The Effect of Diabetes and the Diabetogenic *TBC1D4* p.Arg684Ter Variant on Kidney Function in Inuit in Greenland

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Abstract

Objective

Diabetes prevalence in Greenland is high and increasing. 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.

Research Design and Methods

Health survey data and *TBC1D4* genotypes from 5,336 Greenlanders was used to estimate odds ratios (ORs) of albuminuria (>30 mg/g creatinine) and chronic kidney disease (CKD, eGFR<60 ml/min/1.73m2), comparing individuals with and without diabetes. Using baseline and follow-up data from individuals who participated in two surveys we examined the effect of diabetes on eGFR and urinary albumin creatinine ratio (UACR) at follow-up, stepwise adjusting for baseline confounders including the *TBC1D4* variant.

Results

A total of 9.3% had diabetes of the 3,909 participants with complete data. Albuminuria and CKD was found in 27.6% and 9.5% among those with and without diabetes respectively. Diabetes was associated with 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. Diabetes was not associated with changes in eGFR or UACR over a median of 11.3 years.

Conclusion

Diabetes conferred increased risk of albuminuria and the *TBC1D4* variant was associated with decreased risk of albuminuria, but neither were associated with CKD. The presence/absence of diabetes did not predict changes in eGFR and UACR in longitudinal analyses. The potential renoprotective association of the *TBC1D4* variant on albuminuria calls for further studies.

Objective

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 (15), 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 characterized by chronic hyperglycemia leading to damage of the vascular system with a 3-fold 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 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 study from Greenland analyzing 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 different eGFR cut-off value could be relevant to discuss. 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 hyperglycemia(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.

Research Design 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 (B2018 (2)) 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 three-point follow up.

Participants completed lifestyle questionnaires, clinical examinations and a majority contributed with paraclinical 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 two-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 2006 World Health Organization (WHO) OGTT criteria of fasting plasma glucose ≥7.0 mmol/l, 2 hour plasma glucose ≥11.1mmol/l(20) or self-reported by questionnaire. In a sensitivity analysis diabetes was defined by Hba_{1c} ≥48mmol/l as recommended by WHO in 2011(21).

Kidney function

Frozen samples were used to estimate kidney function. Blood stored at the laboratory at Steno Diabetes Center Copenhagen at -80°C from the years 1999-2001 and 2005-2010 were analyzed for creatinine levels using "Vitros 5600" Ortho Clinical Diagnostics(22). Estimated glomerular filtration rate (eGFR) was calculated using serum creatinine values expressed as milliliters 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/1.73m^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, 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, triacylglycerol (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 also tested the effect of the *TBC1D4* variant and European genetic admixture on microalbuminuria and CKD assuming a recessive effect comparing homozygous (HO) with wildtype (WT) and heterozygous (HT) carriers combined. In an unadjusted model we tested the effect of the *TBC1D4* variant and genetic admixture, 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 eGFR and urinary albumin creatinine ratio (UACR) 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 analyzed 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%) 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%). Genotype distribution of the *TBC1D4* variant among individuals with albuminuria and CKD is shown in Table 2. We found that the HO *TBC1D4* genotype was evenly distributed between those with and without albuminuria and CKD respectively.

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 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 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 (supplementary Table 1). In a model only adjusted for baseline eGFR, diabetes was associated with a decrease in follow-up eGFR of -4.83 ml/min/1.73m^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/1.73m^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/1.73m^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.

Effect of diabetes on UACR at follow-up

The effect of diabetes on UCR 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-up UACR by a factor of 1.79 with 95% CI (1.65,1.95) p<0.001 (supplementary Table 2). The *TBC1D4* variant did not significantly predict changes in UACR and the statistically significant effect of diabetes was not maintained after adjustment in model 3.

Conclusion

Diabetes conferred increased risk of albuminuria and the *TBC1D4* variant was associated with decreased risk of albuminuria, but neither were associated with CKD. The presence/absence of diabetes did not predict changes in eGFR and UACR in longitudinal analyses. The potential renoprotective association of the *TBC1D4* variant on albuminuria calls for further studies.

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Declarations

Conflict of interest and author statements

The manuscript is not under consideration by another journal and has not been published in another journal. All co-authors have made substantial contributions to design, analysis of the research and drafting of the manuscript and have reviewed and accepted the contents of the manuscript prior to its submission. The authors declare no conflicts of interest.

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Tables

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/m²)	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/1.73m^2)	3,526	93.8 [79.2,105.5]	360	88.8 [74.7,100.9]
Chronic Kidney Disease (eGFR < 60 ml/min/1.73m^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*

Genotype distribution	Albuminuria			CKD		
	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 is n and (%) of total.

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

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%. 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 (OR)*

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.

Figures

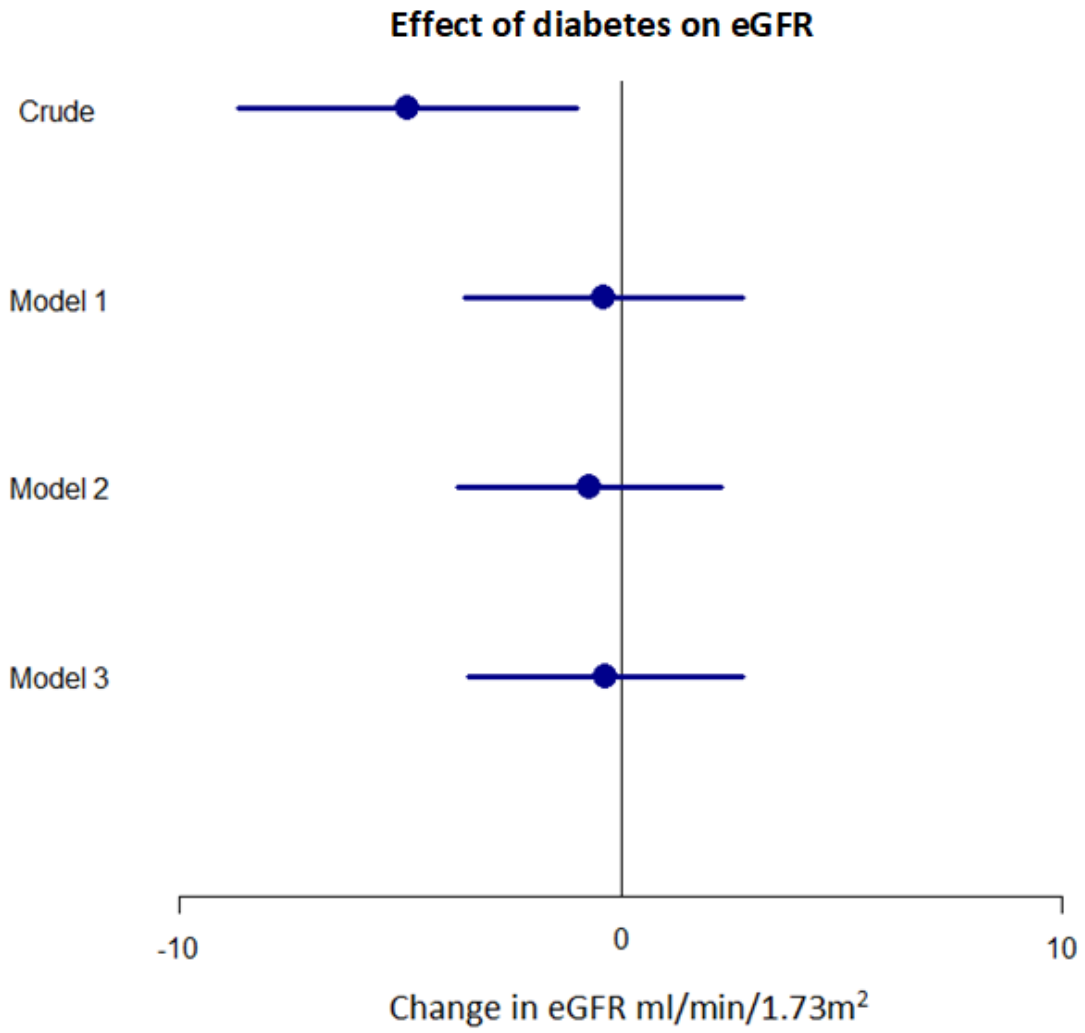

Figure 1

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 supplementary Table 5)

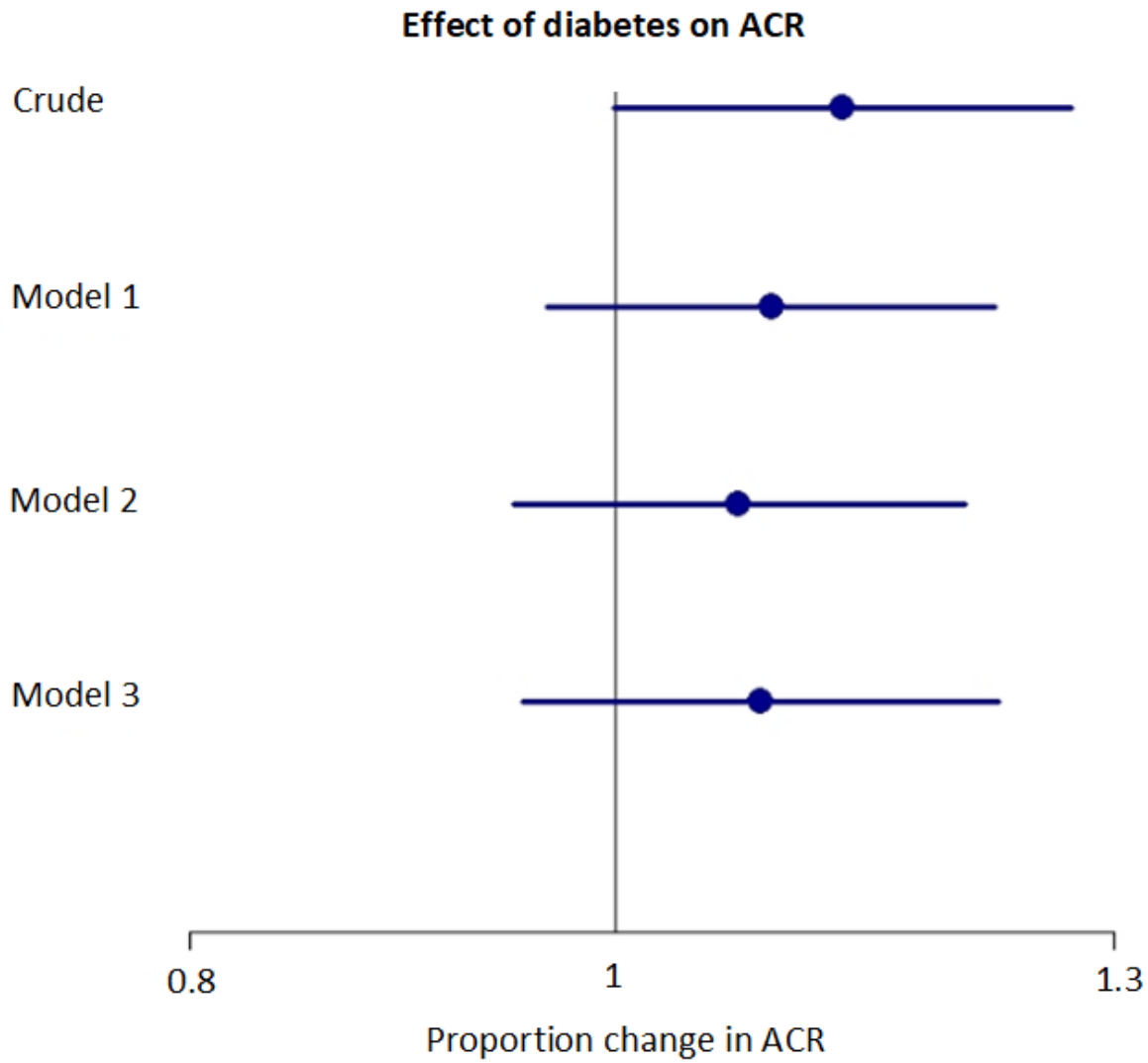

Figure 2

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 supplementary Table 6)

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryTables12.docx