Incidence and risk factors for cancer in people with type 1 diabetes, stratified by stages of diabetic kidney disease: a nationwide Finnish cohort study

Maija Feodoroff,[a,b,c,d] Valma Harjutsalo,[a,b,c] Sari Mäkimattila,[a,b,c,d] and Per-Henrik Groop,[a,b,c,e,*] on behalf of the FinnDiane Study Group

[a]Folkhälsan Institute of Genetics, Folkhälsan Research Centre, Helsinki, Finland
[b]Department of Nephrology, University of Helsinki and Helsinki University Hospital, Finland
[c]Research Program for Clinical and Molecular Metabolism, Faculty of Medicine, University of Helsinki, Finland
[d]Abdominal Center, Endocrinology and Diabetes, University of Helsinki and Helsinki University Hospital, Helsinki, Finland
[e]Department of Diabetes, Central Clinical School, Monash University, Melbourne, VIC, Australia

The Lancet Regional Health - Europe 2024;40: 100884

Published Online xxx
https://doi.org/10.1016/j.lanepe.2024.100884

Summary

Background Individuals with type 1 diabetes (T1D) have been reported to have increased overall risk of cancer. In addition, individuals with a kidney transplant/transplantation (KT) have markedly increased cancer risk due to chronic use of immunosuppressive agents. However, it has not been elucidated whether the observed excess cancer risk is related to KT or whether diabetic kidney disease (DKD) per se is a risk factor for cancer in individuals with T1D.

Methods The study included 5035 individuals from the Finnish Diabetic Nephropathy Study (FinnDiane) and 14,061 control individuals without diabetes. We assessed the standardized incidence ratios (SIRs) for cancers in individuals with T1D compared to controls according to DKD status. Cox regression analyses were used to identify potential risk factors for cancer in individuals with type 1 diabetes.

Findings The SIR for overall cancer for all participants was 1.14 (1.05–1.24), for participants without KT 0.92 (0.83–1.01) and for participants with KT 4.78 (4.02–5.64). Participants without KT had in fact a reduced risk of prostate cancer with a SIR of 0.54 (0.37–0.76), cancer of urinary organs 0.41 (0.21–0.73) and respiratory and intrathoracic organs, 0.62 (0.38–0.97). Participants with KT had on the contrary an increased risk of non-melanoma skin cancer, SIR 14.50 (10.99–18.86), cancer in the lymphoid and hematopoietic tissue 5.38 (2.99–8.96), mouth or pharynx 5.13 (2.08–10.66), melanoma 5.12 [2.38–9.72]) and respiratory and intrathoracic organs 2.77 (1.21–5.49). The risk of thyroid cancer was increased both in participants without KT, SIR 2.14 (1.39–3.16) and with KT 5.30 (1.68–12.78).

Interpretation The excess overall cancer risk in individuals with type 1 diabetes is only seen in KT recipients and in thyroid cancer. The individuals without KT seem to have a decreased risk of some forms of cancer.

Funding Folkhälsan Research Foundation, Academy of Finland [316664], Wilhelm and Else Stockmann Foundation, Liv och Hälsa Society, Novo Nordisk Foundation [NNF OC0013659], Finnish Foundation for Cardiovascular Research, Finnish Diabetes Research Foundation, Medical Society of Finland, Sigrid Jusélius Foundation, and Helsinki University Hospital Research Funds [TYH2018207 and TYH 2020305].

Keywords: Type 1 diabetes; Cancer; Kidney disease; Kidney failure; Kidney transplant; Standardized incidence ratio

Introduction

During the last 20 years the excess cardiovascular mortality in people with diabetes has decreased. However, cancer-related mortality has not declined similarly in people with diabetes compared with people without diabetes.[1] Most of the previous studies regarding the risk of cancer in people with diabetes have included only people with type 2 diabetes or combined type 1 and type 2 diabetes. Based on the few studies including only people with type 1 diabetes, the results have been conflicting and risk of cancer seems to be both site and sex specific. Many previous studies have shown an

*Corresponding author. University of Helsinki and Helsinki University Hospital, Folkhälsan Research Center, Biomedicum Helsinki, Haartmaninkatu 8 (C318b), FIN-00290, Helsinki, Finland.
E-mail address: per-henrik.groop@helsinki.fi (P.-H. Groop).

Research in context

Evidence before this study

We searched MEDLINE, PubMed for studies published by August 31, 2023, using the search terms "type 1 diabetes" and "cancer", without restrictions. Most previous studies, including only people with type 1 diabetes, have shown an increased overall risk of cancer in women. In men, the decreased risk of prostate cancer lowers the overall cancer risk, although the risk of many other forms of cancer, such as stomach, liver, pancreas, and kidney, seems to be elevated also in men. In general population, kidney transplantation increases overall cancer risk 2–3-fold, due to the immunosuppressive medication. Also, proteinuria is associated with increased cancer risk in general population and in people with type 2 diabetes. We found no previous studies addressing the risk of cancer in people with type 1 diabetes, stratified by the kidney status. Also, the previous studies are all register based, and therefore lack the data regarding possible risk factors for cancer in people with type 1 diabetes.

Added value of this study

In large nationwide Finnish cohort of 5035 individuals with type 1 diabetes, we assessed the risk of cancer, stratified by kidney status, and analysed possible risk factors for the development of cancer. Compared with the control population, the overall risk of cancer for all participants was increased. However, when the cancer risk was analysed based on the kidney status, increased risk was only seen in kidney transplant recipients and participants without transplant had in fact a decreased risk of many forms of cancer (prostate, urinary organs, respiratory and intrathoracic organs). Only the risk of thyroid cancer was increased in the whole study population regardless of kidney status. Age and smoking were associated with a higher cancer risk, but none of the diabetes related risk factors, such as insulin dose or HbA_{1c}, were associated with the risk of cancer.

Implications of all the available evidence

This study reveals a potential explanation for the increased risk of cancer in people with type 1 diabetes, reported by many previous studies. Based on our results, type 1 diabetes *per se*, is not associated with a higher cancer risk, but the increased risk is largely explained by the increased cancer risk associated with kidney transplantation. In any future research, regarding cancer risk in individuals with type 1 diabetes, it is essential to knowledge the effect of immunosuppressive medication and separate the analyses for individuals with and without kidney transplant.

increased overall risk of cancer in women with type 1 diabetes.[2–5] Also the most recent study from UK showed an increased risk of ovarian and vulval cancer in women with type 1 diabetes, although the overall risk of cancer was diminished in both men and women.[6] Based on earlier studies, the risk of different forms of gastrointestinal cancers (oesophagus, stomach, pancreas, liver, colon, and rectum) seems to be elevated equally in men and women with type 1 diabetes, as well as the risk of kidney cancer.[2–4,7,8] A decreased risk of breast cancer was shown in one large five-country study, but not confirmed by others.[2–4,6,7] Respectively, the risk of prostate cancer seems to be decreased in men with type 1 diabetes.[2,4] Of note, this risk reduction is not shown in all studies.[3]

These previous cancer studies are mostly based on national diabetes registers and therefore they lack the precise data regarding possible risk factors, such as glycaemic control, BMI, and smoking status, which could affect the risk of cancer in people with type 1 diabetes. Some risk factors such as exogenous insulin, hyperglycaemia, insulin resistance, and increased levels of insulin-like growth factor-1 (IGF-1) due to excess insulin, are only seen in people with diabetes and might explain the increased risk of some forms of cancer.[9] A recent study, using data from the Diabetes Control and Complications Trial (DCCT) and the Epidemiology of Diabetes Interventions and Complications (EDIC) study, showed that age, female sex and daily insulin dose were associated with a higher cancer incidence in people with type 1 diabetes.[10] The specific risk factors for different forms of cancer in people with type 1 diabetes are yet to be studied.

Diabetic kidney disease is associated with a high risk of different micro- and macrovascular complications and higher mortality in people with type 1 diabetes.[11,12] It is not known if impaired kidney function and proteinuria are also associated with a higher risk of cancer in people with type 1 diabetes. Previous studies have addressed the association between chronic kidney disease and risk of cancer in the general population. Based on a large meta-analysis, a decline in estimated glomerular filtration rate (eGFR) per se is not associated with a higher risk of cancer, but people on dialysis have up to 58% higher cancer mortality compared with people with normal kidney function.[13] In the general population, albuminuria is associated with a higher risk of non-prostate cancer, especially lung cancer.[14,15] Also, in people with type 2 diabetes, proteinuria is associated with a higher risk of cancer mortality.[16] In addition to albuminuria, diabetic kidney disease is characterised with other possible risk factors for cancer, such as insulin resistance, increased inflammatory activity and endothelial permeability.

Kidney transplantation, due to any form of chronic kidney disease, is associated with 2–3-fold overall cancer risk.[17,18] The risk is even higher in virally related cancers such as Kaposi's sarcoma, cervical cancer and

post-transplant lymphoproliferative disease.[19] To our knowledge there are no previous studies addressing the risk of cancer at different stages of DKD in people with type 1 diabetes. Therefore, the aim of this study was to elucidate specific risk factors for cancer in people with type 1 diabetes and to determine the risk of cancer at different stages of DKD.

Methods

The present study included 5035 individuals from the Finnish Diabetic Nephropathy Study (FinnDiane), who participated in the FinnDiane Study between the years 1994 and 2019. For each FinnDiane participant, two to three random control individuals matched for sex, age and place of residence in the year of the diagnosis of type 1 diabetes of the FinnDiane participant were selected from the Finnish Population Register Centre, altogether 14,061 control inidividuals were included (see flow-chart in Fig. 1).

FinnDiane is an ongoing, nationwide, multicenter study and its main goal is to find genetic and environmental risk factors for diabetic complications. All adult individuals (≥18 years) with type 1 diabetes were asked to participate during a regular visit to their attending physician or diabetes nurse at all university hospitals, all central hospitals, most of the regional hospitals and major health care centers all over Finland. Age at onset of diabetes <40 years and insulin treatment within one year of diagnosis were required to ensure correct diagnosis of type 1 diabetes. At baseline, the participants underwent a thorough clinical investigation that took place in conjunction with their regular diabetes control visit. Early morning blood samples were drawn for the analysis of HbA_{1c}, creatinine, lipids and lipoproteins. Also, urine was collected, and a wide range of metabolic biomarkers were analyzed from blood and urine. Blood pressure was measured twice in the sitting position. Details of the medical condition, medical history of the participants were obtained from the medical records by the attending physician or nurse using a standardized recruitment questionnaire, and several questionnaires including questions about lifestyle factors such as smoking, and alcohol consumption were completed by the participants.

The DKD status was defined at the baseline visit based on the urinary albumin excretion rate (UAER) measured from two out of three overnight or 24-h urine collections. A normal UAER was defined as <20 μg/min or <30 mg/24 h, moderate albuminuria (previously microalbuminuria) as UAER ≥20 < 200 μg/min or ≥30 < 300 mg/24 h and severe albuminuria (previously macroalbuminuria) as UAER ≥200 μg/min or ≥300 mg/24 h. End-stage kidney disease (ESKD) was defined as ongoing dialysis treatment or having received a kidney transplant. The estimated glomerular filtration rate (eGFR) was determined using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula.

All cancers including in situ cancers (ICD-8/9: 140–208, 230–234, ICD-10: C00–99, D00–D09) were identified from the National Care Register for Health Care and from the Cause of Death Register until the end of year 2020. Cancers were classified according to the Finnish Cancer Register (https://cancerregistry.fi/statistics/cancer-statistics/).

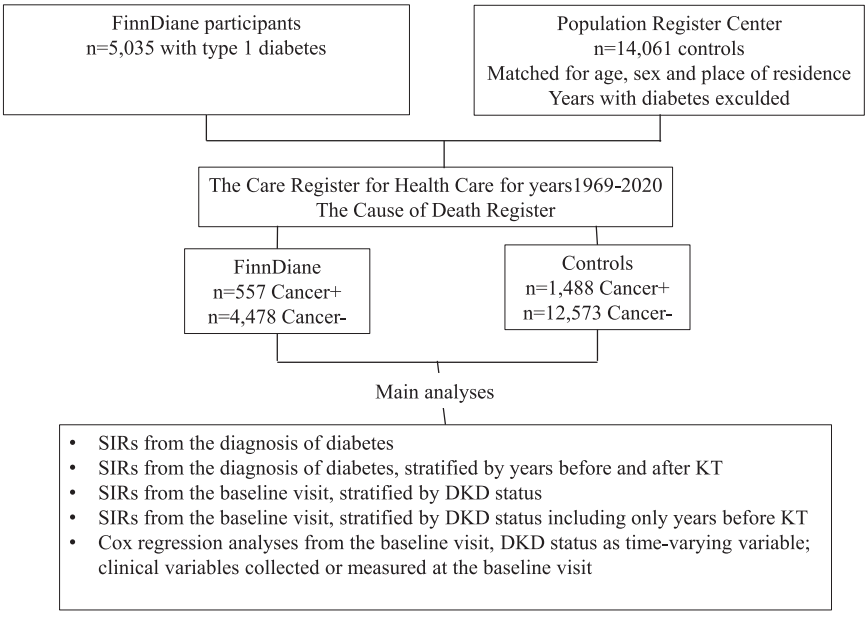

Fig. 1: Flow-chart summarizing the study design. SIRs, standardized incidence ratios; KT, kidney transplant/transplantation; DKD, diabetic kidney disease.

Statistical methods

Clinical characteristics are presented as medians with interquartile range (IQR), or percentages, depending on the variable. Differences between groups with prevalent and incident cancer events and the group without cancer were estimated using the Mann–Whitney U -test or Pearson's $\chi 2$-test, when appropriate.

The analyses were conducted in several ways. The first aim was to study the impact of type 1 diabetes on cancer risk expressed as standardized incidence ratios (SIRs) between individuals with type 1 diabetes and the controls. All participants including those with type I diabetes and their controls were included in the analysis, the follow-up for the participants with type 1 diabetes started from the diagnosis of diabetes. The follow-up for the controls started at the same date as their matched individuals with type I diabetes. The follow-up ended at the time of the cancer, death or at the end of 2020 both in the individuals with type 1 diabetes and the controls. However, if a control individual was diagnosed with diabetes during the follow-up, the follow-up without cancer ended at this date. The second aim was to study, whether kidney transplant/transplantation (KT) impacts the cancer risk in type 1 diabetes expressed as SIRs. For this purpose, one group (KT-) included those without KT and if they had KT during the follow-up the years before the KT. The follow-up ended at the time of the cancer, death, or at the end of 2020 in those without KT but in those with KT during the follow-up the follow-up ended at the date of the KT or at the time of the cancer, if the cancer was diagnosed before the date of the KT. Another group (KT+) included only those with KT, and included only the years after the date of the KT. Therefore, the follow-up started at the date of KT and ended at the time of the cancer, death or at the end of 2020. Site-specific SIRs were calculated for all type 1 diabetes participants, and separately for the KT- and KT + groups (Fig. 2).

The third aim was to study the impact of different stages of DKD, i.e., normal UAER, moderate albuminuria, severe albuminuria and ESKD, on the cancer risk as SIRs. As the DKD status was only available from the baseline visit the follow-up started at the baseline visit and ended at the time of cancer, death or at the end of 2020.

Finally, the fourth aim was to study the possible risk factors including DKD status for the cancer risk in type 1 diabetes using Cox regression analyses. The follow-up started at the baseline visit, as also all clinical variables were measured or collected at the baseline visit, and the follow-up ended at the time of the cancer, death or at the end of 2020.

SIRs were calculated as ratios of observed numbers in type 1 diabetes and expected numbers. The expected numbers were derived by multiplying the number of person-years at risk by sex, 1-year age- and 1-year period-specific morbidity rates observed in the control individuals.

In the Cox regression analyses including individuals with type 1 diabetes the potential risk factors collected or measured at the baseline visit were age, duration of diabetes at baseline visit, sex, DKD status, eGFR, smoking status, BMI, waist-height ratio (WHtR), insulin dose per kg, HbA_{1c}, variability of HbA_{1c} (HbA_{1c} (standard deviation)/HbA_{1c} (mean)) during five years before to five years after the baseline visit, systolic blood pressure, total cholesterol, HDL cholesterol, triglycerides, high-sensitivity C-reactive protein, estimated glucose disposal rate (eGDR). In addition, potential risk factors included also medications that have previously suggested to be associated with cancer risk, namely antibiotic drugs (ATC-code J01) and statins (ATC-code C10AA). As there were only a few users of metformin at baseline, we did not include metformin in the analyses. These data were obtained from the Drug Prescription Register of the Social Insurance Institute of Finland and all individuals with purchases of medications within the time frame of one year before to one year after the baseline visit were considered. DKD status was treated as time varying variable with respect to progression from the earlier stages to dialysis and further to KT.

All analyses were performed using the Statistical Analysis System version 9.4 (SAS Institute, Cary, NC, USA) and the R open-source software version 4.0.5 (http://www.r-project.org).

Role of the funding source

The funders had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Among the 5035 participants, and during total of 191,512 person-years and median (IQR) 38.3 (29.5–46.5) person-years from diagnosis of diabetes 557 cancers were diagnosed, 316 incident cancers were diagnosed before kidney transplantation and 125 after. At baseline visit, 431 participants had ESKD, of which 286 had received a kidney transplant. At the end of the follow-up, the number of participants with ESKD was 901 and 615 had a kidney transplant.

Table 1 presents the clinical characteristics in individuals with type 1 diabetes according to any cancer and incident cancer before and after the kidney transplantation. Cancer after transplantation was more frequently diagnosed in male participants. Participants without cancer were the youngest and had the shortest duration of diabetes at baseline. Participants with cancer after transplantation had the highest HbA_{1c}, but there were only small differences in the glucose control between the groups. Never smokers were least likely to develop cancer during the follow-up. Participants, who developed cancer, had a poorer metabolic profile with more central obesity, measured by waist-to-height-ratio,

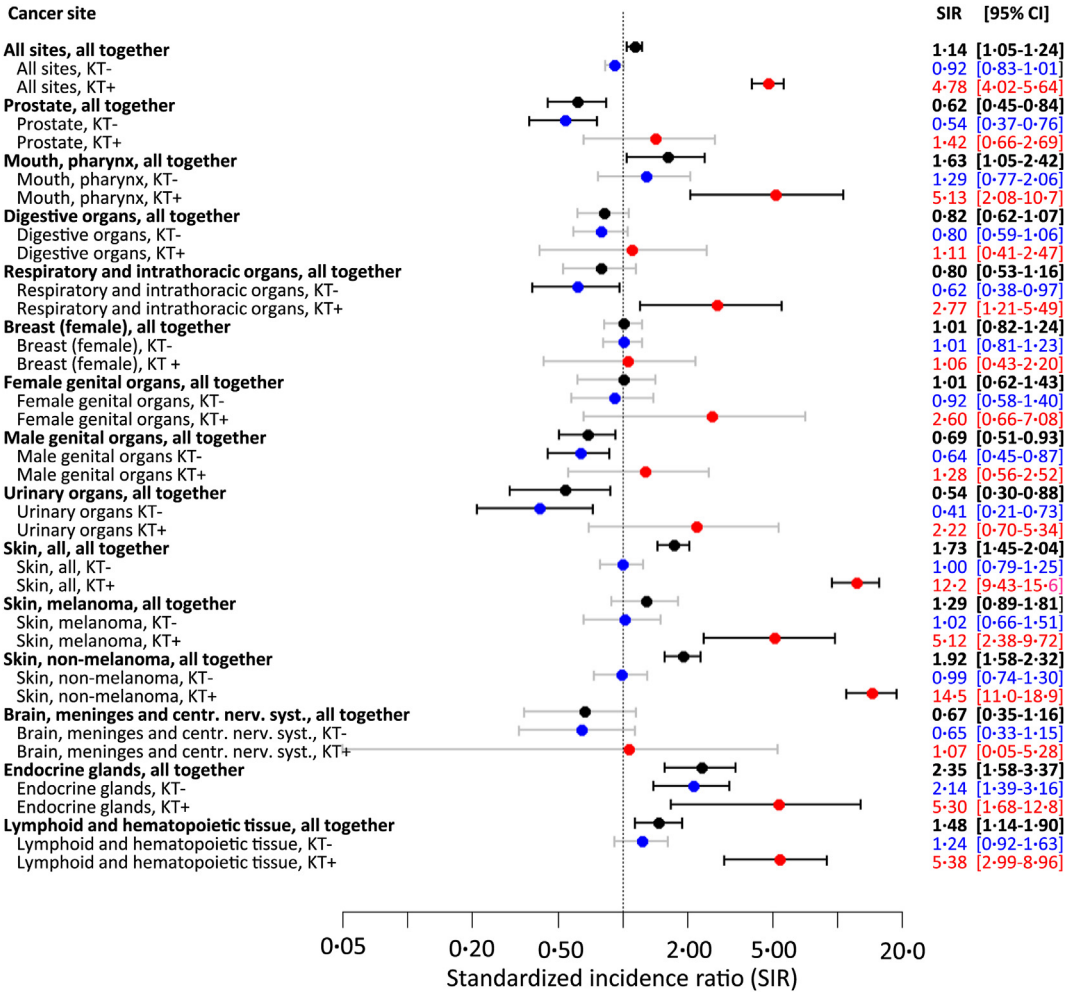

Fig. 2: The standardized incidence ratios (SIRs) with 95% confidence interval between individuals with type 1 diabetes (n = 5035) and the controls (n = 14,061) for the different types of cancer associated with type 1 diabetes; in all individuals with type 1 diabetes together (black), in individuals without kidney transplantation (blue) and in individuals with kidney transplantation (red).

higher blood pressure and higher total and LDL cholesterol compared with the participants without any cancer. The participants who developed cancer after transplantation were the most insulin resistant ones and with the lowest eGDR.

Table 2 presents the distribution of different forms of cancer among study participants, with and without kidney transplantation, and in the control population. The most frequent cancers in participants without kidney transplantation were breast (3.55%), non-melanoma skin (0.97%), lymphoid and hematopoietic tissue (0.95%), digestive organs (0.93%), and cancer in the male genital organs (1.51%). In participants with kidney transplantation the most frequent forms of cancer were non-melanoma skin (8.62%), lymphoid and hematopoietic tissue (2.11%), breast (2.95%), unspecified or in situ carcinoma (2.28), male genital organs (1.85%), and respiratory tract cancers (1.14%). The most frequent cancers in the control population were breast (4.19%), digestive organs (1.40%), cancer in male genital organs (2.47%), non-melanoma skin (1.15%), and lymphoid and hematopoietic tissue (0.89%).

Fig. 1 presents the SIRs for the different types of cancer. The SIR for overall cancer for all participants was 1.14 (1.05–1.24), for participants without kidney transplantation 0.92 (0.83–1.01) and for participants with kidney transplantation 4.78 (4.02–5.64).

The risk of prostate cancer (SIR 0.62 [0.45–0.84]) and cancer of the urinary organs (SIR 0.54 [0.30–0.88]) were decreased in the whole study population and specifically in the participants without kidney transplantation (prostate cancer SIR 0.54 [0.37–0.76] and urinary organs SIR 0.41 [0.21–0.73]). Also, the risk of cancer in respiratory and intrathoracic organs was decreased in

	No cancer n = 4478	Cancer n = 557	Incident cancer before KT[e] n = 316	Incident cancer after KT n = 125
Sex (woman %)	48.6	49.2	52.2	29.6[a]
Age (years)	37.0 (28.3–46.4)	47.5 (39.4–53.9)[a]	46.5 (37.7–55.1)[a]	46.4 (40.0–51.6)[a]
Age at diabetes diagnosis (years)	13.5 (8.8–21.7)	15.8 (10.6–25.7)[a]	18.4 (11.0–27.9)[a]	13.9 (9.1–18.2)
Duration of diabetes	21.4 (12.5–30.9)	29.2 (20.7–37.0)[a]	26.6 (16.9–35.5)[a]	31.2 (25.9–36.4)[a]
DKD N status[c]				
Normal UAER (%)	2811 (62.8)	253 (45.4)	NA	NA
Moderate albuminuria (%)	561 (12.5)	67 (12.0)	NA	NA
Severe albuminuria (%)	593 (13.2)	106 (19.1)	NA	NA
ESKD (%)	329 (7.4)	102 (18.3)	NA	NA
Not known	184 (4.1)	29 (5.2)	NA	NA
HbA_{1c} (%)	8.3 (7.4–9.2)	8.5 (7.5–9.2)[d]	8.3 (7.5–9.1)	8.7 (7.7–9.6)[d]
HbA_{1c} (mmol/mol)	67.2 (57.4–77.1)	68.9 (58.5–77.1)[d]	67.2 (58.5–76.0)	71.6 (60.7–81.4)[d]
Smoking status		[c]	[c]	[c]
Current smoker (%)	23.2	24.0	26.6	22.4
Ex-smoker (%)	21.5	28.2	27.5	29.6
Never smoker (%)	51.6	43.8	44.0	40.8
Not known	3.7	4.0	1.9	7.2
Body mass index (kg/m^2)	24.7 (22.5–27.1)	25.0 (22.9–27.5)	25.3 (23.1–27.9)[b]	24.5 (22.0–26.5)
Waist-to-height ratio	0.49 (0.46–0.54)	0.51 (0.47–0.56)[a]	0.51 (0.47–0.55)[c]	0.51 (0.47–0.56)[d]
Systolic blood pressure (mmHg)[d]	131 (121–144)	140 (127–155)[a]	135 (125–149)[b]	153 (141–167)[a]
Diastolic blood pressure (mmHg)[d]	80 (72–86)	80 (73–87)[d]	79 ((71–87)	85 (80–90)[a]
Total cholesterol (mmol/l)	4.80 (4.20–5.44)	4.95 (4.39–5.64)[c]	4.87 (4.37–5.50)	5.24 (4.40–6.08)[b]
LDL cholesterol (mmol/l)	2.96 (2.45–3.56)	3.09 (2.57–3.66)[c]	3.07 (2.52–3.57)	3.46 (2.77–3.97)[b]
HDL cholesterol (mmol/l)	1.32 (1.10–1.59)	1.33 (1.05–1.64)	1.34 (1.10–1.65)	1.21 (0.93–1.50)
Triglycerides (mmol/l)	1.02 (0.77–1.46)	1.10 (0.83–1.55)[d]	0.99 (0.77–1.34)	1.55 (1.15–2.22)[a]
eGDR (mg kg^{-1} min^{-1})	6.3 (4.4–8.6)	4.9 (3.7–7.5)[a]	6.0 (4.2–8.5)	3.9 (2.9–4.7)[a]
Insulin dose (IU kg-1)	0.67 (0.53–0.84)	0.63 (0.50–0.76)[a]	0.64 (0.51–0.76)[b]	0.66 (0.53–0.78)
eGFR (ml min^{-1} 1.73 m^{-2}) (excluding ESKD)	106 (90–121)	94 (71–109)[a]	98 (79–110)[a]	NA
h-CRP (mg/l)	1.85 (1.02–3.88)	2.31 (1.30–4.62)[a]	2.30 (1.26–4.26)[b]	2.44 (1.46–5.38)[b]
Antibiotic purchases during −1 visit +1 year (%)	61.3	66.3[d]	59.5	80.0[a]

Abbreviations: DKD, diabetic kidney disease; UAER, urinary albumin excretion rate; ESKD, end-stage kidney disease; KT, kidney transplant/transplantation; HbA_{1c}, glycated hemoglobin; LDL, low density lipoprotein; HDL, high density lipoprotein; eGFR, estimated glomerular filtration rate calculated by CKD-EPI equation; eGDR estimated glucose disposal rate; h-CRP, high-sensitivity C-reactive protein. The follow-up started at the baseline visit. Data are given as percentages (%) or median and interquartile range. [a]P-value <0.0001. [b]P-value<0.001. [c]P-value<0.01. [d]P-value<0.05. P-value refers to ANOVA, Kruskal–Wallis test or $\chi 2$-test adjusted for age at baseline when applicable. Comparison group is group without cancer. [e]Either without KT or in those with KT before KT.

Table 1: **Clinical characteristics in individuals with type 1 diabetes according to any cancer and incident cancer before and after kidney transplantation.**

participants without kidney transplantation (SIR 0.62 [0.38–0.97]).

In participants with kidney transplantation the highest excess risk was seen for non-melanoma skin cancer (SIR 14.50 [10.99–18.86]). Also, the risk of cancer in the lymphoid and hematopoietic tissue (SIR 5.38 [2.99–8.96]), mouth or pharynx (SIR 5.13 [2.08–10.66]), melanoma (SIR 5.12 [2.38–9.72]) and respiratory and intrathoracic organs (SIR 2.77 [1.21–5.49]) were increased in participants with kidney transplantation.

The risk of cancer in the endocrine glands was increased in the whole study population (SIR 2.35 [1.58–3.37]), as well as in the participants without (SIR 2.14 [1.39–3.16]) and with kidney transplantation (SIR 5.30 [1.68–12.78]).

Table 3 presents the results of the Cox regression analysis of the variables collected at the baseline visit and were associated with cancer risk in individuals with type 1 diabetes. Based on the multivariable Cox regression models, the only independent risk factors for cancer in the whole study population, were age (HR 1.08 [1.07–1.09]), dialysis (HR 3.86 [2.04–7.30]), kidney transplantation (HR 7.20 [5.66–9.16]) and current smoking (HR 1.51 [1.18–1.93]). Sex, kidney function (eGFR), metabolic risk factors (BMI, waist-height ratio, lipids), diabetes related risk factors (insulin dose per kg, HbA_{1c}, variability of HbA_{1c}, eGDR), high-sensitivity C-reactive protein or purchases of antibiotic drugs or statins were not associated with the cancer risk (Supplemental Tables S1 and S2). Supplemental Table S2 shows the HRs for age, DKD status and smoking after adjustment for these variables.

Table 4 presents the SIRs for any cancer based on DKD status at baseline. Both severe albuminuria (1.84 [1.49–2.25]) and ESKD (5.30 [4.24–6.54]) were associated with increased risk of cancer. When the years before and

Total number	Individuals with type 1 diabetes			Controls
	All 557/5035 No. (%)	Without KT (if KT, years before) 424/5035 No. (%)	With KT (years after KT) 133/615 No. (%)	1488/14,061 No. (%)
Mouth, pharynx Lip, tongue, salivary glands, pharynx, other or unspecified mouth	22 (0.44)	16 (0.32)	6 (0.98)	33 (0.23)
Digestive organs Oesophagus, stomach, small intestine, colon, rectum, rectosigmoid, anus, liver, gallbladder, bile ducts, pancreas, other and unspecified digestive organs	52 (1.03)	47 (0.93)	5 (0.81)	197 (1.40)
Respiratory and intrathoracic organs Nose, sinuses, larynx, epiglottis, lung, trachea, other unspecified respiratory or intrathoracic organs	25 (0.50)	18 (0.36)	7 (1.14)	97 (0.69)
Breast (female)	94 (3.84)	87 (3.55)	7 (2.95)	279 (4.19)
Female genital organs Cervix uteri, corpus uteri, ovary, vulva, vagina, placenta, female genital	23 (0.94)	20 (0.82)	3 (1.27)	72 (1.08)
Male genital organs Penis, prostate, testis, other or unspecified male genital	46 (1.78)	39 (1.51)	7 (1.85)	183 (2.47)
Urinary organ Kidney, bladder and urinary tract	14 (0.28)	10 (0.20)	4 (0.65)	81 (0.58)
Skin Melanoma of the skin, skin, squamous cell carcinoma, other skin	133 (2.64)	72 (1.43)	61 (9.92)	234 (1.66)
Skin, melanoma	31 (0.62)	23 (0.46)	8 (1.30)	72 (0.51)
Skin, non-melanoma	102 (2.03)	49 (0.97)	53 (8.62)	162 (1.15)
Eye	2 (0.04)	2 (0.04)	0	9 (0.06)
Brain, meninges and central nervous system Glioma, meningeoma, CNS, nerves sheet tumor, other or unspecified tumor of brain, meninges and central nervous system	11 (0.22)	10 (0.20)	1 (0.16)	51 (0.36)
Endocrine glands Thyroid gland, adrenal gland, other endocrine glands	29 (0.58)	25 (0.50)	4 (0.65)	34 (0.24)
Mesothelioma	3 (0.06)	3 (0.06)	0	1 (0.007)
Bone	2 (0.04)	2 (0.04)	0	5 (0.04)
Soft tissue	4 (0.08)	3 (0.06)	1 (0.16)	16 (0.11)
Peripheral and autonomic nervous system	0	0	0	3 (0.02)
Lymphoid and hematopoietic tissue Hodgkin lymphoma, mature B-cell neoplasm, mature T and NK cell lymphomas/leukemia, acute lymphoplastic leukemia/lymphoma, acute myeloid leukemia, non-Hodgkin lymphoma, other or unspecified, leukemia, other or unspecified, myeloproloferative neoplasms, myelodysplatic syndromes and myelodysplastic/myeloproliferative neoplasms, other, unspecified or mixed hematological diseases	61 (1.21)	48 (0.95)	13 (2.11)	126 (0.89)
Unspecified or in situ carsinoma	36 (0.71)	22 (0.44)	14 (2.28)	67 (0.48)

Abbreviations: KT, kidney transplant/transplantation; CNS, central nervous system.

Table 2: **Distribution of different forms of cancer among individuals with type 1 diabetes and the controls without diabetes.**

after kidney transplantation were analyzed separately, the risk of cancer was significantly increased only after kidney transplantation (4.78 [4.02–5.64]), not with severe albuminuria or dialysis before transplantation. In men without kidney transplantation, the risk of cancer was lower (0.83 [0.72–0.96]) compared with men in the control group.

Because the increased risk of cancer was only seen after kidney transplantation, the possible predictors for cancer were also analysed excluding the years with kidney transplantation (Table 5). Again, age and current smoking were associated with higher cancer risk in both men and women. In women also central obesity and previous smoking were associated with increased risk of cancer. During the whole follow-up period, there was no difference in the risk of cancer between men and women with diabetes, but during the years after kidney transplantation, the risk of developing cancer was higher in men (HR 1.64 [1.07–2.51]) compared with women (only in text).

Discussion

Our study provided a novel finding, that people with type 1 diabetes, without kidney transplantation, have similar overall risk of cancer compared to the background population. The risk of cancer in prostate, respiratory and intrathoracic organs, and urinary organs, was even lower in people with type one diabetes without kidney transplantation compared with controls. In people with type 1 diabetes, who have undergone kidney transplantation, we could demonstrate a nearly five-fold excess risk of cancer. This was largely explained by the increased risk of non-melanoma skin cancer but also the risk of many solid organ cancers, and cancer of the

	Hazard ratio (95% CI)	p-value
Men	0.89 (0.73–1.08)	0.24
Age (years)	1.08 (1.07–1.09)	<0.0001
DKD status		
Normal UAER	1.00	
Moderate albuminuria	1.10 (0.78–1.51)	0.57
Severe albuminuria	1.33 (0.95–1.87)	0.10
Dialysis	3.86 (2.04–7.30)	<0.0001
Kidney transplantation	7.20 (5.66–9.16)	<0.0001
Smoking status		
Never	1.00	
Current	1.51 (1.18–1.93)	0.001
Ex-smokers	1.18 (0.93–1.49)	0.18

Abbreviations: DKD, diabetic kidney disease; UAER, urinary albumin excretion rate.

Table 3: **The variables that were associated with cancer risk and the corresponding hazard ratios (HRs) in individuals with type 1 diabetes from baseline visit adjusted for sex.**

lymphoid and hematopoietic tissues were increased after kidney transplantation. Cancer of the endocrine glands was the only form of cancer that was increased in all people with type 1 diabetes with or without kidney transplantation.

	Number at risk, type 1 diabetes	Number of cancer events, type 1 diabetes	Standardized incidence ratio (95% CI)
All[a,d]	5035	557	1.14 (1.05–1.24)
Women[a,d]	2451	274	1.13 (1.01–1.28)
Men[a,d]	2584	283	1.15 (1.02–1.29)
DKD status at baseline[b,d]			
Normal UAER	3007	196	0.84 (0.73–0.97)
Moderate albuminuria	612	51	0.96 (0.72–1.25)
Severe albuminuria	684	91	1.84 (1.49–2.25)
ESKD	411	82	5.30 (4.24–6.54)
Years before kidney transplantation[e]			
All[a]	5035	424	0.92 (0.83–1.01)
Women[a]	2451	232	1.00 (0.88–1.14)
Men[a]	2584	192	0.83 (0.72–0.96)
DKD status at baseline[b]			
Normal UAER	3007	196	0.84 (0.73–0.97)
Moderate albuminuria	612	48	0.91 (0.68–1.20)
Severe albuminuria	684	49	1.21 (0.91–1.59)
Dialysis	142	3	2.77 (0.71–7.55)
Years after kidney transplantation[c,f]			
All	598	133	4.78 (4.02–5.64)
Women	225	42	3.80 (2.77–5.09)
Men	373	91	5.42 (4.39–6.63)

Abbreviations: DKD, diabetic kidney disease; UAER, urinary albumin excretion rate; ESKD, end-stage kidney disease. [a]Follow-up from the diagnosis of diabetes. [b]Follow-up from the baseline visit. [c]Follow-up from the transplantation date. [d]Irrespective of whether a kidney transplant has been received during follow-up. [e]Follow-up until the transplantation date for those who had undergone a kidney transplant. [f]Cancer events before kidney transplantation excluded.

Table 4: **Standardized incidence ratios between individuals with type 1 diabetes (n = 5035) and the controls without diabetes (n = 14,061) for any cancer based on nephropathy status at baseline and stratified during follow-up by kidney transplantation.**

	Hazard ratio (95% CI)	p-value
Men		
Age (years)	1.08 (1.07–1.10)	<0.0001
Smoking status		
Never	1.00	
Current	1.49 (1.00–2.24)	0.051
Ex-smokers	1.13 (0.77–1.67)	0.54
Women		
Age (years)	1.06 (1.04–1.07)	<0.0001
Waist to height ratio (per 10)	1.37 (1.09–1.72)	0.006
Smoking status		
Never	1.00	
Current	1.60 (1.09–2.37)	0.02
Ex-smokers	1.47 (1.00–2.17)	0.049

Table 5: **The variables that were associated with cancer risk and the corresponding hazard ratios (HRs) for incident cancers from baseline visit in men and women with type 1 diabetes separately excluding the years with kidney transplant.**

Previous studies including people with type 1 diabetes have reported a similar or lower risk of cancer in men and 7–19% elevated risk of cancer in women, compared with the background population. Based on our data, stratified by the kidney status, the risk of cancer in women, without kidney transplantation was similar to that in the controls. The corresponding risk was 17% lower in men without kidney transplantation. The lower cancer risk in men with type 1 diabetes is mostly explained by the lower risk of prostate cancer, that is shown in some but not all previous studies. Also in our study, we found a decreased risk of prostate cancer in the whole study population. However, after the groups were stratified by the prevalent kidney transplantation, the 50% lower risk of prostate cancer was only seen in men without kidney transplantation. Previous data from the FinnDiane study showed that participants, whose diabetic kidney disease did not progress, had lower total and free testosterone levels and higher sex-hormone binding globulin levels compared to the ones with progressing kidney disease.[20] Testosterone binds to androgen receptors in prostate cells and promotes cell proliferation of both normal and malignant cells.[21] Prostate cancer is treated with testosterone lowering androgen deprivation therapy and therefore one would expect a lower incidence of prostate cancer among men with lower testosterone levels.[22]

We also found a lower risk of cancer in respiratory and intrathoracic organs and urinary organs in participants without kidney transplantation. This is a novel finding, only seen when cancer risk is analysed based on the kidney transplantation status. Smoking is the most important risk factor for lung cancer, causing around 90% of all lung cancer cases.[23] The risk of cancer in the urinary tract is also three-fold higher in current smokers compared with nonsmokers.[24] We have previously

shown, that both current and ex-smokers have a higher cumulative risk of developing ESKD.[25] Therefore, this shared risk factor could explain the difference in the cancer risk between participants with and without kidney transplantation.

The large five-country cancer study by Carstensen et al. found a decreased risk of breast cancer in people with type 1 diabetes, a finding that was not confirmed in our study, or in previous studies from UK, Australia, Taiwan, and Sweden.[2–4,6,7] Based on our results the risk of breast cancer was similar in people with type 1 diabetes, both with and without kidney transplantation, compared to the control population. It is unlikely that this finding is due to a low number of breast cancer cases, because breast cancer was the second most prevalent form of cancer (94 cases) in the whole study population and no trend towards lower risk was seen in any of the groups. It is possible, that differences in some breast cancer specific confounding factors, such as parity or proportions of pre- and post-menopausal women, could explain these conflicting findings.

Previous studies have shown an increased risk of several cancers of the digestive organs, such as pancreas, liver, oesophagus, stomach, and colorectal cancer in people with type 1 diabetes.[2,4,7] These results have varied between the origin of cancer, and between men and women. In our study, there was no difference in the combined risk of cancer of the digestive organs between participants with or without kidney transplantation, and the risk was also similar compared to the controls.

In our study, the cancer of endocrine glands was only due to thyroid cancer, which was the only form of cancer that showed an increased incidence rate in participants without and with kidney transplantation. Our results are in line with studies by Carstensen et al. and Harding et al. who showed an increased risk of thyroid cancer in women with type 1 diabetes. The incidence of thyroid cancer is increasing steadily worldwide, however, the mortality rate in thyroid cancer remains low. This epidemiological pattern is attributed to overdiagnosis, that is estimated to account for up to 50–90% of the cancer cases in high-income countries.[26,27] Individuals with type 1 diabetes are followed-up by endocrinologists, internists or general practitioners regularly. Thyroid function tests are also recommended for individuals with autoimmune diabetes. Therefore, it is likely that individuals with type 1 diabetes are also more often referred to ultrasound examination of the thyroid gland and part of the excess risk of thyroid cancer could be explained by improved diagnostics during the regular healthcare contacts for people with type 1 diabetes. Also, some other underlying mechanisms or shared risk factors could explain the increased risk of thyroid cancer in people with type 1 diabetes. Due to this exceptional finding, compared with other forms of cancer, further research is needed to elucidate possible mechanisms behind the association between type 1 diabetes and thyroid cancer.

Compared with two previous Finnish studies on kidney transplant recipients, the overall cancer risk was higher in our study (SIR 4.78, compared with 2.7 in Kyllönen et al. from 1994 to 3.6 in Friman et al. from 2021).[17,18] In all studies, including ours, the incidence of skin cancer, especially non-melanoma skin cancer was higher in the transplant recipients compared with the background population. In our study including only people with type 1 diabetes, the risk of cancer in the respiratory tract and endocrine organs was higher and the risk of cancer in the urinary tract lower, compared with the studies including people with different underlying kidney diseases. It is of note, that in the study by Friman et al., no cancer cases were found among the 77 pancreas-kidney transplants recipients, all with type 1 diabetes. However, the follow up was shorter, only 2.9 years in this combination transplantation group, compared with 9.6, in kidney-alone transplant recipients.

Immunosuppressive medication, especially a high overall immunosuppressive dose is the most important factor associated with higher cancer risk in kidney transplant recipients.[28] Especially older immunosuppressive agents such as cyclosporine and azathioprine are associated with a higher cancer risk, but the cancer risk is lower with the newer mTOR inhibitors.[29] Immunosuppressive medication causes decreased immunosurveillance of cancer cells, reduced DNA-repairment capacity and reduced antiviral response, leading to increased risk of infection or activation of carcinogenic viruses such as the Ebstein-Barr virus, Human herpesvirus 8 and Human papilloma virus. Kaposi's sarcoma, oropharynx and anogenital cancer and several forms of lymphoma and specifically post-transplant lymphoproliferative disease have viral aetiology, and are more common among transplantation recipients.[19] Also in our study, the recipients of kidney transplantation had a higher risk of cancer in mouth or pharynx and cancer of lymphoid and hematopoietic tissue including lymphoma. Risk of cancer in female genital organs was not significantly increased, but a trend towards a higher risk was observed (HR 2.60 [0.66–7.08]). In line with previous studies, kidney transplantation was associated with significantly increased risk of all forms of skin cancer. The risk of melanoma was increased five-fold and non-melanoma skin cancer up to 14-fold compared with controls.

To our knowledge this is the first study presenting precise data regarding possible risk factors for cancer in people with type 1 diabetes. Previous larger studies are based on register data and therefore lack the information on many clinically important parameters. Risk of cancer is increased with older age, and based on our results, in people with type 1 diabetes, the risk of cancer is increased by 7% per each year. Sex was not an

independent risk factor for cancer in the whole study population, and the SIRs for all forms of cancer were similar in men and women. This is contradictory to the previous studies, that have shown an elevated cancer risk only in women.[2–4] Also in our study, the cancer risk in men was lower during the years before kidney transplantation compared with men in the control population. But after kidney transplantation the risk of all cancer was elevated in both men and women, and the risk was 64% higher in men compared with women with type 1 diabetes.

The HbA1c level was the highest and eGDR the lowest among participants who developed cancer after kidney transplantation, but based on the multivariate analysis, none of the parameters of glucose control or insulin sensitivity (HbA_{1c}, variability of HbA_{1c}, insulin dose per kg or estimated glucose disposal rate) were independently associated with the risk of cancer. These results differ from a recent study from Hong Kong, showing a positive association between high glucose variability and risk of cancer, but our results are largely in line with a recent study from the UK Biobank, that could not demonstrate any positive association between a higher HbA_{1c} and the risk of cancer, apart from the risk of pancreatic cancer.[30,31] Smoking is a known risk factor for cancer and based on our results, men with type 1 diabetes, who were current smokers had 50% higher risk of cancer compared with never smokers. The corresponding risk increase in smoking women was 60%. In women, also previous smoking was associated with 47% higher cancer risk.

Within individuals with type 1 diabetes, both dialysis treatment and kidney transplantation were associated with a higher cancer risk compared with individuals with normal UAER. However, when the cancer risk was evaluated separately during the years before kidney transplantation and after, and compared to individuals without diabetes (SIR), the increased risk was only seen during the years after transplantation and the risk of cancer was not elevated in individuals going on dialysis treatment during the years before kidney transplantation or without kidney transplantation. Therefore, based on our findings, the strongest risk factor for cancer in people with type 1 diabetes was kidney transplantation. This is a novel finding, not shown in previous studies, that did not take diabetic kidney disease or kidney transplantation into account, when evaluating the risk of cancer in people with type 1 diabetes.

Compared with previous, register based studies, our study included only people with type 1 diabetes, and it is of note that precise clinical data regarding the kidney status and different risk factors were available for each participant. Other strengths of our study are the long follow-up time from the diagnosis of diabetes or from the baseline visit. All cancer cases were identified from the National Care Register for Health Care (HILMO) and from the Cause of Death Register. Both are high-quality registers, HILMO being one of the oldest individual-level hospital discharge registers in the world, that covers information on all hospitalisations in Finland since 1967, including day-surgical procedures codes since 1996 and specialised outpatient care since 1998. Although FinnDiane is not by definition a population-based study, the participants were recruited across the country and the number of participants from each region matches the demographic population density of Finland. We consider the findings applicable to similar populations, but further studies are needed to confirm the findings in different populations such as low-income countries and ethnically more diverse populations.

Despite the large cohort of participants with type 1 diabetes, the number of some specific types of cancer, such as liver and pancreas, was low and the exact risk could not be estimated. One limitation of our study was, that, instead of reporting separate risks for all site-specific cancers, we combined cancers within the same organ group. In our study the combined risk of cancer in any of the digestive organs was not elevated, although previous studies have shown an increased risk of both liver and pancreas cancer in individuals with type 1 diabetes.[2,4] Carstensen et al. also reported an elevated risk of kidney cancer in individuals with type 1 diabetes, but the risk of bladder cancer was similar compared with the background population.[4] In our study, we combined all cancers of the urinary organs, and the risk was lower in the whole study population and especially in the participants without kidney transplantation. This discrepancy in the findings might be explained by the low number of urinary organ cancer cases, 10 in participants without kidney transplantation and 4 in participants with transplantation. Also, the sex-specific analyses were limited due to the relatively small number of different cancer cases. Therefore, our results are not fully comparable with the even larger register-based studies, that have reported exact risk estimates for all common site-specific cancers and separately for women and men.

In conclusion, our study demonstrates, that in people with type 1 diabetes, the cancer risk is higher mainly among kidney transplant recipients. In fact, the risk of some forms of cancer, such as the prostate, cancer in respiratory and intrathoracic organs and urinary organs, is even lower in people with type 1 diabetes, without kidney transplantation.

Contributors

MF, SM and VH designed this sub-study of the FinnDiane Study. VH acquired the data and performed the statistical analyses. MF interpreted the data, ensured the integrity of the data, wrote, and critically reviewed the manuscript. VH interpreted the data, wrote and critically reviewed the manuscript. SM and P-HG interpreted the data and critically reviewed the manuscript. VH verified the underlying data. P-HG had

final responsibility for the decision to submit for publication. All authors had full access to the data.

Data sharing statement

Study data will not be available because the General Data Protection Regulation does not allow the distribution of individual-level data.

Declaration of interests

P–HG has received investigator–initiated research grants from Eli Lilly and Roche, is an advisory board member for AbbVie, Astellas, AstraZeneca, Bayer, Boehringer Ingelheim, Cebix, Eli Lilly, Janssen, Medscape, Merck Sharp & Dohme, Mundipharma, Nestlé, Novartis, Novo Nordisk and Sanofi; and has received lecture fees from AstraZeneca, Bayer, Boehringer Ingelheim, Eli Lilly, Elo Water, Genzyme, Merck Sharp & Dohme, Medscape, Novartis, Novo Nordisk, PeerVoice, Sanofi and Sciarc.

Other authors declare no conflict of interest.

Acknowledgements

The authors thank all physicians and nurses at each FinnDiane center participating in recruitment and characterization of the participants. A complete list of the physicians and nurses is presented in the Supplemental Table S3.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lanepe.2024.100884.

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