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Maternal altitude and risk of low birthweight: A systematic review and meta-analyses

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ABSTRACT

Background: Previous studies conducted in high altitude regions showed that maternal altitude was associated with low birth weight. The effect size of birth weight reduction is inclusive with unknown effects due to preterm birth. We systematically reviewed the literature and synthesize evidence on associations between altitude elevation from sea level and birth weight.

Method: We searched MEDLINE/PubMed, Embase, Scopus, Web of Science, and Cochrane database, from inception to May 5, 2020 for studies that reported maternal altitude and birth weight. Bayesian multilevel effect models were employed to estimate the effect size on birth weight (and gestational age) associated with altitude. Bayesian multilevel effect models were employed to estimate the effect size on birth weight (and gestational age) associated with altitude.

Results: The systematic search identified 1020 articles, with 52 articles meeting the inclusion criteria providing 207 estimates for the association of altitude and birth weight ($n = 4,428,563$), and with 22 articles providing 71 estimates for gestational age ($n = 2,149,627$). A reduction in mean birth weight of 96.98 g was associated with every 1000 m increase in altitude across 52 studies. A statistically significant but numerically minimal effect of maternal altitude elevation was observed on the gestational age (0.3 days), corresponding to a negligible estimation of 5 g lower birth weight. A relatively high heterogeneity of between-study association ($I^2 > 84.1\%$) and small study effect was found.

Conclusion: A clinically meaningful birth weight reduction was associated with maternal altitude elevation beginning from sea level. Future longitudinal studies are needed to elucidate the causal association and to understand the late effect of maternal altitude.

1. Introduction

Low birth weight is the leading risk factor for infant mortality and morbidity [1]. The negative impact of low birth weight persists through adolescence presenting as increased risks of asthma, low intelligence quotient, and mild problems in cognition [2–4]. More importantly, adverse birth outcomes have been recognized as an early life risk factor for a wide range of health outcomes over the course of life. In recent years, associations of low birth weight with increased risks of several chronic conditions in adulthood have been documented, including

cardiovascular disease, type 2 diabetes, and metabolic syndromes [5–7].

Factors influencing infants' birth weight are multifaceted. Epidemiological studies suggested that infant weight differs by fetal sex [8], with boys being heavier than girls at the population level [9]. Several maternal factors have also been identified as key determinants for low birth weight including young and advanced maternal age [10,11], social economics status [12], cigarette smoking [13], primiparity [14], poor maternal nutrition, and low pre-pregnancy weight [15]. Another strong determinant for low birth weight is residential altitude.

Earlier studies suggested that decrease in birth weight occurs above

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2000 m, a threshold for a critical barometric pressure reaching a hypoxic effect [16]. A lower birth weight associated with high (2500–4500 m) altitude had been reported in several [17–21] but not all studies [22,23]. More recently, an altitude associated reduction in birth weight had been reported in low to medium (below 2000 m) altitude [24,25]. However, histories on residential altitude are not routinely being considered when it comes to maternal care. This is important because our recent analysis, which investigated the effect of change in women's residential altitude on offspring birth weight between the first and second pregnancy in a total of 433,624 pairs of pregnancies, was the first to demonstrate a longitudinal effect of maternal altitude elevation on the reduced birth weight that occurred below 2000 m, suggesting a causal effect [26]. To date, the effect size of birth weight reduction associated with different levels of altitude elevation is unclear, as not all studies used sea level as a reference group. Furthermore, there is a linear association between gestational age and birth weight between 37 and 42 weeks with a mean weight gain of 12.7 g per day [27]. Despite previous studies differentiated full term and preterm infants using a cut off at 37 weeks, it is unclear whether elevated altitude may impact birth weight through shortened gestational age.

Therefore, we aim to systematically review the available evidence to determine to what extent the maternal altitude affects low birth weight with the consideration of gestational age. We synthesized evidence from the existing observational studies, which examined an association of maternal altitude with birth weight, to determine the direction and magnitude of the effect of maternal altitude on low birth weight.

2. Methods

2.1. Data sources

This systematic review was *a priori* registered (CRD42019135620) and executed following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement guidelines [28]. Two authors searched the electronic databases MEDLINE/PubMed, Embase, Scopus, Web of Science, and Cochrane database from inception to October 18, 2019 with the following search keys: (altitude) and (birth-weight OR “birth weight” OR “low-birth-weight” OR “fetal weight” OR “fetal growth retardation” OR “premature birth” OR “preterm birth” OR “small for gestational age”). Additionally, we hand-searched the reference lists of eligible articles and narrative overviews of systematic reviews/meta-analyses that were ineligible to be included in the present review. We performed an updated search on May 5, 2020 to detect additional published studies since the initial search.

2.2. Study selection and data extraction

All potentially relevant titles and abstracts were screened for eligibility independently by two reviewers (VHP, TW). In cases of disagreement, the consensus was reached through discussion and consulting a third reviewer (LY). We included observational studies (cross-sectional, case-control, or retrospective and prospective cohort studies) that investigated the association of maternal altitude with low birth weight or preterm birth. Studies had to report a residential altitude and an associated mean birth weight. We included only studies published in English.

For each included study, one reviewer (VHP) extracted the data, then a second reviewer (TW) verified the extracted data, and made a summary assessment of study validity. The first reviewer (VHP) then verified the assessment of validity and any discrepancies were resolved by discussion.

The following data were extracted for each included study: study ID, first author name, year of publication, journal, country, setting, objective, study design, sample size, number of births, maternal altitude (in meters), measures of birth weight (gram), definitions of preterm birth, measures of birth weight, delivery method, reference group in any

statistical modeling, results of any statistical tests reported, subgroup analyses, and any evidence relating to effects on other birth outcomes. Altitude that was reported in feet was converted to the metric meter when necessary. If altitude was reported as a range, the mean of the range was used.

2.3. Synthesis

A statistical description of the studies and the results related to the association of maternal altitude with low birth weight and gestational age were performed. To estimate the association between birth weight and maternal altitude, a Bayesian multilevel effect model was employed to estimate the summary effect size using a fixed and random effect for the intercept, as well as a fixed and random coefficient for altitude. The effect size was presented by change in grams per 1000 m increase in altitude. The model was estimated in Winbugs Version 1.4.3 (Winbugs 1996–2007: Imperial College and MRC, UK) using 3 chains with a burn in phase of $n = 100000$ and sampling phase of $n = 100000$. The convergence of chains was checked visually and by Gelman-Rubins statistic. Variability of the estimated parameters was given by the 2.5% and 97.5% percentile of the posterior distribution, which corresponded to a 95% confidence interval. Between-study association was estimated with the I^2 metric; values greater than 50% was indicative of high heterogeneity, while values above 75% suggested very high heterogeneity [29,30]. Also, we calculated the evidence of small-study effects (i.e., whether small studies would have inflated effect sizes compared to larger ones).

Sensitivity analysis was carried out by excluding studies with large sample sizes to test for their influence on the overall effect estimation. Six studies that comprised approximately 95% of total meta-analyzed sample size were excluded one by one and then altogether. Forest and funnel plots were used to illustrate the distribution and potential of bias due to the imprecision of the estimated effects. Data handling and figures were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

To this end, we used the regression asymmetry test developed by Egger and colleagues [31]. Finally, the quality of the included studies was assessed with the Newcastle-Ottawa scale for observational studies [32].

3. Results

3.1. Study selection and characteristics

A flowchart depicting the literature search and selection process is presented in Fig. 1. The literature search generated a total of 1020 articles. After removing the duplicates, 514 articles were screened based on title and abstract, and 155 articles were screened by full text. Of the 155 articles, 103 articles were excluded for various reasons (see Fig. 1), leaving 52 eligible articles to be included in the meta-analyses. Of the 52 eligible articles, 22 studies provided data on gestational age (see supplementary eTables 1).

The risk of bias of the articles included in the analysis is shown in the supplementary eTable 2. The studies included in this review had a low risk of bias. Based on the Newcastle-Ottawa scale, the majority of the studies were of good quality (71% scored 5 out of 7, 27% scored 6 out of 7, 2% scored 7 out of 7).

The included studies represented birth weight data on 4,428,563 newborns and gestational age data on 2,149,627 newborns. In all the studies, birth weight and gestational age were reported and determined using official national or regional registries, and maternal altitude was acquired by the location of the participants' residence. The confounding factor adjustments were largely inconsistent across different studies; therefore an un-adjusted effect size was estimated and reported. The year of exposure assessment ranged from 1957 to 2019.

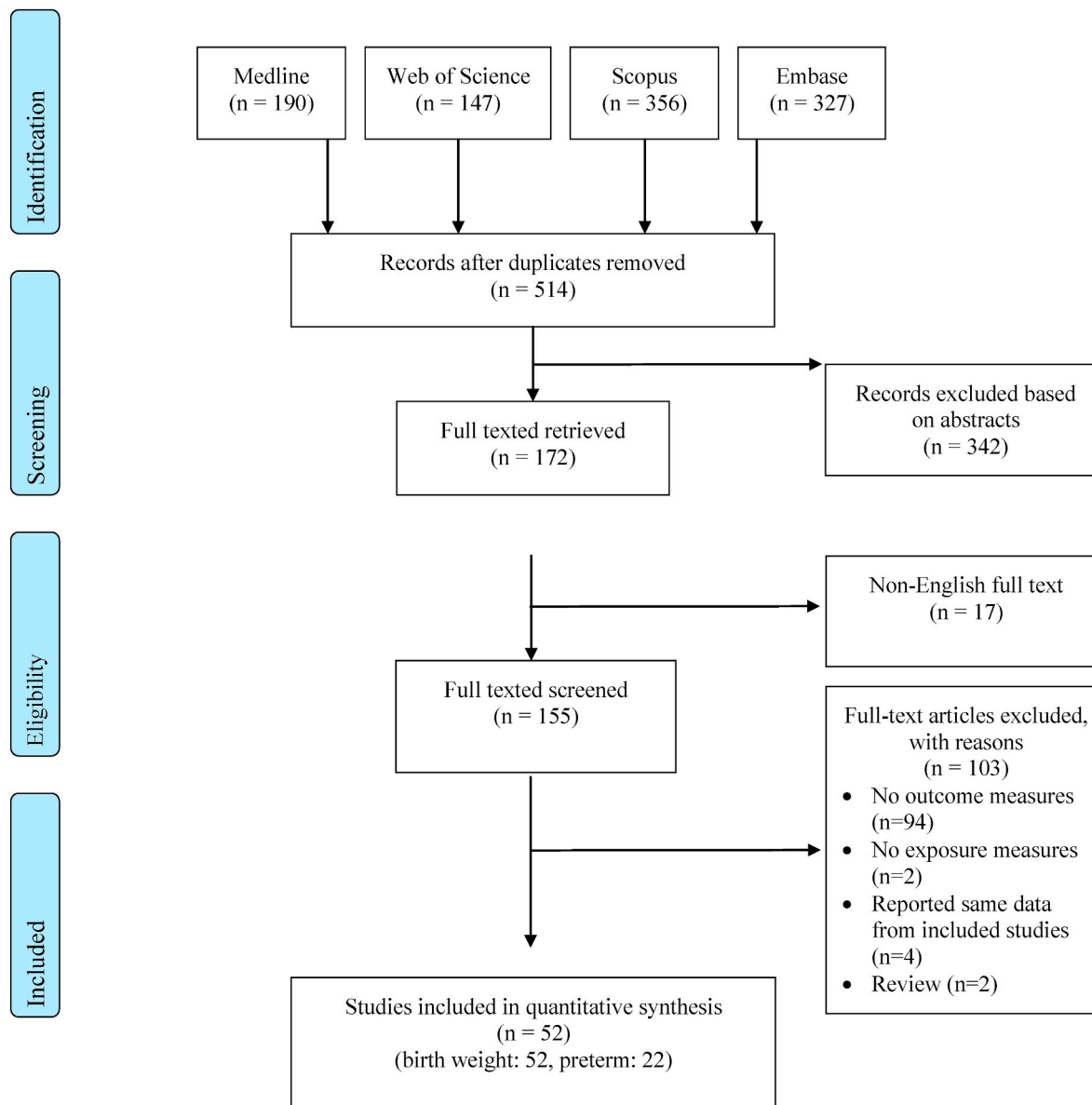


Fig. 1. Study flowchart for study selection.

3.2. Quantitative analysis

Data from 52 studies were included in the analysis, which consisted of 207 estimates on a mean birth weight associated with altitude. Among the analyzed studies, birth weight ranged from 2655 to 3645 g, while altitude ranged from zero to 4602 m. In Fig. 2, the observed mean birth weights were plotted against altitude, demonstrating a negative linear association, such that a decrease in birth weight was observed as altitude increases.

In the Bayesian multilevel regression model, a significant effect of altitude in mean birth weight was observed (Table 1). The fixed intercept (the estimated grand/pooled mean of birth weights of all included studies) was 3389 (SD = 19.09) grams. A fixed effect of altitude per 1000 m increase in altitude was associated with a reduction in mean birth weight of 96.98 g on average across 52 studies. The corresponding 2.5% and 97.5% percentiles (−84.82, −109.7 g) show a clear non-random deviation from zero. The parameter random sigma altitude, with an effect size of 36.95, describes the random variation of the effect of altitude on birth weight (96.98 g lower per 1000 m) due to heterogeneity between 52 studies. This estimate roughly leads to a

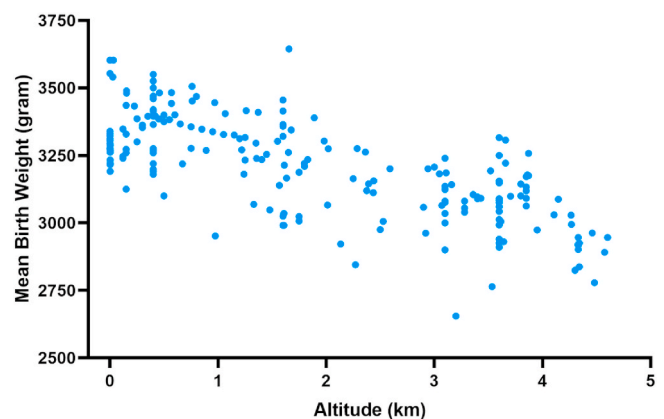


Fig. 2. Scatterplot of raw data on observed mean birth weights against altitude of 207 estimates from 52 included studies.

Table 1

Bayesian multilevel regression model estimating the average effect of per 1000 m altitude elevation on the mean birth weight among 52 included studies.

Parameters	Mean	95% interval ^a	Standard Deviation	Median
Fixed: Intercept ^b	3389	(3352–3428)	19.09	3389
Fixed: Altitude ^c	−96.98	(−109.7 to −84.82)	6.274	−96.97
Random: Sigma_Intercept ^d	117.4	(92.93–148.4)	14.17	116.3
Random: Sigma_Altitude ^e	36.95	(28.17–48.03)	5.068	36.56

^a 95% interval: the range between 2.5% and 97.5% percentiles, which shows a non-random deviation from zero.

^b Fixed intercept: the estimated grand mean of birth weight.

^c Fixed effect of altitude: mean birth weight reduction (gram) associated with per 1000 m increase in altitude.

^d Random sigma intercept: random variation of the mean birth weight of the studies varies around the grand mean due to the heterogeneity between 52 studies.

^e Random sigma altitude: random variation of the effect of altitude on birth weight due to the heterogeneity between 52 studies.

corresponding 95% interval of 24.6–169.4, which indicates the range of birth weight reduction associated with per 1000 m' increase in altitude when considering heterogeneity between studies. The estimated effects of altitude on birth weight and confidence intervals from the 52 studies are presented in forest plots and centered around the fixed effect of 96.98 g (Fig. 3).

Sensitivity analysis, excluding the six largest studies, showed minimal impact on the estimated effect of reduction in birth weight associated with altitude in the model including all studies. The biggest difference is by 1.26 g (95.81 vs. 96.98 g). Similar findings were observed when excluding all six studies (99.75 vs 96.98 g (Supplementary eTable 3)).

Relatively high heterogeneity of between-study association was found ($I^2 = 84.1\%$), which could be due to the heterogeneity in the study design and new-born ethnicities among included studies, and small within-study variation given most studies included large sample size. The funnel plot (Fig. 4) demonstrates that the larger the imprecision of the estimated effect the larger the effect is in absolute terms. Small-sized studies exhibit a larger decrease in birth weight than studies including a large sample size (Egger test for asymmetry, $p < 0.05$).

Among the 52 studies that were included in the present meta-analyses, 22 studies ($n = 2,149,627$) reported data on gestational age, which consisted of 71 estimated mean gestational age values associated with maternal altitude. The multilevel regression model including all 71 estimates, resulting in a small, but statistically significant effect of maternal altitude elevation on the gestational age. This result indicated an average of 0.0418 weeks (0.3 days) smaller gestational age was associated with per 1000 m in maternal altitude elevation (Fig. 5). This corresponded to a conservative estimation of 5 g lower birth weight [27], which is well below our estimated 96.98 g birth weight reduction associated with per 1000 m in maternal altitude elevation. Also, among studies included for gestational age meta-analysis, a large study ($n = 194,526$) conducted by McCullough and colleagues [33] reported a mean gestational age of 37 weeks, but the proportion preterm (<38 weeks) was around 20%. Hence, we suspected the gestational age estimates were likely to be errors in reporting. Overall, it is unlikely that altitude could influence gestational age in the present analyses.

4. Discussion

Our meta-analysis of 4,428,563 participants indicated a lower birth weight associated with higher maternal residential altitude, such that an average of 96.98 g lower birth weight was found for every 1000 m elevated maternal altitude. Also, the lower birth weight did not appear

to be a result of shortened gestation age, which did not appear to differ among babies delivered by women who had higher or lower maternal residential altitude.

To the best of our knowledge, this is the first study that synthesized all available data on the effect of maternal altitude on birth weight across global regions. We observed a non-influential effect of maternal altitude on gestational age; therefore, the reduced birth weight is likely due to a negative impact of maternal altitude on fetal growth rather than preterm birth. At present, the mechanisms through which altitude influences fetal growth is not completely understood [16]. Based on the findings from the present meta-analysis, a reduced birth weight associated with shortened gestational age is unlikely. Ever thought authors from several studies noted that their studies only included termed babies, more studies are required to examine the effect of altitude on preterm birth and gestational age, given that authors from several studies noted that their studies only included termed babies.

Plausible biological pathways have been proposed to explain the birth weight reduction associated with altitude. Elevated altitude is thought to result in the maternal oxygen deprivation pathway, which may induce growth limiting hypobaric hypoxia [19,34–36]. Alternatively, the lower arterial glucose concentrations at a higher altitude may lower the glucose delivery to and consumption by the fetus [37–39]. Furthermore, this effect may be furthered by higher peripheral insulin sensitivity at high altitude in comparison with sea level in the presence of similar insulin secretion [40]. Meanwhile, immigration studies suggested a compensatory genetic or epigenetic process towards high altitude adaption, where the altitude-associated reduction in birth weight appeared to be greater in shorter staying high-altitude residents compared to those of longer staying [34,36,41,42].

The majority of studies were conducted in regions with an altitude over 2000 m, such as the Andes, Himalaya, and the American Rockies [17–21]. An elevation of 2000 m has been considered as a threshold for critical barometric pressure reaching a hypoxic effect which may restrict fetal growth [16,20]. The estimated mean birth weight reduction is around 102–133 g with 1000 m increased altitude in regions at medium-to-high altitude, with minimal model adjustments [20,43]. An intriguing finding in genetic adaption has shown epigenetic changes in Tibetan and Andean women (longer stay in high altitude), whose babies' birth weight reduction associated with elevated altitude was smaller than that of European and Han Chinese women (with a shorter-stay in high altitude) [44].

A few studies have demonstrated a clear effect of altitude elevation on birth weight among babies of women residing in areas of altitude lower than 2000 m. Our group previously demonstrated a crude estimate of 150 g decline in birth weight per 1000 m of altitude in Austrian mothers residing at low-to-medium (up to 1600 m) altitude [24]. Furthermore, Wehby et al. [18] reported a multivariable-adjusted estimation of 70–100 g decline in birth weight per 1000 m altitude ranging between 5 and 1280 m using a “low altitude” sample from South America. Previous studies and the present meta-analyses show a consistent association between elevated altitude and birth weight reduction in altitude of a wide range including well below 2000 m.

All included studies were cross-sectional analyses by design, including one conducted by our group. Using the same dataset, our group was able to investigate this research question using a longitudinal design. We linked national data on infant birth weight of the first and second pregnancies from the same women from all Austrian birth certificates between 1984 and 2016 [26]. This population-based study demonstrated the negative impact of high altitude on birth weight from first to second-born siblings within the same mother living in Austria with low to moderate residential altitude. After taking consideration of maternal and infant characteristics, we found a 32 g decrease in birth weight estimated per 1000 m higher altitude (moving from an altitude of 200 m up to 1200 m), and an 84 g per 1000 m increase in birth weight (moving from 1200 m down to 200 m). Although this finding could not be generalized to a wider population outside Austria, such data suggest

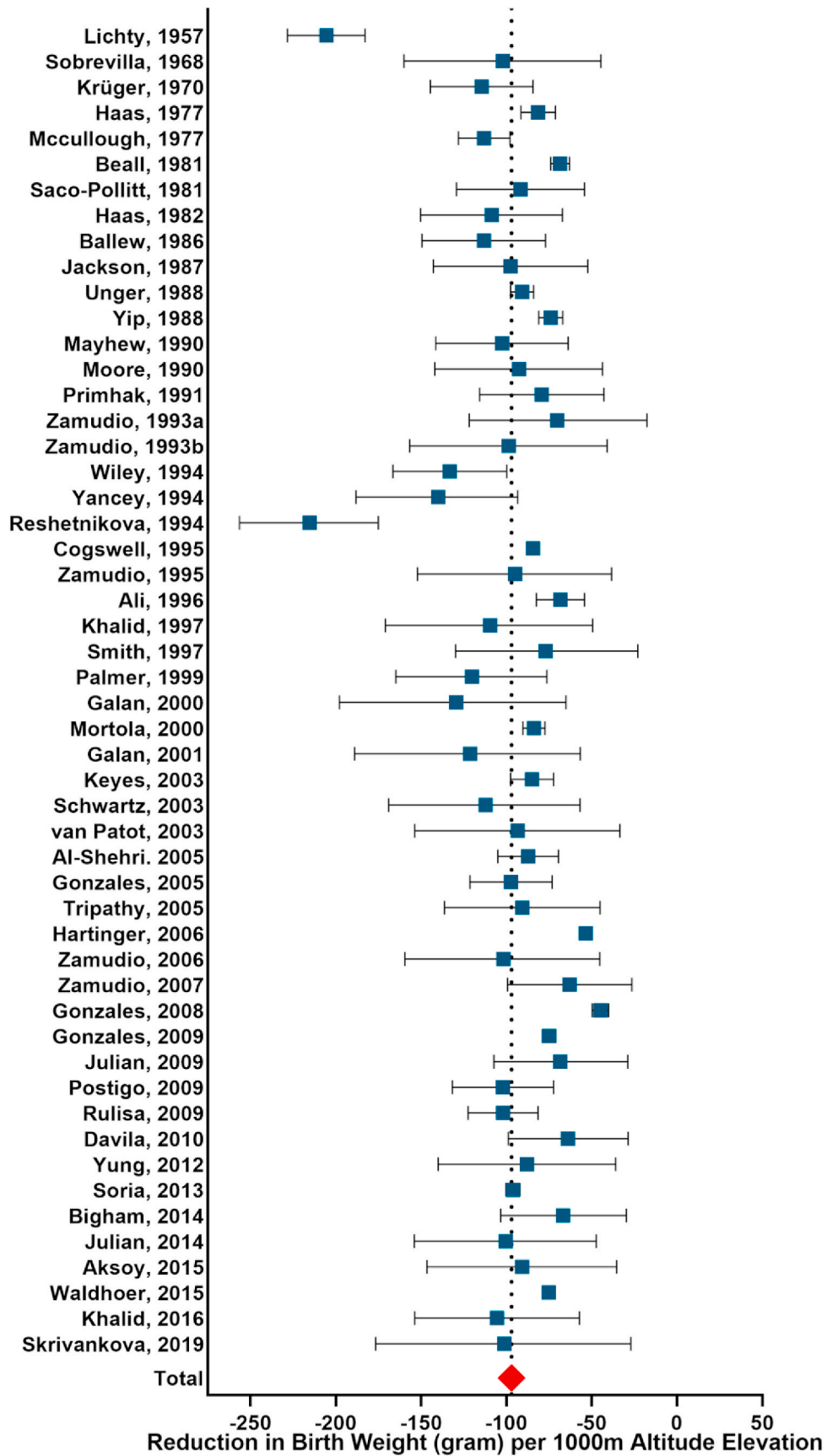


Fig. 3. Forest plot for estimated effects of altitude on birth weight and confidence intervals from 52 studies and centered around the fixed effect of 96.98 g.

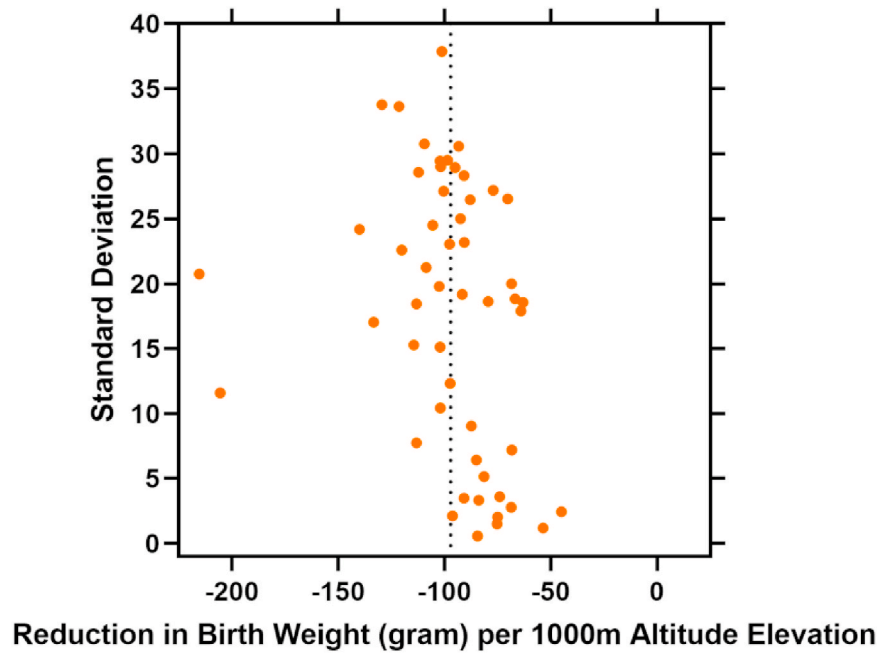


Fig. 4. Funnel plot from the meta-analyses of 52 observational studies that analyzed the association of altitude elevation with birth weight reduction.

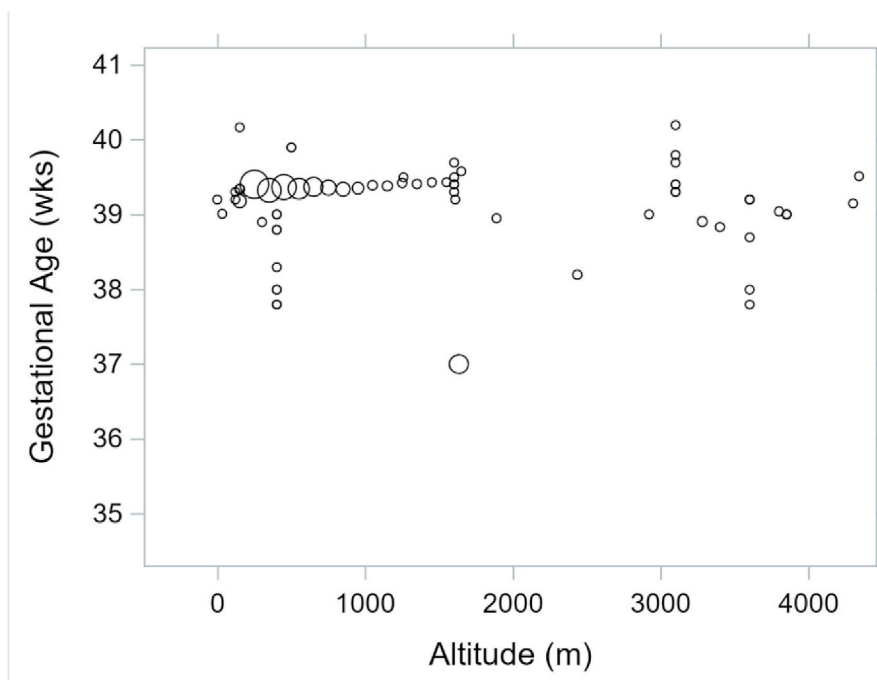


Fig. 5. Association of altitude with gestational age in 22 studies with data available among 52 studies included in the meta-analysis.

that the association between altitude and birth weight is likely to be causal and need to be confirmed in data from other regions using a longitudinal design.

There are several strengths and limitations to this meta-analysis. This meta-analysis included a large number of studies and a study population across global regions. We examined both birth weight and gestational age to rule out the potential influence on low birth weight of small gestational age. Also, we conducted a series of analyses to detect and assess the risk of bias of included studies. Nevertheless, the present analysis was limited to high between-study heterogeneity. Another limitation was the lack of control for potential confounding factors. Both

limitations reflect the inadequate design of the available studies to provide precise and unbiased estimates. Further research is needed to adopt a longitudinal design, taking into consideration of maternal characteristics (maternal age, education, paternal biometric measures), infant and birth-related characteristics (sex, time to the previous born, and gestational age and birth length of the second born). Future studies need to consider lifestyle factors (gestational weight gain and nutrition, cigarette smoking, alcohol consumption, and general morbidity) to identify the potential impact to develop behavior interventions targeting pregnant women who are at higher risk of delivering low birth weight babies.

Another important area of future research is to understand the longitudinal effect of altitude on other pregnancies related outcomes (maternal hypertension, preeclampsia) and the late effect on babies. Previous research has suggested a low birth weight paradox phenomenon, such that there is no impact on mortality from altitude-induced weight reduction among termed babies [45]. Nevertheless, the weight reduction might be detrimental among premature babies, or negatively impact morbidly, which should be investigated in further studies. At the present time, global migration is more than ever before, with 1 billion people in the world today are on the move [46]; therefore, the change in altitude alongside with migration history must be considered in maternal care for movers.

5. Conclusions

Our meta-analyses of 4,428,563 participants indicated an average of 96.98 g lower birth weight for every 1000 m in elevated maternal altitude. There was no evidence supporting an impact of maternal altitude on birth weight through gestational age; suggesting that the reduced birth weight is likely due to a negative impact of maternal altitude on fetal growth. With the current rising trend in global migration, further studies need to elucidate a causal association, and to understand the late effect of altitude elevation on women and babies, and identify behavioural interventions to minimize these effects.

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Declaration of competing interest

All authors declare that they have no potential conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.placenta.2020.09.010>.

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