–22.1)
Adjusted prevalence (95% CI)[e]	10.6 (10.4–10.8)	10.3 (10.0–10.6)	13.1 (12.7–13.5)	13.0 (12.5–13.5)
Advanced CKD				
n	1443	820	719	536
Unadjusted prevalence (95% CI)	2.1 (1.9–2.2)	2.2 (2.0–2.4)	2.9 (2.7–3.1)	3.4 (3.1–3.7)
Adjusted prevalence (95% CI)	1.2 (1.1–1.3)	1.2 (1.1–1.3)	2.0 (1.8–2.2)	2.2 (2.0–2.4)

a. The overall population patient population includes all patients with a serum creatinine measurement in the laboratory database regardless of the type of physician ordering the measurement and the clinical setting.
b. The outpatient population includes all patients with their last serum creatinine measurement ordered in the outpatient clinic.
c. The patient population allowing to test for chronicity are all patients with ≥2 serum creatinine measurements at least three months apart.
d. The prevalence is based on the number of CKD patients identified using the eGFR-based definition of CKD.
e. Adjusted for the age and sex distribution in the total Dutch population.

Sensitivity

Total. Figure 3.1 presents the sensitivity of the claim-based diagnoses of CKD and advanced CKD. Sensitivity of the claim-based diagnosis of CKD was 20% when using CKD_{single} as reference group. This means that 20% of the patients with an eGFR <60 mL/min/1.73 m^2 could be traced to have a CKD-related health claim (Figure 3.1). Sensitivity of CKD was 27% when the chronicity criterion was taken into account (CKD_{chron}). In patients with advanced CKD, sensitivity was 42% when using advanced CKD_{single} as reference group, and 51% when using advanced CKD_{chron} as reference group.

In general, the sensitivity of health claims data was higher in patients with advanced CKD as opposed to those with CKD. In addition, the sensitivity of health claims data was always higher when using eGFR based diagnoses satisfying the chronicity criterion as the reference group.

By age group and sex. Sensitivity was highest for patients aged 20–59 years and lowest in those ≥75 years of age, for all eGFR-based CKD definitions as reference group. In young patients with advanced CKD, sensitivity was 72% when using advanced CKD_{chron} as reference group (Figure 3.1). Overall, the sensitivity was higher in men than in women (Figure 3.1). In contrast, in patients with advanced CKD below the age of 75 years, sensitivity was higher in women than in men. Of note, young female patients (20–59 years) with advanced CKD were most accurately identified with a sensitivity of 76% using CKD_{chron} as reference group.

Age <75 years. Since the sensitivity of claims data was relatively low in patients ≥75 years of age, we performed a subgroup analysis with patients <75 years. As a result, the sensitivity increased, for example, in advanced CKD the sensitivity increased from 51% (Figure 3.1) to 62% when using advanced CKD_{chron} as reference group (Figure 3.2).

Specificity, PPV, NPV

Overall and in all subgroups based on age and sex, the specificity of CKD and advanced CKD was 99% or higher (see online supplementary file). PPVs ranged from 72% to 99% and NPVs ranged from 40% to 100%.

Age <75 years. Specificity, PPV, and NPV of the subgroup of patients under 75 years of age were comparable and are presented in the appendix (see online supplementary file).

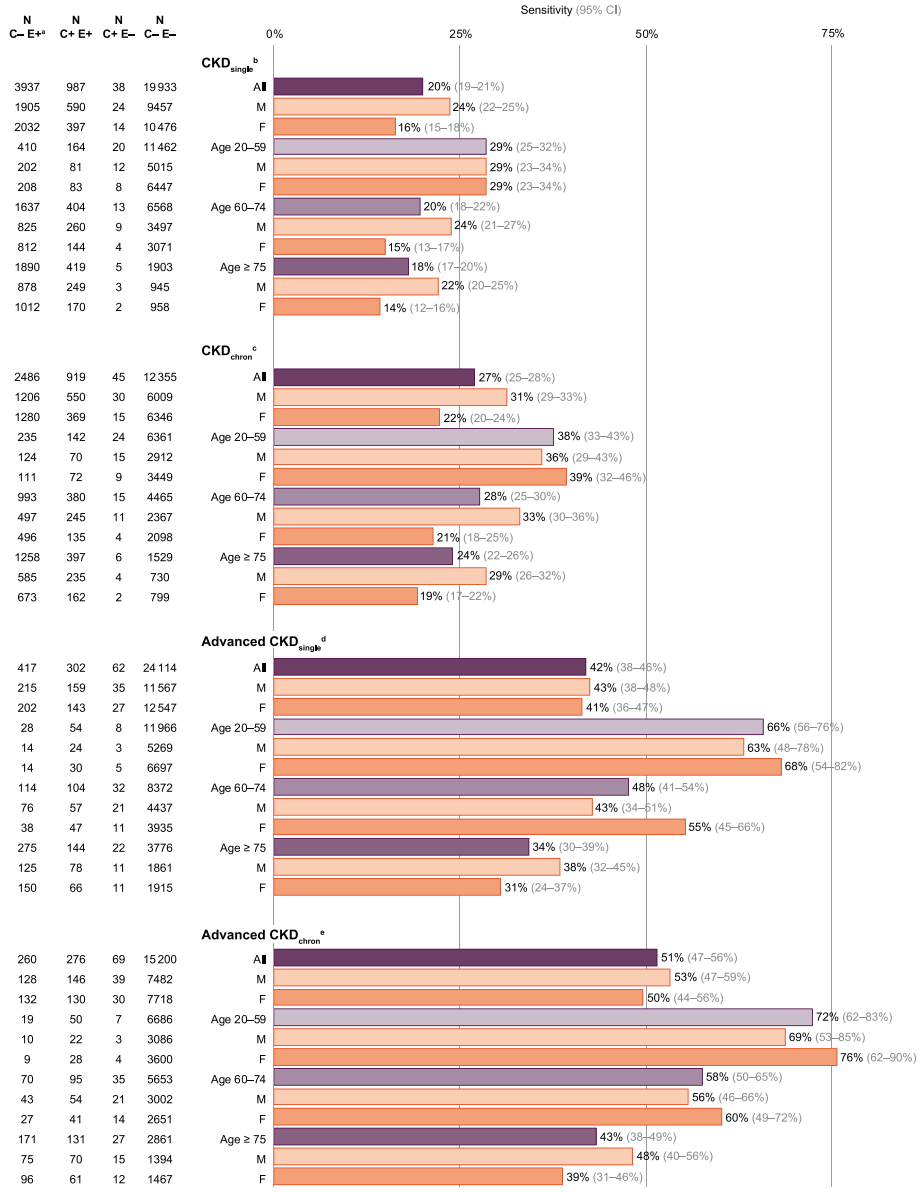


Figure 3.1: Sensitivity of claim-based diagnosis of CKD and advanced CKD using four eGFR-based CKD definitions as the reference group, by age group and sex.

Abbreviations: F, female; M, male.
a. C, claim-based CKD diagnosis; E, eGFR-based CKD diagnosis. b. CKDsingle, one eGFR calculation <60 mL/min/1.73 m^2. c. CKDchron, ≥2 eGFR calculations <60 mL/min/1.73 m^2 at least three months apart. d. Advanced CKDsingle, one eGFR calculation <30 mL/min/1.73 m^2. e. Advanced CKDchron, ≥2 eGFR calculations <30 mL/min/1.73 m^2 at least three months apart.

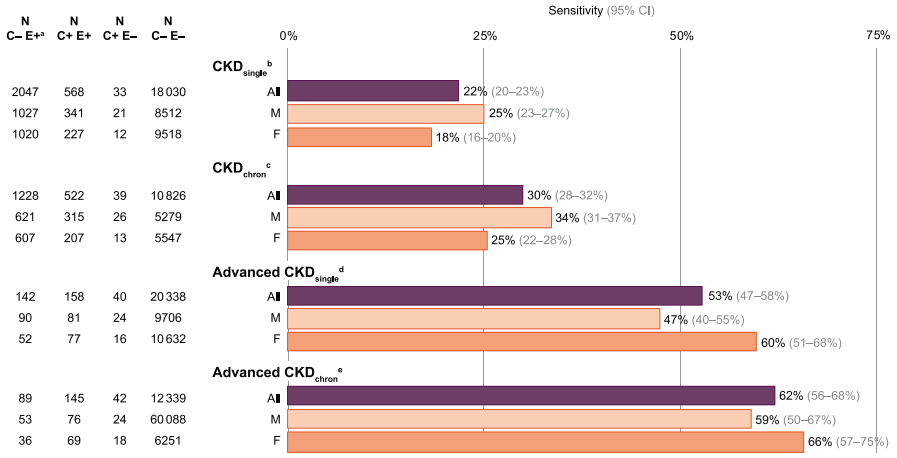


Figure 3.2: Sensitivity of claim-based diagnosis of CKD and advanced CKD using four eGFR-based CKD definitions as the reference group, in patients <75 years.

Abbreviations: F, female; M, male.
a. C, claim-based CKD diagnosis, E, eGFR-based CKD diagnosis. b. CKD_{single}, one eGFR calculation <60 mL/min/1.73 m^2. c. CKD_{chron}, ≥2 eGFR calculations <60 mL/min/1.73 m^2 at least three months apart. d. Advanced CKD_{single}, one eGFR calculation <30 mL/min/1.73 m^2. e. Advanced CKD_{chron}, ≥2 eGFR calculations <30 mL/min/1.73 m^2 at least three months apart.

Nephrological care

The majority of CKD patients without a concordant CKD health claim received adequate nephrological care (60%) (defined as having health claims related to CKD, nephrology, or diabetes care). In CKD patients under the age of 75 years, this was even more than 90% (see online supplementary file).

GP and inpatient population

The baseline characteristics of the GP and inpatient study populations are described in the appendix (see online supplementary file). Here we also present the results of the overall, GP and inpatient study populations.

Discussion

This study describes the validity of Dutch health claims data for the estimation of CKD prevalence, overall and in patient subgroups, in a hospital-based study. Since this study primarily assesses the value of health claims when estimating CKD prevalence in different patient subgroups, we mainly focus on the sensitivity. The

'overall' sensitivity of health claims data for the identification of CKD patients using the chronicity criterion as the reference group was 27%. The sensitivity of health claims data increased to 51% for patients with advanced CKD. Sensitivity of the claim-based diagnoses of CKD was substantially higher in young patients (age 20–59 years) and in men. A maximum of 76% was reached in young women with advanced CKD. The specificity of CKD and advanced CKD was consistently high, whereas the PPV and NPV varied between the patient subgroups.

Sensitivity of health claims data in the estimation of CKD prevalence

Our study is the first describing the validity of claims data in a European healthcare system for the identification of CKD patients. So far, four studies in Canada and the USA have assessed the validity of health claims data in identifying patients with CKD by comparing estimates of claim-based CKD prevalence with an eGFR-based CKD prevalence as reference group.[20,52–54] All studies were able to validate a claim-based diagnosis of CKD while two were additionally able to validate a claim-based diagnosis of advanced CKD.[52,53] Only in one study, the eGFR-based CKD definition was based on ≥2 eGFR calculations, making it possible to take the chronicity criterion into account.[52]

In line with our results, these studies concluded that health claims data have low sensitivity and high specificity for the identification of CKD patients.[20,52–54] The sensitivity for the identification of CKD patients ranged from 2.7% to 19.4% in patients with CKD and from 56.0% to 58.8% in patients with advanced CKD. The accuracy of health claims data in identifying CKD Stages G3-G5 is slightly higher in our study using the chronicity criterion (sensitivity 27%), while slightly lower for advanced CKD using the chronicity criterion (in our case 51%). This comparison between studies is hampered because of differences in the definition of the reference group.

Up to now, studies have provided limited information on the validity of health claims data in specific subgroups. Only one of the four previous studies included patients <65 years of age.[52] That study showed a higher sensitivity in patients with advanced CKD under the age of 65 years compared with patients >65 years (sensitivity 85.8% versus 68.1%). Our data show a similar trend, with a sensitivity considerably higher in patients <75 years compared with patients ≥75 years.

It is not surprising that health claims data in the Netherlands have low accuracy for the estimation of the CKD prevalence in the general population and in particular for elderly patients. In the Netherlands, only hospital claims include information on diagnosis while primary care claims do not. As a consequence, one can only detect

CKD patients referred to a nephrologist, and not CKD patients treated by the GP. Patients with advanced CKD have an indication for referral, while the majority of CKD patients in earlier stages are cared for in primary care, especially at older age.[105,106] This also holds true for many end-stage kidney disease (ESKD) patients on comprehensive conservative management. The results of our study indeed indicate that in daily practice elderly patients with impaired kidney function are more often treated by a GP or do not receive specific nephrology-related care at all.[107] Of note, with this health claims database we can demonstrate that adequate nephrological care is registered for 91% of advanced CKD patients aged <75 years.

Our study shows that considerably fewer elderly women with advanced CKD could be identified with health claims data than similarly aged men. It is known that sex differences exist in the epidemiology and outcomes of CKD. Studies show that more women than men have CKD (not on KRT) while men show a faster decline in kidney function and more often progress to ESKD.[108] Although current guidelines do not involve sex-specific recommendations in the treatment of CKD, this study suggests that at least in our study sample elderly women with advanced CKD were less likely to be treated by a nephrologist than men. Possibly because elderly women are more likely to choose comprehensive conservative management, which can also be done by a GP, than men.[109,110]

Overall, sensitivity differs considerably across patient subgroups defined by the severity of kidney disease, age, and sex. This could suggest that clinicians, among other things, take into account an individual's lifetime risk of developing ESKD while considering the need for nephrological care.[111] This risk estimation is among other things based on a person's age, sex, and the severity of kidney failure. As a result, particularly young patients, men, and advanced CKD (Stage G4-G5) patients satisfying the chronicity criterion are known within the confines of nephrological care and can thus be identified using health claims data.

Estimating CKD prevalence with populations surveys versus health claims data

Numerous studies have evaluated the prevalence of CKD using population surveys[112,113], showing that CKD prevalence varies widely with estimations of CKD Stages G3-G5 prevalence in Europe varying between 1.0% and 5.9%,[113] and in the Netherlands ranging from 1.3% to 4.8%.[114,115] However, an accurate comparison of CKD prevalence across studies remains challenging since different studies used different CKD definitions and different methods for the assessment of kidney function.[116,117] Moreover, these studies

are always based on samples from the general population. Therefore, when estimating CKD prevalence in population surveys, sampling bias cannot be avoided.

The unadjusted (eGFR-based) CKD prevalence (eGFR <60 mL/min/1.73 m^2) in previous studies using health claims data ranged from 19% in a sample of the general population[52] to 67% using patients hospitalized for myocardial infarction.[20] Since studies use different methods as the reference group, comparison between studies is difficult. The estimated unadjusted prevalence of CKD Stages G3-G5 of 22% in our study, using a regional laboratory for the CKD diagnosis, approximates the prevalence of other studies using a sample of the general population as a reference.

Our results suggest that health claims data have low sensitivity for the estimation of overall CKD in the general population, especially in the case of elderly CKD patients and patients with less advanced CKD. However, our results also indicate that health claims data may have value in estimating CKD prevalence in specific subgroups, particularly in young patients and those with advanced CKD. In addition, the sensitivity of young patients (20-59 years) with advanced CKD is similar to those described in validity studies testing claims data for the identification of dialysis patients,[56–58] a population for which is generally assumed that health claims data provide reliable estimates of the actual population receiving dialysis treatment.

Strengths and limitations

The strength of our study is the availability of a large laboratory database including all adults with a serum creatinine measurement, allowing its use as the reference group. This enabled us to define CKD in two ways: based on a single and on ≥2 creatinine measurements in accordance with the chronicity criterion. We consider ≥2 measurements as optimal since it is in accordance with the clinical guidelines. In addition, we were able to differentiate between patients with an eGFR <60 mL/min/1.73 m^2 and an eGFR <30 mL/min/1.73 m^2, and by age and sex.

Several limitations of our study also need consideration. First, primary care claims, in contrast to hospital claims, do not include diagnosis information. Therefore, CKD patients treated by a GP cannot be detected. Moreover, in the Netherlands, a referral from the GP is always required to consult a medical specialist and therefore Dutch health claims data represent those patients with an indication for referral. Although the outpatient population was considered the best proxy for the general population, the CKD prevalence of individuals treated by the GP and with undetected CKD remains unknown. In this study, we focus on CKD Stages G3-G5 since there is no specific health

claim for earlier CKD stages and these patients are often undetected or are cared for in primary care.

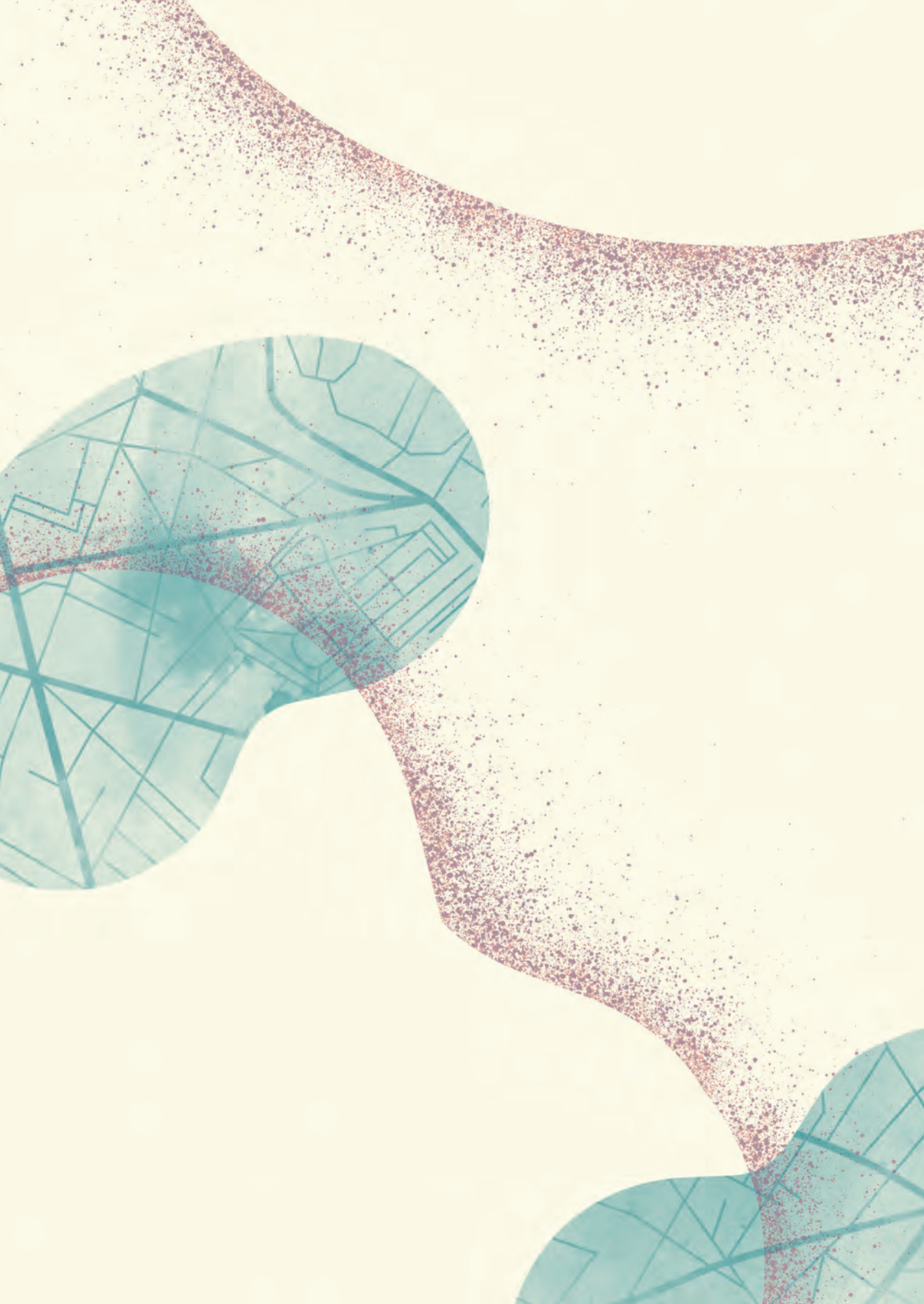
Secondly, the unadjusted CKD prevalence in our database estimated with eGFR was 21.5% for CKD Stages G3–G5 and 3.4% for CKD Stage G4–G5 and decreased to 13.0% and 2.2%, respectively, after adjustment for age and sex. This means that in our study population elderly individuals were over-represented. This can be expected since we select persons with a performed laboratory test, who are likely to be older than persons from the general population. The unadjusted CKD prevalence estimated by claims data was 6.1% for CKD Stages G3–G5 and 2.2% for CKD Stage G4–G5 and decreased to 4.0% and 1.5% after adjustment for age and sex. Likely the CKD prevalence estimated with claims data is underestimated as this study shows that the overall sensitivity is low. Finally, the results of this hospital-based study may not be generalizable to a national level due to differences in coding between regions or hospitals in the Netherlands. In addition, generalizability of the results to other countries could be hampered by differences in coding for claims in different healthcare systems.

Conclusion

This study shows that the sensitivity of the claim-based diagnoses of CKD and advanced CKD varies largely across patient subgroups. Although overall sensitivity was low, in general, sensitivity was much higher in young patients compared with elderly patients and higher in men than in women. Moreover, health claims data were more accurate in the identification of patients with advanced CKD than of those with CKD.

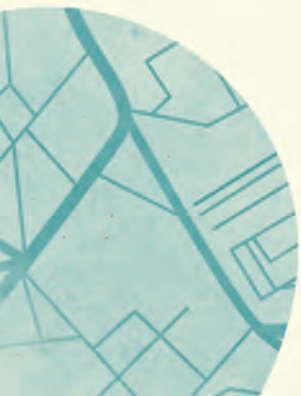
When using health claims data for the estimation of CKD prevalence, it is important to take into account the characteristics of the population at hand. According to this study, the younger the subjects and the more advanced the stage of CKD the higher the sensitivity of such data. Understanding which patients are selected using health claims data and which patients are not is crucial for a correct interpretation of study results.

Bearing this in mind and considering their specific advantages health claims data can have added value for the monitoring of trends in disease prevalence and healthcare costs over time. The linkage of health claims databases to other administrative databases or clinical data can result in a more accurate identification of CKD patients and could thereby improve the usage and value of health claims data for health research even more.[26]



Part 3

Healthcare costs



4

Healthcare costs of patients on different kidney replacement therapy modalities: analysis of Dutch health insurance claims data

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Abstract

Background The aim of this study is to present average annual healthcare costs for Dutch kidney replacement therapy (KRT) patients for seven treatment modalities.

Methods Health insurance claims data from 2012–2014 were used. All patients with a 2014 claim for dialysis or kidney transplantation were selected. The KRT related and KRT unrelated average annual healthcare costs were analyzed for five dialysis modalities [in-center hemodialysis (CHD), home hemodialysis (HHD), continuous ambulatory peritoneal dialysis (CAPD), automated peritoneal dialysis (APD), and multiple dialysis modalities in a year (Mix group)] and two transplant modalities (kidney from living and deceased donor, respectively).

Results The total average annual healthcare costs in 2014 ranged from €77 566 (SD €27 237) for CAPD patients to €105 833 (SD €30 239) for patients in the Mix group. For all dialysis modalities, the vast majority (72%–84%) of costs was KRT related. Patients on hemodialysis ≥4x/week had significantly higher average annual costs compared with those dialyzing 3x/week (Δ€19 122). Costs for kidney transplant recipients were €85 127 (SD €39 679) in the year of transplantation and rapidly declined in the first and second year after successful transplantation (resp. €29 612 (SD €34 099) and €15 018 (SD €16 186)). Transplantation with a deceased donor kidney resulted in higher costs (€99 450, SD €36 036)) in the year of transplantation compared with a living donor kidney transplantation (€73 376, SD €38 666).

Conclusions CAPD patients have the lowest costs compared with other dialysis modalities. Costs in the year of transplantation are 25% lower for patients with kidneys from living versus deceased donors. After successful transplantation, annual costs decline substantially to a level that is approximately 14%–19% of annual dialysis costs.

Introduction

End-stage kidney disease (ESKD) is ranked among the top 20 leading causes of decrease in quality of life and loss of life years and has one of the highest disease burdens worldwide.[118,119] In the Netherlands on January 1st 2015, 16 277 people were dependent on kidney replacement therapy (KRT) with an annual incidence of approximately 2000 patients.[120] Although in the Netherlands the incidence rate of KRT has stabilized, the number of prevalent patients continues to rise due to a relatively high number of kidney transplantations.[121] This implies that the economic burden of KRT treatment increases as well. Healthcare systems face a major challenge as a considerable amount of the often limited healthcare budget is spent on KRT.[122] According to the National Institute of Public Health and the Environment (RIVM), the total healthcare cost for chronic kidney failure was 800 million Euros in 2011.[119] As the vast majority of these costs is related to KRT, this implies that 1% of the national healthcare budget of the Netherlands was spent on 0,1% of the population.[123]

KRT has always served as a classical example of lifesaving treatment with very high per person costs and this essentially has not changed over the past decennia. However, comprehensive cost estimates of KRT in the Netherlands are based on a study from the 1990s.[123] More recent studies only incorporated one or a few KRT modalities.[124,125] Also, recent developments, such as living-donor-related kidney transplantation and high-frequency dialysis, necessitate a comprehensive costing study that includes such new therapeutic possibilities.

Several European studies have recently used health insurance claims to investigate national healthcare expenditures related to KRT.[63,126–128] Dutch health insurance claims contain details on expenditures and treatment of different KRT modalities and enable to perform a comprehensive study on healthcare expenditure of patients on different KRT modalities with nationwide coverage.

This study aims to provide detailed estimates of the average annual costs per patient for seven KRT modalities. Besides distinguishing between dialysis therapies, we also include transplantation costs by source of kidney donor, living or deceased, and hemodialysis (HD) costs by frequency of dialysis.

Methods

Data source

In the Netherlands healthcare insurance is obligatory; almost all citizens have healthcare insurance.[129] Vektis collects and manages claims data of all Dutch health insurance companies. These claims are related to all healthcare procedures covered by the Health Insurance Act, including the costs of compulsory co-payments.[30] The Vektis database covers 99% of insured people living in the Netherlands and contains demographic information, including sex, year of birth, and date of death. To ensure privacy, Vektis pseudonymized the persons' national identification number and allowed data access only in a secured environment. All authors only had access to de-identified data. For the use of this national data, the permission of all contributing insurance companies was provided (see online supplementary file).

Study population

From all adults (≥19 years) in the Vektis claims database who had at least one health insurance claim related to KRT we included those patients on chronic KRT and excluded those with incidental use (e.g. acute dialysis) or unjustified (erroneous) claims. Dialysis patients were selected using health claims in the year 2014 and kidney transplant patients were identified using claims in the period 1 January 2012 to 31 December 2014. We differentiated seven KRT modalities: (1) in-center hemodialysis (CHD), (2) home hemodialysis (HHD), (3) continuous ambulatory peritoneal dialysis (CAPD), (4) automated peritoneal dialysis (APD), (5) multiple dialysis modalities within a year (Mix), (6) living kidney donor transplant recipients and (7) deceased kidney donor transplant recipients (Figure 4.1A and 4.1B, see also online supplementary file). After classification, we validated the number of patients per modality in an external database, the Dutch Renal Registry (Renine), which serves as gold standard because of its complete coverage of chronic KRT. Correspondence between the two databases was high (93.8–99.1%, see online supplementary file).

Cost variables

We estimated healthcare costs by using registered health claims (reimbursement data). Costs were distinguished according to different healthcare components. First, costs directly related to KRT, based on diagnosis-related group codes (DRGs), were identified and included all costs of the dialysis procedure (including access surgery and hospitalization for access surgery), the kidney transplant (including donor expenses)

as well as the pre- and post-transplant care. More specifically, KRT related costs include all medications used during dialysis (e.g. EPO, phosphate binders), staff costs, including physician fees, laboratory assessments, and other diagnostics as included in KRT clinical guidelines (e.g. chest X-ray). Also, equipment and devices needed, e.g. dialysis machines for home dialysis, are included here. Finally, overhead costs, e.g. for water and energy are included. Second, non-KRT costs were defined as all remaining in- and outpatient DRG costs not directly related to KRT, such as primary care, mental healthcare, medication, medical devices, transportation, healthcare costs incurred abroad, and other healthcare costs. These non-KRT costs may incur dialysis-related costs as well, e.g. transportation costs to and from the dialysis center, but these costs cannot be attributed with 100% certainty to KRT.

Cost data are provided as annual costs, averaged over all patients in a specific modality group. To provide meaningful cost estimates for patients that are not a full year on KRT, e.g. incident and deceased patients, we calculated average 4-week healthcare costs for these patient subgroups.

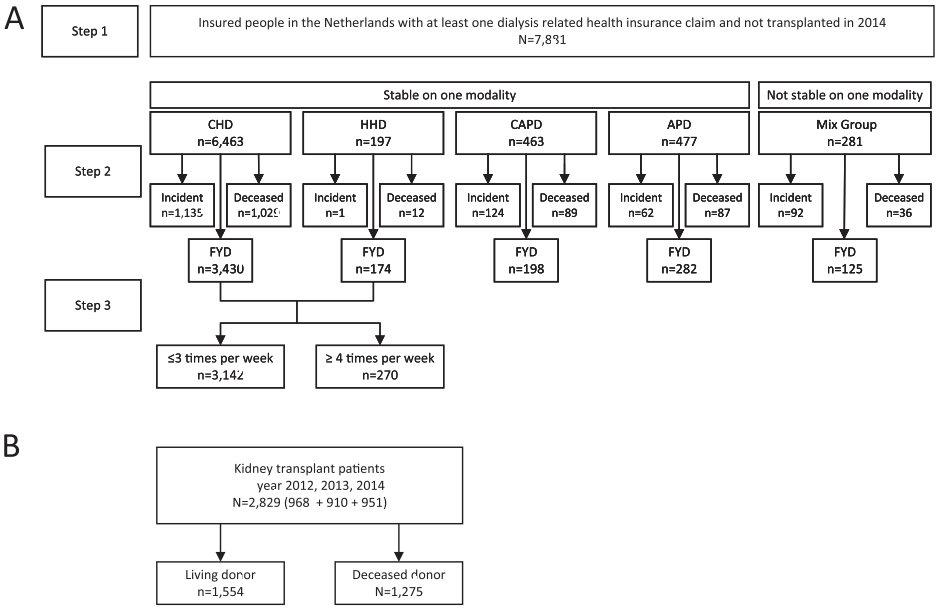

Figure 4.1: Classification of KRT modalities.

A. Classification of dialysis patients; CHD = Center Hemodialysis; HHD = Home Hemodialysis; APD = Automated Peritoneal Dialysis; CAPD = Continuous Ambulatory Peritoneal Dialysis; Mix Group = dialysis modality changed in 2014; FYD = full year on dialysis;
B. Classification of transplantation patients. We included only the first received kidney transplantation in the study period of 2012–2014.
* Excluded patients are not represented in the figure.

Statistical analysis

Descriptive statistics (age, gender, and co-morbidity) are presented per treatment modality. The presence of comorbidities was based on medication (see online supplementary file). Healthcare costs are presented as mean with standard deviation. The average annual costs of hemodialysis patients were calculated depending on weekly dialysis frequency. To test for statistical significance of differences in healthcare expenditure between groups (lower and higher frequency of hemodialysis; donor source), we applied the non-parametric Wilcoxon-Mann-Whitney test, as cost data were non-normally distributed. Finally, healthcare costs were calculated per treatment state. To accommodate for differences in total treatment time between incident, full-year on dialysis (FYD), and deceased patients, we calculated the cost of 4 weeks of treatment (4-week costs) per treatment state, as the sum of yearly costs divided by total treatment time (TTT) in days * 28 days. All costs are reported in euros (1 euro = 1.11454 US dollar–exchange rate of 31 July 2019) and converted to the year 2014 according to the Dutch Consumer Price Index (2012 to 2014: 1.035; 2013 to 2014: 1.010).[130] All analyses were conducted using SAS, version 9.4 (SAS Institute Inc., Cary, NC).

Results

Patient characteristics by KRT modality

Overall, 7827 persons could reliably be attributed to one of seven KRT modalities in 2014 (Table 4.1). Of these, 6876 were dialysis patients and 951 patients received a kidney transplant. On average, HHD patients and transplant recipients were younger and had fewer comorbidities than patients on other modalities, whereas more males than females received KRT.

Annual healthcare costs per dialysis modality

Table 4.2 shows the average annual healthcare costs in 2014 of FYD patients by modality. KRT costs ranged from €61 025 for CAPD patients to €76 531 for Mix group patients. The vast majority of costs were related to the dialysis itself, with relatively small amounts for pre-transplant procedures and dialysis access, but not in the Mix group. This group experiences by definition a change between modalities necessitating costs for access procedures. Three non-KRT healthcare components stand out with relatively high amounts, i.e. hospital costs, medication, and transportation costs. Hospital costs unrelated to KRT for patients in the Mix group (€16 286) were much higher than in other groups. The third most expensive cost item was medication

(outside the hospital) with the lowest costs for CAPD (€3939) and, again, the highest costs for the Mix group (€4690). Transportation costs (taxi costs) were highest in CHD patients (€5455), while home dialysis patients (HHD and (C)APD) had almost ten-fold lower expenditure, obviously related to the less frequent hospital visits of these groups. KRT related costs of HHD were in the same order of magnitude as costs of CHD, this is related to the possibility to use individual nursing assistance at home for HHD patients.

Table 4.1: Patient characteristics per KRT modality (>75% TTT[a]) in the year 2014.

	Dialysis patients					**Kidney transplant recipients**	
	On Hemodialysis (HD)		**On Peritoneal dialysis (PD)**		**Mix between dialysis treatments** [a]	**Performed Transplants**[c]	
	CHD [b]	**HHD** [b]	**APD** [b]	**CAPD** [b]	**Mix Group** [b]	**Deceased donor**	**Living donor**
N (%)	5594 (81%)[d]	187 (3%)	431 (6%)	411 (6%)	253 (4%)	441 (46%) [e]	510 (54%)
Age (mean, SD)	69.6 (13.9)	58.3 (13.5)	65.7 (14.3)	69.0 (13.1)	63.3 (14.9)	57.0 (12.6)	50.7 (13.7)
Gender (% men)	59%	65%	62%	61%	66%	63%	60%
Nr. of comorbidities (mean, SD)	1.0 (0.9)	0.7 (0.8)	1.1 (0.9)	1.2 (0.9)	1.0 (0.9)	1.0 (0.8)	0.7 (0.8)

a. TTT = Total Treatment Time in the year 2014 applies to dialysis patients only. KRT modality groups are exclusive, implying that patients are only part of one 'stable' KRT modality.
b. CHD = Center Hemodialysis; HHD = Home Hemodialysis; APD = Automated Peritoneal Dialysis; CAPD = Continuous Ambulatory Peritoneal Dialysis; Mix Group = dialysis modality changed in 2014.
c. We included only patients with a first kidney transplantation in 2014 in the study period of 2012–2014.
d. Reading example: 81% of the dialysis patients were categorized as CHD patients.
e. Reading example: 46% of kidney transplant recipients received a deceased donor kidney.

Annual healthcare costs by dialysis frequency

A reliable dialysis frequency pattern could be established for 3412 out of 3604 FYD hemodialysis patients (Figure 4.1). Only 8% of these patients dialyzed ≥4 times/week. Of these, the vast majority dialyzed 4 or 5 times/week while 19 patients (7%) received ≥6 sessions/week.

Table 4.2: Average annual healthcare costs per dialysis modality, for FYD patients (Full Year on Dialysis) (€ 2014).

	Hemodialysis (HD)						Peritoneal dialysis (PD)											
	CHD [a] (*n* = 3430)			HHD [a] (*n* = 174)			CAPD [a] (*n* = 198)			APD [a] (*n* = 282)			Mix Group [a] (*n* = 125)					
	Mean (Std Dev)		% users	Mean (Std Dev)		% users	Mean (Std Dev)		% users	Mean (Std Dev)		% users	Mean (Std Dev)		% users	Mean (Std Dev)		% users
Dialysis modality	€ 69 887	(7274)	100%	€ 71 409	(5645)	100%	€ 60 084	(3693)	100%	€ 73 437	(3620)	100%	€ 73 055	(10 002)	100%			
Dialysis access	€ 1645	(2885)	42%	€ 1 187	(2420)	36%	€ 529	(1530)	15%	€ 385	(1475)	12%	€ 3137	(3568)	64%			
Pre-transplant procedures	€ 201	(1379)	11%	€ 239	(791)	19%	€ 413	(1805)	20%	€ 392	(1468)	20%	€ 339	(1186)	22%			
Total KRT costs	**€ 71 734**	**(8106)**	**100%**	**€ 72 834**	**(6338)**	**100%**	**€ 61 025**	**(4644)**	**100%**	**€ 74 215**	**(4152)**	**100%**	**€ 76 531**	**(10 747)**	**100%**			
Hospital (no KRT)	€ 8563	(13 813)	93%	€ 5785	(7775)	93%	€ 9115	(22 633)	90%	€ 7611	(13 401)	91%	€ 16 286	(21 181)	99%			
Primary care	€ 395	(606)	98%	€ 340	(520)	97%	€ 351	(437)	97%	€ 346	(508)	99%	€ 446	(756)	98%			
Mental healthcare	€ 236	(2630)	5%	€ 13	(78)	3%	€ 164	(1617)	3%	€ 87	(601)	4%	€ 414	(3239)	9%			
Medication [b]	€ 4325	(3395)	98%	€ 4277	(4081)	99%	€ 3939	(3383)	98%	€ 4382	(6199)	99%	€ 4690	(6392)	99%			
Medical devices	€ 911	(1787)	70%	€ 2808	(2068)	90%	€ 1726	(1535)	95%	€ 1991	(1515)	95%	€ 2684	(2955)	96%			
Healthcare abroad	€ 171	(846)	9%	€ 355	(917)	21%	€ 1	(17)	2%	€ 202	(2266)	2%	€ 12	(96)	2%			
Transportation	€ 5455	(5499)	96%	€ 570	(973)	49%	€ 504	(1015)	41%	€ 461	(964)	34%	€ 2856	(2633)	87%			
Other	€ 827	(4007)	20%	€ 69	(489)	13%	€ 739	(3785)	12%	€ 639	(3668)	13%	€ 1914	(5756)	27%			
Total average annual costs	**€ 92 616**	(21 500)	**100%**	**€ 87 051**	(12 648)	**100%**	**€ 77 566**	(27 237)	**100%**	**€ 89 932**	(18 890)	**100%**	**€ 105 833**	(30 239)	**100%**			

a. CHD = Center Hemodialysis; HHD = Home Hemodialysis; APD = Automated Peritoneal Dialysis; CAPD = Continuous Ambulatory Peritoneal Dialysis; Mix Group = dialysis modality changed in 2014. b. Medication is all medication distributed by a pharmacy outside the hospital. Other types of costs, i.e. dialysis modality and hospitalization may also include medication costs. In the Netherlands, inpatient medication is part of the DRG and can therefore not be detected as a separate expenditure in claims data.

Table 4.3 shows that frequent users had higher average costs related to KRT (€88 200) in comparison with less frequent users (€69 744). Hospital costs unrelated to KRT did not differ between these groups. Primary care, medical devices, healthcare abroad and transportation costs did however differ between the two groups (although with small differences in euros). Overall, cost differences between the high- and normal-intensity hemodialysis patients amounted to €19 122, in favor of those who dialyze ≤3 times/week.

Table 4.3: Total average annual costs (€) depending on the frequency of hemodialysis, for FYD patients (Full Year on Dialysis) only.

	≤ 3 times per week (*n* = 3142)		**≥4 times per week (*n* = 270)**	
	Mean (Std Dev)	% users	Mean (Std Dev)	% users
n	3142		270	
Total KRT costs*	**€ 69 744 (5067)**	**100%**	**€ 88 200 (10 985)**	**100%**
Hospital costs not related to KRT	€ 8301 (13425)	92%	€ 8818 (13 968)	95%
Primary care*	€ 396 (607)	98%	€ 335 (564)	99%
Mental healthcare	€ 244 (2736)	5%	€ 47 (469)	4%
Medication[a]	€ 4292 (3410)	98%	€ 4349 (3483)	99%
Medical devices*	€ 907 (1734)	70%	€ 1714 (2274)	77%
Healthcare abroad*	€ 169 (831)	9%	€ 213 (727)	13%
Transportion*	€ 5219 (5276)	96%	€ 5186 (7516)	77%
Other	€ 848 (4074)	20%	€ 379 (2803)	17%
Total average annual costs*	**€ 90 119 (19 981)**		**€ 109 241 (23 295)**	

*Significance at P<0.05 two-sided.
a. Medication is all medication disctributed by the pharmacy outside the hospital. Other types of costs, i.e. dialysis modality and hospitalization may also include medication costs. In the Netherlands, inpatient medication is part of the DRG and can therefore not be detected as a separate expenditure in claims data.

4-week healthcare costs per treatment state and dialysis modality

Figure 4.2 shows the 2014 average 4-week healthcare costs of three dialysis subgroups (indicated as "treatment states"): (1) FYD patients, (2) incident patients, and (3) deceased patients. Hence, independent of the TTT or period alive, Figure 4.2 enables a comparison of the five dialysis modalities per treatment state while including all healthcare spending over the year 2014. Incident and deceased HHD patient numbers were too low in number to allow meaningful analysis. Figure 4.2 confirms that most costs of FYD are related to KRT. The highest 4-week expenditures (€15 560) were made

for patients starting CHD. For all dialysis modalities, incident and deceased patients had high non-KRT related costs, while FYD patients had low non-KRT related costs. The highest 4-week costs are associated with patients starting CHD and the lowest 4-week costs were registered for stable CAPD patients.

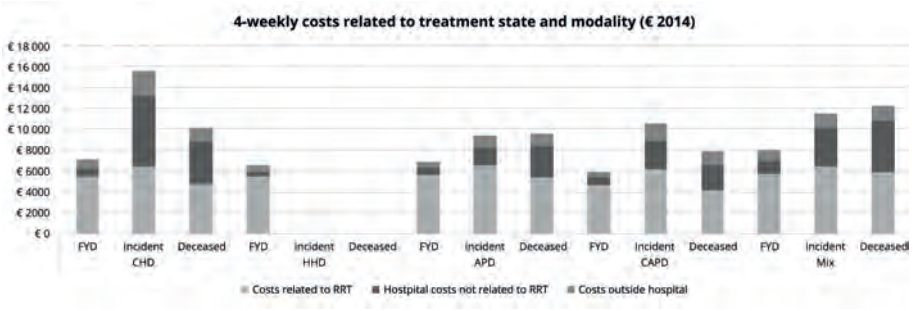

Figure 4.2: 4-week average mean healthcare costs related to treatment states, per modality.

FYD = full year on dialysis; Incident = incident patients starting treatment in 2014; Deceased = patients who died in 2014; CHD = Center Hemodialysis; HHD = Home Hemodialysis; APD = Automated Peritoneal Dialysis; CAPD = Continuous Ambulatory Peritoneal Dialysis; Mix Group = dialysis modality changed in 2014.

Annual healthcare costs of kidney transplantation

Table 4.4 shows that the average annual healthcare costs in the year *of* transplantation are high (€85 127) and comparable to the annual healthcare costs of dialysis patients (€77 566 - €105 833, see Table 4.2). The annual healthcare costs decline with time after surgery, with total annual healthcare costs of €29 612 in the first and €15 018 in the second year after successful transplantation.

At the beginning of the second year after transplantation, 911 out of 968 patients transplanted in 2012 were alive, however, 105 of these patients had experienced graft failure, as appeared from claims indicating another kidney transplantation or a return to dialysis. Of the patients with functioning graft (Table 4.4, last column, n = 806), the average annual healthcare expenditure was €5139 lower than the average second-year costs of all patients alive, irrespective of graft functioning.

Annual healthcare costs of patients according to donor source

Over a three-year period (2012–2014) 1554 patients received a kidney transplant from a living kidney donor and 1275 patients obtained a kidney from a deceased person (Table 4.5). KRT related costs were most prominent in both groups, varying from 72% of all healthcare costs (living donor) to 75% of costs (deceased donor). Absolute KRT

Table 4.4: Total average annual healthcare costs per phase of transplantation.

	Year of transplantation		First year[a] after transplantation		Second year after transplantation		Second year after successful transplantation	
	Mean (Std Dev)	% users	Mean (Std Dev)	% users	Mean (Std Dev)	% users	Mean (Std Dev)	% users
n	2829		1825		911		806	
Preparatory research	€ 1954 (7911)	45%	€ 100 (857)	5%	€ 29 (223)	4%	€ 19 (205)	2%
Transplant operation	€ 22 748 (11 267)	100%	€ 1150 (4454)	9%	€ 242 (2374)	2%	€ 55 (731)	1%
Guidance[b]	€ 474 (1154)	17%	€ 106 (474)	7%	€ 99 (394)	8%	€ 108 (413)	9%
After care	€ 6803 (9641)	74%	€ 4396 (6438)	85%	€ 1831 (2777)	82%	€ 1817 (2566)	86%
Donor expenses	€ 2608 (5466)	23%	€ 246 (1623)	5%	€ 6 (102)	1%	€ 5 (84)	1%
Dialysis procedure (incl. access)	€ 28 020 (26 007)	74%	€ 5048 (15 442)	21%	€ 3635 (14 738)	10%	€ 0 (0)	0%
KRT related costs	**€ 62 607 (31 064)**	**100%**	**€ 11 046 (18 815)**	**92%**	**€ 5842 (15 612)**	**90%**	**€ 2004 (2647)**	**90%**
Hospital (no KRT)	€ 9550 (17 670)	97%	€ 7242 (23 245)	87%	€ 5698 (16 520)	86%	€ 4694 (12 782)	86%
Primary care	€ 246 (328)	99%	€ 276 (377)	100%	€ 285 (506)	100%	€ 281 (522)	100%
Mental healthcare	€ 147 (1597)	6%	€ 263 (3392)	6%	€ 195 (1306)	6%	€ 204 (1380)	6%
Medication[c]	€ 9227 (6458)	100%	€ 8776 (5422)	100%	€ 6536 (4253)	100%	€ 6587 (4258)	100%
Medical devices	€ 678 (1395)	62%	€ 616 (1375)	51%	€ 664 (1640)	49%	€ 648 (1671)	47%
Healthcare abroad	€ 215 (1243)	10%	€ 59 (710)	4%	€ 74 (1128)	5%	€ 52 (1143)	4%
Transportation	€ 2237 (3504)	70%	€ 1041 (2307)	47%	€ 608 (1999)	26%	€ 343 (1099)	21%
Other	€ 220 (1808)	13%	€ 293 (2471)	12%	€ 256 (2969)	10%	€ 180 (2641)	11%
Total average annual costs	**€ 85 127 (39 679)**	**100%**	**€ 29 612 (34 099)**	**100%**	**€ 20 156 (26 571)**	**100%**	**€ 15 018 (16 186)**	**100%**

a. A 'year' refers to a calendar year. For example, when the transplantation has taken place in 2014, the first year after transplantation was 2015
b. Guidance are costs for the process before the transplantation
c. Medication is all medication distributed by pharmacy outside the hospital. Other types of costs, i.e. dialysis modality and hospitalization may also include medication costs. In the Netherlands, inpatient medication is part of the DRG and can therefore not be detected as a separate expenditure in claims data.

related costs were almost €22 000 higher in deceased donor kidney recipients. This was mostly due to higher dialysis and transplant surgery-related costs in recipients of a deceased donor kidney. On average, a transplant from a deceased donor resulted in higher costs in all healthcare components, except donor expenses, compared with receiving a transplant from a living donor. As a result, the total costs related to a deceased donor kidney transplant were substantially higher (€99 450 per year) compared with those of a transplant with a living donor kidney (€73 376).

Table 4.5: Total average annual costs of transplantation (year 0) by source of kidney donor (€).

	Deceased donor		**Living donor**		**Cost**	
	Mean (Std Dev)	% users	Mean (Std Dev)	% users	**difference**	
n	1275		1554			
Preparatory research	€ 578 (2254)	29.3%	€ 3083 (10 343)	58.0%	€ 2505	*
Transplant operation	€ 27 034 (12 083)	100.0%	€ 19 232 (9162)	100.0%	-€ 7802	*
Guidance	€ 256 (847)	10.9%	€ 652 (1329)	22.4%	€ 396	*
After care	€ 7485 (11 034)	73.3%	€ 6244 (8287)	75.4%	-€ 1241	
Donor expenses	€ 28 (254)	1.7%	€ 4725 (6663)	39.9%	€ 4697	*
Dialysis procedure (incl. access)	€ 39 223 (24 281)	94.0%	€ 18 828 (23 674)	56.8%	-€ 20 394	*
Total KRT costs	**€ 74 604 (28 121)**	**100.0%**	**€ 52 764 (29 889)**	**100.0%**	**-€ 21 839**	*****
Hospital (no KRT)	€ 10 571 (18 771)	97.6%	€ 8712 (16 672)	95.9%	-€ 1859	*
Primary care	€ 249 (352)	99.5%	€ 243 (307)	99.2%	-€ 6	
Mental healthcare	€ 210 (2122)	6.8%	€ 96 (972)	5.2%	-€ 114	
Medication[a]	€ 9442 (6143)	99.8%	€ 9051 (6703)	99.8%	-€ 391	*
Medical devices	€ 743 (1376)	69.6%	€ 625 (1409)	55.5%	-€ 118	*
Healthcare abroad	€ 317 (1578)	10.6%	€ 131 (868)	9.3%	-€ 186	
Transportation	€ 3001 (3934)	76.4%	€ 1611 (2966)	63.9%	-€ 1390	*
Other	€ 313 (2092)	14.4%	€ 144 (1533)	11.6%	-€ 169	*
Total average annual costs	**€ 99 450 (36 036)**	**100.0%**	**€ 73 376 (38 666)**	**100.0%**	**-€ 26 074**	*****

*Significance at P<0.05 two-sided.
a. Medication is all medication disctributed by the pharmacy outside the hospital. Other types of costs, i.e. dialysis modality and hospitalization may also include medication costs. In the Netherlands, inpatient medication is part of the DRG and can therefore not be detected as a separate expenditure in claims data.

Discussion

Our study using health insurance claims showed high expenses for all dialysis modalities, with annual expenditure ranging between €77 566 for CAPD to €92 616 for CHD and €105 833 for patients of the Mix group. The vast majority of total healthcare expenses was related to KRT. Patients who dialyzed more frequently had higher overall expenditure because higher KRT related costs were not compensated by lower non-KRT related costs. In the year of kidney transplantation, patients had expenses similar to those on dialysis, but expenses declined steadily in the years post-transplant to €15 018 in the second year for those with a surviving graft after transplantation. Our study found substantial higher expenditure for those who received a kidney from a deceased donor compared with a living donor.

The fact that dialysis treatment is expensive confirms findings of both older[123] and more recent[63,124–128] studies. Our study also confirms that expenses for CAPD are the lowest among the dialysis modalities.[131,132] Our study does not confirm observations from small cohort studies showing that hemodialysis patients who dialyze more frequently have lower overall costs.[133–135] The higher KRT related costs of patients who dialyze ≥4 times/week appeared not to be compensated by lower expenses for other healthcare use. Here, we cannot exclude the possibility that selection bias plays a role, with patients in more severe condition qualifying for more intensive dialysis, leaving open the option that their costs would have been higher should they have received regular dialysis three times per week. As our study only concerns costs, and not health outcomes (more intensive dialysis is reflected in better patient outcomes, such as mortality and physical health[136], a separate cost-effectiveness analysis comparing more and less intensive dialysis treatment would be needed to find out whether additional costs are balanced by better outcomes. Such a cost-effectiveness analysis should be undertaken from a societal perspective, to include types of costs that we currently could not address, such as out-of-pocket costs of patients and productivity costs related to the patients' ability to maintain employment.

Expenses for patients of the Mixed group were remarkably higher in many categories of healthcare use, such as access procedures and medication. In particular, non-KRT related hospital care expenditure in this group was higher than in patients stable on one dialysis modality. This suggests that the switch between dialysis modalities may not only be rooted in therapy failure itself, but also in the occurrence of other diseases that prevent continuation of the initial modality and that are associated with higher non-KRT costs in itself. Indeed, a study from the US[137] showed infections

and cardiovascular diseases, mainly fluid overload, to be the most important causes of a switch from peritoneal dialysis to hemodialysis. Also, patient characteristics such as higher BMI and having diabetes were found to be associated with a switch between dialysis modalities. We only had access to a few background characteristics of patients, such as age, sex, and the number of comorbidities. Patients switching between modalities were somewhat younger than most other dialysis groups, except HHD, but had a similar number of comorbidities. Patient groups may have also differed with regard to other, non-measured, predictors of switching between modalities.

Our study shows a clear cost advantage of transplantation using living donor kidneys compared with deceased donor kidneys, despite additional health expenses for the donor. There was a large difference in dialysis costs, i.e. the dialysis costs were higher for the group who received a kidney from a deceased donor. This is likely related to a substantial proportion of living donor kidney procedures being pre-emptive in the Netherlands. Indeed, 33% of patients receiving a graft from a living donor did not receive dialysis at all during the year of transplantation. Other factors possibly related to lower expenses for those who receive a living donor kidney are better survival[138,139] and fewer post-operative complications. The latter was confirmed in a recent Japanese study also using health claims data. This study showed longer hospitalization and more urinary tract infections, sepsis, and pneumonia in recipients of post-mortal donor kidneys.[66] One further explanation for higher overall costs in patients receiving a deceased kidney organ is the more frequent occurrence of delayed graft function, associated with the need for short-term post-transplant dialysis.[140]

Annual costs decline fast in the first and second years after transplantation, with medication costs being the highest (30%–32% of total cost) component of expenses. These figures include those for non-successful transplantation (n = 105), hence for patients with graft failure who had to return to dialysis and patients who died. Combined with the cost advantages of pre-emptive transplantation as discussed above and the ongoing shortage of deceased donor organs, this stresses the importance of discussing and exploring the possibility of a living donor transplantation in pre-dialysis patients. Recently, the Dutch Parliament accepted a change from opting-in for transplantation after death to an opt-out system, which is expected to increase the number of deceased donor transplantations in the future. Given the small cost differences between pre-emptive transplantation and deceased donor transplantation, relative to the large cost-differences between any transplantation and dialysis, every transplantation is expected to contribute to a decrease in costs of KRT.

Following from the source of the data, being insurance claims, we have to face several limitations of our data. First, we have no guarantees that all transplantation-related costs of living donors were registered on the ID of the recipient, with the possible consequence of underestimating the costs of living donors. Second, the donor costs of deceased donors are not at all part of the claims data, as these are reimbursed outside the basic health insurance. Moreover, societal costs (e.g. incapability to work) and out-of-pocket costs were not part of this study, whereas the limited time frame of two post-transplant years prevents us from predicting cost levels of former transplantation patients in later years. However, as annual costs decline fast after transplantation and are lowest in those without graft failure, there is no reason to expect that the cost difference between dialysis and having a functioning transplant kidney will fade out in later years.

One general limitation to studying costs in terms of expenditure is that expenditure is only to be seen as an administrative proxy for real costs, implying that it is unknown whether these costs reflect "true" resource use (both staff and material resources) needed to provide healthcare to these patients. Another important limitation is that we have not related observed differences in expenditure between modalities to differences in patient characteristics, as we only had limited information on the background characteristics of patients. A previous study on dialysis patients shows that age is associated with expenditures where elderly dialysis patients often have lower healthcare costs than younger dialysis patients.[141] This knowledge is important when interpreting the results of our study, where patients in the CHD and CAPD groups were somewhat older than in other dialysis groups. At least, the number of comorbid diseases was similar across groups. Other important characteristics, such as frailty, were not known to us. Summing up, it is likely that differences in expenditures between modalities are related to (non-)observed differences in patient characteristics and not due to modality characteristics per se. We feel however that in this specific study it is not the statistical significance of cost differences between groups that is of primary interest, but more the actual differences in expenses, as these are meaningful for health insurers and health policymakers.

Strengths of our study include the national coverage (>99% of the population) of our data, the inclusion of all KRT modalities, the inclusion of all healthcare use covered by the Health Insurance Act and not only the part that is related to KRT, the good validation of the data with another national database of KRT patients, and data coverage over a three-year period. We used a rigorous approach of classifying

patients into one of five dialysis groups and two different transplantation groups and excluded all patients with erroneous or temporary KRT claims, as well as patients for whom we had diverging information, e.g. with regard to the weekly number of dialysis procedures. For the included patients we have high levels of confidence that expenditure figures can be attributed correctly to the dialysis modality. Furthermore, as a consequence of our assignment of patients to different treatment groups, we were able to show a clear picture of cost differences between stable patients using different dialysis modalities. Because we present cost data also for periods of 4-weeks, we could show that incident and deceased patients have much higher non-KRT related costs than patients who are stable on one dialysis modality.

Our data stress the fact that CAPD has a clear cost advantage compared with other home-based therapy and CHD. Starting as many patients as possible on CAPD could reduce the high budget impact of KRT to a certain extent. Approximately 1750 patients start dialysis treatment annually in the Netherlands, of whom 20% start PD (CAPD and APD aggregated).[120] It is clear that not all patients are suitable candidates to start with PD, and that a mismatch between the requirements of the dialysis modality and the patient's capacity may have detrimental effects, both on costs and outcomes. However, historically, much higher numbers have started with peritoneal dialysis in the Netherlands, and even today, center differences in patients starting with PD range from 1% to 46%. This leaves us to conclude that advantages of several million euros annually could be reached if a start on PD would be considered more often. Obviously, careful pre-dialysis education followed by shared decision-making should ensure that only patients who are fit for PD are selected to start with this modality. Furthermore, recent research suggested that the utmost should be done to prevent the progression of kidney diseases to kidney failure, and that prevention holds the promise of spending fewer healthcare resources on KRT.[69,141,142]

We conclude that annual healthcare expenditures of KRT patients are high while showing relevant differences between dialysis modalities at the same time. Frequent hemodialysis patients have higher KRT-related expenditure compared with patients with regular dialysis frequency with similar non-KRT costs. Dialysis patients of the Mix group have the highest annual expenditure, in particular in the KRT unrelated costs. Annual healthcare costs in the year of transplantation are high but decline fast in the years after transplantation. Living donor kidney transplantation incurs lower costs compared with transplantation with a deceased donor kidney. Therefore, our results indicate that the current practice in the Netherlands, where (pre-emptive)

living donor procedures are actively encouraged by nephrologists, is associated with cost advantages in both the short and longer term. At the same time, the budget impact of KRT could be diminished to a certain extent when more patients would start treatment with home-based therapies, especially CAPD.

5

Age-related difference in healthcare use and costs of patients with chronic kidney disease and matched controls: analysis of Dutch healthcare claims data

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Abstract

Background The financial burden of chronic kidney disease (CKD) is increasing due to the aging population and increased prevalence of comorbid diseases. Our aim was to evaluate age-related differences in healthcare use and costs in Stage G4-G5 CKD without kidney replacement therapy (KRT), dialysis, and kidney transplant patients and compare them with the general population.

Methods Using Dutch healthcare claims, we identified CKD patients and divided them into three groups: CKD Stage G4-G5 without KRT, dialysis, and kidney transplantation. We matched them with two controls per patient. Total healthcare costs and hospital costs unrelated to CKD treatment are presented in four age categories (19–44, 45–64, 65–74, and ≥75 years).

Results Overall, healthcare costs of CKD patients ≥75 years of age were lower than costs of patients 65–74 years of age. In dialysis patients, costs were highest in patients 45–64 years of age. Since costs of controls increased gradually with age, the cost ratio of patients versus controls was highest in young patients (19–44 years). CKD patients were in greater need of additional specialist care than the general population, which was already evident in young patients.

Conclusion Already at a young age and in the earlier stages of CKD, patients are in need of additional care with corresponding healthcare costs far exceeding those of the general population. In contrast to the general population, the oldest patients (≥75 years) of all CKD patient groups have lower costs than patients 65–74 years of age, which is largely explained by lower hospital and medication costs.

Introduction

Patients with chronic kidney disease (CKD), including those needing kidney replacement therapy (KRT), contribute significantly to healthcare expenditures.[70,122,123,142,143] The prevalence of CKD is increasing as a result of both population aging and the increasing prevalence of diseases like hypertension and diabetes mellitus. Therefore the financial burden for society is also likely to increase substantially.[131,144,145]

Important factors affecting the high healthcare costs of patients with CKD include specific kidney treatment costs and the fact that a significant number of patients need additional care for their CKD-related comorbid conditions.[146] Nevertheless, it is largely unknown how many patients need additional care and for which diagnosis this additional care is needed. Since studies have shown that the prevalence of comorbidities in young patients is lower than in the elderly and that the burden of comorbidities in CKD patients increases with age, attention has mainly been drawn to the clinical management of elderly CKD patients. However, the impact of age on healthcare use and costs of CKD-related comorbidities has rarely been studied.[90,147]

Better knowledge of the age-related differences in healthcare use and costs leads to a better understanding of the impact of comorbidities on CKD patients in different age categories and will potentially lead to improved, age-specific, clinical management of CKD patients. Furthermore, a comparison with care delivered to individuals of similar age in the general population is needed to gain insights into the extra care provided to CKD patients and the additional costs. Therefore the aim of this study was to assess the age-related differences in healthcare use and costs of patients with advanced CKD (Stage G4-G5) without KRT, on dialysis and kidney transplant patients, and to compare the results with the general population.

Methods

Data

To identify kidney patients and to study healthcare costs, we used Dutch healthcare claims from 2016. These claims are related to all healthcare procedures covered by the Health Insurance Act, including the costs of compulsory co-payments.[30] The Vektis database contains healthcare claims and demographic data from all health insurance companies in the Netherlands. The database covers 99% of all insured residents, and since healthcare insurance is obligatory in the Netherlands, almost all Dutch residents are insured (99%).

Demographic data include the year of birth, sex, postal code, and date of death, if applicable. A person's socio-economic status (SES) was determined by the Netherlands Institute for Social Research and was based on a person's postal code.[31] The SES score is a reflection of the mean income, education, and position in the labour market of people living in a postal code area. The mean SES score has been set at 0 and ranges from −6.75 to 3.06; lower scores indicating a lower SES and higher scores indicating a higher SES. To ensure privacy, Vektis pseudonymized the persons' national identification number and allowed data access only in a secured environment.

Study population

We selected adult patients (i.e. ≥20 years of age) with advanced CKD [Stage G4 with an estimated glomerular filtration rate (eGFR) of 15–29 mL/min/1.73 m^2 and Stage G5 with an eGFR ≤15 mL/min/1.73 m^2] with or without KRT using healthcare claims in the year 2016 and who were alive and insured during the whole year. Patients with incomplete data on year of birth or sex were excluded from the analysis. Patients were divided into four age categories: young (20–44 years), middle-aged (45–64 years), elderly (65–74 years), and ≥75 years of age.

CKD patients were divided into three groups: CKD Stage G4-G5 patients without KRT, CKD patients with dialysis treatment, and CKD patients with a kidney transplantation. A detailed list of all diagnosis-related groups (DRGs) used for allocation to groups is provided in an online supplementary file.

CKD Stage G4-G5 We selected patients with CKD Stage G4-G5 not treated with KRT. In the Netherlands, DRGs are based on healthcare claims of specialist care delivered in the hospital. Primary care has no comparable disease-specific healthcare claims. Hence we were unable to identify patients with CKD Stage G4-G5 treated solely in primary care. Patients with health claims for dialysis or kidney transplantation and those who died in the same year were excluded from this group.

Dialysis We selected CKD patients who were on dialysis treatment in 2016 for the entire year regardless of their dialysis modality. Patients who started dialysis, received a kidney transplant or died in 2016 were excluded. Analyses were performed for the whole dialysis group and separately for hemodialysis and peritoneal dialysis.

Kidney transplantation We selected CKD patients with a health claim for a new kidney transplantation or for follow-up care after a kidney transplantation during 2016. We excluded transplant patients who started dialysis or died in 2016.

Controls For every patient in each patient group, we randomly selected two controls, matched for age, sex, and SES score (four groups based on quartiles). Controls were randomly selected out of the entire Vektis database, provided they had no healthcare claim for CKD. In both cases and controls, patients of ≥90 years of age were clustered.

Cost variables

The Vektis data contain DRG claims related to the use of healthcare resources. As DRG claims are based on negotiated administrative prices for high-level groups of diagnoses, the expenses are an approximation of the real costs. For ease of reference, we will refer to these expenses as 'costs'. Costs were expressed per calendar year. The total annual costs consisted of all costs reimbursed through health insurance in a year.

Total healthcare costs encompassed costs of primary care, specialist care delivered in the hospital (inpatient and outpatient), mental health care, prescription medication (excluding medication administered in a hospital and during dialysis treatment, as these are covered by the respective hospital DRGs), transportation and other costs. It should be noted that, in the Netherlands, some prescribed drugs need (co-)payment by the patient. A patient's costs for drugs not covered by the healthcare system (including over-the-counter drugs) are not included in the health claims database and are therefore not covered in our study. Hospital costs are based on DRG claims: the reimbursement of a DRG is a negotiated price covering all costs related to the diagnosis and treatment, including, for example, all laboratory assessments and other diagnostics (e.g. chest X-ray, echocardiographs, or electrocardiograms).

Hospital costs related to CKD included the costs of all DRG claims for nephrological inpatient and outpatient care, costs of dialysis (including access surgery and maintenance), and the costs of kidney transplant care (including the costs for transplant surgery). Moreover, these DRGs encompassed costs for hospital admission related to CKD, medication administered in the hospital and during dialysis treatment, staff costs (such as physician fees), and diagnostic procedures related to CKD.

Hospital costs unrelated to CKD were all other inpatient and outpatient DRG costs. Since DRGs are categorized by medical specialty, we were able to categorize hospital costs into the costs related to consultation of internists, cardiologists, dermatologists, and surgeons, as these four medical specialties are of special importance to CKD patients. In the Netherlands, specialist consultation is carried out in a hospital (inpatient and outpatient care) and therefore all specialist care costs were included in this study. Costs were estimated by calculating the average costs of all DRG claims

assigned to the specified medical specialties. Within the groups of specialist care, we analyzed the most frequently claimed DRG codes per year.

Statistical analysis

We used descriptive statistics to examine the characteristics of the patient groups and their matched controls in four age categories. The average annual costs are presented as mean per person with 25th and 75th percentiles. We used percentiles instead of standard deviations, as these better represent the distribution of the data. Cost ratios were calculated by dividing the mean healthcare costs of patients by the mean costs of matched controls. Moreover, we calculated the percentage of users per group that incurred costs for care in that specific cost category. Statistical analyses were performed using SAS, version 9.4 (SAS Institute, Cary, NC, USA).

Results

Baseline characteristics

We identified 18 340 patients with CKD Stage G4-G5 not on KRT, 4474 dialysis patients, and 9260 patients with a functioning kidney transplant (Table 5.1). Eight percent of these transplant patients were in the first year of transplantation, leaving 92% of patients who were in later years after a successful transplantation. Of CKD Stage G4-G5 patients not on KRT, 2% were categorized as young, 14% as middle-aged, 26% as elderly, and 59% as ≥75 years. In dialysis patients, these were 7%, 26%, 26%, and 41% and in transplant patients 21%, 48%, 25%, and 6%, respectively. In all age groups, more than half of the patients were men. The median SES scores were similar. The matching was successful with respect to age and sex (Table 5.1).

Total healthcare costs

Average annual costs and cost ratios Figure 5.1 shows average annual costs for all three patient groups per age category and the cost ratios between patients and their controls. Total healthcare costs of dialysis patients were higher than those of CKD Stage G4-G5 or transplant patients (Figure 5.1). Overall, the costs of patients ≥75 years of age were lower than the costs of patients 65–74 years of age, the age category with the highest costs. In dialysis patients, costs were highest in middle-aged patients. Costs for patients on peritoneal dialysis were lower than for hemodialysis patients in all age groups (see online supplementary file).

Young CKD Stage G4-G5 patients had 7.6 times higher costs than controls, whereas costs were 2.2 times higher in patients ≥75 years of age (Figure 5.1). Young dialysis patients had 69.1 times higher costs than controls and this cost ratio decreased to 15.9 in the oldest patients. Costs of young transplant patients were 12.4 times higher than controls, decreasing to 3.4 in patients ≥75 years of age.

Costs per segment of healthcare Total healthcare costs can be differentiated into six main segments of healthcare [i.e. primary care, specialist care delivered in the hospital (inpatient and outpatient), mental health care, prescription medication, transportation, and other costs] (see online supplementary file). Young CKD patients had 9.9 times higher medication costs than controls, which decreased to 2.7 in patients ≥75 years of age. Medication costs of young dialysis patients were 56.2 times higher than those of controls and decreased to 49 in patients ≥75 years of age. In transplantation patients, medications costs were 43.0 times higher in young patients and 6.6 times higher in the oldest patients compared with controls.

Hospital costs related to the treatment of CKD

Average annual costs Approximately 80% of total healthcare costs of dialysis patients were related to kidney treatment, and this was ~10% for CKD Stage G4-G5 and roughly 20% for transplantation (see online supplementary file). Costs for CKD Stage G4-G5 patients ranged from €1045 in patients ≥75 years of age to €1191 in middle-aged patients. In both dialysis and transplant patients, costs were highest in young patients (€70 682 and €5223, respectively) and lowest in patients ≥75 years of age (€66 306 and €3 838, respectively).

Hospital costs unrelated to the treatment of CKD

Average annual costs and cost ratios Hospital costs unrelated to kidney treatment in dialysis patients were higher than those in controls, in particular in middle-aged dialysis patients (€10 989 versus €1272) (Figure 5.2). At 13.0, the cost ratio was highest in young dialysis patients, declining to 2.6 in patients ≥75 years of age. Costs for peritoneal dialysis patients were lower than costs for hemodialysis patients in all age groups (see online supplementary file). The decrease in cost ratios with age was similar for both dialysis modalities. Also in CKD Stage G4-G5 and transplant patients, these costs were markedly higher than those in controls, and the cost ratios, again, showed that this is especially true at a younger age. In CKD Stage G4-G5 patients, cost ratios decreased with age from 8.1 to 2.1, comparable to transplant patients, in whom cost ratios declined from 7.1 to 2.5.

Table 5.1: Baseline characteristics of CKD Stage G4-G5 not on KRT, dialysis, and kidney transplant patients and matched controls by age category.

	CKD Stage G4-G5		Dialysis		Kidney transplantation	
Age group	**Patients**	**Controls**	**Patients**	**Controls**	**Patients**	**Controls**
Age 20–44 years						
n (%)	388 (2)	776 (2)	315 (7)	630 (7)	1908 (21)	3816 (21)
Age (years), median (25th–75th percentile)	38 (32–42)	38 (32–42)	37 (31–41)	37 (31–41)	37 (30–41)	37 (30–41)
Sex (male), %	54	54	59	59	60	60
SES score, median (25th–75th percentile)	−0.3 (−1.2–0.4)	−0.2 (−1.1–0.4)	−0.6 (−1.3–0.4)	−0.4 (−1.4–0.4)	−0.2 (−1.2–0.5)	−0.2 (−1.2–0.5)
Age 45–64 years						
n (%)	2502 (14)	5004 (14)	1163 (26)	2326 (26)	4489 (48)	8978 (48)
Age (years), median (25th–75th percentile)	59 (54–62)	59 (54–62)	57 (52–61)	57 (52–61)	55 (51–60)	55 (51–60)
Sex (male), %	52	52	59	59	60	60
SES score, median (25th–75th percentile)	−0.2 (−1.1–0.5)	−0.2 (−1.1–0.5)	−0.4 (−1.4–0.3)	−0.4 (−1.3–0.3)	−0.1 (−1.0–0.6)	−0.1 (−1.0–0.6)
Age 65–74 years						
n (%)	4705 (26)	9410 (26)	1166 (26)	2332 (26)	2267 (24)	4534 (24)
Age (years), median (25th–75th percentile)	70 (68–72)	70 (68–72)	70 (68–72)	70 (68–72)	69 (67–71)	69 (67–71)
Sex (male), %	58	58	58	58	60	60
SES score, median (25th–75th percentile)	−0.2 (−1.0–0.5)	−0.2 (−1.0–0.5)	−0.4 (−1.3–0.4)	−0.4 (−1.3–0.4)	−0.1 (−1.0–0.6)	−0.1 (−0.9–0.6)
Age ≥75 years						
n (%)	10 745 (59)	21 490 (59)	1830 (41)	3660 (41)	598 (6)	1196 (6)
Age (years), median (25th–75th percentile)	82 (78–86)	82 (78–86)	81 (78–84)	81 (78–84)	77 (76–79)	77 (76–79)
Sex (male), %	53	53	58	58	60	60
SES score, median (25th–75th percentile)	−0.2 (−1.0–0.4)	−0.2 (−1.0–0.5)	−0.2 (−1.1–0.4)	−0.2 (−1.1–0.4)	−0.1 (−1.0–0.5)	−0.1 (−1.0–0.5)

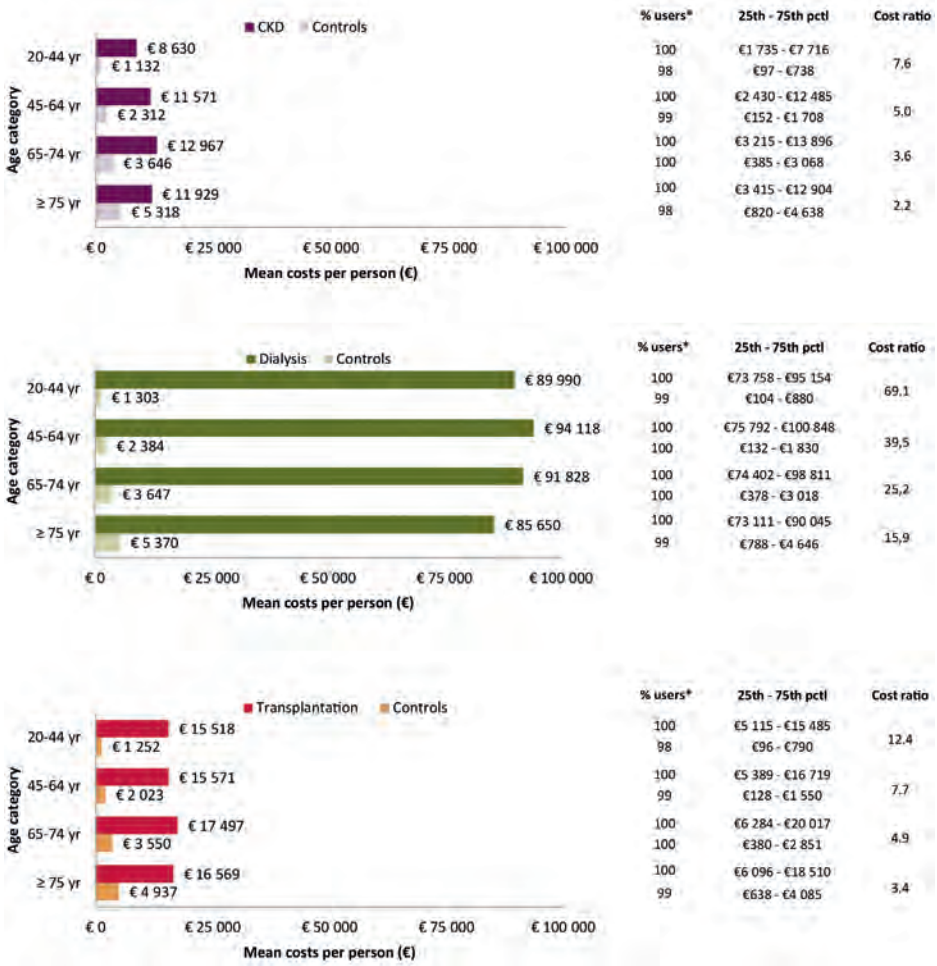

Figure 5.1: Total annual healthcare costs of CKD Stage G4-G5 not on KRT, dialysis, and kidney transplant patients versus matched controls.

*Denotes the percentage of users per group that incurred costs for care in that specific cost category.

Percentage healthcare users In CKD Stage G4-G5 patients, as well as in transplant recipients, hospital costs unrelated to the treatment of CKD were already substantial at a young age (€4020 and €4181, respectively) (Figure 5.2). More than 70% of these young patients used this care compared with only 30% of young controls. In CKD Stage G4-G5 patients ≥75 years of age, 89% used hospital care unrelated to the treatment of CKD, and 92% of transplant patients ≥75 years of age used hospital care unrelated to treatment compared with ~70% of controls. Remarkably, 88% of young dialysis patients needed additional hospital care versus 31% of controls. This increased to 93% in the oldest dialysis patients compared with 73% of controls.

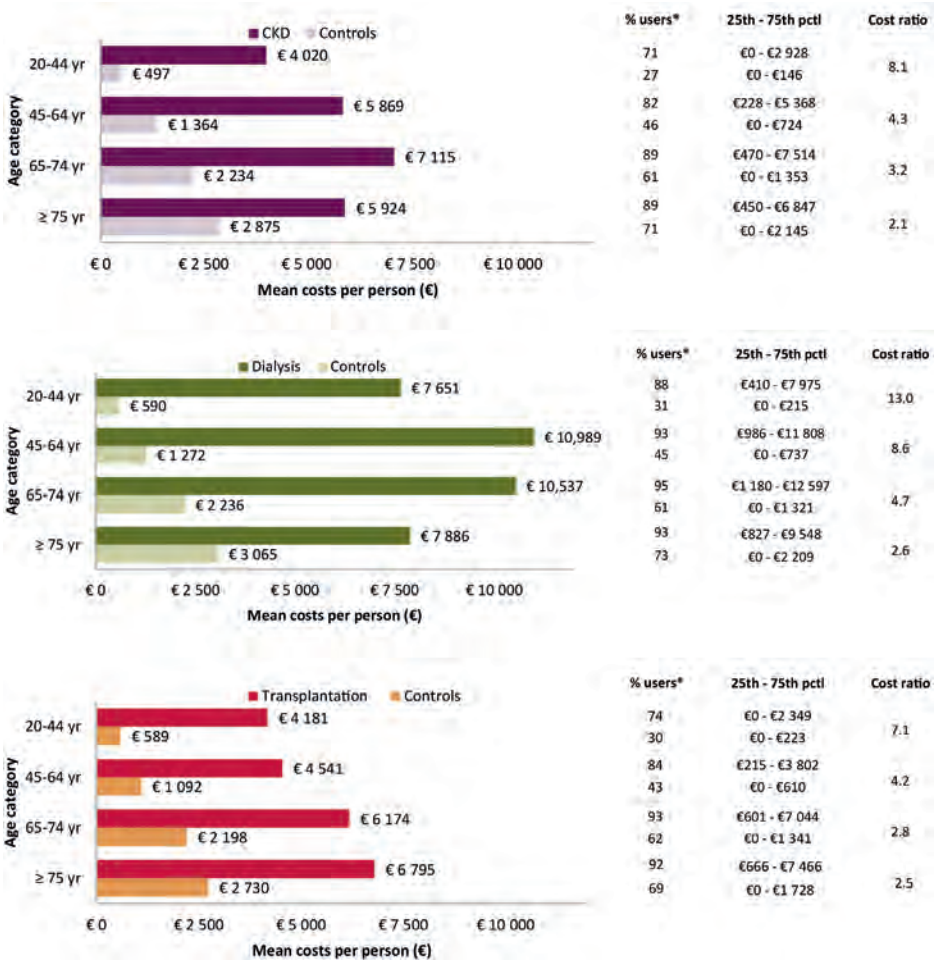

Figure 5.2: Hospital costs unrelated to the treatment of CKD Stage G4-G5 not on KRT, dialysis, and kidney transplant patients versus hospital costs of matched controls.

*Denotes the percentage of users per group that incurred costs for care in that specific cost category.

Annual healthcare costs and healthcare utilization per medical specialty

Figures 5.3a and 5.3b and the online supplementary file, show that CKD Stage G4-G5, dialysis, and kidney transplant patients had 1.5–93.4 times higher costs related to care of internal medicine, cardiologists, dermatologists, and surgeons. In all categories, cost ratios were high in young patients and decreased with age.

Internal medicine Almost 40% of all CKD Stage G4-G5 patients needed internal medicine care (Figure 5.3a). In young dialysis patients, 43% received internal medicine

care, increasing to ~50% in elderly patients. In dialysis patients ≥75 years of age, this was 44%. This proportion was 27% in young transplant patients and increased with age. Regardless of age, most resources were spent on care related to diabetes mellitus and infectious diseases (i.e. sepsis/bacteremia and pneumonia) (see online supplementary file). In controls, diabetes mellitus–related care was also the major part of internal medicine care. In addition, the majority of claims in the elderly controls were related to oncology care (breast cancer).

Cardiology A total of 43% of young dialysis patients needed cardiology care compared with 2% of controls (Figure 5.3b). This increased to 54% and 58% in middle-aged and elderly patients, respectively, compared with 8% and 16% in controls, respectively. With 15% and 11% use of cardiology care in young CKD Stage G4-G5 and transplantation patients, respectively, this was substantially higher than controls (2%). Almost half of all CKD Stage G4-G5 patients ≥75 years of age visited a cardiologist at least once a year.

Cardiology claims in patients were mostly related to ischemia-related disorders (i.e. angina pectoris, acute coronary syndrome, or follow-up after coronary angioplasty or coronary artery bypass graft), whereas in controls the majority of cardiology care was assigned to ischemia-related disorders and cardiac arrhythmia disorders (see online supplementary file).

Dermatology Almost one-quarter of young and more than half of transplant recipients ≥75 years of age used dermatology resources, compared with 4% and 13% of controls, respectively (see online supplementary file). In CKD Stage G4-G5 and dialysis patients, this ranged from 7% to 25%. In all patients, the treatment of malignant and premalignant skin lesions was the most common reason for dermatological care; 38% of elderly transplant patients and 45% of transplant patients ≥75 years of age needed dermatological care for these reasons, compared with only 6% and 10% of controls, respectively.

Surgery Twenty-nine percent of young dialysis patients and 40% of elderly patients needed surgical care versus 5% and 12% of controls, respectively (see online supplementary file). In the oldest dialysis patients, this was 35%. For both CKD Stage G4-G5 and transplant patients, surgery costs were lower for patients ≥75 years of age than for patients 65–74 years of age.

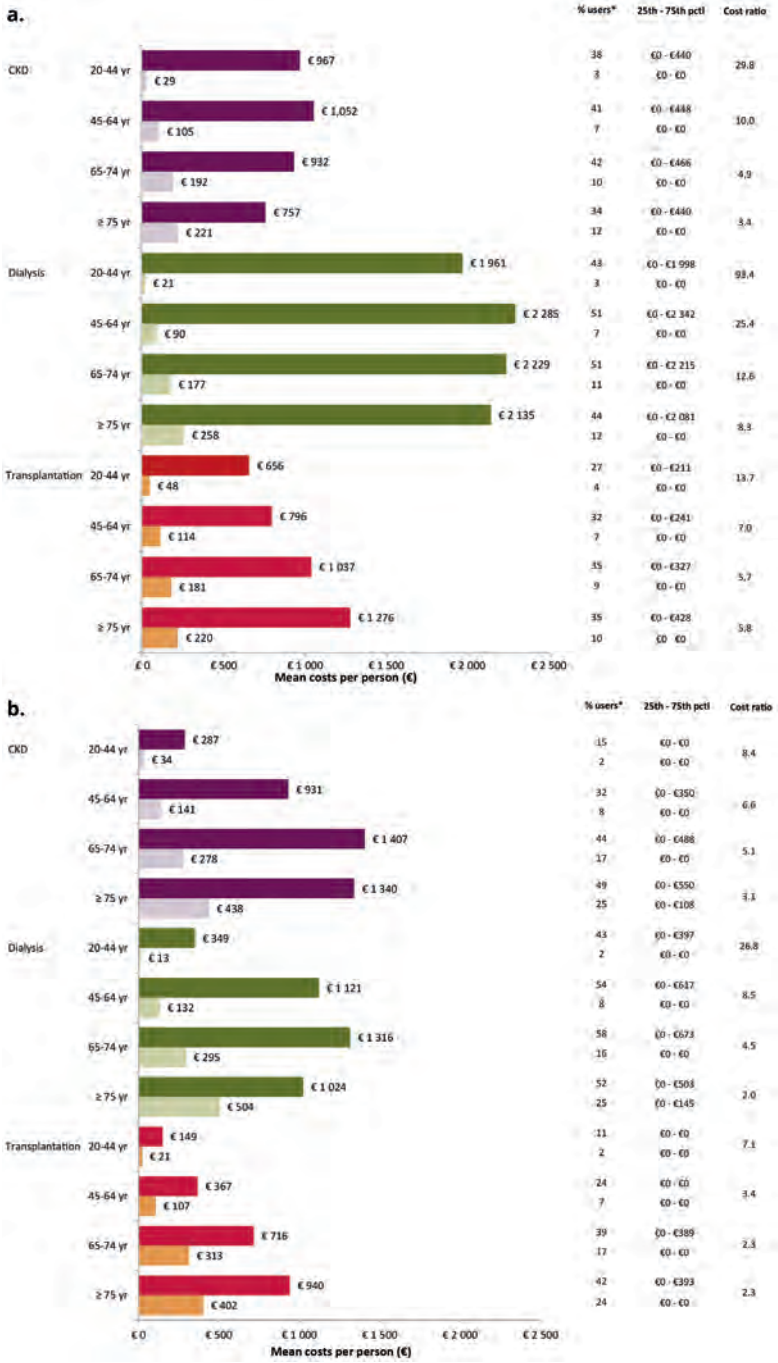

Figure 5.3. Annual health care costs of CKD Stage G4-G5 not on KRT, dialysis, and kidney transplant patients per medical specialty versus matched controls; **(a)** Internal medicine **(b)** Cardiology.

*Denotes the percentage of users per group that incurred costs for care in that specific cost category.

In general, surgical care was mainly related to vascular disorders like peripheral arterial occlusive disease, ischaemic ulcers, and diabetic foot ulcers (see online supplementary file). Approximately 8% of elderly dialysis patients needed surgical care for peripheral arterial occlusive disease, more than elderly CKD Stage G4-G5 patients (5%) or elderly transplant patients (3%). Surgical care in controls was related to a wider variety of conditions, such as malignancies (breast cancer), abdominal aortic aneurysm, or inguinal or femoral hernia.

Discussion

In this study, we describe for the first time the age-related differences in healthcare costs and healthcare use in CKD Stage G4-G5 not on KRT, dialysis, and kidney transplant patients compared with matched controls from the general Dutch population.

As is already known, KRT is expensive; in our study, annual treatment-related costs for CKD patients ranged from €1045 in CKD Stage G4-G5 patients ≥75 years of age to €70 682 in young dialysis patients. However, the additional hospital costs unrelated to CKD treatment ranged from €4020 (young CKD Stage G4-G5 patients) to €10 989 (middle-aged dialysis patients), whereas these hospital costs in the control population ranged from €497 to €3065.

Regarding age differences, in controls, healthcare costs increased gradually with age. This contrasts with our three patient groups, where costs were often equivalent in different age categories, or young and middle-aged patients were more costly than elderly patients. Of note, costs for CKD Stage G4-G5 and dialysis patients ≥75 years of age were lower than for patients 65–74 years of age. We further demonstrated that young patients, in particular, incur considerably higher costs than controls, which is reflected by the decreasing cost ratios with age. Furthermore, we showed that kidney patients were in greater need of additional specialist care because of kidney disease-related comorbidities. Although it is known that the burden of comorbidities is higher in elderly CKD patients, this study shows that costs related to comorbid illness in young patients are similar to that of elderly patients.

Age-related difference of healthcare costs in CKD patients

We demonstrated that healthcare costs for kidney patients did not differ as much with age as in the general population. Several studies have shown rising healthcare costs with age in the general population,[148–150] whereas studies in CKD and KRT patients have

shown no consistent effect of age on healthcare costs.[63,126,127] An interesting finding in our study is that the annual healthcare costs of CKD Stage G4-G5 and dialysis patients ≥75 years of age were lower than for patients 65–74 years of age. This is mainly driven by a decrease in hospital and medication costs with age. An explanation for this observation can possibly be found in the fact that a nephrologist determines for every patient the need for a specific treatment or diagnostic procedure. This thoughtful weighing of harms and benefits may result in different outcomes in the geriatric patient, leading to more conservative treatment options and thus a lowering of total healthcare expenses.

Our study shows that a comparison of costs within the general population is essential to fully understand the additional costs of kidney patients in different age categories. Only two studies have presented costs of CKD and KRT patients compared with those of matched controls in the general population, and none of these took age into account. One study from the USA focusing on patients with CKD Stages G2–G4 found that the total healthcare costs of patients were twice as high compared with those of matched controls.[46] This study was based on aggregated cost data from 2001. Another paper compared costs of CKD Stage G4-G5 not on KRT, dialysis, and kidney transplant patients with matched controls using a population-based cohort in Sweden.[151] The study populations in that study are comparable to ours and the described mean annual costs of CKD, dialysis, and transplant patients are in line with our results. Although an analysis of different age categories is missing, the cost ratios of the Swedish study are similar to those in middle-aged patients in our study. Extremely high cost ratios in young patients were not described.

Costs and utilization of additional hospital care

In this study, we discriminated between treatment-related and non-treatment-related hospital costs. Non-treatment-related hospital costs are a good measure of patients' comorbidities since they reflect the additional hospital care needed apart from treatment of the kidney disease.[127,152] It is well-known that patients in different stages of CKD suffer from comorbidities with a significant financial impact.[146,153] In our study, ~80% of total hospital costs in CKD Stage G4-G5 patients were unrelated to specific kidney treatment. In transplant patients, this varied between 48% and 71% across age categories, whereas in dialysis patients only 10%–14% of hospital costs were unrelated to treatment. This effect is far more pronounced in young than in elderly kidney patients (all modalities). These results show that the majority of kidney patients need substantially more additional hospital care apart from their kidney treatment, reflecting a high prevalence of comorbidities already at a young age.

Specialized care for CKD-related comorbidities

Not only the costs of additional specialist care in kidney patients are higher than those in controls, but also the diagnoses underlying these costs are different. We showed that a significant number of kidney patients need cardiology care and this proportion increases with age. We also showed that cardiology resources of kidney patients are mainly directed to ischemia-related diseases, whereas controls from the general population are more often affected by cardiac arrhythmias. Regarding surgery, resources for patients turned out to be predominantly used in care related to vascular disorders, whereas healthcare use in controls is more often related to malignant diseases. These results confirm that kidney patients are frequently affected by cardiovascular complications, which are associated with higher costs.[152]

Previous research revealed that CKD patients with diabetes have higher costs.[63,127] This is in line with our study, which also shows that kidney patients have relatively high costs for internal medicine care, and most resources were spent on diabetes-related care. In addition, infectious disease-related care was shown to be frequent in kidney patients. In dermatology care, we observed that with age, transplant patients increasingly suffer from malignant and premalignant skin lesions. This is consistent with literature showing that not only elderly patients but also long-term survivors after kidney transplantation have a higher incidence of skin malignancies associated with the use of immunosuppressive drugs.[154]

Strengths and limitations

The main strength of our study is the use of a healthcare claims database with nationwide coverage. This enabled us to identify all CKD Stage G4-G5 not on KRT, dialysis, and kidney transplant patients in the Netherlands treated in the hospital with an insurance health claim. The database also provided a unique opportunity to select matched controls from the general population. The comprehensiveness of the cost data allowed for an analysis of healthcare costs beyond the direct kidney treatment costs.

A general limitation of studying costs with the use of healthcare claims data is that healthcare expenditures may not reflect the actual costs, since expenditures are actually negotiated prices between health insurance companies and caregivers. Another limitation is the accuracy of the identification of patients with the use of healthcare claims data. Although identification of patients on KRT was shown to be very accurate,[67] the identification of patients with advanced CKD using claims data is subject to underidentification, as we could only select patients actively treated

for CKD in a hospital (including outpatient clinics). As a consequence, CKD patients solely treated in primary care could not be identified with claims data. Next, the SES score used for the matching of patients with controls is based on a persons' postal code and may not reflect the true SES of the individual. Next, by excluding patients who died during the study year and patients starting dialysis treatment, we did not report end-of-life costs and costs related to the start of dialysis treatment. Finally, by including newly transplanted patients during the study year, as healthcare costs are given per calendar year in this database, this results in an inaccurate estimation of true transplantation procedure costs. However, the costs before transplantation still reflect the costs of a CKD patient preparing for transplantation therapy.

Conclusion

In conclusion, this study found that CKD Stage G4-G5 not on KRT, dialysis, and kidney transplant patients have notably higher healthcare costs than the general population. We show for the first time that, already at a young age, additional healthcare costs of CKD patients are significantly higher than the healthcare costs of people of the same age in the general population. Additionally, we demonstrate that non-treatment-related hospital costs of CKD Stage G4-G5 patients not on KRT are similar to those of transplant patients in all age groups, although markedly lower than in dialysis patients. This indicates that at a young age and in earlier stages of CKD, patients are in need of additional care far exceeding the needs of people in the general population. While total healthcare costs for the general population continue to increase with age, we observe a decrease in costs in all patient groups ≥75 years of age, which is largely explained by a decrease in hospital and medication costs.

This study provides insight into the specific diagnoses for which patients need additional hospital care. This knowledge of the specific use of hospital resources reveals that the consequences of the comorbidity burden in kidney patients are already present at a young age, which supports the importance of age-specific management of CKD patients aimed at prevention and early treatment of comorbid diseases.

Part 4

Medication prescription

6

Polypharmacy and medication use in patients with chronic kidney disease with and without kidney replacement therapy compared with matched controls

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Abstract

Background This study aims to examine polypharmacy prevalence in patients with CKD Stage G4-G5, and patients with kidney replacement therapy (KRT), in comparison with matched controls from the general population. Furthermore, we examine risk factors for polypharmacy and describe the most commonly dispensed medications.

Methods Dutch health claims data was used to identify three patient groups, i.e. CKD Stage G4-G5, dialysis, and kidney transplant patients. Each patient was matched to two controls based on matched for age, sex, and SES score. We differentiated between 'all medication use' and 'chronic medication use'. Polypharmacy was defined at three levels: use of ≥5 medications (polypharmacy, PP), ≥10 medications (excessive polypharmacy, EPP), and ≥15 medications (hyperpolypharmacy, HPP).

Results The PP prevalence for all medication use was 87%, 93%, and 95% in CKD Stage G4-G5, dialysis, and kidney transplant patients, respectively. For chronic medication use, this was 66%, 70%, and 75%, respectively. PP and comorbidity prevalence were higher in patients than in controls. EPP was 42 times more common in young CKD Stage G4-G5 patients (aged 20-44 years) than in controls, while this ratio was 3.8 in patients ≥75 years. Older age (65-74 years and ≥75 years) was a risk factor for polypharmacy in CKD Stage G4-G5 and kidney transplant patients. Dialysis patients aged ≥75 years had a lower risk of polypharmacy compared with their younger counterparts. Additional risk factors in all patients were low socioeconomic status, diabetes mellitus, vascular disease, hospitalization, and an emergency room visit. The most commonly dispensed medications were proton pump inhibitors (PPIs) and statins.

Conclusion CKD Stage G4-G5 patients and patients with KRT have a high medication burden, far beyond that of individuals from the general population, as a result of their kidney disease and large burden of comorbidities. A critical approach to medication prescription in general, and of specific medications like PPIs and statins (in the dialysis population), could be a first step towards a more appropriate medication use.

Introduction

Polypharmacy, defined as the concomitant use of medications by one individual, is a frequent phenomenon in clinical practice.[155,156] Older age and multimorbidity are associated with the growing polypharmacy prevalence.[156–158] Chronic kidney disease (CKD) patients have often a large burden of comorbidities and commonly require a multitude of medications in relation to their kidney disease, to prevent further progression of CKD, to treat its complications, and to treat comorbidities.[159] This makes polypharmacy a part of their life.[153,160,161] Polypharmacy puts patients at risk of medication-related problems, such as drug-drug interactions, suboptimal therapeutic response, a higher risk of adverse drug events, and decreased medication adherence.[159,162] Additionally, polypharmacy is associated with poorer quality of life, increased healthcare utilization with higher healthcare costs, and a higher risk of morbidity and mortality.[156,163,164] Whether the poor outcomes associated with polypharmacy are merely a reflection of a person's poor health remains unclear. Nevertheless, findings from previously published papers suggest an association between polypharmacy and mortality, also after adjustment for measured confounders such as comorbidities.[165]

The prevalence of polypharmacy varies across countries and stages of CKD.[153,160,161,163,166–170] Current studies mostly report on elderly patients, and only a few studies have used nationwide data and most studies lack comparison with the general population.[160,161,168] This study aims to examine polypharmacy in patients with CKD Stage G4-G5 and patients with kidney replacement therapy (KRT), in comparison to matched general population controls of similar age, sex, and socioeconomic status (SES), while making use of a national health insurance database encompassing the complete known Dutch kidney disease population. Furthermore, we aim to determine risk factors for polypharmacy and commonly dispensed medications.

Methods

Vektis insurance claims database

We used the Vektis database which includes virtually all Dutch citizens.[29] Vektis contains reimbursement data on all medical procedures covered by the Health Insurance Act and demographic data, such as sex, year of birth, area of residence, SES (see online supplementary file), and date of death.[30]

All hospital procedures in the Netherlands are reimbursed via physician claims named Diagnosis-Treatment Combinations (DBC).[38] Vektis also includes pharmacy dispensing data on Anatomical Therapeutic Chemical code level, the defined daily dose (DDD), and the quantity of supplied medication per year. A DDD is a technical unit that reflects the assumed average maintenance dose per day for a medication used for its main indication.[32] The annual quantity supplied of a specific medication is a product of the DDD and the number of days a medication was dispensed. Information on over-the-counter medications and medications administered during hospital admission or dialysis treatment are missing since the costs for the latter are covered by the hospital DBC. Since health claims databases lack clinical data, we used proxies (e.g. Pharmaceutical Cost Groups), to assess the prevalence and number of chronic conditions (see online supplementary file).[171,172] Hospitalization, intensive care unit (ICU) admission, and emergency room (ER) visits were identified by specific healthcare operation codes, an element of the DBC code (see online supplementary file).

Study population

We selected adults (i.e. ≥20 years) with CKD Stage G4-G5 or with KRT using 2017 healthcare claims data. Patients were divided into three patient groups; CKD Stage G4-G5 [estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2)] without KRT, dialysis patients, and kidney transplant patients. Patients were excluded if they switched between groups in 2017 (i.e. from CKD Stage G4-G5 to KRT and vice versa or between KRT modalities), if they died in 2017, or if matching was impossible (Figure 6.1).

CKD Stage G4-G5 without KRT We selected patients with a CKD Stage G4-G5 health claim on 1 January 2017. Since primary care does not have disease-specific claims comparable to DBCs, we could not identify patients solely treated in primary care.

Dialysis Patients with a health claim for dialysis on 1 January 2017 were selected regardless of dialysis modality.

Kidney transplantation Patients with a health claim for kidney transplantation on 1 January 2017 were selected.

Control groups Two controls per patient, matched for age, sex, and SES (per quartile) were selected, provided they had no CKD-related healthcare claim.

Polypharmacy

Medications with a cumulative annual DDD ≥15 (except for antibiotic treatment) and medications with a cumulative annual DDD ≥180 were selected. The first group (DDD ≥15), further indicated as 'all medication use', to prevent inclusion of medication dispensed for a very short period. The second cut-off (DDD ≥180) was to select 'chronic medication use'.

We defined polypharmacy at three levels: concurrent use of ≥5 medications (polypharmacy, PP), ≥10 medications (excessive polypharmacy, EPP), and ≥15 medications (hyperpolypharmacy, HPP). For combination medications, the individual substances could not be extracted and therefore were counted as one.

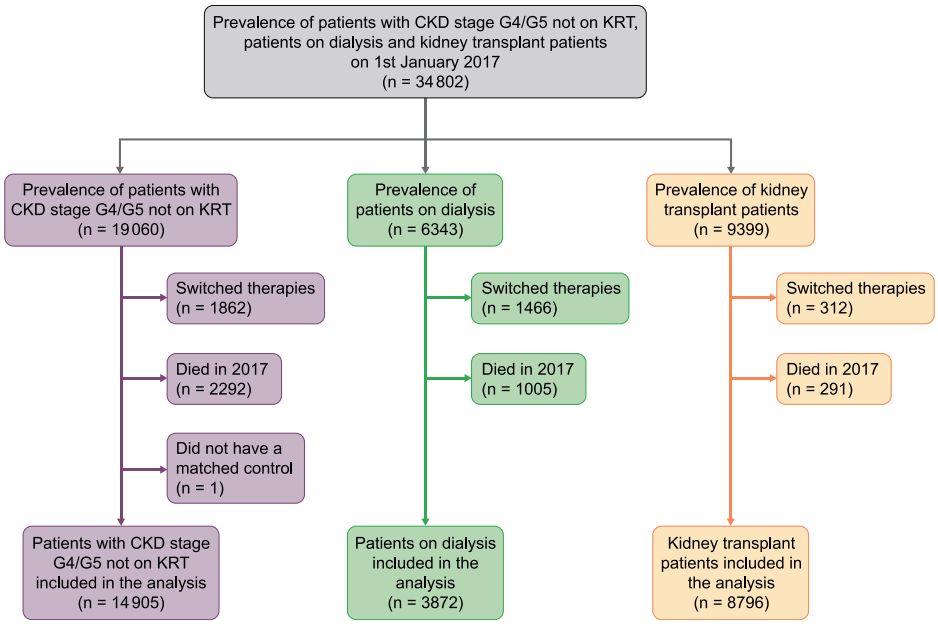

Figure 6.1: Flow chart study participants.

Statistical analysis

To describe baseline characteristics, we used means and standard deviation for continuous variables and frequency distributions with percentages for categorical variables. To compare baseline characteristics between patients and controls we used the chi-squared test for categorical variables and the Mann-Whitney *U*-test for not normally distributed continuous variables. We calculated the PP, EPP, and HPP prevalence in all patient (sub)groups and controls, and expressed them as

percentages. These analyses were repeated in a sensitivity analysis, also including all patients who died in 2017. Ratios were calculated by dividing the polypharmacy prevalence of patients by the respective prevalence in controls. Univariate and multivariate logistic regression was used to analyze the association between the independent variables [e.g. age, sex, diabetes mellitus (DM)] and the outcome (i.e. EPP based on chronic medication use). The EPP prevalence was low (i.e. ≤15%) and therefore the rare disease assumption for logistic regression was met.[173] For the identification of confounders we took the criteria for confounding into account.[174] Associations were expressed as odds ratios (ORs) with 95% confidence intervals (CIs). We considered a P-value <0.05 as statistically significant. Analyses were performed in SAS, version 9.4 (SAS Institute, Cary, NC, USA).

Results

Baseline characteristics

We included 27 573 individuals: 14 905 CKD Stage G4-G5 without KRT, 3872 dialysis, and 8796 transplant patients, with mean ages of 75.6, 70.8, and 56.5 years, respectively (Table 6.1). Chronic comorbidity conditions were 2.9 times more prevalent in CKD Stage G4-G5 patients than in controls (1.92 versus 0.68); 3.0 times higher in dialysis patients (1.86 versus 0.61), and 4.4 times higher in transplant patients (1.46 versus 0.33). In all patient groups, the prevalence of DM, macrovascular disease, and hypertension were significantly higher than in controls.

Number of dispensed medications

All medication use The median number of dispensed medications was 10 for CKD Stage G4-G5 patients, 12 for dialysis patients, and 11 for transplant patients compared with 1, 1, and 0 in controls, respectively (Figure 6.2).

Chronic medication use The median number of dispensed medications was six in all patient groups, compared with zero in controls (Figure 6.3).

Polypharmacy

Figure 6.4 presents the prevalence and ratio of polypharmacy in patients versus controls for 'all medication use' (left panel) and 'chronic medication use' (right panel). The results of the sensitivity analyses were consistent with the results of the main analyses (see online supplementary file).

Overall

All medication use The PP, EPP, and HPP prevalence was 87.4%, 56.6%, and 22.8%, respectively, in patients with CKD Stage G4-G5; 93.4%, 69.3%, and 31.5%, respectively, in dialysis patients; and 94.8%, 60.0%, and 21.5%, respectively, in transplant patients (Figure 6.4). For all comparisons, the PP, EPP, and HPP prevalence were much higher in patients than in controls, with ratios ranging from 2.6 (PP in CKD patients versus controls) to 23.9 (EPP in transplant patients versus controls).

Chronic medication use Overall, polypharmacy based on chronic medication use was less common than polypharmacy based on all medication use (Figure 6.4). The PP, EPP, and HPP prevalence was 66.1%, 13.3%, and 0.9%, respectively, in CKD Stage G4-G5 patients; 70.0%, 15.1%, and 1.2%, respectively, in dialysis patients; and 75.0%, 14.9%, and 1.0%, respectively, in transplant patients. Ratios ranged from 3.7 (PP in CKD patients) to 25.8 (EPP in transplant patients).

Patient subgroups

Tables 6.2 and 6.3 show the prevalence and ratio of polypharmacy in patients versus controls for different subgroups, for 'all' and 'chronic medication use'. Since the PP prevalence for 'all medication use' was very high and HPP prevalence for 'chronic medication use' was very low, these results are not shown.

All medication use In CKD Stage G4-G5 and in transplant patients, the EPP and HPP prevalences were highest in patients ≥75 years of age (CKD G4-G5: 60.0% and 24.4%; transplantation: 77.4% and 34.2%). EPP was 42.0 times more common in young CKD patients (aged 20-44 years) than in controls, and this ratio declined with age to 3.8 in patients ≥75 years (Table 6.2). Polypharmacy was more common in both patients and controls with chronic conditions, such as diabetes or macrovascular disease, with EP prevalence ranging from 78.1% to 89.8% in patient groups and 24.6% to 47.5% in controls. The highest polypharmacy prevalence (EPP 90.8%) was found in transplant patients with coronary artery disease.

Table 6.1: Baseline characteristics of CKD Stage G4-G5 without KRT, dialysis, and kidney transplant patients and matched controls.

	CKD Stage G4-G5			**Dialysis**			**Kidney transplantation**		
Characteristics	**Patients (n = 14 905)**	**Matched controls (n = 29 810)**	**P-*value***	**Patients (n = 3872)**	**Matched controls (n = 7744)**	**P-*value***	**Patients (n = 8796)**	**Matched controls (n = 17 592)**	**P-*value***
Age (years), median (25th–75th percentile)	78.0 (70.0–84.0)	78.0 (70.0–84.0)	*0.99*	74.0 (64.0–80.0)	74.0 (64.0–80.0)	*1.00*	58.0 (48.8–67.0)	58.0 (48.8–67.0)	*1.00*
Age (years), mean (SD)	75.6 (11.2)	75.6 (11.2)	*0.99*	70.8 (13.2)	70.8 (13.2)	*1.00*	56.5 (13.6)	56.5 (13.6)	*1.00*
Age (years), %									
20–44	1.8	1.8	–	4.5	4.5	–	19.6	19.6	–
45–64	12.2	12.2	–	22.5	22.5	–	48.4	48.4	–
65–74	25.0	25.0	–	25.8	25.8	–	24.6	24.6	–
≥75	61.0	61.0	*1.00*	47.3	47.3	*1.00*	7.5	7.5	*1.00*
Sex (male), %	52.8	52.8	*1.00*	58.8	58.8	*1.00*	59.8	59.8	*1.00*
SES score, median (25th–75th percentile)	−0.20 (−1.04–0.45)	−0.18 (−1.01–0.45)	*0.16*	−0.35 (−1.21–0.33)	−0.32 (−1.21–0.36)	*0.25*	−0.09 (−1.03–0.57)	−0.11 (−1.01–0.57)	*0.61*
Quartiles, %									
Q1	28.1	28.1	–	33.6	33.6	–	27.6	27.6	–
Q2	26.5	26.5	–	26.6	26.6	–	24.9	24.9	–
Q3	25.2	25.2	–	22.4	22.4	–	23.7	23.7	–
Q4	20.2	20.2	*1.00*	17.4	17.4	*1.00*	23.9	23.9	*1.00*

Table 6.1: *(continued)*

Characteristics	CKD Stage G4-G5			Dialysis			Kidney transplantation		
	Patients (n = 14 905)	Matched controls (n = 29 810)	P-*value*	Patients (n = 3872)	Matched controls (n = 7744)	P-*value*	Patients (n = 8796)	Matched controls (n = 17 592)	P-*value*
No. of chronic conditions, mean (SD)	1.92 (11.2)	0.68 (0.98)	*<0.0001*	1.86 (1.15)	0.61 (0.96)	*<0.0001*	1.46 (0.95)	0.33 (0.71)	*<0.0001*
Chronic conditions, %									
0	10.8	55.2	–	13.2	63.3	–	12.6	77.8	–
1	25.9	21.0	–	24.3	19.3	–	45.7	14.1	–
≥2	63.4	23.8	*<0.0001*	62.6	17.3	*<0.0001*	41.7	8.1	*<0.0001*
DM, %	35.9	11.0	*<0.0001*	31.1	9.8	*<0.0001*	28.3	5.4	*<0.0001*
Macrovascular disease, %	17.7	5.2	*<0.0001*	29.2	4.8	*<0.0001*	11.3	2.4	*<0.0001*
Coronary artery disease, %	8.7	4.3	*<0.0001*	13.2	4.3	*<0.0001*	6.0	2.5	*<0.0001*
Peripheral artery disease, %	8.4	2.0	*<0.0001*	16.9	1.8	*<0.0001*	4.9	0.82	*<0.0001*
CVA/TIA, %	2.5	1.7	*<0.0001*	3.6	1.5	*<0.0001*	1.6	0.67	*<0.0001*
Malignancy, %	13.7	7.4	*<0.0001*	16.4	6.9	*<0.0001*	19.2	3.6	*<0.0001*
Hypertension, %	88.0	35.7	*<0.0001*	82.7	31.7	*<0.0001*	86.6	17.2	*<0.0001*
Hospitalization, %	28.7	8.7	*<0.0001*	52.3	7.8	*<0.0001*	28.8	4.4	*<0.0001*
ICU admittance, %	2.6	0.78	*<0.0001*	8.4	0.81	*<0.0001*	2.5	0.35	*<0.0001*
ER visit, %	28.5	10.1	*<0.0001*	49.5	9.2	*<0.0001*	32.2	5.6	*<0.0001*

Abbreviations: Q, quartile; CVA/TIA, cerebrovascular accident/transient ischaemic attack.

Chronic medication use PP was most common in CKD patients (69.4%) and dialysis patients (73.5%) aged 65-74 years and in transplant patients (85.0%) ≥75 years of age. Ratios between patient and control groups decreased with increasing age. The prevalence of polypharmacy was high in patients with chronic conditions in all patient groups (Table 6.3).

Risk factors for polypharmacy

Table 6.4 presents the unadjusted and adjusted association between patient demographics and disease-related variables and EPP (≥10 medications, 'chronic medication use'). Below we discuss the fully adjusted models if adjustment for potential confounders was possible.

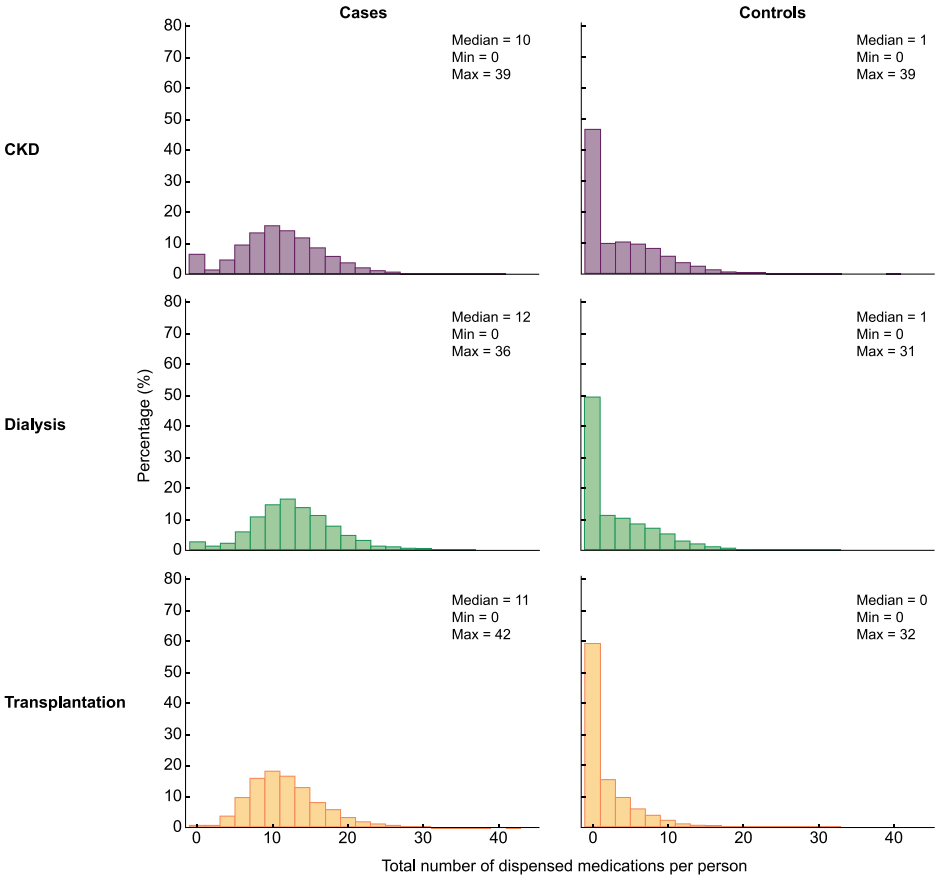

Figure 6.2: Total number of dispensed medication per percentage of CKD Stage G4-G5 not on KRT patients, dialysis, and kidney transplant patients versus matched controls; all medication use.

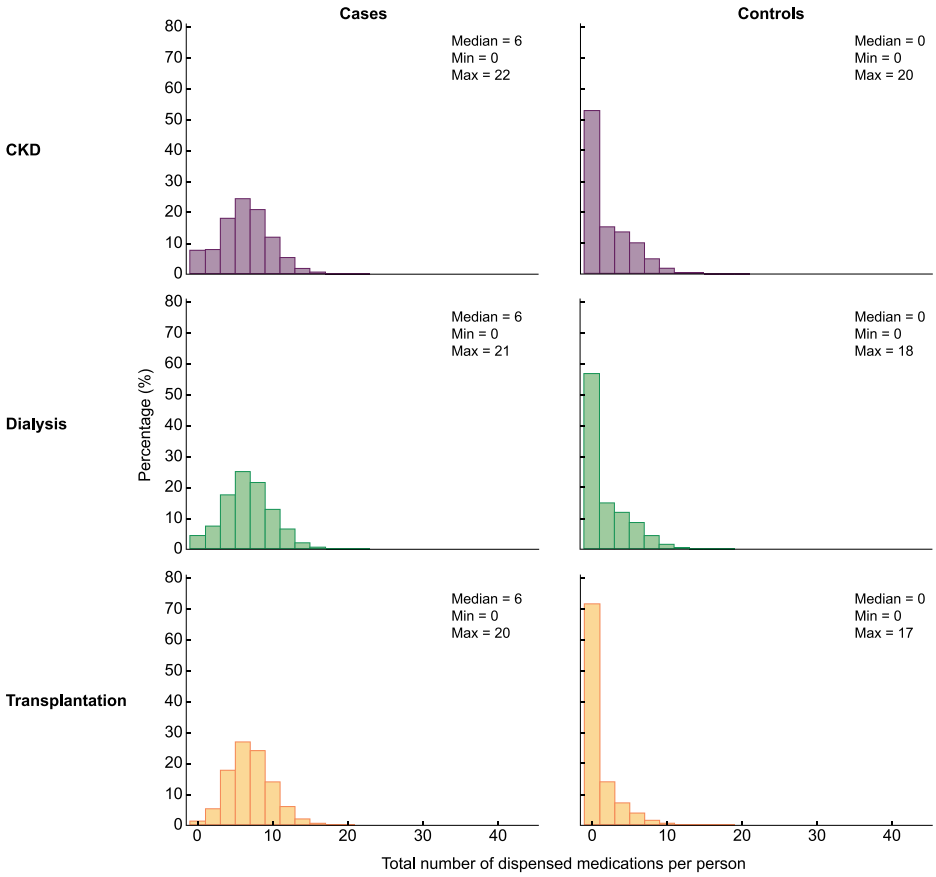

Figure 6.3: Total number of dispensed medication per percentage of CKD Stage G4-G5 not on KRT patients, dialysis, and kidney transplant patients versus matched controls; chronic medication use.

CKD Stage G4-G5 without KRT Patients aged 65-74 years (OR 1.57, 95% CI 1.33-1.85) and ≥75 years (OR 1.24, 95% CI 1.06-1.44) had a higher EPP risk compared with patients aged 20-64 years. In addition, an SES score in the lowest two quartiles compared with an SES score in the highest quartile (OR 1.34, 95% CI 1.17-1.55 versus OR 1.23, 95% CI 1.07-1.43), diabetes (OR 4.98, 95% CI 4.51-5.54) or vascular disease (OR 2.01, 95% CI 2.12-2.62), as well as hospitalization (OR 1.35, 95% CI 1.17-1.55) and an ER visit (OR 1.69, 95% CI 1.53-1.88) were significantly associated with PP.

Dialysis Patients ≥75 years of age had a lower risk of EPP (OR 0.74, 95% CI 0.59-0.91) compared with patients aged 20-64 years. The most pronounced risk factors for EPP in dialysis patients were diabetes (OR 3.69, 95% CI 3.08-4.43) and vascular disease (OR 2.08, 95% CI 1.72-2.51).

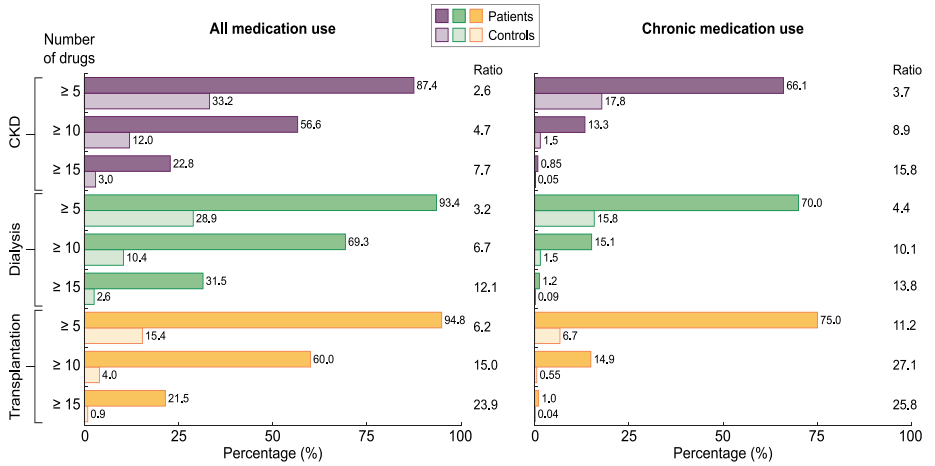

Figure 6.4: Percentage and ratio of polypharmacy of CKD Stage G4-G5 without KRT, dialysis, and kidney transplant patients versus matched controls for (left) all medication use and (right) chronic medication use.

Kidney transplantation Patients aged 65-74 years (OR 3.69, 95% CI 2.89-4.71) and ≥75 years (OR 5.88, 95% CI 4.60-7.51) had a higher EPP risk compared with patients aged 20-64 years. In addition, being male (OR 1.19, 95% CI 1.05-1.34), having an SES score in the lowest two quartiles compared with an SES score in the highest quartile (OR 1.34, 95% CI 1.13-1.59 versus OR 1.29, 95% CI 1.09-1.54), diabetes (OR 5.59, 95% CI 4.91-6.36) or vascular disease (OR 2.51, 95% CI 2.14-2.96), hospitalization (OR 1.29, 95% CI 1.09-1.52), and an ER visit (OR 1.76, 95% CI 1.54-2.00) were significantly associated with EPP.

Dispensed medication classes

Table 6.5 shows the most commonly dispensed chronic medication. Proton pump inhibitors (PPIs) were among the most commonly dispensed medications in patients, with ≥50% of patients using a PPI versus 8%-19% of controls. Also, statins were commonly dispensed (53%, 51%, and 40% in CKD Stage G4-G5, transplant, and dialysis patients, respectively). Dispensed medication classes for all medication use are shown in online supplementary file. Of note, 3%-12% of CKD patients with DM do not use antidiabetic medication, whereas 17-19% of controls with DM are diet-controlled (see online supplementary file). Furthermore, 63%-75% of CKD patients with DM chronically use antidiabetic medication compared with 61%-65% in controls (Table 6.5).

Table 6.2: Percentage and ratio of polypharmacy *(all medication use)* in different subgroups of CKD Stage G4-G5 without KRT patients (*n* = 14 905), dialysis patients (*n* = 3872) and kidney transplant patients (*n* = 8796) versus matched controls (resp. *n* = 29 810, *n* = 7744, *n* = 17 592).

	All medication use																	
	CKD Stage G4-G5						**Dialysis**						**Kidney transplantation**					
	Excessive polypharmacy ≥ 10 drugs			**Hyperpolypharmacy ≥ 15 drugs**			**Excessive polypharmacy ≥ 10 drugs**			**Hyperpolypharmacy ≥ 15 drugs**			**Excessive polypharmacy ≥ 10 drugs**			**Hyperpolypharmacy ≥ 15 drugs**		
	Patients	**Matched controls**	**Ratio**	**Patients**	**Matched controls**	**Ratio**	**Patients**	**Matched controls**	**Ratio**	**Patients**	**Matched controls**	**Ratio**	**Patients**	**Matched controls**	**Ratio**	**Patients**	**Matched controls**	**Ratio**
Polypharmacy overall (%)	56.6	12.0	4.7	22.8	3.0	7.6	69.3	10.4	6.7	31.5	2.6	11.9	60.0	4.0	14.9	21.5	0.90	23.9
Age 20-44 years (%)	23.0	0.55	42.0	6.6	0.0	-	47.4	0.87	54.7	19.7	-	-	38.5	0.49	78.1	8.5	0.09	98.0
Age 45-64 years (%)	45.1	3.1	14.4	16.2	0.60	26.8	67.0	3.8	17.4	32.6	1.2	27.0	59.2	2.8	21.1	20.0	0.69	28.8
Age 65-74 years (%)	56.7	7.6	7.5	23.3	1.6	14.9	74.0	7.6	9.7	36.4	1.9	19.1	73.4	6.8	10.8	31.0	1.3	23.1
Age ≥ 75 years (%)	60.0	16.0	3.8	24.4	4.2	5.8	69.8	15.9	4.4	29.5	4.0	7.4	77.4	12.0	6.4	34.2	2.9	11.9
Male	56.6	11.7	4.8	21.9	2.8	7.7	69.1	9.9	7.0	31.2	2.5	12.3	59.1	3.8	15.6	19.7	0.73	26.9
Female	56.7	12.4	4.6	23.9	3.2	7.4	69.5	11.1	6.3	32.1	2.8	11.4	61.4	4.4	14.0	24.2	1.1	21.1
SES Q1 (%)	58.4	13.7	4.2	24.7	3.7	6.7	68.7	11.9	5.8	29.4	3.2	9.3	62.4	4.4	14.0	23.3	1.1	22.2
SES Q2 (%)	57.6	12.1	4.8	23.7	3.0	8.0	70.8	9.9	7.2	33.5	2.9	11.7	60.9	4.5	13.5	21.5	1.1	20.0
SES Q3 (%)	55.4	11.2	4.9	21.8	2.8	7.9	67.6	9.4	7.2	32.6	2.3	14.1	60.1	3.7	16.4	21.6	0.67	32.1
SES Q4 (%)	54.5	10.6	5.1	20.4	2.5	8.2	70.3	9.7	7.3	31.6	1.8	17.8	56.3	3.4	16.5	19.4	0.76	25.4
0 chronic conditions	6.2	0.63	10.0	0.62	0.08	7.9	24.0	0.55	43.5	5.3	-	-	21.3	0.21	100.6	2.7	0.04	73.9
1 chronic conditions	31.4	11.4	2.8	6.1	1.5	4.0	53.8	10.8	5.0	14.6	1.5	9.9	47.4	6.1	7.7	9.6	0.72	13.3
≥2 chronic conditions	75.5	46.6	1.6	33.4	13.3	2.5	84.8	45.9	1.8	43.6	13.6	3.2	85.5	37.0	2.3	40.2	9.5	4.2

Table 6.2 *(continued)*

	All medication use																	
	CKD Stage G4-G5						Dialysis						Kidney transplantation					
	Excessive polypharmacy ≥ 10 drugs			Hyperpolypharmacy ≥ 15 drugs			Excessive polypharmacy ≥ 10 drugs			Hyperpolypharmacy ≥ 15 drugs			Excessive polypharmacy ≥ 10 drugs			Hyperpolypharmacy ≥ 15 drugs		
	Patients	Matched controls	Ratio	Patients	Matched controls	Ratio	Patients	Matched controls	Ratio	Patients	Matched controls	Ratio	Patients	Matched controls	Ratio	Patients	Matched controls	Ratio
Diabetes Mellitus (%)	78.1	42.5	1.8	37.9	12.4	3.0	86.9	41.0	2.1	51.1	13.0	3.9	86.0	29.7	2.9	41.6	7.4	5.7
Macrovascular disease (%)	79.0	47.5	1.7	39.7	15.3	2.6	84.6	45.2	1.9	48.2	14.7	3.3	89.8	36.0	2.5	49.4	7.9	6.3
Coronary artery disease (%)	84.6	36.5	2.3	44.0	11.5	3.8	89.4	38.2	2.3	56.0	13.6	4.1	90.8	24.6	3.7	53.2	5.1	10.4
Peripheral artery disease (%)	75.9	41.1	1.8	37.6	14.6	2.6	82.7	34.1	2.4	46.2	8.7	5.3	90.8	35.2	2.6	49.7	7.6	6.5
CVA/TIA (%)	77.3	38.3	2.0	41.0	10.8	3.8	84.8	32.7	2.6	42.8	8.8	4.8	87.9	17.8	4.9	48.9	3.4	14.4
Malignancy (%)	66.4	27.8	2.4	29.8	8.8	3.4	74.2	25.5	2.9	38.6	6.3	6.1	67.0	18.4	3.6	28.0	4.1	6.8
Hyper-tension (%)	62.8	30.7	2.0	25.6	8.0	3.2	77.1	29.7	2.6	35.9	8.0	4.5	65.3	19.6	3.3	23.9	4.4	5.4
Hospitali-zation (%)	78.2	47.1	1.7	42.9	17.1	2.5	79.2	44.4	1.8	43.0	14.5	3.0	81.8	28.2	2.9	42.6	9.5	4.5
ICU admit-tance (%)	85.4	60.5	1.4	52.0	23.6	2.2	83.1	60.3	1.4	50.3	25.4	2.0	90.8	50.8	1.8	59.0	24.6	2.4
ER visit (%)	78.5	42.6	1.8	43.5	15.1	2.9	78.4	41.1	1.9	41.3	14.8	2.8	78.0	22.8	3.4	38.5	7.5	5.1

Abbreviations: CKD, chronic kidney disease; KRT, kidney replacement therapy; SES, socioeconomic status; Q, quartile; CVA/TIA, cerebrovascular accident/transient ischemic attack; ICU, intensive care unit, ER, emergency room

Table 6.3: Percentage and ratio of polypharmacy (*chronic medication use)* in different subgroups of CKD Stage G4-G5 without KRT patients (*n* = 14 905), dialysis patients (*n* = 3872), and kidney transplant patients (*n* = 8796) versus matched controls (resp. *n* = 29 810, *n* = 7744, *n* = 17 592).

	Chronic medication use																	
	CKD Stage G4-G5						**Dialysis**						**Kidney transplantation**					
	Polypharmacy ≥ 5 drugs			**Excessive polypharmacy ≥ 10 drugs**			**Polypharmacy ≥ 5 drugs**			**Excessive polypharmacy ≥ 10 drugs**			**Polypharmacy ≥ 5 drugs**			**Excessive polypharmacy ≥ 10 drugs**		
	Patients	**Matched controls**	**Ratio**	**Patients**	**Matched controls**	**Ratio**	**Patients**	**Matched controls**	**Ratio**	**Patients**	**Matched controls**	**Ratio**	**Patients**	**Matched controls**	**Ratio**	**Patients**	**Matched controls**	**Ratio**
Polypharmacy overall (%)	66.1	17.8	3.7	13.3	1.5	9.0	70.0	15.8	4.4	15.1	1.5	10.4	75.0	6.7	11.3	14.9	0.55	27.3
Age 20-44 years (%)	28.1	0.7	38.5	3.3	-	-	50.9	0.9	58.7	5.2	-	-	56.2	0.52	107.6	4.5	0.03	154.0
Age 45-64 years (%)	56.5	5.3	10.6	11.8	0.58	20.5	68.6	5.8	11.8	18.6	0.80	23.1	77.0	4.6	16.8	14.7	0.39	37.9
Age 65-74 years (%)	69.4	12.6	5.5	15.9	1.1	14.1	73.5	12.8	5.7	18.5	1.0	18.4	83.1	11.9	7.0	21.3	1.0	20.9
Age ≥ 75 years (%)	67.7	23.0	2.9	12.9	1.8	7.0	70.6	23.6	3.0	12.6	2.2	5.8	85.0	18.8	4.5	22.4	1.4	16.4
Male	67.5	18.5	3.6	13.8	1.7	8.1	71.0	16.3	4.3	16.0	1.4	11.0	77.6	6.7	11.6	15.8	0.56	28.1
Female	64.4	17.1	3.8	12.9	1.2	10.5	68.5	15.0	4.6	13.8	1.5	9.4	71.3	6.6	10.7	13.6	0.52	26.0
SES Q1 (%)	68.3	19.7	3.5	14.8	1.9	7.6	69.4	17.3	4.0	15.4	1.9	8.2	75.9	7.6	10.0	16.4	0.62	26.4
SES Q2 (%)	66.8	17.9	3.7	13.8	1.5	8.9	71.2	15.8	4.5	15.6	1.6	10.0	76.4	7.5	10.2	15.9	0.48	33.0
SES Q3 (%)	64.7	17.3	3.7	12.8	1.1	11.3	70.2	14.8	4.8	16.3	1.2	13.4	73.6	5.9	12.5	14.5	0.55	26.2
SES Q4 (%)	63.6	15.9	4.0	11.5	1.2	9.7	69.4	14.5	4.8	12.5	0.82	15.3	74.1	5.5	13.4	12.7	0.52	24.3
0 chronic conditions	5.3	0.6	9.2	0.12	0.01	11.1	18.9	0.4	44.1	0.20	-	-	27.6	0.13	210.0	0.18	-	-
1 chronic conditions	46.3	20.8	2.2	0.91	0.12	7.9	53.5	20.3	2.6	2.4	0.20	12.2	71.1	11.8	6.0	4.3	0.08	53.2
≥2 chronic conditions	84.5	66.2	1.3	20.7	7.2	2.9	87.2	67.0	1.3	23.1	8.2	2.8	93.7	60.2	1.6	31.0	6.6	4.7

Table 6.3 *(continued)*

	Chronic medication use																	
	CKD Stage G4-G5						Dialysis						Kidney transplantation					
	Polypharmacy ≥ 5 drugs			Excessive polypharmacy ≥ 10 drugs			Polypharmacy ≥ 5 drugs			Excessive polypharmacy ≥ 10 drugs			Polypharmacy ≥ 5 drugs			Excessive polypharmacy ≥ 10 drugs		
	Patients	Matched controls	Ratio	Patients	Matched controls	Ratio	Patients	Matched controls	Ratio	Patients	Matched controls	Ratio	Patients	Matched controls	Ratio	Patients	Matched controls	Ratio
Diabetes Mellitus (%)	86.2	61.8	1.4	25.6	8.3	3.1	84.3	63.5	1.3	27.6	9.6	2.9	91.8	52.0	1.8	34.2	6.1	5.6
Macrovascular disease (%)	84.3	61.1	1.4	23.0	7.4	3.1	79.7	60.2	1.3	24.1	7.0	3.5	90.7	50.9	1.8	34.1	6.0	5.6
Coronary artery disease (%)	87.8	51.5	1.7	25.8	6.3	4.1	88.1	49.7	1.8	31.9	8.2	3.9	93.3	39.4	2.4	38.2	3.9	9.7
Peripheral artery disease (%)	83.6	52.3	1.6	22.9	7.6	3.0	74.6	50.0	1.5	20.4	2.9	7.0	90.8	52.4	1.7	34.2	8.3	4.1
CVA/TIA (%)	78.7	44.8	1.8	18.3	4.2	4.3	74.6	40.7	1.8	19.6	1.8	11.1	83.0	25.4	3.3	28.4	-	-
Malignancy (%)	71.8	35.0	2.1	15.2	3.7	4.1	73.2	33.7	2.2	15.3	3.7	4.1	78.4	25.3	3.1	17.0	2.1	8.2
Hyper-tension (%)	73.2	45.9	1.6	15.1	4.0	3.8	77.6	45.5	1.7	17.5	4.4	3.9	80.8	33.5	2.4	17.0	2.9	5.8
Hospitali-zation (%)	76.7	45.4	1.7	20.0	5.5	3.6	72.1	43.2	1.7	18.1	6.3	2.9	81.7	30.7	2.7	22.5	5.0	4.5
ICU admit-tance (%)	77.3	52.8	1.5	16.4	8.2	2.0	69.6	54.0	1.3	22.1	9.5	2.3	79.3	55.7	1.4	28.1	9.8	2.9
ER visit (%)	77.4	44.5	1.7	20.1	5.1	3.9	71.2	42.1	1.7	18.2	5.6	3.2	80.5	24.3	3.3	21.7	3.2	6.9

Abbreviations: CKD, chronic kidney disease; KRT, kidney replacement therapy; SES, socioeconomic status; Q, quartile; CVA/TIA, cerebrovascular accident/transient ischemic attack; ICU, intensive care unit, ER, emergency room

Table 6.4: Unadjusted and adjusted analysis of variables associated with polypharmacy (defined as ≥10 medications for chronic medication use*) in CKD Stage G4-G5 without KRT patients, dialysis patients, and kidney transplant patients, using logistic regression.

	CKD Stage G4-G5						Dialysis						Kidney transplantation					
	Unadjusted		Age, sex, SES-adjusted model		Fully adjusted model		Unadjusted		Age, sex, SES-adjusted model		Fully adjusted model		Unadjusted		Age, sex, SES-adjusted model		Fully adjusted model	
Variables	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
Age (categories)																		
Age 20-64 years	Ref.						Ref.						Ref.					
Age 65-74 years	1.57	1.33-1.85	na[b]		na[b]		1.16	0.92-1.46	na[b]		na[b]		3.69	2.89-4.71	na[b]		na[b]	
Age ≥75 years	1.24	1.06-1.44	na[b]		na[b]		0.74	0.59-0.91	na[b]		na[b]		5.88	4.60-7.51	na[b]		na[b]	
Age (continuous, per 10 years)	1.01	0.96-1.05	na[b]		na[b]		0.96	0.90-1.03	na[b]		na[b]		1.51	1.44-1.59	na[b]		na[b]	
Sex (male)																		
Female	Ref.						Ref.						Ref.					
Male	1.08	0.98-1.19	na[b]		na[b]		1.18	0.99-1.42	na[b]		na[b]		1.19	1.05-1.34	na[b]		na[b]	
SES (categories)																		
Q1	1.34	1.17-1.55	na[b]		na[b]		1.28	0.97-1.68	na[b]		na[b]		1.34	1.13-1.59	na[b]		na[b]	
Q2	1.23	1.07-1.43	na[b]		na[b]		1.29	0.97-1.72	na[b]		na[b]		1.29	1.09-1.54	na[b]		na[b]	
Q3	1.14	0.98-1.32	na[b]		na[b]		1.36	1.02-1.82	na[b]		na[b]		1.16	0.97-1.39	na[b]		na[b]	
Q4	Ref.						Ref.						Ref.					
Diabetes Mellitus	5.00	4.51-5.54	4.98	4.50-5.52	na[b]		3.64	3.04-4.36	3.69	3.08-4.43	na[b]		6.59	5.81-7.48	5.59	4.91-6.36	na[b]	
Vascular disease	2.36	2.12-2.62	2.36	2.12-2.63	2.01[c]	1.80-2.25	2.46	2.06-2.95	2.49	2.08-2.99	2.08[c]	1.72-2.51	3.64	3.14-4.22	2.86	2.45-3.33	2.51[c]	2.14-2.96
Hospitalization	2.10	1.91-2.31	2.10	1.90-2.31	1.35[d]	1.17-1.55	1.66	1.38-1.99	1.66	1.39-1.99	1.13[d]	0.90-1.42	2.16	1.91-2.44	1.99	1.76-2.25	1.29[d]	1.09-1.52
ICU admittance	1.29	0.98-1.69	1.28	0.98-1.69	0.64[e]	0.47-0.86	1.68	1.27-2.21	1.66	1.26-2.19	1.10[e]	0.81-1.49	2.29	1.70-3.10	1.99	1.46-2.71	1.10[e]	0.78-1.55
ER visit	2.12	1.92-2.33	2.11	1.92-2.33	1.69[f]	1.53-1.88	1.62	1.35-1.94	1.63	1.37-1.96	1.34[f]	1.11-1.62	2.09	1.85-2.35	2.01	1.78-2.27	1.76[f]	1.54-2.00

Abbreviations: CKD, chronic kidney disease; KRT, kidney replacement therapy; SES, socioeconomic status; Q, quartile; ICU, intensive care unit, ER, emergency room

Table 6.4 *(continued)*
a. the overall polypharmacy rates (for polypharmacy defined as ≥10 medications for chronic medication use) are considered rare enough to reasonably allow for the rare disease assumption for logistic regression.
b. for this variable no confounders could be identified considering the criteria for confounding.
c. model adjusted for age, sex, SES, and diabetes mellitus
d. model adjusted for age, sex, SES, diabetes mellitus, vascular disease, and ER visits
e. model adjusted for age, sex, SES, diabetes mellitus, vascular disease, hospitalization, and ER visits
f. model adjusted for age, sex, SES, diabetes mellitus, vascular disease

Table 6.5: Percentage of most commonly dispensed medication classes of CKD Stage G4-G5 without KRT patients, dialysis patients, and kidney transplant patients and matched controls; medication classes defined for chronic medication use.

	Chronic medication use					
	CKD Stage G4-G5		**Dialysis**		**Kidney transplantation**	
	Patients (%) (*n* = 14 905)	**Matched controls (%) (*n* = 29 810)**	**Patients (%) (*n* = 3872)**	**Matched controls (%) (*n* = 7744)**	**Patients (%) (*n* = 8796)**	**Matched controls (%) (*n* = 17 592)**
Medication classes						
Cardiovascular drugs						
ACE inhibitors	23.6	11.1	11.4	10.4	24.6	5.3
ARB	27.9	9.8	13.2	7.9	17.6	4.8
Beta blockers	29.1	9.1	25.1	7.9	29.6	3.7
Ca channel blockers	39.8	9.3	29.7	8.5	43.4	4.2
Diuretics	43.1	10.1	44.3	8.6	19.1	3.8
Statins	52.8	19.3	39.5	18.3	50.8	10.2
Proton pump inhibitors	51.9	19.4	65.5	16.8	54.0	8.2
Vitamin D analogues	50.6	12.5	43.4	9.9	48.5	4.7
Antithrombotic agents	45.2	19.2	50.3	17.2	29.6	7.6
Platelet aggregation inhibitors	38.8	15.3	44.6	13.9	23.9	6.2
Vitamin K antagonist	5.6	2.1	6.3	1.8	4.3	0.67
Heparin	0.27	0.14	0.44	0.10	0.47	0.06
DOAC/NOAC	1.1	1.9	0.03	1.6	1.4	0.76
Antidiabetics	25.8	6.6	19.6	6.4	21.3	3.5
Insulin	15.8	2.1	14.8	2.1	11.2	1.0
Metformin	2.2	4.7	0.03	4.8	9.2	2.6
Sulfonureumderivate	10.3	2.9	4.5	2.5	7.1	1.5

Abbreviations: CKD, chronic kidney disease; KRT, kidney replacement therapy; DDD, daily defined dose; ACE, angiotensin converting-enzyme; ARB, angiotensin II receptor blocker; DOAC/NOAC, direct oral anticoagulant/ novel oral anticoagulant

Discussion

This study using Dutch health claims data demonstrates that polypharmacy is highly prevalent in CKD Stage G4-G5 patients and patients with KRT compared with the general population. Since multimorbidity is one of the driving factors of polypharmacy, we must note that chronic comorbid conditions were three to four times more prevalent in patients than in controls. In our study, PP prevalence based on 'all medication use' ranged from 87% in CKD Stage G4-G5 to 94%-95% in dialysis and transplant patients. The prevalence was lower for chronic medication use. Older age was an important risk factor for PP in CKD Stage G4-G5 and transplant patients, whereas dialysis patients aged ≥75 years had a lower risk of polypharmacy compared with younger counterparts. For all patients, additional risk factors were lower SES, DM, vascular disease, hospitalization, and an ER visit during the year. The polypharmacy prevalence ratio between patients and controls declined with age. The most commonly dispensed medications were PPIs and statins, with more than half of patients using these medications.

Strengths and limitations

The main strength of this paper is the use of a health claims database with almost complete national coverage of Stage G4-G5 CKD patients, by which we could study CKD Stage G4-G5 and KRT patients in the same cohort and compare them with the general population. Pharmacy dispensing data was complete and contained all dispensed medication by the pharmacy. This is in contrast to other studies which used data from patient questionnaires which heavily relies on patient memory. Another strength of pharmacy dispensing data is that they only include prescribed medication that was actually dispensed and do not cover prescribed medications that were never collected at the pharmacy. Although information on medication adherence is often missing in studies describing medication use, the regular dispensing of medication in a health claims database is an indirect yet strong indication that the medication was routinely taken.

We must consider several limitations. First, although the identification of dialysis and transplant patients is accurate using health claims data,[67] we were unable to identify patients with CKD treated in primary care, being mostly elderly patients.[55] Furthermore, data on medication adherence is missing. In addition, we were unable to identify medication given during dialysis sessions. Therefore, the polypharmacy levels of dialysis patients reported in this study are likely an underestimation of their actual medication burden. Finally, the estimation of chronic conditions in our study was based on proxies that are vulnerable to inaccuracy.

Prevalence of polypharmacy

The comparison of the prevalence of polypharmacy with other studies is challenging due to the substantial differences in patient selection, definition of polypharmacy, and data collection. Almost all previously performed studies collected cross-sectional medication data via patient reports or medical charts. Our study is unique in the approach to use pharmacy dispensing data, which enabled us to monitor all dispensed medication. The availability of the annual quantity of supplied medications makes it possible to differentiate between all and chronic medication use.

The considerably higher PP prevalence based on all medication use compared with chronic medication use suggests that patients often receive short-term medication or experience medication changes. Although PP prevalence based on chronic medication use better reflects the structural medication burden, this type of medication use is not reported in other studies. Therefore, we can only discuss our findings on the PP prevalence from the perspective of other studies on all medication use.

CKD Stage G4-G5 without KRT Current literature describes polypharmacy prevalence in different stages of CKD, using different definitions of polypharmacy, and mainly in elderly patients. Two studies describe polypharmacy prevalence in CKD Stage G4-G5 patients. Of these, Schmidt et al. reported a PP prevalence of 92% (eGFR <30 mL/min/1.73 m^2).[160] Hayward et al. describe prevalences of 91% (≥5 medications) and 43% (≥10 medications) in a group of elderly (>65 years) patients (eGFR <20 mL/min/1.73 m^2) of different European countries.[168] Within the subset of Dutch patients in this study, a prevalence of 91% (≥5 medications) and 43% (≥10 medications) was described. All results are comparable to our findings. Lower PP prevalence was found in patients with CKD Stages G1-G3.[153,160,161]

Dialysis It is well-known that dialysis patients have a high medication burden.[166,175,176] A pooled analyses report that dialysis patients use 12 different medications.[163,176] We report a median of 12 medications. A study from Saudi Arabia with 95 hemodialysis patients reports a 98% PP prevalence (>5 medications)[169], which is comparable to our PP prevalence. A Canadian study reports that 93.1% of elderly hemodialysis patients (age ≥65 years) used five or more medications.[163] No previous studies reported on EP and HP prevalence and we are the first study in a much larger cohort of dialysis patients of all ages.

Kidney transplantation A high pill buren is also described in transplant patients, ranging from 7-32 pills per day, depending on the time period after transplantation.[177–179]

An Argentinean study described a mean of 7.8 different medications, while we describe a median of 10 different medications.[180] Only one Polish study reported polypharmacy prevalence in a much smaller group of 136 transplant patients, being 56% (5-9 medications) and 17% (≥10 medications).[170] We demonstrated a considerably higher PP and EP prevalence in our larger cohort of transplant patients.

Comparison with the general population To our knowledge, this is the first study comparing the polypharmacy prevalence of CKD Stage G4-G5 patients and KRT patients with a matched control group from the general population. We demonstrate that polypharmacy prevalence is already substantially higher in young patients compared with controls, probably reflecting the high number of comorbidities in CKD patients, already at a young age. The ratio of polypharmacy between patients and controls decreases with increasing age, because medication use increases more with age in the general population than it does in patients.[181]

Risk factors for polypharmacy

We confirm a positive association between polypharmacy and older age in CKD Stage G4-G5 and transplant patients.[153,160,170,182] The inverse association between polypharmacy and age ≥75 years in dialysis patients may suggest some reluctance to prescribe medication in the elderly dialysis patient with limited life expectancy being at high risk for medication-related problems. We confirm that the presence of chronic conditions like DM and cardiovascular disease are risk factors for polypharmacy in all patients.[160,163,169,183]

Next, we described a positive association between low SES and polypharmacy, for CKD Stage G4-G5 and transplant patients, in line with other studies.[153,160] A possible explanation is that individuals with a low SES often have low health literacy and are more vulnerable to comorbid illness. Lastly, we are the first to demonstrate a positive association between polypharmacy and hospitalization or an ER visit. We hypothesize that patients with an indication for an ER visit or hospital admission likely have severe comorbid conditions or complications of their CKD, for which they need additional medication prescription. Moreover, polypharmacy itself may be associated with hospitalization in the elderly population[184,185], although this was not confirmed elsewhere.[186]

Medication dispensing

The increased cardiovascular risk of CKD patients is reflected by the high number of medications to prevent or treat cardiovascular conditions. Recent guidelines

recommend statin prescription to CKD Stage G4-G5 patients.[187] Although (almost) all CKD Stage G4-G5 patients would be expected to fulfill the criteria for statin prescription, only half of the patients in our study used statins. Conversely, several studies question the benefit of statin therapy for dialysis patients.[188–190] Guidelines suggest that statins should not be routinely initiated, though continued when patients already use statins when initiating dialysis treatment.[191] We suggest a critical evaluation of statin treatment in dialysis patients to reduce some of the medication burden. This also may be the case for PPIs.[192] More than 50% of CKD Stage G4-G5 and transplant patients, and even >65% of dialysis patients used a PPI in our study. Previous studies reported PPI use of 30%, 50%, and 52% in hemodialysis patients and 33%, 49%, and 62% in CKD Stage G4-G5 patients.[163,168,183] The literature reports that the indication for PPI use in dialysis patients was unknown in more than 25% of the time.[193] Since the long-term use of PPIs can have negative consequences, deprescribing of PPIs should be considered.[194]

Conclusion

Our study demonstrates that patients with CKD Stage G4-G5 and patients on KRT have a very high medication burden, far beyond that of individuals from the general population. Important polypharmacy risk factors are age, SES, DM, vascular disease, hospitalization, and an ER visit.

Medication treatment of CKD patients is a challenging balance between the benefits of pharmacotherapy for the treatment of kidney disease and comorbidities and the disadvantages of potentially inappropriate prescribing or adverse drug interaction.[195] Although physicians often check whether the prescribed medication in their patient is appropriate it is not easy to minimize the medication burden. As directed by the Hippocratic Oath, physicians strive for an optimal treatment of their patients, while avoiding those twin traps of overtreatment and therapeutic nihilism. Undertreatment has been repeatedly associated with unfavorable outcomes in dialysis patients.[196] Despite the fact that therapeutic nihilism should be avoided at all times, we propose that a critical approach to the prescription of specific medications like PPIs, in all CKD patients, and statins, in the dialysis population, could be a first step towards a more appropriate medication use. Finding a proper balance between potentially beneficial medication, and needless use of medications with adverse effects will remain a challenge.

7

Chronic prescription of antidepressant medication in patients with chronic kidney disease with and without kidney replacement therapy compared with matched controls in the Dutch population

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Abstract

Background Chronic kidney disease (CKD) is associated with a higher prevalence of depression, neuropathic pain, and insomnia. These conditions are often treated pharmaceutically. In this study, we aimed to determine the prevalence of chronic antidepressant use among CKD patients with and without kidney replacement therapy (KRT).

Method By using the Dutch health claims database, we were able to determine the prevalence, type, and dosage of chronic antidepressant prescription in patients with CKD Stage G4-G5 without KRT (*n* = 14 905), patients on dialysis (*n* = 3872), and patients living on a functioning graft (*n* = 8796) and compared these with age, sex, and socioeconomic status (SES)-matched controls from the general population.

Results Our data show that the prevalence of chronic antidepressant prescription is 5.6%, 5.3%, and 4.2% in CKD Stage G4-G5, dialysis, and kidney transplant patients, respectively, which is significantly higher than in matched controls. Although our data revealed higher prescription in female patients and the age category 45-64 years, our data did not show any association between antidepressant prescription and SES. Selective serotonin reuptake inhibitors were the most prescribed drugs in all patient groups and controls. Tricyclic antidepressants were more often used in patients compared with controls.

Conclusion This nationwide analysis revealed that chronic antidepressant prescription in the Netherlands is higher in CKD patients with and without KRT than in controls, higher in middle-aged patients and women, unrelated to socioeconomic status, and lower than chronic use reported in other countries.

Introduction

Chronic kidney disease (CKD) is associated with substantial comorbidity. In addition to well-known cardiovascular pathology, CKD is associated with a number of neuropsychiatric conditions such as neuropathic pain, sleep disorders, depressive mood disorder, and anxiety.[197–199] Various non-pharmaceutical therapies are available for these conditions, such as lifestyle modification or cognitive behavioural therapy. If these prove ineffective or when the disease burden is high, pharmaceutical intervention by prescribing antidepressant medication can be considered. The results of several studies suggest that in CKD, the use of antidepressants is associated with higher mortality [200,201] although this is not persistently demonstrated.[202]

Current literature suggests that antidepressant use in CKD with and without kidney replacement therapy (KRT) varies between 5.2% and 29.1%.[201–204] In CKD patients without KRT, antidepressant use appears to be substantially higher than in age and sex matched controls without CKD.[204] However, so far in studies on antidepressant use in dialysis-dependent and kidney transplant patients a control group has been lacking. Moreover, previous studies were restricted to samples and did not use comprehensive, nationwide data.[205,206] Our study aims to examine chronic antidepressant use in patients with CKD Stage G4-G5 without KRT, patients on dialysis treatment, and patients with a functioning kidney transplant in comparison to matched controls from the general population. To this end, we analyzed data derived from a national health insurance database that covers the entire Dutch CKD population.

Methods

Vektis database

For this study, we used Dutch health claims data from the Vektis database. Since health insurance is mandatory in the Netherlands approximately 99% of Dutch residents are insured, of whom 99% are included in the database. This database contains all reimbursement data for healthcare products covered by the Dutch Health Insurance Act, as well as demographic data such as an individual's year of birth, sex, postal code, socioeconomic status (SES), and date of death (if applicable).[30] The SES of each individual is based on a person's postal code and is a reflection of the average income, educational level, and position on the labour market in that area of residence.[207] The mean SES score in the Netherlands has been set at 0 and ranges

from -6.75 to +3.06, where a lower score indicates a lower SES and higher scores indicate a higher SES.[207]

In the Netherlands, all hospital procedures are reimbursed via physician claims named Diagnosis Treatment Combinations (DBC).[38] Every DBC corresponds to a given medical diagnosis in a given medical discipline. Furthermore, Vektis contains pharmacy dispensing data with information regarding the WHO's Anatomical Therapeutic Chemical (ATC) classification system, the daily defined dose (DDD), and the annual quantity of a supplied medication.[32] The DDD reflects the assumed average maintenance dose per day for a medication used for its main indication. The annual quantity of a specific medication is a product of the DDD and the number of days a medication was dispensed. For example, an annual DDD of 180 may indicate the use of medication in its routine dose during 180 days or half of the routine dose during 360 days. Vektis has no information on medication administered in intramural settings, such as during a hospital admission, during dialysis treatment, or a nursing home stay. Furthermore, Vektis does not include data on over-the-counter drugs.

Since the Vektis database lacks detailed clinical information, we used proxies to assess the prevalence of chronic conditions in our study population. The variables diabetes mellitus, macrovascular disease (coronary artery disease, peripheral artery disease, and CVA/TIA), and malignancies were based on combinations of DBC codes, primary care codes, and medication use.[208] The variables COPD and Parkinson's disease were based on medication profiles, i.e. Pharmaceutical Cost Groups, which have been shown to provide reliable estimates of chronic disease burden.[101,171,209,210] The variables hospitalization and intensive care unit (ICU) admission were based on operational codes, an element of the DBC code. See online supplementary file for the variable definitions.

Study population

We identified adults (i.e. ≥20 years of age) with CKD Stage G4-G5 (estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2) without KRT, patients on dialysis treatment (regardless of dialysis modality), and patients with a functioning kidney transplant. Patients were identified and allocated to the patient groups by a DBC for CKD Stage G4-G5, dialysis, or kidney transplantation on 1 January 2017. Patients with CKD Stage G4-G5 without KRT who started KRT in 2017 and patients switching KRT modality in 2017 (from dialysis to kidney transplantation or vice versa) were excluded from the

study (*n* = 7229). Furthermore, individuals were excluded in case of incomplete data, if they died during the study year or if we were unable to match them to controls.

A control group was created for each patient group separately by randomly selecting two controls per patient out of all individuals in the Vektis database provided that they had no CKD-related healthcare claim in 2017. Controls were matched for age, sex, and SES score.

Antidepressant prescription

Antidepressant prescription was defined by drugs listed in WHO's ATC classification system, code N06A Antidepressants (see online supplementary file for drugs listed to code N06A).[211] We selected antidepressants with a cumulative annual DDD of ≥180 to define chronic antidepressant use as our main outcome. In addition, total antidepressant prescription was defined as a DDD>0.

Statistical analyses

Baseline characteristics were described using medians and percentiles for continuous variables that were not normally distributed and frequency distributions with percentages for categorical variables. For the variable age, which was not normally distributed, we also presented the mean and standard deviation (SD). We calculated antidepressant prescription in all patients (sub)groups and controls and expressed it as a percentage. Baseline characteristics and antidepressant prescription in subgroups were compared using a Student's *t*-test for normally distributed continuous variables, the Mann-Whitney *U*-test for not normally distributed continuous variables, and the chi-squared test for categorical variables. We considered a P-value of <0.05 as statistically significant. Analyses were performed in SAS, version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Patient characteristics

In total, 14 905 CKD G4-G5, 3872 dialysis, and 8796 transplant patients were included. Baseline characteristics are shown in Table 7.1. Mean age varied between 56.5 years in transplant patients to 75.6 years in CKD Stage G4-G5 patients, whereas the percentage of males varied between 52.8% in the CKD Stage G4-G5 patients to 59.8% in transplant patients. Median SES ranged from -0.1 (kidney transplantation) to -0.4 (dialysis). The percentage of patients suffering from diabetes mellitus, macrovascular disease,

and COPD was significantly higher in patients compared with controls (P <0.001). Furthermore, the percentage of patients with malignancy, hospitalization, or ICU admission was higher in all patients compared with controls (P <0.001).

Chronic antidepressant prescription

Figure 7.1 shows the percentage of chronic antidepressant prescription in patients and controls. Overall, antidepressant prescription was higher in patients than in controls; i.e. CKD Stage G4-G5 patients (5.6% versus 2.8%, P <0.001), dialysis patients (5.3% versus 3.0%, P <0.001), and transplant patients (4.1% versus 2.7%, P <0.001). In both patients and controls, the antidepressant prescription was highest between 45 and 64 years of age and lowest in patients and controls aged 20-44 years, with the exception of CKD Stage G4-G5 patients, where prescription was lowest in patients aged ≥75 years. In both patients and controls, women were prescribed antidepressants more often than men (Figure 7.1). Frequencies ranged from 5.5% to 7.9% in female patients and from 3.3% to 4.1% in males while in controls this was 3.7% to 4.3% in women and 2.0% to 2.1% in men (Figure 7.1). Variation in prescriptions between the different SES groups was small.

In an online supplementary file we present the percentage of total antidepressant prescription (DDD>0) in patients and controls. Similar patterns were observed as in chronic antidepressant prescription, albeit at higher prescription frequencies. Total antidepressant prescriptions were higher in patients than in controls (CKD G4-G5: 10.6% versus 5.6%, P <0.001, dialysis: 12.1% versus 5.4%, P <0.001, transplantation 7.8% versus 4.4%, P <0.001).

Type of antidepressants

Among patients who were prescribed antidepressant medication, selective serotonin reuptake inhibitors (SSRIs) were the most prevalent type of antidepressant medication, ranging from 55.1% in CKD Stage G4-G5 to 65.1% in transplant patients (Table 7.2). SSRI prescription was consistently lower in patients compared with controls, although this difference was only statistically significant in the CKD group (55.1% versus 62.0%, P = 0.004). The frequency of tricyclic antidepressant (TCA) prescription was 23.4%, 23.0%, and 18.7% in CKD Stage G4-G5, dialysis, and transplant patients, respectively, and was significantly higher in all patient groups compared with controls. Citalopram and paroxetine were the most often prescribed SSRIs (Table 7.2). Regarding TCAs, amitriptyline was significantly more often prescribed in all three patient groups

Table 7.1: Baseline characteristics of CKD Stage G4-G5 without kidney replacement therapy, dialysis, and kidney transplant patients with matched controls.

	CKD Stage G4-G5			Dialysis			Kidney transplantation		
	Patients (*n* = 14 905)	**Matched controls (*n* = 29 810)**	**P-*value***	**Patients (*n* = 3872)**	**Matched controls (*n* = 7744)**	**P-*value***	**Patients (*n* = 8796)**	**Matched controls (*n* = 17 592)**	**P-*value***
Mean age (SD)	75.6 (11.2)	75.6 (11.2)	*1.00*	70.8 (13.2)	70.8 (13.2)	*1.00*	56.5 (13.6)	56.5 (13.6)	*1.00*
Median age (25-75p)	78.0 (70.0-84.0)	78.0 (70.0-84.0)	*1.00*	74.0 (64.0-80.0)	74.0 (64.0-80.0)	*1.00*	58.0 (48.0-67.0)	58.0 (48.0-67.0)	*1.00*
Age 20-44 years (%)	1.8	1.8		4.5	4.5		19.6	19.6	
Age 45-64 years (%)	12.2	12.2	*1.00*	22.5	22.5	*1.00*	48.4	48.4	*1.00*
Age 65-74 years (%)	25.0	25.0		25.7	25.7		24.5	24.5	
Age ≥75 years (%)	61.0	61.0		47.3	47.3		7.5	7.5	
Sex (% M)	52.8	52.8	*1.00*	58.8	58.8	*1.00*	59.8	59.8	*1.00*
Median SES (Q1-Q3)	-0.2 (-1.0-0.5)	-0.2 (-1.0-0.5)	*1.00*	-0.4 (-1.2-0.3)	-0.3 (-1.2-0.4)	*1.00*	-0.1(-1.0-0.6)	-0.1 (-1.0-0.6)	*1.00*
Q1 (%)	28.1	28.1		33.6	33.6		27.6	27.6	
Q2 (%)	26.5	26.5	*1.00*	26.6	26.6	*1.00*	24.9	24.9	*1.00*
Q3 (%)	25.2	25.2		22.4	22.4		23.7	23.7	
Q4 (%)	20.2	20.2		17.4	17.4		23.9	23.9	
Diabetes Mellitus (%)	32.3	8.9	*<0.001*	29.6	8.8	*<0.001*	27.8	4.4	*<0.001*
Macrovascular disease (%)	17.7	5.4	*<0.001*	29.2	4.8	*<0.001*	11.3	2.4	*<0.001*
Coronary artery disease (%)	8.7	4.6	*<0.001*	13.2	4.5	*<0.001*	5.9	2.3	*<0.001*
Peripheral artery disease (%)	8.4	1.9	*<0.001*	16.9	1.8	*<0.001*	4.9	0.7	*<0.001*
CVA/TIA (%)	2.5	1.7	*<0.001*	3.6	1.4	*<0.001*	1.6	0.8	*<0.001*
COPD (%)	7.1	3.1	*<0.001*	5.6	2.7	*<0.001*	2.1	1.2	*<0.001*
Parkinson (%)	0.6	0.6	*0.832*	0.6	0.5	*0.789*	0.4	0.2	*0.001*
Malignancies (%)	13.7	7.5	*<0.001*	16.4	7.9	*<0.001*	19.2	3.6	*<0.001*
Hospitalization (%)	28.7	8.7	*<0.001*	52.3	7.6	*<0.001*	28.8	4.3	*<0.001*
ICU admittance (%)	2.6	0.7	*<0.001*	8.4	0.5	*<0.001*	2.5	0.4	*<0.001*

Abbreviations: CKD, chronic kidney disease; SD, standard deviation; SES, socioeconomic status; Q, quartile; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; TIA, transient ischemic attack; ICU, intensive care unit

compared with their control groups (P <0.01). In transplant patients, also nortriptyline was more often prescribed than in controls (P = 0.034). Mirtazapine (tetracyclic antidepressant) and venlafaxine (selective noradrenalin reuptake inhibitor) were the most commonly prescribed 'other' types of antidepressants.

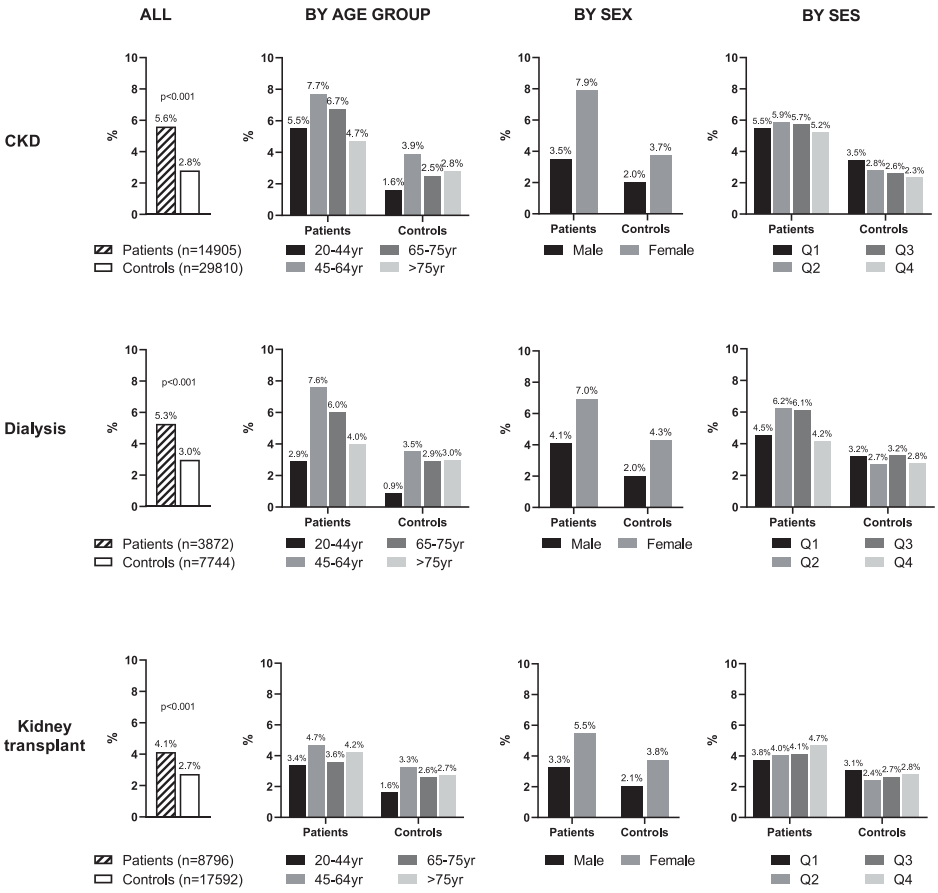


Figure 7.1: Percentage of chronic antidepressant prescription (DDD≥180) in CKD Stage G4-G5 without kidney replacement therapy, dialysis, and kidney transplant patients versus matched controls, and by age, sex, and socioeconomic status.

Abbreviations: CKD, chronic kidney disease; SES, socioeconomic status; Q, quartile; DDD, defined daily dose

Table 7.2: Prescription rates of the different classes of antidepressants and individual antidepressants in CKD Stage G4-G5, dialysis, and kidney transplantation patients and matched controls using antidepressants[a].

	CKD Stage G4-G5			Dialysis			Kidney transplantation		
	Patients	**Controls**	**P-value**	**Patients**	**Controls**	**P-value**	**Patients**	**Controls**	**P-value**
SSRI (%)	**55.1**	**62.0**	**0.004**	**61.3**	**67.1**	**0.206**	**65.1**	**69.7**	**0.156**
Citalopram	19.6	21.5	0.334	26.0	19.0	0.083	21.7	21.0	0.792
Paroxetine	19.0	22.8	0.056	20.6	28.1	0.068	20.6	25.1	0.125
Sertraline	6.5	5.9	0.640	4.4	8.7	0.076	10.7	8.9	0.383
Escitalopram	4.1	5.8	0.103	4.9	4.8	0.946	5.8	6.6	0.605
Other*	6.6	7.5	n.d.	5.9	7.4	n.d.	7.4	9.8	n.d.
TCA (%)	**23.4**	**19.5**	**0.048**	**23.0**	**14.7**	**0.026**	**18.7**	**11.0**	**0.002**
Amitriptyline	13.1	8.3	0.002	17.7	7.8	0.002	11.3	4.8	<0.001
Nortriptyline	7.3	7.4	0.980	4.9	4.3	0.776	4.7	2.1	0.034
Other#	3.5	3.9	n.d.	2.0	3.0	n.d.	3.3	4.2	n.d.
Other (%)	**30.4**	**28.9**	**0.489**	**27.9**	**26.4**	**0.720**	**26.4**	**28.4**	**0.509**
Mirtazapine	16.8	15.8	0.568	20.6	14.3	0.083	12.6	10.8	0.405
Venlafaxine	8.8	10.0	0.399	7.8	8.7	0.758	8.2	13.1	0.026
Other+	6.1	5.3	n.d.	3.9	5.6	n.d.	5.6	6.4	n.d.

a. The table shows the percentages of (type of) antidepressants prescribed in individuals on antidepressant prescription. The prescription rates of SSRI, TCA, and other add up to more than 100% which indicates that some individuals were prescribed more than one antidepressant from different classes.
Abbreviations: CKD, chronic kidney disease; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant
*fluvoxamine and fluoxetine
#clomipramine, imipramime, doxepine, maprotiline, dosulepine
+bupropion, duloxetine, trazodone, agomelatine, vortioxetine, mianserine

Discussion

We conducted the first nationwide study assessing chronic antidepressant prescription in patients with CKD Stage G4-G5 with and without KRT compared with age, sex, and SES-matched controls. In this study, the percentage of prescribed antidepressants was higher in CKD patients than in the matched general population without CKD. Around 6% of CKD Stage G4-G5 patients, 5% of dialysis patients, and 4% of transplant patients were chronically prescribed antidepressants compared with around 3% in the control groups. The antidepressant prescription was highest in patients aged 45-64 years. Both in patients and controls, women were more likely to

be prescribed antidepressant medication. Furthermore, antidepressant prescribing in CKD patients was comparable across SES categories which suggests that there is no association between educational level and chronic antidepressant prescribing. SSRI was the antidepressant of choice in patients being prescribed antidepressants; with 55% of CKD, 61% of dialysis, and 65% of kidney transplant patients using a drug from this class of antidepressants. Interestingly, TCAs were prescribed significantly more often in patients compared with controls.

Strengths and limitations

In this study, we used a comprehensive data source of routinely collected health claims data comprising approximately 98% of all Dutch inhabitants. This enabled us to study CKD Stage G4-G5 patients with and without KRT in the same study cohort and to select a matched control group from the general population. Pharmacy dispensing data, which was used to determine antidepressant prescription in this study, is generally considered the most accurate way to determine medication use in large populations as opposed to medication reviews from patient interviews or medical charts which are vulnerable to recall bias or incomplete registration.[212] Furthermore, our data allowed for the selection of chronically prescribed antidepressant medication representing a group of patients with clinically significant depressive symptoms present for a prolonged period of time. An additional advantage of pharmacy dispensing data is that they only represent prescribed medication that is truly dispensed by the pharmacy and accordingly collected by the patient. Although medication adherence remains difficult to quantify, regular medication dispensing by a pharmacy is a strong indicator that this medication was routinely used by the patient.

Several limitations of this study must also be acknowledged. First, the validity of study results must be discussed when health claims codes are being used to identify a study population. Previously, we showed that Dutch health claims data from the Vektis database provide reliable estimates of the Dutch dialysis and kidney transplantation population since the correspondence between the Dutch renal registry data and the Vektis data was very high (99%).[67] The overall sensitivity to identify patients with CKD Stage G4-G5 (eGFR <30 mL/min/1.73 m^2) using Dutch health claims data was low (51%), although sensitivity was higher in younger patients. The relatively low validity can be explained by the fact that patients solely treated in primary care cannot be identified using hospital claims data. As a result, especially elderly patients and patients with limited comorbidities are underrepresented in the CKD Stage G4-G5

group.[69] Consequently, there is a chance that unidentified CKD patients in our study are selected as controls.

Second, we were unable to determine the indication for the prescription of antidepressants. Besides the treatment of depressive symptoms, antidepressants can be prescribed for other diagnoses such as neuropathic pain or anxiety, which are both more common among CKD patients than in the general population.[197–199]

Antidepressant use

CKD Stage G4-G5 without KRT Antidepressant use in CKD patients without KRT has been described in previous studies originating from the USA and the UK.[12,201,203,204,213] The 2020 USRDS report describes SSRI prescription drug coverage, based on 6 months prescriptions, in CKD Stage G4 and Stage G5 patients being 22.4% and 21.8%, respectively (of note: this USRDS report only described patients aged >65 years and coverage of other antidepressants is not reported).[12] Two studies by Fischer et al. report antidepressant use, derived from patient interviews, in CKD patients (eGFR <60 mL/min/1.73 m^2) using data from two different US cohorts among patients with a mean age of around 60 years.[203,213] Antidepressant use of 18.2% was reported in the Chronic Renal Insufficiency Cohort and 5.4% in the African American Study of Kidney Disease and Hypertension cohort.[203,213] Finally, Balogun et al. reported an antidepressant use of 29.1% using Medicare pharmacy dispensation data from the national Veterans Affairs Health System database, a cohort of elderly (mean age 74 years) CKD patients (eGFR <60 mL/min/1.73 m^2).[201] The study by Iwagami et al. is the only one comparing antidepressant use of CKD patients (eGFR <60 mL/min/1.73 m^2) with matched controls from the general population.[204] This UK study reported that 16.3% of CKD patients with a mean age of 76 years were taking antidepressants, defined as a prescription for a period of at least 6 months, compared with 11.9% in the controls.

The chronic antidepressant prescription in CKD Stage G4-G5 patients in the Netherlands, being 5.6% as reported in this study, is considerably lower than described in literature with the exception of the African American Study of Kidney Disease and Hypertension cohort. It is unknown why this African American cohort reported such low rates of antidepressant use, although it has been suggested that depression is undertreated in African American populations. The low antidepressant prescription rates in our study cannot likely be explained by the age of the included participants as these were comparable across the different studies. Furthermore,

the fact that we only included patients with an eGFR <30 mL/min/1.73 m^2 is unlikely to be related to the observed differences in antidepressant prescription since other studies describe no clear relationship between the level of eGFR and antidepressant use.[203,204,213] Indeed, the percentage of prescribed antidepressants in our study might be lower due to the selection of chronic prescriptions. Nevertheless, antidepressant prescription in the Netherlands seems to be remarkably lower than reported by the USRDS (although only reporting SSRI prescriptions) and the UK study, both based on 6 months prescriptions.[12,204] Furthermore, we report a 10.6% prevalence of total antidepressant prescription which is still remarkably lower than previously reported.

Dialysis The 2020 USRDS report describes the percentage of patients undergoing hemodialysis and peritoneal dialysis using SSRI in the USA, which is 21.5% and 19.3% respectively.[12] Guirguis et al. reports that 11% of hemodialysis patients use antidepressants, based on a small set of UK patients who were interviewed.[214] Finally, Lopes et al. report antidepressant use, derived from medical charts, of approximately 13% in a cross-sectional analysis of the DOPPS II cohort including hemodialysis patients from 12 different countries.[215] Again we find a lower prevalence of chronic antidepressant prescriptions in dialysis patients compared with other studies. Where the USRDS reports chronically prescribed medication, the duration of prescriptions is not known for the other two studies where antidepressant use was based on patient interviews and chart review.[12,214,215] The results of these latter studies are in concordance with our reported total antidepressant prescription rate of 12.1% in dialysis patients.[214,215]

Kidney transplantation Information on antidepressant use in kidney transplant patients is scarce. The 2020 USRDS report described an SSRI use of 19.6% in transplant patients.[12] Lentine et al. studied antidepressant prescriptions in the year before and after transplantation using US pharmacy claims data. Antidepressant prescriptions were 12.8% in the year before transplantation, of which 51.8% of the patients continued use after transplantation and 13.2% started use after transplantation.[200] Among transplant patients, we found a lower prevalence of both chronic (4.1%) and total (7.8%) prescription of antidepressants in comparison to other studies.

Prescribing patterns

The Dutch clinical practice guideline advises SSRIs for the treatment of patients with depressive disorders, because of their lower risk of side effects compared with TCAs, and prefers the prescription of SSRIs citalopram and sertraline and the TCA

nortriptyline in older individuals.[216] In line with this guideline, the results of our study show that most older patients were prescribed citalopram. However, the results of our study do not show a preference for nortriptyline over amitriptyline in older individuals. This may change in the coming years as prescribers may gradually become aware of the beneficial effects of nortriptyline.[217] Our data is broadly consistent with previously conducted studies in CKD patients describing the preference of SSRIs over TCAs.[200,203,204,213] Data on the specific type of antidepressant is scarce, but two studies by Iwagami et al. and Guirguis et al. report that citalopram is the most commonly prescribed antidepressant in CKD and dialysis patients respectively.[204,214]

Prescription of antidepressants in the general population

The antidepressant prescription of approximately 3% in our matched control groups is lower compared with data from the general population in the Netherlands showing that around 6% of all Dutch inhabitants were prescribed antidepressants in 2019.[218] This difference might be explained by the older age of the matched control groups, as our results suggest that antidepressant use decreases with age. Antidepressant use in adults seems to be higher in the US (13.2%) compared with Europe (7.2%).[205] Of note, the percentage of antidepressant use in Europe varies widely per country, from 15.7% in Portugal to 2.7% in Greece.[205]

Factors related to antidepressant prescription

Variations in antidepressant prescription between countries are the result of a complex interplay of factors like the prevalence of depression, certain stigmata about depression, a country's healthcare spending and coverage, and the availability of other treatment options for depression.[205,206] The high percentage of antidepressant prescriptions of CKD patients in the US is in line with the known high antidepressant rates in the US population, which is among the highest in the world.[206] On the other hand a recent study by Hayward et al. demonstrated that the chance of hyperpolypharmacy in older patients with advanced CKD was twice as high in the Netherlands as in the UK.[168] In light of this study it is perhaps remarkable that this does not hold true for antidepressants – the prescription of antidepressants in CKD patients with and without KRT seems to be lower in the Netherlands than in the UK. The results of the study by Hayward et al. imply a generally reserved prescribing approach of UK physicians towards patients with CKD, whereas the results of our study suggest a restrictive prescribing approach of particularly antidepressants in the Netherlands.

Conclusion

This nationwide analysis of Dutch pharmacy dispensing data shows that chronic antidepressant prescription was significantly higher in CKD patients with and without KRT compared with their matched controls from the general population. The prescription was lower in elderly patients and men, yet unrelated to SES. This study reveals an importantly lower prescription rate of antidepressants in Dutch CKD patients than reported in CKD patient populations elsewhere. It is difficult to assess to what extent the intercountry variation is a result of underprescription or overprescription.

8

General discussion

This thesis aimed to assess the value and validity of health claims data for kidney research (Part 1 and 2) and examine healthcare expenditure and medication use of patients with advanced CKD (i.e. CKD Stage G4-G5 without KRT and CKD Stage G5 with KRT, being either dialysis or kidney transplantation) (Part 3 and 4) using Dutch health claims data. This general discussion discusses the results and methods used in the studies described in this thesis and elaborates on the possibilities of Dutch health claims data for kidney research. Furthermore, the development of the online Dutch Kidney Atlas focusing on the burden of CKD patients (e.g. CKD Stage G4-G5 not treated with KRT, dialysis, and kidney transplantation) and its regional variation in the Netherlands is addressed (Part 5).

Part 1 – Value and use of Dutch health claims data for kidney research

Opportunities of using the Dutch health claims database

Chapter 2 discussed the principal strengths of health claims data in general and described health claims databases used for kidney research around the world. This knowledge derived from existing literature, together with the experience gained while working with the Dutch health claims database (Vektis database), provided valuable insight into the possibilities of Dutch health claims data for kidney research.

One of the major advantages of the Vektis database is its nationwide coverage. Because of the mandatory nature of basic health insurance in the Netherlands, the database includes data on nearly all (98%) Dutch citizens resulting in an almost complete representation of the Dutch population, including individuals of all ages and socioeconomic backgrounds.[29,30,129] This important feature of the Dutch database also applies to other countries with universal healthcare coverage in which health claims databases are available for kidney research, such as France, Japan, South Korea, and Taiwan.[42–45] This is in contrast to countries without universal healthcare coverage, such as the USA and China, where health claims databases can be large but not representative of the entire population. For example, the US Medicare program only provides health insurance for American citizens aged 65 years and older as well as for patients with severe diseases such as those suffering from CKD requiring KRT, resulting in an overrepresentation of elderly individuals in this database.[48] The Chinese Commercial Health Insurance database covers Chinese citizens with commercial health insurance and is thereby likely a selection of people with higher socioeconomic status.[43] This illustrates that in countries without universal healthcare coverage, one should be aware of the differences between the insured and the uninsured population when generalizing these results to a broader population.[22,24]

Since health claims data is routinely collected as a by-product of payment processes, data collection usually needs limited time and expenses to comprise many individuals. This makes it possible to study data of large samples or rare diseases with relatively little effort.[22] With Vektis data it is possible to study all Dutch CKD patients treated in hospitals which, unlike many other studies, enables to include CKD Stage G4-G5 patients with and without KRT in the same cohort. In addition, it is possible to compare results in the CKD population with those on a sample of the general population, by selecting a matched control group from the Vektis database.

Another major advantage of health claims databases is the unique set of data; data that is often lacking or less detailed in other datasets. For example, the Vektis database contains unique information on the use of healthcare resources, healthcare costs, and pharmacy dispensing data in combination with geographical data. This observational data reflects healthcare in real-life clinical practice and represents a complete care pathway of a patient from the first contact with a nephrologist until the last treatment.[33]

Challenges of using the Dutch health claims database

Chapter 2 discussed the challenges of using health claims data for kidney research in general. Below we will specifically discuss the main limitations of using Dutch health claims data for kidney research, based on our own studies and experience.

Missing information and misclassification

First of all, health claims data is structured for healthcare delivery and financing systems meaning that the data is not collected and designed for clinical research purposes.[18,26,100] This results in two major challenges of using health claims data for kidney research, that is missing information and misclassification. As for the missing information, the Vektis database lacks important information on the diagnosis of kidney diseases, information on disease severity and progression of kidney disease, variables such as smoking or body weight, and laboratory data to estimate kidney function.[23,33] As a result, the identification of kidney disease patients for our research was purely based on diagnosis and procedure codes using hospital claims data. Within the Vektis database, diagnosis information of patients treated by the general practitioner (GP) is missing since primary care claims, in contrast to hospital claims, do not include diagnosis information. Depending on the specific diagnosis, this has varying impact on the identification of patients within the Vektis database since Dutch GPs play a dominant role in the treatment of patients with chronic conditions. Another consequence of unmeasured variables is that, for outcome research, this might lead to an incomplete adjustment for potential confounders.[22,219]

Proxy variables can be used to address the issue of missing clinical information.[26,219] A proxy is based on measured variables from the database (such as medication prescription data) and aims to approximate the unmeasured variable (e.g. a specific chronic condition). We developed proxies for several chronic conditions (diabetes mellitus, hypertension, malignancy, and macrovascular disease) based on a combination of pharmaceutical claims, health claims for primary care activities, and

hospital claims (DBCs). In addition, we made use of Pharmaceutical Cost Groups (PCGs) as a proxy for several other chronic conditions [e.g. chronic obstructive pulmonary disease (COPD), Parkinson's disease]. PCGs have been shown to provide reliable estimates of certain chronic conditions through identification by claims for specific prescribed drugs.[171,172101,171,172,209,210] They were developed by 'Zorginstituut Nederland' (National Health Care Institute) and used for risk-adjustment in the Dutch healthcare system.[171] Another possibility to overcome missing information is by linking health claims data to other datasets containing clinical information.[26,219] Due to privacy issues we were unable to link the Vektis database to other databases for our research projects. The linkage capacity of a database greatly expands its research possibilities provided privacy is protected.[26] If a common patient identifier is available in both databases, one could link the Vektis database to for example hospital data (including clinical and laboratory variables) or to the Dutch Renal Registry (Renine) database of dialysis and kidney transplant patients (including primary kidney disease, quality indicators, and patient-reported outcome measures).

Misclassification of information concerns discrepancies between the diagnoses registered in the database and the actual disease of a patient which could be the result of overcoding and undercoding.[20,22,28] Overcoding (accidental or intentional inclusion of more diagnostic codes than necessary) can be related to coding optimization; i.e. a diagnosis with higher reimbursement fees is more likely to be coded than the ones with lower fees. This automatically leads to undercoding (incomplete inclusion of diagnostic codes) of diagnoses with lower reimbursement fees. Another reason for undercoding may have occurred in our research, as Dutch health insurance limits the number of active DBCs of one individual. For example, a patient with diabetic nephropathy cannot have a claim for both diabetes mellitus and CKD at the same time, resulting in undercoding of at least one of these disorders.

Missing information and misclassification both potentially compromise the validity of study results.[20,21,27,28] Therefore, validation studies are needed to investigate whether health claims data can provide reliable estimates of the frequency of certain diseases.[22,26] Part 2 of this discussion addresses the validity of Vektis data regarding the identification of CKD patients.

Data processing and accessibility

There are several challenges concerning data processing and data accessibility that could limit the use of health claims data for clinical research.[41] First, the large size and

complexity of health claims databases make research difficult and labor-intensive requiring a significant amount of time and expertise.[19,23] Furthermore, health claims databases consist of an enormous amount of unprocessed raw data that needs processing before it becomes a useful dataset for a specific research question. To conduct the analyses within this thesis, we had to make many micro-decisions while processing the data, e.g. how to cope with missing data, how to reclassify unsuitable data, how to overcome inconsistent or possibly incorrect registrations, which variables to use and in what way, how to select a research population, and how to define incident or prevalent cases. Box 8.1 presents an example to illustrate the steps of processing 'raw' data into data that could be used for the cost analysis of chapter 2.

Accessing the Vektis database requires application procedures and is expensive.[49] Vektis charges a fee for the hours they spend on preparing the dataset and supervision, as well as a fee for the use of the workstations and use of the data. In addition, conducting kidney research using health claims data usually requires a financial budget for people of different expertise (e.g. data analyst specialized in big data, nephrologist, epidemiologist, PhD student). Funding can therefore be difficult to obtain, especially for lump-sum grant applications (e.g. reimbursement of the salary costs of the PhD student only). Barriers to data accessibility differ considerably between countries and seem to influence the utility of health claims databases for clinical research.[41,42,71] Taiwan is the leading example that low costs and insignificant technical barriers for the reuse of health claims data dramatically increase the use of claims data for research purposes.[42]

Box 8.1. Data processing steps preceding cost analysis with Vektis data - an example

Chapter 4 describes, among other things, the estimation of the annual healthcare costs of dialysis patients. Within the Vektis database, healthcare costs are registered per calendar year. For a correct cost estimation, we therefore had to select patients who were on dialysis treatment for the full year. In order to do so, we had to take several steps to define our research population. First, all patients with at least one health claim related to dialysis in 2014 were selected (newly transplanted patients in 2014 were excluded). However, procedure codes for dialysis treatment are registered per 7 days. As a consequence, for a full year of dialysis one would expect 52 dialysis claims with a standard duration of 7 days. From the database of 2014 we extracted 7883 individuals with a dialysis-related health claim of which 54% (4253) had registered dialysis claims for less than 365 days in total. The Dutch Renal Registry (Renine) reports

6446 prevalent dialysis patients on 1 January 2014 and 1414 incident dialysis patients in 2014. From this, we concluded that a part of the dialysis claims in the database appeared to be inconsistent, incomplete, or possibly even incorrect. To include as many 'prevalent' dialysis patients as possible (in correspondence to the Renine data) we defined a patient with 'full year dialysis' to have at least 337 days with an active dialysis-related claim. This relatively arbitrary cutoff of 337 days, intended to improve data quality and utility, might have resulted in a small bias through unjustified in- or exclusion of dialysis patients in the final research population.

In the next step, we wanted to differentiate patients into the different dialysis treatment modalities (i.e. in-center hemodialysis, home hemodialysis, CAPD, APD). According to the health claims data, a considerable number of patients had different dialysis modalities in one year. For example, a home hemodialysis patient may temporarily have in-center hemodialysis during a hospital admittance, and a CAPD-patient may shift to in-centre hemodialysis because of a catheter-related problem. In order to allocate as many patients as possible to their 'true' dialysis modality, patients were attributed to a dialysis modality if they were treated with one modality for ≥75% of their total treatment time. Total treatment time was defined as the number of days in 2014 with a dialysis related claim. Patients with less than 75% of their total treatment time on one dialysis modality were allocated to the 'Mix' dialysis group (patients on different dialysis treatment modalities in one year). Again, by trying to improve the utility of the data for our research, we may have introduced a bias.

Part 2 – Validity of Dutch health claims data

Validation studies help to understand whether the studied populations derived from health claims databases are representative of the entire population of interest and which subgroups may be underrepresented or overrepresented.[20,27] Information on the validity of diagnosis codes or proxies should be provided in all research articles using health claims data.[20,27]

Validity to identify dialysis and kidney transplantation patients

The accuracy of the codes used to identify dialysis and kidney transplant patients in the Vektis database was found to be very high. The numbers of dialysis and kidney transplant patients were validated using the data of the Dutch Renal Registry (Renine) as a reference.[220] Since linkage on an individual basis between the two datasets was not feasible, sensitivity could not be calculated. Nonetheless, the

correspondence between the datasets was high (99%) for the total number of hemodialysis and peritoneal dialysis patients, as well as for the number of performed kidney transplantations per year. The correspondence was also high (94%-99%) for the different dialysis modalities (i.e. in-center hemodialysis, home hemodialysis, CAPD, APD) and type of kidney donors (i.e. living or deceased). The high validity of the identification of dialysis and kidney transplant patients in the Vektis database was expected because almost all KRT patients are cared for in the hospital and the financial incentive for correct code registration is high.

Validity to identify CKD patients without KRT

Chapter 3 describes the results of a validation study in which we tested the validity of Dutch health claims data from a regional hospital in Zwolle for identifying CKD Stages G3-G5 patients using a laboratory database as a reference. Sensitivity for the identification of CKD Stages G3-G5 patients (eGFR <60 mL/min/1.73 m^2) without KRT was low (27%). The sensitivity was higher for patients with CKD Stage G4-G5 (eGFR <30 mL/min/1.73 m^2), being 51%. Furthermore, the validity of Vektis data in identifying CKD patients was remarkably high in young patients compared with elderly patients, and higher in men than in women. For example, sensitivity was 72% in CKD Stage G4-G5 patients aged 20-59 years compared with 43% in patients aged ≥75 years. This lower validity can be explained by the fact that a substantial part of elderly patients is cared for by a GP, and therefore they cannot be identified using hospital claims data.

This validation study demonstrated that Dutch health claims data has low sensitivity for the estimation of overall CKD prevalence in the general population, especially in the case of elderly CKD patients and patients with less advanced CKD. Nonetheless, health claims data may be of value in estimating CKD prevalence in specific subgroups, particularly in young patients and those with advanced CKD, as they are more likely under the care of a nephrologist.

Part 3 – Healthcare costs

Healthcare costs of patients on different kidney replacement modalities

Chapter 4 provides estimates of the average annual healthcare costs of patients treated with a KRT modality in the Netherlands, replacing the previous estimates dating from the 1990s.[123] The annual healthcare costs of prevalent dialysis patients were quantified as well as costs of recently transplanted patients and the evolution of

costs during the first years post transplantation, thereby providing new and valuable information which can be used to project future healthcare expenditures.

This study demonstrates that the average annual healthcare expenditures of patients on all dialysis modalities are high, ranging from €78 000 for CAPD patients to €106 000 for patients with different treatment modalities in 2014. CAPD patients have the lowest costs compared with other dialysis modalities. A direct comparison of costs between modalities is not possible, as some of the observed cost differences may be related to unknown differences in patient characteristics. For example, it is known that older age, lower SES, and the presence of comorbidities are associated with in-center hemodialysis treatment[221–225] and higher healthcare costs.[67] Nevertheless, our results suggest that an increase in the number of patients starting CAPD could reduce the overall financial burden of ESKD to some extent. Although 'PD-first initiatives' have been advocated in the Netherlands, aiming to increase the use of PD as initial dialysis treatment[226], the number of patients starting PD treatment in the Netherlands remained fairly stable over time (335 in 2005 versus 342 in 2020).[220]

Furthermore, this study demonstrates that the average annual healthcare costs in the year of transplantation are high and comparable to the costs of dialysis patients (€80 000). However, where dialysis costs are presumed to remain fairly stable over time, the annual costs of kidney transplant patients decline substantially to 14%-19% of annual dialysis costs within two years after successful transplantation. Besides the clear survival and quality-of-life benefits from kidney transplantation, our data, therefore, shows additional benefits of kidney transplantation from a societal cost point of view.

(Age-related) Healthcare utilization in CKD patients and controls

Chapter 5 describes the age-related differences in healthcare use and costs of CKD Stage G4-G5, dialysis, and kidney transplant patients in comparison to matched controls from the general population. Previously we showed that the high healthcare costs of KRT patients are caused by two factors: the high costs related to the treatment of the kidney disease itself and the costs related to the additional care needed for the CKD-related comorbid conditions.[146] In this chapter we distinguish 'treatment-related' hospital costs and 'non-treatment-related' hospital costs, the latter being a good proxy of patients' comorbidities as they reflect the hospital care required in addition to the treatment of their kidney disease.[127,152] We compared our results with a matched control group from the general population and presented the results by age group.

This study demonstrated that in CKD patients (treated with or without KRT) healthcare utilization is very high and corresponding healthcare costs are far exceeding those of the general population. This can already be seen at a young age and in the earlier stages of CKD. Interestingly, while healthcare costs of the general population rise with age, we observed a decrease in costs in all kidney patient groups aged 75 years or older; this decrease was largely explained by the lower hospital and medication costs. This study revealed that among CKD patients the consequences of their comorbidity burden are already present at a young age, supporting the relevance of age-tailored and early management of CKD patients aimed at prevention and treatment of comorbid illness. Finally, the results of the studies described in chapters 4 and 5 help to understand the societal cost impact of CKD and KRT which is essential information to keep the ever-increasing healthcare costs under control.

Advantages of cost data

The cost data derived from health claims databases has specific strengths compared with other cost data from different data sources. The combination of information on medical resource utilization and associated reimbursement costs enable a real-world evaluation of the financial burden of a disease or procedure.[21,227–229] Furthermore, the longitudinal nature of health claims data together with the detailed documentation of costs per procedure and healthcare services offers unique research opportunities.[227,230] Health claims data enable two types of economic evaluation namely cost analysis, as described in chapters 4 and 5, and cost-effectiveness analysis.[227] Although cost-effectiveness studies provide essential information to health policymakers about the trade-off between costs and outcomes, they fall outside the scope of the research presented in this thesis.

Challenges of cost data

Studying healthcare costs with health claims data also has its shortcomings. First, one should consider that healthcare reimbursement amounts represent only one cost definition, namely, the negotiated prices that health insurance companies pay for the services delivered by healthcare providers. This does not necessarily reflect the value of resource use (such as staff and material resources) needed to produce these healthcare services to patients.[228,230] In line with this, health claims data can only estimate direct medical costs as these are associated with medical resource utilization. Indirect medical costs (i.e. the expenses incurred from lost work productivity as a result of the morbidity and mortality associated with the disease) cannot be estimated. Second, health claims data is limited to procedures and

expenses covered by the health insurer. The out-of-pocket expenses by the patient or patient cost-sharing amounts can therefore not be identified.[230] Third, a general issue in working with medical cost data is that it is right-skewed. This means that the bulk of individuals are nonusers of medical resources with zero costs, while a relatively small number of individuals are extremely frequent users.[229,230] Because of their non-normal distribution, cost data is difficult to analyze with standard methods. In the studies in this thesis the average annual cost data is presented as mean per person. Although the median is the most valid parameter for skewed data, it is often difficult to interpret for the reader. To better represent the distribution of the data we used percentiles instead of standard deviations to complement the mean. A specific drawback of the cost data within the Vektis database is that it is registered per calendar year. For the cost estimation of KRT patients, it was therefore needed to select patients who were on dialysis treatment for the full year (see Box 8.1).

Part 4 – Medication prescription

Polypharmacy in CKD patients

Chapter 6 describes the prevalence of polypharmacy in CKD patients in the Netherlands. Using pharmacy dispensing data from the Vektis database it was demonstrated that polypharmacy (use of ≥5 medications) is highly prevalent in CKD patients with and without KRT compared with matched samples from the general population. The prevalence of polypharmacy ranged between 87%-95% in CKD Stage G4-G5, dialysis, and kidney transplant patients, while in controls this ranged from 15%-33%. The prevalence was lower for chronic medication use, ranging from 66%-75% in patients and 7%-18% in controls. Proton pump inhibitors and statins were the most commonly prescribed medications in CKD patients. Analyzing medication use in relation to clinical variables showed that polypharmacy prevalence among patients with advanced CKD is associated with older age, low SES, the presence of chronic conditions like diabetes mellitus or vascular disease, hospitalization, and an emergency room visit.

Prescription of medication to CKD patients requires carefully balancing between the potential beneficial effects of the treatment of the disease and its comorbidities on the one hand and the risk of inappropriate prescribing or adverse effects on the other hand. Physicians are constantly balancing between overtreatment and therapeutic nihilism since both are associated with unfavorable outcomes. Minimizing the medication burden is therefore challenging. The results of this study suggest that a

first step towards a more appropriate medication use could be a critical approach to the prescription of specific medications like proton pump inhibitors in all CKD patients and statins in dialysis patients.

Antidepressant prescription in CKD patients

Chapter 7 evaluates chronic antidepressant prescription in advanced CKD patients with and without KRT compared with matched controls. Chronic antidepressant prescription was significantly higher in patients than in controls, ranging from 4%-6% in patients compared with 3% in controls. Prescription was highest in patients aged 45-64 years and in women, yet unrelated to SES. This study shows a considerably lower prescription rate of antidepressants in Dutch CKD patients than reported in CKD populations elsewhere. The underlying cause for this variation is complex and could be influenced by the prevalence of depression, a country's wealth and the wellbeing of its citizens, but also by cultural differences towards depression, use of antidepressants or cognitive therapy.

Advantages of medication prescription data

Health claims data is highly suitable for drug utilization studies because of the availability of pharmacy dispensing data in combination with diagnostic and procedure information to define study outcomes and covariates.[212] Pharmacy dispensing data is commonly seen as the gold standard for information on medication exposure as compared with patient interviews or records of physician prescribing from medical charts. Problems like poor patient recall or missed recording of prescribed medication in medical charts do not apply within pharmacy data, which is therefore considered the most accurate way of determining drug exposure in large populations.[212] Moreover, pharmacy dispensing data only include prescribed medication that was actually dispensed.[24,231] Whereas information on medication adherence is an issue in most studies describing medication use, with pharmacy dispensing data the regular recurrence of dispensed prescriptions of a specific medication is an indirect yet strong indication that the medication was routinely taken. Next, prescription data can be used as a proxy for disease.[22] For example, the prescription of antidepressants has shown to be a valid marker for the presence of clinically significant depression.[231,232] Within the Vektis database, PCGs which are based on health claims data for specific prescribed medications were used as a marker for chronic conditions.

The pharmaceutical data within the Vektis database is very complete as a result of the universally accessible and mandatory health insurance in the Netherlands

which covers most dispensed medication within the basic health insurance package, although co-payment is sometimes required. This is in contrast to some other countries, where reimbursement policies may differ from state to state or depend upon a patient's age.[231]

Challenges of medication prescription data

Vektis does not contain data on over-the-counter medications. Also, nursing home medication is missing since these medications are not dispensed to residents via the individual pharmacies but via the nursing home itself. In addition, medications administered during hospital admission or in the process of dialysis treatment cannot be identified with Vektis data since these medications are reimbursed via the (fixed) total price of a DBC. This might lead to an underestimation of medication use in dialysis patients. Another limitation is the lack of clinical data for comparative outcome research. Physicians describe medication in the light of the clinical characteristics of a patient and these characteristics are often not registered in a health claims database. If these characteristics are unevenly distributed between users and non-users and also independent risk factors of the study outcome, this can lead to confounding since one cannot control for these unmeasured characteristics.[212]

Part 5 – Dutch Kidney Atlas

Until now health claims data have been mainly used to evaluate disease incidence, prevalence, follow-up data, and costs resulting in scientific papers in medical journals. The work within this thesis has been used to develop the first publicly accessible Dutch Kidney Atlas (www.nieratlas.nl) using data from the Vektis database. This novel application of health claims data provides insight into healthcare services for CKD patients for consecutive years and is easily accessible for a broad audience. The website provides information on the number of patients, healthcare costs, treatment (besides KRT), medication, outcomes, and other conditions of advanced CKD patients (Stage G4-G5 not on KRT, dialysis patients, and patients with a kidney transplant) in the Netherlands (see Figure 8.1 and 8.2 for an overview of the content of the Dutch Kidney Atlas). The data is presented on a national and a regional level [by province and Municipal Health Services areas (Gemeentelijke Gezondheidsdiensten, GGD)] and provides absolute numbers and numbers per million population with a 95% confidence interval (see Figure 8.3 for examples from the Dutch Kidney Atlas). The Dutch Kidney Atlas presents unadjusted results as well as results standardized for the age and sex distribution of the Dutch general population. Furthermore, data is also

reported by age group and sex and a selection of results are compared with matched controls of the general population. The website includes data since 2012 and will be updated on an annual basis. The website primarily aims to provide information to healthcare researchers and policymakers but is also accessible for CKD patients and the public at large.

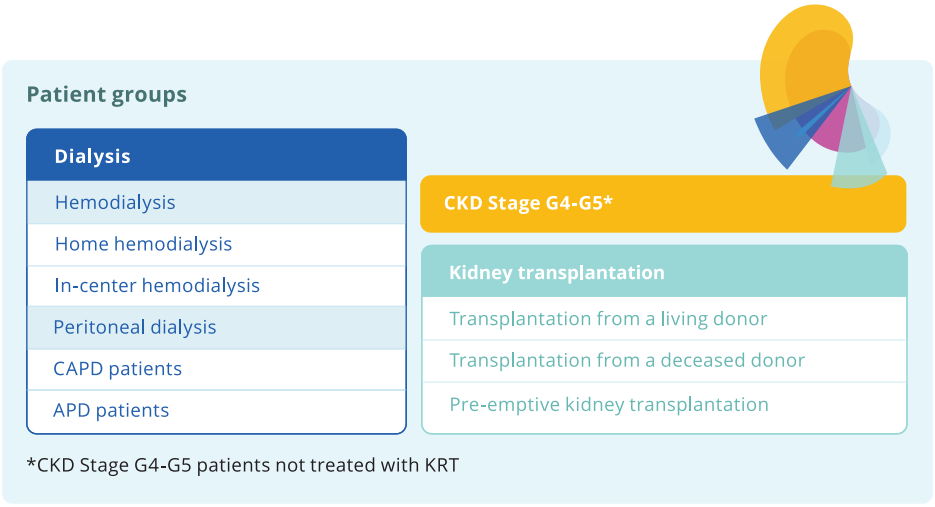


Figure 8.1: Patient groups and subgroups included in the Dutch Kidney Atlas

The data published on the Dutch Kidney Atlas may provide a basis for future research regarding the prevention of kidney diseases and their complications. Furthermore, its content can be used as input for improvements in (quality of) healthcare for CKD patients. This ideally could result in a reduction of health problems and healthcare costs. The Dutch Kidney Atlas might also serve as an example for other countries, where health claims data could also be used for a similar national atlas on CKD patients. In this perspective, the United States Renal Data System (USRDS) yearly publishes the USRDS Annual Data Report containing information on CKD patients (with and without KRT) using US health claims data from Medicare fee-for-service beneficiaries. Uniformity in patient selection and definition of patient subgroups and variables may enhance the comparability between the different atlases. Only then, it is possible to compare health utilization across international populations with different demographics and with different health system characteristics.[25]

Number of patients

Incidence on day 1[1]
Incidence on day 91[2]
Prevalence[3]
Number of performed kidney transplants[4]

Healthcare costs

Total healthcare costs
Hospital-related costs
Non-hospital related costs

Medication

Insulin
Statins
ACE-inhibitors
Anticoagulants
Antidepressants
Sleep medication
Other antidiabetic medication
Other lipid-lowering medication

Outcomes

Mortality
Kidney biopsy
Visit to emergency room
Visit to outpatient clinic
Hospital admittance
Treatment for peripheral vascular disease

Treatment

Consultation of:
- cardiologist
- internist
- surgeon
- dermatologist
- physical therapist
- dietitian

ICU admittance
Dialysis treatment on ICU
Screening for kidney transplantation
Intervention for dialysis access

Other conditions

Diabetes mellitus
Malignant tumor
Macrovascular disease
Coronary artery disease
Peripheral vascular disease
CVA/TIA
Hypertension

[1]only available for CKD Stage G4-G5 without KRT and dialysis patients
[2]only available for dialysis patients
[3]available for CKD Stage G4-G5, dialysis, and kidney transplantation patients
[4]only available for kidney transplantation patients

Figure 8.2: Content per theme of the Dutch Kidney Atlas

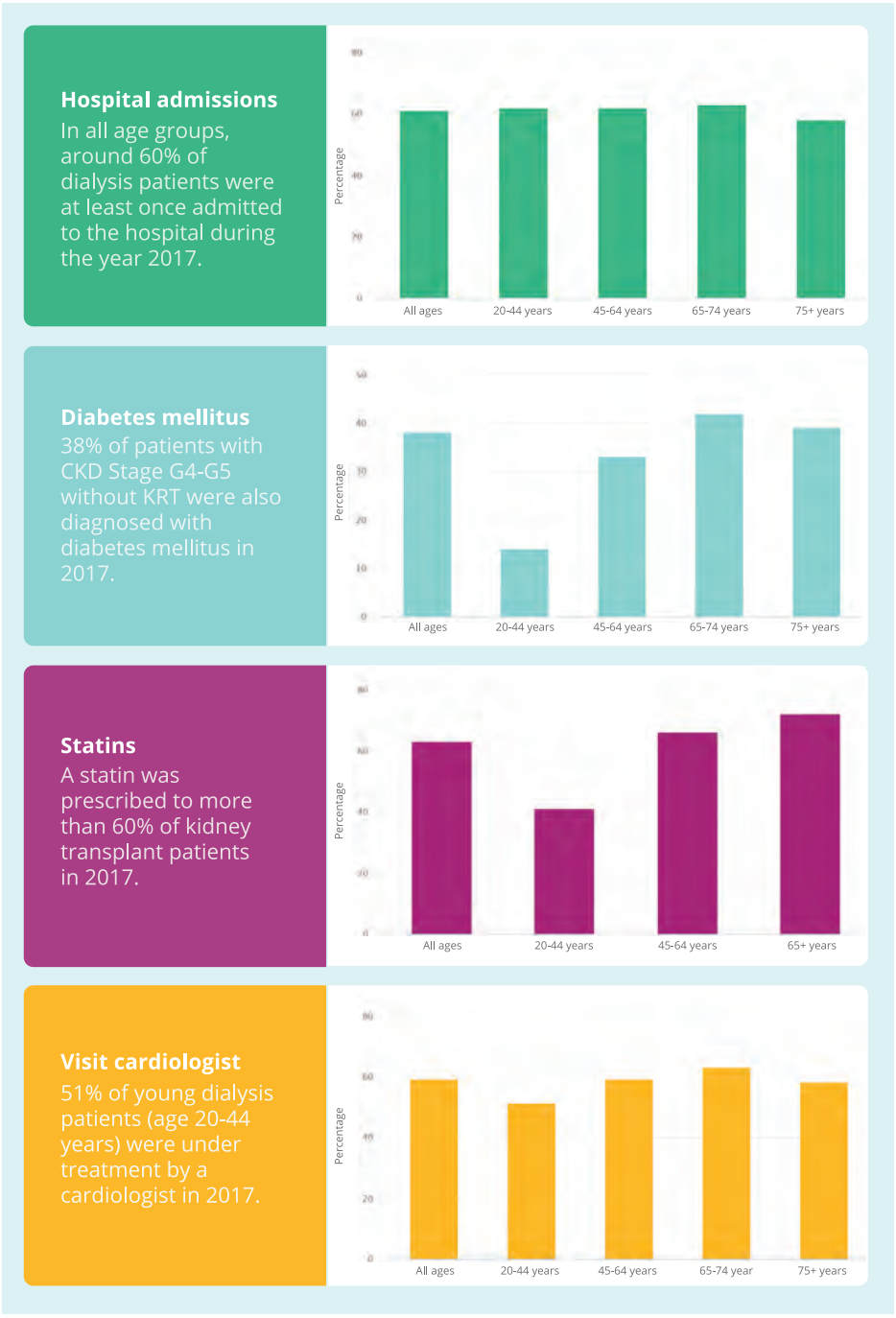
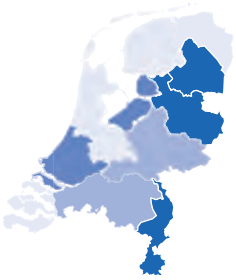
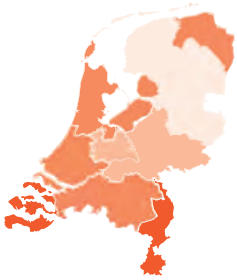


Figure 8.3 Examples from the Dutch Kidney Atlas, data from 2017

Number of patients
The number of patients initiating dialysis treatment was higher than the national average in the provinces Overijssel, Drenthe, and Limburg (data per million insured population and standardized for age).



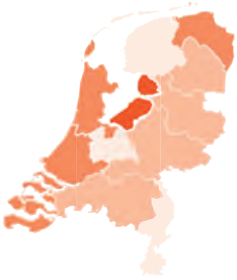
2017



Healthcare costs
Total healthcare costs per patient with CKD Stage G4-G5 without KRT were highest in Zeeland (€ 13 134) and lowest in Overijssel (€ 10 643). The national average was € 11 697.

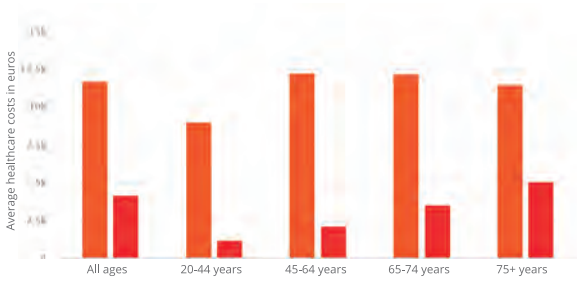
2017

Healthcare costs
Total healthcare costs of patients with a kidney transplantation were highest in Flevoland; € 23 757 per patient per year. This compared with the national average of € 17 735 per year.



2017

Healthcare costs
The total annual healthcare costs of CKD Stage G4-G5 patients in 2017 were € 11 697 per patient. This was €4171 in the matched controls.



Conclusion and future perspectives

To our knowledge, prior to the work outlined in this thesis, Dutch health claims data has never been used to conduct scientific research on CKD patients. The Vektis database has the potential to become a long-lasting data source for Dutch nephrology research. Most notably, it provides opportunities to study distinctive data (such as healthcare costs and medication use) in a large set of patients (enabling the study of patient subgroups based on for example age, sex, and SES) with the possibility to make comparisons with a matched subset of individuals from the general population. Next, Dutch health claims data has high accuracy in the identification of dialysis and kidney transplant patients. Although Vektis data is not suitable for the estimation of CKD prevalence in the general population, it may have value for the estimation of CKD prevalence in specific subgroups, particularly young patients and patients with advanced CKD, and for the study of CKD patients under the care of a nephrologist. The work in this thesis has also led to the development of the publicly accessible Dutch Kidney Atlas: a novel way to describe and present information regarding Dutch CKD patients.

Valuable steps could be taken to further improve the usability of the health claims database which may encourage more researchers to work with Vektis data. First, optimal use of Vektis data for research could be enhanced by reducing barriers to data accessibility. Simple data application processes, low data access fees, and practical guidelines on how to work with the complex data could make Vektis data more attractive for researchers with limited experience in big data analysis. However, not all procedures can be written down in practical guidelines, and the expertise of Vektis employees will remain necessary. Next, the exchange of knowledge and expertise between researchers may stimulate the further use of Vektis data. Prior knowledge of the properties and possibilities of the Vektis database is essential before transforming a valid research question into an adequate research proposal. To prevent every researcher from reinventing the wheel, making use of the expertise from researchers who worked with this data in the past and their knowledge on work processes is desirable and can help save a lot of time and money. That is why a sounding board was established after the completion of the Dutch Kidney Atlas. One of the main tasks of the sounding board is to advise both researchers and Vektis on new research proposals concerning kidney disease patients by assessing its content and feasibility, and by informing the researcher about the preconditions of working with the database. Finally, linkage of Vektis data to other datasets would greatly

improve its research potential, provided that personal information is protected. In this way, clinical data may be added to the Vektis dataset, which may also enhance the identification of CKD Stage G4-G5 patients not treated with KRT.

A

Appendices

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Summary

Chronic kidney disease (CKD) is considered a major public health problem due to its negative impact on a patients' quality of life and life expectancy and its association with high healthcare costs and healthcare utilization. A better understanding of CKD, its treatment, and outcomes is essential to improve healthcare for CKD patients. Health claims data is a relatively new source of data that offers new research opportunities for large populations of patients with kidney disease and health outcomes in a non-experimental setting. Despite the growing international popularity of health claims data, so far the use of health claims data for kidney research in the Netherlands was still in its infancy.

This thesis examines the possibilities of Dutch health claims data (stored in the Vektis database) for research in advanced CKD patients, being Stage G4-G5 CKD patients without kidney replacement therapy (KRT) and Stage G5 CKD patients with KRT (i.e. dialysis or kidney transplantation). The first aim of this thesis was to examine the value and limitations of health claims data for kidney research. The second aim was to study healthcare expenditure and use of healthcare resources (including medication use) of CKD patients using Dutch health claims data.

This thesis consists of four parts: part 1 provides insight into the value and use of health claims data for kidney research, part 2 describes the validity of Dutch health claims data for the identification of CKD patients, and parts 3 and 4 describe the use of health claims data for measuring healthcare costs and medication use of CKD patients. The content of this thesis is summarized below.

Part 1 – Value and use of health claims data for kidney research

Chapter 2 provides an overview of international health claims databases that were used for kidney research. With a literature search, we identified 13 of such health claims databases in 10 countries. We discussed the similarities and distinctions between the databases, the differences in accessibility, the main publications in the area of nephrology, and highlighted the Dutch health claims database. Further, we discussed the strengths and limitations of health claims data. Finally, we introduced the online Dutch Kidney Atlas which was developed with the research presented in this thesis. This website is an innovative way of describing Dutch CKD patients based on health claims data. It describes the burden of CKD in the Netherlands, in terms of numbers of patients, healthcare expenditures, treatment (besides KRT), medication, outcomes, and other conditions associated with CKD and outlines the geographical variation per region in the Netherlands.

Part 2 – Validity of Dutch health claims data

Validation studies help to understand whether the studied populations derived from health claims databases are representative of the entire population of interest and which subgroups may be underrepresented or overrepresented. **Chapter 3** describes the results of a validation study in which we tested the validity of Dutch health claims data from a regional hospital in Zwolle in identifying CKD Stages G3-G5 patients using a laboratory database as a reference. We compared a claim-based diagnosis of CKD (Stages G3-G5) and advanced CKD (Stage G4-G5) with one based on eGFR definitions of CKD (eGFR <60 mL/min/1.73 m^2) and advanced CKD (eGFR <30 mL/min/1.73 m^2). Analyses were stratified by age and sex. Sensitivity was higher in advanced CKD patients (51%) than in CKD patients (27%). Moreover, the validity of claims data in identifying CKD patients was remarkably higher in young patients compared with elderly patients and higher in men than in women. This validation study demonstrated that Dutch health claims data have low sensitivity for the estimation of overall CKD prevalence in the general population, especially in the case of elderly CKD patients and patients with less advanced CKD. Nonetheless, health claims data may have value in estimating CKD prevalence in specific subgroups, particularly in young patients and those with advanced CKD.

Part 3 – Healthcare costs

Chapters 4 and 5 describe the estimation of healthcare costs of CKD patients using Dutch health claims data from the Vektis database. In **chapter 4** we used Vektis data from 2012-2014 to estimate the healthcare costs of patients on different modalities of KRT. Continuous ambulatory peritoneal dialysis (CAPD) patients had the lowest costs compared with other dialysis modalities. Total average annual healthcare costs in 2014 ranged from €77 566 for CAPD patients to €105 833 for patients with different treatment modalities in one year. Costs of kidney transplant recipients were €85 127 in the year of transplantation and rapidly declined in the first (€29 612) and second (€15 018) year after successful transplantation. This is approximately 14%-19% of annual dialysis costs. Costs in the year of transplantation were 25% lower for patients with kidneys from a living versus a deceased donor. On top of the clear survival and quality-of-life benefits from kidney transplantation, our data also shows cost advantages of kidney transplantation as compared with dialysis treatment.

Chapter 5 describes the age-related differences in healthcare use and healthcare costs of CKD Stage G4-G5, dialysis, and kidney transplant patients in comparison to matched controls from the general population. In patients and controls, we studied total healthcare costs and hospital costs unrelated to CKD treatment which were presented in four age categories (19-44, 45-64, 65-74, and ≥75 years). We found that healthcare utilization and corresponding healthcare costs of CKD patients (treated with or without KRT) were very high and far exceeding those of the general population. Remarkably, this was already present at a young age and in the earlier stages of CKD indicating an early burden of comorbidities in CKD patients. Noteworthy, while healthcare costs of the general population rise with age, our study demonstrated a decrease in healthcare costs in CKD patients (with or without KRT) aged 75 years or older, which was mainly explained by lower hospital and medication costs.

Part 4 – Medication prescription

This part of the thesis describes the use of pharmacy dispensing data within the Vektis database to describe medication use in CKD patients (i.e. CKD Stage G4-G5 not treated with KRT and CKD Stage G5 treated with dialysis or kidney transplantation).

Chapter 6 reports on the prevalence of polypharmacy (concomitant use of ≥5 medications) in CKD patients and matched controls, focuses on risk factors associated with polypharmacy, and describes the most commonly prescribed medications.

We differentiated between all medication prescribed and chronically prescribed medication in 2017. This study demonstrated that polypharmacy was highly prevalent in CKD patients (with and without KRT) compared with matched controls. The polypharmacy prevalence for all medication use was 87%, 93%, and 95% in CKD Stage G4-G5, dialysis, and kidney transplant patients, respectively, while in controls this ranged from 15%-33%. The prevalence was lower for chronic medication use, ranging from 66%-75% in patients and 7%-18% in controls. Risk factors for polypharmacy in patients were older age, low socioeconomic status, diabetes mellitus, vascular disease, hospitalization, and an emergency room visit. Proton pump inhibitors and statins were the most commonly prescribed medications in patients. The high medication burden of CKD patients (with or without KRT) was a result of their kidney disease and the large burden of comorbidities and minimizing the medication burden is therefore challenging. Nonetheless, a critical approach to medication prescription while balancing between overtreatment and therapeutic nihilism is essential for appropriate medication use.

In **chapter 7** we evaluated the prescription of antidepressant medication in CKD patients with and without KRT as compared with a matched control group. The prevalence of chronic antidepressant prescription was is 5.6%, 5.3%, and 4.2% in CKD Stage G4-G5, dialysis, and kidney transplant patients respectively, while being 3% in controls. Antidepressant prescription rates were higher in women and middle-aged (45-64 years) patients, however, no association was found between antidepressant prescription and socioeconomic status. This nationwide analysis revealed a remarkably lower antidepressant prescription rate in Dutch CKD patients than reported in CKD populations from other countries. The underlying cause of this difference was difficult to assess since prescription rates are influenced by many factors like a country's prevalence of depression, its health system and coverage, the happiness of its citizens, and the availability of other treatment options for depression. It was therefore impossible to determine to what extent the intercountry variation was related to underprescription in the Netherlands or overprescription elsewhere.

Conclusion

Chapter 8 discusses the findings of this thesis and elaborates on the possibilities of Dutch health claims data for kidney research. Furthermore, the results presented in this thesis were used to develop the first publicly accessible online Dutch Kidney Atlas (www.nieratlas.nl) using Vektis data.

The main conclusion of this thesis is that the Vektis database has the potential to be an important data source for observational nephrology research in the Netherlands. The characteristics of the Vektis database provide opportunities to study unique information (such as healthcare costs, healthcare utilization, and medication use) on a national level with the possibility to make comparisons with a matched subset from the general population. Nonetheless, valuable steps regarding data accessibility, knowledge exchange, and data linkage, could be taken to further improve the research potential of the Vektis database. For this reason, a sounding board was established after the completion of this PhD trajectory and the development of the website. One of the main tasks of the sounding board is to advise both researchers and staff members of Vektis on new research proposals concerning kidney disease patients by assessing its content and feasibility, and by informing researchers about the possibilities and preconditions of working with the Vektis database.

Nederlandse samenvatting

Chronische nierschade (CNS) is een belangrijk probleem voor de volksgezondheid doordat het de kwaliteit van leven en de levensverwachting van patiënten verlaagt en tevens hoge zorgkosten en frequent gebruik van gezondheidszorg met zich meebrengt. Onderzoek naar het voorkomen, de behandeling en uitkomsten van CNS is essentieel om de gezondheidszorg voor CNS-patiënten te verbeteren. Zorgdeclaratiedata is een relatief nieuwe gegevensbron die mogelijkheden biedt voor onderzoek naar patiënten met nierziekten op nationaal niveau in een niet-experimentele setting. Ondanks de groeiende internationale populariteit van het gebruik van zorgdeclaratiedata voor onderzoeksdoeleinden, stond het gebruik hiervan voor onderzoek bij patienten met nierziekten in Nederland tot nu toe nog in de kinderschoenen.

Dit proefschrift beschrijft de mogelijkheden van Nederlandse zorgdeclaratiedata (uit de zogenaamde Vektis database) voor onderzoek bij patiënten met gevorderde CNS, namelijk patiënten in stadium G4-G5 zonder nierfunctievervangende therapie en patiënten in stadium G5 met nierfunctievervangende therapie (dialyse of niertransplantatie). De eerste doelstelling van dit proefschrift betreft het onderzoeken van de mogelijkheden en beperkingen van zorgdeclaratiedata voor nefrologisch onderzoek. De tweede doelstelling heeft betrekking op het onderzoeken van de zorguitgaven en het gebruik van zorgmiddelen (inclusief medicatiegebruik) van CNS-patiënten met behulp van Nederlandse zorgdeclaratiedata.

Dit proefschrift bestaat uit vier delen: deel 1 gaat over de toepassing en mogelijkheden van zorgdeclaratiedata voor onderzoeksdoeleinden binnen de nefrologie, deel 2 beschrijft de validiteit van Nederlandse zorgdeclaratiedata voor de identificatie van CNS-patiënten, deel 3 en 4 beschrijven zorgkosten en medicatiegebruik van CNS-patiënten gebruikmakend van zorgdeclaratiedata. De inhoud van dit proefschrift is hieronder samengevat.

Deel 1 – Mogelijkheden en gebruik van zorgdeclaratiedata voor nefrologisch onderzoek

Hoofdstuk 2 geeft een overzicht van internationale zorgdeclaratie databases die zijn gebruikt voor onderzoek binnen de nefrologie. Met een literatuuronderzoek identificeerden we 13 van deze zorgdeclaratie databases in 10 verschillende landen. We hebben gekeken naar de overeenkomsten en verschillen tussen de databases in bijvoorbeeld de toegankelijkheid en het aantal wetenschappelijke publicaties op het gebied van de nefrologie, waarbij we specifieke aandacht hebben geschonken aan de Nederlandse Vektis database. Verder hebben we de sterke punten en de beperkingen van zorgdeclaratiedata voor onderzoeksdoeleinden beschreven. Tenslotte beschrijft dit hoofdstuk de Nieratlas website (www.nieratlas.nl) welke tijdens dit promotieonderzoek is ontwikkeld. Deze website is een nieuwe manier om Nederlandse CNS patiënten in kaart te brengen met behulp van zorgdeclaratiedata. Het brengt de impact van CNS in Nederland in kaart in termen van aantallen patiënten, zorgkosten, behandeling (naast nierfunctievervangende therapie), medicatiegebruik, uitkomsten, en andere aandoeningen die verband houden met CNS, en geeft tevens de geografische variatie van deze data weer per regio in Nederland.

Deel 2 – Validiteit van Nederlandse zorgdeclaratiedata

Validatiestudies zijn nodig om te onderzoeken of de patiënten populaties die zijn geïdentificeerd met zorgdeclaratiedata ook daadwerkelijk representatief zijn voor de gehele beoogde onderzoekspopulatie en te achterhalen welke subgroepen onder- of oververtegenwoordigd kunnen zijn. **Hoofdstuk 3** beschrijft de resultaten van een dergelijke studie waarin we de validiteit van zorgdeclaratiedata van een regionaal ziekenhuis in Zwolle hebben onderzocht voor de identificatie van patiënten met CNS stadium G3-G5 waarbij een laboratoriumdatabase als referentie werd gebruikt. Daartoe hebben we een diagnose van CNS (stadium G3-G5) en gevorderde CNS (stadium G4-G5) afgeleid uit de zorgdeclaratiedata vergeleken met een diagnose gebaseerd op een eGFR-definitie van CNS (eGFR <60 mL/min/1.73 m^2) en gevorderde CNS (eGFR <30 mL/min/1.73 m^2). Analyses werden gestratificeerd naar leeftijd en geslacht. Hieruit bleek dat de sensitiviteit van zorgdeclaratiedata voor gevorderde CNS-patiënten (51%) hoger was dan bij CNS-patiënten (27%). Bovendien was de nauwkeurigheid van zorgdeclaratiedata bij het identificeren van CNS-patiënten opmerkelijk veel hoger bij jonge patiënten in vergelijking met oudere patiënten, en hoger bij mannen dan bij vrouwen. Deze validiteitsstudie toonde aan dat Nederlandse

zorgdeclaratiedata een lage sensitiviteit heeft voor een schatting van de algehele CNS-prevalentie in de algemene bevolking. Met name in het geval van oudere CNS-patiënten en patiënten met minder gevorderde CNS blijkt de data minder nauwkeurig. Desalniettemin kunnen zorgdeclaratiedata waardevol zijn bij het schatten van de prevalentie van CNS in specifieke subgroepen, in het bijzonder bij jonge patiënten en patiënten met gevorderde CNS.

Deel 3 – Zorgkosten

De hoofdstukken 4 en 5 van het proefschrift beschrijven de schatting van de zorgkosten van CNS-patiënten met behulp van Nederlandse zorgdeclaratiedata uit de Vektis database. In **hoofdstuk 4** hebben we Vektis data van 2012-2014 gebruikt om de zorgkosten van patiënten bij verschillende vormen van nierfunctievervangende therapie te berekenen. Patiënten met continue ambulante peritoneale dialyse (CAPD) hadden de laagste kosten in vergelijking met andere dialysemodaliteiten. De totale jaarlijkse zorgkosten in 2014 varieerden gemiddeld van €77 566 voor CAPD-patiënten tot €105 833 voor patiënten met verschillende behandelingsmodaliteiten in één jaar. De gemiddelde kosten voor niertransplantatiepatiënten bedroegen €85 127 in het jaar van transplantatie en daalden snel in het eerste (€29 612) en tweede (€15 018) jaar na succesvolle transplantatie. Dit betreft ongeveer 14%-19% van de jaarlijkse dialysekosten. De kosten in het jaar van transplantatie waren gemiddeld 25% lager voor patiënten met nieren van een levende versus een overleden donor. Naast de duidelijke voordelen ten aanzien van overleving en kwaliteit van leven van een niertransplantatie laten onze gegevens ook kostenvoordelen zien van een niertransplantatie in vergelijking met dialysebehandeling.

Hoofdstuk 5 beschrijft de aan leeftijd gerelateerde verschillen in zorggebruik en zorgkosten van patienten met CNS stadium G4-G5, dialyse- en niertransplantatie-patiënten in vergelijking met gematchte controles uit de algemene populatie. Bij patiënten en controles deden we onderzoek naar de totale zorgkosten en de ziekenhuiskosten die geen verband hielden met de behandeling van CNS, waarbij de uitkomsten werden gepresenteerd in vier leeftijdscategorieën (19-44, 45-64, 65-74 en ≥75 jaar). We vonden dat het zorggebruik en de bijbehorende zorgkosten van CNS-patiënten (behandeld met of zonder nierfunctievervangende therapie) erg hoog waren, veel hoger dan die van de algemene bevolking. Opmerkelijk is dat dit verschil al op jonge leeftijd en in de eerdere stadia van CNS aanwezig was. Dit wijst op een relatief vroege aanwezigheid van comorbiditeiten bij CNS-patiënten. Opmerkelijk is ook dat, hoewel de zorgkosten bij de algemene bevolking stijgen met de leeftijd, onze

studie een daling van de zorgkosten aantoonde bij CNS-patiënten (met of zonder nierfunctievervangende therapie) van 75 jaar of ouder. Dit kon voornamelijk worden toegeschreven aan lagere ziekenhuiskosten en lagere medicatiekosten.

Deel 4 – Medicatievoorschrift

Dit deel van het proefschrift beschrijft het gebruik van apotheekgegevens uit de Vektis database met als doel het medicatiegebruik bij CNS-patiënten in kaart te brengen (d.w.z. CNS-stadium G4-G5 niet behandeld met nierfunctievervangende therapie, dan wel CNS-stadium G5 behandeld met dialyse of niertransplantatie).

Hoofdstuk 6 rapporteert over de prevalentie van polyfarmacie (het tegelijktijdig gebruik van ≥5 medicijnen) bij CNS-patiënten en gematchte controles, alsmede over denkbare risicofactoren die samenhangen met polyfarmacie en beschrijft de meest voorgeschreven medicijnen. Voor het jaar 2017 maakten we onderscheid tussen alle voorgeschreven medicijnen in dat jaar en alle chronisch voorgeschreven medicatie. Dit onderzoek toonde aan dat polyfarmacie vaker voorkomt bij CNS-patiënten (met en zonder nierfunctievervangende therapie) in vergelijking met gematchte controles. De prevalentie van polyfarmacie gebaseerd op al het jaarlijks medicatiegebruik van patiënten in CNS-stadium G4-G5, dialysepatiënten en niertransplantatiepatiënten was respectievelijk 87%, 93% en 95%, terwijl dit bij controlepatiënten varieerde van 15% tot 33%. De prevalentie was lager voor chronisch medicatiegebruik, variërend van 66% tot 75% bij alle patiëntengroepen en van 7% tot 18% bij de controle groepen. Risicofactoren voor polyfarmacie bij patiënten waren hogere leeftijd, lagere sociaal economische status, diabetes mellitus, hart- en vaatziekten, ziekenhuisopname en een bezoek aan de eerste hulp. Protonpompremmers en statines waren de meest voorgeschreven medicijnen bij patiënten. De hoge medicatielast van CNS-patiënten (met of zonder nierfunctievervangende therapie) was een gevolg van hun nierziekte en bijkomende comorbiditeit en het minimaliseren van de medicatielast is daarom een uitdaging. Een kritische benadering van het voorschrijven van medicijnen en het kiezen van een passende middenweg tussen overbehandeling en therapeutisch nihilisme, is essentieel om te komen tot doelmatig medicatiegebruik.

Hoofdstuk 7 beschrijft het voorschrijven van antidepressiva bij CNS-patiënten met of zonder nierfunctievervangende therapie in vergelijking met een gematchte controlegroep. De prevalentie van het chronisch voorschrijven van antidepressiva was bij patiënten in CNS-stadium G4-G5, bij dialysepatiënten, en bij niertransplantatiepatiënten, respectievelijk 5,6%, 5,3% en 4,2%, terwijl dit bij

de controlegroep 3% was. Het percentage voorgeschreven antidepressiva was hoger bij vrouwen en bij patiënten van middelbare leeftijd (45-64 jaar), maar er werd geen verband gevonden tussen het voorschrijven van antidepressiva en sociaaleconomische status. Deze landelijke analyse onthulde een opmerkelijk lager percentage voorgeschreven antidepressiva bij Nederlandse CNS-patiënten dan gerapporteerd over CNS-populaties uit andere landen. De onderliggende oorzaak van dit verschil was moeilijk te beoordelen, aangezien het voorschrijven van antidepressiva wordt beïnvloed door veel factoren, zoals de prevalentie van depressie in een land, het gezondheidssysteem en de vergoeding uit de zorgverzekering, het welbevinden van zijn burgers en de beschikbaarheid van andere behandelopties voor depressie. In hoeverre het verschil tussen Nederland en die andere landen verband hield met een ondervoorschrijven in Nederland of juist een te veel voorschrijven elders was daarom niet vast te stellen.

Conclusie

Hoofdstuk 8 bediscussieert de bevindingen van dit proefschrift en gaat dieper in op de mogelijkheden van Nederlandse zorgdeclaratiedata voor nefrologisch onderzoek. Verder zijn de in dit proefschrift gepresenteerde resultaten gebruikt om de eerste publiek toegankelijke website van de Nieratlas (www.nieratlas.nl) te ontwikkelen met behulp van Vektis data.

De belangrijkste conclusie van dit proefschrift is dat de Vektis database de potentie heeft om een belangrijke databron te zijn voor observationeel nefrologisch onderzoek in Nederland. De kenmerken van de Vektis database bieden mogelijkheden om unieke informatie te analyseren (zoals zorgkosten, zorggebruik en medicatiegebruik) op nationaal niveau met daarnaast de mogelijkheid om vergelijkingen te maken met gematchte subgroepen uit de algemene bevolking. Om het onderzoekspotentieel van de Vektis database te verbeteren en het gebruik te stimuleren kunnen nog belangrijke stappen worden gezet op het gebied van datatoegankelijkheid, kennisuitwisseling en datakoppeling. Om die reden is er na de afronding van dit promotietraject en de ontwikkeling van de website een klankbordgroep opgericht. Eén van de belangrijkste taken van de klankbordgroep is de ondersteuning van zowel onderzoekers als medewerkers bij Vektis bij nieuwe onderzoeksvoorstellen aangaande nierpatiënten door de inhoud en haalbaarheid ervan te beoordelen en onderzoekers te informeren over de mogelijkheden en randvoorwaarden van het werken met de Vektis database.

Portfolio

Name PhD student: Manon Johanna Magdalena van Oosten
PhD period: April 2016 – December 2021
Name PhD supervisor: prof. dr. K.J. Jager, prof. dr. J.G. Bilo

1. PhD training

	Year	ECTS
General courses		
Project Management – AMC, Amsterdam	2018	0.6
Scientific writing – AMC, Amsterdam	2018	1.5
Practical biostatistics – AMC, Amsterdam	2018	1.1
Specific courses		
ERA EDTA Introduction to Epidemiology course - Cyprus	2017	0.9
Systematic Reviews – AMC, Amsterdam	2018	0.7
Evaluation of Medical Tests – AMC, Amsterdam	2018	0.9
Randomized Controlled Trials – AMC, Amsterdam	2017	0.6
Seminars, workshops and masterclasses		
Nephrology workshop Papendal	2017	0.6
Nephrology workshop Papendal	2019	0.6
Presentations (oral)		
Nederlandse Nefrologiedagen – Veldhoven: The value of the kidney atlas	2020	0.5
Internistendagen – Maastricht: Age-related difference in healthcare use and costs of patients with chronic kidney disease and matched controls	2019	0.5
Nederlandse Nefrologiedagen – Veldhoven: Healthcare costs of patients on different renal replacement modalities – analysis of Dutch health claims data	2018	0.5
Internistendagen – Maastricht: The financial burden of CKD	2018	0.5
Lowlands Health Economic Study Group (LolaHESG) conference – Rotterdam: Healthcare costs of patients on different renal replacement modalities	2017	0.3
Presentation (poster)		
56th ERA-EDTA Congress – Budapest: The validity of Dutch health claims data in identifying patients with CKD	2019	0.5
56th ERA-EDTA Congress – Budapest: Age-related difference in healthcare use and costs of patients with CKD and matched controls: analysis of Dutch health claims data	2019	0.5
Nederlandse Nefrologiedagen (Dutch Nephrology Days) – Veldhoven: Age-related difference in healthcare use and costs of patients with CKD and matched controls	2019	0.5
Nederlandse Nefrologiedagen (Dutch Nephrology Days) – Veldhoven: The validity of Dutch health claims data in identifying patients with CKD	2019	0.5

	Year	ECTS
Presentation (poster) *(continued)*		
Nederlandse Nefrologiedagen – Veldhoven: Worldwide health insurance claims databases in kidney research and a new initiative: the Dutch Kidney Atlas	2018	0.5
55th ERA-EDTA Congress – Copenhagen: Healthcare costs of CKD, dialysis and kidney transplant patients compared with matched controls	2018	0.5
55th ERA-EDTA Congress – Copenhagen: Healthcare costs of patients on different renal replacement modalities – analysis of Dutch health claims data	2018	0.5
(Inter)national conferences		
54th ERA-EDTA Congress – Madrid, Spain	2017	1
55th ERA-EDTA Congress – Copenhagen, Denmark	2018	1
Internistendagen – Maastricht	2018	1
Internistendagen – Maastricht	2019	1
Internistendagen – Maastricht	2021	1
Nederlandse Nefrologiedagen – Veldhoven	2018	1
Nederlandse Nefrologiedagen – Veldhoven	2020	1
Lowlands Health Economic Study Group (LolaHESG) conference – Rotterdam	2017	0.5
Other		
PhD day KIK	2019	0.3
PhD day KIK	2018	0.3
Amstelsymposium	2018	0.3
PLAN scientific symposium – AMC, Amsterdam	2017	0.3
PLAN scientific symposium – Radboud UMC, Nijmegen	2016	0.3
Winterschool Dutch Kidney Foundation	2017	1

2. Teaching

	Year	ECTS
Supervising		
Dan Koning: Antidepressant use in CKD	2021	2.5
Toya Ahmed: 2-month master Medical Informatics internship, Polypharmacy in CKD	2020	2.5

3. Parameters of esteem

	Year
Grants	
ERA EDTA travel grant 'Introductory Course on Epidemiology'	2017

List of publications

Publications in this thesis

Chronic prescription of antidepressant medication in patients with chronic kidney disease with and without kidney replacement therapy compared with matched controls in the Dutch general population.
Manon JM van Oosten*, Dan Koning*, Susan JJ Logtenberg, Martijn JH Leegte, Henk JG Bilo, Marc H Hemmelder, Kitty J Jager, Vianda S Stel.
Accepted for publication in *Clinical Kidney Journal*, 2021. doi: https://doi.org/10.1093/ckj/sfab242

Polypharmacy and medication use in patients with chronic kidney disease with and without kidney replacement therapy compared to matched controls.
Manon JM van Oosten, Susan JJ Logtenberg, Marc H Hemmelder, Martijn JH Leegte, Henk G Bilo, Kitty J Jager, Vianda S Stel.
Clinical Kidney Journal, Volume 14, Issue 12, December 2021, Pages 2497–2523. https://doi.org/10.1093/ckj/sfab120

The validity of Dutch health claims data for identifying patients with chronic kidney disease: a hospital-based study in the Netherlands.
Manon JM van Oosten, Richard M Brohet, Susan JJ Logtenberg, Anneke Kramer, Lambert D Dikkeschei, Marc H Hemmelder, Henk JG Bilo, Kitty J Jager, Vianda S Stel.
Clinical Kidney Journal, Volume 14, Issue 6, June 2021, Pages 1586–1593. https://doi.org/10.1093/ckj/sfaa167

Health claims databases used for kidney research around the world.
Manon JM van Oosten, Susan JJ Logtenberg, Mireille A Edens, Marc H Hemmelder, Kitty J Jager, Henk JG Bilo, Vianda S Stel.
Clinical Kidney Journal, Volume 14, Issue 1, January 2021, Pages 84–97. https://doi.org/10.1093/ckj/sfaa076

Age-related difference in health care use and costs of patients with chronic kidney disease and matched controls: analysis of Dutch health care claims data.
Manon JM van Oosten, Susan JJ Logtenberg, Martijn JH Leegte, Henk JG Bilo, Sigrid M Mohnen, Leona Hakkaart-van Roijen, Marc H Hemmelder, G Ardine de Wit, Kitty J Jager, Vianda S Stel.
Nephrology Dialysis Transplantation, Volume 35, Issue 12, December 2020, Pages 2138–2146, https://doi.org/10.1093/ndt/gfz146

Healthcare costs of patients on different renal replacement modalities – Analysis of Dutch health insurance claims data
Sigrid M Mohnen*, **Manon JM van Oosten***, Jeanine Los*, Martijn JH Leegte, Kitty J Jager, Marc H Hemmelder, Susan JJ Logtenberg, Vianda S Stel, Leona Hakkaart-van Roijen, G. Ardine de Wit.
PLOS One 14(8), Augustus 2019, eCollection, e0220800. https://doi.org/10.1371/journal.pone.0220800

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Other publications

Polymorphisms in the glucocorticoid receptor gene that modulate glucocorticoid sensitivity are associated with rheumatoid arthritis.
Manon JM van Oosten, Radboud J Dolhain, Jan W. Koper, Elisabeth FC van Rossum, Marieke Emonts, Khik H Han, Jacques MGW Wouters, Johanne MW Hazes, Steven WJ Lamberts, Richard A Feelders.
Arthritis Research Therapy. 12(4): R159. 2010. Epub 2010 Aug 21. doi: 10.1186/ar3118

Authors' contributions

Chapter 2

Manon J.M. van Oosten
Conceptualization, Methodology, Data collection, Data interpretation, Data curation, Writing – original draft

Susan J.J. Logtenberg
Conceptualization, Methodology, Data collection, Data interpretation, Supervision, Writing – review & editing

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Chapter 3

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Chapter 7

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About the author

Manon Johanna Magdalena van Oosten, daughter of Daan van Oosten and Magda Eversdijk, was born on 28 June 1984 in Heinkenszand, Zeeland, and grew up with her brother Edwin. After graduating secondary school at St. Willibrord College in Goes in 2002, she moved to Rotterdam to start her medical education at the medical faculty of the Erasmus University Rotterdam. During the second year of medical school Manon started a Master of Science in Clinical Epidemiology at the Netherlands Institute for Health Sciences (NIHES). This resulted in a research project at the department of endocrinology of Erasmus MC in Rotterdam (dr. R.A. Feelders and prof. dr. S.W.J. Lamberts) and her graduation in 2007 after which she was registered as Epidemiologist A. She completed her medical studies (cum laude) in 2009 and started as a resident in internal medicine at Erasmus MC. A few months later she started her specialist training in internal medicine at St. Franciscus Gasthuis (drs. A.P. Rietveld) and Erasmus MC (prof. dr. J.L.C.M. van Saase and prof. dr. S.C.E. Klein Nagelvoort-Schuit) followed by her training in nephrology (prof. Dr. R. Zietse) in 2014.

In 2016, Manon relocated from Rotterdam to Amsterdam where she got the opportunity to work on a PhD project of the Dutch Kidney Atlas under supervision of prof. dr. Kitty Jager, prof. dr. Henk Bilo, dr. Vianda Stel and dr. Susan Logtenberg. This project fulfilled her long-held desire to conduct research in the field of two of her main professional interests, namely nephrology and epidemiology. This thesis is the product of this research project. Alongside her PhD research, she completed her nephrology training at Amsterdam UMC (dr. N.C. van der Weerd) and was registered as an internist-nephrologist in August 2019. Since then, Manon worked as a nephrologist at Rode Kruis Ziekenhuis in Beverwijk and currently at Noordwest Ziekenhuisgroep in Alkmaar.

Manon currently lives in Amsterdam with her partner Rogier Dieks and their two children Daniël Levi and Lotte Lena.

Dankwoord

‘Wat is belangrijker,’ vroeg Grote Panda,
‘de reis of de bestemming?’

‘Het gezelschap,’ zei Kleine Draak.

From ‘Big Panda and Tiny Dragon’ by James Norbury

Ik dank mijn promotieteam voor het geloof in mij.
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