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REVIEW ARTICLE

Obstetrics

Fetal growth and spontaneous preterm birth in high-altitude pregnancy: A systematic review, meta-analysis, and meta-regression

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Abstract

Objective: To understand the relationship between birth weight and altitude to improve health outcomes in high-altitude populations, to systematically assess the impact of altitude on the likelihood of low birth weight (LBW), small for gestational age (SGA), and spontaneous preterm birth (sPTB), and to estimate the magnitude of reduced birth weight associated with altitude.

Methods: PubMed, OvidEMBASE, Cochrane Library, Medline, Web of Science, and clinicaltrials.gov were searched (from inception to November 11, 2020). Observational, cohort, or case-control studies were included if they reported a high altitude (>2500 m) and appropriate control population.

Results: Of 2524 studies identified, 59 were included ($n = 1\,604\,770$ pregnancies). Data were abstracted according to PRISMA guidelines, and were pooled using random-effects models. There are greater odds of LBW (odds ratio [OR] 1.47, 95% confidence interval [CI] 1.33–1.62, $P < 0.001$), SGA (OR 1.88, 95% CI 1.08–3.28, $P = 0.026$), and sPTB (OR 1.23, 95% CI 1.04–1.47, $P = 0.016$) in high- versus low-altitude pregnancies. Birth weight decreases by 54.7 g (± 13.0 g, $P < 0.0001$) per 1000 m increase in altitude. Average gestational age at delivery was not significantly different.

Conclusion: Globally, the likelihood of adverse perinatal outcomes, including LBW, SGA, and sPTB, increases in high-altitude pregnancies. There is an inverse relationship between birth weight and altitude. These findings have important implications for the increasing global population living at altitudes above 2500 m.

KEYWORDS

growth restriction, high-altitude pregnancy, low birth weight, small for gestational age

1 | INTRODUCTION

Pregnancy at high altitudes (>2500 m) involves the physiological challenge of adapting to pregnancy with altered physiology from

environmental hypobaric hypoxia. Studies performed in different global locations^{1–8} suggest that infants born at high altitudes are lighter^{4,5,7,9} with reduced body length^{2,3,7,10,11} compared to those born at low altitudes. Lower birth weights are associated

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with short- and long-term adverse health outcomes, including increased risk of neonatal death,¹² childhood stunting,¹³ and increased risk of obesity¹⁴ and cardiovascular disease later in life.^{15,16} Studies suggest higher rates of pregnancy complications associated with reduced birth weight in high-altitude populations, including stillbirth,¹⁰ pre-eclampsia,⁷ and gestational hypertension.^{11,17} However, estimates of the impact of altitude on pregnancy vary widely across global contexts,^{4,5,7} with some studies finding no significant impact.^{18,19}

There are multiple possible etiologies of altitude-associated reduction in fetal growth. A contributing factor may be uterine artery diameter, which is reduced in high-altitude pregnancies.²⁰ Above 2500 m, uterine artery blood flow is reduced by approximately 30%,²¹ and consequently there is reduced exchange of oxygen and nutrients at the chorionic villi.^{21,22} There are also metabolic changes within the high-altitude placenta that prioritize glycolysis to preserve oxygen for fetal metabolism^{23,24} and modifications in fetal oxygen consumption.^{25,26} These adaptations may ensure fetal survival at the expense of fetal growth.

The number of pregnancies at high altitudes globally continues to increase.^{27,28} As low-altitude areas become more heavily populated, more people are pushed to live at higher elevations worldwide,²⁹ with climate change likely to perpetuate this trend. With an increasing fraction of the global population exposed to high altitudes in utero, it is essential that any increase in adverse pregnancy outcomes associated with fetal growth restriction at a high altitude is recognized and quantified.

In order to fully understand the implications of pregnancy at elevations above 2500 m on fetal growth, the aim of the present study was to systematically assess the impact of increasing altitude on the likelihood of low birth weight (LBW), small for gestational age (SGA), and spontaneous preterm birth (sPTB). The secondary aim was to derive an estimate of the magnitude of any reduction in birth weight associated with altitude.

2 | METHODS

The present systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines.³⁰ The systematic review protocol was registered using PROSPERO (CRD42019125620; Appendix S1).

2.1 | Literature searches and search strategies

A systematic literature search was performed using prespecified search terms (Appendix S2) in PubMed, Ovid EMBASE, Cochrane Library, Medline, Web of Science, and clinicaltrials.gov. All searches were performed from the time of inception of the database to November 11, 2020. No restrictions regarding filters, language, or location were applied to any of the searches.

2.2 | Inclusion criteria

Observational, cohort, or case-controlled study designs in human populations were included. Studies were eligible for inclusion if they had a high-altitude group above 2500 m and a control group below 2500 m, either within the same country or within 600 km. Although some studies have reported the association of birth weight with altitude as low as 1600 m,³¹ others report an "inflection point" at around 2000–2500 m.⁵ By choosing 2500 m, a widely utilized cutoff point,^{32–35} it was ensured that the included studies measured the desired effects, and had appropriately comparable control groups with regard to ethnicity. Of the studies included, none had a control group at an altitude higher than 2000 m. Studies were excluded if data were collected more than 50 years ago, as high-altitude populations may have changed significantly under the influence of migration trends or nutritional differences in the intervening years.³⁶ Studies were excluded if they did not report specified outcomes. No exclusions were applied with regard to standards used to assess SGA. Full inclusion and exclusion criteria are available in Table S1.

The data from conference abstracts would have been included if sufficient detail for assessment was present; however, none met this standard. If insufficient information was available for assessment in a full manuscript, then the authors were contacted for more information. Three authors were contacted and all responded. All papers that met the inclusion criteria were obtained.

2.3 | Study selection

Two reviewers (IDG and CEA) independently assessed each study using predetermined inclusion/exclusion criteria (Table S1). A third reviewer (DAG) was available to resolve any cases where eligibility was unclear. A screening of titles and abstracts was performed, followed by an in-depth full-text analysis (Figure S1).

2.4 | Data extraction

The extraction of data from the included studies was conducted independently by two reviewers (IDG and CEA). Outcome measures were birth weight, sex, gestational age at birth, sPTB (birth <37 weeks), LBW (birth weight <2500 g), and SGA (birth weight <10th centile). Full-term delivery was defined as delivery occurring after 37 completed weeks of gestation.

Study details, including geographical location of the population, cutoff altitudes defining the high- and low-altitude groups, and ethnicity of the participants (where available) were also recorded (Table S2).

Where studies reported multiple low- or high-altitude groups, or multiple groups at the same altitude, these subgroups were combined into a single high- or low-altitude group for the overall birth weight meta-analysis. For meta-regression, multiple high- and low-altitude groups from the same study were kept separate to improve

the precision of estimates of birth weight at different elevations in our meta-regression.

Where studies quoted elevation ranges or gave only a maximum bound for altitude, an online elevation resource was used³⁷ to determine the true mean elevation above sea level of the geographical region specified for population recruitment. Where an elevation was given as a range, the mean of the quoted elevation range was used, for example an altitude in the range of 5–905 m would be assigned 455 m. Where a maximum or minimum bound only was quoted, a conservative value of 500 m less than the maximum bound was used, for example a study giving a control altitude range of below 2000 m would be assigned 1500 m. For the 40 included studies, it was possible to determine the altitude directly from the information given, for 12 studies, the mean elevations were determined from location or elevation range, and for seven studies elevation values were assigned from maximum bounds as specified.

2.5 | Quality assessment of included studies (risk of bias in individual studies)

Each study was independently assessed by two reviewers (IDG and CEA) for quality and validity using the Newcastle-Ottawa Risk of Bias tool. Eight of the nine domains were relevant and assessed for each study, with each study either achieving or failing the domain (Table S3). All risk of bias assessment was performed at the study level.

Data were summarized as mean difference for continuous data and unadjusted odds ratios (OR) for dichotomous data. Meta-analysis was performed using the “metaphor” package in R version 3.5.1.³⁸ Funnel plots and Egger test (for groups with five or more studies) were used to assess publication bias. Heterogeneity between studies was assessed using the I^2 statistic. Any outcome showing significant inter-study heterogeneity was analyzed using a random-effects model. Sensitivity analysis was performed using leave-one-out analysis (LOOA) and by conducting relevant subgroup analyses (studies with low numbers, studies with high risk of bias, and studies that only included infants born at term).

2.6 | Statistical analysis

Where P values are reported, an alpha level less than 0.05 was considered significant. For meta-regression, a mixed-effects model was used.

3 | RESULTS

3.1 | Study selection

Electronic searches of the prespecified databases yielded a total of 2524 studies. After removing duplicates and carrying out a screening of titles and abstracts, 247 studies underwent full-text analysis.

After applying the eligibility criteria, a total of 59 studies remained eligible for inclusion, representing 1 604 770 pregnancies (Figure S1).

The 59 included studies encompassed a range of geographical locations, with variation in average high and low altitudes (Table S2). The majority of areas globally with elevations above 2500 m are represented in the studies, with the exception of areas in Africa, Mexico, Iran, Afghanistan, Papua New Guinea, and northern Italy (Figure S2).

The risk of bias was moderate to low in the majority of included studies: 20 studies had a very low risk of bias; 18 had a low risk of bias; 16 had a moderate risk of bias; and five studies had a high to very high risk of bias. Subgroup meta-analyses were performed excluding the studies with a high risk of bias, and their removal did not significantly change any outcomes; therefore, all studies were included (Figure S3).

The likelihood of single studies significantly influencing the overall results using LOOA was assessed (Table S4). Birth weight meta-analysis as a whole was robust to LOOA, as were birth weight split by male and female infants, term-only birth weight, gestational age, and LBW meta-analyses. sPTB and SGA were not robust to LOOA, with the exclusion of two different studies (for sPTB^{8,39} and SGA^{11,39}) significantly altering the findings and thus reducing confidence in interpreting these results. Funnel plots for all outcomes were assessed visually and using the Egger test (for outcomes with five or more studies) (Figure S4). All funnel plots for the reported analyses appeared symmetric and passed the Egger test.

3.2 | Low birth weight

Six studies reported a prevalence of LBW ($n = 717\ 865$). Infants born at high altitudes were 47% more likely to be born weighing less than 2500 g (LBW) compared to infants born at low altitudes (OR 1.47, 95% CI 1.33–1.62, $P < 0.001$) (Figure 1).

3.3 | Small for gestational age

Nine studies reported a prevalence of SGA infants ($n = 476\ 305$). Infants born at high altitudes were 88% more likely to be SGA (OR 1.88, 95% CI 1.08–3.28, $P = 0.026$) (Figure 2).

3.4 | Preterm birth

Fifteen studies ($n = 1\ 229\ 576$) reported data on sPTB. There was an increased prevalence of sPTB at high altitudes compared to those at low altitudes (OR 1.23, 95% CI 1.04–1.47, $P = 0.016$) (Figure 3).

3.5 | Birth weight

A total of 55 studies ($n = 1\ 537\ 912$ pregnancies) reported data on birth weight. When a meta-regression plot was drawn, calculating

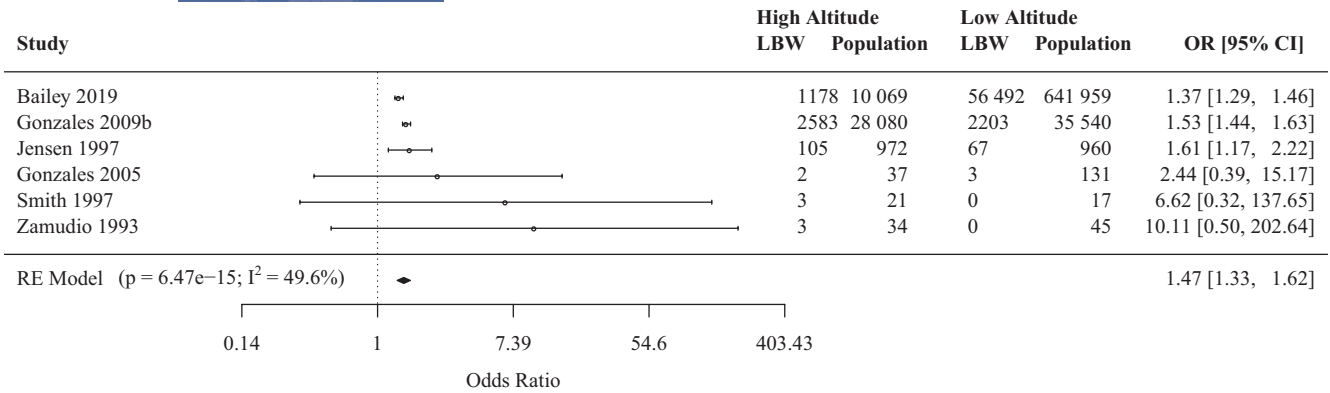


FIGURE 1 LBW (≤ 2500 g) meta-analysis; expressed as OR (random-effects model) with 95% CI. Black diamond represents overall effect. Abbreviations: CI, confidence interval; LBW, low birth weight; OR, odds ratio

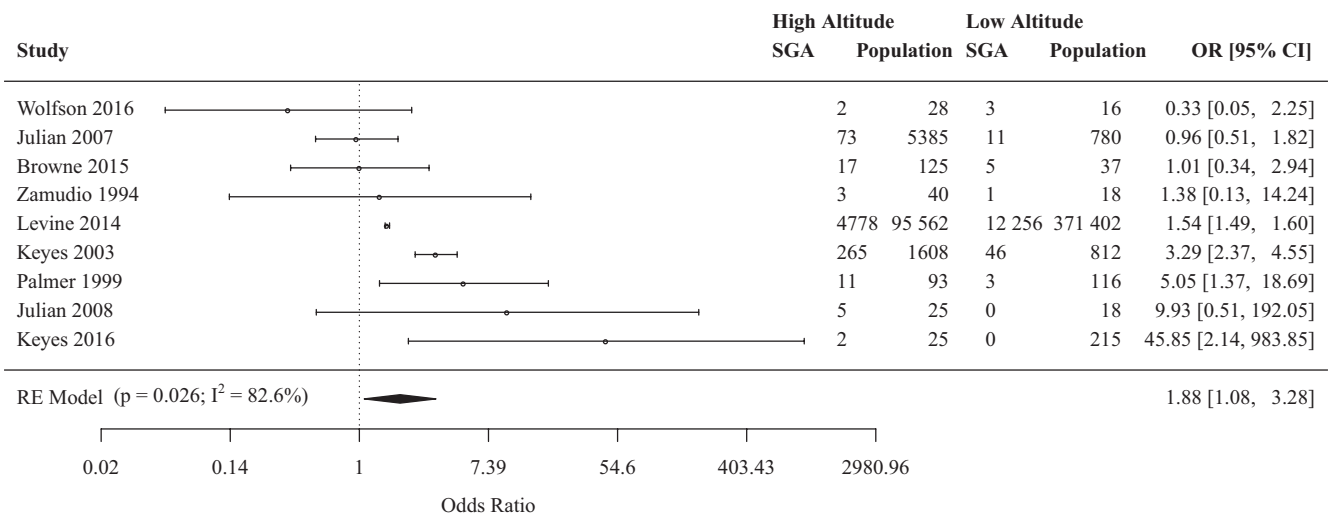


FIGURE 2 SGA (<10th centile) meta-analysis; expressed as OR (random-effects model) with 95% CI. Black diamond represents overall effect. Abbreviations: CI, confidence interval; OR, odds ratio; SGA, small for gestational age

the decrease in birth weight against the increase in elevation, there was a decrease of 54.7 ± 13.0 g ($R^2 = 0.285$, $P < 0.0001$) in birth weight per 1000-m increment in altitude (Figure 4). The 95% CI lines of the meta-regression line included the origin (-143 to 10 g birth weight difference, $P = 0.09$).

Overall birth weight at high altitudes was reduced by 239 g (95% CI 207–271, $P < 0.001$) compared to low altitudes (Figure 5). Where studies reported birth weight separately for male and female infants (nine studies, $n = 118\ 303$) (Figure S5), there was no significant difference in the magnitude of decrease in birth weight at high altitudes between male and female infants. Male infants (nine studies, $n = 60\ 981$) weighed on average 222 g less (95% CI 130–314, $P < 0.001$), and female infants (nine studies, $n = 57\ 322$) weighed 187 g less (95% CI 112–262, $P < 0.001$), at high altitudes compared to low altitudes. Thirteen studies ($n = 32\ 382$) allowed the identification of infants born at full term. Term infants born at high altitudes were on average 307 g lighter (95% CI 196–418, $P < 0.001$) (Figure S6) than those born at low altitudes. A total of 37 studies

($n = 1\ 340\ 607$) reported gestational age at delivery. There was no significant difference in gestational age between infants born at high altitudes versus those born at low altitudes (mean 0.04 ± 0.11 weeks earlier, equivalent to 7 h 40 min earlier at high altitudes, $P = 0.446$) (Figure 6).

4 | DISCUSSION

4.1 | Main findings

The results of the present study show that, globally, infants born at high altitudes (>2500 m) are more likely to experience clinically significant growth restriction in utero than those born at altitudes below 2000 m. The present study shows an increase of 47% in the likelihood of LBW and an increase of 88% in the likelihood of SGA in populations at high altitudes versus those at low altitudes. Infants in high-altitude groups are also 23% more likely to have a sPTB.

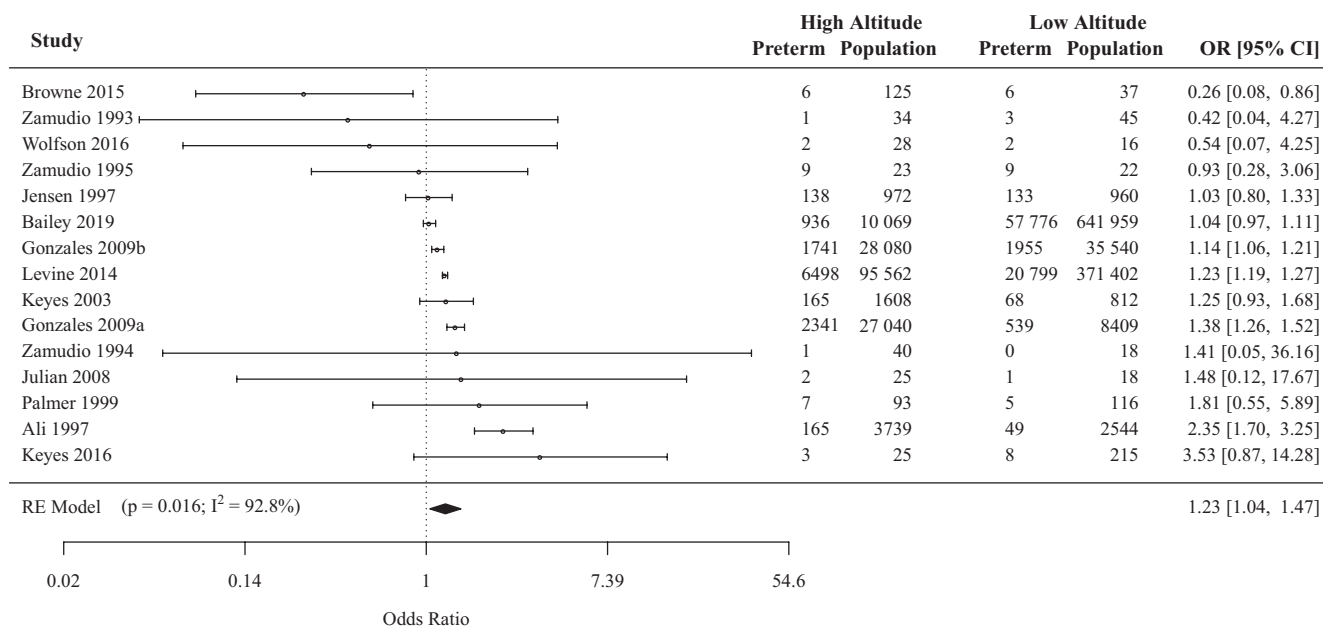


FIGURE 3 Spontaneous preterm birth meta-analysis; expressed as OR (random-effects model) with 95% CI. Black diamond represents overall effect. Abbreviations: CI, confidence interval; OR, odds ratio

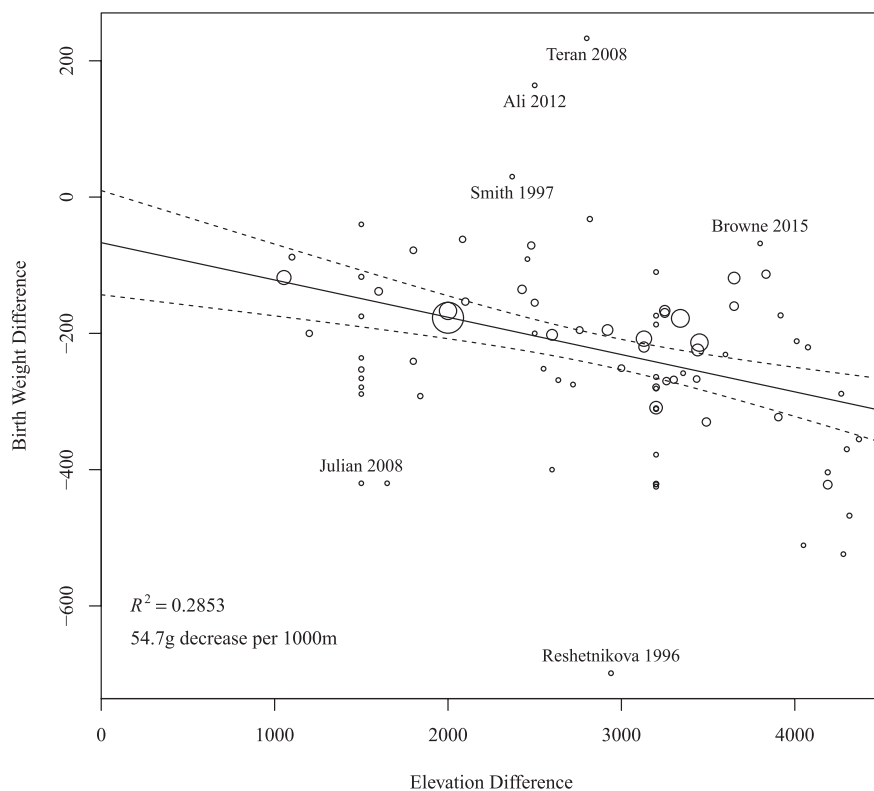


FIGURE 4 Birth weight meta-regression; circle size represents study weighting based on numbers in each study. Visual outliers are labelled with study ID. Solid line: line of best fit, dashed line: 95% CI

There is an inverse linear correlation between altitude and birth weight, with birth weight decreasing by an average of 54.7g per 1000 m elevation. The effect of altitude on birth weight is robust across studies conducted in different global settings and in both sexes. On average, infants born at high altitudes are 239 g lighter

(95% CI 207–271), which is a clinically significant decrease. Despite infants being more likely to be born preterm, average gestational age at delivery is not significantly different between populations at low and high altitudes, indicating that the observed difference in average birth weight is not solely a result of shortened gestation.

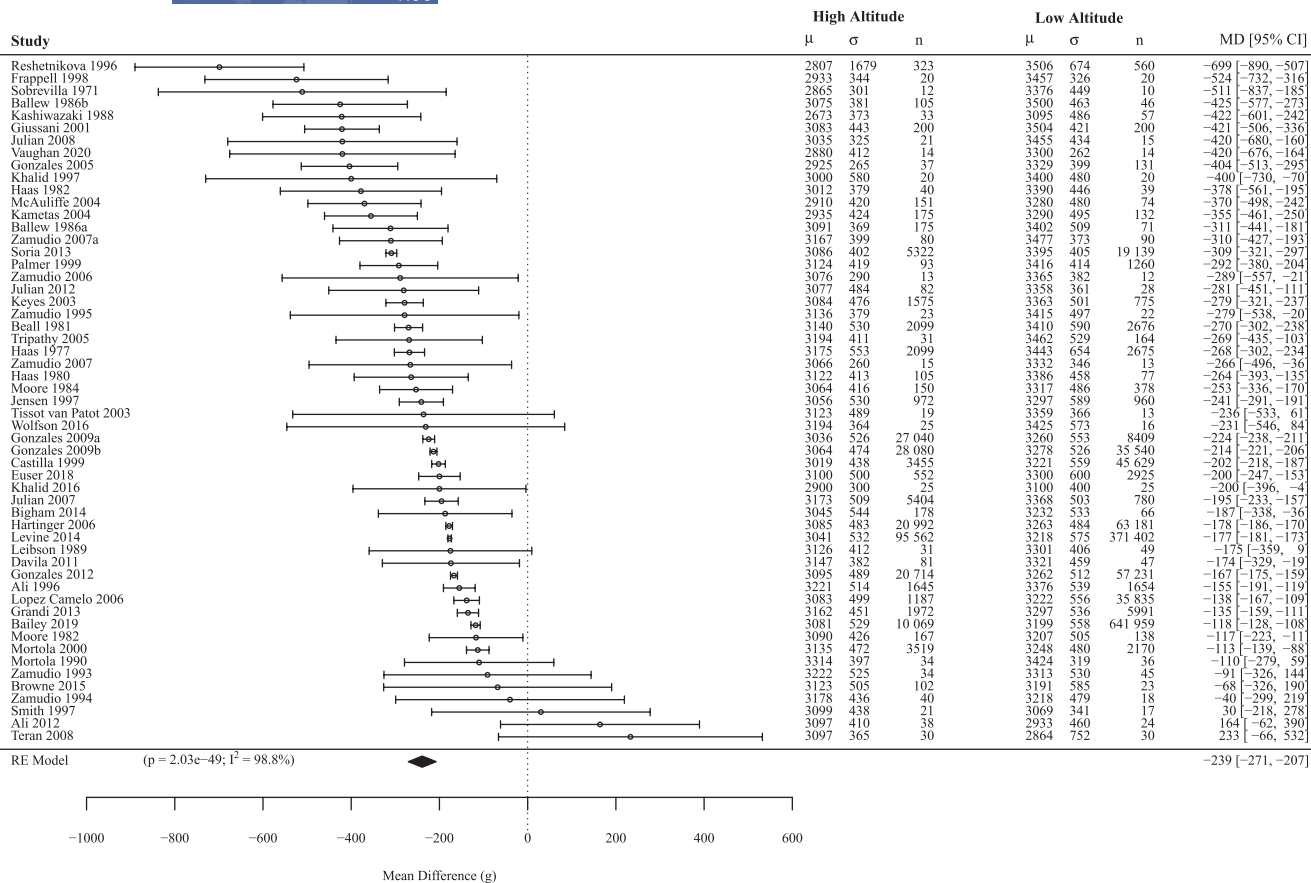


FIGURE 5 Birth weight meta-analysis; results expressed as MD (random-effects model) with 95% CI. Black diamond represents overall effect. Abbreviations: CI, confidence interval; MD, mean difference

4.2 | Strengths and limitations

A large number of high-quality studies from a range of contexts are included in the analysis. Confidence in the results is further increased by the robustness of the conclusions between both sexes. Where possible, multiple sensitivity analyses were performed to take account of other variables, for example limiting the analysis to term-only deliveries. The data are robust to checks including LOOA, funnel plot analysis, and Egger test, with the exception of the small subgroup analyses highlighted.

The present study has some limitations. One limitation is the high heterogeneity between the included studies. This may reflect the difficulty in identifying suitable low-altitude control groups that are demographically similar to high-altitude populations. However, given that studies are included from diverse populations across the globe, it is unsurprising that the heterogeneity is high.

There are geographical regions that are significantly under-represented in the available data. There is a wealth of studies carried out in North and South America, but very few in the Tibetan Plateau and other high-altitude regions through India and China. Given that a significant proportion of the global population reside in these countries, high-quality data from these settings are an important future research goal.

A further limitation was that no study specifically reported how long on average the participants had spent at the study altitude before pregnancy or before delivery. However, compared to the overall duration of pregnancy, acclimatization would be expected to occur relatively rapidly. Moreover, a detailed set of other covariates affecting pregnancy outcome, for example intrauterine infection, was not available.

4.3 | Interpretation

Infants born at high altitude are significantly more likely to be born LBW, SGA, or preterm. Moreover, there is also a significant reduction in birth weight in term infants born at high altitudes versus those born at low altitudes. These findings are likely to significantly impact the health of populations at high altitudes, both in the short term, with regard to growth,⁴⁰ neurodevelopment,⁴¹ and survival in childhood,⁴² but also with respect to long-term consequences of fetal growth restriction, including diseases such as obesity and cardiovascular disease.¹⁴⁻¹⁶

The relationship between birth weight and altitude is linear over the range of altitudes where data are available. However, some studies at the highest elevations (>4000 m) show a greater decrease

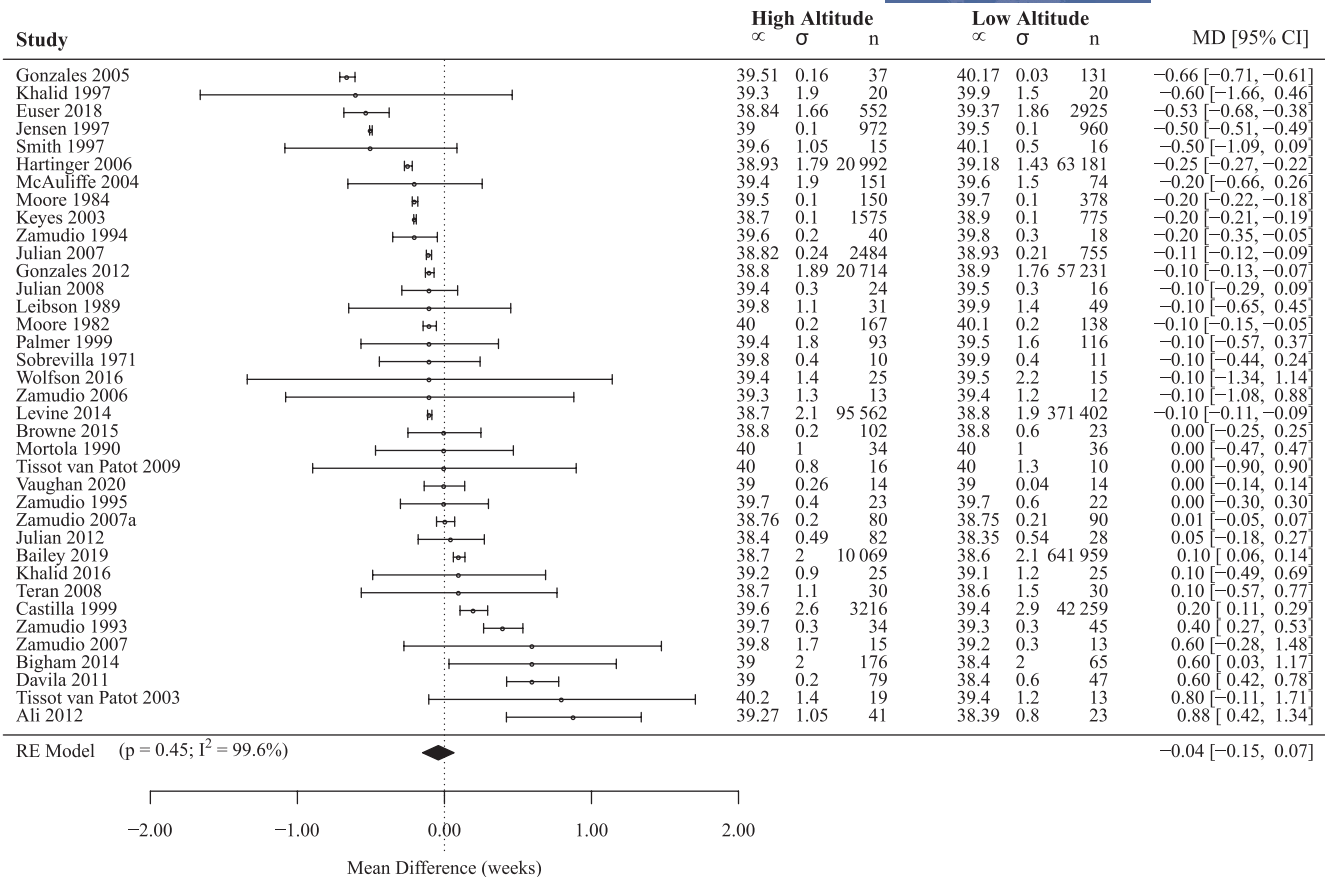


FIGURE 6 Gestational age meta-analysis (weeks); expressed as MD (random-effects model) with 95% CI. Black diamond represents overall effect. Abbreviations: CI, confidence interval; MD, mean difference

birth weight than the line of best fit would predict (Figure 3).^{5,8,43,44} It is possible that the relationship between birth weight and altitude is non-linear above 4000 m, but insufficient data are available to draw robust conclusions. Above 4500 m there are significant logistical and physiological challenges to permanent human settlement. Consequently, there are almost no large settlements above 4500 m worldwide and hence future large-scale studies are unlikely to be feasible at higher altitudes.

If the entire magnitude of birth weight difference between the high- and low-altitude groups is attributable solely to the impact of altitude, then the line of best fit in the birth weight meta-regression would be expected to intersect with the origin, that is at 0 m of elevation difference, there would be 0 g difference in birth weight between groups. Although the 95% CI for the estimate of birth weight difference at 0 m encompasses the origin (-143 to 10 g), there may still be differences other than elevation between the groups at low altitudes and high altitudes that significantly impact birth weight. Populations at high altitudes have historically been more likely to be of lower socioeconomic status,⁴⁵ which is associated with reduced birth weight in other contexts.^{46,47} Areas of high and low altitude experience significant environmental differences such as temperature, humidity, and ultraviolet exposure, as well as access to different sources of nutrition, and genetic differences.^{2,3} Such

factors are difficult to account for adequately in the context of a large meta-regression.

5 | CONCLUSION

Across the world, infants born at high altitudes are more likely to be born LBW, SGA, or preterm. Birth weight decreases by an average of 54.7 g per 1000-m increase in elevation. This results in clinically meaningful reductions in birth weight between populations at high and low altitudes that cannot be accounted for by differences in gestational age at delivery.

Populations at high altitudes are increasing in number and diversity around the world. The results of the present study provide important insight into the increased risk of complications associated with pregnancy at high altitude, particularly LBW due to fetal growth restriction. Fetal growth restriction and preterm birth are major causes of perinatal death worldwide and independent predictors of future health risks in surviving infants.

IG performed the initial searches, analyzed the data, and wrote the paper. IG and CEA performed title and abstract analysis, and full-text analysis. DAG was available to resolve conflicts. CEA and DAG edited and advised on the manuscript.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest.

AUTHOR CONTRIBUTIONS

IG performed the initial searches, analyzed the data, and wrote the paper. IG and CA performed title and abstract analysis, and full text analysis. DG was available to resolve conflicts. CA and DG edited and advised on the manuscript. All authors contributed to and approved of the final version of the manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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