

# The associations of low birth weight with primary hypertension in later life: A systematic review and meta-analysis

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**Background:** The purpose of this study was to evaluate the role of LBW on EH in children and by studying the existing published literature. **Materials and Methods:** A comprehensive literature search for original studies was conducted in Clarivate Analytics Web of Science, PubMed, Scopus, and Embase until July 2019. The search used all of the main keywords and its synonyms include essential hypertension, primary hypertension, essential arterial hypertension, idiopathic hypertension, spontaneous hypertension; child, childhood, children, pediatric, pediatrics, infant, infancy, newborn, neonatal, adolescence, teenagers; and BW, newborn weight, neonatal weight, BW. **Results:** Twelve articles were eligible for the final evaluation. Due to the difference among studies in the report, studies were divided into two-part. The first part, articles were reported in the LBW and NBW groups (interested outcome were SBP and DBP), and the second part was composed as the EH and NR groups (interested outcome were LBW and NBW). In the first part, SMD for SBP was -1.09 with 95% CI (-1.91,-0.26), and was statistically significant ( $Z=2.58$ ,  $P=0.010$ ). As well, SMD for DBP was -0.68 with 95% CI (-1.32,-0.05) statistically significant ( $Z=2.10$ ,  $P=0.036$ ). In the second part, SMD for SBP was 0.77 with 95% CI (-0.85, 2.39), and was statistically significant ( $Z=0.93$ ,  $P=0.352$ ). Subgroup analysis was performed on the pre-term and full-term babies. SMD for SBP was -0.08 with 95% CI (-0.51, 0.35) in the pre-term, and the full-term was -2.07 with 95% CI (-3.47, -0.67). As well, SMD for DBP was -0.02 with 95% CI (-0.20, 0.17) in the preterm, and the term was -1.35 with 95% CI (-1.57, -1.13). **Conclusion:** Although findings of the correlation between BW and EHTN have conflicted. To our knowledge, this is the first report that attempts to a conclusion.

**Key words:** Full-term, low birth weight, primary hypertension, term

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## INTRODUCTION

Essential (primary) hypertension (EH) is the most common form of hypertension in adults with a prevalence of 20% to 30% worldwide. The prevalence of EH seems to be in a range of 4.7%–19.4% in children and adolescents. Based on the 2017 American Academy of Pediatric guidelines on hypertension,

the etiopathogenesis of EH is multifactorial in origin. Because EH remains a major modifiable contributor for premature death and disabling conditions in adults, it is diagnosed and treatment at earlier stages remains vital. There are other factors in childhood that can predict EH in adulthood.<sup>[1,2]</sup> Among these factors is low birth weight (LBW). The prevalence of LBW has been estimated between 15% and 20% of all births worldwide;

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in other words, it is more than 20 million births a year. Some epidemiologic studies have reported an increased risk of childhood-onset EH in LBW infants,<sup>[3,4]</sup> possibly due to alterations in their renal or vascular<sup>[5-7]</sup> systems related to reduced growth *in utero*, while others reported that high birth weight (BW), which may have long-term adverse metabolic effects, including insulin resistance<sup>[8-11]</sup> is also a risk factor for the development of EH in childhood.<sup>[5,9,10]</sup> The aim of this meta-analysis was to study the role of LBW on EH in children by analyzing the existing published literature.

## MATERIALS AND METHODS

### Search strategy and study selection

A comprehensive literature search for original studies was conducted in Clarivate Analytics-Web of Science, PubMed, Scopus, and Embase until July 2019. The search used all of the main keywords and its synonyms include essential hypertension, primary hypertension, essential arterial hypertension, idiopathic hypertension, spontaneous hypertension; child, childhood, children, pediatric, pediatrics, infant, infancy, newborn, neonatal, Adolescence, teenagers; and BW, newborn weight, neonatal weight, BW. Figure 1 presents the search results.

The inclusion criteria were original research articles, containing participants with a mean age  $\leq 18$  years, studies

that definitely determine that the subjects had EH, studies that reported data for meta-analysis, studies whose full text are available in English, and studies whose data set has been used in one study, and studies using the same data set from an earlier publication (salami slicing) were excluded.

### Data extraction and quality assessment

Independent reviewers (MRS and DRN) screened abstracts and titles for eligibility. When the reviewers felt that the abstract or title was potentially useful, full copies of the article were retrieved and considered for eligibility by both reviewers. If discrepancies occurred between reviewers, the reasons were identified and a final decision was made based on a third reviewer (MM) agreement. We evaluated the quality of the included observational studies with the Newcastle–Ottawa quality-assessment scale (NOS).<sup>[12]</sup> Studies that scored  $\geq 7$  were defined as of high quality.

### Statistical analysis

Standardized mean differences (SMDs) and related 95% confidence intervals (CIs) of different outcomes were retrieved in observational studies. Some studies that expressed outcomes as median and Interquartile range, the median and Interquartile range were transformed to the mean and standard deviation. We evaluated the degree of heterogeneity between studies using inconsistency index ( $I^2$ ). Values of  $I^2 = 25\%$ ,  $50\%$ , and  $75\%$  were considered to indicate low, moderate, and high heterogeneity, respectively.

If  $I^2 < 50\%$ , a fixed-effects model (DerSimonian–Laird method) was applied; otherwise, a random-effects model was used. With the purpose of exploring the sources of heterogeneity, all the enrolled studies were sequentially excluded to demonstrate the overall impact of individual study and performed with sub-group analysis of preterm or term status where  $I^2 > 50\%$ . Statistical meta-analysis was performed in Stata software version 14 (StataCorp. 2015, Stata Statistical Software: Release 14, College Station, TX) to generate forest plots of pooled SMDs with 95% CIs (Stata Corp LP, College Station, TX, USA). A two-sided  $P < 0.05$  was considered statistically significant. The potential publication bias was assessed using both Begg's and Egger's test ( $P < 0.05$  as statistically significant). To evaluate the influence of an individual study on the pooled estimate, we performed sensitivity analysis by excluding one study at a time. We also limited the analysis to high-quality studies (NOS score  $\geq 7$ ) to examine the robustness of our results.

## RESULTS

### Study characteristics

From 145 retrieved and limited study according to mentioned

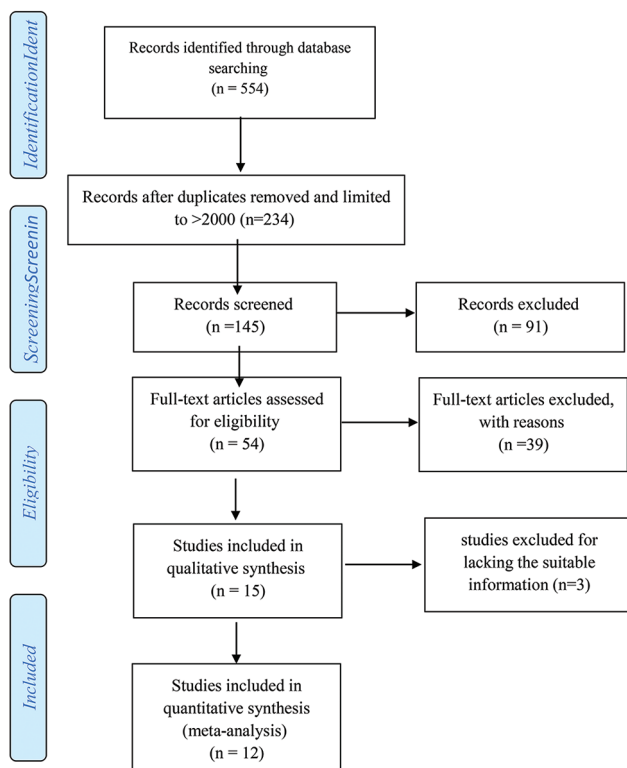


Figure 1: Flowchart of the study selection process

year (January 2000-July 2019) and article type (original articles), 54 records were found eligible regarding their title and abstract. In the next step, with studies including full-text article, 39 records were extracted. Finally, 12 articles were eligible for the final evaluation. The details of these studies are summarized in Table 1. Due to the difference among studies in the report, studies were divided into two parts. The first part, articles were reported in the low birth weight (LBW) and normal birth weight (NBW) groups (interested outcome were systolic blood pressure [SBP] and diastolic blood pressure [DBP]), and the second part was composed as the EH and NR groups (interested outcome were LBW and NBW). The studies were generally of high quality (NOS score  $\geq 7$ ).

### Change in systolic blood pressure and diastolic blood pressure

Eight studies (first part) with 1028 participants met the inclusion criteria to enter the first part of the meta-analysis. The minimum sample size was represented by the study of Boguszewski *et al.*<sup>[23]</sup> and the maximum sample size was represented by the study of Goloba *et al.*<sup>[24]</sup> All studies were published between 2001 and 2019.<sup>[17,23-28]</sup>

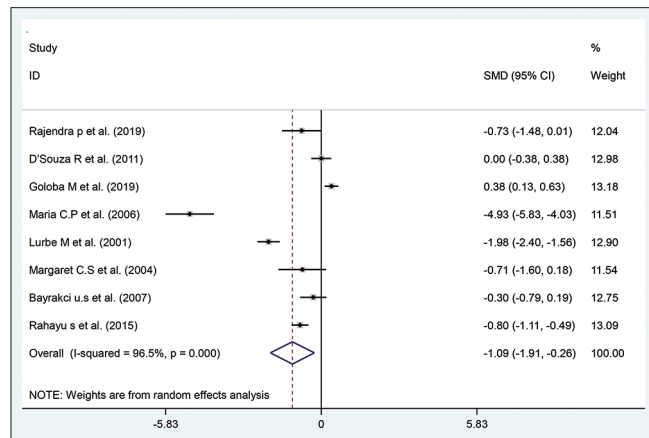


Figure 2: Forest plot of mean difference of systolic blood pressure (normal birth weight - low birth weight)

Figures 2 and 3 depict the forest plot for the SBP and DBP respectively, where the middle point in each line demonstrates the mean difference, and the length of each line indicates the 95% CI of each study. The diamonds represent the 95% CI for the pooled mean difference of the eight studies.

There was evidence of a high heterogeneity among the selected eight studies for SBP ( $I^2 = 96.5\%$ ,  $P = 0.001$ ). In addition, high heterogeneity was observed in DBP ( $I^2 = 94.3\%$ ,  $P = 0.001$ ). The pooled estimate of mean difference for SBP based on a random-effects model was  $-1.09$  (95% CI:  $-1.91, -0.26$ ), and was statistically significant ( $Z = 2.58$ ,  $P = 0.010$ ). As well, the pooled estimate of mean difference for DBP based on a random-effects model was  $-0.68$  (95% CI:  $-1.32, -0.05$ ), which was statistically significant ( $Z = 2.10$ ,  $P = 0.036$ ). Therefore, the BW was as an influencing factor for EH.

### Change in birth weight

In the second part (four studies), 480 participants met the inclusion criteria to enter this meta-analysis. Figure 4

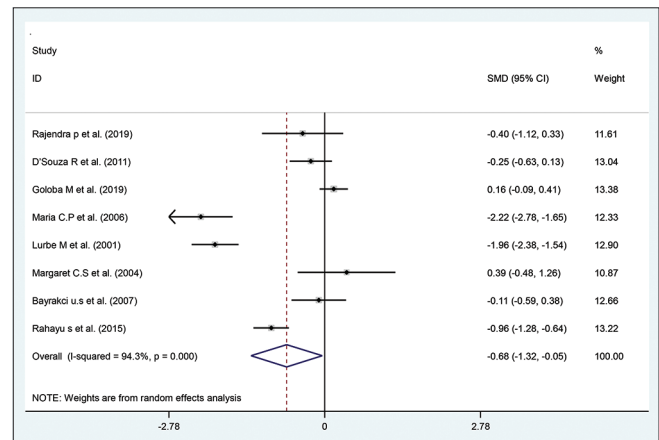


Figure 3: Forest plot of mean difference of diastolic blood pressure (normal birth weight - low birth weight)

Table 1: Details of the studies included in this systematic review and meta-analysis

First author	Year of publication	Outcome	Group	N1	N2	MD	SE (MD)
Raghuraman <i>et al.</i> <sup>[5]</sup>	2019	SBP and DBP	LBW/NBW	16	14	-0.73	0.38
D'Souza <i>et al.</i> <sup>[26]</sup>	2011	SBP and DBP	LBW/NBW	44	71	0	0.19
Goloba <i>et al.</i> <sup>[24]</sup>	2019	SBP and DBP	LBW/NBW	77	284	0.38	0.13
Franco <i>et al.</i> <sup>[17]</sup>	2006	SBP and DBP	LBW/NBW	42	36	-4.93	0.46
Lurbe <i>et al.</i> <sup>[25]</sup>	2001	SBP and DBP	LBW/NBW	35	150	-1.98	0.21
Boguszewski <i>et al.</i> <sup>[23]</sup>	2004	SBP and DBP	LBW/NBW	12	9	-0.71	0.46
Bayrakci <i>et al.</i> <sup>[27]</sup>	2007	SBP and DBP	LBW/NBW	41	27	-0.31	0.25
Rahayu <i>et al.</i> <sup>[28]</sup>	2015	SBP and DBP	LBW/NBW	85	85	-0.80	0.16
Mario <i>et al.</i>	2004	BW	NR/EH	92	103	-0.45	0.15
Daniel <i>et al.</i> <sup>[40]</sup>	2004	BW	NR/EH	45	75	4.00	0.32
Cruickshaw <i>et al.</i>	1935	BW	NR/EH	48	58	-0.56	0.20
Ankwlb <i>et al.</i> <sup>[41]</sup>	2015	BW	NR/EH	36	23	0.16	0.27

SBP=Systolic blood pressure; DBP=Diastolic blood pressure; BW=Birth weight; LBW=Low birth weight; NBW=Normal birth weight; NR=Normal; EH=Essential hypertension; N1=Sample size in LBW or NR; N2=Sample size in NBW or EH; MD=Mean difference; SE=Standard error

depicts the forest plot for the mean difference in BW. There was evidence of a high heterogeneity among studies ( $I^2 = 98.3\%$ ,  $P = 0.001$ ). In addition, a high heterogeneity was observed in DBP ( $I^2 = 94.3\%$ ,  $P = 0.0001$ ). The pooled estimate of mean difference for SBP based on a random-effects model was 0.77 (95% CI: -0.85, 2.39), and was not statistically significant ( $Z = 0.93$ ,  $P = 0.352$ ).

### Subgroup analysis

As the eligible studies have different features, which may contribute to a certain degree of heterogeneity, subgroup analysis was executed, and the results are depicted in Figures 5 and 6. This subgroup analysis was performed on the pre- and full-term babies. The pooled estimate of mean difference for SBP based on a random-effects model was -0.08 (95% CI: -0.51, 0.35) in preterm babies and that in the full-term babies was -2.07 (95% CI: -3.47, -0.67). As well, the pooled estimate of mean difference for DBP based on a random-effects model was -0.02 (95% CI: -0.20, 0.17) in preterm babies and that in the full-term babies was -1.35 (95% CI: -1.57, -1.13). Therefore, the results showed that there is a difference between full- and pre-term groups.

### Publication bias

No evidence of publication bias was found for the SBP (Begg's test:  $P = 0.138$ , Egger's test:  $P = 0.108$ ), and there was no publication bias for the DBP (Begg's test:  $P = 1.00$ , Egger's test:  $P = 0.511$ ). However, publication bias was observed for BW (Begg's test:  $P = 0.042$ , Egger's test:  $P = 0.214$ ).

## DISCUSSION

Birth weight is a major contributor to the development of hypertension, whereby there exists a consistently positive relationship between body weight and blood pressure (BP). Childhood hypertension has been considered a strong predictive factor for hypertension in adulthood. The leading causes of abnormal BP in children can be poor weight management and childhood metabolic syndrome.<sup>[29]</sup>

Barker *et al.* have demonstrated that fetal LBW can lead to raised BP in later life.<sup>[30,31]</sup> EH is a multifactorial disorder that is thought to result from both genetic and environmental components, and is a major risk factor for the development of cardiovascular disease. Several studies have demonstrated that LBW is related to increased BP throughout various stages of life.<sup>[6-9]</sup> In addition, some systematic reviews and meta-analysis have reported that there exists an inverse relationship between BW and BP.<sup>[10,11]</sup>

Our results show decreased change in mean differences (NBW - LBW) of SBP and DBP. In addition, an increased

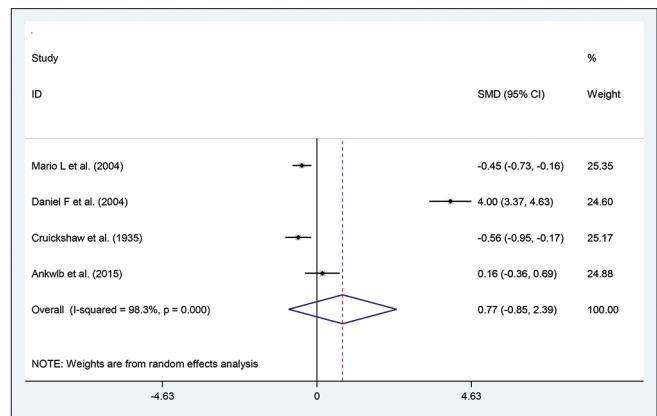


Figure 4: Forest plot of mean difference of birth weight (normal - essential hypertension)

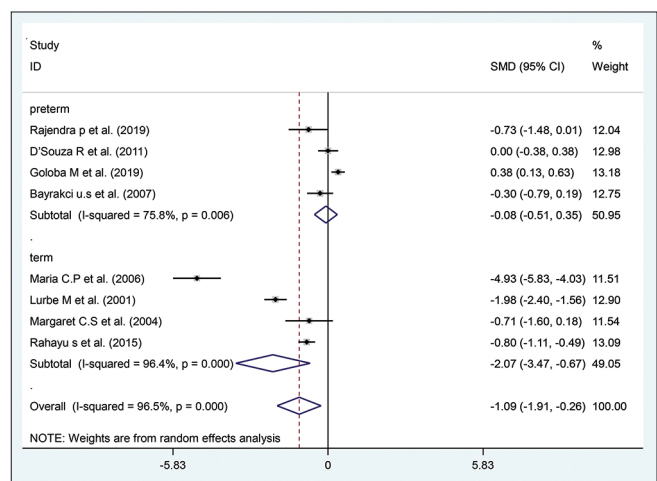


Figure 5: Forest plot for the subgroup analysis according to systolic blood pressure

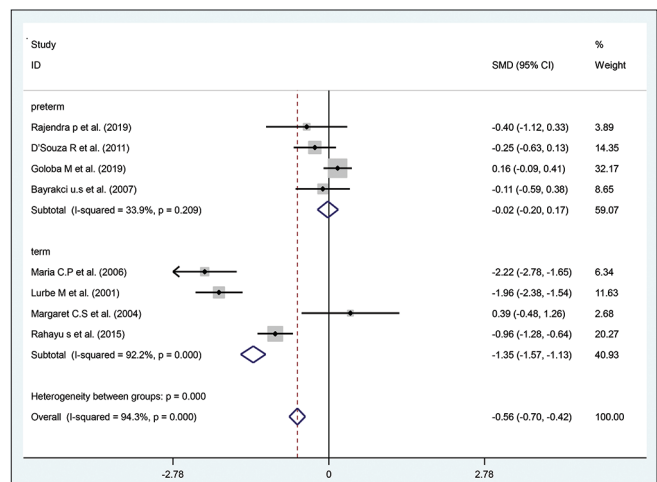


Figure 6: Forest plot for the subgroup analysis according to diastolic blood pressure

change was found in the mean differences (NR - EH) of BW. The subgroup analysis was executed on preterm and term babies according to DBP and SBP. The result of this analysis represented a decreased change in the mean



differences (NBW minus LBW) of SBP and DBP on preterm and no evidence differences on term babies.

BW and gestational age (GA) are considered risk factors of cardiovascular disease especially EH,<sup>[10,25]</sup> as well as diabetes and obesity. However, several studies on BW and GA showed contradictory findings.<sup>[8-11,17,25,28-31]</sup> Some showed a positive association of LGA at birth with EH and ultimately metabolic syndrome in future,<sup>[12,32-34]</sup> while others did not show this association.<sup>[10,25]</sup> Some of these studies believe that microvasculature anomaly and impaired tissue perfusion are the key factors in the pathogenesis of EH.<sup>[35]</sup> Capillary rarefaction is a hallmark of EH, and evidence suggests that rarefaction precedes the onset of rise in BP.<sup>[36]</sup> Today, there are definite findings which report that LBW is accompanied by anatomical and functional anomalies in microvasculature and also EH. D'Souza *et al.* showed that not only there isn't capillary rarefaction in LBW infant at birth but also in those capillary density is higher than NBW infant.<sup>[26]</sup> In addition, they showed this capillary rarefaction that seen in the patient with EH that is programmed in intra uterine period dose not start at that time necessarily. In fact, there is a process as early-accelerated capillary remodeling that cause fast change in high capillary density at birth to capillary rarefaction in the next month and to intensify by oxygen therapy in the early of neonatal period.<sup>[5,24,26]</sup> Several studies believe that the vascular endothelial dysfunction is a key role in the causation of EH in LBW.<sup>[13]</sup> Furthermore, some studies believe that the serum concentration of uric acid could be an important factor in the pathogenesis of EH.<sup>[14,15]</sup> Franco *et al.* showed that increase in the level of uric acid (UA) is associated with EH and also the level of UA is in LBW.<sup>[17]</sup> This finding is consistent with that of other studies.<sup>[16,18-20]</sup> They showed a continuous linear correlation between serum concentration of UA and SBP (increase of 1 mg/dL in UA causes a rise of 3 mmHg in SBP). Maria *et al.* also showed that flow-mediated dilation in capillary as a marker of endothelial function is decreased in LBW infants compared to that of NBW infants. Another mechanism that may cause EH in LBW is sympathetic neuronal activity. Margaret *et al.* showed that ton of sympathetic nerve system in small for gestational age infant is higher than appropriate for gestational age infant. Moreover, they reported that this increase in neuronal activity may be due to central programming and could be important for the later development of EH and cardiovascular disease.<sup>[23]</sup> Some authors believe that LBW (IUGR) with effect on a number of renal glomeruli may cause development of EH.<sup>[21,22,37-39]</sup> As mentioned above, findings on the correlation of BW and EH are contradicting. To our knowledge, this is the first report that has attempted to evaluate previous findings.

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Nil.

#### Conflicts of interest

There are no conflicts of interest.

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