OPEN

Citation: Nutrition & Diabetes (2014) 4, e112; doi:10.1038/nutd.2014.9

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ORIGINAL ARTICLE

Maternal history of diabetes is associated with increased cardiometabolic risk in Chinese

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OBJECTIVE: Positive family history is associated with increased type 2 diabetes (T2D) risk, and reflects both genetic and environmental risks. Several studies have suggested an excess maternal transmission of T2D, although the underlying mechanism is unknown. We aimed to examine the association between maternal diabetes and cardiometabolic risk in the offspring.
METHODS: Parental history of diabetes and clinical data including anthropometric traits, fasting plasma glucose and insulin (FPG, FPI), blood pressure and lipid profile were collected from 2581 unrelated Chinese offspring (2026 adolescents from a population-based school survey and 555 adults from a community-based health screening programme). A subset of subjects ($n = 834$) underwent oral glucose tolerance test to measure the glucose and insulin concentrations at 0, 15, 30, 60 and 120 min for evaluation of the areas under the curve (AUC) of glucose and insulin at 0–120 min, homoeostasis model assessment of insulin resistance (HOMA-IR) and bell-cell function, insulinogenic index, insulin sensitivity index (ISI) and oral disposition index (DI).
RESULTS: A positive parental history of diabetes was associated with increased risk of obesity (odd ratios (OR) (95% confidence interval (CI)) = 1.48 (1.10–2.00)), central obesity (OR (95% CI) = 1.67 (1.21–2.32)), higher FPI, HOMA-IR, 2-h insulin, AUC of glucose at 0–120 min, triglycerides, reduced ISI and DI. Compared with individuals without parental diabetes, offspring with diabetic mother had significantly increased risk of obesity (OR (95% CI) = 1.59 (1.07–2.35)), central obesity (OR (95% CI) = 1.88 (1.23–2.88)), higher glucose levels and BP, were more insulin resistant but also had impaired first-phase insulin response and worse lipid profile. However, paternal history of diabetes had no effect on any of the studied traits, except higher body mass index, waist circumference in females and FPG.
CONCLUSIONS: Our findings suggested that maternal history of diabetes conferred increased risk of cardiometabolic abnormalities, and was associated with both insulin resistance and impaired first-phase insulin secretion. Further investigation into the mechanism of transgenerational diabetes is warranted.

Nutrition & Diabetes (2014) **4,** e112; doi:10.1038/nutd.2014.9; published online 10 March 2014

INTRODUCTION

With the adoption of a modern lifestyle and the lack of physical activity, there has been a twofold increase in the prevalence of type 2 diabetes (T2D) in China during the last two decades.[1] T2D is a multifactorial disease resulting from the interaction between genetic and environmental factors, leading to insulin resistance and β-cell dysfunction.[2] The genetic component has been strongly supported by the familial clustering of the disease in multiple populations.[3–9] These studies have shown that a positive family history (FH) of diabetes is associated with an increased risk of T2D[3–9] and an earlier age of onset in the offspring.[10,11] Moreover, a study conducted in Singapore demonstrated the association between FH of T2D and the presence of cardiometabolic risk factors, including obesity, increased homoeostasis model assessment of insulin resistance (HOMA-IR), fasting triglyceride (TG), and reduced high-density lipoprotein (HDL) cholesterol and homoeostasis model assessment of β-cell function (HOMA-β).[8]

Recently, evidence of excess maternal inheritance of T2D has accumulated from epidemiological studies and animal models. For example, our previous study observed a higher frequency of diabetes in mother than in father among T2D patients.[6] Moreover, women with gestational diabetes have been more frequently reported to have a diabetic mother than a diabetic father.[12] Animal models also demonstrated the effect of maternal diabetes on impaired glucose tolerance in their offspring.[13] Some[6,8,14–27] but not all[5,7,28–30] studies reported that offspring with maternal history of diabetes are more likely to develop diabetes and cardiometabolic disorders such as obesity, impaired glucose tolerance, insulin resistance, hyperinsulinaemia and dyslipidaemia compared with those with paternal history of diabetes. However, only limited data are available on the association between the parental history (PH) of diabetes and cardiometabolic risk. Therefore, we aimed to examine the associations of cardiometabolic risk factors with (1) PH of diabetes (at least one parent diagnosed with diabetes); (2) paternal history of diabetes; (3) maternal history of diabetes; and (4) biparental history of diabetes in two independent cohorts of Chinese adolescents and adults. Finally, we estimate the odd ratios (ORs) (95% confidence intervals (CIs)) for obesity and central obesity by comparing subjects with PH of diabetes to those without PH of diabetes.

MATERIALS AND METHODS

Subjects

The study design, ascertainment, inclusion criteria and phenotyping of the study subjects have been described previously.[31–33] All subjects were of southern Han Chinese ancestry residing in Hong Kong. Our study cohorts

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Received 15 January 2014; accepted 5 February 2014

consist of 2309 adolescents and 559 adults selected from a population-based school survey for risk factor assessment and a community-based health screening programme, respectively. All participants or parents of adolescents were asked to complete a questionnaire including questions on FH of diabetes. We did not document the age at which the parents were diagnosed with diabetes. Positive PH was defined as having at least one diabetic parent. To estimate the parental transmission of cardiometabolic traits, participants with a positive PH of diabetes were further divided into three groups: (1) paternal history was defined as having only father with diabetes; (2) maternal history was defined as having only mother with diabetes; and (3) biparental history was defined as having both parents with diabetes. These groups were mutually exclusive. We excluded 283 (12.3%) adolescents and 4 (0.7%) adults with unknown diabetes status of their parents. Finally, 2026 adolescents (mean age 15.6 ± 2.0 years, 45.5% male) and 555 adults (mean age 43.5 ± 8.2 years, 48.3% male) were included in the subsequent analyses. This study was approved by the Clinical Research Ethics Committee of the Chinese University of Hong Kong. All participants or parents of adolescents gave written informed consent as appropriate.

Clinical studies

All study subjects were examined in the morning after an overnight fast. Anthropometric indices including body weight and height (BW), waist and hip circumference (WC and HC), and systolic and diastolic blood pressure (SBP and DBP) were measured. The body fat percentage (FAT) was measured by bioimpedence analysis (Tanita Corp., Tokyo, Japan). Body mass index (BMI) was calculated as weight (kg) divided by squared height (m^2). Waist–hip ratio (WHR) was calculated as WC (cm) divided by HC (cm). A random spot specimen of urine was collected for the measurements of albumin-creatinine ratio (ACR). Fasting blood samples were collected for the measurements of fasting plasma glucose and insulin (FPG and FPI), as well as lipid profile (total cholesterol, TG, HDL cholesterol and low-density lipoprotein cholesterol). HOMA-IR was calculated as (FPI × FPG)÷22.5, and HOMA-β was calculated as FPI × 20÷(FPG − 3.5).[34]

A subset of the subjects (279 adolescents and 555 adults) also underwent a 75 g oral glucose tolerance test (OGTT) to measure the glucose and insulin concentrations at 0, 15, 30, 60 and 120 min. Areas under the curve (AUC) for glucose and insulin during OGTT at 0–120 min were calculated using the trapezoid rule. Insulinogenic index was assessed as (insulin during OGTT at 30 min − 0 min)÷(glucose during OGTT at 30 min − 0 min).[35] Insulin sensitivity index (ISI) was estimated using the formula proposed by Matsuda and DeFronzo:[36] 10 000÷square root of [FPG × FPI × (mean glucose during OGTT) × (mean insulin during OGTT)]. Oral disposition index (DI) was calculated as (insulin during OGTT at 30 min − 0 min)÷(glucose during OGTT at 30 min − 0 min)÷HOMA-IR.[37]

In adolescents, overweight or obesity was defined on the basis of the age- and sex-specific cutoff for BMI from an international survey.[38] Central obesity was defined using the 90th percentile of WC or adult cutoff if lower.[39] In adults, overweight and obesity were defined as BMI $\geqslant$25 and $\geqslant$30 kg m^{-2}, respectively. Central obesity was defined as WC $\geqslant$90 cm for male or 80 cm for female.[39]

Statistical analysis

All statistical analyses were performed using SPSS for Windows v.18 (SPSS, Chicago, IL, USA). Two-tailed *P*-values <0.05 were considered statistically significant.

Data are presented as percentage (*n*), mean ± s.d. or geometric mean (95% CI) (where appropriate). FPI, HOMA-IR, HOMA-β, insulin concentrations during OGTT at 0, 15, 30, 60 and 120 min, insulin AUC during OGTT at 0–120 min, insulinogenic index, ISI, DI, TG and ACR were log transformed due to skewed distributions. Each cardiometabolic trait was winsorized separately in adult and adolescent cohorts by replacing the extreme values with four s.d. from the mean. In total, 0.25% and 0.31% of data in adolescents and adults were replaced, respectively.

Within each cohort, associations between cardiometabolic risk factors and PH categories were tested by multiple linear regression analysis, adjusted for sex and age. Three dummy variables were used to code for the PH categories (paternal, maternal and biparental history of diabetes) and each group was compared with the group without diabetic parent. We conducted the logistic regression analysis to estimate the ORs with 95% CIs for dichotomous traits (overweight or obesity and central obesity). To combine the results from the two cohorts, meta-analyses under fixed- and random-effects models were performed by weighting the β-coefficient of each study using the inverse of their variance. Cochran's Q statistic and I^2 index were used to assess heterogeneity of effects across cohorts. The Q test informs us about the presence versus the absence of heterogeneity, whereas I^2 index quantifies the degree of heterogeneity in meta-analysis. I^2 values around 25, 50 and 75% would mean low, medium and high heterogeneity, respectively. Multiple testing of phenotypic traits was corrected by a sharper Bonferroni procedure suggested by Hochberg.[40]

RESULTS

Cohort description

The demographic characteristics of the participants are summarized in Table 1. Among 2026 adolescents, 1861 (91.86%) subjects had no PH of diabetes, whereas 95 (4.69%) had a diabetic father, 69 (3.41%) had a diabetic mother and 1 (0.05%) had two diabetic parents. In this cohort, the prevalence of T2D, obesity and central obesity were 0.05%, 13.0% and 7.4%, respectively. Among 555 adults, 411 (74.05%) subjects had no PH of diabetes, whereas 45 (8.11%) had a diabetic father, 84 (15.14%) had a diabetic mother and 15 (2.70%) had two diabetic parents. In this cohort, the prevalence of T2D, obesity and central obesity were 6.8%, 32.3% and 24.5%, respectively. Tables 2 and 3 show the cardiometabolic characteristics of the individuals stratified by parental diabetes status.

Effect of PH of diabetes on cardiometabolic risk factors

Of the adolescents, a positive PH of diabetes was significantly associated with higher BW, BMI, WC in female, WHR, FAT, FPI, HOMA-IR but lower DI ($0.0013<P<0.0393$) (Table 2). Among adults, a positive parental diabetes was associated with higher BMI, FPG, FPI, HOMA-IR, 2-h glucose, glucose AUC during OGTT at 0-120 min (Figure 1 and Supplementary Table 1), SBP, DBP, TG, low-density lipoprotein cholesterol and lower body height, ISI and DI ($2.1\times10^{-4}<P<0.0488$) (Table 2). In the meta-analysis, we observed significant associations for body height, BW, BMI, WC in male and female, HC, WHR, FAT, FPI, HOMA-IR, 2-h insulin, glucose AUC at OGTT 0–120 min, ISI, DI and TG ($2.6\times10^{-5}<P<0.0495$) under the absence of heterogeneity between the two cohorts ($P>0.05$ in Q test) (Table 2). The differences in BMI, HOMA-IR, ISI and DI still remained significant after correction of multiple comparisons.

Paternal and maternal transmission of cardiometabolic risk factors

Next, we examined the paternal and maternal transmission effect on cardiometabolic traits. Adolescents with a maternal history of diabetes had significantly higher BW, BMI, FAT, FPI, HOMA-IR and

Table 1. Demographic characteristics of 2026 and 555 Chinese adolescents and adults, respectively

	Adolescents	*Adults*
N	2026	555
Sex (male %)	45.5% (922)	48.3% (268)
Age (years)	15.6 ± 2.0	43.5 ± 8.2
Parental history of diabetes		
No parental history (%)	91.86% (1861)	74.05% (411)
Paternal history (%)	4.69% (95)	8.11% (45)
Maternal history (%)	3.41% (69)	15.14% (84)
Biparental history (%)	0.05% (1)	2.70% (15)
Proportion of participants with OGTT data (%)	13.8% (279)	100.0% (555)
Type 2 diabetes (%)	0.05% (1)	6.8% (38)
Overweight or obesity (%)	13.0% (264)	32.3% (179)
Central obesity (%)	7.4% (150)	24.5% (136)

Abbreviation: OGTT, oral glucose tolerance test. Data were expressed as % (*n*) or mean ± s.d.

Table 2. Clinical and cardiometabolic characteristic of adolescents and adults stratified by parental history (yes/no)

	Adolescents			*Adults*			*Meta-analysis*			
	Parental diabetic history		$P_{adjusted}$	*Parental diabetic history*		$P_{adjusted}$	P_{fixed}	P_{random}	*Heterogeneity test*	
	No	*Yes*		*No*	*Yes*				P_Q	I^2
N	1861	165	—	411	144	—	—	—	—	—
Sex (male %)	44.8% (833)	53.9% (89)	0.0239	199 (48%)	69 (48%)	0.9174	—	—	—	—
Age (years)	15.55 ± 2.04	15.76 ± 2.08	0.1265	43.9 ± 8.35	42.51 ± 7.74	0.0807	—	—	—	—
Obesity traits										
Body height (cm)	161.4 ± 8.3	162.3 ± 9.6	0.7238	161.6 ± 8.1	160.4 ± 8.8	0.0108	0.0440	0.2009	0.1058	0.6177
Body weight (kg)	52.1 ± 11.2	55.3 ± 12.9	0.0081	61.8 ± 10.9	63 ± 12.6	0.1988	0.0048	0.0048	0.3908	0.0000
Body mass index (kg m^{-2})	19.9 ± 3.4	20.9 ± 3.9	0.0013	23.6 ± 3.3	24.4 ± 4	0.0071	2.6×10^{-5}	2.6×10^{-5}	0.9882	0.0000
Waist circumference (cm)										
Male	71.2 ± 8.5	72.8 ± 9.3	0.1382	83.8 ± 8.2	85.5 ± 9.5	0.1378	0.0370	0.0370	0.7954	0.0000
Female	65.6 ± 6.6	67.5 ± 8	0.0219	74.1 ± 8.3	74.9 ± 9.2	0.3339	0.0150	0.0150	0.5939	0.0000
Hip circumference (cm)	88.9 ± 7.7	90.4 ± 8.8	0.0693	93.7 ± 5.8	94.6 ± 7.1	0.1562	0.0224	0.0224	0.7465	0.0000
Waist–hip ratio	0.77 ± 0.05	0.78 ± 0.05	0.0122	0.84 ± 0.07	0.84 ± 0.08	0.1768	0.0045	0.0045	0.8264	0.0000
Body fat percentage (%)	21.2 ± 6.9	21.9 ± 7.9	0.0292	27.5 ± 6.6	28.6 ± 7.5	0.0565	0.0037	0.0037	0.9854	0.0000
Glucose-related traits										
Fasting plasma glucose (mmol l^{-1})	4.7 ± 0.35	4.72 ± 0.36	0.5558	4.96 ± 0.62	5.18 ± 0.75	2.1×10^{-4}	0.0381	0.2760	0.0016	0.9001
Fasting plasma insulin (pmol l^{-1})	46.8 (45.8–47.7)	49.8 (46.4–53.4)	0.0377	44.4 (41.3–47.8)	53.6 (47.9–60.1)	0.0113	0.0028	0.0314	0.1753	0.4555
HOMA-IR	1.62 (1.59–1.66)	1.73 (1.61–1.87)	0.0393	1.62 (1.51–1.75)	2.05 (1.82–2.31)	0.0023	0.0013	0.0638	0.0675	0.7009
HOMA-β	135.8 (132.8–139)	143.5 (133.1–154.7)	0.1113	109 (100.9–117.8)	115.5 (102.1–130.6)	0.6061	0.0993	0.0993	0.7663	0.0000
2-h glucose (mmol l^{-1})[a]	6.05 ± 1.61	6.15 ± 1.5	0.6928	6.39 ± 2.31	6.79 ± 2.75	0.0488	0.0732	0.0732	0.3577	0.0000
2-h insulin (pmol l^{-1})[a]	460.8 (415.9–510.5)	492 (376–643.8)	0.6031	271.4 (252.8–291.5)	313.7 (276.3–356.3)	0.0535	0.0495	0.0495	0.6937	0.0000
Glucose AUC during OGTT at 0–120 min[a]	814.9 ± 160.9	835.7 ± 140.3	0.4652	893.8 ± 224	954.5 ± 263.4	0.0027	0.0045	0.0318	0.2151	0.3492
Insulin AUC during OGTT at 0–120 min[a]	59702 (55381–64360)	56779 (45538–70795)	0.7045	36227 (34372–38182)	40664 (36720–45032)	0.0587	0.1274	0.3453	0.2353	0.2899
Insulinogenic index[a]	32 (29–35.4)	27.6 (21–36.1)	0.3145	13.2 (12.2–14.3)	12.8 (10.9–15.1)	0.5342	0.3028	0.3028	0.5594	0.0000
Insulin sensitivity index[a]	68.2 (62.7–74.3)	63.3 (49.8–80.4)	0.4803	93.8 (88.4–99.6)	77 (69.2–85.6)	0.0014	0.0015	0.0015	0.4284	0.0000
Oral disposition index[a]	17.64 (15.9–19.57)	12.64 (10.36–15.43)	0.0294	8.46 (7.65–9.36)	6.21 (5.15–7.48)	0.0015	1.1×10^{-4}	1.1×10^{-4}	0.9682	0.0000
Blood pressure										
Systolic blood pressure (mm Hg)	116.8 ± 12.6	118.4 ± 13.8	0.3760	117 ± 17.8	119.3 ± 19	0.0387	0.0654	0.1319	0.1947	0.4055
Diastolic blood pressure (mm Hg)	72.6 ± 9.2	71.8 ± 9.9	0.3419	75.5 ± 10.7	77.1 ± 11.7	0.0419	0.6244	0.6748	0.0281	0.7926
Lipid profile										
Total cholesterol (mmol l^{-1})	4.17 ± 0.7	4.19 ± 0.72	0.5544	5.21 ± 0.93	5.32 ± 0.98	0.0849	0.1500	0.1842	0.2624	0.2038
Triglycerides (mmol l^{-1})	0.76 (0.75–0.77)	0.77 (0.73–0.82)	0.4085	1.07 (1.01–1.12)	1.18 (1.08–1.29)	0.0183	0.0465	0.1481	0.1275	0.5696
HDL cholesterol (mmol l^{-1})	1.6 ± 0.31	1.6 ± 0.32	0.9900	1.59 ± 0.42	1.53 ± 0.4	0.0970	0.3504	0.4095	0.1691	0.4713
LDL cholesterol (mmol l^{-1})	2.2 ± 0.6	2.21 ± 0.65	0.6292	3.06 ± 0.84	3.19 ± 0.85	0.0351	0.1275	0.2445	0.1234	0.5788
Cardiovascular risk factor										
Albumin-creatinine ratio	0.61 (0.58–0.64)	0.58 (0.49–0.68)	0.7971	0.81 (0.73–0.89)	0.88 (0.73–1.08)	0.2856	0.6159	0.6159	0.3280	0.0000

Abbreviations: AUC, areas under the curve; HDL, high-density lipoprotein; HOMA-IR, homoeostasis model assessment of insulin resistance; HOMA-β, homoeostasis model assessment of β-cell function; LDL, low-density lipoprotein; OGTT, oral glucose tolerance test. Data were expressed as *n*, %, mean ± s.d. or geometric mean (95% confidence interval). $P_{adjusted}$ refers to *P*-value obtained from linear regression adjusted by sex and age. P_{fixed} and P_{random} refer to *P*-value obtained from meta-analysis using fixed- and random-effect model, respectively. P_Q refers to *P*-value of Cochran's Q statistics in heterogeneity test. I^2 index is used to quantify the degree of heterogeneity of β-coefficient. I^2 values around 25, 50 and 75% would mean low, medium and high heterogeneity. [a]Indicates only a subset of samples (285 adolescents and 555 adults) who were included in the analysis.

Table 3. Clinical and cardiometabolic characteristic of adolescents and adults stratified by parental history categories

Phenotype	*Parental history categories*	*Adolescent*		*Adults*		*Meta-analysis*			
		Value	$P_{adjusted}$	*Value*	$P_{adjusted}$	P_{fixed}	P_{random}	P_Q	I^2
N	No parental	1861 (91.86%)	—	411 (74.05%)	—	—	—	—	—
	Paternal	95 (4.69%)	—	45 (8.11%)	—	—	—	—	—
	Maternal	69 (3.41%)	—	84 (15.14%)	—	—	—	—	—
	Both	1 (0.05%)	—	15 (2.70%)	—	—	—	—	—
Sex (male %)	No parental	833 (44.8%)	—	199 (48%)	—	—	—	—	—
	Paternal	55 (57.9%)	0.0130	23 (51%)	0.7316	—	—	—	—
	Maternal	34 (49.3%)	0.4597	39 (46%)	0.7395	—	—	—	—
	Both	—	—	7 (47%)	0.8939	—	—	—	—
Age (years)	No parental	15.55 ± 2.04	—	43.9 ± 8.35	—	—	—	—	—
	Paternal	15.88 ± 2.13	0.0649	42.04 ± 7.35	0.1373	—	—	—	—
	Maternal	15.6 ± 2.03	0.7743	43.26 ± 7.99	0.5398	—	—	—	—
	Both	—	—	39.67 ± 7.12	0.0505	—	—	—	—
Obesity traits									
Body height (cm)	No parental	161.4 ± 8.3	Reference	161.6 ± 8.1	Reference	—	—	—	—
	Paternal	162.7 ± 9.7	0.6420	160.9 ± 7.7	0.1312	0.1999	0.1999	0.3541	0.0000
	Maternal	161.9 ± 9.5	0.9869	160.1 ± 9.1	0.0434	0.1289	0.2875	0.1805	0.4423
	Both	—	—	160.4 ± 10.6	0.2393	—	—	—	—
Body weight (kg)	No parental	52.1 ± 11.2	Reference	61.8 ± 10.9	Reference	—	—	—	—
	Paternal	54.9 ± 13.8	0.2115	63 ± 10.3	0.6155	0.1924	0.1924	0.7335	0.0000
	Maternal	55.9 ± 11.7	0.0083	63.6 ± 14	0.0727	0.0020	0.0020	0.4299	0.0000
	Both	—	—	59.5 ± 10.9	0.3407	—	—	—	—
Body mass index ($kg\,m^{-2}$)	No parental	19.9 ± 3.4	Reference	23.6 ± 3.3	Reference	—	—	—	—
	Paternal	20.6 ± 4	0.1224	24.3 ± 3.6	0.1480	0.0367	0.0367	0.7275	0.0000
	Maternal	21.2 ± 3.7	0.0016	24.7 ± 4.2	0.0042	2.0×10^{-5}	2.0×10^{-5}	0.8105	0.0000
	Both	—	—	23.1 ± 3.2	0.7137	—	—	—	—
Waist circumference									
Male (cm)	No parental	71.2 ± 8.5	Reference	83.8 ± 8.2	Reference	—	—	—	—
	Paternal	72.2 ± 8.9	0.6683	82.7 ± 7	0.5537	0.9611	0.9611	0.4653	0.0000
	Maternal	73.9 ± 9.9	0.0550	87.8 ± 10.4	0.0066	0.0010	0.0010	0.5472	0.0000
	Both	—	—	81.9 ± 8.5	0.6483	—	—	—	—
Female (cm)	No parental	65.6 ± 6.6	Reference	74.1 ± 8.3	Reference	—	—	—	—
	Paternal	67.7 ± 8.2	0.0554	76.7 ± 11.5	0.0745	0.0107	0.0107	0.5503	0.0000
	Maternal	67.2 ± 8	0.1923	74.9 ± 8.4	0.5364	0.1626	0.1626	0.7129	0.0000
	Both	—	—	69.6 ± 5.1	0.2156	—	—	—	—
Hip circumference (cm)	No parental	88.9 ± 7.7	Reference	93.71 ± 5.83	Reference	—	—	—	—
	Paternal	90.2 ± 9.3	0.3157	94.36 ± 6.6	0.6054	0.2703	0.2703	0.8074	0.0000
	Maternal	90.5 ± 8.3	0.1078	95.16 ± 7.61	0.0482	0.0108	0.0108	0.9690	0.0000
	Both	—	—	92.3 ± 5.1	0.3331	—	—	—	—
Waist–hip ratio	No parental	0.77 ± 0.05	Reference	0.8 ± 0.1	Reference	—	—	—	—
	Paternal	0.78 ± 0.04	0.0651	0.8 ± 0.1	0.4977	0.0510	0.0510	0.8090	0.0000
	Maternal	0.78 ± 0.06	0.0717	0.85 ± 0.08	0.0736	0.0116	0.0116	0.7682	0.0000
	Both	—	—	0.81 ± 0.07	0.3082	—	—	—	—
Body fat percentage (%)	No parental	21.2 ± 6.9	Reference	27.5 ± 6.6	Reference	—	—	—	—
	Paternal	21.3 ± 8.3	0.3101	28.1 ± 7.8	0.3868	0.1843	0.1843	0.8927	0.0000
	Maternal	22.7 ± 7.2	0.0295	29.1 ± 7.5	0.0372	0.0026	0.0026	0.8841	0.0000
	Both	—	—	27.3 ± 6.1	0.8967	—	—	—	—

Table 3. (Continued)

Phenotype	*Parental history categories*	*Adolescent*		*Adults*		*Meta-analysis*			
		Value	$P_{adjusted}$	*Value*	$P_{adjusted}$	P_{fixed}	P_{random}	P_Q	I^2
Glucose-related traits									
Fasting plasma glucose (mmol l^{-1})	No parental	4.7 ± 0.35	Reference	4.96 ± 0.62	Reference	—	—	—	—
	Paternal	4.75 ± 0.36	0.1505	5.15 ± 0.69	0.0461	0.0427	0.1580	0.1620	0.4886
	Maternal	4.68 ± 0.35	0.5541	5.18 ± 0.82	0.0026	0.3461	0.4565	0.0033	0.8838
	Both	—	—	5.23 ± 0.56	0.0560	—	—	—	—
Fasting plasma insulin (pmol l^{-1})	No parental	46.8 (45.8–47.7)	Reference	44.4 (41.3–47.8)	Reference	—	—	—	—
	Paternal	47.7 (43.7–52.1)	0.4590	46.3 (38.3–56.1)	0.8039	0.4357	0.4357	0.9584	0.0000
	Maternal	52.8 (47.2–59)	0.0122	59.8 (51.6–69.4)	7.8×10^{-4}	1.1×10^{-4}	0.0178	0.0958	0.6395
	Both	—	—	45 (30.3–66.8)	0.9490	—	—	—	—
HOMA-IR	No parental	1.62 (1.59–1.66)	Reference	1.62 (1.51–1.75)	Reference	—	—	—	—
	Paternal	1.68 (1.53–1.84)	0.3453	1.77 (1.44–2.16)	0.5560	0.2727	0.2727	0.8515	0.0000
	Maternal	1.82 (1.62–2.05)	0.0222	2.29 (1.96–2.67)	2.1×10^{-4}	1.2×10^{-4}	0.0444	0.0382	0.7671
	Both	—	—	1.73 (1.14–2.64)	0.8010	—	—	—	—
HOMA-β	No parental	135.8 (132.8–139)	Reference	109 (100.9–117.8)	Reference	—	—	—	—
	Paternal	132.7 (119.8–147.1)	0.8636	101.1 (82.4–124)	0.4317	0.6347	0.6347	0.5156	0.0000
	Maternal	157.3 (141.1–175.3)	0.0093	129.2 (109.6–152.4)	0.0877	0.0019	0.0019	0.9499	0.0000
	Both	—	—	91 (63.8–129.9)	0.2390	—	—	—	—
2-h glucose[a] (mmol l^{-1})	No parental	6.05 ± 1.61	Reference	6.39 ± 2.31	Reference	—	—	—	—
	Paternal	5.85 ± 1.24	0.7081	6.04 ± 2.6	0.4750	0.4389	0.4389	0.8190	0.0000
	Maternal	6.52 ± 1.73	0.3097	7.17 ± 2.79	0.0055	0.0041	0.0041	0.4661	0.0000
	Both	—	—	6.97 ± 2.67	0.2277	—	—	—	—
2-h insulin[a] (pmol l^{-1})	No parental	460.8 (415.9–510.5)	Reference	271.4 (252.8–291.5)	Reference	—	—	—	—
	Paternal	409.2 (302.1–554.3)	0.6941	270.9 (219.1–335)	0.9497	0.7959	0.7959	0.7616	0.0000
	Maternal	613.8 (390.4–964.9)	0.2193	348.8 (295.2–412.1)	0.0057	0.0024	0.0024	0.9633	0.0000
	Both	—	—	269.3 (172.7–419.9)	0.9047	—	—	—	—
Glucose AUC during OGTT at 0–120 min[a]	No parental	814.9 ± 160.9	Reference	893.8 ± 224	Reference	—	—	—	—
	Paternal	817 ± 134.7	0.8978	901.7 ± 247.3	0.6728	0.6912	0.6912	0.8468	0.0000
	Maternal	858.1 ± 148.1	0.3296	974.9 ± 269.3	0.0022	0.0019	0.0019	0.3891	0.0000
	Both	—	—	999.5 ± 270.6	0.0361	—	—	—	—
Insulin AUC during OGTT at 0–120 min[a]	No parental	59702 (55381–64360)	Reference	36227 (34372–38182)	Reference	—	—	—	—
	Paternal	50525 (40950–62340)	0.3569	40645 (33874–48770)	0.2762	0.6612	0.9291	0.1740	0.4588
	Maternal	65970 (43200–100743)	0.6458	42057 (36831–48025)	0.0319	0.0307	0.0307	0.6810	0.0000
	Both	—	—	33719 (24145–47090)	0.4542	—	—	—	—
Insulinogenic index[a]	No parental	32 (29–35.4)	Reference	13.2 (12.2–14.3)	Reference	—	—	—	—
	Paternal	27.4 (19.5–38.4)	0.4985	15.4 (11.7–20.4)	0.3373	0.6863	0.7705	0.2697	0.1793
	Maternal	27.8 (17.6–44.1)	0.4254	12.6 (10.3–15.5)	0.5838	0.4084	0.4084	0.6139	0.0000
	Both	—	—	8.1 (4.5–14.7)	0.0114	—	—	—	—
Insulin sensitivity index[a]	No parental	68.2 (62.7–74.3)	Reference	93.8 (88.4–99.6)	Reference	—	—	—	—
	Paternal	74.2 (57–96.5)	0.8120	85.4 (71.5–101.9)	0.3830	0.5361	0.5361	0.5091	0.0000
	Maternal	51.6 (33.9–78.4)	0.1701	70.9 (61.8–81.4)	2.0×10^{-4}	6.9×10^{-5}	6.9×10^{-5}	0.8594	0.0000
	Both	—	—	88.8 (60.3–130.7)	0.7915	—	—	—	—
Oral disposition index[a]	No parental	17.6 (15.9–19.6)	Reference	8.46 (7.65–9.36)	Reference	—	—	—	—
	Paternal	14 (11–18)	0.2193	8.54 (6.1–11.95)	0.9802	0.4158	0.4158	0.3552	0.0000
	Maternal	11 (8–15.2)	0.0458	5.55 (4.4–7)	5.7×10^{-4}	6.3×10^{-5}	6.3×10^{-5}	0.9445	0.0000
	Both	—	—	4.66 (2.38–9.16)	0.0178	—	—	—	—

Table 3. (Continued)

Phenotype	*Parental history categories*	*Adolescent*		*Adults*		*Meta-analysis*			
		Value	$P_{adjusted}$	*Value*	$P_{adjusted}$	P_{fixed}	P_{random}	P_Q	I^2
Blood pressure									
Systolic blood pressure (mm Hg)	No parental	116.8 ± 12.6	Reference	117 ± 17.8	Reference	—	—	—	—
	Paternal	118.9 ± 14	0.4134	114.2 ± 17.9	0.5031	0.6635	0.6635	0.3351	0.0000
	Maternal	118.1 ± 13.3	0.5032	121.9 ± 19.4	0.0044	0.0237	0.1744	0.0605	0.7162
	Both	—	—	119.4 ± 18	0.2091	—	—	—	—
Diastolic blood pressure (mm Hg)	No parental	72.6 ± 9.2	Reference	75.5 ± 10.7	Reference	—	—	—	—
	Paternal	72.2 ± 9.7	0.7737	73.8 ± 10.2	0.3681	0.4725	0.4725	0.5387	0.0000
	Maternal	71.3 ± 10.4	0.2821	79 ± 12.1	0.0014	0.1548	0.6080	0.0021	0.8940
	Both	—	—	76.1 ± 11.6	0.5041	—	—	—	—
Lipid profile									
Total cholesterol ($mmol\,l^{-1}$)	No parental	4.17 ± 0.7	Reference	5.21 ± 0.93	Reference	—	—	—	—
	Paternal	4.23 ± 0.73	0.2548	5.17 ± 0.91	0.9495	0.2990	0.2990	0.6369	0.0000
	Maternal	4.13 ± 0.71	0.6784	5.37 ± 1.02	0.0864	0.4542	0.5534	0.1095	0.6097
	Both	—	—	5.46 ± 0.95	0.1044	—	—	—	—
Triglycerides ($mmol\,l^{-1}$)	No parental	0.76 (0.75–0.77)	Reference	1.07 (1.01–1.12)	Reference	—	—	—	—
	Paternal	0.76 (0.71–0.82)	0.6747	1.11 (0.95–1.29)	0.5535	0.5171	0.5171	0.7423	0.0000
	Maternal	0.79 (0.72–0.88)	0.3486	1.27 (1.12–1.43)	0.0019	0.0073	0.1144	0.0656	0.7050
	Both	—	—	0.94 (0.76–1.15)	0.5206	—	—	—	—
HDL cholesterol ($mmol\,l^{-1}$)	No parental	1.6 ± 0.31	Reference	1.59 ± 0.42	Reference	—	—	—	—
	Paternal	1.64 ± 0.32	0.1688	1.51 ± 0.34	0.2617	0.4943	0.9986	0.1010	0.6282
	Maternal	1.54 ± 0.3	0.1040	1.5 ± 0.43	0.0413	0.0107	0.0107	0.5793	0.0000
	Both	—	—	1.72 ± 0.4	0.1742	—	—	—	—
LDL cholesterol ($mmol\,l^{-1}$)	No parental	2.2 ± 0.6	Reference	3.06 ± 0.84	Reference	—	—	—	—
	Paternal	2.22 ± 0.67	0.5528	3.14 ± 0.8	0.3705	0.3522	0.3522	0.5901	0.0000
	Maternal	2.19 ± 0.62	0.9907	3.2 ± 0.88	0.0857	0.2957	0.3828	0.1714	0.4653
	Both	—	—	3.28 ± 0.87	0.1410	—	—	—	—
Cardiovascular risk factor									
Albumin-creatinine ratio	No parental	0.61 (0.58–0.64)	Reference	0.81 (0.73–0.89)	Reference	—	—	—	—
	Paternal	0.59 (0.47–0.73)	0.9103	0.62 (0.49–0.78)	0.1625	0.4879	0.5028	0.2226	0.3277
	Maternal	0.56 (0.43–0.73)	0.5823	1.07 (0.79–1.45)	0.0233	0.1983	0.5440	0.0505	0.7386
	Both	—	—	0.88 (0.66–1.17)	0.6263	—	—	—	—

Abbreviations: AUC, areas under the curve; HDL, high-density lipoprotein; HOMA-IR, homoeostasis model assessment of insulin resistance; HOMA-β, homoeostasis model assessment of β-cell function; LDL, low-density lipoprotein; OGTT, oral glucose tolerance test. Data were expressed as *n*, %, mean ± s.d. or geometric mean (95% confidence interval). $P_{adjusted}$ refers to *P*-value obtained from linear regression adjusted by sex and age. P_{fixed} and P_{random} refer to *P*-value obtained from meta-analysis using fixed- and random-effect model, respectively. P_Q refers to *P*-value of Cochran's Q statistics in heterogeneity test. I^2 index is used to quantify the degree of heterogeneity of β-coefficient. I^2 values around 25, 50 and 75% would mean low, medium and high heterogeneity. Each group (paternal, maternal and both parental history of diabetes) was compared with the reference group (no parental history of diabetes) in linear regression analysis. [a]Indicates only a subset of samples (285 adolescents and 555 adults) who were included in the analysis.

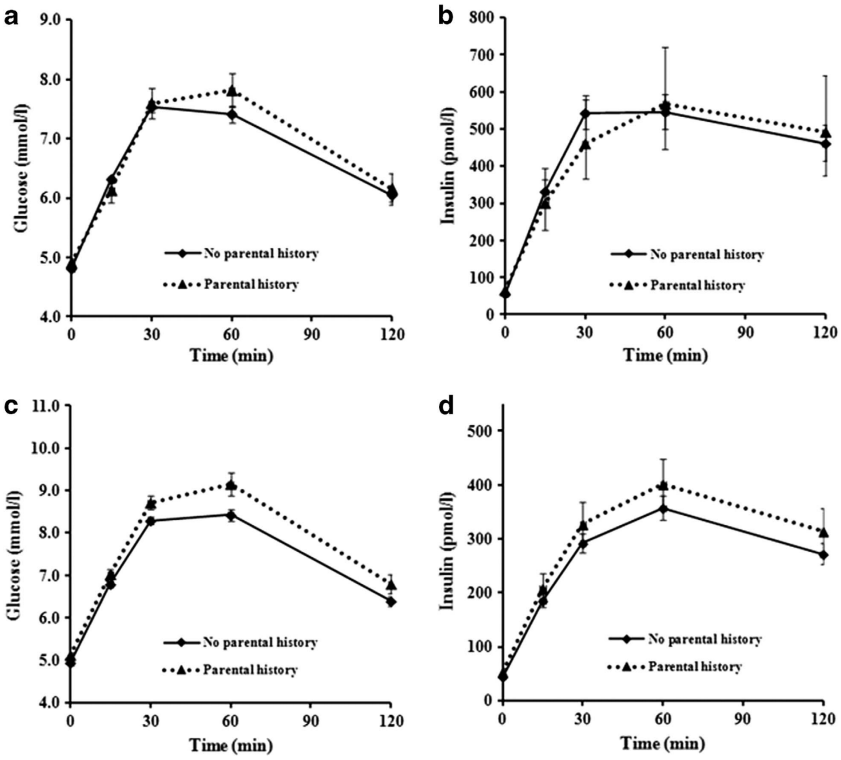

Figure 1. Plasma glucose and insulin concentrations at 0, 15, 30, 60 and 120 min during oral glucose tolerance test (OGTT) in (**a**, **b**) adolescents ($n = 279$) and (**c**, **d**) adults ($n = 555$) stratified by parental history (yes/no). Data were expressed as mean ± s.e. Associations between glucose/insulin concentrations and parental history for each time point during OGTT were shown in Supplementary Table 1.

HOMA-β but lower DI ($0.0016 < P < 0.0458$) compared with those without PH of diabetes (Table 3). Likewise, adults with a maternal history of diabetes had higher BMI, WC in male, HC, FAT, FPG, FPI, HOMA-IR, 2-h glucose, 2-h insulin, glucose and insulin AUC during OGTT at 0–120 min (Figure 2 and Supplementary Table 2), SBP, DBP, TG and ACR, but lower body height, ISI, DI and HDL, ($2.0 \times 10^{-4} < P < 0.0482$), compared with individuals with no parental diabetes (Table 3). In the meta-analysis, there were significant associations for positive maternal history of diabetes with higher BW, BMI, WC in male, HC, WHR, FAT, FPI, HOMA-IR, HOMA-β, 2-h glucose, 2-h insulin, glucose and insulin AUC during OGTT at 0–120 min, SBP and TG, as well as lower ISI, DI and HDL ($2.0 \times 10^{-5} < P < 0.0444$) (Table 3). Conversely, a paternal history of diabetes had no effect on any of the cardiometabolic traits, except for the higher FPG levels in adults ($P = 0.0461$), as well as higher BMI ($P = 0.0367$), WC in female ($P = 0.0107$) and FPG ($P = 0.0427$) in the combined analysis (Table 3). Associations between maternal history of diabetes and BMI, WC in male, FPI, ISI and DI remained significant after considering multiple testing. When we compared the cardiometabolic traits between offspring with diabetic mother to diabetic father, significant associations were still observed for higher WC in male, FPI, HOMA-IR, HOMA-β, 2-h glucose, 2-h insulin, SBP, DBP, ACR, as well as lower ISI, DI and HDL in either individual or combined cohorts (Supplementary Table 3). Among adults, we also found that offspring with two diabetic parents have more impaired β-cell function indicated by the increased glucose AUC during OGTT at 0–120 min (Figure 2 and Supplementary Table 2) and the reduced insulinogenic index and DI compared with those without parental diabetes (Table 3).

Associations of obesity and central obesity with PH

Lastly, we investigated the transmission pattern of obesity and central obesity according to the diabetes status of parents. Subjects with at least one diabetic parent are more obese (OR (95% CI) = 1.48 (1.10–2.00) in overall) and centrally obese (OR (95% CI) = 1.67 (1.21–2.32) in overall) than those without parental diabetes (Figures 3a and b). In addition, subjects with diabetic father had increased odds of central obesity of 1.69 (95% CI = 1.06–2.70 in overall), whereas subjects with diabetic mother had ORs of 1.59 (95% CI = 1.07–2.35 in overall) and 1.88 (95% CI = 1.23–2.88 in overall) for obesity and for central obesity, respectively, compared with offspring without PH of diabetes (Figures 3a and b).

DISCUSSION

T2D has been recognized as a familial disease, passed through from one generation to the next. Recently, several Caucasian studies have indicated that the gender of a diabetic parent may be an important factor in the transmission of the disease to the offspring.[14,15,17,24] In our previous study, we have found evidence for familial clustering of diabetes and maternal influence on increasing total cholesterol level in Chinese patients with T2D.[6] Here we further investigated the effect of parental diabetes on the cardiometabolic traits, which are useful predictors for the development of T2D, in two Chinese cohorts consisting of 2026 adolescents and 555 adults.

In this study, we have confirmed that a positive PH of diabetes conferred increased risk of cardiometabolic abnormalities, including obesity, central obesity, hyperinsulinaemia, hyperglycaemia, insulin resistance, impaired first-phase insulin response, hypertension and dyslipidaemia, in Chinese. Our findings are in line with most of the earlier studies in other populations, which demonstrated familial aggregation of diabetes and related phenotypes.[3–9,41] For example, Abbasi *et al.*[41] reported that PH of diabetes is associated with higher BMI, WC, HC and BP, whereas a Korean study found that offspring with parental diabetes have increased risk for abnormal glucose homoeostasis, compared with offspring without PH.[5] On the other hand, a study conducted in

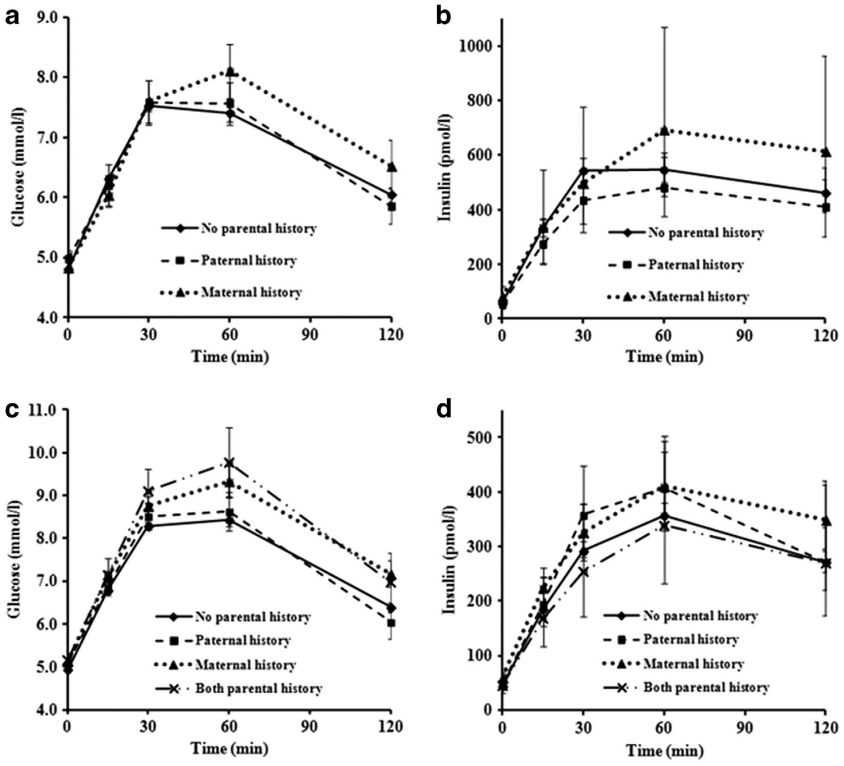

Figure 2. Plasma glucose and insulin concentrations at 0, 15, 30, 60 and 120 min during oral glucose tolerance test (OGTT) in (**a**, **b**) adolescents ($n = 279$) and (**c**, **d**) adults ($n = 555$) according to parental history categories of diabetes. Data were expressed as mean ± s.e. Associations between glucose/insulin concentrations and parental history categories for each time point during OGTT were shown in Supplementary Table 2.

Italy showed that T2D patients with parental diabetes were younger at diagnosis and more likely to be insulin-treated than those without familial diabetes.[10] In the EPIC-InterAct study,[3] a higher frequency of positive FH was observed among T2D patients with more risk alleles in a genetic score. Nevertheless, the genetic score alone explains only 2% of the FH-associated risk of T2D,[3] suggesting that more genes and/or interactions between them have yet to be detected. Taken together, these suggest that positive PH of diabetes in fact reflects the interaction between genetic and shared environmental/lifestyle factors.

Of note, we found that the effect of parental diabetes is largely confined to the maternal side. Our results demonstrated a predominance of maternal influence on the cardiometabolic risk, which strongly support the clinical observations of a greater risk of T2D transmission from the mother than from the father.[6,10,11,14–20,22,26,27,41] Despite consistent findings from these studies, it is worth noting that the Framingham study and a few others have failed to detect such an effect.[5,7,28,42,43] We noted in our study that when compared with either the group without parental diabetes or the group with paternal diabetes, offspring with maternal diabetes were more obese, more centrally obese and insulin resistant, had higher glucose levels and BP, and worse lipid profiles in the present study. Recently, similar findings have been also reported by Tan *et al.*,[8] Groop *et al.*,[18] Ekoe *et al.*,[44] Kasperska-Czyzyk *et al.*,[45] Bjornholt *et al.*[16] and Sasaki *et al.*[46] In addition, we found that positive maternal history of diabetes was associated with impaired first-phase insulin secretion (at 0–30 min during OGTT). Interestingly, our finding is in agreement with the observation reported by Praveen *et al.*,[47] Otabe *et al.*[48] and Kasperska-Czyzyk *et al.*[45] that maternal diabetes was associated with a trend towards lower DI (0–120 min) and β-cell dysfunction.

Several possible mechanisms have been proposed to explain the greater effect of maternal diabetes than paternal diabetes. Recent data reported by Harder *et al.* and Omar *et al.*[49,50] observed a higher prevalence of T2D on the maternal-grandmaternal line than on the paternal-grandpaternal line among the T2D patients. Several studies also showed that a younger onset of maternal diabetes (that is, diabetes present in women of child-bearing age) was associated with an increased risk of impaired glucose tolerance or T2D in the offspring.[3,7,51] Furthermore, the classical study in Pima Indians by Pettitt *et al.* had noted the deleterious effect of gestational diabetes on the offspring, including obesity and abnormal glucose tolerance, which in turn may contribute to pass on the risk for developing the same problems through subsequent generations. Taken together, these findings point towards a genetic background of T2D contributed by mutations or deletions of maternally inherited mitochondrial DNA. Other potential mechanisms include epigenetic changes, the role of imprinted genes whose expression is determined by the parent that contributed them, as well as postnatal lifestyle, which may be preferentially influenced by the mother. Interestingly, there is evidence also suggesting the importance of the intrauterine environment (that is, maternal nutrition) and maternal weight gain during pregnancy for the development of T2D in the offspring.[24] Although the maternal diabetes status defined in the present study was not necessarily diagnosed before or during pregnancy, a mother who is diagnosed with diabetes after pregnancy is more likely to be prediabetic or insulin resistant at the time of her pregnancy and perhaps present an abnormal intrauterine environment to their offspring.

In this study, the maternal history of diabetes was consistently associated with obesity, insulin resistance and loss of first-phase insulin secretion in both adolescents and adults. We further noted adverse effects of maternal diabetes on BP, lipid profiles and ACR in adults, although we failed to observe the same in adolescents. This may be due to the stronger influence of confounding factors, such as age or lifestyle, compared with that of the intrauterine environment or genetic factors. In addition, due to the younger

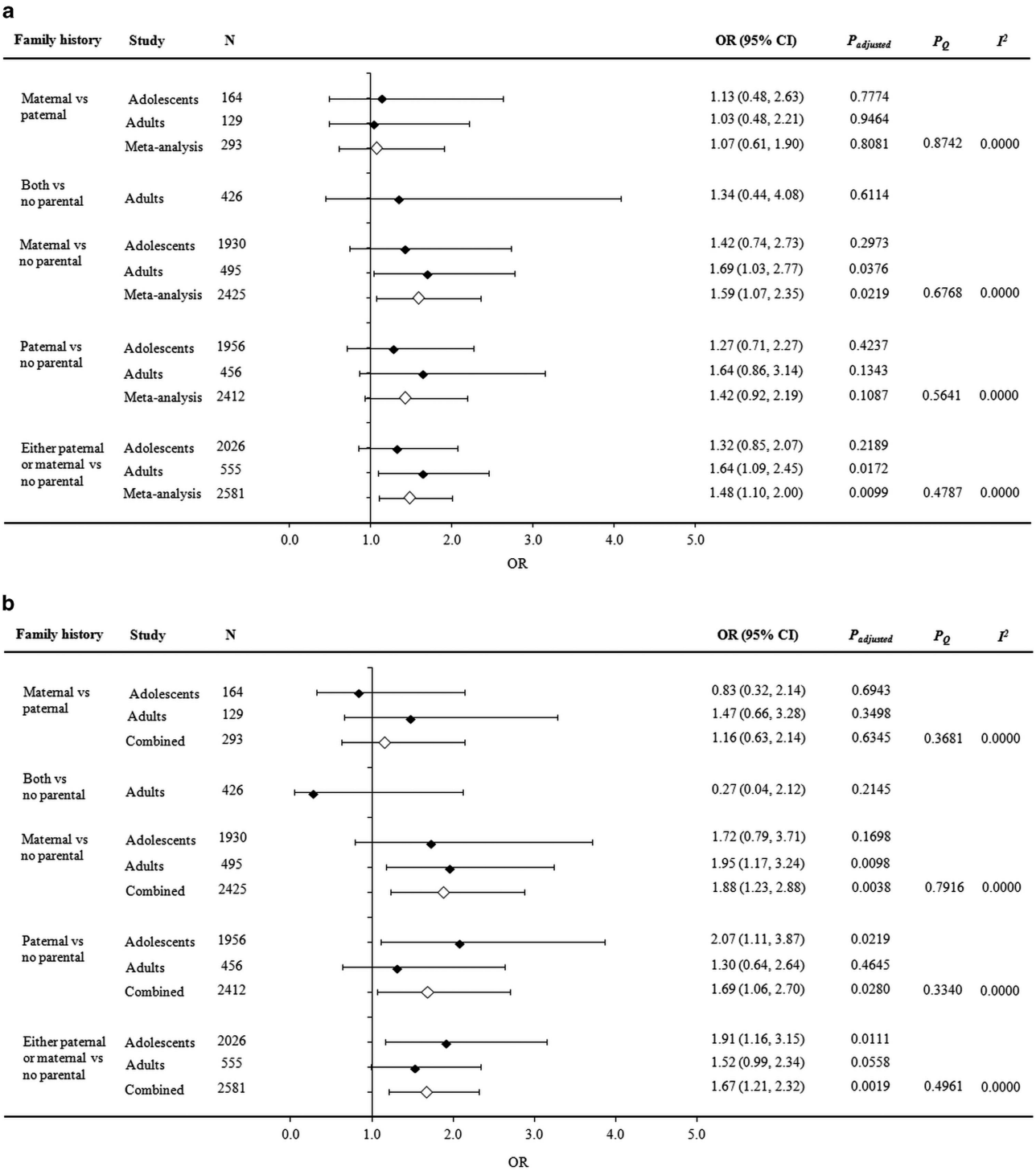

Figure 3. Association of degrees of parental history with risk of (**a**) overweight or obesity and (**b**) central obesity adjusted for sex, age and/or study. Reference groups were individuals with no reported parental history of diabetes or with paternal history of diabetes in testing maternal versus paternal history of diabetes.

age of parents of the adolescents, the prevalence of maternal diabetes in adolescents is much lower than that in adult offspring (3.41% versus 15.14%). This may also explain the absence of associations in adolescents.

The strengths of this study include the inclusion of two representative samples in Chinese adolescents and adults, as well as the detailed clinical assessment of the cardiometabolic risk factors. However, some limitations of this study need to be considered. First, the PH of diabetes collected from questionnaires is self-reported and this collection method did not allow for confirming the diabetes status of parents. Potential censoring and report biases suggested by Cox[52] could contribute to the excess maternal transmission observed in the present study. Therefore, we test for potential biases by comparing the cardiometabolic risk factors among responders and non-responders in adolescents (we did not test for the biases in adults because of the high

response rate). We found that the cardiometabolic traits of the non-responders did not differ from those of responders, except for BMI and WHR (Supplementary Table 4). In addition, we observed similar proportion of unknown paternal status and unknown maternal status (12.6% versus 12.3%) in adolescents. Compared with adults, the difference in the proportion of affected fathers and mothers was smaller in adolescents (affected father versus affected mother 4.69% versus 3.41% in adolescents and 8.11% versus 15.14% in adults), those for whom both parents were most likely to be living. However, we observed a consistent effect of maternal diabetes on cardiometabolic risk factors in both cohorts. On the whole, these results indicate that our data is a representative sample of the Hong Kong Chinese population. Moreover, our study could be further improved by obtaining parental BMI, diagnosed age of diabetes, history of gestational diabetes and information of sharing familial environment, which may help to dissect the underlying mechanism of the association between maternal diabetes and T2D.

In conclusion, we showed that a positive PH of diabetes confers increased risk of cardiometabolic abnormalities in Chinese adolescents and adults, concordant with Caucasian studies. This effect is more pronounced in offspring with maternal history of diabetes, who are more obese, insulin resistant but also had impaired first-phase insulin secretion. Our studies highlight the need for public health schemes including targeted screening, lifestyle modifications and early intervention in offspring with parental diabetes, which may help to circumvent the vicious cycle of cardiometabolic defects through generations.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGEMENTS

We are grateful to all study participants. We thank the Chinese University of Hong Kong Information Technology Services Centre for providing computing resources. Special thanks are extended to all nursing and medical staff at the PWH Diabetes and Endocrine Centre for their dedication and professionalism. This study was supported by the Hong Kong Foundation for Research and Development in Diabetes established under the auspices of the Chinese University of Hong Kong, the Liao Wun Yuk Diabetes Research Memorial Fund, the Hong Kong Governments Research Grant Committee Central Allocation Scheme (CUHK 1/04C), Research Grants Council Earmarked Research Grant (CUHK4055/01M, CUHK4727/07M), General Research Fund (CU471713), the Innovation and Technology Fund (ITS/088/08 and ITS/487/09FP), the Focused Investment Fund of the Chinese University, the Research Fund of the Department of Medicine and Therapeutics, and the Diabetes and Endocrine Research Fund of the Chinese University of Hong Kong.

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