Preterm Birth as a Risk Factor for Metabolic Syndrome and Cardiovascular Disease in Adult Life: A Systematic Review and Meta-Analysis

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Objective To determine if preterm birth is associated with components of the metabolic syndrome in adult life.

Study design A structured literature search was performed using PubMed. All comparative studies reported metabolic and cardiovascular outcomes in adults (≥18 years of age) born preterm (<37 weeks of gestation) compared with adults born at term (37-42 weeks of gestation) and published through March 2018 were included. The major outcomes assessed were body mass index, waist circumference, waist-to-hip ratio, fat mass, systolic blood pressure (SBP), diastolic blood pressure (DBP), 24-hour SBP, 24-hour DBP, endothelium-dependent brachial artery flow-mediated dilation, carotid intima-media thickness, pulse wave velocity, fasting glucose and insulin, Homeostasis Model Assessment-Estimated Insulin Resistance Index, and lipid profiles. Quality appraisal was performed using a modified version of the Newcastle-Ottawa scale. A meta-analysis was performed for comparable studies which reported sufficient data.

Results Forty-three studies were included, including a combined total of 18 295 preterm and 294 063 term-born adults. Prematurity was associated with significantly higher fat mass ($P = .03$), SBP ($P < .0001$), DBP ($P < .0001$), 24-hour SBP ($P < .001$), and 24-hour DBP ($P < .001$). Furthermore, preterm-born adults presented higher values of fasting glucose ($P = .01$), insulin ($P = .002$), Homeostasis Model Assessment-Estimated Insulin Resistance Index ($P = .05$), and total cholesterol levels ($P = .05$) in comparison with adults born at term, in random effect models. No statistically significant difference was found between preterm and term-born adults for the other outcomes studied.

Conclusions Preterm birth is strongly associated with a number of components of the metabolic syndrome and cardiovascular disease in adult life. *(J Pediatr 2019;210:69-80)*.

The metabolic syndrome and cardiovascular disease constitute major public health burdens, as leading causes of disability and death in both the developed and developing world.[1] Low birth weight and/or gestational age are classified among factors influencing the cardiovascular risk, a condition referred to as cardiovascular perinatal programming.[1,2] According to the Barker hypothesis, low birth weight is a risk factor for the later development of cardiovascular disease and noninsulin-dependent diabetes mellitus.[3] Evidence is less strong as regards preterm birth and its link with the development of components of the metabolic syndrome. It has been reported that adults who were born prematurely present elevated arterial blood pressure,[4-9] differences in glucose tolerance, serum insulin levels,[10-12] and/or lipid profiles,[7,13-15] higher total body fat mass (FM), and increased risk for obesity[16,17] in comparison with individuals who were born after a full-term pregnancy. However, other studies support that there is no association between prematurity and subsequent features of metabolic syndrome.[6,17-22] In addition, a small number of studies tried to detect a link between prematurity and endothelial dysfunction in the long term with conflicting results; reduced endothelium-dependent brachial artery flow-mediated dilation (FMD)[23] and pulse wave velocity (PWV),[24] and an increased mean carotid intima-media thickness (cIMT)[24,25] have been reported by some of them, whereas other studies failed to show that any association exists.[6,26] Thus, it remains a controversial issue whether prematurity constitutes an independent risk factor for the subsequent development of cardiovascular disease and the metabolic syndrome.

Systematic reviews and meta-analyses have identified a significant association between preterm birth and arterial blood pressure (systolic blood pressure [SBP], diastolic blood pressure [DBP], 24-hour SBP, and 24-hour DBP)[6,8]; however, they failed to

AGA	Appropriate for gestational age	HOMA-IR	Homeostasis Model Assessment-Estimated Insulin Resistance Index
BMI	Body mass index	IUGR	Intrauterine growth restriction
cIMT	Carotid intima-media thickness	LDL	Low-density lipoprotein
DBP	Diastolic blood pressure	PWV	Pulse wave velocity
FM	Fat mass	SBP	Systolic blood pressure
FMD	Brachial artery flow-mediated dilation	SGA	Small for gestational age
HDL	High-density lipoprotein	TG	Triglycerides
		WHR	Waist-to-hip ratio

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find any association with other features of cardiovascular risk, such as body mass index (BMI), waist-to-hip ratio (WHR), total body FM, glucose and insulin levels, or lipid profile. Nevertheless, a number of studies investigating preterm birth as a risk factor for the metabolic syndrome and cardiovascular disease in adult life have been published since then.[5,13,15,17,24,27-41] Our aim was to conduct a systematic review and meta-analysis to reevaluate the hypothesis that individuals born preterm present with components of the metabolic syndrome and/or additional indicators of increased cardiovascular risk in adult life.

Methods

This systematic review and meta-analysis was based on the guidelines of the PRISMA statement[42] and the broader EQUATOR guidelines.[43] A predefined protocol was used.

Literature Search

A systematic research of the PubMed database from inception through March 31, 2018, was conducted by 2 independent authors. The following keywords were used [(prematurity) OR (premature birth) OR (premature infant) OR (low birth weight) OR (preterm)] AND [(metabolic syndrome) OR (cardiovascular risk) OR (cardiovascular disease) OR (metabolic syndrome, components) OR (atherosclerosis) OR (vascular disease) OR (hypertension) OR (high blood pressure) OR (insulin resistance) OR (glucose intolerance) OR (obesity) OR (overweight) OR (fat mass) OR (dyslipidemia) OR (hypercholesterolemia) OR (diagnostic techniques, cardiovascular). Reference lists of the above research and review articles were also checked for relevant bibliography.

Study Selection

To be included in the systematic review and meta-analysis, studies had to fulfill the following inclusion criteria: (a) to be conducted in human participants, (b) to be written in English, (c) to have a full-text source available, (d) to be conducted in any country, (e) to represent a cohort study, a case-control study, or a cross-sectional study, (f) to be published before March 31, 2018, (g) to include adult participants (≥18 years old) born preterm (<37 weeks of gestation) in comparison with adult participants born at term (37-42 weeks of gestation), and (h) to evaluate components of the metabolic syndrome and cardiovascular risk factors as outcomes, including (1) anthropometric measures (BMI [kg/m^2], waist circumference [cm], WHR, and percent of FM), (2) blood pressure (systolic/SBP [mm Hg], diastolic/DBP [mm Hg], 24-hour ambulatory systolic/24-hour SBP [mm Hg], 24-hour ambulatory diastolic/24-hour DBP [mm Hg]), (3) biomarkers of vascular dysfunction (FMD [%], cIMT [mm], PWV [m/s]), (4) glucose tolerance/insulin sensitivity (fasting glucose [mmol/L], fasting insulin [mU/L], Homeostasis Model Assessment-Estimated Insulin Resistance Index [HOMA-IR]), and (5) lipid profile (fasting total cholesterol [mmol/L], fasting high-density lipoprotein [HDL; mmol/L], fasting low-density lipoprotein [LDL; mmol/L], and fasting triglycerides [TG; mmol/L]).

Studies in nonhuman participants or those conducted in children and/or adolescents (<18 years old), systematic reviews/meta-analyses, case reports, and studies published from April 1, 2018, and onward, were not eligible for this systematic review and meta-analysis; furthermore, studies comparing participants with low birth weight (<2500 g) or very low birth weight (<1500 g) or extremely low birth weight (<1000 g) with normal birth weight infants, when no information about their gestational age was provided, as well as studies presenting outcomes different than those mentioned in the inclusion criteria, were also excluded. For studies with a mixed children and/or adolescent and adult population that fulfilled the rest of the inclusion criteria, authors would be contacted to extract the outcomes mentioned for the adult population.

Data Extraction

The titles and abstracts of all the articles resulting from the search were used to assess eligibility and were scanned twice to exclude irrelevant studies. If the title and abstract contained insufficient information to exclude an article, the full text was retrieved. Authors were contacted where additional data were required. Where multiple reports of the same cohort existed, the study reporting the largest sample number was used (provided that all studies of the same cohort received identical quality assessment scores). Author information, study design, study location and year, population characteristics, methods of outcome measurement, potential sources of bias (inclusion and exclusion criteria, blinding of assessors to gestational age and/or birth weight when evaluating the outcomes), and the mean and SD of the outcomes mentioned, for preterm and term adult groups, were extracted. For inclusion, outcomes were presented unadjusted and measured using the same technique for the preterm and term groups.

Quality Assessment of Studies

A modified version of the Newcastle-Ottawa scale,[44] as previously described,[6] was implemented to assess the methodological quality of each study included in the meta-analysis. The Newcastle-Ottawa scale consists of 6 items with 3 subscales: selection, comparability, and outcome. The total maximum score for these 3 subsets is 7 stars. In the comparability section, studies examining the low birth weight and/or small for gestational age as a potential confounder were awarded 1 star.

Meta-Analysis

For the meta-analysis, the Revman (version 5.3; The Cochrane Collaboration, 2011) was applied to examine differences of each outcome between preterm and term groups using the inverse variance method.[45] For inclusion in the meta-analysis, the SE of change, where applicable, was converted to the SD using the equation: $SD = SE \times \sqrt{N}$. A random effect model was applied for the mean difference

of outcomes between groups. Results are shown as pooled mean difference (95% CI) between the preterm and term groups and are presented using forest plots.

When a study presented subgroups of preterm and/or term adults, pooled means and SDs were calculated for the whole population of preterm or term adults, respectively. Studies comparing groups by birth weight (ie, low birth weight, very low birth weight, or extremely low birth weight vs normal birth weight participants) were included if the mean gestational age ±2 SD did not lie outside 37 weeks for preterm and 37-42 weeks for term participants.

Fasting glucose and insulin levels, as well as fasting lipid profile (total cholesterol, HDL, LDL, and TG levels) were standardized across studies to SI units using established conversion rates.[46] When a geometric mean was provided as a summary measure, it was converted to an arithmetic mean for inclusion in the meta-analysis.[47] Variables were considered to have a skewed distribution if their mean value was less than twice the SD.[48] For skewed outcomes, a meta-analysis of log-transformed data was conducted, as Parkinson et al performed[6]; if the log values were not provided, published summary measures (geometric and arithmetic means) were converted to approximate log values.[47] The pooled mean difference and 95% CIs of the log values were transformed back and represent the percentage difference between the term and preterm groups.

Outcomes of BMI, WHR, FM, SBP, and DBP were analyzed separately for men and women.

Study Heterogeneity

An I^2 test was used to measure heterogeneity between studies, and a value of >50% was considered to reflect high heterogeneity.[49] Random effect models were used throughout; as previously described,[6] if heterogeneity was low ($I^2 < 50\%$), a fixed effect model was carried out to check the sensitivity of conclusions. Because heterogeneity tests have low power when study numbers are small, a fixed effect model was not carried out for analysis with <5 studies.

The sex of participants was examined for causing heterogeneity in Revman (version 5.3; The Cochrane Collaboration, 2011).[45] Other potential sources of study heterogeneity, including the place of origin of the study (a qualitative variable; as the continent where the study was conducted), the mean age of participants at evaluation, as well as the mean gestational age of preterm group (quantitative variables), were examined by meta-regression in STATA 13 (Statacorp, Houston, Texas).[50]

To investigate the impact of being born small for gestational age, as a potential confounder, on the association of prematurity per se and the components of the metabolic syndrome, we extracted the results of studies providing additional comparisons among adults born prematurely and appropriate for gestational age (preterm AGA), adults born prematurely and small for gestational age (preterm SGA), and adults born at term and AGA (control AGA). Specifically, we examined whether the inclusion of the preterm AGA population only in the meta-analysis, instead of the total preterm population of these studies, might lead to changes in our results.

Publication Bias

The existence of publication bias was investigated by funnel plots; in the absence of publication bias, the studies distributed symmetrically around the combined effect size. In addition, the Egger test was performed for each mean difference between preterm and term groups.[51] If the P value for the test was significant ($P \leq .05$), a trim and fill analysis was performed to estimate the pooled effect in the absence of publication bias.[52]

Results

The systematic search strategy returned 6838 articles, and 23 additional records were identified through bibliographic review (**Figure 1**; available at www.jpeds.com); 6394 were excluded based on the screening of titles and abstracts. A total of 467 records were reviewed in full text, which led to the exclusion of another 420 records. After applying the selection criteria, a total of 47 studies were suitable for systematic review (**Table I**; available at www.jpeds.com). Overall, 43 studies were eligible for inclusion in the meta-analysis, and data from 4 studies were excluded. Specifically, data from Oren at al and Pilgaard et al were excluded, because they were presented as adjusted for age and sex.[53,54] Data from Evensen et al were also adjusted for sex,[22] and data from Breukhoven et al were not suitable for inclusion because the outcomes were presented as median and range.[17] Part of the data from 2 studies were not eligible for inclusion in the meta-analysis; data on plasma lipids from Cooper et al were excluded because they were obtained from nonfasting samples and data on cIMT from Bassareo et al were also excluded because the values were almost 10-fold higher than those reported in other relevant studies.[23,55] Data on sex-specific analysis of BMI and WHR from Leeson et al were obtained from Parkinson et al (**Table I**).[6]

Eight studies conducted retrospective analysis of low birth weight or preterm cohorts[16,23,24,27,28,56-58]; 29 studies were longitudinal follow-up of low birth weight or preterm cohorts compared with full-term ones, and 6 studies were population based.[4,26,55,69-71] Concerning the place of origin, 34 studies were conducted in Europe,[4,5,7,15,16,20-29,31-33,40,41,55-59,63-71] 5 were conducted in Oceania,[36,37,39,61,62] 3 in the US,[9,38,60] and 1 in Asia.[30] For 6 studies, additional information on the population characteristics and the measurement of outcomes was obtained by authors after personal contact.[23,38,55,61,67,68]

Overall, a total of 18 295 prematurely born (16 119 males; 2176 females) and 294 063 at term born (284 788 males; 9275 females) adults were included in the meta-analysis. The mean ± SD gestational age of the entire study population of prematurely born adults was 30.4 ± 3.4 weeks (range, 22.5-34.9 weeks), whereas the mean ± SD chronological age at outcome assessment was 19.4 ± 5.1 years (range, 18-58 years). The results of the meta-analyses for each of

the outcomes are presented in Table II. The number of studies and participants varied considerably for each outcome.

Prematurely born adults demonstrated a higher percentage of FM in both random and fixed effect models (random mean difference, 1.5%; 95% CI, 0.1-2.8; $P = .03$, and fixed mean difference, 1.2%; 95% CI, 0.3-2.1; $P = .009$) compared with adults born at term (Figure 2). FM was estimated by bioelectrical impedance, dual-energy x-ray absorptiometry, or whole body MRI. No significant differences were observed between preterm and at term born adults in BMI, waist circumference, or WHR (Table II).

Furthermore, adults born prematurely showed significantly higher levels of SBP (random mean difference, 4.2 mm Hg; 95% CI, 3.0-5.5; $P < .0001$; Figure 3, A), DBP (random mean difference, 2.3 mm Hg; 95% CI, 1.2-3.3; $P < .0001$; Figure 3, B), as well as 24-hour SBP (random mean difference, 4.6 mm Hg; 95% CI, 2.0-7.2; $P < .001$, Figure 3, C) and 24-hour DBP (random mean difference, 1.7 mm Hg; 95% CI, 0.9-2.5; $P < .001$; Figure 3, D).

Differences in the diurnal pattern of ambulatory blood pressure monitoring were also observed between groups; sleeping SBP (random mean difference, 3.3 mm Hg; 95% CI, 1.2-5.3; $P = .002$) and DBP (random mean difference, 1.3 mm Hg; 95% CI, 0.4-2.1; $P = .003$), as well as awake SBP (random mean difference, 4.8 mm Hg; 95% CI, 2.5-7.1; $P < .001$) and DBP (random mean difference, 1.9 mm Hg; 95% CI, 1.0-2.7; $P < .001$) were significantly higher in adults born prematurely compared with adults born at term. Sleeping SBP and DBP were significantly lower than awake SBP and DBP values in both preterm (by 15.9 mm Hg [95% CI, 14.7-17.2; $P < .001$] and 14.9 mm Hg [95% CI, 13.8-16.1; $P < .001$], respectively) and at term born adults (by 14.7 mm Hg [95% CI, 13.5-16.0; $P < .001$] and 14.5 mm Hg [95% CI, 13.0-16.0; $P = .005$], respectively).

Prematurely born adults demonstrated increased fasting levels of glucose in both random (mean difference, 0.07 mmol/L; 95% CI, 0.02-0.1; $P = .01$) and fixed effect models (mean difference, 0.06 mmol/L; 95% CI, 0.02-0.1; $P = .008$; Figure 4, A) in comparison with adults born at

Table II. Results of meta-analyses of study outcomes: Associations between preterm birth (gestational age of <37 weeks) and components of the metabolic syndrome/cardiovascular risk factors in adult life

Outcomes	No. of studies	No. of participants	Pooled mean difference (95% CI)	FE/RE *P* value	Heterogeneity (I^2 *P* value)	Egger test (*P* value)
BMI	22	P: 16 185 T: 287 296	RE: 0.04 kg/m^2 (−0.22 to 0.31) FE: −0.02 kg/m^2 (−0.07 to 0.04)	RE: $P = .75$ FE: $P = .53$	I^2: 35%; $P = .05$	.42
Waist circumference	7	P: 609 T: 2174	RE: 0.84 cm (−0.3 to 1.99) FE: 0.84 cm (−0.3 to 1.99)	RE: $P = .15$ FE: $P = .15$	I^2: 0%; $P = .86$	.32
WHR	4	P: 157 T: 181	RE: 0.01 (−0.02 to 0.05)	RE: $P = .52$	I^2: 85%; $P = .0002$	.70
Percent FM	9	P: 602 T: 656	RE: 1.46% (0.13 to 2.79) FE: 1.22% (0.31 to 2.14)	**RE: $P = .03$** **FE: $P = .009$**	I^2: 45%; $P = .07$	.23
SBP	20	P: 16 520 T: 291 446	RE: 4.22 mm Hg (2.98 to 5.45)	**RE: $P < .0001$**	I^2: 82%; $P < .00001$	**<.001**
DBP	19	P: 16 201 T: 291 283	RE: 2.27 mm Hg (1.22 to 3.31)	**RE: $P < .0001$**	I^2: 86%; $P < .00001$	**.001**
24-Hour SBP	6	P: 569 T: 458	RE: 4.62 mm Hg (2.04 to 7.21)	**RE: $P = .0005$**	I^2: 77%; $P < .001$	.68
24-Hour DBP	6	P: 569 T: 458	RE: 1.69 mm Hg (0.89 to 2.48) FE: 1.69 mm Hg (0.89 to 2.48)	**RE: $P < .0001$** **FE: $P < .0001$**	I^2: 0%; $P = .62$	.31
FMD*	4	P: 448 T: 1180	RE: −7% (−30 to 15)	RE: $P = .53$	I^2: 94%; $P < .0001$	.85
cIMT	4	P: 579 T: 1391	RE: 0.04 mm (−0.01 to 0.08)	RE: $P = .1$	I^2: 97%; $P < .0001$	.19
PWV	2	P: 234 T: 281	RE: 0.05 m/s (−0.12 to 0.22)	RE: $P = .56$	I^2: 0%; $P = .33$	—
Glucose	10	P: 650 T: 2069	RE: 0.07 mmol/L (0.02 to 0.13) FE: 0.06 mmol/L (0.02 to 0.1)	**RE: $P = .01$** **FE: $P = .008$**	I^2: 26%; $P = .2$	.31
Insulin*	8	P: 578 T: 2022	RE: 16% (6 to 26)	**RE: $P = .002$**	I^2: 82%; $P < .001$	.18
HOMA-IR*	4	P: 178 T: 154	RE: 24% (0 to 47)	**RE: $P = .05$**	I^2: 55%; $P = .08$	.76
Total cholesterol	8	P: 432 T: 740	RE: 0.17 mmol/L (0.00 to 0.34) FE: 0.17 mmol/L (0.04 to 0.29)	**RE: $P = .05$** **FE: $P = .008$**	I^2: 40%; $P = .11$	.89
HDL	10	P: 615 T: 2400	RE: 0.03 mmol/L (−0.01 to 0.08) FE: 0.03 mmol/L (0.00 to 0.07)	RE: $P = .13$ FE: $P = .07$	I^2: 16%; $P = .13$	.52
LDL	7	P: 489 T: 1982	RE: 0.06 mmol/L (−0.04 to 0.16) FE: 0.06 mmol/L (−0.04 to 0.16)	RE: $P = .21$ FE: $P = .21$	I^2: 0%; $P = .74$	.93
TG*	10	P: 890 T: 2568	RE: 6% (−5 to 17)	RE: $P = .26$	I^2: 76%; $P < .001$	.44

FE, fixed effect model; *P*, preterm-born adults; *RE*, random effect model; *T*, term-born adults. Statistical significance is defined by $P \leq .05$. Significant results are shown in bold type.
*Skewed variables were logarithm transformed before meta-analysis.

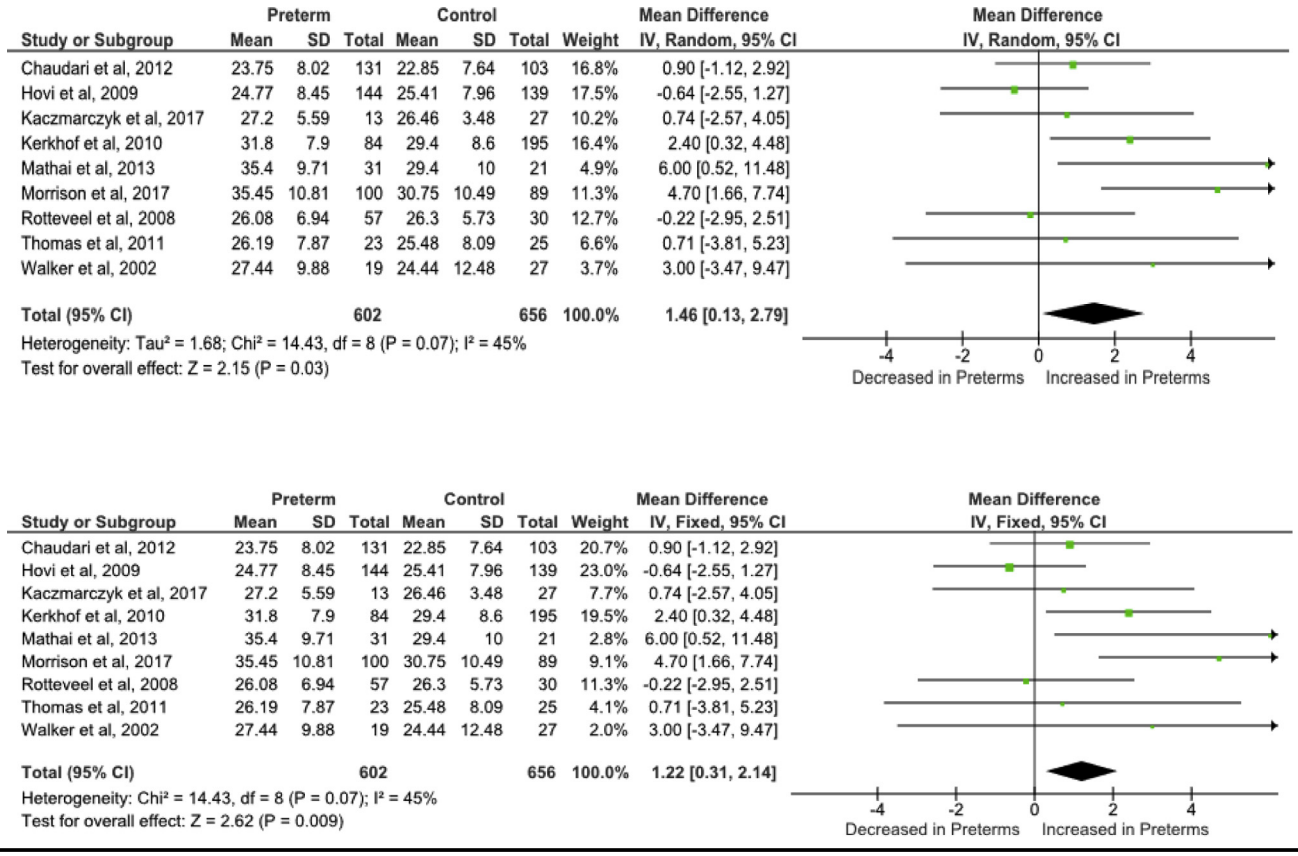


Figure 2. Forest plots showing the unadjusted pooled association between premature birth (gestational age of <37 weeks) and percent FM (random and fixed effect model). *IV*, inverse variance.

term. In addition, after logarithm transforming for skewness, a significant increase in fasting insulin (random mean difference, 16%; 95% CI, 6%-26%; $P = .002$; **Figure 4**, B) and HOMA-IR (random mean difference, 24%; 95% CI, 0.0-47%; $P = .05$, **Figure 4**, C) values were observed in preterm-born adults.

Significantly increased fasting total cholesterol levels in both random (mean difference, 0.2 mmol/L; 95% CI, 0.0-0.3; $P = .05$) and fixed effect models (mean difference, 0.2 mmol/L; 95% CI, 0.04-0.3; $P = .008$; **Figure 5**; available at www.jpeds.com) were observed in adults born prematurely, whereas no significant differences were found in fasting HDL, LDL, and TG levels between groups (**Table II**).

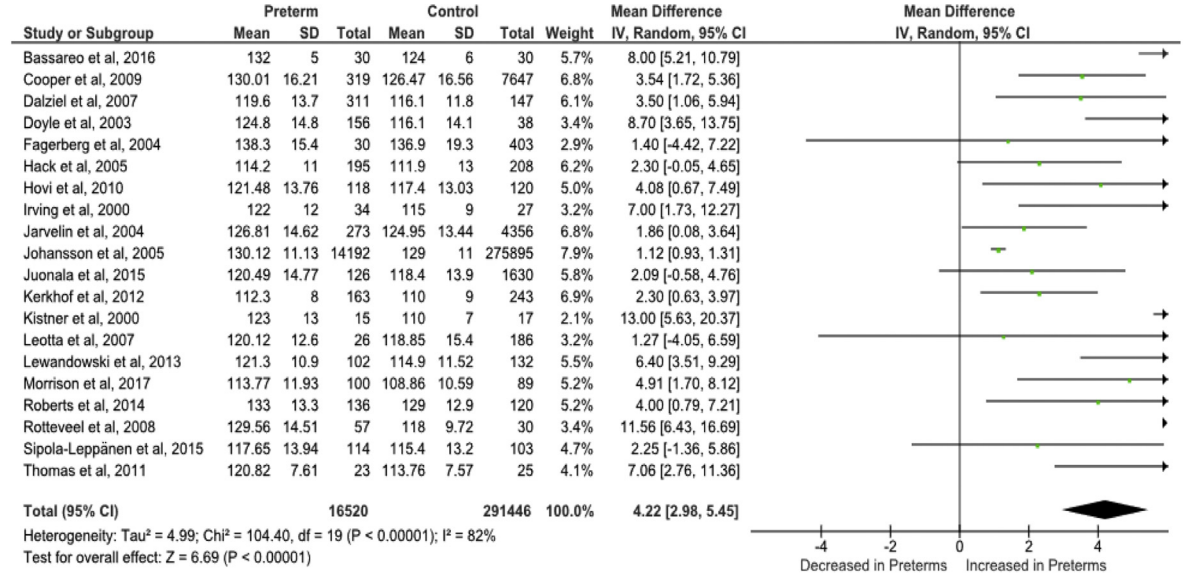
Differences in the cIMT, FMD, and PWV between preterm and at term born participants were not statistically significant (**Table II**).

Sex-specific analyses were also performed; no differences between preterm-born and term-born adults were observed in BMI, WHR, or FM when these variables were analyzed separately for men and women (**Table III**; available at www.jpeds.com). SBP and DBP were higher in both men and women born prematurely compared with their counterparts born at term (men: SBP random mean difference, 2.0 mm Hg; 95% CI, 0.6-3.4; $P = .007$; DBP random mean difference, 1.3 mm Hg; 95% CI, 0.1-2.5; $P = .03$; women: SBP random mean difference, 4.9 mm Hg; 95% CI, 3.3-6.6; $P < .001$; SBP fixed mean difference, 4.2 mm Hg; 95% CI, 3.1-5.3; $P < .001$; DBP random mean difference, 2.9 mm Hg; 95% CI, 1.6-4.2; $P < .001$; DBP fixed mean difference, 2.6 mm Hg; 95% CI, 1.7-3.4; $P < .001$; **Table III**). Sex-specific analysis revealed significantly higher 24-hour SBP (random mean difference, 3.5 mm Hg; 95% CI, 1.4-5.6; $P = .001$) and 24-hour DBP (random mean difference, 1.6 mm Hg; 95% CI, 0.0-3.1; $P = .04$) for women born prematurely compared with women born at term, but not for men (**Table III**).

Study Heterogeneity and Metaregression

Sex was examined as a cause of heterogeneity; a significant increase in the preterm–term difference of WHR (random mean difference, 0.02; 95% CI, 0.0-0.03; $P = .05$) and percent FM (random mean difference, 0.9%; 95% CI, 0.1-1.7; $P = .03$; fixed mean difference, 0.9%; 95% CI, 0.2-1.6; $P = .02$) was observed in men compared with women (**Table III**). In contrast, the preterm–term differences for SBP, DBP, and 24-hour SBP were higher in women than in men by 3.5 mm Hg (95% CI, 2.3-4.8; $P < .001$), 2.1 mm Hg (95% CI, 1.1-3.1; $P < .001$), and 3.2 mm Hg (95% CI, 1.0-5.4; $P = .005$), respectively (**Table III** and **Figure 6**, A-C

A



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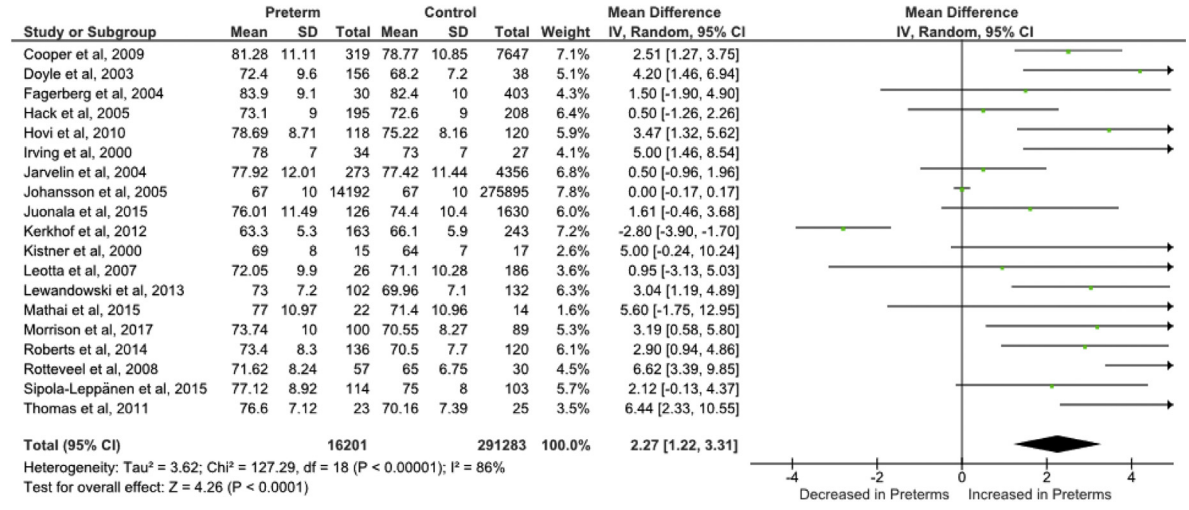

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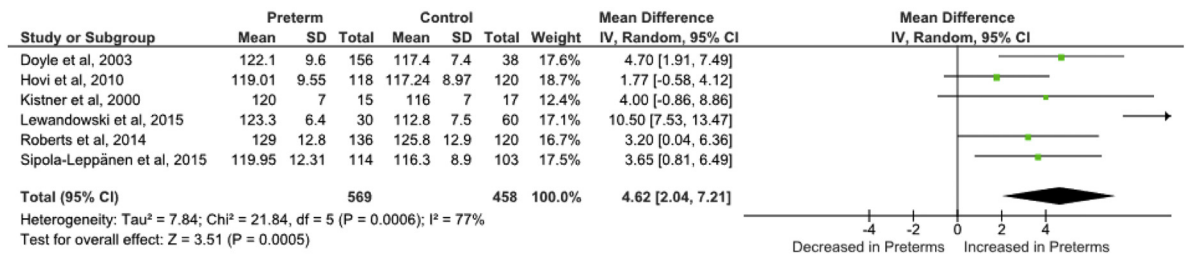

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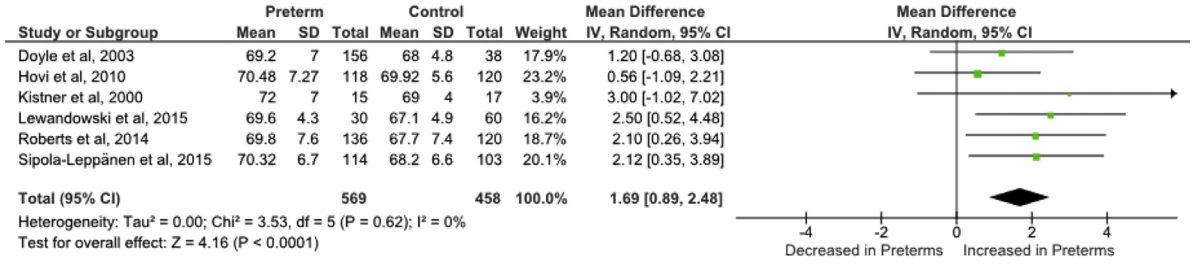

Figure 3. Forest plots showing the unadjusted pooled association between premature birth (gestational age <37 weeks) and **A**, SBP, **B**, DBP, **C**, 24-hour SBP, and **D**, 24-hour DBP.

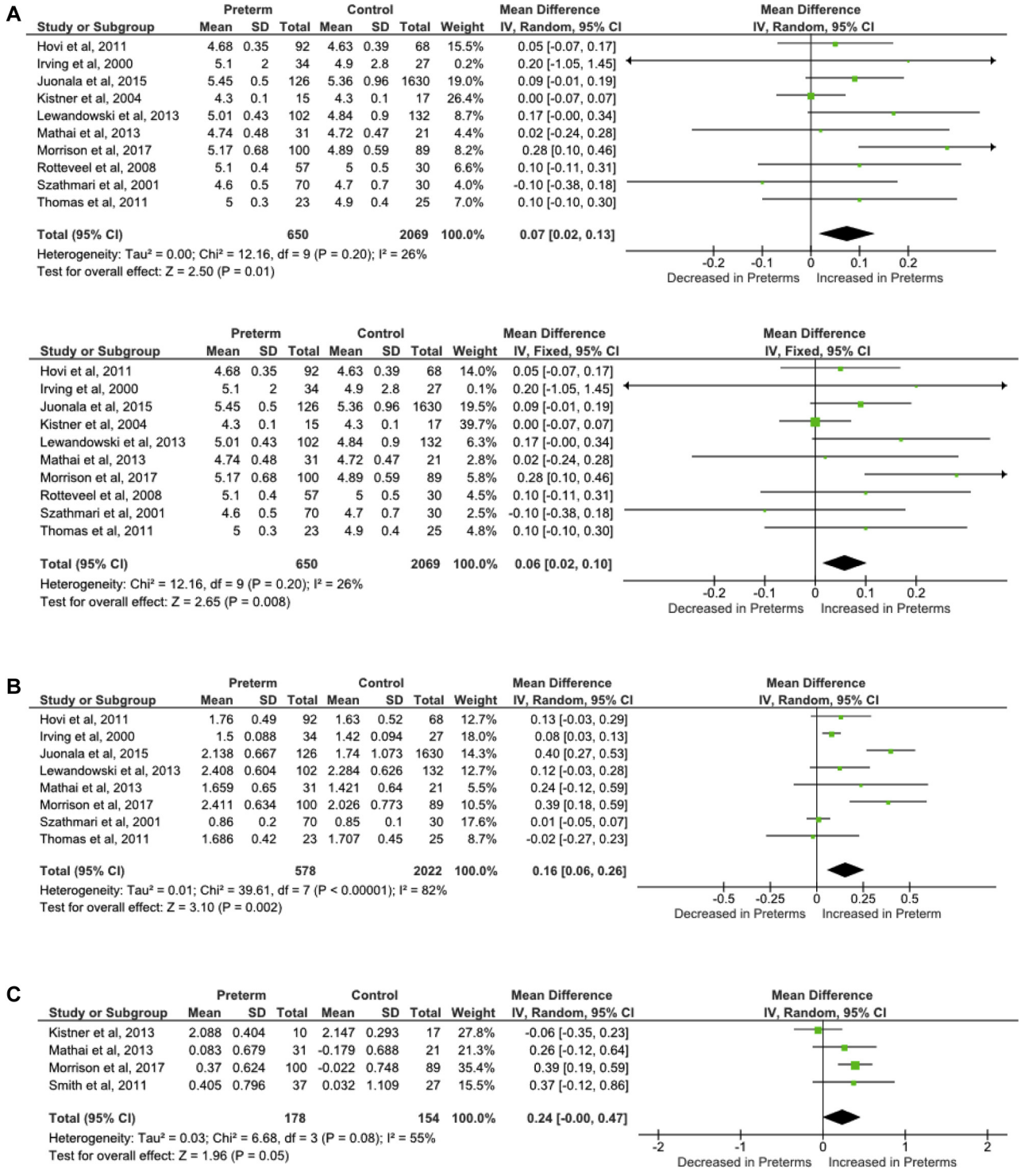

Figure 4. Forest plots showing the unadjusted pooled association between premature birth (gestational age <37 weeks) and **A**, glucose (random and fixed effect model), **B**, insulin, and **C**, HOMA-IR.

[available at www.jpeds.com]), whereas no significant difference, by sex was observed for BMI and 24-hour DBP (**Table III** and **Figure 6**, D [available at www.jpeds.com]).

Metaregression analyses revealed that preterm–term differences in BMI were associated with the mean participants' age at which BMI was measured (coefficient [SE] = 0.03 [0.01]; 95% CI, 0-0.1; P = .04). Furthermore, preterm–term differences in SBP were found to correlate with the mean gestational age of participants born prematurely (coefficient [SE] = 0.1 [0.04]; 95% CI, 0.02-0.2; P = .02). No significant

association was observed between preterm–term differences for any other outcome studied and either the mean age of participants or mean gestational age of prematurely born ones.

When the continent of origin of the included studies was taking into account, metaregression revealed a statistically significant correlation between preterm–term TG differences and European origin of studies (coefficient [SE] = −0.5 [0.2]; 95% CI, −0.9 to −0.06; $P = .03$), as well as between preterm–term HDL differences and studies from Oceania (coefficient [SE] = −0.8 [0.3]; 95% CI, −1.5 to −0.1; $P = .02$). No significant association was found between preterm–term differences for any other studied outcome and place of origin of the study.

Seven studies attempted to address the impact of low birth weight and/or SGA, as a potential confounder, by comparing preterm AGA adults, preterm SGA adults, or adults born prematurely with intrauterine growth restriction (preterm IUGR), and control AGA adults.[20,21,24,30,31,33,68] When the preterm AGA population replaced the total preterm population of these studies in the meta-analysis, the significant preterm–term differences of outcomes assessed retained their size and statistical significance. Specifically, prematurely born adults demonstrated higher percentage of FM (random mean difference, 1.6%; 95% CI, 0.2-3.0; $P = .03$), higher levels of SBP (random mean difference, 4.2 mm Hg; 95% CI, 2.9-5.5; $P < .001$), DBP (random mean difference, 2.3 mm Hg; 95% CI, 1.3-3.4; $P < .001$), 24-hour SBP (random mean difference, 4.6 mm Hg; 95% CI, 2.0-7.2; $P < .001$), and 24-hour DBP (random mean difference, 1.7 mm Hg; 95% CI, 0.9-2.5; $P < .001$) compared with adults born at term. Prematurely born adults also demonstrated increased fasting levels of glucose (random mean difference, 0.07 mmol/L; 95% CI, 0.004-0.1; $P = .03$) and insulin (random mean difference, 15.8%; 95% CI, 5.8%-25.4%; $P = .01$), HOMA-IR values (random mean difference, 23.7%; 95% CI, 0.2-47%; $P = .05$), and total cholesterol levels (random mean difference, 0.2 mmol/L; 95% CI, 0.0-0.4; $P = .05$) in comparison with adults born at term.

Publication Bias

In a pooled analysis of SBP and DBP, funnel plots demonstrated significant asymmetry (**Figure 7**; available at www.jpeds.com), and the Egger test was significant for both outcomes ($P < .001$ for SBP and $P = .001$ for DBP; **Table II**). The trim and fill method was used to identify and correct for funnel plot asymmetry arising from publication bias; for SBP, a slightly reduced pooled effect was revealed (3.6 mm Hg; 95% CI, 2.4-4.8; $P < .001$), and a similar effect was observed for DBP (1.6 mm Hg; 95% CI, 0.6-2.5; $P = .001$). Funnel plots demonstrated some visual asymmetry for WHR, percent FM, and total cholesterol, LDL, and TG; however, the results of the Egger test were not statistically significant for these outcomes (**Table II**).

In sex-specific analyses, there was some visual evidence of asymmetry for all outcomes measured; however, the Egger test revealed publication bias only in studies of DBP in men ($P = .03$; **Table III**) and of SBP in women ($P = .002$; **Table III**). A trim and fill analysis gave a reduced difference in SBP in women (3.6 mm Hg; 95% CI, 1.9-5.4; $P < .001$), and no difference in DBP in men ($P = .9$).

Quality Assessment of Studies

In the modified version of the Newcastle-Ottawa scale,[44] we considered a score of 0-2 stars to indicate poor quality of study, a score of 3-5 stars to indicate acceptable study quality, and a score of 6-7 stars to indicate a good quality of study.[72] Among the 43 studies included in meta-analysis, 8 studies were scored as of good quality, 34 studies of acceptable quality, and 1 study of poor quality (**Table I**).

Discussion

In this systematic review and meta-analysis, preterm birth was found to be associated with significantly higher total body FM and arterial blood pressure, including the 24-hour ambulatory blood pressure, in adult life. Furthermore, prematurely born adults exhibited higher fasting glucose and insulin levels, as well as elevated HOMA-IR values and total cholesterol levels, in comparison with adults born at term. No difference was found between preterm adults and those born at term in other outcomes examined, including BMI, waist circumference, WHR, FMD, cIMT, PWV, HDL, LDL, and TG.

A previous systematic review and meta-analysis showed similar results regarding increased arterial blood pressure (SBP, DBP, 24-hour SBP) in adults born preterm in comparison with adults born after a full-term pregnancy[6]; however, no difference was found regarding other outcomes associated with the metabolic syndrome, such as BMI, WHR, FM, 24-hour DBP, cIMT, FMD, PWV, glucose and insulin levels, or total cholesterol, HDL, and TG levels. A smaller meta-analysis investigating the association between prematurity and SBP from neonatal to adult life also reported increased SBP in individuals born preterm.[8] Meanwhile, because the possible association of prematurity with the metabolic syndrome and/or cardiovascular disease is an interesting field of research, a number of new studies have been published, although with conflicting results[5,13,15,17,24,27-41]; thus, a repeat systematic review and meta-analysis would be useful to provide up-to-date knowledge. Our systematic review and meta-analysis indeed showed additional associations between prematurity and outcomes related to the metabolic syndrome, beyond increased arterial blood pressure; the greater number of included studies compared with the previous systematic reviews and meta-analyses is the main strength of our study.

In our meta-analysis, asymmetry of the funnel plots of SBP and DBP mean difference between preterm- and term-born adults, as well as the statistically significant results of the Egger test, are suggestive of publication bias. Publication bias arises from the greater possibility of publication of studies that found a positive association between prematurity and increased arterial blood pressure; furthermore, studies with small populations may conclude in larger effects. Thus, as

Parkinson et al have reported in their meta-analysis,[6] the statistically significant difference of arterial blood pressure between preterm- and term-born adults may have been overestimated. Nevertheless, a trim and fill analysis used to identify and correct for funnel plot asymmetry also indicated a statistically significant mean difference of SBP and DBP between preterm and term adults. Regarding 24-hour ambulatory monitoring of SBP and DBP, and its greater reliability for assessing blood pressure, the mean differences were significant between groups despite the limited number of studies. Interestingly, a nocturnal decrease in blood pressure (dipper pattern) in preterm-born adults is maintained, at least at this young age; the absence of a dipper pattern in blood pressure is a well-established cause of cardiovascular risk.

Endothelial dysfunction plays a role in the development of cardiovascular disease, because it is considered the initial step in the process of atherosclerosis.[1] However, only a small number of studies have been conducted so far to detect an association between prematurity and endothelial dysfunction, with conflicting results.[6,23-26] This meta-analysis showed no association between prematurity and biomarkers of endothelial dysfunction, including FMD, cIMT, and PWV; nevertheless, the number of studies examining this association was quite small, and differences in the methodology applied among studies may act as barriers to reveal any significant correlation with prematurity.

A sex-specific analysis revealed significantly higher 24-hour SBP and 24-hour DBP in women born prematurely compared with women born at term, and by examining sex as a cause of heterogeneity, the preterm–term differences in SBP, DBP, and 24-hour SBP were greater in women than in men. However, it is difficult to reach a firm conclusion as to whether prematurely born women are at a greater risk for hypertension compared with prematurely born men; the number of studies that evaluated the 24-hour SBP and 24-hour DBP is rather small, the total number of women studied was significantly lower compared with the total number of men, and also information regarding gestational age at birth, separately for male and female participants, is missing. Nevertheless, several studies have shown that there is a positive association between catchup growth and arterial blood pressure[73]; interestingly, the velocity of weight gain during childhood and adolescence is higher in women with very low birth weight compared with very low birth weight men.[74]

Controversy exists so far whether total FM is increased in preterm-born individuals. Recent studies have shown that prematurity is associated with a higher percentage of body fat, as estimated by bioelectrical impedance, dual-energy x-ray absorptiometry, and whole body MRI.[16,20,32,36,38,56,57,63,68] In contrast, in other studies, adults born prematurely exhibit no difference in FM percentage in comparison with adults born at term; in addition, they are shorter, and have a lower BMI and total lean mass.[12,22,60] We found that prematurity was associated with a higher percent of total body fat; heterogeneity was low, despite the use of different methodologies among studies. Although no difference was found in BMI between adults born prematurely and those born at term, metaregression revealed a positive correlation between preterm–term differences in BMI and the mean participants' age. The average age at assessment of outcomes in our study population was low. The evaluation of preterm-born individuals at an older age may reveal a positive association between preterm birth and BMI.

The finding of increased levels of total cholesterol in adults born prematurely contradicts the results of the previously published meta-analysis showing only higher LDL levels in this group in comparison with adults born at term.[6] We found that preterm–term differences in TG levels were lower in individuals participating in European studies in comparison with those participating in studies conducted in the US, Asia, or Oceania; the increasing prevalence of components of the metabolic syndrome recently across Europe may offer an explanation for the small preterm–term difference of TG levels in European studies.[75] Furthermore, preterm–term HDL level differences were lower in participants in studies conducted in Oceania. Data from the 2011-2012 Australian Health Survey showed that almost 23% of the adult Australian population demonstrated low HDL levels,[76] and several reports described extremely low HDL levels in Australian indigenous populations, resulting from a complex interplay of environmental and genetic factors.[77]

A significant and novel finding of our meta-analysis is the increased levels of fasting glucose and insulin, and the elevated HOMA-IR, in adults born prematurely compared with adults born at term. In contrast with the previous relevant meta-analysis,[6] which included 27 studies, our meta-analysis examined 43 studies providing more data on glucose and insulin levels of preterm born adults compared with adults born at term.

Being born SGA is a potential confounding factor in the observed association between prematurity and components of the metabolic syndrome/cardiovascular disease in adult life. In our systematic review and meta-analysis, 7 studies attempted to address this issue by comparing adults born prematurely and AGA (preterm AGA), adults born prematurely and SGA (preterm SGA) or with IUGR (preterm IUGR), and adults born at term and AGA (control AGA).[20,21,24,30,31,33,68] No significant difference between preterm AGA and preterm SGA or IUGR was reported in any of the outcomes assessed in these studies; only Juonala et al found a significantly higher SPB in preterm SGA in comparison with preterm AGA.[31] In the majority of the studies discussed, the significant preterm–term differences retained their statistical significance when preterm AGA and control AGA were compared. Furthermore, when only the preterm AGA population instead of the total preterm population of these studies was included in our meta-analysis, the significant preterm–term differences of outcomes assessed remained significant. This fact possibly indicates that the risk for metabolic syndrome and cardiovascular disease in individuals born preterm is independent of being born SGA or IUGR.

Limitations of our systematic review and meta-analysis are the following. There was a limited number of studies examining waist circumference, WHR, 24-hour SBP, 24-hour DBP, FMD, cIMT, PWV, and HOMA-IR, thus decreasing the ability to detect any existing association. Furthermore, the pooled effects of the outcomes examined were not adjusted for possible confounding factors, such as age and sex; nevertheless, metaregression revealed no impact of several confounding factors on the majority of the outcomes. Adults participating in studies included in the meta-analysis were of a young mean age; more studies are needed to evaluate the components of the metabolic syndrome at an older age (ie, >30-40 years of age) to determine more precisely the associations between preterm birth and cardiovascular risk factors.

An early, constant, and prolonged follow-up program, as well as an intervention plan, for prematurely born individuals, may be useful for the prevention, early detection, and appropriate treatment of disorders leading to the metabolic syndrome and cardiovascular disease in later life. ■

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References

1. Visentin S, Grumolato F, Nardelli GB, Di Camillo B, Grisan E, Cosmi E. Early origins of adult disease: low birth weight and vascular remodeling. Atherosclerosis 2014;237:391-9.
2. Bayman E, Drake AJ, Piyasena C. Prematurity and programming of cardiovascular disease risk: a future challenge for public health? Arch Dis Child Fetal Neonatal Ed 2014;99:510-4.
3. de Boo HA, Harding JE. The developmental origins of adult disease (Barker) hypothesis. Aust N Z J Obstet Gynaecol 2006;46:4-14.
4. Johansson S, Iliadou A, Bergvall N, Tuvemo T, Norman M, Cnattingius S. Risk of high blood pressure among young men increases with the degree of immaturity at birth. Circulation 2005;112:3430-6.
5. Lewandowski AJ, Davis EF, Yu G, Digby JE, Boardman H, Whitworth P, et al. Elevated blood pressure in preterm-born offspring associates with a distinct antiangiogenic state and microvascular abnormalities in adult life. Hypertension 2015;65:607-14.
6. Parkinson JR, Hyde MJ, Gale C, Santhakumaran S, Modi N. Preterm birth and the metabolic syndrome in adult life: a systematic review and meta-analysis. Pediatrics 2013;131:1240-63.
7. Sipola-Leppänen M, Karvonen R, Tikanmäki M, Matinolli HM, Martikainen S, Pesonen AK, et al. Ambulatory blood pressure and its variability in adults born preterm. Hypertension 2015;65:615-21.
8. de Jong F, Monuteaux MC, van Elburg RM, Gillman MW, Belfort MB. Systematic review and meta-analysis of preterm birth and later systolic blood pressure. Hypertension 2012;59:226-34.
9. Hack M, Schluchter M, Cartar L, Rahman M. Blood pressure among very low birth weight (<1.5 kg) young adults. Pediatr Res 2005;58:677-84.
10. Hofman PL, Regan F, Jackson WE, Jefferies C, Knight DB, Robinson EM, et al. Premature birth and later insulin resistance. N Engl J Med 2004;351:2179-86.
11. Kajantie E, Strang-Karlsson S, Hovi P, Wehkalampi K, Lahti J, Kaseva N, et al. Insulin sensitivity and secretory response in adults born preterm: the Helsinki Study of Very Low Birth Weight Adults. J Clin Endocrinol Metab 2015;100:244-50.
12. Hovi P, Andersson S, Eriksson JG, Järvenpää AL, Strang-Karlsson S, Mäkitie O, et al. Glucose regulation in young adults with very low birth weight. N Engl J Med 2007;356:2053-63.
13. Sipola-Leppänen M, Vääräsmäki M, Tikanmäki M, Matinolli HM, Miettola S, Hovi P, et al. Cardiometabolic risk factors in young adults who were born preterm. Am J Epidemiol 2015;181:861-73.
14. Hirschler V, Bugna J, Roque M, Gilligan T, Gonzalez C. Does low birth weight predict obesity/overweight and metabolic syndrome in elementary school children? Arch Med Res 2008;39:796-802.
15. Hovi P, Kajantie E, Soininen P, Kangas AJ, Järvenpää AL, Andersson S, et al. Lipoprotein subclass profiles in young adults born preterm at very low birth weight. Lipids Health Dis 2013;12:57.
16. Thomas EL, Parkinson JR, Hyde MJ, Yap IK, Holmes E, Doré CJ, et al. Aberrant adiposity and ectopic lipid deposition characterize the adult phenotype of the preterm infant. Pediatr Res 2011;70:507-12.
17. Breukhoven PE, Kerkhof GF, Willemsen RH, Hokken-Koelega AC. Fat mass and lipid profile in young adults born preterm. J Clin Endocrinol Metab 2012;97:1294-302.
18. Willemsen RH, Leunissen RW, Stijnen T, Hokken-Koelega AC. Prematurity is not associated with reduced insulin sensitivity in adulthood. J Clin Endocrinol Metab 2009;94:1695-700.
19. Singhal A, Kattenhorn M, Cole TJ, Deanfield J, Lucas A. Preterm birth, vascular function, and risk factors for atherosclerosis. Lancet 2001;358:1159-60.
20. Rotteveel J, van Weissenbruch MM, Twisk JW, Delemarre-Van de Waal HA. Abnormal lipid profile and hyperinsulinaemia after a mixed meal: additional cardiovascular risk factors in young adults born preterm. Diabetologia 2008;51:1269-75.
21. Irving RJ, Belton NR, Elton RA, Walker BR. Adult cardiovascular risk factors in premature babies. Lancet 2000;355:2135-6.
22. Evensen KA, Steinshamn S, Tjønna AE, Stølen T, Høydal MA, Wisløff U, et al. Effects of preterm birth and fetal growth retardation on cardiovascular risk factors in young adulthood. Early Hum Dev 2009;85:239-45.
23. Bassareo PP, Fanos V, Puddu M, Demuru P, Cadeddu F, Balzarini M, et al. Reduced brachial flow-mediated vasodilation in young adult ex extremely low birth weight preterm: a condition predictive of increased cardiovascular risk? J Matern Fetal Neonatal Med 2010;23:121-4.
24. Kerkhof GF, Breukhoven PE, Leunissen RW, Willemsen RH, Hokken-Koelega AC. Does preterm birth influence cardiovascular risk in early adulthood? J Pediatr 2012;161:390-6.
25. Lazdam M, de la Horra A, Pitcher A, Mannie Z, Diesch J, Trevitt C, et al. Elevated blood pressure in offspring born premature to hypertensive pregnancy: is endothelial dysfunction the underlying vascular mechanism? Hypertension 2010;56:159-65.
26. Skilton MR, Viikari JS, Juonala M, Laitinen T, Lehtimäki T, Taittonen L, et al. Fetal growth and preterm birth influence cardiovascular risk factors and arterial health in young adults: the Cardiovascular Risk in Young Finns Study. Arterioscler Thromb Vasc Biol 2011;31:2975-81.
27. Bassareo PP, Fanos V, Puddu M, Flore G, Mercuro G. Advanced intrauterine growth restriction is associated with reduced excretion of asymmetric dimethylarginine. Early Hum Dev 2014;90:173-6.
28. Bassareo PP, Fanos V, Puddu M, Marras S, Mercuro G. Epicardial fat thickness, an emerging cardiometabolic risk factor, is increased in young adults born preterm. J Dev Orig Health Dis 2016;7:369-73.
29. Breij LM, Kerkhof GF, Hokken-Koelega AC. Risk for nonalcoholic fatty liver disease in young adults born preterm. Horm Res Paediatr 2015;84:199-205.
30. Chaudhari S, Otiv M, Khairnar B, Pandit A, Hoge M, Sayyad M. Pune low birth weight study, growth from birth to adulthood. Indian Pediatr 2012;49:727-32.
31. Juonala M, Cheung MM, Sabin MA, Burgner D, Skilton MR, Kähönen M, et al. Effect of birth weight on life-course blood pressure levels among children born premature: the Cardiovascular Risk in Young Finns Study. J Hypertens 2015;33:1542-8.
32. Kaczmarczyk K, Pituch-Zdanowska A, Wiszomirska I, Magiera A, Ronikier A. Long-term effects of premature birth on somatic development in women through adolescence and adulthood. J Int Med Res 2018;46:44-53.

33. Kistner A, Vanpée M, Hall K. Leptin may enhance hepatic insulin sensitivity in children and women born small for gestational age. Endocr Connect 2013;2:38-49.
34. Lewandowski AJ, Bradlow WM, Augustine D, Davis EF, Francis J, Singhal A, et al. Right ventricular systolic dysfunction in young adults born preterm. Circulation 2013;128:713-20.
35. Prickett TCR, Darlow BA, Troughton RW, Cameron VA, Elliott JM, Martin J, et al. New insights into cardiac and vascular natriuretic peptides: Findings from young adults born with very low birth weight. Clin Chem 2018;64:363-73.
36. Mathai S, Derraik JG, Cutfield WS, Dalziel SR, Harding JE, Biggs J, et al. Increased adiposity in adults born preterm and their children. PLoS One 2013;8:e81840.
37. Mathai S, Derraik JG, Cutfield WS, Dalziel SR, Harding JE, Biggs JB, et al. Blood pressure abnormalities in adults born moderately preterm and their children. Int J Cardiol 2015;181:152-4.
38. Morrison KM, Ramsingh L, Gunn E, Streiner D, Van Lieshout R, Boyle M, et al. Cardiometabolic health in adults born premature with extremely low birth weight. Pediatrics 2016;138:e20160515.
39. Roberts G, Lee KJ, Cheong JL, Doyle LW. Group of Victorian Infant Collaborative Study. Higher ambulatory blood pressure at 18 years in adolescents born less than 28 weeks' gestation in the 1990s compared with term controls. J Hypertens 2014;32:620-6.
40. Sharafi M, Duffy VB, Miller RJ, Winchester SB, Huedo-Medina TB, Sullivan MC. Dietary behaviors of adults born prematurely may explain future risk for cardiovascular disease. Appetite 2016;99:157-67.
41. Smith CM, Wright NP, Wales JK, Mackenzie C, Primhak RA, Eastell R, et al. Very low birth weight survivors have reduced peak bone mass and reduced insulin sensitivity. Clin Endocrinol (Oxf) 2011;75:443-9.
42. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ 2009;339:2700.
43. Simera I, Moher D, Hoey J, Schulz KF, Altman DG. A catalogue of reporting guidelines for health research. Eur J Clin Invest 2010;40:35-53.
44. Deeks JJ, Dinnes J, D'Amico R, Sowden AJ, Sakarovitch C, Song F, et al. Evaluating non-randomised intervention studies. Health Technol Assess 2003;7:1-173.
45. Collaboration TC. Cochrane handbook for systematic reviews of interventions version 5.1.0. Copenhagen: The Nordic Cochrane Centre; 2011.
46. Staten MA, Stern MP, Miller WG, Steffes MW, Campbell SE. Insulin Standardization Workgroup. Insulin assay standardization: leading to measures of insulin sensitivity and secretion for practical clinical care. Diabetes Care 2010;33:205-6.
47. Higgins JP, White IR, Anzures-Cabrera J. Meta-analysis of skewed data: combining results reported on log-transformed or raw scales. Stat Med 2008;27:6072-92.
48. Altman DG, Bland JM. Detecting skewness from summary information. BMJ 1996;313:1200.
49. Hardy RJ, Thompson SG. Detecting and describing heterogeneity in meta-analysis. Stat Med 1998;17:841-56.
50. Harbord R, Higgins J. Meta-regression in Stata. Stata J 2008;8:493-519.
51. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629-34.
52. Duval S, Tweedie R. Trim and fill: a simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. Biometrics 2000;56:455-63.
53. Oren A, Vos LE, Uiterwaal CS, Grobbee DE, Bots ML. Aortic stiffness and carotid intima-media thickness: two independent markers of subclinical vascular damage in young adults? Eur J Clin Invest 2003;33:949-54.
54. Pilgaard K, Færch K, Carstensen B, Poulsen P, Pisinger C, Pedersen O, et al. Low birthweight and premature birth are both associated with type 2 diabetes in a random sample of middle-aged Danes. Diabetologia 2010;53:2526-30.
55. Cooper R, Atherton K, Power C. Gestational age and risk factors for cardiovascular disease: evidence from the 1958 British birth cohort followed to mid-life. Int J Epidemiol 2009;38:235-44.
56. Kerkhof GF, Leunissen RW, Willemsen RH, de Jong FH, Stijnen T, Hokken-Koelega AC. Influence of preterm birth and birth size on gonadal function in young men. J Clin Endocrinol Metab 2009;94:4243-50.
57. Kerkhof GF, Leunissen RW, Willemsen RH, de Jong FH, Visser JA, Laven JS, et al. Influence of preterm birth and small birth size on serum anti-Müllerian hormone levels in young adult women. Eur J Endocrinol 2010;163:937-44.
58. Szathmári M, Vásárhelyi B, Tulassay T. Effect of low birth weight on adrenal steroids and carbohydrate metabolism in early adulthood. Horm Res 2001;55:172-8.
59. Hovi P, Turanlahti M, Strang-Karlsson S, Wehkalampi K, Järvenpää AL, Eriksson JG, et al. Intima-media thickness and flow-mediated dilatation in the Helsinki study of very low birth weight adults. Pediatrics 2011;127:304-11.
60. Saigal S, Stoskopf B, Streiner D, Paneth N, Pinelli J, Boyle M. Growth trajectories of extremely low birth weight infants from birth to young adulthood: a longitudinal, population-based study. Pediatr Res 2006;60:751-8.
61. Dalziel SR, Parag V, Rodgers A, Harding JE. Cardiovascular risk factors at age 30 following pre-term birth. Int J Epidemiol 2007;36:907-15.
62. Doyle LW, Faber B, Callanan C, Morley R. Blood pressure in late adolescence and very low birth weight. Pediatrics 2003;111:252-7.
63. Hovi P, Andersson S, Järvenpää AL, Eriksson JG, Strang-Karlsson S, Kajantie E, et al. Decreased bone mineral density in adults born with very low birth weight: a cohort study. PLoS Med 2009;6:e1000135.
64. Hovi P, Andersson S, Räikkönen K, Strang-Karlsson S, Järvenpää AL, Eriksson JG, et al. Ambulatory blood pressure in young adults with very low birth weight. J Pediatr 2010;156:54-9.
65. Kistner A, Celsi G, Vanpee M, Jacobson SH. Increased blood pressure but normal renal function in adult women born preterm. Pediatr Nephrol 2000;15:215-20.
66. Kistner A, Jacobson SH, Celsi G, Vanpee M, Brismar K. IGFBP-1 levels in adult women born small for gestational age suggest insulin resistance in spite of normal BMI. J Intern Med 2004;255:82-8.
67. Lewandowski AJ, Augustine D, Lamata P, Davis EF, Lazdam M, Francis J, et al. Preterm heart in adult life: cardiovascular magnetic resonance reveals distinct differences in left ventricular mass, geometry, and function. Circulation 2013;127:197-206.
68. Walker BR, Irving RJ, Andrew R, Belton NR. Contrasting effects of intrauterine growth retardation and premature delivery on adult cortisol secretion and metabolism in man. Clin Endocrinol (Oxf) 2002;57:351-5.
69. Fagerberg B, Bondjers L, Nilsson P. Low birth weight in combination with catch-up growth predicts the occurrence of the metabolic syndrome in men at late middle age: the Atherosclerosis and Insulin Resistance study. J Intern Med 2004;256:254-9.
70. Järvelin MR, Sovio U, King V, Lauren L, Xu B, McCarthy MI, et al. Early life factors and blood pressure at age 31 years in the 1966 northern Finland birth cohort. Hypertension 2004;44:838-46.
71. Leotta G, Rabbia F, Milan A, Mulatero P, Veglio F. Effects of birth weight on spontaneous baroreflex sensitivity in adult life. Nutr Metab Cardiovasc Dis 2007;17:303-10.
72. Wells GA, Shea B, O'Connel D. The Newcastle-Ottawa scale (NOS) for assessing the quality of nonrandomized studies in meta-analyses [updated 2009]. http://www.ohri.ca/programs/clinical epidemiology/oxford.htm. Accessed November 20, 2018.
73. Gerber LM, Stern PM. Relationship of body size and body mass to blood pressure: sex-specific and developmental influences. Hum Biol 1999;71:505-28.
74. Hack M, Schluchter M, Cartar L, Rahman M, Cuttler L, Borawski E. Growth of very low birth weight infants to age 20 years. Pediatrics 2003;112:e30-8.

75. Kjeldsen SE, Naditch-Brule L, Perlini S, Zidek W, Farsang C. Increased prevalence of metabolic syndrome in uncontrolled hypertension across Europe: the Global Cardiometabolic Risk Profile in Patients with hypertension disease survey. J Hypertens 2008;26:2064-70.

76. Australian Health Survey. Biomedical results for chronic diseases 2013. www.abs.gov.au/australianhealthsurvey. Accessed January 15, 2019.

77. Lyons JG, O'Dea K, Walker KZ. Evidence for low high-density lipoprotein cholesterol levels in Australian indigenous peoples: a systematic review. BMC Public Health 2014;14:545.

50 Years Ago in *THE JOURNAL OF PEDIATRICS*

Culturing Beta Hemolytic Streptococci in Pediatric Practice – Observation After Twenty Years

Breese BB. J Pediatr 1969;75:164-166.

In 1969, Dr Burtis Burr Breese reported that, since the end of World War II and the advent of penicillin, he and Dr Frank Disney, both of whom had been impressed by the aid that bacteriologic cultures had provided in the management of streptococcal pharyngitis among military recruits, performed cultures for beta-hemolytic streptococci on site in their "4-man" private pediatric practice in Rochester, New York. He mused that more than 3 decades later, 150 000 such cultures had been performed. In the 20 years leading up to their 1969 report in *The Journal*, >10 000 cultures were performed, and 20% were positive.

Dr Breese published extensively over the following decades on the nuances of culture findings (especially regarding density of organisms) and clinical aspects of group A streptococcal pharyngitis, rheumatic fever, and poststreptococcal glomerulonephritis. The world of clinical microbiology, quality control in laboratory medicine, and antigen detection of *Streptococcus pyogenes* also developed exponentially over this timeframe. For several valid reasons, few practices currently go beyond antigen testing on site. The systems and turnaround times for culture results to back up negative antigen tests have improved. The current cost of using a clinical laboratory would not match up to Dr Breese's on-site culture cost, which he estimated in the 1960s to be 30 cents (including technician's time, media, etc.), nor would it substitute for the closeness he felt to his patients' problems, or their parents' appreciation for his personal investment.

In honor of the contributions of B.B. Breese, in 2006 his family and supporters established an award held in the Pediatric Infectious Diseases Society (PIDS) to be given annually to the authors of the article published in *The Pediatric Infectious Disease Journal* that best illustrated Dr Breese's principles and practices. Dr Breese's major legacy in pediatric infectious diseases was his daughter, Dr Caroline Breese Hall who garnered international acclaim for her clinical and laboratory research, especially in respiratory syncytial virus and human herpesvirus 6. In 2013, after her death, the PIDS award became the Caroline B. Hall Clinically Innovative Research Award for junior investigators.

Dr Hall liked to begin a chapter or end an editorial with a bit of poetry. Not having such talent, suffice it for us to remember fondly a father and a daughter who were lifetime personifications of our "better selves" (William Wordsworth).

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St. Christopher's Hospital for Children
Philadelphia, Pennsylvania

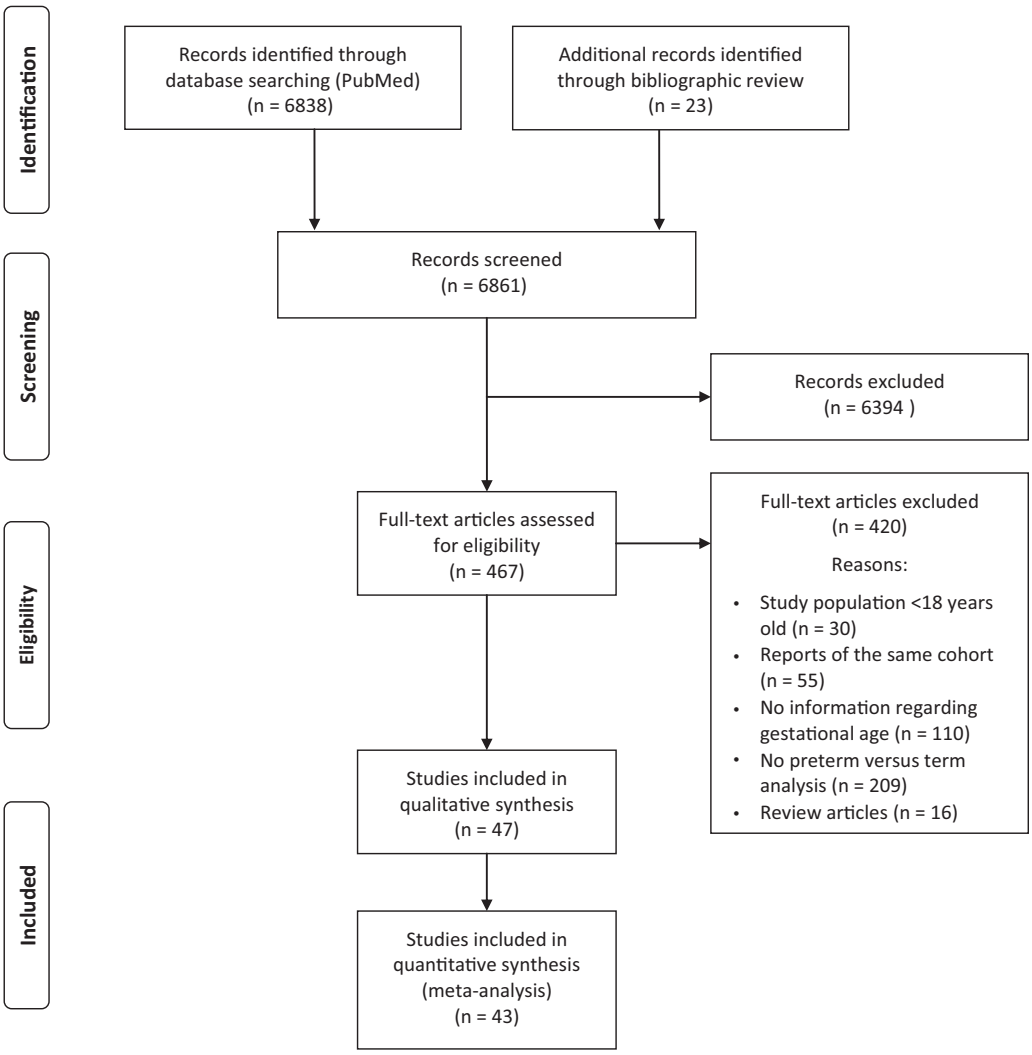

Figure 1. Workflow of systematic review and meta-analysis.

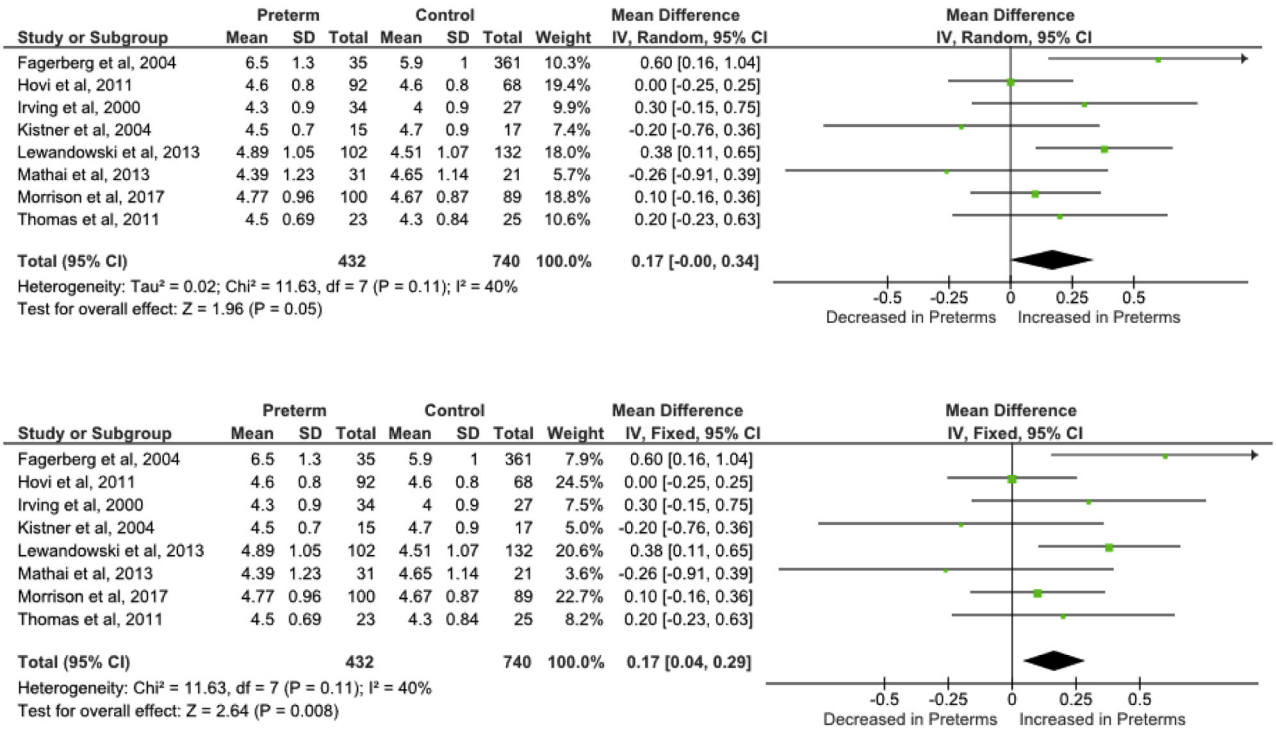

Figure 5. Forest plots showing the unadjusted pooled association between premature birth (gestational age of <37 weeks) and total cholesterol (random and fixed effect model). *IV*, inverse variance.

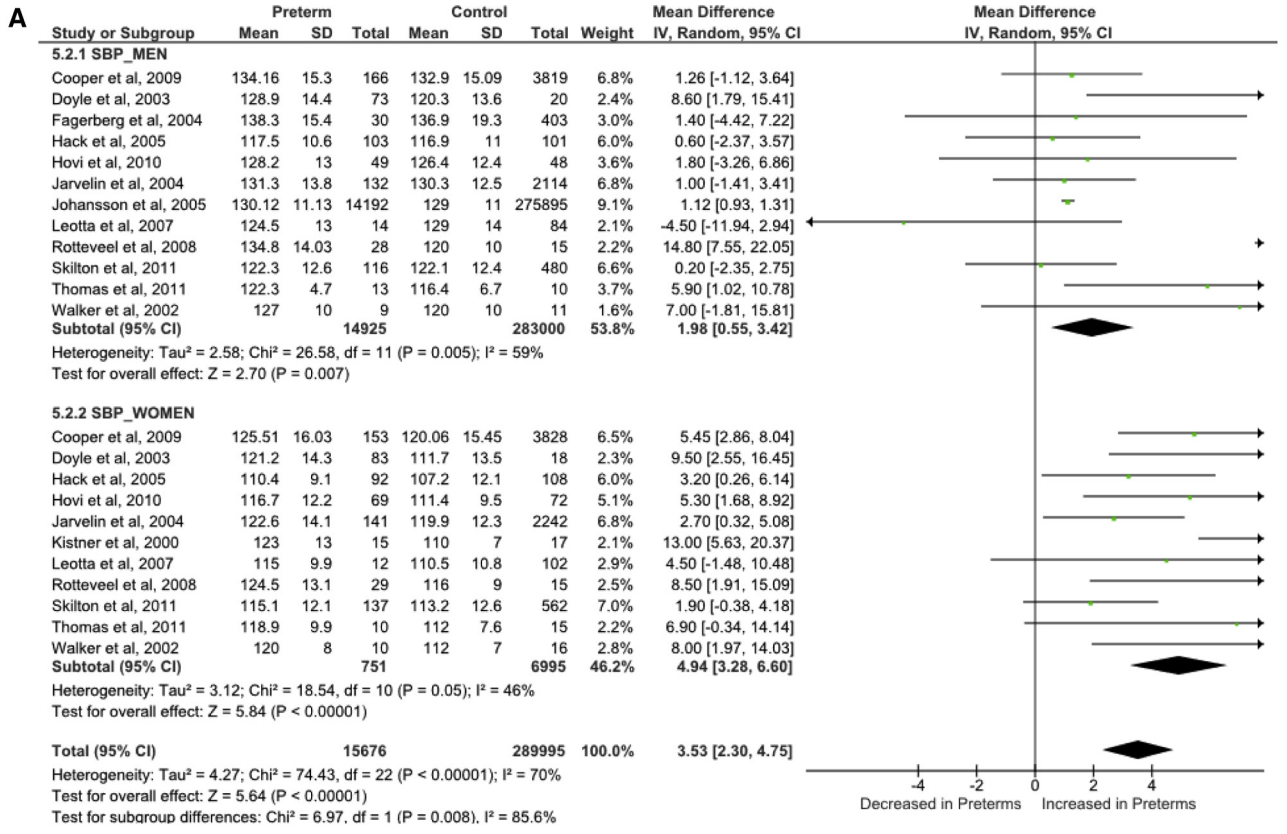

Figure 6. Forest plots showing the unadjusted pooled association between premature birth (gestational age of <37 weeks) and **A**, SBP, **B**, DBP, **C**, 24-hour SBP, and **D**, 24-hour DBP in men and women. *(Continues on next page)*

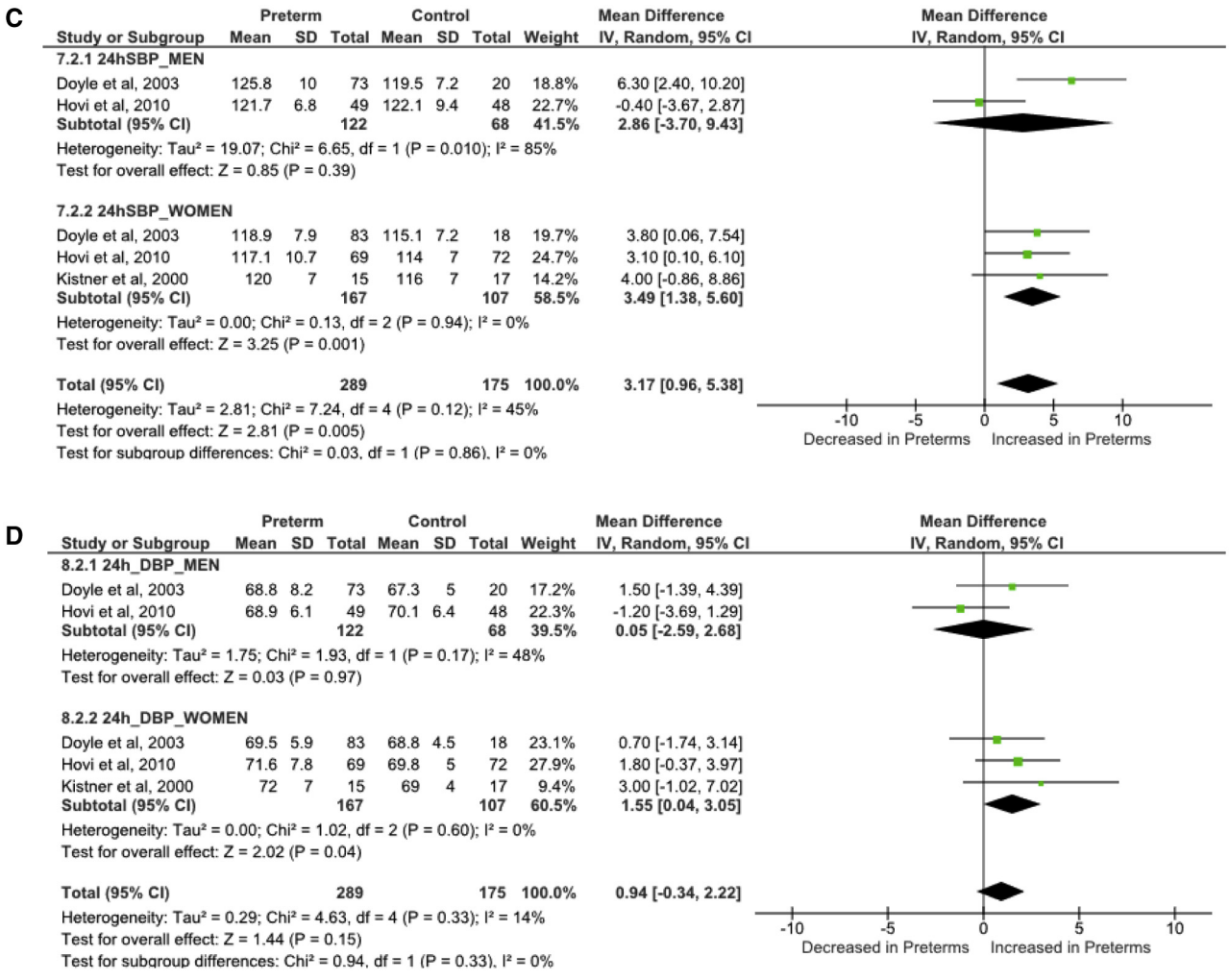

Figure 6. Continued

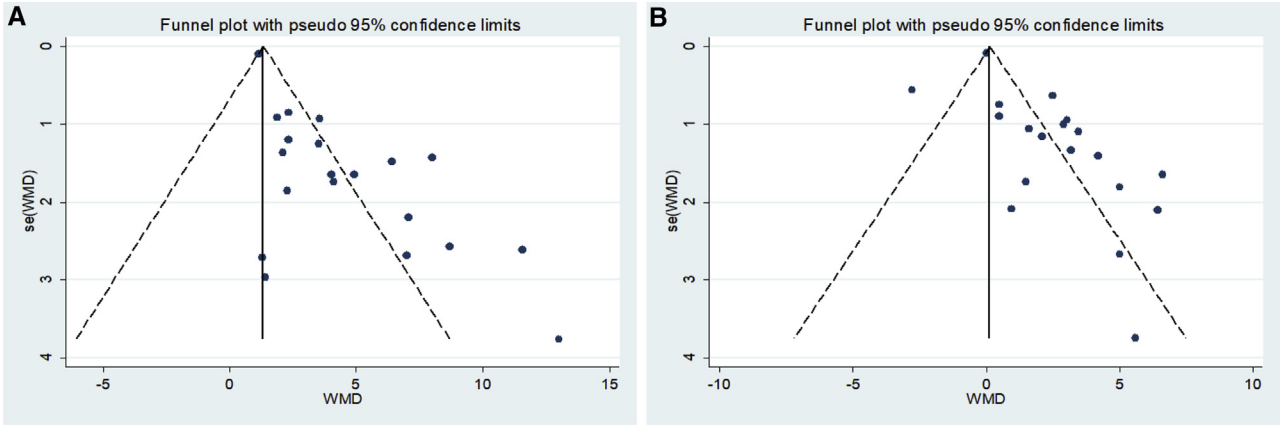

Figure 7. Funnel plots showing the unadjusted pooled association between premature birth (gestational age of <37 weeks) and **A**, SBP and **B**, DBP in adult life. *WMD*, weighted mean difference.

Table III. Results of meta-analyses of study outcomes: Associations between preterm birth (gestational age of <37 weeks) and components of the metabolic syndrome/cardiovascular risk factors in adult men and women

Outcome	No. of studies	No. of participants	Pooled mean difference (95% CI)	FE/RE *P* value	Heterogeneity (I^2, *P* value)	Sex-specific pooled mean difference (95% CI) and *P* value	Egger test (*P* value)
BMI							
Men	15	P: 14 947 T: 281 038	RE: −0.07 kg/m^2 (−0.49 to 0.34)	RE: *P* = .72	I^2: 53%; *P* = .008	RE: −0.03 kg/m^2 (−0.31 to 0.24); *P* = .82 FE: −0.02 kg/m^2 (−0.08 to 0.03); *P* = .44	.74
Women	16	P: 902 T: 5189	RE: 0.04 kg/m^2 (−0.36 to 0.44) FE: 0.04 kg/m^2 (−0.32 to 0.41)	RE: *P* = .85 FE: *P* = .81	I^2: 14%; *P* = .29		.48
WHR							
Men	3	P: 69 T: 68	RE: 0.02 (−0.0 to 0.04)	RE: *P* = .08	I^2: 43%; *P* = .17	**RE: 0.02 (−0.0 to 0.03); *P* = .05**	-
Women	4	P: 88 T: 113	RE: 0.01 (−0.02 to 0.04)	RE: *P* = .4	I^2: 65%; *P* = .04		.5
Percent FM							
Men	6	P: 271 T: 271	RE: 1.27% (−0.38 to 2.93)	RE: *P* = .13 FE: *P* = .08	I^2: 53%; *P* = .06	**RE: 0.92% (0.09 to 1.74); *P* = .03** **FE: 0.85% (0.15 to 1.55); *P* = .02**	.12
Women	7	P: 285 T: 397	RE: 0.78% (−0.14 to 1.71) FE: 0.78% (−0.14 to 1.71)	RE: *P* = .1 FE: *P* = .1	I^2: 0%; *P* = .57		.67
SBP							
Men	12	P: 14 925 T: 283 000	RE: 1.98 mm Hg (0.55 to 3.42)	**RE: *P* = .007**	I^2: 59%; *P* = .005	**RE: 3.53 mm Hg (2.3 to 4.75); *P* < .0001**	.18
Women	11	P: 751 T: 6995	RE: 4.94 mm Hg (3.28 to 6.6) FE: 4.18 mm Hg (3.09 to 5.27)	**RE: *P* < .001** **FE: *P* < .001**	I^2: 46%; *P* = .05		**.002**
DBP							
Men	11	P: 14 916 T: 282 989	RE: 1.29 mm Hg (0.13 to 2.45)	**RE: *P* = .03**	I^2: 65%; *P* = .001	**RE: 2.13 mm Hg (1.14 to 3.11); *P* < .0001**	**.03**
Women	10	P: 741 T: 6979	RE: 2.89 mm Hg (1.61 to 4.16) FE: 2.57 mm Hg (1.72 to 3.41)	**RE: *P* < .001** **FE: *P* < .001**	I^2: 45%; *P* = .06		.12
24-Hour SBP							
Men	2	P: 122 T: 68	RE: 2.86 mm Hg (−3.7 to 9.43)	RE: *P* = .39	I^2: 85%; *P* = .01	**RE: 3.17 mm Hg (0.96 to 5.38); *P* = .005**	-
Women	3	P: 167 T: 107	RE: 3.49 mm Hg (1.38 to 5.6)	**RE: *P* = .001**	I^2: 0%; *P* = .94		-
24-Hour DBP							
Men	2	P: 122 T: 68	RE: 0.05 mm Hg (−2.59 to 2.68)	RE: *P* = .97	I^2: 48%; *P* = .17	RE: 0.94 mm Hg (−0.34 to 2.22); *P* = .15	-
Women	3	P: 167 T: 107	RE: 1.55 mm Hg (0.04 to 3.05)	**RE: *P* = .04**	I^2: 0%; *P* = .6		-

FE, fixed effect model; *P*, preterm-born adults; *RE*, random effect model; *T*, term-born adults. Statistical significance is defined by P ≤ 0.05. Significant results are shown in bold type.