Elevated Metabolic Score for Insulin Resistance During Early Midpregnancy Predicts Higher Risk of Gestational Diabetes Mellitus: a Prospective Cohort Study

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Research Article

Keywords: gestational diabetes mellitus, glucose, triglyceride, metabolic score for insulin resistance

Posted Date: March 21st, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1334495/v1

Abstract

Purpose: To evaluate the clinical implication of metabolic score for insulin resistance (METS-IR) during early midpregnancy on subsequent risk of gestational diabetes mellitus (GDM) in Chinese women.

Methods: A total of 1747 pregnant women without pre-existing diabetes from the Tongji Maternal and Child Health Cohort (TMCHC) were included in this analysis. Blood glucose and lipid profiles (triglyceride [TG], total cholesterol [TC], high-density lipoprotein cholesterol [HDL-C] and low-density lipoprotein cholesterol [LDL-C]) were measured during 15-19 weeks and 75-g 2-h oral glucose tolerance test was conducted during 24-28 weeks to diagnose GDM. METS-IR was calculated by a modified formula which originally as follows: Ln(2×FPG[mg/dl]+TG[mg/dl])×BMI[kg/m^2] /Ln(HDL-C[mg/dl]).

Results: The median (interquartile range) of age was 28 (26-30) years, and 19.7% of them were underweight and 11.7% were overweight/obese before pregnancy. The overall incidence of GDM was 9.4% and median (interquartile range) of METS-IR was 27.36 (24.57-31.07). The median METS-IR was significantly increased with the increasing pre-pregnancy BMI categories (22.92 vs 27.72 vs 35.55, *P*＜0.001). Based on quartiles of METS-IR in women with normal pre-pregnancy BMI, participants were classified into 4 groups. Compared with women in the lowest quartile of METS-IR (＜25.52) , the adjusted RRs (95% CIs) of GDM were 2.15 (1.23-3.74), 1.34 (0.72-2.49), and 3.63 (2.22-5.95) for women in quartile 2 (25.52-27.71), quartile 3 (27.72-30.39) and quartile 4 (≥30.40) after adjusting potential confounds. In addition, a significant increase risk of GDM (adjusted RR [95% CI]: 2.55 [1.83-3.55]) was found in women within the highest quartile of METS-IR (≥30.40) compared to the other 3 lower quartiles (＜30.40).

Conclusions: Women with METS-IR (≥30.40) during early midpregnancy were more likely to develop GDM, thus the index might be a reliable early indicator for identifying women at high risk of GDM.

Introduction

Gestational diabetes mellitus (GDM) is classified as glucose intolerance with onset or first recognition during pregnancy and is one of the most common pregnancy metabolic complications. Women with GDM and their offspring are at elevated risk of future type 2 diabetes mellitus (T2DM), cardiovascular disease and associated metabolic diseases [1–4]. In the past few decades, the prevalence of GDM has been increasing globally. A latest systematic review and meta-analysis including 25 studies and 79,064 Chinese participants showed that the total incidence of GDM in mainland China was 14.8% (95% confidence interval 12.8–16.7%), according to International Association of Diabetes and Pregnancy Study Groups (IADPSG) criteria [5]. The most effective way to prevent the disease and its adverse effects is early identification of women with high risk of subsequent GDM.

Insulin resistance, an ineffective state of insulin action, is the critical mechanism of the pathogenesis of GDM [1]. The gold standard to define insulin resistance is the euglycemic-hyperinsulinemic clamp technique [6], but the technique is difficult to use in a clinical setting because it is invasive, complex, and costly. Therefore, a more simple, accurate, and practical insulin resistance index is needed. In 2018, a

novel metabolic score for insulin resistance (METS-IR) calculated using fasting plasma glucose (FPG), triglyceride (TG), and high-density lipoprotein cholesterol (HDL-C) along with body mass index (BMI) has been suggested as an inexpensive and reliable surrogate indicator to identify insulin resistance and predict type 2 diabetes [7, 8]. It was later confirmed to be associated with arterial stiffness, hypertension and prehypertension [9–11]. Till now, there is scant research addressing the correlation between METS-IR and GDM. To explore the possible association, we analyzed the link between METS-IR during early midpregnancy and the risk of subsequent GDM.

Subjects And Methods

Study population

This study was part of the Tongji Maternal and Child Health Cohort (TMCHC) study, which was a prospective cohort study designed to investigate the association between maternal diet during pregnancy and the outcomes of mother-offspring pairs in Wuhan, China. Pregnant women attending their antenatal care appointment before 16 weeks of gestation in one of three public hospitals in Wuhan, between January 2013 and May 2016 were recruited to join the cohort [12]. All procedures and study protocols were approved by the Ethics Review Committee of Tongji Medical College of Huazhong University of Science and Technology (NO. 201302) and written informed consent was obtained at enrollment.

In the current analysis, we included TMCHC participants met the following criteria: (1) with a singleton pregnancy, (2) completed an oral glucose tolerance test (OGTT), (3) had complete information on anthropometric measurements, blood glucose and lipid profiles (TG, total cholesterol [TC], HDL-C and low-density lipoprotein cholesterol [LDL-C]) during 15-19 gestational weeks. Women without information on blood pressure at enrollment (n=6) were excluded. Women with known diseases prior to pregnancy (e.g., chronic viral hepatitis, hypertension, diabetes) (n=47) or fasting plasma glucose ≥7.0 mmol/L at first prenatal visit (n=38) were excluded. Those with the outliers of fasting plasma glucose concentrations and/or lipid profiles (n=63) were excluded. Finally, a total of 1747 women were involved (Fig. 1).

Data collection and measurement

Basic information was obtained by questionnaire in an in-person interview at enrollment. The content of the standardized self-reported questionnaire included age, education level, average personal income, lifestyle (including smoking, alcohol habits and physical activity), medical history, and family history of diseases including diabetes, hypertension and hyperlipidemia. The educational level was classified according to the number of completed academic years. Maternal height was measured without shoes at enrollment. Their weight before pregnancy was self-reported, and current weight was measured by our trained staffs in each regular antenatal examination. Pre-pregnancy BMI was calculated as pre-pregnancy weight in kilograms divided by the square of the height in meters, and was classified as underweight (pre-pregnancy BMI□18.5), normal (18.5≤pre-pregnancy BMI□24.0) and overweight/obese (pre-pregnancy BMI≥24.0) [13]. Alcohol consumers were defined as those consuming alcohol before pregnancy or currently. Participants were defined as smokers if they smoked before or during pregnancy. Physical

activity during pregnancy was assessed and classified according to whether they take moderate or vigorous intensity exercise more than 3 times per week for more than 30 min once.

Blood samples were obtained after an overnight fast. Blood glucose was measured through the glucose oxidase method, TG was measured with GPO-PAP method, TC was measured with CHOD-PAP method, HDL-C was measured with catalase scavenging method and LDL-C was measured with surfactant scavenging method using commercially available kits (Biosino, Bio-technology and Science Inc. Beijing, China), by Mindray BS-200 automatic biochemical analyzer (Shenzhen, China). METS-IR was calculated by applying the modified formula, as Ln(2×FPG[mg/dl]+TG[mg/dl])×BMI[kg/m^2]/Ln(HDL-C[mg/dl]) [7]. Considering progressive weight gain during pregnancy, we used “pre-pregnancy BMI×current gestational weight/ideal gestational weight” instead of the BMI in the original formula to take in account the influence of both pre-pregnancy BMI and gestational weight gain. The ideal gestational weight was calculated using pre-pregnancy weight plus the ideal weight gain which was determined by recommendation of Institute of Medicine (IOM), based on the gestational age of blood testing and pre-pregnancy BMI of each participant [14].

A 75-g 2-h OGTT was performed during 24 and 28 gestational weeks. According to the criteria recommended by IADPSG, GDM was diagnosed when fasting plasma glucose ≥5.1 mmol/L, or 1-h plasma glucose ≥10.0 mmol/L, or 2-h plasma glucose ≥8.5 mmol/L [15].

Statistical analysis

All continuous variables were described as median (interquartile range) because of skewed distribution, and categorical variables were presented as number (percentage). The Kruskal-Wallis H tests and chi-square test were used to compare continuous and categorical variables between groups, respectively.

Participants were classified into 4 groups based on quartiles of METS-IR in pre-pregnancy normal-weight women. A modified Poisson regression model [16] was used to estimate risk ratio (RR) and 95% confidence interval (CI) for the association of METS-IR during early midpregnancy with incident GDM. In adjusted models, we controlled potential confounders including age, parity, family history of diabetes, family history of hypertension, family history of hyperlipidemia, systolic blood pressure (SBP), diastolic blood pressure (DBP), gestational week at blood sampling, TC and LDL-C. Stratified and interaction analyses were also conducted. Statistical analyses were done using SAS 9.4 (SAS Inst., Cary, NC, USA). Two-sided P 0.05 was considered statistically significant.

Results

Participant characteristics

1747 pregnant women (median age 28 years [interquartile range 26-30]) were included in the study. 19.7% of them were underweight and 11.7% were overweight/obese before pregnancy. The overall rate of GDM was 9.4% (165/1747) and the median (interquartile range) of METS-IR during early midpregnancy was

27.36 (24.57-31.07). The median METS-IR was significant different among women with various pre-pregnancy BMI, with highest value in women with pre-pregnancy overweight/obese and lowest in those with pre-pregnancy underweight (Table 1).

Table 1
Median and interquartile rang of METS-IR in whole study population and different pre-pregnancy BMI groups.

	GDM/Total (%)	METS-IR	*P* value
Whole study population	165/1747 (9.4)	27.36 (24.57-31.07)	
Pre-pregnancy BMI (kg/m^2)			<0.001
<18.5	16/344 (4.7)	22.92 (21.65-24.53)	
18.5-23.9	104/1198 (8.7)	27.72 (25.52-30.40)	
≥24.0	45/205 (22.0)	35.55 (33.10-38.30)	
Date are median (interquartile range) or n (%).			
METS-IR, metabolic score for insulin resistance; BMI, body mass index; GDM, gestational diabetes mellitus.			

Table 2 presented basic characteristics of the participants based on their METS-IR levels, according to quartiles of METS-IR in women with normal pre-pregnancy BMI. 594 (34.0%), 342 (19.6%), 315 (18.0%) and 496 (28.4%) of all participants were categorized into quartile1 to quartile 4 respectively. Age, pre-pregnancy BMI, SBP and DBP were increased with increasing quartiles of METS-IR (all P<0.05). Women within the higher quartile of METS-IR were more likely to be nulliparous and with family history of diabetes or hypertension. FPG, TG and LDL-C levels were increased and HDL-C level was decreased with increasing METS-IR levels (all P<0.001). The incident of GDM was highest among women within quartile 4 of METS-IR.

Table 2
Characteristics of study participants.

	METS-IR				*P* value
	Quartile 1 (<25.52) n=594	Quartile 2 (25.52-27.71) n=342	Quartile 3 (27.72-30.39) n=315	Quartile 4 (≥30.40) n=496	
Age (years)	27.0 (25.0-29.0)	27.0 (26.0-29.0)	27.0 (26.0-30.0)	29.0 (27.0-31.0)	<0.001
Pre-pregnancy weight (kg)	48.0 (45.0-50.0)	52.0 (48.0-55.0)	54.0 (51.0-57.5)	60.0 (55.0-65.0)	<0.001
Pre-pregnancy BMI (kg/m^2)	18.5 (17.7-19.5)	20.2 (19.4-21.1)	21.1 (20.2-22.0)	23.4 (21.8-24.9)	<0.001
Education level* (year)					0.482
<16	219 (38.0)	124 (36.8)	120 (38.6)	202 (41.7)	
≥16	357 (62.0)	213 (63.2)	191 (61.4)	282 (58.3)	
Average personal income* (CNY)					0.426
<5000 per month	207 (35.6)	114 (33.9)	101 (32.8)	187 (38.1)	
≥5000 per month	375 (64.4)	222 (66.1)	207 (67.2)	304 (61.9)	
Nulliparous (yes)	542 (91.3)	296 (86.6)	273 (86.7)	393 (79.2)	<0.001
Family history of diabetes* (yes)	35 (6.0)	25 (7.6)	29 (9.3)	56 (11.4)	0.013
Family history of hypertension* (yes)	128 (22.3)	70 (21.3)	87 (27.9)	146 (30.0)	0.006
Family history of hyperlipidemia* (yes)	27 (4.7)	20 (6.2)	25 (8.1)	41 (8.5)	0.066
Alcohol intake (yes)	90 (15.2)	44 (12.9)	37 (11.8)	69 (13.9)	0.515
Smoking (yes)	88 (14.8)	49 (14.3)	36 (11.4)	74 (14.9)	0.496

Date are median (interquartile range) or n (%).

P values (< 0.05 with asterisk) were obtained from the Kruskal-Wallis H tests, Chi square test.

METS-IR, metabolic score for insulin resistance; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; GDM, gestational diabetes mellitus.

*Partial data deletion.

	METS-IR				*P* value
	Quartile 1 (<25.52) n=594	Quartile 2 (25.52-27.71) n=342	Quartile 3 (27.72-30.39) n=315	Quartile 4 (≥30.40) n=496	
Physical activity during pregnancy (yes)	96 (16.2)	66 (19.3)	59 (18.7)	112 (22.6)	0.064
SBP (mmHg)	111.0 (105.0-118.0)	112.0 (105.0-120.0)	111.0 (105.0-121.0)	116.0 (109.0-124.0)	<0.001
DBP (mmHg)	70.0 (64.0-76.0)	69.0 (63.0-75.0)	69.0 (64.0-76.0)	72.0 (67.0-78.0)	<0.001
Gestational week at blood sampling (week)	17.0 (16.4-17.6)	17.0 (16.4-17.6)	17.0 (16.4-17.7)	17.0 (16.4-17.6)	0.343
FPG (mmol/l)	4.14 (3.76-4.52)	4.24 (3.86-4.64)	4.26 (3.90-4.73)	4.51 (4.06-5.16)	<0.001
TC (mmol/l)	4.76 (4.32-5.40)	4.81 (4.16-5.40)	4.76 (4.19-5.39)	4.74 (4.13-5.33)	0.677
TG (mmol/l)	1.34 (1.09-1.61)	1.49 (1.27-1.85)	1.63 (1.37-2.00)	1.94 (1.53-2.53)	<0.001
HDL-C (mmol/l)	2.00 (1.71-2.28)	1.74 (1.52-2.05)	1.65 (1.40-1.86)	1.46 (1.16-1.70)	<0.001
LDL-C (mmol/l)	2.23 (1.78-2.67)	2.39 (1.88-2.83)	2.40 (1.92-3.02)	2.48 (1.97-3.02)	<0.001
GDM (yes)	22 (3.7)	32 (9.4)	19 (6.0)	92 (18.6)	<0.001
Date are median (interquartile range) or n (%).					
P values (< 0.05 with asterisk) were obtained from the Kruskal-Wallis H tests, Chi square test.					
METS-IR, metabolic score for insulin resistance; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; GDM, gestational diabetes mellitus.					
*Partial data deletion.					

Association of METS-IR during early midpregnancy with GDM

Table 3 demonstrated the association of METS-IR with incident GDM by modified Poisson regression analysis. Higher METS-IR was correlated with increased risk of GDM after adjustment for age, parity, family history of diabetes, family history of hypertension, family history of hyperlipidemia, SBP, DBP,

gestational week at blood sampling, TC and LDL-C. Compared with lowest quartile of METS-IR, the adjusted RRs (95% CIs) of GDM were 2.15 (1.23-3.74), 1.34 (0.72-2.49), and 3.63 (2.22-5.95) for women within quartile 2, quartile 3 and quartile 4.

Table 3
Associations of METS-IR during early midpregnancy with incident GDM.

METS-IR	GDM/Total (%)	Unadjusted model	Model 1*	Model 2*	Model 3*
Quartile 1 (<25.52)	22/594 (3.7)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Quartile 2 (25.52-27.71)	32/342 (9.4)	2.53 (1.49-4.28)	2.40 (1.41-4.07)	2.25 (1.29-3.91)	2.15 (1.23-3.74)
Quartile 3 (27.72-30.39)	19/315 (6.0)	1.63 (0.90-2.96)	1.50 (0.82-2.74)	1.44 (0.78-2.68)	1.34 (0.72-2.49)
Quartile 4 (≥30.40)	92/496 (18.6)	5.01 (3.19-7.85)	4.27 (2.68-6.83)	4.07 (2.52-6.59)	3.63 (2.22-5.95)
Quartile 1-3 (<30.40)	73/1251 (5.8)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Quartile 4 (≥30.40)	92/496 (18.6)	3.18 (2.38-4.24)	2.79 (2.06-3.77)	2.77 (2.00-3.83)	2.55 (1.83-3.55)
Data are risk ratios (RRs) and 95% confidence intervals (95% CIs).					
METS-IR, metabolic score for insulin resistance; GDM, gestational diabetes mellitus.					
*Model 1: adjusted for age. Model 2: model 1 + parity, family history of diabetes, family history of hypertension, family history of hyperlipidemia, systolic blood pressure, diastolic blood pressure and gestational week at blood sampling. Model 3: model 2 + total cholesterol and low-density lipoprotein cholesterol levels.					

As GDM incidence among women within quartile 4 (18.6%) was significantly higher than that of quartile 1 (3.7%), quartile 2 (9.4%), and quartile 3 (6.0%), we compared women within highest quartile of METS-IR with those within the other 3 lower quartiles. The unadjusted modified Poisson regression analysis indicated that the higher METS-IR level (above 30.40) was associated with more than 3-fold risk of GDM than the lower level (RR [95% CI]: 3.18 [2.38-4.24]). After adjustment for age, parity, family history of diabetes, family history of hypertension, family history of hyperlipidemia, SBP, DBP, gestational week at blood sampling, TC and LDL-C, the relative risk (adjusted RR [95% CI]: 2.55 [1.83-3.55]) remained significant.

Table 4 presented analysis between the association of higher METS-IR with incident GDM stratified by age, parity, family history of diseases including diabetes or hypertension or hyperlipidemia, and gestational week at blood sampling. Stratified analysis indicated that the positive association between higher METS-IR and GDM risk remained significant regardless of age, parity, and gestational week at

blood sampling. The associations were stronger in women without family history of diseases or when the gestational age of assessment was >17 weeks(*P* for interaction<0.05).

Table 4
Stratified analysis: Associations of METS-IR during early midpregnancy with incident GDM in various population*

METS-IR	GDM/Total (%)	Quartile 1-3 (<30.40)	Quartile 4 (≥30.40)	*P* for interaction
Age (years)				0.321
≤27	63/853 (7.4)	1.00 (ref.)	3.39 (2.08-5.52)	
>27	102/894 (11.4)	1.00 (ref.)	2.32 (1.53-3.53)	
Parity				0.747
Primiparous	129/1504 (8.6)	1.00 (ref.)	2.51 (1.75-3.61)	
Multiparous	36/243 (14.8)	1.00 (ref.)	2.38 (1.10-5.15)	
Family history of diseases including diabetes or hypertension or hyperlipidemia†				0.045
No	99/1165 (8.5)	1.00 (ref.)	3.31 (2.20-4.98)	
Yes	60/532 (11.3)	1.00 (ref.)	1.48 (0.89-2.49)	
Gestational week at blood sampling (week)				0.001
≤17.0	84/937 (9.0)	1.00 (ref.)	1.67 (1.05-2.64)	
>17.0	81/810 (10.0)	1.00 (ref.)	3.86 (2.36-6.32)	

Data are risk ratios (RRs) and 95% confidence intervals (95% CIs).

METS-IR, metabolic score for insulin resistance; GDM, gestational diabetes mellitus.

*Adjusted for age, parity, family history of diabetes, family history of hypertension, family history of hyperlipidemia, systolic blood pressure, diastolic blood pressure, gestational week at blood sampling, total cholesterol and low-density lipoprotein cholesterol. Each of the above groups was adjusted for all covariates except itself.

†Partial data deletion.

Discussion

This is the first prospective cohort study to explore the predictive value of METS-IR during early midpregnancy on subsequent GDM risk. Women with higher METS-IR (≥30.40) in early midpregnancy had a 2.55-fold risk of developing GDM, compared with those with lower METS-IR (<30.40). These findings suggested that early assessment of METS-IR during pregnancy could be used as a valuable indicator to identify women at higher risk for subsequent GDM.

METS-IR was first reported as a novel score in 2018 to evaluate cardio-metabolic risk by screening insulin sensitivity in Mexican population [7]. Subsequently, several studies supported the importance of METS-IR in predicting the onset and progression of cardio-metabolic disease. Furthermore, elevated METS-IR was found to be related to a higher risk of arterial stiffness, hypertension, and prehypertension [9–11]. In recent, an increased baseline METS-IR and 6-year METS-IR change were found positively associated with risk of incident T2DM in a rural Chinese population [8]. To the best of our knowledge, our study has shown for the first time, that higher METS-IR during early midpregnancy was significant association with subsequent GDM.

METS-IR was a comprehensive index derived from the general individuals that included FPG, TG, HDL-C and BMI [7]. Previous studies suggested that pre-pregnancy obesity and excessive gestational weight gain were associated with increased risk of GDM [17, 18]. To include both these two influencing factors, we used “pre-pregnancy BMI×current gestational weight/ideal gestational weight” instead of the BMI in the original formula.

Besides pre-pregnancy obesity and excessive gestational weight, many other characters were found associated with increased GDM risk [19]. Several observational studies demonstrated that about 30% of normal-weight people have metabolic abnormalities (called MONW-like phenotype) [20, 21]. Data from the Korean study showed that women with MONW before pregnancy exhibited a significantly increased risk of developing GDM that required treatment with oral hypoglycemic agents or insulin compared to metabolically healthy and normal weight women [22]. Asians had a higher risk of being MONW than Europeans due to a greater amount of metabolically active visceral adipose tissue with the same BMI [23, 24]. Women with normal pre-pregnancy BMI were more likely to be ignored in early detection, and effective methods to early identify women at high GDM risk were lacking. Our results showed that METS-IR≥30.40 during early midpregnancy was associated with significant increased risk of developing GDM later. It could be used as a simple and reliable indicator to identify women at high GDM risk.

Although the potential mechanism underlying the association of METS-IR with GDM remains unclear, insulin resistance and β-cell impairment are considered central events in the development of GDM [1]. METS-IR was significantly correlated with visceral, intrahepatic and intra-pancreatic fat content, known pathophysiological components of insulin resistance [7]. Hepatic insulin resistance due to fat accumulation in the liver may alter blood glucose and lipid homeostasis, which translate into hyperglycemia and impaired lipemia and increases in body weight, all of which are mechanisms evaluated by METS-IR [25–28].

The strengths of our study were its prospective cohort design with collection of standardized data and biological samples, the use of available clinical and biochemical measures, and adjustment for a large number of potential confounders. Nevertheless, there were several limitations of our study. Firstly, we did not compare METS-IR with the homeostatic model assessment of insulin resistance (HOMA-IR) as indicator for GDM, because insulin levels were not routine measured in routine clinical practice. Secondly, we could not guarantee that all participants were free from any potential illness which might influence blood glucose, lipid profiles or impair insulin secretion or action, although we excluded women with medical history of chronic viral hepatitis, hypertension, diabetes prior to pregnancy. Finally, because almost all participants were Chinese Han, the utility and applicability of METS-IR during early midpregnancy for predicting GDM should be further confirmed in other ethnic populations.

Conclusion

In conclusion, our study suggests a significant association between higher METS-IR during early midpregnancy and increased risk of subsequent GDM in Chinese population. METS-IR can be used as an effective indicator for identifying women at high GDM risk to prevent the development of GDM.

Declarations

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions

The authors' contributions were as follows- N.H.Y. and M.H.T.: designed the research. M.H.T., G.Q.S., M.W., X.Y.C., X.Z., T.Q.T., C.R.Z., L.H., R.J.C., X.Z.Z., Q.L., X.C., L.X.L., S.Y., and G.P.X.: contributed to the acquisition and curation of data for the study. X.F.Y., L.P.H. and N.H.Y.: supervised the study conduct. M.H.T.: performed the statistical analysis and wrote the manuscript under supervision of N.H.Y.. All authors rigorously reviewed the draft and approved the final manuscript. The authors report no conflict interest.

Funding

This research was supported by the National Program on Basic Research Project of China (NO.2013FY114200) and the Fundamental Research Funds for the Central Universities (HUST: 2019kfyXMPY008) for Nianhong Yang.

Compliance with ethical standards

Conflict of interest

The authors report no conflicts of interest or personal relationships that could affect the work reported in this study.

Ethical approval

All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the Ethics Review Committee of Tongji Medical College of Huazhong University of Science and Technology (NO. 201302).

Consent to participate

Informed consent was obtained from all individual participants included in the study.

Consent for publication

Patients signed informed consent regarding publishing their data.

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Acknowledgments

This research was supported by the National Program on Basic Research Project of China (NO.2013FY114200) and the Fundamental Research Funds for the Central Universities (HUST: 2019kfyXMPY008) for Nianhong Yang. The authors thank all the women who participated in this cohort study, the practices who allowed us to access their databases and the staff of the primary care science research center who helped to manage the project.

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Figures

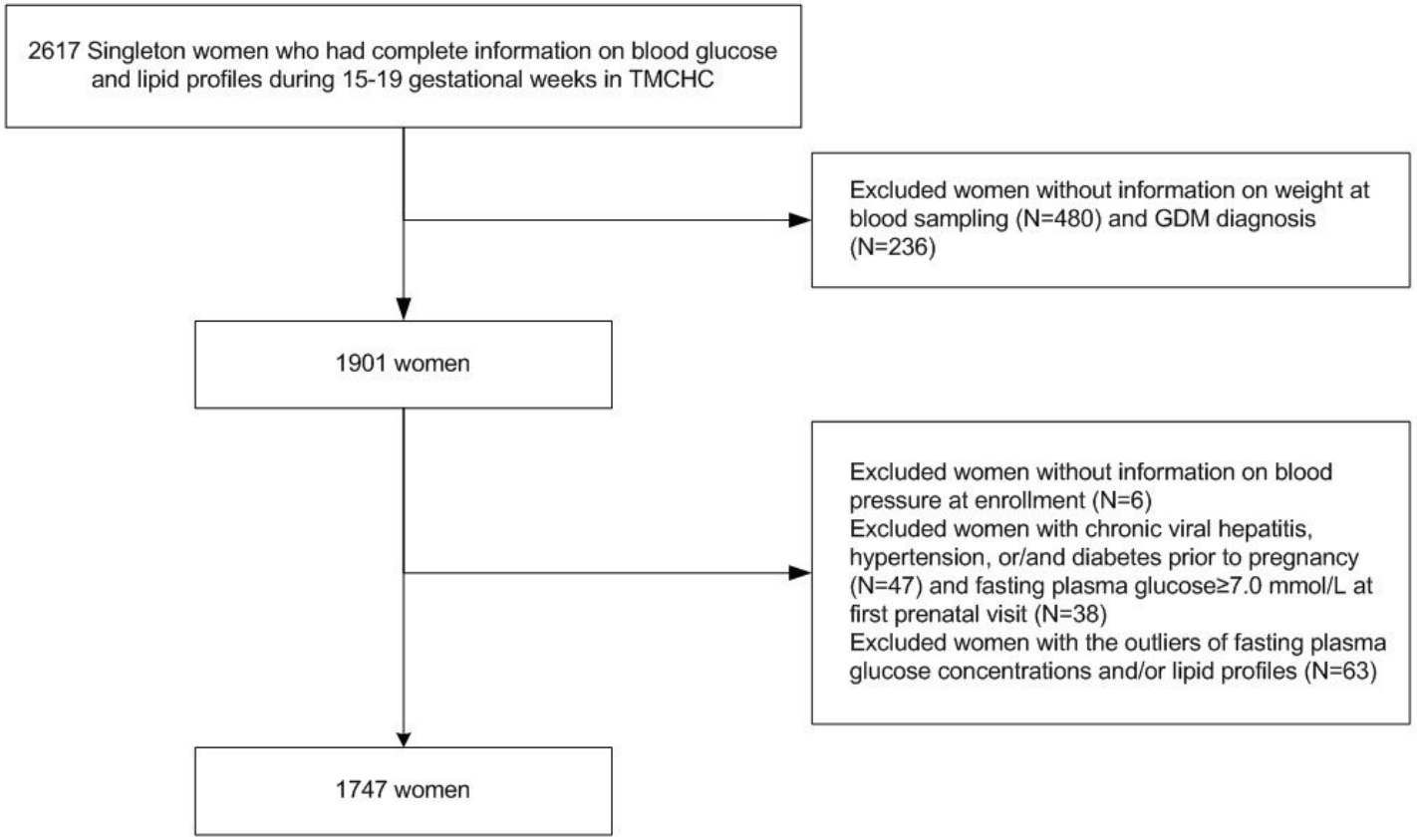

Figure 1

Flowchart of the participants in final analysis