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Long-term maternal cardiometabolic outcomes 22 years after gestational diabetes mellitus

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ABSTRACT

Aims/Introduction: Women with gestational diabetes mellitus are at increased risk for type 2 diabetes. We characterized the association between maternal glycemia during pregnancy with long-term outcomes.

Methods and Methods: In this prospective nested case–cohort study, participants were recalled for follow up with detailed evaluation including oral glucose tolerance test at 8, 15 and 22 years. Logistic regression was used to estimate the risk of developing impaired glucose tolerance/type 2 diabetes and metabolic syndrome at follow up. The association between maternal glycemia at pregnancy and follow up was evaluated by linear regression. We also charted trajectory of β-cell function during follow up.

Results: The analysis included 121 women with a mean follow-up period of 22.5 years, and a mean age of 50.3 years. Gestational diabetes was associated with an adjusted odds ratio of 2.48 (95% confidence interval 1.03–5.99) for combined diabetes/impaired glucose tolerance at follow up ($P = 0.04$). Women with a pre-pregnancy body mass index ≥23 had an odds ratio of 5.43 (95% confidence interval 1.87–15.72) for metabolic syndrome at follow up, compared with those with body mass index <23 ($P = 0.002$). Both fasting and 2-h glucose during pregnancy were strongly associated with glycemic indices at follow up (*P*-value <0.001–0.016). Gestational diabetes was associated with impaired β-cell function that remained relatively stable after the index pregnancy.

Conclusions: Chinese women with a history of gestational diabetes have a high prevalence of impaired glucose tolerance/type 2 diabetes at 22-year follow up. Glucose levels during mid-pregnancy are strongly associated with those of middle age.

INTRODUCTION

The global estimate for hyperglycemia during pregnancy in women aged 20–49 years is 16.2%, with approximately 85% of cases being attributable to gestational diabetes mellitus (GDM)[1]. In 1961, O'Sullivan explored the natural history of transient diabetes in pregnancy or GDM, where he reported 7% had developed overt diabetes by 6 weeks postpartum, and 29% within 5.5 years[2]. A 2002 systematic review of the literature reported similar findings. That said, just six of the 28 studies included were of ≥10 years duration, and only one with a follow-up period of >20 years. Studies with approximately 10 years of follow up found crude conversion rates to type 2 diabetes of approximately 10%, except a study in ethnic Navajo Indian women from the USA, where the cumulative incidence was 42%. In the one study with a multi-ethnic population and follow-up period of 28 years, the rate reported was 49.9%. The authors noted the cumulative incidence of type 2 diabetes increased significantly in the postpartum period up to 5 years, moderated between 5 and 10 years, and then plateaued after 10 years. Pregnancy fasting plasma glucose (FPG) was the risk factor most likely to be associated with the future risk of type 2 diabetes[3]. A meta-analysis that included 20 studies carried out between 1960 and 2009 concluded that women with prior GDM had a relative risk of 7.43 (95% confidence interval [CI] 4.79–11.51) for developing type 2 diabetes compared with those with a normal glucose tolerance (NGT) pregnancy, with little

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heterogeneity associated with either patient characteristics or the GDM diagnostic criteria applied[4].

Women with a history of GDM also face increased risks for other comorbidities, principally cardiovascular disease, but also metabolic syndrome (MetS). There have been relatively few long-term studies examining cardiovascular risk in GDM populations. A retrospective cohort study using healthcare administrative databases matched 8,191 women with GDM to 81,262 controls, and reported after a median follow-up period of 11.5 years that the hazard ratio for cardiovascular events was 1.71 (95% CI 1.08–2.69), and 1.13 (95% CI 0.67–1.89) after adjustment for subsequent type 2 diabetes[5]. A recent study aimed to determine if the increased risk for cardiovascular disease in women with a history of GDM was dependent on the development of subsequent type 2 diabetes. The authors reported that for macrovascular outcomes, women with GDM with or without subsequent type 2 diabetes showed increased risks of cardiovascular disease and coronary artery disease ($P < 0.01$ for both)[6]. Women with a prior history of GDM are also at approximately threefold increased risk for MetS[7], including GDM defined by the International Association of Diabetes and Pregnancy criteria[8]. A recent meta-analysis supported the relationship between GDM and MetS[9].

The risk for conversion to manifest type 2 diabetes in women with a history of GDM is well known. However, the natural history of these patients has rarely been examined beyond 10 years after pregnancy. The issue of glycemic levels in pregnancy that are below thresholds for frank GDM, and future diabetes and cardiometabolic risk has also not been adequately explored. Accordingly, the purpose of the present study was to examine the risk of developing abnormal glucose tolerance (AGT) to include IGT and IFG, or diabetes and MetS in Hong Kong Chinese women with a history of GDM or gestational impaired glucose tolerance (GIGT; defined as FPG <7.0 mmol/L, 2-h glucose 7.8–11.0 mmol/L), and to characterize the association between maternal glycemia during pregnancy with long-term cardiometabolic outcomes.

METHODS

In the present prospective nested cohort study, eligible participants were identified from a consecutive cohort of 1,032 women recruited at the antenatal clinic, Prince of Wales Hospital, Shatin, Hong Kong, between 1992 and 1994 who underwent screening for GDM between 24 and 28 weeks' gestation[10] (for STROBE statement please refer to Appendix S1). Women were recalled for follow up and a detailed evaluation including an oral glucose tolerance test (OGTT) at 8 and 15 years' postpartum[11,12]. At the 8-year follow-up visit, each GDM case (diagnosed according to the World Health Organization [WHO] 1999 criteria, including both GIGT and GDM), was matched 1:2 with two women with NGT (FPG <7.0 mmol/L and 2 h PG <7.8 mmol/L), and invited to return for follow-up evaluation. Women were invited to participate in the current study between July and November 2015, so long as they had completed the 8-year assessment. This study was approved by the Joint Chinese University of Hong Kong-New Territories East Cluster Clinical Research Ethics Committee. All participants provided written informed consent. A detailed medical history, parity and assessment of anthropometry including bodyweight (kg), height (cm), hip and waist circumference (cm), blood pressure (mmHg), and blood biochemical analysis were documented at all time points. Fasting blood was collected for complete blood count, renal function and liver function tests, plasma glucose, C-peptide, and lipid biochemistry (triglyceride, total cholesterol, high-density lipoprotein cholesterol and low-density lipoprotein cholesterol). A 75-g OGTT was administered after an 8-h overnight fast, apart from those who had been previously diagnosed with type 2 diabetes, in which case a FPG was carried out, along with glycated hemoglobin. Venous blood samples were collected at 0, 30, 60 and 120 min after glucose challenge. Plasma glucose was measured using the hexokinase method (DP Modular Analytics; Roche Diagnostics, Indianapolis, IN, USA). Insulin assay was carried out by enzyme-linked immunosorbent assay (Dako Insulin ELISA Kit; Dako Denmark, A/S, Glostrup, Denmark), which was the same as that used for the 8- and 15-year assessments. Insulin resistance was assessed using the homeostasis model assessment insulin resistance index (HOMA[2]-IR) and the quantitative insulin sensitivity check index (QUICKI) calculated as QUICKI = 1/(log[insulin 0 min]) + (log[FPG 18]), where insulin is measured in uIU/mL and glucose in mmol/L. Pancreatic β-cell function was determined by HOMA(2)-β, and the oral disposition index (ODI) was calculated as (insulin 30 min − insulin 0 min) / (glucose 30 min − glucose 0 min) / HOMA(2) IR, where insulin was measured in uIU/mL and glucose in mmol/L. HOMA(2)-β was calculated through the HOMA Calculator v2.2.3 (Diabetes Trials Unit, The Oxford Centre for Diabetes, Endocrinology and Metabolism, University of Oxford, Oxford, UK; https://www.dtu.ox.ac.uk/homacalculator/), 8 January 2013. The area under the curve = (30 [fasting + 2 30 min + 60 min] + 60 [60 min + 120 min]) / 2, where fasting, 30, 60 and 120 min are respective insulin or glucose values at OGTT sampling points. Maternal overweight was defined as body mass index (BMI) ≥23 kg/m^2 at booking. MetS was defined according to the International Diabetes Federation definition of 2005[13] (to compare with the previous analysis of the cohort), using the Asian-specific definition for central obesity. MetS was deemed present if three or more of five risk factors existed: waist circumference ≥80 cm, FPG ≥5.6 mmol/L, systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg, fasting plasma triglyceride ≥1.7 mmol/L, or high-density lipoprotein cholesterol <1.3 mmol/L.

Data are expressed as the mean or median, and between-group differences were compared using the Student's *t*-test for continuous data, Fisher's exact test for categorical contingency data or the Mann–Whitney *U*-test for non-parametric data. A *P*-value <0.05 (two-tailed) was considered to be significant. Logistic regression was used to estimate the risk of developing

AGT/type 2 diabetes and MetS at 22-year follow up. Linear regression was applied to estimate the association between maternal glycemia at pregnancy and follow up. Skewed data were transformed by natural log to meet assumptions for linear regression analysis. All statistical analyses were carried out using the SPSS 22.0 (SPSS, Chicago, IL, USA) statistics program.

RESULTS

Cohort description

A total of 118 women completed the follow-up assessment at 22 years' postpartum (Figure 1). The mean age of the participants was 50.3 years, and the mean follow-up period from index pregnancy was 22.5 years. Patient characteristics were similar between the two groups. Of the 118 women, 80 had NGT at pregnancy, 34 had GIGT and four had GDM, as defined by the WHO 1999 diagnostic criteria[14]. There were 20 total cases of type 2 diabetes in the follow-up population (16.9%), with half being newly diagnosed, and 44 participants had either diabetes or AGT. MetS was present in 24 women (20.3%). The median plasma glucose during OGTT was higher in women with a history of GDM/GIGT compared with participants with NGT at all time points (P = 0.001 or <0.001). The median ODI, a measure of β-cell function, was significantly lower in women with GDM/GIGT compared with participants with NGT (68.7 vs 108.6, P = 0.016), whereas HOMA(2)-β, HOMA(2)-IR and QUICKI were not significantly different (Table 1).

Results from multiple logistic regression analysis show a history of GDM/GIGT was associated with an odds ratio of 2.78 (95% CI 1.18–6.55) for a combination of type 2 diabetes/AGT at follow up, after adjusting for pregnancy age, parity, family

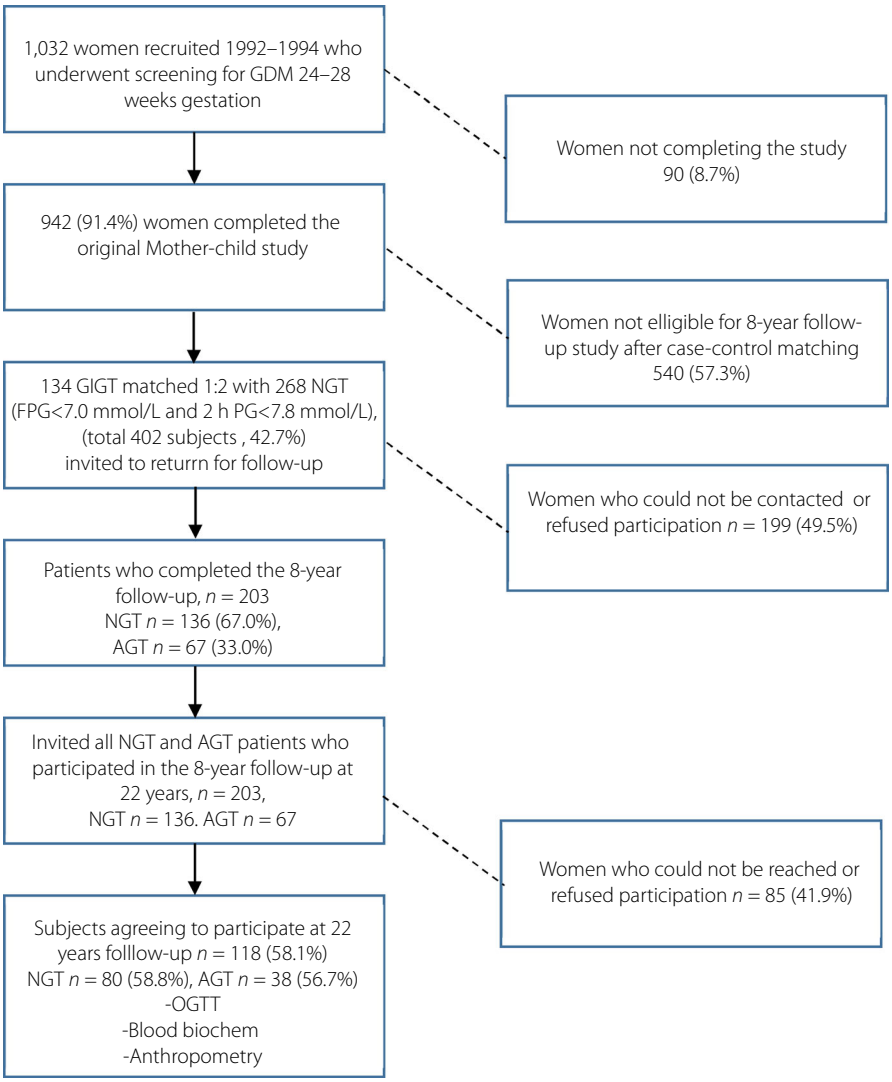

Figure 1 | Patient disposition and study scheme for 22-year follow up to the Screening Test for Gestational Impaired Glucose Tolerance and Gestational Diabetes Mellitus Study. Abnormal glucose tolerance (AGT) is gestational diabetes mellitus (GDM)/gestational impaired glucose tolerance (GIGT). FPG, fasting plasma glucose; NGT, normal glucose tolerance.

Table 1 | Baseline characteristics at the 22-year follow up for women with normal glucose tolerance or gestational diabetes mellitus/gestational impaired glucose tolerance during the index pregnancy

Maternal characteristics	*n*	Mean/median	IQR/SD	*n*	Mean/median	IQR/SD	*P*
	Non-GDM/GIGT			GDM/GIGT			
Age (years)	80	49.9	±4.45	38	51.2	±3.72	0.130
Follow up (years)	80	22.4	±0.84	38	22.5	±0.89	0.549
Adiposity/blood pressure							
BMI (kg/m^2)	80	24.6	±3.9	38	24.1	±4.3	0.518
WHR	80	0.82	±0.07	38	0.84	±0.09	0.229
Waist circumference (cm)	80	90.3	±11.3	38	90.2	±11.7	0.959
Systolic BP (mmHg)	80	117	±14	38	121	±15	0.136
Diastolic BP (mmHg)	80	75	±11	38	77	±9	0.344
Plasma lipids							
Total cholesterol (mmol/L)	80	5.1	±0.9	38	5.1	±0.7	0.790
HDL-C (mmol/L)	80	1.7	±0.5	38	1.6	±0.4	0.736
TG (mmol/L) (median)	80	0.9	0.7–1.3	38	1.0	0.7–1.5	0.176
LDL-C (mmol/L)	80	2.9	±0.8	38	2.9	±0.7	0.917
NHDL (mmol/L)	80	3.4	±0.9	38	3.5	±0.8	0.758
OGTT PG (mmol/L)							
Fasting (median)	80	4.8	4.6–5.1	38	5.3	4.8–5.4	0.001
30-min (median)	76	8.2	7.2–9.3	33	9.1	8.3–9.9	0.001
60-min (median)	76	7.9	6.6–10.1	33	11.0	8.1–12.6	<0.001
120-min (median)	76	5.9	5.2–7.9	33	7.4	6.2–10.7	0.001
AUC glucose (median)	76	865	746–999	33	1,078	858–1,265	<0.001
OGTT insulin (uIU/mL)							
Fasting (median)	80	6.6	4.3–10.4	38	7.7	4.3–10.2	0.940
30-min (median)	76	54.5	54.5–93.7	33	42.5	29.3–97.3	0.649
60-min (median)	76	58.1	41.0–102.4	33	59.1	34.1–81.0	0.410
120-min (median)	76	44.6	32.8–84.7	33	72.3	44.1–126.3	0.025
AUC insulin (median)	76	5,973	4,417–9,707	33	6,748	4,102–8,771	0.869
HOMA(2)-β (%)	80	89.9	±43.6	38	78.2	±35.9	0.154
HOMA(2)-IR (%) (median)	80	0.7	0.48–1.16	38	0.9	0.48–1.17	0.831
ODI (median)	80	108.6	72.8–224.5	38	68.7	50.2–165.5	0.016
QUICKI	80	0.36	±0.04	38	0.36	±0.04	0.642

AUC, area under curve; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); BP, blood pressure; GDM/GIGT, gestational diabetes mellitus/gestational impaired glucose tolerance; HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; NHDL, non-high-density lipoprotein cholesterol; ODI, oral disposition index; OGTT, oral glucose tolerance test; PG, plasma glucose; SD, standard deviation; TG, triglyceride; WHR, waist-to-hip ratio.

history of diabetes and BMI ≥23 kg/m^2 at first antenatal visit (P = 0.02; Table S1). Women with a pregnancy BMI ≥23 kg/m^2 had an odds ratio of 5.42 (95% CI 1.87–15.72) for the presence of MetS at follow up compared with those with BMI <23 kg/m^2 after adjusting for pregnancy age, parity, family history of diabetes and GDM/GIGT status at pregnancy (P = 0.002). A BMI ≥23 kg/m^2 was not itself associated with dysglycemia at follow up, and similarly, a history of GDM/GIGT did not predict MetS at 22 years, although it remains suggestive (P = 0.09; Table S1). Multiple linear regression analysis showed that both FPG and 2-h glucose during mid-pregnancy were strongly associated with glycemic indices at follow up (Table S2). After adjustment for maternal age, parity, education and BMI, FPG at pregnancy was significantly associated with follow-up FPG, glucose 30-min and area under the curve glucose (P < 0.01–0.016). The 2-h glucose at pregnancy was strongly associated with glucose levels at all OGTT time points at follow up (P < 0.001 for all). The ODI at follow up was found to be inversely associated with the 2-h plasma glucose, but not FPG at pregnancy (P = 0.012 and 0.923, respectively).

Longitudinal changes in dysglycemia, and measures of β-cell function and other covariates

Indices of insulin resistance and β-cell function, as well as their covariates, were evaluated longitudinally to assess changes over successive assessments. Selected characteristics from the intact patient population (n = 943) and for those of the current population at booking (n = 118) are presented in Table S3. Figure 2 shows the conversion to type 2 diabetes/AGT in the two groups. By 8 years' postpartum, 40.3% of the GDM/GIGT

participants showed dysglycemia compared with 17.7% of the women with NGT ($P = 0.001$). At 15 years, the figures were 51.1% and 20.2%, respectively ($P < 0.001$). By 22 years' follow up, 52.6% of GDM/GIGT women had type 2 diabetes/AGT compared with 30.0% for women with NGT ($P = 0.025$).

Figure 3 shows the changes in FPG and 2-h glucose at 8-, 15- and 22-year follow up. At 8 years, the 2-h glucose was higher in GDM/GIGT (8.09 mmol/L vs 6.33 mmol/L, $P = 0.003$). At 15 years, both the FPG (5.33 mmol/L vs 4.85 mmol/L, $P = 0.001$) and 2-h glucose (7.76 mmol/L vs 6.42, $P = 0.013$ mmol/L) were higher in the GDM/GIGT group. At 22 years, the 2-h glucose was seen to be greater in the GDM/GIGT participants (8.69 mmol/L vs 6.81 mmol/L, $P = 0.005$).

BMI significantly increased in both the GDM/GIGT and NGT groups from booking to 8 years. BMI was unchanged thereafter in the women with GDM/GIGT, with a mean BMI of 24.1 kg/m^2 at 22 years' postpartum, whereas BMI continued to increase modestly in the NGT group from 8 to 15 years, and from 15 to 22 years (Figure S1). Similarly, waist circumference increased markedly from 8 to 15 years (Figure S2). The derived measure HOMA(2)-β declined in both groups between eight and 15 years ($P < 0.001$ for both), but not significantly thereafter (P for trend, $P < 0.001$ GDM/GIGT, $P = 0.003$ NGT). There were no between-group differences at any follow up (Figure S3). Measures of QUICKI were lower in the GDM/GIGT group at all time points, although differences were not statistically significant (Figure S4).

Calculation of the ODI is illustrated in Figure 4 for 8- and 22-year follow up. No estimate was possible for the 15-year assessment, as a 30-min OGTT blood sample was not collected. The ODI was significantly lower in the GDM/GIGT participants, as compared with NGT at both time points (8 years 68.2 vs 103.3, $P = 0.004$; 22 years 76.9 vs 121.8, $P = 0.021$, respectively), although there was no significant change in this measure over the assessment period in either group.

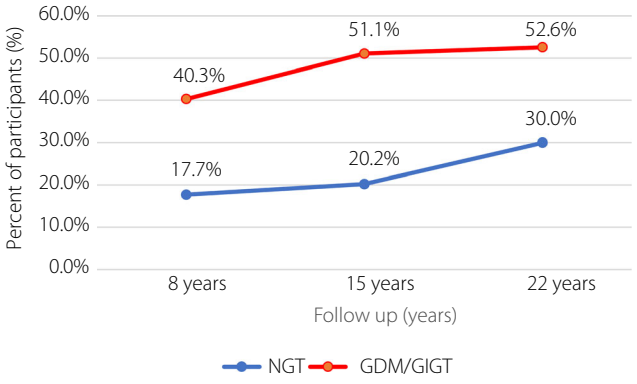

Figure 2 | Conversion to combination of impaired glucose tolerance or diabetes at 8-, 15- and 22-year follow up.

DISCUSSION

In the present longitudinal study of women with a previous history of GDM/GIGT, approximately 53% developed some form of AGT at 22 years' postpartum compared with 30% among unaffected women. GDM/GIGT was associated with 2.78-fold risk for a combination of type 2 diabetes/AGT after adjusting for covariates. These findings are not unexpected. Indeed, a previous report from this same cohort noted after 8 and 15 years that 40.3% of these women had AGT by 8 years, and 51.0% at 15 years, compared with 17.6% and 20.2%, respectively, in unaffected women. Odds ratios for AGT and

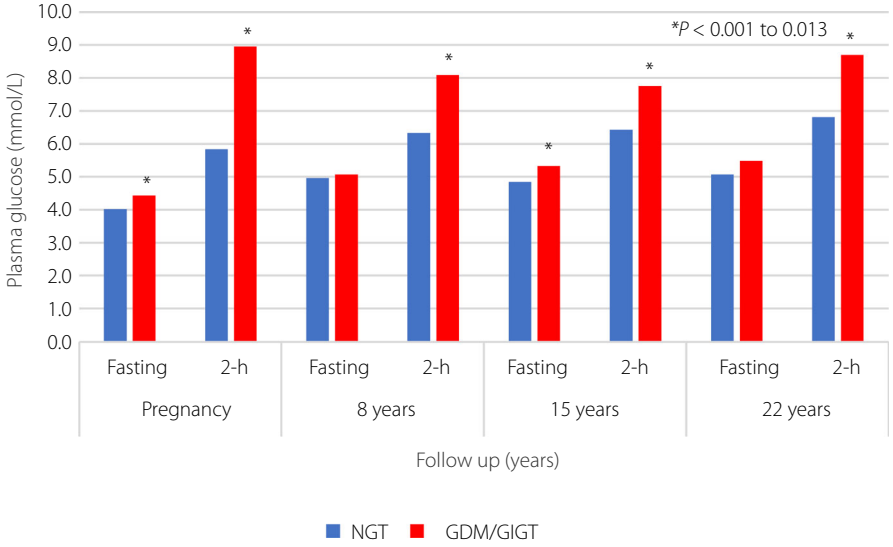

Figure 3 | Changes in fasting and 2-h plasma glucose (mmol/L) at 8-, 15- and 22-year follow up. GDM, gestational diabetes mellitus; GIGT, gestational impaired glucose tolerance; NGT, normal glucose tolerance.

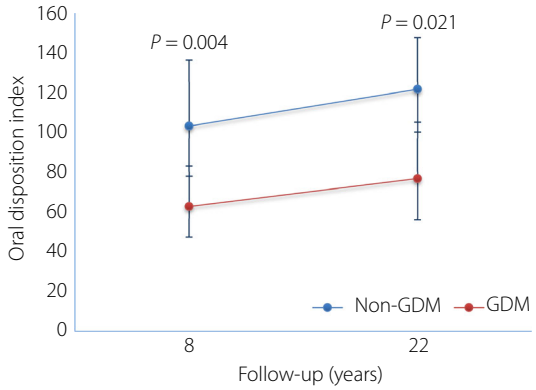

Figure 4 | Changes in oral disposition index at 8- and 22-year follow up. GDM, gestational diabetes mellitus.

diabetes among women with a GDM history at 15 years were 5.2 (95% CI 2.2–12.1) and 8.0 (95% CI 2.2–28.3), respectively[11]. The predictive strength of a history of GDM for subsequent AGT has moderated with longer follow up, as more women who had NGT at pregnancy develop dysglycemia, presumably associated with middle age (20.2% to 30.0% from 15 to 22 years). Linné *et al.*[22] reported results from a small cohort of 80 women (including 28 with GDM) followed for 15 years, in which 35% of the women with GDM had developed type 2 diabetes versus none in the NGT group. Although weight gain during the follow-up period was not different between the two groups (8.2 kg), among those where diabetes developed, the mean weight gain was almost twice that, at 15.1 kg[15]. In another study of Spanish women followed for 11 years, the cumulative incidence of type 2 diabetes was 13.8% in women with prior GDM, and 0% in women with NGT ($P = 0.02$), whereas the corresponding rates for AGT in this population were 42.4% and 2.8%, respectively ($P < 0.001$)[16]. The relative risk for diabetes after GDM has been reported to be 7.43 in a large meta-analysis that included a fairly broad range of risk observations[3]. Similar findings were noted in a more recent systematic review and meta-analysis, which noted women with prior GDM had substantially increased risk of diabetes, with the risk highest during the 3–6 years after GDM[17]. A similar observation was reported in a large retrospective cohort study that included >185,000 gravid women[18]. These reports showed that a high proportion of GDM-positive women developed dysglycemia in the postpartum period, yet interestingly, roughly half did remain NGT >20 years postpartum. It is noteworthy that in the current study, there were very few participants in the GDM/GIGT group who were classified as having GDM. Indeed, of the 38 participants who had some form of hyperglycemia at pregnancy, just four met the 1999 WHO diagnostic criteria for GDM, suggesting that the present cohort represents a group that might be at lower risk for diabetes compared to those with a formal diagnosis of GDM at the time of the study. In a recent report from the Hyperglycemia and Adverse Pregnancy Outcome Follow-up Study, 52.2% of women with GDM (diagnosed by International Association of Diabetes and Pregnancy/WHO 2013 criteria) developed a disorder of glucose metabolism approximately 11 years after pregnancy compared with 20.1% of mothers without GDM (OR 3.44, 95% CI 2.85–4.14)[19]. Taken together, the observation that approximately half of the women with GDM had AGT or type 2 diabetes at follow up strongly indicate that any level of dysglycemia during mid-pregnancy OGTT imparts a substantial risk for subsequent AGT or type 2 diabetes in middle age.

Increasing adiposity and weight gain are well-known risk factors for type 2 diabetes. In the present study, women in both groups showed substantial weight gain postpartum, and as a population, are considered overweight using Asian diagnostic BMI cut-offs. In a population of Korean women with a previous history of GDM, weight gain after pregnancy was associated with an adjusted hazard ratio of 1.27 (95% CI 1.04–1.56, P = 0.021) for diabetes [20]. Similarly, in the current study, waist circumference increased markedly after pregnancy to >80 cm by 15 years postpartum. This is an important indicator of central obesity and one of the elements defining MetS. Accordingly, there was a high rate of dysglycaemia and MetS in this study. The presence of GDM/GIGT was not predicative of MetS at follow up, although BMI ≥23 kg/m^2 at booking was highly predictive of future MetS after adjustment for covariates. Clearly, a high BMI at booking is a more significant driver of cardiometabolic risk, as compared with high glucose. Previous reports found an increased risk for MetS among women with a GDM history[6,8]. Earlier analyses from this cohort did not show any difference in the rate of MetS between GDM/GIGT and women with NGT[21]. These observations might be related to evidence that obesity duration and its severity are associated with incident MetS. An analysis of 2,748 participants in the Multi-Ethnic Study of Atherosclerosis study followed for 10 years showed that higher obesity severity and obesity duration were both associated with a higher odds of incident MetS and its components[22]. Women in the current population had a BMI of ~24 kg/m^2 at booking, and this increased modestly over the follow-up period. Hence, participants were overweight by Asian criteria, and endured persistent elevated adiposity, which might have outweighed more modest glucose effects.

Results from multiple linear regression analysis showed that both FPG and 2-h glucose at pregnancy were associated with post-challenge glucose at follow up. However, the 2-h pregnancy glucose exhibited a stronger and more consistent association. When FPG and 2-h glucose values are examined longitudinally, it is apparent that although the FPG was modestly elevated in GDM/GIGT participants, the 2-h measure was markedly higher at all follow-up assessments. To better understand these observations, HOMA(2)-β was compared longitudinally, and although declines were seen in both groups between 8 and 15 years, there were no between-group differences at the follow-up examinations. The insulin sensitivity measure, QUICKI, increased significantly between 8 and 15 years in all

women with no between-group difference at any time point, although it is notable that those with a history of GDM/GIGT had a lower QUICKI score at all assessments, but differences did not reach statistical significance. These data suggest this population shifted to the right along the hyperbolic insulin sensitivity/secretion curve, particularly between 8 and 15 years. Also, at 8 years, the mean QUICKI value in women with GDM/GIGT was 0.345, with a QUICKI score of <0.357 suggestive of metabolic abnormalities[23]. Similarly, the ODI was assessed longitudinally, although it could only be calculated at 8 and 22 years. The median ODI was observed to be inversely associated with the 2-h plasma glucose, but not FPG at pregnancy, consistent with it being an indicator of β-cell function. Furthermore, the ODI was significantly lower in women with GDM/GIGT at both the 8- and 22-year follow up, with no apparent change over the assessment period in either group. The hyperbolic insulin sensitivity/secretion curve shows the physiological regulation of glucose homeostasis that requires β-cells to balance changes in insulin sensitivity by adjusting insulin secretion. The indices HOMA(2)-β and QUICKI assess individual components of the hyperbolic curve, and thus are not by themselves an appropriate measure of β-cell function. Insulin secretion must be evaluated in the context of ambient insulin sensitivity, thus the ODI shows whether the population is on the hyperbolic curve or to the left of the curve. An elegant study by Elbein *et al.* carried out in a Caucasian population with two siblings with diabetes showed that the ODI was substantially more heritable than either of its components, which might help explain a higher diabetes family history among those affected with GDM/GIGT[24]. Because women with GDM/GIGT in the present study showed similar HOMA(2)-β and QUICKI, and a consistently lower ODI across the follow-up period compared with women with NGT, taken together, these data show that the GDM/GIGT population had shifted to the right, similar to women with NGT, although the curve of their β-cell function falls to the left of the hyperbolic insulin sensitivity/secretion curve of women with NGT. It is important to note that the serial analysis of the ODI over time in the present study excluded participants with type 2 diabetes (as women with known type 2 diabetes did not undergo the OGTT), although the ODI has been shown to be a predictor of future diabetes above and beyond the 2-h glucose level in adults[25]. In lean Japanese women with NGT, insulin sensitivity was reportedly the same between GDM and healthy controls 6 months' postpartum, although tissue glucose sensitivity and first-phase insulin secretion were markedly lower. Acute insulin response was found to be reduced by 44% in women with GDM. The ODI was also significantly reduced, suggesting impairment of acute β-cell response to glucose. When insulin secretion was plotted against insulin sensitivity on a hyperbolic insulin sensitivity/secretion curve, those with previous GDM fall to the left of controls[26]. Although the present study included women with a continuum of adiposity levels, comparable findings were observed. Insulin sensitivity was similar between groups, whereas measures of ODI were consistently reduced. Rottenkolber *et al.*[27] found at 3–16 months' postpartum that women with GDM had reduced insulin sensitivity and ODI, although the women in the post-GDM group had a significantly higher BMI, which might account for the lower insulin sensitivity. Xiang *et al.*[28] reported findings from a group of non-diabetic Mexican American women with or without a history of GDM at 10 years' postpartum who were matched for age, BMI and parity, and followed for 4 years. Insulin sensitivity was not different between the groups at baseline and declined modestly in both groups, but significantly more so in women with GDM. The ODI was also comparatively lower in women with GDM at both baseline and follow up, and declined more in women with GDM over the observation period[28]. In another report, ODI was assessed in in 126 women diagnosed with GDM according to the International Association of Diabetes and Pregnancy criteria. As previously observed, the ODI in women with GDM was significantly lower than in non-GDM participants, and was a negative correlate of glucose values, and ODI was progressively lower from NGT to three abnormal OGTT glucose values[29].

There were 20 total cases of type 2 diabetes in this follow-up population, with half being newly diagnosed. Tam *et al.*[12] found that 10 of the 16 women with type 2 diabetes at the 15-year follow up were newly diagnosed (62.5%). These figures are alarming and should be cause for concern. Postpartum screening rates for diabetes after a diagnosis of GDM are low across many high-income countries, ranging from 20% to 58% up to 1 year after delivery[30]. Subsequent annual follow-up rates plateau at 20%[31]. This low compliance to post-GDM screening is highlighted by an audit of 229 women with a history of GDM at Southampton, UK, where 98.3% received FPG testing before discharge, 34.3% had glucose testing in the first year postpartum and, subsequently, 12.2% were screened at 2 years, postpartum, and by ≥3 years postpartum, just 17.8% had been screened[30]. More structured follow-up assessments are required for this high-risk population with GDM.

We acknowledge several limitations of this study. First, the sample size was rather small and the participants represent only a subgroup of the original cohort. However, no major differences were observed between the original cohort and the current study population. Furthermore, most of the women who did return for the current assessment had also joined both the 8- and 15-year assessments, thus providing a unique opportunity to evaluate the evolution of pathogenic factors leading to AGT and type 2 diabetes. Second, we were not able to ascertain the glycemic status of women who declined to participate or who were lost to follow up, as well as if they had higher or lower rates of type 2 diabetes. It is possible that women in the GDM/GIGT group who had already developed diabetes might have declined to participate in the latest follow up, thus attenuating the change in cumulative incidence observed between 15 and 22 years. Also, a 30-min blood sample was not part of the study design for the 15-year follow up, thus the ODI could not be evaluated at all three

assessments. This is of minor consequence, as the bracketing assessments were calculated with findings remarkably similar to those from an earlier study by Xiang *et al.*[28] Finally, the diagnostic criteria of GDM used in the present study were somewhat different to contemporary definitions of GDM.

In summary, Chinese women with a history of GDM/GIGT have a high prevalence of diabetes/AGT at 22-year follow-up. Glucose levels during mid-pregnancy are strongly associated with those of middle age, and are highly predictive of future dysglycemia. Conversion to type 2 diabetes/AGT occurred more rapidly after a GDM/GIGT pregnancy and plateaued after 15 years, whereas the rate of incident dysglycemia in the NGT women continued to increase over this later period. β-Cell function measured as ODI was consistently lower in women with GDM/GIGT, although it remained stable during follow up. A high pre-pregnancy BMI confers a substantial increased risk for the subsequent development of MetS. There is a need to raise awareness regarding this at-risk population, and to implement active surveillance to prevent associated morbidity and mortality.

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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 | Predictors of maternal cardiometabolic traits at 22 years.

Table S2 | Association between maternal plasma glucose at pregnancy with plasma glucose and oral disposition index at 22-years follow up.

Table S3 | Characteristics for the original mother–child study population, current patients at booking and 22-year follow up.

Figure S1 | Changes in body mass index at booking, and 8-, 15- and 22-year follow up.

Figure S2 | Changes in waist circumference at 8-, 15- and 22-year follow up.

Figure S3 | Changes in homeostasis model assessment of β-cell function (HOMA[2]-) at 8-, 15- and 22-year follow up.

Figure S4 | Changes in quantitative insulin sensitivity check index (QUICKI) at 8-, 15- and 22-year follow up.

Appendix S1 | STROBE Statement – checklist of items that should be included in reports of observational studies.