Effect of the interaction between advanced maternal age and pre-pregnancy BMI on pre-eclampsia and GDM in Central China

Mengting Sun,[1] Manjun Luo,[1] Tingting Wang,[1,2] Jianhui Wei,[1] Senmao Zhang,[1] Jing Shu,[1] Taowei Zhong,[1] Yiping Liu,[1] Qian Chen,[1] Ping Zhu,[3] Jiabi Qin [1,2,4]

ABSTRACT

Introduction To investigate the independent and combined effects of advanced maternal age and pre-pregnancy body mass index (BMI) on the risk of pre-eclampsia and gestational diabetes mellitus (GDM).

Research design and methods Logistic regression models were used to estimate the OR and 95% CIs of pre-eclampsia and GDM with advanced maternal age and pre-pregnancy BMI, respectively, and the interaction between advanced maternal age and pre-pregnancy BMI. We also used causal mediation analysis to assess the mediating role of pre-pregnancy BMI on maternal age–pre-eclampsia/GDM associations.

Results In this study, 788 cases (2.31%) were diagnosed with pre-eclampsia and 5430 cases (15.92%) were diagnosed with GDM. We found that advanced maternal age was associated with a higher risk for pre-eclampsia and GDM, with adjusted ORs (aORs) of 1.74 (95% CI 1.49–2.05) and 1.76 (95% CI 1.65–1.89) after adjusting for potential confounders, respectively. In addition, maternal pre-pregnancy overweight/obesity was associated with the risk of pre-eclampsia and GDM, with the corresponding aORs of 3.64 (95% CI 3.12–4.24) and 1.71 (95% CI 1.60–1.85), respectively. We also observed the interaction between maternal age and pre-pregnancy BMI for the risk of pre-eclampsia/GDM (all p for interaction <0.001). In the mediating effect analysis, we found that maternal pre-pregnancy BMI mediated the associations between maternal age and the development of pre-eclampsia and GDM.

Conclusions Advanced maternal age and pre-pregnancy BMI were respectively associated with the risk of pre-eclampsia/GDM, and there was an interaction between the two risk factors. In addition, we found that pre-pregnancy BMI served as a mediator of the association between advanced maternal age and the risk of pre-eclampsia/GDM, providing an essential target for the prevention of maternal overweight/obesity.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Many studies have analyzed the association between advanced maternal age and pre-pregnancy body mass index (BMI) with the risk of pre-eclampsia/gestational diabetes mellitus (GDM), but the results are still controversial. Few studies have analyzed the interaction between advanced maternal age, pre-pregnancy BMI and the risk of diseases.

WHAT THIS STUDY ADDS

⇒ Advanced maternal age and pre-pregnancy BMI were respectively associated with the risk of pre-eclampsia/GDM during pregnancy, and there was an interaction between the two risk factors. In addition, we found that pre-pregnancy BMI serves as a mediator of the association between advanced maternal age and the risk of pre-eclampsia/GDM, providing an important target for the prevention of maternal overweight/obesity.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ We suggest that the community health service center should provide more prenatal guidance to women with advanced age and/or high BMI who plan to conceive so that they can understand the potential risk factors of maternal and infant-related complications. At the same time, women are encouraged to bear at the right age, so as to achieve better pregnancy outcomes.

INTRODUCTION

Pre-eclampsia and gestational diabetes mellitus (GDM) are common and significant maternal pregnancy complications worldwide, posing a severe threat to maternal and newborn morbidity and mortality. It is reported that the global prevalence of pre-eclampsia is between 2% and 4%.[1] Furthermore, it is associated with about 46 000 maternal deaths annually, especially in developing countries.[2] In China, Liu *et al*[3] reported an overall prevalence of pre-eclampsia of 2.4% in 2019, which is still increasing. Additionally, numerous epidemiological studies have demonstrated that pre-eclampsia contributes significantly to women's long-term risk of cardiovascular disease and other

chronic diseases.[4 5] GDM is traditionally defined as glucose intolerance with onset or first recognition during pregnancy. It affects an estimated 14.0% of pregnant women worldwide.[6 7] The prevalence of GDM in different regions of China fluctuated between 8.1% and 24.2%, showing a sharp upward trend.[8–11] Similarly, GDM has an important impact on the long-term health risks of mothers, including type 2 diabetes and metabolic syndrome. It also has a great hidden danger to the adverse pregnancy outcome of offspring and the occurrence of obesity, diabetes, and other diseases after growing up.[12]

With the improvement of social and economic levels, the opening of the two-child policy, the extension of schooling time, work pressure, and other reasons, the average childbearing age of women in China has been increasing.[13] However, it may also lead to an increased risk of pre-eclampsia and GDM in pregnant women. A Finnish study reported that the incidence of pre-eclampsia in pregnant women of advanced maternal age (≥35 years old) (9.4%) was higher than that in younger pregnant women (6.4%).[14] A meta-analysis of 120 million participants found that the risk of GDM increases linearly with maternal age.[15] The reasons may be related to higher nutrient intake, weight gain, higher circulating adipokine, and oxidative stress in pregnant women of advanced maternal age.[16] However, a study in China suggested that the prevalence of GDM peaked in pregnant women between the ages of 30 and 34 and then declined after the age of 35.[17] Given the inconsistencies in research evidence and the enormous burden of disease, it is of great practical importance to clarify the degree of age-related risk for pre-eclampsia and GDM.

Presently, obesity is spreading rapidly all over the world,[18 19] accompanied by the fact that pre-pregnancy overweight and obesity in pregnant women have also become an increasingly severe global public health problem. It is estimated that China's contribution to the global prevalence of overweight and obesity among pregnant women is as high as 11.0%, ranking second only to India (11.1%).[20] Overweight or obesity before pregnancy in pregnant women increases the incidence of adverse pregnancy complications and threatens the adverse pregnancy outcomes in their offspring.[21 22] Conversely, underweight pregnant women may have a protective effect on maternal and fetal health.[23] The world's largest and most comprehensive meta-analysis of pre-pregnancy body mass index (BMI) in 20 328 777 women included in 86 studies found that pre-pregnancy overweight and obesity significantly increased the risk of pre-eclampsia and GDM during pregnancy. The OR for obesity was 4.10 and 3.57, respectively.[24] There was evidence in different populations that pre-pregnancy overweight and obesity were associated with an approximately twofold to fourfold increased risk of pre-eclampsia and GDM.[25–27]

Although many studies have investigated the risk factors associated with pre-eclampsia and GDM, the interaction effect between advanced maternal age and pre-pregnancy BMI on the development of pre-eclampsia/GDM during pregnancy has received less attention in China. It has been reported that modern women with advanced reproductive age are more likely to have a higher BMI before pregnancy. Therefore, the purpose of this study was to evaluate the interaction effect between advanced maternal age and pre-pregnancy BMI on pre-eclampsia and GDM and its possible mediating effect.

MATERIALS AND METHODS
Study design and participant enrollment
The prospective cohort study was conducted at the Hunan Maternal and Child Health Hospital in Central China, the first third level of first-class maternal and child healthcare hospital with a long history in Hunan Province. The study period was from 13 March 2013 to 31 December 2019. Couples who received prenatal care for the first time in the reproductive center, obstetrics department, ultrasound department, and other departments of our hospital during this period and planned to receive prenatal care and deliver in our hospital during the whole pregnancy were recruited as subjects to establish a cohort. All included participants provided written informed consent.

Gestational weeks were estimated through the data of the last menstrual period, and if menstruation was irregular, an ultrasound was used for confirmation. The inclusion criteria for this study were (1) single pregnancy, (2) availability of complete medical information, and (3) eventual completion of the entire follow-up process. The exclusion criteria for this study included (1) pregnant women using assisted reproductive technology, (2) pregnant women with twin or more pregnancies (including the natural extinction of one of the original twin pregnancies), (3) termination of pregnancy due to miscarriage, stillbirth and induced labor, (4) pre-GDM, (5) pre-pregnancy hypertension or a history of serious heart disease before pregnancy, and (6) pregnant women with severe mental disorders who were unable to cooperate in completing the survey. Overall, the total number of subjects was 34 104 pregnant women after the final exclusion of lost follow-up.

Data collection
This study designed a structured questionnaire based on maternal and child health information, which covered the maternal sociodemographic characteristics, obstetrical or reproductive history, maternal behavioral characteristics, and medical history before and in the early stage of pregnancy and complications during pregnancy. Meanwhile, the sociodemographic and behavioral characteristics of the spouse were collected. The investigators surveyed through a one-to-one interview questionnaire and telephone follow-up. All investigators have undergone rigorous uniform training. Information on

pregnancy complications and postpartum offspring was reconfirmed in the electronic medical record system.

Exposure

The age information of all participants was calculated based on the birth date on their resident ID cards. The height and weight information was reported from measurements taken with light clothing and shoes removed. BMI was calculated as the ratio of weight (kilogram) to the square of height (meter). Underweight was defined as BMI<18.5 kg/m^2, normal weight was defined as 18.5≤BMI<24.0 kg/m^2, and overweight/obesity was defined as BMI≥24.0 kg/m^2.[28]

Outcome

The outcomes of interest in this study were pre-eclampsia and GDM, obtained from the electronic medical record system. In this study, pre-eclampsia was defined as newly diagnosed hypertension and proteinuria after 20 weeks of pregnancy. Hypertension referred to the systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg measured twice at an interval of 4 hours. Proteinuria referred to ≥300 mg/24-hour urine volume, or protein/creatinine ≥0.3, or a single random urine sample containing at least 1+ protein detected by test paper.

GDM was diagnosed according to the standards of the International Association of Diabetes and Pregnancy Study Groups. If the 75 g oral glucose tolerance test was performed during 24–28 weeks of pregnancy, venous blood glucose was measured at 0 hour on an empty stomach, 1 hour, and 2 hours after administration. Any of the three blood glucose levels reached or exceeded the diagnostic limit: fasting plasma glucose >5.10 mmol/L, 1-hour plasma glucose (1hPG) after a meal >10.00 mmol/L, and 2-hour plasma glucose (2hPG) after a meal >8.50 mmol/L. The level of venous plasma glucose was measured by an automatic analyzer (Toshiba TBA-120FR, Tokyo, Japan) in the Central Laboratory of Hunan Maternal and Child Health Hospital.

Statistical analysis

The data information of this study was input by EpiData V.3.1, and a two-person input mechanism was adopted to ensure the accuracy of the data. For the description of participants' sociodemographic characteristics, median and IQR were used to represent the continuous variables, number and frequency distribution were used to represent the categorical variables. The χ^2 test and Mann-Whitney U test were used to compare the classification variables and skewness distribution of continuous variables between groups. The logistic regression model was used to estimate the OR and 95% CIs between pre-eclampsia or GDM and advanced maternal age and pre-pregnancy BMI, and the interaction between advanced maternal age and pre-pregnancy BMI. Then, the maternal age was stratified by 35 years to estimate the association between pre-eclampsia, GDM and maternal pre-pregnancy BMI. Model 1 was adjusted for demographic characteristics,

including maternal age, residence location, education, nationality, and monthly household income. Model 2 was further adjusted for maternal pre-pregnancy BMI, drinking in early pregnancy, passive smoking in early pregnancy, smoking in early pregnancy, parity, folic acid supplementation, family history of hypertension, and family history of hyperglycemia. When the variable was the maternal age, model 1 did not adjust the maternal age; when the variable was the maternal pre-pregnancy BMI, model 2 did not adjust the maternal pre-pregnancy BMI. In addition, we further conducted the combined analysis to assess the impact of advanced maternal age and pre-pregnancy BMI on pre-eclampsia and GDM, respectively. We further performed a combined analysis to evaluate the effect of maternal age and pre-pregnancy BMI on the risk of pre-eclampsia and GDM and visualized the interactions using the R language Visreg package.

We used causal mediation analysis to assess the mediating role of pre-pregnancy BMI on maternal age–pre-eclampsia/GDM associations. The mediation model was fitted by taking the maternal pre-pregnancy BMI as a response and using the potential covariables in the regression equation as predictors. Next, the fitting of the outcome model used outcome variables pre-eclampsia or GDM as responses, respectively, and pre-pregnancy BMI and potential covariates in the regression equation as predictors. The direct and indirect effects of maternal age on pre-eclampsia or GDM were calculated by the '*mediation*' function in the R mediation package, and the proportion of pre-pregnancy BMI was estimated. We further conducted a sensitivity analysis to enhance the stability of the results by controlling for the influence of different ethnic groups and including only the Han population in the analysis (there are 55 ethnic groups in China besides the Han population). All statistical analyses were performed by SPSS V.26.0 (SPSS) and R V.4.1.2 (R Foundation for Statistical Computing, Vienna, Austria). Two-sided p values less than 0.05 were defined as statistically significant.

RESULTS

Participant characteristics

In the study population, 34 104 pregnant women were included, of which 788 cases (2.31%) were diagnosed with pre-eclampsia and 5430 cases (15.92%) were diagnosed with GDM. According to pre-pregnancy BMI, most pregnant women were of normal weight (70.15%, 23 925/34 104), while underweight and overweight/obese pregnant women accounted for 14.43% (4920/34 104) and 15.42% (5259/34 104), respectively. The average age of the study participants was 31.12±4.51 years old, and pregnant women with advanced age (≥35 years old) accounted for 22.46%. Table 1 shows the baseline characteristics of participants according to pre-pregnancy BMI.

The incidence (% and 95% CI) of pre-eclampsia and GDM according to advanced maternal age and pre-pregnancy BMI is shown in table 2. The incidence of

Table 1 Baseline characteristics of participants by pre-pregnancy maternal BMI

Characteristics	Total	Underweight	Normal weight	Overweight/obesity	P value
Maternal age (year), median (IQR)	30 (28, 34)	29 (27, 31)	31 (28, 34)	32 (29, 35)	<0.001
Maternal age, n (%)					0.001
<35 years	26 445 (77.5)	4378 (89.0)	18 297 (76.5)	3770 (71.7)	
≥35 years	7659 (22.5)	542 (11.0)	5628 (23.5)	1489 (28.3)	
Residence location, n (%)					0.415
Urban area	21 074 (61.8)	3075 (62.5)	14 732 (61.6)	3267 (62.1)	
Rural area	13 030 (38.2)	1845 (37.5)	9193 (38.4)	1992 (37.9)	
Education level, n (%)					<0.001
Junior high and below	2547 (7.5)	367 (7.5)	1572 (6.6)	608 (11.6)	
High school or technical secondary school	9695 (28.4)	1338 (27.2)	6599 (27.6)	1758 (33.4)	
College degree	15 594 (45.7)	2399 (48.8)	11 091 (46.4)	2104 (40.0)	
Bachelor's degree or above	6268 (18.4)	816 (16.6)	4663 (19.5)	789 (15.0)	
Nationality, n (%)					0.098
Han nationality	33 656 (98.7)	4871 (99.0)	23 601 (98.6)	5184 (98.6)	
Minority nationality	448 (1.3)	49 (1.0)	324 (1.4)	75 (1.4)	
Monthly household income (¥), n (%)					0.490
≤2500	5892 (17.3)	825 (16.8)	4126 (17.2)	941 (17.9)	
2500–5000	18 206 (53.4)	2672 (54.3)	12 737 (53.2)	2797 (53.2)	
>5000	10 006 (29.3)	1423 (28.9)	7062 (29.5)	1521 (28.9)	
Drinking in early pregnancy, n (%)					0.091
No	33 606 (98.5)	4863 (98.8)	23 555 (98.5)	5188 (98.6)	
Yes	498 (1.5)	57 (1.2)	370 (1.5)	71 (1.4)	
Passive smoking in early pregnancy, n (%)					0.007
No	31 752 (93.1)	4539 (92.3)	22 278 (93.1)	4935 (93.8)	
Yes	2352 (6.9)	381 (7.7)	1647 (6.9)	324 (6.2)	
Smoking in early pregnancy, n (%)					0.659
No	33 650 (98.7)	4849 (98.6)	23 507 (98.7)	5194 (98.8)	
Yes	454 (1.3)	71 (1.4)	318 (1.3)	65 (1.2)	
Parity, n (%)					<0.001
Primiparous	10 493 (30.8)	1986 (40.4)	7254 (30.3)	1253 (23.8)	
Multiparous	23 611 (69.2)	2934 (59.6)	16 671 (69.7)	4006 (76.2)	
Folic acid supplementation, n (%)					0.176
No	32 556 (95.5)	4708 (95.7)	22 807 (95.3)	5041 (95.7)	
Yes	1548 (4.5)	212 (4.3)	1118 (4.7)	218 (4.1)	
Family history of hypertension, n (%)					
No	33 200 (97.3)	4821 (98.0)	23 294 (97.4)	5085 (96.7)	<0.001
Yes	904 (2.7)	99 (2.0)	631 (2.6)	174 (3.3)	
Family history of hyperglycemia, n (%)					
No	33 618 (98.6)	4873 (99.0)	23 592 (98.6)	5153 (98.0)	<0.001
Yes	486 (1.4)	47 (1.0)	333 (1.4)	106 (2.0)	

Underweight (BMI: <18.5 kg/m^2), normal weight (BMI: 18.5–23.9 kg/m^2), overweight/obesity (BMI: ≥24.0 kg/m^2).
BMI, body mass index.

Table 2 Incidence (% and 95% CI) of pre-eclampsia and GDM according to advanced maternal age and pre-pregnancy BMI

Variables	Pre-eclampsia		GDM	
	n	Incidence % (95% CI)	n	Incidence % (95% CI)
Total	788	2.31 (2.15–2.47)	5430	15.92 (15.53–16.31)
Maternal age (years)				
<35	513	1.94 (1.77–2.11)	3706	14.01 (13.60–14.43)
≥35	275	3.59 (3.17–4.01)	1724	22.51 (21.57–23.45)
Pre-pregnancy BMI				
Underweight	64	1.30 (0.98–1.62)	448	9.11 (8.30–9.91)
Normal weight	390	1.63 (1.47–1.79)	3696	15.45 (14.99–15.91)
Overweight/obesity	334	6.35 (5.69–7.01)	1286	24.45 (23.29–25.62)

Underweight (BMI: <18.5 kg/m^2), normal weight (BMI: 18.5–23.9 kg/m^2), overweight/obesity (BMI: ≥24.0 kg/m^2).
BMI, body mass index; GDM, gestational diabetes mellitus.

pre-eclampsia (3.59% vs 1.94%) and GDM (22.51% vs 14.01%) in pregnant women aged ≥35 years was higher than those in pregnant women aged <35 years. Similarly, the incidence of pre-eclampsia and GDM varied according to maternal pre-pregnancy BMI status. The incidence of pre-eclampsia and GDM ranged from 1.30% to 6.35% and 9.11% to 24.45% in underweight to overweight/obese women, respectively.

Associations of advanced maternal age and pre-pregnancy BMI with pre-eclampsia and GDM

Table 3 shows the associations of advanced maternal age and pre-pregnancy BMI with pre-eclampsia and GDM during pregnancy, respectively. We found that advanced maternal age was associated with a higher risk for pre-eclampsia and GDM during pregnancy, with adjusted ORs (aORs) of 1.74 (95% CI 1.49–2.05) and 1.76 (95% CI 1.65–1.89) after adjusting for potential confounders,

respectively. In addition, maternal pre-pregnancy overweight/obesity was associated with the risk of pre-eclampsia and GDM during pregnancy, with the corresponding aOR values of 3.64 (95% CI 3.12–4.24) and 1.71 (95% CI 1.60–1.85) after adjusting for potential confounders, respectively. This study showed that the prevalence of GDM was lower in underweight women than those who were normal weight (aOR=0.62, 95% CI 0.56–0.70).

The interaction effect between advanced maternal age and pre-pregnancy BMI on pre-eclampsia and GDM

There was a significant statistical interaction between maternal age (<35 years, ≥35 years) and pre-pregnancy BMI in the risk of pre-eclampsia and GDM during pregnancy after adjusting for potential confounding factors (all p for interaction <0.001, table 4). We found that maternal pre-pregnancy overweight/obesity was

Table 3 ORs (95% CIs) for pre-eclampsia and GDM by advanced maternal age and pre-pregnancy body mass index

Variables	Pre-eclampsia		GDM	
	Model 1	Model 2	Model 1	Model 2
Maternal age (years)				
<35	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
≥35	1.80 (1.55–2.09)*	1.74 (1.49–2.05)*	1.79 (1.68–1.91)*	1.76 (1.65–1.89)*
Pre-pregnancy BMI				
Underweight	0.84 (0.64–1.09)	0.84 (0.64–1.10)	0.63 (0.56–0.70)*	0.62 (0.56–0.70)*
Normal weight	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Overweight/obesity	3.67 (3.15–4.27)*	3.64 (3.12–4.24)*	1.72 (1.59–1.84)*	1.71 (1.60–1.85)*

Underweight (BMI: <18.5 kg/m^2), normal weight (BMI: 18.5–23.9 kg/m^2), overweight/obesity (BMI: ≥24.0 kg/m^2).
Model 1 was adjusted for demographic characteristics including maternal age, residence location, education, nationality, and monthly household income. Model 2 was further adjusted for maternal pre-pregnancy body mass index, drinking in early pregnancy, passive smoking in early pregnancy, smoking in early pregnancy, parity, folic acid supplementation, family history of hypertension, and family history of hyperglycemia. When the variable was the maternal age, model 1 did not adjust for the maternal age; when the variable was the maternal pre-pregnancy BMI, model 2 did not adjust for the maternal pre-pregnancy BMI.
*P<0.001.
BMI, body mass index; GDM, gestational diabetes mellitus.

Table 4 ORs (95% CIs) for pre-eclampsia and GDM by maternal pre-pregnancy body mass index, stratified by maternal age

Outcome	Age <35 years			Age ≥35 years			P value for interaction
	Underweight	Normal weight	Overweight/obesity	Underweight	Normal weight	Overweight/obesity	
Pre-eclampsia							<0.001
Model 1	0.77 (0.57–1.05)	1.00 (Ref)	3.78 (3.13–4.57)*	1.19 (0.69–2.06)	1.00 (Ref)	3.48 (2.69–4.49)*	
Model 2	0.77 (0.56–1.05)	1.00 (Ref)	3.84 (3.18–4.64)*	1.28 (0.74–2.21)	1.00 (Ref)	3.39 (2.61–4.39)*	
GDM							<0.001
Model 1	0.61 (0.55–0.69)*	1.00 (Ref)	1.82 (1.67–1.99)*	0.48 (0.37–0.63)*	1.00 (Ref)	1.60 (1.40–1.82)*	
Model 2	0.62 (0.55–0.69)*	1.00 (Ref)	1.80 (1.65–1.97)*	0.48 (0.37–0.63)*	1.00 (Ref)	1.61 (1.40–1.83)*	

Underweight (BMI: <18.5 kg/m^2), normal weight (BMI: 18.5–23.9 kg/m^2), overweight/obesity (BMI: ≥24.0 kg/m^2).
Model 1 was adjusted for demographic characteristics including maternal residence location, education, nationality and monthly household income. Model 2 was further adjusted for maternal drinking in early pregnancy, passive smoking in early pregnancy, parity, folic acid supplementation, family history of hypertension, and family history of hyperglycemia.
*P<0.001.
BMI, body mass index; GDM, gestational diabetes mellitus.

associated with a higher risk of pre-eclampsia in both groups with maternal ages of <35 and ≥35 years, with aOR values of 3.84 (95% CI 3.18–4.64) and 3.39 (95% CI 2.61–4.39) after adjusting for potential confounding factors, respectively. Similarly, maternal pre-pregnancy overweight/obesity was associated with GDM during pregnancy in both groups with maternal ages of <35 and ≥35 years, with aOR values of 1.80 (95% CI 1.65–1.97) and 1.61 (95% CI 1.40–1.83) after adjusting for potential confounding factors, respectively. However, maternal pre-pregnancy underweight was associated with a reduced risk of GDM in both groups with maternal ages of <35 and ≥35 years, with corresponding aOR values of 0.62 (95% CI 0.55–0.69) and 0.48 (95% CI 0.37–0.63) after adjusting for potential confounding factors, respectively.

In addition, we further performed a combined analysis to evaluate the effect of maternal age and pre-pregnancy BMI on the risk of pre-eclampsia and GDM (table 5, online supplemental figure S1). Compared with those aged <35 years and of pre-pregnancy normal weight, those with maternal pre-pregnancy overweight/obesity and aged ≥35 years had a 5.66-fold odds of pre-eclampsia (OR=5.66, 95% CI 4.50–7.12). Moreover, pregnant women who were pre-pregnancy overweight/obese and aged ≥35 years had a 2.80 times (OR=2.80, 95% CI 2.48–3.15) higher risk of developing GDM than those who were of pre-pregnancy normal weight and aged <35 years. We further visualized the interaction between maternal age (as a continuous variable) and pre-pregnancy BMI with the risk of developing pre-eclampsia and GDM (online supplemental figure S2). It was clear that the risk of developing pre-eclampsia/GDM increased with maternal age, especially in women who were pre-pregnancy overweight/obese.

The mediation effects of pre-pregnancy BMI on maternal age–pre-eclampsia/GDM associations

As shown in online supplemental figure S3, maternal pre-pregnancy BMI mediated the associations between maternal age and the development of pre-eclampsia and GDM during pregnancy. More specifically, pre-pregnancy overweight/obesity mediated the association between advanced maternal age and pre-eclampsia (proportion mediated: 23.1% (95% CI 17.1%–32.0%)). Similarly, pre-pregnancy overweight/obesity mediated the association between advanced maternal age and GDM (proportion mediated: 15.2% (95% CI 13.0%–16.0%)). We then performed sensitivity analyses that excluded ethnic minority populations, and the results were similar, suggesting the robustness of the results (there are 55 ethnic groups in China besides the Han population) (online supplemental figure S4).

DISCUSSION

In this prospective cohort study in Central China, women diagnosed with pre-eclampsia and GDM during pregnancy accounted for 2.31% and 15.92%, respectively. We found that advanced maternal age (≥35 years) was

Table 5 ORs (95% CIs) for pre-eclampsia and GDM by the interaction between maternal age and pre-pregnancy body mass index

Maternal age (years)	BMI	Pre-eclampsia	GDM
<35	Underweight	0.78 (0.57–1.06)	0.62 (0.55–0.69)**
<35	Normal weight	1.00 (Ref)	1.00 (Ref)
<35	Overweight/obesity	3.82 (3.16–4.61)**	1.81 (1.65–1.97)**
≥35	Underweight	2.05 (1.20–3.48)*	0.85 (0.65–1.11)
≥35	Normal weight	1.68 (1.35–2.09)**	1.74 (1.61–1.88)**
≥35	Overweight/obesity	5.66 (4.50–7.12)**	2.80 (2.48–3.15)**

Underweight (BMI: <18.5 kg/m^2), normal weight (BMI: 18.5–23.9 kg/m^2), overweight/obesity (BMI: ≥24.0 kg/m^2).
Adjusted for maternal demographic characteristics including residence location, education, nationality, monthly household income, drinking in early pregnancy, passive smoking in early pregnancy, smoking in early pregnancy, parity, folic acid supplementation, family history of hypertension, and family history of hyperglycemia.
**P<0.001; *p<0.01.
BMI, body mass index; GDM, gestational diabetes mellitus.

associated with an increased risk of pre-eclampsia and GDM during pregnancy after adjusting for potential confounders. Similarly, maternal pre-pregnancy BMI was associated with the risk of pre-eclampsia and GDM after adjustment for potential confounders. We further observed a statistically significant interaction between maternal age and pre-pregnancy BMI with the risk of developing pre-eclampsia and GDM during pregnancy after adjusting for potential confounders. In the mediation effect analysis, maternal pre-pregnancy BMI mediated the associations between maternal age and the occurrence of pre-eclampsia and GDM during pregnancy.

Advanced maternal age has attracted the attention of clinicians and researchers due to its gradual social generalization. In different racial and ethnic groups, many epidemiological studies have reported positive associations between advanced maternal age and pre-eclampsia and GDM, which was consistent with our findings. A study in Hubei, China, found that the trend of advanced maternal age (age ≥35) increased by 75% from 2011 to 2019, and noted that advanced maternal age was associated with an increased risk of pre-eclampsia (OR=1.6) and GDM (OR=2.5) after adjusting for confounding factors.[29] Shan *et al* found that the risk of pre-eclampsia increased dramatically with maternal age. In addition, older pregnant women have a twofold to threefold risk of being diagnosed with GDM.[30] Similarly, Makgoba *et al* reported a strong positive association between the increase in maternal age and the occurrence of GDM, particularly in black African and South Asian women.[31] We also found that the risk of pre-eclampsia/GDM increased with maternal age, especially among pre-pregnancy overweight/obese women. This may provide a scientific basis for exploring the degree of age-related risk of pre-eclampsia and GDM. However, the associations between advanced maternal age and pre-eclampsia and GDM have not been well described. The association between advanced maternal age and pre-eclampsia may be due to aging's association with endothelial dysfunction caused by reduced nitric oxide availability and high

oxidative stress.[32] This idea has also been validated in animal experiments.[33] Changes in endothelial function make placental perfusion unable to meet the actual birth needs of the pregnant woman and lead to more oxidative stress, which increases the risk of maternal pre-eclampsia.[34] Glucose tolerance is known to be associated with insulin sensitivity and secretory function. The increased risk of GDM in advanced maternal age may be explained by impaired islet β-cell function, decreased insulin sensitivity, dysregulation of lipid metabolism, and high oxidative stress with aging.[16 35 36] However, metabolic disorders, oxidative stress and other reactions may also affect placental function. It is known that the placenta is the main organ for the mother to transport nutrients to the fetus. At present, it has been found that placental dysfunction may be the direct cause of abnormal growth and development of the offspring of pregnant women with GDM through proteomics.[37] This view deserves our attention and also provides new ideas for our next research.

At present, there is also literature suggesting that advanced maternal age may affect pre-eclampsia or GDM through inflammatory dysregulation. Increasing age is known to trigger proinflammatory tendencies and elevated oxidative stress, both of which are strongly associated with pregnancy pathology.[38] In animal experiments, interleukin-10 knockout mice were found to cause increased susceptibility to inflammatory stimuli, leading to exacerbation of vascular symptoms of pre-eclampsia.[39] A population-based study has found altered biomarkers of circulating inflammation and oxidative stress in older pregnant women with adverse pregnancy outcomes.[40] Therefore, the age-related decline in anti-inflammatory cytokines may increase the vulnerability of older women to inflammation. Both pre-eclampsia and GDM are associated with inflammatory response. Uteroplacental ischemia in pre-eclampsia may cause adverse reactions such as angiogenesis dysregulation and systemic inflammatory response.[41] One study found that blood inflammatory indicators such as neutrophil to lymphocyte ratio,

platelet to lymphocyte ratio, white cell count, and neutrophil count in GDM pregnant women are higher than those in healthy pregnant women.[42] Therefore, larger prospective cohort studies as well as laboratory data are needed to provide a scientific basis for the pathogenesis of the disease.

Studies also confirmed positive associations between high pre-pregnancy BMI and pre-eclampsia and GDM during pregnancy.[43 44] A birth cohort study in Lanzhou, China, showed a 1.81-fold increased risk of pre-eclampsia in overweight/obese women compared with women with a normal pre-pregnancy BMI, which was consistent with our findings.[45] Another cross-sectional study of 16 hospitals in five provinces in Mainland China reported that pre-pregnancy BMI was a risk factor for pre-eclampsia (OR=1.16) and GDM (OR=1.19).[46] The sample size of our study was more extensive, which strengthened the credibility of the evidence. Similar findings have been found in Italian, Indian and Japanese populations.[47–49] The pathogenesis of maternal pre-pregnancy overweight/obesity and pre-eclampsia and GDM during pregnancy is complex and not yet fully understood. There is a consensus that overweight and obesity are known to be chronic inflammatory diseases that can lead to insulin resistance, high oxidative stress, inflammatory markers, and high cytokine levels,[50–52] which can lead to endothelial dysfunction/elevated blood glucose, resulting in clinical symptoms of pre-eclampsia or GDM.[19 53 54]

In the stratified analysis of this study, maternal pre-pregnancy underweight was associated with a reduced risk of GDM in both groups with maternal ages of <35 and ≥35 years. This was consistent with the results of a meta-analysis conducted by Vats *et al*.[24] There were also studies that show no association between pre-pregnancy underweight and GDM.[26 55] Potential causes of this ambiguity include restrictions on specific ethnicity as well as different definitions of BMI and different inclusion and exclusion criteria. To look at a problem requires multiple perspectives. Although we found that pre-pregnancy underweight may be a protective factor for GDM, some studies have found that pre-pregnancy underweight may increase the risk of preterm birth, low birth weight, and small for gestational age in the offspring.[24] Therefore, we still advocate maintaining an appropriate BMI before pregnancy to reduce the burden of maternal and infant diseases.

An interesting finding of our study is that we found a statistically significant interaction between advanced maternal age and pre-pregnancy BMI on the risk of pre-eclampsia and GDM during pregnancy after adjusting for potential confounders. Specifically, we found that women aged ≥35 years who were pre-pregnancy overweight/obese had a 5.66-fold higher risk of developing pre-eclampsia than women aged <35 years who were of pre-pregnancy normal weight. Similarly, pregnant women who were pre-pregnancy overweight/obese and aged ≥35 years had a 2.80 times higher risk of developing GDM than those who were of pre-pregnancy normal weight and

aged <35 years. Current studies suggest that the interaction between maternal age and BMI may influence breast milk's fat and calorie content, which may adversely affect the birth weight of offspring.[56] However, there were few studies on the interaction between maternal age and BMI and the risk of adverse pregnancy complications. Dong *et al* reported that increased pre-pregnancy BMI increased the risk of GDM, especially in advanced maternal age.[57] Our study provided further evidence for this view. Therefore, our study highlights that pregnant women with pre-pregnancy overweight/obesity plus advanced age should pay more attention to weight control during pregnancy preparation and strengthen the attention of this population to prenatal examination.

Studies have found that obesity is more common in older women.[30] In our study, advanced maternal age was associated with an increased risk of pre-eclampsia and GDM during pregnancy. Therefore, we further assessed the mediating role of pre-pregnancy BMI on advanced maternal age–pre-eclampsia/GDM association. Most notably, our results suggested that 23.1% of the increased risk of pre-eclampsia and 15.2% of the increased risk of GDM were mediated by pre-pregnancy overweight/obesity after adjusting for potential confounders. The latter is a new finding that provides important clues to the mechanism between the difference in the development of severe pregnancy complications and the social determinants and provides an essential target for the prevention of obesity in pregnant women. It has important guiding significance for female pregnancy. Siddiqui *et al*[58] found that pre-pregnancy obesity played an intermediary role between the mother's place of birth and the development of severe pre-eclampsia, which was partly similar to our study.

The main strengths of this study were the large sample size and the fact that pregnant-related data were prospectively collected to minimize recall bias. In addition, we investigated the effect of the interaction between advanced maternal age and pre-pregnancy BMI on the risk of pre-eclampsia/GDM during pregnancy and the mediation effect of pre-pregnancy BMI. This provides a new perspective for the study of pregnancy complications and may have important practical significance. Currently, there is a lack of internationally recognized early screening methods to prevent the occurrence of pre-eclampsia and GDM. Pregnant women with advanced age and pre-pregnancy overweight/obesity may have a higher risk of pre-eclampsia and GDM, which is more meaningful for predicting pre-eclampsia and GDM. At the same time, advanced age and overweight/obesity may be accompanied by potential inflammatory mechanisms, which may provide new targets for diagnosing pre-eclampsia and GDM. This still needs to be verified by epidemiological investigations and animal experiments.

Some limitations should be taken into account when interpreting our results. First, all the study population recruited came from the same hospital, which is challenging to avoid selection bias. Second, we failed to collect

information about pregnant women's diet, exercise, and weight gain before or during the early pregnancy, which limited us from further exploring the etiology of pre-eclampsia and GDM. Third, since the process and results of pregnancy in pre-eclampsia and GDM vary by race and nationality, it is necessary to carry out this study in a larger population of different nationalities and compare the results. Fourth, we adjusted for many confounders in model 2, and it is still possible that some confounders were not captured.

CONCLUSION

In conclusion, we found that both advanced maternal age and pre-pregnancy overweight/obesity were associated with an increased risk of pre-eclampsia and GDM during pregnancy, respectively, and that there was an interaction between the two risk factors in terms of their impact on the disease. We suggest that the community health service center provide more prenatal guidance to women with advanced age and high BMI who plan to conceive of understanding the potential risk factors of maternal and infant-related complications. At the same time, women are encouraged to bear at the right age to achieve better pregnancy outcomes. Further research is needed to identify appropriate interventions to reduce the risk of pre-eclampsia and GDM in advanced maternal age.

Author affiliations
[1]Department of Epidemiology and Health Statistics, Xiangya School of Public Health, Central South University, Changsha, Hunan, China
[2]National Health Committee (NHC) Key Laboratory of Birth Defect for Research and Prevention, Hunan Provincial Maternal and Child Health Care Hospital, Changsha, Hunan, China
[3]Guangdong Cardiovascular Institute, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, Guangzhou, Guangdong, China
[4]Hunan Provincial Key Laboratory of Clinical Epidemiology, Changsha, Hunan, China

ORCID iD
Jiabi Qin http://orcid.org/0000-0002-9360-4991

REFERENCES

1 Longo DL, Magee LA, Nicolaides KH, *et al*. Preeclampsia. *N Engl J Med* 2022;386:1817–32.
2 Kassebaum NJ, Barber RM, Bhutta ZA, *et al*. Global, regional, and national levels of maternal mortality, 1990–2015: a systematic analysis for the global burden of disease study 2015. *The Lancet* 2016;388:1775–812.
3 Liu Y, Li N, Li Z, *et al*. Impact of gestational hypertension and preeclampsia on fetal gender: a large prospective cohort study in china. *Pregnancy Hypertens* 2019;18:132–6.
4 Stuart JJ, Tanz LJ, Rimm EB, *et al*. Cardiovascular risk factors mediate the long-term maternal risk associated with hypertensive disorders of pregnancy. *J Am Coll Cardiol* 2022;79:1901–13.
5 Oshunbade AA, Lirette ST, Windham BG, *et al*. Hypertensive diseases in pregnancy and kidney function later in life: the genetic epidemiology network of arteriopathy (genoa) study. *Mayo Clin Proc* 2022;97:78–87.
6 Wang H, Li N, Chivese T, *et al*. IDF diabetes atlas: estimation of global and regional gestational diabetes mellitus prevalence for 2021 by international association of diabetes in pregnancy Study Group's criteria. *Diabetes Research and Clinical Practice* 2022;183:109050.
7 Giorgione V, Ridder A, Kalafat E, *et al*. Incidence of postpartum hypertension within 2 years of a pregnancy complicated by pre-eclampsia: a systematic review and meta-analysis. *BJOG* 2021;128:495–503.
8 Leng J, Shao P, Zhang C, *et al*. Prevalence of gestational diabetes mellitus and its risk factors in Chinese pregnant women: a prospective population-based study in Tianjin, China. *PLoS ONE* 2015;10:e0121029.
9 Li G, Wei T, Ni W, *et al*. Incidence and risk factors of gestational diabetes mellitus: a prospective cohort study in Qingdao, China. *Front Endocrinol* 2020;11:636.
10 Zhang H, Wang Q, Benmarhnia T, *et al*. Assessing the effects of non-optimal temperature on risk of gestational diabetes mellitus in a cohort of pregnant women in Guangzhou, China. *Environment International* 2021;152:106457.
11 Wang C, Jin L, Tong M, *et al*. Prevalence of gestational diabetes mellitus and its determinants among pregnant women in Beijing. *J Matern Fetal Neonatal Med* 2022;35:1337–43.
12 Zhong C, Li X, Chen R, *et al*. Greater early and mid-pregnancy gestational weight gain are associated with increased risk of gestational diabetes mellitus: a prospective cohort study. *Clin Nutr ESPEN* 2017;22:48–53.
13 Matthews TJ, Hamilton BE. First births to older women continue to rise. *NCHS Data Brief* 2014;2014:1–8.
14 Lamminpää R, Vehviläinen-Julkunen K, Gissler M, *et al*. Preeclampsia complicated by advanced maternal age: a registry-

based study on primiparous women in Finland 1997-2008. *BMC Pregnancy Childbirth* 2012;12:47.

15 Li Y, Ren X, He L, *et al*. Maternal age and the risk of gestational diabetes mellitus: a systematic review and meta-analysis of over 120 million participants. *Diabetes Research and Clinical Practice* 2020;162:108044.

16 Fontana L, Eagon JC, Trujillo ME, *et al*. Visceral fat adipokine secretion is associated with systemic inflammation in obese humans. *Diabetes* 2007;56:1010–3.

17 Zhang F, Dong L, Zhang CP, *et al*. Increasing prevalence of gestational diabetes mellitus in Chinese women from 1999 to 2008. *Diabet Med* 2011;28:652–7.

18 Livingston EH. Reimagining obesity in 2018: A JAMA theme issue on obesity. *JAMA* 2018;319:238–40.

19 Neeland IJ, Poirier P, Després J-P. Cardiovascular and metabolic heterogeneity of obesity: clinical challenges and implications for management. *Circulation* 2018;137:1391–406.

20 Chen C, Xu X, Yan Y, *et al*. Estimated global overweight and obesity burden in pregnant women based on panel data model. *PLoS ONE* 2018;13:e0202183.

21 Lewandowska M, Więckowska B, Sajdak S. Pre-pregnancy obesity, excessive gestational weight gain, and the risk of pregnancy-induced hypertension and gestational diabetes mellitus. *J Clin Med* 2020;9:1980.

22 Li L, Chen Y, Lin Z, *et al*. Association of pre-pregnancy body mass index with adverse pregnancy outcome among first-time mothers. *PeerJ* 2020;8:e10123.

23 Ratnasiri AWG, Lee HC, Lakshminrusimha S, *et al*. Trends in maternal prepregnancy body mass index (BMI) and its association with birth and maternal outcomes in California, 2007-2016: a retrospective cohort study. *PLoS One* 2019;14:e0222458.

24 Vats H, Saxena R, Sachdeva MP, *et al*. Impact of maternal pre-pregnancy body mass index on maternal, fetal and neonatal adverse outcomes in the worldwide populations: a systematic review and meta-analysis. *Obes Res Clin Pract* 2021;15:536–45.

25 Mrema D, Lie RT, Østbye T, *et al*. The association between pre pregnancy body mass index and risk of preeclampsia: a Registry based study from Tanzania. *BMC Pregnancy Childbirth* 2018;18.

26 Sun Y, Shen Z, Zhan Y, *et al*. Effects of pre-pregnancy body mass index and gestational weight gain on maternal and infant complications. *BMC Pregnancy Childbirth* 2020;20:390.

27 Kim S, Hong S, Kim Y, *et al*. Maternal pre-pregnancy body mass index and the risk for gestational diabetes mellitus in women with twin pregnancy in South Korea. *Taiwanese Journal of Obstetrics and Gynecology* 2021;60:863–8.

28 National health commission of the people's republic of china: criteria of weight for adults. 2013. Available: http//www.nhc.gov.cn/ewebeditor/uploadfile/2013/08/20130808135 [Accessed 6 Jan 2022].

29 Li H, Fan C, Mubarik S, *et al*. The trend in delayed childbearing and its potential consequences on pregnancy outcomes: a single center 9-years retrospective cohort study in hubei, china. *BMC Pregnancy Childbirth* 2022;22:514.

30 Shan D, Qiu P-Y, Wu Y-X, *et al*. Pregnancy outcomes in women of advanced maternal age: a retrospective cohort study from China. *Sci Rep* 2018;8.

31 Makgoba M, Savvidou MD, Steer PJ. An analysis of the interrelationship between maternal age, body mass index and racial origin in the development of gestational diabetes mellitus. *BJOG* 2012;119:276–82.

32 Taddei S, Virdis A, Ghiadoni L, *et al*. Endothelium, aging, and hypertension. *Curr Hypertens Rep* 2006;8:84–9.

33 Care AS, Bourque SL, Morton JS, *et al*. Effect of advanced maternal age on pregnancy outcomes and vascular function in the rat. *Hypertension* 2015;65:1324–30.

34 Gilbert JS, Ryan MJ, LaMarca BB, *et al*. Pathophysiology of hypertension during preeclampsia: linking placental ischemia with endothelial dysfunction. *Am J Physiol Heart Circ Physiol* 2008;294:H541–50.

35 Fulop T, Larbi A, Douziech N. Insulin receptor and ageing. *Pathol Biol (Paris)* 2003;51:574–80.

36 Kolovou GD, Bilianou HG. Influence of aging and menopause on lipids and lipoproteins in women. *Angiology* 2008;59(2 Suppl):54S–7S.

37 Assi E, D'Addio F, Mandò C, *et al*. Placental proteome abnormalities in women with gestational diabetes and large-for-gestational-age newborns. *BMJ Open Diab Res Care* 2020;8:e001586.

38 Syslová K, Böhmová A, Mikoška M, *et al*. Multimarker screening of oxidative stress in aging. *Oxid Med Cell Longev* 2014;2014:562860.

39 Chatterjee P, Chiasson VL, Kopriva SE, *et al*. Interleukin 10 deficiency exacerbates Toll-like receptor 3–induced preeclampsia-like symptoms in mice. *Hypertension* 2011;58:489–96.

40 Lean SC, Jones RL, Roberts SA, *et al*. A prospective cohort study providing insights for markers of adverse pregnancy outcome in older mothers. *BMC Pregnancy Childbirth* 2021;21:706.

41 Wedn AM, El-Bassossy HM, Eid AH, *et al*. Modulation of preeclampsia by the cholinergic anti-inflammatory pathway: therapeutic perspectives. *Biochem Pharmacol* 2021;192:114703.

42 Wang L, Yao H, Shen W, *et al*. Gestational diabetes mellitus is associated with blood inflammatory indicators in a Chinese pregnant women population. *Gynecological Endocrinology* 2022;38:153–7.

43 Santos S, Voerman E, Amiano P, *et al*. Impact of maternal body mass index and gestational weight gain on pregnancy complications: an individual participant data meta-analysis of European, North American and Australian cohorts. *BJOG* 2019;126:984–95.

44 Najafi F, Hasani J, Izadi N, *et al*. Risk of gestational diabetes mellitus by pre-pregnancy body mass index: a systematic review and meta-analysis. *Diabetes Metab Syndr* 2021;15:102181.

45 Shao Y, Qiu J, Huang H, *et al*. Pre-pregnancy BMI, gestational weight gain and risk of preeclampsia: a birth cohort study in lanzhou, China. *BMC Pregnancy Childbirth* 2017;17:400.

46 Li M, Zhang CY, Yue CY. Effects of pre-pregnancy BMI and gestational weight gain on adverse pregnancy outcomes and complications of GDM. *Journal of Obstetrics and Gynaecology* 2022;42:630–5.

47 Masturzo B, Franzè V, Germano C, *et al*. Risk of adverse pregnancy outcomes by pre-pregnancy body mass index among Italian population: a retrospective population-based cohort study on 27,807 deliveries. *Arch Gynecol Obstet* 2019;299:983–91.

48 Naik R, Karmali D, Nagarsenkar A, *et al*. Effect of pre-pregnancy maternal body mass index on obstetric outcomes in a tertiary care hospital in goa, india. *J Obstet Gynaecol India* 2022;72:141–6.

49 Toma R, Aoki S, Fujiwara K, *et al*. Associations of pre-pregnancy obesity with adverse pregnancy outcomes and the optimal gestational weight gain in japanese women. *Clin Exp Obstet Gynecol* 2017;44:190–4.

50 Ziccardi P, Nappo F, Giugliano G, *et al*. Reduction of inflammatory cytokine concentrations and improvement of endothelial functions in obese women after weight loss over one year. *Circulation* 2002;105:804–9.

51 Walsh SW. Obesity: a risk factor for preeclampsia. *Trends Endocrinol Metab* 2007;18:365–70.

52 Plows JF, Stanley JL, Baker PN, *et al*. The pathophysiology of gestational diabetes mellitus. *Int J Mol Sci* 2018;19:3342.

53 Opichka MA, Rappelt MW, Gutterman DD, *et al*. Vascular dysfunction in preeclampsia. *Cells* 2021;10:3055.

54 Johns EC, Denison FC, Norman JE, *et al*. Gestational diabetes mellitus: mechanisms, treatment, and complications. *Trends Endocrinol Metab* 2018;29:743–54.

55 Simko M, Totka A, Vondrova D, *et al*. Maternal body mass index and gestational weight gain and their association with pregnancy complications and perinatal conditions. *Int J Environ Res Public Health* 2019;16:1751.

56 Hahn W-H, Jeong T, Park S, *et al*. Content fat and calorie of human milk is affected by interactions between maternal age and body mass index. *J Matern Fetal Neonatal Med* 2018;31:1385–8.

57 Dong B, Yu H, Wei Q, *et al*. The effect of pre-pregnancy body mass index and excessive gestational weight gain on the risk of gestational diabetes in advanced maternal age. *Oncotarget* 2017;8:58364–71. 10.18632/oncotarget.17651 Available: https://www.oncotarget.com/lookup/doi/10.18632/oncotarget.v8i35

58 Siddiqui A, Deneux-Tharaux C, Luton D, *et al*. Maternal obesity and severe pre-eclampsia among immigrant women: a mediation analysis. *Sci Rep* 2020;10.