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Increased incidence of neurodegenerative diseases in Finnish individuals with type 1 diabetes

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ABSTRACT

Introduction Diabetes is linked to neurodegenerative diseases (NDs), but data in type 1 diabetes are scarce. Our aim was to assess the standardized incidence ratios (SIRs) of different NDs in type 1 diabetes, and to evaluate the impact of diabetic vascular complications and age at diabetes onset.

Research design and methods In this observational cohort study, we included 4261 individuals with type 1 diabetes from the Finnish Diabetic Nephropathy study, and 11 653 matched population-based controls without diabetes. NDs were identified from registers until the end of 2017. Diabetic complications were assessed at the baseline study visit. SIRs were calculated from diabetes onset, except for impact of complications that was calculated from baseline study visit.

Results The SIRs for NDs were increased in type 1 diabetes: any dementia 2.24 (95% CI 1.79 to 2.77), Alzheimer's disease 2.13 (95% CI 1.55 to 2.87), vascular dementia 3.40 (95% CI 2.08 to 5.6), other dementias 1.70 (95% CI 1.22 to 2.31), and Parkinson's disease 1.61 (95% CI 1.04 to 2.37). SIR showed a twofold increased incidence already in those without albuminuria (1.99 (1.44–2.68)), but further increased in presence of diabetic complications: kidney disease increased SIR for Alzheimer's disease, while cardiovascular disease increased SIR for both Alzheimer's disease and other dementias. Diabetes onset <15 years, compared with ≥15 years, increased SIR of Alzheimer's disease, 3.89 (2.21–6.35) vs 1.73 (1.16–2.48), p<0.05, but not the other dementias.

Conclusions ND incidence is increased 1.7–3.4-fold in type 1 diabetes. The presence of diabetic kidney disease and cardiovascular disease further increased the incidence of dementia.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ There is evidence of a link between type 1 diabetes and cognition decline, but less is known whether this will translate into an increased risk of neurodegenerative diseases (ND).

⇒ The impact of vascular complications of diabetes on the incidence of NDs is not known.

WHAT THIS STUDY ADDS

⇒ With our study setting we could assess the standardized incidence ratio of different NDs since diabetes onset onward with long follow-up period.

⇒ As a novel finding, our results indicate that the incidence of NDs was increased even in individuals without vascular complications, but the presence of vascular complications further modified this risk.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ All NDs, especially dementias, increase the burden of treatment of type 1 diabetes in several ways. Further investigations are needed to identify the risk factors and causes for NDs in type 1 diabetes, to be able to evaluate the benefit of screening and ultimately improve brain health in individuals with diabetes.

INTRODUCTION

The life expectancy of individuals with type 1 diabetes has improved in recent years. In the Pittsburgh Epidemiology of Diabetes Complications study, the life expectancy at birth was 15 years longer among individuals with diagnosed type 1 diabetes during 1965–1980 compared with those diagnosed during 1950–1964.[1] In a recent Finnish register study, the survival probability was further improved in those diagnosed with type 1 diabetes in 2000–2017, compared with 1964–1999.[2]

The main reason for the life expectancy improvement is the improved prevention and treatment of the chronic complications of diabetes.[1 3 4] The improved life expectancy exposes, however, individuals with type 1 diabetes to aging-related diseases, and conditions, such as cognitive impairment, which may have an impact on well-being and safe self-management.[5] Type 1 diabetes is linked to milder degrees of cognitive decline.[5–8] The identified risk factors include poor glycemic control, elevated blood pressure,[6 8] depression,[9] sleeping disorders,[10] and longer duration of type 1 diabetes.[6 11] Chronic

hyperglycemia and diabetic ketoacidosis during childhood are especially harmful to the developing brain,[5 7 8] and these may be linked to reduced brain growth.[12] The cognitive changes are usually mild, appearing typically as a decline of psychomotor and mental efficiency and flexibility, as well as problems with verbal episodic memory and language.[5 7 8]

In brain MRI studies, type 1 diabetes has been linked to signs of focal brain atrophy and cerebral small-vessel disease.[13 14]

Whether these early signs of cognitive impairment translate into increased risk for different neurodegenerative diseases (ND) is not clear. We know that in type 2 diabetes, the overall risk of dementia is increased 1.5–2-fold,[15 16] but less is known about type 1 diabetes. There is also some evidence that type 2 diabetes is associated with increased risk of Parkinson's disease,[17] but studies in type 1 diabetes show conflicting results.[18–20]

The aim of this study was to examine whether the incidences of different NDs are increased in individuals with type 1 diabetes compared with the background population without diabetes. To achieve this goal, we calculated standardized incidence ratios (SIRs) between these two groups. We also evaluated the impact of diabetic kidney disease, severe retinopathy, history of cardiovascular events, and age at onset of type 1 diabetes on the incidences of NDs.

RESEARCH DESIGN AND METHODS

Study design and participants

This study is part of the nationwide Finnish Diabetic Nephropathy (FinnDiane) study, a prospective cohort study, initiated in 1997.[21] The participants were recruited at hospitals and primary healthcare diabetes clinics all around Finland in 1997–2017 (online supplemental table 1).

Study cohort

For this study, we included all 4261 adult FinnDiane study individuals with type 1 diabetes, with their baseline visit prior to December 31, 2017, without NDs before their diabetes diagnosis, and with matched controls available (figure 1). For 700 individuals, we did not have matched controls available. Their clinical characteristics compared with the current study cohort are presented in online supplemental table 2. Those with missing controls had their first FinnDiane study visit more recently (median calendar year 2014 vs 2000). They were older, had an earlier diabetes onset, and thus a longer diabetes duration. Furthermore, they were less often current smokers, had better metabolic profile (eg, glycemic control, diastolic blood pressure, and lipid profile), but more diabetic complications at baseline visit. Only 43 (6.2%) excluded participants died during follow-up versus 845 (19.8%) in the study group. They did not differ with respect to NDs during follow-up, except for less Alzheimer's disease in those excluded.

Control cohort without diabetes

For each FinnDiane participant that entered the study before 2009, three population-based controls without diabetes were retrieved from the Finnish Population Register Centre, by matching for age, sex, and place of residence at the time of diagnosis of type 1 diabetes (figure 1). The Finnish Population Registry contains information such as birth date, sex, and place of residence of Finnish citizens and foreign citizens residing in Finland. For the 11 653 controls, only register-based data were available, and controls were diabetes free during the entire follow-up period.

Procedure

FinnDiane baseline visit

The FinnDiane baseline visit included a thorough evaluation by the participant's attending physician, including anthropometrics, office blood pressure measurements,

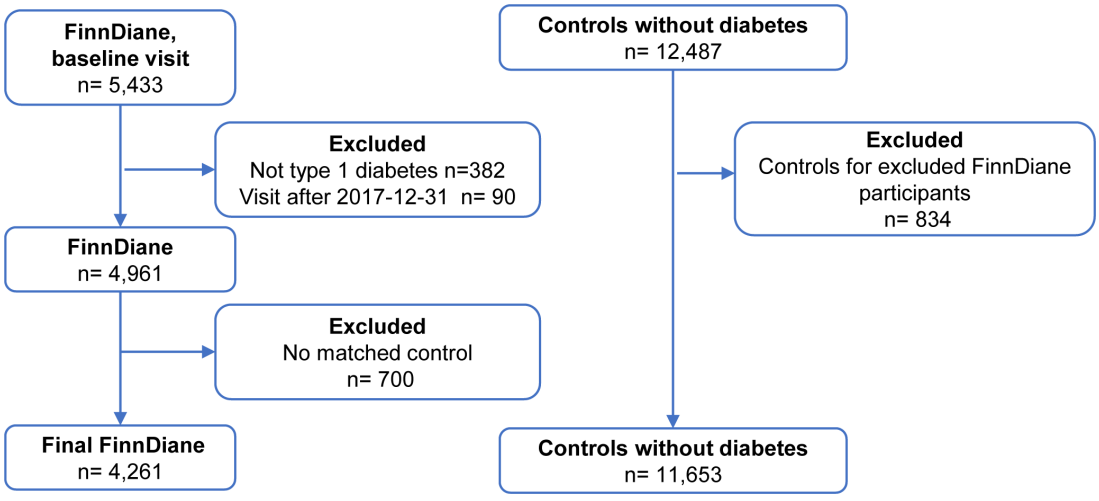

Figure 1 Selection of the Finnish Diabetic Nephropathy (FinnDiane) cohort and their matched controls without diabetes.

history of diabetes and review of complications status, blood samples and urine collections, as well as questionnaires about lifestyle, such as smoking habits.[21] Definition of type 1 diabetes was diabetes onset before 40 years of age and insulin initiation within 1 year of diagnosis. Blood was drawn and analyzed for HbA1c, creatinine, lipids, and lipoproteins. Estimated glomerular filtration rate (eGFR) was estimated with the Chronic Kidney Disease Epidemiology Collaboration formula. Albuminuria was defined based on two out of three urine collections into normal urinary albumin excretion rate (AER <20 µg/min or <30 mg/24 hours), moderate albuminuria (AER 20–200 µg/min or 30–300 mg/24 hours), or severe albuminuria (AER >200 µg/min or >300 mg/24 hours). Kidney replacement therapy included ongoing dialysis or history of kidney transplantation. Diabetic kidney disease was defined as any albuminuria or kidney replacement therapy. Severe diabetic retinopathy was defined as a history of retinal photocoagulation. Cardiovascular disease included history of acute myocardial infarction, coronary revascularization, stroke, lower limb revascularizations, or amputations.

Follow-up data

Follow-up data were retrieved for all participants from the Care Register for Health Care (Finnish Institute for Health and Welfare), Register of Primary Health Care Visits (Finnish Institute for Health and Welfare), and the Finnish Cause of Death Register (Statistics Finland). Data from the Register of Primary Health Care Visits are available only since 2011. These three registers cover all International Classification of Diseases (ICD) diagnoses of healthcare visits, hospitalization, specialized outpatient care and deaths in Finland. The diagnoses we registered were Alzheimer's disease (ICD-8/9 code 3310; ICD-10 codes G30 and F00), vascular dementia (ICD-9 code 4378; ICD-10 code F01), other dementias (ICD-8 code 290; ICD-9 codes 290, 3212, 3311, and 3312; ICD-10 codes G31, F02, and F03), and Parkinson's disease and other extrapyramidal disorders (ICD-8/9 codes 3320–3321 and 3330; ICD-10 codes G20 and G21). For all diagnoses, we registered the time point when the diagnosis of the specific ND occurred for the first time. Any dementia was defined as any of Alzheimer's disease, vascular dementia, or other dementias. For analysis, Parkinson's disease and other extrapyramidal disorders were combined and denominated Parkinson's disease.

Follow-up began at the diagnosis of type 1 diabetes when evaluating the incidences of NDs and none of the participants were diagnosed with ND within 1 year from the diabetes diagnosis. For the impact of diabetic complications on NDs, the follow-up began at FinnDiane baseline visit, excluding those with NDs between diabetes diagnosis and FinnDiane study visit (n=5). Follow-up continued until a diagnosis of ND was made, death occurred, or the end of 2017 was reached. None of the FinnDiane participants moved abroad during the follow-up period, meaning full follow-up period for each participant.

Statistical analysis

Normally distributed continuous variables were analyzed with the t-test and presented as means±SD, and non-normally distributed with the Mann-Whitney U test and presented as median with IQR. Categorical variables were analyzed with the χ^2 test and presented as n (%).

To determine differences in the risk of NDs between individuals with and without type 1 diabetes, two approaches were applied. First, SIRs were calculated as ratios of observed and expected number of cases. The expected numbers in individuals with diabetes were derived by multiplying the number of person-years at risk by sex, age and period-specific incidence rates observed in the individuals without diabetes. The controls without diabetes were selected to match the type 1 diabetes cohort for sex, age, and place of residence at the time of diagnosis of type 1 diabetes, which means that the analyses for risk determination are accounted for in the analyses. No other confounders were included in the analyses. The 95% CIs were calculated assuming Poisson distribution. SIRs were calculated separately for different types of NDs, separately for childhood-onset diabetes (<15 years) and adult-onset diabetes (15–39 years) and according to

Table 1 Number of events, standardized incidence ratios (SIR), and subdistribution HRs (SHR) for different neurodegenerative diseases

Disease	Type 1 diabetes n=4261 n (%)	Controls, no diabetes n=11 653 n (%)	SIR (95% CI)	SHR (95% CI)	P value
Vascular dementia	18 (0.42)	15 (0.13)	3.40 (2.08 to 5.26)	2.87 (1.43 to 5.76)	0.003
Alzheimer's disease	44 (1.03)	43 (0.37)	2.29 (1.68 to 3.05)	2.51 (1.64 to 3.83)	<0.001
Other dementias	39 (0.90)	68 (0.58)	1.70 (1.22 to 2.31)	1.43 (0.96 to 2.12)	0.080
Any dementia	85	102	2.32 (1.86 to 2.86)	2.07 (1.55 to 2.75)	<0.001
Parkinson's disease	23 (0.50)	40 (0.34)	1.61 (1.04 to 2.37)	1.38 (0.82 to 2.32)	0.230

SHR is based on Fine and Gray competing risk analyses from the time of diagnosis of diabetes for participants with type 1 diabetes compared with controls without diabetes.
CI, Confidence Interval.

microvascular and macrovascular complications assessed at baseline visit.

Second, since the mortality is higher in individuals with type 1 diabetes than without, survival analyses by Fine and Gray competing risk analyses (with subdistribution HRs (SHRs)) were performed. Cumulative incidence figures were produced based on the Fine and Gray competing risk analyses.

Statistical significance was set at p<0.05. Analyses were performed using IBM SPSS Statistics V.25 software (IBM) and Statistical Analysis System V.9.4 (SAS Institute).

RESULTS

Of the 4261 participants with type 1 diabetes, 2226 (52.2%) were men and the median age at onset of diabetes was 13.9 (IQR 9.2, 22.1) years. The 11 653 controls without diabetes were matched for this sex and age distribution.

At the FinnDiane baseline visit, median age was 37.4 (28.7, 46.6) years, duration of type 1 diabetes was 21.4 years (12.0, 30.9), and mean HbA1c was 8.4±1.5% (69±16.3 mmol/mol). Diabetic kidney disease was present in 1605 (37.7%) of participants, and 1438 (34.4%) had a history of severe retinopathy and 493 (9.5%) had a history of cardiovascular events. During a median follow-up of 37.5 (28.5, 45.5) years from the time of diabetes diagnosis, 845 (19.8%) individuals with type 1 diabetes died, while the number of deaths was 1062 (9.1%) in the control cohort, p<0.001 (online supplemental table 2).

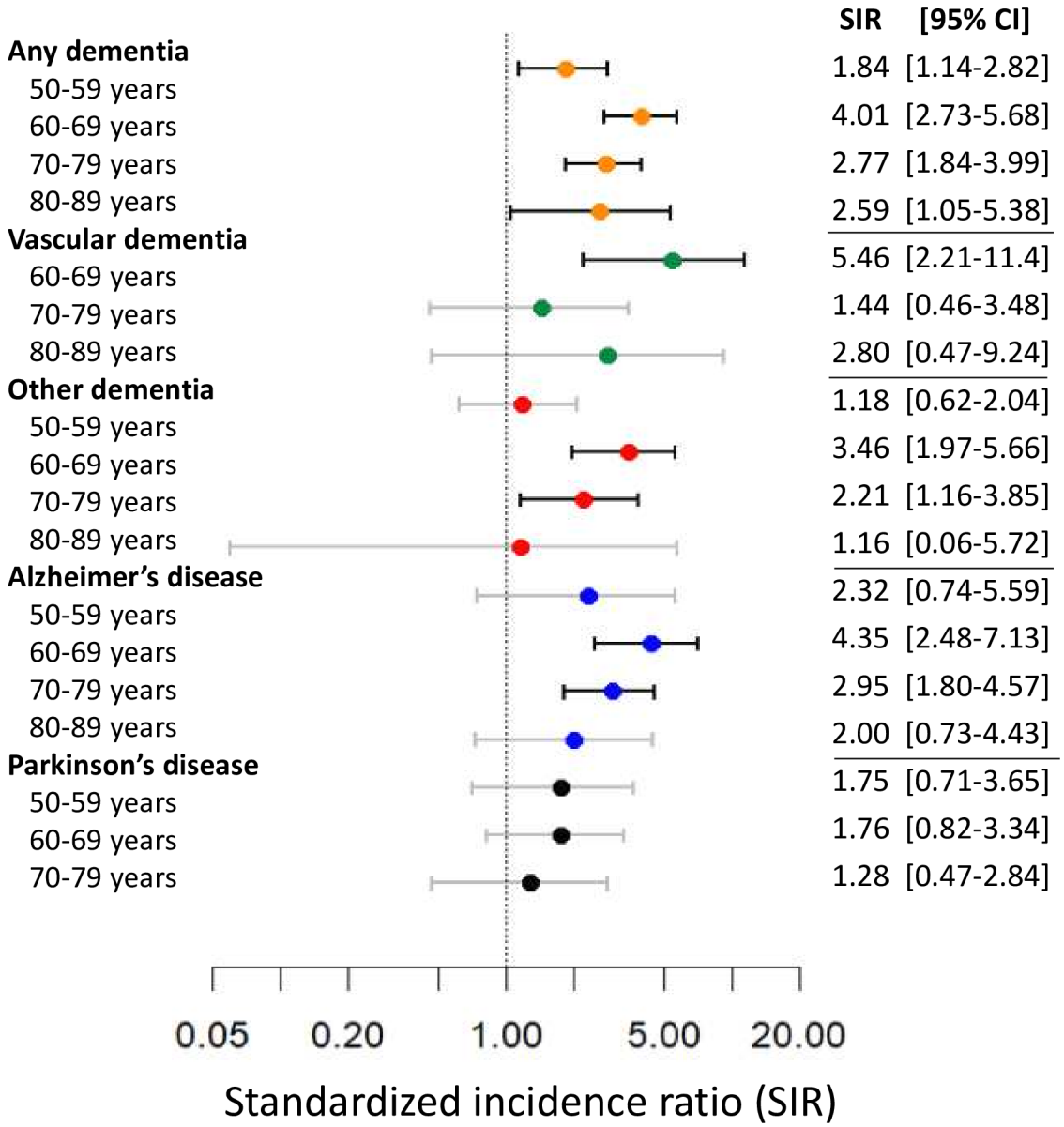

Figure 2 Standardized incidence ratios (SIRs) of neurodegenerative diseases between individuals with type 1 diabetes and controls without diabetes in 10-year age groups.

Risk of NDs in people with type 1 diabetes

The SIRs for the different NDs are presented in table 1 and divided by the age of the participants at the onset of ND in figure 2. Cumulative incidences for different NDs are provided in online supplemental figure 1 and median age at NDs in online supplemental table 2.

Competing risk of death

Also, the SHRs for the different NDs were higher in individuals with type 1 diabetes compared with individuals without diabetes, except for Parkinson's disease and other dementias (table 1).

Impact of vascular complications

The impact of diabetic vascular complications on SIRs of NDs is presented in table 2 comparing SIRs by presence and absence of diabetic complication at the FinnDiane baseline visit. The number of events in each group is provided in online supplemental table 3. The median follow-up time was 16.8 (14.0, 18.8) years. For vascular dementia, SIRs were increased both in the presence and absence of complications compared with control population, and similarly for Alzheimer's disease except for those without severe retinopathy. For other dementias, SIRs were increased only in the presence of any of diabetic complications, while SIR for Parkinson's disease was increased only in those with diabetic kidney disease.

Diabetic kidney disease was significantly associated with higher SIR of Alzheimer's disease, while cardiovascular disease was linked to higher SIR of both Alzheimer's disease and other dementias. Severe retinopathy was not associated with increased SIRs of any ND (table 2).

Impact of kidney disease severity

The worsening of diabetic kidney disease severity increased the SIRs of any dementia. SIR was increased in individuals with diabetes already in those with normal AER SIR of 1.99 (1.44–2.68), and 2.28 (1.24–3.88) in moderate albuminuria, 2.92 (1.66–4.78) in severe albuminuria, and 4.93 (2.40–9.04) in those with kidney replacement therapy. The between-group comparison was significant for those with kidney replacement therapy versus normal AER (SIR ratio 4.93, p=0.002).

Impact of age at onset of type 1 diabetes

Age at onset of type 1 diabetes did not have a major impact on most of the NDs (online supplemental table 4). The incidence of Alzheimer's disease was, however, significantly higher in those diagnosed under 15 years of age, compared with those diagnosed at 15 years or older, SIR 3.89 (2.21–6.35) vs 1.73 (1.16–2.48), p=0.001 for between-group comparison.

DISCUSSION

In this study of 4261 individuals with type 1 diabetes, the incidences of dementias were increased compared with the background population without diabetes. Our study setting enables us to assess the standardized incidences of

Table 2 Standardized incidence ratios (SIRs) for the different neurodegenerative diseases by the presence and absence of the different diabetic vascular complications

	Diabetic kidney disease			Severe retinopathy			Cardiovascular disease		
	SIR (95% CI)			SIR (95% CI)			SIR (95% CI)		
	Yes	No	SIR ratio	Yes	No	SIR ratio	Yes	No	SIR ratio
Vascular dementia	5.21 (2.54 to 9.56)	2.46 (1.08 to 4.87)	2.11 (0.70–6.68)	4.16 (2.25 to 7.07)	2.99 (1.10 to 6.63)	1.39 (0.45–5.03)	6.00 (2.63 to 11.87)	3.23 (1.70 to 5.61)	1.86 (0.61–5.25)
Alzheimer's disease	3.98 (2.00 to 5.76)	1.69 (1.12 to 2.46)	2.64* (1.27–5.29)	2.74 (1.74 to 4.11)	1.59 (0.97 to 2.46)	1.72 (0.87–3.43)	5.18 (2.95 to 8.48)	1.64 (1.10 to 2.36)	3.15* (1.53–6.23)
Other dementias	2.31 (1.41 to 3.58)	1.53 (0.92 to 2.40)	1.51 (0.73–3.11)	2.07 (1.32 to 3.11)	1.42 (0.79 to 2.37)	1.46 (0.70–3.17)	4.41 (2.51 to 7.23)	1.35 (0.87 to 2.01)	3.27* (1.55–6.69)
Parkinson's disease	2.62 (1.42 to 4.45)	1.08 (0.50 to 2.06)	2.42 (0.90–6.82)	1.78 (0.90 to 3.17)	1.52 (0.77 to 2.70)	1.67 (0.43–3.12)	NA	1.94 (1.20 to 2.97)	NA

The data are SIRs and SIR ratios with 95% CIs
*P<0.05 for between-group comparisons.
CI, Confidence Interval.

NDs already since diabetes onset onward, and this has not been reported previously to our knowledge. As a novel finding, our results indicate that the incidence of NDs was increased even in individuals without vascular complications, but the presence of vascular complications further modified this risk. Diabetic kidney disease increased the incidence of Alzheimer's disease, and the presence of cardiovascular diseases increased the incidence of both Alzheimer's disease and other dementias. Severe diabetic retinopathy was not associated with increased incidence of any NDs. Younger onset of type 1 diabetes (<15 years) increased the incidence of Alzheimer's disease, but not other NDs.

In this study, we found the highest SIR for vascular dementia, which was 3.4. This is in line with findings from other studies showing an excess risk of especially vascular dementia in relation to type 1 diabetes.[16 22] This finding is expected, since type 1 diabetes is linked to cerebrovascular disease, both to cerebral small-vessel disease,[14] and to overt stroke.[4] Cerebrovascular disease is also known to predispose to dementia in the general population and type 2 diabetes.[23]

We found increased SIR also for Alzheimer's disease at 2.3, other dementias at 1.7, and for any dementia at 2.3 compared with controls without diabetes. These ratios are slightly higher than the risk ratios in a large British register-based study that included hospitalized individuals with type 1 diabetes and assessed the prevalence of dementia in comparison to individuals hospitalized for other causes.[16] They found the overall risk ratio of Alzheimer's disease to be slightly, but significantly increased, risk ratio at 1.1, and the risk ratio of any dementia at 1.7. The SIR in our study cannot be directly compared with risk ratios in this cross-sectional setting, but differences in reference population (general population vs hospitalized individuals) probably explain some of the observed differences. In the British study, there was, interestingly, a clear tendency toward higher relative risk ratios for any dementia in younger age groups, being, for example, fourfold in 40–60 year-olds.[16]

In a Danish national registry-based study, the HR for dementia was assessed for approximately 10 years of follow-up.[22] Especially the younger individuals with type 1 diabetes were found to have a higher risk of developing dementia. Type 1 diabetes increased the risk of any dementia 2.8-fold in those diagnosed with dementia under 65 years of age, and 1.3-fold in those diagnosed after 65 years, compared with matched controls without diabetes.[22] In the present study, we observed the highest relative risk of dementia in the 60–69 year-olds, 4.0-fold for any dementia (figure 2).

There are several possible etiological features that link diabetes with dementia. Diabetes is thought to cause dysfunction of the blood–brain barrier, structural and morphological chances in hippocampus and other parts of the brain, chronic inflammation, and/or oxidative stress.[23 24] In the Diabetes Control and Complications Trial (DCCT) cohort, the apolipoprotein E and ACE genes were not associated with cognitive decline in middle-aged individuals with type 1 diabetes.[25] As well, the recent genetic study with Mendelian randomization approach showed no significant association between genetically determined type 1 diabetes and Alzheimer's disease, suggesting a lesser genetic susceptibility than in the general population, in support of our hypothesis that the metabolic risk factors, such as long-term hyperglycemia, might be more important in type 1 diabetes.[20]

Interestingly, Ouwens *et al* found elevated levels of phosphorylated tau, ß-amyloid 42, and soluble lipoprotein receptor-related protein 1 in cerebrospinal fluid of individuals with type 1 diabetes compared with controls; and in type 1 diabetes, increased tau levels were associated with the decreased integrity of the white matter of right fronto-occipital tract.[26] The meaning of this finding is unclear, considering that in Alzheimer's disease tau levels in cerebrospinal fluid are elevated, but ß-amyloid 42 levels reduced.[27] In addition, frequent severe hypoglycemia and hyperglycemia are also associated with sixfold risk of dementias.[28]

As a novel finding, our study showed a higher incidence of Alzheimer's disease in individuals with diabetic kidney disease and cardiovascular disease. The latter was also linked to other dementias. We also explored the impact of diabetic kidney disease severity on different NDs and found that incidence of any dementia was increased already in those without albuminuria, and further increased by kidney disease severity, but reached statistical difference in between-group comparison only between those with kidney replacement therapy compared with those with normal urinary albumin excretion.

We did not, however, find any association with severe retinopathy and increased incidence of any NDs, which is in line with a study by Rodill *et al*, where they assessed dementia risk in a type 1 diabetes register cohort with and without severe retinopathy.[29]

This finding is surprising, since the retinal vasculature is thought to mirror the vasculature of the brain, and diminishing of retinal diameter has been associated with cognitive decline.[30] We have also reported that diabetic retinopathy severity is associated with cerebral small-vessel disease in individuals with type 1 diabetes.[31] In the present study, the incidence of NDs was clearly increased also in individuals without severe retinopathy, also including individuals with milder forms of retinopathy. We did not assess milder forms of retinopathy, so we cannot rule out an impact of milder forms of retinopathy on the ND risk in those without severe diabetic retinopathy. For Parkinson's disease, a large Danish register-based study showed no link between Parkinson's disease and retinopathy,[32] which is in line with our findings.

Parkinson's disease has been linked to diabetes in several studies.[17] The reason for comorbidity between Parkinson's disease and diabetes is still unclear, but speculations include oxidative stress, mitochondrial dysfunction, inflammation, and common genetic pathways.[17] There are conflicting results on the association

between type 1 diabetes and Parkinson's disease based on recent genetic and experimental studies, with indications that the genetic predisposition might play a lesser role in type 1 diabetes compared with the general population.[18–20] In the present study, the standardized incidence of Parkinson's disease was 1.6-fold in individuals with type 1 diabetes, but the SHR was not increased between the study group and controls. In addition, the presence of diabetic vascular complications did not influence the standardized incidence of Parkinson's disease. Our partly conflicting results can be a result of the relatively low number of events, influencing statistical power.

For age at diabetes onset, we found little or no impact on the risk of NDs. Alzheimer's disease was, however, clearly increased in those with diabetes onset before 15 years, indicating that a long disease duration inevitably has some negative impact on brain health. As a positive message, it is reassuring that our observations show that this is not apparent for all NDs.

The strengths of our study include the nationwide thoroughly characterized cohort of people with type 1 diabetes with population-based matched controls without diabetes, enabling us to assess the SIRs. For both groups, we had complete register-based data on NDs over a long follow-up time. Despite this, the relatively low number of NDs limited somewhat the statistical power in subgroup analyses. The excess mortality in people with type 1 diabetes might influence our results since NDs increase with aging. We explored the impact of death as a competing factor but found it not to influence our main results. This could be since those with excess mortality might be partly the same individuals who have a higher relative risk of NDs at a younger age.

We excluded 700 individuals with type 1 diabetes without matched controls. The excluded individuals did not have controls available due to later enrollment in the study. The excluded individuals showed better metabolic risk factor control, reflecting the treatment improvements over the years. The median follow-up for the excluded individuals was shorter, and thus there were a limited number of NDs in this group. Assessing temporal trends in incidence of NDs and the impact of improved control of metabolic risk factors on both survival and ND incidence would be of interest, and will be possible, when we have longer follow-up available.

Another limitation is that the NDs were assessed only based on register data, and thus potential misclassification is possible. This is, however, the same between those with type 1 diabetes and the controls without diabetes. In addition, Solomon *et al* showed that the validity of diagnosis of dementias and Alzheimer's disease is good in Finnish registers.[33] It is not either always easy to separate different dementia types based on ICD codes only, and dementia types, for example, vascular dementia and Alzheimer's disease, often co-occur. This should, however, not influence the results for any dementia, where all different dementia diagnoses were pooled.

A strength of our study is that the diabetic vascular complications were verified at the clinical study visit, and they are, thus, not based on register data. It would have been of interest also to assess the association between diabetic neuropathy and risk of NDs, but unfortunately, we did not have sufficient data on neuropathy. Further investigation is still needed to explore the risk factors for NDs and to assess their similarities and potential dissimilarities to that of classic diabetic vascular complications.

Taken together, our results and previous findings make it apparent that type 1 diabetes is linked to increased risk of dementia, similarly to that observed in type 2 diabetes.[15 22] We show that the incidences are increased even without the presence of vascular complications, but the presence of diabetic kidney disease and cardiovascular disease further increases the incidences of dementias. The positive finding is that the absolute risk of NDs is modest. Further investigations are needed to identify the risk factors and causes for NDs in type 1 diabetes, to identify possible prevention targets and subpopulations of interests. Studies are also needed to assess whether screening for NDs is beneficial in specific subpopulations in type 1 diabetes to be able to improve the brain health in individuals with diabetes.

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Collaborators The FinnDiane Study Group.

Contributors SIS-A, VH, and LMT were responsible for study design and statistical analyses. SIS-A, VH, MIE, and LMT were responsible for the acquisition and preparing of data for analyses. SIS-A, VH, and LMT were responsible for preparation of the first draft of the manuscript. All the authors interpreted the results and gave critical comments for the final version of the manuscript. LMT is the guarantor of this work and has full access to all data in this study.

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Competing interests MIE is a shareholder of BCB Medical. P-HG reports receiving lecture fees from Astellas Pharma, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Elo Water, Genzyme, Medscape, Merck, Sharp & Dohme, Mundipharma, Novartis, Novo Nordisk, PeerVoice, Sanofi, and Sciarc. P-HG reports being an advisory board member for AbbVie, Astellas Pharma, AstraZeneca, Bayer, Boehringer Ingelheim, Eli

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Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by the ethics committee of Helsinki University Hospital (ID: 491/E5/2006, 238/13/03/00/2015, HUS/3313/2018). The study was performed in accordance with the Declaration of Helsinki. Participants gave informed consent to participate in the study before taking part.

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Data availability statement Data are available upon reasonable request. Individual-level data for the study participants are not publicly available because of the restrictions due to the study consent provided by the participant at the time of data collection. The readers may propose collaboration to research the individual-level data with correspondence with the lead investigator.

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