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The effect of diabetes and the diabetogenic *TBC1D4* p.Arg684ter variant on kidney function in Inuit in Greenland

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ABSTRACT

The aim of this study was to examine the effect of diabetes and the diabetogenic TBC1D4 variant on kidney function in Greenland in a population-based setting. Health survey data and TBC1D4 genotypes from 5,336 Greenlanders were used to estimate odds ratios (ORs) of albuminuria (>30 mg/g creatinine) and chronic kidney disease (CKD, eGFR <60 ml/min/1.73m^2), comparing individuals with and without diabetes, including the effect of TBC1D4 variant. Of the 3,909 participants with complete data, 9.3% had diabetes. Albuminuria was found in 27.6% and 9.5% and CKD was found in 10.8% and 6.3% among those with and without diabetes, respectively. Diabetes was cross-sectionally associated with an increased risk of albuminuria (OR (95% CI) = 2.37 (1.69,3.33); p < 0.001) and the TBC1D4 variant protected against albuminuria (OR (95% CI) = 0.44 (0.22,0.90); p = 0.02) in a multivariable model. Neither diabetes nor the TBC1D4 variant significantly associated with CKD. The presence/absence of diabetes did not predict changes in eGFR and UACR in longitudinal analyses. Diabetes conferred an increased risk of albuminuria, and the TBC1D4 variant was associated with a decreased risk of albuminuria, but neither was associated with CKD. The potential renoprotective association of the TBC1D4 variant on albuminuria calls for further studies.

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Introduction

Diabetes prevalence has increased globally from 180 to 463 million from 1980 to 2019 [1]. In Greenland, the same trend has been seen over the past 60 years, with diabetes increasing from being almost non-existent to ~10% currently affected [2–5]. Reasons for this rapid increase are found in the unique genetic architecture, the ageing population and the social transition from a traditional active lifestyle with a marine-based diet to a more western sedentary lifestyle with higher consumption of imported foods of dubious quality [6]. Consequently, the burden of diabetes risk factors like obesity, physical inactivity, hypertension and dyslipidemia has increased [7].

Diabetes is characterised by chronic hyperglycaemia, leading to damage of the vascular system with a threefold increased risk of cardiovascular disease (CVD) [8]. A large proportion of people with diabetes also develop microvascular complications like retinopathy, neuropathy and diabetic kidney disease [9]. Diabetic kidney disease is a chronic nephropathic condition that typically begins with microalbuminuria that progresses to macroalbuminuria, eventually resulting in decreased renal function, ultimately leading to end-stage kidney failure and death [10]. Both microalbuminuria and chronic kidney disease (CKD) are found in around 40% of individuals with diabetes [11], but ethnic differences in complication rates exist [12].

Two register-studies from the capital Nuuk (2010 and 2018) [13,14] and one study (2019) [15] representative of most of Greenland (except the east and parts of the north) examined microvascular diabetes complications among residents from Greenland registered with a diabetes diagnosis in medical records. The studies found rates of nephropathy (albuminuria or CKD) from 25% to 48%. Comparing Greenlanders and non-Greenlanders with diabetes, Greenlanders had a lower frequency of microalbuminuria (25% vs. 38%). A 2015

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study from Greenland analysing 24-h urine samples found lower urinary creatinine excretion in Greenlanders compared to non-Greenlanders, both for males (n1,344) and females (n1,807) (mg/24 h and 894/1259 mg/24 h; $p = 0.002/0.02$ for males and females respectively) [16], suggesting a higher UACR value for a given level of albumin excretion. Concluding on the limited literature from Greenland, studies support diabetes being a risk factor for kidney disease in Inuit, however perhaps to a lesser extent than in non-Inuit.

An important factor that could influence diabetic kidney disease rates in Greenland is the recently identified *TBC1D4* p.Arg684Ter variant. It was discovered in 2014 with 4% homozygous (HO) carriers in the population and an allele frequency of 17%, and it is associated with severe muscular insulin resistance and postprandial hyperglycaemia [17]. HO carriers have an odds ratio of 10.3 for developing diabetes and in total, this variant explains 15% of all diabetes in Greenland. The clinical consequences of the *TBC1D4* variant remain to be fully elucidated, and with its large impact and a high prevalence, it is necessary to test its potential influence on diabetes complications, in this case, diabetic kidney disease. The aim of this study was therefore to examine the effect of diabetes and the *TBC1D4* variant on kidney function in Inuit in Greenland in a population-based setting.

Materials and methods

Study design

The initial study population was 5,336 adult Greenlanders who had participated in population-based health surveys conducted in the years 1999–2001, 2005–2010 and 2017–2019, respectively: The Population Study in Greenland 1999 (B99 [18]), Inuit Health in Transition (IHIT [19]) and the Population Survey in Greenland 2018 (B20182) with nationwide sampling. A total of 3,820 participated once and 1,516 participated twice in B99 or IHIT at baseline and follow-up in either IHIT or B2018. A small sample participated in all three surveys, but missing data on key variables made it infeasible to make a 3-point follow-up.

Participants completed lifestyle questionnaires and clinical examinations, and a majority contributed with data from blood samples, oral glucose tolerance tests (OGTTs) and random spot urine samples. We therefore had information on age, sex, height, weight, systolic and diastolic blood pressure, smoking status, blood glucose levels (HbA_{1c}, fasting and 2-hour glucose values from the OGTT), serum creatinine, urinary albumin creatinine ratio (UACR), low-density lipoprotein (LDL) cholesterol and triacyl glycerol (TG).

All participants in the health surveys provided oral and written informed consent. The health surveys were conducted in accordance with the Helsinki Declaration and were approved by the Ethics Committee for Medical Research in Greenland. Details of the B99 study [18], the IHIT study [19] and the B2018 study [2] are found elsewhere.

Diabetes

We defined diabetes according to the 2006 World Health Organization (WHO) OGTT criteria of fasting plasma glucose ≥7.0 mmol/l, 2-hour plasma glucose ≥11.1 mmol/l [20] or self-reported by questionnaire. In a sensitivity analysis, diabetes was defined by HbA_{1c} ≥48 mmol/l as recommended by the WHO in 2011 [21].

Kidney function

Frozen samples were used to estimate kidney function. Blood stored at the laboratory at the Steno Diabetes Center, Copenhagen, at −80°C from the years 1999–2001 and 2005–2010 was analysed for creatinine levels using "Vitros 5600" Ortho Clinical Diagnostics [22]. Estimated glomerular filtration rate (eGFR) was calculated using serum creatinine values expressed as millilitres per minute and adjusted for mean body surface area of 1,73 m^2, age and sex according to the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) formula with CKD cut-off at eGFR <60 ml/min/1.73 m^2. We used Danish guidelines [23] similar to the 2012 KDIGO guidelines (Kidney Disease: Improving Global Outcomes) defining albuminuria as urine albumin creatinine ratio in a random spot urine >30 mg/g [24].

Genotyping

The *TBC1D4* variant was genotyped using the KasPAR assay (LGC Genomics, Hoddesdon, the UK), and European admixture proportions were estimated with a proportion of one equal to 100% Inuit ancestry and zero equal to 100% European ancestry, using data from the Illumina MetaboChip [17].

Analyses

For cross-sectional analyses, we used baseline data from individuals at the time of their first visit. We examined the effect of diabetes on kidney function expressed as dichotomous outcomes albuminuria yes/no and CKD yes/no

using logistic regression. For both outcomes, we performed a crude analysis of the effect of diabetes, and in model 1, we adjusted for age and sex. In model 2, we further adjusted for body mass index (BMI), systolic and diastolic blood pressure, low-density lipoprotein (LDL) cholesterol, triacyl glycerol (TG) and smoking. In model 3, we further adjusted for the *TBC1D4* variant and genetic admixture. We did a sensitivity analysis using HbA_{1c} diabetes criteria instead of OGTT criteria and ran analyses again to quantify differences in associations between the two diagnostic measures. We used an additive model of the effect of the *TBC1D4* variant and European genetic admixture on microalbuminuria and CKD assuming a comparing homozygous (HO) with wild-type (WT) and heterozygous (HT) carriers combined. In separate analyses, we also tested a recessive model but found no clinical effect with that assumption. In an unadjusted model, we tested the effect of the *TBC1D4* variant and genetic admixture, and then in model 1, we adjusted for age and sex.

Using baseline and follow-up data for those who participated twice, we used linear regression to test predictors of continuous measures of kidney function, measured as changes in urinary albumin creatinine ratio (UACR) and eGFR from baseline to follow-up, adjusted for baseline values. For both outcomes, we first tested the effect of diabetes on eGFR and UACR adjusted for baseline values. In model 1, we adjusted for age and sex. In model 2, we further adjusted for BMI, systolic and diastolic blood pressure, LDL cholesterol, TG, smoking and years between baseline and follow-up, and in model 3, we further adjusted for the effect of the *TBC1D4* variant and genetic admixture. We checked the normality of distributions of covariates and log10 transformed UACR to get a better fit. We back transformed for interpretation of parameter estimates that therefore reflect proportional changes in UACR.

Statistical significance level was set at 5% using complete cases. Data was managed and analysed using SAS 9.4 [25–27].

Results

Baseline characteristics of study population

Baseline characteristics of the 3,909 with complete OGTT information are shown in Table 1. For those with normoglycemia, median age was 45.2 years and 44.5% were male. Median age was 57.4 years and 47.8% were male, among the 362 individuals (9.3%)

Table 1. Baseline characteristics of participants.

	Normoglycemia		Diabetes	
	N total	Median [IQR] or n	N total	Median[IQR] or n
N total	3,547	3.547	362	362
Age (years)	3,547	45.2 [36.7,55.0]	362	57.4 [48.1,67.6]
Males (%)	3,547	1,577 (44.5)	362	173 (47.8)
BMI (kg/m^2)	3515	25.5 [22.6,29.3]	350	28.2 [23.2,32.5]
Systolic blood pressure (mmHg)	3,523	124.0 [113.0,137.0]	360	136.5 [123.5,153.0]
Diastolic blood pressure (mmHg)	3,524	76.0 [69.0,84.0]	360	80.0 [71.0,88.5]
Hba_{1c} (mmol/mol)	3,537	38.1 [35.5,41.0]	361	42.1 [38.8,46.4]
Blood glucose at 0 minutes (mmol/L)	3,547	5.6 [5.2,5.9]	362	7.1 [6.1,7.6]
Blood glucose at 120 minutes (mmol/L)	3,547	5.3 [4.3,6.5]	362	9.9 [6.4,13.6]
Total cholesterol mmol/l	3,547	5.8 [5.0,6.6]	361	6.0 [5.3,6.9]
LDL (mmol/l)	3,524	3.5 [2.9,4.3]	357	3.6 [2.9,4.4]
TG (mmol/l)	3,547	1.0 [0.8,1.4]	361	1.2 [0.8,1.8]
TBC1D4 (HO)	3,065	70 (2.3)	306	46 (15.0)
TBC1D4 (HT)	3.065	834 (27.2)	306	79 (25.8)
Inuit genetic admixture (%)	3,126	0.77 [0.61,0.91]	316	0.8 [0.64,0.97]
Smoking (%)	3,159	2,197 (70.5)	316	180 (57.0)
Albumin/creatinine ratio (mg/g)	3,241	7.0 [5.0,13.0]	322	14.0 [7.0,35.0]
Albuminuria yes/no (mg/g)	3,241	309 (9.5)	322	89 (27.6)
eGFR ($ml/min/1.73\ m^2$)	3,526	93.8 [79.2,105.5]	360	88.8 [74.7,100.9]
Chronic kidney disease ($eGFR<60\ ml/min/1.73\ m^2$)	3,526	223 (6.3)	360	39 (10.8)

Data are median [interquartile range] and n (%). Diabetes is screen detected by OGTT criteria and self-reported..

Table 2. TBC1D4 genotype distribution among individuals with and without albuminuria and CKD.

	Albuminuria			CKD		
Genotype distribution	N	Yes	No	N	Yes	No
TBC1D4 HO (% of total)	126 (3.7)	13 (3.4)	113 (3.7)	142 (3.7)	8 (3.1)	134 (3.7)
TBC1D4 HT (% of total)	893 (26.3)	105 (27.6)	788 (26.1)	1,060 (27.3)	60 (23.4)	1,000 (27.6)
TBC1D4 WT (% of total)	2,382 (70.0)	262 (69.0)	2,120 (70.2)	2,682 (69.0)	180 (73.5)	2,493 (68.7)
Total (%)	3,401 (100)	380 (11.2)	3,021 (88.8)	3,884 (100)	257 (6.6)	270 (93.4)

Data are n and (%) of total.

with diabetes. Comparing individuals with and without diabetes, more had albuminuria (27.6% vs. 9.5%) and CKD (10.8% vs. 6.3%) and more were homozygous for the *TBC1D4* variant (15% vs. 2.3%). The genotype distribution of the *TBC1D4* variant among individuals with albuminuria and CKD is shown in Table 2.

Cross-sectional effect of diabetes on albuminuria

A crude effect of diabetes on albuminuria using logistic regression gave an OR of 3.6 with 95% CI (2.76, 4.75) $p < 0.001$ (Table 3). In the fully adjusted model 3, diabetes remained associated with an increased risk of albuminuria with an OR of 2.37, 95% CI (1.69, 3.33) $p < 0.001$. Also in model 3, the HO *TBC1D4* genotype was associated with a decreased risk of albuminuria with an OR of 0.44, 95% CI (0.22, 0.90) $p = 0.02$.

In a sensitivity analysis, we used HbA_{1c} criteria as diabetes definition instead of OGTT criteria and ran all analyses again. Statistically significant associations were maintained except in model 3 where the *TBC1D4* variant was no longer associated with a lower OR of albuminuria (data not shown).

Cross-sectional effect of diabetes on chronic kidney disease (CKD)

The crude effect of diabetes on CKD was also estimated with logistic regression and gave an OR of 1.8 with 95% CI (1.3, 2.6) $p = 0.001$ (Table 4). *TBC1D4* HO carrier status conferred a decreased but statistically insignificant effect on CKD. In a sensitivity analysis using HbA_{1c} criteria for diabetes definition instead of OGTT criteria, all models and statistically significant associations were unchanged (data not shown).

Effect of diabetes on UACR at follow-up

The effect of diabetes on UACR adjusted for baseline UACR showed a proportionate increase in UACR by a factor of 1.13 with 95% CI (1.00,1.27) $p = 0.05$, and baseline UACR gave a proportionate increase in follow-

Table 3. Cross-sectional analysis of the effect of diabetes on albuminuria: stepwise logistic regression presented as odds ratios (ORs).

Outcome albuminuria	Crude OR	P value	Model 1 OR	P value	Model 2 OR	P value	Model 3 OR	P value
Diabetes vs. no diabetes	3.6 (2.76,4.75)	**<0.001**	2.34 (1.76,3.11)	**<0.001**	2.13 (1.55,2.93)	**<0.001**	2.37 (1.69,3.33)	**<0.001**
Male vs. female			0.88 (0.71,1.09)	0.25	0.81 (0.63,1.03)	0.09	0.83 (0.64,1.06)	0.14
Age (years)			1.05 (1.04,1.06)	**<0.001**	1.04 (1.03,1.05)	**<0.001**	1.04 (1.03,1.05)	**<0.001**
BMI (kg/m^2)					0.98 (0.95,1.00)	0.07	0.98 (0.95,1.01)	0.14
Systolic blood pressure (mmHg)					1.02 (1.01,1.03)	**<0.001**	1.02 (1.01,1.03)	**<0.001**
Diastolic blood pressure (mmHg)					1.00 (0.99,1.01)	0.83	1.00 (0.99,1.01)	0.76
LDL (mmol/l)					0.96 (0.86,1.07)	0.45	0.93 (0.83,1.05)	0.25
TG (mmol/l)					1.24 (1.03,1.50)	**0.02**	1.32 (1.09,1.60)	**0.01**
Smoking vs. no smoking					0.85 (0.66,1.11)	0.23	0.84 (0.64,1.10)	0.21
HO vs (HT+WT)							0.44 (0.22,0.90)	**0.02**
Inuit genetic admixture (per % point increase)							1.01 (1.00,1.01)	**0.001**

Data are odds ratio (OR) with confidence limits, and p values are considered significant below 5% (shown in bold). The crude model shows the effect of diabetes on CKD. Model 1: adjusted for age and sex. Model 2: model 1 + BMI, systolic and diastolic blood pressure, LDL cholesterol, TG and smoking. Model 3: model 2 + the TBC1D4 variant and Inuit genetic admixture.

Table 4. Cross sectional analysis of the effect of diabetes on CKD: stepwise logistic regression presented as odds ratios (ORs).

Outcome CKD	Crude OR	P value	Model 1 OR	P value	Model 2 OR	P value	Model 3 OR	P value
Diabetes vs. no diabetes	1.8 (1.3,2.6)	**0.001**	1.01 (0.69,1.5)	0.97	0.78 (0.51,1.19)	0.24	0.85 (0.55,1.32)	0.47
Male vs. female			1.07 (0.83,1,38)	0.62	1.03 (0.78,1.35)	0.84	1.01 (0.76,1.33)	0.95
Age (years)			1.06 (1.05,1.07)	**<0.001**	1.05 (1.04,1.06)	**<0.001**	1.05 (1.04,1.06)	**<0.001**
BMI (kg/m^2)					0.95 (0.92,0.98)	**0.001**	0.94 (0.92,0.97)	**0.003**
Systolic blood pressure (mmHg)					1.01 (1.00,1.02)	**0.009**	1.01 (1.00,1.02)	**0.02**
Diastolic blood pressure (mmHg)					1.00 (0.98,1.01)	0.74	1.00 (0.99,1.01)	0.94
LDL (mmol/l)					1.07 (0.95,1.21)	0.28	1.09 (0.96,1.23)	0.17
TG (mmol/l)					1.71 (1.40,2.08)	**<0.001**	1.62 (1.32,2.00)	**<0.001**
Smoking vs. no smoking					0.88 (0.65,1.19)	0.40	0.96 (0.70,1.30)	0.80
HO vs (HT+WT)							0.76 (0.34,1.71)	0.50
Inuit genetic admixture (per % point increase)							0.99 (0.99,1.0)	**0.03**

Data are odds ratio (OR) with confidence limits, and p values are considered significant below 5%. The crude model shows the effect of diabetes on CKD. Model 1: adjusted for age and sex. Model 2: model 1 + BMI, systolic and diastolic blood pressure, LDL cholesterol, TG and smoking. Model 3: model 2 + the TBC1D4 variant and genetic admixture.

up UACR by a factor of 1.79 with 95% CI (1.65,1.95) $p < 0.001$ (Table S1 and Figure 1). The *TBC1D4* variant was associated with lower UACR during follow-up, although not statistically significant. The statistically significant effect of diabetes was not maintained after adjustment in model 3.

Effect of diabetes on eGFR at follow-up

We estimated the effect of diabetes at baseline on eGFR at follow-up adjusted for baseline eGFR values using a linear regression model (Table S1 and Figure 2). In a model only adjusted for baseline eGFR, diabetes was associated with a decrease in follow-up eGFR of −4.83 ml/min/1.73 m^2 with 95% CI (−8.66,-1.01), $p = 0.01$, and baseline eGFR was positively associated with follow-up eGFR with an increase of 0.42 ml/min/1.73 m^2 with 95% CI (0.37,0.47) $p < 0.001$. In further adjusted models; however, diabetes was not associated with eGFR at follow-up. An increase in baseline eGFR was associated with follow-up eGFR, with an increase of 0.34 ml/min/1.73 m^2, 95% CI (0.30,0.38) $p < 0.001$ for a one-unit increase in baseline eGFR. Further adjustment for the *TBC1D4* variant did not alter effect sizes significantly.

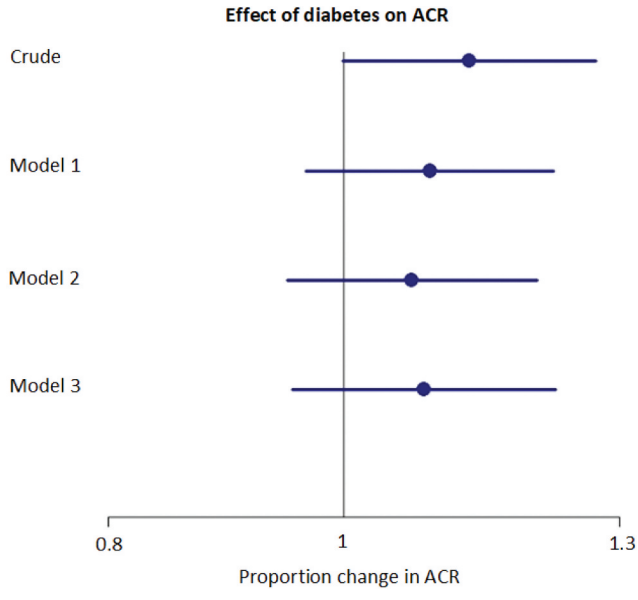

Figure 1. The effect of diabetes on eGFR at follow-up adjusted for baseline eGFR using linear regression, expressed as a proportion change in follow-up eGFR. Model 1: adjusted for age and sex. Model 2: model 1 + BMI, systolic and diastolic blood pressure, LDL cholesterol, TG, smoking and years between baseline and follow-up. Model 3: model 2 + the TBC1D4 variant and admixture (from Table S2).

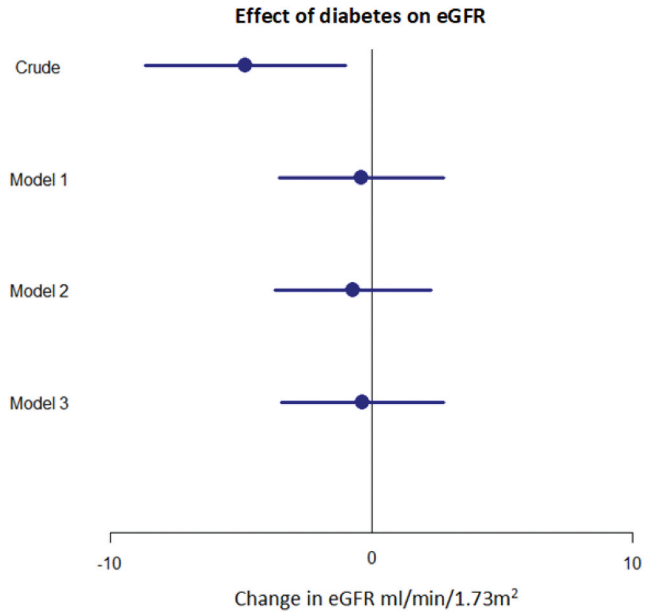

Figure 2. The effect of diabetes on ACR at follow-up adjusted for baseline ACR using linear regression, expressed as a proportion change in follow-up ACR. Model 1: adjusted for age and sex. Model 2: model 1 + BMI, systolic and diastolic blood pressure, LDL cholesterol, TG, smoking and years between baseline and follow-up. Model 3: model 2 + the TBC1D4 variant and admixture (from Table S1).

Discussion

Diabetes in Greenland was cross-sectionally associated with an elevated risk of albuminuria, but not with an elevated risk of CKD. A HO *TBC1D4* genotype conferred an increased risk of diabetes and indicated a protective effect on albuminuria. A sensitivity analysis diagnosing diabetes by HbA_{1c} criteria did not significantly change estimates of diabetes by OGTT criteria, except for the potential renoprotective effect of the *TBC1D4* variant on albuminuria in the cross-sectional model 3 that was not maintained. Diabetes did not significantly predict changes in eGFR or UACR from baseline to follow-up in the longitudinal analyses in adjusted models.

Diabetes conferred increased risk of albuminuria with maintained effect after adjustments for multiple confounders, OR 2.37, 95% CI (1.69, 3.33) $p < 0.001$. This corresponds well to the findings in European and North American white populations [26,27]. Smoking did not increase the risk of albuminuria, possibly related to the fact that there were fewer smokers among individuals with diabetes than those without (Table 1: 57.0% vs. 70.5%). Fewer individuals who smoke among those with diabetes may relate to changes in health behaviour leading to smoking cessation after a diabetes diagnosis.

HO *TBC1D4* carriers had a lower risk of albuminuria than non-HO carriers with OR 0.44, CI (0.22,0.90) $p = 0.02$. The

potential renoprotective effect of the variant could be due to the diabetes form that it induces, with intermittent postprandial hyperglycaemia, which is different from the cardiometabolic diabetes types that we know from the rest of the world. Consequently, the risk of microvascular complications could be lower, a theory that could be supported by a recent study finding a low prevalence of retinopathy among Greenlandic Inuit with diabetes [28]. This idea also supports the concept of glucose homoeostasis improvement through a *TBC1D4* independent pathway, for instance via physical activity [29]. Physical activity is also shown to increase skeletal muscle myokine production, allowing for cross-talk between muscles and other organs like the pancreas, gut, adipose tissue and brain, which may play a role in this case [30]. Moreover, low-grade albuminuria may also reflect generalised vascular damage and defect endothelial function, thereby also constituting a cardiovascular risk [31]. Accordingly, an association may exist between albuminuria and CVD in this study.

Diabetes did not confer an increased risk of CKD; however, we cannot convincingly rule out that there could be an effect. CKD represents prolonged kidney damage and is usually preceded by albuminuria. One reason for not finding increased CKD risk for individuals with diabetes may relate to diabetes being screen detected, and thus the condition may have been identified before symptoms would have led the individual to get checked by a health care professional. As such, we may have studied the early stages of diabetes, when complication rates are low or not yet present. A weakness of this study is the inability to replicate the findings in a larger or different population. Another reason for not finding an association with more serious kidney outcomes may lie in the unique genetic background that characterises this isolated population, where risk variants are present with high effect sizes [32]. Genetic variants carry a significant weight in explaining diabetes causes in the Greenlandic population, and although multiple variants have been identified, there are undoubtedly more to be found.

Accordingly, diabetes among Inuit in Greenland may be a different type of diabetes. The *TBC1D4* variant may confer one of many diabetes types, like MODY (maturity onset diabetes of the young) identified in 1974 as a dominantly inherited non-insulin diabetes type in a European population [33]. Today, MODY is defined by beta cell dysfunction caused by known mutations in different genes, the most frequent types being the *GCK* and *HNF1A* genes [34,35]. Mutations in *GCK* (also called MODY2) confer mild fasting hyperglycaemia throughout, but patients do not tend to get diabetes complications and do not require treatment. Diabetes in Greenland could be a combination of *TBC1D4* diabetes and other yet unknown genetic forms like MODY, without increased risk of complications.

In the longitudinal analyses we did not find that diabetes predicted significant changes in UACR or eGFR. Baseline values of age and time between baseline and follow-up were associated with UACR and eGFR, respectively. Reasons for this may again relate to early detection of diabetes, which may lead to kidney protective medicaments and the large genetic contribution to developing diabetes in the first place. Also competing risk from mortality and loss-to-follow up for other reasons could be reasons for not finding significant associations.

A strength of this study is the inclusion of participants from all regions in Greenland, from both settlements and towns. Another strength is using both a cross-sectional design and follow-up of a large proportion of participants. As such the association of diabetes with albuminuria and CKD was tested in a larger population than in a clinical setting and had the potential to detect predictive parameters for changes in UACR and eGFR.

From a clinical point of view, the results of this study bring forward the potential relevance of genetic testing of individuals with diabetes in Greenland. It is not unlikely that the clinical implications of the *TBC1D4* diabetes form are milder and complication screening intervals could be reduced for homozygous carriers, provided neuropathy risk is also lower. We recently examined the effect of the variant on cardiovascular disease (CVD) in Greenland and could not convincingly rule out increased risk of CVD for HO carriers nor could we convincingly conclude that diabetes increases the risk of CVD [36].

In conclusion, we found that diabetes in Greenland is associated with an increased risk of albuminuria, but not CKD. Diabetes did not predict changes UACR or eGFR over time. It is difficult to confirm or reject an effect of the *TBC1D4* variant on kidney function, but an unexpected potential renoprotective effect calls for further studies. Diabetes in Greenland seems to be dissimilar to the diabetes form that we know from the rest of the world and is determined to a larger extent by genetics. It would be relevant in the future to combine epidemiological and genetic studies with patient records to get unbiased measures of kidney function and albuminuria.

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Disclosure statement

MO and LJD now work at Novo Nordisk.

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