


BMJ Open Effects of family history of diabetes on pancreatic β -cell function and diabetic ketoacidosis in newly diagnosed patients with type 2 diabetes: a cross-sectional study in China

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To cite: Xiong X, Wei L, Xiao Y, *et al.* Effects of family history of diabetes on pancreatic β -cell function and diabetic ketoacidosis in newly diagnosed patients with type 2 diabetes: a cross-sectional study in China. *BMJ Open* 2021;**11**:e041072. doi:10.1136/bmjopen-2020-041072

► Prepublication history and additional material for this paper are available online. To view these files, please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2020-041072>).

Received 01 June 2020
Revised 14 December 2020
Accepted 28 December 2020



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ABSTRACT

Objective To investigate the association between a parental and/or sibling history of diabetes and clinical characteristics.

Design A cross-sectional study.

Setting The data were collected from the endocrinology department of The Second Xiangya Hospital of Central South University from June 2017 to October 2019.

Participants A total of 894 newly diagnosed patients with type 2 diabetes were recruited. Data on clinical characteristics were collected from patient medical records. Pancreatic β -cell function and insulin resistance were calculated with the homeostatic model assessment. SPSS V.25.0 was used to perform the analysis.

Results The percentages of patients with parental and sibling histories of diabetes were 14.8% and 9.8%, respectively. The prevalence of diabetic ketoacidosis (DKA) was 3.9%. Compared with those with no parental history of diabetes, patients with a parental history of diabetes were characterised by early-onset disease (41.70 \pm 10.88 vs 51.17 \pm 14.09 years), poor glycaemic control of fasting blood glucose (10.84 \pm 5.21 vs 8.91 \pm 4.38 mmol/L) and a high prevalence of DKA (7.6% vs 3.3%). The patients with a sibling history of diabetes had later disease onset (56.05 \pm 9.86 vs 49.09 \pm 14.29 years) and lower BMI (24.49 \pm 3.48 vs 25.69 \pm 3.86 kg/m²) than those with no sibling history of diabetes. Univariate regression suggested that both parental history ($p=0.037$) and sibling history ($p=0.011$) of diabetes were associated with β -cell function; however, multiple regression analysis showed that only a sibling history of diabetes was associated with β -cell function ($p=0.038$). Univariate regression revealed a positive correlation between parental history of diabetes ($p=0.023$, OR=2.416, 95% CI 1.132 to 5.156) and DKA. Unfortunately, this correlation was not statistically significant for either patients with a parental history ($p=0.234$, OR=1.646, 95% CI 0.724 to 3.743) or those with a sibling history ($p=0.104$, OR=2.319, 95% CI 0.841 to 6.389) after adjustments for confounders.

Conclusion A sibling history of diabetes was associated with poor β -cell function, and a parental history of diabetes was associated with poor glycaemic control and a high prevalence of DKA.

Strengths and limitations of this study

- This is the first study to investigate the relationship between a family history of diabetes and diabetic ketoacidosis (DKA) in type 2 diabetes.
- Patients with type 2 diabetes were susceptible to poor β -cell function and DKA if their family members had a history of diabetes.
- Prospective, multicentre studies and studies including patients with type 1 diabetes should be conducted in the future.

INTRODUCTION

Globally, there has been an unprecedented increase in diabetes mellitus (DM) such that 366 million people lived with diabetes in 2011, and this number is estimated to rise to 552 million by 2030.¹ The incidence and prevalence of type 2 diabetes mellitus (T2DM) are much higher in low-income to middle-income countries than in high-income countries, accounting for 80% of global cases.² For instance, China, as the major epicentre of diabetes in Asia, has a prevalence of 10.9% and 35.7% for diabetes and pre-diabetes, respectively.³

A family history of diabetes (FHD), which is a common and medically significant finding in medical history records, is a risk factor for various diseases, such as subclinical atherosclerosis,⁴ colorectal cancer⁵ and gestational hypertensive disease.⁶ A previous study suggested that patients with an FHD tended to have a higher risk of colorectal cancer (men, HR=1.19, 95% CI 1.04 to 1.36; women, HR=1.06, 95% CI 0.96 to 1.17) than those without an FHD.⁵ Moreover, an FHD also plays an important role in the prevalence of pre-diabetes,⁷ diabetes risk,⁸ glycaemic control,⁹ and insulin secretion

and sensitivity.¹⁰ A multicentre study that included 8106 participants without diabetes revealed that an important risk factor for pre-diabetes (OR=1.26, 95% CI 1.14 to 1.40) was an FHD, even after adjustments for potential confounders.⁷ Moreover, data from 9756 Chinese participants noted that their siblings, mothers and fathers had diabetes prevalence rates of 39.3%, 38.3% and 36.4%, respectively.⁸ Additionally, patients with a parental history of diabetes appeared to have an early disease onset and high body mass index (BMI).⁹

Several studies have concentrated on the long-term complications of patients with diabetes who have an FHD,^{11 12} such as diabetic retinopathy (DR).¹¹ A retrospective study focusing on the parental history of diabetes and DR found that a parental history of diabetes was a risk factor for DR (OR=1.9, 95% CI 1.09 to 3.5) after adjusting for potential confounding factors.¹¹ However, little attention has been given to an FHD and diabetic ketoacidosis (DKA), a life-threatening complication mainly characterised by hyperglycaemic and ketosis with a 1%–5% fatality rate.¹³ It remains unclear whether DKA is associated with an FHD and whether the association degree may differ among different first-degree relatives, such as parents and siblings.

In addition, some studies have found that an FHD also plays an important role in residual β -cell function, but the results remain controversial.^{14–16} On the one hand, one study demonstrated that patients with an FHD had significantly lower levels of C-peptide than those without an FHD.¹⁵ On the other hand, another study reported that the impact of an FHD on the C-peptide level was definitely weak.¹⁶ Moreover, a Japanese study suggested that an FHD was associated with β -cell function and that the association degree differed based on the type of first-degree relationship, such as a sibling history of diabetes or a parental history of diabetes.¹⁴ However, multiple studies have focused on T2DM with a long duration, and no reports have accurately shown the relationship between an FHD and various clinical characteristics, such as residual β -cell function and glycaemic control, in newly diagnosed Chinese patients with T2DM.

Under such a background, this study aimed to investigate the relationship between a parental or sibling history of diabetes and clinical data, particularly glycaemic control, residual β -cell function and DKA.

METHODS

Study population

The study included 894 patients who were newly diagnosed with type 2 diabetes in the endocrinology department of The Second Xiangya Hospital of Central South University from June 2017 to October 2019. The exclusion criteria were as follows: type 1 diabetes, latent autoimmune diabetes in adults, age under 18 years, known pancreatic disease such as pancreatitis or pancreatic cancer, or missing data pertaining to the FHD.

Data collection and measurements

Data on the following clinical characteristics of the patients were collected: sex, age, drinking habits, BMI, waist-to-hip ratio (WHR), FHD, complications and use of drugs. Additionally, the following laboratory data were collected: fasting blood glucose (FBG), glycosylated haemoglobin (HbA_{1c}), albumin (Alb), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglyceride (TG) and serum C-peptide levels in fasting samples.

Haemoglobin concentrations and platelet (PLT) counts were measured with an ADVIA 2120 automated haematology analyser (Siemens Healthcare Diagnostics, Germany). Blood chemistry testing, measuring FBG, Alb, TC, TG and serum creatinine, was performed with standard automated enzymatic methods (Hitachi 912 automated analyzer). The measurement of HDL-C and LDL-C was based on lipoprotein electrophoresis and the Friedewald formula,¹⁷ respectively. In addition, automatic high-performance liquid chromatography (VARIANT-II Haemoglobin Testing System; Bio-Rad Laboratories, Hercules, California, USA) was applied to evaluate HbA_{1c} levels. The chemiluminescence method was applied to evaluate the fasting C-peptide level using the Adiva Centaur Systema kit (Siemens, Munich, Germany).

Definitions

The diagnosis of DM was based on the criteria of the American Diabetes Association.¹⁸ An FHD was defined as a first-degree family member (parents, siblings, excluding children) with the presence or absence of diabetes. Calculations of BMI and WHR were based on the following formulas: weight (kg)/height (m²) and waist circumference/hip circumference, respectively. Patients with a drinking history of more than 1 year were defined as drinkers. Drug use referred to regular medications taken for more than 3 months. Hypertension (HTN) was defined as systolic blood pressure (SBP) greater than 130 mm Hg and/or diastolic blood pressure (DBP) greater than 80 mm Hg with three sequential measurements at different time points.¹⁹ The definition of DKA was based on the following criteria: a concentration of blood bicarbonate of <15 mmol/L, or pH of <7.25 (venous) or <7.30 (arterial or capillary), or a diagnosis of DKA in the medical records.²⁰

Calculation of β -cell function and insulin sensitivity

The homeostasis model assessment (HOMA) was used to estimate β -cell function (homeostatic model assessment 2-B (HOMA2-B)) and insulin resistance (homeostatic model assessment 2-insulin resistance (HOMA2-IR)) based on FBG and fasting C-peptide, which were calculated with the HOMA calculator (University of Oxford, Oxford, UK), as described in previous studies.^{21 22}

Statistical analysis

Quantitative variables were recorded as the mean \pm SD, and qualitative variables were described as percentages. A

t-test or the χ^2 test was applied to compare the differences between two groups. A non-parametric Mann-Whitney U test was used when the p value of the one-sample Shapiro-Wilk test was less than 0.05. Partial correlation was performed to identify the association between an FHD and clinical characteristics, such as SBP, DBP, metabolic parameters and complications, when adjusted for confounders of sex, age and BMI. Regression was used to evaluate the relationship among β -cell function, DKA and an FHD after adjustments for confounders, including sex, age, BMI and HbA_{1c} confounders. Quantitative variables in the logistic regression were defined as positive or negative by a cut-off value as follows: HbA_{1c} (%): '0' refers to '<10' and '1' refers to '≥10'; BMI (kg/m²): '0' refers to '<24' and '1' refers to '≥24'. The data were analysed by SPSS V.25.0, and a p value of less than 0.05 was regarded as indicative of statistical significance.

RESULTS

Clinical characteristics of the whole cohort

A total of 894 newly diagnosed patients with T2DM were enrolled in the study. The mean age of this cohort was 49.78±14.07 years, and most of them were men, accounting for 66.8% of the study participants. The mean BMI and WHR were 25.58±3.8 kg/m² and 0.95±0.07, respectively. A total of 14.8% and 9.8% of the participants had a parental history and a sibling history of diabetes, respectively. Moreover, 26.8% of the patients had a drinking habit. The mean FBG was 9.20±4.56 mmol/L, and the mean HbA_{1c} was 10.13%±2.8%. The mean HOMA2-IR and HOMA2-B were 1.44±1.34 and 50.89%±50.03%, respectively. Regarding complications, the prevalence of DKA was 3.9%, and that of HTN was 39.4% (table 1).

Clinical characteristics based on a parental history of DM

Patients with T2DM with a parental history were characterised by early-onset disease (p<0.001), worse glycaemic control with higher FBG (p<0.001) and HbA_{1c} (p=0.005), higher levels of TG (p=0.01) and TC (p=0.012), and worse β -cell dysfunction (p<0.001) than those with no parental history of DM. Moreover, the prevalence of DKA was higher among participants with a parental history of diabetes (p=0.028) than among those with no parental history of DM. Furthermore, there were no significant differences between groups regarding the distributions of other variables, such as sex, BMI, HOMA2-IR and the use of medications (table 2). Next, the study also investigated the clinical characteristics based on paternal diabetes and maternal diabetes. As with the basic characteristics, there were no significant differences in laboratory data, complications or medications between those with and without paternal and maternal histories of diabetes (p>0.05) (online supplemental table 1).

Clinical characteristics based on a sibling history of DM

The patients with a sibling history of DM had later disease onset (p<0.001), a lower proportion of men (p<0.001),

Table 1 Clinical characteristics of the whole cohort presented as mean±SD or percentages

Basic characteristics	
N	894
Age (years)	49.78±14.07
Men (%)	597 (66.8)
BMI (kg/m ²)	25.58±3.84
WHR	0.95±0.07
SBP (mm Hg)	134.78±18.32
DBP (mm Hg)	83.88±12.73
Parent history of diabetes (%)	132 (14.8)
Sibling history of diabetes (%)	88 (9.8)
Drinking (%)	240 (26.8)
Laboratory data	
Hb (g/L)	137.60±19.84
PLT (*10 ⁹ /L)	219.75±88.10
FBG (mmol/L)	9.20±4.56
HbA _{1c} (%)	10.13±2.8
Alb (g/L)	37.24±4.90
TC (mmol/L)	4.63±1.44
LDL (mmol/L)	2.87±1.02
HDL (mmol/L)	0.98±0.30
TG (mmol/L)	2.70±3.37
sCre (μmol/L)	68.45±38.07
HOMA2-IR (%)	1.44±1.34
HOMA2-B (%)	50.89±50.03
Complications	
DKA	35 (3.9)
HTN	352 (39.4)
Medications	
ACEI (%)	126 (14.1)
ARB (%)	134 (15)
Lipid-lowering agents (%)	564 (63.1)

HOMA2-B and HOMA2-IR were applied to estimate the function of β -cell and insulin resistance, respectively, which were calculated using fasting plasma glucose and C-peptide. ACEI, ACE inhibitor; Alb, albumin; ARB, angiotensin receptor blocker; BMI, body mass index; DBP, diastolic blood pressure; DKA, diabetic keto acidosis; DM, diabetes mellitus; FBG, fasting blood glucose; Hb, haemoglobin; HbA_{1c}, glycosylated haemoglobin; HDL, high-density lipoprotein; HOMA2-B, homoeostatic model assessment 2-B; HOMA2-IR, homoeostatic model assessment 2-insulin resistance; HTN, hypertension; LDL, low-density lipoprotein; PLT, platelet; SBP, systolic blood pressure; sCre, serum creatinine; TC, total cholesterol; TG, triglyceride; WHR, waist-to-hip ratio.

lower BMI (p=0.011) and worse β -cell dysfunction (p=0.062) than those with no sibling history of DM. No significant differences were found in other parameters (table 3).

Table 2 Clinical characteristics based on parental history of DM

	No parental history of DM (n=762)	Parental history of DM (n=132)	P value
Basic characteristics			
Age (years)	51.17±14.09	41.70±10.88	< 0.001
Men (%)	502 (65.9)	95 (72.0)	0.193
BMI (kg/m ²)	25.49±3.86	26.06±3.70	0.108
WHR	0.94±0.06	0.95±0.06	0.938
SBP (mm Hg)	135.02±18.51	133.40±17.14	0.362
DBP (mm Hg)	83.68±12.81	85.00±12.22	0.212
Drinking (%)	202 (26.5)	38 (28.8)	0.731
Laboratory data			
Hb (g/L)	136.71±20.02	142.73±20.02	0.003
PLT (×10 ⁹ /L)	218.22±90.17	228.58±74.77	0.029
FBG (mmol/L)	8.91±4.38	10.84±5.21	<0.001
HbA _{1c} (%)	10.03±2.86	10.73±2.48	0.005
Alb (g/L)	37.08±4.95	38.12±4.44	0.057
TC (mmol/L)	4.56±1.34	4.99±1.88	0.012
LDL (mmol/L)	2.86±1.01	2.97±1.08	0.195
HDL (mmol/L)	0.98±0.29	0.96±0.34	0.193
TG (mmol/L)	2.53±3.0	3.72±4.88	0.01
sCre (µmol/L)	69.26±39.93	63.83±24.43	0.266
HOMA2-IR (%)	1.43±1.29	1.48±1.53	0.803
HOMA2-B (%)	52.41±50.46	42.28±46.83	<0.001
Complications			
DKA	25 (3.3)	10 (7.6)	0.027
HTN	305 (40.0)	47 (35.6)	0.385
Medications			
ACEI (%)	112 (14.7)	20 (15.1)	0.786
ARB (%)	115 (15.1)	19 (14.4)	0.896
Lipid-lowering agents (%)	479 (62.9)	85 (64.4)	0.747

HOMA2-B and HOMA2-IR were applied to estimate the function of β -cell and insulin resistance, respectively, which were calculated using fasting plasma glucose and C-peptide.

*Refers to $p < 0.05$.

ACEI, ACE inhibitor; Alb, albumin; ARB, angiotensin receptor blocker; BMI, body mass index; DBP, diastolic blood pressure; DKA, diabetic ketoacidosis; DM, diabetes mellitus; FBG, fasting blood glucose; Hb, haemoglobin; HbA_{1c}, glycosylated haemoglobin; HDL, high-density lipoprotein; HOMA2-B, homeostatic model assessment 2-B; HOMA2-IR, homeostatic model assessment 2-insulin resistance; HTN, hypertension; LDL, low-density lipoprotein; PLT, platelet; SBP, systolic blood pressure; sCre, serum creatinine; TC, total cholesterol; TG, triglyceride; WHR, waist-to-hip ratio.

Correlation between an FHD and clinical characteristics

A parental history of DM showed a positive association with TGs, TC, FBG, HbA_{1c} and DKA, and a negative association with age and HOMA2-B. When the analysis was adjusted for sex, age and BMI, only FBG and HbA_{1c} showed a statistically significant association with a parental history of DM. A positive association was found between a sibling history of DM and age, while a sibling history of DM had a negative association with sex, BMI and HOMA2-B. After adjustments for confounders, FBG and HOMA2-B were correlated with a sibling history of DM (table 4).

Regression analysis between HOMA2-B and DKA and an FHD

The results of the linear regression analysis showed that a parental history ($p=0.037$) and a sibling history ($p=0.011$) of DM were associated with HOMA2-B. After adjustments for sex, age, BMI and HbA_{1c}, a sibling history of DM remained related to HOMA2-B ($p=0.038$) (table 5). In addition, a parental history of DM, but not a sibling history of DM, was associated with DKA (OR=1.622, 95% CI 1.070 to 2.461). Unfortunately, no significant associations for either a parental history or a sibling history remained after adjustment for confounders (table 6).

Table 3 Clinical characteristics based on sibling history of DM

	No sibling history of DM (n=806)	Sibling history of DM (n=88)	P value
Basic characteristics			
Age (years)	49.09±14.29	56.05±9.86	< 0.001
Men (%)	555 (68.9)	42 (47.7%)	< 0.001
BMI (kg/m ²)	25.69±3.86	24.49±3.48	0.011*
WHR	0.95±0.07	0.94±0.06	0.059
SBP (mm Hg)	134.99±18.26	132.89±18.87	0.413
DBP (mm Hg)	83.88±12.79	83.84±12.21	0.992
Drinking (%)	218 (27)	22 (25)	0.819
Laboratory data			
Hb (g/L)	137.87±19.98	135.17±18.47	0.109
PLT (×10 ⁹ /L)	219.13±88.22	225.44±87.34	0.57
FBG (mmol/L)	9.16±4.62	9.57±3.97	0.079
HbA _{1c} (%)	10.10±2.86	10.43±2.43	0.232
Alb (g/L)	37.27±4.95	36.88±4.36	0.247
TC (mmol/L)	4.62±1.44	4.70±1.45	0.786
LDL (mmol/L)	2.86±1.04	2.99±0.88	0.196
HDL (mmol/L)	0.98±0.30	0.99±0.24	0.366
TG (mmol/L)	2.75±3.42	2.28±2.88	0.358
sCre (µmol/L)	68.99±39.27	63.56±23.95	0.12
HOMA2-IR (%)	1.45±1.38	1.31±0.86	0.639
HOMA2-B (%)	52.37±51.80	37.81±27.09	0.062
Complications			
DKA	30 (3.7%)	5 (5.7%)	0.379
HTN	314 (39.0%)	38 (43.2%)	0.491
Medications			
ACEI (%)	117 (14.5)	9 (10.2)	0.334
ARB (%)	117 (14.5)	17 (19.3)	0.269
Lipid-lowering agents (%)	506 (62.8)	58 (65.9)	0.642

HOMA2-B and HOMA2-IR were applied to estimate the function of β -cell and insulin resistance, respectively, which were calculated using fasting plasma glucose and C-peptide.

*Refers to $p < 0.05$.

ACEI, ACE inhibitor; Alb, albumin; ARB, angiotensin receptor blocker; BMI, body mass index; DBP, diastolic blood pressure; DKA, diabetic keto acidosis; DM, diabetes mellitus; FBG, fasting blood glucose; Hb, haemoglobin; HbA_{1c}, glycosylated haemoglobin; HDL, high-density lipoprotein; HOMA2-B, homeostatic model assessment 2-B; HOMA2-IR, homeostatic model assessment 2-insulin resistance; HTN, hypertension; LDL, low-density lipoprotein; PLT, platelet; SBP, systolic blood pressure; sCre, serum creatinine; TC, total cholesterol; TG, triglyceride; WHR, waist-to-hip ratio.

DISCUSSION

In this study, we found that patients with a parental history or a sibling history of diabetes had different clinical characteristics. Moreover, a parental history of diabetes was associated with poor glycaemic control and a high prevalence of DKA, and a sibling history of diabetes was associated with poor β -cell function.

In our study, we found that an FHD was, to the greatest extent, associated with poor β -cell function, as demonstrated by several studies.^{10 14 15 23} A population-based study found that participants with more than three siblings with a history of diabetes plus parents with a history of

diabetes presented with the worst glycaemic control and lowest insulin secretion levels among participants in all groups, including those with negative personal, sibling and parental histories of diabetes.¹⁰ Another study demonstrated similar results, in which a positive history of diabetes was related to insulinopenia in a middle-aged population with diabetes.²³ In our study, we observed that a sibling history rather than a parental history of diabetes was associated with β -cell function.

An FHD is reflected by not only genetic factors but also environmental factors.²⁴ With the advancement of emerging genetic technologies, numerous candidate

Table 4 Correlation between family history of diabetes and clinical characteristics

	Parental history of DM				Sibling history of DM			
	r	P	a-r	a-P	r	P	a-r	a-P
Sex	0.046	0.171			-0.134	< 0.001		
Age	-0.237	< 0.001			0.125	< 0.001		
SBP	-0.031	0.357	-0.031	0.357	-0.037	0.266	-0.034	0.319
DBP	0.032	0.334	0.002	0.958	-0.015	0.653	-0.002	0.951
BMI	0.06	0.077			-0.088	0.01		
TG	0.075	0.028	0.026	0.45	-0.018	0.6	0.011	0.753
TC	0.07	0.041	0.054	0.125	0.038	0.273	0.045	0.204
HDL	-0.063	0.066	-0.04	0.256	0.019	0.581	-0.031	0.383
LDL	0.045	0.179	0.03	0.376	-0.011	0.741	-0.021	0.542
FBG	0.141	< 0.001	0.119	0.001*	0.054	0.109	0.075	0.028
HbA _{1c}	0.101	0.003	0.071	0.038	0.005	0.87	0.01	0.777
HOMA2-IR (%)	-0.022	0.521	-0.039	0.275	-0.015	0.673	0.008	0.83
HOMA2-B (%)	-0.093	0.007	-0.066	0.061	-0.07	0.044	-0.096	0.007
DKA	0.079	0.019	0.05	0.146	0.03	0.369	0.05	0.142

a-r and a-p: correlation adjusted for sex, age and BMI.

HOMA2-B and HOMA2-IR were applied to estimate the function of β -cell and insulin resistance, respectively, which were calculated using fasting plasma glucose and C-peptide.

*Refers to $p < 0.05$.

BMI, body mass index; DBP, diastolic blood pressure; DKA, diabetic keto acidosis; DM, diabetes mellitus; FBG, fasting blood glucose; HbA_{1c}, glycosylated haemoglobin; HDL, high-density lipoprotein; HOMA2-B, homoeostatic model assessment 2-B; HOMA2-IR, homoeostatic model assessment 2-insulin resistance; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride; WHR, waist-to-hip ratio.

genes related to T2DM have been identified. Many of them, such as *RGS16*, *SYT13* and *ENTPD3*, are involved in insulin secretion.²⁵ It was reported that the Genetic Risk Score (GRS), calculated based on the summation of trait-associated risk alleles of the variants, has a close relationship with clinical parameters, including β -cell function, glycaemic control and diabetes risk.^{26–28} A study conducted by Walker *et al* showed that β -cell sensitivity would be reduced by 39% if the individuals had more than five risk alleles compared with those who had five or fewer among participants without diabetes.²⁶ Moreover, the GRS has been shown to be strongly associated with an FHD.^{29–30} One study that calculated a GRS using 33 type 2 diabetes-related variants and examined the relationship between the GRS and a parental history of diabetes found that the mean GRS was increased in accordance with the degree of parental diabetes (zero, one or two

parents with a history of diabetes led to a GRS=16.8, 16.9 and 17.1, respectively).²⁹ Thus, from the aforementioned reports, we speculated that impaired β -cell function may be impacted by the GRS.

Surprisingly, in our study, parental history showed no significant association with β -cell function, while sibling history was related to poor β -cell function. Several findings have indicated an important role for a sibling history of diabetes.^{31–32} A prospective study with 2960 enrolled participants demonstrated that sibling history played a more important role in diabetes risk than parental history.³¹ However, the possible mechanism remains unclear. The study reported that many environmental or lifestyle factors contributed to the prevalence and incidence of diabetes, such as poor eating habits, a lack of exercise, sleep insufficiency and long duration of depression and stress; among them, many factors may not target

Table 5 Linear regression between HOMA2-band family history of diabetes

	Univariate regression			Multivariate regression		
	β	P value	95% CI	β	P value	95% CI
Parental history of DM	-0.072	0.037*	-19.628 to -0.617	-0.028	0.371	-12.156 to 4.54
Sibling history of DM	-0.088	0.011*	-25.761 to -3.357	-0.063	0.038*	-20.352 to -0.57

Multivariate regression adjusted for sex, age, body mass index, glycosylated haemoglobin and HOMA2-B.

*Refers to $p < 0.05$.

DM, diabetes mellitus; HOMA2-B, homoeostatic model assessment 2-B.

Table 6 Logistic regression between DKA and family history of diabetes

	Univariate regression			Multivariate regression		
	Wald	P value	OR (95% CI)	Wald	P value	OR (95% CI)
Parental history of DM	5.205	0.023*	2.416 (1.132 to 5.156)	1.415	0.234	1.646 (0.724 to 3.743)
Constant	276.847	<0.001	0.034	43.37	<0.001	0.016
Sibling history of DM	0.798	0.372	1.558 (0.589 to 4.125)	2.639	0.104	2.319 (0.841 to 6.389)
Constant	305.636	<0.001	0.039	72.229	<0.001	0.08

Multivariate logistic regression adjusted for sex, age, body mass index and HbA_{1c}.

*Refers to p<0.05.

DKA, diabetic ketoacidosis; DM, diabetes mellitus.

β-cells directly but have distant sites of action.³³ It is likely that the siblings shared more genetic and environmental factors, such as lifestyle, eating habits and exercise load, which may be attributed to poor β-cell function. Furthermore, insulin resistance also leads to poor β-cell function.³⁴ However, there was no statistically significant association between a sibling history of diabetes and insulin resistance in our study.

An FHD, an easily obtainable and relatively useful screening tool, has been proven to be a potential risk factor for T2DM.^{31 35–37} Our study showed that the patients with a parental history of diabetes were younger than those with no parental history of diabetes, which was consistent with several published studies.^{14 38} Currently, whether genetic predisposition or lifestyle transformation is responsible for early disease onset in those with a parental history of diabetes is controversial. Alternatively, the improved awareness of diabetic symptoms of those patients could be explained by early disease onset.³⁹ In addition, a strong association between FBG or HbA_{1c} and parental history was observed, even after adjustments for sex, age and BMI, suggesting that the relationship was not influenced by those factors. Gong *et al*⁴⁰ indicated that individuals with a parental history of diabetes were more familiar with the symptoms of T2DM, which made them underestimate the seriousness of the disease, as they may have observed no immediate consequences of higher blood glucose levels in their family members. Moreover, patients with a parental history of DM had higher TG and TC. However, the results of this partial analysis, adjusted for BMI, age and sex, were not statistically significant. Unhealthy lifestyles, such as drinking and a lack of exercise, are also risk factors for T2DM.⁴¹ However, our study observed no obvious association between a parental history of diabetes and drinking. A Swedish study incorporating 1 575 49 patients with T2DM revealed that there was a low risk of adoptees developing T2DM if their adopted parents had T2DM, while there was a relatively small increase in the risk if their spouse had T2DM, suggesting a limited impact of environmental factors.³⁶ In addition, we found no significant differences in BMI or WHR between patients with no parental history of diabetes and those with a parental history of diabetes, in contrast to the results of several other studies.^{9 37 41}

Previous studies focusing on type 1 diabetes have shown that an FHD is associated with DKA.^{20 42} To our knowledge, no studies related to DKA and FHD in T2DM have been reported. In our study, we found that the prevalence of DKA was higher among patients with a parental history than among those without. One study examined the relationship between DKA and gene polymorphisms in gestational diabetes. The results showed that a single-nucleotide polymorphism, rs184187143 in the SLC26A6 gene, was a risk factor for DKA, indicating a possible role for this gene in DKA.⁴³ Due to the limited number of observations in large samples and the inclusion of multiple racial backgrounds, the mechanism of genetic inheritance and DKA remains unclear. Moreover, the multivariate regression in our study indicated no association between parental or sibling history and diabetes, which demonstrates a limited impact of genetic inheritance on DKA, and other factors, including poor glycaemic control, may be mainly responsible for it.

In our study, the patients with a sibling history of diabetes were older at the time of diagnosis. The reason for this remains unclear. A possible explanation is their increased awareness of diabetes prevention, which may be due to their observation of the negative impact of the disease on their siblings. Additionally, abnormalities in lipid parameters, such as TC and TG, were not different between those with and those without a sibling history of diabetes, contradicting the results of the Alharithy *et al*⁹ study. This may be due to adequate use of lipid-lowering agents.

The prevalence of DKA in our study was different from that in a Japanese study (3.8% vs 0.48%).⁴⁴ Possible reasons are as follows. First, the study population was different. The whole cohort included in our study was newly diagnosed patients with type 2 diabetes, while the Japanese population included both diagnosed and newly diagnosed patients. Second, all of the patients were inpatients in our study, but all 36 674 patients recruited in the Japanese study were from outside of the hospital. Additionally, race, clinical differences, and the use of medication may contribute to the differences in the prevalence of DKA.⁴⁵ Compared with that in the Japanese study, the mean age at diagnosis was lower (49.78 vs 51.9 years), and the mean HbA_{1c} was higher (10.13 vs 7.0) in our cohort.

There are several limitations of this study that should be mentioned. First, detailed FHD information, including whether the parents and siblings had type 1 diabetes or type 2 diabetes, was not collected. Second, this was a cross-sectional study, and more prospective and multi-centre studies should be conducted in the future.

In conclusion, patients with a parental history of diabetes had poor glycaemic control and a high prevalence of DKA, while patients with a sibling history of diabetes had poor β -cell function.

Contributors The data were collected by XX, LW and YX, and the manuscript was written by XX, LW, YX, YH, JY, HZ and MY. LS was responsible for data integrity and accuracy.

Funding This study was assisted by the National Key R&D Program of China (2018YFC1314002 and 2016YFC1305501) and the National Natural Science Foundation of China (81730018).

Competing interests None declared.

Patient consent for publication Not required.

Ethics approval This study was approved by the human research ethics committees of The Second Xiangya Hospital of Central South University, China. All participants in this study provided informed consent prior to their inclusion in the study.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. Data used in this study can be obtained from the corresponding author.

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