

Maternal and paternal histories differentially influence risks for diabetes, insulin secretion and insulin resistance in a Chinese population

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ABSTRACT

Aims/Introduction: To investigate the differential effects of maternal versus paternal history of diabetes on the risks for diabetes and prediabetes, as well as on insulin secretion and resistance in Chinese individuals.

Materials and Methods: From the 2007 to 2008 China National Diabetes and Metabolism Disorders Study, 39,244 participants were included and divided into four categories: negative parental history, paternal history only (PH), maternal history only (MH), and both paternal and maternal history.

Results: The age- and sex-standardized prevalence rates of diabetes in the negative parental history, PH, MH, and both paternal and maternal history groups were 8.59, 12.56, 15.86 and 29.81%, respectively. The prevalence rates of impaired glucose metabolism were 24.13, 25.41, 31.13 and 50.80%, with the prevalence in the MH group being significantly higher than that in the PH group. Compared with that in the FH0 group, the risks of diabetes in the PH, MH, and both paternal and maternal history groups were 2.01-, 2.67- and 6.37-fold greater, and the risks of impaired glucose metabolism were 1.28-, 1.65- and 3.45-fold greater. In addition, MH had a significantly greater impact on impaired glucose metabolism than PH ($P_{MHvsPH} = 0.0292$). Regression analyses suggested MH was associated with homeostatic model assessment for β -cell function ($\beta[SE] = -0.0910[0.0334]$, $P = 0.0065$), insulinogenic index ($-0.1866[0.0550]$, $P = 0.0007$), homeostatic model assessment for insulin resistance ($0.0662[0.0227]$, $P = 0.0036$) and Matsuda Index [$-0.0716(0.0203)$, $P = 0.0004$]. PH was specifically associated with homeostatic model assessment for insulin resistance ($0.1343[0.0267]$, $P < 0.0001$) and Matsuda Index ($-0.1566[0.0243]$, $P < 0.0001$), but the effects were stronger than those of MH ($P_{MHvsPH} = 0.0431, 0.0054$).

Conclusions: MH and PH differentially influence the risks for diabetes, insulin secretion, and insulin resistance in the Chinese population, suggesting they participate in the pathogenesis of diabetes through different mechanisms.

INTRODUCTION

Diabetes is emerging as a major healthcare problem worldwide, and already causes a great health economic burden that continues to grow. China has the largest population of diabetes patients in the world, with an estimated diabetes prevalence of 10.9% in 2013¹. Meanwhile, the prevalence of prediabetes, a high-risk state for diabetes, has reached 35.7%¹. The prevention

of diabetes is of great clinical importance and a great challenge in China.

Diabetes is well known to be aggregated in families. A family history (FH) of diabetes is one of the most important risk factors for diabetes, and is frequently applied in the assessment of diabetes risk in clinical practice. The similar genetic background and shared environmental components among family members are critical mediators of the FH-associated disease risk². Studies have shown that a positive FH is associated with an elevation in the risk of type 2 diabetes in offspring by two- to sixfold,

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depending on the number of first-degree relatives affected^{3–6}. In addition to the risk for diabetes, diabetes patients with a positive FH have a higher risk of complications of diabetes⁷, and worse glycemic control^{8,9}.

Notably, most epidemiological evidence has shown a greater impact of a maternal history (MH) of diabetes than a paternal history (PH) on the risk for diabetes and other metabolic disorders in offspring^{4,7,10,11,12}. However, the greater maternal transmission of type 2 diabetes is still debated. Several studies have suggested equivalent maternal and paternal effects on the risk for diabetes among offspring^{3,13,14}. Also, the heterogeneity of the population could lead to the discrepancy, such as sex or age subpopulations^{12,15,16}. Overall, a precise assessment of the parental influence on the risk for diabetes is still required.

The pathophysiological mechanisms underlying different patterns of familial transmission of diabetes remain to be further explored. In the Chinese population, previous research on whether maternal and paternal transmission of diabetes share the same or distinct pathways involving impaired insulin secretion and/or insulin resistance showed controversial results^{6,14,17}.

In the present study, based on the national representative population in the China National Diabetes and Metabolism Disorders Study (DMS)¹⁸ with a sample size as 39,244, we estimated the prevalence rates of diabetes, prediabetes and impaired glucose metabolism according to parental history categories, and compared the transmission of diabetes to offspring with a MH and PH. Furthermore, we investigated and compared the effects of MH and PH on insulin secretion and insulin resistance.

METHODS

Study participants

From June 2007 to May 2008, the DMS was carried out using a complex multistage, stratified sampling method, and the detailed methods were described elsewhere¹⁸. In brief, representative regions (including 152 urban districts and 112 rural villages) were selected across the country by considering the geographical distribution, economic development and level of urbanization.

The DMS initially recruited 46,239 adult participants (aged ≥ 20 years) from mainland China¹⁸. Parental history of diabetes was obtained by self-reporting during the interview, including the diabetes history of their mother, father, siblings and offspring¹⁸. In the present analyses, all of the individuals with complete data for both paternal and maternal history of diabetes were included in the present study (39,244 individuals

comprising of 15,573 men and 23,671 women). Individuals with self-reported paternal and/or maternal history missing were excluded from the present study ($n = 6,995$).

Ethics statement

The study protocol was carried out in accordance with the Declaration of Helsinki II, and approved by the ethics committee of the China-Japan Friendship Hospital (Beijing, China). Written informed consent was obtained from each participant.

Definitions

Diabetes was identified according to the 1999 World Health Organization criteria of fasting plasma glucose (FPG) ≥ 7.0 mmol/L, 2-h post-prandial plasma glucose ≥ 11.1 mmol/L or a self-reported history of diabetes. Prediabetes was defined as FPG ≥ 6.1 and < 7.0 mmol/L, and/or 2-h post-prandial plasma glucose ≥ 7.8 and < 11.1 mmol/L. "Impaired glucose metabolism" was defined as a collective term for both diabetes and prediabetes.

Overweight was defined by a body mass index (BMI) ≥ 24 and < 28 kg/m². Obesity was defined as a BMI ≥ 28 kg/m². A collective term "overweight/obesity" was defined as a BMI ≥ 24 kg/m².

Assessment of parental history

Parental history of diabetes was obtained by self-reporting during the interview. The participants were then categorized as those with a negative parental history of diabetes (FH0 group), those with paternal history only (PH group), those with maternal history only (MH group), and those with both paternal and maternal history (FH2 group).

Clinical information and laboratory measurements

Demographic and anthropometric characteristics were examined as previously described¹⁸. Bodyweight and height were measured using standard methods. BMI was calculated as weight / height² (kg/m²). At enrollment, each participant completed a 75-g oral glucose tolerance test after overnight fasting. Blood samples were obtained at 0, 30 min and 2 h during the oral glucose tolerance. Serum insulin was measured by radioimmunoassay. The homeostatic model assessment for β -cell function (HOMA-B) and insulinogenic indices were calculated to evaluate β -cell function. The homeostatic model assessment for insulin resistance (HOMA-IR) index and Matsuda Index (ISIm) were used to assess insulin sensitivity. The formulas are shown below^{20–22}:

$$\text{HOMA-B} = \text{fasting serum insulin} \times 20 / (\text{FPG} - 3.5) \text{ (with serum insulin in mU/L and plasma glucose in mmol/L)}$$

$$\text{Insulinogenic index} = (\text{serum insulin at 30 min} - \text{fasting serum insulin}) / (\text{plasma glucose at 30 min} - \text{FPG}) \\ \times (\text{with serum insulin in mU/L and plasma glucose in mmol/L})$$

$$\text{HOMA-IR} = \text{fasting serum insulin} \times \text{FPG} / 22.5 (\text{with serum insulin in mU/L and plasma glucose in mmol/L})$$

$$\text{ISIm} = 10,000 / (\text{FPG} \times \text{fasting serum insulin} \times \text{mean OGTT glucose} \times \text{mean OGTT insulin})^{1/2}$$

× (with serum insulin in mU/L and plasma glucose in mg/dL)

Statistical analysis

All statistical analyses were carried out with the use of SUDAAN software (version 10; Research Triangle Institute, Research Triangle Park, NC, USA). All calculations involved in the present study were weighted to represent the total population of Chinese adults (\geq aged 20 years) on the basis of Chinese population data from 2006 and the study sampling scheme, as previously described¹⁸. In brief, several features of the survey were taken into account, including oversampling for women and urban residents, non-response, economic development, and other demographic or geographic differences between the sample and total populations. All *P*-values were two-tailed, and a *P*-value <0.05 was considered statistically significant.

Mean values were determined according to different parental history categories, as well as within the subpopulations. Prevalence estimates for diabetes, prediabetes and impaired glucose metabolism were also calculated. The differences in means and frequencies between parental history categories were tested using the PAIRWISE procedure in the SUDAAN software.

A multinomial logistic analysis was used to test the association of different parental history categories with the risk of diabetes and prediabetes. A binomial logistic analysis was applied to examine the association with impaired glucose metabolism. The odds ratio (OR) and 95% confidence interval (CI) were calculated. Regression analysis was applied to determine the effects of parental history on the insulin secretion-related or insulin resistance-related indices. All non-Gaussian distributed quantitative traits were natural logarithmically transformed before the regression analyses. Furthermore, the effects of MH on the dependent variables were compared with the effects of PH using the EFFECTS procedure. For the aforementioned calculations, sex, age and BMI were adjusted. To examine the interaction effects of sex and age, the interaction terms (gender \times parental history, age \times parental history) were further included in these models. Furthermore, the association studies were also carried out in male versus female subpopulations, as well as in participants aged <45 versus ≥ 45 years, separately.

RESULTS

Clinical characteristics

As shown in Table 1, from among the 39,244 participants, the FH0, PH, MH and FH2 groups had 34,913, 1,628, 2,378 and 325 participants. Compared with those in the FH0 group (mean age 44.35 years, 95% CI 44.01–44.69 years), participants in the PH (mean age 39.76 years, 95% CI 38.93–40.59 years) or MH (mean age 41.18 years, 95% CI 40.33–42.03 years) group

were younger. The mean age of the MH group was older than that of the PH group ($P_{\text{MHvsPH}} = 0.0104$).

Among the four subgroups, FH0 group showed the lowest BMI, prevalence of overweight and overweight/obesity, and fasting and 2-h oral glucose tolerance glucose and insulin levels, whereas the FH2 group showed the highest values for these indices. No significant differences in clinical measurements were observed between the MH and PH groups, except for a significantly lower fasting insulin level in the MH group ($P_{\text{MHvsPH}} = 0.0194$).

The FH0 group had the best insulin secretion capacity (assessed by HOMA-B and insulinogenic index) and insulin sensitivity (assessed by HOMA-IR and ISIm indices), whereas the FH2 group showed the worst. The mean insulinogenic index of the MH group (13.54, 95% CI 10.59–16.49) was significantly lower than that of the PH group (18.06, 95% CI 13.04–23.09; $P_{\text{MHvsPH}} = 0.0434$), but the MH group had a significantly higher mean ISIm (7.58, 95% CI 7.22–7.94) than did the PH group (6.93, 95% CI 6.63–7.24; $P_{\text{MHvsPH}} = 0.0276$).

Prevalence rates of diabetes, prediabetes and impaired glucose metabolism according to different parental history categories

For age- and sex-standardized prevalence rates of diabetes, prediabetes or impaired glucose metabolism, the FH2 group had the highest estimates (diabetes/prediabetes/impaired glucose metabolism: 29.81%/20.98%/50.80%), whereas the FH0 group had the lowest estimates (8.59%/15.54%/24.13%). Notably, the estimated prevalence rates of diabetes and prediabetes within the MH group (15.86%/15.27%) were higher than those of the PH group (12.56%/12.85%; $P_{\text{MHvsPH}} = 0.0606/0.1606$), whereas only the prevalence of impaired glucose metabolism in the MH group (31.13%) was significantly higher than that in the PH group (25.41%; $P_{\text{MHvsPH}} = 0.0134$; Table 2).

The age- and sex-standardized prevalence rates were then calculated in subpopulations stratified by sex and age of the offspring. As expected, men or participants aged ≥ 45 years generally had higher prevalence rates of diabetes, prediabetes and impaired glucose metabolism. For each subpopulation, individuals with FH2 showed the highest prevalence rates. Then, when compared between MH and PH groups, for female sex, the MH group showed significantly higher prevalence rates of diabetes (14.11%) and impaired glucose metabolism (27.50%) than did the PH group (7.13%/19.81%; $P_{\text{MHvsPH}} < 0.0001/0.0026$). For those aged ≥ 45 years, the prevalence of impaired glucose metabolism in the MH group (45.90%) was significantly higher

Table 1 | Clinical characteristics of the study participants according to parental history of diabetes

	FH0	PH	MH	FH2
<i>n</i>	34,913	1,628	2,378	325
<i>n</i> _{Male}	13,895	678	884	116
Mean age, years (95% CI)	44.35 (44.01–44.69)	39.76 (38.93–40.59) [†]	41.18 (40.33–42.03) ^{†,‡}	44.76 (42.62–46.90)
Mean BMI, kg/m ² (95% CI)	23.72 (23.65–23.79)	24.51 (24.23–24.78) [†]	24.56 (24.31–24.81) [†]	24.61 (24.11–25.12) [†]
Prevalence of overweight, % (95% CI)	31.52 (30.63–32.42)	35.70 (32.10–39.47) [†]	38.77 (35.20–42.47) [†]	44.15 (34.90, 53.83) [†]
Prevalence of obesity, % (95% CI)	12.01 (11.44–12.61)	17.12 (14.35–20.29) [†]	15.76 (13.62–18.17) [†]	12.38 (8.24–18.21)
Prevalence of overweight/obesity, % (95% CI)	43.53 (42.57–44.50)	52.82 (48.99–56.61) [†]	54.53 (50.77–58.24) [†]	56.54 (46.93–65.68) [†]
Mean fasting plasma glucose, mmol/L (95% CI)	5.22 (5.18–5.26)	5.47 (5.34–5.59) [†]	5.54 (5.42–5.66) [†]	6.30 (5.85–6.75) [†]
Mean 2-h OGTT glucose, mmol/L (95% CI)	6.81 (6.73–6.88)	7.24 (6.95–7.52) [†]	7.55 (7.30–7.79) [†]	9.06 (8.20–9.92) [†]
Mean fasting serum insulin, mU/L (95% CI)	8.22 (8.08–8.37)	9.37 (8.81–9.92) [†]	8.81 (8.38–9.24) ^{†,‡}	10.05 (8.58–11.52) [†]
Mean 2-h OGTT insulin, mU/L (95% CI)	36.86 (35.83–37.89)	43.69 (40.23–47.15) [†]	42.33 (39.40–45.25) [†]	40.69 (33.63–47.74)
Mean HOMA-B (95% CI)	144.13 (136.93–151.32)	131.72 (122.14–141.30)	155.68 (100.75–210.61)	105.32 (88.06–122.58) [†]
Mean insulinogenic index (95% CI)	14.64 (13.92–15.37)	18.06 (13.04–23.09)	13.54 (10.59–16.49) [‡]	13.36 (9.50–17.22)
Mean HOMA-IR (95% CI)	1.96 (1.92–2.00)	2.35 (2.17– 2.53) [†]	2.26 (2.10–2.42) [†]	2.82 (2.38–3.26) [†]
Mean ISIm (95% CI)	8.55 (8.44–8.67)	6.93 (6.63–7.24) [†]	7.58 (7.22–7.94) ^{†,‡}	6.41 (5.49–7.34) [†]

Data are shown as the mean (95% confidence interval [CI]) and estimated prevalence (95% CI). All mean values and the prevalences for overweight, obesity, and overweight/obesity were weighted to represent the total population of Chinese adults (aged ≥20 years) on the basis of Chinese population data from 2006. All non-Gaussian distributed quantitative traits were natural logarithmically transformed before the comparisons. The differences in means or prevalences between the parental history categories were tested using the PAIRWISE procedure in SUDAAN software. *P* < 0.05 is considered statistically significant.

BMI, body mass index; CI, confidence interval; FH2, both parents affected with diabetes; HOMA-B, the homeostasis model assessment for β-cell function; HOMA-IR, the homeostasis model assessment for insulin resistance; ISIm, Matsuda Index; OGTT, oral glucose tolerance test.

[†]Significant difference from negative parental history of diabetes (FH0).

[‡]Significant difference between maternal history of diabetes only (MH) and paternal history of diabetes only (PH).

than that in the PH group (36.04%; *P*_{MHvsPH} = 0.0156; Table 2).

Association of parental history of diabetes with disease risks, insulin secretion and insulin sensitivity in the overall cohort

Compared with the FH0 group, the risks of diabetes in the PH, MH and FH2 groups were elevated by 2.01-, 2.67- and 6.37-fold, after adjustment for age, sex and BMI (all *P* < 0.0001) in the overall cohort, and FH2 was associated with an increased risk of prediabetes (OR 2.17, 95%CI 1.27–3.71, *P* = 0.0046). This suggests a larger impact of MH than PH on elevating the disease risk, although no significant difference was observed (*P*_{MHvsPH} = 0.0909; Table 3). When using impaired glucose metabolism as the outcome, PH, MH and FH2 increased its risk by 1.28-, 1.65- and 3.45-fold (*P* = 0.0094, <0.0001, <0.0001), respectively, and MH showed a significantly stronger influence than PH (*P*_{MHvsPH} = 0.0292; Table 3).

In regression analyses, FH2 was found to be associated with decreased HOMA-B (β −0.2623 [standard error; SE 0.0989], *P* = 0.0080), elevated HOMA-IR (β 0.3254 [SE 0.0696], *P* < 0.0001), and decreased ISIm (β −0.2402 [SE 0.0721], *P* = 0.0009). Interestingly, only MH, but not PH, contributed significantly to worsened insulin secretion, as assessed by HOMA-B (MH: β −0.0910 [SE 0.0334], *P* = 0.0065; PH: β −0.0381 [SE 0.0332], *P* = 0.2508) and insulinogenic index (MH: β −0.1866 [SE 0.0550], *P* = 0.0007; PH: β −0.0602 [SE

0.0504], *P* = 0.2320). The effective size of MH on HOMA-B was not significantly different from that of PH (*P*_{MHvsPH} = 0.2413), and the effective sizes on insulinogenic index were not significantly different between MH and PH (*P*_{MHvsPH} = 0.0809). Both MH and PH were associated with increased HOMA-IR (MH: β 0.0662 [SE 0.0227], *P* = 0.0036; PH: β 0.1343 [SE 0.0267], *P* < 0.0001) and reduced ISIm (MH: β −0.0716 [SE 0.0203], *P* = 0.0004; PH: β −0.1566 [SE 0.0243], *P* < 0.0001). Also, PH had significantly larger effective sizes than MH on HOMA-IR (*P*_{MHvsPH} = 0.0431) and ISIm (*P*_{MHvsPH} = 0.0054; Table 4).

Influences of parental history of diabetes on disease risk in subpopulations

The present study identified that parental history interacted significantly with sex (*P*_{Sex×parental history interaction} = 0.0122) and age (*P*_{Age×parental history interaction} = 0.0111) as a determinant of risks for diabetes and prediabetes. Thus, these results support that the effects of parental history on disease risk in men or participants aged <45 years were significantly greater than those in women or participants aged ≥45 years (Table 3). Similarly, significant interactions were identified between them for the risk of impaired glucose metabolism (Table 3).

In women, MH showed a significantly larger influence on the risk for diabetes (OR 2.58, 95% CI 2.02–3.30, *P* < 0.0001) compared with the effective sizes of PH (OR 1.32, 95% CI

Table 2 | Age- and sex-standardized prevalence rates of diabetes, prediabetes, and impaired glucose metabolism according to parental history of diabetes in the overall cohort and subpopulations stratified by gender and age

	Prevalence of diabetes, % (95% CI)	Prevalence of prediabetes, % (95% CI)	Prevalence of impaired glucose metabolism, % (95% CI)
Overall cohort			
FH0	8.59 (8.08–9.12)	15.54 (14.82–16.29)	24.13 (23.29–24.98)
PH	12.56 (10.24–15.32) [†]	12.85 (10.63–15.46)	25.41 (22.29–28.80)
MH	15.86 (13.66–18.34) [†]	15.27 (13.04–17.81)	31.13 (28.06–34.38) ^{†,‡}
FH2	29.81 (21.29–40.02) [†]	20.98 (13.60–30.95)	50.80 (41.39–60.15) [†]
Males			
FH0	9.36 (8.61–10.16)	16.24 (15.19–17.35)	25.60 (24.37–26.87)
PH	17.65 (13.64–22.54) [†]	13.01 (9.76–17.14)	30.66 (25.66–36.17)
MH	17.64 (14.09–21.86) [†]	17.19 (13.55–21.57)	34.83 (29.66–40.39) [†]
FH2	33.37 (19.90–50.23) [†]	27.42 (15.07–44.59)	60.79 (46.29–73.60) [†]
Females			
FH0	7.83 (7.16–8.57)	14.85 (13.88–15.87)	22.68 (21.56–23.84)
PH	7.13 (5.38–9.38)	12.68 (9.91–16.08)	19.81 (16.49–23.60)
MH	14.11 (11.61–17.05) ^{†,‡}	13.39 (10.94–16.28)	27.50 (24.12–31.16) ^{†,‡}
FH2	26.28 (17.21–37.94) [†]	14.58 (8.40–24.10)	40.86 (30.36–52.27) [†]
Age <45 years			
FH0	3.40 (3.02–3.83)	10.42 (9.67–11.21)	13.82 (12.99–14.69)
PH	8.42 (6.10–11.53) [†]	11.88 (9.30–15.05)	20.30 (16.84–24.27) [†]
MH	9.51 (7.50–11.99) [†]	13.77 (10.98–17.13) [†]	23.28 (19.80–27.18) [†]
FH2	26.19 (15.43–40.82) [†]	20.33 (11.32–33.80)	46.52 (33.63–59.90) [†]
Age ≥45 years			
FH0	14.65 (13.69–15.68)	21.53 (20.29–22.82)	36.18 (34.78–37.61)
PH	21.17 (16.38–26.91) [†]	14.87 (10.97–19.85) [†]	36.04 (30.16–42.37)
MH	27.79 (23.32–32.76) [†]	18.10 (14.71–22.08)	45.90 (40.84–51.04) ^{†,‡}
FH2	33.61 (21.42–48.45) [†]	21.66 (11.23–37.68)	55.27 (42.17–67.68) [†]

Prevalence estimates for diabetes and prediabetes, as well as for impaired glucose metabolism, were calculated and weighted to represent the total population of Chinese adults (aged ≥20 years) on the basis of Chinese population data from 2006 and the study sampling scheme. The differences in the prevalence rates between the groups with different family history patterns were tested using the PAIRWISE procedure in SUDAAN software. $P < 0.05$ is considered statistically significant.

CI, confidence interval; FH2, both parents affected with diabetes.

[†]Significant difference from negative parental history of diabetes (FH0) within the certain subpopulation.

[‡]Significant difference between maternal history of diabetes only (MH) and paternal history of diabetes only (PH) within the certain subpopulation.

0.94–1.87, $P = 0.1134$; $P_{MHvsPH} = 0.0040$). The effective size of MH on diabetes risk was greater than that of PH in participants aged ≥45 years, which showed a strong tendency toward statistical significance (PH: OR 1.73, 95% CI 1.25–2.40, $P = 0.0011$; MH: OR 2.68, 95% CI 2.06–3.47, $P < 0.0001$; $P_{MHvsPH} = 0.0559$; Table 3). Furthermore, we identified a significantly stronger influence of MH on the risk for impaired glucose metabolism compared with that of PH in women and participants aged ≥45 years (all $P_{MHvsPH} < 0.05$; Table 3).

Influences of parental history of diabetes on insulin secretion and insulin resistance in subpopulations

We identified significant interactions between parental history and age on HOMA-B ($P_{Age \times \text{parental history interaction}} < 0.0001$) and HOMA-IR ($P_{Age \times \text{parental history interaction}} = 0.0176$; Table 4).

In men, PH showed significant contributions to elevated HOMA-IR (β 0.1647 (SE 0.0445), $P = 0.0002$) and decreased

ISIm (β -0.1979 [SE 0.0396], $P < 0.0001$), whereas MH did not influence HOMA-IR (β 0.0357 [SE 0.0369], $P = 0.3344$) or ISIm (β -0.0636 [SE 0.0328], $P = 0.0529$). Also, the differences between them were statistically significant ($P_{MHvsPH} = 0.0201$, 0.0069; Table 4).

In women, only MH was associated with a worse HOMA-B (β -0.1155 [SE 0.0332], $P = 0.0005$) and insulinogenic index (β -0.2523 [SE 0.0604], $P < 0.0001$), but PH was not related to these indices [HOMA-B: β 0.0101 [SE 0.0373], $P = 0.7870$; insulinogenic index: β -0.0766 [SE 0.0636], $P = 0.2287$]. Significant differences were observed ($P_{MHvsPH} = 0.0089$, 0.0390; Table 4).

In participants aged <45 years, PH was strongly associated with an elevated HOMA-IR (β 0.1154 [SE 0.0306], $P = 0.0002$) and a decreased ISIm (β -0.1623 [SE 0.0288], $P < 0.0001$), of which the effective sizes were greater than those of MH (HOMA-IR: β 0.0386 [SE 0.0297], $P = 0.1938$, $P_{MHvsPH} =$

Table 3 | Associations of parental history of diabetes with the risks for diabetes, prediabetes or impaired glucose metabolism in the overall cohort and the subpopulations stratified by sex and age

Population	Multinomial logistic regression				Binomial logistic				
	Diabetes		Prediabetes		Impaired glucose metabolism		$P_{MH \text{ vs PH}}$		
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	
Overall cohort	(age, sex, BMI and parental history)								
FH0	As reference	—	As reference	—	As reference	—	As reference	—	0.0292*
PH	2.01 (1.57–2.59)	<0.0001*	0.96 (0.76–1.21)	0.7276	1.28 (1.06–1.54)	0.0094*	1.28 (1.06–1.54)	0.0094*	
MH	2.67 (2.21–3.23)	<0.0001*	1.21 (0.99–1.47)	0.0587	1.65 (1.42–1.91)	<0.0001*	1.65 (1.42–1.91)	<0.0001*	
FH2	6.37 (3.91–10.38)	<0.0001*	2.17 (1.27–3.71)	0.0046*	3.45 (2.32–5.12)	<0.0001*	3.45 (2.32–5.12)	<0.0001*	
Males	(age, BMI and parental history)								
FH0	As reference	—	As reference	—	As reference	—	As reference	—	0.1932
PH	2.53 (1.81–3.52)	<0.0001*	0.93 (0.66–1.32)	0.6962	1.44 (1.11–1.88)	0.0062*	1.44 (1.11–1.88)	0.0062*	
MH	2.77 (2.08–3.69)	<0.0001*	1.35 (1.00–1.82)	0.0501	1.80 (1.43–2.27)	<0.0001*	1.80 (1.43–2.27)	<0.0001*	
FH2	8.24 (3.77–17.98)	<0.0001*	3.42 (1.56–7.48)	0.0021*	4.95 (2.65–9.23)	<0.0001*	4.95 (2.65–9.23)	<0.0001*	
Females	(age, BMI and parental history)								
FH0	As reference	—	As reference	—	As reference	—	As reference	—	0.0413*
PH	1.32 (0.94–1.87)	0.1134	1.00 (0.74–1.35)	0.9846	1.09 (0.85–1.41)	0.5002	1.09 (0.85–1.41)	0.5002	
MH	2.58 (2.02–3.30)	<0.0001*	1.07 (0.84–1.36)	0.5973	1.49 (1.24–1.80)	<0.0001*	1.49 (1.24–1.80)	<0.0001*	
FH2	4.98 (2.88–8.55)	<0.0001*	1.28 (0.67–2.44)	0.4480	2.36 (1.50–3.72)	0.0002*	2.36 (1.50–3.72)	0.0002*	
$P_{\text{Sex} \times \text{parental history interaction}}$	(age, sex, BMI, parental history, and sex parental history)								0.0379*
Age <45 years	(age, sex, BMI and parental history)								
FH0	As reference	—	As reference	—	As reference	—	As reference	—	0.3557
PH	2.18 (1.47–3.23)	0.0001*	1.07 (0.79–1.43)	0.6663	1.34 (1.04–1.73)	0.0236*	1.34 (1.04–1.73)	0.0236*	
MH	2.50 (1.87–3.35)	<0.0001*	1.25 (0.95–1.64)	0.1068	1.56 (1.25–1.93)	0.0001*	1.56 (1.25–1.93)	0.0001*	
FH2	10.48 (5.00–21.95)	<0.0001*	2.73 (1.35–5.53)	0.0051*	4.59 (2.62–9.05)	<0.0001*	4.59 (2.62–9.05)	<0.0001*	
Age ≥45 years	(age, sex, BMI and parental history)								
FH0	As reference	—	As reference	—	As reference	—	As reference	—	0.0171*
PH	1.73 (1.25–2.40)	0.0011*	0.78 (0.54–1.13)	0.1879	1.14 (0.87–1.50)	0.3333	1.14 (0.87–1.50)	0.3333	
MH	2.68 (2.06–3.47)	<0.0001*	1.12 (0.86–1.47)	0.4101	1.72 (1.39–2.12)	<0.0001*	1.72 (1.39–2.12)	<0.0001*	
FH2	3.91 (2.17–7.04)	<0.0001*	1.61 (0.72–3.57)	0.2458	2.49 (1.48–4.17)	0.0006*	2.49 (1.48–4.17)	0.0006*	
$P_{\text{Age} \times \text{parental history interaction}}$	(age, sex, BMI, parental history and age x parental history)								0.0059*

All calculations were weighted on the basis of Chinese population data and the study sampling scheme. Multinomial logistic models were used to test the impact of each parental history category compared with negative parental history of diabetes (FH0) on the risk for diabetes and prediabetes. Binomial logistic models were used to test the impact of each parental history category compared with FH0 on the risk for impaired glucose metabolism. The odds ratio (OR) and 95% confidence interval (CI) were calculated. The effects of maternal history of diabetes only (MH) on disease risk were compared with the effects of paternal history of diabetes only (PH) using the EFFECTS procedure. The interaction terms (sex x parental history, age x parental history) were further included in these models separately to examine the interaction effects. Variables included in the logistic models are denoted in parentheses. * P -values <0.05.

BMI, body mass index; FH2, both parents affected with diabetes.

Table 4 | Associations of parental history of diabetes with the insulin secretion-related and insulin resistance-related indices in the overall cohort and subpopulations stratified by sex and age

Population	Ln HOMA-B			Ln Insulinogenic index			Ln HOMA-IR			Ln ISIm		
	β (SE)	P	$P_{MH \text{ vs PH}}$	β (SE)	P	$P_{MH \text{ vs PH}}$	β (SE)	P	$P_{MH \text{ vs PH}}$	β (SE)	P	$P_{MH \text{ vs PH}}$
Overall cohort	(age, sex, BMI and parental history)											
FH0	As reference	—	0.2413	As reference	—	0.0809	As reference	—	0.0431*	As reference	—	0.0054*
PH	-0.0381 (0.0332)	0.2508		-0.0602 (0.0504)	0.2320		0.1343 (0.0267)	<0.0001*		-0.1566 (0.0243)	<0.0001*	
MH	-0.0910 (0.0334)	0.0065*		-0.1866 (0.0550)	0.0007*		0.0662 (0.0227)	0.0036*		-0.0716 (0.0203)	0.0004*	
FH2	-0.2623 (0.0989)	0.0080*		-0.0595 (0.1145)	0.6030		0.3254 (0.0696)	<0.0001*		-0.2402 (0.0721)	0.0009*	
Males	(age, BMI and parental history)											
FH0	As reference	—	0.7662	As reference	—	0.6864	As reference	—	0.0201*	As reference	—	0.0069*
PH	-0.0887 (0.0548)	0.1057		-0.0748 (0.0784)	0.3401		0.1647 (0.0445)	0.0002*		-0.1979 (0.0396)	<0.0001*	
MH	-0.0663 (0.0570)	0.2449		-0.1220 (0.0917)	0.1832		0.0357 (0.0369)	0.3344		-0.0636 (0.0328)	0.0529	
FH2	-0.4252 (0.1755)	0.0154*		-0.0202 (0.1580)	0.8984		0.3052 (0.1139)	0.0074*		-0.2081 (0.1238)	0.0927	
Females	(age, BMI and parental history)											
FH0	As reference	—	0.0089*	As reference	—	0.0390*	As reference	—	0.9496	As reference	—	0.5170
PH	0.0101 (0.0373)	0.7870		-0.0766 (0.0636)	0.2287		0.0924 (0.0293)	0.0016*		-0.0999 (0.0272)	0.0002*	
MH	-0.1155 (0.0332)	0.0005*		-0.2523 (0.0604)	<0.0001*		0.0947 (0.0260)	0.0003*		-0.0777 (0.0235)	0.0009*	
FH2	-0.0977 (0.0780)	0.2101		-0.1070 (0.1651)	0.5170		0.3431 (0.0784)	<0.0001*		-0.2708 (0.0664)	<0.0001*	
$P_{\text{sex} \times \text{parental history interaction}}$	(age, sex, BMI, parental history and sex X parental history)		0.1409			0.4180			0.2214			0.0712
Age <45 years	(age, sex, BMI and parental history)											
FH0	As reference	—	0.6390	As reference	—	0.0987	As reference	—	0.0595	As reference	—	0.0048*
PH	-0.0275 (0.0424)	0.5161		0.0093 (0.0628)	0.8820		0.1154 (0.0306)	0.0002*		-0.1623 (0.0288)	<0.0001*	
MH	-0.0555 (0.0458)	0.2255		-0.1470 (0.0753)	0.0510		0.0386 (0.0297)	0.1938		-0.0581 (0.0255)	0.0231*	
FH2	-0.4087 (0.1557)	0.0087*		-0.0782 (0.1539)	0.6113		0.3530 (0.0749)	<0.0001*		-0.2379 (0.0821)	0.0038*	
Age \geq 45 years	(age, sex, BMI and parental history)											
FH0	As reference	—	0.1295	As reference	—	0.7098	As reference	—	0.4551	As reference	—	0.5376
PH	-0.0459 (0.0511)	0.3693		-0.1699 (0.0795)	0.0327*		0.1968 (0.0512)	0.0001*		-0.1744 (0.0439)	0.0001*	
MH	-0.1382 (0.0373)	0.0002*		-0.2068 (0.0651)	0.0015*		0.1526 (0.0331)	<0.0001*		-0.1418 (0.0320)	<0.0001*	
FH2	-0.0744 (0.1096)	0.4969		0.0167 (0.1657)	0.9196		0.3274 (0.1200)	0.0064*		-0.2852 (0.1188)	0.0164*	

Table 4 (Continued)

Population	Ln HOMA-B		Ln Insulinogenic index		Ln HOMA-IR		Ln ISIm	
	β (SE)	P	β (SE)	P	β (SE)	P	β (SE)	P
P_{Age} parental history interaction (age, sex, BMI, parental history and age x parental history)								
		<0.0001*				0.1744		0.0176*
								0.0684

All calculations were weighted on the basis of Chinese population data and the study sampling scheme. Regression analysis was used to determine the effects of parental history (negative parental history of diabetes [FH0] was used as reference) on the insulin secretion-related or insulin resistance-related indices (the homeostasis model assessment for β -cell function [HOMA-B], insulinogenic index; the homeostasis model assessment for insulin resistance [HOMA-IR], Matsuda Index [ISIm]). All non-Gaussian distributed quantitative traits were natural logarithmically transformed before the regression analyses. Furthermore, the effects of maternal history of diabetes only (MH) on the dependent variables were compared with the effects of paternal history of diabetes only (PH) using the EFFECTS procedure. The interaction terms (sex X parental history, age X parental history) were further included in these models separately to examine the interaction effects. Variables included in the regression models are denoted in parentheses. * P -values <0.05. BMI, body mass index; CI, confidence interval; FH2, both parents affected with diabetes; SE, standard error.

0.0595; ISIm: β -0.0581 [SE 0.0255], $P = 0.0231$; $P_{\text{MHvsPH}} = 0.0048$; Table 4).

DISCUSSION

Based on the weighted data from 39,244 participants of the DMS, we reported the nationally representative prevalence rates for diabetes, prediabetes and impaired glucose metabolism in each parental history category. The results of the present study show that impaired glucose metabolism was significantly more prevalent among participants with a MH of diabetes than among those with a PH of diabetes. Logistic analyses showed MH had greater influences on the elevated disease risks than PH, especially in women and participants aged ≥ 45 years. Regression analyses suggested that MH could contribute to the diseases through its impact on both insulin secretion impairment and insulin resistance, whereas the contribution of PH could rely on its specific impact on insulin resistance. The current findings highlight the mechanisms underlying the contributions of the maternal and paternal sides of diabetes history in the Chinese population, as well as emphasize the importance of a personalized management strategy for the at-risk population with recognition of parental history along with sex and age.

Epidemiological evidence showed excess transmission of maternal-side history of diabetes to offspring worldwide, including in China^{7,11,12,23,24}. For example, a study including >2,310 Chinese patients diagnosed with late-onset type 2 diabetes showed that a MH of diabetes was more prevalent (17.6%) than a PH of diabetes (10.7%)¹¹. Sheu *et al.*²³ reported MH and PH rates of 22.5 and 12.0%, in 449 Chinese patients with type 2 diabetes aged between 35 and 74 years. Wei *et al.*¹² reported that Chinese children with a MH had a higher risk for type 2 diabetes than children with a PH. Also, several studies have failed to identify excess transmission of MH-related diabetes. In the Framingham offspring study, individuals with a MH or PH showed comparable increased risks for type 2 diabetes with ORs of 3.4 and 3.5⁴. In Korea, both PH and MH increased the risk for diabetes comparatively³. Abbasi *et al.*¹³ reported, in a prospective cohort with a median follow-up period of 10.2 years, that the paternal and maternal transmission rates of diabetes were equal. In a Chinese population, Chien *et al.*¹⁴ observed similar effects of MH and PH on the risk for diabetes. We speculate that these discrepancies can be explained either by the sample sizes or by the study design, because most of the previous studies included <2,000 patients with diabetes and none with normal glycemic regulation, and each study population was only representative for a limited region. In the current study, 39,244 individuals including 4,019 diabetes patients were enrolled through the DMS, which was a relatively larger sample size than those of previous studies and was nationally representative. Importantly, the estimated prevalence rates derived from the present study were also weighted to represent the total population of Chinese adults. Therefore, it could be more reliable for generalization in the Chinese population.

The results confirmed an excessive impact from the maternal side. We also observed that MH had a larger effective size in determining the risk for diabetes and impaired glucose metabolism than did PH. After all, the present results suggest that MH needs to be emphasized in the assessment of diabetes risk in China.

Biological studies have shown that the paternal side and maternal side influence the metabolism of the offspring through different mechanisms, differently. Notably, the findings from the current study strongly support that MH and PH likely contribute to diabetes through different mechanisms. First, impaired insulin secretion was significantly associated with MH, but could not be attributed to PH. Similarly, a previous study reported that Chinese participants who had a MH of diabetes showed significantly lower insulin secretion⁶. Another study in China showed that a MH was associated with both insulin resistance and impaired first-phase insulin secretion²⁵. Therefore, among those with a positive MH of diabetes, the decline in β -cell function should be carefully monitored and promptly treated. The results also suggest the transmission of diabetes from the maternal side could be partly explained by the impact of the unique maternal factors on β -cell function. For example, the mitochondria, which are inherited specifically from the maternal side, are responsible for producing adenosine triphosphate, which is tightly linked to insulin secretion from β -cells. Genetic defects in mitochondria can lead to a rapid decline in β -cell function in humans, such as maternally inherited diabetes and deafness²⁶. Variants in mitochondrial deoxyribonucleic acid were also proposed to be associated with an increased risk for diabetes²⁷. Maternal disorders during pregnancy might induce epigenetic modifications in the infant, resulting in dysregulation of β -cell development²⁸. Nutrition factors, both pre- and postnatal nutrition, have essential roles in the development of diabetes, as well as the reduced β -cell mass^{29,30}. For prenatal nutrition factors, maternal nutrition during pregnancy and intrauterine nutrition is well known to be predominant in health outcomes of offspring. For the postnatal stage, mothers are usually responsible for the diet structure and calories intake, as well as the cooking style, in most Chinese families. Thus, both pre- and postnatal nutrition of the offspring are mainly depended on mothers, which could be an unignorable reason for the excessive maternal transmission of diabetes.

It was also noticed that the MH group showed an older age than the PH group, along with a significantly lower insulinogenic index and a higher prevalence of impaired glucose metabolism in the present study. Aging is an essential risk factor for impaired β -cell function, so that the observed difference in insulinogenic index and risk for impaired glucose metabolism might be confounded by the difference in age. Then, age was adjusted in each regression model to exclude its confounding effects. The present authors previously reported worse β -cell function in older Chinese without diabetes³¹. In the present study, we built both the univariate and multivariate models

to explore the associations of age with β -cell function (Table S1), the results of which supported both aging and parental history having independent negative impacts on β -cell function. In the future, a longitudinal study design will be ideal to investigate the changing of β -cell function during the aging process in participants with different parental history patterns.

The present study also showed that reduced insulin sensitivity could be attributed to both MH and PH, and PH had significantly greater effects on promoting insulin resistance than did MH. We speculated that factors that can be affected by both parents might be major contributors to the determinant of insulin sensitivity in the offspring, such as insulin sensitivity-related genetic variants inherited from both parents or postnatal lifestyle characteristics learned from the environment that have an impact on insulin sensitivity. A study of white people showed that both maternal glucose and paternal insulin resistance were independently associated with the umbilical cord insulin concentration of the fetus³², implying the importance of the exposures from both the maternal side and the paternal side on insulin resistance of the offspring. However, why PH made a stronger contribution to insulin resistance than MH still requires further elucidation. One possible explanation could be that diabetes risk-related exposures are more frequent in men. It was previously reported that in China, diabetes risk-related exposures, including smoking, alcohol consumption and obesity, are more frequent in men than women¹⁸. It is also recognized that paternal exposures could impact the risk of metabolic diseases in offspring through epigenetic modification in sperm^{33,34}, such as paternal obesity³⁴, paternal cigarette smoking^{34,35} and paternal alcohol consumption³⁵. For example, an experimental study showed that paternal obesity could then induce insulin resistance through the actions of sperm non-coding ribonucleic acids³⁶.

It is speculated that the parental transmission of diabetes depends on the sex and age of the offspring. In China, male patients were more likely to have a father with diabetes than were female patients¹¹. In Japan, Otabe *et al.*¹⁵ observed excessive maternal transmission of diabetes only in offspring with type 2 diabetes (<20 years). In the present study, excessive maternal transmission of diabetes and impaired glucose metabolism was observed in women, which is partly consistent with the stronger influence of MH on decreased insulin secretion in women. Also, excessive maternal transmission of diabetes and impaired glucose metabolism was observed in those aged ≥ 45 years. In addition, PH had a greater contribution than MH to elevated insulin resistance in men or participants aged <45 years. However, the biological mechanisms were unclear. Although detailed analyses should be carried out to pursue more precise estimates for the influence of parental history, the results from subpopulations in the current study show the necessity for a more precise personalized management of diabetes.

Also, in Table 4, MH showed a significant association with HOMA-B and insulinogenic index in women, whereas FH2

did not show any association with these indices. We speculated that there are several reasons for these findings. First, in the female subgroup, there were 209 individuals with FH2 and 1,494 individuals with MH only. Thus, compared with FH2, the statistical power to detect the effect of MH could be larger due to the larger sample size of MH group. Second, we did not exclude the participants previously diagnosed as diabetes and those who already received glucose-lowering interventions, of whom insulin secretion or sensitivity indices could be influenced. In the female subgroup of the present study, there were significantly more participants with diabetes or impaired glucose metabolism in the FH2 group than in the MH group (Table 2; both $P < 0.05$). Thus, a larger proportion of individuals in the FH2 group than in the MH group could have received interventions. Also, it is possible that women with both parents affected by diabetes will have a greater awareness of the disease and engage in a better lifestyle to prevent diabetes. Thus, it might attenuate the associations of FH2 with HOMA-B or insulinogenic index.

Additionally, we found that the parental history of diabetes contributed to even greater diabetes risks in men and those aged <45 years. Thus, we speculate that for men or individuals aged <45 years, common genetic factors and family environment provided by the parents, which could be represented by FH, could make major contributions to the disease pathogenesis, whereas for women or individuals aged ≥ 45 years, habits acquired later in life could be more critical. These results also suggest the possibility of the existence of a stronger parental imprint specific to male offspring.

Furthermore, some studies showed that a sibling history of diabetes was more strongly associated with the risk for diabetes than parental history^{6,14}. We compared the participants with sibling diabetes history with parental diabetes history only in the present study (Appendix S1). The sibling history only group had worse insulin secretion capacity and insulin sensitivity than the parental history only group (Table S2). The estimated prevalence of diabetes and impaired glucose metabolism were significantly higher in the sibling history only group than in the parental history only group (Table S3). A significantly larger effective size of sibling history on the risk for diabetes and impaired glucose metabolism than those with parental history was identified (Table S4). These findings were consistent with the previous report. It is suggested that the recognition of sibling history of diabetes is especially important in the assessment of diabetes risk for those with one or more siblings. In fact, China's one-child policy was established by the government to restrict China's population growth and limited each couple to have only one child since 1980. Thus, it will be difficult to obtain any sibling history among the adults born after 1980. However, during recent years, China's two-child policy has gradually liberalized, so the assessment of both sibling and parental history will be of greatly increased importance in the future.

The current study had the following strengths. The present study was based on a relatively large population recruited from a large national representative population. Calculations in the present study were weighted on the basis of Chinese population data and the sampling scheme. Therefore, the results can be generalized among individuals of Chinese ancestry. Meanwhile, the present study provided insight into the different mechanisms that underpin MH and PH, and carried out subgroup analyses. This study also has a limitation. MH included both a history of diabetes during pregnancy and a history of diabetes after pregnancy, with no ability to distinguish them. Studies have shown that these forms of diabetes have different influences on the metabolism of offspring¹⁰. Thus, longitudinal studies are required to test the robustness of findings.

In conclusion, we reported the estimated prevalence rates of diabetes, prediabetes and impaired glucose metabolism in different parental history categories of Chinese participants, and observed that the MH group had a significantly higher prevalence of impaired glucose metabolism than did the PH group. These findings show that MH had greater influences on the elevated disease risks than did PH, especially in women and those aged ≥ 45 years. The findings also showed that MH has strong impacts on both insulin resistance and impaired insulin secretion, whereas PH had a specifically pronounced contribution to insulin resistance, suggesting that different biological mechanisms underpin the roles of MH and PH in the pathogenesis of diabetes. In addition, the current study showed that parental transmission of diabetes depends on the sex and age of the offspring. In this respect, it emphasizes the importance of detailed FH investigation, specifically the parental sides of diabetes transmission, in the risk assessment and development of a personalized management strategy for the at-risk population.

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DISCLOSURE

There are no patents, products in development or marketed products to declare. Outside the submitted work, WY has attended the advisory board of Novo Nordisk; received investigator-initiated trial research funds from AstraZeneca; been a speaker for Novo Nordisk, Bayer, Sanofi Aventis, Merck Sharp & Dohme China, AstraZeneca, Eli Lilly, Boehringer-Ingelheim and Servier; and received honorarium and travel support as the advisory boards' member from Merck & Co., Inc. The other authors declare no conflict of interest

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1 | Univariate and multivariate regressions of age on insulin secretion-related indices in the overall cohort.

Table S2 | Clinical characteristics of the study participants according to parental history and sibling history of diabetes.

Table S3 | Age- and sex-standardized prevalence rates of diabetes, prediabetes, and impaired glucose metabolism according to parental history and sibling history of diabetes in the overall cohort.

Table S4 | Associations of parental history and sibling history of diabetes with the risks for diabetes, prediabetes or impaired glucose metabolism in the overall cohort.

Appendix S1 | Materials and methods for the appendix data.