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Rate of gestational weight gain, pre-pregnancy body mass index and preterm birth subtypes: a retrospective cohort study from Peru

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Abstract

Objective—To examine the shape (functional form) of the association between the rate of gestational weight gain, pre-pregnancy body mass index (BMI), and preterm birth and its subtypes.

Design—Retrospective cohort study.

Setting—National reference obstetric centre in Lima, Peru.

Population—Pregnant women who delivered singleton babies during the period 2006–2009, resident in Lima, and beginning prenatal care at 12 weeks of gestation ($n = 8964$).

Methods—Data were collected from the centre database. The main analyses consisted of logistic regression with fractional polynomial modelling.

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Disclosure of interests

None to declare.

Contribution to authorship

AMC conceived the idea of the study, contributed to the design of the study, undertook the statistical analysis and drafted the article. CRM and PJG contributed to the study design and coordinated the data collection. All authors contributed to the final article and approved its contents.

Details of ethics approval

This study was exempted from ethical review by the Research Ethics Committee of the Instituto Nacional Materno-Perinatal (ref. no. 149-DG-440-OEAIDE-INMP-11) and the Institutional Review Board of Universidad Peruana Cayetano Heredia (project no. 57628), Lima, Peru.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Predicted gestational age at delivery and 95% confidence intervals by rate of gestational weight gain (kg/week) and pre-pregnancy body mass index categories.

Table S1. Bias analysis to quantify the potential effect of smoking and previous preterm births (unmeasured confounding factors) on the study results: comparison of insufficient and adequate weight gains.

Table S2. Bias analysis to quantify the potential effect of smoking and previous preterm birth (unmeasured confounding factors) on the study results: comparison of excessive and adequate weight gains.

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Main outcome measures—Preterm birth and its subtypes.

Results—Preterm birth occurred in 12.2% of women, being mostly idiopathic (85.7%). The rate of gestational weight gain was independently associated with preterm birth, and the shape of this association varied by pre-pregnancy BMI. In women who were underweight, the association was linear (per 0.1 kg/week increase) and protective (OR 0.88; 95% CI 0.82–1.00). In women of normal weight or who were overweight, the association was U-shaped: the odds of delivering preterm increased exponentially with rates <0.10 or >0.66 kg/week, and <0.04 or >0.50 kg/week, respectively. In women who were obese, the association was linear, but nonsignificant (OR 1.01; 95% CI 0.95–1.06). The association described for preterm birth closely resembled that of idiopathic preterm birth, although the latter was stronger. The rate of gestational weight gain was not associated with indicated preterm birth or preterm prelabour rupture of membranes.

Conclusions—In Peruvian pregnant women starting prenatal care at 12 weeks of gestation, the rate of gestational weight gain is independently associated with preterm birth, mainly because of its association with idiopathic preterm birth, and the shape of both associations varies by pre-pregnancy BMI.

Keywords

body mass index; pregnancy; premature birth; weight gain

Introduction

Preterm birth is an increasingly important global health problem,^{1,2} which causes significant mortality,^{3,4} and longterm disability.^{5,6} Thus, prematurity represents a high economic burden for health care,^{7,8} particularly in developing countries, where it is considerably more frequent.⁹ Despite having been studied for decades, the causal pathways underlying preterm birth remain largely unknown, and the preventive strategies implemented have been, for the most part, unsuccessful. This has been attributed to the heterogeneous and multifactorial nature of prematurity; in order to revert the current scenario, further etiological studies focusing on plausible causal pathways are needed, and these should divide the disease into subtypes based on underlying pathophysiological mechanisms.¹⁰ An area of growing interest is the potential link between the maternal nutritional status in pregnancy, a potentially modifiable attribute, and the occurrence of preterm birth.

Multiple lines of evidence have established that maternal nutritional factors are important determinants of pregnancy outcomes, and there is growing evidence suggesting that maternal nutritional status is a significant determinant of preterm birth.^{11–13} Specifically, several studies have reported that a low or high pre-pregnancy body mass index (BMI),^{14–17} anaemia, and iron, folate, calcium, magnesium, and zinc deficiencies are associated with an elevated risk of preterm birth. Potential mechanisms linking nutritional status and preterm birth include: decreased uteroplacental blood flow; increased risk of infection/inflammation; decreased antioxidant activity; myometrial hyper-reactivity; and the development of obstetric complications (e.g. pre-eclampsia and fetal distress).^{2,12,18,19} Considerably fewer studies have evaluated the association between gestational weight gain and preterm birth, in many cases with contradictory results.^{20–28} Furthermore, these studies have generally failed

to distinguish between the different preterm birth subtypes, and have categorised the rates of weight gain, limiting their ability to delineate the dose–response relationship between gestational weight gain and preterm birth subtypes. In addition, previous studies have been conducted in different contexts than those prevailing in Latin America and/or Peru. This is important, as racial, cultural, and socio-economic factors are associated with preterm birth.^{29–31} In particular, it has been shown that obesity-related obstetric complications vary by race,³² and that Hispanic women are at an increased risk of preterm birth and many of its risk factors (including obesity).^{29–31} Moreover, although obesity is currently on the rise worldwide, malnutrition persists as an important complication of pregnancy in developing countries: in Peru, 1.5–11.9% of pregnant women are malnourished, and 5.4–20.1% of women are obese.^{33–35} Consequently, much uncertainty persists on the dose–response relationship between gestational weight gain and preterm birth and its subtypes, complicating any interpretation of the role of weight gain during pregnancy on the risk of preterm birth and its subtypes, and the possible mechanisms involved. In this context, we aimed to examine the shape of the association (i.e. the functional form of the relationship) between the rate of gestational weight gain, the pre-pregnancy BMI, and preterm birth and its subtypes in a national reference obstetric centre in Peru.

Methods

We conducted a retrospective cohort study based on the data for pregnant women who delivered singleton babies during the period 2006–2009 in the Instituto Nacional Materno-Perinatal (INMP) in Lima, Peru, which is the national reference centre and largest obstetric centre in Peru. We used the INMP electronic database to obtain information for all pregnant women who delivered in the INMP during the period 2006–2009 ($n = 66\,630$, 100%), and selected women who delivered singleton babies, lacked selected comorbidities, and had complete weight and height data ($n = 27\,203$, 40.8%). We excluded women with multiple pregnancies to simplify and homogenise the calculations of weight gain rates ($n = 1233$, 1.9%), as well as women with comorbidities that could interfere with gestational weight gain [HIV infection ($n = 338$, 0.5%), tuberculosis ($n = 256$; 0.4%) and congenital malformations ($n = 52$, 0.1%)]. We further excluded women who started prenatal care after 12 weeks of pregnancy in order to limit potential inaccuracies in the pre-pregnancy weight recorded ($n = 18\,117$, 27.2%). In addition, we excluded women who resided outside of Lima (the main capture area of the INMP), in order to diminish the potential of a referral bias ($n = 83$, 0.1%). Finally, we excluded 39 women (<0.1%) with implausible weight measurements, leaving 8964 (13.5%) women available for the analysis. Figure 1 shows the process of selection of women in the study.

The main outcome of the study was the occurrence of preterm birth, defined as delivery occurring before 37 completed weeks of gestation, and its subtypes. Gestational age at delivery was determined by a physical examination of the newborn. Although controversial,^{36–38} the most widely used classification divides preterm birth into three clinical subtypes: idiopathic preterm birth; preterm prelabour rupture of membranes (PPROM); and indicated preterm birth.^{2,9} The diagnoses of preterm birth, and its subtypes, were obtained from the medical records of the women: indicated preterm birth included cases resulting from medical intervention, PPRM included cases with a diagnosis of

spontaneous rupture of membranes before the onset of labour; and idiopathic preterm birth included cases with a diagnosis of idiopathic preterm birth or those otherwise not classified (i.e. not resulting from medical intervention or from the rupture of membranes preceding labour).

The measure of weight gain during pregnancy used in the study was the rate of gestational weight gain, calculated by subtracting the women's weight at delivery from her weight at the first prenatal care visit, and dividing this weight by the gestational age at delivery minus the gestational age at the start of prenatal care. This measure is preferable to the total gestational weight gain, as the latter measure is intrinsically linked to the length of pregnancy, and thus to preterm birth. Nevertheless, the rate of gestational weight gain is still weakly linked to the gestational duration, as it overlooks the normal pattern of weight gain during pregnancy: i.e. a low rate of weight gain during the first trimester, followed by a high and linear rate of weight gain, respectively, in the second and third trimesters of pregnancy.^{39,40} Thus, women with shorter pregnancies tend to have a lower rate of gestational weight gain because of the relatively greater influence of the slow rate of weight gain during the first trimester of pregnancy.¹⁹ Preferable measures include the pattern of weight gain, or separating the rate of weight gain by trimesters. However, because we did not have information on the women's weight at different times in pregnancy, we had to rely solely on the rate of gestational weight gain (see Discussion). The women's weight and gestational age at the first prenatal care visit and at delivery, used to calculate the rates of gestational weight gain, were obtained from the women's medical records.

Other covariates measured included the pre-pregnancy BMI, maternal age, number of prenatal care visits, parity, number of previous miscarriages/terminations of pregnancy, socio-economic status, and history of pre-eclampsia/eclampsia and chronic arterial hypertension, which were also obtained from the women's medical records.

Statistical analysis was conducted using *STATA/IC* 11.1 for windows (StataCorp LP, College Station, TX, USA). Bivariate analyses were performed using the Student's *t* test, the Mann–Whitney *U* test, Analysis of variance, or the Kruskal–Wallis test for continuous variables, and the chisquared test or Fisher's exact test for categorical variables, as appropriate. Confidence intervals were calculated using standard formulae for statistics with known sampling distributions, and using bootstrap methods for those with unknown sampling distributions (e.g. Spearman's rank correlation coefficient). For the multivariate analysis, we fitted separate multiple logistic regression models using fractional polynomial modelling, in order to calculate the adjusted odds ratios with 95% confidence intervals for preterm birth, and each of its subtypes. This approach permitted the modelling of continuous predictors, thereby avoiding categorisation and its drawbacks,⁴¹ and, most importantly, allowing the evaluation of the shape of the association between the rate of gestational weight gain and preterm birth subtypes. During the model-building process, we evaluated the linearity assumption using graphical methods and the fractional polynomial closed test (to control the significance level),⁴² and accounted for nonlinearities by using fractional polynomial transformations. We constructed the final logistic regression model by evaluating the inclusion and best transformation of each predictor (the default transformation was linear) in terms of the deviance of nested models.⁴² Finally, we added into the final model any

covariate that was thought to be an important confounding factor on theoretical grounds. Selection of the polynomial transformations was mainly statistical, but also considered the clinical plausibility of the resulting models. We preferred using fractional polynomial regression over other methods that handle continuous predictors (such as splines, non-parametric or complete polynomial regression), because of the existence of an established method for model building, the decreased potential for artifacts, the flexibility and goodness of fit provided, and the parsimony and interpretability of fractional polynomial models.⁴³ We evaluated the goodness of fit of the models with the Hosmer–Lemeshow test and residual analysis. In addition, we searched for alternative more complex, betterfitting transformations by using a less stringent fractional polynomial selection probability ($\alpha = 0.10$). Finally, we assessed the stability of the models using bootstrap analysis.⁴² We also tested the inclusion of two interaction terms (between the pre-pregnancy BMI and rate of gestational weight gain, and between the pre-pregnancy BMI and parity) using the MFPIgen algorithm,⁴² but neither was significant in any of the preterm birth subtypes. Nevertheless, we stratified all models by pre-pregnancy BMI (using the WHO classification), based on previous reports of an interaction between the pre-pregnancy BMI and the rate of gestational weight gain, and between the pre-pregnancy BMI and parity,^{17,24–27,44–46} and the theoretical plausibility of such effect modification, as well as the importance of the maternal pre-pregnancy BMI on previous reports and recommendations. Also, because of the possibility of residual confounding, we included the pre-pregnancy BMI as a continuous covariate in the multivariate models. We centred all continuous variables to give our models a more intuitive interpretation.

In addition, we performed a bias analysis to determine whether smoking and a previous preterm birth (important unmeasured confounding factors) could account for the observed association between the rate of gestational weight gain and preterm birth, by conducting an external adjustment, as described by Lin et al.⁴⁷ Because this approach can only accommodate categorical predictors, we categorised the weight gain, according to the 2009 Institute of Medicine (IOM) recommendations,⁴⁸ into three categories: insufficient, adequate, and excessive weight gain. The bias parameters were extracted from previous studies; however, the paucity of information on the preterm birth subtypes necessarily restricted the bias analysis to preterm birth (all subtypes combined). For smoking, we hypothesised that the prevalence of smoking in women with adequate weight gain (reference) varied between 1 and 20%, and that women with insufficient and excessive weight gain were 1.50 and 1.20 times as likely to smoke, respectively (estimates calculated from previous reports ranged from 0.40 to 1.49 and from 0.49 to 1.17, respectively).^{49–57} We also assumed that smokers had 1.27 (95% CI 1.22–1.31) times the odds of delivering preterm than women who did not smoke.⁵⁸ For the antecedent of a previous preterm birth, we hypothesised that the prevalence of such an antecedent in women with adequate weight gains varied between 1 and 10%, and that women with insufficient and excessive weight gains were 0.83 and 0.67 times as likely to have such an antecedent as women with adequate weight gains, respectively (estimates calculated from a previous report).⁵⁹ We also assumed that women with a previous preterm birth had 2.90 (95% CI 2.80–3.00) times the odds of delivering preterm than those without a previous preterm birth.⁶⁰

Finally, as a secondary analysis, we examined the association between the gestational age at delivery and the rate of gestational weight gain using a multiple regression analysis with fractional polynomial modelling, stratified by the pre-pregnancy BMI (using the WHO classification). Assumptions for the linear regression model were assessed through residual analysis. The model-building strategy and the assessment of the model's stability was the same as described above for the main analysis.

Results

A total of 8964 women were included in the study. Table 1 shows the sociodemographic and clinical characteristics of the cohort. Of these, 276 women (3.1%) were underweight, 5867 (65.5%) had normal weights, 2267 (25.3%) were overweight, and 554 (6.2%) were obese. The median gestational age at the start of prenatal care was 9 weeks of gestation (bootstrap bias-corrected accelerated 95% CI: 8–10 weeks). The mean rate of gestational weight gain was 0.38 ± 0.19 kg/ week. Finally, 1094 (12.2%) women had preterm birth: 937 (85.7%) of these were idiopathic, 99 (9.0%) were indicated, and 58 (5.3%) were the result of PPROM.

The pre-pregnancy BMI was inversely associated with the rate of gestational weight gain, and was positively associated with maternal age, parity, and the number of previous miscarriages/terminations of pregnancy. No differences were noted in the gestational age at which women started prenatal care, the prevalence of chronic hypertension, or in socio-economic status (Table 2). In addition, the rate of gestational weight gain decreased slightly as the pre-pregnancy BMI increased (Spearman's $\rho = -0.25$; bootstrap bias-corrected accelerated 95% CI -0.27 to -0.23 ; data not shown).

Table 3 shows the adjusted odds ratio and 95% confidence intervals of preterm birth and its subtypes by rate of gestational weight gain, with categories based on the 2009 IOM recommendations.

Preterm birth (all subtypes)

The association between the rate of gestational weight gain and preterm birth varied by the pre-pregnancy BMI (see Figure 2). In women who were underweight, the association was linear and protective: the odds of preterm birth decreased by 9% with every increase of 0.1 kg/week (OR 0.91; 95% CI 0.82–1.00). In women of normal weight and women who were overweight, the association was curvilinear (U-shaped): compared with women who gained 0.38 kg/week (reference), both low rates of weight gain (<0.10 and <0.04 kg/week for women of normal weight and women who were overweight, respectively) and high rates of weight gain (>0.66 and >0.50 kg/week, respectively) were associated with exponentially increasing odds of preterm birth (doubling at -0.42 and 1.18 kg/week for women of normal weight; doubling at -0.27 and 1.02 kg/ week for women who were overweight). In obese women, the association was linear: the odds of preterm birth increased by 1% with every increase of 0.1 kg/week, although this increase was not statistically significant (OR 1.01; 95% CI 0.95–1.06).

Idiopathic preterm birth

The association between the rate of gestational weight gain and idiopathic preterm birth closely resembled that of preterm birth, although the former was stronger (see Figure 3). In women who were underweight, the association was linear: the odds of idiopathic preterm birth decreased by 12% with every increase of 0.1 kg/week (OR 0.88; 95% CI 0.79–0.98). In women of normal weight and in women who were overweight, the association was curvilinear (U-shaped): compared with women who gained 0.38 kg/week (reference), both low rates of weight gain (<0.22 and <0.11 kg/week for women of normal weight and women who were overweight, respectively) and high rates of weight gain (>0.76 and >0.51 kg/week, respectively) were associated with exponentially increasing odds of preterm birth (doubling at –0.60 and 1.15 kg/week for women of normal weight; doubling at –0.27 and 1.02 kg/week for women who were overweight). In women who were obese, the association was linear: the odds of preterm birth decreased by 1% with every increase of 0.1 kg/week, although this increase was not statistically significant (OR 0.99; 95% CI 0.93–1.05).

Indicated preterm birth

We found no association between rates of gestational weight gain and indicated preterm birth in any of the BMI strata. The relationship between the rate of gestational weight gain and indicated preterm birth was linear and direct for all BMI categories, although this was not statistically significant: every increase of 0.1 kg/week increased the odds of indicated preterm birth by 4% in women who were underweight (OR 1.04; 95% CI 0.75–1.45), by 7% in women of normal weight (OR 1.07; 95% CI 0.99–1.15), by 3% in women who were overweight (OR 1.03; 95% CI 0.93–1.13), and by 9% in women who were obese (OR 1.09; 95% CI 0.96–1.24).

Preterm prelabour rupture of membranes (PPROM)

The rate of gestational weight gain was not independently associated with PPRM in any BMI strata. The relationship between the rate of gestational weight gain and indicated preterm birth was linear, although not statistically significant, and with marked heterogeneity between BMI categories. In women who were underweight or overweight, every increase of 0.1 kg/week increased the odds of PPRM by 5% (OR 1.05; 95% CI 0.76–1.44) and 6% (OR 1.06; 95% CI 0.90–1.24), respectively. However, in women of normal weight and in women who were obese, every increase of 0.1 kg/week decreased the odds of PPRM by 2% (OR 0.98; 95% CI 0.89–1.07) and 11% (OR 0.89; 95% CI 0.67–1.18), respectively.

The bias analysis conducted allowed the evaluation of the effect of smoking and a previous preterm birth (unmeasured confounding factors) on the observed association between the rate of gestational weight gain and preterm birth (Tables S1 and S2). The observed adjusted odds ratio of preterm birth comparing women with adequate weight gains (referent) against women with insufficient and excessive weight gains was 1.20 (95% CI 1.09–1.31) and 1.10 (95% CI 1.04–1.18), respectively. An increase in the prevalence of smoking or the smoking/preterm birth risk ratio resulted in a decrease of the externally adjusted odds ratio of preterm birth: up to 5.0% (to 1.14; 95% CI 1.04–1.25) when comparing women with insufficient and adequate weight gains, and 11.0% (to 1.07; 95% CI 1.02–1.13) when comparing women

with excessive and adequate weight gains. In addition, an increase in the prevalence of a previous preterm birth or the previous preterm birth/preterm birth risk ratio resulted in an increase of the externally adjusted odds ratio of preterm birth: up to 19.9% (to 1.44; 95% CI 1.31–1.57) when comparing women with insufficient and adequate weight gains, and 36.2% (to 1.63; 95% CI 1.56–1.72) when comparing women with excessive and adequate weight gains. Under all the scenarios tested, the externally adjusted odds ratio of preterm birth remained statistically significant.

The multiple linear regression analysis performed revealed that the gestational age at delivery was independently associated with the rate of gestational weight gain, and that this association varied by the pre-pregnancy BMI: in women who were underweight, the association was linear but non-significant; in women of normal weight and women who were overweight, the association exhibited a 'reversed-U' shape: both low rates of weight gain (<-0.26 and <0.38 kg/week for women of normal weight and women who were overweight, respectively) and high rates of weight gain (>1.19 and >1.18 kg/week, respectively) resulted in a shortened length of gestation (<37 weeks). Finally, in obese women, the association was linear, but not statistically significant (Figure S1). These findings closely parallel those described earlier for preterm birth and idiopathic preterm birth.

Discussion

In this retrospective cohort study of Peruvian pregnant women, we found that preterm birth was independently associated with the rate of gestational weight gain, and that the association varied by pre-pregnancy BMI. In women who were underweight, the association was linear and protective, and in women of normal weight, the association was U-shaped: both very low rates (<0.10 kg/week) and very high rates (>0.68 kg/week) of gestational weight gain were associated with an increase in the odds of delivering preterm, compared with women who gained 0.38 kg/week. In women who were overweight, the association was also U-shaped: both very low rates (<0.04 kg/week) and very high rates (>0.50 kg/week) of gestational weight gain were associated with an increase in the odds of delivering preterm, compared with women who gained 0.38 kg/week. Finally, in women who were obese, the association was linear and risk-bearing, but not significant. The association between idiopathic preterm birth and the rate of gestational weight gain closely resembled that of preterm birth, although it was a stronger association. PPRM and indicated preterm birth exhibited a slight, linear relationship with the rate of gestational weight gain (direct and heterogeneous, respectively), although it was not significant. Although differences in the shape of the association between preterm birth subtypes may reflect true heterogeneity, they have most likely resulted from the limited number of PPRM and indicated preterm birth cases ($<10\%$ each), which limited the power of study to evaluate these associations.

Most previous studies have reported that low rates of pregnancy weight gain may increase the risk of preterm birth,^{19,22,24,25,28,61–64} although several studies have also suggested that excessive rates of weight gain may increase the risk of preterm birth.^{23,26,27,37,44,59,65} Although these results may seem inconsistent with the U-shaped association we have reported, the underlying explanation may be two-fold. First, as most studies have evaluated

categorised rates of weight gain, they may have missed part of the association by averaging the effects of dissimilar rates of weight gain. This is supported by the fact that most studies that evaluated rates of weight gain continuously, or used narrow categories, have found results consistent with a U-shaped association.^{26,44,65} Also, as the effect of increasing rates of weight gain may be greater at low rates of weight gain, this may explain why most studies have detected a protective effect of increasing rates of weight gain. Second, the failure to distinguish between the different preterm birth subtypes may have diluted any association that was specific to a particular subtype. Indeed, rates of weight gain affect the preterm birth subtypes differently: spontaneous preterm birth is associated mainly with low rates of weight gain; indicated preterm birth is associated with high rates of weight gain; and PPROM is not associated with rates of weight gain.^{25,27,37,59,61} Thus, by distinguishing between the preterm birth subtypes and modelling the rate of weight gain as a continuous variable, we avoided several of the shortcomings of previous studies, permitting a better delineation of the shape of the association between the rates of gestational weight gain and preterm birth, and its subtypes. The ranges of insufficient/excessive rates of gestational weight gain we found are consistent with those previously reported, although such comparisons are complicated by the arbitrariness of the categories used, the lack of stratification by pre-pregnancy BMI, and the aggregation of preterm birth subtypes. For preterm birth, insufficient rates of weight gain were in the range of <0.18 – 0.37 kg/week,^{25,27,28,37,59,61,63} and excessive rates of weight gain were in the range >0.45 – 0.79 kg/week.^{26,37,44} For idiopathic preterm birth, insufficient rates of weight gain were <0.18 – 0.37 kg/week,^{25,27,37,59,61} and excessive rates of weight gain were >0.52 kg/week.⁵⁹

The reported shapes of the association between the rate of weight gain and preterm birth, and its subtypes, are biologically plausible and in agreement with previous knowledge, and may be explained by the different hypothesised mechanisms acting at the extremes of weight-gain rates.^{2,12,13} As previously stated, low rates of weight gain may be associated with an increased risk of preterm birth because of its association with the poor expansion of plasma volume, diminished uteroplacental blood flow, impaired antioxidant activity, micronutrient deficiencies, and an increased risk of infection and/or inflammation. On the other hand, the mechanisms linking excessive rates of weight gain and preterm birth are less well defined, but may result from induction of a pro-inflammatory state and, consequently, labour.² Although the fluid retention associated with pre-eclampsia may partly explain the relationship between high rates of weight gain and preterm birth, this is challenged by the persistence of an increased risk of preterm birth after controlling for pre-eclampsia/eclampsia.²⁶ Furthermore, preterm birth has been consistently associated with both low and high rates of gestational weight gain in studies with varying methodologies, conducted in different population groups (albeit mainly from affluent countries). This study adds to such consistency by reporting an association (and its functional form) between the rate of gestational weight gain and preterm birth, and its subtypes, in an ethnically and culturally varied population from a developing country. Despite these arguments, considerable uncertainty remains about whether the association between gestational weight gain and preterm birth is causal, and further and more definitive information is needed before this issue can be resolved. Evidence supporting this association has come mainly from observational studies that, as stated above, have failed to distinguish between the preterm

birth subtypes, have been unable to evaluate the shape (dose–response relationship) of the association, and have been carried out almost exclusively in developed countries. In addition, because of the observational nature of such evidence, there is a significant probability of confounding and other biases. The situation is compounded by the fact that the rate of gestational weight gain is an nonspecific marker of many different physiological/pathological processes, in addition to nutritional status, making it difficult to determine whether it is the cause of preterm birth or just a marker of other processes associated with preterm birth. In this context, experimental evidence is needed to disentangle the independent effect of gestational weight gain on preterm birth. Experimental studies oriented to modulate gestational weight gain have been limited, but the few small trials conducted have provided some evidence that it is possible to regulate weight gain during pregnancy.⁶⁶ Larger trials are needed to determine whether such interventions may have an impact on preterm birth. In sum, we cannot consider the observed association as causal until more definitive supporting evidence (both, epidemiological and experimental) is available.

Our study has several limitations that should be considered when interpreting its results, most of which stem from its retrospective nature. First, as women start prenatal care after the diagnosis of pregnancy, the pre-pregnancy weight is seldom available on their medical records. Thus, we had to rely on weight in early pregnancy as a surrogate of pre-pregnancy weight, and assuming that any weight gain resulting from pregnancy at that time was small, and possibly negligible. To increase the accuracy of the pre-preg-nancy weight, we restricted the study population to pregnant women who started prenatal care before or at 12 weeks of gestation, limiting any weight gained because of pregnancy. Although we recognise that the pre-preg-nancy weight may have still been inaccurate, it is reasonable to assume that such misclassification would probably be small. Second, as we had no information on the weight of women at different times during pregnancy, we had to rely on the rate of gestational weight gain as a measure of weight gain. As mentioned above, this measure is less preferable than the pattern of weight gain, as it is slightly related to the length of the pregnancy, resulting in a lower overall weight gain rate in women who deliver preterm. Nevertheless, such bias is probably small,^{44,59} as it is the rate of weight gain in late pregnancy that is associated with preterm birth,^{19,26,40} and as the lower rate of gestational weight gain in women with shorter pregnancies, is partly offset by the smaller influence of the slower rate of weight gain in the third trimester (in comparison with the rate of weight gain in the second trimester) in such women. Third, data on important theoretical confounding factors, such as maternal smoking and the antecedent of a previous preterm delivery, was not available for the analysis, resulting in uncontrolled confounding. Because both smoking and a previous preterm delivery are associated with an increased risk of preterm birth,^{58,67} and lower rates of weight gain during pregnancy,^{67,68} the failure to adjust for these confounding factors would theoretically result in an overesti-mation of the association. However, it is unlikely that such confounding accounts completely for the strong association reported, given that smoking and a previous preterm birth, although strong predictors of preterm birth, are not strongly associated with the rate of gestational weight gain. The bias analysis confirmed that it is unlikely that confounding by smoking and previous preterm birth accounts for the reported association, as it remained statistically significant under the most conservative scenarios (and even after diluting the effect of

extreme weight gains by categorisation). Finally, our analysis of the association between the rate of gestational weight gain and PPRM, and indicated preterm birth, was limited by the scarce number of these outcomes, thereby undermining the power of the study to examine these associations. This may have resulted from the study setting (a national reference centre), the selection criteria employed, and the difficulty in discriminating between PPRM and idiopathic preterm birth.

Despite these limitations, the study has several strengths worth considering. First, it benefited from a relatively large sample size (to our knowledge, the largest published study of a Peruvian pregnant population) that allowed the examination of the shape of the association between rates of weight gain and preterm birth subtypes. Second, the fractional polynomial modelling used also permitted the evaluation of the shape of this association, and, in addition, it maximised the power of the study, and avoided categorisation and its drawbacks. In addition, the stability and goodness-of-fit analyses performed ensured that the models selected were supported by most of the data. Third, the selection criteria employed helped to ensure the validity of its results, by limiting the potential of information (misclassification) and selection (referral) bias. Fourth, the bias analysis and secondary analysis corroborated the robustness of our findings and argue in favour of their validity. Finally, the study setting, a national reference obstetric centre with an electronic database, guaranteed the quality and homogeneity of the data, and may determine a greater external validity of its results, as the INMP serves a large population with varied cultural and socioeconomic backgrounds.

These findings are important from both a public health and clinical perspective. The study provides evidence of an independent association between the rate of gestational weight gain and preterm birth, and idiopathic preterm birth, which varies by the pre-pregnancy BMI. By elucidating the shape of the association for each of the preterm birth subtypes, these findings may contribute to our understanding the mechanisms underlying preterm birth. Although the association identified is plausible and consistent, we would not yet recommend any nutritional intervention on gestational weight gain to prevent preterm birth until more definitive evidence is available (including experimental evidence). Nevertheless, irrespective of whether the association is causal or not, gestational weight gain may serve to identify women at high risk of preterm birth (and other complications), and may constitute a useful marker of a favourable evolution of pregnancy, particularly in women with risk factors for delivering preterm. Furthermore, the study provides direct estimates of adequate rates of gestational weight gain, which may serve to develop guidelines on weight gain during pregnancy for Peruvian and/or Latin American women, an understudied population at an increased risk of inadequate gestational weight gain (both, insufficient and excessive) and preterm birth, for whom there are no specific guidelines on weight gain during pregnancy.

Conclusion

In Peruvian pregnant women who started prenatal care before 12 weeks of gestation, the rate of gestational weight gain exhibited an independent association with preterm birth, which varied by the pre-pregnancy BMI. This association was explained mainly by that of idiopathic preterm birth, as the other preterm birth subtypes were not associated with the rate

of gestational weight gain. These findings are plausible, and of public health and clinical relevance, and highlight the need for further studies in Peruvian and Latin American women (including longitudinal and experimental studies) to confirm our results and expand our knowledge on the aetiology of preterm birth.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Selection of women included in the study. The percentages refer to the total number of women who delivered in the Instituto Nacional Materno-Perinatal (INMP) in Lima, Peru, during 2006–2009 ($n = 66\,630$). †Comorbidities excluded from the study: tuberculosis ($n = 256$, 0.4%), human immunodeficiency virus (HIV) infection ($n = 338$, 0.5%), and congenital malformations ($n = 52$, 0.1%).

Figure 2.

Adjusted odds ratios (AORs) of preterm birth (all subtypes) and 95% confidence intervals (95% CIs) by rate of gestational weight gain (kg/week) and pre-pregnancy body mass index categories; AORs, solid lines; 95% CIs, broken lines. The natural logarithm of the odds of preterm birth was calculated from the following models: (A) underweight, $\ln y = -18.838 - 0.077(\text{rate} + 1) - 0.144(\text{BMI}) + 4.444(\text{PCV})^{-1} + 2.072(\text{PCV})^{-1} \ln(\text{PCV}) - 0.055(\text{GA}) - 0.075(\text{parity} + 1) + 0.014(\text{age}) + 16.994(\text{SES2}) + 17.061(\text{SES3}) + 0.653(\text{HTN})$; (A, B) normal weight, $\ln y = -2.235 - 2.2885(\text{rate} + 1)^{1/2} + 0.204(\text{rate} + 1)^3 - 0.019(\text{BMI}) + 9.270 \ln(\text{PCV}) - 26.780(\text{PCV})^{1/2} - 0.049(\text{GA}) - 0.003(\text{parity} + 1)^{-2} + 0.678(\text{age})^{-1} + 0.266(\text{SES2}) + 0.348(\text{SES3}) + 0.431(\text{HTN})$; (C) overweight, $\ln y = -2.745 + 1.753(\text{rate} + 1)^{-1} + 0.195(\text{rate} + 1)^3 - 0.056(\text{BMI}) + 20.657(\text{PCV})^{-1/2} + 7.322(\text{PCV})^{-1/2} \ln(\text{PCV}) - 0.051(\text{GA}) + 0.080(\text{parity} + 1) + 0.009(\text{age}) + 0.573(\text{SES2}) + 0.621(\text{SES3}) + 0.287(\text{HTN})$; (D) obese, $\ln y = -2.133 + 0.022(\text{rate} + 1) + 0.022(\text{BMI}) - 0.026(\text{PCV})^3 - 0.045(\text{GA}) + 0.052(\text{parity} + 1) - 0.002(\text{age}) + 0.424(\text{SES2}) + 0.394(\text{SES3}) + 0.342(\text{HTN})$, where y is the odds of preterm birth, rate is the rate of gestational weight gain (kg/week), BMI is the body mass index (kg/m^2), GA is the gestational age at the start of prenatal care (weeks), PCV is the number of prenatal care visits, SES2 is medium socio-economic status, SES3 is high socio-economic status, and HTN is history of gestational hypertension. The reference weight gain rate during pregnancy was 0.38 kg/week (mean).

Figure 3.

Adjusted odds ratios (AORs) of idiopathic preterm birth and 95% confidence intervals (95% CIs) by rate of gestational weight gain (kg/week) and pre-pregnancy body mass index categories; AORs, solid lines; 95% CIs, broken lines. The natural logarithm of the odds of idiopathic preterm birth was calculated from the following models: (A) underweight, $\ln y = -19.056 - 1.242(\text{rate} + 1) - 0.152(\text{BMI}) - 0.337(\text{PCV})^{-2} + 2.264(\text{PCV})^{-1} - 0.044(\text{GA}) - 0.349(\text{parity} + 1) + 0.007(\text{age}) + 16.980(\text{SES2}) + 17.001(\text{SES3}) + 0.825(\text{HTN})$; (B) normal weight, $\ln y = -2.432 - 1.188(\text{rate} + 1)^2 + 0.538(\text{rate} + 1)^3 - 0.015(\text{BMI}) + 9.751 \ln(\text{PCV}) - 27.905(\text{PCV})^{1/2} - 0.049(\text{GA}) - 0.003(\text{parity} + 1)^{-2} + 1.107(\text{age})^{-2} + 0.295(\text{SES2}) + 0.347(\text{SES3}) + 0.608(\text{HTN})$; (C) overweight, $\ln y = -2.780 + 2.142(\text{rate} + 1)^{-1} + 0.225(\text{rate} + 1)^3 - 0.063(\text{BMI}) - 12.636(\text{PCV})^{1/2} - 9.498 \ln(\text{PCV}) - 0.051(\text{GA}) + 0.077(\text{parity} + 1) + 0.005(\text{age}) + 0.417(\text{SES2}) + 0.435(\text{SES3}) + 0.482(\text{HTN})$; (D) obese, $\ln y = -2.384 - 0.101(\text{rate} + 1) - 0.014(\text{BMI}) - 1.305(\text{PCV})^3 - 0.040(\text{GA}) + 0.071(\text{parity} + 1) - 0.002(\text{age}) + 0.216(\text{SES2}) + 0.209(\text{SES3}) + 0.584(\text{HTN})$, where y is the odds of idiopathic preterm birth, rate is the rate of gestational weight gain (kg/week), BMI is the body mass index (kg/m^2), GA is the gestational age at the start of prenatal care (weeks), PCV is the number of prenatal care visits, SES2 is medium socio-economic status, SES3 is high socio-economic status, and HTN is a history of gestational hypertension. The reference weight gain rate during pregnancy was 0.38 kg/week (mean).

Table 1

Maternal characteristics in the study population

Characteristic	N
Preterm birth	1.094 (12.2%)
Idiopathic preterm birth	937 (85.7%)
PPROM	58 (5.3%)
Indicated preterm birth	99 (9.0%)
Gestational weight gain rate (Kg/week) *	0.38 (0.37, 0.38)
<0.12	867 (9.7%)
0.12–0.45	4711 (52.6%)
0.46–0.91	3217 (35.9%)
0.92–1.11	134 (1.5%)
1.12	35 (0.4%)
Pre-gestational BMI (Kg/m²) *	23.9 (23.8, 23.9)
Underweight (<18.5 Kg/m ²)	276 (3.1%)
Normal weight (18.5–24.9 Kg/m ²)	5867 (65.5%)
Overweight (25.0–29.9 Kg/m ²)	2267 (25.3%)
Obese (>30 Kg/m ²)	554 (6.2%)
Maternal age (years) *	26.4 (26.2, 26.5)
GA at the start of prenatal care (weeks) †	9 (8, 10)
Number of prenatal care visits †	9 (8, 19)
Parity	
0	4417 (49.3%)
1+	4547 (50.7%)
Previous miscarriages/TOP	
0	6667 (74.4%)
1+	2297 (25.6%)
Chronic arterial hypertension	
Present	20 (0.2%)
Absent	8944 (99.8%)
Socioeconomic status	
Low	3467 (38.7%)
Medium	5365 (59.9%)
High	132 (1.5%)

BMI, body mass index (in kg/m); PPRM, preterm premature rupture of membranes; GA, gestational age (in weeks); TOP, termination of pregnancy.

* Mean (95% confidence Intervals),

† median (95% confidence intervals), otherwise *n* (%).

Table 2

Distribution of maternal characteristics by pre-gestational body mass index categories

Variable	Underweight (<18.5 Kg/m ²)	Normal weight (18.5 – 24.9 Kg/m ²)	Overweight (25.0 – 29.9 Kg/m ²)	Obese (>30 Kg/m ²)
Gestational weight gain rate (kg/week) *	0.49 (0.47, 0.52)	0.41 (0.40, 0.41)	0.33 (0.32, 0.33)	0.25 (0.23, 0.26)
Maternal age (years) *	23.09 (22.44, 23.74)	25.36 (25.21, 25.52)	28.29 (28.03, 28.54)	30.20 (29.70, 30.70)
GA at the start of prenatal care †	9 (8, 10)	9 (8, 10)	9 (3, 10)	10 (7, 10)
Number of prenatal care visits †	10 (9, 16)	11 (10, 20)	2 (1, 8)	6 (2, 10)
Parity †	0 (0, 5)	0 (0, 4)	0 (0, 3)	1 (0, 5)
Previous miscarriages/TOP †	0 (0, 2)	0 (0, 2)	0 (0, 4)	0 (0, 3)
Chronic arterial hypertension				
Present	2 (0.7%)	11 (0.2%)	5 (0.2%)	2 (0.4%)
Absent	274 (99.3%)	1092 (99.8%)	2262 (99.8%)	552 (99.6%)
Socioeconomic status				
Low	116 (42.0%)	2207 (37.6%)	904 (39.9%)	240 (43.3%)
Medium	157 (56.9%)	3569 (60.8%)	1333 (58.8%)	306 (55.2%)
High	3 (1.1%)	91 (1.6%)	30 (1.3%)	8 (1.5%)

BMI, body mass index (categories based on the WHO classification); GA, gestational age (in weeks); TOP, termination of pregnancy.

* Mean (95% confidence intervals),

† Median (95% confidence intervals), otherwise *n* (%).

Adjusted odds ratio (OR) and 95% confidence intervals (95% CI) of preterm birth subtypes by gestational weight gain rate categories based on the 2009 Institute of Medicine (IOM) Recommendations^{*,†}

Table 3

Gestational weight gain rate (kg/week)		All subtypes		Idiopathic preterm birth		Indicated preterm birth	
Category	Range [‡]	OR	95% CI	OR	95% CI	OR	95% CI
Underweight							
Insufficient	<0.32	1.99	1.26, 3.13	2.03	1.25, 3.30	0.92	0.18, 4.68
Adequate	0.32–0.46	1.00	Reference	1.00	Reference	1.00	Reference
Excessive	>0.46	0.76	0.48, 1.24	0.69	0.41, 1.16	1.50	0.24, 9.29
Normal weight							
Insufficient	<0.28	1.26	1.12, 1.41	1.29	1.14, 1.45	0.85	0.59, 1.22
Adequate	0.28–0.40	1.00	Reference	1.00	Reference	1.00	Reference
Excessive	>0.40	1.14	0.98, 1.32	1.14	0.97, 1.34	1.06	0.67, 1.69
Overweight							
Insufficient	<0.17	1.00	0.82, 1.20	1.08	0.88, 1.32	0.70	0.41, 1.18
Adequate	0.17–0.28	1.00	Reference	1.00	Reference	1.00	Reference
Excessive	>0.28	0.88	0.73, 1.07	0.94	0.77, 1.16	1.07	0.78, 1.57
Obese							
Insufficient	<0.13	0.98	0.64, 1.49	1.00	0.63, 1.56	0.60	0.21, 1.68
Adequate	0.13–0.23	1.00	Reference	1.00	Reference	1.00	Reference
Excessive	0.23	1.26	0.85, 1.85	1.16	0.76, 1.76	1.53	0.64, 3.66

* Adjusted for body mass index (kg/m²), maternal age (years), socioeconomic status, number of prenatal visits, gestational age at start of prenatal care (weeks), parity, and history of gestational hypertension.

[‡] Based on the 2009 IOM Recommendations on weight gain during pregnancy; the gestational weight gain rate categories were calculated using the approach of Schieve et al.⁴⁴