

SYSTEMATIC REVIEW UPDATE

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Low birth weight as a predictor of adverse health outcomes during adulthood in twins: a systematic review and meta-analysis

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Abstract

Background: Low birth weight might affect adverse health outcomes during a lifetime. Our study analyzes the association between low birth weight and negative health outcomes during adulthood in twin populations.

Methods: Searches were conducted using databases inclusive of MEDLINE, CINAHL, Web of Science, and EBSCO. Observational studies on twins with low birth weight and adverse health outcomes during adulthood were included. Two reviewers independently screened the papers, and a third reviewer resolved the conflicts between the two reviewers. Following abstract and title screening, full-texts were screened to obtain eligibility. Eligible full-text articles were then assessed for quality using a modified Downs and Black checklist. Studies with a score within one standard deviation of the mean were included in the analysis. A fixed-effect model was used for analysis.

Results: 3987 studies were screened describing low birth weight as a risk factor for adverse health outcomes during adulthood for all twelve-body systems (circulatory, digestive, endocrine, lymphatic, muscular, nervous, reproductive, respiratory, skeletal, urinary, and integumentary systems). One hundred fourteen articles made it through full-text screening, and 14 of those articles were assessed for quality. Five papers were selected to perform two meta-analyses for two outcomes: asthma and cerebral palsy. For asthma, the meta-analyses of three studies suggested a higher odds of low birth weight twins developing asthma (OR 1.33, 95% CI 1.24-1.44, $I^2 = 77%$). Meta-analysis for cerebral palsy included two studies and suggested a 4.88 times higher odds of low birth weight twins developing cerebral palsy compared to normal birth weight twins (OR 4.88, 95% CI 2.34-10.19, $I^2 = 79%$). We could not find enough studies for other adverse health outcomes to pool data for a Forest plot.

Conclusions: The odds of low birth weight were found to be high in both asthma and cerebral palsy. There are not enough studies of similar nature (study types, similar body systems) to ensure a meaningful meta-analysis. We recommend that future research considers following up on twins to obtain data about adverse health outcomes during their adult lives.

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Background

According to the World Health Organization, it is estimated that 15-20% of all births worldwide are low birth weight, which equates to more than 20 million births per year [1]. Low birth weight, defined as being born less than or equal to 2500 grams, is extensively related to a poor child and adult health outcomes [2, 3]. Babies born with more severe low birth weights are more likely to develop chronic illness and difficulty with cognition [3, 4]. One study suggested that lower birth weight is associated with short telomere length and lower cognitive ability [5]. Another study demonstrates that low birth weight is associated with later development of non-insulin-dependent diabetes mellitus, six indicating a positive relationship between being born low birth weight and adverse health outcomes.

Previous studies have confirmed that twin gestations are associated with higher perinatal morbidity and mortality when compared to gestations of singleton pregnancies [6, 7], and multiple pregnancies are among the significant risk factors for preterm births [8]. Babies born in multiple pregnancies are more likely to be low birth weight when compared to their singleton counterparts [9, 10]. In 2015, in the USA, according to the Centers for Disease Control and Prevention (CDC), about 55% of twins were born low birth weight, and about 6% of singletons were reported as low birth weight, utilizing the same threshold for low birth weight singletons and in twins [10]. Thus, twins are at a higher risk of being born low birth weight when compared to singletons, and by extension, are more likely to develop adverse health outcomes that are associated with being born low birth weight [11].

Twin studies give us information about the potential epigenetic etiologies of disease [12–14]. One study examined the association between birth weight and rheumatoid arthritis (RA) in twins discordant for RA, concluding that birth weight was not associated with the development of RA in adult life when adjusted for appropriate confounders [15]. Another study found a positive association between low birth weight and development of type 2 diabetes when comparing within-pair differences in twins, suggesting that genetic factors contribute to outcomes later on in life [16]. Thus, twin studies provide us with valuable information regarding the etiology and epigenetic roots of health and disease.

From the preceding section, it is proven that twins are at higher risk of being born low birth weight and, by extension, are at a higher risk of developing diseases and conditions that are associated with their birth weight. To our knowledge, there is no systematic review that studies the impact of low birth weight on future adult health outcomes in twin populations. Additionally, literature examining these outcomes focuses on one sole outcome

rather than grouping these outcomes into a similar category, such as bodily systems. We compared longitudinal outcomes of twins of low birth weight compared with normal birth weight twins. The methodology that our review follows is the Cochrane method of screening, analysis, and quality assessment. To our knowledge, there is no systematic review that uses this method and analyzes how low birth weight affects longitudinal outcomes in twins through the body systems we are investigating; thus, our study is unique in that sense. We studied this association across all body systems: circulatory, digestive, endocrine, lymphatic, muscular, nervous, reproductive, respiratory, skeletal, urinary, and integumentary systems.

Study question and objective

Our study question attempted to answer this question: Does low birth weight among twins have a long-term impact during adulthood? Our study investigates the association between low birth weight among twins and long-term outcomes during adulthood.

Methods

The target population of this systematic review is adult twin populations that have data on birth weights. The exposure is low birth weight, and the comparator is average birth weight. The study outcomes are any adult health outcomes classified by the bodily system through clinical measurements. Finally, the study design is further described below.

The methodology follows the MOOSE statement and is explained under seven categories: search strategy, inclusion and exclusion criteria, databases, study selection, data extraction, quality assessment, and statistical analysis.

Search strategy

Searches were conducted using databases inclusive of MEDLINE, CINAHL, Web of Science, and EBSCO. A comprehensive list of Mesh terms was obtained by three means (see [Appendix 2](#)). Firstly, the definition of each concept was extracted from MEDLINE. Secondly, gray literature, conference proceedings, and reference lists of published articles were explored. Thirdly, specialists in the field were consulted to identify the Mesh terms. These included: “low birth weight,” “twin studies,” “longitudinal outcome(s),” “adult outcome(s),” “multiple pregnancies,” “twin pregnancy,” and “observational studies.” Boolean logic was used to combine the concepts and eliminate irrelevant articles. Filters were employed to limit the search to observational studies only. The search was limited to English literature.

Inclusion and exclusion criteria

The target population of this systematic review is adult twin populations (P) that have data on birth weights. The exposure is the low birth weight (I), and the comparator is a normal birth weight (C). The study outcomes are any adult adverse health outcomes, including those related to twelve-body systems (circulatory, digestive, endocrine, lymphatic, muscular, nervous, reproductive, respiratory, skeletal, urinary, and integumentary systems). (O) The bodily system can classify that through clinical measurements. Finally, the study design is observational studies (S). Low birth weight was defined as birth weight less than 2500 grams. Clinical diagnosis of chronic conditions and illnesses by a medical doctor, presented by the authors, was considered to substantiate such conditions.

Databases

The following databases were searched, from the earliest available date (mentioned in brackets) to March 10, 2018: MEDLINE (1996), Cochrane Central Register of Controlled Trials (1991), CINAHL (1982), Database of abstracts of reviews of effects (1991), Web of Science (1990), and EBSCO (1946). The references of the full papers included in the study analysis were checked to find additional articles. Articles were stored in a reference manager, EndNote, version 18. References were then imported into a systematic review manager, Covidence, and duplicates were deleted.

Study selection

The screening process was done on Covidence. Two reviewers were involved in the screening process. Two individuals completed the screening; if consensus was not reached about whether to include a study in the subsequent screening or final analysis, a third reviewer determined if a study was included. Cohen's kappa coefficient for the level of agreement for the first 100 abstracts was 0.78. Differences of opinions were resolved by consensus.

Articles were initially stored in Endnote®, a reference manager, and duplicates were deleted. The remaining articles were transferred to Covidence, an online application designed to facilitate literature screening and data extraction. Two reviewers screened article titles for appropriateness and relevance, with those not meeting the study criteria or recognized as duplicates were eliminated (stage 1a). Abstracts of all potentially relevant articles were then retrieved and screened in a similar manner (stage 1b).

Data extraction

Articles were excluded or promoted to the next stage based on the responses entered to each question on the

relevant form. Data extraction for systematic reviews and original studies involved using a standard data extraction form embedded in Covidence. This form included the following information: Study title, authors, year of publication, country of origin, sample size, enrollment period, outcome reported, maternal age, gestational age, zygosity, and sex of the twins in each group. The outcome reported included the following information: The OR, 95% confidence interval (95% CI), test statistics for the interaction, and statistical significance of the analysis were extracted from selected studies. For papers, not reporting OR and 95% CI, the raw data (i.e., number of events and the total number of samples in the exposed and unexposed groups) were used to estimate OR and 95% CI. For eligible studies, two review authors extracted the data using Covidence. Data were entered into Review Manager Software (RevMan, 2018).

Quality assessment

The risk of bias and quality assessment of selected studies was assessed through a modified Downs and Black checklist for methodological quality assessment of health care interventions [17]. We chose to utilize this checklist for quality assessment because it was developed specifically for health care interventions. Additionally, this checklist provides an overall quality index and four subscales of quality assessment (reporting, external quality, internal validity-bias, and internal validity-confounding). [Appendix 1](#) shows the full checklist that was used in the quality assessment. We did not exclude any study based on quality. Both SJ and SH screened the articles, and JI was the third reviewer. JC was the advisor.

Statistical analysis

Meta-analyses were conducted using the generic inverse variance with a fixed- or random-effect model in Revman 5.2. We compared the odds between fixed effect and random effect to adjust for weighting. If the effect measure was found to be the same, we reported the fixed effect. The I^2 test quantified the heterogeneity across individual studies. Low, moderate, or high degrees of heterogeneity were approximated by I^2 values of 25%, 50%, and 75%, respectively. Reasons for heterogeneity were investigated by eyeballing extreme OR and sensitivity analysis.

We planned to conduct subgroup analyses using the following variables: zygosity (monozygotic or dizygotic), gestational age (yes or no), sex of twins (discordant or concordant), maternal age (yes or no), and twin data comparisons (if low birth weight was compared with singleton or twin standards of birth weight). However, we were unable to do this because of a lack of studies.

Sensitivity analysis was conducted by excluding data points with extreme OR or maximum weight to examine

their impact on the overall OR. We were planning to investigate the publication bias using inverted funnel plots. However, the plots can only be drawn if meta-analyses include more than ten studies.

Results

Three thousand nine hundred eighty-seven studies were identified through database searching. Duplicates were removed ($n = 1356$), and 2631 abstracts were screened. One hundred fourteen full-text articles were assessed for eligibility, and 22 studies were evaluated for quality using a modified Downs and Black checklist [17] (see [Appendix 1](#) for modified checklist). Studies were included in the quantitative analysis if their scores were within one standard deviation of the mean quality score. Figure 1 shows the PRISMA flow chart summarizing how articles were screened and how many were ultimately eligible for inclusion in this study; Table 1 shows the 14 studies that

were eligible for quality assessment. Table 2 presents a description of included studies.

Although 14 studies were eligible for inclusion in the final model, the outcomes that these studies looked into were distinct from each other; outcomes included attention-deficit disorders, colorectal cancer, and motor development. Each of these papers suggested a positive correlation between low birth weight in twins and the outcomes above. In order to be included in the meta-analyses, we needed at least two studies per body system to study the impact of low birth weight on longitudinal outcomes that are a part of each body system. Thus, two outcomes that are a part of two different body systems were included in the final meta-analysis: asthma (respiratory system) and cerebral palsy (nervous system). Tables 2 and 3 include descriptions of the last five articles that were included in the meta-analyses. The five articles included were all cross-sectional studies using data from

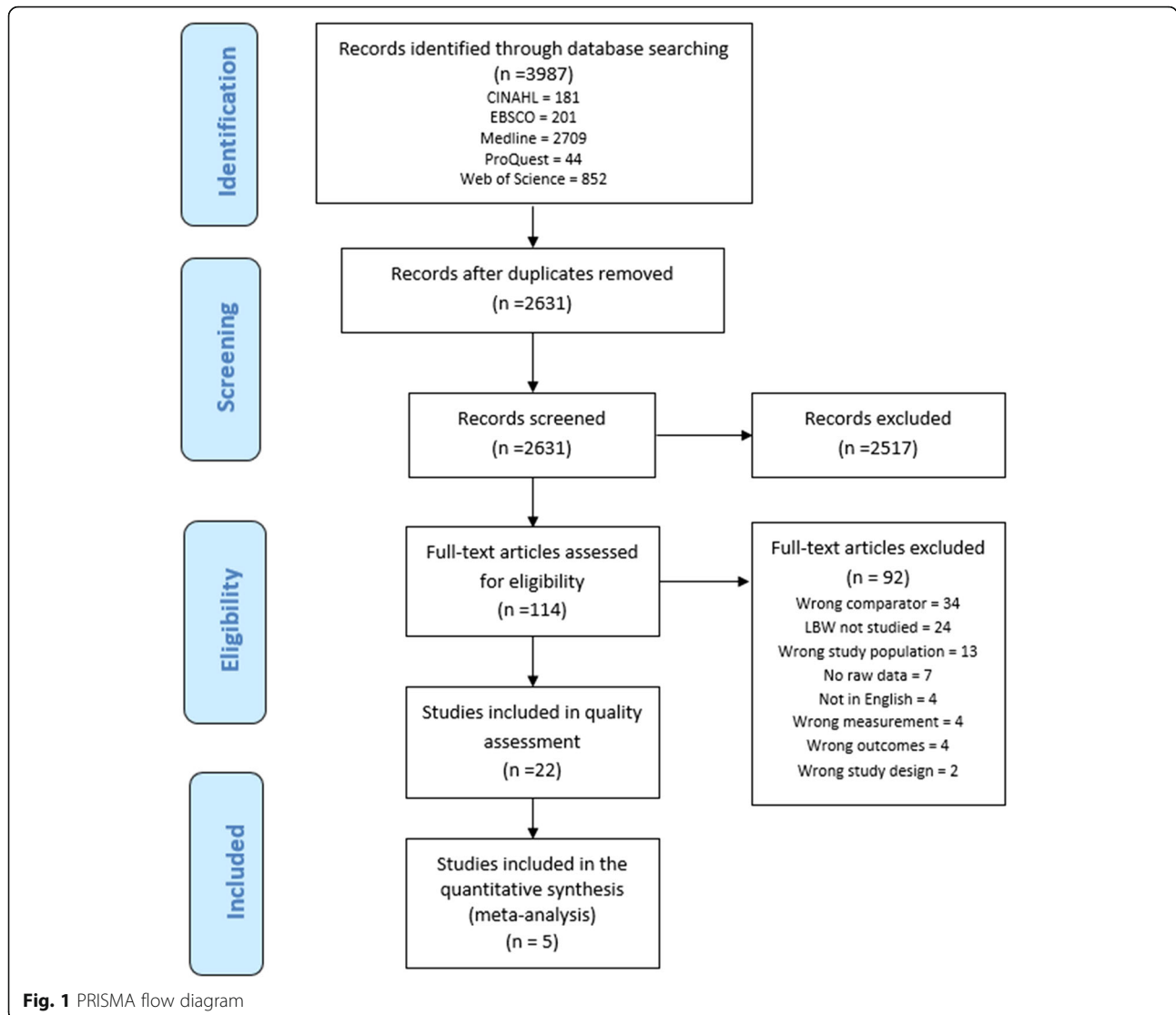


Table 1 Quality assessment of the articles reviewed

| Study ID (author, year) | Clarity | External validity | Internal validity | | Total score |
|--------------------------|---------|-------------------|-------------------|-------------|--------------|
| | | | Bias | Confounding | |
| Alin Akerman 1995 [18] | 4 | 2 | 5 | 2 | 13 |
| Bergvall 2007 [19] | 5 | 2 | 5 | 3 | 15 |
| Cnattingius 2009 [20] | 5 | 2 | 5 | 3 | 15 |
| De Zeeuw 2012 [21] | 4 | 2 | 5 | 2 | 13 |
| Groen-Blokhuis 2011 [22] | 3 | 2 | 5 | 2 | 12 |
| Hestbaek 2003 [23] | 4 | 2 | 5 | 2 | 13 |
| Hultman 2007 [24] | 4 | 2 | 5 | 3 | 14 |
| Gardner 1995 [25] | 3 | 2 | 5 | 2 | 12 |
| Ortqvist 2009 [11] | 5 | 2 | 5 | 3 | 15 |
| Rasanen 2000 [26] | 5 | 2 | 5 | 3 | 15 |
| Suvanand 1997 [27] | 3 | 2 | 5 | 3 | 15 |
| Villamor 2009 [28] | 5 | 2 | 5 | 3 | 15 |
| Williams 1996 [29] | 4 | 2 | 5 | 3 | 14 |
| Yokoyama 2007 [30] | 5 | 2 | 4 | 3 | 14 |
| Median (range) | 4 (3-5) | 2 (2-2) | 5 (4-5) | 3 (2-3) | 13.5 (12-15) |

Table 2 Description of the articles included in meta-analyses. All study designs are cross-sectional, and all studies used singleton standards to classify low birth weight

| Study ID (author, year) | Country | Number of participants | Enrollment period | Outcome | Maternal age | Gestational age | Zygosity (MZ/DZ) | Sex (MM/MF/FF) |
|-------------------------|---------|------------------------|-------------------|----------------|--|---|--|--|
| Ortqvist 2009 [11] | Sweden | 10918 | 2004-2007 | Asthma | ≤ 19: 18.4% 20-24: 16.1% 25-29: 13.9% 30-34: 13.9% ≥ 35: 11.8% | ≤31: 24.8% 32-34: 18.1% 35-36: 14.1% 37-38: 11.7% 39-40: 10.7% ≥ 41: 12.9% | MZ: 13.4% DZ: 28.4% Unknown: 11.7% | - |
| Rasanen 2000 [26] | Finland | 4502 | 1975-1979 | Asthma | < 25: 31.4% 25-30: 38.8% > 30: 29.8% | < 33: 7.1% 33-36: 29.0% 37-40: 60.6% > 40: 3.3% | - | - |
| Villamor 2009 [28] | Sweden | 32580 | 1926-1958 | Asthma | < 20: 2.7% 20-24: 17.0% 25-29: 29.9% 30-34: 27.4% ≥ 35: 22.9% Missing: 0.1% | 31-34: 12.9% 35-36: 20.0% 37-41: 58.7% 42-45: 3.5% Missing: 4.8% | - | MM: 47.2% FF: 52.8% |
| Gardner 1995 [25] | USA | 1079 | 1959-1966 | Cerebral palsy | - | - | MZ: 31.9% DZ: 58.6% Unknown: 9.4% | Concordant: 63.9% Discordant: 36.1% |
| Suvanand 1997 [27] | India | 250 | 1993-1994 | Cerebral palsy | - | - | - | - |

Table 3 Impact of low birth weight on longitudinal outcomes by body system

| Body system | Outcome | Number of studies | Number of participants | OR (95%CI) | Heterogeneity (%) |
|-------------|----------------|-------------------|------------------------|-------------------|-------------------|
| Nervous | Cerebral palsy | 2 | 1318 | 4.88 (2.34-10.19) | 79% |
| Respiratory | Asthma | 3 | 37,008 | 1.33 (1.24-1.44) | 77% |

four countries, consisting of over 35,000 twin participants.

Asthma

Asthma is defined as a respiratory condition marked by spasms in the bronchi of the lungs, causing difficulty in breathing. It usually results from an allergic reaction or other forms of hypersensitivity. Figure 2 shows the meta-analysis for the association between low birth weight and the development of asthma later on in life. Three studies were included in this meta-analysis, with just over 37,000 twins being studied. A fixed-effect model was used, and the meta-analysis showed $I^2 = 77%$ and OR (95% CI) = 1.33 (1.24-1.44). A random-effect model was tested to adjust weighting. However, no change in the effect was observed. Hence, the fixed effect is reported. However, the results were significant ($p < 0.00001$); this outcome shows high heterogeneity and ultimately favored low birth weight.

Cerebral palsy

Table 3 lists the studies used to analyze outcomes of cerebral palsy. Figure 3 shows the meta-analysis for the association between low birth weight in twins and the development of cerebral palsy. This meta-analysis included two studies that looked at about 1300 twin participants. A fixed-effect model was used and yielded $I^2 = 79%$ and OR (95% CI) = 4.88 (2.34-10.19). A random-effect model was tested to adjust the weight. However, the effect measure did not change. Thus a fixed-effect model was kept and is shown in Fig. 3.

We performed sensitivity analysis on the asthma outcome due to having more than two studies in our meta-analysis. Sensitivity analysis was impossible for the cerebral palsy outcome due to not eliminating a study, as there were only two studies eligible for the meta-analysis. However, we were able to perform

sensitivity analysis for the asthma outcome. Figure 4 shows the meta-analysis without Ortqvist 2009 included. This study provided 46.5% of the weight of the comparison; when eliminating the study, heterogeneity decreased from 77 to 54%, and new OR (95% CI) is 1.21 (1.09-1.35), previously was OR (95% CI) was 1.33 (1.24-1.44).

Other studies

Table 4 shows all these studies were longitudinal studies from European or Asian countries (e.g., Denmark, Japan). Various outcomes were studied; hence, meta-analysis was not possible—the majority adjusted for zygosity as well as other socio-demographic characteristics.

Discussion

Our review investigated published articles that explored the association between low birth weight and adverse health outcomes during adulthood. To our knowledge, there is no systematic review that examined this particular exposure and subsequent outcomes in twins.

Our review indirectly explored the concept of the fetal origins of adult disease (FOAD), initially popularized by Dr. David Barker in the twentieth century [32], and how it applies to twin studies. Dr. Barker initially observed that events during early development and intrauterine environmental exposures impact the risk of development of disease in adulthood. The first evidence of the validity of this hypothesis was a study published in 1989 that showed that low birth weight was associated with an increased risk of coronary artery disease [33]. This hypothesis has been applied to a number of studies to understand if there is a correlation between early developmental factors and adult health outcomes, particularly the development of chronic disease [32]. Twin studies, in particular, are valuable to understanding the FOAD hypothesis as they control for genetic and environmental

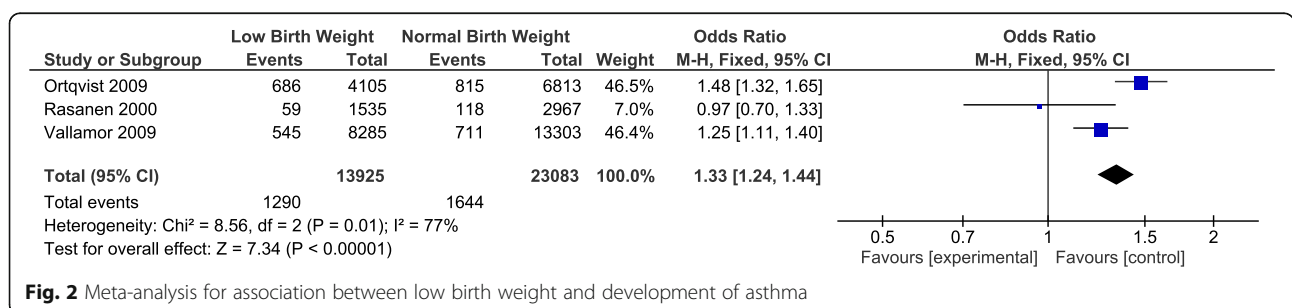


Fig. 2 Meta-analysis for association between low birth weight and development of asthma

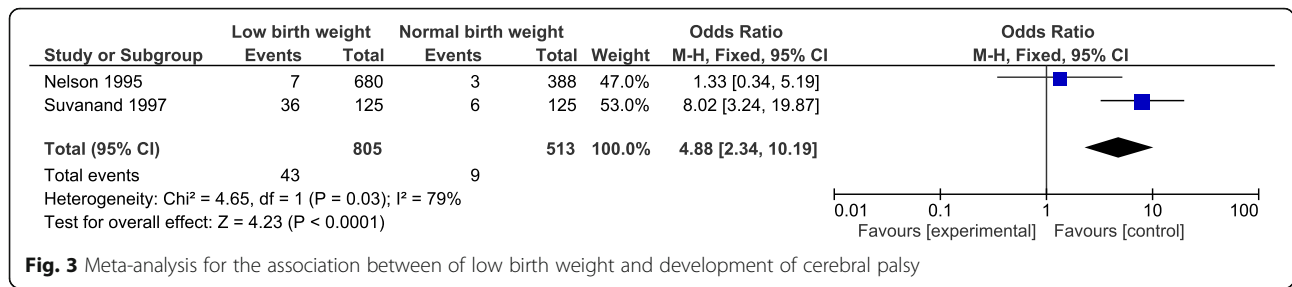


Fig. 3 Meta-analysis for the association between of low birth weight and development of cerebral palsy

confounding factors [14, 31], thus helping understand how epigenetic factors apply to health outcomes [12]. Twins also share an intra-uterine environment and can share a childhood environment if not separated at birth.

Asthma

Because our methodology did not yield many studies, we could only perform two meta-analyses for two outcomes. The first meta-analysis was performed on three twin studies to assess the development of asthma in normal vs. low birth weight twin participants. This meta-analysis (shown in Fig. 2) showed high heterogeneity (I² = 77%) among the three included studies. Thus, there was high variation among these three studies. It is already known that children born with low gestational age or low birth weight are at an increased risk of asthma [34, 35]. Furthermore, it is known that twins are more likely to be born at a lower gestational age and lower birth weight than their singleton counterparts [36]. Although this fact was found valid in several past studies; interestingly, our results show high heterogeneity across the three studies that were assessed in our review.

Asthma is a chronic disease that is typically developed during childhood [29]. The Copenhagen Studies on Asthma in Childhood concluded that 40% of lower lung function cases had asthma present at birth; 26 in other words, children who developed asthma later in life (in this study, at the age of 7) demonstrated lung function deficits in the neonatal period, suggesting support for the hypothesis that later chronic disease can be predicted by early developmental factors [31]. However, other studies have suggested the opposite; these studies essentially attribute asthma development more to

environmental exposures rather than to lung function at birth and subsequent lung functioning later on in life [37, 38].

Although this is not an exhaustive review on all studies investigating asthma development, these examples of conflicting results can explain that confounders are to be included to reduce the bias. After following the previously described methodology, we only had three studies in our review, which can also be attributed to high variation in results. Thus, to concretely conclude that there is a positive or negative association between low birth weight and the development of asthma, more studies need to be done to assess this relationship.

Cerebral palsy

Cerebral palsy is a lifelong physical disability associated with movement and posture disorders and impairments in communication, intellectual ability, and neurological functioning [32]. Worldwide, cerebral palsy is estimated to affect 17 million people, affecting about 1 in 500 neonates [39, 40]. The onset of cerebral palsy is during childhood, and there is currently no cure for the disorder [39, 41]. After following the methodology for our present review, we performed a meta-analysis on two articles that investigated the impact of low birth weight on cerebral palsy development in twin study participants.

Although studies have been conducted for several years regarding the etiology and pathways of cerebral palsy, there is still little known about the risk factors of developing the disorder [40]. However, it is known that multiple pregnancies increase the risk of cerebral palsy twofold in each twin, and twins conceived via in vitro fertilization each have a fourfold risk of

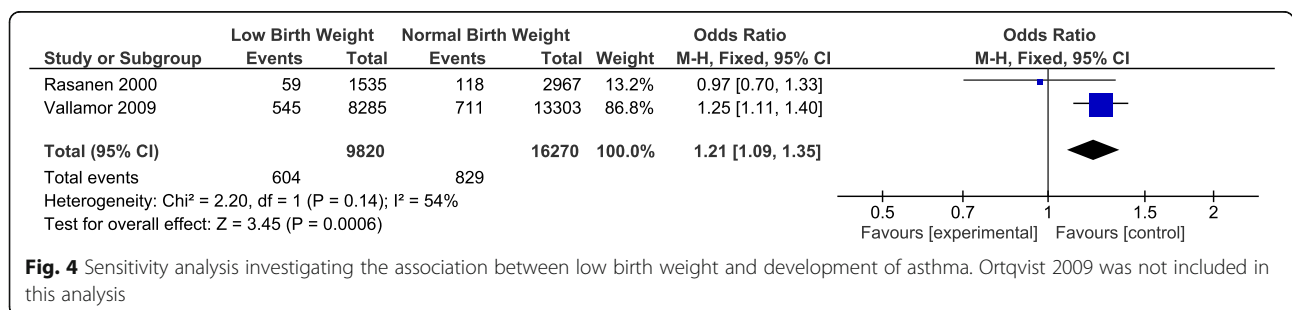


Fig. 4 Sensitivity analysis investigating the association between low birth weight and development of asthma. Orqvist 2009 was not included in this analysis

Table 4 Characteristics of studies that were not included in the meta-analysis

| Author, year | Study design | Confounders | Outcome | Result |
|--------------------------|--------------|---|--|---|
| Antoniades 2003 [17] | Cohort study | Height, age | Bone Mineral density (BMD) and bone mineral content (BMC) at the lumbar spine, Hip and forearm | No association was found with LBW |
| Bergvall 2007 [31] | Cohort study | Zygosity and socioeconomic factors, genetic factors, shared familial environment, BMI | Hypertension | Decreased birth weight was found to be associated with increased risk of hypertension |
| Cnattingius 2009 [19] | Cohort study | Mother's short status | Late fetal death rates | The risk of late fetal death is greatly increased in twin fetuses |
| De Zeeuw 2012 [20] | Cohort study | Mode of delivery, gestational age and zygosity | Educational achievement in primary school | Low birth weight were the most important risk factors for lower educational achievement of twins in primary school |
| Groen-Blokhuis 2011 [21] | Cohort study | Zygosity | Attention problems | Association of birth weight and attention problems represented a causal relationship |
| Hestbaek 2003 [22] | Cohort study | Birth factors and anthropometric measures in adolescence | Low back pain | The odds ratio for the lifetime prevalence of low back pain increases from 1.21 (0.94-1.56) for a birth weight of 2000-2500 g to 1.97 (1.35-2.88) for a birth weight of > 3500 g compared to the smallest weight group (< 2000 g) in males, whereas there is a small statistically insignificant, positive association for females. |
| Hultman 2007 [23] | Cohort study | Fetal growth restriction | Attention-deficit/hyperactivity disorder in childhood and early adolescence | Low birth weight was a risk factor for symptoms of attention-deficit/hyperactivity disorder and the associations did not diminish when we controlled for genetic influence |
| Williams 1996 [24] | Cohort study | Gestational age | Cerebral palsy | The relative risk was greatest in twins weighing more than 2499 g (4.5). However, after adjusting for reduced birthweight of twins it was the relative risk of twins weighing less than 1400 g that was significantly increased. |
| Yokoyama 2007 [29] | Cohort study | Gestational age | Motor development in early life | The mean age at achieving milestones was slower in twins with normal birth weight than singletons |

developing cerebral palsy, mainly because of the predisposition to cerebral damage that twins have when compared to singletons [42, 43]. In twins, zygosity and sex pairing have previously been studied in cerebral palsy development and survival [44]. This study showed that the prevalence of cerebral palsy was higher in the low birth weight and same-sex twin groups, suggesting evidence for the role of low birth weight in the disorder's etiology [44].

The high heterogeneity observed in the meta-analysis (shown in Fig. 3) for the association between low birth weight and development of cerebral palsy can be attributed to several factors, primarily due to the lack of studies that assessed the association between low birth weight and cerebral palsy. Past studies have indicated that there is a correlation between the two. Still, after going through our review's methodology, we could only perform a meta-analysis for two studies for this particular outcome. Thus, this likely affected the variation of results across the two studies. To have more valid and reliable results for this meta-analysis, more studies are necessary.

Clinical implications and limitations of study

The above results can help adopt preventative measures for the development of asthma. Early intervention to prevent asthma can be done in a more aggressive manner when twins are born low birth weight. Cerebral palsy, however, is largely not preventable; there are few underlying causes of cerebral palsy that have been confirmed through research [45–50]. The present review further suggests that studies on the etiology and possible prevention methods of cerebral palsy should be explored and researched.

The present study included several limitations. Firstly, the number of studies that were included in the final review is low. It can be argued that reliable conclusions cannot be made due to the low number of studies as well as their corresponding heterogeneity. Though we were able to make conclusions for two distinct adult health outcomes, differences in diagnosis were not considered, which is a potential confounder that was not adjusted for in this review. It is possible that diagnosis of cerebral palsy and asthma may vary across countries and clinics. Therefore, this may have affected results.

The quality of evidence in this review was 13.5 ± 1.14 and range of 12 to 15. The maximum total score of short versions of Dawn and Black's quality assessment criteria is 18. Hence, the quality of studies entered into this review might not be optimal.

Conclusion

In conclusion, the present systematic review screened almost 4000 articles to study the association between low birth weight and long-term health outcomes in both children and adults. The two outcomes assessed were asthma and cerebral palsy, and we were able to conclude that low birth weight twins were more likely to develop these outcomes when compared to their normal birth weight counterparts. It is important to note that there were a low number of studies that passed inclusion criteria; thus, we recommend that future twin studies collect data regarding low birth weight as a potential risk factor for developing longitudinal outcomes to draw more viable conclusions. According to one of the reviewers of this paper and I quote, "There is a need to connect maternal-child health outcomes with the noncommunicable disease better later in life. It is tempting to think about these categories of conditions as fully separate and unrelated, but as we establish relationships between health in early and later life, we will better understand how to prevent the exploding epidemic of noncommunicable disease in nearly every country in the world."

Appendix 1

Modified Downs and Black quality assessment tool

Study clarity:

- 1) Is the objective clearly described?
- 2) Are the main outcomes to be measured clearly described?
- 3) Is the exposure clearly described?
- 4) Are the principal confounders in each group of subjects to be compared clearly described?
- 5) Are the main findings of the study clearly described?

External validity:

- 6) Were the subjects asked to participate in the study representative of the entire population from which they were recruited?
- 7) Was there an overall participation rate of at least 70%?

Internal validity – bias:

- 8) If any of the results of the study were based on data dredging, was this made clear?

- 9) In case-control studies, is the time period between the exposure and outcome the same for cases and controls? In cohort studies, do the analyses adjust for different lengths of follow-up for subjects?
- 10) In case-control studies, was the exposure misclassification likely to bias the reported association toward the null? In cohort studies, did the exposure status change during the follow-up?
- 11) Were the statistical tests used to assess the main outcomes appropriate?
- 12) Were the main outcome measurements clearly described, and valid and reliable?

Internal validity – confounding (selection bias):

- 13) In case-control studies, were the cases and controls recruited from the same population? In cohort studies, were study subjects in different exposure groups recruited from the same population?
- 14) Were study subjects recruited over the same period of time?
- 15) Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?

Appendix 2

Search strategy

1. exp Pregnancy, Multiple/ or exp Twins/
2. exp Birth Weight/
3. ((birth weight or birthweight) adj3 discordan*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
4. ((birth weight or birthweight) adj3 differen*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
5. or/2-4
6. 1 and 5
7. exp Epidemiologic studies/
8. (cohortadj (study or studies)).tw.
9. Cohort analy\$.tw.
10. (Follow up adj (study or studies)).tw.
11. (observationaladj (study or studies)).tw.
12. Longitudinal.tw.
13. Retrospective.tw.
14. 7-15
15. 6 and 14
16. All bodily systems and similar terminology related to them were added. The search strategy is truncated for consideration related to space.

Abbreviations

MEDLINE: Medical Literature Analysis and Retrieval System Online; CINA HL: Cumulative Index to Nursing and Allied Health Literature; EBSCO: Elton B. Stephens Company; CDC: Centers for Disease Control and Prevention; RA: Rheumatoid arthritis; MOOSE: Meta-analysis of Observational Studies in Epidemiology; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; FOAD: Fetal origins of adult disease

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Authors' contributions

SJ conceived of the presented idea. SH performed the search, conducted the screening, and wrote the manuscript. SJ conducted the meta-analysis and interpreted the output, verified the analytical methods. SJ also supervised the findings of this work and contributed to the final manuscript. JI oversees the project, participated as the third reviewer, and contributed critical comments on the manuscript. He also supervised the work. CJ was the mentor for this project. The authors read and approved the final manuscript.

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Ethics approval and consent to participate

Not applicable

Consent for publication

All authors have seen and verified the content for publication.

Competing interests

The authors have no conflict of interest. Neither of the authors has any financial disclosure.

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