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

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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.

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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.

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.

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.

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's (CDC/RTI) ~~model and the UK Prospective Diabetes Study (UKPDS)~~

~~model~~ [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]. ~~Owing~~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].

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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).

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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.

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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.

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amputation. Similarly, in a
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ıdity problem between conditions of
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ındness, amputation) in years with two
ɹ, in the longitudinal view, there can be gaps
ɹplications (retinopathy/blindness,
ɹtoris, diabetic foot) resulting from incomplete
and irregular visits to the doctor (see Table S2 in
ıterial). For example, a chronic diagnosis was
ıt was missing in 2014. These types of gaps of one or
ɹed as possible missing information, which can influence
ı patterns. We therefore examined the effect of different
ɹor such possible missing diagnoses (details on the imputation
ɔnales can be found in “Supplementary Appendix II” in the
ınentary material). It was decided, based on preliminary regression
observed and imputed data, to correct for missing diagnoses in the
ɔry of diabetic foot and retinopathy. For all other conditions, the original
data were used.

Statistical Analysis

ɔ account for the non-independence of observations within each subject, we used a generalized estimating equations (GEE) model with a~~n~~ first-order autocorrelation structure (AR(1)) ~~autocorrelation structure~~. A near normality of the sample means

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atients with a mean age of ~ 66 years; over 60%
aracteristics in Table 1 provide a first indication
with different population characteristics. Out of the
omplications at baseline, 26% had one complication,
more complications. It was found that the proportion of
r of complications (~ 69% in the group with at least two
ly, the mean age and share of participants in a structured
program for type 2 diabetes is the highest in this group, with
roximately 72 years. The proportion of patients receiving no
tment was maximal (~ 42%) in the group with no complications,
roportion of an insulin-based therapy (insulin only or combined with
) is highest in the group with two or more complications (~ 35%).
g other comorbidities and risk factors, hypertension is the most frequent,
round 98% in the group with two or more complications compared with the
rall average of ~ 86%.

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, ATC N06A)	22.6	21.0	23.6	27.8

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* ischemic heart disease, *MI* myocardial infarction

or ATC N06A)	22.0	21.0	25.0	27.8
Obesity (E66)	**Overall (n = 316,220)** 20.1	**No complications at baseline (n = 193,166)** 12.2	**One complication (n = 82,360)** 31.8	**At least two complications (n = 40,694)** 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* ischemic heart disease, *MI* myocardial infarction				

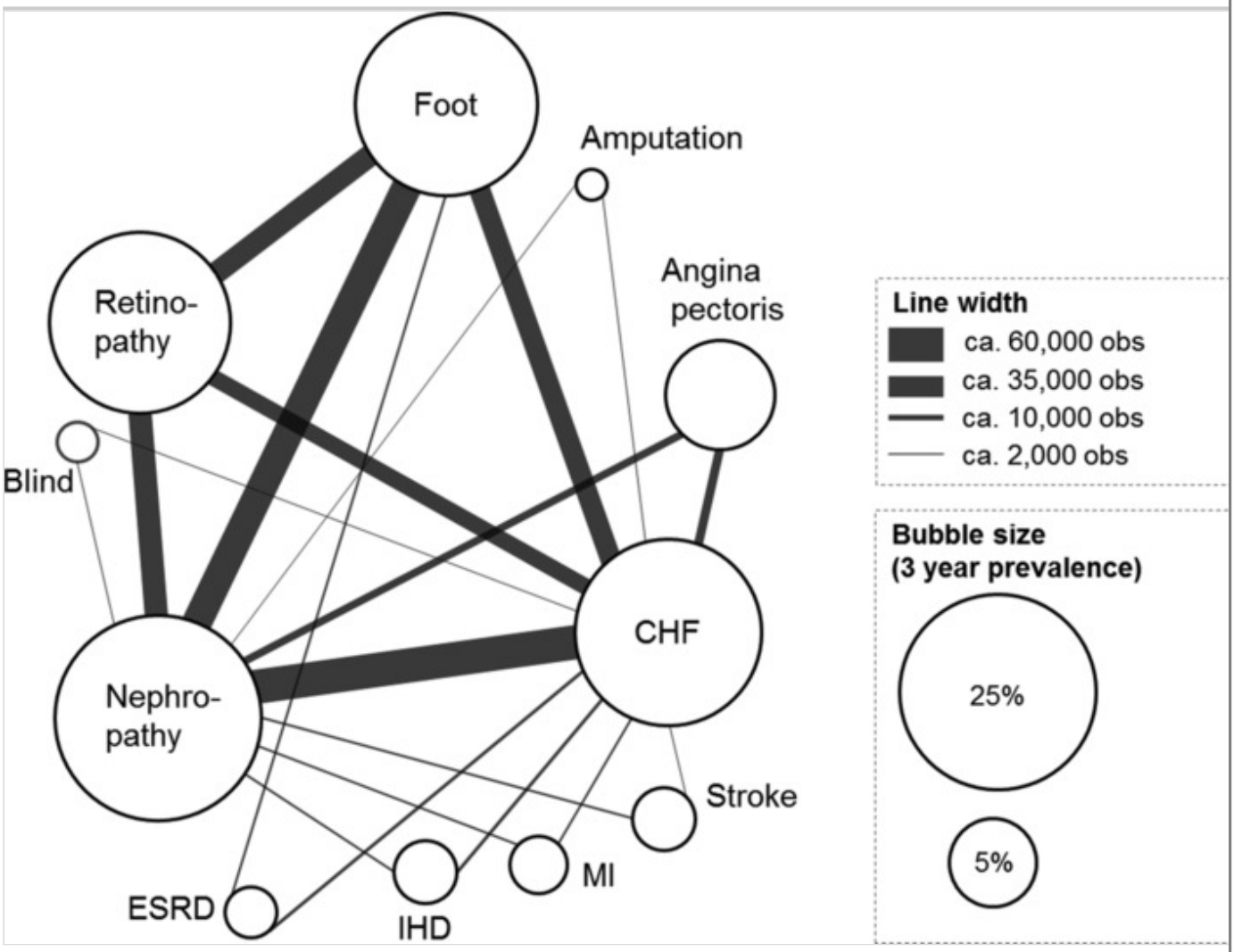
3.2. Descriptive Analysis

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 conditions are likely to appear together with nephropathy and CHF.

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



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 ~~co-occurrence~~presence of multiple microvascular complications ~~interacts~~ showed a negative~~ly~~ effect ~~with regard to the~~on total costs (particularly to correct for the overestimation of inpatient costs), ~~the interaction between~~ multiple macrovascular complications or interactions between micro- and macrovascular complications ~~is~~were ~~significantly~~ 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 *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 ~~pairing~~interactions, a history of retinopathy, diabetic foot, or angina pectoris led to a negative ~~interactions with regard to~~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.

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)

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Variable	Strategy 1

Variable	Strategy 1
~~Basic set, estimate (SE), €~~**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]~~	
~~Multimorbidity measure~~Number of complications[b], ~~estimate (SE), €~~**estimate (SE), €**	
2	296*** (58)
3	1126*** (108)
≥ 4	2618*** (197)
R-squared, %	

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

Variable	Strategy 1
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	
*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$	
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)	
The following complications were considered: retinopathy, blindness, diabetic foot, amputation, nephropathy, ESRD, angina, CHF, MI, stroke, and IHD	

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*** (522)	25,731*** (672)
Stroke	12,270*** (259)	13,085*** (258)
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		
*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$		
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)		
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)		

	(259)	(258)
Variable	**Strategy 2**	**Strategy 3**
MI	7581*** (244)	6829*** (230)
IHD	6497*** (206)	5694*** (161)
Angina	968*** (85)	1703*** (59)
CHF	2828*** (55)	2465*** (55)
Death	6365*** (162)	6253*** (162)

Interactions	**Pathophysiological groups~~based~~**	**Model** Please reformat the columns as suggested in my response. **state-specific**	
Multimorbidity measures, estimate (SE), €			
	Micro ≥ 1 and macro = 1	716*** (85)	Neuropathy × nephropathy	− 520*** (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 (macro = 0)	–234*** (65)	Angina × amputation	− 5282** (1965)

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

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

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)

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)

Variable				
	Micro ≥ 2 and macro ≥ 2	Strategy 3	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

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

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)

Variable	Strategy 2	Strategy 3
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	4347*** (223)
MI	5219*** (191)
IHD	3955*** (162)

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

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

[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)

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)

Variable	Strategy 4
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)

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

Interactions Multimorbidity Chronological occurrence

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

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)	Diabetic foot (history) × stroke (incident)	− 1534** (587)
	Angina (history) × CHF (incident)	− 571* (266)
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)	Retinopathy (history) × diabetic foot (incident)	− 293* (117)

Please reformat the columns as suggested in my response.
AQ10

Variable	Strategy 4	
	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	

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

AQ10

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

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)

Variable	Strategy 4
QIC	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)

AQ7

AQ8

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.

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, 25, 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 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.

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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.

6. Electronic supplementary material

Below is the link to the electronic supplementary material.

Supplementary material 1 (DOC 411 kb)

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