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Intergenerational transmission of birth weight: a systematic review and meta-analysis

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Abstract

The objectives of this study were (1) to systematically review the literature on the association between birth weight in children born in the first and second generation and (2) to quantify this association by performing a meta-analysis. A systematic review was carried out in six databases (PubMed, Science Direct, Web of Science, Embase, Scopus, CINAHL and LILACS), in January 2021, for studies that recorded the birth weight of parents and children. A meta-analysis using random effects to obtain a pooled effect of the difference in birth weight and the association of low birth weight (LBW) between generations was performed. Furthermore, univariable meta-regression was conducted to assess heterogeneity. Egger's tests were used to possible publication biases. Of the 9878 identified studies, seventy were read in full and twenty were included in the meta-analysis (ten prospective cohorts and ten retrospective cohorts), fourteen studies for difference in means and eleven studies for the association of LBW between generations (twenty-three estimates). Across all studies, there was no statistically significant mean difference (MD) birth weight between first and second generation (MD 19·26, 95 % CI 28·85, 67·36; $P = 0·43$). Overall, children of LBW parents were 69 % more likely to have LBW (pooled effect size 1·69, 95 % CI (1·46, 1·95); I^2:85·8 %). No source of heterogeneity was identified among the studies and no publication bias. The average birth weight of parents does not influence the average birth weight of children; however, the proportion of LBW among the parents seems to affect the offspring's birth weight.

Keywords: Birth weight: Intergenerational relations: Cohort studies: Meta-analysis

Maternal birth weight has been considered an anthropometric indicator for predicting the birth weight of children[1,2]. Studies that assessed the intergenerational transmission of birth weight identified relationships between low birth weight (LBW) in the mother and LBW in the child. At the same time, the relationships of higher birth weights between mothers and their children have also been evidenced in some studies[3–6]. In addition, studies also evaluated the association between paternal birth weight and offspring birth weight[7,8].

A systematic review of the intergenerational transmission of birth weight suggests that a 100 g increase in the mother's birth weight leads to a 10–20 g gain in the child's birth weight. Paternal birth weight was also associated with child birth weight, but this association was not as strong as maternal birth weight[9]. Thus, this difference in the strength of association is possibly due to the fact that birth weight is related to maternal anthropometric factors, such as height and pre-pregnancy BMI, in addition to maternal weight gain during pregnancy. The influence of the maternal lineage on the birth weight of children, which possibly indicates an additional effect represented by intra-uterine influences on birth weight, resulting from maternal health conditions, behaviour and socio-economic status[10], what would explain this difference in the intergenerational relationship among mothers/fathers and their children.

The relationship between the birth weight of both parents and children has been studied previously[9], and a meta-analysis has examined intergenerational differences in birth weight[11]. In this context, the purposes of this study were (1) to systematically review the literature on the evidence of the intergenerational transmission of birth weight from parents to their children and (2) to quantify this association by performing a meta-analysis.

Methods

Protocol and registration

The review was carried out following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses[12]. The study protocol was registered in the International Prospective Register of Systematic Reviews – (registration number: CRD42021230962).

Abbreviations: MD, mean difference; LBW, low birth weight.

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Selection of studies

Potentially relevant papers were identified by searching the electronic databases PubMed, Science Direct, Web of Science, Embase, Scopus, CINAHL and LILACS completed on 21st of January 2021 (Fig. 1). The literature search used the following terms: 'birth weight' OR 'birthweight' OR 'birth-weight' OR 'size at birth' AND 'family' OR 'parents' OR 'mother*' OR 'father*' OR 'offspring' AND 'intergenerational' OR 'generation'.

After excluding the duplicates, two independent reviewers (RRO and EPS) screened the titles to remove irrelevant studies. The full texts of the remaining studies were retrieved and those studies that were eligible for this review were identified. In addition to the electronic search, reference lists of the selected studies were examined to identify manuscripts that had not been captured by the database search. Disagreements were solved by a third reviewer. Additional search was made by scanning the reference lists of the identified studies and the previously published systematic reviews.

Selection criteria

We included original studies, performed in humans, that evaluated the intergenerational transmission of birth weight. Thus, studies presenting birth weight data from two generations were selected, including mothers, fathers or parents in the first generation, and daughters, sons or children in the second generation. We excluded those studies that included review studies, editorials, comments and studies conducted with animals. Studies were excluded if they did not provide birth weight data; studies with a different design than the longitudinal; studies focused on fetal growth or prematurity and studies focused on specific samples, such as studies performed with twins.

Exposure and outcome

Study exposure was first-generation birth weight, including studies conducted with fathers and mothers. Outcome was second-generation birth weight for both offsprings, sons or daughters. In some studies, when available, birth weight in both generations was considered a continuous variable (measured in grams), and the combined mean difference (MD) between the first and second generations was analysed. Other studies, with available data on OR and other measures of effect, were included for the LBW analysis.

Extraction and quality assessment

The extraction of data and assessment of quality were performed separately and blindly by two reviewers (RRO and EPS) using a structured form generated in Microsoft Excel 2016 (Microsoft). Differences were resolved by consensus and discussion with a third reviewer (DPG). We extracted the following information from each manuscript: publication year; country of data collection; data source; sample size; exposure; outcome; control for confounding and main results.

When reported, mean birth weight and standard deviation or OR and 95 % CI were extracted. If these data were not informed or could not be calculated, the first author of the study was contacted by email.

Study quality

Methodological quality assessment was based on the Newcastle–Ottawa scale[13], a quality assessment scale for cohort studies. For each study, a maximum of nine points could be achieved. The Grading of Recommendations Assessment, Development and Evaluation approach was used to assess the overall quality and strength of evidence. By this approach, the quality of the totality of evidence can be graded as 'very low', 'low', 'moderate' or 'high'. Evidence derived from observational studies receives an initial grade of 'low'.

Data analysis

Two meta-analyses were conducted. The first one used mean birth weights of both generations and their respective standard deviations, obtaining the MD and 95 % CI which were calculated for each study, as well as a pooled estimate. The second study outcome, an intergenerational assessment of LBW, was assessed by OR, and 95 % CI for LBW was generated for each study as well as pooled estimate in the second meta-analysis. For the mean birth weight meta-analysis, when the study contained information on the mean birth weight of both parents or children of both sexes, the weighted mean and standard deviation were calculated for each study. In the OR meta-analysis, we followed the birth weight classifications in groups established by the studies, with more than one estimate being performed in each study. Pooled summary statistics were calculated using a random-effects model. Forest plots were generated to explore heterogeneity, graphically.

To evaluate the pooled effect size, we used the random-effects models and evaluated the heterogeneity among studies using the I^2 statistics. To explore the heterogeneity sources of this association, the variables year of publication (before 2010 and after 2010), study design (retrospective cohort and prospective cohort), sample (<1000, 1000–5000 and >5000), setting (high-income country, middle/low-income country), relationship (parents, mothers and fathers) and adjustment for confounding variables confounding (no and yes). Meta-regression was performed to evaluate the pooled effect according to the characteristics of the studies. Funnel plots and the Egger's test were used to evaluate publication bias under variables (year, study design, sample, setting, relationship, control for confounding). Analysis was performed using Stata 16.

A sensitivity analysis was performed to assess the robustness of the observed results. Therefore, according to the Newcastle–Ottawa scale, studies of low quality, less than or equal to five points, were excluded in the sensitivity analysis.

Results

Study characteristics

Fig. 1 shows the study selection flow chart. The search identified 9878 studies. After excluding duplicates (n 1873), 8005 titles were read and 154 abstracts were selected. Of these, eighty-four abstracts were excluded mainly because they did not assess birth weight and did not include two generations or related birth weight of children with socio-demographic, behavioural and

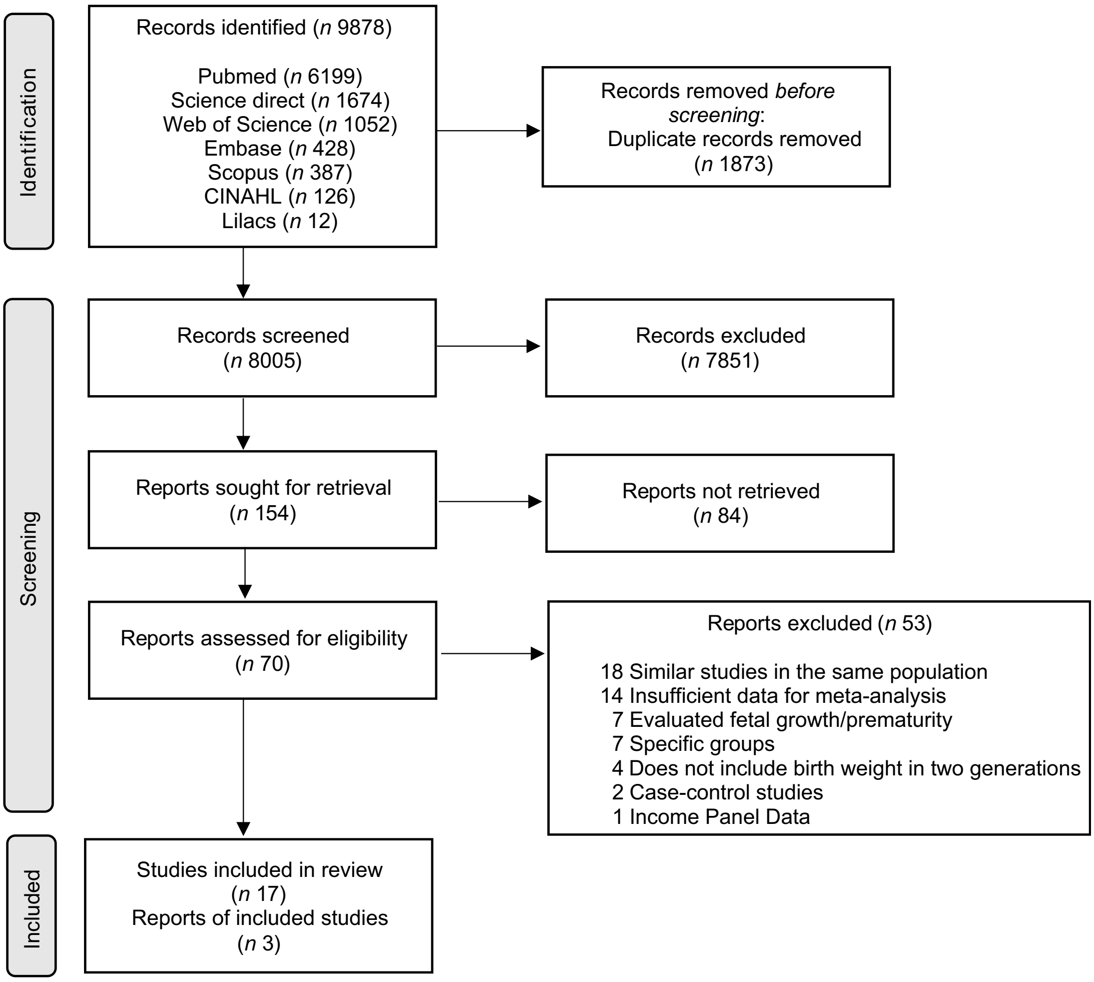

Fig. 1. Flow chart of the study selection.

health characteristics of the parents. After excluding the abstracts, seventy manuscripts read in full were selected.

Of these, fifty-three were excluded, and the reasons for this exclusion were presented in the flow chart (Fig. 1). Other three studies were identified through a search in the references of the manuscripts selected. For studies in which we were unable to extract mean birth weight and standard deviation or OR and 95 % CI, we sent an email to the authors. In case they did not respond to the email or did not provide the necessary data, we excluded the meta-analysis study (*n* 12).

Thus, twenty studies were included in the meta-analysis, fourteen in the MD analysis[14–27] and eleven in the OR[3,8,15,18,23,26–31]. Table 1 shows a description of the studies included in the meta-analysis.

All studies were cohort studies, of which ten were prospective and ten retrospective cohorts. The studies were conducted in the USA (*n* 8), Israel (*n* 2), Sweden (*n* 2), England (*n* 1), Malta (*n* 1), Spain (*n* 1), Argentina (*n* 1), India (*n* 1), Brazil (*n* 1), Norway (*n* 1) and a study by the Consortium on Health Oriented Research in Transitional Societies with a sample of the countries Brazil, Guatemala, India and the Philippines.

Mean birth weight

Fig. 2 shows the results of the overall meta-analysis of mean birth weight. The pooled MD in birth weight (measured in grams) between the first generation and second generation, across all studies, was not statistically significant (fourteen studies; MD 19·26, 95 % CI 28·85, 67·36; $P = 0·43$). Using a random-effects model, these results were found to be highly heterogeneous ($I^2 = 99·96$ %).

Low birth weight

The pooled association between LBW in the first generation and LBW in the second generation is shown in Fig. 3. Offspring of LBW parents were 69 % more likely to have LBW (effect size 1·69, 95 % CI 1·46, 1·95; I^2:85·8 %). These results were found to be statistically significant and of high heterogeneity.

The subgroup analysis (Fig. 4) was carried out on studies performed with mothers (eight studies, ten estimates; OR 1·80, 95 % CI 1·59, 2·03), with parents (three studies, seven estimates; OR 1·55, 95 % CI 1·22, 1·97) and with fathers (one study, two estimates; OR 2·19, 95 % CI 1·00, 4·80).

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Table 1. Description of studies included in meta-analysis (*n* 20)

Author, year	Country	Survey year	Data source	Sample size	Exposure	Outcome	Adjustment for confounders	Mains results
Klebanoff *et al.*, 1984[3]	USA	1959–1966	Buffalo cohort of the Collaborative Perinatal Project	1·348 mothers/off-spring	Maternal BW	Offspring BW	Maternal weight, height, weight/height kg/cm', maximum pregnancy weight gain, age, socio-economic index, smoking, parity and education	Compared with mothers who weighed 3·6 kg or more at birth, mothers who weighed 1·8–2·7 kg were at 3·46 times the risk of having a LBW infant, and mothers who weighed 2·7–3·6 kg at birth were at 1·66 times the risk of having a LBW infant2·7–3·6 kg (OR: 1·66; 95 % CI 0·82, 3·39) 1·8–2·7 kg (OR: 3·46; 95 % CI 1·51, 7·93)
Little *et al.*, 1987[14]	USA	No information	Group Health Cooperative of Puget Sound in Seattle, Washington (prenatal clin-ics)	377 parents–off-spring	Parental BW	Offspring BW	Parents' usual weights and races; maternal height, parity, pregnancy weight gain, mother's and father's drinking before conception, and mother's smoking before and during pregnancy	The parent–infant birth weight correla-tions ranged between 0·14 and 0·16, except for the mother–daughter corre-lation, which was about double these values (0·32). Increase of 100 g in the father's birth weight predicts an increase of about 13 g in the son's birth weight and about 11 g in the daughter's birth weight. An increase of 100 g in the mother's birth weight predicts an increase of 17 g in the daughter's birth weight
Coutinho *et al.*, 1997[8]	USA	1956–1975 parents 1989–1991 offspring	Illinois vital records	132 995 parents/ offspring	Parental BW	Offspring BW	No adjustment	For African Americans, the LBW rate was 17·9 % among those born to LBW mothers compared with 10·8 % among those born to non-LBW mothers For whites, the LBW rate was 8·5 % among those born to LBW mothers compared with 4·8 % among those born to non-LBW mothers African Americans mother: (OR: 1·99; 95 % CI1·74, 2·27) White mother: (OR: 1·71; 95 % CI 1·55, 1·87) African Americans father: (OR: 1·41; 95 % CI 1·21, 1·66) White father: (OR: 0·87; 95 % CI0·75, 0·99)
Winkvist *et al.*, 1998[21]	Sweden	Mothers 1955–1972 Offspring 1973–1990	Swedish Medical Birth Registry (mothers) Registered in obstetric clin-ics (offspring)	4746 mothers/off-spring	Characteristics of maternal birth (length of gestation and types of growth retar-dation)	Family trends in prema-ture and small births for gesta-tional age (SGA)	Maternal age Parity Sex	Mothers who had themselves been pre-term at birth were not at increased risk of any of the outcomes studied. Mothers who had themselves been SGA at birth had an almost 50 % higher risk (NS) of giving birth to either a preterm or an SGA infant than had mothers who had not been (OR: 1·47; 95 % CI0·35, 6·08)

Table 1. (*Continued*)

Author, year	Country	Survey year	Data source	Sample size	Exposure	Outcome	Adjustment for confounders	Mains results
Hypponen *et al.*, 2004[22]	England	1958 (G2 = cohort members) 1970–2000 (First-born offspring (G3)	1958 British national birth cohort	4566 mothers 4050 offspring	Parent's growth in height and BMI from childhood to adulthood	Offspring BW	G2: Social class and birth order G3: Gestational age and sex	Mother's birth weight (standardised for gestational age and sex) was the strongest determinant of offspring birth weight (effect size per SDS 112 g (95 % CI 97, 128)), which was little affected by adjustment for maternal height or BMI (ES 95 g and 105 g, respectively)
Cuestas *et al.*, 2007[23]	Argentina	2007	Maternity of the Private Hospital Centro Medico De Cordoba	180 mothers/ offspring	Maternal BW	Offspring BW	No adjustment	The correlation coefficient between maternal birth weight and child birth weight for males was 0·321 (*P* 0·001) and for females was 0·216 (*P* 0·053) Where it is observed that the lean mass mother's birth predicts significantly the birth weight of the firstborn males ($\beta = 0{\cdot}321$)
Agnihotri *et al.*, 2008[24]	India	1969–1973 (parents) 2002–2004 (research)	Longitudinal studies in human repro- duction – Vellore	472 fathers 422 mothers 1525 offspring	Parental BW	Offspring BW	Sex of the offspring, parity of the mother, BMI, adult height and SES score of parents	A LBW mother had times risk (OR: 2·76, 95 % CI 1·20, 6·40) of delivering a LBW baby and a LBW father was twice as likely to produce a LBW baby (OR: 2·19; 95 % CI 1·00, 4·80) Every 100 g increase in maternal BW was associated with an increase in off- spring BW of 14 g; the equivalent fig- ure for paternal BW was 18·1 g
Nordtveit *et al.*, 2009[25]	Norway	1967–2006	Medical Birth Registry	272 674 mothers/ offspring	Mother's birth order	Offspring BW	Mother's year of birth, grandmother's age and education	Mother's birth weight increased steadily with increasing birth order from 3369 g for first born to 3538 g for fourth or later born mothers. In contrast, there was a monotonic decrease in offspring mean birth weight with increasing mother's birth order (9·1 g/birth order (95 % CI 6·8, 11·4))
Mattsson *et al.*, 2012[26]	Sweden	1973 or later parents 1994–2006 offspring	Swedish Population Register, Medical Birth Register and Multi- Generation Register	137 538 parents/ offspring	Parental BW	Offspring BW	Maternal and paternal age, infant ges- tational length, infant sex, parity, maternal smoking, and maternal BMI and height	For every 1000 g rise in birth weight of the mother and father, a difference in offspring birth weight by 164 g (95 % CI 159, 170) and 149 g (95 % CI 145, 154), respectively.
Agius *et al.*, 2013[27]	Malta	1987 G2 2004–2010 G3	Department of Obstetrics and Gynaecology at Mater Dei University Hospital in Malta	182 grandmothers 182 mothers 233 infants	Maternal BMI and BW (G2) Grandmothers' pre-pregnancy BMI (G3)	Offspring BW	No adjustment	The higher birth weight infants born to high BMI first-generation mothers were more likely to become obese in later life (22·69 + 4·21 *v.* 24·83 + 4·40) and in turn have infants with higher mean birth weights themselves (3·12 + 0·47 *v.* 3·40 + 0·54)
	USA				Maternal BW	Offspring BW		

British Journal of Nutrition

Table 1. (*Continued*)

Author, year	Country	Survey year	Data source	Sample size	Exposure	Outcome	Adjustment for confounders	Mains results
Chapman *et al.*, 2014[30]		1960–1997 2005–2009	The Virginia Intergeneratio-nal Linked Birth File	69 702 mothers/off-spring			Education, age at delivery, marital status, insurance status, adequacy of prenatal care index and smoking during pregnancy	Maternal risk factors in the current pregnancy, non-Hispanic black (OR: 1·60; 95 % CI 1·42, 1·79) and non- Hispanic white (OR: 2·03; 95 % CI 1·78, 2·30) infants had increased odds of being born LBW if their mother was born LBW
Addo *et al.*, 2015[28]	Brazil Guatemala India Philippines	1982–2012 (Brazil) 1969/1977–2004 (Guatemala) 1969/1972–1998/2002 (India) 1983/1984–2009 (Philippines)	1982 Pelotas Birth Cohort (Brazil) Central American Nutrition Institute and Panama Cohort of Nutrition (Guatemala) New Delhi Birth Cohort (India) Longitudinal Survey of Health and Nutrition in Cebu (Philippines)	3392 parents 5506 offspring	Parental birth weight (BW) and post-natal anthropometry	Offspring BW and LBW	Parental early childhood SES (quintiles); maternal/paternal firstborn status, offspring sex and firstborn status, nutrition supplementation status, site, maternal age at delivery and sibling clustering	The increase per 1 SD was 102·3 g (95 % CI79·5, 125·2) with maternal birth weight. Paternal birth weight was associated with 57·3 g (95 % CI 25·9, 88·6), increase in offspring birth weight Parental birth weight was independently associated with reduced risk of offspring LBW, with prevalence ratio (PR) 50·7 (95 % CI 0·6, 0·8) for mother–offspring; and (PR) 50·87 (95 % CI 0·8, 1·0) for father–offspring models
Costa e Silva *et al.*, 2015[16]	Brazil	2012–2014	'Hospital Universitário' of the University of São Paulo	773 mother/off-spring	Maternal BW	Child's LBW	No adjustment	The child's weight at birth ≤2500 g showed associated with maternal weight (OR: 2·10; 95 % CI 0·70, 6·20)
Kane *et al.*, 2015[17]	USA	2010 (G3)	National Longitudinal Survey of Youth (NLSY79)	1·580 mothers/ daughters G1 = mothers NLSY79 G2 = CNLSY79 daughters G3 = infants	Maternal BW	Infant's BW Social inequality can transmit from mothers to children via birth weight	G0: education G1: race-ethnicity, family structure in adolescence G2: race-ethnicity, preterm birth, birth order G3: race-ethnicity, preterm birth, sex, birth order	The path coefficient from G2 birth weight to G3 birth weight indicates that for each additional gram of G2 birth weight, G3 birth weight is, on average, 0·13 g heavier
Giuntella *et al.*, 2016[18]	USA	1970–1985 e 1989–2009	Birth Statistical Master File provided by the Office of Vital Record	4·704·571 births	Birth weight of second-generation Hispanics born in California and Florida	Birth weight of third-generation Hispanics born in California and Florida	Child's sex, parity, type of birth, year of birth, maternal marital status, prenatal care, maternal and paternal education	The generational decline in the birth outcomes of immigrant descendants of Hispanic origin in the USA. Children of first-generation Hispanic immigrant women have lower incidence of LBW and heavier average birth weight than children of US-born white women. These differences become larger when controlling for socio-demographic characteristics
	USA				Maternal LBW			

Table 1. (*Continued*)

Author, year	Country	Survey year	Data source	Sample size	Exposure	Outcome	Adjustment for confounders	Mains results
Ncube *et al.*, 2017[31]		Mothers 1979–1998 Offspring 2009–2011	Cohort study in Allegheny County, Pennsylvania	6633 mother/offspring		Offspring LBW (and LBW subgroup) status	Mothers' race, age, marital status, educational attainment, health insurance, neighbourhood racial, composition and poverty	Maternal LBW was associated with (OR: 1·53 95 % CI 1·15, 2·02) fold increases in risk of infant LBW
Drukker *et al.*, 2018[32]	Israel	1982–1997 parents 2000–2015 offspring	Shaare Zedek Medical Center birth certificate Birth and death certificate registries of the Israel Ministry of Health	377 very low birth weight (VLBW)	Fertility of parents with VLBW – <1500 g	1. VLBW risk in offspring 2. Offspring BW	Year of birth Parents' age	Both female and male first-generation patients from the LBW group had half the reproductive rate relative for the normal birth weight group. After adjusting for parental age, male and female LBW survivors had no significant risk for a LBW neonate in the next generation Mother <2·500 g (OR: 1·94; 95 % CI 1·72, 2·21) Father <2·500 g (OR: 1·44; 95 % CI 1·18, 1·76)
Sepúlveda *et al.*, 2019[29]	Spain	1975–1993	Hospital Sant Joan de Déu in Barcelona Small-for-gestational age (SGA) Appropriate growth for gestational age (AGA)	152 adults (72 born small-for-gestational age (SGA) and 80 with appropriate intra-uterine growth)	Maternal SGA	Offspring SGA	Sex, salary, educational level, body surface area and smoking status	Descendants from SGA adults presented lower birth weight percentile (median 26 *v.* 43) and higher prevalence of SGA (40·3 % *v.* 16·3 %) Parental SGA background was associated with an almost three-fold increased risk of subsequent SGA or any placental mediated disease in the following generation (OR: 2·90; 95 % CI 1·06, 7·91)
Sherf *et al.*, 2019[19]	Israel	1991–2013	Soroka University Medical Center	2311 familial triads 1490 F1 (mothers) 1616 F2 (daughters) 2311 F3 (children)	Maternal LBW	Offspring LBW	Maternal age at delivery, parity, placental pathology, preeclampsia, lack of prenatal care, ethnicity	LBW in mothers (F2), adjusted for possible confounders, was found to be a significant predictor for LBW in offspring (OR: 1·60; 95 % CI 1·02, 2·60)
Liu *et al.*, 2020[20]	USA	1995–2005 Mothers 2010–2018 Offspring	Nebraska Mother Index (NMI)	5·118 mothers/offspring	Mothers' adverse birth outcomes LBW and preterm birth (PTB)	Offspring LBW and PTB	Age at delivery Marital status Educational level Urban or rural area Ethnicity Diabetes, hypertension Smoking in pregnancy Caesarean delivery	Mothers born LBW preterm were more likely to deliver LBW (OR 1·94; 95 % CI 1·39, 2·71) than mothers born with normal weight or at term

BW, birth weight; LBW, low birth weight; SES, socio-economic status.

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Table 2. Meta-analysis showing heterogeneity and meta-regression of the associations between low birth weight (LBW) in the first generation and LBW in the second generation (eighteen estimates from eleven studies) (Odds ratios and 95 % confidence intervals)

		ES pooled		I^2	Meta-regression		
Variables	Number of estimates	OR	95 % CI	%	OR	*P*	% Heterogeneity explained (R^2)
Year of publication							
Before 2010	9	1·52	1·43, 1·61	91·2	Index	0·52	−0·29
After 2010	9	1·77	1·67, 1·89	49·9	1·10		
Type of study							
Retrospective cohort	11	1·63	1·56, 1·71	91·1	Index	0·25	−4·21
Prospective cohort	7	1·80	1·45, 2·25	0·0	1·25		
Sample							
<1000	6	1·81	1·64, 2·01	39·9	Index	0·51	−9·42
1000–5000	4	1·83	1·30, 2·58	0·0	0·99		
>5000	8	1·60	1·52, 1·68	93·2	0·83	0·25	2·89
Setting							
High-income country	15	1·63	1·56, 1·71	88·1	Index		
Middle/low-income country	3	2·36	1·42, 3·92	0·0	1·43	0·43	1·06
Relationship							
Parents	7	1·57	1·49, 1·66	94·0	Index		
Mothers	10	1·78	1·65, 1·92	28·5	1·19		
Fathers	1	2·19	1·00, 4·80	0·0	1·42		
Control for confounding						0·22	2·51
No	7	1·52	1·43, 1·61	93·1	Index		
Yes	11	1·78	1·67, 1·90	48·3	1·20		

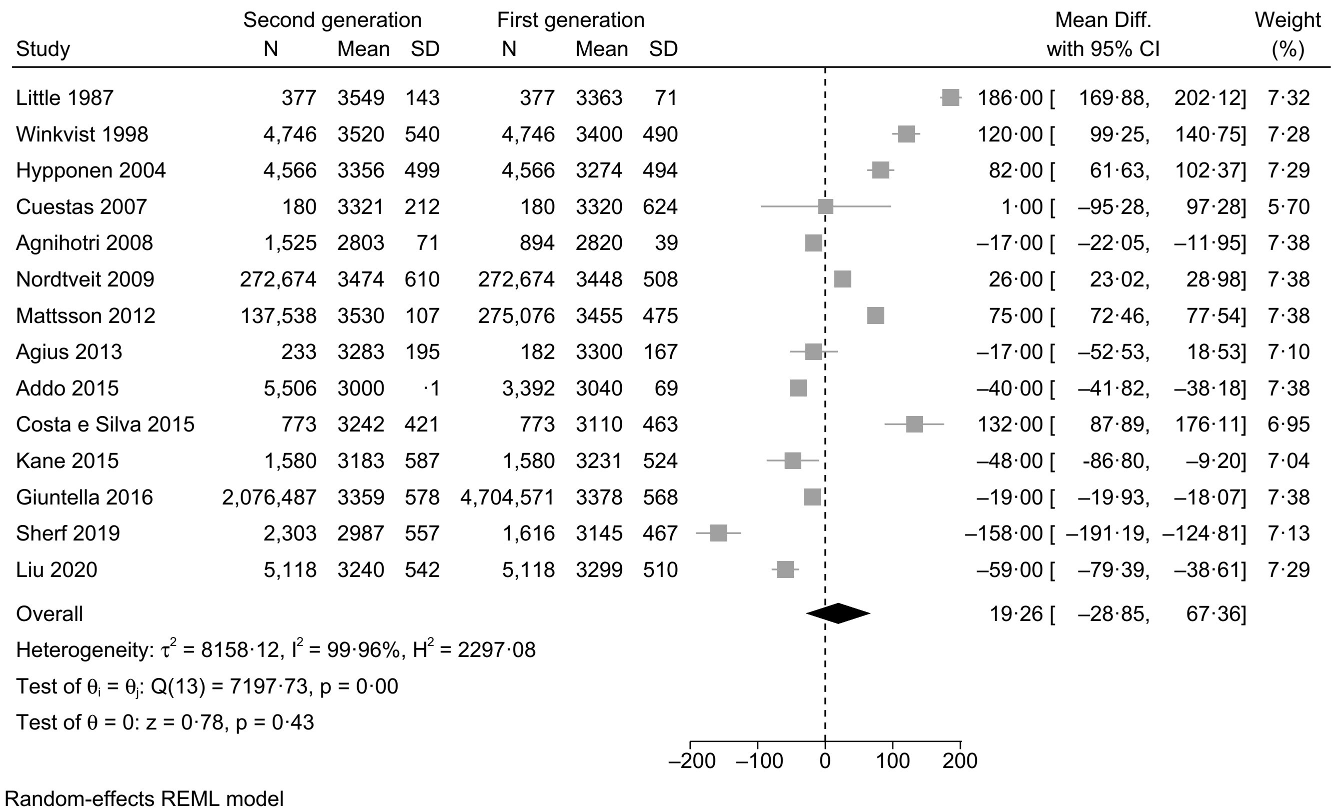

Fig. 2. Meta-analysis of mean birth weight. The pooled mean difference (MD) in birth weight (measured in grams) between the first generation and second generation (fourteen studies).

When performing meta-regression, no significant differences were observed between year of publication ($P = 0·70$), type of study ($P = 0·47$), sample ($P = 0·34$), setting ($P = 0·17$), relationship ($P = 0·49$) and control by confounding ($P = 0·29$) (Table 2). Despite the funnel plot showing evidence of publication bias (Fig. 5), the Egger's test was not significant ($P = 0·67$).

British Journal of Nutrition

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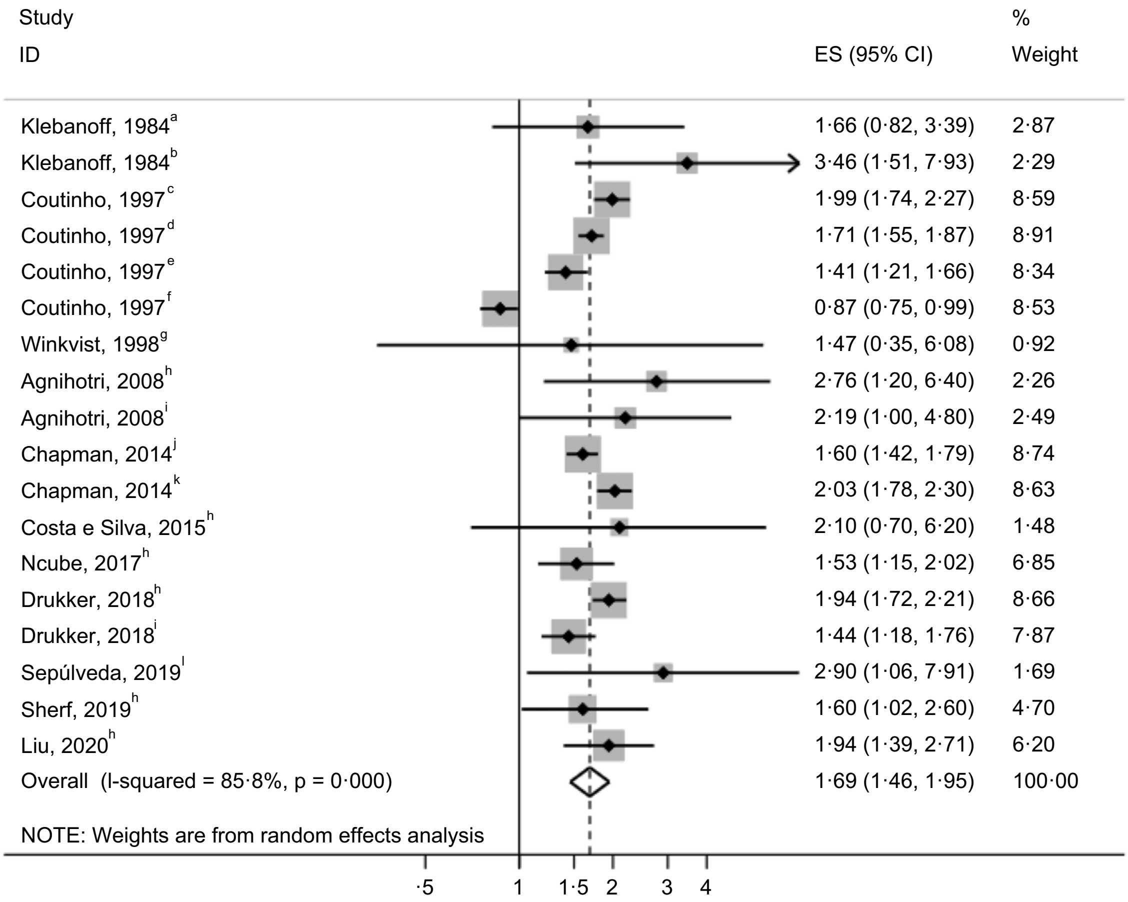

Fig. 3. Meta-analysis on the association of the low birth weight between the first generation and the second generation (random effect). ES effect size (eighteen estimates from eleven studies). [a]Mother born with 2,7-3,6kg [b]Mother born with 1,8-2,7kg [c]African americans mother [d]White mother [e]African americans father [f]White father [g]Mother small for gestational age [h]Mother with LBW [i]Father with LBW [j]Non-hispanic black LBW [k]Non-hispanic white LBW [l]Parents small for gestational age

Quality assessment

The results of the literature quality evaluation are shown in Table 3. Of the twenty studies included in this review, seventeen studies met more than half of the methodological quality criteria score[3,14–16,18–31]. Furthermore, three studies had four points in methodological quality[8,17,23]. The overall strength and quality of the evidence were assessed by Grading of Recommendations Assessment, Development and Evaluation, the default level for observational studies (Table 4).

In the sensitivity analysis, after excluding low-quality studies[15,17,23,26], we found that there were no significant changes in mean birth weight (ten studies; MD, 17·33, 95 % CI 30·32, 64·97; $P = 0·48$). In the sensitivity analysis of LBW, after excluding low-quality articles[3,8,15,23,26], the result of our study was more evident (six studies, thirteen estimates; OR 1·76, 95 % CI 1·58, 1·95; $P = 0·04$).

Discussion

In this systematic review and meta-analysis, we assessed the association between intergenerational birth weight. The overall mean birth weight was slightly higher among offspring, compared with parents' birth weight; however, this association was not statistically significant. We also assessed the association between LBW over the generations. Children of parents with LBW at birth had a higher risk of being born with LBW. In this sense, we can observe the roles that intergenerational factors can play on the birth weight of the next generation.

Intergenerational factors are characteristics of pregnancy, childbirth, exposure to events, situations and/or substances that affect the health status of one generation and can affect the growth and development of the next generation[32]. Furthermore, maternal social environment, socio-economic status at birth and the child growth pattern are important factors in predicting the weight of children at birth[33,34].

The associations between the birth weight of the parents and children are well known, with most of these studies reporting a stronger relationship with the birth weight of the mother rather than with the birth weight of the father[9]. This difference in the strength of the association between mothers and fathers is possibly due to birth weight related to maternal anthropometric factors, such as height and pre-pregnancy BMI, and maternal weight gain during pregnancy. Moreover, birth weight results

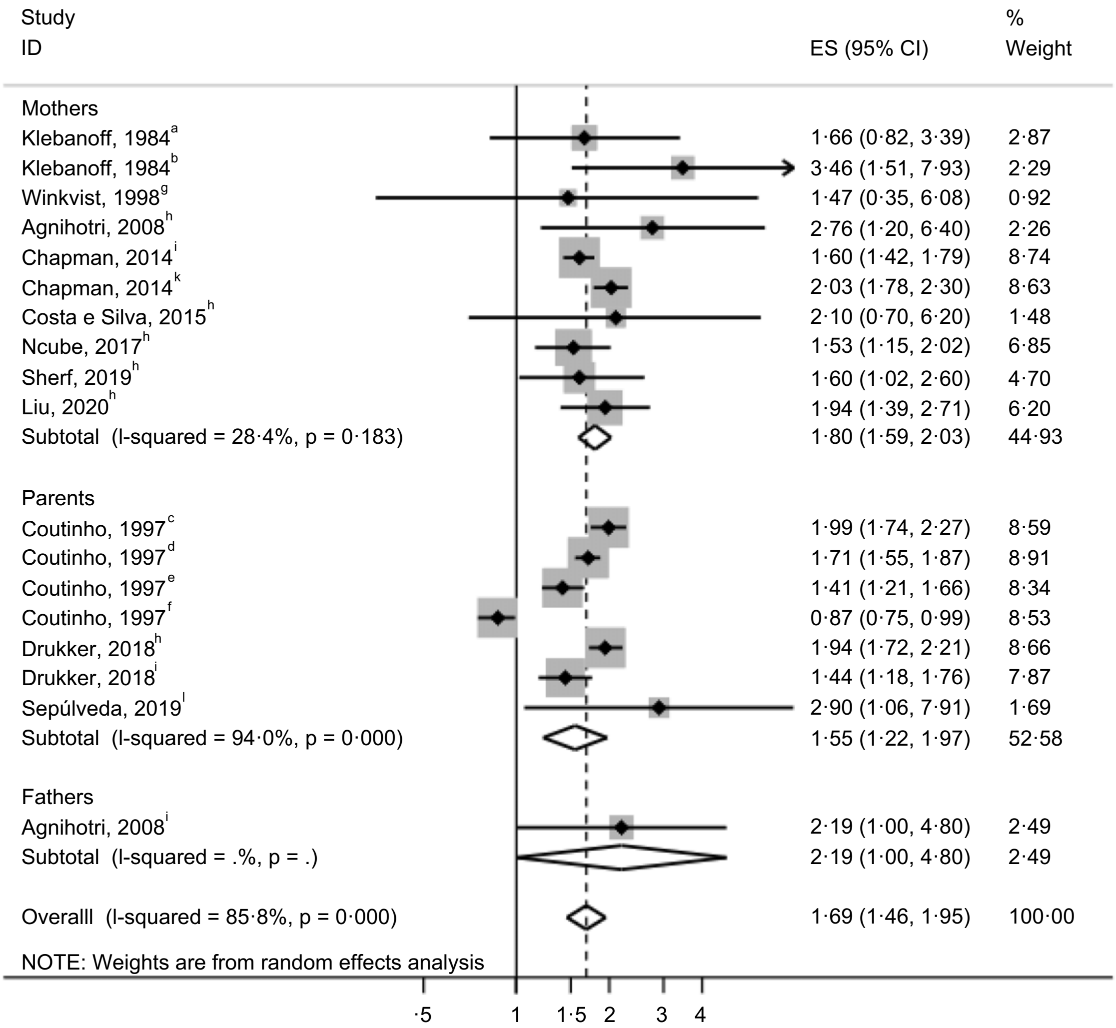

Fig. 4. Meta-analysis of low birth weight between the first generation and second generation by subgroup. [a]Mother born with 2,7-3,6kg [b]Mother born with 1,8-2,7kg [c]African americans mother [d]White mother [e]African americans father [f]White father [g]Mother small for gestational age [h]Mother with LBW [i]Father with LBW [j]Non-hispanic black LBW [k]Non-hispanic white LBW [l]Parents small for gestational age

from maternal factors such as smoking, diabetes and hypertension during the gestational period. Some studies suggest the effects of paternal smoking during pregnancy, that is, passive smoking, can influence the reduction of birth weight of children[35,36].

Our meta-analysis found that the LBW of the parents increases the chance of the child having LBW. The WHO defines LBW as a birth weight of less than 2500 g and remains a significant public health problem worldwide. According to data from UNICEF and from WHO[37], almost 15 % of all children in the world are born with LBW, undermining their survival, health and development. Hence, reducing LBW is one of the global nutritional targets – WHO intends to reduce LBW by 30 % worldwide by 2025[38,39].

As we have seen, LBW has an intergenerational transmission. The consequences of LBW are both short and long term, including neonatal mortality and morbidity, and an increased probability of stunted growth, poor cognitive development[40] and lower[41]. In adulthood, the risk of chronic diseases such as obesity, diabetes and CVD increases[40,42].

Most studies were carried out in high-income countries. It is known that there is considerable variation in the prevalence of LBW among regions worldwide and within each country. Nevertheless, the vast majority of people with LBW occur in low- and middle-income countries and especially in the most vulnerable populations[43,44]. Between 2000 and 2015, almost 95 % of LBW children were found in less developed region[37]. In less developed regions, LBW is mainly caused by low fetal growth associated with maternal malnutrition before and during pregnancy. In more developed regions, LBW is associated with prematurity (defined as a baby born before 37 weeks of pregnancy) due to high maternal age, smoking, multiparity and caesarean delivery[45]. Most studies investigating the intergenerational transmission of birth weight have been based on American or European populations.

This is the first meta-analysis on the intergenerational transmission of birth weight, with the inclusion of longitudinal studies as a strong point. In relation to the publication bias, although visual inspection of the funnel plot showed asymmetry, the Egger's test did not confirm publication bias. However, this study

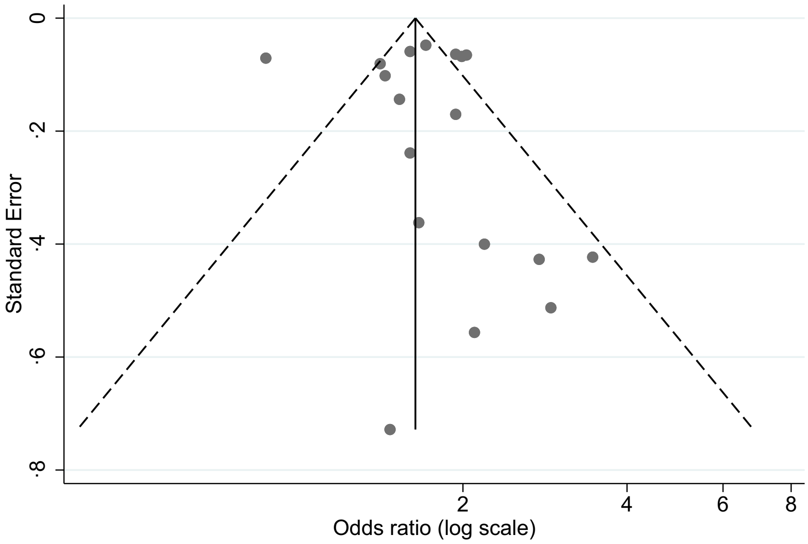

Fig. 5. Funnel plot of the effects measured by the studies of low birth weight included in meta-analysis (eighteen estimates from eleven studies).

Table 3. Example of Newcastle–Ottawa scale for assessment of quality of cohort studies

	Selection				Comparability		Outcome			
Studies	1	2	3	4	5a	5b	6	7	8	Score
Klebanoff *et al.*, 1984[3]	*	*			*	*			*	5
Little *et al.*, 1987[14]		*			*	*	*	*	*	6
Coutinho *et al.*, 1997[8]	*	*	*				*			4
Winkvist *et al.*, 1998[15]	*	*	*			*	*			5
Hypponen 2004[16]	*	*	*	*	*	*		*	*	8
Cuestas *et al.*, 2007[17]	*	*	*				*			4
Agnihotri *et al.*, 2008[18]	*	*	*	*	*	*	*	*	*	9
Nordtveit *et al.*, 2009[19]	*	*	*		*	*	*			6
Mattsson *et al.*, 2012[20]	*	*	*			*	*		*	6
Agius *et al.*, 2013[21]	*	*	*	*			*	*	*	7
Chapman *et al.*, 2014[28]	*	*	*		*	*	*			6
Addo *et al.*, 2015[22]	*	*	*	*	*	*		*	*	8
Costa e Silva *et al.*, 2015[23]	*	*	*				*			4
Kane *et al.*, 2015[24]	*	*	*		*	*	*			6
Giuntella *et al.*, 2016[25]	*	*	*		*	*	*			6
Ncube *et al.*, 2017[29]	*	*	*		*	*	*		*	7
Drukker *et al.*, 2018[30]	*	*	*	*	*		*	*	*	8
Sepúlveda-Martínez *et al.*, 2019[31]	*	*	*		*	*	*			6
Sherf *et al.*, 2019[26]	*	*	*			*	*			5
Liu *et al.*, 2020[27]	*	*	*		*	*	*		*	7

*Represents a point on the scale score.

presents some limitations that should be considered. Initially, there was a lack of information in some studies, such as mean birth weight and standard deviation, making it impossible to include it in the meta-analysis. Second, the high heterogeneity was observed both in the mean birth weight and in the LBW analysis through the OR. We used meta-regression to investigate the source of heterogeneity, which is used to explore associations between study characteristics and the effect found, but we were unable to obtain an explanation with the variables included in our analyses. Furthermore, regarding the assumption of independence of the data that regular meta-analysis packages assume, we can consider these data as paired and not independent. However, in the meta-analysis we have the variability between studies, but we would not be able to do a meta-analysis with the variability within the studies.

Therefore, some methodological differences identified in the studies must be taken into consideration. Although the variables did not explain the high heterogeneity between studies, the possible explanation could be the source of information on birth weight, which varied between studies. Some of them used measurements from population records and hospital records; others collected information through a parent questionnaire.

In addition, some studies have been adjusted for few variables. For instance, important socio-economic variables that influence birth weight have not been adjusted, so the pooled estimates of associations may be affected by residual confounding. However, some studies that controlled for confusion seem to have included possible mediators in the model. Adjusting for a mediator may underestimate the magnitude of the association. Accordingly, it is clear that further studies should use an adequate conceptual framework when analysing the association of birth weight of parents and children.

Conclusions

This meta-analysis did not find an effect on mean birth weight between parents and offspring. However, we have found that having a LBW parent increases the odds of their child being born with LBW. Thus, more studies are needed, especially to assess the intergenerational transmission of birth weight in low- and middle-income countries. We also need more studies in order to understand the potential determinants, confounding factors and possible mediators of the association between birth weight of parents and children.

British Journal of Nutrition

Table 4. Grading of Recommendations Assessment, Development and Evaluation assessment

Certainty assessment							
No. of studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Other considerations	Overall quality (very low ⊕; low ⊕⊕; moderate ⊕⊕⊕; high ⊕⊕⊕⊕)
Difference in birth weight between generations							
14	Not serious	Not serious	Serious*	Not serious	Undetected	Undetected	⊕◯◯◯ Very low *Due to inconsistency
Low birth weight between generations							
11	Not serious	Not serious	Serious†	Not serious	Undetected	Undetected	⊕◯◯◯ Very low †Due to inconsistency

* Evidence of significant inter-study heterogeneity (I^2 = 99·96 %).
† Evidence of significant inter-study heterogeneity (I^2 = 82·3 %) that cannot be explained by meta-regression.

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RRO participated in all stages of the manuscript (definition and search in databases, selecting, reading articles, extracting data, and analyzing), interpreted the results, and wrote down the text. EPS participated in the selection, reading of articles, and extracting data. TRF collaborated with data analyses, and did a critical review of the manuscript. DPG guided and critically reviewed the manuscript.

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