Aus dem Institut für Gesundheitsökonomie und Management im Gesundheitswesen des

Helmholtz Zentrum Münchens – Deutsches Forschungszentrum für Gesundheit und Umwelt

Institutsleiter: Prof. Dr. Reiner Leidl

Modeling the Health Care Costs of Multiple Type 2 Diabetes-Related Complications Based on Patient-Level Real-World Data in Germany

A Methodological and Empirical Study of a Large Statutory Sickness Fund Population

Dissertation

zum Erwerb des Doktorgrades der Humanbiologie

an der Medizinischen Fakultät der

Ludwig-Maximilians-Universität München

vorgelegt von

Katharina Kähm (geb. Schremser)

aus Qaratau (Kasachstan)

2018

Mit Genehmigung der Medizinischen Fakultät

der Universität München

Betreuer/Berichterstatter:	Prof. Dr. Rolf Holle
	_____
Mitberichterstatter(in):	Prof. Dr. Eva Grill, MPH
	Prof. Dr. Bärbel Otto
Dekan:	Prof. Dr. Reinhard Hickel
Tag der mündlichen Prüfung:	06.05.2019

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München, den 10. August 2019

Katharina Kähm

“Do not go where the path may lead.

Instead, go where there is no path and leave a trail.”

Emerson

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List of abbreviations

aDCSI	adapted Diabetes Complications Severity Index
ATC	Anatomical Therapeutic Chemical (Classification)
CHF	Chronic Heart Failure
CDC	Center for Disease Control and Prevention
CoDiM	Costs of Diabetes Mellitus
DMP	Disease Management Program
DRG	Diagnoses Related Group
EBM	Uniform Value Scale (“Einheitlicher Bewertungsmaßstab”)
ESRD	End-Stage Renal Disease
GEE	Generalized Estimating Equation
GLM	Generalized Linear Model
HRQoL	Health-Related Quality of Life
ICD-10	International Statistical Classification of Diseases and Related Health Problems, 10th version
IHD	(other) Ischemic Heart Disease
LE	Lower Extremities
MI	Myocardial Infarction
OAD	Oral Antidiabetics
OPS	Operation Procedure Codes
PVD	Peripheral Vascular Disease
QIC	Quasi Information Criterion
RCT	Randomized Controlled Trial
RTI	Research Triangle Institute
SE	Standard Error
SHI	Statutory Health Insurance
UKPDS	United Kingdom Prospective Diabetes Study

Zusammenfassung

Hintergrund

Die derzeitigen Entwicklungen hin zu einer alternden Bevölkerung und ungünstigen Lebensstilveränderungen haben dazu beigetragen, dass immer mehr Menschen immer länger mit Typ 2 Diabetes und den damit einhergehenden Folgen von Multimorbidität leben. Verschiedene mikro- und makrovaskuläre Komplikationen sind als bedeutende Ursache der gesteigerten Morbidität und Mortalität bekannt und stellen eine signifikante ökonomische Belastung dar. Mathematische Diabetesmodelle bieten ein nützliches Instrument, um den Krankheitsprozess zu simulieren, klinisch relevante Ereignisse und Kosten vorherzusagen und Entscheidungsträger somit in der Abschätzung möglicher Folgen neuer Therapie- und Managementansätze für Patienten zu unterstützen. Trotz des internationalen Einsatzes, gibt es derzeit noch kein basierend auf individuellen Patientendaten angepasstes Diabetesmodell für den deutschen Kontext. Zu diesem Zweck und um detailliertere Kosteninformationen zu ermitteln, stellen sogenannte „Real World"-Daten eine der umfangreichsten und bedeutendsten Datenquellen dar. In diesem Zusammenhang müssen geeignete methodische Ansätze entwickelt werden, um auf Basis dieser Daten spezifische Modellparameter valide schätzen zu können.

Ziele

Diese Dissertation mit ihren Teiluntersuchungen verfolgt eine systematische Analyse von Routinedaten der größten bundesweiten Krankenkasse mit der übergeordneten Leitidee möglichst umfangreiche und differenzierte Informationen zu den direkten Kosten des Typ 2 Diabetes und seiner assoziierten Folgekomplikationen für Diabetesmodelle bereitzustellen. Damit sollen insbesondere zwei Ziele erreicht werden: Zum einen geht es darum, aktuelle empirische Evidenz zu den ökonomischen Folgen von Typ 2 Diabetes-Komplikationen zu generieren. Zum anderen sollen konzeptionelle und methodische Ansätze erarbeitet werden, die einen Umgang mit Validitätsproblemen in Krankenkassendaten erlauben und der Komplexität des Krankheitsbildes durch Multimorbidität Rechnung tragen. Die erste Studie liefert zu diesem Zweck detaillierte Kostenschätzer für die Erstdiagnose verschiedener Typ 2 Diabetes-Komplikationen im Längsschnitt. Die zweite Studie umfasst

vor allem eine fundierte methodische Vertiefung verschiedener Strategien, um die ökonomischen Auswirkungen mehrerer gleichzeitig bestehender Typ 2 Diabetes-Komplikationen und ihre Interaktionensmuster zu untersuchen.

Methoden

Diese Dissertation basiert auf bundesweiten Patientendaten von 316.220 (über 18 Jahre alten) Versicherten mit Typ 2 Diabetes der Techniker Krankenkasse im Basisjahr 2012 und 3-Jahres-Follow-up von 2013-2015. Alle diabetesassoziierten Folgekomplikationen, die typischerweise in internationalen Diabetesmodellen beschrieben werden, wurden basierend auf ambulanten und stationären Diagnosedaten sowie abgerechneten Leistungen identifiziert. Hierzu standen quartalsweise Beobachtungen pro Kalenderjahr und Patient zur Verfügung. Direkte Kosten (Bezugsjahr 2015) beinhalten Kosten für ambulante und stationäre Leistungen, Arzneimittel, Rehabilitation und Heil- und Hilfsmittel. Als Erweiterung zu gängigen generalisierten linearen Modellen (GLM) wurden Generalized Estimating Equations (GEE)-Modelle verwendet, um wiederholte Beobachtungen am selben Patienten zu berücksichtigen. Aufgrund der hinreichend großen Population und dem niedrigen Anteil an Nullkosten wurde im Basisfall jeweils eine Normalverteilung der Kosten angenommen. In der ersten Studie wurde ein GEE-Modell entwickelt, welches die Gesamtkosten für einen Patienten mit Typ 2 Diabetes pro Quartal vorhersagt, adjustiert nach Altersgruppen, Geschlecht, Auftreten verschiedener Komplikationen, Vorgeschichte der Komplikationen im Basisjahr und Tod (aus anderen Gründen als den berücksichtigten Komplikationen). Zusätzlich zur Unterscheidung zwischen inzidenten und prävalenten Komplikationen, lag ein weiterer Schwerpunkt auf der Differenzierung von nichttödlich oder tödlich verlaufenden akuten makrovaskulären Ereignissen, sowie auf der Quantifizierung der Kosten sowohl im Quartal des Ereignisses/Krankheitsbeginns als auch in den Folgequartalen unter der Berücksichtigung von alters- und geschlechtsspezifischen Interaktionen. Darauf aufbauend untersucht die zweite Studie vier unterschiedlich granulare Strategien, mit dem Ziel die ökonomischen Auswirkungen der diabetesassoziierten Multimorbidität zu untersuchen, angefangen mit der groben Berücksichtigung der Anzahl prävalenter Komplikationen, über das gemeinsame Bestehen von mikro- und makrovaskulären Komplikationen, bis hin zur Berücksichtigung spezifischer Interaktionen und dem

Auftreten inzidenter Komplikationen neben bereits bestehenden chronischen Komplikationen. Hierfür wurden GEE-Modelle entwickelt und auf die jährlichen Beobachtungsdaten angewandt, um die statistische Power zu erhöhen.

Ergebnisse

Der additive Ansatz (unter Berücksichtigung eines GEE-Models mit Normalverteilung) zeigte einen besseren Modellfit verglichen mit einem multiplikativen Modell basierend auf einem Gamma-GEE-Modell. Ausgehend von dem Beispiel eines 60 bis 69 Jahre alten Mannes, wurden in der ersten Studie folgende Gesamtkosten für das erste Diagnosequartal der Komplikationen ermittelt: diabetischer Fuß 1.293€, Amputation 14.284€, Retinopathie 671€, Erblindung 2.933€, Nephropathie 3.353€, chronisches Nierenversagen 22.691€, nichttödlicher Schlaganfall 9.769€, tödlicher Schlaganfall 11.176€, nichttödlicher Myokardinfarkt/Herzstillstand 8.035€, tödlicher Myokardinfarkt/Herzstillstand 8.700€, nichttödliche (andere) ischemische Herzkrankheit (IHK) 6.548€, tödliche IHK 20.842€, chronische Herzinsuffizienz 3.912€, and Angina pectoris 2.695€. In den Folgequartalen reichten die Kosten von 681€ für Retinopathie bis zu 6.130€ für chronisches Nierenversagen. Männer und Frauen unterschiedlicher Altersgruppen unterschieden sich hinsichtlich ihrer Kosten für Komplikationen. Die zweite Studie konnte darüber hinaus zeigen, dass die gestiegene Anzahl von aufgetretenen Komplikationen mit signifikant höheren jährlichen Gesamtkosten pro Patient assoziiert ist. Weitere Untersuchungen haben ergeben, dass makrovaskuläre Komplikationen (z.B. chronische Herzinsuffizienz) und kostenintensive Komplikationen (z.B. chronisches Nierenversagen, Amputation) zu signifikant positiven Interaktionseffekten hinsichtlich der jährlichen Gesamtkosten führen, während die Beobachtung früher mikrovaskulärer Veränderungen (z.B. Retinopathie) zu negativen Interaktionseffekten führen kann. Die chronologische Abfolge des Komplikationsgeschehens stellte sich ebenfalls als wichtiger Einflussfaktor in der Schätzung von Interaktionseffekten heraus.

Schlussfolgerungen

Die Ergebnisse dieser Dissertation haben wichtige Implikationen für verschiedene Akteure im Gesundheitswesen. Für den wissenschaftlichen Bereich, insbesondere für die Diabetesmodellierung, liefern die Studien nicht nur umfangreiche empirische Kostenschätzer zur Parametrisierung eines auf den deutschen Kontext adaptierten Typ 2-Diabetesmodells, sondern liefern auch wichtige konzeptionelle und strategische Ansätze zur Analyse von großen Krankenkassenpopulationen. Die empirische Fundierung dieser Arbeit sowie die methodische Aufbereitung des Themas können zu einer höheren Genauigkeit von zukünftigen Kosten-Effektivitäts-Analysen beitragen, in der insbesondere Multimorbiditätsaspekte und Interaktionsmuster stärker berücksichtigt werden. Aus einer gesundheitspolitischen oder Krankenkassen-Perspektive, liefern die Studien wertvolle Informationen zur Unterstützung einer optimalen Ressourcenallokation zwischen verschiedenen Präventions- und Behandlungsprogrammen für Patienten mit Typ 2 Diabetes. Zudem unterstreichen die Forschungsergebnisse die Forderung nach ganzheitlich integrierten Ansätzen, welche vorbestehende oder begleitende Erkrankungen stärker berücksichtigen. Aus klinischer Perspektive schärfen diese umfassenden Ergebnisse das Bewusstsein für die derzeitige ökonomische Belastung durch Typ 2 Diabetes-assoziierte Komplikationen. Weitere Beobachtungsstudien werden benötigt, um ein vollständigeres Verständnis von den zu Grunde liegenden gemeinsamen pathologischen Mechanismen des Typ 2 Diabetes und seiner Komplikationen zu erhalten. Real World-Daten, zu denen die Routinedaten der gesetzlichen Krankenversicherung gehören, können klinische Studiendaten sinnvoll ergänzen. Um den Mehrwert dieser Daten in der Zukunft zu steigern, gilt es die im Rahmen dieser Studien aufgezeigten Validierungslücken weiter zu untersuchen und so weit wie möglich zu schließen.

Abstract

Background

In the context of an ageing population and unfavorable trends in lifestyle factors, more people are living longer with type 2 diabetes and associated multimorbidity. Various micro- and macrovascular complications have been shown to contribute substantially to the morbidity, mortality and economic burden of type 2 diabetes. Mathematical models of diabetes provide a useful tool that can help to simulate the disease process, predict clinical and economic outcomes, and thereby assist decision makers in assessing the possible impact of a range of new diabetes interventions. At present, internationally available type 2 diabetes models are not well adapted to German patient level data. To achieve this, and especially to obtain detailed cost information, real-world health insurance data are one of the most powerful data sources to be used. However, methodological approaches to map these data into model parameters have to be further developed.

Objectives

This dissertation with its sub-studies seeks to systematically analyze routine data of a large statutory health insurance fund to inform diabetes simulation models on the direct costs of type 2 diabetes-related complications. In particular, this work has the two-fold aims, to provide new empirical evidence on diabetes-related costs for Germany, and to develop conceptual and methodological approaches that are capable of dealing with validity issues of routine data and the complexity due to multimorbidity in the diabetes population. In this context, the first study provides detailed estimates on the longitudinal costs associated with the diagnosis of various complications. The second study is more focused on pursuing the methodological depth in this research by exploring different strategies that address the economic impact of multiple type 2 diabetes-related complications and their interactions. In addition, this study describes important interaction patterns of co-occurring complications.

Methods

This dissertation is based on nationwide claims data of 316,220 (over 18 years-old) type 2 diabetes patients who were insured by the Techniker Krankenkasse in the baseline year 2012 and the 3-year follow-up period from 2013-2015. All diabetes-related complications that are typically included in international diabetes models were identified based on outpatient and inpatient diagnoses and procedures. Quarterly observations were available for each year and patient. Direct health care costs (in 2015 euros) include costs for outpatient and inpatient care, medication, rehabilitation, and the provision of aids and appliances. Generalized estimating equations (GEE) models are used to account for repeated observations per patient as an extension to traditional generalized linear models. As the base case, a normal distribution of the mean costs was assumed, given the large population size and small proportion of zero costs. In particular, in the first study, a GEE model predicting quarterly total costs was developed, adjusted for the age group, sex, occurrence of different (incident) complications, history of prevalent complications at baseline, and death for other reasons. In addition to distinguishing incident/prevalent complications, special emphasis was given to differentiate between fatal/nonfatal acute macrovascular events, to quantify costs at the quarter of event/onset and in subsequent quarters, and to consider interactions of complications with age or sex. Building on this, the second study explores four strategies of different granularity to assess the economic impact of diabetes-related multimorbidity, including the number of prevalent complications, co-occurrence of micro- and macrovascular complications, disease–disease interactions of prevalent complications, and interactions of incident on top of already prevalent complications. For this, different GEE models were developed and applied to the annual observations to increase the statistical power.

Results

The additive approach (using a GEE model with a normal distribution) showed a better model fit compared to a multiplicative approach with a gamma-based GEE model. Using the example of a 60-69 year old man, the first study estimated the following total costs in the quarter of first diagnosis of the complication: diabetic foot €1,293, amputation €14,284, retinopathy €671, blindness €2,933, nephropathy €3,353, end-stage renal disease (ESRD) €22,691, nonfatal stroke €9,769, fatal stroke

€11,176, nonfatal myocardial infarction/cardiac arrest (MI/CA) €8,035, fatal MI/CA €8,700, nonfatal other ischemic heart disease (IHD) €6,548, fatal IHD €20,842, chronic heart failure €3,912, and angina pectoris €2,695. In the subsequent quarters, costs ranged from €681 for retinopathy to €6,130 for ESRD. Men and women from different age groups differed in their costs for complications. In addition, the second study showed that the increased number of complications is significantly associated with higher annual total costs per patient. Further assessment of interactions revealed that macrovascular complications (e.g., CHF) and high cost complications (e.g., ESRD, amputation) lead to significant positive interactions on annual costs, whereas early microvascular complications (e.g., retinopathy) caused negative interactions. The chronology of the onset of these complications turned out to have an additional impact on the cost estimates of interactions.

Conclusions

The results of this dissertation have important implications for different healthcare stakeholders. From a modeler's or researcher's perspective, the two studies provide comprehensive empirical estimates for the economic parametrization of type 2 diabetes models, especially for Germany, as well as methodological approaches for the claims-based analysis of large diabetes populations. These concepts will also help to further improve the accuracy of international cost-effectiveness evaluations by addressing multimorbidity, and especially interaction patterns. From a policy or SHI perspective, the studies provide valuable information to support the optimal resource allocation across different intervention programs for the prevention and management of type 2 diabetes complications. In addition, the results encourage a more integrated approach that takes better account of preexisting or co-occurring conditions. From a clinician's perspective, the empirical findings may increase the awareness of the economic burden of complications in patients with type 2 diabetes. Further observational studies are still needed to gain a more complete understanding of the multiple shared pathogenic mechanisms of diabetes and its complications. Real world data, including health insurance claims data, can be used to successfully complement clinical data. To increase the added value of these data, remaining validation gaps need to be further examined and closed.

Preface

"Everyone dealing with health care today knows there is an elephant in the room, impossible to miss but frequently ignored—the cost of diabetes care."

Matthew C. Riddle

This metaphor symbolizes diabetes as a major challenge, standing in the way of patients and their families every day and putting healthcare providers, payers and regulators under increasing pressure [1]. What is also known as the burden of disease (Introductory section 1.1), does not appear overnight, but rather develops over a longer period of time. This also means to think of diabetes (particularly type 2 diabetes) as a continuum of disease that may begin with overweight and other risk factors, then becomes prediabetes, then diabetes, and ultimately leads to the progression of a wide range of diabetic complications (section 1.2). Diabetes simulation models strive to account for this dynamic disease process, multiple complications, and related health care costs in health economic evaluations of new diabetes interventions and programs (section 1.4). Since the validity of a model highly depends on the inputs, data sources and methods should be used carefully to inform such health economic models (section 1.3). The following thesis, with its sub-studies, has been written in light of this context. Primary aim was to use real-world data of a large health insurance fund to contribute new empirical evidence and methodological perspectives on the evaluation of costs of complications in patients with type 2 diabetes for the economic parametrization of diabetes models.

1 Introductory summary and motivation

1.1 Identifying type 2 diabetes and its complications as a high burden disease and research priority

"*Diabetes, long thought of as a Cinderella disease, has become a major challenge of the 21st century*" Paul Zimmet [2]

The burden of diabetes can be viewed from at least three perspectives: morbidity (including health-related quality of life (HRQoL)), mortality, and economic impact. In short, this section aims to provide an overview of the burden of diabetes in order to understand the various demands on diabetes research, the central role of complications and the confluence of these perspectives in the examination of the economy of diabetes.

In terms of morbidity at a population level, an increasing global trend in the prevalence of type 2 diabetes is expected due to demographic changes and shifts in population dietary patterns and physical inactivity (e.g., increases in diabetes cases in youth, continued rise of the numbers of older patients with diabetes) [3-5]. In Germany, the prevalence of known type 2 diabetes was estimated to be 7–8% of the adult population in 2011, which is slightly above the global average [6-8]. As a serious chronic disease, diabetes also belongs to the top five causes of long-term disability [9]. A closer look at the individual patient level reveals that patients often make substantial changes to their lifestyle behavior and in their physical and psychological health [10]. Consequently, one of the main causes of the severity of diabetes is the development of various complications and (multi-)morbidity patterns that vary widely in their manifestations [11]. Considering these factors, German cohort studies showed a faster decline in the HRQoL score of patients with diabetes (compared to people without diabetes) and especially those with multiple complications [12, 13].

As on the second point (burden of mortality), it has to be considered that better glucose-lowering drugs, structured education programs and improved prognosis of other chronic diseases (e.g., myocardial infarction, renal insufficiency) have contributed to life expectancy improvements in diabetes patients [14, 15]. Although diabetes is not a leading cause of death in Germany, the diabetes-related excess mortality in people >40 years of age was estimated to be 21% (all diabetes types) and 16% (type 2) in 2010, which is above what was measured in international studies (8%) [16, 17]. Again, beyond different

data sources and methods, diabetes complications turned out to play an important and challenging role in estimating the diabetes-related mortality, because most people die of diabetes complications and comorbidities and not of diabetes itself.

Finally, the economic burden of type 2 diabetes (that is typically measured by cost of illness studies) is mainly a result of the other two points integrated in a complex national health care and legislative system. Although there is literature on this field, it is important to note that cost of illness studies are systematically different from other study designs due to their characteristic interest to quantify the total (excess) costs attributable to the disease rather than its specific components. Since 1999, there are few studies on the societal total costs of diabetes (including direct and indirect costs) extrapolated to the entire German population [18, 19]. The Costs of Diabetes Mellitus (CoDiM) study reports a rise in the direct cost burden of diabetes from €15 billion in 2001 to €21 billion in 2009 based on a retrospective bottom-up analysis of ~30,000 insured diabetes patients (all types) and matched controls in the Hessian AOK [20-22]. A recent study by a German group used a top-down approach to look at the global economic burden of diabetes in 180 countries in 2015 [23]. They estimated direct and indirect costs of all diabetes types of approximately US$38 and 17 billion for Germany, compared to a global burden of US$1.3 trillion that was expected to increase in the future [24]. Other population-based German studies without extrapolation report excess costs of €3,625 (59% indirect costs) per patient with type 2 diabetes [25]. Moreover, these studies indicate that, apart from a long duration of diabetes and treatment with insulin, complications play a significant role in the assessment of the economic burden [25-27].

What this thesis is able to add to the research, particularly on the economic burden of type 2 diabetes, is carving out the detailed economic impact of complications in patients with type 2 diabetes, specified morbidity patterns and risk of mortality. This includes (1) discriminating type 2 from other diabetes types, (2) effectively analyzing longitudinal data rather than to conduct serial cross-sectional studies, (3) not excluding patients who died in the follow-up (e.g., due to fatal diabetes complications), and (4) providing robust cost estimates based on a larger population dataset.

1.2 Focusing on the costs of diabetes-related complications and associated multimorbidity

"1+1+1 = Multimorbidity is more than the addition of monopathologies" Cornel C. Sieber [28]

Type 2 diabetes is a multisystem chronic disease that is associated with a wide range of complications that share similar risk factors [29-31]. Traditionally, complications are divided into those with primarily microvascular origins, affecting small blood vessels (i.e., retinopathy/blindness, nephropathy/end-stage renal disease (ESRD), diabetic foot/lower-extremity amputation), and those with macrovascular origins, affecting large blood vessels (i.e., myocardial infarction (MI), chronic heart failure (CHF), angina pectoris, other ischemic heart disease (IHD), stroke). Information on yearly incidence rates of these complications in patients with type 2 diabetes are scarce in Germany, but generally, reported rates range from rather rare (e.g., <1% for amputations or blindness [32-34]) to moderately high (e.g. up to 6% for diabetic foot [35]). In addition, studies suggest that the actual lifetime prevalence rates are even higher (e.g., almost everyone with diabetes develops some degree of retinopathy) [36]. Taking also into account that multimorbidity is increasingly prevalent in the heterogeneous population of aging patients (especially those with diabetes), the term "high-need, high cost patients" has become widely used in recent years [37-39]. In the field of diabetes, associated complications have shown to make up the most common multimorbidity cluster [40]. Here, economic evaluations have found higher hospitalization costs due to macrovascular complications, and that costs gradually increase with the number of complications and higher levels of morbidity scores (i.e., adapted Diabetes Complications Severity Index) [41, 42]. However, a detailed examination of the longitudinal costs and the effect of specific interactions is missing. In addition, despite the growing scientific evidence, clinical guidelines still inconsistently consider aspects of multimorbidity in the development of recommendations for treatment and integrated disease control [43].

What this thesis is able to add to the research of type 2 diabetes complications is a more differentiated and methodologically sophisticated analysis of the economic impact of various micro- and macrovascular complications and their co-occurrence. This includes, first, differentiating incident and prevalent complications and quantifying the longitudinal costs before and after the occurrence of new acute events or onset of chronic complications and, second, exploring different granularity levels of

combining complications (e.g., from an aggregated count level to micro-/ macrovascular groups to specific complications) and quantifying the economic impact of diabetes-related multimorbidity and underlying interactions.

1.3 Revealing potentials and pitfalls of claims data in the context of latest data trends

"Imperfect data can still provide important answers" Raymond J. Gibbons [44]

A crucial point in research is the realization that there is no database free of any bias. In short, this section aims to provide an essential understanding of the scientific value of health insurance claims data in the context of emerging paradigm shifts, and what this means for researching the costs of diabetes and its complications. Generally, in clinical research, randomized controlled trials (RCTs) are considered the gold standard in demonstrating the efficacy and safety of interventions [45]. However, long-term studies are rather rare, difficult and expensive to conduct and have its own limitations (e.g., limited generalizability and power to analyze rare outcomes). In addition, economic aspects are, if at all, only partly taken into account. Here, other data sources have become well-established, including data from various payer sources [46, 47]. In Germany, the vast majority of people (90%) are covered by over 100 statutory health insurance (SHI) funds that can vary in size, demographic characteristics and diabetes prevalence [48]. The content of these claims data is mostly regulated in the Fifth Book of the Social Law Code (§§ 294-303 SGB V). Although the data are primarily collected for reimbursement reasons, they contain many detailed information on (socio-)demographic characteristics, diagnoses and health services from outpatient and inpatient care, pharmaceuticals, rehabilitation and costs that are particularly useful for retrospective cohort studies [49, 50]. The two fast-growing research streams of real-world data and big data recognize health insurance claims data as an important contributing source [51]. Whereas "big data" is more focused on data management and analytic opportunities, "real-world data" is more related to a specific type of evidence generated from routine practice (e.g., on effectiveness, safety and economic impacts of interventions and care patterns). What both have in common is the potential to analyze larger volumes of data with high coverage and speed of availability, based on a wide variety of accepted statistical methods. In addition, studies based on real-world data can be more representative of the patient population and actual health care setting than in traditional

RCTs, are often cheaper to conduct and enable the examination of multiple interventions, outcomes and their interactions. However, SHI data in particular have also critical limitations that need to be considered throughout the study process, from data preparation/validation to interpretation of results. Some of the well-known limitations are limited or even lacking clinical and laboratory information (e.g., HbA1c, blood pressure, and lipids), the only quarterly documentation of outpatient diagnoses, time lags in the availability of claims data, and the maximum of four years of data storage for outpatient data (resulting in a reduced interpretability of the length of diabetes and its complications). Of at least similar importance are the hidden pitfalls of claims data resulting, for example, from selection effects within the SHI system or from physicians' incomplete or implausible coding of diagnoses and other information that do not affect the payment. Regarding the first point, selection effects are one reason for differences in the prevalence rates of diabetes between various German SHI funds [48, 52, 53]. The second point, the coding practice, does not only affect the differentiation between diabetes types, but also the identification of chronic complications in the longitudinal setting and thus and the analysis of multimorbidity patterns and the accuracy of cost estimates.

What this thesis is able to add to the research of real-world claims data is exploring key challenges and develop methodological strategies for claims data analyses of type 2 diabetes in Germany's largest nationwide SHI fund based on a large population and longitudinal setting. This especially includes applying and developing transparent validation routines not only in the data itself but also in the further processing and analysis (e.g., more accurate definition of type 2 versus type 1 and unspecified diabetes, and dealing with irregular patterns in the diagnosis of chronic complications).

1.4 Strengthening the use of accurate diabetes models to inform healthcare decisions

"A model is a simplified representation of reality used to aid the understanding of key relationships and dynamics in the care process, and to evaluate the likely impact of changes before implementation." Syed Mohiuddin [54]

In short, this section aims to highlight the importance of accurately parametrized health economic diabetes models, to explain how simulation models work, and to identify important data and methodological requirements and possibilities for the economic parametrization of such a model. Two of the best-known non-commercial type 2 diabetes models are the United Kingdom Prospective Diabetes Study (UKPDS) model and the US model by the CDC (Center for Disease Control and Prevention) and RTI International (Research Triangle Institute) [55, 56]. Beyond the national context, key distinguishing features are primarily of methodological relevance, and include the model type (UKPDS microsimulation vs. CDC/RTI Markov cohort model) and scope (newly diagnosed diabetes in the UKPDS vs. additional screening for prediabetes/diabetes in the CDC/RTI model). Despite these differences, the core models are ought to produce same or similar results, given the fact that the CDC/RTI model is largely based on data from the 30-year UKPDS landmark trial. In particular, the UKPDS model (version 2.0) can be viewed as two parts. The epidemiological part contains the so-called "Risk Engine" that first calculates the lifetime probabilities of developing complications in individual patients based on their demographic characteristics (ethnicity, age, gender, duration of diabetes, weight, height), risk factor values (i.e., HbA1c, blood pressure, heart rate, HDL, LDL, hemoglobin, white blood cell count, smoking status, albuminuria status) and pre-existing events. The second part, the actual outcomes model, then assigns age group- and sex specific cost and quality of life values to different complication outcomes (no complications, fatal/nonfatal IHD, fatal/nonfatal MI, CHF, fatal/nonfatal stroke, amputation, blindness, end-stage renal disease, diabetic foot ulcer), both at the time of event and in subsequent years. As it is characteristic for a Markov model, the CDC/RTI model also computes the transition from early to late-stage complications (e.g., micro-/ macroalbuminuria leading to nephropathy and subsequently to ESRD, or retinopathy leading to blindness). Both models have been used, for example, to estimate the cost-effectiveness of intensified glycemic and hypertension control strategies, cholesterol-reducing medications, and lifestyle intervention programs [57-59]. In addition, the models

are regularly tested in validation challenges at the Mount Hood diabetes modeling conference that addresses the need for well-parametrized, robust and transparent models [60]. While there is currently no German type 2 diabetes model available, joint efforts of a research group at the German Diabetes Center in Düsseldorf and the Helmholtz Zentrum München are underway in this direction. This process includes three major steps: first, the examination of the adaptability of a comparable type 2 diabetes model to the German context, second, the collection of relevant data and parametrization of the (adapted) model and, third, the extensive validation and application of the model. Focusing on the second point, it has to be remembered that different sets of parameters require different data sources, e.g. efficacy data and transition probabilities of prevention and health care strategies are mostly gathered from clinical trials, whereas HRQoL values (utilities) are likely to be generated by cohort studies [61]. Regarding costs, diabetes models usually focus on direct medical costs. In particular, two major types of costs have to be distinguished here: intervention costs and complication costs [62]. While intervention costs can be directly derived from the trials itself, complication costs can be obtained either from separate literature sources (additive cost function) or from a single data-based regression of all predictors (additive or multiplicative cost function). For the regression approach, it is important to know that cost data usually follow a highly skewed distribution with a heavy tail and considerable number of zeros [63-65]. Traditionally, the additive cost function refers to the use of multiple sources, which can be biased due to heterogeneity reasons (e.g., different populations, time periods and settings) [62]. In diabetes modeling, the term is particularly used for the summative evaluation of the unit costs of complications (e.g., the costs of having both CHF and retinopathy would equal the costs of having CHF plus the costs of having retinopathy). The multiplicative approach is always a regression-based method that assumes a multiplicative linking of costs and may need transformation routines to obtain directly interpretable estimates. In the UKPDS model, Alva et al. used data of ~3500 patients to estimate an additive cost function based on a two-part model and bootstrap technique for inpatient costs (involving a logit and gamma generalized linear model (GLM) with identity link transformation), and a one-part gamma GLM for outpatient costs [66]. The CDC/RTI model reports both, an additive cost function based on multiple data sources, and a multiplicative cost function that mainly consists of baseline costs multiplied with the product of several multipliers associated with demographic variables, diabetes-

related complications, and diabetes-related treatments [67]. In addition, the presence of disease interactions can indicate a more than additive relationship between complications (in other words, the effect of the co-occurring diseases is more than could be expected from adding their individual effects). The optimal choice of regression method should be carefully considered with regard to the study aims and may also depend on other factors, including convergence and computational performance, interpretability of results, quality of estimates (e.g., mean-squared error of the predictions vs. observed data), and ease of sensitivity analyses [68]. The availability of a large database provides a greater flexibility and variety in methods to assess diabetes costs, including the assumption of a normal distribution of costs with favorable properties for run-time efficiency, the quantification of probabilistic uncertainty, and direct interpretability of the results [64].

What this thesis is able to add to the field of type 2 diabetes modeling is providing methodological input and empirical evidence on quantifying the costs of relevant complications, in order to improve the accuracy of model-based cost-effectiveness evaluations or even to build a German diabetes model. At first, this includes the development of a study design that is tailored to the economic parametrization of a type 2 diabetes model and its specific health states (e.g., incident/prevalent and fatal/nonfatal complications). Furthermore, this involves a more thorough examination of the additive or multiplicative linkage of diabetes costs and finally, a robust and detailed quantification of the total direct costs of complications (e.g., by using a larger dataset, considering time-dependent structures, and measuring interactions of specific complications with age, sex or other complications).

1.5 Guiding through this dissertation

1.5.1 Goal of this dissertation and scope of published sub-studies

This dissertation is based on a retrospective analysis of real-world patient-level data of the largest nationwide SHI fund, the Techniker Krankenkasse (10.2 million insured in mid-2018). The primary aim and long-term perspective of this dissertation was to contribute new empirical evidence and methodological approaches on the economic evaluation of various diabetes-related complications and, particularly, to inform the parametrization of type 2 diabetes models. The two sub-studies are based on quarterly data from 2012 (baseline year) and 3-year follow-up, on a total of 316,220 patients with type 2 diabetes (63% male, mean age 65.6 years), who were selected based on the diagnostic codes E11 and E14, the prescription of oral antidiabetic medications, and participation in a disease management program for type 2 diabetes.

The first study (published in Diabetes Care) describes the collection of the study population and focuses on providing robust empirical evidence on the total direct costs associated with the occurrence of diabetes-related complications. In detail, the study addresses the following questions:

- How much do various incident complications of patients with type 2 diabetes cost the SHI system in the quarter of event/onset and thereafter?
- How can type 2 diabetes and its complications be identified in claims data that are checked for consistency and plausibility?
- Are there significant interactions between age, sex and the occurrence of complications on total costs?
- How do the results compare with what is known from international diabetes models and other literature on the burden of diabetes?

The second study (published in PharmacoEconomics) adds more in-depth empirical and especially methodological knowledge on the annual total costs associated with diabetes-related multimorbidity, with a strong focus on developing and exploring measures of different granularity.

In detail, the study addresses the following questions:

- What is the economic impact of different strategies to assess the co-occurrence of multiple complications on total healthcare costs (ranging from an aggregated count level to the differentiation of micro-/ macrovascular groups to interactions between specific incident/prevalent complications)?
- Which interaction patterns can be observed and visualized?
- What validity issues arise from the cross-sectional and longitudinal analysis of claims data and how can they possibly be dealt with in standard routines?
- How can the results be usefully implemented in diabetes simulation models?

1.5.2 Individual contribution of the author

The author (KK) of this cumulative thesis contributed substantially to all included articles. The conceptual ideas, study design and statistical analysis plan originated from or were substantially shaped by the author. KK selected, prepared and analyzed the data of the two studies independently at the Techniker Krankenkasse in Hamburg. She composed and finalized the underlying manuscripts and acted as corresponding author for the published articles.

1.6 References

1. Riddle MC, Herman WH. The cost of diabetes care - an elephant in the room. Diabetes Care. 2018 May;41(5):929-32.

2. Zimmet PZ, Magliano DJ, Herman WH, Shaw JE. Diabetes: a 21st century challenge. The Lancet Diabetes & Endocrinology. 2014 Jan;2(1):56-64.

3. Oggioni C, Lara J, Wells JC, Soroka K, Siervo M. Shifts in population dietary patterns and physical inactivity as determinants of global trends in the prevalence of diabetes: an ecological analysis. Nutrition, Metabolism, and Cardiovascular Diseases. 2014 Oct;24(10):1105-11.

4. Brinks R, Tamayo T, Kowall B, Rathmann W. Prevalence of type 2 diabetes in Germany in 2040: Estimates from an epidemiological model. European Journal of Epidemiology. 2012 Oct;27(10):791-7.

5. Cho NH, Shaw JE, Karuranga S, Huang Y, da Rocha Fernandes JD, Ohlrogge AW, et al. IDF Diabetes Atlas: Global estimates of diabetes prevalence for 2017 and projections for 2045. Diabetes Research and Clinical Practice. 2018 Apr;138:271-81.

6. Heidemann C, Du Y, Schubert I, Rathmann W, Scheidt-Nave C. [Prevalence and temporal trend of known diabetes mellitus: Results of the German Health Interview and Examination Survey for Adults (DEGS1)]. Bundesgesundheitsblatt, Gesundheitsforschung, Gesundheitsschutz. 2013 May;56(5-6):668-77.

7. Tamayo T, Brinks R, Hoyer A, Kuss OS, Rathmann W. The prevalence and incidence of diabetes in Germany. Deutsches Arzteblatt International. 2016 Mar 18;113(11):177-82.

8. Whiting DR, Guariguata L, Weil C, Shaw J. IDF diabetes atlas: global estimates of the prevalence of diabetes for 2011 and 2030. Diabetes Research and Clinical Practice. 2011 Dec;94(3):311-21.

9. Global Burden of Disease Study 2013 Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990-2013: A systematic analysis for the Global Burden of Disease Study 2013. The Lancet. 2015 Aug;386(9995):743-800.

10. Cummings M, Cunha-Vaz J. Treatment of neovascular age-related macular degeneration in patients with diabetes. Clinical Ophthalmology. 2008 Jun;2(2):369-75.

11. Chang HY, Weiner JP, Richards TM, Bleich SN, Segal JB. Validating the adapted Diabetes Complications Severity Index in claims data. The American Journal of Managed Care. 2012 Nov;18(11):721-6.

12. Hunger M, Thorand B, Schunk M, Doring A, Menn P, Peters A, et al. Multimorbidity and health-related quality of life in the older population: results from the German KORA-age study. Health and Quality of Life Outcomes. 2011 Jul;9:53.

13. Schunk M, Reitmeir P, Ruckert-Eheberg IM, Tamayo T, Schipf S, Meisinger C, et al. Longitudinal change in health-related quality of life in people with prevalent and incident type 2 diabetes compared to diabetes-free controls. PLOS ONE. 2017 May;12(5):e0176895.

14. Heidemann C, Scheidt-Nave C. Prevalence, incidence and mortality of diabetes mellitus in adults in Germany - A review in the framework of the diabetes surveillance. Journal of Health Monitoring. 2017;2(3):98–121.

15. Fuchs S, Henschke C, Blumel M, Busse R. Disease management programs for type 2 diabetes in Germany: A systematic literature review evaluating effectiveness. Deutsches Arzteblatt International. 2014 Jun;111(26):453-63.

16. Jacobs E, Hoyer A, Brinks R, Kuss O, Rathmann W. Burden of mortality attributable to diagnosed diabetes: A nationwide analysis based on claims data from 65 Million people in Germany. Diabetes Care. 2017 Dec;40(12):1703-9.

17. IDF Diabetes Atlas Group. Update of mortality attributable to diabetes for the IDF Diabetes Atlas: Estimates for the year 2013. Diabetes Research and Clinical Practice. 2015 Sep;109(3):461-5.

18. Stock SA, Redaelli M, Wendland G, Civello D, Lauterbach KW. Diabetes – prevalence and cost of illness in Germany: A study evaluating data from the statutory health insurance in Germany. Diabetic Medicine. 2006 Mar;23(3):299-305.

19. Jonsson B. Revealing the cost of type II diabetes in Europe. Diabetologia. 2002 Jul;45(7):S5-12.

20. Köster I, Schubert I, Huppertz E. [Follow up of the CoDiM-Study: Cost of diabetes mellitus 2000-2009]. Deutsche Medizinische Wochenschrift. 2012 May;137(19):1013-6.

21. Köster I, Huppertz E, Hauner H, Schubert I. Direct costs of diabetes mellitus in Germany - CoDiM 2000-2007. Experimental and Clinical Endocrinology & Diabetes. 2011 Jun;119(6):377-85.

22. Köster I, von Ferber L, Ihle P, Schubert I, Hauner H. The cost burden of diabetes mellitus: the evidence from Germany - the CoDiM study. Diabetologia. 2006 Jul;49(7):1498-504.

23. Bommer C, Heesemann E, Sagalova V, Manne-Goehler J, Atun R, Barnighausen T, et al. The global economic burden of diabetes in adults aged 20-79 years: A cost-of-illness study. The Lancet Diabetes & Endocrinology. 2017 Jun;5(6):423-30.

24. Bommer C, Sagalova V, Heesemann E, Manne-Goehler J, Atun R, Barnighausen T, et al. Global economic burden of diabetes in adults: Projections from 2015 to 2030. Diabetes Care. 2018 May;41(5):963-70.

25. Ulrich S, Holle R, Wacker M, Stark R, Icks A, Thorand B, et al. Cost burden of type 2 diabetes in Germany: results from the population-based KORA studies. BMJ Open. 2016 Nov 21;6(11):e012527.

26. von Ferber L, Koster I, Hauner H. Medical costs of diabetic complications total costs and excess costs by age and type of treatment results of the German CoDiM Study. Experimental and Clinical Endocrinology & Diabetes. 2007 Feb;115(2):97-104.

27. von Ferber L, Koster I, Hauner H. [Costs of the treatment of hyperglycemia in patients with diabetes mellitus. The impact of age, type of therapy and complications: results of the German CoDiM study]. Medizinische Klinik - Intensivmedizin und Notfallmedizin. 2006 May;101(5):384-93.

28. Sieber C. [1+1+1 = Multimorbidity is more than the addition of monopathologies]. Deutsche Medizinische Wochenschrift. 2017 Aug;142(15):1089.

29. Ahlqvist E, Storm P, Karajamaki A, Martinell M, Dorkhan M, Carlsson A, et al. Novel subgroups of adult-onset diabetes and their association with outcomes: A data-driven cluster analysis of six variables. The Lancet Diabetes & Endocrinology. 2018 May;6(5):361-9.

30. Chawla A, Chawla R, Jaggi S. Microvasular and macrovascular complications in diabetes mellitus: Distinct or continuum? Indian Journal of Endocrinology and Metabolism. 2016 Jul-Aug;20(4):546-51.

31. Wilke T, Mueller S, Groth A, Fuchs A, Seitz L, Kienhofer J, et al. Treatment-dependent and treatment-independent risk factors associated with the risk of diabetes-related events: A retrospective analysis based on 229,042 patients with type 2 diabetes mellitus. Cardiovascular Diabetology. 2015 Feb;14:14.

32. Kröger K, Berg C, Santosa F, Malyar N, Reinecke H. Lower limb amputation in Germany: An analysis of data from the German Federal Statistical Office between 2005 and 2014. Deutsches Ärzteblatt International. 2017;114(8):130-6.

33. Buckley CM, O'Farrell A, Canavan RJ, Lynch AD, De La Harpe DV, Bradley CP, et al. Trends in the incidence of lower extremity amputations in people with and without diabetes over a five-year period in the Republic of Ireland. PLOS ONE. 2012;7(7):e41492.

34. Abholz HH, Egidi G, Zitterbart EU. Prävalenz von Folgeerkrankungen und Nutzen der Glukosesenkung bei Diabetes mellitus Typ 2. Deutscher Ärzte-Verlag | Zeitschrift für Allgemeinmedizin. 2015;91(5):220-6.

35. Bundesärztekammer (BÄK), Kassenärztliche Bundesvereinigung (KVB), Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF). Typ 2 Diabetes: Präventions- und Behandlungsstrategien für Fußkomplikationen. 2010; Available from: https://www.awmf.org/leitlinien (last accessed 6th Sept 2018).

36. Marshall SM, Flyvbjerg A. Prevention and early detection of vascular complications of diabetes. BMJ. 2006;333(7566):475-80.

37. Hartmann J, Jacobs S, Eberhard S, von Lengerke T, Amelung V. Analysing predictors for future high-cost patients using German SHI data to identify starting points for prevention. European Journal of Public Health. 2016;26(4):549-55.

38. Blumenthal D, Chernof B, Fulmer T, Lumpkin J, Selberg J. Caring for high-need, high-cost patients - An urgent priority. The New England Journal of Medicine. 2016;375(10):909-11.

39. Lin PJ, Pope E, Zhou FL. Comorbidity type and health care costs in type 2 diabetes: A retrospective claims database analysis. Diabetes Therapy. 2018 Aug 10 [Epub ahead of print].

40. Alonso-Moran E, Orueta JF, Esteban JI, Axpe JM, Gonzalez ML, Polanco NT, et al. Multimorbidity in people with type 2 diabetes in the Basque Country (Spain): Prevalence, comorbidity clusters and comparison with other chronic patients. European Journal of Internal Medicine. 2015 Apr;26(3):197-202.

41. Nuno-Solinis R, Alonso-Moran E, Arteagoitia Axpe JM, Ezkurra Loiola P, Orueta JF, Gaztambide S. Healthcare costs of people with type 2 diabetes mellitus in the Basque Country (Spain). Endocrinología y Nutrición. 2016 Dec;63(10):543-50.

42. Chen HL, Hsu WW, Hsiao FY. Changes in prevalence of diabetic complications and associated healthcare costs during a 10-year follow-up period among a nationwide diabetic cohort. Journal of Diabetes and its Complications. 2015 May-Jun;29(4):523-8.

43. Hughes LD, McMurdo ME, Guthrie B. Guidelines for people not for diseases: the challenges of applying UK clinical guidelines to people with multimorbidity. Age and Ageing. 2013 Jan;42(1):62-9.

44. Gibbons RJ. Imperfect data can still provide important answers. JACC: Cardiovasc Imaging. 2018 June 8 [Epub ahead of print].

45. Claxton K, Cohen JT, Neumann PJ. When is evidence sufficient? Health Affairs. 2005 Jan-Feb;24(1):93-101.

46. Harpe SE. Using secondary data sources for pharmacoepidemiology and outcomes research. Pharmacotherapy. 2009 Feb;29(2):138-53.

47. Schubert I, Köster I, Küpper-Nybelen J, Ihle P. Versorgungsforschung mit GKV-Routinedaten. Bundesgesundheitsblatt - Gesundheitsforschung - Gesundheitsschutz. 2008 October 01;51(10):1095-105.

48. Hoffmann F, Icks A. Diabetes prevalence based on health insurance claims: large differences between companies. Diabetic Medicine. 2011 Aug;28(8):919-23.

49. Gansen FM. Health economic evaluations based on routine data in Germany: A systematic review. BMC Health Services Research. 2018 Apr;18(1):268.

50. Kreis K, Neubauer S, Klora M, Lange A, Zeidler J. Status and perspectives of claims data analyses in Germany - A systematic review. Health Policy. 2016 Feb;120(2):213-26.

51. Einav L, Levin J. Economics in the age of big data. Science. 2014 Nov 7;346(6210):1243089.

52. Hoffmann F, Icks A. [Structural differences between health insurance funds and their impact on health services research: Results from the Bertelsmann Health-Care Monitor]. Gesundheitswesen. 2012 May;74(5):291-7.

53. Altenhofen L, Hagen B, Kretschmann J, Groos S, Graf von Stillfried D. Collective was not representative. Deutsches Ärzteblatt International. 2011;108(42):722.

54. Mohiuddin S, Busby J, Savovic J, Richards A, Northstone K, Hollingworth W, et al. Patient flow within UK emergency departments: A systematic review of the use of computer simulation modelling methods. BMJ Open. 2017 May;7(5):e015007.

55. Govan L, Wu O, Lindsay R, Briggs A. How do diabetes models measure up? A review of diabetes economic models and ADA guidelines. Journal of Health Economics and Outcomes Research. 2015;3(2):132-52.

56. Tarride JE, Hopkins R, Blackhouse G, Bowen JM, Bischof M, Von Keyserlingk C, et al. A review of methods used in long-term cost-effectiveness models of diabetes mellitus treatment. PharmacoEconomics. 2010;28(4):255-77.

57. Laxy M, Wilson ECF, Boothby CE, Griffin SJ. Incremental costs and cost-effectiveness of intensive treatment in individuals with type 2 diabetes detected by screening in the ADDITION-UK trial: An update with empirical trial–based cost data. Value in Health. 2017.

58. Zhuo X, Zhang P, Gregg EW, Barker L, Hoerger TJ, Tony P-C, et al. A nationwide community-based lifestyle program could delay or prevent type 2 diabetes cases and save $5.7 billion in 25 years. Health Affairs. 2012 Jan;31(1):50-60.

59. The CDC Diabetes Cost-Effectiveness Group. Cost-effectiveness of intensive glycemic control, intensified hypertension control, and serum cholesterol level reduction for type 2 diabetes. JAMA. 2002 May;287(19):2542-51.

60. Palmer AJ, Si L, Tew M, Hua X, Willis MS, Asseburg C, et al. Computer modeling of diabetes and its transparency: A report on the Eighth Mount Hood Challenge. Value in Health. 2018.

61. Paisley S. Classification of evidence in decision-analytic models of cost-effectiveness: a content analysis of published reports. International Journal of Technology Assessment in Health Care. 2010 Oct;26(4):458-62.

62. Hoerger TJ. Using costs in cost-effectiveness models for chronic diseases: lessons from diabetes. Medical Care. 2009 Jul;47(7 Suppl 1):S21-7.

63. Barber J, Thompson S. Multiple regression of cost data: Use of generalised linear models. Journal of Health Services Research & Policy. 2004 Oct;9(4):197-204.

64. Mihaylova B, Briggs A, O'Hagan A, Thompson SG. Review of statistical methods for analysing healthcare resources and costs. Health Economics. 2011 Aug;20(8):897-916.

65. Gregori D, Petrinco M, Bo S, Desideri A, Merletti F, Pagano E. Regression models for analyzing costs and their determinants in health care: an introductory review. International Journal for Quality in Health Care. 2011 Jun;23(3):331-41.

66. Alva ML, Gray A, Mihaylova B, Leal J, Holman RR. The impact of diabetes-related complications on healthcare costs: New results from the UKPDS (UKPDS 84). Diabetic Medicine. 2015 Apr;32(4):459-66.

67. Brandle M, Zhou H, Smith BR, Marriott D, Burke R, Tabaei BP, et al. The direct medical cost of type 2 diabetes. Diabetes Care. 2003 Aug;26(8):2300-4.

68. Pagano E, Petrelli A, Picariello R, Merletti F, Gnavi R, Bruno G. Is the choice of the statistical model relevant in the cost estimation of patients with chronic diseases? An empirical approach by the Piedmont Diabetes Registry. BMC Health Services Research. 2015 Dec 30;15:582.

2 Article 1: "Health care costs associated with incident complications in patients with type 2 diabetes in Germany"

Published in:

Kähm K., Laxy M., Schneider U., Rogowski W.H., Lhachimi S.K., Holle R.: Health care costs associated with incident complications in type 2 diabetes in Germany. Diabetes Care 2018; 41(5): 971-978.

Diabetes Care Volume 41, May 2018

Health Care Costs Associated With Incident Complications in Patients With Type 2 Diabetes in Germany

Katharina Kähm,[1,2] Michael Laxy,[1,2] Udo Schneider,[3] Wolf H. Rogowski,[4] Stefan K. Lhachimi,[5,6] and Rolf Holle[1,2]

Diabetes Care 2018;41:971–978 | https://doi.org/10.2337/dc17-1763

OBJECTIVE

The aim of this study is to provide reliable regression-based estimates of costs associated with different type 2 diabetes complications.

RESEARCH DESIGN AND METHODS

We used nationwide statutory health insurance (SHI) data from 316,220 patients with type 2 diabetes. Costs for inpatient and outpatient care, pharmaceuticals, rehabilitation, and nonmedical aids and appliances were assessed in the years 2013–2015. Quarterly observations are available for each year. We estimated costs (in 2015 euro) for complications using a generalized estimating equations model with a normal distribution adjusted for age, sex, occurrence of different complications, and history of complications at baseline, 2012. Two- and threefold interactions were included in an extended model.

RESULTS

The base case model estimated total costs in the quarter of event for the example of a 60- to 69-year-old man as follows: diabetic foot €1,293, amputation €14,284, retinopathy €671, blindness €2,933, nephropathy €3,353, end-stage renal disease (ESRD) €22,691, nonfatal stroke €9,769, fatal stroke €11,176, nonfatal myocardial infarction (MI)/cardiac arrest (CA) €8,035, fatal MI/CA €8,700, nonfatal ischemic heart disease (IHD) €6,548, fatal IHD €20,942, chronic heart failure €3,912, and angina pectoris €2,695. In the subsequent quarters, costs ranged from €681 for retinopathy to €6,130 for ESRD.

CONCLUSIONS

Type 2 diabetes complications have a significant impact on total health care costs in the SHI system, not only in the quarter of event but also in subsequent years. Men and women from different age-groups differ in their costs for complications. Our comprehensive estimates may support the parametrization of diabetes models and help clinicians and policy makers to quantify the economic burden of diabetes complications in the context of new prevention and treatment programs.

In Germany, the prevalence of type 2 diabetes was estimated at ~7% in 2011, which is slightly above the global average (1,2). Type 2 is the most common form of diabetes, accounting for >90% of all diabetes cases, and is largely the result of lifestyle and behavioral risk factors. The shift in risk factors as well as demographics is contributing to the increasing prevalence worldwide, especially among younger age-groups (3). This increased prevalence adds to the growing social and economic burden of diabetes, which is further driven by the occurrence of multiple heterogeneous complications (4).

[1]Institute of Health Economics and Health Care Management, Helmholtz Zentrum München (GmbH)–German Research Center for Environmental Health (GmbH), Neuherberg, Germany
[2]German Center for Diabetes Research (DZD), München-Neuherberg, Germany
[3]Scientific Institute of the Techniker Krankenkasse for Benefit and Efficiency in Health Care, Techniker Krankenkasse, Hamburg, Germany
[4]Department of Health Care Management, Institute of Public Health and Nursing Research, Health Sciences, University of Bremen, Bremen, Germany
[5]Research Group Evidence-Based Public Health, Leibniz Institute for Epidemiology and Prevention Research (BIPS), Bremen, Germany
[6]Health Sciences Bremen, Institute for Public Health and Nursing, University of Bremen, Bremen, Germany

Corresponding author: Katharina Kähm, katharina.kaehm@helmholtz-muenchen.de.

Received 23 August 2017 and accepted 15 December 2017.

This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc17-1763/-/DC1.

See accompanying articles, pp. 917, 929, 933, 940, 949, 956, 963, 979, 985, and e72.

As new diabetes treatments and prevention programs are introduced to address these issues, economic evaluations are becoming more important. Tools such as systematic disease models can assist decision makers in assessing the impact on clinical outcomes and economic performance. The two widely used noncommercial type 2 diabetes models that have a substantive overlap include the Centers for Disease Control and Prevention/RTI International (CDC/RTI) model and the UK Prospective Diabetes Study (UKPDS) Outcomes Model (5,6). Both models follow patients over a lifetime horizon and simulate the development of various complications, including microvascular complications (nephropathy, diabetic foot, and retinopathy) as well as macrovascular complications. These models have, for example, been used to estimate the cost-effectiveness of an intensive glycemic control regimen, a cholesterol-reducing regimen, or other intervention programs (7,8). So far, there is no literature on a comparable German model for type 2 diabetes. Although the risk engines are probably transferable to Caucasian populations, costs mostly remain country specific. Reliable estimates are therefore needed for the use of diabetes models in the German context. To date, there are only a few related studies focusing on the health care costs of diabetes complications in Germany. However, none of these studies fulfills all the requirements necessary for a complete implementation and parametrization of such a diabetes model. Specifically, they do not distinguish between type 1 and type 2 diabetes, do not account for the temporal distribution of costs, exclude deaths, use a restrictive sample (e.g., from the state Hesse), or focus on just one single complication (9–11). With regard to the data source to be used, health claims data are the most suitable source because of the large sample size, wide coverage, and detailed cost data covering several years.

This study therefore uses nationwide health insurance data from Germany to comprehensively estimate the short- and medium-term costs of typical type 2 diabetes–related complications within a regression approach. These estimates can be used for the parametrization of diabetes models such as UKPDS and CDC/RTI and are helpful for clinicians and decision makers in quantifying the economic burden of diabetes complications.

RESEARCH DESIGN AND METHODS

Research Setting

In Germany, every citizen is required to have health insurance (either private or statutory). Currently, there are >100 statutory health insurance (SHI) funds, which are mainly historically evolved and cover ~90% of the population.

Each person is assigned a unique pseudonymous identification number, which allows every insurance fund to capture information from the same person until death, end of insurance, or even with interruptions in the insurance history. In this retrospective cohort study, we use claims data from the Techniker Krankenkasse (TK), which is the largest nationwide SHI provider in Germany, covering ~9.8 million insured people in the first half of 2017 throughout Germany.

Health claims data (especially outpatient service data) are by German social laws only available for the last 4 years. The data extraction was performed at the end of 2016; therefore, the baseline year was 2012. The development of complications and costs was then assessed during the follow-up period in 2013–2015. All analyses were performed at the WINEG institute (Scientific Institute of TK for Benefit and Efficiency in Health Care), who approved the intended use of the data. According to official guidelines, the consultation of an ethics committee is not required because of the retrospective design of the study and the on-site evaluation of data at the WINEG institute (12).

Selection of Study Population: Inclusion and Exclusion Criteria

The definition of type 2 diabetes follows a recent publication on the incidence and prevalence of diabetes in Germany (13). In this study, Tamayo et al. (13) propose a way of distinguishing between different groups of patients with diabetes based on outpatient and inpatient ICD-10 diagnoses E10–E14, namely type 1, type 2, unclear type 1 or 2, unspecified, or other diabetes. For our analysis, we concentrated on the group of patients with clear type 2 diabetes but also considered potential type 2 diabetes in the group with an unclear or unspecified diabetes diagnosis. Therefore, we linked the inclusion criteria to the prescription of oral antidiabetes medications and participation in a disease-management program (DMP) for type 2 diabetes. Regarding the first point, for example, the most commonly prescribed antidiabetes agent metformin is not licensed for individuals without diabetes in Germany. On the second point, it should be noted that >60% of the population with diabetes participates in a DMP for type 2 diabetes (14,15). A more detailed technical definition can be found in Supplementary Table 1. Before beginning the data selection, we also compared the diabetes prevalence calculated based on the TK population (standardized to the German population in 2011) with other literature. Exclusion criteria included age <18 years, certain diseases such as gestational diabetes mellitus (ICD-10 O24), pancreoprivic diabetes (E13), and pancreatic cancer, and participation in a DMP for type 1 diabetes. Furthermore, we excluded patients with an incomplete insurance history until death in the follow-up period and patients with unknown residence or residence abroad at baseline. The flowchart for the cohort selection is shown in Fig. 1.

Identification of Diabetes-Associated Complications

This study investigates macrovascular complications, including angina pectoris, chronic heart failure (CHF), myocardial infarction (MI)/cardiac arrest (CA), stroke, and other ischemic heart diseases (IHDs), as well as microvascular complications, including retinopathy, blindness, diabetic foot, lower-extremity amputation (LEA), nephropathy, and end-stage renal disease (ESRD). These are the complications in the UKPDS and CDC/RTI diabetes model, which were identified based on corresponding medical codes that were collected from the literature and publicly accessible databases (see Supplementary Tables 2 and 3 for full details of the operationalization of complications, risk factors, and medications) (16–28). Inclusion criteria for complications required that at least one outpatient or one primary or secondary inpatient ICD diagnosis was documented in the follow-up period. Complications with only one suspected diagnosis in one quarter were not taken into account. For some complications (i.e., LEA or dialysis-dependent renal insufficiency), inpatient operation/procedure codes and outpatient service codes were also used. Moreover, acute macrovascular complications (MI/CA, stroke, and IHD) were defined as nonfatal or fatal events that were limited to hospitalizations with primary diagnosis. Fatal macrovascular

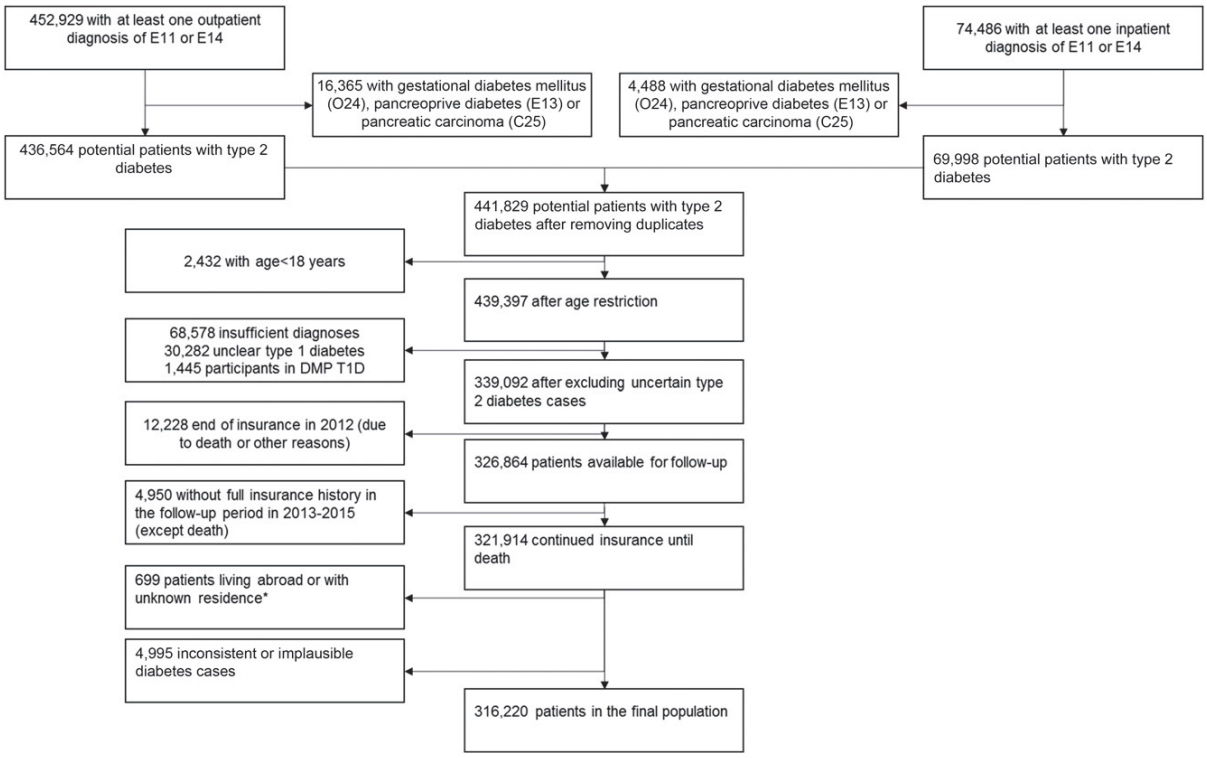

Figure 1—Selection algorithm for patients with type 2 diabetes (baseline year 2012). *At time of data selection (December 2016). Therefore, patients with temporary stay abroad are still included in the population. T1D, type 1 diabetes.

complications additionally required death as the discharge reason. The quarter of an incident complication was detected in the follow-up period by requiring a washout period of 1 year (that is the baseline year 2012) free of diagnoses of the specific complication. If a complication was present at baseline, patients were assigned as having a history of the complication.

Resources and Costs

By applying an SHI perspective, health care costs include costs for outpatient and inpatient services, medication, rehabilitation, and the provision of aids and appliances. Therefore, copayments to medical services covered by SHI are included in the data set, whereas patients' out-of-pocket payments for other services are not. All costs are expressed in 2015 euros using official inflation data from the Federal Statistical Office (29). Outpatient diagnoses are only available on a quarter level. For inpatient data, the admission and discharge dates are available. In line with an SHI perspective, we used the discharge date to determine the corresponding quarter.

Data Preprocessing and Statistical Analysis

Before the actual statistical analysis, data were subjected to quality and plausibility checks as requested by common guidelines for secondary data analysis (12). This included, for example, checking for negative or zero total hospital payments, implausible lengths of stay in hospital, or charged costs after death (see Supplementary Table 4). Additionally, cost data were plotted in a boxplot and histogram to identify possible outliers. We prepared the data in the form of 12 observation periods of 3 months per patient, representing the number of calendar quarters in the 3-year follow-up period. We allowed for deviations of the time of onset of the complication by consecutively numbering quarters without complication with zero, the quarter of event with 1, and the following quarters with 2 to up to 12. In accordance with the requirements of the implementation of costs in diabetes models, we estimated the impact of complications in at least two time periods: within the quarter in which the complication occurs and in subsequent quarters (i.e., $<$1 year after the onset of complication and $>$1 year after the onset of complication). Similar to Alva et al. (22), we assume that the later time periods are likely to reflect the ongoing impact of complications, including subsequent events of the same type. Patients who already experienced this complication at baseline are extracted in separate dummy variables, which stay the same during the follow-up period. All patients were followed up until death or end of 2015. A generalized estimating equations (GEE) model was used to account for the nonindependence of observations within each subject during the period of the study (see Supplementary Statistical Appendix for the detailed model notation). In line with literature recommendations, we can assume a near normality of the sample means, as the sample size is sufficiently large and the proportion of zero costs relatively small ($<$2%) (30). Furthermore, the GEE model with a normal distribution showed better model fit based on the mean square error and residual plot compared with a γ-based GEE model where €1 was assigned for patients with zero costs. While the normal distribution also has favorable properties

for run-time efficiency, the quantification of probabilistic uncertainty, and the interpretability of results, other data transformation methods, such as the logarithmic transformation, have several drawbacks on their own (31). To address challenges associated with extreme outliers, costs were winsorized at 99.9% (by sex) in a sensitivity analysis. Winsorization is a way to minimize the influence of outliers in the data by replacing extreme values based on percentiles. All analyses were performed using SAS Enterprise Guide version 7.1 with SAS version 9.4 (SAS Institute Inc., Cary, NC).

RESULTS

Sample Characteristics

Table 1 describes the baseline sociodemographic and clinical characteristics of the study sample, which consisted of 316,220 patients. Approximately 61% of the population was found to participate in a DMP for type 2 diabetes in 2012. Hypertension and obesity were frequently present in ~81% and 30%, respectively. Obesity and depression were thereby more frequent in women (34% vs. 28% and 26% vs. 14%), whereas alcohol and tobacco abuse and malignant cancer were more frequent in men (10% vs. 7% and 16% vs. 13%). Men also exhibited a slightly higher adapted Diabetes Complication Severity Index (aDCSI) score of 1.9 vs. 1.5 (see Supplementary Tables 5 and 6 for further details on the calculation of the aDCSI score and distribution in the population) (25).

Diabetes Prevalence

In the TK population, the standardized prevalence of clear type 2 diabetes cases (ICD E11) was calculated at 5.6% in 2012 (6.15% for men and 5.10% for women). When taking all diabetes forms into account (including unclear or unspecified type 2 diabetes but also type 1 and other types of diabetes), an overall prevalence of 8.5% and 7.0% was calculated for men and women, respectively.

Descriptive Analysis

In our population, complications occurred with the following frequencies: nephropathy (17.7% observed new cases), diabetic foot (15.5%), CHF (13.4%), retinopathy (11.3%), angina pectoris (5.5%), stroke (2.5%), MI/CA (2.0%), other IHD (2.0%), ESRD (1.2%), amputation (0.6%), and blindness (0.6%).

On the cost side, total raw mean costs increased from €4,688 in 2013 by ~5.6% to €4,949 in 2015 (see Supplementary Fig. 1*A* and *B*). Most of the costs are related to inpatient care (42%), pharmaceuticals (27%), and physician care (20%). In age-groups <60 years, costs were higher in women, whereas costs were higher in men in higher age-groups. Figure 2 shows the development of costs before, during, and after the occurrence or onset of certain complications (information on the number of patients that were included in the calculations as well as the cost factor relative to the absence of complications can be found in Supplementary Fig. 2). Costs in the quarter of event were the highest for LEA, ESRD, and all three acute events (MI/CA, stroke, and other IHD), ranging from €9,309 to €30,739 for nonfatal and fatal IHD, respectively. The distribution of costs indicates no or only a slight peak for chronically evolving complications such as retinopathy, nephropathy, or foot complications at the quarter of first diagnosis. The costs here are growing slowly or remain stagnant. This is in contrast to acute or very severe complications such as LEA, ESRD, and acute macrovascular events, where a clear high peak can be identified. There is also a difference between LEA and acute macrovascular complications, showing that the decline in costs is relatively slower for acute macrovascular complications in the subsequent periods.

Table 1—Baseline characteristics in 2012

	Overall (*n* = 316,220)	Female (*n* = 116,010)	Male (*n* = 200,210)
Participation in the DMP for type 2 diabetes (%)*	61.2	61.0	61.3
Sex (%)		36.7	63.3
Age, years, mean (min, max)	65.9 (18, 106)	66.3 (18, 101)	65.6 (18, 106)
Age-group, years, %			
<50	8.6	9.3	8.2
50–59	19.4	18.2	20.1
60–69	29.6	28.0	30.5
70–79	32.4	32.1	32.6
>80	10.0	12.4	8.5
Type of antidiabetes treatment, %			
None	37.9	42.3	35.3
Only oral	47.4	44.6	48.9
Oral + insulin	9.2	8.1	9.9
Only insulin	5.5	5.0	5.9
aDCSI score, mean (min, max)	1.747 (0, 12)	1.545 (0, 12)	1.864 (0, 12)
Risk factors (ICD codes), %			
Hypertension (I10–I15)	80.5	80.0	80.7
Alcohol/tobacco (F10, F17)	9.0	6.6	10.4
Depression (F32–F34)	18.4	26.3	13.8
Obesity (E66)	30.1	34.2	27.7
Sleeping disorder (G47, F51)	12.9	12.0	13.4
Malignant cancer (C00–C97)	14.7	13.1	15.7

max, maximum; min, minimum. *Participation for at least 1 day.

Regression Analysis

Table 2 shows the estimated coefficients obtained from the GEE model. Because the estimates are directly interpreted as costs, the intercept of €780 represents fixed costs for a female patient aged 70–79 years without any complications for a 3-month period, which corresponds to about €3,120 for a whole year. The same patient with a diabetic foot diagnosis would have additional costs of around €640 for the quarter of diagnosis and around €370 of additional costs in the following quarters. Owing to the large sample size, confidence intervals will be small. Supplementary Tables 7 and 8 report estimates and predictions of costs from the regression, including interaction effects between age, sex, and complications. Total costs were calculated separately for men, women, and age-groups to meet the basic requirements for model parametrization. In addition, results are also presented on an annualized basis. The annualized costs per complication (in 2015 euros) for the example of a 60- to 69-year-old man ranged from €2,539 for retinopathy to €34,547 for ESRD in the year of event, and from €2,469 to €24,662 for retinopathy and ESRD in the following years, respectively. Costs

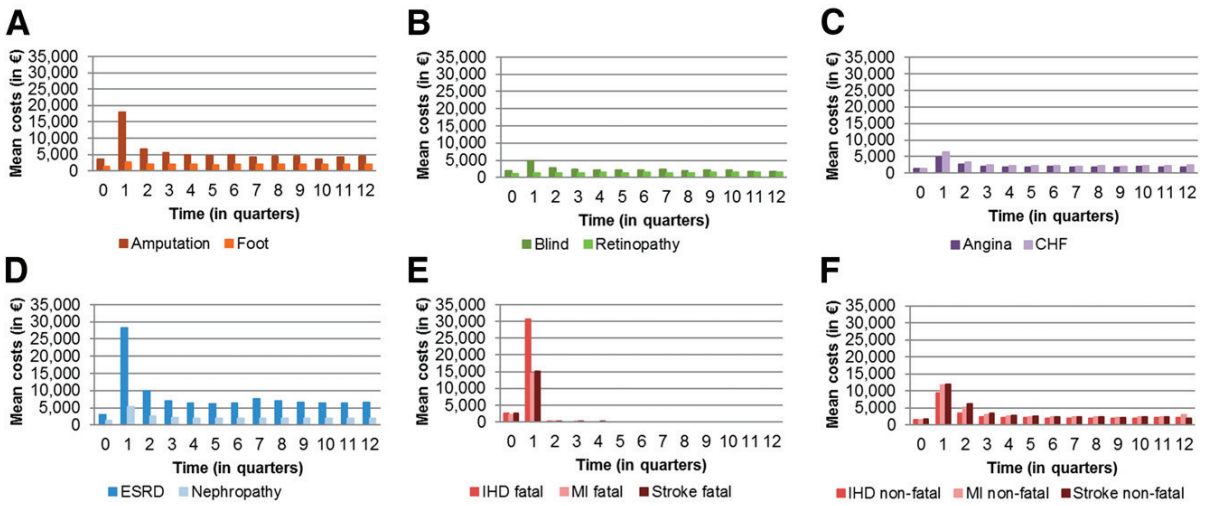

Figure 2—Distribution of raw total costs before and after the occurrence of acute events or onset of chronic complications in quarterly intervals. Costs were not standardized and refer to the patients who were alive or died in the same quarter during the follow-up period (see Supplementary Fig. 2 for further details). Time zero is the mean over patients and quarters without complication; "1" is the quarter where the complication occurs/starts. *A*: Lower-extremity complications. *B*: Eye complications. *C*: Chronic heart complications. *D*: Renal complications. *E*: Acute fatal macrovascular complications. *F*: Acute nonfatal macrovascular complications.

of other fatal IHD were also estimated to be very high, but the SE is the highest because of the small number of patients. It is also noticeable that men have higher costs in most age-groups in the event quarter for macrovascular complications, severe renal complications, and LEA. The differences range from ~5% higher costs for LEA to >80% for fatal MI and more than double for fatal IHD. For acute macrovascular complications, sex differences are higher for fatal than for nonfatal events. Women, in contrast, have higher costs in the first quarter of microvascular complications such as diabetic foot, retinopathy, and blindness, and for macrovascular complications only in specific age-groups. The differences here range from 20% to 30% higher costs for blindness to >50% for retinopathy in the younger age-groups. For retinopathy and diabetic foot, sex differences in costs decrease with higher age-group or even reverse, as for diabetic foot complications. In addition, women also have higher costs in the follow-up quarters for the majority of complications except ESRD. This especially applies to the younger age-groups, whereas the effect often declines in older age-groups. Additional cross-validation was performed by relatively comparing our results with the UKPDS Outcomes Model (version 2) based on the example of a 70- to 79-year-old patient (see Supplementary Table 9).

Sensitivity Analysis

In the sensitivity analysis using winsorization, estimates have generally not changed greatly (results are available on request). The largest changes of 11%–42% reduced costs were mainly related to those complications that are known to be rather rare and expensive (e.g., ESRD, amputation, and fatal macrovascular events).

CONCLUSIONS

There is, to our knowledge, no comparable study that provides an overall picture of the impact of many diabetes-related complications on health care costs in Germany. This study is, therefore, the first providing sufficiently detailed information on the real-life costs of patients with type 2 diabetes for a variety of acute or chronic microvascular and macrovascular complications based on nationwide German claims data for 2012–2015. The results not only show that costs are increased in the quarter in which the event/disease occurs but also show that they continue to be elevated in subsequent years. Second, it becomes apparent that women and men in different age-groups differ in the costs of their complications.

Comparison and Cross-Validation With Other Studies

In 2012, the standardized prevalence of clear type 2 diabetes cases (ICD E11) was lower compared with the estimate of Tamayo et al. (13) for 2010 (5.6% vs. 7.1%). This is in line with a comparison study between different health insurance funds in Germany that resulted in a prevalence of 5.8% for the TK compared with 6.9% overall (32). However, given knowledge about the large numbers of misdiagnosed diabetes cases, the total diabetes prevalence of 8.5% and 7.0% for men and women is overall comparable with other literature (2,33). This also reflects the importance of choosing an appropriate selection strategy for potential type 2 diabetes cases. The proportion of patients who had no antidiabetes treatment at baseline was relatively high (37.9%) compared with the literature (20% for Germany) (34). However, the widely published Costs of Diabetes Mellitus (CoDiM) study also reported a higher percentage of 29.4%, which is comparable to our findings for DMP participants (28.6%) (35). The reason for this higher value cannot be fully determined; it could be because of a healthier patient sample, improved disease monitoring, or false-positive or less severe/prediabetic cases.

Total raw mean costs of €4,688 (2013) are in the same range as reported in other studies, including the CoDiM study and others (€5,993 and €4,377 in 2010, respectively) (21,36). We also cross-validated our results by comparing calculated cost factors for each complication (relative to no complications) with the UKPDS Outcomes Model based on the example of a 70- to 79-year-old patient. Generally,

Table 2—Effects of acute events and chronic type 2 diabetes complications on total costs per quarter in GEE normal regression

Variable	Coefficient estimate (SE)		
Constant	779.7*** (7.9)		
Sex: male (Ref = female)	−57.1*** (6.3)		
Age-group (Ref = 70–79 years), years†			
<50	−128.3*** (12.6)		
50–59	−116.3*** (9.2)		
60–69	−69.2*** (8.4)		
>80	−195.1*** (12.0)		
	Coefficient estimate (SE)		
Event/condition (Ref = no)	Quarter/time of event	<1 year after the event‡	>1 year after the event‡
Diabetic foot	639.3*** (30.8)	369.2*** (17.0)	356.0*** (23.0)
Amputation	13,630.3*** (482.0)	2,665.9*** (168.8)	1,967.9*** (319.3)
Retinopathy	17.5 (16.0)	27.2 (14.2)	39.1* (18.0)
Blindness	2,279.9 (177.3)	487.1 (67.6)	316.2 (80.3)
Nephropathy	2,699.3*** (47.2)	702.0*** (19.3)	432.7*** (21.4)
ESRD	22,037.6*** (700.4)	5,476.4*** (195.5)	4,605.9*** (293.0)
Fatal MI	8,046.2*** (950.8)	NA	NA
Nonfatal MI	7,381.7*** (152.6)	820.8*** (73.5)	220.6** (71.3)
Fatal IHD	20,288.4*** (5,251.3)	NA	NA
Nonfatal IHD	5,894.9*** (141.4)	523.3*** (69.9)	171.2*** (52.3)
CHF	3,258.5*** (55.3)	868.7*** (24.0)	549.7*** (24.4)
Fatal stroke	10,522.9*** (903.5)	NA	NA
Nonfatal stroke	9,115.6*** (155.5)	2,168.8*** (88.7)	642.6*** (54.8)
Angina pectoris	2,041.9*** (50.4)	242.2*** (27.6)	106.3** (35.7)
Death for other reasons	5,589.0*** (124.2)	NA	NA
History in 2012 (Ref = no)	Coefficient estimate (SE)		
Diabetic foot	372.5*** (13.9)		
Amputation	2,017.4*** (171.1)		
Retinopathy	63.2*** (9.3)		
Blindness	196.2*** (47.5)		
Nephropathy	408.8*** (11.1)		
ESRD	6,902.3*** (164.3)		
Nonfatal MI	52.1 (46.3)		
Nonfatal IHD	566.1*** (25.4)		
CHF	532.6*** (12.8)		
Angina pectoris	−11.6 (19.4)		
Nonfatal stroke	635.2*** (46.5)		
Number of observations	3,663,240		
Number of patients	316,220		

NA, not applicable; Ref, reference. *P <0.05. **P <0.01. ***P <0.001. †The interactions between age and sex as well as threefold interactions with complications are omitted here for visibility reasons. The extended model as well as estimated costs by age-group and sex can be found in Supplementary Tables 7 and 8. ‡"Event" refers to the quarter when the diabetes complication first occurred/started.

a reasonable level of congruence was observed, with greater deviations for IHD and diabetic foot. However, greater uncertainty has to be considered in our regression model regarding IHD. In the publication by Alva et al. (22) on the updated cost estimations in the UKPDS model, female patients in most age-groups and complications were assumed to have higher costs (except for ESRD and foot ulcer, where the same costs are assumed in the model). When considering interactions between age, sex, and complications, it was noticeable that our study reveals more differences between men and women. Accordingly, in the event quarter, men had higher costs in most age-groups for ESRD, LEA, and macrovascular complications, whereas women had higher costs for other microvascular complications. Also, women had higher costs in the follow-up quarters for the majority of complications except ESRD. However, because of a lower number of cases in some age-groups, interaction estimates do not always show significant effects and should be interpreted with caution. Important reasons for these sex differences in health care costs could be potentially different causes of the disease (e.g., hemorrhagic versus ischemic stroke and role of psychological factors in women), different severity, or differences in disease management (e.g., less invasive treatments in women with MI) (37). From a methodological point of view, it is also important to consider the age distribution in the different age-groups. Mean age is the same in the middle age-groups, whereas women are 2 years younger than men in the age-group <50 years (44 vs. 42 years) and 1 year older than en in the group >80 years (83 vs. 84 years).

Strengths and Weaknesses of This Study

This study uses the method of regression analysis to provide reliable estimates of

costs associated with different type 2 diabetes complications, adjusted for age, sex, a large set of preexisting complications at baseline, and other two- or three-factor interactions. It was considered to not control for other chronic comorbidities for several reasons, which might have an effect on the results. First, to avoid overadjustment, it would be a crucial point to identify functionally fully independent conditions that are unrelated to the complications of interest. This is especially difficult, since diabetes and its complications are affecting the whole body system. Second, we have good evidence that age is the main predictor of comorbidity (38). Third, we explored the potential bias using the example of obesity, showing that most of the estimates do not differ much at all or at least not significantly.

The analysis itself was based on health insurance data that can be regarded as the best available data source for health care costs in Germany; however, inherent advantages and disadvantages must be considered. First, the representativeness of the data has to be assessed. Despite the high population coverage and the nationwide scope of the TK database, a small selection bias cannot be excluded for any of the insurance providers (32). In this case, the age distribution of the TK population is slightly skewed toward younger people (compared with the general population); however, the mean age of patients with diabetes in our population is comparable with other studies (35).

Second, there are only limited clinical data covered by health claims data. This means that the identification of complications is relying on accurate clinical diagnoses and clinical history information at baseline and that the length of diabetes is unknown. However, regarding the latter point, most diabetes models by their nature require mean cost values as input parameters for practical modeling reasons. What we also have is relatively robust information on the severity of diabetes at baseline (e.g., from treatment type, aDCSI score, and presence of certain risk factors). In addition, we use the information on the history of complications at baseline as an indicator to cope with not having prospective clinical data from newly diagnosed patients with diabetes (as in the UKPDS). It is important that most of these clinical trials are very expensive to conduct and are often still too short to measure the complication costs for many chronic diseases (39). When focusing on cost data, a major strength of this study can therefore be seen in the real-world setting in which the costs are incurred by a large population experiencing natural heterogeneity. The sample size of >300,000 patients with type 2 diabetes also guaranteed the statistical power to investigate rather rare complications (i.e., ESRD, blindness, and amputation). In addition, claims data are not subjected to recall bias, which can be an issue in clinical trials. Finally, another strength of this study is the reference to international diabetes models, which allows better cross-validation. A lack of a sharp boundary between diabetes-related and -unrelated complications remains an important aspect. This applies, for instance, to tumors, injury/poisoning, or psychiatric and psychological illnesses. As for the injuries, it cannot be ruled out that peripheral neuropathy and foot deformities are associated with increased risk of injuries. This is why no diseases beyond type 1 and other diabetes were excluded here. In addition, the relatively large sample size already ensures the stability of the results and that certain groups are not overrepresented by chance.

Summary and Implications

Type 2 diabetes complications have a significant impact on total health care costs in the SHI system, with varying size dependent on age, sex, and type of complication. Our comprehensive estimates may further inform diabetes models and support politicians and health care actors in evaluating the optimal resource allocation across different prevention and intervention programs for the management of type 2 diabetes complications. For high-frequency complications, it is of particular interest for future studies to investigate a deeper analysis of interactions between complications and the importance of the severity of complications. It is also to be expected that this study will motivate future research in the field of diabetes modeling in Germany.

Funding. This research was performed on behalf of Helmholtz Zentrum München, the German Research Center for Environmental Health (HMGU), which is a member of the German Center for Diabetes Research (DZD). The HMGU is an independent organization funded by the German and Bavarian governments. There was no special funding for this study.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

Author Contributions. K.K. paved the way for cooperation with TK for data access; planned the overall study design; performed cohort selection, data processing, and statistical data analysis; and drafted and revised the manuscript. M.L. drafted and revised the manuscript. U.S. was the key contact person at the WINEG/TK and provided continuous technical support during data processing and analysis. W.H.R. paved the way for cooperation with TK for data access and provided methodological input. S.K.L. provided methodological input. R.H. planned the overall study design, provided methodological input, supervised all steps of the work, and drafted and revised the manuscript. All authors critically reviewed the manuscript and approved its final version. K.K. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

References

1. Shaw JE, Sicree RA, Zimmet PZ. Global estimates of the prevalence of diabetes for 2010 and 2030. Diabetes Res Clin Pract 2010;87:4–14

2. Heidemann C, Du Y, Schubert I, Rathmann W, Scheidt-Nave C. Prevalence and temporal trend of known diabetes mellitus: results of the German Health Interview and Examination Survey for Adults (DEGS1). Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz 2013;56:668–677 [in German]

3. Chen L, Magliano DJ, Zimmet PZ. The worldwide epidemiology of type 2 diabetes mellitus–present and future perspectives. Nat Rev Endocrinol 2011;8:228–236

4. Seuring T, Archangelidi O, Suhrcke M. The economic costs of type 2 diabetes: a global systematic review. Pharmacoeconomics 2015;33:811–831

5. Clarke PM, Gray AM, Briggs A, et al.; UK Prospective Diabetes Study (UKDPS) Group. A model to estimate the lifetime health outcomes of patients with type 2 diabetes: the United Kingdom Prospective Diabetes Study (UKPDS) outcomes model (UKPDS no. 68). Diabetologia 2004;47:1747–1759

6. CDC Diabetes Cost-effectiveness Group. Cost-effectiveness of intensive glycemic control, intensified hypertension control, and serum cholesterol level reduction for type 2 diabetes. JAMA 2002;287:2542–2551

7. Laxy M, Wilson ECF, Boothby CE, Griffin SJ. Incremental costs and cost-effectiveness of intensive treatment in individuals with type 2 diabetes detected by screening in the ADDITION-UK trial: an update with empirical trial–based cost data. Value Health 2017;20:1288–1298

8. Zhuo X, Zhang P, Gregg EW, et al. A nationwide community-based lifestyle program could delay or prevent type 2 diabetes cases and save $5.7 billion in 25 years. Health Aff (Millwood) 2012;31:50–60

9. Hoffmann F, Claessen H, Morbach S, Waldeyer R, Glaeske G, Icks A. Impact of diabetes on costs before and after major lower extremity amputations in Germany. J Diabetes Complications 2013;27:467–472

10. von Ferber L, Köster I, Hauner H. Medical costs of diabetic complications total costs and excess costs by age and type of treatment results of the German CoDiM Study. Exp Clin Endocrinol Diabetes 2007;115:97–104
11. Martin S, Schramm W, Schneider B, et al. Epidemiology of complications and total treatment costs from diagnosis of Type 2 diabetes in Germany (ROSSO 4). Exp Clin Endocrinol Diabetes 2007;115:495–501
12. Swart E, Gothe H, Geyer S, et al. Good practice of secondary data analysis (GPS): guidelines and recommendations. Gesundheitswesen 2015; 77:120–126 [in German]
13. Tamayo T, Brinks R, Hoyer A, Kuß OS, Rathmann W. The prevalence and incidence of diabetes in Germany. Dtsch Arztebl Int 2016;113:177–182
14. Schäfer I, Küver C, Gedrose B, et al. Selection effects may account for better outcomes of the German Disease Management Program for type 2 diabetes. BMC Health Serv Res 2010;10:351
15. Fuchs S, Henschke C, Blümel M, Busse R. Disease management programs for type 2 diabetes in Germany: a systematic literature review evaluating effectiveness. Dtsch Arztebl Int 2014;111:453–463
16. Kuo RN, Dong YH, Liu JP, Chang CH, Shau WY, Lai MS. Predicting healthcare utilization using a pharmacy-based metric with the WHO's Anatomic Therapeutic Chemical algorithm. Med Care 2011;49:1031–1039
17. Hoffmann F, Haastert B, Koch M, Giani G, Glaeske G, Icks A. The effect of diabetes on incidence and mortality in end-stage renal disease in Germany. Nephrol Dial Transplant 2011;26:1634–1640
18. National Association of Statutory Health Insurance Physicians. Uniform Value Scale [Internet], 2016. Available from http://www.kbv.de/html/ebm.php. Accessed 8 January 2018 [in German]
19. Icks A, Haastert B, Trautner C, Giani G, Glaeske G, Hoffmann F. Incidence of lower-limb amputations in the diabetic compared to the non-diabetic population. findings from nationwide insurance data, Germany, 2005-2007. Exp Clin Endocrinol Diabetes 2009;117:500–504
20. Icks A, Claessen H, Morbach S, Glaeske G, Hoffmann F. Time-dependent impact of diabetes on mortality in patients with stroke: survival up to 5 years in a health insurance population cohort in Germany. Diabetes Care 2012;35:1868–1875
21. Köster I, Huppertz E, Hauner H, Schubert I. Costs of Diabetes Mellitus (CoDiM) in Germany, direct per-capita costs of managing hyperglycaemia and diabetes complications in 2010 compared to 2001. Exp Clin Endocrinol Diabetes 2014;122: 510–516
22. Alva ML, Gray A, Mihaylova B, Leal J, Holman RR. The impact of diabetes-related complications on healthcare costs: new results from the UKPDS (UKPDS 84). Diabet Med 2015;32: 459–466
23. German Institute of Medical Documantation and Information (DIMDI). Official classification for operations and procedures (OPS catalogue) [Internet], 2016. Available from https://www.dimdi.de/static/en/dimdi/index.htm. Accessed 8 January 2018
24. Institute for the Hospital Remuneration System (InEK GmbH). General and special guidelines for the coding of diseases and procedures, version 2017 [Internet], 2016. Available from http://www.dkgev.de/media/file/26001.Deutsche_Kodierrichtlinien_Version_2017_Endversion.pdf. Accessed 8 January 2018 [in German]
25. Chang HY, Weiner JP, Richards TM, Bleich SN, Segal JB. Validating the adapted Diabetes Complications Severity Index in claims data. Am J Manag Care 2012;18:721–726
26. Kassenärztliche Bundesvereinigung. Guide for diabetic foot syndrome: ICD-10 codes for diagnoses of various clinical presentations [Internet], 2015. Available from http://www.kbv.de/media/sp/20150107_wegweiser_diabetes_mellitus_fuss.pdf. Accessed 8 January 2018 [in German]
27. Lundström H, Siersma V, Nielsen AB, et al. The effectiveness of structured personal care of type 2 diabetes on recurrent outcomes: a 19 year follow-up of the study Diabetes Care in General Practice (DCGP). Diabetologia 2014;57:1119–1123
28. GKV-Spitzenverband. Medical aids register [Internet], 2016. Available from https://hilfsmittel.gkv-spitzenverband.de/hmvAnzeigen_input.action. Accessed 8 January 2018 [in German]
29. Federal Statistical Office. *Consumer Price Indices for Germany, Annual Report 2016* [Internet], 2017. Available from https://www.destatis.de/DE/Publikationen/Thematisch/Preise/Verbraucherpreise/VerbraucherpreisindexJahresbericht.html. Accessed 8 January 2018 [in German]
30. Mihaylova B, Briggs A, O'Hagan A, Thompson SG. Review of statistical methods for analysing healthcare resources and costs. Health Econ 2011;20:897–916
31. Malehi AS, Pourmotahari F, Angali KA. Statistical models for the analysis of skewed healthcare cost data: a simulation study. Health Econ Rev 2015;5:11
32. Hoffmann F, Icks A. Diabetes prevalence based on health insurance claims: large differences between companies. Diabet Med 2011;28: 919–923
33. Robert Koch Institute. *Diabetes Mellitus: Fact Sheet for GEDA 2012: Results of the "Health in Germany Study 2012."* Berlin, Robert Koch Institute, 2014
34. Jonsson B. Revealing the cost of type II diabetes in Europe. Diabetologia 2002;45:S5–S12
35. Koster I, Hauner H, von Ferber L. Heterogeneity of costs of diabetic patients: the Cost of Diabetes Mellitus Study. Dtsch Med Wochenschr 2006;131:804–810 [in German]
36. Müller N, Heller T, Freitag MH, et al. Healthcare utilization of people with type 2 diabetes in Germany: an analysis based on health insurance data. Diabet Med 2015;32:951–957
37. Regitz-Zagrosek V. Sex and gender differences in health. Science & society series on sex and science. EMBO Rep 2012;13:596–603
38. GBD 2015 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet 2016;388: 1545–1602
39. Hoerger TJ. Using costs in cost-effectiveness models for chronic diseases: lessons from diabetes. Med Care 2009;47(Suppl. 1):S21–S27

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Supporting Information to 'Healthcare costs associated with incident complications in type 2 diabetes patients in Germany'

Katharina Kähm, Michael Laxy, Udo Schneider, Wolf H. Rogowski, Stefan K. Lhachimi, Rolf Holle

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I. Statistical appendix

The basecase model is therefore noted as follows:

$y_{ij} = \beta_0 + \beta_1 Z_{1i} + \beta_{2l} Z_{2li} + \beta_{3k} Z_{3ki} + \beta_4 Z_{4ij} + \beta_{5km} Z_{5kmij} + e_{ij}$

where:

i = patient i

j = observation j (quarters 1-12)

k = complication k

l = age group l

m = time period m for a new complication

y_{ij} = outcome/total healthcare costs for patient i and observation j

β_0 = coefficient for the intercept

β_1 = coefficient for sex

Z_{1i} = dummy variable for sex (0='female', 1='male')

β_{2l} = coefficient for age group l

Z_{2li} = dummy variables for the age group

(l=1: '<50'=1,else 0 ,
l=2: '50-60'=1 else 0,
l=3: '60-70'=1 else 0,
l=4: '>80'=1 else 0)

β_{3k} = coefficient for pre-existing complication k in 2012

Z_{3ki} = for each complication k: 1 if present at baseline, 0 otherwise

β_4= coefficient for death of other reasons

Z_{4ij} = 1 (for death of other reasons), 0 otherwise

β_{5km} = coefficient for new complication k, in time period m

Z_{5kmij} = dummy variables for complication k, in time period m

(m=1: 'quarter of event*'=1 else 0,
m=2: 'follow-up quarter'< 1 year'=1 else 0,
m=3: 'follow-up quarter'>1 year'=1 else 0)

e_{ij} = error term for patient i, observation j

* 'Event' refers to quarter when the diabetes complication first occurred/started.

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II. Tables

Table S1: Technical definition of type 2 diabetes

Criteria/ diabetes group	ICD*-E11 (IPC)	ICD-E11 (OPC)	ICD-E10 (IPC)	ICD-E10 (OPC)	ICD-E14 (IPC)	ICD-E14 (OPC)	OAD†	DMP type 2
(1) Type 2	(≥1 OR	≥2) AND	0 AND	0				
		≥1 AND	0 AND	0 AND	(≥1 OR	≥1)		
		≥1 AND	0 AND	0		AND	(Yes OR	Yes)
(2) Unclear with type 2 indication	(≥1 OR	≥1) AND	(≥1 OR	≥1)		AND	(Yes OR	Yes)
(3) Unspecified with type 2 indication	0 AND	0 AND	0 AND	0 AND	(≥1 AND	≥2) AND	(Yes OR	Yes)

* E10, type 1 diabetes; E11, type 2 diabetes, E14, unspecified diabetes.

† At least one prescription of oral antidiabetics in 2012.

Abbrevations: DMP, disease management program; ICD, international classification of diseases; ipc, inpatient care; OAD, oral antidiabetic drugs; opc, outpatient care.

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Table S2: Identification of relevant complications and events based on ICD-10-GM, OPS- and EBM-codes (1-13)

Microvascular complications	**ICD-, OPS- or EBM-codes**
Eye complications	
Retinopathy	ICD-codes E10-E14.3- (diabetes with eye complications), H36.0 (diabetic retinopathy), H35.0 (background retinopathy and retinal vascular changes), H35.2 (other proliferative retinopathy)
Blindness in one or two eyes	ICD-codes H54.0 (blindness, both eyes), H54.4 (blindness, one eye)
Renal complications	
Renal insufficiency	E11.2- (or E14.2-) (diabetes with renal complications), ICD-codes N17 (acute renal failure), N18 (chronic renal failure, without N18.5), N19 (not other specified renal failure)
ESRD	ICD-code N18.5 (terminal renal insufficiency)
→ with or without dialysis	ICD-codes Z49 (dialysis), Z99.2 (long-term dialysis in renal insufficiency) OPS-codes 8-854 (hemodialysis), 8-855 (hemodiafiltration), 8-857 (peritoneal dialysis), 8-85a (dialysis after failed kidney transplant) EBM-codes 13602-13622 w/o 13621 (dialysis fees), 40815-40838 (material cost fee)
Neuropathic complications	
Diabetic foot syndrome (with polyneuropathy and peripheral angiopathy)	ICD-codes E10-E14.74 and .75 (diabetes with multiple complications, with diabetic foot syndrome) or ICD-code for peripheral neuropathy G63.2 (diabetic polyneuropathy) + one of the ICD-codes for PVD: E11.5 (or E14.5) (diabetes with peripheral vascular complications), I70.2 (atherosclerosis of extremities), I73.9 (peripheral vascular disease, not other specified), I79.2 (diabetic peripheral angiopathy), R02 (gangrene) or

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	EBM-code 02311 (treatment of diabetic foot)
Amputation of lower extremities	OPS-codes 5-864 (amputation of lower extremity), 5-865 (amputation of the foot)
Macrovascular complications	
Cardiovascular complications	
Angina pectoris	ICD-code I20 (angina pectoris)
Chronic heart failure (CHF)	ICD-codes I50 (heart failure) , I11.0 (hypertensive heart disease with heart failure), I13.0 (hypertensive heart and chronic kidney disease with heart failure), I13.2 (Hypertensive heart and chronic kidney disease with heart failure and with end stage renal disease)
Myocardial infarction/cardiac arrest (non-fatal event)	ICD-codes I21 (acute myocardial infarction), I46.0 or .9 (cardiac arrest)
Myocardial infarction/cardiac arrest (fatal event)	In addition, see hospital death
Other IHD (non-fatal event)	ICD-codes I22 (recurrent myocardial infarction), I24 (other acute ischemic heart disease), I25 (chronic ischemic heart disease)
Other IHD (fatal event)	In addition, see hospital death
Cerebrovascular complications	
Stroke* (non-fatal event)	ICD-codes I60 (subarachnoidal haemorrhage), I61 (intracerebral bleeding), I62 (other non-traumatic intracranial bleeding), I63 (brain infarction), I64 (stroke)
Stroke (fatal event)	In addition, see hospital death
Other events/death	
Hospital death	Reason for discharge is death
Death due to other reasons (including unknown causes)	Reason for termination of membership due to death

* Stroke includes bleeding inside the brain (hemorrhagic stroke).

Abbreviations: CHF, chronic heart failure; EBM, uniform value scale for outpatient services; ESRD, end-stage renal disease; GM, german modification; ICD, International Classification of Diseases; IHD, ischemic heart disease; OPS, operation procedure codes; PVD, peripheral vascular disease.

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Table S3: Identification of risk factors and antidiabetic treatment based on ICD-10-GM and ATC-codes

Risk factor	**ICD-codes**
Derailed diabetes (derailment of glucose metabolism)	E10-E14 plus 1, 3 or 5 as fifth digit
Diabetes without complications	E10-E14 plus 9 as fourth digit
Hypertension	I10-I15
Hazardous alcohol consumption or smoking	F10 (Alcohol related disorders), F17 (Nicotine dependence)
Depression	F32 (single depressive episode), F33 (recurrent depressive disorder), F34 (persistent affective disorder)
Obesity	E66
Cancer	C00-C99
Sleeping disorder	G47 (sleep disorders), F51 (sleep disorders not due to a substance or known physiological condition)
Antidiabetic treatment	**ATC-codes**
Antidiabetic treatment type	No antidiabetics, OAD alone (ATC-code A10B), insulin+OAD (A10A and A10B) or insulin alone (A10A)

Abbreviations: ATC, anatomical therapeutic chemical; GM, german modification; ICD, International Classification of Diseases; OAD, oral antidiabetics.

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Table S4: Quality assurance activities (December 2016-March 2017)

Quality aspect	Observed, n	Activity
Inpatient care		
No or zero total payments	5057 and 221 inpatient and outpatient hospital cases	Cases were deleted, patients remain included
Negative total payments	5 cases	Cross-checked with sum of invoice values, otherwise cut to zero
Implausible length of stay (>365 days) compared to the amount of payment	1 case	Not necessary
Incorrect discharge reason death	1 case	Corrected
Hospital visits abroad	945 cases	Those cases remain included
Pharmaceuticals		
Date of prescription after date of handling by the pharmacy	No	-
Charged costs after death	Yes, 822 observations (781 cases)	Charged costs after the quarter of death are not considered

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Table S5: Calculation of the adapted Diabetes Complication Severity Index (aDCSI) based on ICD-10-GM [further adapted from (10)]

Complication	**ICD-9-CM**	**aDCSI Score***	**ICD-10-GM**
Retinopathy			
Diabetic ophthalmologic disease	250.5x	●	E10-E14.3-, H36.0
Background retinopathy	362.01	●	E10-E14.3
Other retinopathy	362.1	●	H35.0
Retinal edema	362.83	●	H35.8
Clinically Significant Macular Edema (CSME)	362.53	●	H35.3
Other retinal disorders	362.81, 621.82	●	H35.6, H35.8
Proliferative retinopathy	362.02	●●	H35.2
Retinal detachment	361.xx	●●	H33
Blindness	369.xx .00-.99	●●	H54
Vitreous hemorrhage	379.23	●●	H43.1
Nephropathy			
Diabetic nephropathy	250.4	●	E10-E14.2-
Acute glomerulonephritis	580	●	N00
Nephrotic syndrome	581	●	N04
Hypertension, nephrosis	581.81	●	N08
Chronic glomerulonephritis	582	●	N03
Nephritis/nephropathy	583	●	N05, N08, N17
Chronic renal failure	585	●●	N18
Rental failure, not otherwise specified	586	●●	N19
Renal insufficiency	593.9	●●	N28.9
Neuropathy			
Diabetic neuropathy	250.6, 356.9	●	E10-E14.4-, G60.9
Amyotrophy	358.1	●	G73.0, G73.3
Cranial nerve palsy	951.0, 951.1, 951.3	●	S04.1, S04.2
Mononeuropathy	354.0-355.9	●	G56-G59
Charcot's anthropathy	713.5	●	M14.6
Polyneuropathy	357.2	●	G62, G63.2
Cerebrovascular			
Transient ischemic attack (TIA)	435	●	G45
Stroke	431, 433, 434, 436	●●	I61, I63, I66, I67
Cardiovascular			
Atherosclerosis	440.xx	●	I70

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Other ischemic heart disease (IHD)	411	●	I24
Angina pectoris	413	●	I20
Other chronic IHD	414	●	I25
Myocardial infarction	410	●●	I21
Ventricular fibrillation, arrest	427.1, 427.3	●●	I47.2, I48
Atrial fibrillation, arrest	427.4, 427.5	●●	I49.0
Other atherosclerotic cardiovascular disease (ASCVD)	429.2	●	I25.1
Old myocardial infarction	412	●●	I25.2
Heart failure	428	●●	I50
Atherosclerosis, severe	440.23, 440.24	●●	I70.24, I70.25
Aortic aneurysm/dissection	441	●●	I71
Peripheral vascular disease (PVD)			
Diabetic PVD	250.7	●	E10-E14.5-
Other aneurysm, lower extremities (LE)	442.3	●	I72.4
PVD	443.81, 443.9	●	I79.2/8, I73.9
Foot wound + complication	892.1	●	S91
Claudication, intermittent	443.9	●	I73.9
Embolism/thrombosis (LE)	444.22	●●	I74.3
Gangrene	785.4	●●	I96
Gas gangrene	0.4	●●	A48.0
Ulcer of lower limbs	707.1	●●	L97
Metabolic			
Ketoacidosis	250.1	●●	E10-E14.1
Hyperosmolar	250.2	●●	E10-E14.0
Other coma	250.3	●●	E10-E14.0

* Seven complications which in each case can be rated with 0-2 points (except for neuropathy), thus the total score ranges from 0-13.

Abbreviations: aDSCI, adapted Diabetes Complications Severity Index, GM, german modification; ICD, International Classification of Diseases; LE, lower extremities.

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Table S6: Adapted Diabetes Complication Severity Index (aDCSI) in the population by age and sex (at baseline)

Sex	Age group	N	Mean	Std Dev	Minimum	Maximum
Male	<50 yrs	16374	0.6	1.1	0	10
	50-59 yrs	40320	1.1	1.4	0	11
	60-69 yrs	61142	1.7	1.7	0	11
	70-79 yrs	65336	2.5	2.0	0	12
	>80 yrs	17038	3.3	2.1	0	11
Female	<50 yrs	10738	0.5	1.0	0	8
	50-59 yrs	21056	0.9	1.2	0	9
	60-69 yrs	32520	1.3	1.5	0	10
	70-79 yrs	37265	2.0	1.8	0	11
	>80 yrs	14431	2.8	2.0	0	12

Abbreviations: aDCSI, adapted Diabetes Complications Severity Index; std dev, standard deviation; yrs, years.

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Table S7: Effects of acute events and chronic type 2 diabetes complications on total costs in GEE normal regression considering interactions* with age and sex

* All three-fold interactions of complications with age and sex are considered here, except for rare complications with low incidences (amputation, blindness, ESRD, fatal MI, fatal stroke, fatal IHD). Here the interaction gender x complication is considered though.

† Due to statistical reasons, it was not differentiated between the follow-up period <1 year and >1 year.

Abbreviations: CHF, chronic heart failure; ESRD, end-stage renal disease; IHD, ischemic heart disease; MI, myocardial infarction; QTR, quarter.

Parameter	Manifestations			Estimate	Standard Error (SE)	p Value
Intercept				762.9	9.4	<.0001
Age group	**<50**			-12.7	19.4	0.5127
Age group	**50-59**			-40.7	13.3	0.0022
Age group	**60-69**			-46.8	12.3	0.0001
Age group	**>80**			-165.9	15.4	<.0001
Age group	**70-79**			0.0	0.0	.
Gender	**Male**			-35.1	11.5	0.0023
Gender	**Female**			0.0	0.0	.
Foot	**Qtr of event**			570.8	71.3	<.0001
Foot	**Follow-up qtr †**			324.5	38.0	<.0001
Foot	**No**			0.0	0.0	.
Amputation	**Qtr of event**			13074.1	851.1	<.0001
Amputation	**Follow-up qtr**			2498.2	692.4	0.0003
Amputation	**No**			0.0	0.0	.
Retinopathy	**Qtr of event**			-20.1	45.8	0.6599
Retinopathy	**Follow-up qtr**			35.6	35.4	0.3145
Retinopathy	**No**			0.0	0.0	.
Blindness	**Qtr of event**			2573.5	353.0	<.0001
Blindness	**Follow-up qtr**			524.0	95.0	<.0001
Blindness	**No**			0.0	0.0	.
Nephropathy	**Qtr of event**			2784.8	115.4	<.0001
Nephropathy	**Follow-up qtr**			625.4	40.0	<.0001
Nephropathy	**No**			0.0	0.0	.
ESRD	**Qtr of event**			17349.1	1051.1	<.0001
ESRD	**Follow-up qtr**			4176.2	294.2	<.0001
ESRD	**No**			0.0	0.0	.
Stroke. nonfatal	**Qtr of event**			9197.1	423.2	<.0001
Stroke. nonfatal	**Follow-up qtr**			1688.0	154.6	<.0001
Stroke. nonfatal	**No**			0.0	0.0	.
Stroke. fatal	**Qtr of event**			9387.2	1059.0	<.0001
Stroke. fatal	**No**			0.0	0.0	.
Myocardia linfarction. nonfatal	**Qtr of event**			7848.1	569.1	<.0001
Myocardia linfarction. nonfatal	**Follow-up qtr**			773.6	202.6	0.0001
Myocardia linfarction. nonfatal	**No**			0.0	0.0	.
Myocardial infarction. fatal	**Qtr of event**			4677.9	686.6	<.0001

Parameter	Manifestations			Estimate	Standard Error (SE)	p Value
Myocardial infarction. fatal	No			0.0	0.0	.
Other IHD, nonfatal	Qtr of event			5040.1	428.2	<.0001
Other IHD, nonfatal	Follow-up qtr			476.2	156.7	0.0024
Other IHD, nonfatal	No			0.0	0.0	.
IHD. fatal	Qtr of event			8248.2	3335.7	0.0134
IHD. fatal	No			0.0	0.0	.
Angina pectoris	Qtr of event			1803.1	154.7	<.0001
Angina pectoris	Follow-up qtr			191.7	61.9	0.0019
Angina pectoris	No			0.0	0.0	.
CHF	Qtr of event			3345.3	139.5	<.0001
CHF	Follow-up qtr			717.7	44.1	<.0001
CHF	No			0.0	0.0	.
Death for other reasons	Qtr of event			5621.2	124.7	<.0001
Death for other reasons	No			0.0	0.0	.
History of foot complications	Yes			369.6	13.9	<.0001
History of foot complications	No			0.0	0.0	.
History of amputation	Yes			2004.1	171.7	<.0001
History of amputation	No			0.0	0.0	.
History of retinopathy	Yes			62.1	9.3	<.0001
History of retinopathy	No			0.0	0.0	.
History of blindness	Yes			198.8	47.6	<.0001
History of blindness	No			0.0	0.0	.
History of nephropathy	Yes			407.5	11.2	<.0001
History of nephropathy	No			0.0	0.0	.
History of ESRD	Yes			6883.0	160.4	<.0001
History of ESRD	No			0.0	0.0	.
History of stroke	Yes			626.7	46.4	<.0001
History of stroke	No			0.0	0.0	.
History of MI	Yes			48.1	45.2	0.2864
History of MI	No			0.0	0.0	.
History of IHD	Yes			555.0	25.3	<.0001
History of IHD	No			0.0	0.0	.
History of angina	Yes			-12.5	19.1	0.512
History of angina	No			0.0	0.0	.
History of CHF	Yes			529.2	12.9	<.0001
History of CHF	No			0.0	0.0	.
Age group*gender	<50	Male		-189.7	23.1	<.0001
Age group*gender	<50	Female		0.0	0.0	.
Age group*gender	50-59	Male		-113.1	17.5	<.0001
Age group*gender	50-59	Female		0.0	0.0	.
Age group*gender	60-69	Male		-37.4	16.1	0.0203
Age group*gender	60-69	Female		0.0	0.0	.
Age group*gender	>80	Male		77.4	22.3	0.0005
Age group*gender	>80	Female		0.0	0.0	.

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Parameter	Manifestations			Estimate	Standard Error (SE)	p Value
Age group*gender	70-79	Male		0.0	0.0	.
Age group*gender	70-79	Female		0.0	0.0	.
Age group*gender*MI	<50	Male	Qtr of event	-562.9	1010.7	0.5776
Age group*gender*MI	<50	Male	Follow-up qtr	-107.7	372.9	0.7726
Age group*gender*MI	<50	Male	No	0.0	0.0	.
Age group*gender*MI	<50	Female	Qtr of event	-2510.5	1337.2	0.0605
Age group*gender*MI	<50	Female	Follow-up qtr	-131.6	551.7	0.8115
Age group*gender*MI	<50	Female	No	0.0	0.0	.
Age group*gender*MI	50-60	Male	Qtr of event	-786.5	740.5	0.2882
Age group*gender*MI	50-60	Male	Follow-up qtr	-275.5	266.7	0.3015
Age group*gender*MI	50-60	Male	No	0.0	0.0	.
Age group*gender*MI	50-60	Female	Qtr of event	-1449.2	803.7	0.0714
Age group*gender*MI	50-60	Female	Follow-up qtr	-368.6	312.8	0.2386
Age group*gender*MI	50-60	Female	No	0.0	0.0	.
Age group*gender*MI	60-70	Male	Qtr of event	-6.2	644.0	0.9924
Age group*gender*MI	60-70	Male	Follow-up qtr	-261.9	240.3	0.2758
Age group*gender*MI	60-70	Male	No	0.0	0.0	.
Age group*gender*MI	60-70	Female	Qtr of event	-1629.3	693.7	0.0188
Age group*gender*MI	60-70	Female	Follow-up qtr	64.8	343.8	0.8505
Age group*gender*MI	60-70	Female	No	0.0	0.0	.
Age group*gender*MI	>80	Male	Qtr of event	-1714.3	693.7	0.0135
Age group*gender*MI	>80	Male	Follow-up qtr	-380.6	266.2	0.1528
Age group*gender*MI	>80	Male	No	0.0	0.0	.
Age group*gender*MI	>80	Female	Qtr of event	-2543.3	670.8	0.0001
Age group*gender*MI	>80	Female	Follow-up qtr	-464.1	276.0	0.0926
Age group*gender*MI	>80	Female	No	0.0	0.0	.
Age group*gender*MI	70-80	Male	Qtr of event	-31.0	651.8	0.9621
Age group*gender*MI	70-80	Male	Follow-up qtr	-107.2	227.6	0.6378
Age group*gender*MI	70-80	Male	No	0.0	0.0	.
Age group*gender*MI	70-80	Female	Qtr of event	0.0	0.0	.
Age group*gender*MI	70-80	Female	Follow-up qtr	0.0	0.0	.
Age group*gender*MI	70-80	Female	No	0.0	0.0	.
Age group*gender*MI, fatal	Male	Qtr of event		4472.4	1420.9	0.0016
Age group*gender*MI, fatal	Male	No		0.0	0.0	.
Age group*gender*MI, fatal	Female	Qtr of event		0.0	0.0	.
Age group*gender*MI, fatal	Female	No		0.0	0.0	.
Gender*IHD, fatal	Male	Qtr of event		14596.8	7244.9	0.0439
Gender*IHD, fatal	Male	No		0.0	0.0	.
Gender*IHD, fatal	Female	Qtr of event		0.0	0.0	.
Gender*IHD, fatal	Female	No		0.0	0.0	.
Age group*gender*IHD	<50	Male	Qtr of event	153.5	793.4	0.8466
Age group*gender*IHD	<50	Male	Follow-up qtr	-481.6	260.6	0.0646
Age group*gender*IHD	<50	Male	No	0.0	0.0	.
Age group*gender*IHD	<50	Female	Qtr of event	-681.3	1093.2	0.5332

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Parameter	Manifestations			Estimate	Standard Error (SE)	p Value
Age group*gender*IHD	<50	Female	Follow-up qtr	546.6	963.5	0.5705
Age group*gender*IHD	<50	Female	No	0.0	0.0	.
Age group*gender*IHD	50-60	Male	Qtr of event	1182.4	753.1	0.1164
Age group*gender*IHD	50-60	Male	Follow-up qtr	112.1	258.5	0.6645
Age group*gender*IHD	50-60	Male	No	0.0	0.0	.
Age group*gender*IHD	50-60	Female	Qtr of event	2588.4	1316.3	0.0493
Age group*gender*IHD	50-60	Female	Follow-up qtr	-81.1	297.8	0.7855
Age group*gender*IHD	50-60	Female	No	0.0	0.0	.
Age group*gender*IHD	60-70	Male	Qtr of event	1010.9	506.7	0.046
Age group*gender*IHD	60-70	Male	Follow-up qtr	-29.2	193.7	0.8801
Age group*gender*IHD	60-70	Male	No	0.0	0.0	.
Age group*gender*IHD	60-70	Female	Qtr of event	377.7	885.7	0.6698
Age group*gender*IHD	60-70	Female	Follow-up qtr	-288.7	204.2	0.1574
Age group*gender*IHD	60-70	Female	No	0.0	0.0	.
Age group*gender*IHD	>80	Male	Qtr of event	94.1	577.8	0.8706
Age group*gender*IHD	>80	Male	Follow-up qtr	-69.2	245.3	0.7779
Age group*gender*IHD	>80	Male	No	0.0	0.0	.
Age group*gender*IHD	>80	Female	Qtr of event	-150.3	761.0	0.8434
Age group*gender*IHD	>80	Female	Follow-up qtr	134.8	298.0	0.6509
Age group*gender*IHD	>80	Female	No	0.0	0.0	.
Age group*gender*IHD	70-80	Male	Qtr of event	874.8	467.0	0.061
Age group*gender*IHD	70-80	Male	Follow-up qtr	-278.3	172.5	0.1067
Age group*gender*IHD	70-80	Male	No	0.0	0.0	.
Age group*gender*IHD	70-80	Female	Qtr of event	0.0	0.0	.
Age group*gender*IHD	70-80	Female	Follow-up qtr	0.0	0.0	.
Age group*gender*IHD	70-80	Female	No	0.0	0.0	.
Age group*gender*stroke	<50	Male	Qtr of event	89.0	1151.4	0.9384
Age group*gender*stroke	<50	Male	Follow-up qtr	-224.0	532.7	0.6741
Age group*gender*stroke	<50	Male	No	0.0	0.0	.
Age group*gender*stroke	<50	Female	Qtr of event	935.0	1992.7	0.6389
Age group*gender*stroke	<50	Female	Follow-up qtr	6092.3	4133.8	0.1405
Age group*gender*stroke	<50	Female	No	0.0	0.0	.
Age group*gender*stroke	50-60	Male	Qtr of event	22.2	992.9	0.9822
Age group*gender*stroke	50-60	Male	Follow-up qtr	-392.5	246.0	0.1106
Age group*gender*stroke	50-60	Male	No	0.0	0.0	.
Age group*gender*stroke	50-60	Female	Qtr of event	-690.8	1282.0	0.59
Age group*gender*stroke	50-60	Female	Follow-up qtr	1098.7	782.7	0.1604
Age group*gender*stroke	50-60	Female	No	0.0	0.0	.
Age group*gender*stroke	60-70	Male	Qtr of event	102.3	583.7	0.8608
Age group*gender*stroke	60-70	Male	Follow-up qtr	185.8	225.5	0.4099
Age group*gender*stroke	60-70	Male	No	0.0	0.0	.
Age group*gender*stroke	60-70	Female	Qtr of event	80.8	685.6	0.9062
Age group*gender*stroke	60-70	Female	Follow-up qtr	229.4	299.8	0.4442
Age group*gender*stroke	60-70	Female	No	0.0	0.0	.

SUPPLEMENTARY DATA

Parameter	Manifestations			Estimate	Standard Error (SE)	p Value
Age group*gender*stroke	>80	Male	Qtr of event	-508.9	560.5	0.3639
Age group*gender*stroke	>80	Male	Follow-up qtr	-823.9	207.7	<.0001
Age group*gender*stroke	>80	Male	No	0.0	0.0	.
Age group*gender*stroke	>80	Female	Qtr of event	-1339.7	536.2	0.0125
Age group*gender*stroke	>80	Female	Follow-up qtr	-790.3	198.0	<.0001
Age group*gender*stroke	>80	Female	No	0.0	0.0	.
Age group*gender*stroke	70-80	Male	Qtr of event	-136.2	502.2	0.7862
Age group*gender*stroke	70-80	Male	Follow-up qtr	-75.6	188.6	0.6884
Age group*gender*stroke	70-80	Male	No	0.0	0.0	.
Age group*gender*stroke	70-80	Female	Qtr of event	0.0	0.0	.
Age group*gender*stroke	70-80	Female	Follow-up qtr	0.0	0.0	.
Age group*gender*stroke	70-80	Female	No	0.0	0.0	.
Age group*gender*stroke, fatal	Male	Qtr of event		2013.3	1699.3	0.2361
Age group*gender*stroke, fatal	Male	No		0.0	0.0	.
Age group*gender*stroke, fatal	Female	Qtr of event		0.0	0.0	.
Age group*gender*stroke, fatal	Female	No		0.0	0.0	.
Age group*gender*CHF	<50	Male	Qtr of event	-28.3	658.0	0.9657
Age group*gender*CHF	<50	Male	Follow-up qtr	186.3	207.8	0.3698
Age group*gender*CHF	<50	Male	No	0.0	0.0	.
Age group*gender*CHF	<50	Female	Qtr of event	-280.2	592.7	0.6363
Age group*gender*CHF	<50	Female	Follow-up qtr	256.0	243.1	0.2923
Age group*gender*CHF	<50	Female	No	0.0	0.0	.
Age group*gender*CHF	50-60	Male	Qtr of event	2.3	338.2	0.9946
Age group*gender*CHF	50-60	Male	Follow-up qtr	107.8	92.8	0.2451
Age group*gender*CHF	50-60	Male	No	0.0	0.0	.
Age group*gender*CHF	50-60	Female	Qtr of event	-348.9	344.8	0.3116
Age group*gender*CHF	50-60	Female	Follow-up qtr	-47.4	119.9	0.6928
Age group*gender*CHF	50-60	Female	No	0.0	0.0	.
Age group*gender*CHF	60-70	Male	Qtr of event	-216.6	188.8	0.2513
Age group*gender*CHF	60-70	Male	Follow-up qtr	62.8	69.7	0.3672
Age group*gender*CHF	60-70	Male	No	0.0	0.0	.
Age group*gender*CHF	60-70	Female	Qtr of event	-222.9	230.9	0.3345
Age group*gender*CHF	60-70	Female	Follow-up qtr	115.5	80.1	0.1491
Age group*gender*CHF	60-70	Female	No	0.0	0.0	.
Age group*gender*CHF	>80	Male	Qtr of event	-450.4	204.4	0.0275
Age group*gender*CHF	>80	Male	Follow-up qtr	-72.5	72.3	0.3163
Age group*gender*CHF	>80	Male	No	0.0	0.0	.
Age group*gender*CHF	>80	Female	Qtr of event	-624.6	189.8	0.001
Age group*gender*CHF	>80	Female	Follow-up qtr	-289.4	64.0	<.0001
Age group*gender*CHF	>80	Female	No	0.0	0.0	.
Age group*gender*CHF	70-80	Male	Qtr of event	144.4	172.6	0.4028
Age group*gender*CHF	70-80	Male	Follow-up qtr	48.7	56.5	0.3885
Age group*gender*CHF	70-80	Male	No	0.0	0.0	.
Age group*gender*CHF	70-80	Female	Qtr of event	0.0	0.0	.

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Parameter	Manifestations			Estimate	Standard Error (SE)	p Value
Age group*gender*CHF	70-80	Female	Follow-up qtr	0.0	0.0	.
Age group*gender*CHF	70-80	Female	No	0.0	0.0	.
Age group*gender*foot	<50	Male	Qtr of event	187.6	425.0	0.6589
Age group*gender*foot	<50	Male	Follow-up qtr	-21.8	71.4	0.7601
Age group*gender*foot	<50	Male	No	0.0	0.0	.
Age group*gender*foot	<50	Female	Qtr of event	305.7	237.2	0.1974
Age group*gender*foot	<50	Female	Follow-up qtr	252.6	200.7	0.2081
Age group*gender*foot	<50	Female	No	0.0	0.0	.
Age group*gender*foot	50-60	Male	Qtr of event	-24.7	98.5	0.802
Age group*gender*foot	50-60	Male	Follow-up qtr	67.0	59.5	0.26
Age group*gender*foot	50-60	Male	No	0.0	0.0	.
Age group*gender*foot	50-60	Female	Qtr of event	-93.0	94.6	0.326
Age group*gender*foot	50-60	Female	Follow-up qtr	13.2	60.9	0.828
Age group*gender*foot	50-60	Female	No	0.0	0.0	.
Age group*gender*foot	60-70	Male	Qtr of event	-63.9	89.9	0.477
Age group*gender*foot	60-70	Male	Follow-up qtr	40.5	54.4	0.4558
Age group*gender*foot	60-70	Male	No	0.0	0.0	.
Age group*gender*foot	60-70	Female	Qtr of event	-37.3	95.7	0.697
Age group*gender*foot	60-70	Female	Follow-up qtr	58.6	58.6	0.3179
Age group*gender*foot	60-70	Female	No	0.0	0.0	.
Age group*gender*foot	>80	Male	Qtr of event	377.4	133.1	0.0046
Age group*gender*foot	>80	Male	Follow-up qtr	-51.5	71.4	0.4703
Age group*gender*foot	>80	Male	No	0.0	0.0	.
Age group*gender*foot	>80	Female	Qtr of event	208.9	123.0	0.0894
Age group*gender*foot	>80	Female	Follow-up qtr	-157.2	63.1	0.0127
Age group*gender*foot	>80	Female	No	0.0	0.0	.
Age group*gender*foot	70-80	Male	Qtr of event	190.1	99.6	0.0563
Age group*gender*foot	70-80	Male	Follow-up qtr	45.9	51.0	0.3681
Age group*gender*foot	70-80	Male	No	0.0	0.0	.
Age group*gender*foot	70-80	Female	Qtr of event	0.0	0.0	.
Age group*gender*foot	70-80	Female	Follow-up qtr	0.0	0.0	.
Age group*gender*foot	70-80	Female	No	0.0	0.0	.
Age group*gender*retinopathy	<50	Male	Qtr of event	-11.4	74.8	0.8787
Age group*gender*retinopathy	<50	Male	Follow-up qtr	73.9	106.7	0.4887
Age group*gender*retinopathy	<50	Male	No	0.0	0.0	.
Age group*gender*retinopathy	<50	Female	Qtr of event	20.6	82.2	0.8018
Age group*gender*retinopathy	<50	Female	Follow-up qtr	72.3	78.0	0.3534
Age group*gender*retinopathy	<50	Female	No	0.0	0.0	.
Age group*gender*retinopathy	50-60	Male	Qtr of event	95.6	64.7	0.1394
Age group*gender*retinopathy	50-60	Male	Follow-up qtr	55.6	51.4	0.2794
Age group*gender*retinopathy	50-60	Male	No	0.0	0.0	.
Age group*gender*retinopathy	50-60	Female	Qtr of event	212.5	87.9	0.0156
Age group*gender*retinopathy	50-60	Female	Follow-up qtr	73.7	54.1	0.1729
Age group*gender*retinopathy	50-60	Female	No	0.0	0.0	.

SUPPLEMENTARY DATA

Parameter	Manifestations			Estimate	Standard Error (SE)	p Value
Age group*gender*retinopathy	60-70	Male	Qtr of event	23.9	55.8	0.6686
Age group*gender*retinopathy	60-70	Male	Follow-up qtr	-61.9	44.9	0.1684
Age group*gender*retinopathy	60-70	Male	No	0.0	0.0	.
Age group*gender*retinopathy	60-70	Female	Qtr of event	44.3	62.4	0.4775
Age group*gender*retinopathy	60-70	Female	Follow-up qtr	-28.1	47.2	0.552
Age group*gender*retinopathy	60-70	Female	No	0.0	0.0	.
Age group*gender*retinopathy	>80	Male	Qtr of event	136.2	105.1	0.1949
Age group*gender*retinopathy	>80	Male	Follow-up qtr	-6.6	72.2	0.9269
Age group*gender*retinopathy	>80	Male	No	0.0	0.0	.
Age group*gender*retinopathy	>80	Female	Qtr of event	178.3	94.3	0.0587
Age group*gender*retinopathy	>80	Female	Follow-up qtr	59.0	76.2	0.4383
Age group*gender*retinopathy	>80	Female	No	0.0	0.0	.
Age group*gender*retinopathy	70-80	Male	Qtr of event	-33.8	58.7	0.5644
Age group*gender*retinopathy	70-80	Male	Follow-up qtr	-49.1	46.0	0.2854
Age group*gender*retinopathy	70-80	Male	No	0.0	0.0	.
Age group*gender*retinopathy	70-80	Female	Qtr of event	0.0	0.0	.
Age group*gender*retinopathy	70-80	Female	Follow-up qtr	0.0	0.0	.
Age group*gender*retinopathy	70-80	Female	No	0.0	0.0	.
Age group*gender*nephropathy	<50	Male	Qtr of event	-753.8	465.0	0.105
Age group*gender*nephropathy	<50	Male	Follow-up qtr	-240.0	97.0	0.0134
Age group*gender*nephropathy	<50	Male	No	0.0	0.0	.
Age group*gender*nephropathy	<50	Female	Qtr of event	-1430.6	330.7	<.0001
Age group*gender*nephropathy	<50	Female	Follow-up qtr	-159.8	138.0	0.2469
Age group*gender*nephropathy	<50	Female	No	0.0	0.0	.
Age group*gender*nephropathy	50-60	Male	Qtr of event	-478.2	218.7	0.0287
Age group*gender*nephropathy	50-60	Male	Follow-up qtr	28.1	73.0	0.7
Age group*gender*nephropathy	50-60	Male	No	0.0	0.0	.
Age group*gender*nephropathy	50-60	Female	Qtr of event	-945.8	214.9	<.0001
Age group*gender*nephropathy	50-60	Female	Follow-up qtr	-16.8	89.4	0.8506
Age group*gender*nephropathy	50-60	Female	No	0.0	0.0	.
Age group*gender*nephropathy	60-70	Male	Qtr of event	177.8	187.0	0.3415
Age group*gender*nephropathy	60-70	Male	Follow-up qtr	122.3	60.8	0.0442
Age group*gender*nephropathy	60-70	Male	No	0.0	0.0	.
Age group*gender*nephropathy	60-70	Female	Qtr of event	-593.7	178.5	0.0009
Age group*gender*nephropathy	60-70	Female	Follow-up qtr	-86.4	64.0	0.1771
Age group*gender*nephropathy	60-70	Female	No	0.0	0.0	.
Age group*gender*nephropathy	>80	Male	Qtr of event	171.8	192.6	0.3724
Age group*gender*nephropathy	>80	Male	Follow-up qtr	-164.8	64.3	0.0103
Age group*gender*nephropathy	>80	Male	No	0.0	0.0	.
Age group*gender*nephropathy	>80	Female	Qtr of event	96.9	176.0	0.5818
Age group*gender*nephropathy	>80	Female	Follow-up qtr	-104.3	60.2	0.0834
Age group*gender*nephropathy	>80	Female	No	0.0	0.0	.
Age group*gender*nephropathy	70-80	Male	Qtr of event	55.5	145.4	0.7027
Age group*gender*nephropathy	70-80	Male	Follow-up qtr	-71.8	51.1	0.1595

SUPPLEMENTARY DATA

Parameter	Manifestations			Estimate	Standard Error (SE)	p Value
Age group*gender*nephropathy	70-80	Male	No	0.0	0.0	.
Age group*gender*nephropathy	70-80	Female	Qtr of event	0.0	0.0	.
Age group*gender*nephropathy	70-80	Female	Follow-up qtr	0.0	0.0	.
Age group*gender*nephropathy	70-80	Female	No	0.0	0.0	.
Age group*gender*angina	<50	Male	Qtr of event	-79.6	279.5	0.7758
Age group*gender*angina	<50	Male	Follow-up qtr	215.6	227.0	0.3421
Age group*gender*angina	<50	Male	No	0.0	0.0	.
Age group*gender*angina	<50	Female	Qtr of event	-597.4	272.4	0.0283
Age group*gender*angina	<50	Female	Follow-up qtr	59.5	155.4	0.7017
Age group*gender*angina	<50	Female	No	0.0	0.0	.
Age group*gender*angina	50-60	Male	Qtr of event	80.7	209.3	0.6998
Age group*gender*angina	50-60	Male	Follow-up qtr	-25.6	105.7	0.809
Age group*gender*angina	50-60	Male	No	0.0	0.0	.
Age group*gender*angina	50-60	Female	Qtr of event	-636.4	215.2	0.0031
Age group*gender*angina	50-60	Female	Follow-up qtr	-80.0	106.5	0.4526
Age group*gender*angina	50-60	Female	No	0.0	0.0	.
Age group*gender*angina	60-70	Male	Qtr of event	433.2	190.0	0.0226
Age group*gender*angina	60-70	Male	Follow-up qtr	-111.4	80.1	0.1643
Age group*gender*angina	60-70	Male	No	0.0	0.0	.
Age group*gender*angina	60-70	Female	Qtr of event	-160.5	208.1	0.4405
Age group*gender*angina	60-70	Female	Follow-up qtr	-48.1	89.9	0.5926
Age group*gender*angina	60-70	Female	No	0.0	0.0	.
Age group*gender*angina	>80	Male	Qtr of event	469.5	260.6	0.0716
Age group*gender*angina	>80	Male	Follow-up qtr	46.1	111.5	0.6793
Age group*gender*angina	>80	Male	No	0.0	0.0	.
Age group*gender*angina	>80	Female	Qtr of event	5.7	268.3	0.9831
Age group*gender*angina	>80	Female	Follow-up qtr	13.0	109.9	0.906
Age group*gender*angina	>80	Female	No	0.0	0.0	.
Age group*gender*angina	70-80	Male	Qtr of event	491.7	186.8	0.0085
Age group*gender*angina	70-80	Male	Follow-up qtr	7.6	77.1	0.9217
Age group*gender*angina	70-80	Male	No	0.0	0.0	.
Age group*gender*angina	70-80	Female	Qtr of event	0.0	0.0	.
Age group*gender*angina	70-80	Female	Follow-up qtr	0.0	0.0	.
Age group*gender*angina	70-80	Female	No	0.0	0.0	.
Gender*ESRD	Male	Qtr of event		6340.7	1369.8	<.0001
Gender*ESRD	Male	Follow-up qtr		1345.7	371.0	0.0003
Gender*ESRD	Male	No		0.0	0.0	.
Gender*ESRD	Female	Qtr of event		0.0	0.0	.
Gender*ESRD	Female	Follow-up qtr		0.0	0.0	.
Gender*ESRD	Female	No		0.0	0.0	.
Gender*blindness	Male	Qtr of event		-523.9	398.6	0.1888
Gender*blindness	Male	Follow-up qtr		-178.8	120.2	0.137
Gender*blindness	Male	No		0.0	0.0	.

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Parameter	Manifestations			Estimate	Standard Error (SE)	p Value
Gender*blindness	Female	Qtr of event		0.0	0.0	.
Gender*blindness	Female	Follow-up qtr		0.0	0.0	.
Gender*blindness	Female	No		0.0	0.0	.
Gender*amputation	Male	Qtr of event		632.8	1019.5	0.5348
Gender*amputation	Male	Follow-up qtr		-125.3	712.1	0.8603
Gender*amputation	Male	No		0.0	0.0	.
Gender*amputation	Female	Qtr of event		0.0	0.0	.
Gender*amputation	Female	Follow-up qtr		0.0	0.0	.
Gender*amputation	Female	No		0.0	0.0	.

SUPPLEMENTARY DATA

Table S8: Expected total costs per quarter and year for type 2 diabetes patients of varying age and gender*

* All three-fold interactions of complications with age and sex are considered here (see Table S7), except for rare complications with low incidences (amputation, blindness, ESRD, fatal MI, fatal stroke, fatal IHD). Here the interaction gender x complication is considered though.

† Due to statistical reasons, it was not differentiated between the follow-up period <1 year and >1 year.

‡ A mean case scenario was assumed to account for the possibility that complications can occur in one of four quarters.

Abbreviations: CHF, chronic heart failure; ESRD, end-stage renal disease; IHD, ischemic heart disease; MI, myocardial infarction; QTR, quarter.

Type of complication	Age group (in years)	Total estimated costs (in €) in the quarter of event (and follow-up quarter†)				Annualized total costs (in €) in the year of event‡ (and follow-up year)			
		Male		Female		Male		Female	
		Qtr of event	Follow-up qtr	Qtr of event	Follow-up qtr	Year of event	Follow-up year	Year of event	Follow-up year
Foot	<50	1,284	828	1,627	1,327	3,314	3,313	4,743	5,309
	50-59	1,120	965	1,200	1,060	3,429	3,862	3,873	4,240
	60-69	1,150	1,009	1,250	1,099	3,629	4,034	3,972	4,396
	70-79	1,489	1,098	1,334	1,087	4,228	4,393	4,109	4,350
	>80	1,510	912	1,377	764	3,838	3,649	3,419	3,057
Amputation	<50	14,232	2,898	13,824	3,248	19,368	11,594	19,823	12,994
	50-59	14,281	2,947	13,796	3,220	19,562	11,788	19,710	12,882
	60-69	14,350	3,017	13,790	3,214	19,841	12,066	19,686	12,857
	70-79	14,435	3,101	13,837	3,261	20,178	12,403	19,873	13,045
	>80	14,346	3,012	13,671	3,095	19,824	12,049	19,210	12,381
Retinopathy	<50	494	635	751	858	2,235	2,540	3,164	3,433
	50-59	649	665	915	832	2,508	2,661	3,245	3,326
	60-69	647	617	740	724	2,539	2,469	2,900	2,895
	70-79	674	714	743	799	2,837	2,857	3,085	3,194
	>80	678	668	755	692	2,640	2,674	2,688	2,767
Blindness	<50	2,575	871	3,324	1,274	4,669	3,483	6,361	5,097
	50-59	2,624	919	3,296	1,246	4,864	3,677	6,248	4,985
	60-69	2,693	989	3,290	1,240	5,142	3,955	6,224	4,960
	70-79	2,777	1,073	3,336	1,287	5,479	4,292	6,411	5,148
	>80	2,689	985	3,171	1,121	5,125	3,939	5,748	4,484
Nephropathy	<50	2,557	911	2,104	1,216	4,711	3,644	5,054	4,864
	50-59	2,881	1,228	2,561	1,331	5,583	4,910	5,641	5,323
	60-69	3,606	1,391	2,907	1,255	6,658	5,565	5,864	5,021
	70-79	3,568	1,281	3,548	1,388	6,582	5,126	6,775	5,553
	>80	3,519	1,100	3,479	1,118	6,128	4,400	6,052	4,473
ESRD	<50	24,215	6,047	18,099	4,926	34,075	24,189	26,614	19,706
	50-59	24,264	6,096	18,071	4,898	34,269	24,384	26,502	19,594
	60-69	24,333	6,165	18,065	4,892	34,547	24,662	26,478	19,569
	70-79	24,418	6,250	18,112	4,939	34,884	24,999	26,665	19,756
	>80	24,329	6,161	17,946	4,773	34,530	24,645	26,002	19,093

SUPPLEMENTARY DATA

Type of complication	Age group (in years)	Total estimated costs (in €) in the quarter of event (and follow-up quarter†)				Annualized total costs (in €) in the year of event‡ (and follow-up year)			
		Male		Female		Male		Female	
		Qtr of event	Follow-up qtr	Qtr of event	Follow-up qtr	Year of event	Follow-up year	Year of event	Follow-up year
Nonfatal stroke	<50	9,812	1,990	10,882	8,531	13,584	7,958	24,804	34,123
	50-59	9,793	1,870	9,229	3,509	13,459	7,478	15,575	14,036
	60-69	9,943	2,517	9,994	2,634	14,684	10,070	15,018	10,534
	70-79	9,789	2,340	9,960	2,451	14,391	9,361	14,781	9,804
	>80	9,250	1,504	8,455	1,495	12,465	6,014	11,592	5,979
Fatal stroke	<50	11,926	na	10,137	na	12,765	na	11,263	na
	50-59	11,975	na	10,109	na	12,874	na	11,193	na
	60-69	12,044	na	10,103	na	13,031	na	11,177	na
	70-79	12,128	na	10,150	na	13,220	na	11,295	na
	>80	12,040	na	9,984	na	13,021	na	10,880	na
Nonfatal MI	<50	7,811	1,191	6,088	1,392	10,386	4,765	9,302	5,569
	50-59	7,636	1,072	7,121	1,127	10,105	4,289	9,895	4,509
	60-69	8,485	1,155	6,935	1,554	11,184	4,621	10,341	6,218
	70-79	8,545	1,394	8,611	1,537	11,728	5,577	12,060	6,146
	>80	6,696	1,032	5,902	907	9,203	4,130	8,157	3,626
Fatal MI	<50	9,676	na	5,428	na	10,515	na	6,554	na
	50-59	9,724	na	5,400	na	10,624	na	6,483	na
	60-69	9,794	na	5,394	na	10,780	na	6,468	na
	70-79	9,878	na	5,441	na	10,970	na	6,585	na
	>80	9,790	na	5,275	na	10,771	na	6,171	na
Nonfatal IHD	<50	5,719	520	5,109	1,773	7,287	2,080	8,894	7,092
	50-59	6,796	1,162	8,351	1,117	9,401	4,649	11,110	4,469
	60-69	6,695	1,091	6,134	904	9,296	4,362	8,563	3,614
	70-79	6,643	926	5,803	1,239	9,123	3,703	8,806	4,957
	>80	5,696	1,046	5,487	1,208	8,225	4,186	8,195	4,832
Fatal IHD	<50	23,371	na	8,998	na	24,209	na	10,124	na
	50-59	23,419	na	8,970	na	24,319	na	10,054	na
	60-69	23,489	na	8,964	na	24,475	na	10,038	na
	70-79	23,573	na	9,011	na	24,665	na	10,156	na
	>80	23,484	na	8,845	na	24,466	na	9,741	na
Angina pectoris	<50	2,249	933	1,956	1,002	4,436	3,731	4,584	4,006
	50-59	2,458	740	1,889	834	4,429	2,961	4,223	3,336
	60-69	2,880	724	2,359	860	4,931	2,896	4,722	3,439
	70-79	3,023	927	2,566	955	5,505	3,709	5,142	3,819
	>80	2,835	877	2,406	802	5,110	3,509	4,504	3,207
CHF	<50	3,842	1,430	3,815	1,724	6,775	5,718	7,527	6,896
	50-59	3,922	1,400	3,719	1,393	6,882	5,598	6,891	5,570
	60-69	3,772	1,424	3,839	1,549	6,874	5,696	7,237	6,197
	70-79	4,218	1,494	4,108	1,481	7,551	5,977	7,474	5,923
	>80	3,457	1,285	3,318	1,025	6,343	5,139	5,751	4,101
No complication	<50	526		750		2,102		3,001	

SUPPLEMENTARY DATA

Type of complication	Age group (in years)	Total estimated costs (in €) in the quarter of event (and follow-up quarter†)				Annualized total costs (in €) in the year of event‡ (and follow-up year)			
		Male		Female		Male		Female	
		Qtr of event	Follow-up qtr	Qtr of event	Follow-up qtr	Year of event	Follow-up year	Year of event	Follow-up year
	50-59	574		722		2,296		2,889	
	60-69	644		716		2,574		2,864	
	70-79	728		763		2,911		3,052	
	>80	639		597		2,558		2,388	

Table S9: Comparing relative cost factors* with the UKPDS Outcomes Model (Version 2) based on the example of 70-79 years old patients†

* Cost factors were calculated by dividing the total costs for each complication by the total costs in absence of complications.

† The extended model with all three-fold interactions of complications with age and sex was used here (see Table S8).

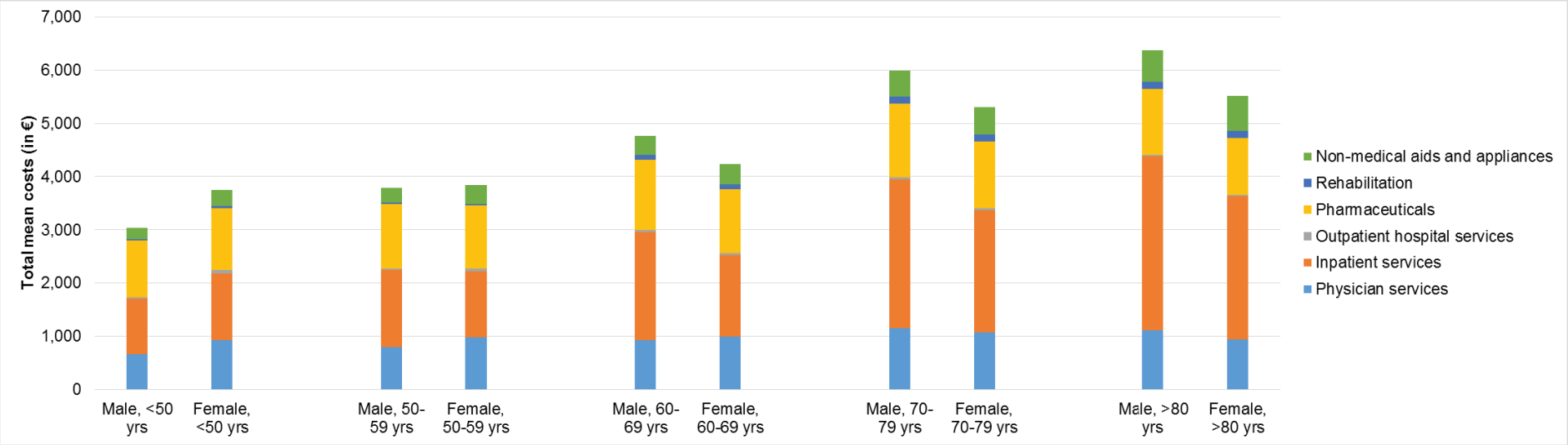
Abbreviations: CHF, chronic heart failure; ESRD, end-stage renal disease; IHD, ischemic heart disease; MI, myocardial infarction; na, not available.

	Male						Female					
Type of complication	Year of event (in €)	Cost Factor	Cost Factor (UKPDS)	Follow-up year (in €)	Cost Factor	Cost Factor (UKPDS)	Year of event (in €)	Cost Factor	Cost Factor (UKPDS)	Follow-up year (in €)	Cost Factor	Cost Factor (UKPDS)
Foot	4,228	1.5	3.9	4,393	1.5	0.6	4,109	1.3	3.2	4,350	1.4	0.5
Amputation	20,178	6.9	7.9	12,403	4.3	2.8	19,873	6.5	6.9	13,045	4.3	2.6
Retinopathy	2,837	1.0	na	2,857	1.0	na	3,085	1.0	na	3,194	1.0	na
Blindness	5,479	1.9	2.6	4,292	1.5	1.1	6,411	2.1	2.4	5,148	1.7	1.1
Nephropathy	6,582	2.3	na	5,126	1.8	na	6,775	2.2	na	5,553	1.8	na
ESRD	34,884	12.0	11.2	24,999	8.6	11.2	26,665	8.7	9.4	19,756	6.5	9.4
Non-fatal stroke	14,391	4.9	5.9	9,361	3.2	1.8	14,781	4.8	5.2	9,804	3.2	1.8
Fatal stroke	13,220	4.5	3.4	na	na	na	11,295	3.7	3.1	na	na	na
Non-fatal MI	11,728	4.0	4.9	5,577	1.9	1.8	12,060	4.0	4.3	6,146	2.0	1.7
Fatal MI	10,970	3.8	2.0	na	na	na	6,585	2.2	1.8	na	na	na
Non-fatal IHD	9,123	3.1	7.2	3,703	1.3	1.9	8,806	2.9	6.3	4,957	1.6	1.8
Fatal IHD	24,665	8.5	3.2	na	na	na	10,156	3.3	2.9	na	na	na
Angina pectoris	5,505	1.9	na	3,709	1.3	na	5,142	1.7	na	3,819	1.3	na
CHF	7,551	2.6	3.1	5,977	2.1	2.3	7,474	2.4	2.8	5,923	1.9	2.1
No complication	2,911	1.0	1.0	2,911	1.0	1.0	3,052	1.0	1.0	3,052	1.0	1.0

Figures

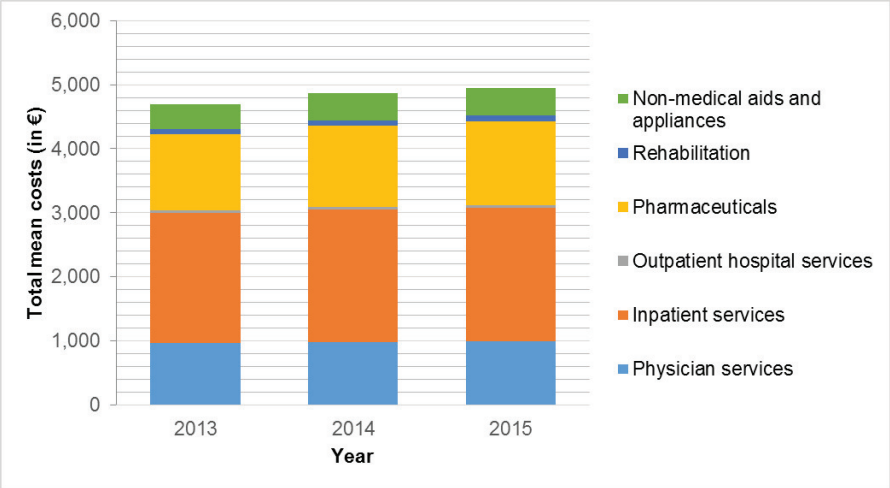
Figure S1. Descriptive analysis of the non-standardized total healthcare costs 2013-2015

A. Shares of total healthcare costs by age, sex, and healthcare sector



SUPPLEMENTARY DATA

B. Shares of total healthcare costs by healthcare sector und year



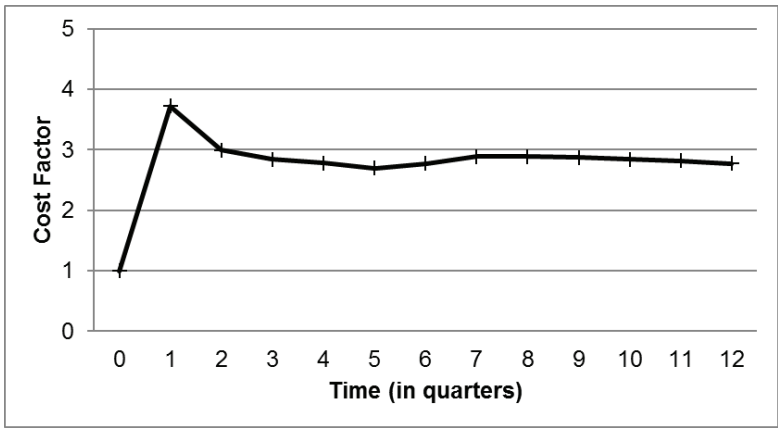
SUPPLEMENTARY DATA

Figure S2: Relative cost factor* at time and after the occurrence of acute events or onset of chronic complications in quarterly intervals†

* Cost factor was calculated by dividing total costs in quarter x by mean costs in a quarter of no complications (€703).

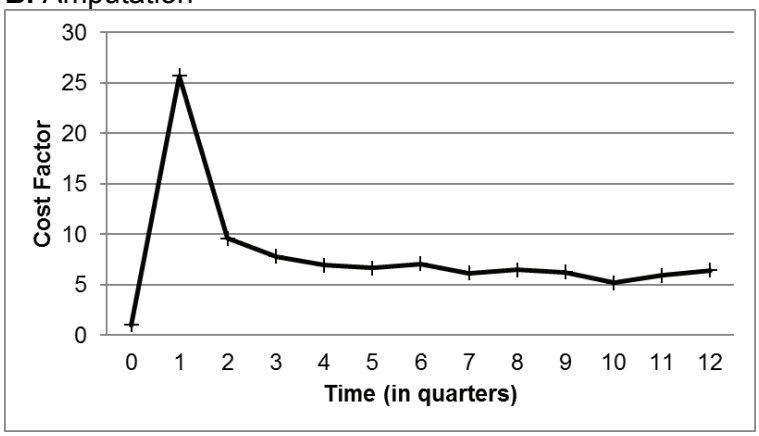
† The method of linear interpolation was used between quarterly data points.

A. Diabetic foot



Time	0	1	2	3	4	5	6	7	8	9	10	11	12
n	41,481	44,689	38,576	33,036	29,488	25,649	21,943	18,083	15,338	12,130	8,999	5,879	2,803

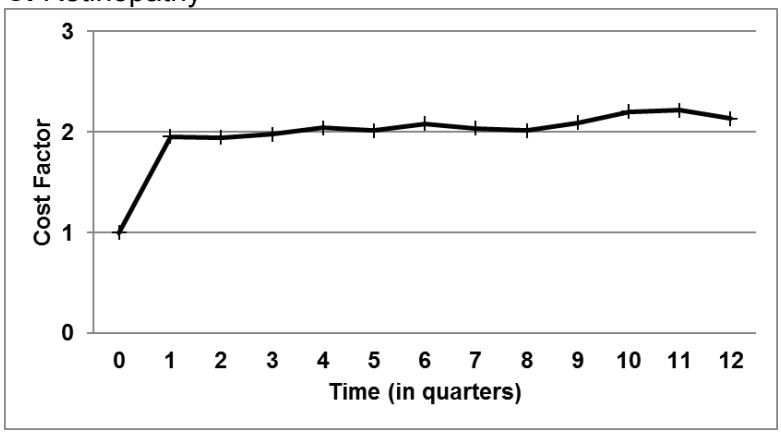
B. Amputation



Time	0	1	2	3	4	5	6	7	8	9	10	11	12
n	1,726	1,887	1,510	1,273	1,086	924	764	652	518	413	314	184	94

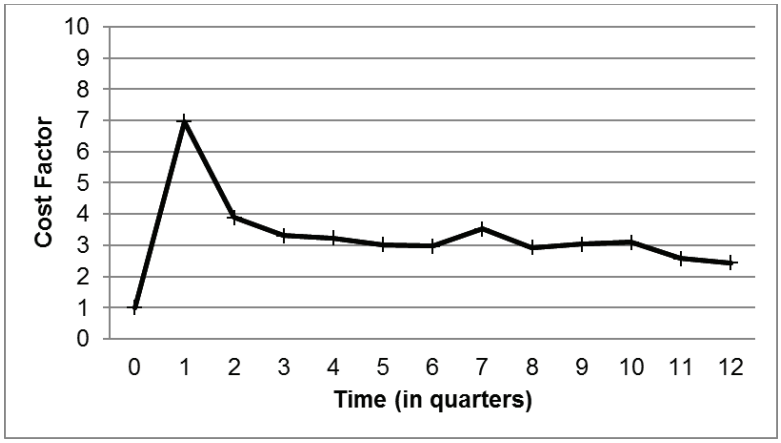
SUPPLEMENTARY DATA

C. Retinopathy



Time	0	1	2	3	4	5	6	7	8	9	10	11	12
n	26,190	30,408	28,564	26,627	24,641	22,463	20,248	18,057	15,779	12,997	10,200	7,296	3,949

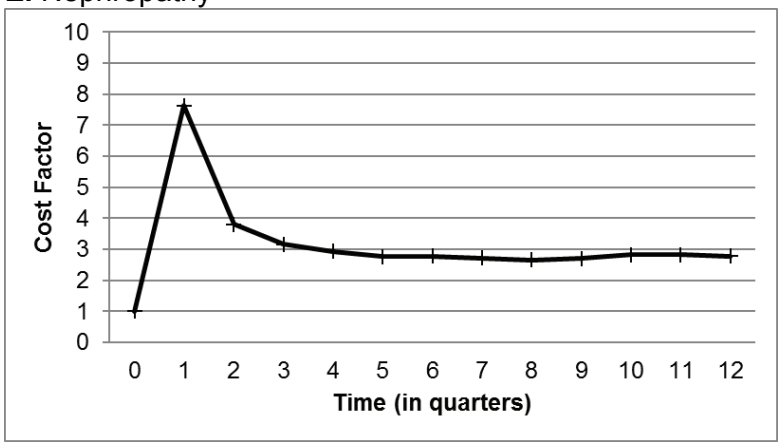
D. Blindness



Time	0	1	2	3	4	5	6	7	8	9	10	11	12
n	1,771	1,949	1,746	1,549	1,383	1,240	1,079	920	765	619	460	303	144

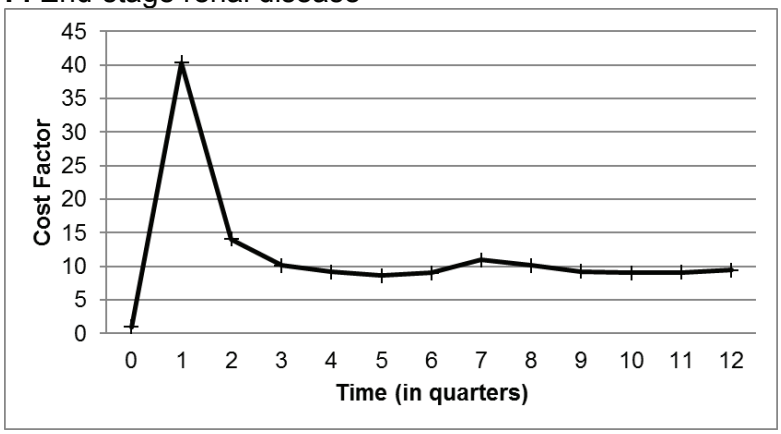
SUPPLEMENTARY DATA

E. Nephropathy



Time	0	1	2	3	4	5	6	7	8	9	10	11	12
n	43,302	47,463	41,028	36,179	31,909	28,018	24,444	20,962	17,535	13,718	10,009	6,589	3,320

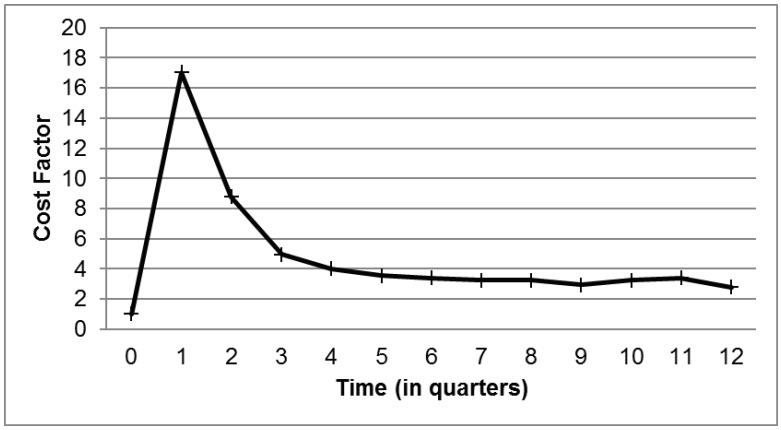
F. End-stage renal disease



Time	0	1	2	3	4	5	6	7	8	9	10	11	12
n	3,470	3,775	2,308	1,874	1,581	1,350	1,137	952	775	606	422	271	114

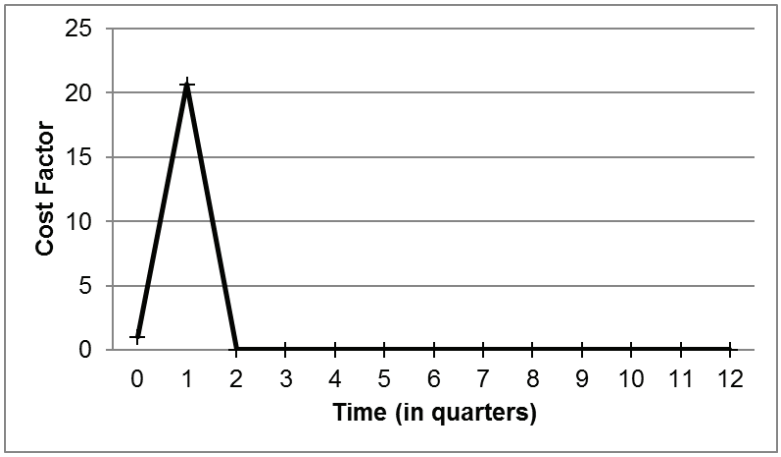
SUPPLEMENTARY DATA

G1. Non-fatal stroke



Time	0	1	2	3	4	5	6	7	8	9	10	11	12
n	6,628	7,192	6,281	5,452	4,747	4,116	3,499	2,919	2,365	1,869	1,376	848	403

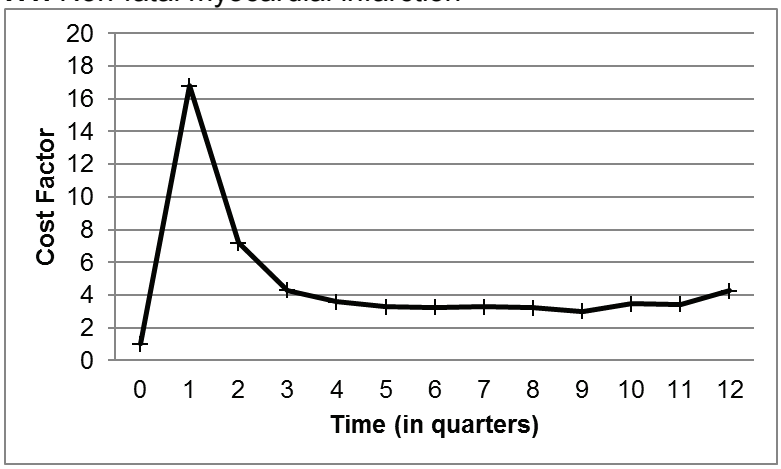
G2. Fatal stroke



Time	0	1		2	3	4	5	6	7	8	9	10	11	12
n	686	739		690	632	575	495	415	355	297	228	169	110	53

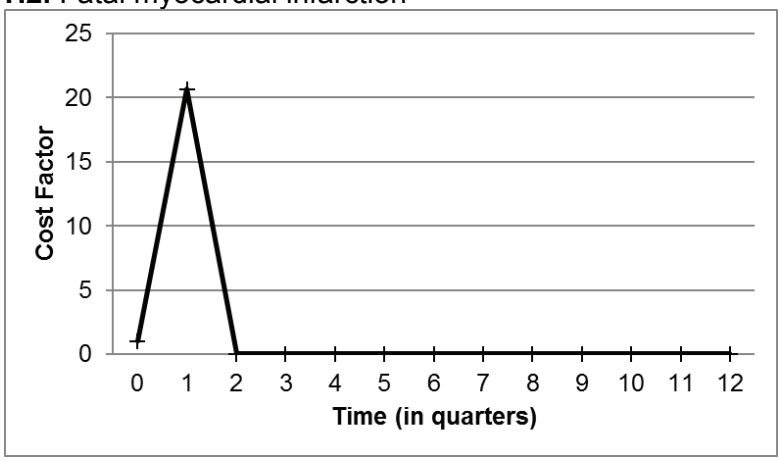
SUPPLEMENTARY DATA

H1. Non-fatal myocardial infarction



Time	0	1	2	3	4	5	6	7	8	9	10	11	12
n	5,168	5,650	4,980	4,408	3,913	3,423	2,866	2,434	1,989	1,553	1,150	773	395

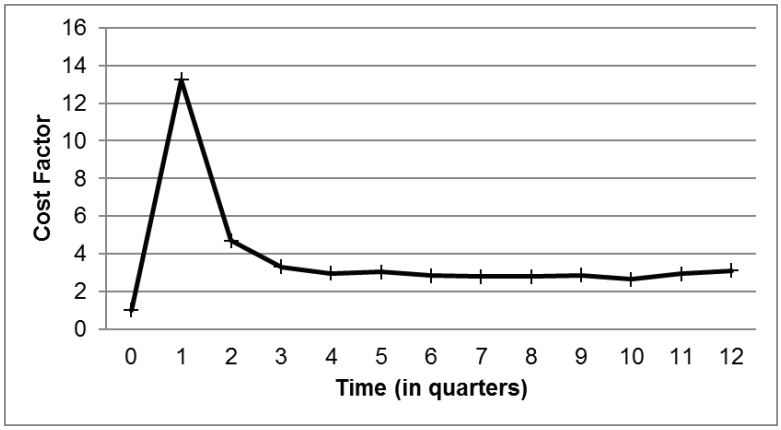
H2. Fatal myocardial infarction



Time	0	1	2	3	4	5	6	7	8	9	10	11	12
n	726	790	716	655	576	502	421	354	282	218	168	123	64

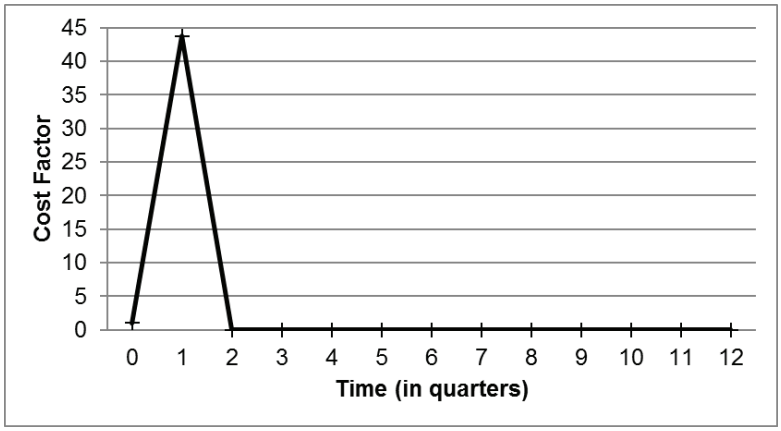
SUPPLEMENTARY DATA

I1. Non-fatal other ischemic heart disease



Time	0	1	2	3	4	5	6	7	8	9	10	11	12
n	5,918	6,345	5,749	5,157	4,557	3,949	3,439	2,892	2,396	1,838	1,321	836	397

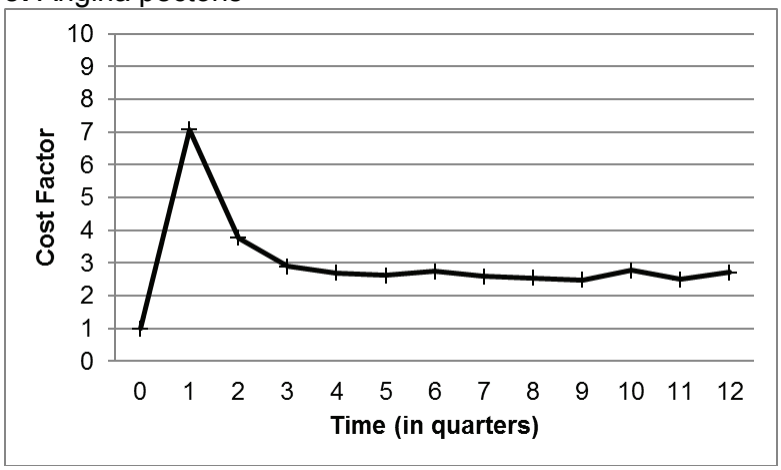
I2. Fatal other ischemic heart disease



Time	0	1	2	3	4	5	6	7	8	9	10	11	12
n	55	57	53	46	39	35	27	23	20	14	7	5	2

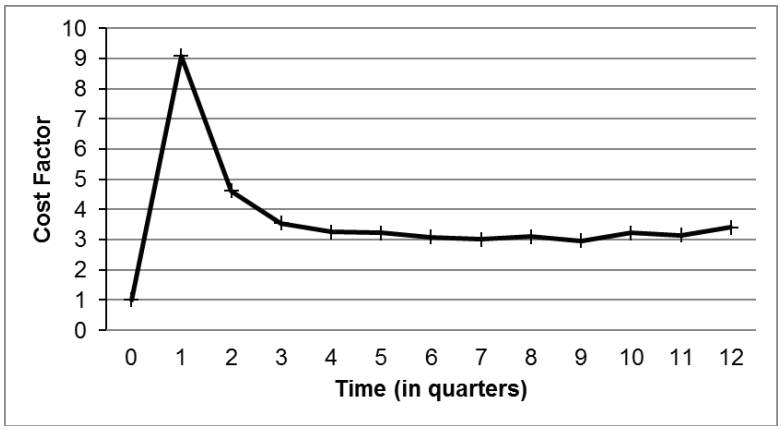
SUPPLEMENTARY DATA

J. Angina pectoris



Time	0	1	2	3	4	5	6	7	8	9	10	11	12
n	14,781	16,491	15,123	13,878	12,683	11,298	9,901	8,552	7,236	5,762	4,336	3,004	1,563

K. Chronic heart failure



Time	0	1	2	3	4	5	6	7	8	9	10	11	12
n	33,142	36,825	32,378	29,103	26,072	23,093	20,438	17,653	14,725	11,462	8,602	5,728	2,859

SUPPLEMENTARY DATA

References

1. Kuo RN, Dong YH, Liu JP, Chang CH, Shau WY, Lai MS. Predicting healthcare utilization using a pharmacy-based metric with the WHO's Anatomic Therapeutic Chemical algorithm. Medical care. 2011;49(11):1031-9.
2. Hoffmann F, Haastert B, Koch M, Giani G, Glaeske G, Icks A. The effect of diabetes on incidence and mortality in end-stage renal disease in Germany. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association. 2011;26(5):1634-40.
3. National Association of Statutory health Insurance Physicians. Uniform Value Scale 2016 [Available from: http://www.kbv.de/html/ebm.php.
4. Icks A, Haastert B, Trautner C, Giani G, Glaeske G, Hoffmann F. Incidence of lower-limb amputations in the diabetic compared to the non-diabetic population. findings from nationwide insurance data, Germany, 2005-2007. Experimental and clinical endocrinology & diabetes : official journal, German Society of Endocrinology [and] German Diabetes Association. 2009;117(9):500-4.
5. Icks A, Claessen H, Morbach S, Glaeske G, Hoffmann F. Time-dependent impact of diabetes on mortality in patients with stroke: survival up to 5 years in a health insurance population cohort in Germany. Diabetes care. 2012;35(9):1868-75.
6. Köster I, Huppertz E, Hauner H, Schubert I. Costs of Diabetes Mellitus (CoDiM) in Germany, direct per-capita costs of managing hyperglycaemia and diabetes complications in 2010 compared to 2001. Experimental and clinical endocrinology & diabetes : official journal, German Society of Endocrinology [and] German Diabetes Association. 2014;122(9):510-6.
7. Alva ML, Gray A, Mihaylova B, Leal J, Holman RR. The impact of diabetes-related complications on healthcare costs: new results from the UKPDS (UKPDS 84). Diabetic medicine : a journal of the British Diabetic Association. 2015;32(4):459-66.
8. German Institute of Medical Documantation and Information (DIMDI). Official classification for operations and procedures (OPS catalogue) 2016 [Available from: https://www.dimdi.de/static/en/dimdi/index.htm.
9. Deutsche Krankenhausgesellschaft (DKG) G-S, Verband der privaten Krankenversicherung (PKV), Institut für das Entgeltsystem im Krankenhaus (InEK GmbH). Allgemeine und spezielle Kodierrichtlinien für die Verschlüsselung von Krankheiten und Prozeduren. 2015.
10. Chang HY, Weiner JP, Richards TM, Bleich SN, Segal JB. Validating the adapted Diabetes Complications Severity Index in claims data. The American journal of managed care. 2012;18(11):721-6.
11. Kassenärztliche Bundesvereinigung. Wegweiser Diabetisches Fußsyndrom: ICD-10-Kodes für Diagnosen, die zum klinischen Bild gehören 2015 [Available from: http://www.kbv.de/media/sp/20150107_wegweiser_diabetes_mellitus_fuss.pdf.
12. Lundström H, Siersma V, Nielsen AB, Brodersen J, Reventlow S, Andersen PK, et al. The effectiveness of structured personal care of type 2 diabetes on recurrent outcomes: a 19 year follow-up of the study Diabetes Care in General Practice (DCGP). Diabetologia. 2014;57(6):1119-23.
13. GKV-Spitzenverband. Medical aids register 2016 [Available from: https://hilfsmittel.gkv-spitzenverband.de/hmvAnzeigen_input.action.

3 Article 2: "Exploring different strategies of assessing the economic impact of multiple diabetes-associated complications and their interactions: A large claims-based study in Germany"

Published in:

Kähm K., Laxy M., Schneider U., Holle R. Exploring different strategies of assessing the economic impact of multiple diabetes-associated complications and their interactions: A large claims-based study in Germany. PharmacoEconomics 2018 Aug 30 [Epub ahead of print].

PharmacoEconomics
https://doi.org/10.1007/s40273-018-0699-1

ORIGINAL RESEARCH ARTICLE

Exploring Different Strategies of Assessing the Economic Impact of Multiple Diabetes-Associated Complications and Their Interactions: A Large Claims-Based Study in Germany

Katharina Kähm[1,2] · Michael Laxy[1,2] · Udo Schneider[3] · Rolf Holle[1,2]

Abstract

Background In the context of an aging population with increasing diabetes prevalence, people are living longer with diabetes, which leads to increased multimorbidity and economic burden.

Objective The primary aim was to explore different strategies that address the economic impact of multiple type 2 diabetes-related complications and their interactions.

Methods We used a generalized estimating equations approach based on nationwide statutory health insurance data from 316,220 patients with type 2 diabetes (baseline year 2012, 3 years of follow-up). We estimated annual total costs (in 2015 euros) for type 2 diabetes-related complications and, in addition, explored different strategies to assess diabetes-related multimorbidity: number of prevalent complications, co-occurrence of micro- and macrovascular complications, disease–disease interactions of prevalent complications, and interactions between prevalent/incident complications.

Results The increased number of complications was significantly associated with higher total costs. Further assessment of interactions showed that macrovascular complications (e.g., chronic heart failure) and high-cost complications (e.g., end-stage renal disease, amputation) led to significant positive effects of interactions on costs, whereas early microvascular complications (e.g., retinopathy) caused negative interactions. The chronology of the onset of these complications turned out to have an additional impact on the interactions and their effect on total costs.

Conclusions Health economic diabetes models and evaluations of interventions in patients with diabetes-related complications should pay more attention to the economic effect of specific disease interactions. Politically, our findings support the development of more integrated diabetes care programs that take better account of multimorbidity. Further observational studies are needed to elucidate the shared pathogenic mechanisms of diabetes complications.

Key Points for Decision Makers

Researchers can choose from various strategies of different granularity to assess the economic impact of multiple co-occurring diseases and their interactions.

The inclusion of interaction patterns of multiple diabetes-related complications can improve the accuracy of model-based cost-effectiveness evaluations.

Longitudinal analysis of real-world claims data revealed validity issues in the diagnosis of chronic conditions that should be considered in evaluations.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s40273-018-0699-1) contains supplementary material, which is available to authorized users.

✉ Katharina Kähm
katharina.kaehm@helmholtz-muenchen.de

1 Institute of Health Economics and Health Care Management, Helmholtz Zentrum München (GmbH)-German Research Center for Environmental Health (GmbH), Ingolstädter Landstraße 1, 85758 Neuherberg, Germany

2 German Center for Diabetes Research (DZD), Munich, Neuherberg, Germany

3 Scientific Institute of TK for Benefit and Efficiency in Health Care, Techniker Krankenkasse (TK), Hamburg, Germany

Published online: 30 August 2018

1 Introduction

Type 2 diabetes is not only becoming increasingly prevalent worldwide (7% in Germany in 2011), but is also emerging as an important comorbidity in daily clinical practice [1, 2]. Demographic changes as well as improved prognosis of life-threatening and chronic diseases (e.g., myocardial infarction [MI], renal insufficiency) are contributing to an aging population with diabetes and growing multimorbidity. In response to the arising economic challenges, the term "high-need, high-cost" has been introduced in recent years to characterize a growing group of usually older patients who are suffering from multiple diseases such as diabetes, require multiple medications, and tend to have more frequent health behavior problems and hospital admissions. What is lacking in the literature is a systematic analysis of the impact of diabetes-related multimorbidity and underlying heterogeneity from disease interactions on healthcare costs [3]. Statistically, such disease interactions can have a positive or negative effect on the outcome variable (costs, clinical outcomes and quality of life), which means that the effect of the co-occurring diseases is either more or less than could be expected from their individual effects. In detail, the typical multimorbidity cluster in diabetes patients is characterized by one or more of the following diabetes-related acute or chronic complications: coronary heart disease (CHD), chronic heart failure (CHF), stroke, retinopathy, renal insufficiency, and peripheral vascular disease [4]. It is to be expected that the coexistence of multiple diseases will be a major contributing factor to the increasing economic burden of diabetes, which is currently estimated at US$1.3 trillion worldwide [5]. Therefore, to conduct thorough health economic evaluations of new diabetes and complication treatments or prevention programs, diabetes models that consider complex interaction patterns are becoming increasingly important. Two of the best known non-commercial international type 2 diabetes models are the UK Prospective Diabetes Study (UKPDS) model and the model developed by the Center for Disease Control and Prevention/Research Triangle Institute (CDC/RTI) [6, 7]. For example, the CDC/RTI model uses five individual disease paths for the most common complications and integrates their interactions through a faster progression on these paths (e.g., presence of hypertensive nephropathy leads to faster progression of chronic heart disease compared to the absence of nephropathy). As another example, a study of UKPDS data found no significant effect of the co-occurrence of complications on patient's quality of life [8], whereas a German study showed that patients with diabetes, coronary events, and a history of stroke had a worse quality of life than could be expected from the separate effects [9]. However, there are only limited data and evidence to inform diabetes models about the economic consequences of disease interactions [10]. Due to their special focus and time- and budget-restricted nature, randomized trials, if they investigate interactions at all, generally concentrate on interactions between frequent outcomes. Moreover, in Germany, data sources such as routinely collected statutory health insurance (SHI) data may be better suited because of their large sample size, extensive population coverage (around 90%), and detailed cost data over several years [11].

The primary aim of this study was to use a large claims data set to explore regression-based strategies for analyzing the economic impact of multiple type 2 diabetes-related complications and their interactions on total costs. A secondary purpose of this study is to describe the patterns of these disease interactions. This study builds on a previous study, where we presented the data together with a longitudinal analysis of quarterly costs for incident complications, but without considering interactions [12]. In addition to presenting new empirical evidence for Germany, this study has a strong methodological focus that addresses data accuracy issues and differentiates between the co-occurrence of prevalent complications or disease groups and the development of incident complications on top of prevalent complications. Our methodology and findings will serve as an important input for data scientists, and especially developers of diabetes and related models.

2 Methods

2.1 Data and Research Design

A core component of Germany's healthcare system is its SHI, covering ~90% of the population. This retrospective cohort study is based on data from the largest SHI provider in Germany, the Techniker Krankenkasse (TK), which included around 10 million insured people in 2017. In addition to basic demographic data, the claims contain detailed information on, for example, healthcare costs, outpatient and inpatient diagnoses and procedures, and medication data. Although outpatient diagnoses are only documented on a quarterly level, admission and discharge dates are available for inpatient data. The selection of type 2 diabetes patients was defined on the basis of two outpatient diagnoses in two different quarters and/or one inpatient diagnosis (International Statistical Classification of Diseases and Related Health Problems, 10th revision, German Modification [ICD-10-GM] codes E11 and E14), prescription of oral antidiabetics, and participation in a disease management program for type 2 diabetes. All patients who met the inclusion criteria and passed the exclusion criteria in the baseline year (2012)

were included in the analysis. Full details on the iterative selection algorithm were published recently [12] (a summary can be found in the electronic supplementary material; see "Supplementary Appendix I" on the "selection of study population"). The follow-up period of this study covered 3 years, from 2013 to 2015, so that every person had up to three observations, one for each calendar year. The whole time horizon is 4 years, because outpatient service data are only stored for a limited time, according to social laws. Healthcare costs include outpatient and inpatient services, medication, rehabilitation, and the provision of aids and appliances. All costs are expressed in 2015 euros using official inflation data from the Federal Statistical Office (14).

2.2 Choice and Identification of Prevalent and Incident Complications

The following complications were considered and are characteristically used in diabetes models, such as the CDC/RTI model and the UKPDS outcomes model: macrovascular complications, including angina pectoris, CHF, MI/cardiac arrest (CA), stroke, and other ischemic heart diseases (IHD), and microvascular complications including retinopathy, blindness, diabetic foot, lower extremity amputation, nephropathy, and end-stage renal disease (ESRD). All these complications are known to belong to the most common comorbidity clusters among patients with diabetes [4]. The complications were identified based on ICD diagnoses and outpatient and inpatient procedure codes (see Table S1 in the electronic supplementary material or the previous publication) [12]. A distinction can be made between prevalent and incident complications in order to address different research aspects (descriptive and causal). The definition of prevalent complications required that at least one outpatient or one primary or secondary inpatient ICD diagnosis was documented in a specific year at baseline or follow-up [12]. Uncertain diagnoses were not considered. In the case of acute macrovascular complications (MI/CA, stroke, and IHD), only hospitalizations with a primary diagnosis were considered. On the other hand, the definition of incident complications additionally required that patients were free from diagnoses of the disease at baseline (2012). Otherwise, patients were defined as having a prevalent history of the complication, which was assumed to continue throughout the follow-up.

2.3 Strategies to Address Diabetes-Related Multimorbidity and Interactions

Figure S1 (see the electronic supplementary material) shows important analytical aspects of multimorbidity, including the type of measurement, chronology of diseases, differentiation between diabetes-related complications and unrelated comorbidities, effect of interactions, and subgroup effects. As this study focuses on diabetes-related multimorbidity, four different strategies were explored to develop a comprehensive yet granular understanding of the economic effect of co-occurring complications and their specific interactions. Before looking at specific pairwise interactions, we start with the most common method in the literature to indicate whether the presence of multimorbidity is associated with higher costs.

- *Strategy 1* evaluates diabetes-related multimorbidity by simply counting multiple prevalent complications (i.e., two, three, or more complications). It makes the assumption of independence of the type of complication and is helpful for comparison reasons.

To add complexity, the next two strategies considered interactions between groups of prevalent complications or single prevalent complications in each year.

- *Strategy 2* divides the spectrum of complications into two main pathophysiological groups (microvascular and macrovascular) without looking at the relationship between specific complications [13].
- *Strategy 3* looks at specific interactions of prevalent complications (e.g., between present retinopathy and diabetic foot).

Finally, the last strategy helps to understand the possible chronological dependence structure of diabetes-related multimorbidity and temporal causality of interactions.

- *Strategy 4* distinguishes between chronic complications that were present since baseline and incident complications that started or occurred in the follow-up (e.g., prevalent CHF since baseline and incident MI in the follow-up). Interactions between prevalent and incident complications are referred to as sequential interactions.

2.4 Data Accuracy and Interaction Patterns Emerging from the Data

There are two important issues arising from the data that we have to address in this study of the influence of interaction patterns on healthcare costs. The first is that we have to decide whether different stages of the same disease in a given time period contribute to multimorbidity. The second is that claims data by nature only reflect real-world clinical practice records; to improve data accuracy, it can be necessary to correct irregular diagnostic patterns of chronic diseases. On the first point, in the annual cross-sectional data, there is a strong correlation between ESRD and nephropathy, amputation and foot complications, and blindness and retinopathy, which practically means that the majority of patients

with ESRD, amputation, or blindness were also diagnosed with the earlier stages of the complication in the same year (but not vice versa). This is not surprising as it reflects the natural progression of complications, e.g., a foot ulcer normally precedes an amputation. Similarly, in a Markov model setting, patients are always modeled as transitioning from an early to an advanced stage. In order to avoid a multimorbidity problem between conditions of the same complication family, we applied this perspective and considered the advanced stage of a complication (ESRD, blindness, amputation) in years with two competing diagnoses. On the second point, in the longitudinal view, there can be gaps in the diagnostic validity of chronic complications (retinopathy/blindness, nephropathy/ESRD, CHF, angina pectoris, diabetic foot) resulting from incomplete coding of diagnoses by physicians and irregular visits to the doctor (see Table S2 in the electronic supplementary material). For example, a chronic diagnosis was recorded in 2013 and 2015, but was missing in 2014. These types of gaps of one or more years can be interpreted as possible missing information, which can influence the analysis of interaction patterns. We therefore examined the effect of different algorithms to impute for such possible missing diagnoses (details on the imputation routine and our rationales can be found in "Supplementary Appendix II" in the electronic supplementary material). It was decided, based on preliminary regression analyses of the observed and imputed data, to correct for missing diagnoses in the chronic history of diabetic foot and retinopathy. For all other conditions, the original diagnoses data were used.

2.5 Statistical Analysis

To account for the non-independence of observations within each subject, we used a generalized estimating equations (GEE) model with a first-order autocorrelation structure (AR(1)). A near normality of the sample means was assumed. This assumption is justified by literature recommendations, based on the large sample size and the relatively low proportion of zero costs (<2%) [14]. In addition, the additive approach has been verified to provide a better model fit based on the mean square error compared with a multiplicative model with a gamma log-link GEE model where €1 was assigned for patients with zero costs. *Strategies 1–3* are based on a prevalence approach, which leads to the following set of variables (see "Statistical Appendix" in the electronic supplementary material for full model notation): age (in five age groups), sex, age–sex interaction, presence of different complications, plus the number of complications or interactions (according to the strategy). *Strategy 4* leads to the extended set of the following variables: age groups, sex, age–sex interaction, occurrence of different incident complications, presence of prevalent chronic complications at baseline, plus sequential interactions. For *strategies 3* and *4*, which require careful variable selection, interactions were included using a stepwise approach based on a *p* value of 0.05 [15]. All analyses were performed at the Scientific Institute of TK for Benefit and Efficiency in Health Care (WINEG) that approved the intended use of the data.

3 Results

3.1 Sample Characteristics

The study sample included 316,220 patients with a mean age of ~66 years; over 60% of them were men. The baseline characteristics in Table 1 provide a first indication that multimorbidity is associated with different population characteristics. Out of the total population, 61% had no complications at baseline, 26% had one complication, and 13% had at least two or more complications. It was found that the proportion of men rises with the number of complications (~69% in the group with at least two complications). Similarly, the mean age and share of participants in a structured disease management program for type 2 diabetes is the highest in this group, with over 72% and approximately 72 years. The proportion of patients receiving no antidiabetic treatment was maximal (~42%) in the group with no complications, whereas the proportion of an insulin-based therapy (insulin only or combined with oral agents) is highest in the group with two or more complications (~35%). Regarding other comorbidities and risk factors, hypertension is the most frequent, with around 98% in the group with two or more complications compared with the overall average of ~86%.

3.2 Descriptive Analysis

Figure 1 shows what the diabetes-related multimorbidity network looks like in this population. The 3-year prevalence rates of the complications (2013–2015) are mapped as well as the most frequent interactions between different types of complications. Further details on the frequencies of interactions can be found in Table S3 (see the electronic supplementary material). We did not include hypertension because the majority already had diagnosed hypertension or received antihypertensive agents. Nephropathy (~28%), CHF (~23%), and foot complications (22%) had the highest 3-year prevalence. Owing to the higher frequency, the co-occurrence of these conditions is also more likely. Nephropathy and CHF is the most frequent interaction (41% of CHF observations), followed by nephropathy and foot complications (37% of diabetic foot observations), and retinopathy and foot complications (25% of retinopathy observations). It is also noticeable that most cardio- and cerebrovascular

Table 1 Baseline characteristics in 2012, stratified by number of known diabetes-related complications

	Overall ($n = 316,220$)	No complications at baseline ($n = 193,166$)	One complication ($n = 82,360$)	At least two complications ($n = 40,694$)
Participation in the DMP for type 2 diabetes (%)	61.2	56.7	66.3	72.1
Sex, male (%)	63.3	61.7	64.4	68.9
Mean age (years)	65.9	63.4	68.1	71.6
Age group (%)				
< 50 years	8.6	11.5	4.9	1.9
50–59 years	19.4	23.5	15.0	9.0
60–69 years	29.6	31.0	29.1	24.1
70–79 years	32.4	27.5	38.2	44.3
> 80 years	10.0	6.4	12.9	20.8
Type of antidiabetic treatment (%)				
No antidiabetics	37.9	41.7	34.4	27.1
Only oral	47.4	49.0	47.9	38.5
Oral + insulin	9.2	6.4	11.4	18.2
Only insulin	5.5	2.9	6.4	16.3
Mean aDCSI score	1.7	0.9	2.4	4.4
Other comorbidities (%)				
Hypertension (ICD codes I10–I15 or ATC C02–C09)	85.8	80.1	93.0	98.1
Depression (F32–F32 or ATC N06A)	22.6	21.0	23.6	27.8
Obesity (E66)	30.1	27.5	31.8	38.9
Malignant cancer (C00–C97)	14.7	12.2	17.3	21.3

The following complications were considered: retinopathy, blindness, diabetic foot, amputation, nephropathy, ESRD, angina, CHF, MI, stroke, and IHD. There is no overlap between retinopathy and blindness, nephropathy and ESRD, and foot and amputation

aDCSI adapted Diabetes Complications Severity Index, *ATC* Anatomical Therapeutic Chemical Classification System, *CHF* chronic heart failure, *DMP* disease management program, *ESRD* end-stage renal disease, *ICD* International Classification of Diseases, *IHD* (other) ischemic heart disease, *MI* myocardial infarction

conditions are likely to appear together with nephropathy and CHF.

3.3 Regression Analysis

Tables 2 and 3 show the results for *strategies 1–3* that are based on a cross-sectional prevalence approach. Depending on the strategy used, prevalent complications were associated with the following additional costs per year (compared with a population without complications): diabetic foot €1100–1300, amputation €18,200–20,600, retinopathy –€200 to over €200, blindness €1800–2100, nephropathy €2500–2600, ESRD €26,000–30,000, stroke €12,300–13,000, MI €6800–7700, IHD €5700–6800, angina pectoris €1000–1700, and CHF €2500–3200. In *strategy 1* (Table 2), we can only see that the number of complications (2, 3, and ≥ 4) has a significant impact on total costs. The implementation of more advanced strategies is needed to interpret specific interaction effects. In *strategy 2* (Table 3), we gain more information on the relevance of pathophysiological groups of complications (microvascular and macrovascular). Although the presence of multiple microvascular complications showed a negative effect on total costs (particularly to correct for the overestimation of inpatient costs), multiple macrovascular complications or interactions between micro- and macrovascular complications were positively associated with total costs. In addition, the size of the effect significantly depends on the number of micro- or macrovascular complications. In *strategy 3*, we extensively analyzed specific disease–disease interactions of prevalent conditions. Out of 52 possible interactions, 13 interactions had a significant impact on total costs. CHF has been shown to be of particular importance in the pairwise interactions (especially for cardiovascular conditions, but also for microvascular complications). Most of the interactions had a positive effect on total costs, ranging from approximately €180 for retinopathy and diabetic foot to around €13,600 for ESRD and IHD. Negative effects on total costs were found for certain interactions with retinopathy and angina pectoris. As an indicator for the economic relevance of specific interactions, Table S4 (see the electronic supplementary material) shows the relative proportions of interaction estimates to the mean estimates of complications. Generally, the percentage is far over 10%, indicating a moderate to high relevance. In

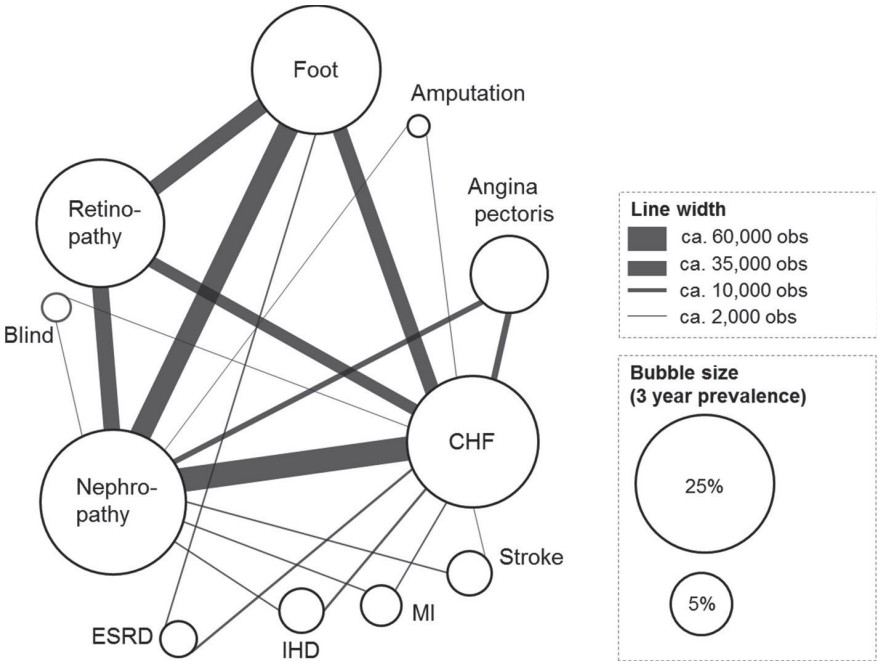


Fig. 1 Multimorbidity network based on most important type 2 diabetes complications. The bubble size corresponds to the 3-year prevalence of ever having the disease in 2013–2015, and should take account of the visibility of rare complications. For reasons of clarity and to avoid unnecessary complexity, all disease pairings with more than 10,000 observations are shown. In the case of less frequent diseases (ESRD, IHD, MI, stroke, blindness), the two most common combinations are presented. The thickness of the lines therefore corresponds to the relative frequency (with the most frequent pair, CHF and nephropathy, as reference). The relative position of the bubbles is not specified and is mainly a result of better visibility and grouping of similar micro- and macrovascular complications. *CHF* chronic heart failure, *ESRD* end-stage renal disease, *IHD* (other) ischemic heart disease, *MI* myocardial infarction, *obs* observations

strategy 4 (Table 4), the sequence of specific disease–disease interactions was assessed using an incidence approach. Annual costs for incident complications ranged from €40 for retinopathy to around €26,000 for ESRD. Out of 60 possible interactions, 15 sequential interactions were found to have a significant impact on total costs. Again, history of CHF followed by ESRD was frequently involved in positive interactions. In some interactions, a history of retinopathy, diabetic foot, or angina pectoris led to a negative effect on total costs. Switching incident and historical conditions led to either reversed effects (from positive to negative and vice versa) or positive but smaller effects. Although not all these interactions were significant in the overall model, it indicates that the chronology of diseases is important.

4 Discussion

This study provides novel methodological and empirical findings on the assessment of the economic impact of multiple diabetes-related complications and their interactions. At an empirical level, there is currently no other German study providing similarly detailed cost information on model-relevant diabetes complications. At a methodological level, there is no international study exploring the economic effect of interactions between multiple disease complications in a comparably structured way. Methodology and results on interaction patterns and economic effects can be used to inform other research in diabetes, especially health economic models or even to build a German diabetes model. The results of the regression models gradually revealed the complexity of diabetes-related multimorbidity that goes beyond the simple counting of comorbidities/complications. In detail, this study adds additional evidence for diabetes models, indicating that the effect of diabetes-related multimorbidity is less than multiplicative yet more than additive. In support of this, we systematically identified significant interactions between disease groups and single complications based on additive GEE models, where the interactions predominantly had a positive effect on total healthcare costs. Some of the interactions (such as nephropathy and CHF) had already been identified to be epidemiologically important based on a multimorbidity network. Apart from highly prevalent complications, expensive conditions (such as amputations) were also found to be more sensitive for interactions. In addition, the sequence of the occurrence of complications revealed an additional impact on the interpretation of interactions.

Table 2 Effects of prevalent type 2 diabetes complications and the number of complications on total costs per year in GEE normal regression (strategy 1)

Variable	Strategy 1
Basic set, estimate (SE), €	
Population-average constant (no complications)[a]	2893
Complication/condition (Ref. = no)	
Diabetic foot	1118*** (42)
Amputation	20,352*** (676)
Retinopathy	− 179*** (33)
Blindness	1799*** (176)
Nephropathy	2542*** (43)
ESRD	29,693*** (526)
Stroke	12,648*** (259)
MI	7694*** (238)
IHD	6788*** (193)
Angina	1334*** (69)
CHF	3160*** (49)
Death	6396*** (162)
Multimorbidity measure	
Number of complications[b], estimate (SE), €	
2	296*** (58)
3	1126*** (108)
≥4	2618*** (197)
R-squared, %	
With adjustment for main effects of complications (reference case)	22.0
Without adjustment for main effects of complications (count = 1, 2, 3, ≥4)	12.2

CHF chronic heart failure, *ESRD* end-stage renal disease, *GEE* generalized estimating equations, *IHD* (other) ischemic heart disease, *MI* myocardial infarction, *Ref.* reference, *SE* standard error

*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$

[a]Includes intercept, weighted age- and sex-specific estimates, and interaction between age groups and sex (see "Statistical Appendix" in the electronic supplementary material for full model notation)

[b]The following complications were considered: retinopathy, blindness, diabetic foot, amputation, nephropathy, ESRD, angina, CHF, MI, stroke, and IHD

4.1 Comparison and Cross-Validation with Other Studies

Direct evidence on the economic impact of diabetes-related multimorbidity, specifically on disease–disease interactions, is barely available. Although there is some international evidence indicating that costs increase gradually with the number of comorbidities/complications and higher levels of the adapted Diabetes Complications Severity Index (aDCSI) [16, 17], detailed studies on specific interactions are lacking. In addition, there is a study that showed higher hospitalization costs for type 2 diabetes resulting from macrovascular rather than microvascular complications; however, it did not consider a combination of both [18]. Regarding specific interactions, epidemiological literature was found on associations between diabetic foot and retinopathy [19], amputation and chronic kidney disease [20, 21], retinopathy and chronic kidney disease [22, 23], chronic kidney disease and cardiovascular disease [24–26], and diabetic foot and cardio- and cerebrovascular diseases [27, 28]. Interactions were often reflected in increased severity and faster progression to more advanced stages or death. In addition, these studies support the involvement of microvascular diseases in the development of macrovascular diseases in patients with diabetes.

4.2 Interpretation and Integration of Interactions in Diabetes Models

An important point for discussion is the challenge of integrating evidence on multimorbidity in diabetes simulation models. Modeling a heterogeneous population of patients with a systemic disease and multiple complications is challenging since a complex network of patient characteristics, pathophysiological processes, and different treatment approaches have to be translated into a formal computer simulation [29]. Diabetes is one of the few examples of whole disease models, where multiple comorbidities are modeled simultaneously (e.g., using a summarized state transition matrix as in the CDC/RTI model) [30]. Although these models by nature focus on well-known diabetes-related complications, they are constantly updated as soon as new evidence emerges. In these complex structures, multimorbidity is often taken into account by including covariates (e.g., blood pressure) that have multiple effects and can thus cause interactions. The most common interactions are usually two-way disease interactions that lead to a faster progression on each of the disease paths. The detailed analysis of specific disease-disease interactions in this study is of particular interest for cost-effectiveness analyses based on microsimulation models, as the prediction of costs in patients with specific complications can be improved. Markov cohort models, in contrast, are more focused on population mean costs of complications rather than on individual variations due to interactions. In particular, such methods and findings can be used to refine interaction patterns and assign detailed cost information to specific health states. In this context, the following assumptions and constraints have to be considered. First, the exact lapse of time between two co-occurring conditions cannot be determined; however, most of the complications are chronic, and diabetes models typically use 1-year intervals. Second, we do not account for the longitudinal development of disease interactions; however, at least in *strategy 4*, we were still

Table 3 Effects of prevalent type 2 diabetes complications and interactions on total costs per year in GEE normal regression (strategies 2 and 3)

Variable	Strategy 2		Strategy 3	
Basic set, estimate (SE), €				
Population-average constant (no complications)[a]	2881		2900	
Complication/condition (Ref. = no)				
Diabetic foot	1330*** (41)		1294*** (40)	
Amputation	20,582*** (672)		18,248*** (648)	
Retinopathy	− 3 (34)		242*** (30)	
Blindness	1990*** (176)		2119*** (175)	
Nephropathy	2653*** (43)		2454*** (42)	
ESRD	29,798*** (523)		25,731*** (672)	
Stroke	12,270*** (259)		13,085*** (258)	
MI	7381*** (244)		6829*** (230)	
IHD	6497*** (206)		5694*** (161)	
Angina	968*** (85)		1703*** (59)	
CHF	2828*** (55)		2465*** (55)	
Death	6365*** (162)		6253*** (162)	
Multimorbidity measure	Pathophysiological groups		Model state-specific	
Interactions, estimate (SE), €				
	Micro ≥ 2 (macro = 0)	–234*** (65)	Angina × amputation	− 5282** (1965)
	Micro = 1 and macro = 1	716*** (85)	Retinopathy × nephropathy	− 530*** (83)
	Macro ≥ 2 (micro = 0)	988*** (198)	Retinopathy × CHF	− 320** (111)
	Micro ≥ 2 and macro = 1	1443*** (130)	Foot × retinopathy	183* (82)
	Micro = 1 and macro ≥ 2	2327*** (231)	CHF × angina	305* (145)
	Micro ≥ 2 and macro ≥ 2	3487*** (308)	Diabetic foot × CHF	554*** (119)
			Nephropathy × CHF	2056*** (92)
			IHD × CHF	2286*** (332)
			MI × CHF	2298*** (436)
			Amputation × CHF	3504** (1277)
			ESRD × CHF	6982*** (942)
			Amputation × ESRD	8923* (3772)
			ESRD × IHD	13,599* (3373)
R-squared (%)	22.1		22.3	
ΔQICu (compared to strategy 1)[b]	3		10	

AIC Akaike information criterion, *CHF* chronic heart failure, *ESRD* end-stage renal disease, *GEE* generalized estimating equations, *IHD* (other) ischemic heart disease, *macro* macrovascular complications, *MI* myocardial infarction, *micro* microvascular complications, *QIC* quasi information criterion, *Ref.* reference, *SE* standard error

*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$

[a]Includes intercept, weighted age- and sex-specific estimates, and interaction between age groups and sex (see "Statistical Appendix" in the electronic supplementary material for full model notation)

[b]The QIC is an adaptation of the AIC in GEE models. Whereas individual QIC values are not interpretable, their differences (deltas) indicate a more or less parsimonious model (higher is less parsimonious)

Table 4 Effects of incident type 2 diabetes complications in addition to prevalent chronic complications (at baseline) on total costs per year in GEE normal regression (strategy 4)

Variable	Strategy 4	
Basic set, estimate (SE), €		
Population-average constant (no complications)[a]	2653	
Complication/condition (Ref. = no)		
Diabetic foot	993*** (53)	
Amputation	14,489*** (531)	
Retinopathy	41 (44)	
Blindness	2529*** (242)	
Nephropathy	2920*** (57)	
ESRD	25,921 *** (663)	
Stroke	9347*** (223)	
MI	5219*** (191)	
IHD	3935*** (162)	
Angina	1362*** (78)	
CHF	3998*** (71)	
Death	6529*** (165)	
History in 2012 (Ref. = no)		
Diabetic foot	1385*** (54)	
Amputation	6450*** (621)	
Retinopathy	292*** (38)	
Blindness	734*** (194)	
Nephropathy	1439*** (47)	
ESRD	23,875*** (660)	
Stroke	2284*** (180)	
MI	111 (174)	
IHD	2072 (99)	
Angina	107 (76)	
CHF	1682*** (53)	
Multimorbidity measure	Chronological occurrence	
Interactions, estimate (SE), €		
	Diabetic foot (history) × stroke (incident)	–1534** (577)
	Angina (history) × CHF (incident)	−571* (266)
	Retinopathy (history) × diabetic foot (incident)	−295* (117)
	Nephropathy (history) × diabetic foot (incident)	644*** (147)
	CHF (history) × nephropathy (incident)	881*** (159)
	CHF (history) × diabetic foot (incident)	971*** (179)
	CHF (history) × angina (incident)	1137*** (249)
	CHF (history) × IHD (incident)	1486* (622)
	Diabetic foot (history) × IHD (incident)	1844 (749)
	CHF (history) × amputation (incident)	2860* (1390)
	ESRD (history) × diabetic foot (incident)	3176* (1502)
	ESRD (history) × CHF (incident)	3720** (1350)
	Amputation (history) × CHF (incident)	4592* (2240)
	Amputation (history) × blindness (incident)	10,459* (5120)
	ESRD (history) × IHD (incident)	12,257*** (3661)
R-squared (%)	19.7	
ΔQICu (compared to strategy 1)[b]	23	

Table 4 (continued)

AIC Akaike information criterion, *CHF* chronic heart failure, *ESRD* end-stage renal disease, *GEE* generalized estimating equations, *IHD* (other) ischemic heart disease, *MI* myocardial infarction, *QIC* quasi information criterion, *Ref.* reference, *SE* standard error

$^{*}p < 0.05$; $^{**}p < 0.01$; $^{***}p < 0.001$

[a]Includes intercept, weighted age- and sex-specific estimates, and interaction between age groups and sex (see "Statistical Appendix" in the electronic supplementary material for full model notation)

[b]The QIC is an adaptation of the AIC in GEE models. Whereas individual QIC values are not interpretable, their differences (deltas) indicate a more or less parsimonious model (higher is less parsimonious)

able to integrate a time component in our analysis. In detail, most of the significant disease–disease interactions (*strategy 3* and *4*) were positively associated with higher costs. This can be due to several factors: causal interactions within the pathogenesis, severity, disease management, or progression (i.e., more severe in combination with renal failure, less severe in combination with retinopathy). These factors, however, do not change the interpretation of the economic effect of the interactions. Although positive interactions are often easier to interpret, it has to be considered for negative interactions that certain costs may be covered in the main estimates, so that negative interactions reduce double counting of costs. One reason for possible double counting is that total cost estimates include inpatient costs for hospital admissions due to primary and other (secondary) diagnoses (e.g., CHF and retinopathy). In addition, negative interactions are influenced by the severity of complications that can be different depending on the presence of early stages of other conditions (e.g., CHF with concurrent retinopathy may be less severe than average CHF). Beyond the interpretation of the direction of interactions (positive or negative), it is important to understand the economic relevance of specific disease interactions. Our study could show that just counting complications (*strategy 1*) is not sufficient to dissect and quantify potential interactions within multimorbidity. In the example of two complications, estimated additional costs were relatively low because all types of complications and their (significant and non-significant) interactions are mixed up in one estimate. Therefore, the usefulness of a model strategy is not only a question of the goodness-of-fit, but highly depends on the intended purpose of analysis (e.g., as adjustment variable for prediction, or to investigate the underlying effects of diabetes-related multimorbidity).

4.3 Further Strengths and Weaknesses of this Study

Among the core strengths of this study is its large population size that is less vulnerable to outliers. The analysis was based on real-world data from a nationwide health insurance fund that can be regarded as the best available data source for healthcare costs in Germany. However, some limitations must be considered. These include a lack of clinical data (e.g., severity), unknown duration of diabetes, and reliance on diagnostic accuracy. Beyond the mere comparison of sensitivity and specificity of disease definitions over multiple years in the literature [31], we were able to specify the incomplete patterns of diagnoses and proposed a way to handle this issue in claims data. In addition, several factors can explain diagnoses restricted to 1 year, including acute episodes of chronic conditions, accidental findings, remissions, or false-positive cases. Another key feature of this study is our effort to inform health economic diabetes models. Therefore, and to avoid an overfitting of the model, we did not adjust for other comorbidities than model-relevant complications. In addition, the included complications have been shown to make up the most important comorbidity clusters [4]. The exception is that we did not adjust for hypertension, because the vast majority of patients already had diagnosed/treated hypertension at baseline. Finally, it is important that this study primarily provides information on statistical cost interactions and can only touch upon the issue of causal interactions. Despite there being more to be done, these findings provide a broad basis for discussion and further research investigations in this area.

5 Future Implications

The results of this study have several implications for different healthcare stakeholders. From a modeler's perspective, future diabetes models should pay more attention to computing multimorbidity, and especially interactions, which may have a considerable effect on both health effects and costs. From a policy perspective, our findings encourage the implementation and further development of more integrated prevention and disease management programs that take better account of preexisting or co-occurring conditions. At the same time, a complete clinical/epidemiological view requires further observational studies to unravel the complex interplay between multiple shared pathogenic mechanisms of diabetes and its complications.

Data Availability Statement The data are owned by the Techniker Krankenkasse. To fulfill the legal requirements to obtain the data, researchers must obtain permission

for a specific research question from the German Federal (Social) Insurance Office. Additionally, researchers must conclude a contract with the statutory health insurer regarding data access. The study must also be approved by the data protection officer both at the statutory health insurer and the research institute as well as the local ethics committee.

Acknowledgements This research is carried out on behalf of the Helmholtz Zentrum München, the German Research Center for Environmental Health (HMGU), which is a member of the German Center for Diabetes Research (DZD). The HMGU is an independent organization funded by the German and Bavarian governments.

Author Contributions KK and RH planned the study design. Cohort selection, data processing, and statistical data analysis were conducted by KK. US was the key contact person at the WINEG/TK and provided continuous technical support during data processing and analysis. The manuscript was drafted and improved by KK, ML, and RH. RH and ML provided methodological input. All authors critically reviewed the manuscript and approved its final version. RH supervised all steps of the work. The overall guarantor for the content of this paper is KK.

Compliance with Ethical Standards

Conflict of interest KK, ML, US, and RH have no financial, academic or other conflicts of interest to declare.

References

1. Battegay E, Cheetham M, Holzer BM, Nowak A, Schmidt D, Rampini S. Multimorbidity management and the physician's daily clinical dilemma. Der Internist. 2017;58(4):344–53.
2. Workneh MH, Bjune GA, Yimer SA. Prevalence and associated factors of tuberculosis and diabetes mellitus comorbidity: a systematic review. PLoS One. 2017;12(4):e0175925.
3. Ording AG, Sorensen HT. Concepts of comorbidities, multiple morbidities, complications, and their clinical epidemiologic analogs. Clin Epidemiol. 2013;5:199–203.
4. Alonso-Moran E, Orueta JF, Esteban JI, Axpe JM, Gonzalez ML, Polanco NT, et al. Multimorbidity in people with type 2 diabetes in the Basque Country (Spain): prevalence, comorbidity clusters and comparison with other chronic patients. Eur J Int Med. 2015;26(3):197–202.
5. Bommer C, Sagalova V, Heesemann E, Manne-Goehler J, Atun R, Barnighausen T, et al. Global economic burden of diabetes in adults: projections from 2015 to 2030. Diabetes Care. 2018;41(5):963–70.
6. Clarke PM, Gray AM, Briggs A, Farmer AJ, Fenn P, Stevens RJ, et al. A model to estimate the lifetime health outcomes of patients with type 2 diabetes: the United Kingdom Prospective Diabetes Study (UKPDS) Outcomes Model (UKPDS no. 68). Diabetologia. 2004;47(10):1747–59.
7. The CDC Diabetes Cost-Effectiveness Group. Cost-effectiveness of intensive glycemic control, intensified hypertension control, and serum cholesterol level reduction for type 2 diabetes. Jama. 2002;287(19):2542–51.
8. Alva M, Gray A, Mihaylova B, Clarke P. The effect of diabetes complications on health-related quality of life: the importance of longitudinal data to address patient heterogeneity. Health Econ. 2014;23(4):487–500.
9. Hunger M, Thorand B, Schunk M, Doring A, Menn P, Peters A, et al. Multimorbidity and health-related quality of life in the older population: results from the German KORA-age study. Health Qual Life Outcomes. 2011;18(9):53.
10. Palmer AJ, Clarke P, Gray A, Leal J, Lloyd A, Grant D, et al. Computer modeling of diabetes and its complications: a report on the Fifth Mount Hood challenge meeting. Value Health J Int Soc Pharm Outcomes Res. 2013;16(4):670–85.
11. Kreis K, Neubauer S, Klora M, Lange A, Zeidler J. Status and perspectives of claims data analyses in Germany—a systematic review. Health Policy (Amst Neth). 2016;120(2):213–26.
12. Kähm K, Laxy M, Schneider U, Rogowski WH, Lhachimi SK, Holle R. Health care costs associated with incident complications in patients with type 2 diabetes in Germany. Diabetes Care. 2018;41(5):971–8.
13. Krentz AJ, Clough G, Byrne CD. Interactions between microvascular and macrovascular disease in diabetes: pathophysiology and therapeutic implications. Diabetes Obes Metab. 2007;9(6):781–91.
14. Mihaylova B, Briggs A, O'Hagan A, Thompson SG. Review of statistical methods for analysing healthcare resources and costs. Health Econ. 2011;20(8):897–916.
15. Walter S, Tiemeier H. Variable selection: current practice in epidemiological studies. Eur J Epidemiol. 2009;24(12):733–6.
16. Nuno-Solinis R, Alonso-Moran E, Arteagoitia Axpe JM, Ezkurra Loiola P, Orueta JF, Gaztambide S. Healthcare costs of people with type 2 diabetes mellitus in the Basque Country (Spain). Endocrinologia y nutricion : organo de la Sociedad Espanola de Endocrinologia y Nutricion. 2016;63(10):543–50.
17. Chen HL, Hsu WW, Hsiao FY. Changes in prevalence of diabetic complications and associated healthcare costs during a 10-year follow-up period among a nationwide diabetic cohort. J Diabetes Complicat. 2015;29(4):523–8.
18. Dimitrova M, Doneva M, Valov V, Yordanova S, Manova M, Savova A, et al. Cost of hospitalizations due to microvascular and macrovascular complications in type 1 and type 2 diabetic patients in Bulgaria. Biotechnol Biotechnol Equip. 2015;29(4):805–13.
19. Hwang DJ, Lee KM, Park MS, Choi SH, Park JI, Cho JH, et al. Association between diabetic foot ulcer and diabetic retinopathy. PloS One. 2017;12(4):e0175270.
20. Lavery LA, Hunt NA, Ndip A, Lavery DC, Van Houtum W, Boulton AJ. Impact of chronic kidney disease on survival after amputation in individuals with diabetes. Diabetes Care. 2010;33(11):2365–9.
21. Ndip A, Lavery LA, Boulton AJ. Diabetic foot disease in people with advanced nephropathy and those on renal dialysis. Curr Diabetes Rep. 2010;10(4):283–90.
22. Jeng CJ, Hsieh YT, Yang CM, Yang CH, Lin CL, Wang IJ. Diabetic retinopathy in patients with diabetic nephropathy: development and progression. PloS One. 2016;11(8):e0161897.
23. Grunwald JE, Alexander J, Ying GS, Maguire M, Daniel E, Whittock-Martin R, et al. Retinopathy and chronic kidney disease in the Chronic Renal Insufficiency Cohort (CRIC) study. Arch Ophthalmol. (Chicago, Ill : 1960). 2012;130(9):1136–44.
24. Damman K, Valente MA, Voors AA, O'Connor CM, van Veldhuisen DJ, Hillege HL. Renal impairment, worsening renal function, and outcome in patients with heart failure: an updated meta-analysis. Eur Heart J. 2014;35(7):455–69.
25. Silverberg D, Wexler D, Blum M, Schwartz D, Iaina A. The association between congestive heart failure and chronic renal disease. Curr Opin Nephrol Hypertens. 2004;13(2):163–70.

26. Palsson R, Patel UD. Cardiovascular complications of diabetic kidney disease. Adv Chron Kidney Dis. 2014;21(3):273–80.
27. Tuttolomondo A, Maida C, Pinto A. Diabetic foot syndrome as a possible cardiovascular marker in diabetic patients. J Diabetes Res. 2015;2015:268390.
28. Banerjee A, Fowkes FG, Rothwell PM. Associations between peripheral artery disease and ischemic stroke: implications for primary and secondary prevention. Stroke J Cereb Circ. 2010;41(9):2102–7.
29. Lappenschaar M, Hommersom A, Lucas PJ. Probabilistic causal models of multimorbidity concepts. In: AMIA annual symposium proceedings/AMIA symposium AMIA symposium. 2012;2012:475–84.
30. Brennan A, Chick SE, Davies R. A taxonomy of model structures for economic evaluation of health technologies. Health Econ. 2006;15(12):1295–310.
31. Khokhar B, Jette N, Metcalfe A, Cunningham CT, Quan H, Kaplan GG, et al. Systematic review of validated case definitions for diabetes in ICD-9-coded and ICD-10-coded data in adult populations. BMJ Open. 2016;6(8):e009952.

Supporting Information to “Exploring different strategies of assessing the economic impact of multiple diabetes-associated complications and their interactions: A large claims-based study in Germany”

Katharina Kähm, Michael Laxy, Udo Schneider, Rolf Holle

I. Selection of study population

The first step was to identify patients who had at least one outpatient or inpatient type 2 (ICD-10 E11) or unspecified diagnosis (E14) in the baseline year, 2012, without other diagnoses of gestational diabetes (O24), pancreoprive diabetes (E13), or pancreatic carcinoma (C25). At the end of step 1, a total of 441,829 potential type 2 diabetes patients were identified. Further exclusion criteria were applied in subsequent steps: age <18 years (2,432 patients excluded), insufficient diagnoses (68,578), unclear type 1 diabetes (30,282), participation in a disease management program for type 1 diabetes (1,445), end of insurance in 2012 (due to death or other reasons) (12,228), lack of full insurance history in the follow-up period 2013-2015 (except death) (4,950), unknown residence or residence abroad (699), and inconsistent or implausible diabetes cases (4,995). Insufficient/uncertain type 2 diabetes diagnosis was supposed when a patient had less than two outpatient diagnoses in separate quarters, only unspecified diabetes diagnoses (E14), or a competing type 1 diagnosis (E10). In these cases, we considered additional criteria, including the prescription of oral antidiabetics or the participation in a disease management program for type 2 diabetes. The final population consisted of 316,220 patients.

For a figure of the selection algorithm, please additionally see Kähm et al. 2018 [1].

II. Data validation: Imputation of missing values in the diagnostic course of chronic complications

Patients with continuously higher costs are relevant, even without showing the diagnosis in every year (e.g., incomplete coding of diagnoses by physicians, irregular visits to the doctor). Information on the successful treatment and cure of diseases is not directly available from claims data, and derivatives of the likelihood are difficult to analyze considering the diversity of complications and the available period of 4 years.

Therefore, we examined the effect of different algorithms to impute for possible missing diagnosis information (see **Table S1**) by including separate variables for observed and imputed data in the regression and comparing the similarity of the cost estimates. Since corrections to diagnoses can only be performed prospectively from the first diagnosis onward, we tested the following consecutive strategies:

- *First*, a missing diagnosis in 1 year is corrected (e.g., diagnosis was recorded in 2013 and 2015, but was missing in 2014).
- *Second*, missing diagnoses in up to 2 consecutive years are corrected (diagnosis was recorded in 2012 and 2015, but was missing in 2013 and 2014).
- *Third*, in addition to the last point, the disease is assumed to continue until death or the end of the study for patients with two consecutive years of disease.

Preliminary regression analyses of the observed and imputed diagnostic data showed no significant difference in the estimated costs for observed and imputed diabetic foot or observed and imputed retinopathy based on all three imputation algorithms (e.g., 95% confidence intervals for imputed diabetic foot €1231 [€768, €1693] and observed diabetic foot €1435 [€1359, €1511]). Therefore, diagnostic gaps for these two conditions were imputed according to the last strategy. For all other conditions, the original diagnoses data were used.

III. Statistical appendix

The basic regression model for strategy 1 is noted as follows*:

$y_{ij} = \beta_0 + \beta_1 Z_{1i} + \beta_{2l} Z_{2il} + \beta_{3l} Z_{1i} Z_{2il} + \beta_{4k} Z_{4ijk} + \beta_5 Z_{5ij} + \beta_{6m} Z_{2ijm} + e_{ij}$

where:
i = patient i
j = observation j (year 2013–2015)
k = complication k (diabetic foot/amputation, retinopathy/blindness, nephropathy/ESRD, MI, CHF, stroke, IHD, angina pectoris)
l = age group l
m = number of complications

y_{ij} = outcome/total healthcare costs for patient i and observation j
β_0 = coefficient for the intercept

β_1 = coefficient for sex
Z_{1i} = dummy variable for sex (0="female", 1="male")

β_{2l} = coefficient for age group l
Z_{2il} = dummy variables for the age group
(l=1: "<50"=1,else 0 ,
l=2: "50–60"=1 else 0,
l=3: "60–70"=1 else 0,
l=4: ">80"=1 else 0)

β_{3l} = coefficient for interaction term of male sex and age group l

β_{4k} = coefficient for prevalent complication k
Z_{4ijk} = dummy variables for complication k: 1 if present, 0 otherwise

β_5= coefficient for death from other reasons
Z_{5ij} = 1 (for death from other reasons), 0 otherwise

β_{6m} = coefficient for number of complications m
Z_{6ijm} = dummy variables for the number of complications
(m=2: 1, else 0 ,
m=3: 1, else 0,
m≥4: 1, else 0)

e_{ij} = error term for patient i, observation j

* Strategies 2 and 3 build on the first strategy. Instead of the crude number of complications, interactions between micro- and macrovascular complications (strategy 2) and disease–disease interactions (strategy 3) are considered. No interactions within the same group of complication were considered.

The regression model for strategy 4 is different from the others and noted as follows:

$y_{ij} = \beta_0 + \beta_1 Z_{1i} + \beta_{2l} Z_{2il} + \beta_{3l} Z_{1i} Z_{2il} + \beta_{4k} Z_{4ik} + \beta_5 Z_{5ij} + \beta_{6k} Z_{6ijk} + \beta_{7kk} Z_{4ik} Z_{6ijk} + e_{ij}$

where:
i = patient i
j = observation j (year 2013–2015)
k = complication k (diabetic foot/amputation, retinopathy/blindness, nephropathy/ESRD, MI, CHF, stroke, IHD, angina pectoris)
l = age group l

y_{ij} = outcome/total healthcare costs for patient i and observation j
β_0 = coefficient for the intercept

β_1 = coefficient for sex
Z_{1i} = dummy variable for sex (0="female", 1="male")

β_{2l} = coefficient for age group l
Z_{2il} = dummy variables for the age group
(l=1: "<50"=1,else 0 ,
l=2: "50–60"=1 else 0,
l=3: "60–70"=1 else 0,
l=4: ">80"=1 else 0)

β_{3l} = coefficient for interaction term of male sex and age group l

β_{4k}= coefficient for history of complication k in 2012
Z_{4ik} = for each complication k: 1 if present at baseline, 0 otherwise

β_5= coefficient for death from other reasons
Z_{5ij} = 1 (for death from other reasons), 0 otherwise

β_{6k} = coefficient for new complication k
Z_{6ijk} = dummy variables for new complication k: 1 with onset of the disease, 0 otherwise

β_{7kk} = coefficient for interaction between a history of prevalent complication k and incident complication k*

e_{ij} = error term for patient i, observation j

* No interactions within the same group of complication. In addition, only the history of chronic complications was considered (diabetic foot, retinopathy, blindness, nephropathy, end-stage renal disease, angina pectoris, chronic heart failure).

Abbreviations: CHF, chronic heart failure; ESRD, end-stage renal disease; IHD, (other) ischemic heart disease; MI, myocardial infarction.

IV. Tables

Table S1: Identification of relevant complications and events based on ICD-10-GM, OPS- and EBM-codes

Microvascular complications	**ICD-, OPS- or EBM-codes**
Eye complications	
Retinopathy	ICD-codes E10-E14.3- (diabetes with eye complications), H36.0 (diabetic retinopathy), H35.0 (background retinopathy and retinal vascular changes), H35.2 (other proliferative retinopathy)
Blindness in one or two eyes	ICD-codes H54.0 (blindness, both eyes), H54.4 (blindness, one eye)
Renal complications	
Renal insufficiency	E11.2- (or E14.2-) (diabetes with renal complications), ICD-codes N17 (acute renal failure), N18 (chronic renal failure, without N18.5), N19 (not other specified renal failure)
ESRD	ICD-code N18.5 (terminal renal insufficiency)
→ with or without dialysis	ICD-codes Z49 (dialysis), Z99.2 (long-term dialysis in renal insufficiency) OPS-codes 8-854 (hemodialysis), 8-855 (hemodiafiltration), 8-857 (peritoneal dialysis), 8-85a (dialysis after failed kidney transplant) EBM-codes 13602-13622 w/o 13621 (dialysis fees), 40815-40838 (material cost fee)
Neuropathic complications	
Diabetic foot syndrome (with polyneuropathy and peripheral angiopathy)	ICD-codes E10-E14.74 and .75 (diabetes with multiple complications, with diabetic foot syndrome) or ICD-code for peripheral neuropathy G63.2 (diabetic polyneuropathy) + one of the ICD-codes for PVD: E11.5 (or E14.5) (diabetes with peripheral vascular complications), I70.2 (atherosclerosis of extremities), I73.9 (peripheral vascular disease, not other specified), I79.2 (diabetic peripheral angiopathy), R02 (gangrene) or EBM-code 02311 (treatment of diabetic foot)
Amputation of lower extremities	OPS-codes 5-864 (amputation of lower extremity), 5-865 (amputation of the foot)
Macrovascular complications	
Cardiovascular complications	
Angina pectoris	ICD-code I20 (angina pectoris)
Chronic heart failure (CHF)	ICD-codes I50 (heart failure) , I11.0 (hypertensive heart disease with heart failure), I13.0 (hypertensive heart and chronic kidney disease with heart failure), I13.2 (Hypertensive heart and chronic kidney disease with heart failure and with end stage renal disease)
Myocardial infarction/cardiac arrest	ICD-codes I21 (acute myocardial infarction), I46.0 or .9 (cardiac arrest)

Other IHD	ICD-codes I22 (recurrent myocardial infarction), I24 (other acute ischemic heart disease), I25 (chronic ischemic heart disease)
Cerebrovascular complications	
Stroke*	ICD-codes I60 (subarachnoidal haemorrhage), I61 (intracerebral bleeding), I62 (other non-traumatic intracranial bleeding), I63 (brain infarction), I64 (stroke)
Death	
All-cause death	Reason for termination of membership due to death

* Stroke includes bleeding inside the brain (hemorrhagic stroke).

Abbreviations: CHF, chronic heart failure; EBM, uniform value scale for outpatient services; ESRD, end-stage renal disease; GM, german modification; ICD, International Classification of Diseases; IHD, ischemic heart disease; OPS, operation procedure codes; PVD, peripheral vascular disease.

Table S2: Examination of the completeness of diagnostic coding of chronic diseases (in % of patients with the specific complication)*

Indicator for completeness and distribution of missing diagnoses	Data example (X= diagnosis was recorded, ?= missing diagnosis)				ESRD	Diabetic Foot	Angina pectoris	CHF	Retinopathy	Blindness	Nephropathy
	2012	2013	2014	2015							
Continuous diagnoses[a]	X	X	X	X	56%	51%	23%	53%	46%	43%	60%
No further diagnoses after two consecutive years of disease (without death)	X	X	?	?	2%	5%	8%	6%	11%	7%	4%
Diagnostic gaps[b]											
of 1 year		X	?	X	2%	4%	5%	5%	9%	4%	4%
of 2 years	X	?	?	X	0%	1%	2%	1%	2%	1%	1%
of up to 2 years followed by death		X	?	Death	3%	1%	3%	2%	2%	3%	1%
Only one year of diagnosis in 2012–2015 (including incident cases in 2015)			X	?	37%	37%	61%	32%	31%	41%	29%

*Column-wise interpretation. This is an average over patients who either already had the complication at baseline or developed it later in follow-up. Patients who develop a complication later in follow-up have less observed years and therefore higher chance of gaps.

[a]There were no years without recorded diagnosis since the onset of the disease or since baseline year.

[b]There were gaps of up to two consecutive years without recorded diagnosis.

Table S3: Average annual frequencies of two-way disease interactions in diabetes patients with complications*

	Total (observations) 2013–2015	Foot	Amputation	Retinopathy	Blind	Nephropathy	ESRD	MI	Stroke	IHD	Angina pectoris	CHF
Foot	133,966	X	1.4%	27.0%	1.3%	39.5%	2.6%	1.4%	1.5%	1.5%	5.9%	26.5%
Amputation	2,322	82.1%	X	26.4%	2.4%	60.6%	13.5%	3.0%	2.6%	2.2%	6.3%	49.3%
Retinopathy	141,833	25.5%	0.4%	X	1.2%	28.1%	1.4%	0.8%	1.0%	1.2%	5.3%	19.2%
Blind	6,290	26.9%	0.9%	26.1%	X	34.6%	2.6%	1.2%	2.4%	1.1%	5.9%	29.0%
Nephropathy	187,631	28.2%	0.7%	21.3%	1.2%	X	4.3%	1.9%	1.8%	2.0%	6.9%	33.4%
ESRD	8,700	39.9%	3.6%	23.0%	1.9%	92.7%	X	5.2%	2.6%	3.4%	8.1%	55.8%
MI	7,105	25.6%	1.0%	16.3%	1.1%	49.4%	6.4%	X	2.4%	12.4%	24.9%	59.1%
Stroke	8,579	23.5%	0.7%	17.2%	1.8%	40.1%	2.6%	2.0%	X	1.7%	6.1%	33.4%
IHD	8,703	23.7%	0.6%	19.6%	0.8%	42.7%	3.4%	10.2%	1.6%	X	31.3%	52.7%
Angina pectoris	38,407	20.7%	0.4%	19.5%	1.0%	33.6%	1.8%	4.6%	1.4%	7.1%	X	39.3%
CHF	143,094	24.8%	0.8%	19.1%	1.3%	43.8%	3.4%	2.9%	2.0%	3.2%	10.6%	X
Total	925,073											

* Row-wise interpretation. Lower (green) and higher (red) frequencies are highlighted in color. Please note that the co-occurrence of multiple complications of the same disease family (e.g., ESRD and nephropathy) in a given year was not considered as a typical disease interaction, and therefore not shown in the network analysis of Figure 1.

Abbreviations: CHF, chronic heart failure; ESRD, end-stage renal disease; IHD, (other) ischemic heart disease; MI, myocardial infarction.

Table S4: Strategy 3: Economic relevance of disease-disease interactions, expressed as the percentage of the main estimates

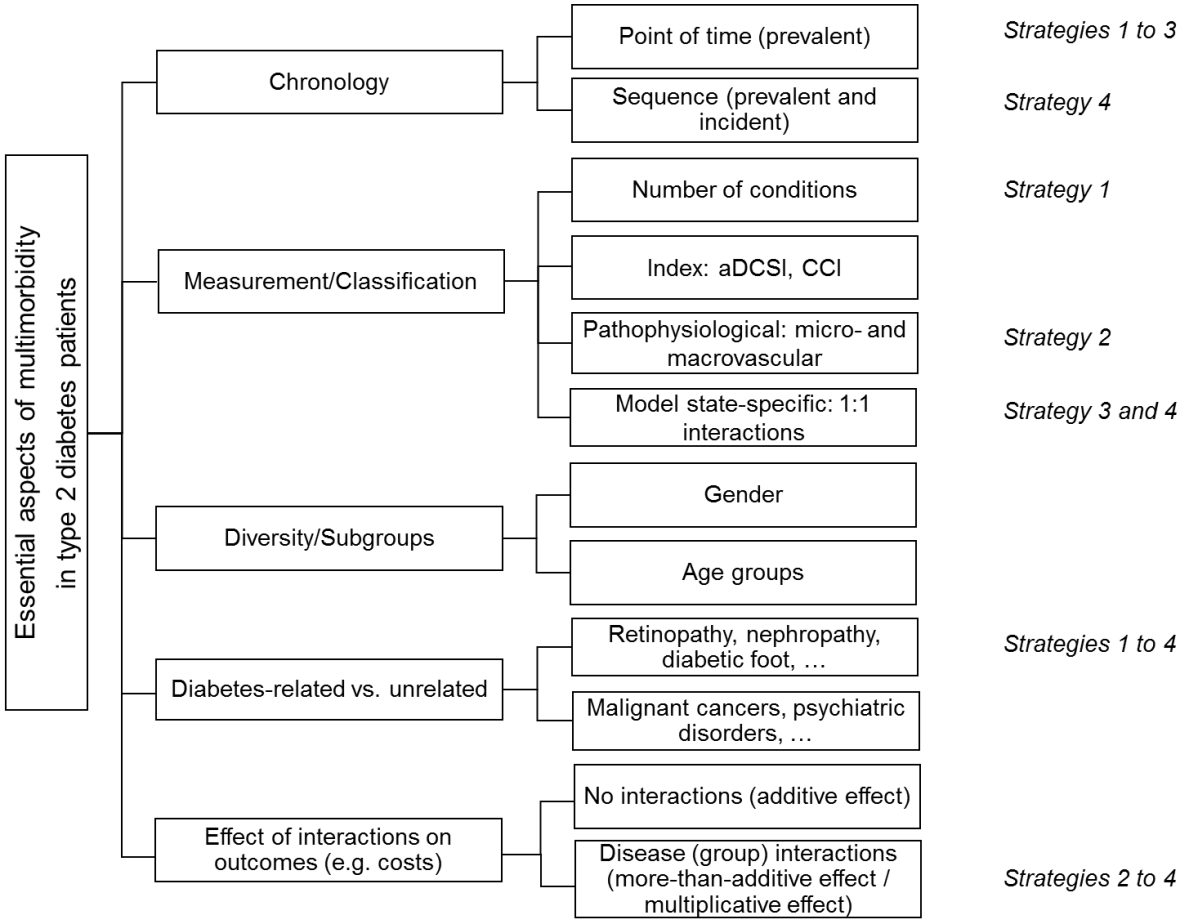
Main estimates	**Estimate (in €)**	**Lower 95% CI (in €)**	**Upper 95% CI (in €)**
Diabetic Foot	1,294	1,216	1,372
Amputation	18,248	16,978	19,517
Retinopathy	242	182	301
Blindness	2,119	1,775	2,463
Nephropathy	2,454	2,371	2,537
ESRD	25,731	24,413	27,048
Stroke	13,085	12,580	13,590
MI	6,829	6,378	7,281
IHD	5,694	5,378	6,009
Angina pectoris	1,703	1,588	1,818
CHF	2,465	2,357	2,573
Interactions	**Estimate (in €)/ in %**	**Lower 95% CI (in €)/ in %**	**Upper 95% CI (in €)/ in %**
Diabetic foot x retinopathy	183	22	343
in % of diabetic foot	14%	2%	25%
in % of retinopathy	76%	12%	114%
Diabetic foot x CHF	554	320	788
in % of diabetic foot	43%	26%	57%
in % of CHF	22%	14%	31%
Retinopathy x nephropathy	-530	-693	-368
in % of retinopathy	-219%	-380%	-122%
in % of nephropathy	-22%	-29%	-14%
Retinopathy x CHF	-320	-537	-103
in % of retinopathy	-132%	-294%	-34%
in % of CHF	-13%	-23%	-4%
Amputation x ESRD	8,923	1,530	16,315
in % of amputation	49%	9%	84%
in % of ESRD	35%	6%	60%
Amputation x angina	-5,282	-9,134	-1,430
in % of amputation	-29%	-54%	-7%
in % of angina	-310%	-575%	-79%
Amputation x CHF	3,504	1,000	6,007
in % of amputation	19%	6%	31%
in % of CHF	142%	42%	233%
Nephropathy x CHF	2,056	1,876	2,237
in % of nephropathy	84%	79%	88%
in % of CHF	83%	80%	87%
ESRD x IHD	13,599	6,989	20,208
in % of ESRD	53%	29%	75%
in % of IHD	239%	130%	336%
ESRD x CHF	6,982	5,136	8,829

in % of ESRD	27%	21%	33%
in % of CHF	283%	218%	343%
MI x CHF	2,298	1,443	3,154
in % of MI	34%	23%	43%
in % of CHF	93%	61%	123%
IHD x CHF	2,286	1,636	2,936
in % of IHD	40%	30%	49%
in % of CHF	93%	69%	114%
Angina x CHF	305	22	588
in % of angina	18%	1%	32%
in % of CHF	12%	1%	23%

Abbreviations: CHF, chronic heart failure; CI, confidence interval; ESRD, end-stage renal disease; IHD (other) ischemic heart disease; MI, myocardial infarction.

V. Figures

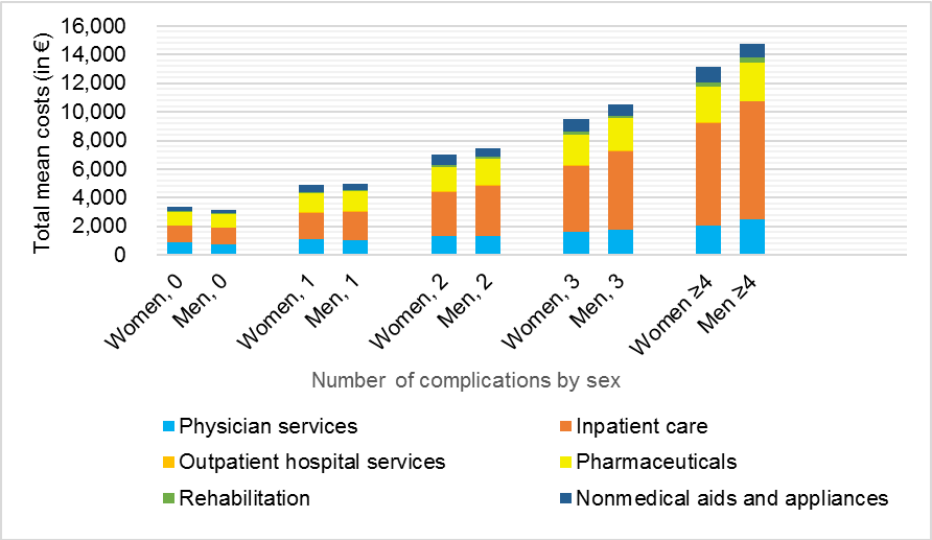
Figure S1: Essential analytical aspects of multimorbidity in type 2 diabetes patients [2-4]



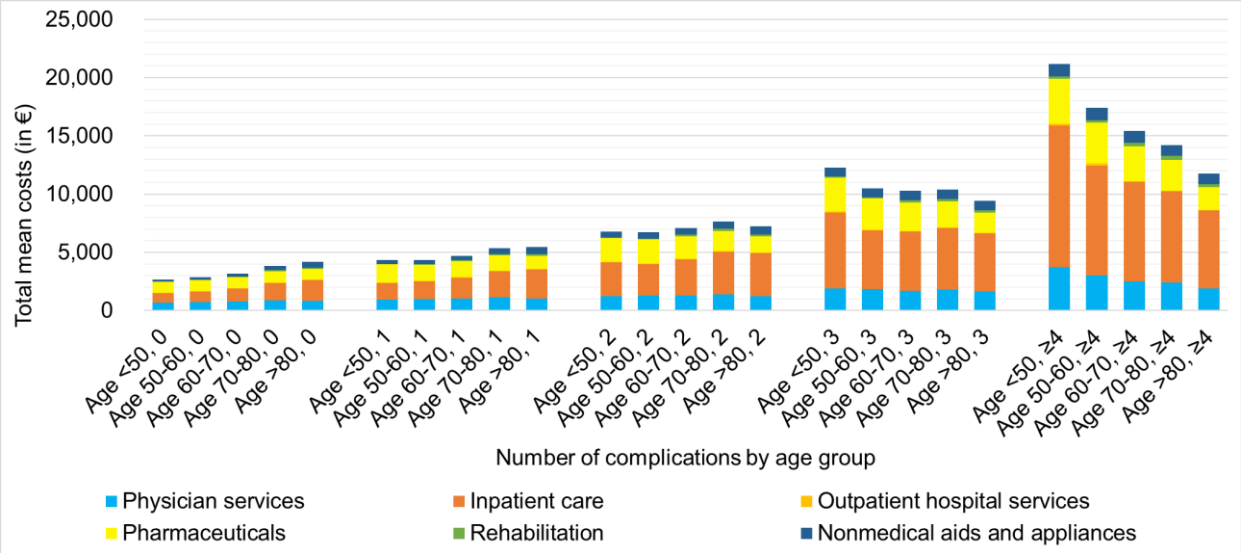
Abbreviations: aDCSI, adapted Diabetes Complications Severity Index; CCI, Charlson Comorbidity Index.

Figure S2: Descriptive analysis of the non-standardized total healthcare costs 2013–2015 by number of complications* and healthcare sector

A. by sex



B. by age groups



* Number of complications was considered each year. Therefore, same patient can be counted in multiple categories.

References

1. Kähm K, Laxy M, Schneider U, Rogowski WH, Lhachimi SK, Holle R. Health care costs associated with incident complications in patients with type 2 diabetes in Germany. Diabetes Care. 2018 May;41(5):971-8.
2. Krentz AJ, Clough G, Byrne CD. Interactions between microvascular and macrovascular disease in diabetes: pathophysiology and therapeutic implications. Diabetes, Obesity & Metabolism. 2007 Nov;9(6):781-91.
3. Sambamoorthi U, Tan X, Deb A. Multiple chronic conditions and healthcare costs among adults. Expert Review of Pharmacoeconomics & Outcomes Research. 2015;15(5):823-32.
4. Valderas JM, Starfield B, Sibbald B, Salisbury C, Roland M. Defining comorbidity: implications for understanding health and health services. Annals of Family Medicine. 2009 Jul-Aug;7(4):357-63.

Danksagung

Diese Dissertation entstand während meiner Tätigkeit als wissenschaftliche Mitarbeiterin am Institut für Gesundheitsökonomie und Management im Gesundheitswesen des Helmholtz Zentrums München. All denen, die zum Entstehen dieser Arbeit beigetragen haben, möchte ich an dieser Stelle meinen Dank aussprechen.

Der größte Dank gilt meinem Doktorvater, Prof. Dr. Rolf Holle, für seine ausgezeichnete fachliche Betreuung und für das entgegengebrachte Vertrauen in meine Person und Ideen. Er hat mein wissenschaftliches Denken und Arbeiten nachhaltig geprägt und meine Begeisterung für gesundheitsökonomische Fragen und Methoden neu geweckt.

Herzlich danken möchte ich auch allen Koautoren, die mich unterstützt haben und mich durch ihr konstruktives Feedback stets motiviert haben, das Beste aus den Arbeiten herauszuholen. Ein spezieller Dank gilt meinem Kollegen, Dr. Michael Laxy, für seinen erfahrenen perspektivischen Blick und die stets wertvollen Anregungen. Weiterhin gilt mein Dank auch den Gutachtern und Editoren, die mit ihren kritischen Anmerkungen zur wissenschaftlichen Qualität dieser Artikel beigetragen haben.

Bedanken möchte ich mich auch bei den Wissenschaftlern der Techniker Krankenkasse, allem voran bei Dr. Udo Schneider, für den ermöglichten Datenzugang und die stets produktive Zusammenarbeit. Darüber hinaus möchte ich mich auch bei allen nicht erwähnten aktuellen und ehemaligen Kollegen vom Institut für Gesundheitsökonomie und Management im Gesundheitswesen für die stets angenehme Arbeitsatmosphäre sowie die interessanten Projekte bedanken.

Nicht zuletzt möchte ich mich bei meinen Eltern, Valentina und Jakob, sowie meinem Ehemann und besten Freund Otto bedanken, ohne die ich es nicht so weit geschafft hätte.
Von tiefem Herzen ein Danke!

List of publications

Publications included in the cumulative thesis

Kähm K., Laxy M., Schneider U., Holle R. Exploring different strategies of assessing the economic impact of multiple diabetes-associated complications and their interactions: A large claims-based study in Germany. PharmacoEconomics 2018 Aug 30 [Epub ahead of print].

Kähm K., Laxy M., Schneider U., Rogowski W.H., Lhachimi S.K., Holle R.: Health care costs associated with incident complications in type 2 diabetes in Germany. Diabetes Care 2018; 41(5): 971-978.

Other publications

Kähm K., Holle R., Laxy M. Diabetes mellitus: Kosten von Komplikationen erstmals detailliert berechnet. Deutsches Ärzteblatt 2018; 115(17) Supplement: Perspektiven der Diabetologie 1/2018: 14-16.

Kähm K. Simulation models in a world of 'big data' [blog post]. Mt hood diabetes challenge network. February 7, 2018, URL: www.mthooddiabeteschallenge.com/blog.

Schremser K., Butzke B., Wilman N., Brandes A., Rogowski W. Managed Entry Agreements in Deutschland - Konzepte, rechtliche Grundlagen und systematischer Review. Gesundheitsökonomie und Qualitätsmanagement 2017; 22(1): 20-34.

Schremser K., Rogowski W. H., Adler-Reichel S., Tufman A. L., Huber R. M., Stollenwerk B. Cost-effectiveness of an individualized first-line treatment strategy offering erlotinib based on EGFR mutation testing in advanced lung adenocarcinoma patients in Germany. PharmacoEconomics 2015; 33(11): 1215-28.

Hatz M.H., *Schremser K.,* Rogowski W.H.: Is individualized medicine more cost-effective? A systematic review. Pharmacoeconomics 2014; 32(5): 443-455.