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## Systematic Review and Meta-Analysis of Preterm Birth and Later Systolic Blood Pressure

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# Systematic Review and Meta-Analysis of Preterm Birth and Later Systolic Blood Pressure

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See Editorial Commentary, pp 189–190

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**Abstract**—Lower birth weight because of fetal growth restriction is associated with higher blood pressure later in life, but the extent to which preterm birth (<37 completed weeks' gestation) or very low birth weight (<1500 g) predicts higher blood pressure is less clear. We performed a systematic review of 27 observational studies that compared the resting or ambulatory systolic blood pressure or diagnosis of hypertension among children, adolescents, and adults born preterm or very low birth weight with those born at term. We performed a meta-analysis with the subset of 10 studies that reported the resting systolic blood pressure difference in millimeters of mercury with 95% CIs or SEs. We assessed methodologic quality with a modified Newcastle-Ottawa Scale. The 10 studies were composed of 1342 preterm or very low birth weight and 1738 term participants from 8 countries. The mean gestational age at birth of the preterm participants was 30.2 weeks (range: 28.8–34.1 weeks), birth weight was 1280 g (range: 1098–1958 g), and age at systolic blood pressure measurement was 17.8 years (range: 6.3–22.4 years). Former preterm or very low birth weight infants had higher systolic blood pressure than term infants (pooled estimate: 2.5 mm Hg [95% CI: 1.7–3.3 mm Hg]). For the 5 highest quality studies, the systolic blood pressure difference was slightly greater, at 3.8 mm Hg (95% CI: 2.6–5.0 mm Hg). We conclude that infants who are born preterm or very low birth weight have modestly higher systolic blood pressure later in life and may be at increased risk for developing hypertension and its sequelae. (*Hypertension*. 2012;59:226-234.) • **Online Data Supplement**

**Key Words:** blood pressure ■ meta-analysis ■ systematic review ■ preterm birth ■ very low birth weight

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More than 12% of infants in the United States are born preterm (at <37 completed weeks' gestation),<sup>1</sup> and the majority now survives to adulthood.<sup>2</sup> Although researchers have focused considerable attention on the adverse neurodevelopmental consequences of preterm birth, particularly for those infants born very low birth weight (VLBW; <1500 g),<sup>3,4</sup> relatively little is known about other aspects of later childhood and adult health that may also be associated with preterm and VLBW birth.

Lower birth weight is associated with higher blood pressure (BP) later in life.<sup>5</sup> Other authors have implicated prenatal programming of BP by impaired fetal growth and its determinants, such as poor maternal nutrition,<sup>6</sup> hypertensive disorders,<sup>7,8</sup> and smoking,<sup>9</sup> during pregnancy. Few, however, have examined the role of shortened gestation. Evidence is now emerging that lower birth weight resulting from preterm birth may also be associated with higher BP later in life,<sup>10</sup> but most studies have been relatively small and/or included participants born at a single center.

It is important to gain a clear understanding of the extent to which preterm birth predicts higher BP later in life, to inform

medical and preventive care for survivors of preterm birth as they reach adulthood, and to increase scientific understanding of mechanisms underlying the fetal and postnatal programming of BP. The aim of this study was to perform a systematic review of the literature and meta-analysis to test the hypothesis that children, adolescents, and adults who were born preterm or VLBW have higher systolic BP (SBP) and hypertension prevalence, as compared with those born at term.

## Methods

### Search Strategy

We followed the Meta-Analysis of Observational Studies in Epidemiology<sup>11</sup> guidelines regarding the design, implementation, analysis, and reporting of this study. We searched for all of the observational studies that compared the resting and/or ambulatory BP or the hypertension prevalence of former preterm or VLBW children (>2 years old), adolescents, or adults with those born at term, published from January 1946 through June 2011. We included studies of preterm and VLBW children because virtually all of the VLBW children are preterm. We included the following databases in our

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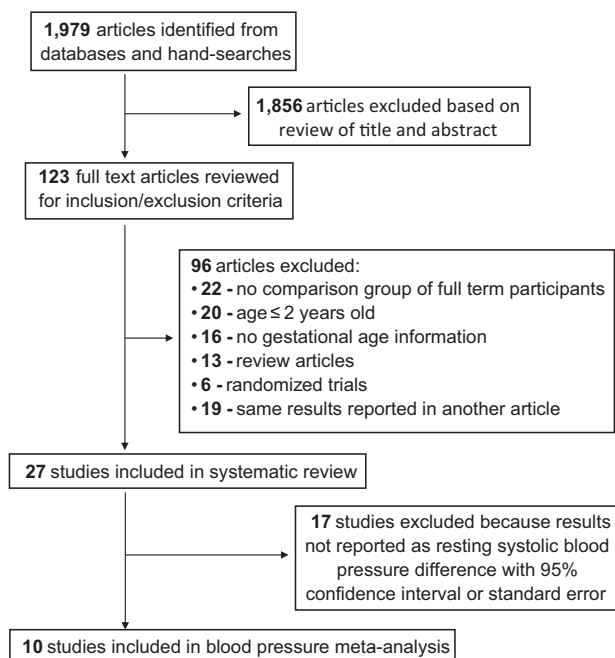
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**Figure 1.** Screening and selection of studies included in the systematic review and meta-analysis.

search: PubMed, Excerpta Medica Database, ISI Web of Knowledge, and Cumulative Index to Nursing and Allied Health Literature and used the following medical subject headings and key words: “preterm birth” OR “prematurity” OR “very low birth weight” OR “low birth weight” AND “blood pressure” OR “hypertension” OR “cardiovascular risk factors” OR “cardiovascular disease.” To identify additional pertinent articles, we used the “related citations” function in PubMed and hand-searched bibliographies of all of the articles that met our inclusion criteria, as well as review articles.

### Selection of Articles

Of the 1979 identified articles, we excluded 1856 based on a review of the title and abstract conducted by 1 author (Figure 1). Two authors reviewed the full text of the remaining 123 articles to determine inclusion or exclusion. Any differences were resolved through discussion, resulting in agreement for all of the included and excluded articles. We excluded 96 articles for the following reasons: (1) no comparison group of term infants (22 articles); (2) age at measurement  $\leq 2$  years old (20 articles); (3) lack of data about birth weight or gestational age (16 articles); (4) review articles (13 articles); and (5) randomized trials (6 articles). We excluded 19 articles that reported results also reported in another article. If an article reported duplicate results from the same cohort or a subset of the cohort, we included the article with the largest sample size; in 1 case, identical results were published separately in English<sup>12</sup> and French,<sup>13</sup> so we included the article published in English. For studies that reported outcomes at different ages in separate articles, we included the article reporting results at the oldest age. Twenty-seven studies met inclusion criteria for the systematic review. For 1 article<sup>13,14</sup> published in Hungarian, a neonatologist who is a fluent speaker assisted with reviewing the article for inclusion criteria and extracting the data.

Of the 27 studies included in the systematic review, for the meta-analysis we included the 10 studies that reported the resting SBP difference in millimeters of mercury with 95% CI or SEs. We could not perform a meta-analysis for hypertension prevalence or ambulatory BP because of the small number of studies, heterogeneity of methodology, and lack of reported 95% CIs and SEs.

### Data Extraction

From the 27 included articles, 2 authors independently extracted the following information: (1) birth year(s); (2) location of cohort; (3)

selection criteria for preterm or VLBW group; (4) sample size; (5) proportions of men and women; (6) prevalence of small for gestational age (SGA); (7) mean birth weight, gestational age, and age at BP measurement; (8) method of BP measurement and number of measurements; (9) hypertension definition; (10) SBP difference in millimeters of mercury between preterm and term participants for resting or ambulatory BP; (11) relative risk of hypertension; (12) 95% CI or SE around the effect estimates; and (13) *P* value. We focused on SBP because it is at least as good a predictor of later cardiovascular risk as diastolic BP and is measured with more accuracy in youth.<sup>15</sup> The 2 authors compared extracted data and resolved any differences by discussion.

Because some articles reported  $>1$  multivariable model and different studies adjusted for different sets of covariates, from each article we recorded estimates from the models adjusted for the fewest and most covariates. We categorized each model as having the following: (1) no adjustment apart from age and sex; (2) adjustment for any measure of socioeconomic status; (3) adjustment for any measure of fetal growth; and (4) adjustment for participant size at the time of BP measurement. If studies reported models adjusted separately for  $>1$  measure of participant size, we used the height-adjusted estimate; if not reported, we used the body mass index-adjusted estimate, and, if that was not reported, we used the weight-adjusted estimate.

For studies that did not report an unadjusted (or only age- and sex-adjusted) estimate of SBP difference, we calculated the unadjusted SBP difference as the mean SBP of the preterm or VLBW participants minus the mean of the term participants. One study<sup>16</sup> reported unadjusted SBP differences stratified by sex, so we calculated a weighted average SBP difference for the men and women combined. Similarly, for studies that did not report the relative risk or odds ratio of hypertension, we calculated the unadjusted relative risk as the percentage of preterm or VLBW participants with hypertension divided by the percentage of term participants with hypertension. For studies that reported the SE but not the 95% CI, we calculated the 95% CI as the estimated SBP difference  $\pm 1.96$  times the SE. For studies that separately analyzed  $>1$  term group (eg, SGA and appropriate for gestational age), we used the appropriate for gestational age term group for comparison. For studies that only reported results separately for SGA and appropriate for gestational age preterm or VLBW participants, we extracted both estimates. We did not attempt to contact authors regarding missing data.

### Assessment of Methodologic Quality

We used a modified version of the Newcastle-Ottawa Scale<sup>17</sup> to assess the methodologic quality of each study (Figure 2). We awarded studies a maximum of 7 stars, summed from up to 3 stars for selection and 2 each for comparability and outcome assessment, with more stars indicating better quality. Some studies reported  $>1$  outcome (resting SBP, hypertension diagnosis, and ambulatory BP), so we rated the quality of those studies separately for each outcome. Two authors independently assessed the quality of each study. Initial agreement between the 2 authors on the quality score was 91%. All of the differences were resolved by discussion.

### Statistical Analysis

For the meta-analysis of resting SBP difference, to calculate effect estimates, we used random-effects models,<sup>18</sup> which allow for sampling variability within and between studies. To assess the proportion of total variability in the effect estimate attributable to between-study heterogeneity, we calculated the  $I^2$  statistic and associated *P* value. We also created funnel plots and tested for asymmetry using the method of Egger et al.<sup>19</sup> Funnel plot asymmetry may reflect selective publication of positive studies or lower methodologic quality of individual studies.<sup>20</sup> When we identified significant heterogeneity ( $P < 0.05$ ) or funnel plot asymmetry, we performed an influence analysis in which we omitted the results of one study at a time and recalculated the pooled effect estimate.

For the primary meta-analysis, we used the least and most fully covariate-adjusted estimates from each study with 95% CIs. We also analyzed separately the estimates that were adjusted for any measure

| Criteria  | Rating   | Example                             | Stars |
|---|--|-------------------------------------|-------|
| <b>Selection</b> ★★★                                |  |                                     |       |
| 1. Representativeness of the preterm/VLBW cohort    | • Truly representative of preterm/VLBW infants in the contemporary western world   | Regional NICU or multi-center study | ★     |
|   | • Somewhat representative of preterm/VLBW infants in the contemporary western world  | Single center                       | ★     |
|   | • Selected group of patients<br>• Not reported   | Specialty clinic                    |       |
| 2. Selection of full term cohort                    | • Drawn from the same community as the preterm cohort  | Hospital or school based selection  | ★     |
|   | • Drawn from a different community   | Medical students                    |       |
|   | • Not reported   |                                     |       |
| 3. Ascertainment of gestational age                 | • Hospital medical record  |                                     | ★     |
|   | • Public record  | Birth certificate                   | ★     |
|   | • Not reported   |                                     |       |
| <b>Comparability</b> ★★                             |  |                                     |       |
| 1. Comparability on the basis of design or analysis | • Study reports adjustment for later size  | Weight, height, or BMI              | ★     |
|   | • Study reports adjustment for fetal growth and/or SES   |                                     | ★     |
| <b>Assessment of blood pressure</b> ★★              |  |                                     |       |
| 1. Blood pressure measurement                       | • Direct measurement, assessor blinded to gestational age  |                                     | ★     |
|   | • Direct measurement and no report of blinding   |                                     | ★     |
|   | • Hypertension diagnosis by medical or public health record  |                                     | ★     |
|   | • Not reported   |                                     |       |
| 2. Adequacy of follow-up                            | • Complete follow-up, all subjects accounted for   |                                     | ★     |
|   | • Subjects lost to follow-up unlikely to introduce bias - number lost ≤ 20%, or description provided of those lost suggesting no different from those followed |                                     | ★     |
|   | • Follow-up rate ≤ 80% and no description of those lost or description provided of those lost indicates substantial differences                                |                                     |       |
|   | • Not reported   |                                     |       |

**Figure 2.** Assessment of methodologic quality for observational studies, adapted from the Newcastle-Ottawa Scale.<sup>17</sup> Stars were awarded if the study met the listed criteria. The maximum possible score was 7. VLBW is very low birth weight (<1500 g).

of socioeconomic status and later size. We could not perform a separate meta-analysis with estimates adjusted for fetal growth because there were only 2 studies with this information. We performed one set of secondary analyses restricted to studies of VLBW or very preterm ( $\leq 32$  weeks' gestation) participants, because that group is at highest risk for long-term sequelae of preterm birth. We also stratified by year of birth (<1990 versus  $\geq 1990$ ) and performed a separate meta-analysis for the 5 studies with a quality score of 7 (highest quality). We used Stata 10.0 (Stata Corp LP, College Station, TX) for all of the analyses.

## Results

### Description of Studies Included in the Systematic Review

We identified 27 observational studies, published from 1998 to 2011, describing 25 unique cohorts from 13 countries, although 2 studies<sup>21,22</sup> sampled from a common database and likely had some overlap of participants. Twenty three of the cohorts were from the United States, Europe, Australia, or New Zealand. The other 2 were from China<sup>23,24</sup> and Brazil.<sup>23,24</sup> Of the 24 articles, 22 reported resting SBP (Table 1 and Table S1, available in the online Data Supplement at <http://hyper.ahajournals.org>), 8 reported hypertension diagnosis (Table S2), and 5 reported ambulatory BP (Table S3).

### Resting SBP

Of the 22 studies that reported resting SBP, for the meta-analysis we included the 10 studies<sup>16,23,25–32</sup> that reported estimates with CIs or SEs, composed of 1342 preterm or VLBW

and 1738 term participants from 8 countries (Table 1). Of studies reporting these data, the mean gestational age of the preterm participants was 30.2 weeks (range: 28.8–34.1 weeks), and birth weight was 1280 g (range: 1098–1958 g). Studies used different definitions of SGA status, for example, birth weight for gestational age SD score less than  $-2^8$  or birth weight <10th percentile for gestational age.<sup>25</sup> The SGA proportion ranged from 15% to 51%. The mean age at BP measurement was 17.8 years (range: 6.3–22.4 years). Details of the 12 studies excluded from the meta-analysis are listed in Table S1.

Seven of the 10 studies reported the unadjusted or least-adjusted estimates. The pooled unadjusted estimate of SBP difference was 2.2 mm Hg (95% CI: 1.1–3.3 mm Hg) higher for preterm or VLBW versus term participants. Using the most-adjusted estimates from all 10 of the studies, the pooled estimate was similar, at 2.5 mm Hg (95% CI: 1.7–3.3 mm Hg; Figure 3A). Restricting to the 5 higher quality studies, the most-adjusted pooled SBP difference was 3.8 mm Hg (95% CI: 2.6–5.0 mm Hg), somewhat higher than for the analysis including all 10 of the studies (Figure 3B). Restricting to the 8 studies of former VLBW or very preterm infants, the pooled adjusted SBP difference was 2.5 mm Hg (95% CI: 1.6–3.4 mm Hg; Figure 3C). For the 7 studies of participants born before 1990, the pooled adjusted SBP difference was 4.2 mm Hg (95% CI: 3.2–5.3 mm Hg), higher than for the 3 studies of participants born in 1990 or later (0.0 mm Hg [95% CI:  $-1.2$ –1.3 mm Hg]).

**Table 1. Studies Included in Meta-Analysis of Preterm Birth and/or Very Low Birth Weight and Later Resting SBP**

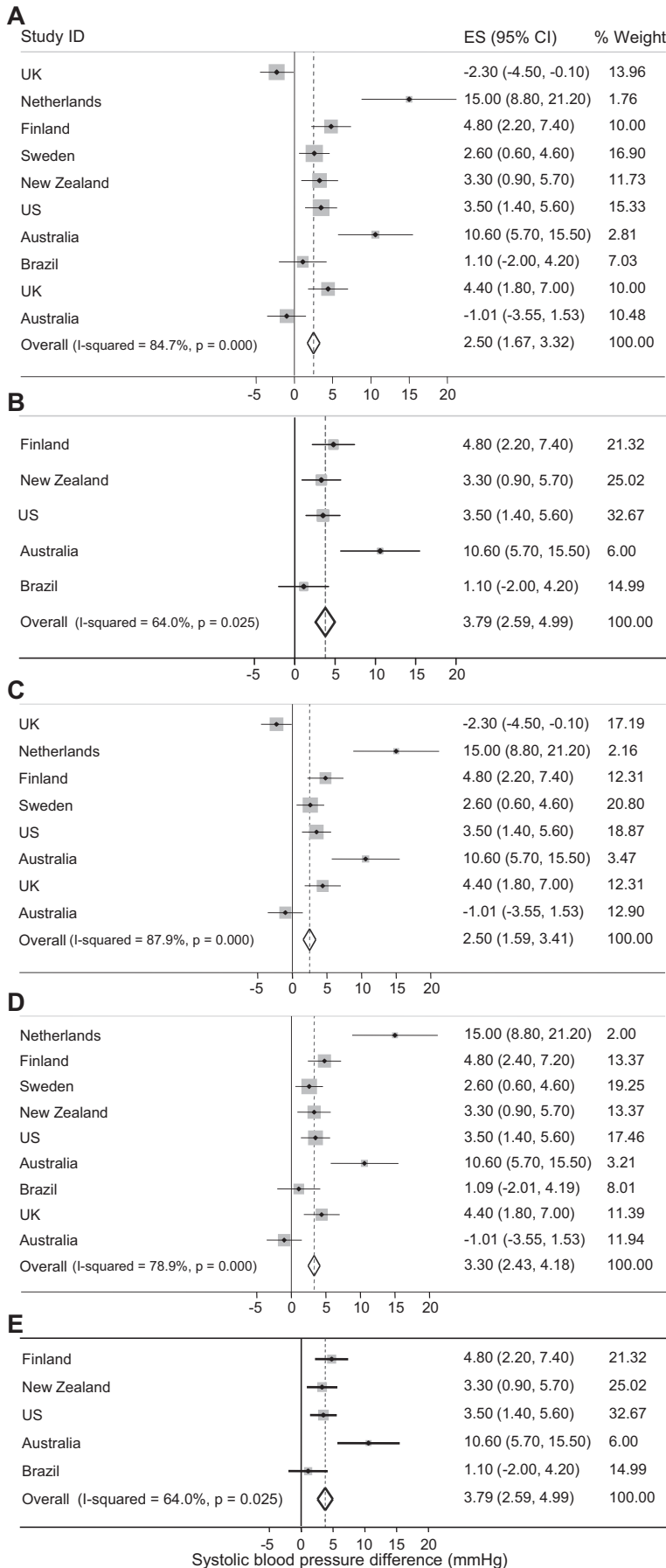
| First Author,<br>Year Published,<br>Country, Year Born                         | Selection of<br>Preterm/VLBW | Sample Size,<br>Preterm/VLBW<br>Term, % SGA<br>(of Preterm/VLBW) | Age, y,<br>Mean±SD,<br>Range | % Follow-Up,<br>Preterm/VLBW,<br>Term | BP Method<br>(No. of<br>Measurements) | Multivariable<br>Adjustment |     |      | Least Adjusted SBP<br>Difference, mm Hg<br>(Preterm/VLBW–Term)<br>95% CI, <i>P</i>  | Most Adjusted SBP<br>Difference, mm Hg<br>(Preterm/VLBW–Term)<br>95% CI, <i>P</i>  |
|--|------------------------------|--|------------------------------|---------------------------------------|---------------------------------------|-----------------------------|-----|------|---|--|
|  |                              |  |                              |                                       |                                       | SES                         | FG  | Size |   |  |
| Chan <sup>26</sup><br>2010<br>Australia<br>1992–1995                           | <1500 g or ≤ 32 wk           | 39<br>32<br>36%  | NR<br>NR<br>(median: 13.9)   | NR<br>NR                              | Manual<br>(2×)                        | No                          | Yes | Yes  | AGA preterm vs term:<br>–2 mm Hg*<br>NR<br>NR<br>SGA preterm vs term:<br>4 mm Hg*<br>NR<br>NR   | –1.0 mm Hg†<br>95% CI–3.6–1.5<br><i>P</i> =0.43  |
| Bracewell et al <sup>27</sup><br>2008<br>United Kingdom<br>and Ireland<br>1995 | <26 wk                       | 214<br>158<br>NR   | 6.3±NR<br>5.2–7.3            | 78%<br>NR                             | Manual<br>(NR)                        | No                          | No  | No   | –2.3 mm Hg†<br>95% CI–4.6 to–0.1<br><i>P</i> =0.04  | –2.3 mm Hg†<br>95% CI–4.6 to–0.1<br><i>P</i> =0.04   |
| Rotteveel et al <sup>28</sup><br>2008<br>Netherlands<br>1983                   | <32 wk and/or<br><1500 g     | 57<br>30<br>49%  | 20.7±NR<br>NR                | 65%<br>NR                             | Automated<br>(3×)                     | No                          | No  | Yes  | AGA preterm vs term:<br>14.0 mm Hg†<br>95% CI: 7.5–20.5<br><i>P</i> <0.0001<br>SGA preterm vs term:<br>8.8 mm Hg†<br>95% CI: 2.2–15.4<br><i>P</i> =0.01 | AGA preterm vs term:<br>15.0 mm Hg†<br>95% CI: 8.8–21.2<br><i>P</i> <0.0001<br>SGA preterm vs term:<br>12.8 mm Hg†<br>95% CI: 6.2–19.4<br><i>P</i> <0.0001 |
| Hovi et al <sup>29</sup><br>2007<br>Finland<br>1978–1985                       | <1500 g                      | 166<br>172<br>33%  | 22.4±NR<br>18.5–27.1         | 65%<br>55%                            | Automated<br>(2×)                     | Yes                         | No  | Yes  | 4.0 mm Hg†<br>95% CI: 1.5–6.5<br><i>P</i> =0.002  | 4.8 mm Hg†<br>95% CI: 2.1–7.4<br><i>P</i> <0.001   |
| Bonamy et al <sup>30</sup><br>2007<br>Sweden<br>1992–1998                      | ≤30 wk                       | 39<br>21<br>51%  | 9.1±1.7<br>7–12              | 63% (preterm+term)                    | Automated<br>(6×)                     | No                          | No  | Yes  | –7.0 mm Hg*<br>NR<br><i>P</i> =0.33   | 2.6 mm Hg†<br>95% CI: 0.6–4.6<br><i>P</i> =0.01  |
| Dalziel et al <sup>25</sup><br>2007<br>New Zealand<br>1969–1974                | <37 wk                       | 311<br>147<br>15%  | 30±NR<br>NR                  | 51%<br>44%                            | Automated<br>(2×)                     | No                          | Yes | Yes  | 3.5 mm Hg†<br>95% CI: 1.0–6.0<br><i>P</i> =0.009  | 3.3 mm Hg†<br>95% CI: 0.9–5.7<br><i>P</i> =0.004   |
| Hack et al <sup>16</sup><br>2005<br>United States<br>1977–1982                 | <1500 g                      | 195<br>208<br>20%  | 20.2±NR<br>NR                | 68%<br>57%                            | Manual<br>(2×)                        | Yes                         | No  | Yes  | 2.3 mm Hg*<br>NR<br>NR  | 3.5 mm Hg†<br>95% CI: 1.4–5.6<br><i>P</i> =0.001   |
| Doyle et al <sup>31</sup><br>2003<br>Australia<br>1977–1982                    | <1500 g and <37 wk           | 156<br>38<br>NR  | 18.6±NR<br>NR                | 74%<br>63%                            | Manual<br>(3×)                        | No                          | No  | Yes  | 8.6 mm Hg†<br>95% CI: 3.4–13.9<br>NR  | 10.6 mm Hg†<br>95% CI: 5.8–15.5<br>NR  |
| Barros and Victora <sup>23</sup><br>1999<br>Brazil<br>1982                     | <37 wk                       | 37<br>811<br>NR  | NR±NR<br>14–15               | 62%<br>76%                            | Manual<br>(2×)                        | Yes                         | No  | Yes  | 0.2 mm Hg†<br>95% CI: –3.2–3.5<br><i>P</i> =0.9   | 1.1 mm Hg†<br>95% CI: –2.0–4.2<br><i>P</i> =0.5  |
| Pharoah et al <sup>32</sup><br>1998<br>United Kingdom<br>1980–1981             | <1500 g                      | 128<br>128<br>NR   | 15±NR<br>NR                  | 74%<br>NR                             | Automated<br>(3×)                     | No                          | No  | Yes  | 3.2 mm Hg†<br>95% CI: 0.4–6.0<br><i>P</i> <0.05   | 4.4 mm Hg†<br>95% CI: 1.8–7.0<br><i>P</i> =0.001   |

VLBW indicates very low birth weight (<1500 g); SBP, systolic blood pressure; SGA, small for gestational age; AGA, appropriate for gestational age; FG, fetal growth; NR, not reported.

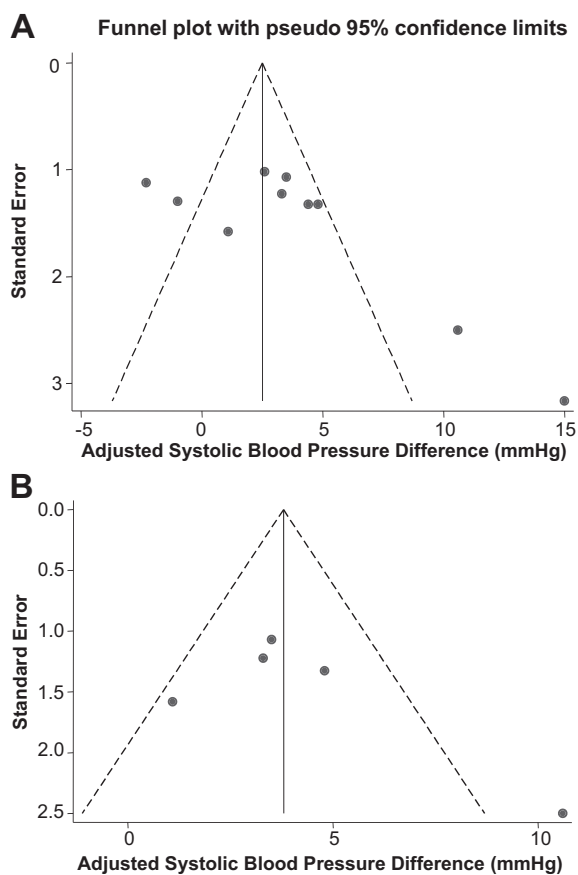
\*Numbers were calculated by authors from data presented in the article; estimate is unadjusted.

†Numbers are the estimated SBP difference as reported in the article.





**Figure 3.** Meta-analysis of the difference in systolic blood pressure (SBP) between participants born preterm or very low birth weight (VLBW) vs term. Small solid circles represent the estimated SBP difference from each study, shaded squares represent the sample size, and solid horizontal lines represent the 95% CIs. The open diamond and dashed vertical line represent the pooled SBP difference, and the solid vertical line represents the null hypothesis, no SBP difference. Weights are from the random effects analysis. **A**, 10 observational studies. **B**, The 3 studies that adjusted for a measure of socioeconomic status. **C**, The 8 studies that adjusted for a measure of attained size (height, weight, or body mass index [BMI]). **D**, Only very preterm ( $\leq 32$  weeks) or VLBW ( $< 1500$  g) participants. **E**, The 5 higher quality studies.



**Figure 4.** Funnel plots with (A) 10 observational studies of preterm or very low birth weight (VLBW) birth and systolic blood pressure (SBP) and (B) 5 higher quality studies. Circles represent studies. Small study effects are visually apparent in A for 2 studies<sup>28,31</sup> with larger effect sizes and greater variability (larger SEs),  $P=0.04$ , and in B for 1 study,<sup>31</sup>  $P=0.29$ .

Nine studies<sup>16,23,25,26,28–32</sup> reported an estimate adjusted for later size; the pooled estimate for those studies was 3.3 mm Hg (95% CI: 2.4–4.2 mm Hg; Figure 3D). Three studies<sup>16,23,29</sup> reported an estimate adjusted for a measure of socioeconomic status; the pooled estimate was 2.7 mm Hg (95% CI: 1.2–4.1 mm Hg; Figure 3E). Only 2 studies<sup>25,26</sup> adjusted for fetal growth, so a separate pooled estimate was not feasible. One study<sup>16</sup> reported adjusted results stratified by sex; the estimated SBP difference was similar for men (3.2 mm Hg [95% CI: 0.1–6.2 mm Hg]) and women (3.8 mm Hg [95% CI: 0.8–6.8 mm Hg]).

Visual inspection of the funnel plot using the most adjusted estimates (Figure 4) revealed asymmetry, with relatively large, positive effect sizes seen for the 2 studies<sup>28,31</sup> with the smallest sample size and greatest variability (largest SE). The Egger et al<sup>19</sup> test  $P$  value was 0.06, suggesting possible undue influence of these small studies on the pooled effect. We also noted significant heterogeneity in that analysis ( $P<0.0001$ ). However, an influence analysis omitting one at a time the 2 studies<sup>28,31</sup> with unbalanced effects on the funnel plot revealed pooled SBP differences of 2.3 mm Hg (95% CI: 1.4–3.1 mm Hg) for each of the 2 analyses, minimally different from the analysis including all 10 studies. Removing each of the other studies one at a time also minimally changed

the estimate (data not shown). A funnel plot of the 5 higher quality studies showed 1 study with an unbalanced effect, but the Egger et al<sup>19</sup> test  $P=0.29$  suggested no small study effects.

Of the 12 studies<sup>12,14,21,24,33–40</sup> excluded from the meta-analysis, 6<sup>33–35,37,39,40</sup> reported that former preterm or VLBW infants had SBP that was statistically higher than the term control group, with the SBP difference ranging from 5.1 to 13.0 mm Hg (Table S1). Two studies<sup>24,36</sup> reported a small, nonsignificant, positive SBP difference; 4<sup>12,14,21,38</sup> did not report statistical testing.

### Hypertension Prevalence

Eight studies<sup>21,22,33,34,41,42</sup> examined hypertension prevalence (Table S2), all but 2<sup>14,25</sup> of which included only VLBW or very preterm participants or analyzed separately a very preterm subgroup. The sample size of former preterm or VLBW infants ranged from 37 to 28 220. Three studies<sup>25,33,34</sup> reported the percentage of preterm or VLBW participants who were also SGA, which ranged from 10.8% to 38.0%. Seven of the 8 studies assessed hypertension in adolescence or adulthood; 1<sup>14</sup> assessed hypertension at a mean age of 9.2 years. Four studies directly measured BP and defined systolic hypertension either as  $>140$  mm Hg<sup>21,34</sup> or  $>95$ th percentile for age.<sup>14,33</sup> One study<sup>41</sup> measured ambulatory BP and used different cutoffs for 24-hour, daytime, and nighttime hypertension. One study<sup>43</sup> used discharge diagnoses, 1<sup>22</sup> used prescriptions for antihypertensive medications, and 1<sup>25</sup> used self-report of hypertension diagnosis. Only 2 studies<sup>21,22</sup> adjusted for potential confounders.

Of the 8 studies, 3<sup>21,22,25</sup> reported a statistically higher relative risk of hypertension in preterm or VLBW participants, ranging from 1.2 to 2.5 compared with term participants. In 1 study<sup>41</sup> that examined ambulatory BP, 6% of preterm or VLBW participants had 24-hour, daytime, and nighttime systolic hypertension, as compared with none of the term participants for 24-hour and daytime BP and 5% for nighttime BP; statistical testing was not reported. One study<sup>42</sup> reported that the difference in hypertension prevalence was not statistically significant; 4<sup>14,33,34,41</sup> did not report statistical testing. Only 3 studies<sup>21,22,42</sup> reported CIs or SEs around the estimates.

### Ambulatory BP

Characteristics of the 5 studies that reported ambulatory SBP are listed in Table S3. Four<sup>31,40,41,44</sup> included only VLBW or very preterm participants. The proportion of preterm or VLBW participants who were also SGA ranged from 27% to 42%. All but 1 study<sup>45</sup> measured BP in adolescence or young adulthood. One study<sup>40</sup> included only female participants. All of the studies used SpaceLabs 90207 to measure ambulatory BP. Only 2 studies<sup>31,44</sup> adjusted for potential confounders.

Results were reported as 24-hour BP, daytime or awake BP, and nighttime or asleep BP. Three of the 5 studies<sup>31,41,44</sup> reported statistically higher 24-hour SBP, 1<sup>31</sup> reported higher awake BP, and 1<sup>45</sup> reported statistically higher nighttime SBP. Only 2 studies<sup>44,46</sup> reported 95% CIs or SEs around the ambulatory BP differences.

**Table 2. Quality Assessment of 10 Studies Included in the SBP Meta-Analysis**

| Study                            | Modified Newcastle-Ottawa Scale |                                |                                   | Total Score<br>(Maximum 7 ★) |
|----------------------------------|---------------------------------|--------------------------------|-----------------------------------|------------------------------|
|                                  | Selection<br>(Maximum 3 ★)      | Comparability<br>(Maximum 2 ★) | Assessment of BP<br>(Maximum 2 ★) |                              |
| Chan et al <sup>26</sup>         | ★★                              | ★★                             | ★                                 | ★★★★★                        |
| Bracewell et al <sup>27</sup>    | ★★★                             |                                | ★                                 | ★★★★                         |
| Rotteveel et al <sup>28</sup>    | ★★                              | ★                              | ★                                 | ★★★★                         |
| Hovi et al <sup>29</sup>         | ★★★                             | ★★                             | ★★                                | ★★★★★★                       |
| Bonamy et al <sup>30</sup>       | ★★★                             | ★                              | ★★                                | ★★★★★★                       |
| Dalziel et al <sup>25</sup>      | ★★★                             | ★★                             | ★★                                | ★★★★★★                       |
| Hack et al <sup>16</sup>         | ★★★                             | ★★                             | ★★                                | ★★★★★★                       |
| Doyle et al <sup>31</sup>        | ★★★                             | ★★                             | ★★                                | ★★★★★★                       |
| Barros and Victora <sup>23</sup> | ★★★                             | ★★                             | ★★                                | ★★★★★★                       |
| Pharoah et al <sup>32</sup>      | ★★★                             | ★                              | ★                                 | ★★★★★                        |

SBP indicates systolic blood pressure; BP, blood pressure.

### Quality Assessment

Table 2 and Table S4 show the assessment of methodologic quality for the 27 studies included in the systematic review. All of the studies received  $\geq 2$  of 3 possible points for selection and  $\geq 1$  of 2 possible points for assessment; however, 17 studies received 0 points for lack of statistical adjustment for important potential confounders. Total scores ranged from 3 to 7.

### Discussion

The results of our systematic review and meta-analysis suggest that preterm and VLBW births are associated with higher resting SBP later in life than term birth. Estimates were not materially changed by adjustment for differences in socioeconomic factors or attained height or weight, suggesting that differences in these factors do not account for the higher SBP observed in participants born preterm or VLBW. In fact, the association was strengthened somewhat by adjustment for attained size.

In our meta-analysis, we found quantitative evidence for small study effects, which can be explained by publication bias and/or poor methodologic quality of individual studies.<sup>20</sup> Although our influence analysis suggested only a minor effect on results by the small studies, we cannot rule out publication bias. The fact that only 2 studies reported lower SBP with preterm birth could suggest publication bias but may just be chance findings. Because all of the studies were observational rather than randomized trials for which trial registration is required, we could not identify unpublished studies.

Our meta-analysis restricted to the higher quality studies suggests that poor methodologic quality of smaller studies does not explain the observed SBP difference. In addition to the 10 studies that met criteria for our meta-analysis, we identified an additional 12 studies of resting SBP difference in our systematic review, but we were not able to quantify the potential effect of publication bias or poor methodologic quality, because those studies did not report CIs or SEs around the estimated SBP difference.

Although the observed resting SBP difference of 2.5 mm Hg is modest, even small differences in BP are important for the population with respect to prevention of cardiovascular disease.<sup>47</sup> The SBP difference that we observed is similar to the SBP increase that is associated with excessive intake of dietary sodium,<sup>48</sup> a recommended target for public health interventions aimed at reducing the incidence of cardiovascular disease in the general US population. Unfortunately, prevention of preterm birth as a means to reduce cardiovascular disease is not feasible, because no effective strategy currently exists.

Our systematic review revealed limited data on the prevalence of hypertension in former preterm or VLBW adults. Only 3 studies reported CIs or SEs, and study methodology including the definition of hypertension differed substantially across studies, making it impossible to calculate pooled estimates, which would have been important given the relatively low observed prevalence of hypertension. Similarly, data are limited on ambulatory BP, although 4 of the 5 studies reported higher 24-hour or nighttime ambulatory SBP in the preterm or VLBW participants.

The survival of preterm and VLBW infants increased markedly in the 1990s because of advances in obstetric and neonatal care. In our meta-analysis, the SBP difference was greater for participants born before 1990 versus in or after 1990. This discrepancy may be related to differences in gestational age or specific care practices but might also be explained by differences in age at SBP measurement, which occurred in adolescence or adulthood for those born before 1990 but at school age for those born in or after 1990. BP differences related to differences in birth weight are known to amplify with increasing age.<sup>49</sup> As the population of preterm and VLBW children born in the modern era of neonatal intensive care reaches adulthood, additional study of hypertension and its sequelae, including coronary heart disease and stroke, will be informative. It will also be important to ascertain whether the effect of preterm birth on later BP is stronger for the smaller, sicker infants who now survive because of advanced neonatal intensive care and also whether



specific practices that lead to better survival also impact the risk of hypertension later in life.

The mechanisms linking preterm birth with later, higher BP may involve both prenatal and postnatal factors. The risk of hypertension may be influenced through the process of fetal programming, which involves long-lasting adaptation to an adverse intrauterine environment during a critical period in development.<sup>50</sup> An adverse intrauterine environment may prompt preterm birth, for example, in the setting of preeclampsia or fetal growth restriction, although existing evidence does not consistently support a link between those conditions and later BP in former preterm or VLBW infants.<sup>16,33,51</sup> In our meta-analysis, we were not able to examine the extent to which fetal growth restriction modifies or confounds the association of shortened gestation with later BP, because only 2 studies adjusted for a measure of fetal growth.

The preterm infant is ex utero during the fetal developmental period from the time of preterm birth to term (40 weeks' postmenstrual age) and typically spends several weeks to months after birth in the NICU. Thus, adverse postnatal conditions could also influence later BP through fetal programming mechanisms. For example, preterm and VLBW infants often experience extrauterine growth restriction during the NICU hospitalization.<sup>52</sup> However, to our knowledge, no study has linked extrauterine growth restriction in preterm infants with later higher BP. In addition, long-term follow-up of randomized trials<sup>53,54</sup> of nutrient-enriched preterm infant formula suggest that more rapid early weight gain may lead to higher BP. After NICU discharge, preterm infants typically experience gains in weight and length resulting in catch-up to their term-born peers by school age.<sup>55</sup> Some<sup>28,33,56</sup> but not all<sup>56,57</sup> studies in preterm populations suggest that more rapid postnatal weight gain after term may lead to higher BP later in life. Although it is possible that altering early nutrition to prevent excessive weight gain may prevent the higher BP seen in former preterm and VLBW infants, one must also consider the risks of such a strategy, such as to neurodevelopment.<sup>56,58</sup>

A strength of our study is that we conducted a thorough and systematic search of multiple databases, so it is likely that we identified all of the relevant publications, although we could not identify unpublished studies. Two authors independently reviewed articles for inclusion/exclusion and extracted the data, improving the validity of our results. We also performed a quality assessment. We identified studies from multiple countries, improving the generalizability of our findings, although they may not apply to settings with fewer resources. Although we identified 22 studies that examined resting SBP in former preterm or VLBW infants, fewer than half reported CIs or SEs around the BP differences, so we could not include all of them in the meta-analysis. We also could not perform a meta-analysis of hypertension prevalence or ambulatory BP because of heterogeneity of methodology and the small number of published studies with CIs or SEs.

## Perspectives

Our results suggest that preterm and VLBW infants have higher SBP later in life than those born at term and may be at

increased risk for developing hypertension and its sequelae. These findings should inform medical and preventive care for survivors of preterm birth as they reach adulthood and also increase scientific understanding of mechanisms underlying the fetal and postnatal programming of BP.

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## Disclosures

None.

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