Acta Diabetologica (2019) 56:995–1003
https://doi.org/10.1007/s00592-019-01332-7

ORIGINAL ARTICLE

Different treatment forms of type II diabetes and the risk of dementia in German health claims data

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Received: 31 December 2018 / Accepted: 22 March 2019 / Published online: 22 May 2019

Abstract

Aims The association between type II diabetes (T2D) and increased all-cause dementia risk is well established. However, to date, there is no definite proof that a specific therapy for diabetes can halt a progress of cognitive decline. Therefore, we analyzed a large longitudinal random sample of German health claims data to focus on associations between T2D and dementia and to elucidate the role of different treatment forms of T2D on the risk for dementia.

Methods We used a longitudinal random sample ($n = 250{,}000$) of claims data of the largest public sickness fund in Germany, the Allgemeine Ortskrankenkasse (AOK). Dementia was defined as ICD-10 codes G31.0, G31.82, G23.1, F00, F01, F02, F03, and F05, and T2D was defined as E11–E14. We performed Cox proportional hazard models to explore the transition into dementia and to calculate the relative risk of dementia dependent on T2D and different T2D treatment forms.

Results All models were adjusted for sex, age, and each patient's history of depression, renal insufficiency, and cardiovascular comorbidities. Non-pharmacologic-treated diabetics showed a 23% increased dementia risk ($p < 0.001$) and oral ADM-treated diabetics showed a 16% increased risk ($p < 0.001$). Insulin-dependent diabetics is still the highest dementia risk (40%; $p < 0.001$) and obesity additionally attenuated this risk (75%; $p < 0.001$) increased risk.

Conclusions We found that diabetes is an independent risk factor for all-cause dementia. An increased risk for dementia in insulin-dependent and obese subjects with diabetes was evident. Longitudinal studies on the effect of different forms of therapy and weight reduction are needed to verify the results of this study.

Keywords Dementia · Diabetes · Obesity · Health claims data · Treatment · Risk factors

Managed by Massimo Porta.

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Introduction

With a prevalence of 5–7%, dementia is among the leading causes of dependency and disability in the elderly population [1]. Identification of potential risk factors and mechanisms involved in cognitive decline are essential for the development of novel prevention and therapy strategies [2].

The association between type 2 diabetes (T2D) and all-cause dementia is well established [3–5]. Brain atrophy, white and gray matter changes, and damage of the blood–brain barrier have been observed in subjects with T2D [6–9]. However, little is known about the possible role of T2D in the development of nonvascular dementia, as cerebrovascular disease is believed to play a leading role in neurodegeneration in T2D [3, 5]. Nevertheless, there is an association between T2D and other forms of dementia, such as Alzheimer`s disease or mixed forms of dementia [3, 10].

Brain atrophy has been observed in T2D, which can occur independently of arteriosclerotic alterations [11–13].

With regard to possible pathophysiological mechanisms, hyper- and hypoglycemic conditions are believed to serve as potential candidates linking T2D with dementia, which could drive the joint appearance of these diseases in a bidirectional manner [13–15]. In addition, obesity seems to play an important role as a consequence of intensive insulin therapy and/or associated with physical inactivity [14].

To date, there is no definite proof for a specific therapy of diabetes to halt a progress of cognitive decline [16]. It is even assumed that, in some cases, especially when cognitive decline has progressed, medication may even have negative consequences, possibly due to more frequent episodes of hypoglycemia [17–19]. There are still sparse data on this state of affairs, although current research provides first hints that specific treatment forms may be beneficial in some patients [20–22].

Here, we analyzed a large longitudinal random sample of German health claims data (data of the Allgemeine Ortskrankenkasse AOK health insurance) to elucidate a possible role of different treatment forms of T2D on the risk of dementia. We studied the possible role of obesity, cerebrovascular diseases, arterial hypertension, hyperlipoproteinemia, micro- and macrovascular diseases, renal insufficiency, and depression in this relationship.

Data and methods

Sample and study design

We used a longitudinal sample of claims data of the largest public sickness fund in Germany, the Allgemeine Ortskrankenkasse (AOK). A random sample ($N = 250{,}000$) of insured persons aged 50 years or above with at least 1 insured day in the first quarter of 2004 was drawn. The data represent outpatient care information, and include information on sex, year, and month of birth, year, and month of death if applicable, a diagnosis part of all inpatient and outpatient diagnoses coded by ICD-10 as well as all filled prescriptions of medications on a quarterly basis. The study was partially funded by the "Deutsches Zentrum für Neurodegenerative Erkrankungen e.V" (DZNE).

Definition of incident dementia cases

Incidence dementia cases were determined in the 5-year period from the first quarter of 2006 through the last quarter of 2010 for all subjects who did not have any dementia diagnosis in the years 2004 and 2005. Dementia was defined as having one of the ICD-10 codes G31.0, G31.82, G23.1, F00, F01, F02, F03, and F05. We did not differentiate by subtype of dementia as over 50% of all incident diagnoses were coded as "unspecified dementia" (F03). All cases without a valid dementia diagnosis (see section "Validation of dementia diagnoses" below) in 2004 and 2005 and a first valid dementia diagnosis in 2006 or later are assumed to represent incident dementia cases.

Definition of diabetes mellitus and treatments

We defined a time-dependent variable distinguishing between person-times without a diabetes diagnosis, person-times with a diabetes diagnosis but without a prescription of oral antidiabetic medication (ADM) whom we labeled as "non-pharmacologic treated", person-times with a diabetes diagnosis and a treatment with oral ADM, and person-times with a diabetes diagnosis and treatment with insulin. Type 2 Diabetes (T2D) was defined as having one of the ICD-10 codes E11–E14. All patients ever having an E10 (type 1 diabetes) diagnosis in their medical history between 2004 and 2010 were excluded from our analyses. Information on medical drug use was obtained from the documented filled prescriptions of the outpatient sector. Active ingredients were coded by the German version of the Anatomical Therapeutic Chemical (ATC) classification system. Diabetes patients with prescriptions of oral ADM (ATC code: A10B) and insulin (ATC code: A10A) were differentiated. The treatment status of the diabetes patients was entered as time-dependent variable.

Definition of obesity

We defined obesity as having the ICD-10 code E66. This variable was treated as time-dependent variable.

Covariates

All models were adjusted for sex, age, and each patient's history of depression (F32, F33, and F34.1), renal insufficiency (N17–N19), and cardiovascular comorbidities, such as cerebrovascular diseases (I60–I69), hypertension (I10–I15), ischemic heart diseases (I20–I25), atrial fibrillation (I48), and hypercholesterolemia (E78.0). The variables take the value of one from the first time, comorbidity was noted in the data, and zero otherwise. With the exception of sex, all covariates were defined as time-dependent variables.

Validation of dementia diagnoses

Since large data of public sickness funds are created for the purpose of cost calculation and reimbursement and are subject to legal changes and data-handling procedures of the health insurers, a two-stage validation procedure was applied to internally validate the dementia diagnoses. This procedure

excluded false-positive diagnoses of dementia which, otherwise, would lead to an overestimation of the true dementia incidence [23]. First, diagnoses from the outpatient sector were taken into account only if the physician had indicated them as verified. Diagnoses from the inpatient sector had to be either discharge or secondary diagnoses. Second, dementia diagnoses had to be confirmed by co-occurrence. Diagnoses were considered valid if they occurred simultaneously in the inpatient and outpatient sectors, or if at least two physicians made a diagnosis of dementia in the same quarter. Furthermore, dementia diagnoses were considered valid by a co-occurrence over time, with all 5 study years being used as the validation period. If the quarter with the first dementia diagnosis was the last observational quarter (due to death or end of the study), the case was considered valid, even though the initial diagnosis could not be confirmed by a second diagnosis.

Statistical analyses

We performed Cox proportional hazard models to explore the transition into dementia and to calculate the risk of an incident dementia diagnosis dependent on the diabetes status, the presence of obesity, and the other covariates. As the proportional hazard assumption was not fulfilled for two control variables in the full model, we performed a stratified model with cerebrovascular diseases and depression as strata variables.

The period of analysis started on January 1st, 2006 and ended at the time point of the first dementia diagnosis. In the case of no dementia diagnosis, analysis time was censored at the time of death, the time of leaving the health insurance or the end of the study period, December 31st, 2010, whatever occurred first. As we had information on diagnoses on a quarterly basis, the incidence of dementia was set in the middle of the respective quarter (which corresponded to 1.5 months in terms of analysis time). In the case of death, the time of death was assumed to be in the middle of the respective month (0.5 months in terms of analysis time). Furthermore, we calculated a model with an interaction term between diabetes status and obesity to explore their combined effects on dementia incidence.

Results

Basic characteristics

Of the 250,000 subjects of the original sample, 142,012 persons aged 60 years and above were found to be free of dementia until 2006 and without diagnosis of type 1 diabetes (E10) in their medical history. They totally contributed 612,027 person-years at risk. 12,784 subjects had an incident dementia diagnosis during the observational period. Characteristics of the study population and dementia incidence rates are given in Table 1. Dementia incidence increased exponentially with increasing age (Fig. 1a), which was also true for the prevalence of diabetes up to the 9th decade of life (Fig. 1b). At age 60, 15% of the subjects suffered from diabetes; at age 88, 34% suffered from diabetes, although with a decline at higher ages. Insulin-dependent diabetes patients with a mean age of 73.5 ± 7.2 years constituted the smallest group among the diabetes patients. With increasing age, the share of non-pharmacologic treated diabetes patients increased resulting in the group with the highest mean age of 75.3 ± 7.4 years. Diabetes patients treated with oral ADM had a mean age of 73.9 ± 6.8 years. As expected, persons without a diabetes diagnosis had the lowest dementia incidence with 17.8 new cases per 1000 person-years compared to diabetes patients without medical treatment (33.5 new cases), diabetes patients treated with oral ADM (23 new cases), and insulin-dependent diabetes patients (28.4 new cases). Surprisingly, subjects with an obesity diagnosis had a significantly lower dementia incidence with 19.3 new cases per 1000 person-years compared to non-obese subjects (21.1 new cases). However, this is mainly caused by the difference in the age distribution (see model results). Patients with hypertension (23.7 new cases) had a significantly higher dementia incidence compared to persons without hypertension (12.1 new cases). Similarly, depressed persons and patients with renal insufficiency had significantly increased incidence rates of dementia. However, in contrast, hypercholesterolemia was associated with a significantly reduced dementia incidence rate.

Model results

Compared to persons without diabetes, non-pharmacologically treated diabetes patients had a 46% increased risk of dementia ($p < 0.001$) when controlled for sex and age (Table 2, Model 1). Diabetic patients with an oral ADM treatment had a 25% increased dementia risk ($p < 0.001$) and insulin-dependent diabetes patients had the highest risk of dementia (Hazard ratio $HR = 1.52$, $p < 0.001$). Moreover, obesity was associated with an increased risk of dementia ($HR = 1.11$, $p < 0.001$) when controlled for age and sex (Table 2, Model 1). In fully adjusted Model 2, however, statistically significance for the dementia-obesity association vanished. Moreover, a considerable proportion of the negative effect of diabetes on dementia was explained by the presence of cardiovascular disease, renal insufficiency and depression (Model 2). However, effects were not fully attenuated with non-pharmacologically treated diabetes patients having a 23% increased dementia

Table 1 Characteristics and dementia incidence of the study population

Variable	Person-years at risk	Subjects with dementia	Dementia incidence rate per 1000 person-years	
	N = 612,027	*N* = 12,784	Rate	95% CI
Sex				
Male	246,981	4145	16.78	16.28–17.30
Female	365,047	8639	23.67	23.17–24.17
Age group				
60–64	55,528	175	3.15	2.72–3.65
65–69	155,462	723	4.65	4.32–5.00
70–74	154,974	1537	9.92	9.43–10.43
75–79	116,238	2548	21.92	21.09–22.79
80–84	77,958	3327	42.68	41.25–44.15
85–89	38,010	2794	73.51	70.83–76.28
90–94	10,464	1195	114.20	107.91–120.87
95+	3,393	485	142.96	130.78–156.26
Diabetes				
No diabetes diagnosis	444,171	7883	17.75	17.36–18.14
Non-pharmacologic-treated diabetes patients	82,257	2752	33.46	32.23–34.73
Treated diabetes patients, oral ADM	52,054	1197	23.00	21.73–24.34
Treated diabetes patients, insulin	33,545	952	28.38	26.63–30.24
Obesity				
No	544,094	11,472	21.08	20.70–21.47
Yes	67,934	1312	19.31	18.30–20.39
Hypertension				
No	146,776	1773	12.08	11.53–12.66
Yes	465,251	11,011	23.67	23.23–24.11
Hypercholesterolemia				
No	425,363	9212	21.66	21.22–22.10
Yes	186,665	3572	19.14	18.52–19.77
Cerebrovascular diseases				
No	490,822	6519	13.28	12.96–13.61
Yes	121,205	6265	51.69	50.43–52.99
Ischemic heart diseases				
No	395,815	6062	15.32	14.93–15.71
Yes	216,213	6722	31.09	30.36–31.84
Atrial fibrillation				
No	539,412	9264	17.17	16.83–17.53
Yes	72,616	3520	48.47	46.90–50.10
Depression				
No	498,662	8657	17.36	17.00–17.73
Yes	113,366	4127	36.40	35.31–37.53
Renal insufficiency				
No	568,655	10,685	18.79	18.44–19.15
Yes	43,373	2099	48.39	46.37–50.51

CI confidence interval, *ADM* antidiabetic medication, Source: AOK claims data 2004–2010

risk ($p < 0.001$) and oral ADM-treated diabetes patients having a 16% increased risk ($p < 0.001$). Nevertheless, insulin-dependent diabetes patients had still the highest dementia risk (HR = 1.40, $p < 0.001$) (Model 2).

Including an interaction effect in Model 2 permitted the analysis of the combined effect of diabetes and obesity on dementia risk. Within each diabetes group, obesity increased the risk of dementia; however, it did not differ statistically

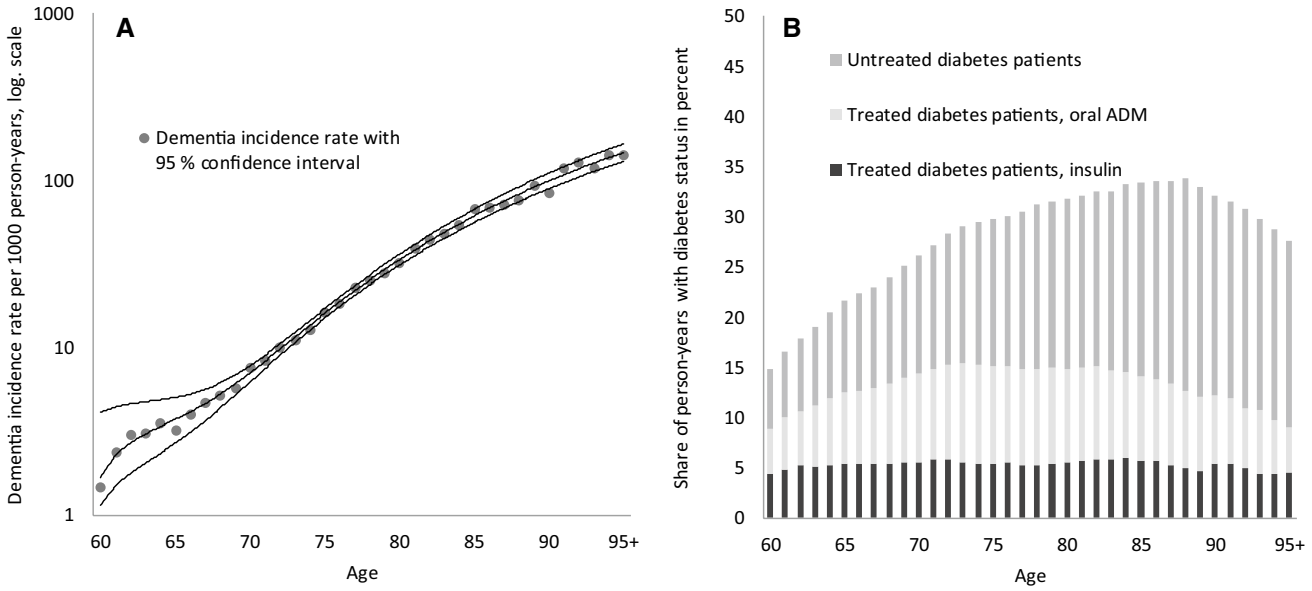

Fig. 1 Dementia incidence rate per 1000 person-years (**a**) and share of person-years with diabetes status in percent (**b**)

Table 2 Hazard ratios of dementia estimated by Cox proportional hazard models

Variable	Model 1*		Model 2**	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Treatment status diabetes				
No diabetes diagnosis	1.00		1.00	
Non-pharmacologic-treated diabetes patients	1.46 (1.39–1.52)	< 0.001	1.23 (1.17–1.28)	< 0.001
Treated diabetes patients, oral ADM	1.25 (1.18–1.33)	< 0.001	1.16 (1.09–1.24)	< 0.001
Treated diabetes patients, insulin	1.52 (1.42–1.62)	< 0.001	1.40 (1.31–1.50)	< 0.001
Obesity	1.11 (1.05–1.18)	< 0.001	1.05 (0.99–1.11)	0.093

Source: AOK claims data 2004–2010

CI confidence interval, *ADM* antidiabetic medication

*Model is adjusted for sex and age

**Model is adjusted for sex, age and comorbidities, and is stratified by the presence of cerebrovascular diseases and depression

from the non-obese individuals with the exception of insulin-dependent diabetes patients. Here, obese insulin-dependent diabetes patients had a significantly increased risk of dementia compared to non-obese insulin-dependent diabetes patients. Controlled for comorbidities, obese non-pharmacologic-treated diabetes patients had a 34% ($p < 0.001$) increased risk and obese diabetes patients with oral ADM had a 20% ($p = 0.008$) increased risk for dementia as compared to persons without a diabetes diagnosis. Obese insulin-dependent diabetes patients had a 75% ($p < 0.001$) increased risk (Fig. 2).

Discussion

In our analysis of a large ($N = 250{,}000$) longitudinal random sample of the largest German health claims data, we found that subjects with T2D had an increased risk of dementia compared to persons without a diagnosis of diabetes. The risk increased over the different types of treatment with oral ADM-treated diabetes patients revealing the lowest risk, followed by non-pharmacologic-treated and insulin-dependent

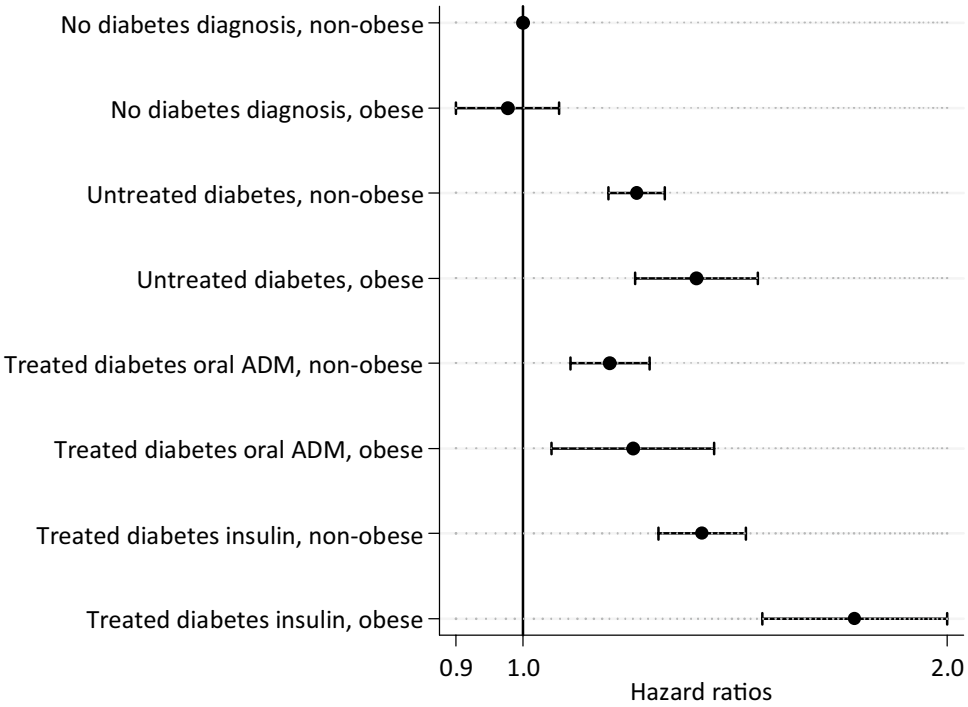

Fig. 2 Hazard ratios of dementia dependent on diabetes status and obesity controlled for sex, age, and comorbidities. Source: AOK claims data 2004–2010

diabetes patients. Moreover, we observed that obesity exerted an additional and independent effect on the risk of dementia, solely in insulin-dependent diabetes patients.

The association between T2D and all-cause dementia (Alzheimer's disease and vascular dementia) has been described earlier and our results are in line with those previous findings [13, 24–26]. To date, control of modifiable cardiovascular risk factors, nutrition, and sports seem to be the most promising approaches to prevent dementia [26–29]. With respect to T2D, however, there is no definite proof that a specific therapy for diabetes can halt a progress of cognitive decline [16]. Whether a strict medical drug control setting in middle years seems preventative is also unknown [13, 30]. Recent studies started to address this issue and suggested that some treatment forms may result in better outcomes regarding cognitive function and the incidence of dementia [20–22]. This assumption is supported by neuropathological studies, which demonstrated reduced amyloid load in T2D patients with antidiabetic treatment compared to not-treated diabetes patients [31]. In line with this observation, our study revealed that subjects who received an oral antidiabetic treatment had the lowest risk for the development of dementia compared to non-pharmacologically treated and insulin-dependent diabetes patients. With respect to medical treatments of T2D, recent studies, see a protective effect of metformin against the development of dementia in T2D [32]. Moreover, Xu et al. found that T2D was associated with vascular dementia in a study cohort of 1,301 elderly subjects. They found that this association was strongest in insulin-treated subjects [33]. This is also in line with our findings. However, this association contradicts the current view that hyperinsulinemia may exhibit an increased risk for the development of dementia [34, 35].

Insulin-induced hypoglycemia might be a crucial aspect in this context. A not negligible aspect with respect to the different treatment forms of T2D is the potential bidirectional association between T2D with dementia, especially with respect to the self-management of T2D in dementia [13]. In our analysis, we found a higher risk of dementia in insulin-dependent diabetes patients in the presence of obesity. The reason is unclear, but may be related to the fact that self-administrated T2D-therapy may become insufficient as a consequence of cognitive impairments. Therefore, the results regarding the risk of dementia with respect to oral ADM or insulin therapy have to be interpreted with caution, as no information about adherence to therapy or markers of T2D severity such as HbA1c was available in our cohort.

When considering the links between T2DM and dementia, it is important to consider the possible role of other diseases which are commonly associated with both T2D and dementia. To clarify this, regression models were adjusted for known risk factors associated with dementia and T2D in our analysis. In the current analysis, we have focused especially on obesity as a common risk factors associated with both T2D and dementia. Obesity is a known risk factor for T2D, and insulin therapy in T2D is associated with weight gain [36, 37]. Notably, in contrast to T2D, there are conflicting data regarding the obesity–dementia association in different lifespans and it is not evident if weight gain in insulin-dependent diabetes patients attenuates the risk for

dementia [38–40]. Thus, the interpretation of obesity as a risk factor for the development of dementia is challenging in subjects with T2D and insulin therapy. Metabolic alterations as observed in obese subjects might favor the development of dementia, especially in midlife or in early stages of T2D [40–42]. Admittedly, a significant reduction in weight is generally observed in the prodromal stage of dementia, a few years before diagnosis. Midlife obesity has consistently been associated with risk of dementia, this has, however, not been observed in elderly subjects, and the influence of different therapy regimes in T2D on these findings has not intensively been researched in elderly subjects [40, 42]. In that regard, we found that subjects with intense treatment had the highest risk for dementia; in particular, diabetes patients with insulin therapy and obesity. From this, it could be deduced that weight control could be one aspect in both treatment of T2D and prevention of cognitive decline. This seems suitable in the early stages of cognitive decline, as weight loss is also seen as a negative consequence of dementia. Thus, neither obesity nor the treatment of insulin itself but hypoglycemic conditions and severity of diabetes could pave the way for future dementia. Nevertheless, recent research suggests that brain alterations are more progressive in T2D patients, if they are obese and brain imaging data were not available for the current analysis [43, 44].

Arterial hypertension, hyperlipoproteinemia, micro- and macrovascular diseases, and depression are known to play important roles in the development of cognitive disorders [45–49]. This is evident also in the results of our study. Patients with hypertension had a significantly higher dementia incidence compared to persons without hypertension. As hypertension is also a strong risk factor for cerebrovascular diseases, such as stroke, ischemic heart diseases, and atrial fibrillation, the gross effect of hypertension vanishes when controlling for those diseases. Notably, no information about efficiency of antihypertensive treatment was available. Thus, subjects with diagnosed hypertension might not be treated to target, which could contribute to the current findings. Surprisingly, hypercholesterolemia, an evident risk factor for cardiovascular disease, was associated with reduced risk for dementia. A missing link between hypercholesterolemia with dementia in subjects with T2D has been found previously, in particular in elderly subjects [30, 50]. In our cohort, this might also be due to sufficient treatment of hypercholesterolemia. Statin therapy has been suggested to be preventive in all types of dementia [51]. However, interpretation of our results is difficult, because definition of hypercholesterolemia was solely based on the ICD E78.0 which does not differentiate between hypercholesterolemia due to elevated LDL-cholesterol concentrations and other forms of hyperlipoproteinemia.

Limitations and strengths of the study

Our results are subject to limitations. An important issue is the study population. Subjects insured in the AOK do not represent the German population in their entirety. There is a compulsory health insurance for all people residing in Germany. The majority of the population is insured under a statutory insurance plan (like the AOK provides); however, a smaller number of subjects, usually with higher incomes, have the option to insure themselves privately. Thus, subjects insured in the AOK health insurance system are on average of a lower socioeconomic level compared to other compulsory insurances. Moreover, our analyses relied on health claims (outcome) data with diagnosis of diseases based on ICD codes. Thus, there were no precise measurement data of e.g. “height” and “weight” for the definition of obesity. These and other diseases may have been underdiagnosed or inaccurately encoded by the treating physicians. This assumption is supported due to the fact that more than 50% of dementia diagnoses were coded as “unspecific”. Moreover, alterations in diagnoses may not compulsorily reflect real changes in the prevalence or incidence of the according diseases. However, we tried to overcome at least part of this problem by applying an internal validation strategy. The group of persons without a diabetes diagnosis, which is used as reference group in our analyses, consisted of persons without diabetes and persons with undiagnosed diabetes that are subject to an increased dementia risk as an effective glycemic control is missing here. Thus, our effect sizes are potentially underestimated. We cannot rule out that the onset of dementia is related to the duration and severity of diabetes which correlates with the treatment form. However, as we use time-varying variables, diabetes patients can change the treatment group over time. Immortal time bias can be ruled out. Furthermore, sensitivity analyses showed that there is no time-related effect between first diabetes diagnosis and dementia incidence in our data. In addition, there are some disease states, which could play a role, but were not analyzed. For example, hyponatremia, endocrinopathies, or vitamin deficient might mimic cognitive impairment in the absence of dementia, and although we adjusted for a number of confounders, these disease states are not well reflected by the current data set and, thus, were not included.

As risk factors like diabetes and hypoglycemic conditions due to medication, but also cardiovascular parameters can favor the development of dementia, the question arises how treatment or prevention of dementia is conceivable. However, there are currently no sufficient data, nor can our study clarify this question. For example, life-style changes or a well-controlled diabetes setting by medication could be approached to treat or prevent dementia in patients with T2D [5].

Our analyses rely on a large sample size. We were able to analyze longitudinal data and 12,784 persons had an incident dementia diagnosis during the observation period, which allows us to draw conclusions on causality. However, different mechanisms may drive the associations found. As already stated, it is likely that the relationship between T2D and Alzheimer's disease is different from that of vascular dementia with T2D. Our data do not allow a specific examination of individual forms of dementia, since dementia was mostly coded as "unspecified dementia" in our dataset. Nevertheless, health claims data are only marginally biased due to attrition for reasons other than death as the data are complete over time and the rate of change between public health insurance funds is low, especially at the oldest ages. The medical diagnoses were not prone to recall bias. Study participants were not recruited, so that selection bias by health care providers or self-selection into the study can be ruled out. Moreover, all insured individuals, regardless of their functional and cognitive status, were included in the study.

Conclusion

In the present analysis of a large longitudinal random sample of German health claims data, we found that diabetes is an independent risk factor for all-cause dementia. We found that different treatment forms of T2D result in different incident rates of dementia with insulin-treated subjects revealing the highest risk for dementia, particularly if they are obese. These results underline that different treatment forms may affect the development of dementia and weight gain seems to intensify this effect. Nevertheless, large and longitudinal intervention trials with detailed drug information are required to enlighten if well-controlled antidiabetic drug intervention and weight reduction could prevent the development of cognitive decline.

Acknowledgements We are grateful to the Scientific Research Institute of the AOK, WIdO, for providing the data. We thank Dr. Maik Gollasch for a critical reading of the manuscript.

Compliance with ethical standards

Conflict of interest Dr. Steinhagen-Thiessen reports grants and personal fees from Sanofi, personal fees from MSD, Fresenius, personal fees from Amgen and Chiesi, outside the submitted work. Dr. Demuth reports grants from Sanofi, personal fees from uniQure biopharma B.V., outside the submitted work. Prof. Doblhammer-Reiter recieved honoraries from Eli Lilly and Novartis not related to the study.

Ethical approval This study involving retrospective, anonymized claims data falls outside the scope of the Declaration of Helsinki and did not require ethical review.

Human and animal rights disclosure This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent For this type of study formal consent is not required.

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