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Gestational weight gain and adverse pregnancy outcomes: a prospective cohort study

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Abstract

Objective To assess the associations of gestational weight gain (GWG) in early, late with subsequent risks of adverse pregnancy outcomes in Chinese women.

Design Prospective cohort study.

Setting Shanghai, China.

Participants We studied 2670 nulliparous singleton pregnant women with complete data on weight gain in early (≤17 weeks of gestation) and late (>17 weeks) pregnancy in the Shanghai Birth Cohort.

Methods GWG was standardized into z-scores by gestational age and categorized as low (z score <-1), normal (-1 to 1), and high (>1). The adjusted relative risks (aRRs) and 95% confidence intervals (CIs) were estimated in log-binomial regression models. Interaction effects were tested, and stratified analyses were performed where appropriate.

Outcome measures Adverse maternal and neonatal outcomes.

Results Independent from GWG in late pregnancy, higher GWG in early pregnancy

was associated with higher risks of gestational diabetes mellitus, caesarean section, and prolonged hospitalization (all $P < 0.05$). Higher GWG in late pregnancy was independently associated with higher risks of caesarean section, large for gestational age, and macrosomia (all $P < 0.05$). In addition, the risk of gestational hypertension increased significantly with increased total GWG. The effects of GWG in late pregnancy on maternal and neonatal outcomes were significantly different between women bearing a female vs. male fetus.

Conclusion The associations with pregnancy outcomes differ for GWG in early and late pregnancy. There might be sex dimorphism in the impacts of late GWG on perinatal outcomes.

Keywords gestational weight gain, pregnancy outcomes, z-scores, fetal sex

Strengths and limitations of this study

- The SBC database contains detailed clinical data including pre-pregnancy weight, weight measurements during pregnancy and last pregnancy weight measurements. This made it possible to study GWG in both early and late pregnancy.
- Our use of GWG z-scores instead of original weight gain to account for the gestational-age-dependent nature of GWG allowed us to disentangle the effects of GWG from the effects of gestational duration (a shorter pregnancy duration should be correlated to less weight gain.
- We only investigated the short-term perinatal outcomes. Further studies on long-term outcomes would provide important evidence regarding the associations between chronic diseases and events during the intrauterine phase.

Introduction

Gestational weight gain (GWG) has been associated with pregnancy outcomes. Insufficient weight gain has been linked with increased risks of low birth weight, small for gestational age (SGA) and preterm birth, while excessive weight gain has been associated with large for gestational age (LGA), gestational diabetes mellitus (GDM), preeclampsia, preterm birth, caesarean section, infant mortality and childhood obesity[1-2]. However, although women are routinely weighed in clinical settings and receive gestational weight gain advice[3-4], a high proportion of pregnant women who gained above or below GWG weight ranges recommended by the guidelines[5]. Based on data from 23 studies involving more than 1.3 million women, GWG was below or above Institute of Medicine (IOM) guidelines[5] in 23% and 47% of pregnancies, respectively[1], and the prevalence of excess gestational weight gain appears to be on the rise [6].

It is well established that total GWG affects pregnancy outcomes[7]. Some studies suggest that GWG during early pregnancy may be more important than late GWG for certain pregnancy outcomes such as GDM and adverse cardio-metabolic profile in the

offspring[8-11]. Overall, studies examining associations of early GWG with perinatal outcomes have been relatively few in numbers, and these studies have often not accounted for the effects of weight gain in other periods of pregnancy[12].

In a prospective pregnancy cohort, we sought to explore in a homogenous Chinese population the associations of GWG during early and late pregnancy with maternal and neonatal outcomes

Materials and Methods

Study design and data source

This prospective cohort study is based on the recently developed Shanghai Birth Cohort (SBC) which has been described in detail elsewhere[13]. Briefly, the SBC cohort recruited 4127 women in pre-conception care (701) or early antenatal care (3426) in Shanghai upon signing an informed consent form commencing on September 1st, 2013, resulting in 3699 live births. The collected data included maternal demographical characteristics, health behaviors, reproductive history, as well as clinical information related to pregnancy, birth and pregnancy outcomes. This study was approved by Xinhua Hospital Research Ethics Committee, Shanghai Jiao Tong University School of

Medicine (reference number: XHEC-F-NSFC-2018-122).

Study population

The present study included all singleton pregnancies in women with age ≥20 years who started antenatal care before 17 weeks' gestation and delivered at ≥28 weeks of gestation with data available on weight gains in early and late gestation in the SBC cohort.

Gestational age was estimated based on the date of last menstruation period and confirmed by first trimester ultrasound dating. Eligibel women must have data available on self-reported pre-pregnancy weight (kg), measured weight and height (cm) in early pregnancy (17 weeks of gestation or less), and measured weight in the last week before delivery. Subjects with implausible weights at early pregnancy (<30 kg or >350 kg) or implausible gestational weight-gain measurements (z-score <-4.0 or >4.0) were excluded, similar to the method of Johansson et al[14]. Women with major pre-pregnancy illnesses such as pre-gestational diabetes, hypo- or hyper-thyroidism (affecting GWG)[15] and heart/liver/kidney diseases were also excluded. A total of 2670 pregnancies constituted the final study sample. Figure 1 illustrates the flowchart in the

selection of study subjects.

Weight measurements

Pre-pregnancy weight (kg) was based on self-reports, while weight at early pregnancy and at delivery was measured to the nearest 0.1 kg using the routinely available electronic weighing device in the prenatal care clinics. Height (cm) at the first prenatal visit was measured to the nearest 0.1 cm using the routinely available electronic stadiometer in the hospital. Pre-pregnancy body mass index (BMI; kg/m^2) was calculated as pre-pregnancy weight (kg) divided by height $(m)^2$ and categorized as underweight (<18.5 kg/m^2), normal weight (18.5-24.9 kg/m^2), overweight (25.0-29.9 kg/m^2), and obese (≥ 30.0 kg/m^2)[16].

Early pregnancy in this study was defined as gestational age ≤17 weeks so as to include virtually all women who started the first antenatal care in the hospital [17]. The 2009 Institute of Medicine (IOM) recommendations suggested that women should gain 0.5-2 kg in early pregnancy[5] and the 50th centile GWG for women at gestational age ≤17 weeks was below 2 kg according to the INTERGROWTH-21st Project[2]. We examined gestational weight gain (GWG) in early pregnancy (weight ≤17 weeks minus pre-

pregnancy weight) and late pregnancy (last measured weight before delivery minus measured weight at ≤17 weeks). Total GWG was calculated as last measured weight before delivery minus pre-pregnancy weight. All GWG values were standardized into z-scores, using BMI category-specific values from the study cohort. The means and standard deviations (SD) of GWGs in early pregnancy and late pregnancy were used to convert the GWG values into z-scores. All GWG z-scores were first examined as continuous variables, and then categorized as <-1.0 (low), -1.0 to +1.0 (normal) and > +1.0 (high) in data analyses. The analyses for GWG in early pregnancy were restricted to women whose GWGs in late pregnancy were normal (-1.0 to +1.0). Similarly, the analyses for late pregnancy weight gain were restricted to women with weight gain value in early pregnancy within -1.0 to +1.0.

Covariates

Co-variables included fetal sex, maternal age (20 to 34, ≥35 years), parity (0, ≥1), pre-pregnancy body mass index (BMI) categories (underweight, normal, overweight/obese), alcohol/tobacco use (yes or no), GDM (yes or no), gestational hypertension (yes or no) and length of gestation (28 to 36, ≥37 weeks)

Outcomes

The outcomes included gestational diabetes mellitus (GDM), gestational hypertension, caesarean section, preterm birth, neonatal intensive care unit (NICU) admission, neonatal prolonged hospitalization (≥5 days), severe neonatal outcomes, neonatal hyperbilirubinemia (12 mg/dL), LGA, SGA, macrosomia (>4000 g) and low birthweight (<2500 g).

All women received a 75 g oral glucose tolerance test (OGTT) during 24-28 weeks of gestation. GDM was diagnosed according to the IADPSG criteria: if anyone of the glucose values fell at or above the following thresholds: fasting 5.1 mmol/L, 1 hour 10.0 mmol/L, 2 hour 8.5 mmol/L. Gestational hypertension was defined as de no hypertension (systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg) after 20 weeks' gestation. Preterm birth was defined as gestational age at delivery <37 weeks. SGA was defined as birth weight ≤10th percentile, and LGA as birth weight ≥90th percentile according to Chinese sex- and gestational age-specific birth weight standards[18]. Severe neonatal outcomes included death, 5 minute APGAR score <7, hypoglycemia (<40 mg/dL), sepsis, cardiopulmonary resuscitation or

ventilator support within 24 hours after birth, severe respiratory disorders (respiratory distress syndrome or transient tachypnea of the newborn), serious birth defects, seizures, necrotizing enterocolitis, and hypoxic-ischemic encephalopathy.

Statistical analyses

Maternal demographic characteristics and clinical factors were compared among gestational weight gain below. Continuous variables were described by mean ± standard deviation (SD) or median (interquartile range, IQR). Categorical variables were described by counts and percentages (%). Analysis of variance or Kruskal-Wallis H tests were performed for continuous data, and chi-square tests or Fisher's exact tests were performed for categorical data.

The incidences of adverse pregnancy outcomes were examined among three GWG groups. Multivariate log-binomial regression models were used to estimate the unadjusted relative risks (RRs), adjusted relative risks (ARRs) and 95% confidence intervals (CIs) of adverse pregnancy outcomes across GWG groups. Regression model for maternal outcomes were adjusted for only co-variables with $p < 0.2$ (maternal age, parity, pre-pregnancy BMI, alcohol/tobacco use, fetal sex and length of gestation).

Neonatal outcomes models were further adjusted for GDM and PIH in addition to the aforementioned factors. Effects between weight gain and fetal sex and other covariates on adverse neonatal outcomes were also tested. Interaction effects between GWG and fetal sex and other covariates (parity, maternal pre-pregnancy BMI, maternal age) on adverse maternal and neonatal outcomes were also tested.

All analyses were performed using the Statistical Analysis System (SAS) for Windows, version 9.4 (SAS Institute, Cary, NC). $P<0.05$ was considered statistically significant.

Patient and public involvement

No patients were involved in the design, or conduct, or reporting, or dissemination plans of our research.

Results

Study population and characteristics

A total of 2670 pregnant women met the study inclusion criteria. Of these, 1605 women gained average weight in late pregnancy (z-score -1 to +1), weight gain above (< -1.0) or below (> +1.0) average in early pregnancy accounted for 11.6% respectively; 1717 women with average weight gain in early pregnancy, 14.4% and 13.7% gained above

and below average in late, respectively (Figure 1).

Table 1 shows the characteristics of all pregnant women in the study. The characteristics of the study population stratified by maternal weight gain in early as well as late pregnancy are presented in Table S1-2.

Weight gain during early pregnancy

The risks of maternal and neonatal outcomes for GWG in early pregnancy are presented in Figure 2A and Table S3. Lower GWG was not significantly associated with pregnancy outcomes, compared with the average GWG. In contrast, the risks of GDM (aRR=1.66; 95% CI: 1.11-2.48), caesarean section (aRR=1.21; 95% CI: 1.05-1.39) and prolonged hospitalization (aRR=1.56; 95% CI: 1.03-2.38) were higher in the group with GWG above average in early pregnancy. No significant interactions between GWG in early pregnancy and covariates were observed.

Weight gain during late pregnancy

Associations of GWG in late pregnancy with perinatal outcomes are presented in Figure 2B and Table S4. In contrast to early pregnancy, the odds for GDM and SGA decreased significantly with increased GWG in late pregnancy, whereas the risks for LGA and

macrosomia increased. Weight gain above average was correlated with a higher risk for caesarean section (aRR=1.24; 95% CI: 1.09-1.41) in late pregnancy. In addition, higher GWG showed a protective effect against neonatal hyperbilirubinemia (aRR=0.64; 95% CI: 0.43-0.94).

Significant interactions were identified between GWG in late pregnancy and fetal sex. Figure 3 and Table S5 shows the associations of late pregnancy weight gain with pregnancy outcomes stratified by fetal sex. The risks for LGA and caesarean section significantly increased in women with higher GWG in late pregnancy, but the odds of GDM increased with less GWG, regardless of fetal sex. However, higher risks of gestational hypertension (aRR=2.31; 95% CI: 1.08-4.95) was only observed in women bearing a female fetus with higher GWG. Conversely, higher GWG in late pregnancy was associated with GDM (aRR=0.30; 95% CI: 0.10-0.96), neonatal hyperbilirubinemia (aRR=0.46; 95% CI: 0.24-0.89) and macrosomia (aRR=2.05; 95% CI: 1.27-3.31) for women having a boy, but not for women having a girl, indicating effect modifications by fetal sex. But when stratified by fetal sex, the lower risk of SGA with higher GWG was no longer observed.

Total weight gain during pregnancy

Figure 2C and Table S6 show results for pregnancy outcomes by total GWG. The effect sizes of GWG in late pregnancy on pregnancy outcomes were almost identical with the effect sizes of total GWG. Similar to late pregnancy, the risks for LGA, macrosomia and gestational hypertension increased significantly with increased total GWG. Higher GWG was also linked with a higher risk for caesarean section (aRR=1.78; 95% CI: 1.14-2.76). Moreover, total GWG below the average was associated with higher risks of GDM (aRR=1.51; 95% CI: 1.15-1.98) and SGA (aRR=1.53; 95% CI: 1.01-2.32). No significant interactions between total GWG and other covariates were observed.

Discussion

Main Findings

In this study, we found that the associations of gestational stage-specific weight gain with maternal and neonatal outcomes were different. Of those, independent of GWG in late pregnancy, higher GWG in early was associated with higher risks of GDM, caesarean section, and neonatal prolonged hospitalization (P <0.05).

Strengths and limitations

There are strengths in our study compared with other studies in the literature. First, the SBC database contains detailed clinical data including pre-pregnancy weight, weight measurements during pregnancy and last pregnancy weight measurements. This made it possible to study GWG in both early and late pregnancy. In addition, our use of GWG z-scores instead of original weight gain to account for the gestational-age-dependent nature of GWG allowed us to disentangle the effects of GWG from the effects of gestational duration (a shorter pregnancy duration should be correlated to less weight gain)[14, 36].

There are limitations in this study. We only investigated the short-term perinatal outcomes. Recently, researchers have linked an individual's susceptibility to chronic disease such as cardio-metabolic disease and obesity in later life to events during the intrauterine phase of development[8, 20, 37]. Further studies on long-term outcomes would provide important evidence regarding the associations between chronic diseases and events during the intrauterine phase.

Interpretation

Associations between insufficient or excessive weight gain during the whole pregnancy

and maternal and child health outcomes have been well described[1-2, 7]. A meta-analysis of pooled 1309136 participant data from 23 cohort studies showed that women who gained high weight were more likely to have LAG, caesarean section and macrosomia, while women who gained less were at an increased risk of SGA[1]. These findings are in line with the association of maternal weight gain with adverse pregnancy outcomes in our study.

There is growing recognition that the impacts of gestational stage-specific weight gain on pregnancy outcomes may vary[8-9, 19-21]. GWG in early pregnancy largely reflects maternal fat deposition, whereas GWG thereafter is mainly attributed to maternal and amniotic fluid expansion, and growth of the fetus, placenta and uterus[5]. In this context, mothers with increased fat deposition during pregnancy may affect the adiposity of the offspring by higher placental transfer of nutrients, such as glucose and free fatty acids, which may lead to maternal pregnancy complications, such as GDM, and permanent fetal and childhood adaptations in appetite, energy metabolism and neuro-endocrine function [21-22]. Therefore, GWG in early pregnancy, prior to the development of pregnancy outcomes, might be as or more important than GWG in late pregnancy with

respect to pregnancy outcomes[9, 14]. A study of 5908 Netherlands mother-offspring pairs reported that higher weight gain in early pregnancy was associated with an adverse cardio-metabolic profile in the offspring [odds ratio (OR)=1.19; 95% CI: 1.10-1.29][8]. Similarly, a study of 5154 UK mother-offspring pairs showed that GWG in the first 14 weeks tended to be incrementally associated with offspring BMI, waist circumference and fat mass in children at age 9 years, but after 14 weeks of gestation, only high levels of GWG were associated with offspring's adiposity measures, highlighting the importance of the timing of weight gain in pregnancy[19].

Studies to clarify the relationship between gestational stage-specific weight gain and adverse pregnancy outcomes have been sporadic. A study of Korean pregnant women found that GWG velocity at early pregnancy was significantly associated with GDM (OR=1.77), gestational hypertension (OR=2.80), cesarean section (OR = 1.65), LGA (OR = 1.77) and macrosomia (OR = 1.93)[12]. However, the analyses have not accounted for the effects of weight gain in other periods of pregnancy. In contrast, our analyses for early/late pregnancy GWG were restricted to women whose GWG z-scores in other pregnancy stage were normal (-1.0 to +1.0), and thus the observed associations

are independent of GWG in different periods. Our data from a large population-based Chinese cohort in Shanghai showed that higher, but not lower, maternal GWG in early pregnancy was associated with increased risks of adverse pregnancy outcomes, including GDM, caesarean section and prolonged hospitalization. In late pregnancy, low weight gain was associated with GDM as well as SGA, and high weight gain was associated with caesarean section, LGA and macrosomia

High GWG in early pregnancy has been associated with an increased risk of GDM, while there are some inconsistent data concerning the associations of GWG in second and third trimester or the whole pregnancy with GDM[11, 23-25]. Our study presented some consistent results with other studies [12, 23, 26] indicating that higher GWG in early pregnancy may increase the risk of developing GDM (aRR=1.66), but higher GWG in late pregnancy showed a reversed association. The discrepancy might be due to that women diagnosed with GDM might have undergone weight control interventions such as prescribled diet and physical exercise after the GDM diagnosis. Avoiding high weight gain in early pregnancy may prevent GDM, and doctors might consider preemptive actions in high-risk pregnant women.

The risk of gestational hypertension increased significantly with higher maternal total GWG. A study of 29861 women from 25 hospitals in America showed that early weight gain over the 2009 IOM recommendation were shown to be associated with the development of gestational hypertension (adjusted OR==1.84; 95% CI: 1.66–2.04)[27]. In a study of 101259 women with chronic hypertension, women who gained weight above IOM guidelines were at increased odds of eclampsia [28]. Given the known vascular permeability and decreased plasma oncotic pressure that accompanies preeclampsia and its association with rapid weight gain[29], excessive GWG may be a cause of hypertensive disease of pregnancy.

Our data suggest effect modification by fetal sex in the association of GWG in late pregnancy with birth outcomes. Recent studies suggest that fetus sex may affect pregnancy outcomes[30-31]. Although not very clear, how fetal sex may influence these outcomes may be explained by several factors. The placenta is an active endocrine organ, a sex-specific maternal-placental-fetal interaction may be involved [19]. Animal studies suggest that maternal baseline BMI and GWG are associated with the hormonal milieu, including insulin resistance[32]. In agreement with this concept, a growing body

of evidence linking early pregnancy GWG with cord blood hormones that may affect fetal growth and development[33]. Previous studies reported fetal sex differences in maternal first trimester hormones concentrations [15, 30, 34]. The resultant intrauterine environment may affect fetal development.

Our findings may have clinical implications. First, from early pregnancy onwards, GWG may affect subsequent maternal and neonatal outcomes. Second, although interventions to limit GWG in late pregnancy are effective, the benefits might be modest at best. To mitigate the harms of excessive weight gain, attention to appropriate weight gain in both early and late pregnancy should be integrated into routine prenatal care[1, 7, 35].

Conclusion

The associations with adverse pregnancy outcomes differ for GWG in early and late pregnancy, and there may be effect modification by fetal sex in the association of GWG in late pregnancy with some pregnancy outcomes. Weight gain management should be integrated into the routine prenatal care to decrease the risks of adverse pregnancy outcomes.

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Contributors YW and SW participated in interpretation of data and involved in drafting the manuscript. SG, ZM and LD analyzed the data and critically revised the manuscript. ZL, JZ and XH made substantial contributions to conception and design, interpreted the data, and critically revised the manuscript. All authors read and approved the final manuscript.

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Competing interests None declared. Completed disclosure of interests form available to view online as supporting information.

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Table 1. Characteristics of pregnant women in the study cohort (n=2670).

Characteristic	Total Gestational Weight Gain			P	Total
	Below (n=392)	Within (n=1842)	Above (n=396)		
Maternal age (year)	29.9 ± 3.8	29.4 ± 3.5	28.5 ± 3.6	<0.0001	29.4 ± 3.6
≥35 years	51 (13)	169 (9.2)	21 (5.3)	0.0002	241 (9.2)
Nulliparous	325 (82.9)	1532 (83.2)	359 (90.7)	0.0027	2216 (84.3)
Education, university degree and above	362 (92.6)	1702 (92.5)	340 (85.7)	0.0007	2404 (91.5)
ART	9 (2.3)	37 (2)	9 (2.3)	0.9834	55 (2.1)
Tobacco smoking	7 (1.8)	41 (2.2)	24 (6.1)	<0.0001	72 (2.7)
Alcohol use	52 (13.3)	240 (13)	46 (11.6)	0.7221	338 (12.9)
Pre-pregnancy BMI (kg/m^2)	21.7 ± 3.1	21.2 ± 3.0	21.5 ± 2.9	0.0139	21.3 ± 3.0
Underweight (< 18.5)	54 (13.8)	292 (15.9)	50 (12.6)		396 (15.1)
Normal weight (18.5-24.9)	298 (76)	1372 (74.5)	310 (78.3)	0.7530	1980 (75.3)
Overweight and obese (≥ 25)	40 (10.2)	178 (9.7)	36 (9.1)		254 (9.7)
Gestational age at the first prenatal visit (week) (Median, IQR)	14 (13, 16)	15 (13, 16)	15 (13, 16)	0.1986	15 (13, 16)
GWG during early pregnancy (≤17 week) (kg)					
All women	-0.2 ± 2.8	2.1 ± 2.2	4.9 ± 3.2	<0.0001	2.2 ± 2.9
Underweight (< 18.5)	0.9 ± 1.9	2.4 ± 2.0	4.8 ± 3.0	<0.0001	2.5 ± 2.4
Normal weight (18.5-24.9)	0.0 ± 2.8	2.2 ± 2.2	4.9 ± 3.1	<0.0001	2.3±2.8

Overweight and obese (≥ 25)	-2.2 ± 3.3	1.5 ± 2.6	4.7 ± 4.4	<0.0001	1.4±3.6
GWG during late pregnancy (>17 week) (kg)					
All women	8.2 ± 3.0	12.6 ± 2.9	17.8 ± 3.6	<0.0001	13.0 ± 3.5
Underweight (< 18.5)	8.9 ± 1.9	12.8 ± 2.5	18.2 ± 3.8	<0.0001	13.0 ± 3.5
Normal weight (18.5-24.9)	8.4 ± 3.0	12.8 ± 2.8	17.8 ± 3.6	<0.0001	12.9 ± 4.0
Overweight and obese (≥ 25)	5.8 ± 3.3	10.8 ± 3.8	17.4 ± 3.8	<0.0001	11.0 ± 4.9
Gestational age at delivery (week) (Median, IQR)	39 (38, 40)	39 (38, 40)	39 (38, 40)	0.0793	39 (38, 40)
Birth weight (gm)	3238 ± 422	3370 ± 438	3540 ± 480	<0.0001	3376 ± 450
Infant gender (male)	194 (50.4)	945 (52)	195 (49.5)	0.7951	1334 (51.4)

Data are mean ± SD or n (%) unless otherwise specified.

SD: standard deviation; BMI: body mass index; ART: assisted reproductive technology; GWG: gestational weight gain

Figure Legend

Figure 1. Study flow chart.

Figure 2. Associations of gestational weight gain with pregnancy outcomes.

(A) Associations of early gestational weight gain (≤17 week) with pregnancy outcomes. (B) Associations of late gestational weight gain (>17 week) with pregnancy outcomes. (C) Associations of total gestational weight gain with pregnancy outcomes.

NICU: neonatal intensive care unit; LGA: large for gestational age; SGA: small for gestational age; GDM: gestational diabetes mellitus; PIH: pregnancy-induced hypertension; GWG: gestational weight gain; ARR: adjusted relative risk. *<0.05

Average GWG group as the reference.

a1 The analysis was adjusted for maternal age, parity, pre-pregnancy BMI and length of gestation.

b1 The analysis was adjusted for parity, pre-pregnancy BMI, fetal sex, GDM and PIH.

c1 The analysis was adjusted for pre-pregnancy BMI, fetal sex, alcohol/tobacco use, length of gestation, GDM and PIH.

d1 The analysis was adjusted for maternal age, alcohol/tobacco use, GDM and PIH.

a2 The analysis was adjusted for maternal age and pre-pregnancy BMI.;

b2 The analysis was adjusted for parity, pre-pregnancy BMI, fetal sex and length of gestation.

c2 The analysis was adjusted for maternal age, parity, pre-pregnancy BM, GDM and PIH.

d2 The analysis was adjusted for parity, pre-pregnancy BMI, fetal sex, GDM and PIH.

e2 The analysis was adjusted for parity, pre-pregnancy BMI, alcohol/tobacco use, length of gestation, GDM and PIH.

f2 The analysis was adjusted for maternal age, alcohol/tobacco use and length of gestation.

a3 The analysis was adjusted for maternal age, parity, pre-pregnancy BMI, alcohol/tobacco use and fetal sex.

b3 The analysis was adjusted for parity, pre-pregnancy BMI and length of gestation.

c3 The analysis was adjusted for parity, pre-pregnancy BMI, length of gestation, GDM and PIH.

d3 The analysis was adjusted for maternal age, parity and length of gestation.

e3 The analysis was adjusted for pre-pregnancy BMI, fetal sex, length of gestation, GDM and PIH.

Figure 3. Associations of late gestational weight gain (>17 week) with pregnancy outcomes, stratified by fetal sex.

NICU: neonatal intensive care unit; LGA: large for gestational age; SGA: small for gestational age; GDM: gestational diabetes mellitus; PIH: pregnancy-induced hypertension; GWG: gestational weight gain; ARR: adjusted relative risk.

*<0.05

Average GWG group as the reference.

[a] The analysis was adjusted for maternal age and pre-pregnancy BMI.

[b] The analysis was adjusted for maternal age, parity, pre-pregnancy BMI, alcohol/tobacco use and length of gestation.

[c] The analysis was adjusted for maternal age, pre-pregnancy BMI, GDM and PIH.

[d] The analysis was adjusted for parity, pre-pregnancy BMI, alcohol/tobacco use and length of gestation.

[e] The analysis was adjusted for parity, alcohol/tobacco use, length of gestation, GDM and PIH.

[f] The analysis was adjusted for parity, pre-pregnancy BMI, length of gestation, GDM and PIH.

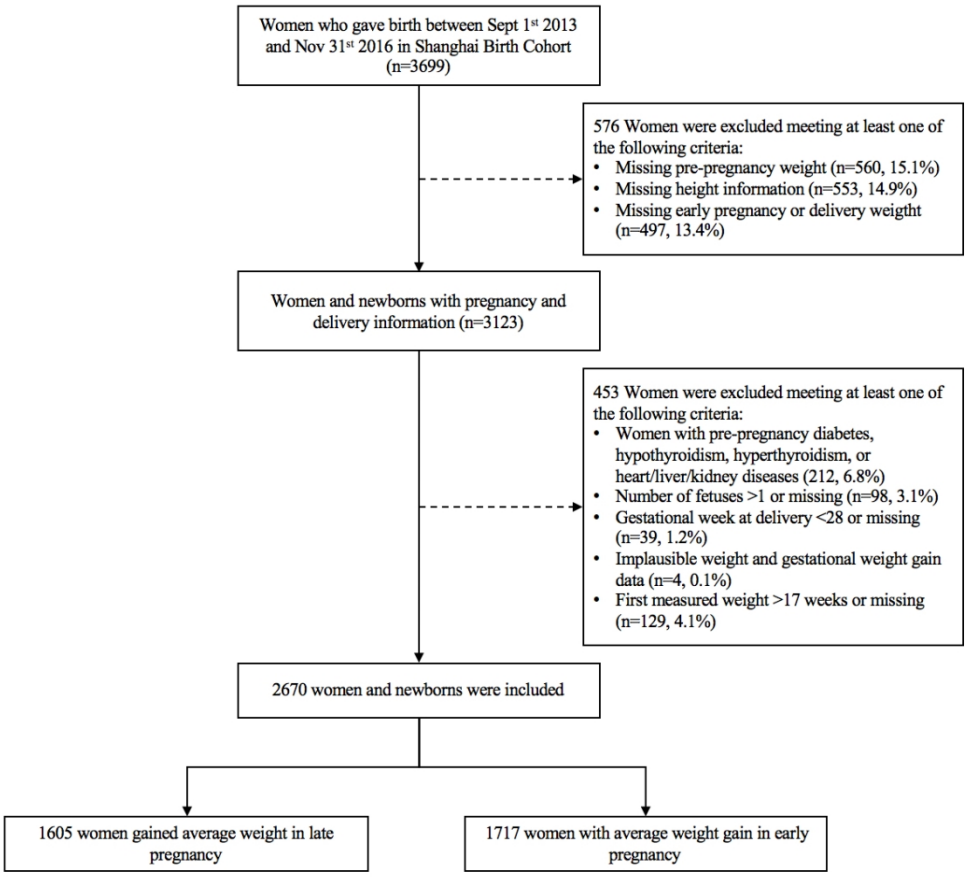

Figure 1. Study flow chart.

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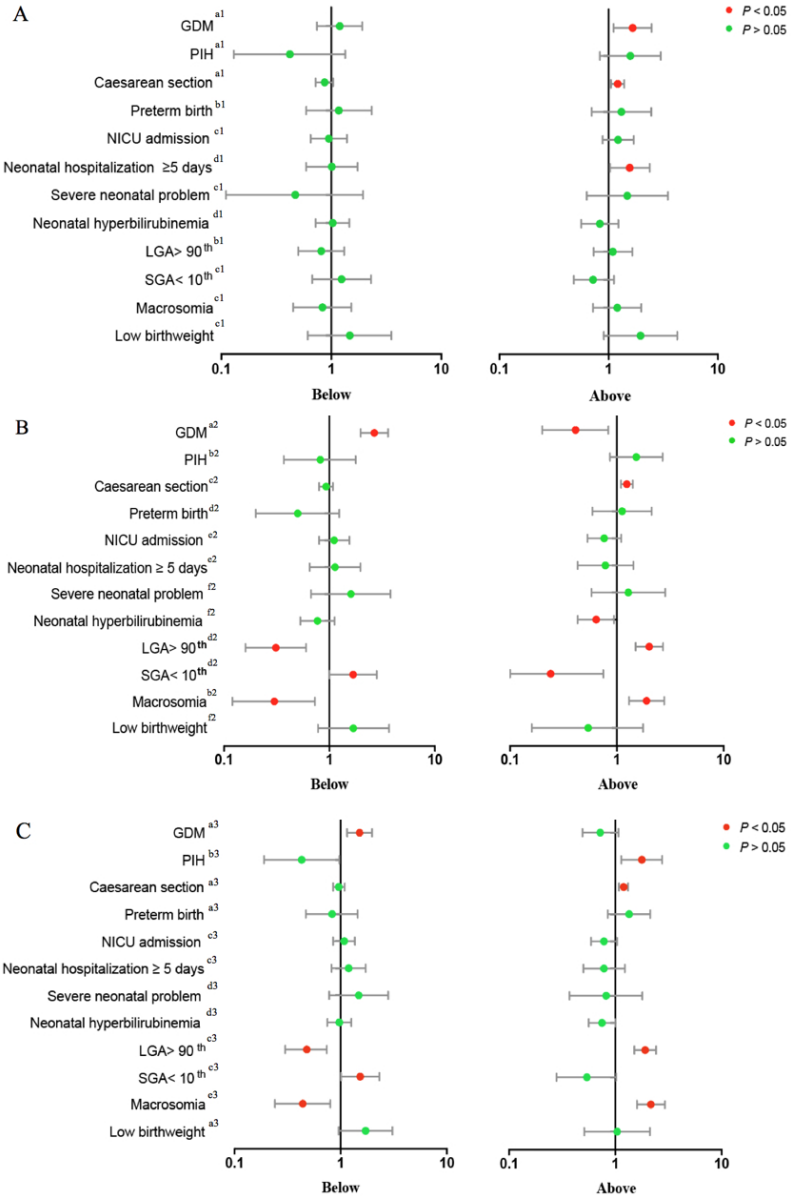

Figure 2. Associations of gestational weight gain with pregnancy outcomes.
(A) Associations of early gestational weight gain (≤17 week) with pregnancy outcomes. (B) Associations of late gestational weight gain (>17 week) with pregnancy outcomes. (C) Associations of total gestational weight gain with pregnancy outcomes.
NICU: neonatal intensive care unit; LGA: large for gestational age; SGA: small for gestational age; GDM: gestational diabetes mellitus; PIH: pregnancy-induced hypertension; GWG: gestational weight gain; ARR: adjusted relative risk. *<0.05

Average GWG group as the reference.
a1 The analysis was adjusted for maternal age, parity, pre-pregnancy BMI and length of gestation.
b1 The analysis was adjusted for parity, pre-pregnancy BMI, fetal sex, GDM and PIH.
c1 The analysis was adjusted for pre-pregnancy BMI, fetal sex, alcohol/tobacco use, length of gestation, GDM and PIH.
d1 The analysis was adjusted for maternal age, alcohol/tobacco use, GDM and PIH.

a2 The analysis was adjusted for maternal age and pre-pregnancy BMI.;
b2 The analysis was adjusted for parity, pre-pregnancy BMI, fetal sex and length of gestation.
c2 The analysis was adjusted for maternal age, parity, pre-pregnancy BM, GDM and PIH.
d2 The analysis was adjusted for parity, pre-pregnancy BMI, fetal sex, GDM and PIH.
e2 The analysis was adjusted for parity, pre-pregnancy BMI, alcohol/tobacco use, length of gestation, GDM and PIH.
f2 The analysis was adjusted for maternal age, alcohol/tobacco use and length of gestation.
a3 The analysis was adjusted for maternal age, parity, pre-pregnancy BMI, alcohol/tobacco use and fetal sex.
b3 The analysis was adjusted for parity, pre-pregnancy BMI and length of gestation.
c3 The analysis was adjusted for parity, pre-pregnancy BMI, length of gestation, GDM and PIH.
d3 The analysis was adjusted for maternal age, parity and length of gestation.
e3 The analysis was adjusted for pre-pregnancy BMI, fetal sex, length of gestation, GDM and PIH.

147x222mm (144 x 144 DPI)

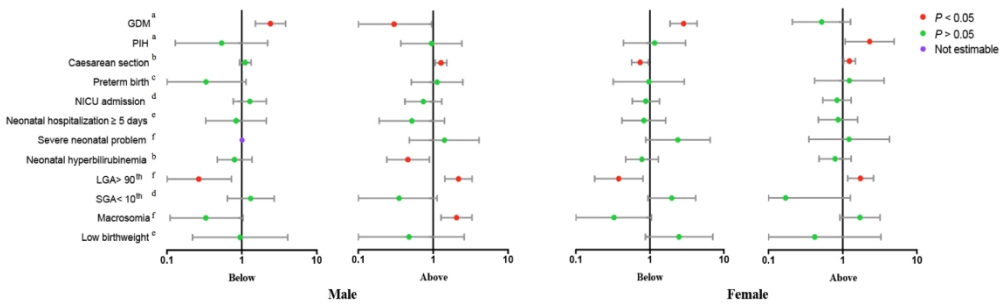

Figure 3. Associations of late gestational weight gain (>17 week) with pregnancy outcomes, stratified by fetal sex.

NICU: neonatal intensive care unit; LGA: large for gestational age; SGA: small for gestational age; GDM: gestational diabetes mellitus; PIH: pregnancy-induced hypertension; GWG: gestational weight gain; ARR: adjusted relative risk.

*<0.05

Average GWG group as the reference.

a The analysis was adjusted for maternal age and pre-pregnancy BMI.

b The analysis was adjusted for maternal age, parity, pre-pregnancy BMI, alcohol/tobacco use and length of gestation.

c The analysis was adjusted for maternal age, pre-pregnancy BMI, GDM and PIH.

d The analysis was adjusted for parity, pre-pregnancy BMI, alcohol/tobacco use and length of gestation.

e The analysis was adjusted for parity, alcohol/tobacco use, length of gestation, GDM and PIH.

f The analysis was adjusted for parity, pre-pregnancy BMI, length of gestation, GDM and PIH.

324x99mm (144 x 144 DPI)

Table S1. Maternal Characteristics in the study of GWG at early pregnancy (n=1605).

Characteristic	Gestational Weight Gain During Early Pregnancy (≤17 week)			
	Below n=186	Average n=1233	Above n=186	*P*
Maternal age (year)	28.2 ± 3.4	29.4 ± 3.7	29.4 ± 3.5	0.0002
≥35 years	11 (5.9)	126 (10.2)	14 (7.5)	0.5946
Nulliparous	165 (88.7)	1011 (82)	155 (83.3)	0.1683
Education, university degree and above	164 (88.1)	1138 (92.4)	162 (87.6)	0.8411
ART	4 (2.2)	27 (2.2)	5 (2.7)	0.9110
Tobacco smoking	4 (2.2)	26 (2.1)	9 (4.8)	0.0924
Alcohol use	15 (8.1)	129 (10.5)	18 (9.37)	0.5876
Pre-pregnancy BMI (kg/m^2)	21.8±3.1	21.2 ± 3.0	21.7 ± 3.1	0.0027
Underweight (< 18.5)	28 (15.1)	193 (15.7)	28 (15.1)	
Normal weight (18.5-24.9)	134 (72)	929 (75.3)	133 (71.5)	0.9848
Overweight and obese (≥ 25)	24 (12.9)	111 (9)	25 (13.4)	
Gestational age at the first prenatal visit (week) (Median, IQR)	14 (13, 16)	14 (13, 16)	15 (13, 16)	0.8298
GWG during early pregnancy (kg)				
All women	-2.5±2.0	2.1 ± 1.5	6.7 ± 2.1	<0.0001
Underweight (< 18.5)	-0.6±1.1	2.1 ± 1.2	6.4 ± 2.1	<0.0001

Normal weight (18.5-24.9)	-2.5±1.7	2.1 ± 1.5	7.0 ± 2.1	<0.0001
Overweight and obese (≥ 25)	-4.7±1.7	1.5 ± 1.8	5.7 ± 1.7	<0.0001
GWG during the late pregnancy (kg)				
All women	12.5 ± 2.3	12.6 ± 2.3	12.3 ± 2.4	0.4854
Underweight (< 18.5)	12.4 ± 1.9	12.7 ± 1.9	12.5 ± 1.8	0.6323
Normal weight (18.5-24.9)	12.8 ± 2.2	12.7 ± 2.2	12.6 ± 2.1	0.8492
Overweight and obese (≥ 25)	10.7 ± 2.2	11.1 ± 3.1	10.4 ± 3.3	0.5676
Gestational age at delivery (week) (Median, IQR)	39 (38, 40)	39 (38, 40)	39 (38, 40)	0.9126
Birth weight (g)	3296 ± 435	3370 ± 446	3382 ± 515	0.0428
Infant sex (male)	92 (50.3)	646 (53.2)	102 (55.4)	0.6091

Data are mean ± SD or n (%) unless otherwise specified.

SD: standard deviation; BMI: body mass index; ART: assisted reproductive technology; GWG: gestational weight gain

Table S2. Maternal Characteristics in the study of GWG at late pregnancy (n=1717).

Characteristic	Gestational Weight Gain During Late Pregnancy (>17 week)			
	Below n=236	Average n=1233	Above n=248	*P*
Maternal age (year)	30.4 ± 3.8	29.4 ± 3.7	27.9 ± 3.5	<0.0001
≥35 years	37 (15.7)	126 (10.2)	10 (4)	<0.0001
Nulliparous	183 (77.5)	1011 (82)	234 (94.4)	<0.0001
Education, university degree and above	222 (94.1)	1138 (92.4)	214 (86.3)	0.0017
ART	7 (3)	27 (2.2)	6 (2.4)	0.7701
Tobacco smoking	4 (1.7)	26 (2.1)	12 (4.8)	0.0234
Alcohol use	20 (8.5)	129 (10.5)	20 (8.1)	0.3841
Pre-pregnancy BMI (kg/m^2) (Median, IQR)	21.6±3.1	21.2±3.0	21.4±3.1	0.0564
Underweight (< 18.5)	29 (12.3)	193 (15.7)	37 (14.9)	
Normal weight (18.5-24.9)	178 (75.4)	929 (75.3)	189 (76.2)	0.3711
Overweight and obese (≥ 25)	29 (12.3)	111 (9)	22 (8.9)	
Gestational age at the first prenatal visit (week)	14 (13, 16)	14 (13, 16)	14 (13, 16)	0.4231
GWG during early pregnancy (kg)				
All women	2.1±1.5	2.1 ± 1.5	2.3 ± 1.4	0.1943
Underweight (< 18.5)	2.7±1.4	2.1 ± 1.2	2.8 ± 1.3	0.0009
Normal weight (18.5-24.9)	2.1±1.5	2.1 ± 1.5	2.2 ± 1.5	0.7273

Overweight and obese (≥ 25)	1.5±1.6	1.5 ± 1.8	2.1 ± 1.2	0.2109
GWG during the late pregnancy (kg)				
All women	7.0 ± 2.1	12.6 ± 2.3	19.1 ± 2.4	<0.0001
Underweight (< 18.5)	7.9 ± 1.2	12.7 ± 1.9	19.2 ± 2.6	<0.0001
Normal weight (18.5-24.9)	7.3 ± 1.9	12.7 ± 2.2	19.1 ± 2.2	<0.0001
Overweight and obese (≥ 25)	4.1 ± 1.9	11.1 ± 3.1	18.3 ± 3.2	<0.0001
Gestational age at delivery (week) (Median, IQR)	39 (38, 40)	39 (38, 40)	39 (38, 40)	0.0872
Birth weight (g)	3261 ± 397	3370 ± 446	3536 ± 461	<0.0001
Infant sex (male)	110 (47.8)	646 (53.2)	120 (49)	0.8381

Data are mean ± SD or n (%) unless otherwise specified.

SD: standard deviation. BMI: body mass index; ART: assisted reproductive technology; GWG: gestational weight gain.

Table S3. Pregnancy outcomes by gestational weight gain during early pregnancy

Outcome	Gestational Weight Gain During Early Pregnancy (≤17 week)				
	Below		Average	Above	
	n (%)	Unadjusted RR (95% CI)	n (%)	n (%)	Unadjusted RR (95% CI)
GDM	18 (9.7)	1.23 (0.76, 1.99)	97 (7.9)	25 (13.4)	1.71 (1.13, 2.58) *
PIH	3 (1.6)	0.45 (0.14, 1.44)	44 (3.6)	11 (5.9)	1.66 (0.87, 3.15)
Caesarean section	71 (41)	0.87 (0.72, 1.05)	548 (47.3)	101 (56.7)	1.20 (1.04, 1.38)*
Preterm birth	9 (4.8)	1.10 (0.55, 2.20)	54 (4.4)	11 (5.9)	1.35 (0.72, 2.53)
NICU admission	24 (12.9)	0.95 (0.64, 1.41)	168 (13.6)	31 (16.7)	1.22 (0.86, 1.74)
Neonatal hospitalization ≥5 days	12 (6.5)	1.12 (0.62, 2.03)	71 (5.8)	17 (9.1)	1.59 (0.96, 2.63)
Severe neonatal problem	2 (1.1)	0.51 (0.12, 2.13)	26 (2.1)	6 (3.2)	1.53 (0.64, 3.67)
Neonatal hyperbilirubinemia	30 (16.1)	1.04 (0.73, 1.48)	191 (15.5)	24 (12.9)	0.83 (0.56, 1.24)
LGA> 90th	17 (9.3)	0.85 (0.53, 1.38)	132 (10.9)	23 (12.5)	1.15 (0.76, 1.74)
SGA< 10th	11 (6)	1.21 (0.65, 2.26)	60 (5)	8 (4.3)	0.62 (0.36, 1.09)
Macrosomia	11 (5.9)	0.86 (0.47, 1.59)	84 (6.9)	16 (8.6)	1.26 (0.75, 2.10)
Low birthweight	6 (3.2)	1.52 (0.64, 3.65)	26 (2.1)	8 (4.3)	2.03 (0.93, 4.42)

NICU: neonatal intensive care unit; LGA: large for gestational age; SGA: small for gestational age; GDM: gestational diabetes mellitus; PIH: pregnancy-induced hypertension; GWG: gestational weight gain. *<0.05

Table S4. Pregnancy outcomes by gestational weight gain in late pregnancy

Outcome	Gestational Weight Gain During Late Pregnancy (>17 week)				
	Below		Average	Above	
	n (%)	Unadjusted RR (95% CI)	n (%)	n (%)	Unadjusted RR (95% CI)
GDM	52 (22)	2.80 (2.06, 3.81) *	97 (7.9)	8 (3.2)	0.41 (0.20, 0.83) *
PIH	7 (3)	0.83 (0.38, 1.83)	44 (3.6)	15 (6.1)	1.69 (0.96, 3.00)
Caesarean section	105 (46.9)	0.99 (0.85, 1.15)	548 (47.3)	129 (56.3)	1.19 (1.05, 1.35)*
Preterm birth	6 (2.5)	0.58 (0.25, 1.33)	54 (4.4)	12 (4.8)	1.10 (0.60, 2.03)
NICU admission	35 (14.8)	1.09 (0.78, 1.52)	168 (13.6)	27 (10.9)	0.80 (0.54, 1.17)
Neonatal hospitalization ≥5 days	14 (5.9)	1.03 (0.59, 1.80)	71 (5.8)	11 (4.4)	0.77 (0.41, 1.43)
Severe neonatal problem	6 (2.5)	1.21 (0.50, 2.90)	26 (2.1)	7 (2.8)	1.34 (0.59, 3.05)
Neonatal hyperbilirubinemia	28 (11.9)	0.77 (0.53, 1.11)	191 (15.5)	25 (10.1)	0.65 (0.44, 0.96) *
LGA> 90th	9 (3.9)	0.36 (0.19, 0.69)*	132 (10.9)	51 (20.8)	1.91 (1.43, 2.56)*
SGA< 10th	17 (7.4)	1.49 (0.89, 2.51)	60 (5)	3 (1.2)	0.25 (0.08, 0.78)*
Macrosomia	5 (2.1)	0.31 (0.13, 0.76)*	84 (6.9)	31 (12.6)	1.83 (1.24, 2.70) *
Low birthweight	8 (3.4)	1.61 (0.74, 3.50)	26 (2.1)	3 (1.2)	0.57 (0.17, 1.88)

NICU: neonatal intensive care unit; LGA: large for gestational age; SGA: small for gestational age; GDM: gestational diabetes mellitus; PIH: pregnancy-induced hypertension; GWG: gestational weight gain. *<0.05

Table S5. Pregnancy outcomes by total gestational weight gain, stratified by fetal sex.

Outcomes	Gestational Weight Gain During Late Pregnancy (>17 week)					
	Male			Female		
	Below (n=110)	Within (Referent) (n=646)	Above (n=120)	Below (n=120)	Within (Referent) (n=569)	Above (n=125)
	n (%)	Unadjusted RR (95% CI)	n (%)	n (%)	Unadjusted RR (95% CI)	n (%)	n (%)	Unadjusted RR (95% CI)
GDM	21 (19.1)	2.33 (1.46, 3.70) *	53 (8.2)	3 (2.5)	0.30 (0.10, 0.96)	29 (24.2)	3.20 (2.08, 4.91) *	43 (7.6)	5 (4)	0.53 (0.21, 1.31)
PIH	2 (1.8)	0.47 (0.11, 1.96)	25 (3.9)	5 (4.2)	1.08 (0.42, 2.76)	5 (4.2)	1.25 (0.48, 3.28)	19 (3.3)	9 (7.2)	2.16 (1.00, 4.65)
Caesarean section	61 (57)	1.20 (0.99, 1.44)	291 (47.5)	62 (56.4)	1.19 (1.00, 1.43)*	41 (36.6)	0.77 (0.60, 1.00)	250 (47.3)	66 (56.4)	1.19 (0.99, 1.43)
Preterm birth	1 (0.9)	0.17 (0.02, 1.21)	35 (5.4)	7 (5.8)	1.08 (0.49, 2.37)	4 (3.3)	1.12 (0.38, 3.26)	17 (3)	4 (3.2)	1.07 (0.37, 3.13)
NICU admission	16 (14.6)	1.09 (0.67, 1.79)	86 (13.3)	12 (10)	0.75 (0.42, 1.33)	16 (13.3)	1.01 (0.61, 1.67)	75 (13.2)	14 (11.2)	0.85 (0.50, 1.45)
Neonatal hospitalization ≥5 days	5 (4.6)	0.70 (0.28, 1.73)	42 (6.5)	4 (3.3)	0.51 (0.19, 1.40)	6 (5)	1.02 (0.43, 2.40)	28 (4.9)	7 (5.6)	1.14 (0.51, 2.55)
Severe neonatal problem	0	NA	17 (2.6)	4 (3.3)	1.27	5 (4.2)	2.63	9 (1.6)	3 (2.4)	1.52

					(0.43, 3.70)		(0.90, 7.72)		(0.42, 5.52)
Neonatal hyperbilirubinemia	13 (11.8)	0.76 (0.44, 1.31)	100 (15.5)	9 (7.5)	0.48 (0.25, 0.93)*	15 (12.5)	0.79 (0.47, 1.32)	90 (15.8)	16 (12.8)	0.81 (0.49, 1.33)
LGA> 90th	2 (1.8)	0.19 (0.05, 0.76)*	62 (9.7)	25 (20.8)	2.16 (1.42, 3.29)*	7 (5.8)	0.47 (0.22, 1.01)	70 (12.3)	26 (20.8)	1.69 (1.13, 2.54)*
SGA< 10th	8 (7.3)	1.26 (0.60, 2.64)	37 (5.8)	2 (1.7)	0.29 (0.07, 1.18)	9 (7.5)	1.86 (0.88, 3.91)	23 (4)	1 (0.8)	0.20 (0.03, 1.45)
Macrosomia	3 (2.7)	0.35 (0.11, 1.10)	50 (7.8)	19 (15.8)	2.03 (1.24, 3.32)*	2 (1.7)	0.29 (0.07, 1.18)	33 (5.8)	12 (9.6)	1.66 (0.88, 3.11)
Low birthweight	2 (1.8)	0.83 (0.19, 3.62)	14 (2.2)	1 (0.8)	0.38 (0.05, 2.88)	5 (4.2)	2.37 (0.83, 6.81)	10 (1.8)	1 (0.8)	0.46 (0.06, 3.52)

NICU: neonatal intensive care unit; LGA: large for gestational age; SGA: small for gestational age; GDM: gestational diabetes mellitus; PIH: pregnancy-induced hypertension; GWG: gestational weight gain. *<0.05

Table S6. Pregnancy outcomes by total gestational weight gain

Outcome	Total Gestational Weight Gain				
	Below		Average	Above	
	n (%)	Unadjusted RR (95% CI)	n (%)	n (%)	Unadjusted RR (95% CI)
GDM	60 (15.3)	1.60 (1.22, 2.10) *	176 (9.6)	27 (6.8)	0.71 (0.48, 1.05)
PIH	6 (1.5)	0.43 (0.19, 0.99) *	65 (3.5)	26 (6.6)	1.86 (1.20, 2.89) *
Caesarean section	163 (45)	1.00 (0.88, 1.13)	778 (45.2)	203 (55.5)	1.22 (1.10, 1.36)*
Preterm birth	15 (3.8)	0.87 (0.51, 1.49)	81 (4.4)	22 (5.6)	1.26 (0.80, 2.00)
NICU admission	61 (15.6)	1.12 (0.86, 1.44)	257 (14)	45 (11.4)	0.81 (0.60, 1.10)
Neonatal hospitalization ≥5 days	27 (6.9)	1.19 (0.79, 1.78)	107 (5.8)	19 (4.8)	0.83 (0.51, 1.33)
Severe neonatal problem	11 (2.8)	1.40 (0.72, 2.71)	37 (2)	7 (1.8)	0.88 (0.40, 1.96)
Neonatal hyperbilirubinemia	58 (14.8)	0.96 (0.74, 1.24)	285 (15.5)	47 (11.9)	0.77 (0.57, 1.02)
LGA> 90th	20 (5.2)	0.49 (0.31, 0.77)*	192 (10.6)	80 (20.4)	1.92 (1.52, 2.44)*
SGA< 10th	27 (7)	1.46 (0.96, 2.22)	87 (4.8)	10 (2.5)	0.53 (0.28, 1.01)
Macrosomia	11 (2.8)	0.45 (0.24, 0.83)*	115 (6.3)	53 (13.5)	2.15 (1.58, 2.93)*
Low birthweight	15 (3.8)	1.72 (0.96, 3.07)	41 (2.2)	9 (2.3)	1.03 (0.50, 2.09)

NICU: neonatal intensive care unit; LGA: large for gestational age; SGA: small for gestational age; GDM: gestational diabetes mellitus; PIH: pregnancy-induced hypertension; GWG: gestational weight gain. *<0.05

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Gestational weight gain and adverse pregnancy outcomes: a prospective cohort study

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Abstract

Objective To assess the associations of gestational weight gain (GWG) in early and late pregnancy with subsequent risks of adverse pregnancy outcomes in Chinese women.

Design Prospective cohort study.

Setting Shanghai, China.

Participants We studied 2630 nulliparous singleton pregnant women with complete data on weight gain in early (≤17 weeks of gestation) and late (>17 weeks) pregnancy in the Shanghai Birth Cohort.

Methods GWG was standardized into z-scores by gestational age and categorized as low (z score <-1), normal (-1 to 1), and high (>1). The adjusted relative risks (aRRs) and 95% confidence intervals (CIs) were estimated through log-binomial regression models. Interaction effects between GWG and some other adjustment factors were tested, further stratified analyses were performed separately where interaction terms were significant.

Outcome measures Adverse maternal and neonatal outcomes.

Results Independent from GWG in late pregnancy, higher GWG in early pregnancy was associated with higher risks of gestational diabetes mellitus (aRR: 1.66; 95% CI: 1.11–2.48), caesarean section (aRR: 1.21; 95% CI: 1.05–1.39), and prolonged hospitalization (aRR: 1.56; 95% CI: 1.03–2.38). Higher GWG in late pregnancy was independently associated with higher risks of caesarean section (aRR: 1.24; 95% CI: 1.09–1.41), large for gestational age (aRR: 2.01; 95% CI: 1.50–2.7), and macrosomia (aRR: 1.90; 95% CI: 1.30–2.78). In addition, the risk of gestational hypertension increased significantly with increased total GWG (aRR: 1.78; 95% CI: 1.14–2.76). The effects of GWG in late pregnancy on maternal and neonatal outcomes were significantly different between the women bearing a female and the women bearing male fetus.

Conclusion GWG is associated with a series of adverse pregnancy outcomes including gestational diabetes mellitus, gestational hypertension, large for gestational age, etc.. And the GWG associations with the pregnancy outcomes can be modified by the timing of GWG and the infant sex.

Keywords gestational weight gain, pregnancy outcomes, z-scores, fetal sex

Strengths and limitations of this study

1. Weight gain data collected before and during pregnancy enabled us to investigate the effect of timing of weight gain on the outcomes.
2. The use of z-scores instead of original weight gain value to account for the gestational-age-dependent nature of GWG allowed us to differentiate the effect caused by weight gain from the effect caused by duration of pregnancy.
3. Effect modification by fetal sex was investigated.
4. Only short-term rather than long-term pregnancy outcomes were investigated.
5. Pre-pregancy weight was self-reported rather than measured.

Introduction

Gestational weight gain (GWG) has been associated with pregnancy outcomes. Insufficient weight gain has been linked with increased risks of low birth weight, small for gestational age (SGA) and preterm birth, while excessive weight gain has been associated with large for gestational age (LGA), gestational diabetes mellitus (GDM), preeclampsia, preterm birth, caesarean section, infant mortality and childhood obesity[1-2]. However, although women are routinely weighed in clinical settings and receive gestational weight gain advice[3-4], a high proportion of pregnant women who gained above or below GWG weight ranges recommended by the guidelines[5]. Based on data collected from 23 studies involving more than 1.3 million women, GWG was below or above the weight gain range suggested by Institute of Medicine (IOM) guidelines in 23% and 47% of pregnancies, respectively[1], and the prevalence of excess gestational weight gain appears to be on the rise[6].

It is well established that total GWG affects pregnancy outcomes[7]. Some studies suggest that GWG during early pregnancy may be more important than GWG at late pregnancy for developing certain pregnancy outcomes such as GDM and adverse

cardio-metabolic profile in the offspring[8-11]. Overall, studies examining associations of early GWG with perinatal outcomes have been relatively few, and these studies have often not accounted for the effects of weight gain during other periods of pregnancy[12]. In the prospective pregnancy cohort study, we conducted a sought to explore in a Chinese population-based study to establish the relationship of GWG during early and late pregnancy with maternal and neonatal outcomes.

Materials and Methods

Study design and data source

This prospective cohort study is based on the recently developed Shanghai Birth Cohort (SBC) which has been described in details elsewhere[13]. Briefly, the SBC is a prospective observational study conducted in Shanghai, China, aiming to examine factors affecting fecundability, pregnancy outcomes, child growth and development, and risks of diseases. The cohort recruited 4127 women in pre-conception care (701) or early antenatal care (3426). The data was collected between September 1, 2013 and November 31, 2016, resulting in 3699 live births. The collected data included maternal demographical characteristics, health behaviors, reproductive history, as well as

clinical information related to pregnancy, birth and pregnancy outcomes. This study was approved by Xinhua Hospital Research Ethics Committee, Shanghai Jiao Tong University School of Medicine (reference number: XHEC-F-NSFC-2018-122).

Study population

The present study collected the data from all singleton pregnancies in women with age ≥20 years old who started antenatal care before 17 weeks' gestation and delivered at ≥28 weeks of gestation with data available on weight gains in early and late gestation in the SBC cohort.

Gestational age was estimated based on the date of last menstruation period and confirmed by first trimester ultrasound date. The eligible data collected in this study were obtained from : (1) self-reported pre-pregnancy weight (kg); (2) weight and height (cm) measured in early pregnancy (17 weeks of gestation or less); and (3) weight measured within the last week of pregnancy. Subjects were excluded if: (1) weight in early pregnancy <30 kg or >350 kg; or (2) z-score of gestational weight gain <-4.0 or >4.0, the methods used in the study were similar to the study conducted by Johansson et al[14]. Women with pre-existing medical conditions such as pre-gestational diabetes,

hypo- or hyper-thyroidism (affecting GWG)[15] and heart/liver/kidney diseases were also excluded.

Weight measurements

Pre-pregnancy weight (kg) was based on self-reporting, while weight at early pregnancy and at delivery was routinely measured to the nearest 0.1 kg using the available electronic weighing device in the prenatal care clinics. Height (cm) at the first prenatal visit was routinely measured to the nearest 0.1 cm using the available electronic stadiometer in the hospital. Pre-pregnancy body mass index (BMI; kg/m^2) was calculated as pre-pregnancy weight (kg) divided by height $(m)^2$ and categorized as underweight (<18.5 kg/m^2), normal weight (18.5-24.9 kg/m^2), overweight (25.0-29.9 kg/m^2), and obese (≥ 30.0 kg/m^2)[16].

Early pregnancy in this study was defined as gestational age ≤17 weeks so as to include virtually all women who started the first antenatal care in the hospital[17]. The 2009 Institute of Medicine (IOM) recommendations suggested that women should gain 0.5-2 kg in early pregnancy[5] and the 50th centile GWG for women at gestational age ≤17 weeks was below 2 kg according to the INTERGROWTH-21st Project[2]. We examined

GWG in early pregnancy (weight measured ≤17 weeks minus pre-pregnancy weight) and late pregnancy (last measurement of weight prior to delivery minus weight measured ≤17 weeks). Total GWG was calculated as last measurement of weight before delivery minus pre-pregnancy weight. All GWG values were standardized into z-scores by gestational age, stratified by BMI categories. The means and standard deviations (SD) of GWGs in early pregnancy and late pregnancy were used to convert the GWG values into z-scores. All GWG z-scores were first examined as continuous variables, and then categorized as <-1.0 (below), -1.0 to +1.0 (average) and > +1.0 (above) in data analyses. The analyses for GWG in early pregnancy were restricted to women whose GWGs in late pregnancy were average (-1.0 to +1.0). Similarly, the analyses for late pregnancy weight gain were restricted to women with weight gain value in early pregnancy within -1.0 to +1.0.

Covariates

Co-variables included fetal sex, maternal age (20 to 34, ≥35 years), parity (0, ≥1), pre-pregnancy body mass index (BMI) categories (underweight, normal, overweight/obese), alcohol/tobacco use (yes or no), GDM (yes or no), gestational hypertension (yes or no)

and length of gestation (28 to 36, ≥37 weeks)

Outcomes

The outcomes included gestational diabetes mellitus (GDM), gestational hypertension, caesarean section, preterm birth, neonatal intensive care unit (NICU) admission, neonatal prolonged hospitalization (≥5 days), severe neonatal outcomes, neonatal hyperbilirubinemia (≤12 mg/dL), LGA, SGA, macrosomia (>4000 g) and low birthweight (<2500 g).

All women received a 75 g oral glucose tolerance test (OGTT) during 24-28 weeks of gestation. GDM was diagnosed according to the IADPSG criteria: if anyone had the glucose values fell at or above the following thresholds: fasting 5.1 mmol/L, 1 hour 10.0 mmol/L, 2 hour 8.5 mmol/L. Gestational hypertension was defined as de novo hypertension (systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg) after 20 weeks' gestation. Preterm birth was defined as gestational age at delivery <37 weeks. SGA was defined as birth weight ≤10th percentile, and LGA as birth weight ≥90th percentile according to Chinese sex- and gestational age-specific birth weight standards[18]. Severe neonatal outcomes included death, 5 minute APGAR

score <7, hypoglycemia (<40 mg/dL), sepsis, cardiopulmonary resuscitation or ventilator support within 24 hours after birth, severe respiratory disorders (respiratory distress syndrome or transient tachypnea of the newborn), serious birth defects, seizures, necrotizing enterocolitis, and hypoxic-ischemic encephalopathy.

Statistical analyses

Maternal demographic characteristics and clinical factors were compared across GWG groups. Continuous variables were described by mean ± standard deviation (SD) or median (interquartile range, IQR). Categorical variables were described by frequencies (%). Analysis of variance or Kruskal-Wallis H tests were performed for continuous data, and chi-square tests or Fisher's exact tests were performed for categorical data.

The incidences of adverse pregnancy outcomes were examined among three GWG groups. Multivariate log-binomial regression models were used to estimate the unadjusted relative risks (RRs), adjusted relative risks (ARRs) and 95% confidence intervals (CIs) of adverse pregnancy outcomes across GWG groups. Regression model for maternal outcomes were adjusted for only co-variables with p <0.2 (maternal age, parity, pre-pregnancy BMI, alcohol/tobacco use, fetal sex and length of gestation).

Neonatal outcomes models were further adjusted for GDM and PIH in addition to the aforementioned factors. Effects between weight gain and fetal sex and other covariates on adverse neonatal outcomes were also investigated. Interaction effects between GWG and fetal sex and other covariates (parity, maternal pre-pregnancy BMI, maternal age) on adverse maternal and neonatal outcomes were also tested.

All analyses were performed using the Statistical Analysis System (SAS) for Windows, version 9.4 (SAS Institute, Cary, NC). $P<0.05$ was considered statistically significant.

Patient and public involvement

No patients were involved in the design, or conduct, or reporting, or dissemination plans of our research.

Results

Study population and characteristics

A total of 2630 pregnant women met the study inclusion criteria (Figure 1). The characteristics of all pregnant women in the study by total GWG is shown in Table 1. Among them, 1605 women who gained average weight in late pregnancy (z-score -1 to +1) were analyzed for the association of GWG in early pregnancy with the outcomes

(Table S1); while 1717 women who gained average weight in early pregnancy were analyzed for the association of GWG in late pregnancy with the outcomes (Table S2). It should be noticed that for the two analytic datasets, the reference group was the same group of women who had average GWG in both early and late pregnancy (n=1233).

Weight gain during early pregnancy

The risks of maternal and neonatal outcomes for GWG in early pregnancy are presented in Figure 2A and Table S3. Lower GWG was not significantly associated with pregnancy outcomes, compared with that of the average GWG. In contrast, the risks of GDM (aRR=1.66; 95% CI: 1.11-2.48), caesarean section (aRR=1.21; 95% CI: 1.05-1.39) and prolonged hospitalization (aRR=1.56; 95% CI: 1.03-2.38) were higher in the group with GWG above average in early pregnancy. No significant interactions between GWG in early pregnancy and covariates were observed.

Weight gain during late pregnancy

Associations of GWG in late pregnancy with perinatal outcomes are presented in Figure 2B and Table S4. In contrast to early pregnancy, the risks for GDM and SGA decreased significantly with increased GWG in late pregnancy, whereas the risks for LGA and

macrosomia increased. Weight gain above average was correlated with a higher risk for caesarean section (aRR=1.24; 95% CI: 1.09-1.41) in late pregnancy. In addition, higher GWG showed a protective effect against neonatal hyperbilirubinemia (aRR=0.64; 95% CI: 0.43-0.94).

Significant interactions were identified between GWG in late pregnancy and fetal sex. Figure 3 and Table S5 shows the associations of late pregnancy weight gain with pregnancy outcomes stratified by fetal sex. The risks for LGA and caesarean section significantly increased in women with higher GWG in late pregnancy, but the odds of GDM increased with less GWG, regardless of fetal sex. However, higher risks of gestational hypertension (aRR=2.31; 95% CI: 1.08-4.95) was only observed in women bearing a female fetus with higher GWG. Conversely, higher GWG in late pregnancy was associated with GDM (aRR=0.30; 95% CI: 0.10-0.96), neonatal hyperbilirubinemia (aRR=0.46; 95% CI: 0.24-0.89) and macrosomia (aRR=2.05; 95% CI: 1.27-3.31) for women bearing a boy, but not for women bearing a girl, indicating effect modifications by fetal sex. But when stratified by fetal sex, the lower risk of SGA with higher GWG was no longer observed.

Total weight gain during pregnancy

Figure 2C and Table S6 show results for pregnancy outcomes by total GWG. The effect sizes of GWG in late pregnancy on pregnancy outcomes were almost identical with the effect sizes of total GWG. Similar to late pregnancy, the risks for LGA, macrosomia and gestational hypertension increased significantly with increased total GWG. Higher GWG was also linked with a higher risk for caesarean section (aRR=1.78; 95% CI: 1.14-2.76). Moreover, total GWG below the average was associated with higher risks of GDM (aRR=1.51; 95% CI: 1.15-1.98) and SGA (aRR=1.53; 95% CI: 1.01-2.32). No significant interactions between total GWG and other covariates were identified.

Discussion

Main Findings

In this study, we found that the associations of gestational stage-specific weight gain with maternal and neonatal outcomes were different. Of those, independent of GWG in late pregnancy, higher GWG in early was associated with higher risks of GDM, caesarean section, and neonatal prolonged hospitalization.

Strengths and limitations

There are strengths in our study. In the study, some improvements have been made when compared with other studies reported in the literatures. First, the SBC database contains detailed clinical data including pre-pregnancy weight, weight measurements during pregnancy and pregnancy weight measurements before delivery. This made it possible to study GWG in both early and late pregnancy. In addition, the use of GWG z-scores in our study instead of using original weight gain to take into consideration(account for the gestational-age-dependent nature of GWG allowed us to differentiate the effects of GWG from the effects of gestational duration (a shorter pregnancy duration should be correlated to less weight gain)[14, 19].

There are also limitations in our study. We only investigated the short-term perinatal outcomes. Recently, researchers have linked an individual's susceptibility to chronic disease such as cardio-metabolic disease and obesity in later life to events during the intrauterine phase of development[8, 20-21]. Further studies on long-term outcomes would provide important evidence regarding the associations between chronic diseases and events during the intrauterine phase.

Interpretation

Associations between insufficient or excessive weight gain during the whole pregnancy and maternal and child health outcomes have been well described[1-2, 7]. A meta-analysis of pooled 1309136 participant data from 23 cohort studies showed that women who gained high weight were more likely to have LAG, caesarean section and macrosomia, while women who gained less weight were at higher risk of SGA[1]. These findings are in line with the association of maternal weight gain with adverse pregnancy outcomes in our study.

There is growing recognition that the impacts of gestational stage-specific weight gain on pregnancy outcomes may vary[8-9, 20, 22-23]. GWG in early pregnancy largely reflects maternal fat deposition, whereas GWG thereafter is mainly attributed to maternal and amniotic fluid expansion, and growth of the fetus, placenta and uterus[5]. In this study, mothers with increased fat deposition during pregnancy may affect the adiposity of the offspring by higher placental transfer of nutrients, such as glucose and free fatty acids, which may lead to maternal pregnancy complications, such as GDM, and permanent fetal and childhood adaptations in appetite, energy metabolism and neuro-endocrine function [23-24]. Therefore, GWG in early pregnancy, prior to the development of

pregnancy outcomes, might be as or more important than GWG in late pregnancy with respect to pregnancy outcomes[9, 14]. A study of 5908 Netherlands mother-offspring pairs reported that higher weight gain in early pregnancy was associated with an adverse cardio-metabolic profile in the offspring[8]. Similarly, a study of 5154 UK mother-offspring pairs showed that GWG in the first 14 weeks tended to be incrementally associated with offspring BMI, waist circumference and fat mass in children at age 9 years, but after 14 weeks of gestation, only high levels of GWG were associated with offspring's adiposity measures, highlighting the importance of the timing of weight gain in pregnancy[22].

Studies to clarify the relationship between gestational stage-specific weight gain and adverse pregnancy outcomes have been sporadic. A study of Korean pregnant women found that GWG velocity at early pregnancy was significantly associated with GDM, gestational hypertension, cesarean section, LGA, and macrosomia[12]. However, the analyses have not accounted for the effects of weight gain in other periods of pregnancy. In contrast, our analyses for early/late pregnancy GWG were restricted to women whose GWG z-scores in other pregnancy stage were normal, and thus the observed

associations are independent of GWG in different periods. Our data from a large population-based Chinese cohort in Shanghai showed that higher, but not lower, maternal GWG in early pregnancy was associated with increased risks of adverse pregnancy outcomes, including GDM, caesarean section and prolonged hospitalization. In late pregnancy, low weight gain was associated with GDM as well as SGA, and high weight gain was associated with caesarean section, LGA and macrosomia.

High GWG in early pregnancy has been associated with an increased risk of GDM, while there are some inconsistent data concerning the associations of GWG in second and third trimester or the whole pregnancy with GDM[11, 25-27]. Our study presents the results which are in consistent with results produced by other studies [12, 25, 28] indicating that higher GWG in early pregnancy may increase the risk of developing GDM, but higher GWG in late pregnancy shows a reversed association. The discrepancy might be due to that women diagnosed with GDM might have undergone weight control interventions such as prescribed diet and physical exercise after the GDM diagnosis. Avoiding high weight gain in early pregnancy may prevent GDM, and doctors might consider preemptive actions in high-risk pregnant women.

The risk of gestational hypertension increases significantly with higher maternal total GWG. A study of 29861 women from 25 hospitals in America showed that early weight gain over the 2009 IOM recommendation were shown to be associated with the development of gestational hypertension[29]. In a study of 101259 women with chronic hypertension, women who gained the amount of weight above the GWG range recommended by IOM guidelines were at increased risks of eclampsia[30]. Given the known vascular permeability and decreased plasma oncotic pressure that accompanies preeclampsia and its association with rapid weight gain[31], excessive GWG may be a cause of hypertensive disease of pregnancy.

Total GWG of average (-1 to +1) in our study were 15.2±2.3 kg for women with pre-pregnancy BMI less than 18.5 (underweight) and 15.0±2.5 kg for those who with pre-pregnancy BMI of 18.5 to 24.9 (normal weight), which corresponded to the 2009 IOM recommendations. Specifically, the 2009 IOM recommendations suggested GWG of 12.5 to 18 kg for underweight women and 11.5 to 16 kg for normal weight women[5]. However, due to the sporadic number of obese women, we analyzed them together with overweight women. Total GWG of average were 12.3±3.7 kg for women with pre-

pregnancy BMI greater than 25.0 (overweight and obese) in our study, which in general was higher than the 2009 IOM recommended GWG range with 7 to 11.5 kg for overweight and 5 to 9 kg for obese[5]. The most important reason for this difference is that the IOM recommendation was derived largely from data collected among white women and may not well represent Chinese Population[32]. Therefore, we plan to establish GWG standards that can be applied to Chinese population.

Our data suggest effect modification by fetal sex in the association of GWG in late pregnancy with birth outcomes. Recent studies suggest that fetus sex may affect pregnancy outcomes[33-34]. Although not very clear, how fetal sex may influence these outcomes may be explained by several factors. The placenta is an active endocrine organ, a sex-specific maternal-placental-fetal interaction may be involved[22]. Animal studies suggest that maternal baseline BMI and GWG are associated with the hormonal milieu, including insulin resistance[35]. In agreement with this concept, a growing body of evidence linking early pregnancy GWG with cord blood hormones that may affect fetal growth and development[36]. Previous studies reported fetal sex differences in maternal first trimester hormones concentrations[15, 33, 37]. The resultant intrauterine

environment may affect fetal development.

Our findings may have clinical implications. First, from early pregnancy onwards, GWG may affect subsequent maternal and neonatal outcomes. Second, although interventions to limit GWG in late pregnancy are effective, the benefits might be modest at best. To mitigate the harms of excessive weight gain, addressing the importance of gaining the appropriate amount of weight in both early and late pregnancy should be integrated into routine prenatal care[1, 7, 38].

Conclusion

The GWG associations with adverse pregnancy outcomes differ at early and late pregnancy, and there may be effect modification by fetal sex in the association of GWG in late pregnancy with some pregnancy outcomes. Weight gain management should be integrated into the routine prenatal care to decrease the risks of adverse pregnancy outcomes.

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drafting the manuscript. SG, ZM and LD analyzed the data and critically revised the manuscript. ZL, JZ and XH made substantial contributions to conception and design, interpreted the data, and critically revised the manuscript. All authors read and approved the final manuscript.

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Table 1. Characteristics of pregnant women in the study cohort (n=2630)

Characteristic	Total	Total gestational weight gain			*P*
		Below (n=392)	Average (n=1842)	Above (n=396)	
Maternal age (year), mean ± SD	29.4 ± 3.6	29.9 ± 3.8	29.4 ± 3.5	28.5 ± 3.6	<0.0001
Maternal age ≥35 years, n (%)	241 (9.2)	51 (13)	169 (9.2)	21 (5.3)	0.0002
Nulliparous, n (%)	2216 (84.3)	325 (82.9)	1532 (83.2)	359 (90.7)	0.0027
Education, university degree and above, n (%)	2404 (91.5)	362 (92.6)	1702 (92.5)	340 (85.7)	0.0007
ART, n (%)	55 (2.1)	9 (2.3)	37 (2)	9 (2.3)	0.9834
Tobacco smoking, n (%)	72 (2.7)	7 (1.8)	41 (2.2)	24 (6.1)	<0.0001
Alcohol use, n (%)	338 (12.9)	52 (13.3)	240 (13)	46 (11.6)	0.7221
Pre-pregnancy BMI (kg/m^2), mean ± SD	21.3 ± 3.0	21.7 ± 3.1	21.2 ± 3.0	21.5 ± 2.9	0.0139
Pre-pregnancy BMI categories, n (%)					
Underweight (< 18.5 kg/m^2)	396 (15.1)	54 (13.8)	292 (15.9)	50 (12.6)	0.7530
Normal weight (18.5–24.9 kg/m^2)	1980 (75.3)	298 (76)	1372 (74.5)	310 (78.3)	
Overweight and obese (≥ 25 kg/m^2)	254 (9.7)	40 (10.2)	178 (9.7)	36 (9.1)	
Gestational age at the first prenatal visit (week), median (IQR)	15 (3)	14 (3)	15 (3)	15 (3)	0.1986
GWG in early pregnancy by BMI categories (kg), mean ± SD					
All women	2.2 ± 2.9	-0.2 ± 2.8	2.1 ± 2.2	4.9 ± 3.2	<0.0001
Underweight (< 18.5 kg/m^2)	2.5 ± 2.4	0.9 ± 1.9	2.4 ± 2.0	4.8 ± 3.0	<0.0001
Normal weight (18.5–24.9 kg/m^2)	2.3±2.8	0.0 ± 2.8	2.2 ± 2.2	4.9 ± 3.1	<0.0001
Overweight and obese (≥ 25 kg/m^2)	1.4±3.6	-2.2 ± 3.3	1.5 ± 2.6	4.7 ± 4.4	<0.0001

GWG in late pregnancy by BMI categories (kg), mean ± SD					
All women	13.0 ± 3.5	8.2 ± 3.0	12.6 ± 2.9	17.8 ± 3.6	<0.0001
Underweight (< 18.5 kg/m^2)	13.0 ± 3.5	8.9 ± 1.9	12.8 ± 2.5	18.2 ± 3.8	<0.0001
Normal weight (18.5–24.9 kg/m^2)	12.9 ± 4.0	8.4 ± 3.0	12.8 ± 2.8	17.8 ± 3.6	<0.0001
Overweight and obese (≥ 25 kg/m^2)	11.0 ± 4.9	5.8 ± 3.3	10.8 ± 3.8	17.4 ± 3.8	<0.0001
GWG in whole pregnancy by BMI categories (kg), mean ± SD					
All women	15.0 ± 4.9	8.1 ± 2.6	14.8± 2.7	22.7 ± 2.9	<0.0001
Underweight (< 18.5 kg/m^2)	15.4 ± 4.2	9.7 ± 1.6	15.2 ± 2.3	23.1 ± 3.0	<0.0001
Normal weight (18.5–24.9 kg/m^2)	15.2 ± 4.7	8.4 ± 2.1	15.0 ± 2.5	22.7 ± 2.8	<0.0001
Overweight and obese (≥ 25 kg/m^2)	12.3 ± 6.1	3.7 ± 2.4	12.3 ± 3.7	22.0 ± 3.6	<0.0001
Gestational age at delivery (week), median (IQR)	39 (2)	39 (2)	39 (2)	39 (2)	0.0793
Birth weight (g), mean ± SD	3376 ± 450	3238 ± 422	3370 ± 438	3540 ± 480	<0.0001
Male infant, n (%)	1334 (51.4)	194 (50.4)	945 (52)	195 (49.5)	0.7951

ART: assisted reproductive technology; BMI: body mass index; GWG: gestational weight gain; IQR: interquartile range; SD: standard deviation.

Figure Legend

Figure 1. Study flow chart.

Figure 2. Associations of gestational weight gain with pregnancy outcomes.

(A) Associations of early gestational weight gain (≤17 week) with pregnancy outcomes. (B) Associations of late gestational weight gain (>17 week) with pregnancy outcomes. (C) Associations of total gestational weight gain with pregnancy outcomes.

NICU: neonatal intensive care unit; LGA: large for gestational age; SGA: small for gestational age; GDM: gestational diabetes mellitus; PIH: pregnancy-induced hypertension; GWG: gestational weight gain; ARR: adjusted relative risk. *<0.05

Average GWG group as the reference.

a1 The analysis was adjusted for maternal age, parity, pre-pregnancy BMI and length of gestation.

b1 The analysis was adjusted for parity, pre-pregnancy BMI, fetal sex, GDM and PIH.

c1 The analysis was adjusted for pre-pregnancy BMI, fetal sex, alcohol/tobacco use, length of gestation, GDM and PIH.

d1 The analysis was adjusted for maternal age, alcohol/tobacco use, GDM and PIH.

a2 The analysis was adjusted for maternal age and pre-pregnancy BMI.;

b2 The analysis was adjusted for parity, pre-pregnancy BMI, fetal sex and length of gestation.

c2 The analysis was adjusted for maternal age, parity, pre-pregnancy BM, GDM and PIH.

d2 The analysis was adjusted for parity, pre-pregnancy BMI, fetal sex, GDM and PIH.

e2 The analysis was adjusted for parity, pre-pregnancy BMI, alcohol/tobacco use, length of gestation, GDM and PIH.

f2 The analysis was adjusted for maternal age, alcohol/tobacco use and length of gestation.

a3 The analysis was adjusted for maternal age, parity, pre-pregnancy BMI, alcohol/tobacco use and fetal sex.

b3 The analysis was adjusted for parity, pre-pregnancy BMI and length of gestation.

c3 The analysis was adjusted for parity, pre-pregnancy BMI, length of gestation, GDM and PIH.

d3 The analysis was adjusted for maternal age, parity and length of gestation.

e3 The analysis was adjusted for pre-pregnancy BMI, fetal sex, length of gestation, GDM and PIH.

Figure 3. Associations of late gestational weight gain (>17 week) with pregnancy outcomes, stratified by fetal sex.

NICU: neonatal intensive care unit; LGA: large for gestational age; SGA: small for gestational age; GDM: gestational diabetes mellitus; PIH: pregnancy-induced hypertension; GWG: gestational weight gain; ARR: adjusted relative risk.

*<0.05

Average GWG group as the reference.

[a] The analysis was adjusted for maternal age and pre-pregnancy BMI.

[b] The analysis was adjusted for maternal age, parity, pre-pregnancy BMI, alcohol/tobacco use and length of gestation.

[c] The analysis was adjusted for maternal age, pre-pregnancy BMI, GDM and PIH.

[d] The analysis was adjusted for parity, pre-pregnancy BMI, alcohol/tobacco use and length of gestation.

[e] The analysis was adjusted for parity, alcohol/tobacco use, length of gestation, GDM and PIH.

[f] The analysis was adjusted for parity, pre-pregnancy BMI, length of gestation, GDM and PIH.

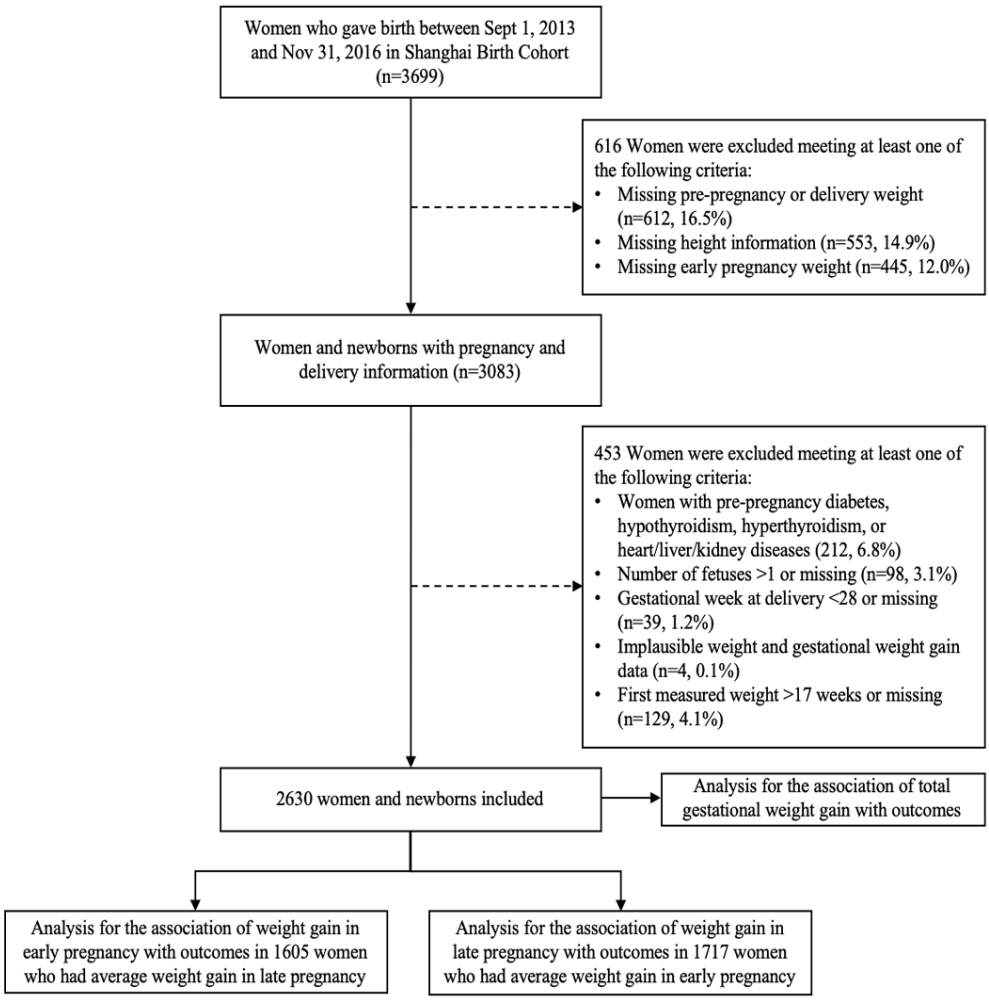

Figure 1. Study flow chart.

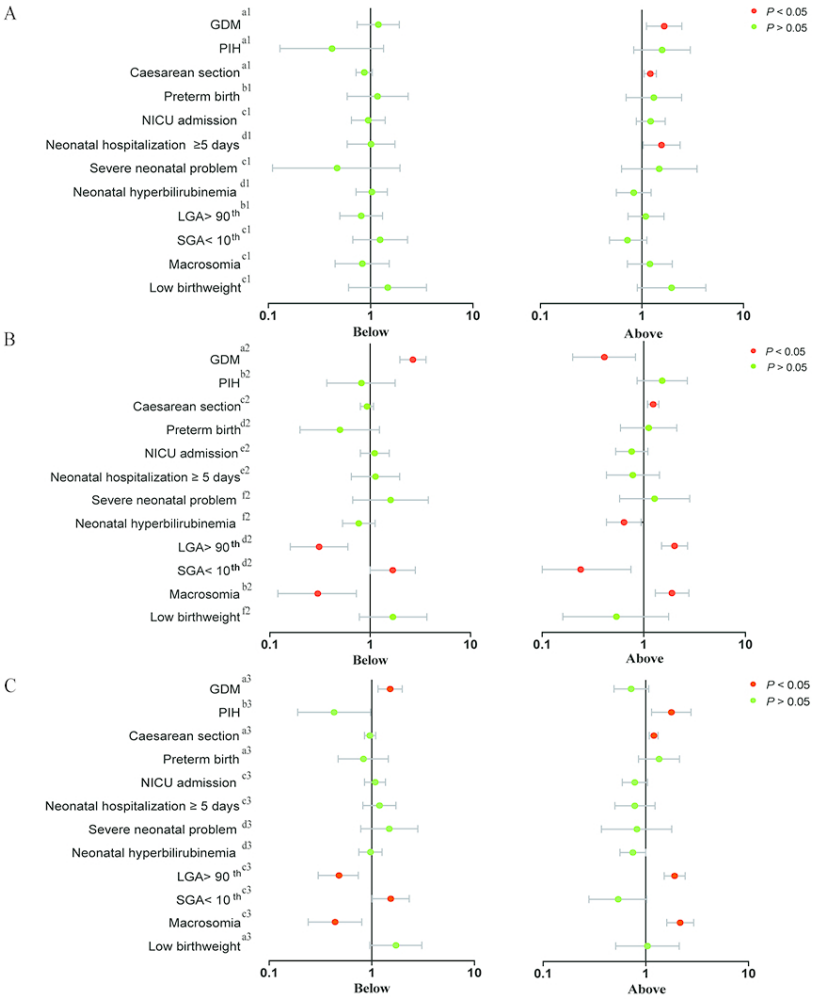

Figure 2. Associations of gestational weight gain with pregnancy outcomes.(A) Associations of early gestational weight gain (≤17 week) with pregnancy outcomes. (B) Associations of late gestational weight gain (>17 week) with pregnancy outcomes. (C) Associations of total gestational weight gain with pregnancy outcomes. NICU: neonatal intensive care unit; LGA: large for gestational age; SGA: small for gestational age; GDM: gestational diabetes mellitus; PIH: pregnancy-induced hypertension; GWG: gestational weight gain; ARR: adjusted relative risk. *<0.05Average GWG group as the reference.a1 The analysis was adjusted for maternal age, parity, pre-pregnancy BMI and length of gestation.b1 The analysis was adjusted for parity, pre-pregnancy BMI, fetal sex, GDM and PIH.c1 The analysis was adjusted for pre-pregnancy BMI, fetal sex, alcohol/tobacco use, length of gestation, GDM and PIH.d1 The analysis was adjusted for maternal age, alcohol/tobacco use, GDM and PIH.a2 The analysis was adjusted for maternal age and pre-pregnancy BMI.; b2 The analysis was adjusted for parity, pre-pregnancy BMI, fetal sex and length of gestation.c2 The analysis was adjusted for maternal age, parity, pre-pregnancy BM, GDM and PIH. d2 The analysis was adjusted for parity, pre-pregnancy BMI, fetal sex, GDM and PIH.e2 The analysis was adjusted for parity, pre-pregnancy BMI, alcohol/tobacco use, length of gestation, GDM and PIH.f2 The analysis was adjusted for maternal age, alcohol/tobacco use and length of gestation.a3 The analysis was adjusted for maternal age, parity, pre-pregnancy BMI, alcohol/tobacco use and fetal sex.b3 The analysis was adjusted for parity, pre-pregnancy BMI and length of gestation.c3 The analysis was adjusted for parity, pre-pregnancy BMI, length of gestation, GDM and PIH.d3 The analysis was adjusted for maternal age, parity and length of gestation.e3 The analysis was adjusted for pre-pregnancy BMI, fetal sex, length of gestation, GDM and PIH.

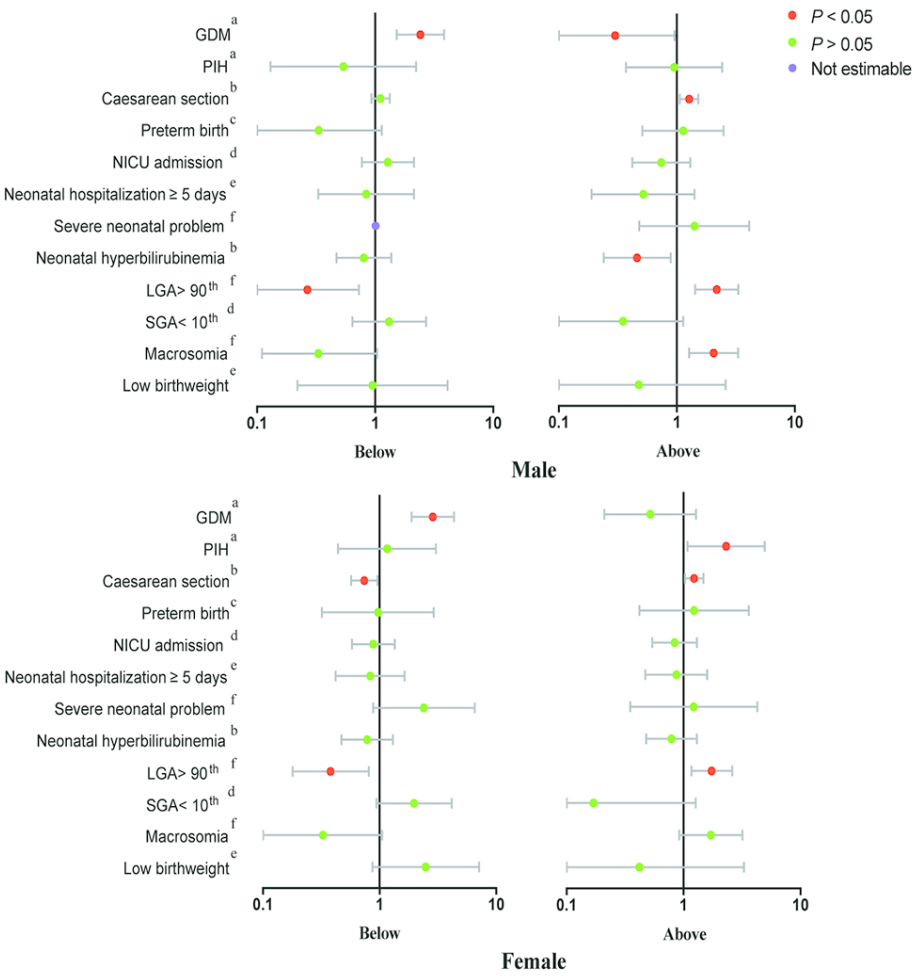

Figure 3. Associations of late gestational weight gain (>17 week) with pregnancy outcomes, stratified by fetal sex.NICU: neonatal intensive care unit; LGA: large for gestational age; SGA: small for gestational age; GDM: gestational diabetes mellitus; PIH: pregnancy-induced hypertension; GWG: gestational weight gain; ARR: adjusted relative risk. *<0.05Average GWG group as the reference.a The analysis was adjusted for maternal age and pre-pregnancy BMI.b The analysis was adjusted for maternal age, parity, pre-pregnancy BMI, alcohol/tobacco use and length of gestation.c The analysis was adjusted for maternal age, pre-pregnancy BMI, GDM and PIH.d The analysis was adjusted for parity, pre-pregnancy BMI, alcohol/tobacco use and length of gestation.e The analysis was adjusted for parity, alcohol/tobacco use, length of gestation, GDM and PIH.f The analysis was adjusted for parity, pre-pregnancy BMI, length of gestation, GDM and PIH.

Table S1. Maternal characteristics in the study of gestational weight gain in early pregnancy (≤17 week)

Characteristic	Below (n=186)	Average (n=1233)	Above (n=186)	*P*
Maternal age (year), mean ± SD	28.2 ± 3.4	29.4 ± 3.7	29.4 ± 3.5	0.0002
Maternal age ≥35 years, n (%)	11 (5.9)	126 (10.2)	14 (7.5)	0.5946
Nulliparous, n (%)	165 (88.7)	1011 (82)	155 (83.3)	0.1683
Education, university degree and above, n (%)	164 (88.1)	1138 (92.4)	162 (87.6)	0.8411
ART, n (%)	4 (2.2)	27 (2.2)	5 (2.7)	0.9110
Tobacco smoking, n (%)	4 (2.2)	26 (2.1)	9 (4.8)	0.0924
Alcohol use, n (%)	15 (8.1)	129 (10.5)	18 (9.37)	0.5876
Pre-pregnancy BMI (kg/m^2), mean ± SD	21.8 ± 3.1	21.2 ± 3.0	21.7 ± 3.1	0.0027
Pre-pregnancy BMI categories, n (%)				
Underweight (< 18.5 kg/m^2)	28 (15.1)	193 (15.7)	28 (15.1)	
Normal weight (18.5–24.9 kg/m^2)	134 (72)	929 (75.3)	133 (71.5)	0.9848
Overweight and obese (≥ 25 kg/m^2)	24 (12.9)	111 (9)	25 (13.4)	
Gestational age at the first prenatal visit (week), median (IQR)	14 (3)	14 (3)	15 (3)	0.8298
GWG in early pregnancy by BMI categories (kg), mean ± SD				
All women	-2.5 ± 2.0	2.1 ± 1.5	6.7 ± 2.1	<0.0001
Underweight (< 18.5 kg/m^2)	-0.6 ± 1.1	2.1 ± 1.2	6.4 ± 2.1	<0.0001
Normal weight (18.5–24.9 kg/m^2)	-2.5 ± 1.7	2.1 ± 1.5	7.0 ± 2.1	<0.0001
Overweight and obese (≥ 25 kg/m^2)	-4.7 ± 1.7	1.5 ± 1.8	5.7 ± 1.7	<0.0001
GWG in late pregnancy by BMI categories (kg), mean ± SD				
All women	12.5 ± 2.3	12.6 ± 2.3	12.3 ± 2.4	0.4854

Underweight (< 18.5 kg/m^2)	12.4 ± 1.9	12.7 ± 1.9	12.5 ± 1.8	0.6323
Normal weight (18.5–24.9 kg/m^2)	12.8 ± 2.2	12.7 ± 2.2	12.6 ± 2.1	0.8492
Overweight and obese (≥ 25 kg/m^2)	10.7 ± 2.2	11.1 ± 3.1	10.4 ± 3.3	0.5676
Gestational age at delivery (week), median (IQR)	39 (2)	39 (2)	39 (2)	0.9126
Birth weight (g), mean ± SD	3296 ± 435	3370 ± 446	3382 ± 515	0.0428
Male infant, n (%)	92 (50.3)	646 (53.2)	102 (55.4)	0.6091

ART: assisted reproductive technology; BMI: body mass index; GWG: gestational weight gain; IQR: interquartile range; SD: standard deviation.

Table S2. Maternal characteristics in the study of gestational weight gain in late pregnancy (>17 week)

Characteristic	Below (n=236)	Average (n=1233)	Above (n=248)	*P*
Maternal age (year), mean ± SD	30.4 ± 3.8	29.4 ± 3.7	27.9 ± 3.5	<0.0001
Maternal age ≥35 years, n (%)	37 (15.7)	126 (10.2)	10 (4)	<0.0001
Nulliparous, n (%)	183 (77.5)	1011 (82)	234 (94.4)	<0.0001
Education, university degree and above, n (%)	222 (94.1)	1138 (92.4)	214 (86.3)	0.0017
ART, n (%)	7 (3)	27 (2.2)	6 (2.4)	0.7701
Tobacco smoking, n (%)	4 (1.7)	26 (2.1)	12 (4.8)	0.0234
Alcohol use, n (%)	20 (8.5)	129 (10.5)	20 (8.1)	0.3841
Pre-pregnancy BMI (kg/m^2), mean ± SD	21.6 ± 3.1	21.2 ± 3.0	21.4 ± 3.1	0.0564
Pre-pregnancy BMI categories, n (%)				
Underweight (< 18.5 kg/m^2)	29 (12.3)	193 (15.7)	37 (14.9)	
Normal weight (18.5–24.9 kg/m^2)	178 (75.4)	929 (75.3)	189 (76.2)	0.3711
Overweight and obese (≥ 25 kg/m^2)	29 (12.3)	111 (9)	22 (8.9)	
Gestational age at the first prenatal visit (week), median (IQR)	14 (3)	14 (3)	14 (3)	0.4231
GWG in early pregnancy by BMI categories (kg), mean ± SD				
All women	2.1 ± 1.5	2.1 ± 1.5	2.3 ± 1.4	0.1943
Underweight (< 18.5 kg/m^2)	2.7 ± 1.4	2.1 ± 1.2	2.8 ± 1.3	0.0009
Normal weight (18.5–24.9 kg/m^2)	2.1 ± 1.5	2.1 ± 1.5	2.2 ± 1.5	0.7273
Overweight and obese (≥ 25 kg/m^2)	1.5 ± 1.6	1.5 ± 1.8	2.1 ± 1.2	0.2109
GWG in late pregnancy by BMI categories (kg), mean ± SD				
All women	7.0 ± 2.1	12.6 ± 2.3	19.1 ± 2.4	<0.0001

Underweight (< 18.5 kg/m^2)	7.9 ± 1.2	12.7 ± 1.9	19.2 ± 2.6	<0.0001
Normal weight (18.5–24.9 kg/m^2)	7.3 ± 1.9	12.7 ± 2.2	19.1 ± 2.2	<0.0001
Overweight and obese (≥ 25 kg/m^2)	4.1 ± 1.9	11.1 ± 3.1	18.3 ± 3.2	<0.0001
Gestational age at delivery (week), median (IQR)	39 (2)	39 (2)	39 (2)	0.0872
Birth weight (g), mean ± SD	3261 ± 397	3370 ± 446	3536 ± 461	<0.0001
Male infant, n (%)	110 (47.8)	646 (53.2)	120 (49)	0.8381

ART: assisted reproductive technology; BMI: body mass index; GWG: gestational weight gain; IQR: interquartile range; SD: standard deviation.

Table S3. Association of pregnancy outcomes by gestational weight gain in early pregnancy (≤17 week)

	Below (n=186)		Average (n=1233)		Above (n=186)	
Outcomes	n (%)	aRR (95% CI)	n (%)	aRR	n (%)	aRR (95% CI)
GDM	18 (9.7)	1.19 (0.74, 1.91)	97 (7.9)	Reference	25 (13.4)	1.66 (1.11, 2.48) *
PIH	3 (1.6)	0.42 (0.13, 1.34)	44 (3.6)	Reference	11 (5.9)	1.58 (0.83, 3.00)
Caesarean section	71 (41)	0.87 (0.72, 1.04)	548 (47.3)	Reference	101 (56.7)	1.21 (1.05, 1.39)*
Preterm birth	9 (4.8)	1.17 (0.59, 2.33)	54 (4.4)	Reference	11 (5.9)	1.31 (0.70, 2.46)
NICU admission	24 (12.9)	0.95 (0.65, 1.39)	168 (13.6)	Reference	31 (16.7)	1.22 (0.88, 1.70)
Neonatal hospitalization ≥5 d	12 (6.5)	1.01 (0.59, 1.73)	71 (5.8)	Reference	17 (9.1)	1.56 (1.03, 2.38)*
Severe neonatal problem	2 (1.1)	0.47 (0.11, 1.94)	26 (2.1)	Reference	6 (3.2)	1.48 (0.63, 3.50)
Neonatal hyperbilirubinemia	30 (16.1)	1.03 (0.72, 1.46)	191 (15.5)	Reference	24 (12.9)	0.83 (0.56, 1.23)
LGA > 90th	17 (9.3)	0.81 (0.50, 1.31)	132 (10.9)	Reference	23 (12.5)	1.09 (0.73, 1.65)
SGA < 10th	11 (6)	1.24 (0.67, 2.30)	60 (5)	Reference	8 (4.3)	0.72 (0.48, 1.12)
Macrosomia	11 (5.9)	0.83 (0.45, 1.52)	84 (6.9)	Reference	16 (8.6)	1.20 (0.72, 1.99)
Low birthweight	6 (3.2)	1.47 (0.61, 3.52)	26 (2.1)	Reference	8 (4.3)	1.96 (0.90, 4.26)

aRR: adjusted relative risk; CI: confidence interval; GDM: gestational diabetes mellitus; LGA: large for gestational age; NICU: neonatal intensive care unit; PIH: pregnancy-induced hypertension; SGA: small for gestational age.

*P <0.05

Table S4. Association of pregnancy outcomes with gestational weight gain in late pregnancy (>17 week)

	Below (n=236)		Average (n=1233)		Above (n=248)	
Outcomes	n (%)	aRR (95% CI)	n (%)	aRR	n (%)	aRR (95% CI)
GDM	52 (22)	2.67 (1.98, 3.61) *	97 (7.9)	Reference	8 (3.2)	0.41 (0.20, 0.83) *
PIH	7 (3)	0.82 (0.37, 1.78)	44 (3.6)	Reference	15 (6.1)	1.52 (0.86, 2.69)
Caesarean section	105 (46.9)	0.93 (0.80, 1.08)	548 (47.3)	Reference	129 (56.3)	1.24 (1.09, 1.41)*
Preterm birth	6 (2.5)	0.50 (0.20, 1.24)	54 (4.4)	Reference	12 (4.8)	1.12 (0.59, 2.12)
NICU admission	35 (14.8)	1.11 (0.80, 1.55)	168 (13.6)	Reference	27 (10.9)	0.76 (0.53, 1.10)
Neonatal hospitalization ≥5 d	14 (5.9)	1.13 (0.65, 1.97)	71 (5.8)	Reference	11 (4.4)	0.78 (0.43, 1.43)
Severe neonatal problem	6 (2.5)	1.60 (0.67, 3.80)	26 (2.1)	Reference	7 (2.8)	1.28 (0.58, 2.84)
Neonatal hyperbilirubinemia	28 (11.9)	0.77 (0.53, 1.12)	191 (15.5)	Reference	25 (10.1)	0.64 (0.43, 0.94) *
LGA > 90th	9 (3.9)	0.31 (0.16, 0.60)*	132 (10.9)	Reference	51 (20.8)	2.01 (1.50, 2.70)*
SGA < 10th	17 (7.4)	1.68 (1.00, 2.82) *	60 (5)	Reference	3 (1.2)	0.24 (0.07, 0.75)*
Macrosomia	5 (2.1)	0.30 (0.12, 0.73)*	84 (6.9)	Reference	31 (12.6)	1.90 (1.30, 2.78)*
Low birthweight	8 (3.4)	1.69 (0.78, 3.68)	26 (2.1)	Reference	3 (1.2)	0.54 (0.16, 1.76)

aRR: adjusted relative risk; CI: confidence interval; GDM: gestational diabetes mellitus; LGA: large for gestational age; NICU: neonatal intensive care unit; PIH: pregnancy-induced hypertension; SGA: small for gestational age.

*P <0.05

Table S5. Association of pregnancy outcomes with gestational weight gain in late pregnancy (>17 week), by infant sex (27 sex unknown)

Outcomes	Male					Female				
	Below (n=110)		Average (n=646) (reference)	Above (n=120)		Below (n=120)		Average (n=569) (reference)	Above (n=125)	
	n (%)	aRR (95% CI)	n (%)	n (%)	aRR (95% CI)	n (%)	aRR (95% CI)	n (%)	n (%)	aRR (95% CI)
GDM	21(19.1)	2.41 (1.52, 3.84)*	53 (8.2)	3 (2.5)	0.30 (0.10, 0.96) *	29(24.2)	2.86 (1.88, 4.35)*	43 (7.6)	5 (4)	0.52 (0.21, 1.28)
PIH	2 (1.8)	0.54 (0.13, 2.22)	25 (3.9)	5 (4.2)	0.95 (0.37, 2.42)	5 (4.2)	1.16 (0.44, 3.04)	19 (3.3)	9 (7.2)	2.31 (1.08, 4.95)
Caesarean section	61 (57)	1.11 (0.93, 1.33)	291 (47.5)	62 (56.4)	1.27 (1.06, 1.52)*	41(36.6)	0.74 (0.57, 0.96)*	250 (47.3)	66 (56.4)	1.23(1.03, 1.48)*
Preterm birth	1 (0.9)	0.16 (0.02, 1.14)	35 (5.4)	7 (5.8)	1.13 (0.51, 2.49)	4 (3.3)	0.97 (0.32, 2.91)	17 (3)	4 (3.2)	1.23 (0.42, 3.62)
NICU admission	16(14.6)	1.28 (0.77, 2.13)	86 (13.3)	12 (10)	0.74 (0.42, 1.30)	16(13.3)	0.88 (0.58, 1.35)	75 (13.2)	14 (11.2)	0.84 (0.54, 1.30)
Neonatal hospitalization ≥5 d	5 (4.6)	0.84 (0.33, 2.13)	42 (6.5)	4 (3.3)	0.52 (0.19, 1.41)	6 (5)	0.83 (0.42, 1.64)	28 (4.9)	7 (5.6)	0.87 (0.47, 1.59)
Severe neonatal problem	0	NA	17 (2.6)	4 (3.3)	1.41 (0.48, 4.10)	5 (4.2)	2.39 (0.88, 6.54)	9 (1.6)	3 (2.4)	1.22 (0.35, 4.27)
Neonatal hyperbilirubinemia	13(11.8)	0.80 (0.47, 1.37)	100 (15.5)	9 (7.5)	0.46 (0.24, 0.89)*	15(12.5)	0.78 (0.47, 1.30)	90 (15.8)	16 (12.8)	0.79 (0.48, 1.30)
LGA > 90th	2 (1.8)	0.18 (0.04, 0.73)*	62 (9.7)	25 (20.8)	2.18 (1.43, 3.32)*	7 (5.8)	0.38 (0.18, 0.81)*	70 (12.3)	26 (20.8)	1.74 (1.17, 2.61)*
SGA < 10th	8 (7.3)	1.31 (0.64, 2.70)	37 (5.8)	2 (1.7)	0.28 (0.07, 1.13)	9 (7.5)	1.97 (0.94, 4.15)	23 (4)	1 (0.8)	0.17 (0.02, 1.27)
Macrosomia	3 (2.7)	0.33 (0.11, 1.04)	50 (7.8)	19 (15.8)	2.05 (1.27, 3.31) *	2 (1.7)	0.26 (0.06, 1.05)	33 (5.8)	12 (9.6)	1.71 (0.92, 3.19)
Low birthweight	2 (1.8)	0.95 (0.22, 4.11)	14 (2.2)	1 (0.8)	0.34 (0.05, 2.59)	5 (4.2)	2.48 (0.87, 7.11)	10 (1.8)	1 (0.8)	0.42 (0.05, 3.29)

aRR: adjusted relative risk; CI: confidence interval; GDM: gestational diabetes mellitus; LGA: large for gestational age; NICU: neonatal intensive care unit; PIH: pregnancy-induced hypertension; SGA: small for gestational age.

*P <0.05

Table S6. Association of pregnancy outcomes with total gestational weight gain

	Below (n=392)		Average (n=1842)		Above (n=396)	
Outcome	n (%)	aRR (95% CI)	n (%)	aRR	n (%)	aRR (95% CI)
GDM	60 (15.3)	1.51 (1.15, 1.98) *	176 (9.6)	Reference	27 (6.8)	0.72 (0.49, 1.07)
PIH	6 (1.5)	0.43 (0.19, 0.97) *	65 (3.5)	Reference	26 (6.6)	1.78 (1.14, 2.76) *
Caesarean section	163 (45)	0.96 (0.85, 1.09)	778 (45.2)	Reference	203 (55.5)	1.20 (1.08, 1.32)*
Preterm birth	15 (3.8)	0.83 (0.47, 1.45)	81 (4.4)	Reference	22 (5.6)	1.35 (0.85, 2.13)
NICU admission	61 (15.6)	1.08 (0.85, 1.36)	257 (14)	Reference	45 (11.4)	0.78 (0.59, 1.04)
Neonatal hospitalization ≥5 d	27 (6.9)	1.19 (0.82, 1.72)	107 (5.8)	Reference	19 (4.8)	0.78 (0.50, 1.23)
Severe neonatal problem	11 (2.8)	1.48 (0.78, 2.81)	37 (2)	Reference	7 (1.8)	0.82 (0.37, 1.79)
Neonatal hyperbilirubinemia	58 (14.8)	0.97 (0.75, 1.26)	285 (15.5)	Reference	47 (11.9)	0.75 (0.56, 1.00)
LGA > 90th	20 (5.2)	0.48 (0.30, 0.74) *	192 (10.6)	Reference	80 (20.4)	1.91 (1.51, 2.42) *
SGA < 10th	27 (7)	1.53 (1.01, 2.32) *	87 (4.8)	Reference	10 (2.5)	0.54 (0.28, 1.02)
Macrosomia	11 (2.8)	0.44 (0.24, 0.80) *	115 (6.3)	Reference	53 (13.5)	2.16 (1.60, 2.93) *
Low birthweight	15 (3.8)	1.72 (0.96, 3.08)	41 (2.2)	Reference	9 (2.3)	1.04 (0.51, 2.12)

aRR: adjusted relative risk; CI: confidence interval; GDM: gestational diabetes mellitus; LGA: large for gestational age; NICU: neonatal intensive care unit; PIH: pregnancy-induced hypertension; SGA: small for gestational age.

*P <0.05

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3-4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6
Objectives	3	State specific objectives, including any prespecified hypotheses	7
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	8
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	n/a
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	9-11
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	9
Bias	9	Describe any efforts to address potential sources of bias	9
Study size	10	Explain how the study size was arrived at	8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	10-11
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	12-13
		(*b*) Describe any methods used to examine subgroups and interactions	12
		(*c*) Explain how missing data were addressed	12
		(*d*) If applicable, explain how loss to follow-up was addressed	12
		(*e*) Describe any sensitivity analyses	n/a
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	13
		(b) Give reasons for non-participation at each stage	fig 1
		(c) Consider use of a flow diagram	fig 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	table 1
		(b) Indicate number of participants with missing data for each variable of interest	n/a
		(c) Summarise follow-up time (eg, average and total amount)	13
Outcome data	15*	Report numbers of outcome events or summary measures over time	table 2-3
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted	14-15

		estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	
		(*b*) Report category boundaries when continuous variables were categorized	n/a
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n/a
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	15
Discussion			
Key results	18	Summarise key results with reference to study objectives	16
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	16-17
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	17-22
Generalisability	21	Discuss the generalisability (external validity) of the study results	22
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	23

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Gestational weight gain and adverse pregnancy outcomes: a prospective cohort study

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Abstract

Objective To assess the associations of gestational weight gain (GWG) in early and late pregnancy with subsequent risks of adverse pregnancy outcomes in Chinese women.

Design Prospective cohort study.

Setting Shanghai, China.

Participants We studied 2630 nulliparous singleton pregnant women with complete data on weight gain in early (≤17 week of gestation) and late (>17 week) pregnancy in the Shanghai Birth Cohort.

Methods GWG was standardized into z-scores by gestational age and categorized as low (z score <-1), normal (-1 to 1), and high (>1). The adjusted relative risks (aRRs) and 95% confidence intervals (CIs) were estimated through log-binomial regression models. Interaction effects between GWG and some other adjustment factors were tested, further stratified analyses were performed separately where interaction terms were significant.

Outcome measures Adverse maternal and neonatal outcomes.

Results Independent from GWG in late pregnancy, higher GWG in early pregnancy was associated with higher risks of gestational diabetes mellitus (aRR: 1.66; 95% CI: 1.11–2.48), caesarean section (aRR: 1.21; 95% CI: 1.05–1.39), and prolonged hospitalization (aRR: 1.56; 95% CI: 1.03–2.38). Higher GWG in late pregnancy was independently associated with higher risks of caesarean section (aRR: 1.24; 95% CI: 1.09–1.41), large for gestational age (aRR: 2.01; 95% CI: 1.50–2.7), and macrosomia (aRR: 1.90; 95% CI: 1.30–2.78). In addition, the risk of gestational hypertension increased significantly with increased total GWG (aRR: 1.78; 95% CI: 1.14–2.76). The effects of GWG in late pregnancy on maternal and neonatal outcomes were significantly different between the women bearing a female and the women bearing male fetus.

Conclusion The GWG associations with adverse pregnancy outcomes differ at early and late pregnancy, and there may be effect modification by fetal sex in the association of GWG in late pregnancy with some pregnancy outcomes.

Keywords gestational weight gain, pregnancy outcomes, z-scores, fetal sex

Strengths and limitations of this study

1. Weight gain data collected before and during pregnancy enabled us to investigate the effect of timing of weight gain on the outcomes.
2. The use of z-scores instead of original weight gain value to account for the gestational-age-dependent nature of GWG allowed us to differentiate the effect caused by weight gain from the effect caused by duration of pregnancy.
3. Effect modification by fetal sex was investigated.
4. Only short-term rather than long-term pregnancy outcomes were investigated.
5. Pre-pregancy weight was self-reported rather than measured.

Introduction

Gestational weight gain (GWG) has been associated with pregnancy outcomes. Insufficient weight gain has been linked with increased risks of low birth weight, small for gestational age (SGA) and preterm birth, while excessive weight gain has been associated with large for gestational age (LGA), gestational diabetes mellitus (GDM), preeclampsia, preterm birth, caesarean section, infant mortality and childhood obesity[1-2]. However, although women are routinely weighed in clinical settings and receive gestational weight gain advice[3-4], a high proportion of pregnant women gain above or below GWG weight ranges recommended by the guidelines[5]. Based on data collected from 23 studies involving more than 1.3 million women, GWG was below or above the weight gain range suggested by Institute of Medicine (IOM) guidelines in 23% and 47% of pregnancies, respectively[1], and the prevalence of excess gestational weight gain appears to be on the rise[6].

It is well established that total GWG affects pregnancy outcomes[7]. Some studies suggest that GWG during early pregnancy may be more important than GWG at late pregnancy for developing certain pregnancy outcomes such as GDM and adverse

cardio-metabolic profile in the offspring[8-11]. Overall, studies examining associations of early GWG with perinatal outcomes have been relatively few, and these studies have often not accounted for the effects of weight gain during other periods of pregnancy[12]. In a Chinese population-based study, our objective was to explore the association of GWG during early and late pregnancy with maternal and neonatal outcomes .

Materials and Methods

Study design and data source

This prospective cohort study is based on the recently developed Shanghai Birth Cohort (SBC) which has been described in details elsewhere[13]. Briefly, the SBC is a prospective observational study conducted in Shanghai, China, aiming to examine factors affecting fecundability, pregnancy outcomes, child growth and development, and risks of diseases. The cohort recruited 4127 women in pre-conception care (701) or early antenatal care (3426). Written informed consent was obtained from the participants. The data was collected between September 1st, 2013 and November 31th, 2016, resulting in 3699 live births. The collected data included maternal demographical characteristics, health behaviors, reproductive history, as well as clinical information

related to pregnancy, birth and pregnancy outcomes. This study was approved by Xinhua Hospital Research Ethics Committee, Shanghai Jiao Tong University School of Medicine (reference number: XHEC-F-NSFC-2018-122).

Study population

The present study collected the data from all singleton pregnancies in women with age ≥20 years old who started antenatal care before 17 week's gestation and delivered at ≥28 week of gestation with data available on weight gains in early and late gestation in the SBC cohort.

Gestational age was estimated based on the date of last menstruation period and confirmed by first trimester ultrasound date. The eligible data collected in this study were obtained from: (1) self-reported pre-pregnancy weight (kg); (2) weight and height (cm) measured in early pregnancy (17 week of gestation or less); and (3) weight measured within the last week of pregnancy. Subjects were excluded if: (1) weight in early pregnancy <30 kg or >350 kg; or (2) z-score of gestational weight gain <-4.0 or >4.0, the methods used in the study were similar to the study conducted by Johansson et al[14]. Women with pre-existing medical conditions such as pre-gestational diabetes,

hypo- or hyper-thyroidism (affecting GWG)[15] and heart/liver/kidney diseases were also excluded.

Weight measurements

Pre-pregnancy weight (kg) was based on self-reporting, while weight at early pregnancy and at delivery was routinely measured to the nearest 0.1 kg using the available electronic weighing device in the prenatal care clinics. Height (cm) at the first prenatal visit was routinely measured to the nearest 0.1 cm using the available electronic stadiometer in the hospital. Pre-pregnancy body mass index (BMI; kg/m^2) was calculated as pre-pregnancy weight (kg) divided by height $(m)^2$ and categorized as underweight (<18.5 kg/m^2), normal weight (18.5 to 24.9 kg/m^2), overweight (25.0 to 29.9 kg/m^2), and obese (≥ 30.0 kg/m^2)[16].

The 2009 IOM recommendations suggested 0.5 to 2 kg weight gain for women in the first trimester (0 to 13 week)[5] and the 50^{th} centile GWG for women at gestational age $\leq$17 week is below 2 kg according to the INTERGROWTH-21^{st} Project[2]. However, early pregnancy in this study was defined as gestational age $\leq$17 week so as to include virtually all women who started the first antenatal care in the hospital[17]. In addition,

the 2009 IOM recommendations suggested total GWG of 12.5 to 18 kg for women with pre-pregnancy BMI less than 18.5 (underweight); 11.5 to 16 kg for those with BMI of 18.5 to 24.9 (normal weight); 7 to 11.5 kg for those with an initial BMI of 25.0 to 29.9 (overweight); and 5 to 9 kg for those with an initial BMI greater than 30.0 (obese) [5]. In this study, due to the sporadic number of obese women, we analyze them together with overweight women. We examined GWG in early pregnancy (the last weight measured ≤17 week minus pre-pregnancy weight) and late pregnancy (last measurement of weight prior to delivery minus the last weight measured ≤17 week). Total GWG was calculated as last measurement of weight before delivery minus pre-pregnancy weight. All GWG values were standardized into z-scores by gestational age, stratified by BMI categories. The means and standard deviations (SD) of GWGs in early pregnancy and late pregnancy were used to convert the GWG values into z-scores. All GWG z-scores were first examined as continuous variables, and then categorized as <-1.0 (below), -1.0 to +1.0 (average) and > +1.0 (above) in data analyses. The analyses for GWG in early pregnancy were restricted to women whose GWGs in late pregnancy were average (-1.0 to +1.0). Similarly, the analyses for late pregnancy

weight gain were restricted to women with weight gain value in early pregnancy within -1.0 to +1.0.

Covariates

Co-variables included fetal sex, maternal age (20 to 34, ≥35 years), parity (0, ≥1), pre-pregnancy body mass index (BMI) categories (underweight, normal, overweight/obese), alcohol/tobacco use (yes or no), GDM (yes or no), gestational hypertension (yes or no) and length of gestation (28 to 36, ≥37 week).

Outcomes

The outcomes included gestational diabetes mellitus (GDM), gestational hypertension, caesarean section, preterm birth, neonatal intensive care unit (NICU) admission, neonatal prolonged hospitalization (≥5 days), severe neonatal outcomes, neonatal hyperbilirubinemia (≤12 mg/dL), LGA, SGA, macrosomia (>4000 g) and low birthweight (<2500 g).

All women received a 75 g oral glucose tolerance test (OGTT) during 24-28 week of gestation. GDM was diagnosed according to the IADPSG criteria: if anyone had the glucose values fell at or above the following thresholds: fasting 5.1 mmol/L, 1 hour

10.0 mmol/L, 2 hour 8.5 mmol/L. Gestational hypertension was defined as de novo hypertension (systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg) after 20 week's gestation. Preterm birth was defined as gestational age at delivery <37 week. SGA was defined as birth weight ≤10th percentile, and LGA as birth weight ≥90th percentile according to Chinese sex- and gestational age-specific birth weight standards[18]. Severe neonatal outcomes included death, 5 minute APGAR score <7, hypoglycemia (<40 mg/dL), sepsis, cardiopulmonary resuscitation or ventilator support within 24 hours after birth, severe respiratory disorders (respiratory distress syndrome or transient tachypnea of the newborn), serious birth defects, seizures, necrotizing enterocolitis, and hypoxic-ischemic encephalopathy.

Statistical analyses

Maternal demographic characteristics and clinical factors were compared across GWG groups. Continuous variables were described by mean with standard deviation (SD) or median with interquartile range (IQR). Categorical variables were described by frequencies (%). Analysis of variance or Kruskal-Wallis H tests were performed for continuous data, and chi-square tests or Fisher's exact tests were performed for

categorical data.

The incidence of adverse pregnancy outcomes were examined among three GWG groups. Multivariate log-binomial regression models were used to estimate the unadjusted relative risks (RRs), adjusted relative risks (ARRs) and 95% confidence intervals (CIs) of adverse pregnancy outcomes across GWG groups. Regression model for maternal outcomes were adjusted for only co-variables with $p < 0.2$ (maternal age, parity, pre-pregnancy BMI, alcohol/tobacco use, fetal sex and length of gestation). Women with GDM or HIP have long been known to be at increased risk for adverse neonatal outcomes, including neonatal intensive care admission, cesarean section, preterm delivery <37 weeks and neonatal morbidity[19, 20]. As a result, neonatal outcomes models were further adjusted for GDM and PIH in addition to the aforementioned factors. Effects between weight gain and fetal sex and other covariates on adverse neonatal outcomes were also investigated. Interaction effects between GWG and fetal sex and other covariates (parity, maternal pre-pregnancy BMI, maternal age) on adverse maternal and neonatal outcomes were also tested.

All analyses were performed using the Statistical Analysis System (SAS) for Windows,

version 9.4 (SAS Institute, Cary, NC). P<0.05 was considered statistically significant.

Patient and public involvement

No patients were involved in the design, or conduct, or reporting, or dissemination plans of our research.

Results

Study population and characteristics

A total of 2630 pregnant women met the study inclusion criteria (Figure 1). The characteristics of all pregnant women in the study by total GWG is shown in Table 1. Among them, 1605 women who gained average weight in late pregnancy (z-score -1 to +1) were analyzed for the association of GWG in early pregnancy with the outcomes (Table S1); while 1717 women who gained average weight in early pregnancy were analyzed for the association of GWG in late pregnancy with the outcomes (Table S2). It should be noticed that for the two analytic datasets, the reference group was the same group of women who had average GWG in both early and late pregnancy (n=1233).

Weight gain during early pregnancy

The risks of maternal and neonatal outcomes for GWG in early pregnancy are presented in Figure 2A and Table S3. Lower GWG was not significantly associated with pregnancy outcomes, compared with the average GWG. In contrast, the risks of GDM (aRR=1.66; 95% CI: 1.11-2.48), caesarean section (aRR=1.21; 95% CI: 1.05-1.39) and prolonged hospitalization (aRR=1.56; 95% CI: 1.03-2.38) were higher in the group with GWG above average in early pregnancy. No significant interactions between GWG in early pregnancy and covariates were observed.

Weight gain during late pregnancy

Associations of GWG in late pregnancy with perinatal outcomes are presented in Figure 2B and Table S4. In contrast to early pregnancy, the risks for GDM and SGA decreased significantly with increased GWG in late pregnancy, whereas the risks for LGA and macrosomia increased. Weight gain above average was correlated with a higher risk for caesarean section (aRR=1.24; 95% CI: 1.09-1.41) in late pregnancy. In addition, higher GWG showed a protective effect against neonatal hyperbilirubinemia (aRR=0.64; 95% CI: 0.43-0.94).

Significant interactions were identified between GWG in late pregnancy and fetal sex.

Figure 3 and Table S5 shows the associations of late pregnancy weight gain with pregnancy outcomes stratified by fetal sex. The risks for LGA and caesarean section significantly increased in women with higher GWG in late pregnancy, but the risk of GDM increased with less GWG, regardless of fetal sex. However, higher risks of gestational hypertension (aRR=2.31; 95% CI: 1.08-4.95) was only observed in women bearing a female fetus with higher GWG. Conversely, higher GWG in late pregnancy was associated with GDM (aRR=0.30; 95% CI: 0.10-0.96), neonatal hyperbilirubinemia (aRR=0.46; 95% CI: 0.24-0.89) and macrosomia (aRR=2.05; 95% CI: 1.27-3.31) for women bearing a boy, but not for women bearing a girl, indicating effect modifications by fetal sex. But when stratified by fetal sex, the lower risk of SGA with higher GWG was no longer observed.

Total weight gain during pregnancy

Figure 2C and Table S6 show results for pregnancy outcomes by total GWG. The effect sizes of GWG in late pregnancy on pregnancy outcomes were almost identical with the effect sizes of total GWG. Similar to late pregnancy, the risks for LGA, macrosomia and gestational hypertension increased significantly with increased total GWG. Higher

GWG was also linked with a higher risk for caesarean section (aRR=1.78; 95% CI: 1.14-2.76). Moreover, total GWG below the average was associated with higher risks of GDM (aRR=1.51; 95% CI: 1.15-1.98) and SGA (aRR=1.53; 95% CI: 1.01-2.32). No significant interactions between total GWG and other covariates were identified.

Discussion

Main Findings

In this study, we found different associations of gestational stage-specific weight gain with maternal and neonatal outcomes. Of those, independent of GWG in late pregnancy, higher GWG in early pregnancy was associated with higher risks of GDM, caesarean section, and neonatal prolonged hospitalization.

Strengths and limitations

There are strengths in our study. In the study, some improvements have been made when compared with other studies reported in the literature. First, the SBC database contains detailed clinical data including pre-pregnancy weight, weight measurements during pregnancy and pregnancy weight measurements before delivery. This made it possible to study GWG in both early and late pregnancy. In addition, it is difficult to

disentangle the effects of GWG on adverse pregnancy outcomes from the effects of the gestation duration, because GWG is highly correlated with the gestational duration. However, the use of GWG z-scores in our study can overcome this limitation. This method ensured that the weight gain of women who experience adverse pregnancy outcomes would be compared with the weight gain of women without adverse outcomes at the same point in pregnancy[14, 21].

There are also limitations in our study. We only investigated the short-term perinatal outcomes. Recently, researchers have linked an individual's susceptibility to chronic disease such as cardio-metabolic disease and obesity in later life to events during the intrauterine phase of development[8, 22-23]. Further studies on long-term outcomes would provide important evidence regarding the associations between chronic diseases and events during the intrauterine phase.

Interpretation

Associations between insufficient or excessive weight gain during the whole pregnancy and maternal and child health outcomes have been well described[1-2, 7]. A meta-analysis of pooled 1309136 participant data from 23 cohort studies showed that women who

gained high weight were more likely to have LGA, caesarean section and macrosomia, while women who gained less weight were at higher risk of SGA[1]. These findings are in line with the association of maternal weight gain with adverse pregnancy outcomes in our study.

There is growing recognition that the impacts of gestational stage-specific weight gain on pregnancy outcomes may vary[8-9, 22, 24-25]. GWG in early pregnancy largely reflects maternal fat deposition, whereas GWG thereafter is mainly attributed to maternal and amniotic fluid expansion, and growth of the fetus, placenta and uterus[5]. In this study, mothers with increased fat deposition during pregnancy may affect the adiposity of the offspring by higher placental transfer of nutrients, such as glucose and free fatty acids, which may lead to maternal pregnancy complications, such as GDM, and permanent fetal and childhood adaptations in appetite, energy metabolism and neuro-endocrine function [25-26]. Therefore, GWG in early pregnancy, prior to the development of pregnancy outcomes, might be as or more important than GWG in late pregnancy with respect to pregnancy outcomes[9, 14]. A study of 5908 Netherlands mother-offspring pairs reported that higher weight gain in early pregnancy was associated with an

adverse cardio-metabolic profile in the offspring[8]. Similarly, a study of 5154 UK mother-offspring pairs showed that GWG in the first 14 week tended to be incrementally associated with offspring BMI, waist circumference and fat mass in children at age 9 years, but after 14 week of gestation, only high levels of GWG were associated with offspring's adiposity measures, highlighting the importance of the timing of weight gain in pregnancy[24].

Studies to clarify the relationship between gestational stage-specific weight gain and adverse pregnancy outcomes have been sporadic. A study of Korean pregnant women found that GWG velocity at early pregnancy was significantly associated with GDM, gestational hypertension, cesarean section, LGA, and macrosomia[12]. However, the analyses have not accounted for the effects of weight gain in other periods of pregnancy. In contrast, our analyses for early/late pregnancy GWG were restricted to women whose GWG z-scores in other pregnancy stage were normal, and thus the observed associations are independent of GWG in different periods. Our data from a large population-based Chinese cohort in Shanghai showed that higher, but not lower, maternal GWG in early pregnancy was associated with increased risks of adverse

pregnancy outcomes, including GDM, caesarean section and prolonged hospitalization. In late pregnancy, low weight gain was associated with GDM as well as SGA, and high weight gain was associated with caesarean section, LGA and macrosomia.

High GWG in early pregnancy has been associated with an increased risk of GDM, while there are some inconsistent data concerning the associations of GWG in second and third trimester or the whole pregnancy with GDM[11, 27-29]. Our study presents results which are in consistent with results produced by other studies [12, 27, 30] indicating that higher GWG in early pregnancy may increase the risk of developing GDM, but higher GWG in late pregnancy shows a reversed association. The discrepancy might be due to that women diagnosed with GDM might have undergone weight control interventions such as prescribed diet and physical exercise after the GDM diagnosis. Avoiding high weight gain in early pregnancy may prevent GDM, and health professionals who assist prenatal care might consider preemptive actions in high-risk pregnant women.

The risk of gestational hypertension increases significantly with higher maternal total GWG. A study of 29861 women from 25 hospitals in America showed that early weight

gain over the 2009 IOM recommendation were shown to be associated with the development of gestational hypertension[31]. In a study of 101259 women with chronic hypertension, women who gained the amount of weight above the GWG range recommended by IOM guidelines were at increased risks of eclampsia[32]. Given the known vascular permeability and decreased plasma oncotic pressure that accompanies preeclampsia and its association with rapid weight gain[33], excessive GWG may be a cause of hypertensive disease of pregnancy.

Total GWG on average (-1 to +1) in our study were 15.2±2.3 kg for women with pre-pregnancy BMI less than 18.5 (underweight) and 15.0±2.5 kg for those who with pre-pregnancy BMI of 18.5 to 24.9 (normal weight), which corresponded to the 2009 IOM recommendations. Specifically, the 2009 IOM recommendations suggested GWG of 12.5 to 18 kg for underweight women and 11.5 to 16 kg for normal weight women[5]. However, due to the sporadic number of obese women, we analyzed them together with overweight women. Total GWG on average were 12.3±3.7 kg for women with pre-pregnancy BMI greater than 25.0 (overweight and obese) in our study, which in general was higher than the 2009 IOM recommended GWG range with 7 to 11.5 kg for

overweight and 5 to 9 kg for obese[5]. The most important reason for this difference is that the IOM recommendation was derived largely from data collected among white women and may not well represent Chinese Population[34]. Therefore, we plan to establish GWG standards that can be applied to Chinese population.

Our data suggest effect modification by fetal sex in the association of GWG in late pregnancy with birth outcomes. Recent studies suggest that fetus sex may affect pregnancy outcomes[35-36]. Although not very clear, how fetal sex may influence these outcomes may be explained by several factors. The placenta is an active endocrine organ, a sex-specific maternal-placental-fetal interaction may be involved[24]. Animal studies suggest that maternal baseline BMI and GWG are associated with the hormonal milieu, including insulin resistance[37]. In agreement with this concept, a growing body of evidence link early pregnancy GWG with cord blood hormones that may affect fetal growth and development[38]. Previous studies reported fetal sex differences in maternal first trimester hormones concentrations[15, 35, 39]. The resultant intrauterine environment may affect fetal development.

Our findings may have clinical implications. First, from early pregnancy onwards,

GWG may affect subsequent maternal and neonatal outcomes. Second, although interventions to limit GWG in late pregnancy are effective, the benefits might be modest at best. To mitigate the harms of excessive weight gain, addressing the importance of gaining the appropriate amount of weight in both early and late pregnancy should be integrated into routine prenatal care[1, 7, 40].

Conclusion

The GWG associations with adverse pregnancy outcomes differ at early and late pregnancy, and there may be effect modification by fetal sex in the association of GWG in late pregnancy with some pregnancy outcomes. Weight gain management should be integrated into the routine prenatal care to decrease the risks of adverse pregnancy outcomes.

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Contributors YW and SW participated in interpretation of data and involved in drafting the manuscript. SG, ZM and LD analyzed the data and critically revised the manuscript. ZL, JZ and XH made substantial contributions to conception and design,

interpreted the data, and critically revised the manuscript. All authors read and approved the final manuscript.

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Table 1. Characteristics of pregnant women in the study cohort (n=2630)

Characteristic	Total	Total gestational weight gain			*P*
		Below (n=392)	Average (n=1842)	Above (n=396)	
Maternal age (year), mean ± SD	29.4 ± 3.6	29.9 ± 3.8	29.4 ± 3.5	28.5 ± 3.6	<0.0001
Maternal age ≥35 years, n (%)	241 (9.2)	51 (13)	169 (9.2)	21 (5.3)	0.0002
Nulliparous, n (%)	2216 (84.3)	325 (82.9)	1532 (83.2)	359 (90.7)	0.0027
Education, university degree and above, n (%)	2404 (91.5)	362 (92.6)	1702 (92.5)	340 (85.7)	0.0007
ART, n (%)	55 (2.1)	9 (2.3)	37 (2)	9 (2.3)	0.9834
Tobacco smoking, n (%)	72 (2.7)	7 (1.8)	41 (2.2)	24 (6.1)	<0.0001
Alcohol use, n (%)	338 (12.9)	52 (13.3)	240 (13)	46 (11.6)	0.7221
Pre-pregnancy BMI (kg/m^2), mean ± SD	21.3 ± 3.0	21.7 ± 3.1	21.2 ± 3.0	21.5 ± 2.9	0.0139
Pre-pregnancy BMI categories, n (%)					
Underweight (< 18.5 kg/m^2)	396 (15.1)	54 (13.8)	292 (15.9)	50 (12.6)	0.7530
Normal weight (18.5–24.9 kg/m^2)	1980 (75.3)	298 (76)	1372 (74.5)	310 (78.3)	
Overweight and obese (≥ 25 kg/m^2)	254 (9.7)	40 (10.2)	178 (9.7)	36 (9.1)	
Gestational age at the first prenatal visit (week), median (IQR)	15 (3)	14 (3)	15 (3)	15 (3)	0.1986
GWG in early pregnancy by BMI categories (kg), mean ± SD					
All women	2.2 ± 2.9	-0.2 ± 2.8	2.1 ± 2.2	4.9 ± 3.2	<0.0001
Underweight (< 18.5 kg/m^2)	2.5 ± 2.4	0.9 ± 1.9	2.4 ± 2.0	4.8 ± 3.0	<0.0001
Normal weight (18.5–24.9 kg/m^2)	2.3±2.8	0.0 ± 2.8	2.2 ± 2.2	4.9 ± 3.1	<0.0001
Overweight and obese (≥ 25 kg/m^2)	1.4±3.6	-2.2 ± 3.3	1.5 ± 2.6	4.7 ± 4.4	<0.0001

GWG in late pregnancy by BMI categories (kg), mean ± SD					
All women	13.0 ± 3.5	8.2 ± 3.0	12.6 ± 2.9	17.8 ± 3.6	<0.0001
Underweight (< 18.5 kg/m^2)	13.0 ± 3.5	8.9 ± 1.9	12.8 ± 2.5	18.2 ± 3.8	<0.0001
Normal weight (18.5–24.9 kg/m^2)	12.9 ± 4.0	8.4 ± 3.0	12.8 ± 2.8	17.8 ± 3.6	<0.0001
Overweight and obese (≥ 25 kg/m^2)	11.0 ± 4.9	5.8 ± 3.3	10.8 ± 3.8	17.4 ± 3.8	<0.0001
GWG in whole pregnancy by BMI categories (kg), mean ± SD					
All women	15.0 ± 4.9	8.1 ± 2.6	14.8± 2.7	22.7 ± 2.9	<0.0001
Underweight (< 18.5 kg/m^2)	15.4 ± 4.2	9.7 ± 1.6	15.2 ± 2.3	23.1 ± 3.0	<0.0001
Normal weight (18.5–24.9 kg/m^2)	15.2 ± 4.7	8.4 ± 2.1	15.0 ± 2.5	22.7 ± 2.8	<0.0001
Overweight and obese (≥ 25 kg/m^2)	12.3 ± 6.1	3.7 ± 2.4	12.3 ± 3.7	22.0 ± 3.6	<0.0001
Gestational age at delivery (week), median (IQR)	39 (2)	39 (2)	39 (2)	39 (2)	0.0793
Birth weight (g), mean ± SD	3376 ± 450	3238 ± 422	3370 ± 438	3540 ± 480	<0.0001
Male infant, n (%)	1334 (51.4)	194 (50.4)	945 (52)	195 (49.5)	0.7951

ART: assisted reproductive technology; BMI: body mass index; GWG: gestational weight gain; IQR: interquartile range; SD: standard deviation.

Figure Legend

Figure 1. Study flow chart.

Figure 2. Associations of gestational weight gain with pregnancy outcomes.

(A) Associations of early gestational weight gain (≤17 week) with pregnancy outcomes. (B) Associations of late gestational weight gain (>17 week) with pregnancy outcomes. (C) Associations of total gestational weight gain with pregnancy outcomes.

NICU: neonatal intensive care unit; LGA: large for gestational age; SGA: small for gestational age; GDM: gestational diabetes mellitus; PIH: pregnancy-induced hypertension; GWG: gestational weight gain; ARR: adjusted relative risk. *<0.05

Average GWG group as the reference.

a1 The analysis was adjusted for maternal age, parity, pre-pregnancy BMI and length of gestation.

b1 The analysis was adjusted for parity, pre-pregnancy BMI, fetal sex, GDM and PIH.

c1 The analysis was adjusted for pre-pregnancy BMI, fetal sex, alcohol/tobacco use, length of gestation, GDM and PIH.

d1 The analysis was adjusted for maternal age, alcohol/tobacco use, GDM and PIH.

a2 The analysis was adjusted for maternal age and pre-pregnancy BMI.;

b2 The analysis was adjusted for parity, pre-pregnancy BMI, fetal sex and length of gestation.

c2 The analysis was adjusted for maternal age, parity, pre-pregnancy BM, GDM and PIH.

d2 The analysis was adjusted for parity, pre-pregnancy BMI, fetal sex, GDM and PIH.

e2 The analysis was adjusted for parity, pre-pregnancy BMI, alcohol/tobacco use, length of gestation, GDM and PIH.

f2 The analysis was adjusted for maternal age, alcohol/tobacco use and length of gestation.

a3 The analysis was adjusted for maternal age, parity, pre-pregnancy BMI, alcohol/tobacco use and fetal sex.

b3 The analysis was adjusted for parity, pre-pregnancy BMI and length of gestation.

c3 The analysis was adjusted for parity, pre-pregnancy BMI, length of gestation, GDM and PIH.

d3 The analysis was adjusted for maternal age, parity and length of gestation.

e3 The analysis was adjusted for pre-pregnancy BMI, fetal sex, length of gestation, GDM and PIH.

Figure 3. Associations of late gestational weight gain (>17 week) with pregnancy outcomes, stratified by fetal sex.

NICU: neonatal intensive care unit; LGA: large for gestational age; SGA: small for gestational age; GDM: gestational diabetes mellitus; PIH: pregnancy-induced hypertension; GWG: gestational weight gain; ARR: adjusted relative risk.

*<0.05

Average GWG group as the reference.

[a] The analysis was adjusted for maternal age and pre-pregnancy BMI.

[b] The analysis was adjusted for maternal age, parity, pre-pregnancy BMI, alcohol/tobacco use and length of gestation.

[c] The analysis was adjusted for maternal age, pre-pregnancy BMI, GDM and PIH.

[d] The analysis was adjusted for parity, pre-pregnancy BMI, alcohol/tobacco use and length of gestation.

[e] The analysis was adjusted for parity, alcohol/tobacco use, length of gestation, GDM and PIH.

[f] The analysis was adjusted for parity, pre-pregnancy BMI, length of gestation, GDM and PIH.

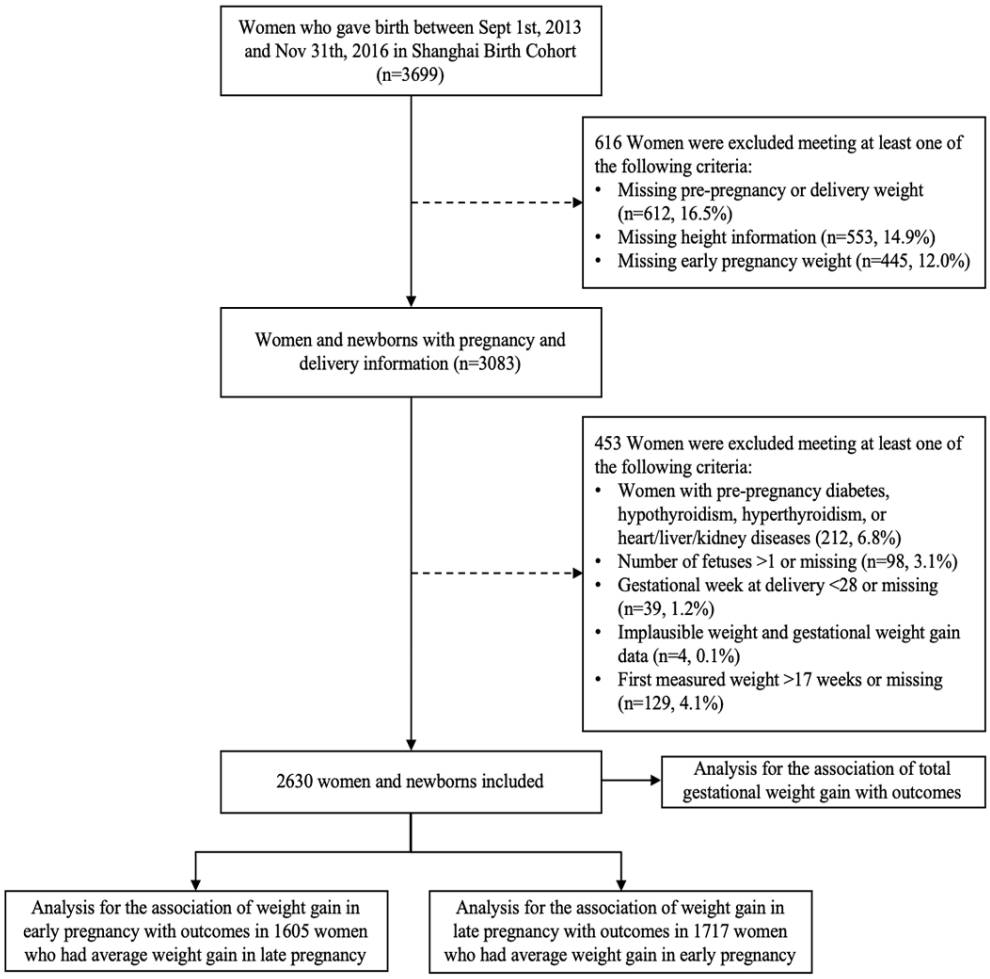

Figure 1. Study flow chart.

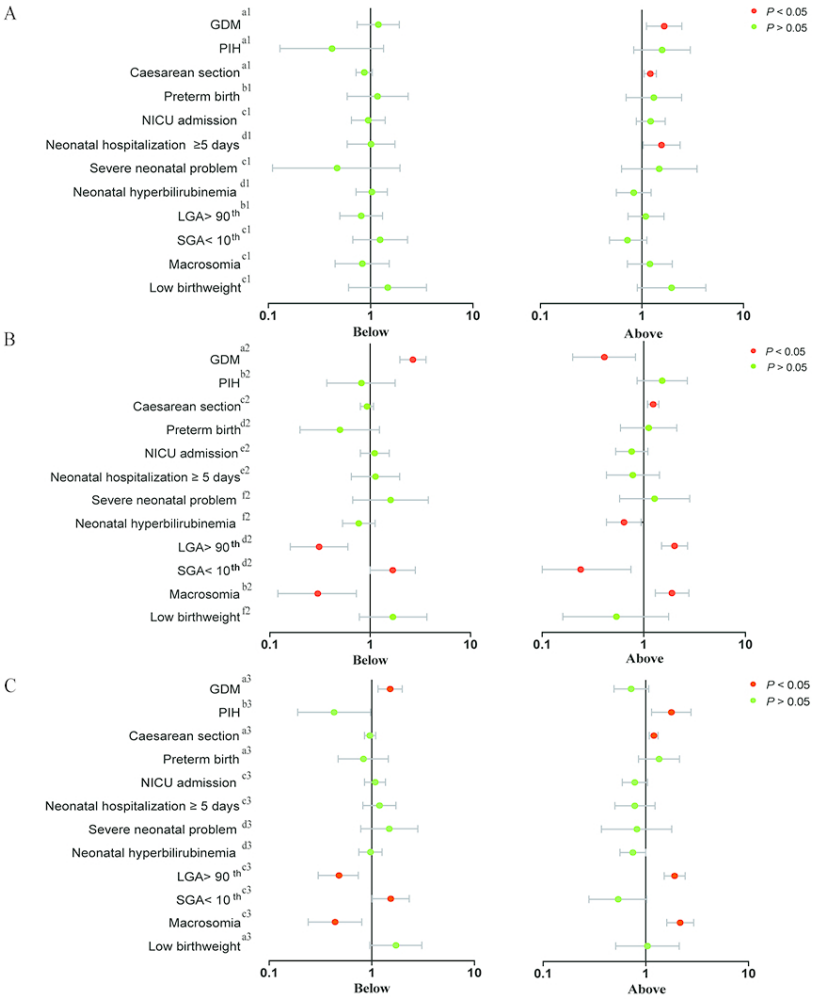

Figure 2. Associations of gestational weight gain with pregnancy outcomes.(A) Associations of early gestational weight gain (≤17 week) with pregnancy outcomes. (B) Associations of late gestational weight gain (>17 week) with pregnancy outcomes. (C) Associations of total gestational weight gain with pregnancy outcomes. NICU: neonatal intensive care unit; LGA: large for gestational age; SGA: small for gestational age; GDM: gestational diabetes mellitus; PIH: pregnancy-induced hypertension; GWG: gestational weight gain; ARR: adjusted relative risk. *<0.05Average GWG group as the reference.a1 The analysis was adjusted for maternal age, parity, pre-pregnancy BMI and length of gestation.b1 The analysis was adjusted for parity, pre-pregnancy BMI, fetal sex, GDM and PIH.c1 The analysis was adjusted for pre-pregnancy BMI, fetal sex, alcohol/tobacco use, length of gestation, GDM and PIH.d1 The analysis was adjusted for maternal age, alcohol/tobacco use, GDM and PIH.a2 The analysis was adjusted for maternal age and pre-pregnancy BMI.; b2 The analysis was adjusted for parity, pre-pregnancy BMI, fetal sex and length of gestation.c2 The analysis was adjusted for maternal age, parity, pre-pregnancy BM, GDM and PIH. d2 The analysis was adjusted for parity, pre-pregnancy BMI, fetal sex, GDM and PIH.e2 The analysis was adjusted for parity, pre-pregnancy BMI, alcohol/tobacco use, length of gestation, GDM and PIH.f2 The analysis was adjusted for maternal age, alcohol/tobacco use and length of gestation.a3 The analysis was adjusted for maternal age, parity, pre-pregnancy BMI, alcohol/tobacco use and fetal sex.b3 The analysis was adjusted for parity, pre-pregnancy BMI and length of gestation.c3 The analysis was adjusted for parity, pre-pregnancy BMI, length of gestation, GDM and PIH.d3 The analysis was adjusted for maternal age, parity and length of gestation.e3 The analysis was adjusted for pre-pregnancy BMI, fetal sex, length of gestation, GDM and PIH.

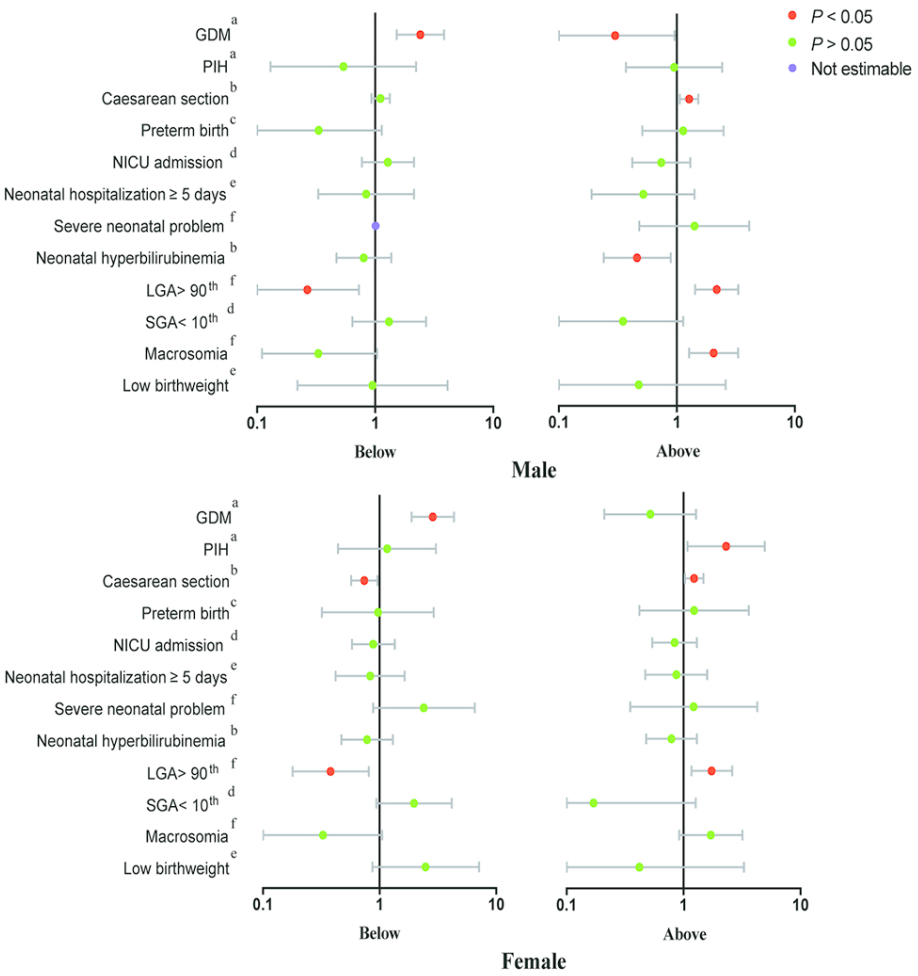

Figure 3. Associations of late gestational weight gain (>17 week) with pregnancy outcomes, stratified by fetal sex.NICU: neonatal intensive care unit; LGA: large for gestational age; SGA: small for gestational age; GDM: gestational diabetes mellitus; PIH: pregnancy-induced hypertension; GWG: gestational weight gain; ARR: adjusted relative risk. *<0.05Average GWG group as the reference.a The analysis was adjusted for maternal age and pre-pregnancy BMI.b The analysis was adjusted for maternal age, parity, pre-pregnancy BMI, alcohol/tobacco use and length of gestation.c The analysis was adjusted for maternal age, pre-pregnancy BMI, GDM and PIH.d The analysis was adjusted for parity, pre-pregnancy BMI, alcohol/tobacco use and length of gestation.e The analysis was adjusted for parity, alcohol/tobacco use, length of gestation, GDM and PIH.f The analysis was adjusted for parity, pre-pregnancy BMI, length of gestation, GDM and PIH.

Table S1. Maternal characteristics in the study of gestational weight gain in early pregnancy (≤17 week)

Characteristic	Below (n=186)	Average (n=1233)	Above (n=186)	*P*
Maternal age (year), mean ± SD	28.2 ± 3.4	29.4 ± 3.7	29.4 ± 3.5	0.0002
Maternal age ≥35 years, n (%)	11 (5.9)	126 (10.2)	14 (7.5)	0.5946
Nulliparous, n (%)	165 (88.7)	1011 (82)	155 (83.3)	0.1683
Education, university degree and above, n (%)	164 (88.1)	1138 (92.4)	162 (87.6)	0.8411
ART, n (%)	4 (2.2)	27 (2.2)	5 (2.7)	0.9110
Tobacco smoking, n (%)	4 (2.2)	26 (2.1)	9 (4.8)	0.0924
Alcohol use, n (%)	15 (8.1)	129 (10.5)	18 (9.37)	0.5876
Pre-pregnancy BMI (kg/m^2), mean ± SD	21.8 ± 3.1	21.2 ± 3.0	21.7 ± 3.1	0.0027
Pre-pregnancy BMI categories, n (%)				
Underweight (< 18.5 kg/m^2)	28 (15.1)	193 (15.7)	28 (15.1)	
Normal weight (18.5–24.9 kg/m^2)	134 (72)	929 (75.3)	133 (71.5)	0.9848
Overweight and obese (≥ 25 kg/m^2)	24 (12.9)	111 (9)	25 (13.4)	
Gestational age at the first prenatal visit (week), median (IQR)	14 (3)	14 (3)	15 (3)	0.8298
GWG in early pregnancy by BMI categories (kg), mean ± SD				
All women	-2.5 ± 2.0	2.1 ± 1.5	6.7 ± 2.1	<0.0001
Underweight (< 18.5 kg/m^2)	-0.6 ± 1.1	2.1 ± 1.2	6.4 ± 2.1	<0.0001
Normal weight (18.5–24.9 kg/m^2)	-2.5 ± 1.7	2.1 ± 1.5	7.0 ± 2.1	<0.0001
Overweight and obese (≥ 25 kg/m^2)	-4.7 ± 1.7	1.5 ± 1.8	5.7 ± 1.7	<0.0001
GWG in late pregnancy by BMI categories (kg), mean ± SD				
All women	12.5 ± 2.3	12.6 ± 2.3	12.3 ± 2.4	0.4854

Underweight (< 18.5 kg/m^2)	12.4 ± 1.9	12.7 ± 1.9	12.5 ± 1.8	0.6323
Normal weight (18.5–24.9 kg/m^2)	12.8 ± 2.2	12.7 ± 2.2	12.6 ± 2.1	0.8492
Overweight and obese (≥ 25 kg/m^2)	10.7 ± 2.2	11.1 ± 3.1	10.4 ± 3.3	0.5676
Gestational age at delivery (week), median (IQR)	39 (2)	39 (2)	39 (2)	0.9126
Birth weight (g), mean ± SD	3296 ± 435	3370 ± 446	3382 ± 515	0.0428
Male infant, n (%)	92 (50.3)	646 (53.2)	102 (55.4)	0.6091

ART: assisted reproductive technology; BMI: body mass index; GWG: gestational weight gain; IQR: interquartile range; SD: standard deviation.

Table S2. Maternal characteristics in the study of gestational weight gain in late pregnancy (>17 week)

Characteristic	Below (n=236)	Average (n=1233)	Above (n=248)	*P*
Maternal age (year), mean ± SD	30.4 ± 3.8	29.4 ± 3.7	27.9 ± 3.5	<0.0001
Maternal age ≥35 years, n (%)	37 (15.7)	126 (10.2)	10 (4)	<0.0001
Nulliparous, n (%)	183 (77.5)	1011 (82)	234 (94.4)	<0.0001
Education, university degree and above, n (%)	222 (94.1)	1138 (92.4)	214 (86.3)	0.0017
ART, n (%)	7 (3)	27 (2.2)	6 (2.4)	0.7701
Tobacco smoking, n (%)	4 (1.7)	26 (2.1)	12 (4.8)	0.0234
Alcohol use, n (%)	20 (8.5)	129 (10.5)	20 (8.1)	0.3841
Pre-pregnancy BMI (kg/m^2), mean ± SD	21.6 ± 3.1	21.2 ± 3.0	21.4 ± 3.1	0.0564
Pre-pregnancy BMI categories, n (%)				
Underweight (< 18.5 kg/m^2)	29 (12.3)	193 (15.7)	37 (14.9)	
Normal weight (18.5–24.9 kg/m^2)	178 (75.4)	929 (75.3)	189 (76.2)	0.3711
Overweight and obese (≥ 25 kg/m^2)	29 (12.3)	111 (9)	22 (8.9)	
Gestational age at the first prenatal visit (week), median (IQR)	14 (3)	14 (3)	14 (3)	0.4231
GWG in early pregnancy by BMI categories (kg), mean ± SD				
All women	2.1 ± 1.5	2.1 ± 1.5	2.3 ± 1.4	0.1943
Underweight (< 18.5 kg/m^2)	2.7 ± 1.4	2.1 ± 1.2	2.8 ± 1.3	0.0009
Normal weight (18.5–24.9 kg/m^2)	2.1 ± 1.5	2.1 ± 1.5	2.2 ± 1.5	0.7273
Overweight and obese (≥ 25 kg/m^2)	1.5 ± 1.6	1.5 ± 1.8	2.1 ± 1.2	0.2109
GWG in late pregnancy by BMI categories (kg), mean ± SD				
All women	7.0 ± 2.1	12.6 ± 2.3	19.1 ± 2.4	<0.0001

Underweight (< 18.5 kg/m^2)	7.9 ± 1.2	12.7 ± 1.9	19.2 ± 2.6	<0.0001
Normal weight (18.5–24.9 kg/m^2)	7.3 ± 1.9	12.7 ± 2.2	19.1 ± 2.2	<0.0001
Overweight and obese (≥ 25 kg/m^2)	4.1 ± 1.9	11.1 ± 3.1	18.3 ± 3.2	<0.0001
Gestational age at delivery (week), median (IQR)	39 (2)	39 (2)	39 (2)	0.0872
Birth weight (g), mean ± SD	3261 ± 397	3370 ± 446	3536 ± 461	<0.0001
Male infant, n (%)	110 (47.8)	646 (53.2)	120 (49)	0.8381

ART: assisted reproductive technology; BMI: body mass index; GWG: gestational weight gain; IQR: interquartile range; SD: standard deviation.

Table S3. Association of pregnancy outcomes by gestational weight gain in early pregnancy (≤17 week)

	Below (n=186)		Average (n=1233)		Above (n=186)	
Outcomes	n (%)	aRR (95% CI)	n (%)	aRR	n (%)	aRR (95% CI)
GDM	18 (9.7)	1.19 (0.74, 1.91)	97 (7.9)	Reference	25 (13.4)	1.66 (1.11, 2.48) *
PIH	3 (1.6)	0.42 (0.13, 1.34)	44 (3.6)	Reference	11 (5.9)	1.58 (0.83, 3.00)
Caesarean section	71 (41)	0.87 (0.72, 1.04)	548 (47.3)	Reference	101 (56.7)	1.21 (1.05, 1.39)*
Preterm birth	9 (4.8)	1.17 (0.59, 2.33)	54 (4.4)	Reference	11 (5.9)	1.31 (0.70, 2.46)
NICU admission	24 (12.9)	0.95 (0.65, 1.39)	168 (13.6)	Reference	31 (16.7)	1.22 (0.88, 1.70)
Neonatal hospitalization ≥5 d	12 (6.5)	1.01 (0.59, 1.73)	71 (5.8)	Reference	17 (9.1)	1.56 (1.03, 2.38)*
Severe neonatal problem	2 (1.1)	0.47 (0.11, 1.94)	26 (2.1)	Reference	6 (3.2)	1.48 (0.63, 3.50)
Neonatal hyperbilirubinemia	30 (16.1)	1.03 (0.72, 1.46)	191 (15.5)	Reference	24 (12.9)	0.83 (0.56, 1.23)
LGA > 90th	17 (9.3)	0.81 (0.50, 1.31)	132 (10.9)	Reference	23 (12.5)	1.09 (0.73, 1.65)
SGA < 10th	11 (6)	1.24 (0.67, 2.30)	60 (5)	Reference	8 (4.3)	0.72 (0.48, 1.12)
Macrosomia	11 (5.9)	0.83 (0.45, 1.52)	84 (6.9)	Reference	16 (8.6)	1.20 (0.72, 1.99)
Low birthweight	6 (3.2)	1.47 (0.61, 3.52)	26 (2.1)	Reference	8 (4.3)	1.96 (0.90, 4.26)

aRR: adjusted relative risk; CI: confidence interval; GDM: gestational diabetes mellitus; LGA: large for gestational age; NICU: neonatal intensive care unit; PIH: pregnancy-induced hypertension; SGA: small for gestational age.

*P <0.05

Table S4. Association of pregnancy outcomes with gestational weight gain in late pregnancy (>17 week)

	Below (n=236)		Average (n=1233)		Above (n=248)	
Outcomes	n (%)	aRR (95% CI)	n (%)	aRR	n (%)	aRR (95% CI)
GDM	52 (22)	2.67 (1.98, 3.61) *	97 (7.9)	Reference	8 (3.2)	0.41 (0.20, 0.83) *
PIH	7 (3)	0.82 (0.37, 1.78)	44 (3.6)	Reference	15 (6.1)	1.52 (0.86, 2.69)
Caesarean section	105 (46.9)	0.93 (0.80, 1.08)	548 (47.3)	Reference	129 (56.3)	1.24 (1.09, 1.41)*
Preterm birth	6 (2.5)	0.50 (0.20, 1.24)	54 (4.4)	Reference	12 (4.8)	1.12 (0.59, 2.12)
NICU admission	35 (14.8)	1.11 (0.80, 1.55)	168 (13.6)	Reference	27 (10.9)	0.76 (0.53, 1.10)
Neonatal hospitalization ≥5 d	14 (5.9)	1.13 (0.65, 1.97)	71 (5.8)	Reference	11 (4.4)	0.78 (0.43, 1.43)
Severe neonatal problem	6 (2.5)	1.60 (0.67, 3.80)	26 (2.1)	Reference	7 (2.8)	1.28 (0.58, 2.84)
Neonatal hyperbilirubinemia	28 (11.9)	0.77 (0.53, 1.12)	191 (15.5)	Reference	25 (10.1)	0.64 (0.43, 0.94) *
LGA > 90th	9 (3.9)	0.31 (0.16, 0.60)*	132 (10.9)	Reference	51 (20.8)	2.01 (1.50, 2.70)*
SGA < 10th	17 (7.4)	1.68 (1.00, 2.82) *	60 (5)	Reference	3 (1.2)	0.24 (0.07, 0.75)*
Macrosomia	5 (2.1)	0.30 (0.12, 0.73)*	84 (6.9)	Reference	31 (12.6)	1.90 (1.30, 2.78)*
Low birthweight	8 (3.4)	1.69 (0.78, 3.68)	26 (2.1)	Reference	3 (1.2)	0.54 (0.16, 1.76)

aRR: adjusted relative risk; CI: confidence interval; GDM: gestational diabetes mellitus; LGA: large for gestational age; NICU: neonatal intensive care unit; PIH: pregnancy-induced hypertension; SGA: small for gestational age.

*P <0.05

Table S5. Association of pregnancy outcomes with gestational weight gain in late pregnancy (>17 week), by infant sex (27 sex unknown)

Outcomes	Male					Female				
	Below (n=110)		Average (n=646) (reference)	Above (n=120)		Below (n=120)		Average (n=569) (reference)	Above (n=125)	
	n (%)	aRR (95% CI)	n (%)	n (%)	aRR (95% CI)	n (%)	aRR (95% CI)	n (%)	n (%)	aRR (95% CI)
GDM	21(19.1)	2.41 (1.52, 3.84)*	53 (8.2)	3 (2.5)	0.30 (0.10, 0.96) *	29(24.2)	2.86 (1.88, 4.35)*	43 (7.6)	5 (4)	0.52 (0.21, 1.28)
PIH	2 (1.8)	0.54 (0.13, 2.22)	25 (3.9)	5 (4.2)	0.95 (0.37, 2.42)	5 (4.2)	1.16 (0.44, 3.04)	19 (3.3)	9 (7.2)	2.31 (1.08, 4.95)
Caesarean section	61 (57)	1.11 (0.93, 1.33)	291 (47.5)	62 (56.4)	1.27 (1.06, 1.52)*	41(36.6)	0.74 (0.57, 0.96)*	250 (47.3)	66 (56.4)	1.23(1.03, 1.48)*
Preterm birth	1 (0.9)	0.16 (0.02, 1.14)	35 (5.4)	7 (5.8)	1.13 (0.51, 2.49)	4 (3.3)	0.97 (0.32, 2.91)	17 (3)	4 (3.2)	1.23 (0.42, 3.62)
NICU admission	16(14.6)	1.28 (0.77, 2.13)	86 (13.3)	12 (10)	0.74 (0.42, 1.30)	16(13.3)	0.88 (0.58, 1.35)	75 (13.2)	14 (11.2)	0.84 (0.54, 1.30)
Neonatal hospitalization ≥5 d	5 (4.6)	0.84 (0.33, 2.13)	42 (6.5)	4 (3.3)	0.52 (0.19, 1.41)	6 (5)	0.83 (0.42, 1.64)	28 (4.9)	7 (5.6)	0.87 (0.47, 1.59)
Severe neonatal problem	0	NA	17 (2.6)	4 (3.3)	1.41 (0.48, 4.10)	5 (4.2)	2.39 (0.88, 6.54)	9 (1.6)	3 (2.4)	1.22 (0.35, 4.27)
Neonatal hyperbilirubinemia	13(11.8)	0.80 (0.47, 1.37)	100 (15.5)	9 (7.5)	0.46 (0.24, 0.89)*	15(12.5)	0.78 (0.47, 1.30)	90 (15.8)	16 (12.8)	0.79 (0.48, 1.30)
LGA > 90th	2 (1.8)	0.18 (0.04, 0.73)*	62 (9.7)	25 (20.8)	2.18 (1.43, 3.32)*	7 (5.8)	0.38 (0.18, 0.81)*	70 (12.3)	26 (20.8)	1.74 (1.17, 2.61)*
SGA < 10th	8 (7.3)	1.31 (0.64, 2.70)	37 (5.8)	2 (1.7)	0.28 (0.07, 1.13)	9 (7.5)	1.97 (0.94, 4.15)	23 (4)	1 (0.8)	0.17 (0.02, 1.27)
Macrosomia	3 (2.7)	0.33 (0.11, 1.04)	50 (7.8)	19 (15.8)	2.05 (1.27, 3.31) *	2 (1.7)	0.26 (0.06, 1.05)	33 (5.8)	12 (9.6)	1.71 (0.92, 3.19)
Low birthweight	2 (1.8)	0.95 (0.22, 4.11)	14 (2.2)	1 (0.8)	0.34 (0.05, 2.59)	5 (4.2)	2.48 (0.87, 7.11)	10 (1.8)	1 (0.8)	0.42 (0.05, 3.29)

aRR: adjusted relative risk; CI: confidence interval; GDM: gestational diabetes mellitus; LGA: large for gestational age; NICU: neonatal intensive care unit; PIH: pregnancy-induced hypertension; SGA: small for gestational age.

*P <0.05

Table S6. Association of pregnancy outcomes with total gestational weight gain

	Below (n=392)		Average (n=1842)		Above (n=396)	
Outcome	n (%)	aRR (95% CI)	n (%)	aRR	n (%)	aRR (95% CI)
GDM	60 (15.3)	1.51 (1.15, 1.98) *	176 (9.6)	Reference	27 (6.8)	0.72 (0.49, 1.07)
PIH	6 (1.5)	0.43 (0.19, 0.97) *	65 (3.5)	Reference	26 (6.6)	1.78 (1.14, 2.76) *
Caesarean section	163 (45)	0.96 (0.85, 1.09)	778 (45.2)	Reference	203 (55.5)	1.20 (1.08, 1.32)*
Preterm birth	15 (3.8)	0.83 (0.47, 1.45)	81 (4.4)	Reference	22 (5.6)	1.35 (0.85, 2.13)
NICU admission	61 (15.6)	1.08 (0.85, 1.36)	257 (14)	Reference	45 (11.4)	0.78 (0.59, 1.04)
Neonatal hospitalization ≥5 d	27 (6.9)	1.19 (0.82, 1.72)	107 (5.8)	Reference	19 (4.8)	0.78 (0.50, 1.23)
Severe neonatal problem	11 (2.8)	1.48 (0.78, 2.81)	37 (2)	Reference	7 (1.8)	0.82 (0.37, 1.79)
Neonatal hyperbilirubinemia	58 (14.8)	0.97 (0.75, 1.26)	285 (15.5)	Reference	47 (11.9)	0.75 (0.56, 1.00)
LGA > 90th	20 (5.2)	0.48 (0.30, 0.74) *	192 (10.6)	Reference	80 (20.4)	1.91 (1.51, 2.42) *
SGA < 10th	27 (7)	1.53 (1.01, 2.32) *	87 (4.8)	Reference	10 (2.5)	0.54 (0.28, 1.02)
Macrosomia	11 (2.8)	0.44 (0.24, 0.80) *	115 (6.3)	Reference	53 (13.5)	2.16 (1.60, 2.93) *
Low birthweight	15 (3.8)	1.72 (0.96, 3.08)	41 (2.2)	Reference	9 (2.3)	1.04 (0.51, 2.12)

aRR: adjusted relative risk; CI: confidence interval; GDM: gestational diabetes mellitus; LGA: large for gestational age; NICU: neonatal intensive care unit; PIH: pregnancy-induced hypertension; SGA: small for gestational age.

*P <0.05

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3-4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6
Objectives	3	State specific objectives, including any prespecified hypotheses	7
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	8
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	n/a
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	9-11
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	9
Bias	9	Describe any efforts to address potential sources of bias	9
Study size	10	Explain how the study size was arrived at	8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	10-11
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	12-13
		(*b*) Describe any methods used to examine subgroups and interactions	12
		(*c*) Explain how missing data were addressed	12
		(*d*) If applicable, explain how loss to follow-up was addressed	12
		(*e*) Describe any sensitivity analyses	n/a
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	13
		(b) Give reasons for non-participation at each stage	fig 1
		(c) Consider use of a flow diagram	fig 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	table 1
		(b) Indicate number of participants with missing data for each variable of interest	n/a
		(c) Summarise follow-up time (eg, average and total amount)	13
Outcome data	15*	Report numbers of outcome events or summary measures over time	table 2-3
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted	14-15

		estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	
		(*b*) Report category boundaries when continuous variables were categorized	n/a
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n/a
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	15
Discussion			
Key results	18	Summarise key results with reference to study objectives	16
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	16-17
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	17-22
Generalisability	21	Discuss the generalisability (external validity) of the study results	22
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	23

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Gestational weight gain and adverse pregnancy outcomes: a prospective cohort study

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Abstract

Objective To assess the associations of gestational weight gain (GWG) in early and late pregnancy with subsequent risks of adverse pregnancy outcomes in Chinese women.

Design Prospective cohort study.

Setting Shanghai, China.

Participants We studied 2630 nulliparous singleton pregnant women with complete data on weight gain in early (≤17 week of gestation) and late (>17 week) pregnancy in the Shanghai Birth Cohort.

Methods GWG was standardized into z-scores by gestational age and categorized as low (z score <-1), normal (-1 to 1), and high (>1). The adjusted relative risks (aRRs) and 95% confidence intervals (CIs) were estimated through log-binomial regression models. Interaction effects between GWG and some other adjustment factors were tested, further stratified analyses were performed separately where interaction terms were significant.

Outcome measures Adverse maternal and neonatal outcomes.

Results Independent from GWG in late pregnancy, higher GWG in early pregnancy was associated with higher risks of gestational diabetes mellitus (aRR: 1.66; 95% CI: 1.11–2.48), caesarean section (aRR: 1.21; 95% CI: 1.05–1.39), and prolonged hospitalization (aRR: 1.56; 95% CI: 1.03–2.38). Higher GWG in late pregnancy was independently associated with higher risks of caesarean section (aRR: 1.24; 95% CI: 1.09–1.41), large for gestational age (aRR: 2.01; 95% CI: 1.50–2.7), and macrosomia (aRR: 1.90; 95% CI: 1.30–2.78). In addition, the risk of gestational hypertension increased significantly with increased total GWG (aRR: 1.78; 95% CI: 1.14–2.76). The effects of GWG in late pregnancy on maternal and neonatal outcomes were significantly different between the women bearing a female and the women bearing male fetus.

Conclusion The GWG associations with adverse pregnancy outcomes differ at early and late pregnancy, and there may be effect modification by fetal sex in the association of GWG in late pregnancy with some pregnancy outcomes.

Keywords gestational weight gain, pregnancy outcomes, z-scores, fetal sex

Strengths and limitations of this study

1. Weight gain data collected before and during pregnancy enabled us to investigate the effect of timing of weight gain on the outcomes.
2. The use of z-scores instead of original weight gain value to account for the gestational-age-dependent nature of GWG allowed us to differentiate the effect caused by weight gain from the effect caused by duration of pregnancy.
3. Effect modification by fetal sex was investigated.
4. Only short-term rather than long-term pregnancy outcomes were investigated.
5. Pre-pregancy weight was self-reported rather than measured.

Introduction

Gestational weight gain (GWG) has been associated with pregnancy outcomes. Insufficient weight gain has been linked with increased risks of low birth weight, small for gestational age (SGA) and preterm birth, while excessive weight gain has been associated with large for gestational age (LGA), gestational diabetes mellitus (GDM), preeclampsia, preterm birth, caesarean section, infant mortality and childhood obesity[1-2]. However, although women are routinely weighed in clinical settings and receive gestational weight gain advice[3-4], a high proportion of pregnant women gain above or below GWG weight ranges recommended by the guidelines[5]. Based on data collected from 23 studies involving more than 1.3 million women, GWG was below or above the weight gain range suggested by Institute of Medicine (IOM) guidelines in 23% and 47% of pregnancies, respectively[1], and the prevalence of excess gestational weight gain appears to be on the rise[6].

It is well established that total GWG affects pregnancy outcomes[7]. Some studies suggest that GWG during early pregnancy may be more important than GWG at late pregnancy for developing certain pregnancy outcomes such as GDM and adverse

cardio-metabolic profile in the offspring[8-11]. Overall, studies examining associations of early GWG with perinatal outcomes have been relatively few, and these studies have often not accounted for the effects of weight gain during other periods of pregnancy[12]. In a Chinese population-based study, our objective was to explore the association of GWG during early and late pregnancy with maternal and neonatal outcomes .

Materials and Methods

Study design and data source

This prospective cohort study is based on the recently developed Shanghai Birth Cohort (SBC) which has been described in details elsewhere[13]. Briefly, the SBC is a prospective observational study conducted in Shanghai, China, aiming to examine factors affecting fecundability, pregnancy outcomes, child growth and development, and risks of diseases. The cohort recruited 4127 women in pre-conception care (701) or early antenatal care (3426). Written informed consent was obtained from the participants. The data was collected between September 1st, 2013 and November 31th, 2016, resulting in 3699 live births. The collected data included maternal demographical characteristics, health behaviors, reproductive history, as well as clinical information

related to pregnancy, birth and pregnancy outcomes. This study was approved by Xinhua Hospital Research Ethics Committee, Shanghai Jiao Tong University School of Medicine (reference number: XHEC-F-NSFC-2018-122).

Study population

The present study collected the data from all singleton pregnancies in women with age ≥20 years old who started antenatal care before 17 week's gestation and delivered at ≥28 week of gestation with data available on weight gains in early and late gestation in the SBC cohort.

Gestational age was estimated based on the date of last menstruation period and confirmed by first trimester ultrasound date. The eligible data collected in this study were obtained from: (1) self-reported pre-pregnancy weight (kg); (2) weight and height (cm) measured in early pregnancy (17 week of gestation or less); and (3) weight measured within the last week of pregnancy. Subjects were excluded if: (1) weight in early pregnancy <30 kg or >350 kg; or (2) z-score of gestational weight gain <-4.0 or >4.0, the methods used in the study were similar to the study conducted by Johansson et al[14]. Women with pre-existing medical conditions such as pre-gestational diabetes,

hypo- or hyper-thyroidism (affecting GWG)[15] and heart/liver/kidney diseases were also excluded.

Weight measurements

Pre-pregnancy weight (kg) was based on self-reporting, while weight at early pregnancy and at delivery was routinely measured to the nearest 0.1 kg using the available electronic weighing device in the prenatal care clinics. Height (cm) at the first prenatal visit was routinely measured to the nearest 0.1 cm using the available electronic stadiometer in the hospital. Pre-pregnancy body mass index (BMI; kg/m^2) was calculated as pre-pregnancy weight (kg) divided by height $(m)^2$ and categorized as underweight (<18.5 kg/m^2), normal weight (18.5 to 24.9 kg/m^2), overweight (25.0 to 29.9 kg/m^2), and obese (≥ 30.0 kg/m^2)[16].

The 2009 IOM recommendations suggested 0.5 to 2 kg weight gain for women in the first trimester (0 to 13 week)[5] and the 50^{th} centile GWG for women at gestational age $\leq$17 week is below 2 kg according to the INTERGROWTH-21^{st} Project[2]. However, early pregnancy in this study was defined as gestational age $\leq$17 week so as to include virtually all women who started the first antenatal care in the hospital[17]. In addition,

the 2009 IOM recommendations suggested total GWG of 12.5 to 18 kg for women with pre-pregnancy BMI less than 18.5 (underweight); 11.5 to 16 kg for those with BMI of 18.5 to 24.9 (normal weight); 7 to 11.5 kg for those with an initial BMI of 25.0 to 29.9 (overweight); and 5 to 9 kg for those with an initial BMI greater than 30.0 (obese) [5]. In this study, due to the sporadic number of obese women, we analyze them together with overweight women. We examined GWG in early pregnancy (the last weight measured ≤17 week minus pre-pregnancy weight) and late pregnancy (last measurement of weight prior to delivery minus the last weight measured ≤17 week). Total GWG was calculated as last measurement of weight before delivery minus pre-pregnancy weight. All GWG values were standardized into z-scores by gestational age, stratified by BMI categories. The means and standard deviations (SD) of GWGs in early pregnancy and late pregnancy were used to convert the GWG values into z-scores. All GWG z-scores were first examined as continuous variables, and then categorized as <-1.0 (below), -1.0 to +1.0 (average) and > +1.0 (above) in data analyses. Previous studies suggested different associations of gestational stage-specific weight gain with maternal and neonatal outcomes[8]. For example, weight gain in early pregnancy is

associated with offspring BMI, whereas weight gain in mid pregnancy tended to be associated with the offspring's metabolic and inflammatory biomarkers[5, 8]. Thus, to disentangle the associations of other periods of GWG with pregnancy outcomes from GWG in specific periods, we restricted the analyses for GWG in early pregnancy in women whose GWGs in late pregnancy were average (-1.0 to +1.0). Similarly, the analyses for late pregnancy weight gain were restricted to women with weight gain value in early pregnancy within -1.0 to +1.0.

Covariates

Co-variables included fetal sex, maternal age (20 to 34, ≥35 years), parity (0, ≥1), pre-pregnancy body mass index (BMI) categories (underweight, normal, overweight/obese), alcohol/tobacco use (yes or no), GDM (yes or no), gestational hypertension (yes or no) and length of gestation (28 to 36, ≥37 week).

Outcomes

The outcomes included gestational diabetes mellitus (GDM), gestational hypertension, caesarean section, preterm birth, neonatal intensive care unit (NICU) admission, neonatal prolonged hospitalization (≥5 days), severe neonatal outcomes, neonatal

hyperbilirubinemia (≤12 mg/dL), LGA, SGA, macrosomia (>4000 g) and low birthweight (<2500 g).

All women received a 75 g oral glucose tolerance test (OGTT) during 24-28 week of gestation. GDM was diagnosed according to the IADPSG criteria: if anyone had the glucose values fell at or above the following thresholds: fasting 5.1 mmol/L, 1 hour 10.0 mmol/L, 2 hour 8.5 mmol/L. Gestational hypertension was defined as de novo hypertension (systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg) after 20 week's gestation. Preterm birth was defined as gestational age at delivery <37 week. SGA was defined as birth weight ≤10th percentile, and LGA as birth weight ≥90th percentile according to Chinese sex- and gestational age-specific birth weight standards[18]. Severe neonatal outcomes included death, 5 minute APGAR score <7, hypoglycemia (<40 mg/dL), sepsis, cardiopulmonary resuscitation or ventilator support within 24 hours after birth, severe respiratory disorders (respiratory distress syndrome or transient tachypnea of the newborn), serious birth defects, seizures, necrotizing enterocolitis, and hypoxic-ischemic encephalopathy.

Statistical analyses

Maternal demographic characteristics and clinical factors were compared across GWG groups. Continuous variables were described by mean with standard deviation (SD) or median with interquartile range (IQR). Categorical variables were described by frequencies (%). Analysis of variance or Kruskal-Wallis H tests were performed for continuous data, and chi-square tests or Fisher's exact tests were performed for categorical data.

The incidence of adverse pregnancy outcomes were examined among three GWG groups. Multivariate log-binomial regression models were used to estimate the unadjusted relative risks (RRs), adjusted relative risks (ARRs) and 95% confidence intervals (CIs) of adverse pregnancy outcomes across GWG groups. Regression model for maternal outcomes were adjusted for only co-variables with $p < 0.2$ (maternal age, parity, pre-pregnancy BMI, alcohol/tobacco use, fetal sex and length of gestation). Women with GDM or HIP have long been known to be at increased risk for adverse neonatal outcomes, including neonatal intensive care admission, cesarean section, preterm delivery <37 weeks and neonatal morbidity[19, 20]. As a result, neonatal outcomes models were further adjusted for GDM and PIH in addition to the

aforementioned factors. Effects between weight gain and fetal sex and other covariates on adverse neonatal outcomes were also investigated. Interaction effects between GWG and fetal sex and other covariates (parity, maternal pre-pregnancy BMI, maternal age) on adverse maternal and neonatal outcomes were also tested.

All analyses were performed using the Statistical Analysis System (SAS) for Windows, version 9.4 (SAS Institute, Cary, NC). $P<0.05$ was considered statistically significant.

Patient and public involvement

No patients were involved in the design, or conduct, or reporting, or dissemination plans of our research.

Results

Study population and characteristics

A total of 2630 pregnant women met the study inclusion criteria (Figure 1). The characteristics of all pregnant women in the study by total GWG is shown in Table 1. Among them, 1605 women who gained average weight in late pregnancy (z-score -1 to +1) were analyzed for the association of GWG in early pregnancy with the outcomes (Table S1); while 1717 women who gained average weight in early pregnancy were

analyzed for the association of GWG in late pregnancy with the outcomes (Table S2). It should be noticed that for the two analytic datasets, the reference group was the same group of women who had average GWG in both early and late pregnancy (n=1233).

Weight gain during early pregnancy

The risks of maternal and neonatal outcomes for GWG in early pregnancy are presented in Figure 2A and Table S3. Lower GWG was not significantly associated with pregnancy outcomes, compared with the average GWG. In contrast, the risks of GDM (aRR=1.66; 95% CI: 1.11-2.48), caesarean section (aRR=1.21; 95% CI: 1.05-1.39) and prolonged hospitalization (aRR=1.56; 95% CI: 1.03-2.38) were higher in the group with GWG above average in early pregnancy. No significant interactions between GWG in early pregnancy and covariates were observed.

Weight gain during late pregnancy

Associations of GWG in late pregnancy with perinatal outcomes are presented in Figure 2B and Table S4. In contrast to early pregnancy, the risks for GDM and SGA decreased significantly with increased GWG in late pregnancy, whereas the risks for LGA and macrosomia increased. Weight gain above average was correlated with a higher risk for

caesarean section (aRR=1.24; 95% CI: 1.09-1.41) in late pregnancy. In addition, higher GWG showed a protective effect against neonatal hyperbilirubinemia (aRR=0.64; 95% CI: 0.43-0.94).

Significant interactions were identified between GWG in late pregnancy and fetal sex. Figure 3 and Table S5 shows the associations of late pregnancy weight gain with pregnancy outcomes stratified by fetal sex. The risks for LGA and caesarean section significantly increased in women with higher GWG in late pregnancy, but the risk of GDM increased with less GWG, regardless of fetal sex. However, higher risks of gestational hypertension (aRR=2.31; 95% CI: 1.08-4.95) was only observed in women bearing a female fetus with higher GWG. Conversely, higher GWG in late pregnancy was associated with GDM (aRR=0.30; 95% CI: 0.10-0.96), neonatal hyperbilirubinemia (aRR=0.46; 95% CI: 0.24-0.89) and macrosomia (aRR=2.05; 95% CI: 1.27-3.31) for women bearing a boy, but not for women bearing a girl, indicating effect modifications by fetal sex. But when stratified by fetal sex, the lower risk of SGA with higher GWG was no longer observed.

Total weight gain during pregnancy

Figure 2C and Table S6 show results for pregnancy outcomes by total GWG. The effect sizes of GWG in late pregnancy on pregnancy outcomes were almost identical with the effect sizes of total GWG. Similar to late pregnancy, the risks for LGA, macrosomia and gestational hypertension increased significantly with increased total GWG. Higher GWG was also linked with a higher risk for caesarean section (aRR=1.78; 95% CI: 1.14-2.76). Moreover, total GWG below the average was associated with higher risks of GDM (aRR=1.51; 95% CI: 1.15-1.98) and SGA (aRR=1.53; 95% CI: 1.01-2.32). No significant interactions between total GWG and other covariates were identified.

Discussion

Main Findings

In this study, we found different associations of gestational stage-specific weight gain with maternal and neonatal outcomes. Of those, independent of GWG in late pregnancy, higher GWG in early pregnancy was associated with higher risks of GDM, caesarean section, and neonatal prolonged hospitalization.

Strengths and limitations

There are strengths in our study. In the study, some improvements have been made

when compared with other studies reported in the literature. First, the SBC database contains detailed clinical data including pre-pregnancy weight, weight measurements during pregnancy and pregnancy weight measurements before delivery. This made it possible to study GWG in both early and late pregnancy. In addition, it is difficult to disentangle the effects of GWG on adverse pregnancy outcomes from the effects of the gestation duration, because GWG is highly correlated with the gestational duration. However, the use of GWG z-scores in our study can overcome this limitation. This method ensured that the weight gain of women who experience adverse pregnancy outcomes would be compared with the weight gain of women without adverse outcomes at the same point in pregnancy[14, 21].

There are also limitations in our study. We only investigated the short-term perinatal outcomes. Recently, researchers have linked an individual's susceptibility to chronic disease such as cardio-metabolic disease and obesity in later life to events during the intrauterine phase of development[8, 22-23]. Further studies on long-term outcomes would provide important evidence regarding the associations between chronic diseases and events during the intrauterine phase.

Interpretation

Associations between insufficient or excessive weight gain during the whole pregnancy and maternal and child health outcomes have been well described[1-2, 7]. A meta-analysis of pooled 1309136 participant data from 23 cohort studies showed that women who gained high weight were more likely to have LGA, caesarean section and macrosomia, while women who gained less weight were at higher risk of SGA[1]. These findings are in line with the association of maternal weight gain with adverse pregnancy outcomes in our study.

There is growing recognition that the impacts of gestational stage-specific weight gain on pregnancy outcomes may vary[8-9, 22, 24-25]. GWG in early pregnancy largely reflects maternal fat deposition, whereas GWG thereafter is mainly attributed to maternal and amniotic fluid expansion, and growth of the fetus, placenta and uterus[5]. In this study, mothers with increased fat deposition during pregnancy may affect the adiposity of the offspring by higher placental transfer of nutrients, such as glucose and free fatty acids, which may lead to maternal pregnancy complications, such as GDM, and permanent fetal and childhood adaptations in appetite, energy metabolism and neuro-endocrine function [25-26]. Therefore, GWG in early pregnancy, prior to the development of

pregnancy outcomes, might be as or more important than GWG in late pregnancy with respect to pregnancy outcomes[9, 14]. A study of 5908 Netherlands mother-offspring pairs reported that higher weight gain in early pregnancy was associated with an adverse cardio-metabolic profile in the offspring[8]. Similarly, a study of 5154 UK mother-offspring pairs showed that GWG in the first 14 week tended to be incrementally associated with offspring BMI, waist circumference and fat mass in children at age 9 years, but after 14 week of gestation, only high levels of GWG were associated with offspring's adiposity measures, highlighting the importance of the timing of weight gain in pregnancy[24].

Studies to clarify the relationship between gestational stage-specific weight gain and adverse pregnancy outcomes have been sporadic. A study of Korean pregnant women found that GWG velocity at early pregnancy was significantly associated with GDM, gestational hypertension, cesarean section, LGA, and macrosomia[12]. However, the analyses have not accounted for the effects of weight gain in other periods of pregnancy. In contrast, our analyses for early/late pregnancy GWG were restricted to women whose GWG z-scores in other pregnancy stage were normal, and thus the observed

associations are independent of GWG in different periods. Our data from a large population-based Chinese cohort in Shanghai showed that higher, but not lower, maternal GWG in early pregnancy was associated with increased risks of adverse pregnancy outcomes, including GDM, caesarean section and prolonged hospitalization. In late pregnancy, low weight gain was associated with GDM as well as SGA, and high weight gain was associated with caesarean section, LGA and macrosomia.

High GWG in early pregnancy has been associated with an increased risk of GDM, while there are some inconsistent data concerning the associations of GWG in second and third trimester or the whole pregnancy with GDM[11, 27-29]. Our study presents results which are in consistent with results produced by other studies [12, 27, 30] indicating that higher GWG in early pregnancy may increase the risk of developing GDM, but higher GWG in late pregnancy shows a reversed association. The discrepancy might be due to that women diagnosed with GDM might have undergone weight control interventions such as prescribed diet and physical exercise after the GDM diagnosis. Avoiding high weight gain in early pregnancy may prevent GDM, and health professionals who assist prenatal care might consider preemptive actions in high-risk

pregnant women.

The risk of gestational hypertension increases significantly with higher maternal total GWG. A study of 29861 women from 25 hospitals in America showed that early weight gain over the 2009 IOM recommendation were shown to be associated with the development of gestational hypertension[31]. In a study of 101259 women with chronic hypertension, women who gained the amount of weight above the GWG range recommended by IOM guidelines were at increased risks of eclampsia[32]. Given the known vascular permeability and decreased plasma oncotic pressure that accompanies preeclampsia and its association with rapid weight gain[33], excessive GWG may be a cause of hypertensive disease of pregnancy.

Total GWG on average (-1 to +1) in our study were 15.2±2.3 kg for women with pre-pregnancy BMI less than 18.5 (underweight) and 15.0±2.5 kg for those who with pre-pregnancy BMI of 18.5 to 24.9 (normal weight), which corresponded to the 2009 IOM recommendations. Specifically, the 2009 IOM recommendations suggested GWG of 12.5 to 18 kg for underweight women and 11.5 to 16 kg for normal weight women[5]. However, due to the sporadic number of obese women, we analyzed them together with

overweight women. Total GWG on average were 12.3 ± 3.7 kg for women with pre-pregnancy BMI greater than 25.0 (overweight and obese) in our study, which in general was higher than the 2009 IOM recommended GWG range with 7 to 11.5 kg for overweight and 5 to 9 kg for obese[5]. The most important reason for this difference is that the IOM recommendation was derived largely from data collected among white women and may not well represent Chinese Population[34]. Therefore, we plan to establish GWG standards that can be applied to Chinese population.

Our data suggest effect modification by fetal sex in the association of GWG in late pregnancy with birth outcomes. Recent studies suggest that fetus sex may affect pregnancy outcomes[35-36]. Although not very clear, how fetal sex may influence these outcomes may be explained by several factors. The placenta is an active endocrine organ, a sex-specific maternal-placental-fetal interaction may be involved[24]. Animal studies suggest that maternal baseline BMI and GWG are associated with the hormonal milieu, including insulin resistance[37]. In agreement with this concept, a growing body of evidence link early pregnancy GWG with cord blood hormones that may affect fetal growth and development[38]. Previous studies reported fetal sex differences in maternal

first trimester hormones concentrations[15, 35, 39]. The resultant intrauterine environment may affect fetal development.

Our findings may have clinical implications. First, from early pregnancy onwards, GWG may affect subsequent maternal and neonatal outcomes. Second, although interventions to limit GWG in late pregnancy are effective, the benefits might be modest at best. To mitigate the harms of excessive weight gain, addressing the importance of gaining the appropriate amount of weight in both early and late pregnancy should be integrated into routine prenatal care[1, 7, 40].

Conclusion

The GWG associations with adverse pregnancy outcomes differ at early and late pregnancy, and there may be effect modification by fetal sex in the association of GWG in late pregnancy with some pregnancy outcomes. Weight gain management should be integrated into the routine prenatal care to decrease the risks of adverse pregnancy outcomes.

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Contributors YW and SW participated in interpretation of data and involved in drafting the manuscript. SG, ZM and LD analyzed the data and critically revised the manuscript. ZL, JZ and XH made substantial contributions to conception and design, interpreted the data, and critically revised the manuscript. All authors read and approved the final manuscript.

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Competing interests None declared. Completed disclosure of interests form available to view online as supporting information.

Patient consent for publication Not required.

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Data sharing statement Data are available upon reasonable request. Prospective scientists who are interested in the SBC are welcomed to contact the authors via e-mail to [junjimzhang@sina.com].

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Table 1. Characteristics of pregnant women in the study cohort (n=2630)

Characteristic	Total	Total gestational weight gain			*P*
		Below (n=392)	Average (n=1842)	Above (n=396)	
Maternal age (year), mean ± SD	29.4 ± 3.6	29.9 ± 3.8	29.4 ± 3.5	28.5 ± 3.6	<0.0001
Maternal age ≥35 years, n (%)	241 (9.2)	51 (13)	169 (9.2)	21 (5.3)	0.0002
Nulliparous, n (%)	2216 (84.3)	325 (82.9)	1532 (83.2)	359 (90.7)	0.0027
Education, university degree and above, n (%)	2404 (91.5)	362 (92.6)	1702 (92.5)	340 (85.7)	0.0007
ART, n (%)	55 (2.1)	9 (2.3)	37 (2)	9 (2.3)	0.9834
Tobacco smoking, n (%)	72 (2.7)	7 (1.8)	41 (2.2)	24 (6.1)	<0.0001
Alcohol use, n (%)	338 (12.9)	52 (13.3)	240 (13)	46 (11.6)	0.7221
Pre-pregnancy BMI (kg/m^2), mean ± SD	21.3 ± 3.0	21.7 ± 3.1	21.2 ± 3.0	21.5 ± 2.9	0.0139
Pre-pregnancy BMI categories, n (%)					
Underweight (< 18.5 kg/m^2)	396 (15.1)	54 (13.8)	292 (15.9)	50 (12.6)	0.7530
Normal weight (18.5–24.9 kg/m^2)	1980 (75.3)	298 (76)	1372 (74.5)	310 (78.3)	
Overweight and obese (≥ 25 kg/m^2)	254 (9.7)	40 (10.2)	178 (9.7)	36 (9.1)	
Gestational age at the first prenatal visit (week), median (IQR)	15 (3)	14 (3)	15 (3)	15 (3)	0.1986
GWG in early pregnancy by BMI categories (kg), mean ± SD					
All women	2.2 ± 2.9	-0.2 ± 2.8	2.1 ± 2.2	4.9 ± 3.2	<0.0001
Underweight (< 18.5 kg/m^2)	2.5 ± 2.4	0.9 ± 1.9	2.4 ± 2.0	4.8 ± 3.0	<0.0001
Normal weight (18.5–24.9 kg/m^2)	2.3±2.8	0.0 ± 2.8	2.2 ± 2.2	4.9 ± 3.1	<0.0001
Overweight and obese (≥ 25 kg/m^2)	1.4±3.6	-2.2 ± 3.3	1.5 ± 2.6	4.7 ± 4.4	<0.0001

GWG in late pregnancy by BMI categories (kg), mean ± SD					
All women	13.0 ± 3.5	8.2 ± 3.0	12.6 ± 2.9	17.8 ± 3.6	<0.0001
Underweight (< 18.5 kg/m^2)	13.0 ± 3.5	8.9 ± 1.9	12.8 ± 2.5	18.2 ± 3.8	<0.0001
Normal weight (18.5–24.9 kg/m^2)	12.9 ± 4.0	8.4 ± 3.0	12.8 ± 2.8	17.8 ± 3.6	<0.0001
Overweight and obese (≥ 25 kg/m^2)	11.0 ± 4.9	5.8 ± 3.3	10.8 ± 3.8	17.4 ± 3.8	<0.0001
GWG in whole pregnancy by BMI categories (kg), mean ± SD					
All women	15.0 ± 4.9	8.1 ± 2.6	14.8± 2.7	22.7 ± 2.9	<0.0001
Underweight (< 18.5 kg/m^2)	15.4 ± 4.2	9.7 ± 1.6	15.2 ± 2.3	23.1 ± 3.0	<0.0001
Normal weight (18.5–24.9 kg/m^2)	15.2 ± 4.7	8.4 ± 2.1	15.0 ± 2.5	22.7 ± 2.8	<0.0001
Overweight and obese (≥ 25 kg/m^2)	12.3 ± 6.1	3.7 ± 2.4	12.3 ± 3.7	22.0 ± 3.6	<0.0001
Gestational age at delivery (week), median (IQR)	39 (2)	39 (2)	39 (2)	39 (2)	0.0793
Birth weight (g), mean ± SD	3376 ± 450	3238 ± 422	3370 ± 438	3540 ± 480	<0.0001
Male infant, n (%)	1334 (51.4)	194 (50.4)	945 (52)	195 (49.5)	0.7951

ART: assisted reproductive technology; BMI: body mass index; GWG: gestational weight gain; IQR: interquartile range; SD: standard deviation.

Figure Legend

Figure 1. Study flow chart.

Figure 2. Associations of gestational weight gain with pregnancy outcomes.

(A) Associations of early gestational weight gain (≤17 week) with pregnancy outcomes. (B) Associations of late gestational weight gain (>17 week) with pregnancy outcomes. (C) Associations of total gestational weight gain with pregnancy outcomes.

NICU: neonatal intensive care unit; LGA: large for gestational age; SGA: small for gestational age; GDM: gestational diabetes mellitus; PIH: pregnancy-induced hypertension; GWG: gestational weight gain; ARR: adjusted relative risk. *<0.05

Average GWG group as the reference.

[a1] The analysis was adjusted for maternal age, parity, pre-pregnancy BMI and length of gestation.

[b1] The analysis was adjusted for parity, pre-pregnancy BMI, fetal sex, GDM and PIH.

[c1] The analysis was adjusted for pre-pregnancy BMI, fetal sex, alcohol/tobacco use, length of gestation, GDM and PIH.

[d1] The analysis was adjusted for maternal age, alcohol/tobacco use, GDM and PIH.

[a2] The analysis was adjusted for maternal age and pre-pregnancy BMI.;

[b2] The analysis was adjusted for parity, pre-pregnancy BMI, fetal sex and length of gestation.

[c2] The analysis was adjusted for maternal age, parity, pre-pregnancy BM, GDM and PIH.

[d2] The analysis was adjusted for parity, pre-pregnancy BMI, fetal sex, GDM and PIH.

[e2] The analysis was adjusted for parity, pre-pregnancy BMI, alcohol/tobacco use, length of gestation, GDM and PIH.

[f2] The analysis was adjusted for maternal age, alcohol/tobacco use and length of gestation.

[a3] The analysis was adjusted for maternal age, parity, pre-pregnancy BMI, alcohol/tobacco use and fetal sex.

[b3] The analysis was adjusted for parity, pre-pregnancy BMI and length of gestation.

[c3] The analysis was adjusted for parity, pre-pregnancy BMI, length of gestation, GDM and PIH.

[d3] The analysis was adjusted for maternal age, parity and length of gestation.

[e3] The analysis was adjusted for pre-pregnancy BMI, fetal sex, length of gestation, GDM and PIH.

Figure 3. Associations of late gestational weight gain (>17 week) with pregnancy outcomes, stratified by fetal sex.

NICU: neonatal intensive care unit; LGA: large for gestational age; SGA: small for gestational age; GDM: gestational diabetes mellitus; PIH: pregnancy-induced hypertension; GWG: gestational weight gain; ARR: adjusted relative risk.

*<0.05

Average GWG group as the reference.

[a] The analysis was adjusted for maternal age and pre-pregnancy BMI.

[b] The analysis was adjusted for maternal age, parity, pre-pregnancy BMI, alcohol/tobacco use and length of gestation.

[c] The analysis was adjusted for maternal age, pre-pregnancy BMI, GDM and PIH.

[d] The analysis was adjusted for parity, pre-pregnancy BMI, alcohol/tobacco use and length of gestation.

[e] The analysis was adjusted for parity, alcohol/tobacco use, length of gestation, GDM and PIH.

[f] The analysis was adjusted for parity, pre-pregnancy BMI, length of gestation, GDM and PIH.

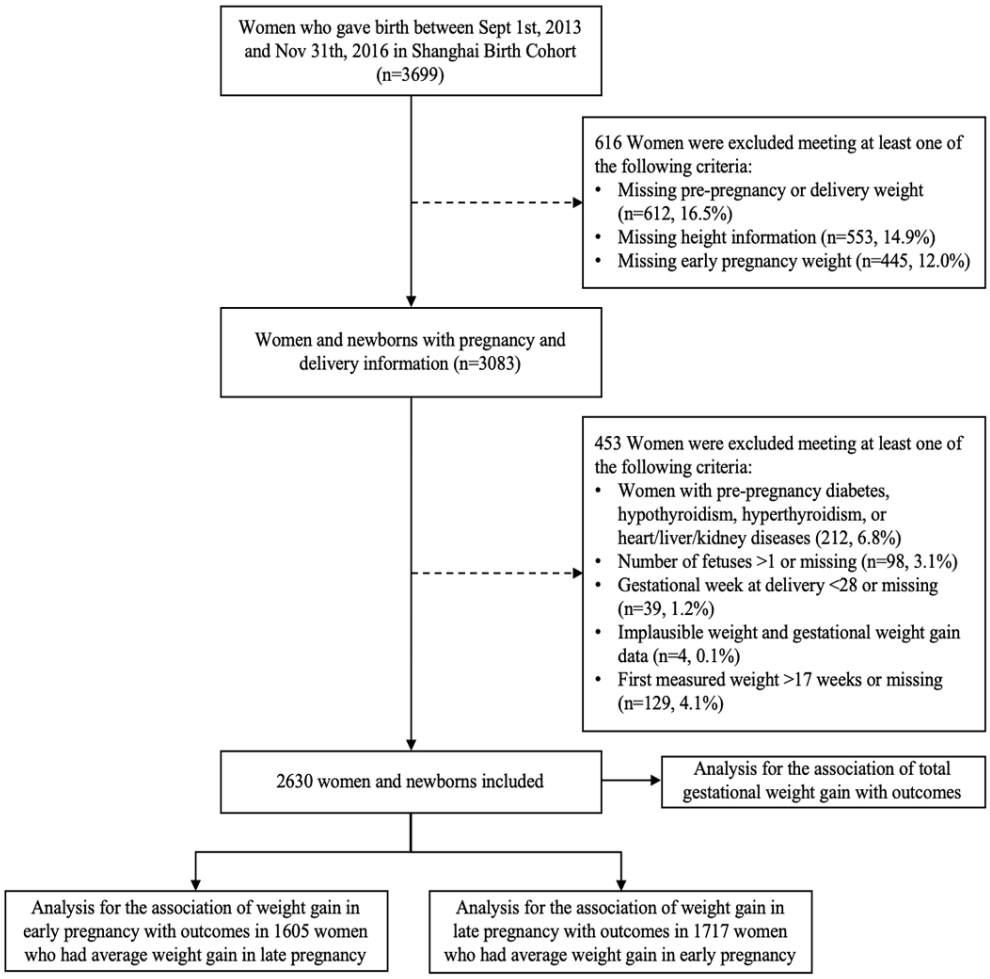

Figure 1. Study flow chart.

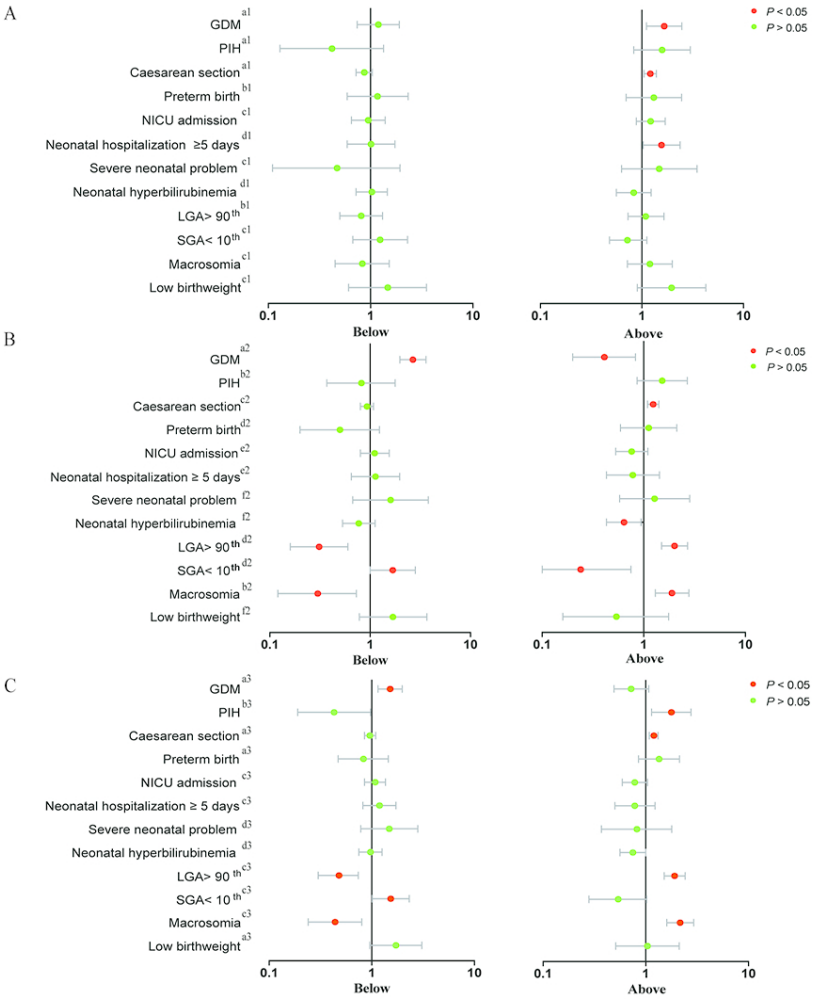

Figure 2. Associations of gestational weight gain with pregnancy outcomes.(A) Associations of early gestational weight gain (≤17 week) with pregnancy outcomes. (B) Associations of late gestational weight gain (>17 week) with pregnancy outcomes. (C) Associations of total gestational weight gain with pregnancy outcomes. NICU: neonatal intensive care unit; LGA: large for gestational age; SGA: small for gestational age; GDM: gestational diabetes mellitus; PIH: pregnancy-induced hypertension; GWG: gestational weight gain; ARR: adjusted relative risk. *<0.05Average GWG group as the reference.a1 The analysis was adjusted for maternal age, parity, pre-pregnancy BMI and length of gestation.b1 The analysis was adjusted for parity, pre-pregnancy BMI, fetal sex, GDM and PIH.c1 The analysis was adjusted for pre-pregnancy BMI, fetal sex, alcohol/tobacco use, length of gestation, GDM and PIH.d1 The analysis was adjusted for maternal age, alcohol/tobacco use, GDM and PIH.a2 The analysis was adjusted for maternal age and pre-pregnancy BMI.; b2 The analysis was adjusted for parity, pre-pregnancy BMI, fetal sex and length of gestation.c2 The analysis was adjusted for maternal age, parity, pre-pregnancy BM, GDM and PIH. d2 The analysis was adjusted for parity, pre-pregnancy BMI, fetal sex, GDM and PIH.e2 The analysis was adjusted for parity, pre-pregnancy BMI, alcohol/tobacco use, length of gestation, GDM and PIH.f2 The analysis was adjusted for maternal age, alcohol/tobacco use and length of gestation.a3 The analysis was adjusted for maternal age, parity, pre-pregnancy BMI, alcohol/tobacco use and fetal sex.b3 The analysis was adjusted for parity, pre-pregnancy BMI and length of gestation.c3 The analysis was adjusted for parity, pre-pregnancy BMI, length of gestation, GDM and PIH.d3 The analysis was adjusted for maternal age, parity and length of gestation.e3 The analysis was adjusted for pre-pregnancy BMI, fetal sex, length of gestation, GDM and PIH.

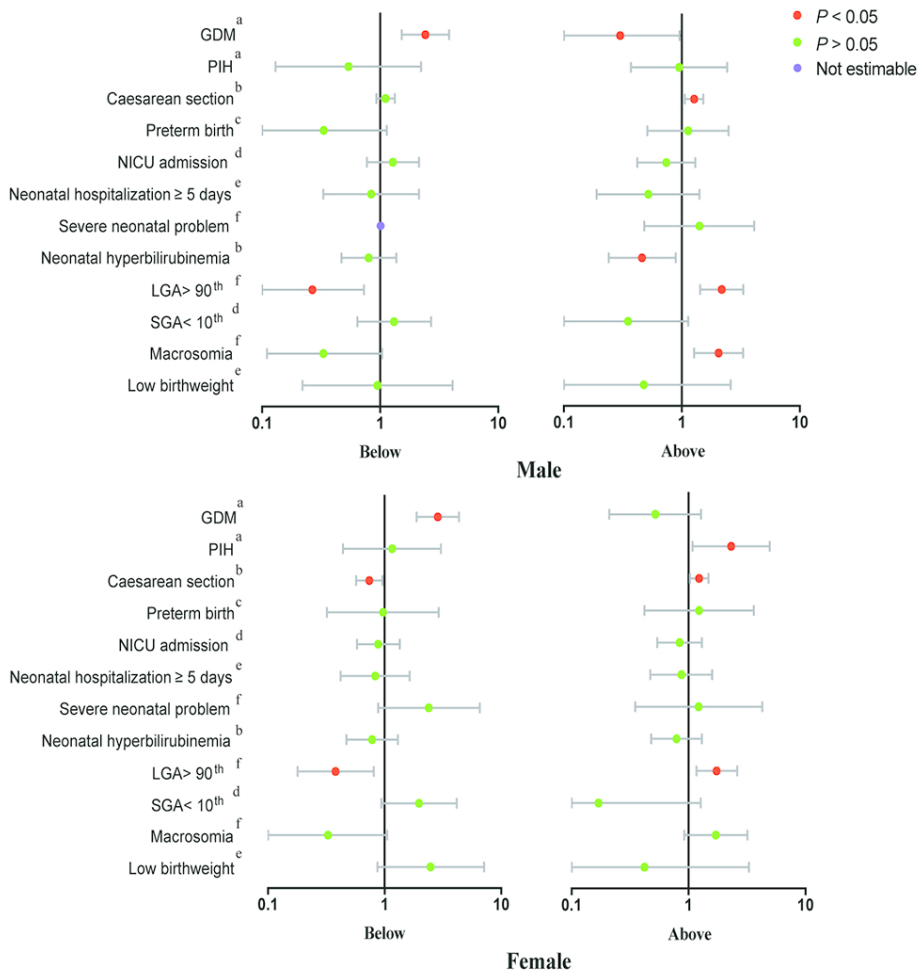

Figure 3. Associations of late gestational weight gain (>17 week) with pregnancy outcomes, stratified by fetal sex.NICU: neonatal intensive care unit; LGA: large for gestational age; SGA: small for gestational age; GDM: gestational diabetes mellitus; PIH: pregnancy-induced hypertension; GWG: gestational weight gain; ARR: adjusted relative risk. *<0.05Average GWG group as the reference.a The analysis was adjusted for maternal age and pre-pregnancy BMI.b The analysis was adjusted for maternal age, parity, pre-pregnancy BMI, alcohol/tobacco use and length of gestation.c The analysis was adjusted for maternal age, pre-pregnancy BMI, GDM and PIH.d The analysis was adjusted for parity, pre-pregnancy BMI, alcohol/tobacco use and length of gestation.e The analysis was adjusted for parity, alcohol/tobacco use, length of gestation, GDM and PIH.f The analysis was adjusted for parity, pre-pregnancy BMI, length of gestation, GDM and PIH.

Table S1. Maternal characteristics in the study of gestational weight gain in early pregnancy (≤17 week)

Characteristic	Below (n=186)	Average (n=1233)	Above (n=186)	*P*
Maternal age (year), mean ± SD	28.2 ± 3.4	29.4 ± 3.7	29.4 ± 3.5	0.0002
Maternal age ≥35 years, n (%)	11 (5.9)	126 (10.2)	14 (7.5)	0.5946
Nulliparous, n (%)	165 (88.7)	1011 (82)	155 (83.3)	0.1683
Education, university degree and above, n (%)	164 (88.1)	1138 (92.4)	162 (87.6)	0.8411
ART, n (%)	4 (2.2)	27 (2.2)	5 (2.7)	0.9110
Tobacco smoking, n (%)	4 (2.2)	26 (2.1)	9 (4.8)	0.0924
Alcohol use, n (%)	15 (8.1)	129 (10.5)	18 (9.37)	0.5876
Pre-pregnancy BMI (kg/m^2), mean ± SD	21.8 ± 3.1	21.2 ± 3.0	21.7 ± 3.1	0.0027
Pre-pregnancy BMI categories, n (%)				
Underweight (< 18.5 kg/m^2)	28 (15.1)	193 (15.7)	28 (15.1)	
Normal weight (18.5–24.9 kg/m^2)	134 (72)	929 (75.3)	133 (71.5)	0.9848
Overweight and obese (≥ 25 kg/m^2)	24 (12.9)	111 (9)	25 (13.4)	
Gestational age at the first prenatal visit (week), median (IQR)	14 (3)	14 (3)	15 (3)	0.8298
GWG in early pregnancy by BMI categories (kg), mean ± SD				
All women	-2.5 ± 2.0	2.1 ± 1.5	6.7 ± 2.1	<0.0001
Underweight (< 18.5 kg/m^2)	-0.6 ± 1.1	2.1 ± 1.2	6.4 ± 2.1	<0.0001
Normal weight (18.5–24.9 kg/m^2)	-2.5 ± 1.7	2.1 ± 1.5	7.0 ± 2.1	<0.0001
Overweight and obese (≥ 25 kg/m^2)	-4.7 ± 1.7	1.5 ± 1.8	5.7 ± 1.7	<0.0001
GWG in late pregnancy by BMI categories (kg), mean ± SD				
All women	12.5 ± 2.3	12.6 ± 2.3	12.3 ± 2.4	0.4854

Underweight (< 18.5 kg/m^2)	12.4 ± 1.9	12.7 ± 1.9	12.5 ± 1.8	0.6323
Normal weight (18.5–24.9 kg/m^2)	12.8 ± 2.2	12.7 ± 2.2	12.6 ± 2.1	0.8492
Overweight and obese (≥ 25 kg/m^2)	10.7 ± 2.2	11.1 ± 3.1	10.4 ± 3.3	0.5676
Gestational age at delivery (week), median (IQR)	39 (2)	39 (2)	39 (2)	0.9126
Birth weight (g), mean ± SD	3296 ± 435	3370 ± 446	3382 ± 515	0.0428
Male infant, n (%)	92 (50.3)	646 (53.2)	102 (55.4)	0.6091

ART: assisted reproductive technology; BMI: body mass index; GWG: gestational weight gain; IQR: interquartile range; SD: standard deviation.

Table S2. Maternal characteristics in the study of gestational weight gain in late pregnancy (>17 week)

Characteristic	Below (n=236)	Average (n=1233)	Above (n=248)	*P*
Maternal age (year), mean ± SD	30.4 ± 3.8	29.4 ± 3.7	27.9 ± 3.5	<0.0001
Maternal age ≥35 years, n (%)	37 (15.7)	126 (10.2)	10 (4)	<0.0001
Nulliparous, n (%)	183 (77.5)	1011 (82)	234 (94.4)	<0.0001
Education, university degree and above, n (%)	222 (94.1)	1138 (92.4)	214 (86.3)	0.0017
ART, n (%)	7 (3)	27 (2.2)	6 (2.4)	0.7701
Tobacco smoking, n (%)	4 (1.7)	26 (2.1)	12 (4.8)	0.0234
Alcohol use, n (%)	20 (8.5)	129 (10.5)	20 (8.1)	0.3841
Pre-pregnancy BMI (kg/m^2), mean ± SD	21.6 ± 3.1	21.2 ± 3.0	21.4 ± 3.1	0.0564
Pre-pregnancy BMI categories, n (%)				
Underweight (< 18.5 kg/m^2)	29 (12.3)	193 (15.7)	37 (14.9)	
Normal weight (18.5–24.9 kg/m^2)	178 (75.4)	929 (75.3)	189 (76.2)	0.3711
Overweight and obese (≥ 25 kg/m^2)	29 (12.3)	111 (9)	22 (8.9)	
Gestational age at the first prenatal visit (week), median (IQR)	14 (3)	14 (3)	14 (3)	0.4231
GWG in early pregnancy by BMI categories (kg), mean ± SD				
All women	2.1 ± 1.5	2.1 ± 1.5	2.3 ± 1.4	0.1943
Underweight (< 18.5 kg/m^2)	2.7 ± 1.4	2.1 ± 1.2	2.8 ± 1.3	0.0009
Normal weight (18.5–24.9 kg/m^2)	2.1 ± 1.5	2.1 ± 1.5	2.2 ± 1.5	0.7273
Overweight and obese (≥ 25 kg/m^2)	1.5 ± 1.6	1.5 ± 1.8	2.1 ± 1.2	0.2109
GWG in late pregnancy by BMI categories (kg), mean ± SD				
All women	7.0 ± 2.1	12.6 ± 2.3	19.1 ± 2.4	<0.0001

Underweight (< 18.5 kg/m^2)	7.9 ± 1.2	12.7 ± 1.9	19.2 ± 2.6	<0.0001
Normal weight (18.5–24.9 kg/m^2)	7.3 ± 1.9	12.7 ± 2.2	19.1 ± 2.2	<0.0001
Overweight and obese (≥ 25 kg/m^2)	4.1 ± 1.9	11.1 ± 3.1	18.3 ± 3.2	<0.0001
Gestational age at delivery (week), median (IQR)	39 (2)	39 (2)	39 (2)	0.0872
Birth weight (g), mean ± SD	3261 ± 397	3370 ± 446	3536 ± 461	<0.0001
Male infant, n (%)	110 (47.8)	646 (53.2)	120 (49)	0.8381

ART: assisted reproductive technology; BMI: body mass index; GWG: gestational weight gain; IQR: interquartile range; SD: standard deviation.

Table S3. Association of pregnancy outcomes by gestational weight gain in early pregnancy (≤17 week)

	Below (n=186)		Average (n=1233)		Above (n=186)	
Outcomes	n (%)	aRR (95% CI)	n (%)	aRR	n (%)	aRR (95% CI)
GDM	18 (9.7)	1.19 (0.74, 1.91)	97 (7.9)	Reference	25 (13.4)	1.66 (1.11, 2.48) *
PIH	3 (1.6)	0.42 (0.13, 1.34)	44 (3.6)	Reference	11 (5.9)	1.58 (0.83, 3.00)
Caesarean section	71 (41)	0.87 (0.72, 1.04)	548 (47.3)	Reference	101 (56.7)	1.21 (1.05, 1.39)*
Preterm birth	9 (4.8)	1.17 (0.59, 2.33)	54 (4.4)	Reference	11 (5.9)	1.31 (0.70, 2.46)
NICU admission	24 (12.9)	0.95 (0.65, 1.39)	168 (13.6)	Reference	31 (16.7)	1.22 (0.88, 1.70)
Neonatal hospitalization ≥5 d	12 (6.5)	1.01 (0.59, 1.73)	71 (5.8)	Reference	17 (9.1)	1.56 (1.03, 2.38)*
Severe neonatal problem	2 (1.1)	0.47 (0.11, 1.94)	26 (2.1)	Reference	6 (3.2)	1.48 (0.63, 3.50)
Neonatal hyperbilirubinemia	30 (16.1)	1.03 (0.72, 1.46)	191 (15.5)	Reference	24 (12.9)	0.83 (0.56, 1.23)
LGA > 90th	17 (9.3)	0.81 (0.50, 1.31)	132 (10.9)	Reference	23 (12.5)	1.09 (0.73, 1.65)
SGA < 10th	11 (6)	1.24 (0.67, 2.30)	60 (5)	Reference	8 (4.3)	0.72 (0.48, 1.12)
Macrosomia	11 (5.9)	0.83 (0.45, 1.52)	84 (6.9)	Reference	16 (8.6)	1.20 (0.72, 1.99)
Low birthweight	6 (3.2)	1.47 (0.61, 3.52)	26 (2.1)	Reference	8 (4.3)	1.96 (0.90, 4.26)

aRR: adjusted relative risk; CI: confidence interval; GDM: gestational diabetes mellitus; LGA: large for gestational age; NICU: neonatal intensive care unit; PIH: pregnancy-induced hypertension; SGA: small for gestational age.

*P <0.05

Table S4. Association of pregnancy outcomes with gestational weight gain in late pregnancy (>17 week)

	Below (n=236)		Average (n=1233)		Above (n=248)	
Outcomes	n (%)	aRR (95% CI)	n (%)	aRR	n (%)	aRR (95% CI)
GDM	52 (22)	2.67 (1.98, 3.61) *	97 (7.9)	Reference	8 (3.2)	0.41 (0.20, 0.83) *
PIH	7 (3)	0.82 (0.37, 1.78)	44 (3.6)	Reference	15 (6.1)	1.52 (0.86, 2.69)
Caesarean section	105 (46.9)	0.93 (0.80, 1.08)	548 (47.3)	Reference	129 (56.3)	1.24 (1.09, 1.41)*
Preterm birth	6 (2.5)	0.50 (0.20, 1.24)	54 (4.4)	Reference	12 (4.8)	1.12 (0.59, 2.12)
NICU admission	35 (14.8)	1.11 (0.80, 1.55)	168 (13.6)	Reference	27 (10.9)	0.76 (0.53, 1.10)
Neonatal hospitalization ≥5 d	14 (5.9)	1.13 (0.65, 1.97)	71 (5.8)	Reference	11 (4.4)	0.78 (0.43, 1.43)
Severe neonatal problem	6 (2.5)	1.60 (0.67, 3.80)	26 (2.1)	Reference	7 (2.8)	1.28 (0.58, 2.84)
Neonatal hyperbilirubinemia	28 (11.9)	0.77 (0.53, 1.12)	191 (15.5)	Reference	25 (10.1)	0.64 (0.43, 0.94) *
LGA > 90th	9 (3.9)	0.31 (0.16, 0.60)*	132 (10.9)	Reference	51 (20.8)	2.01 (1.50, 2.70)*
SGA < 10th	17 (7.4)	1.68 (1.00, 2.82) *	60 (5)	Reference	3 (1.2)	0.24 (0.07, 0.75)*
Macrosomia	5 (2.1)	0.30 (0.12, 0.73)*	84 (6.9)	Reference	31 (12.6)	1.90 (1.30, 2.78)*
Low birthweight	8 (3.4)	1.69 (0.78, 3.68)	26 (2.1)	Reference	3 (1.2)	0.54 (0.16, 1.76)

aRR: adjusted relative risk; CI: confidence interval; GDM: gestational diabetes mellitus; LGA: large for gestational age; NICU: neonatal intensive care unit; PIH: pregnancy-induced hypertension; SGA: small for gestational age.

*P <0.05

Table S5. Association of pregnancy outcomes with gestational weight gain in late pregnancy (>17 week), by infant sex (27 sex unknown)

Outcomes	Male					Female				
	Below (n=110)		Average (n=646) (reference)	Above (n=120)		Below (n=120)		Average (n=569) (reference)	Above (n=125)	
	n (%)	aRR (95% CI)	n (%)	n (%)	aRR (95% CI)	n (%)	aRR (95% CI)	n (%)	n (%)	aRR (95% CI)
GDM	21(19.1)	2.41 (1.52, 3.84)*	53 (8.2)	3 (2.5)	0.30 (0.10, 0.96) *	29(24.2)	2.86 (1.88, 4.35)*	43 (7.6)	5 (4)	0.52 (0.21, 1.28)
PIH	2 (1.8)	0.54 (0.13, 2.22)	25 (3.9)	5 (4.2)	0.95 (0.37, 2.42)	5 (4.2)	1.16 (0.44, 3.04)	19 (3.3)	9 (7.2)	2.31 (1.08, 4.95)
Caesarean section	61 (57)	1.11 (0.93, 1.33)	291 (47.5)	62 (56.4)	1.27 (1.06, 1.52)*	41(36.6)	0.74 (0.57, 0.96)*	250 (47.3)	66 (56.4)	1.23(1.03, 1.48)*
Preterm birth	1 (0.9)	0.16 (0.02, 1.14)	35 (5.4)	7 (5.8)	1.13 (0.51, 2.49)	4 (3.3)	0.97 (0.32, 2.91)	17 (3)	4 (3.2)	1.23 (0.42, 3.62)
NICU admission	16(14.6)	1.28 (0.77, 2.13)	86 (13.3)	12 (10)	0.74 (0.42, 1.30)	16(13.3)	0.88 (0.58, 1.35)	75 (13.2)	14 (11.2)	0.84 (0.54, 1.30)
Neonatal hospitalization ≥5 d	5 (4.6)	0.84 (0.33, 2.13)	42 (6.5)	4 (3.3)	0.52 (0.19, 1.41)	6 (5)	0.83 (0.42, 1.64)	28 (4.9)	7 (5.6)	0.87 (0.47, 1.59)
Severe neonatal problem	0	NA	17 (2.6)	4 (3.3)	1.41 (0.48, 4.10)	5 (4.2)	2.39 (0.88, 6.54)	9 (1.6)	3 (2.4)	1.22 (0.35, 4.27)
Neonatal hyperbilirubinemia	13(11.8)	0.80 (0.47, 1.37)	100 (15.5)	9 (7.5)	0.46 (0.24, 0.89)*	15(12.5)	0.78 (0.47, 1.30)	90 (15.8)	16 (12.8)	0.79 (0.48, 1.30)
LGA > 90th	2 (1.8)	0.18 (0.04, 0.73)*	62 (9.7)	25 (20.8)	2.18 (1.43, 3.32)*	7 (5.8)	0.38 (0.18, 0.81)*	70 (12.3)	26 (20.8)	1.74 (1.17, 2.61)*
SGA < 10th	8 (7.3)	1.31 (0.64, 2.70)	37 (5.8)	2 (1.7)	0.28 (0.07, 1.13)	9 (7.5)	1.97 (0.94, 4.15)	23 (4)	1 (0.8)	0.17 (0.02, 1.27)
Macrosomia	3 (2.7)	0.33 (0.11, 1.04)	50 (7.8)	19 (15.8)	2.05 (1.27, 3.31) *	2 (1.7)	0.26 (0.06, 1.05)	33 (5.8)	12 (9.6)	1.71 (0.92, 3.19)
Low birthweight	2 (1.8)	0.95 (0.22, 4.11)	14 (2.2)	1 (0.8)	0.34 (0.05, 2.59)	5 (4.2)	2.48 (0.87, 7.11)	10 (1.8)	1 (0.8)	0.42 (0.05, 3.29)

aRR: adjusted relative risk; CI: confidence interval; GDM: gestational diabetes mellitus; LGA: large for gestational age; NICU: neonatal intensive care unit; PIH: pregnancy-induced hypertension; SGA: small for gestational age.

*P <0.05

Table S6. Association of pregnancy outcomes with total gestational weight gain

	Below (n=392)		Average (n=1842)		Above (n=396)	
Outcome	n (%)	aRR (95% CI)	n (%)	aRR	n (%)	aRR (95% CI)
GDM	60 (15.3)	1.51 (1.15, 1.98) *	176 (9.6)	Reference	27 (6.8)	0.72 (0.49, 1.07)
PIH	6 (1.5)	0.43 (0.19, 0.97) *	65 (3.5)	Reference	26 (6.6)	1.78 (1.14, 2.76) *
Caesarean section	163 (45)	0.96 (0.85, 1.09)	778 (45.2)	Reference	203 (55.5)	1.20 (1.08, 1.32)*
Preterm birth	15 (3.8)	0.83 (0.47, 1.45)	81 (4.4)	Reference	22 (5.6)	1.35 (0.85, 2.13)
NICU admission	61 (15.6)	1.08 (0.85, 1.36)	257 (14)	Reference	45 (11.4)	0.78 (0.59, 1.04)
Neonatal hospitalization ≥5 d	27 (6.9)	1.19 (0.82, 1.72)	107 (5.8)	Reference	19 (4.8)	0.78 (0.50, 1.23)
Severe neonatal problem	11 (2.8)	1.48 (0.78, 2.81)	37 (2)	Reference	7 (1.8)	0.82 (0.37, 1.79)
Neonatal hyperbilirubinemia	58 (14.8)	0.97 (0.75, 1.26)	285 (15.5)	Reference	47 (11.9)	0.75 (0.56, 1.00)
LGA > 90th	20 (5.2)	0.48 (0.30, 0.74) *	192 (10.6)	Reference	80 (20.4)	1.91 (1.51, 2.42) *
SGA < 10th	27 (7)	1.53 (1.01, 2.32) *	87 (4.8)	Reference	10 (2.5)	0.54 (0.28, 1.02)
Macrosomia	11 (2.8)	0.44 (0.24, 0.80) *	115 (6.3)	Reference	53 (13.5)	2.16 (1.60, 2.93) *
Low birthweight	15 (3.8)	1.72 (0.96, 3.08)	41 (2.2)	Reference	9 (2.3)	1.04 (0.51, 2.12)

aRR: adjusted relative risk; CI: confidence interval; GDM: gestational diabetes mellitus; LGA: large for gestational age; NICU: neonatal intensive care unit; PIH: pregnancy-induced hypertension; SGA: small for gestational age.

*P <0.05

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3-4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6
Objectives	3	State specific objectives, including any prespecified hypotheses	7
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	8
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	n/a
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	9-11
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	9
Bias	9	Describe any efforts to address potential sources of bias	9
Study size	10	Explain how the study size was arrived at	8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	10-11
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	12-13
		(*b*) Describe any methods used to examine subgroups and interactions	12
		(*c*) Explain how missing data were addressed	12
		(*d*) If applicable, explain how loss to follow-up was addressed	12
		(*e*) Describe any sensitivity analyses	n/a
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	13
		(b) Give reasons for non-participation at each stage	fig 1
		(c) Consider use of a flow diagram	fig 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	table 1
		(b) Indicate number of participants with missing data for each variable of interest	n/a
		(c) Summarise follow-up time (eg, average and total amount)	13
Outcome data	15*	Report numbers of outcome events or summary measures over time	table 2-3
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted	14-15

		estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	
		(*b*) Report category boundaries when continuous variables were categorized	n/a
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n/a
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	15
Discussion			
Key results	18	Summarise key results with reference to study objectives	16
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	16-17
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	17-22
Generalisability	21	Discuss the generalisability (external validity) of the study results	22
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	23

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.