Gestational Weight Gain as a Mediator of the Relationship between Pre-Pregnancy Body Mass Index and the Risk of Preterm Birth: A Four-way Decomposition Analysis

Niknam, A., Behboudi-Gandevani, S., Rahmati, M., Firouzi, F., Azizi, F. & Tehrani, F. R.

Published in: International Journal of Gynecology & Obstetrics
DOI: 10.1002/ijgo.15789
Available online: 16 July 2024

Citation:
Behboudi-Gandevani, S., Niknam, A., Rahmati, M. & Tehrani, F. R. (2024). International Journal of Gynecology & Obstetrics. Doi: 10.1002/ijgo.15789

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Short title: Gestational Weight Gain, Pre-Pregnancy BMI and Risk of Preterm Birth

Authors: Atrin Niknam[1], Samira Behboudi-Gandevani[2,] Maryam Rahmati[1], Faegheh Firouzi[3], Fereidoun Azizi[4], Fahimeh Ramezani Tehrani[1,]*

[1]Reproductive Endocrinology Research Center, Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran. [niknamatrin@gmail.com, rahmati.mary@gmail.com, fah.tehrani@gmail.com]
[2]Faculty of Nursing and Health Sciences, Nord University, Bodø, Norway. [samira.behboudi-gandevani@nord.no]
[3]Islamic Azad University, Tehran Medical Branch, Tehran, Iran. faegheh_f7@yahoo.com
[4]Endocrine Research Center, Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran. [azizi@endocrine.ac.ir]

***Corresponding Author.** Reproductive Endocrinology Research Center, Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran.
Tel number: +98-21-22432500; Fax number: +98-21-22416264.
E-mail: ramezani@endocrine.ac.ir, framezan@postharvard.edu, fah.tehrani@gmail.com (Prof. Fahimeh Ramezani Tehrani).

Synopsis
The risk of preterm birth is lowest for underweight mothers with adequate gestational weight gain and highest for obese mothers with excessive GWG

Abstract

Objectives: We aimed to examine and quantify whether the association between preterm birth (PTB) and pre-pregnancy Body Mass Index (BMI) is mediated by Gestational Weight Gain (GWG).

Methods: This is a secondary-analysis of a large randomized-community non-inferiority trial using a cohort-design. The data of 26,101 pregnant women in their first-trimester who sought prenatal-care and met eligibility-criteria were included. The 4-way decomposition method was applied to screen for all types of association effects of pre-pregnancy BMI on the risk of PTB. These effects include the total effect, direct effect, and various indirect effects including pure mediation via GWG, interactive effects with GWG, and mediated interaction with GWG, all adjusted for potential confounders.

Results: Among the study participants, 24,461(93.7%) had term deliveries, while 1,640(6.3%) experienced PTB. The results of the study showed that there was a positive association between pre-pregnancy BMI among those with BMI more than 25 kg/m2 and the risk of PTB and this association was negatively mediated and interacted by GWG, which differed quantitatively between those who had inadequate, adequate, or excessive GWG. The total association effect showed that the risk was lowest for those who had underweight pre-pregnancy BMI and adequate GWG (Excess

relative risk (RR): 0.06,95%CI: 0.01-0.11,P-value:0.022) and was highest for those who had obese pre-pregnancy BMI and excessive GWG (Excess RR:0.67,95%CI:0.35-1.00,P-value<0.001).

Conclusions: The findings of the present prospective population-based study demonstrated that pre-pregnancy BMI >25kg/m2 is directly and positively associated with the risk of preterm birth. The highest risk of preterm birth was observed among individuals with an obese pre-pregnancy BMI who also experienced excessive GWG.

Keywords:

Four-way decomposition Analysis, Gestational weight gain, Pre-pregnancy BMI, Preterm birth, Mediation analysis, indirect association

Name of the registry: Iranian Registry of Clinical Trials, as Primary Registry in the WHO Registry Network.
Registration number: IRCT138707081281N1
URL of registration: https://www.irct.ir/trial/518

Synopsis
The risk of preterm birth is lowest for underweight mothers with adequate gestational weight gain and highest for obese mothers with excessive GWG

1. INTRODUCTION

Preterm birth (PTB), defined as a livebirth before 37 completed weeks of gestation, is an increasingly important issue, with a global incidence rate of about 11% and rising [1]. Prematurity results in long-term disability and imposing a significant economic burden on healthcare systems and society [2]. Despite being studied for decades, the causal pathways underlying preterm birth remain largely unknown, and the risk factors have been, for the most part, controversial [3].

It is now well-established from a variety of studies that maternal pre-pregnancy Body Mass Index (BMI) is an important determinant of pregnancy outcomes [4, 5]. Both extremes of maternal BMI contribute to an increased risk of PTB [6]. However, obesity mainly leads to medically-initiated PTB due to associated medical complications, including hypertensive disorders and gestational diabetes mellitus (GDM) [7]. These complications are correlated with another factor influenced by pre-pregnancy BMI, known as gestational weight gain (GWG) [5, 8]. While fewer studies have explored the effect of GWG on the incidence of PTB, most of those studies have been conducted in high-income countries [9, 10].

Similar to maternal BMI, GWG outside the normal range increases the risk of PTB, although through different mechanisms [11, 12]. However, due to the established association between BMI and GWG, the impact of GWG on PTB might be extend beyond a direct influence, an issue that remains under debate [13, 14].

Mediation analysis is a method employed to understand a known relationship by exploring the underlying mechanism or process through which one variable influences another variable via a mediator variable [15]. Therefore, using the dataset of a large population-based study, this study tried to develop a better understanding of how pre-pregnancy BMI and GWG are correlated in impose their influence on PTB. The aim of this study was to examine and quantify whether the association between PTB and pre-pregnancy BMI is mediated by GWG.

2. MATERIALS AND METHODS

2.1. Study design and participants

This is a secondary analysis of a large, randomized community non-inferiority trial among pregnant women with a cohort approach started from 19.02.2017 to 23.08.2018. Detailed methods of the study have been reported previously [16, 17]. Briefly, the primary objective of the main study was to assess the non-inferiority of less stringent (GDM screening criteria compared with the stringent and rigorous International Association of Diabetes in Pregnancy Study Group (IADPSG) criteria concerning both maternal and neonatal outcomes. A total number of 35,430 pregnant women in their first trimester, aged ≥ 18 years from five different geographic regions of Iran participated in the study. The exclusion criteria were uncertainty regarding the date of the last menstrual period and lack of ultrasound estimation from 6 to 14 weeks of gestation, previous diagnosis of type II diabetes, or other chronic disorders. For the current analysis, we further excluded those with twin pregnancies, pregnancies that terminated before 20 weeks of gestation, and lacking complete data. Finally, a total of 26,101 pregnant women was included in the current analysis.

As part of their regular prenatal care, all participants underwent two phases of screening for GDM during their first and second trimesters of pregnancy. This screening process adhered to a predetermined protocols and involved using fasting plasma glucose (FPG) for the first-trimester screening and either a one-step or a two-step method for the second-trimester screening. All study participants were followed until delivery, and all adverse maternal and neonatal outcomes were recorded in detail.

2.2. Outcome definitions and measurements

The primary outcome was preterm birth, defined as babies born alive before 37 weeks of pregnancy are completed.

Gestational age was determined using the certain date of last menstrual period, or ultrasound estimation between 6 to 14 weeks of gestational age. Participants' weight was recorded using digital scales with an accuracy to the nearest 100 grams. This measurement was taken while participants were wearing minimal clothing and without shoes. Height was measured while participants stood without shoes, using a tape measure with precision to the nearest 0.5 centimeters. Body mass index (BMI) was computed by dividing the weight in kilograms by the square of the height in meters. Further, BMI were categorized into underweight (< 18.5 kg/m^2), normal weight (18.5-24.9 kg/m^2), and overweight (25.0-29.9 kg/m^2) or obese (≥ 30 kg/m^2).

Gestational weight gain was calculated as the difference between the maternal weight at the first and last prenatal visit just prior to delivery, measured in kilograms. It should be noted that the mean timing for prenatal visits during pregnancy was 8 weeks of gestation [16, 17]. We further classified the adequacy of GWG as inadequate, adequate, and excessive. Inadequate GWG was defined as GWG < 12.5 kg in mothers with underweight, < 11.5 kg in mothers with normal-weight, GWG < 7 kg in mothers who were overweight, and < 5 kg in in mothers with obesity.

Adequate GWG was defined as GWG between 12.5-18.5 kg in mothers with underweight, 11.5-16 kg in mothers with normal weight, 7-11.5 kg in mothers who were overweight, and 5-9 kg in mothers with obesity. Excessive GWG was defined as GWG > 18 kg in mothers with underweight, > 16 kg in mothers with normal-weight, > 11.5 kg in mother with overweight, and > 9 kg in mothers with obesity [18].

GDM was screened and diagnosed using one-step 75-gram two-hour oral glucose tolerance test (75g 2h-OGTT) or two step (100g 3h-OGTT) screening approaches.

In one step approach, any values exceeding the cut-off, which included fasting plasma glucose levels of ≥ 92 mg/dL but < 126 mg/dL and/or two-hour OGTT levels of ≥153 mg/dL, resulted in a diagnosis of GDM. Individuals who underwent screening through a two-step (100g 3h-OGTT) were diagnosed with GDM if their glucose levels exceeded certain thresholds. These thresholds included FPG > 95 mg/dL, 1-h glucose level > 180 mg/dL, 2-h glucose level > 155 mg/dL, and 3-h glucose level > 140 mg/dL [19]. The definition of preterm birth in this study was when live birth occurs between 20 and 37 weeks of pregnancy. Preeclampsia was defined as a systolic blood pressure ≥ 140 mmHg or a diastolic blood pressure ≥ 90 mmHg on two occasions at least four hours apart, after 20 weeks of gestation in women with previously normal blood pressure, plus proteinuria ≥ 300 mg per 24 h urine collection, or protein/creatinine ratio ≥ 0.3, or dipstick reading of 1+ and more if other quantitative methods were not available. In

the absence of proteinuria, preeclampsia was defined as new-onset hypertension plus the new onset of thrombocytopenia, renal insufficiency, impaired liver function, pulmonary edema, and cerebral or visual symptoms.

2.3. Ethics approval

This study was approved by the national ethics committee of the National Institute for Medical Research Development (Approval number: IR.NIMAD.REC.1394.013). In addition, the Iranian Ministry of Health and Medical Education (MoHME) approved the study protocol and prespecified GDM modalities were made available to all those provinces as mandatory guidelines. As a result, this was considered a part of routine prenatal care, and specific individual informed consent was not obtained from pregnant women. For further analysis, all participants personal information were deanonymized.

2.4. Statistical analysis

Continuous variables were checked for normality using the Shapiro–Wilk test; those with normal distribution are expressed as mean (standard deviation) and were compared between two groups using a t-test of independent samples. Non-normal distributed variables are expressed as median (interquartile range) and were compared between two groups using an independent sample Mann–Whitney U test. Categorical variables are presented as frequencies (percentages) and were compared using the chi-square test. Locally weighted regression (LOWESS) of GWG on BMI was used to assess nonlinear associations of the variables. LOWESS plots with logit transformation for the dependent variable were applied in the case of nonlinear associations of weight gain or BMI with preterm birth. A generalized linear regression model (GLM) via log and linear link functions were applied for binary (preterm birth) and continuous (GWG) outcomes, respectively. The risk ratio (RR) for binary outcomes and mean difference for continuous outcomes were estimated with 95% confidence intervals.

The approach of four-way decomposition was used to analyze the interaction and mediation effects and their combination. Using this approach, the overall effect of pre-pregnancy BMI on preterm birth, in the presence of GWG, which may interact with BMI, can be decomposed into four components that correspond to the portion of the effect that is due: (i) to neither mediation nor interaction; (ii) to just interaction (but not mediation); (iii) to just mediation (but not interaction); and (iv) to both mediation and interaction. First, two regression models were fitted: a log-binomial model for the preterm birth outcome (as a function of the pre-pregnancy BMI, GWG, the interaction between pre-pregnancy BMI and GWG, and confounders) and a linear regression model for GWG as a mediator (as a function of the pre-pregnancy BMI and confounders). The variance-covariance matrix of the estimated components was

obtained using the multivariate delta method, and excess relative risks were plotted according to the GWG categories. If the 95% confidence interval (95% CI) of the excess relative risk in the four-way decomposition does not include zero, it was considered statistically significant [20]. We could further obtain the proportions of the effects attributable to each component by dividing the estimate of a component by the total excess relative risk. Adjusted variables were maternal age, GDM status, preeclampsia status, infant sex, and assigned protocols. Figure 1 is a conceptual framework that illustrates four decompositions of the relationship between BMI, GWG, and risk of preterm birth. We refined the analysis of how gestational weight gain (GWG) affects the relationship between pre-pregnancy BMI and the risk of preterm birth by decomposing it into four distinct components: the controlled direct effect (CDE), reference interaction (INTref), pure indirect effect (PIE), and mediated interaction (INTmed). The CDE represents the direct influence of BMI on preterm birth risk independent of GWG, illustrated by arrow 1 without arrow 3. The INTref highlights the interaction between BMI and GWG on preterm birth risk, controlling for the effect of BMI on GWG, and is depicted by arrows 3+1, excluding arrow 2. This interaction represents effects solely from the interaction, not mediation. The PIE captures the effect of BMI on preterm birth solely through its impact on GWG, shown by arrows 2+4, indicating an effect purely from mediation without interaction. Lastly, the INTmed occurs only if BMI affects GWG, showcasing a combined effect due to both mediation and interaction, as shown by arrows 2+3+1. This comprehensive approach accounts for potential confounders, including maternal age, GDM status, preeclampsia status, infant sex, and assigned protocols, between the exposure, mediator, and outcome, ensuring a nuanced understanding of these relationships. Statistical analysis was performed using the software package Stata (version 17; STATA Inc., College Station, TX, USA); All statistical tests were two-sided with a statistical significance of $p< 0.05$. The study was approved by the National Institute for Medical Research Development, the national ethics committee of the National Institute of Health Research, and the Iranian Ministry of Health and Medical Education.

3. RESULTS

3.1. Baseline characteristics

A total of 26,101 pregnant women were included in the present study (supplementary Figure 1). Among them, 24,461 (93.7%) had term deliveries, while 1,640 (6.3%) experienced preterm birth. The baseline characteristics of participants in both groups are presented in Table 1. Compared to mothers with term infants, mothers with preterm infants were

more likely to be older, [30.5 (6.2) versus 29.3 (5.8) years (P < 0.001)], exhibited significantly higher BMI [(26.2 (4.7) vs. 25.7 (4.5) kg/m^2, P < 0.001] and lower GWG [(9.0 (4.9) vs. 11.3 (4.5), P < 0.001].

The incidence of GDM (16.5% vs. 13.7%, P = 0.004), preeclampsia (18.5% vs. 11%, P < 0.001), neonatal intensive care unit (NICU) admission (32.5% vs. 3.8%, P < 0.001), hypoglycemia (2.7% vs. 0.9%, P < 0.001), hypocalcemia (1.9% vs. 0.6%, P < 0.001), and birth trauma (4.2% vs. 0.3%, P < 0.001) in mothers with preterm pregnancies was significantly higher that mothers with term pregnancies. The frequency of mothers with term and preterm infants based on BMI and GWG classifications are shown in Table 2. Among those with preterm birth, who classified as normal pre-pregnancy BMI, 391 (64.7) experienced inadequate GWG, 165 (27.2) and 49 (8.1) pregnant women had normal and excessive weight gain, respectively; these values for obese pregnant women with preterm birth were 97 (28.1), 133 (38.6) and, 115 (33.3), respectively (Table 2).

3.2. Exposure, mediator, and outcome associations based on individual regressions

Regarding the association between BMI and GWG, the LOWESS plot indicated a negative association between BMI and GWG (adjusted mean difference= -0.23, 95%CI: (-0.25, -0.22); P < 0.001) (Figure 2-a).

In term of the association between PTB and GWG, preterm birth exhibited a U-shaped relationship with GWG, where increased GWG up to 20 kg was significantly associated with a decreasing trend in the risk of preterm birth (adjusted RR=0.88, 95% CI: (0.87,0.89); P < 0.001), but when the GWG exceeded 20 kg, an increasing trend was observed in relation to preterm birth, although it was not statistically significant (adjusted RR=1.11, 95% CI: 0.98,1.25; P = 0.081) (Figure 2-b).

Regarding the association between BMI and PTB, there is no significant association between them until a BMI of 25 kg/m2. However, an increasing trend in PTB risk with increasing BMI was observed in BMI more than 25 kg/m^2 (Figure 2-c).

3.3. Decomposition Analysis

The results of the four-way decomposition analysis, where the mediator (GWG) is set at various levels of adequate, inadequate, and excessive GWG, are presented in Figure 3. The CDE, considering GWG at all levels, indicates that women with either underweight, over or obese pre-pregnancy BMI are at an increased risk of preterm birth compared to women with a normal pre-pregnancy BMI ($p<0.05$). Among women who had adequate GWG, the controlled direct

effects of all classification of pre-pregnancy BMI on the risk of preterm birth were all significantly positive. Indirect effects were weak but significantly positive for pure indirect effect, and significantly negative for both reference interaction and mediated interaction (Figure 3-a). The results of total effect indicated that within this group of women who experienced adequate GWG showed that (i) those with underweight pre-pregnancy BMI had a statistically significant 6% higher risk of preterm birth compared to women with a normal pre-pregnancy BMI (Excess RR: 0.06, 95% CI: 0.01-0.11, P value: 0.022), (ii) those with overweight pre-pregnancy BMI had a statistically significant 13% higher risk of preterm birth compared to women with a normal pre-pregnancy BMI (Excess RR: 0.13, 95% CI: 0.03-0.23, P value: 0.013) (iii) those with obese BMI had a statistically significant 22% higher risk of preterm birth compared to women with a normal pre-pregnancy BMI (Excess RR: 0.22, 95% CI: 0.06-0.38, P value: 0.011).

Among women who had inadequate GWG, the controlled direct effects of all classification of pre-pregnancy BMI on the risk of preterm birth were all significantly positive. But indirect effects were only observed significantly for pure indirect effect (Figure 3-b). The results of total effect within this group of women who experienced inadequate GWG indicated that (i) Underweight pre-pregnancy BMI was associated with a 11% higher risk of preterm birth (Excess RR: 0.11, 95% CI: 0.06-0.17, P value< 0.001). (ii) Overweight pre-pregnancy BMI was associated with a 26% higher risk of preterm birth (Excess RR: 0.26, 95% CI: 0.14-0.38, P value< 0.001). (iii) Obese pre-pregnancy BMI was associated with a 45% higher risk of preterm birth (Excess RR: 0.45, 95% CI: 0.24-0.678, P value< 0.001). These total excess RR reflect both direct and indirect associations, including mediation and interaction effects, within the decompositions.

Among women who had excessive GWG, the controlled direct effects of all classification of pre-pregnancy BMI on the risk of preterm birth were all significantly positive, although CDE had a predominant influence and PIE played a weaker role. But indirect effects were only observed significantly for pure indirect effect (Figure 3-c). The results of total effect within this group of women who experienced excessive GWG indicated that (i) Underweight pre-pregnancy BMI was associated with a 19% higher risk of preterm birth (Excess RR: 0.19, 95% CI: 0.11-0.27, P value< 0.001). (ii) Overweight pre-pregnancy BMI was associated with a 41% higher risk of preterm birth (Excess RR: 0.41, 95% CI: 0.23-0.60, P value< 0.001). (iii) Obese pre-pregnancy BMI was associated with a 67% higher risk of preterm birth (Excess RR: 0.67, 95% CI: 0.35-1.00, P value< 0.001).

4. DISCUSSION

The findings of the present prospective population-based study demonstrated that pre-pregnancy BMI is directly and positively associated with the risk of preterm birth, and this association is negatively mediated and interacted by GWG, which differed quantitatively between those who had different GWG classifications. Total association effect showed that women who were classified as underweight, overweight, or obese based on their pre-pregnancy BMI exhibited a higher risk of preterm birth compared to those with a normal pre-pregnancy BMI, but the amounts of the risk varied based on GWG classifications: (i) among women who had adequate GWG, those with underweight, overweight and obese pre-pregnancy BMI were significantly associated with 6%, 13% and 22% higher risk of preterm birth compared to normal pre-pregnancy BMI; (ii) among women who had inadequate GWG, those with underweight, overweight and obese pre-pregnancy BMI was significantly associated with 11%, 26% and 45% higher risk of preterm birth compared to normal pre-pregnancy BMI; and finally (iii) among women who had excessive GWG, those with underweight, overweight and obese pre-pregnancy BMI was significantly associated with 19%, 41% and 67% higher risk of preterm birth compared to normal pre-pregnancy BMI. However, the risk was lowest for those who had underweight pre-pregnancy BMI and adequate GWG and was highest for those who had obese pre-pregnancy BMI and excessive GWG.

There is a wealth of literature confirming the association between abnormal maternal BMI and an elevated risk of preterm birth (PTB) [21, 22]. Similar to maternal pre-pregnancy BMI, either excessive or inadequate GWG might contribute to an increased risk of PTB.[4] In agreement, another study carried out in England also identified this association and emphasized the significance of accurately categorizing obese mothers to circumvent misinterpreting PTB risk [23]. Likewise, a study in China confirmed that maternal obesity is associated with all types of PTB, with extremely preterm and medically-indicated PTB exhibiting the most profound risk [24]. Conversely, a systematic review encompassing over one million deliveries reported that underweight women had an increased risk of an LBW infant [25]. Furthermore, in a retrospective cohort study, Girsen et al. (2016) revealed that increasing severity of maternal pre-pregnancy underweight BMI was associated with increasing risk-adjusted PTB at <37 weeks [26].

In the present study, while we have presented robust evidence supporting the positive correlation between BMI and the risk of PTB, aligning with prior research, it is noteworthy that contrary to existing literature, this association was not observed among women categorized as underweight. However, it should be noted that as the number of underweight women who participated in this study was limited, the significance of this association in this population warrants cautious interpretation. In a secondary analysis of multi-center cross-sectional studies in Brazil, authors

revealed that inadequate GWG was associated with a higher prevalence of spontaneous PTB. Additionally, irrespective of maternal BMI, an increased rate of GWG was linked to a heightened occurrence of all PTB subtypes.12 Consistent with a wealth of prior evidence, our study findings highlighted the U-shaped association between GWG and PTB. This indicates that extremes of GWG were linked to an increased risk of PTB.

Furthermore, underweight women with insufficient GWG and overweight women with excessive GWG were the categories that were more agreed upon in the literature [27]. This indicates that extremes of BMI and GWG might synergistically amplify the influence of each other on the risk of PTB. However, these associations were investigated through different definitions, settings, and study designs [28]. Differences in measurements exist all over the literature. Some studies utilized classifications outside WHO guidelines to address their different populations [29]. For GWG, most of the studies used total GWG [27, 29]; other studies used chronological categorization to address the differences between trimesters regarding the embryological processes [8, 29, 30]. However, using a linear association without accounting for the potential mediating effect of GWG might be a significant limitation of prior research in this area.

In the present study, the effect of GWG categories on the association between maternal BMI and the risk of PTB was decomposed into an interaction effect and a mediation-plus-interaction effect. This approach enabled us to examine whether the addition of a mediatory role to GWG and looking beyond a simple linear association between GWG and BMI would change the results. Therefore, controlled direct effects (CDEs) were compared with total effects (TEs) in different categories of BMI and GWG, which led to the discovery that the effect of BMI on the risk of PTB is bias estimated when the mediation effect of GWG is not taken into account. For instance, overweight women with an adequate GWG had 36 percent excessive risk of PTB versus normal weight women in the same category of GWG. However, when the mediatory effect of GWG was taken into account, this excessive risk became 13 percent, which is an important difference influencing clinical decisions.

The present study highlighted the importance of closely monitoring maternal weight gain throughout pregnancy, as doing so can potentially mitigate its impact on the risk of PTB, as well as the influence of pre-pregnancy BMI on the risk of PTB. As such, preconception counseling is a critical component of prenatal care, with an emphasis on achieving a healthy BMI prior to conception, particularly for women who are overweight or obese. This may involve implementing lifestyle modifications such as a well-balanced diet and regular exercise regimen, and in some cases, bariatric surgery. Healthcare providers should provide appropriate guidance and support throughout pregnancy to help women achieve healthy weight gain. This includes regularly monitoring maternal weight and providing guidance on

healthy nutrition and exercise habits. Ultimately, ensuring optimal maternal health prior to and during pregnancy is critical for promoting positive neonatal and maternal outcomes.

This study benefited from a prospective population-based design, a large sample size, and a novel analysis method implemented to gain new perspectives on the ongoing debate regarding the associations between pre-pregnancy BMI, GWG, and the risk of PTB. Another strength of this study is related to its setting, a resource-limited country, which benefits the literature considering the scarcity of population-based studies in this setting. The present study has several limitations that merit discussion. Firstly, the analysis did not account for the impact of nutritional factors on both GWG and PTB, which may have led to an underestimation of the association between these variables. Secondly, the study evaluated GWG as a total rather than as a dynamic process throughout pregnancy, potentially overlooking important associations between trimester specific GWG and the risk of PTB. Thirdly, due to the limited sample size of underweight women, the findings for these groups should be viewed with caution. Finally, the small number of cases of very-early PTB (before 34 weeks of gestation) limited our potential to conduct subgroup analysis according to the time of PTB occurrence. In light of these limitations, future research should aim to account for the influence of relevant nutritional factors, utilize dynamic measures of GWG, and recruit larger samples of underweight women and very-early PTB cases to better elucidate the relationship between maternal weight and the risk of PTB.

In our study, the 4-way decomposition method was used to investigate the relationship between pre-pregnancy BMI, GWG, and risk of preterm birth. The findings demonstrated that pre-pregnancy BMI is directly and positively associated with the risk of preterm birth, and this association is negatively mediated and interacted by GWG, which differed quantitatively between those who had different GWG classifications. Total association effect showed that the risk was lowest for those who had underweight pre-pregnancy BMI and adequate GWG and was highest for those who had obese pre-pregnancy BMI and excessive GWG.

ACKNOWLEDGEMENT

The authors extend their gratitude to Golestan, Bushehr, Birjand, Kurdistan, and Yazd Universities of Medical Sciences for their cooperation in this study.

AUTHOR CONTRIBUTION

AN was involved in study design, data analysis, manuscript drafting, and critical discussion. SB-G and FF substantial contributions to conception and design, revising the manuscript, and critical debate, FRT conceptualized the study and was involved in the study design, interpretation of findings, revising the manuscript, and critical discussion. MR contributed to statistical analysis, interpreting data, and manuscript drafting. FA was involved in made substantial contributions to conception and design, and critical discussion. All authors read and approved the final manuscript.

FUNDING

Research reported in this publication was supported by Elite Researcher Grant Committee under award number IR.NIMAD.REC.1394.013 from the National Institute for Medical Research Development (NIMAD).

CONFLICT OF INTEREST

None.

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Figure legend

Figure 1. Conceptual Framework of the Four-Way Decomposition Analysis

- **Arrow 1 (excluding Arrow 3)**: Controlled Direct Effect (CDE) - The direct effect of maternal BMI on PTB, not mediated by GWG.
- **Arrow 3 + Arrow 1 (excluding Arrow 2): Reference Interaction (INTref)** - The combined effect of BMI and GWG on PTB, considering the interaction but excluding the mediation pathway via GWG.
- **Arrow 2 + Arrow 4: Pure Indirect Effect (PIE)** - The effect of maternal BMI on PTB that is mediated solely through GWG.
- **Arrow 2 + Arrow 3 + Arrow 1: Mediated Interaction (INTmed)** - The interaction effect of BMI and GWG on PTB, which includes both the direct and indirect pathways.

Confounders included in the analysis were Maternal age, GDM status, preeclampsia status, infant sex, and assigned protocols.

Figure 2. Locally weighted regression (LOWESS) plots. (a) GWG to pre-pregnancy BMI; (b) GWG to logit transformed smooth of PTB outcome; (c) pre-pregnancy BMI to logit transformed smooth of PTB outcome. Abbreviations: GWG, gestational weight gain; BMI, body mass index; PTB, preterm birth.

Figure 3. Analysis of the four-way decomposition effects of GWG categories on the association between pre-pregnancy BMI classifications and excess relative risk of PTB. (a) adequate “normal” GWG; (b) inadequate “under” GWG; and (c) excessive “over” GWG. Abbreviations: CI, confidence interval; BMI, body mass index; CDE, controlled direct effect; INTref, reference interaction; INTmed, mediated interaction; PIE, pure indirect effect. Total Effect = CDE + INTref + INTmed + PIE. Adjusted by maternal age, GDM status, preeclampsia status, infant sex, and assigned protocols.

Table 1. Baseline characteristics of the participants.

Variables	Mothers with Preterm infants (N=1,640)	Mothers with Term infants (N=24,461)	P-value
Age (years)	30.5 (6.2)	29.7 (5.8)	<0.001
Maternal weight at first trimester (kg)	66.5 (12.6)	65.6 (12.1)	0.002
Maternal BMI at first trimester (kg/m^2)	26.2 (4.7)	25.7 (4.5)	<0.001
Gravida	2.4 (1.5)	2.2 (1.2)	<0.001
Parity	1.1 (1.0)	1.1 (0.9)	0.021
>1, n (%)	1244 (75.8)	18703 (93.8)	0.501
Gestational Weight gain (kg)	9.0 (4.9)	11.3 (4.5)	<0.001
Gestational age at delivery (weeks)	34.2 (3.0)	39.0 (1.1)	<0.001
Type of delivery (cesarean section), n (%)	859 (52.3)	9481 (38.7)	<0.001
Infant sex (male), n (%)	718 (45.5)	11020 (47.1)	0.212
Birth weight (gr)	2402.9 (691.4)	3243.5 (422.7)	<0.001
GDM, n (%)	268 (16.3)	3363 (13.7)	0.004
Macrosomia, n (%)	102 (6.5)	1432 (6.1)	0.607
LBW, n (%)	888 (56.3)	1439 (6.1)	<0.001
Preeclampsia, n (%)	292 (18.5)	2571 (11.0)	<0.001
NICU admission, n (%)	519 (32.9)	890 (3.8)	<0.001
Hypoglycemia, n (%)	43 (2.7)	201 (0.9)	<0.001
Hypocalcemia, n (%)	30 (1.9)	132 (0.6)	<0.001
IUFD, n (%)	104 (6.6)	67 (0.3)	<0.001
Birth trauma, n (%)	67 (4.2)	67 (0.3)	<0.001

Data are presented as mean (standard deviation) or number (%). Independent t-test, or chi-square test were used as appropriate. Statistically significant result: $p < 0.05$. Abbreviations: BMI, body mass index; GDM, gestational diabetes mellitus; NICU, neonatal intensive care unit; IUFD, intrauterine fetal demise; LBW, low birth weight.

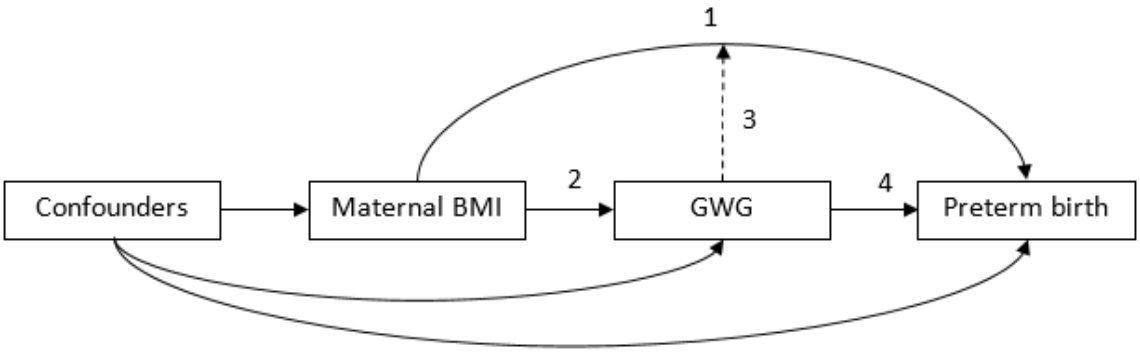
Table 2. Frequency of mothers with term and preterm infants based on BMI and GWG classifications.

Variables	Preterm Birth (n = 1,640)				Term Birth (n = 24,461)			
	GWG				GWG			
BMI	Inadequate	Adequate	Excessive	Total	Inadequate	Adequate	Excessive	Total
Underweight	44 (65.7)	21 (31.3)	2 (3.0)	67 (100)	485 (47.9)	416 (41.1)	111 (11.0)	1012 (100)
Normal weight	391 (64.7)	165 (27.2)	49 (8.1)	605 (100)	4455 (43.6)	3915 (38.3)	1850 (18.1)	10222 (100)
Overweight	215 (34.5)	233 (37.5)	175 (28.0)	623 (100)	1659 (18.2)	3629 (40.0)	3798 (41.8)	9086 (100)
Obese	97 (28.1)	133 (38.6)	115 (33.3)	345 (100)	625 (15.0)	1411 (34.1)	2107 (50.9)	4143 (100)
Total	748 (45.5)	553 (33.7)	341 (20.8)	1640 (100)	7224 (29.5)	9374 (38.3)	7867 (32.2)	24,461 (100)

Data are presented as number (%),
GWG: gestational wight gain; BMI: body mass index.
Underweight was defined as BMI < 18.5 kg/m2, normal weight was defined as BMI: 18.5-24.9 kg/m^2, and overweight was defined as BMI: 25.0-29.9 kg/m^2 and obese was defined as BMI: ≥ 30 kg/m^2. Inadequate GWG was defined as GWG < 12.5 kg in mothers with underweight, < 11.5 kg in mothers with normal-weight, GWG < 7 kg in mothers who were overweight, and < 5 kg in in mothers with obesity. Adequate GWG was defined as GWG between 12.5-18.5 kg in mothers with underweight, 11.5-16 kg in mothers with normal weight, 7-11.5 kg in mothers who were overweight, and 5-9 kg in mothers with obesity. Excessive GWG was defined as GWG > 18 kg in mothers with underweight, > 16 kg in mothers with normal-weight, > 11.5 kg in mother with overweight, and > 9 kg in mothers with obesity.

440 **Figure 1.**

441



442 **Figure 2.**

443

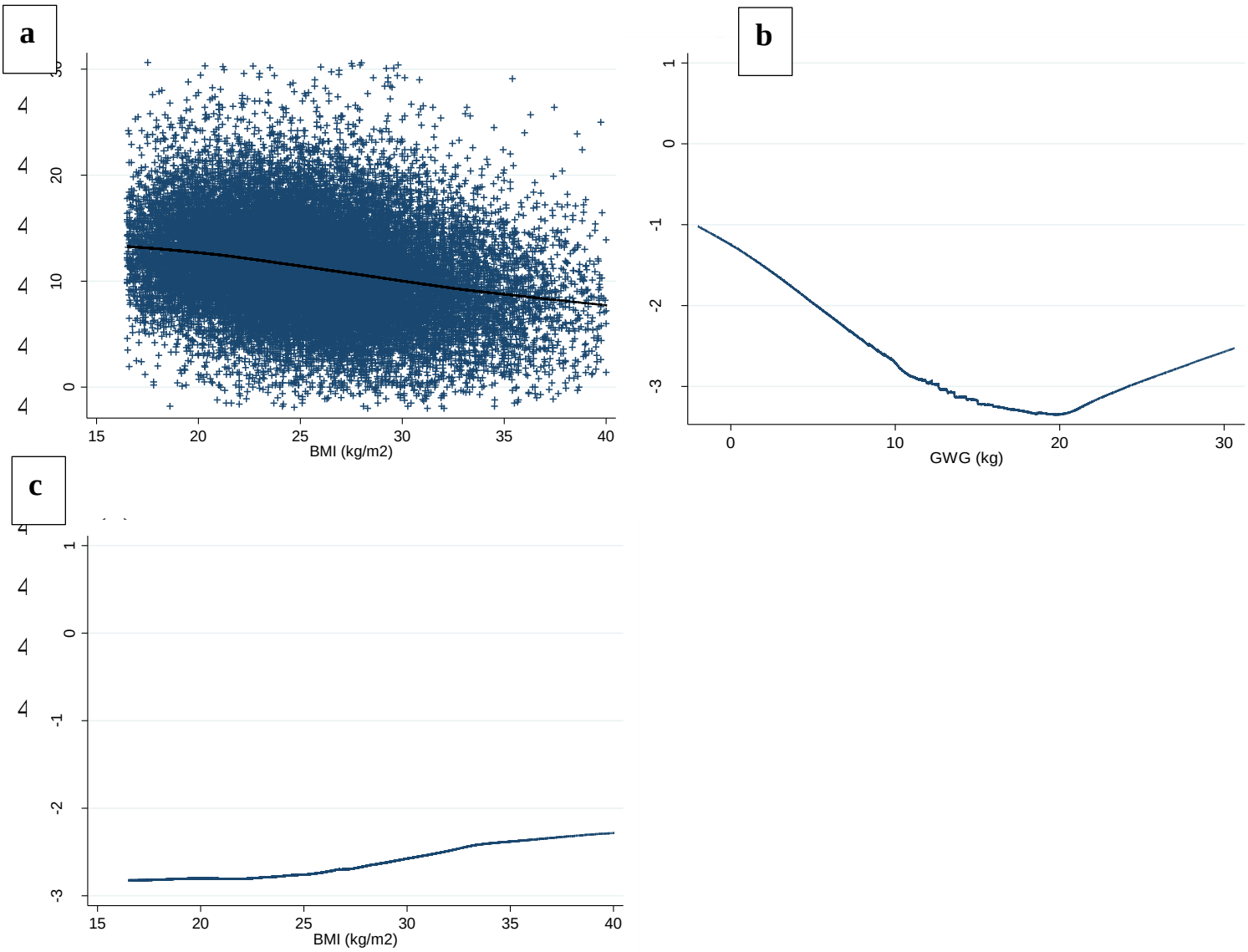
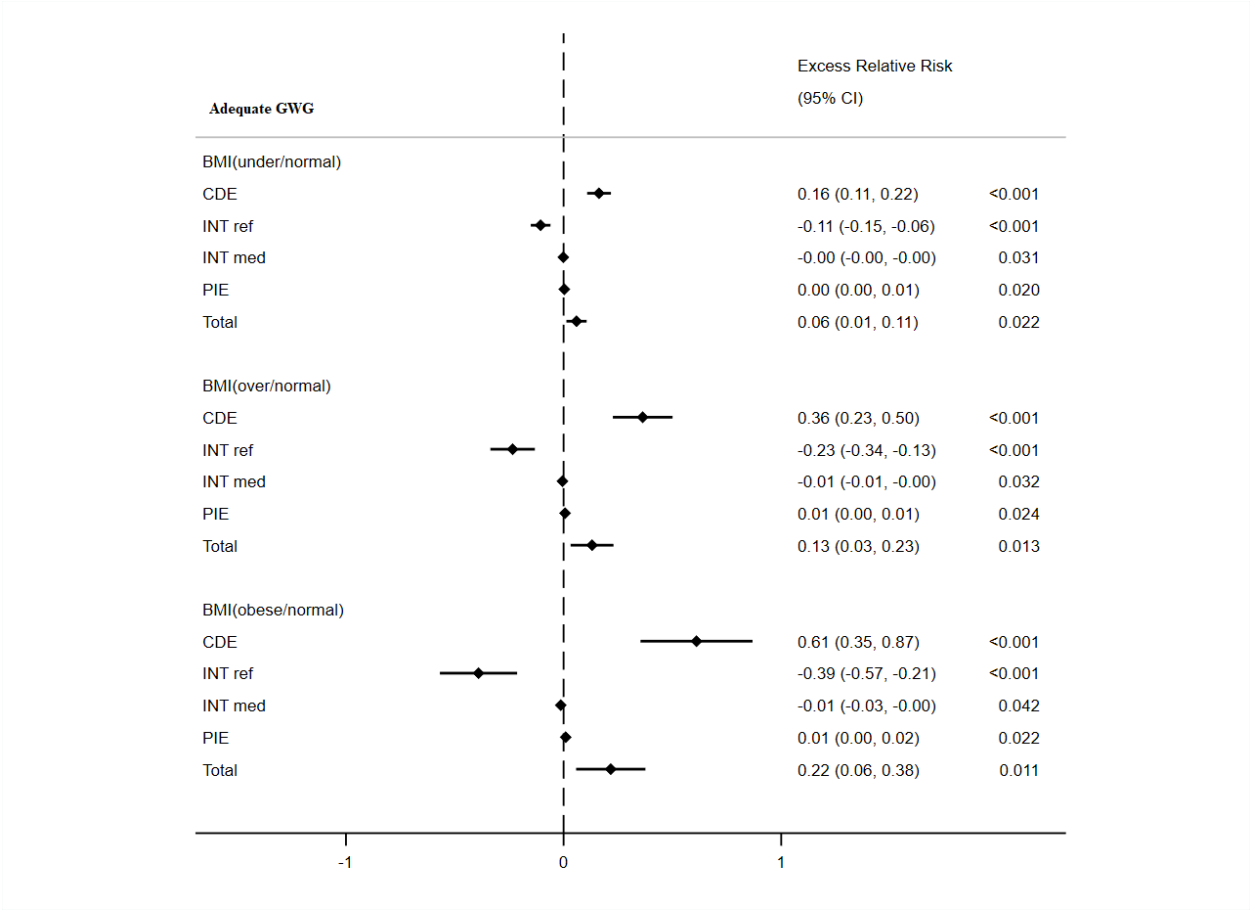
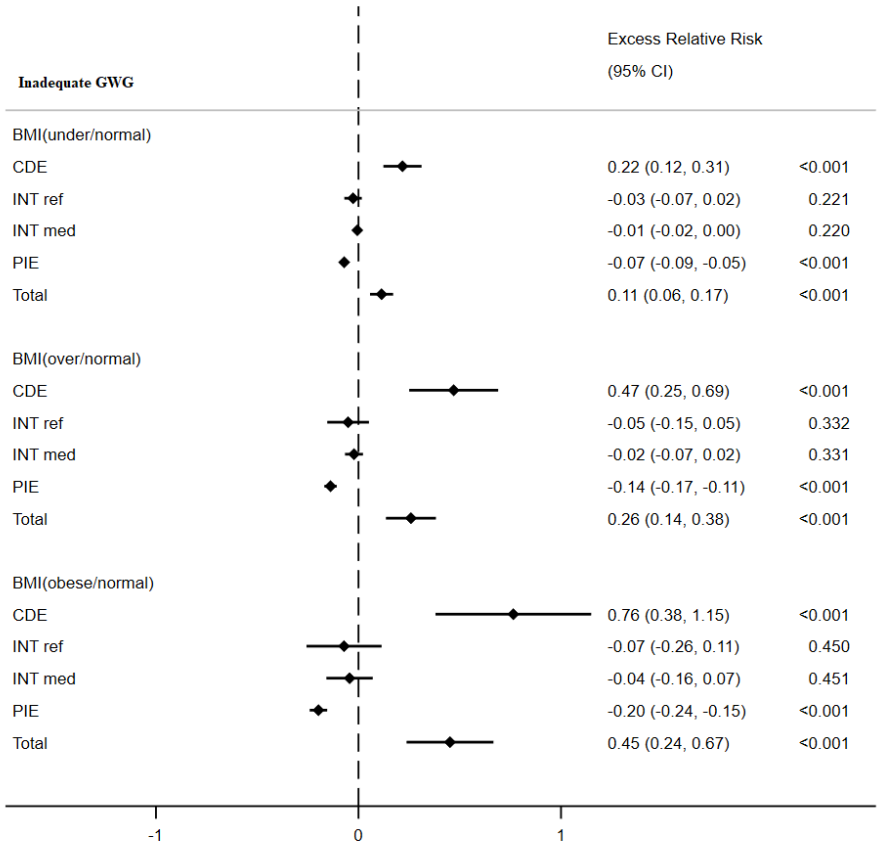


Figure 3.

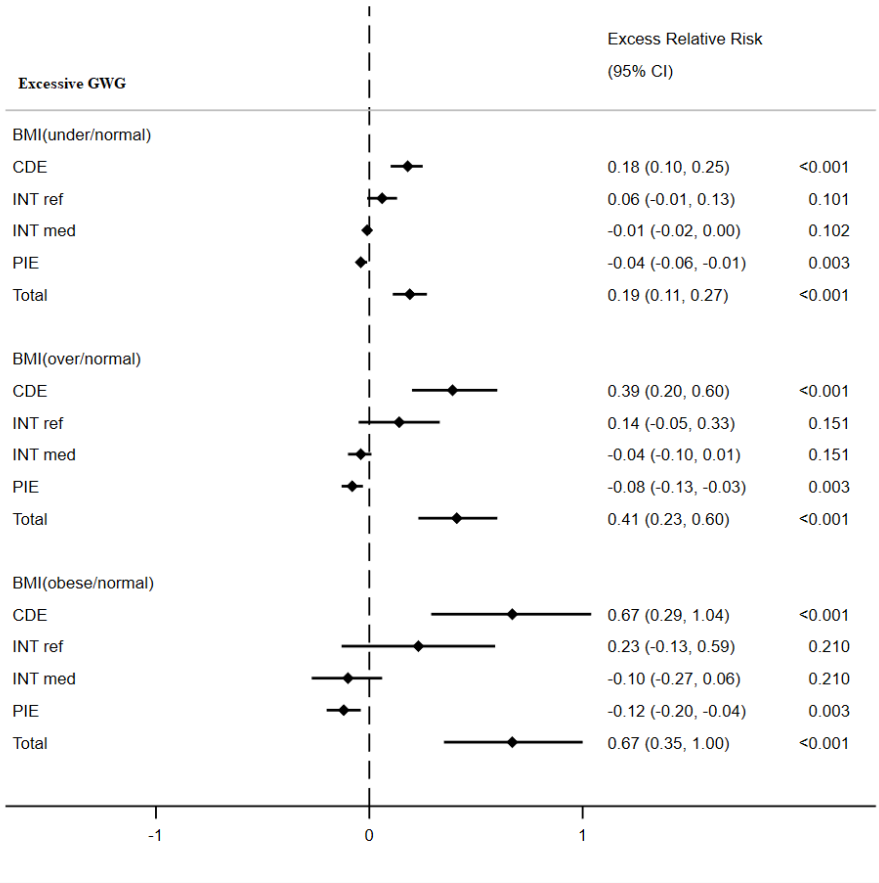
(a)


Adequate GWG
Excess Relative Risk
(95% CI)
BMI(under/normal)
CDE 0.16 (0.11, 0.22) <0.001
INT ref -0.11 (-0.15, -0.06) <0.001
INT med -0.00 (-0.00, -0.00) 0.031
PIE 0.00 (0.00, 0.01) 0.020
Total 0.06 (0.01, 0.11) 0.022
BMI(over/normal)
CDE 0.36 (0.23, 0.50) <0.001
INT ref -0.23 (-0.34, -0.13) <0.001
INT med -0.01 (-0.01, -0.00) 0.032
PIE 0.01 (0.00, 0.01) 0.024
Total 0.13 (0.03, 0.23) 0.013
BMI(obese/normal)
CDE 0.61 (0.35, 0.87) <0.001
INT ref -0.39 (-0.57, -0.21) <0.001
INT med -0.01 (-0.03, -0.00) 0.042
PIE 0.01 (0.00, 0.02) 0.022
Total 0.22 (0.06, 0.38) 0.011
-1
0
1

(b)


Inadequate GWG
Excess Relative Risk
(95% CI)
BMI(under/normal)
CDE 0.22 (0.12, 0.31) <0.001
INT ref -0.03 (-0.07, 0.02) 0.221
INT med -0.01 (-0.02, 0.00) 0.220
PIE -0.07 (-0.09, -0.05) <0.001
Total 0.11 (0.06, 0.17) <0.001
BMI(over/normal)
CDE 0.47 (0.25, 0.69) <0.001
INT ref -0.05 (-0.15, 0.05) 0.332
INT med -0.02 (-0.07, 0.02) 0.331
PIE -0.14 (-0.17, -0.11) <0.001
Total 0.26 (0.14, 0.38) <0.001
BMI(obese/normal)
CDE 0.76 (0.38, 1.15) <0.001
INT ref -0.07 (-0.26, 0.11) 0.450
INT med -0.04 (-0.16, 0.07) 0.451
PIE -0.20 (-0.24, -0.15) <0.001
Total 0.45 (0.24, 0.67) <0.001
-1
0
1

(c)


Excessive GWG
Excess Relative Risk
(95% CI)
BMI(under/normal)
CDE
0.18 (0.10, 0.25)
<0.001
INT ref
0.06 (-0.01, 0.13)
0.101
INT med
-0.01 (-0.02, 0.00)
0.102
PIE
-0.04 (-0.06, -0.01)
0.003
Total
0.19 (0.11, 0.27)
<0.001
BMI(over/normal)
CDE
0.39 (0.20, 0.60)
<0.001
INT ref
0.14 (-0.05, 0.33)
0.151
INT med
-0.04 (-0.10, 0.01)
0.151
PIE
-0.08 (-0.13, -0.03)
0.003
Total
0.41 (0.23, 0.60)
<0.001
BMI(obese/normal)
CDE
0.67 (0.29, 1.04)
<0.001
INT ref
0.23 (-0.13, 0.59)
0.210
INT med
-0.10 (-0.27, 0.06)
0.210
PIE
-0.12 (-0.20, -0.04)
0.003
Total
0.67 (0.35, 1.00)
<0.001
-1
0
1

Supplementary Figure 1. Consort flow chart