Diabetes & Metabolism 45 (2019) 261–267

Available online at
ScienceDirect
www.sciencedirect.com

Elsevier Masson France
EM|consulte
www.em-consulte.com

Original article

The relationship of family history and risk of type 2 diabetes differs by ancestry

Brian G. Kral MD, MPH*, Diane M. Becker ScD, MPH, Lisa R. Yanek MPH, Dhananjay Vaidya MBBS, PhD, Rasika A. Mathias ScD, Lewis C. Becker MD, Rita R. Kalyani MD, MHS

The Johns Hopkins GeneSTAR Research Program, Department of Medicine, The Johns Hopkins Medical Institutions, 1830, East Monument Street, Room 8023, 21287 Baltimore, MD, USA

ARTICLE INFO

Article history:
Received 13 December 2017
Received in revised form 7 May 2018
Accepted 14 May 2018
Available online 21 May 2018

Keywords:
Ancestry
Epidemiology
Family history
Race
Type 2 diabetes

ABSTRACT

Aim. – Type 2 diabetes (T2DM) in a first-degree relative is a risk factor for incident diabetes. Americans of African ancestry (AA) have higher rates of T2DM than Americans of European ancestry (EA). Thus, we aimed to determine whether the presence, number and kinship of affected relatives are associated with race-specific T2DM incidence in a prospective study of participants from the Genetic Study of Atherosclerosis Risk (GeneSTAR), who underwent baseline screening including a detailed family history.
Methods. – Nondiabetic healthy siblings ($n = 1405$) of patients with early-onset coronary artery disease (18–59 years) were enrolled (861 EA and 544 AA) and followed for incident T2DM (mean 14 ± 6 years).
Results. – Baseline age was 46.2 ± 7.3 years and 56% were female. T2DM occurred in 12.3% of EA and 19.1% of AA. Among EA, 32.6% had ≥ 1 affected first-degree relatives versus 53.1% in AA, $P < 0.0001$. In fully adjusted Cox proportional hazard analyses, any family history was related to incident T2DM in EA (*HR* = 2.53, 95% CI: 1.58–4.06) but not in AA (*HR* = 1.01, 0.67–1.53). The number of affected relatives conferred incremental risk of T2DM in EA with *HR* = 1.82 (1.08–3.06), 4.83 (2.15–10.85) and 8.46 (3.09–23.91) for 1, 2, and ≥ 3 affected, respectively. In AA only ≥ 3 affected increased risk (*HR* = 2.45, 1.44–4.19). Specific kinship patterns were associated with incident T2DM in EA but not in AA.
Conclusions. – The presence of any first-degree relative with T2DM does not discriminate risk in AA given the high race-specific prevalence of diabetes. Accounting for the number of affected relatives may more appropriately estimate risk for incident diabetes in both races.

Introduction

A family history of type 2 diabetes (T2DM) in a first-degree relative including a parent or sibling is a strong independent risk factor for T2DM, with greater than two-fold excess risk having an affected parent or sibling compared to no family history [1–4]. Of major public health importance, Americans of African ancestry (AA) have rates of T2DM that are up to two times higher than Americans of European ancestry (EA) [5–7] and are at greater risk of diabetes-associated complications [8–10]. Differences in T2DM risk factors, including age, race, fasting plasma glucose levels, obesity and sedentary lifestyle are in general thought to represent as much as 45% of the observed racial disparity in the disease [11,12]. Most genetic research has focused on EA populations that show a heritability estimate of 72% including a large meta-analysis of international twin registries [13]. The limited data in AA also show strong evidence of heritability with observed clustering of T2DM within families [14]. However, no particularly robust genetic signals that are common to both races have been found to date that would account for any differential T2DM risk by race [15]. A greater risk from maternal T2DM compared to paternal diabetes has been reported in EA, yet little is known about relative kinship risk in AA [16–19]. To date, no studies have examined whether differences in the number or kinship of affected relatives differentially impacts the risk of incident T2DM in persons of different races.

We hypothesized that specific family patterns of prevalent T2DM may be race specific in explaining the much higher incidence of T2DM in AA compared to EA populations. We thus examined the extent to which patterns of family history, including the kinship, sex of the affected relatives and the number of affected

Abbreviations: AA, African American; BMI, body mass index; CAD, coronary artery disease; EA, European American; HDL, high density lipoprotein; LDL, low density lipoprotein; T2DM, type 2 diabetes.

* Corresponding author.
E-mail address: bkral@jhmi.edu (B.G. Kral).

https://doi.org/10.1016/j.diabet.2018.05.004
1262-3636/

family members was associated with the risk of incident T2DM by race in a prospective study of apparently healthy EA and AA individuals from identified families.

Methods

Sample and recruitment

The study population consisted of asymptomatic, healthy siblings from AA and EA families in the ongoing GeneSTAR family cohort where a family index case had documented early-onset coronary artery disease (CAD) as previously described [20]. Index cases did not participate in the longitudinal study but apparently healthy siblings were enrolled from 1983 through 2007 if they were less than 60 years of age and had no known history of CAD.

A total of 1640 siblings were enrolled from 1983 to 2007. We excluded all siblings with known diabetes (history of diabetes and/or use of glucose-lowering medications ($n = 128$) or newly diagnosed diabetes (fasting plasma glucose level ≥ 7 mmol/L or 126 mg/dL) at the time of baseline screening ($n = 42$). We also excluded individuals with missing diabetes status at baseline ($n = 20$) or follow-up ($n = 45$). These individuals were, however, included in family history enumerations. There were no differences in age, sex, African American ancestry, follow-up time or the prevalence of a family history between participants included in the study compared to individuals excluded for missing diabetes status. Thus, the sample included 1405 initially nondiabetic siblings (including 861 EA and 544 AA), representing 763 different families. The study was approved by the Johns Hopkins Medicine Institutional Review Board and all participants gave informed consent.

Baseline screening

Participants underwent a comprehensive baseline risk factor screening following a 12-hour overnight fast. Medical history and current medication use were elicited. Detailed pedigrees and family T2DM history were obtained. Height was determined using a fixed stadiometer and weight was measured on a balance scale with the subject wearing light clothing and no shoes. Body mass index (BMI) was calculated as kg/m^2. Blood pressure was measured three times over the course of the 8-hour day in accordance to the American Heart Association guidelines. Hypertension was defined as an average blood pressure ≥ 140 mmHg systolic, or ≥ 90 mmHg diastolic, and/or use of an antihypertensive drug. Blood was obtained and total cholesterol, high-density lipoprotein (HDL) cholesterol, and triglyceride levels were measured using the United States Centres for Disease Control standardized methods [21]. Low-density lipoprotein (LDL) cholesterol was estimated using the Friedewald formula [22]. Glucose levels were measured using the glucose oxidase method [23]. T2DM was defined as a physician-diagnosed history, a measured fasting plasma glucose level ≥ 7 mmol/L, and/or use of prescribed glucose-lowering medications. In order to assess physical fitness level, all participants underwent a maximal graded treadmill test using a modified Bruce protocol. Maximum metabolic equivalent of task (MET) level and treadmill time was recorded. Total MET minutes were calculated as the product of minutes performed $\times$ MET level for each escalating stage during the treadmill test. Smoking status was assessed by self-report and confirmed by exhaled carbon monoxide (CO), where participants who reported no current smoking but who had exhaled CO ≥ 8 ppm were reclassified as current smokers.

Follow-up screening and assessment of incident T2DM

Participants were followed for the development of T2DM. A standardized instrument was administered every five years via postal mail or via telephone by a trained interviewer to elicit a history of a new diabetes diagnosis and/or the use of medications for diabetes. T2DM was the primary event endpoint. Incident T2DM was assessed at follow-up visits using the same definition for diabetes as described at the baseline-screening visit.

Statistical analyses

Statistical analyses were performed using SAS version 9.2 and R version 3.1.2. Variables were examined for skewness and kurtosis and log-transformed to normality as needed. For continuous variables, frequencies, means and standard deviations were examined. For bivariable analyses among continuous variables, the *t*-test and ANOVA were used; contingency table arrays and the χ^2 statistic were used for the examination of relationships between categorical variables. Laboratory values were expressed using conventional units. Kaplan–Meier survival curves for incident T2DM were used to examine the unadjusted relationship of the number of first-degree relatives affected with T2DM to the outcome, incident T2DM, separately for EA and AA. Cox proportional hazard modelling incorporating a kinship matrix in the R coxme package was performed for incident T2DM with the covariates age, sex, race, any family history of T2DM and an interaction term of race and family history. Cox proportional hazard models predicting incident T2DM were performed stratified by race to examine the predictive significance of:

- any affected first degree relative;
- the number of affected relatives, adjusting for age and sex (Model 1);
- then age, sex, current smoking status, systolic blood pressure, fasting serum glucose, HDL cholesterol, triglycerides, BMI and physical fitness level (Model 2).

Similar hazard models were performed separately for specific affected kinship patterns, including any parent, maternal only, paternal only, both parents, any sibling, parent and sibling, females only, males only, and both female and male family histories, all compared to no history.

Results

Baseline population demographics

Table 1 shows the baseline sample characteristics and follow-up time by race and incident type 2 diabetes status. Overall, 12.3% of EA and 19.1% of AA developed T2DM during follow-up ($P = 0.0005$ for racial difference), although follow-up times were shorter for AA. Incident T2DM at 10 years was 4.0% for EA and 13.8% for AA ($P < 0.0001$ for $n = 1084$ with 10-year follow-up). The rate of T2DM per 1000 person years in our study was 8.1 in EA and 16.3 in AA. AA females had the highest incidence of T2DM that was almost double that of EA females who had the lowest incidence (20.5% versus 10.8%, $P = 0.0002$). The incidence of T2DM was 16.4% in AA males and 13.8% in EA males. In both races, hypertension, higher baseline BMI, fasting glucose and triglycerides as well as lower HDL cholesterol and physical fitness level (total MET minutes) were significantly associated with incident T2DM. In EA, older age, current smoking status and higher total and LDL cholesterol were also associated with incident T2DM. Interestingly, there was no significant racial difference in baseline fasting glucose level among those subjects who developed T2DM. However, obesity (BMI ≥ 30 kg/m^2) was much more prevalent in AA compared to EA among those with incident T2DM (69 versus 43%, $P = 0.0005$) or without (45 versus 24%, $P < 0.0001$).

Table 1
Baseline participant characteristics and follow-up time by incident type 2 diabetes status, in European Americans and African Americans ($n = 1.405$).

	European Americans			African Americans		
	No incident diabetes $n = 755$	Incident diabetes $n = 106$	Within EA *P*-value	No incident diabetes $n = 440$	Incident diabetes $n = 104$	Within AA *P*-value
Age, mean (SD), years	45.6 (7.6)	47.0 (6.2)	0.04	46.7 (6.9)	47.3 (7.3)	0.46
Female sex, n (%)	379 (50.2)	46 (43.4)	0.19	287 (65.2)	74 (71.2)	0.25
Fasting glucose, mean (SD), mmol/L	4.89 (0.57)	5.40 (0.62)	< 0.0001	4.94 (0.61)	5.56 (0.76)	< 0.0001
Current smoker, n (%)	200 (26.5)	41 (38.7)	0.009	135 (30.7)	34 (32.7)	0.69
Hypertension, n (%)	290 (38.4)	41 (62.3)	< 0.0001	227 (51.6)	66 (63.5)	0.03
Total cholesterol, mean (SD), mmol/L	5.80 (1.16)	6.12 (1.37)	0.03	5.47 (1.21)	5.52 (1.30)	0.71
HDL cholesterol, mean (SD), mmol/L	1.40 (0.43)	1.20 (0.38)	< 0.0001	1.47 (0.44)	1.25 (0.35)	< 0.0001
LDL cholesterol, mean (SD), mmol/L	3.69 (1.08)	3.92 (1.16)	0.048	3.47 (1.12)	3.56 (1.22)	0.46
Triglycerides, mean (SD), mmol/L	1.61 (1.23)	2.34 (1.54)	< 0.0001	1.18 (0.63)	1.61 (0.98)	< 0.0001
BMI, mean (SD), kg/m²	27.3 (5.0)	30.2 (4.8)	< 0.0001	30.0 (6.2)	34.4 (7.1)	< 0.0001
BMI category, n (%)						
Normal	251 (33.3)	11 (10.4)	< 0.0001	89 (20.2)	6 (5.8)	< 0.0001
Overweight	326 (43.2)	50 (47.2)		152 (34.6)	26 (25.0)	
Obese	178 (23.6)	45 (42.5)		199 (45.2)	72 (69.2)	
Total MET level (MET minutes)	114.8 (50.3)	96.0 (46.5)	0.0003	80.1 (43.1)	62.5 (35.1)	< 0.0001
Follow-up time, mean (SD), years	15.1 (7.2)	15.4 (5.6)	0.68	12.4 (3.2)	9.1 (3.5)	< 0.0001

AA: African American; BMI, body mass index; EA: European American; HDL: high-density lipoprotein; LDL: low-density lipoprotein; MET: metabolic equivalent of task; NA: not applicable.

Table 2
Family history definitions of type 2 diabetes by incident type 2 diabetes status, in European Americans and African Americans ($n = 1.405$).

	European American			African American		
	No incident diabetes $n = 755$	Incident diabetes $n = 106$	Within EA *P*-value	No incident diabetes $n = 440$	Incident diabetes $n = 104$	Within AA *P*-value
Any first-degree relative, n (%)	229 (30.3)	52 (49.1)	< 0.0001	223 (50.7)	66 (63.5)	0.02
Number of affected first-degree relatives, n (%)						
None	526 (69.7)	52 (49.1)	Reference	217 (49.3)	38 (36.5)	Reference
1	175 (23.2)	33 (31.1)	0.006	127 (28.9)	24 (23.1)	0.79
2	45 (6.0)	12 (11.3)	0.004	75 (17.1)	18 (17.3)	0.32
3 or more	9 (1.2)	9 (8.5)	< 0.0001	21 (4.8)	24 (23.1)	< 0.0001
Any parent affected, n (%)	154 (20.4)	41 (38.7)	< 0.0001	146 (33.2)	48 (46.2)	0.01
Maternal history, n (%)	81 (10.7)	29 (27.4)	< 0.0001	128 (29.1)	44 (42.3)	0.009
Paternal history, n (%)	83 (11.0)	16 (15.1)	0.22	56 (12.7)	30 (28.9)	< 0.0001
Both parents affected, n (%)	5 (0.7)	2 (1.9)	0.21	19 (4.3)	13 (12.5)	0.001
Any full sibling affected, n (%)	114 (15.1)	28 (26.4)	0.003	126 (28.6)	44 (42.3)	0.007
≥2 full siblings affected, n (%)	12 (1.6)	9 (8.5)	< 0.0001	27 (6.1)	21 (20.2)	< 0.0001
Generation(s) of family history, n (%)						
None	526 (69.7)	52 (49.1)	< 0.0001	217 (49.3)	38 (36.5)	< 0.0001
Parental only	115 (15.2)	26 (24.5)		97 (22.1)	22 (21.2)	
Sibling only	70 (9.3)	11 (10.4)		58 (13.2)	5 (4.8)	
Parental and sibling	44 (5.8)	17 (16.0)		68 (15.5)	39 (37.5)	
Sex concordance of family history, n (%)						
No family history	526 (69.7)	52 (49.1)	< 0.0001	217 (49.3)	38 (36.5)	0.007
Female history only (mother and/or sister)	86 (11.4)	24 (22.6)		111 (25.2)	26 (25.0)	
Male history only (father and/or brother)	118 (15.6)	20 (18.9)		49 (11.1)	11 (10.6)	
Both female and male history	25 (3.3)	10 (9.4)		63 (14.3)	29 (27.9)	

Race, family history and incident type 2 diabetes

The overall prevalence of a positive family history of T2DM was higher in AA compared to EA (53.1 versus 32.9%, $P < 0.0001$). Table 2 shows the prevalence of family history patterns by the number and kinship of affected first-degree relatives in AA and EA. Having any affected first-degree relative was significantly more common among those with incident T2DM in both races (49.1% in EA, 63.5% in AA) compared to those without incident T2DM. Additionally, in EA, the prevalence of 1, 2 or ≥ 3 affected first-degree relatives was significantly higher in those with incident T2DM compared to those without incident T2DM. However, AA had a higher prevalence of ≥ 3 affected first degree relatives compared to EA ($P < 0.0001$), particularly among those who developed incident T2DM, including 23.1% of AA with ≥ 3 affected first degree relatives compared to only 8.5% of EA. Within AA, the presence of ≥ 3 affected first-degree relatives was the only significant discriminator of incident diabetes by the number of affected relatives compared to those with no family history ($P < 0.0001$).

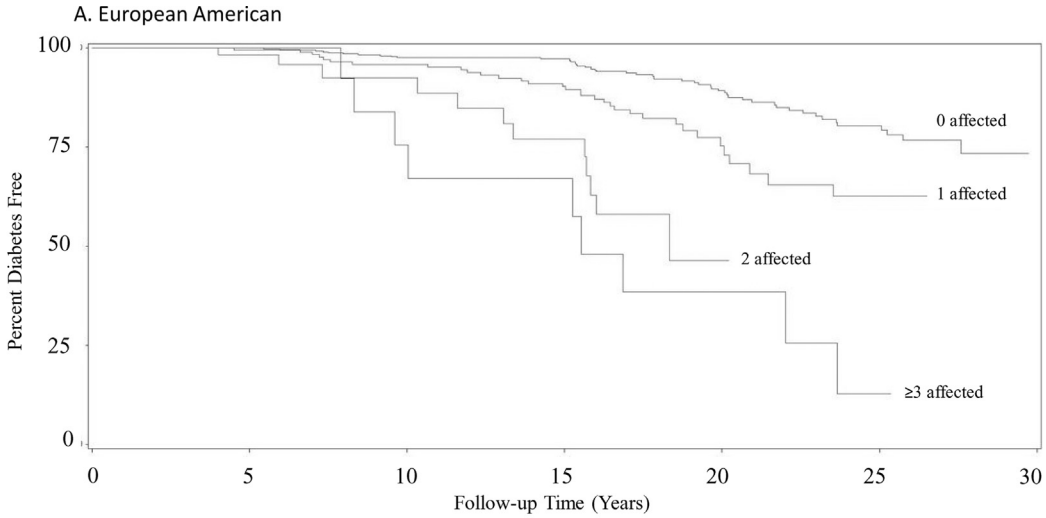
Regarding kinship of affected family members, maternal history was most prevalent among those with incident T2DM in EA (27.4%) and AA (42.3%) compared to any other kinship pattern. Interestingly, paternal history of T2DM did not differ between those with and without incident T2DM in EA but did differ by incident diabetes status in AA. An exclusively female history of T2DM was more common among those with versus without incident T2DM in EA but not in AA. In fact, nearly half of EA with incident T2DM who had a positive family history had a female history of T2DM alone. The combination of having both affected female and male first-degree relatives was a more common familial pattern in AA (27.9%) than in EA (18.9%) with incident T2DM.

Incident type 2 diabetes outcomes

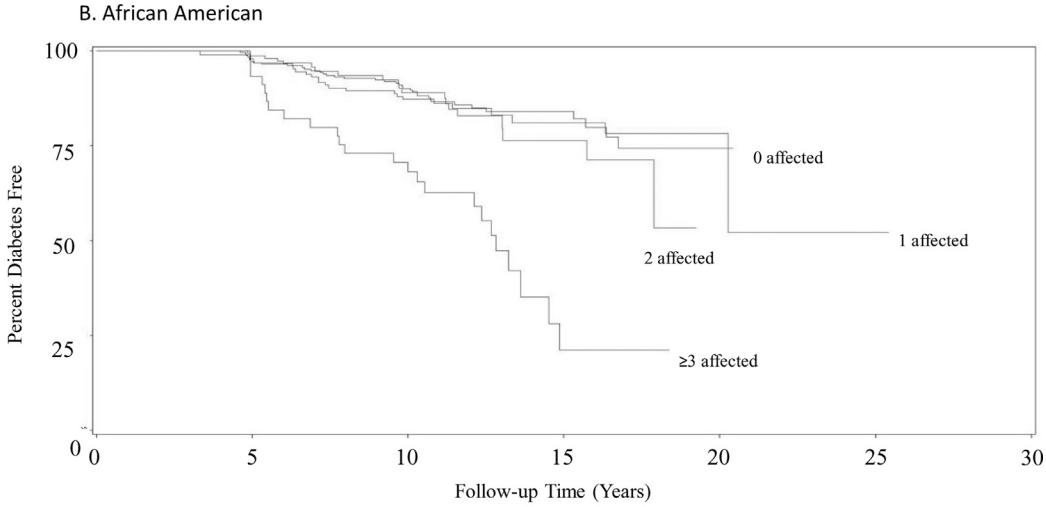
Kaplan–Meier T2DM event-free survival analyses were performed for the entire length of follow-up by number of first-degree relatives affected and stratified by race (Fig. 1). In EA (panel A), an increase in the number of affected relatives decreased event-free survival in a dose responsive manner (log rank *P*-value < 0.0001). In the first 10 years of follow-up, 25% of persons with ≥ 3, 11.1% with 2, 4.7% with 1 and 2.6% with no affected relatives have developed T2DM in EA by 10 years ($n = 605$ with full follow-up). In AA (panel B), there were no differences in event-free survival by number of affected relatives. At 10 years of follow-up, there was minimal separation in event-free survival among AA individuals with 2, 1 or no affected first-degree relatives. However, at 15 years of follow-up, 85% of individuals with ≥ 3 affected relatives developed T2DM compared to 42% with < 3 affected relatives (log-rank *P*-value < 0.0001).

Cox proportional hazard analyses of incident type 2 diabetes

Cox proportional hazard analysis exploring the relationship of any family history of T2DM to incident T2DM with the covariates age, sex, race, any family history and an interaction term of race and any family history showed significant racial differences



0 affected	n=578	n=564	n=406	n=386	n=170	n=76
1 affected	n=208	n=207	n=142	n=123	n=34	n=15
2 affected	n=57	n=50	n=24	n=20	n=1	n=0
≥3 affected	n=18	n=18	n=9	n=8	n=3	n=1
Number of participants studied during 5-year interval by number of affected relatives						



0 affected	n=255	n=247	n=198	n=47	n=3	n=0
1 affected	n=151	n=148	n=111	n=36	n=3	n=1
2 affected	n=93	n=91	n=79	n=18	n=0	n=0
≥3 affected	n=45	n=42	n=29	n=4	n=0	n=0
Number of participants studied during 5-year interval by number of affected relatives						

Fig. 1. Kaplan–Meier T2DM event-free survival by ancestry and number of first degree relatives affected. A. European American: the number of affected relatives decreased event-free survival in a dose responsive manner (log rank *P*-value < 0.0001). B. African American: at 15 years of follow-up, 85% of individuals with ≥ 3 affected relatives developed T2DM compared to 42% with < 3 affected relatives (log-rank *P*-value < 0.0001).

Table 3A
Cox proportional hazards models for incident type 2 diabetes by number of affected first-degree relatives and kinship patterns, in European Americans and African Americans[a]. A. Any affected first-degree relative.

	European American			African American		
	Hazard	95% CI	*P*-value	Hazard	95% CI	*P*-value
Model 1						
Age (per 5 year increments)	1.25	1.06–1.47	0.007	1.11	0.95–1.30	0.17
Female sex	1.02	0.66–1.60	0.92	1.39	0.87–2.22	0.16
Any affected relative	3.49	2.18–5.58	< 0.0001	1.54	0.98–2.41	0.06
Model 2						
Age (per 5 year increments)	1.18	0.99–1.41	0.07	1.05	0.90–1.23	0.51
Female sex	1.34	0.76–2.35	0.31	1.31	0.79–2.15	0.29
Current smoking	2.10	1.30–3.39	0.003	1.32	0.84–2.08	0.22
SBP (per 10 mmHg)	1.10	0.94–1.30	0.23	0.92	0.80–1.05	0.21
Fasting glucose (mmol/L)	2.33	1.56–3.47	< 0.0001	2.82	2.06–3.85	< 0.0001
HDL cholesterol (mmol/L)	0.62	0.29–1.32	0.21	0.45	0.23–0.90	0.02
Triglycerides (mmol/L)	1.09	0.96–1.25	0.19	1.12	0.91–1.39	0.29
Body-mass-index (kg/m^2)	1.11	1.06–1.16	< 0.0001	1.06	1.02–1.09	0.001
Total MET level (per 10 MET minutes)	0.97	0.91–1.03	0.32	0.94	0.88–1.01	0.08
Any affected relative	2.53	1.58–4.06	0.0001	1.01	0.67–1.53	0.97

HDL: high-density lipoprotein; SBP: systolic blood pressure.
[a] Incorporating kinship matrix.

Table 3B
Cox proportional hazards models for incident type 2 diabetes by number of affected first-degree relatives and kinship patterns, in European Americans and African Americans[a]. B. Number of affected first-degree relatives.

	European American			African American		
	Hazard	95% CI	*P*-value	Hazard	95% CI	*P*-value
Model 1						
Age (per 5 year increments)	1.20	1.03–1.41	0.02	1.09	0.93–1.27	0.28
Female sex	1.03	0.67–1.59	0.90	1.52	0.96–2.40	0.08
1 Affected relative	2.43	1.45–4.05	0.0007	0.97	0.56–1.70	0.92
2 Affected relatives	7.72	3.48–17.10	< 0.0001	1.27	0.70–2.34	0.43
≥ 3 Affected relatives	11.13	3.98–31.11	< 0.0001	4.69	2.60–8.46	< 0.0001
Model 2						
Age (per 5 year increments)	1.14	0.96–1.36	0.15	1.06	0.90–1.25	0.51
Female sex	1.43	0.82–2.51	0.21	1.26	0.76–2.09	0.36
Current smoking	2.16	1.34–3.47	0.002	1.48	0.94–2.31	0.09
SBP (per 10 mmHg)	1.11	0.94–1.30	0.22	0.91	0.80–1.01	0.14
Fasting glucose (mmol/L)	2.45	1.64–3.67	< 0.0001	2.84	2.05–3.92	< 0.0001
HDL cholesterol (mmol/L)	0.67	0.32–1.42	0.30	0.53	0.27–1.04	0.06
Triglycerides (mmol/L)	1.10	0.97–1.26	0.14	1.08	0.89–1.31	0.44
Body-mass-index (kg/m^2)	1.10	1.05–1.15	< 0.0001	1.06	1.03–1.10	0.0004
Total MET level (per 10 MET minutes)	0.98	0.92–1.04	0.45	0.95	0.88–1.02	0.12
1 Affected relative	1.82	1.08–3.06	0.02	0.73	0.43–1.23	0.22
2 Affected relatives	4.83	2.15–10.85	0.00001	0.81	0.45–1.44	0.47
≥ 3 Affected relatives	8.46	3.09–23.91	< 0.0001	2.45	1.44–4.19	0.001

[a] Incorporating kinship matrix.

(interaction *P*-value with race = 0.02). Thus, Cox proportional hazard analyses of incident T2DM were performed stratified by race. The presence of any affected first degree relative (Table 3A) was significantly associated with incident T2DM in EA adjusting for age and sex (Model 1; *HR* = 3.49, 95% CI: 2.18–5.58, *P* = 0.007) and remained significant after further adjusting for additional risk factors (Model 2; *HR* = 2.53, 95% CI: 1.58–4.06, *P* = 0.0001). Any family history showed a weaker non-significant association with incident T2DM in AA in the base model (Model 1; *HR* = 1.54, 95% CI: 0.98–1.24, *P* = 0.06) but this association was attenuated after further adjustment (Model 2; *HR* = 1.01, 95% CI: 0.67–1.53, *P* = 0.97).

In EA, the strength of family history (Table 3B) showed a dose response relationship with incident T2DM; the hazard ratio increased from 1.82 (95% CI: 1.08–3.06, *P* = 0.02) with one affected first degree relative to 8.46 (95% CI: 3.09–23.91, *P* < 0.0001) with ≥ 3 affected relatives in the fully adjusted model. In AA, family history was only a significant predictor of incident T2DM if ≥ 3 first degree relatives were affected with a hazard ratio of 2.45 (95% CI: 1.44–4.19, *P* = 0.001) in the fully adjusted model.

Table 3C
Cox proportional hazards models for incident type 2 diabetes by number of affected first-degree relatives and kinship patterns, in European Americans and African Americans[a]. C. Affected kinship patterns[b].

	European American			African American		
	Hazard	95% CI	*P*-value	Hazard	95% CI	*P*-value
Any parent	3.21	1.89–5.46	< 0.0001	1.03	0.66–1.61	0.89
Maternal only	3.59	2.25–6.77	< 0.0001	0.85	0.51–1.41	0.52
Paternal only	3.32	1.54–7.16	0.002	1.81	0.97–3.36	0.06
Both parents	26.17	3.60–190.12	0.001	2.10	0.98–3.85	0.06
Any sibling	2.62	1.42–4.82	0.002	1.07	0.68–1.69	0.76
Parent and sibling	7.11	3.32–15.44	< 0.0001	1.47	0.92–2.36	0.11
Females only	1.84	0.95–3.56	0.07	0.77	0.45–1.31	0.34
Males only	2.73	1.43–5.20	0.002	0.80	0.39–1.65	0.54
Both female and male	8.52	3.19–22.74	< 0.0001	1.29	0.77–2.15	0.34

[a] Incorporating kinship matrix.
[b] Compared to no family history by race, adjusting for age, sex, current smoking status, systolic blood pressure, fasting glucose, HDL cholesterol, triglycerides, body-mass-index and physical fitness level (total MET minutes achieved).

Separate fully adjusted Cox proportional hazard analyses of incident T2DM were performed for specific affected kinship patterns (Table 3C). In EA, maternal only, paternal only and any sibling T2DM history were significantly and independently associated with incident T2DM with similar hazards of 3.59 (95% CI: 2.25–6.77), 3.32 (1.54–7.16) and 2.62 (1.42–4.82), respectively. The highest hazards for incident T2DM in EA were observed with both parents affected, a parent and sibling affected, and both female and male family members affected with hazards of 26.17 (3.60–190.12), 7.11 (3.32–15.44), and 8.52 (3.19–22.74), respectively. In AA, only the pattern of having both parents affected neared statistical significance for an association with incident T2DM (*HR* = 2.10, 0.98–3.85).

Discussion

The major findings of this study did not support our a priori hypothesis that race specific family patterns of prevalent T2DM may explain the much higher incidence of T2DM in AA compared to EA populations, although we found not only that the relationship of any positive family history as a dichotomous variable to incident T2DM differs by race, but also that the number and kinship of affected first-degree relatives with T2DM differentially predicts the development of T2DM in EA versus AA. Most importantly, we found that any positive family history was almost the "norm", with over half of AA participants having at least one affected first degree relative and a quarter with ≥ 3 affected relatives. In fact, statistically family history was not an independent risk factor for T2DM in AA unless multiple family members (≥ 3) were known to be affected given this saturated family structure. In comparison, the number of affected relatives showed a dose–dependent relationship with incident risk of T2DM in EA even after adjustment for other known risk factors. Consequently, our findings emphasize the epidemic of prevalent and incident diabetes in African American families and have important implications for diabetes risk assessment and prediction in multi-ethnic populations.

Our population, all of whom are siblings with a family history of early onset CAD, had a high prevalence of affected family members with T2DM as well as CAD risk factors. The higher background prevalence of any affected family member in AA families compared to EA families likely explains our finding of the limited prognostic utility of a weaker positive family history (i.e. 1 or 2 affected relatives) in the risk of incident T2DM. For example, in a population of persons with similar age, the Coronary Artery Risk Development Study in Young Adults (CARDIA) study [24] reported a prevalence of parental history of T2DM of 14.3% in EA and 22.8% in AA compared to 22.6% and 35.7% in our study, respectively. Notably, higher BMI, which was strongly associated with incident T2DM in EA and AA, and obesity were markedly more prevalent in AA compared to EA. It is possible that race-specific adverse environmental factors such as unhealthy diet and lack of exercise contributed greatly to the high prevalence of T2DM in AA families, thus diminishing the effect of relatedness.

The results of our study for European Americans with one or two affected first-degree relatives is similar to findings from other studies. The recent European Prospective Investigation into Cancer and Nutrition (EPIC)-InterAct Study of incident T2DM in almost 14,000 predominantly white Europeans found that a family history of a first-degree relative conferred a hazard ratio of 2.72 but a biparental history increased the hazard ratio to 5.14 [1]. Although this study did not specifically examine the number of affected first-degree relatives, all types of affected kinship increased risk, including affected mothers, fathers and siblings. These parental hazard ratios are similar to our findings in EA for having one (hazard ratio of 2.43) or two affected relatives (hazard ratio of 7.72). In a population from France, Balkau et al. (2017) [25] recently reported that having either a mother or father with diabetes was significantly associated with incident T2DM in daughters but not sons and, similarly, that having a first-degree relative with diabetes was significantly associated with incident diabetes in women but not men. The results of our U.S. study differ in that having a first-degree relative with diabetes was significantly associated with incident diabetes in both EA males and females when analyses were stratified by sex [fully adjusted hazard ratio (95% CI) was 2.75 (1.56–4.87) and 2.28 (1.08–4.79) in males and females, respectively]. Using a large multi-ethnic cohort, Karter et al. [17] found that the prevalence of T2DM in EA and AA was higher in offspring of affected mothers than affected fathers but having both affected parents almost doubled the risk. Although excess maternal risk has been reported in other studies [16,18,19], results have been inconsistent. In the Framingham Offspring Study, Meigs et al. [2] found equal risk ratios for maternal versus paternal transmission. Our study similarly shows that, in EA, the specific kinship hazards were similar by affected maternal, paternal, or sibling history of T2DM. However, our study further demonstrates that a history of multiple affected relatives is associated with a dose–dependent relationship for developing diabetes in EA. To our knowledge, no previous studies have specifically investigated the presence of a dose–dependent association of the number of affected first-degree relatives with development of type 2 diabetes in AA.

The observed racial differences in family history pedigrees of T2DM and associated race-specific risk of T2DM suggest that genetic factors may contribute to these disparities. For example, in a large-scale admixture genetic analysis in African Americans, Cheng et al. [26] found that greater African ancestry was significantly associated with T2DM after controlling for BMI and socioeconomic variables. However, there remains a paucity of genomic studies for T2DM in AA and most common genetic variants discovered so far in populations of European ancestry, fail to replicate in African Americans [15]. It is possible that AAs carry gene variants putatively associated with T2DM but are so frequent with relatively large effect sizes that they would require targeted or very large study populations to be identified. Analogous to the thrifty gene variant in CREBRF that strongly affects BMI almost exclusively in Samoans [27], a common gene variant with strong environmental interactions in persons of African ancestry but rare in other populations, could explain a high genetic penetrance of T2DM in African Americans and why family history screening is only effective if multiple family members are affected, but this requires further investigation.

While most current risk prediction models for type 2 diabetes include the presence of any affected first-degree relative [28], there is a lack of specific discrimination of risk by the number of affected relatives or kinship, both of which are important particularly for EAs in our study. Our findings suggest that screening for T2DM could be potentially improved by accounting for the apparent dose effect conferred by the number of affected family members for EAs, the apparent dose threshold of 3 or more affected relatives in AAs and the relative frequency of race-specific kinship patterns. Future studies should investigate the performance of risk prediction models for type 2 diabetes with the inclusion of additional information regarding the number and kinship of affected first-degree relatives.

Strengths of our study include a well-characterized cohort with detailed information on family history patterns of T2DM. We included families from both EA and AA ancestry to uniquely study race-specific differences in family history patterns in association with incident T2DM during an extended follow-up period. A limitation is that our study is comprised of high risk individuals

identified from families with early-onset coronary artery disease that may not be generalizable to other populations. For comparison, the rate of T2DM per 1000 person years in our study was 8.1 in EA and 16.3 in AA compared to 8.3 and 12.3 in EA and AA, respectively, in the Multi-Ethnic Study of Atherosclerosis [29]. Although participants were screened for the presence of diabetes at baseline using fasting plasma glucose levels, these laboratory measures were not collected at all follow-up visits and incident diabetes was identified by self-report. We also followed-up incident T2DM at 5 year intervals. AA overall had a shorter follow-up duration compared to EA. Although EA and AA were recruited, screened and followed using the same protocols, AA recruitment was enriched 10 years after the onset of the overall study through a targeted funding mechanism granted by the National Institutes of Health. We did not have information on gestational diabetes or polycystic ovarian syndrome, both risk factors for the development of T2DM. We used fasting glucose and did not have haemoglobin A1c to define T2DM and thus may have underdiagnosed individuals at baseline and follow-up. Information on usual physical activity was not collected, however, physical fitness level on treadmill testing was assessed and included in our study.

Conclusions

The significance of family history to the risk of incident T2DM differs between EA and AA individuals from high risk CAD families. Whereas Americans of European ancestry demonstrate a dose–dependent risk association, Americans of African ancestry have a much more saturated positive family history structure that diminishes the ability to discriminate at risk persons unless multiple family members are affected. This finding alone should lead to essential public health efforts targeting diabetes prevention in African Americans. Further research of genetic, biological and environmental mechanisms leading to racial differences and a better understanding of the relationship between family history and incident T2DM in other races and ethnicities should also lead to better preventive strategies.

Funding Sources

The GeneSTAR Research Program and this work was supported by grants from the National Institutes of Health/National Heart, Lung and Blood Institute (RC1HL099747, K23HL094747, R01HL59684, R01HL071025, U01HL72518, HL49762, R01HL58625, HL092165), the National Institutes of Health/National Institute of Nursing Research (R01NR08153, R01NR0224103), the National Institutes of Health/National Institute of Neurological Disorders and Stroke (R01NS062059), the National Institutes of Health/National Institute of Diabetes, and Digestive and Kidney Disease (R03DK109163), by a grant from the National Institutes of Health/National Center for Research Resources (M01RR000052) to The Johns Hopkins General Clinical Research Center and by a grant (UL1 RR 025005) from the National Center for Research Resources and the National Center for Advancing Translational Sciences, National Institutes of Health to the Johns Hopkins Institute for Clinical & Translational Research.

Disclosure of interest

The authors declare that they have no competing interest.

References

[1] InterAct C, Scott RA, Langenberg C, Sharp SJ, Franks PW, Rolandsson O, et al. The link between family history and risk of type 2 diabetes is not explained by anthropometric, lifestyle or genetic risk factors: the EPIC-InterAct study. Diabetologia 2013;56:60–9.
[2] Meigs JB, Cupples LA, Wilson PW. Parental transmission of type 2 diabetes: the Framingham Offspring Study. Diabetes 2000;49:2201–7.
[3] van't Riet E, Dekker JM, Sun Q, Nijpels G, Hu FB, van Dam RM. Role of adiposity and lifestyle in the relationship between family history of diabetes and 20-year incidence of type 2 diabetes in U.S. women. Diabetes Care 2010;33:763–7.
[4] Klein BE, Klein R, Moss SE, Cruickshanks KJ. Parental history of diabetes in a population-based study. Diabetes Care 1996;19:827–30.
[5] Lipton RB, Liao Y, Cao G, Cooper RS, McGee D. Determinants of incident non-insulin-dependent diabetes mellitus among blacks and whites in a national sample. The NHANES I Epidemiologic Follow-up Study. Am J Epidemiol 1993;138:826–39.
[6] Suchindran S, Vana AM, Shaffer RA, Alcaraz JE, McCarthy JJ. Racial differences in the interaction between family history and risk factors associated with diabetes in the National Health and Nutritional Examination Survey, 1999–2004. Genet Med 2009;11:542–7.
[7] Cowie CC, Rust KF, Ford ES, Eberhardt MS, Byrd-Holt DD, Li C, et al. Full accounting of diabetes and pre-diabetes in the U.S. population in 1988–1994 and 2005–2006. Diabetes Care 2009;32:287–94.
[8] Perneger TV, Brancati FL, Whelton PK, Klag MJ. End-stage renal disease attributable to diabetes mellitus. Ann Intern Med 1994;121:912–8.
[9] Harris MI, Klein R, Cowie CC, Rowland M, Byrd-Holt DD. Is the risk of diabetic retinopathy greater in non-Hispanic blacks and Mexican Americans than in non-Hispanic whites with type 2 diabetes? A U.S. population study. Diabetes Care 1998;21:1230–5.
[10] Carter JS, Pugh JA, Monterrosa A. Non-insulin-dependent diabetes mellitus in minorities in the United States. Ann Intern Med 1996;125:221–32.
[11] Brancati FL, Kao WH, Folsom AR, Watson RL, Szklo M. Incident type 2 diabetes mellitus in African American and white adults: the Atherosclerosis Risk in Communities Study. JAMA 2000;283:2253–9.
[12] Chatterjee R, Brancati FL, Shafi T, Edelman D, Pankow JS, Mosley TH, et al. Non-traditional risk factors are important contributors to the racial disparity in diabetes risk: the atherosclerosis risk in communities study. J Gen Intern Med 2014;29:290–7.
[13] Willemsen G, Ward KJ, Bell CG, Christensen K, Bowden J, Dalgard C, et al. The concordance and heritability of type 2 diabetes in 34,166 Twin Pairs From International Twin Registers: the Discordant Twin (DISCOTWIN) Consortium. Twin Res Hum Genet 2015;18:762–71.
[14] Rotimi C, Cooper R, Cao G, Sundarum C, McGee D. Familial aggregation of cardiovascular diseases in African-American pedigrees. Genet Epidemiol 1994;11:397–407.
[15] Ng MC, Shriner D, Chen BH, Li J, Chen WM, Guo X, et al. Meta-analysis of genome-wide association studies in African Americans provides insights into the genetic architecture of type 2 diabetes. PLoS Genet 2014;10:e1004517.
[16] Vaag A, Lehtovirta M, Thye-Ronn P, Groop L. Metabolic impact of a family history of type 2 diabetes. Results from a European multicentre study (EGIR). Diabet Med 2001;18:533–40.
[17] Karter AJ, Rowell SE, Ackerson LM, Mitchell BD, Ferrara A, Selby JV, et al. Excess maternal transmission of type 2 diabetes. The Northern California Kaiser Permanente Diabetes Registry. Diabetes Care 1999;22:938–43.
[18] Groop L, Forsblom C, Lehtovirta M, Tuomi T, Karanko S, Nissen M, et al. Metabolic consequences of a family history of NIDDM (the Botnia study): evidence for sex-specific parental effects. Diabetes 1996;45:1585–93.
[19] Abbasi A, Corpeleijn E, van der Schouw YT, Stolk RP, Spijkerman AM, van der AD, et al. Maternal and paternal transmission of type 2 diabetes: influence of diet, lifestyle and adiposity. J Intern Med 2011;270:388–96.
[20] Vaidya D, Yanek LR, Moy TF, Pearson TA, Becker LC, Becker DM. Incidence of coronary artery disease in siblings of patients with premature coronary artery disease: 10 years of follow-up. Am J Cardiol 2007;100:1410–5.
[21] Myers GL, Kimberly MM, Waymack PP, Smith SJ, Cooper GR, Sampson EJ. A reference method laboratory network for cholesterol: a model for standardization and improvement of clinical laboratory measurements. Clin Chem 2000;46:1762–72.
[22] Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem 1972;18:499–502.
[23] Pesce AJ, Kaplan LA. Methods in clinical chemistry. St. Louis: Mosby; 1987.
[24] Lacy ME, Wellenius GA, Carnethon MR, Loucks EB, Carson AP, Luo X, et al. Racial differences in the performance of existing risk prediction models for incident type 2 diabetes: the CARDIA Study. Diabetes Care 2016;39:285–91.
[25] Balkau B, Roussel R, Wagner S, Tichet J, Froguel P, Fagherazzi G, et al. Transmission of Type 2 diabetes to sons and daughters: the D.E.S.I.R. cohort. Diabet Med 2017;34:1615–22.
[26] Cheng CY, Reich D, Haiman CA, Tandon A, Patterson N, Selvin E, et al. African ancestry and its correlation to type 2 diabetes in African Americans: a genetic admixture analysis in three U.S. population cohorts. PLoS One 2012;7:e32840.
[27] Minster RL, Hawley NL, Su CT, Sun G, Kershaw EE, Cheng H, et al. A thrifty variant in CREBRF strongly influences body mass index in Samoans. Nat Genet 2016;48:1049–54.
[28] American Diabetes A. Standards of medical care in diabetes-2017 abridged for primary care providers. Clin Diabetes 2017;35:5–26.
[29] Joseph JJ, Echouffo-Tcheugui JB, Carnethon MR, Bertoni AG, Shay CM, Ahmed HM, et al. The association of ideal cardiovascular health with incident type 2 diabetes mellitus: the Multi-Ethnic Study of Atherosclerosis. Diabetologia 2016;59:1893–903.