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Cardiovascular risk factors in those born preterm – systematic review and meta-analysis

Prabha H. Andraweera, Bradley Condon, Gemma Collett, Stefania Gentilcore and Zohra S. Lassi

Adelaide Medical School and The Robinson Research Institute, The University of Adelaide, Adelaide, Australia

Review

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Address for correspondence:
Prabha Andraweera, Discipline of Obstetrics and Gynaecology, Adelaide Medical School and The Robinson Research Institute, The University of Adelaide, Adelaide, Australia
Email prabha.andraweera@adelaide.edu.au

Abstract

Emerging evidence demonstrates a link between preterm birth (PTB) and later life cardiovascular disease (CVD). We conducted a systematic review and meta-analysis to compare conventional CVD risk factors between those born preterm and at term. PubMed, CINAHL, SCOPUS, and EMBASE databases were searched. The review protocol is registered in PROSPERO (CRD42018095005). CVD risk factors including systolic blood pressure (SBP), diastolic blood pressure (DBP), body mass index, lipid profile, blood glucose, and fasting insulin among those born preterm (<37 weeks' gestation) were compared with those born at term (≥37 weeks' gestation). Subgroup analyses based on gender, age, gestational at birth (<32 weeks' gestation and <28 weeks' gestation), and PTB associated with small for gestational age or average for gestational age were also performed. Fifty-six studies provided data on 308,987 individuals. Being born preterm was associated with 3.26 mmHg (95% confidence interval [CI] 2.08 to 4.44) higher mean SBP and 1.32 mmHg (95% CI: 0.61 to 2.04) higher mean DBP compared to being born at term. Subgroup analyses demonstrated that SBP was higher among (a) preterm compared to term groups from early adolescence until adulthood; (b) females born preterm but not among males born preterm compared to term controls; and (c) those born at <32 weeks or <28 weeks compared to term. Our meta-analyses demonstrate higher SBP and DBP among those born preterm compared to term. The difference in SBP is evident from early adolescence until adulthood.

Introduction

Cardiovascular disease (CVD) is a major public health burden and is a leading cause of morbidity and mortality in both developed and developing countries[1]. In addition to suboptimal lifestyle and environmental factors in adult life, early life experiences are believed to contribute to CVD[2]. Preterm birth (PTB) affects 5%–8% of pregnancies worldwide with an estimated 15 million babies born before the completion of 37 weeks' of gestation each year[3]. In addition to being the leading cause of mortality among neonates, infants, and children under 5 years of age, there is an increasing evidence to show that those born preterm are at increased risk of developing CVD in adulthood[4]. With one in 10 babies born preterm and >99% surviving due to improved newborn care, long-term health outcome of those born preterm is a growing health concern[5].

A number of studies have identified PTB as a risk factor for higher blood pressure (BP), higher body mass index (BMI), and type 2 diabetes mellitus (T2DM). A systematic review and meta-analysis reports that PTB associates with an increased risk of T2DM[6]. However, other studies have shown no association between PTB and systolic BP (SBP) or insulin sensitivity. A recent systematic review that evaluated risk factors for CVD among adults (≥ 18 years of age) born preterm reports that PTB is associated with higher SBP, diastolic BP (DBP), 24 h DBP, fat mass, glucose, insulin, and total cholesterol levels[7]. However, whether this elevated risk factor profile is evident from childhood is not known. Therefore, our primary aim was to conduct a systematic review and meta-analysis on the association between PTB and key risk factors for CVD including BP, BMI, fasting glucose, insulin, and lipids using data from studies from birth until adulthood. Our secondary aim was to assess the risk factor profile based on gender, age, gestational age at birth, and PTB associated with small for gestational age (SGA) or average for gestational age (AGA) subgroups.

Methods

Data sources and search strategy

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA),[8] and the review protocol is registered with PROSPERO (CRD42018095005). The electronic databases, PubMed, CINAHL, the Cochrane Library, and EMBASE were searched with an end of search date of

July 14, 2020. A full list of the search terms is included in the Supplementary Material. Earlier reviews of relevant topics and bibliographies of included papers were also checked for relevant publications.

Study section and data extraction

Studies were selected if they compared CVD risk factors in offspring born preterm compared to offspring born at term. "Preterm" was defined as delivery <37 weeks' gestation and "term" was defined as delivery ≥37 weeks' gestation[9]. In addition, studies on very low birthweight infants where gestational age at birth was reported to be prior to 37 weeks' gestation were also included. We included studies that reported on outcome measures including SBP, DBP, BMI, lipid levels (total cholesterol, low density lipoprotein [LDL], high density lipoprotein [HDL], nonHDL, and triglycerides), blood glucose, and fasting insulin. Studies that did not have the above definitions of "preterm" and "term", those that did not define the groups, and those that compared preterm born with another risk group were excluded. When the same cohort was reported in multiple publications at similar ages, the study reporting on the largest sample size was included in the meta-analyses. When the same cohort was reported in multiple publications at different ages, the study reporting at the oldest age was included in the meta-analyses. However, studies reporting outcomes at different age points in separate publications were included in subgroup analyses based on the age of the offspring. All selected studies were published in peer-reviewed journals, undertaken in humans, and published in English. Two reviewers independently screened the titles and abstracts of studies. Data extraction was also conducted by two reviewers independently. Disagreements were resolved by discussion within the team.

Study quality assessment

The methodological quality was assessed by two independent reviewers using the Newcastle–Ottawa Quality Assessment Scale (NOS) which assesses three broad perspectives: the selection of the study groups; the comparability of the groups; and the ascertainment of either the exposure or outcome of interest for case-control or cohort studies, respectively[10]. The total maximum score for these three subsets is seven stars. Disagreements were resolved by discussions within the team.

Data synthesis

For studies that separately analyzed more than one full-term group defined as SGA and AGA, we used the AGA full-term group for comparison. For studies that separately analyzed more than one preterm term group defined as SGA and AGA, we extracted results for both groups. We also performed subgroup analyses based on gender, age, gestational age at birth (<32 weeks' and <28 weeks'), preterm SGA, and preterm AGA groups. Since some articles reported more than one multivariable model, and different studies adjusted for different sets of covariates, we extracted crude mean values for each outcome from each article. The meta-analyses were performed using RevMan software (Review Manager Version 5.1.1). For each outcome measure, standardized mean difference (SMD) or mean difference (MD) and the 95% confidence interval (CI) were calculated using a random effects model. SMD was used when the outcome was measured in different units across trials and MD when units were consistent.[11] When mean and SD were not reported, the results were extracted as presented (i.e., mean ± SEM, mean and CI, or range) and are detailed in Supplementary Table 1. Substantial heterogeneity was considered when I^2 statistic exceeded 50%, and the Chi^2 p-value was less than 0.1.[12] Funnel plots were examined for the evidence of publication bias if more than 10 studies reported data on the same outcome (Supplementary Figs. 8–11).[13]

Subgroup and sensitivity analyses

The robustness of results was evaluated by subgroup and sensitivity analyses. Prespecified subgroup analyses were performed to determine the risk factors based on gender, age group, gestational age at birth, and PTB associated with SGA vs AGA. Sensitivity analyses were performed based on evidence for publication bias.

Results

A total of 2987 articles were identified by the search, of which 105 were eligible for a full-text review (Fig. 1) and a further 33 from bibliographic search. Of these, 56 studies (published as 75 papers) were included in the review, and 40 were included in the meta-analyses (Table 1). Of the selected studies, 25 were population-based cohort studies and the others were case-control studies. The reasons for excluding 63 papers are shown in Fig. 1. Of the studies included in the meta-analyses, 11.5% were of high quality (scored 7–8), 86.9% were of moderate quality (scored 4–6), and 1.6% were of low quality (scored 1–3) as assessed by the NOS (Supplementary Table 2).

Risk factor profile between those born preterm compared to term

Systolic blood pressure

SBP data were available from 35 studies. Of these, 31 were included in the meta-analysis providing data on 308,987 individuals, of whom 18,005 were born preterm (Fig. 2A). The meta-analysis demonstrated that those born preterm have 3.26 mmHg (95% CI: 2.08 to 4.44) higher mean SBP compared to those born at term (Fig. 2A)[14–44]. Four studies could not be included in the meta-analysis[45–48]. Of these, two demonstrated an increase in SBP among preterm compared to term-born individuals[47,48] and one demonstrated a reduction in SBP of 0.53 mmHg (95% CI: 0.32, 0.75) for every 1-week increase in gestational age after adjusting for confounders[46] (Supplementary Table 1).

Diastolic blood pressure

DBP data were available from 32 studies. Of these, 29 were included in the meta-analysis providing data on 308,048 individuals, of whom 17,898 were born preterm (Fig. 2B). The meta-analysis demonstrated that those born preterm have 1.32 mmHg (95% CI: 0.61 to 2.04) higher mean DBP compared to those born at term (Fig. 2B)[16–44]. The three studies that could not be included in the meta-analysis showed an increase in DBP among preterm compared to the term group (Supplementary Table 1)[45–47].

Body mass index

BMI data were available from 34 studies. Of these, 30 were included in the meta-analysis providing data on 311,030 individuals, of whom 18,077 were born preterm (Supplementary Fig. 1). The meta-analysis demonstrated that there was no difference in BMI between those born preterm and at term (MD, 0.13 kg/m^2, 95% CI: −0.40 to 0.14 Supplementary Fig. 1)[16–19,21,22,24,27,29–32,34,36–44,49–56]. Four studies

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Table 1. Characteristics of the included studies

Study	Study design	Country	Definition of PTB (n)	Term (n)	Birthweight cases/ controls (g)	Gestational age cases/ controls (weeks)	Variables for matching cases and controls	Age at follow up (yrs)	Outcome measures reported
Alves *et al.* 2016[14]*	Cohort study	Brazil	< 37 weeks (67)	67	1751.7 ± 399.5/ 3345.0 ± 271.4	33.2 ± 2.0/39.2 ± 1.2	Month of birth	10–20	SBP, DBP, BMI, TC, LDL, HDL, VLDL, FG
Baross *et al.* 1999[15]*	Cohort study	Brazil	< 37 weeks (239)	4275	411/5249 (g)	239/4275 (g)		14–15	BMI, DBP, SBP
Bassareo *et al.* 2010[49]*	Case control	Italy	Extremely LBW (GA 27.8+2.2) ($n = 32$)	32	837.7+115.5/ 3137.9 ± 758.8	27.8+2.2/39.4 ± 1.6	Sex, age, BMI	17–28	BMI
Bayrakci *et al* 2007[16]*	Case control	Turkey	< 37 weeks (41)	27	900–2500/2900 – 3750	26–36/38–41	Sex, age, height, BMI	5–17	SBP, DBP
Bonamy *et al.* 2005[17]*	Case control	Sweden	≤ 34 weeks (34)	32	1343 ± 81/3602 ± 58	29.1 ± 0.5/39.6 ± 0.2	Age	16.5	SBP, DBP, BMI
Bonamy *et al.* 2007[18]*	Case control	Sweden	≤ 30 weeks (39)	21	1106 ± 305/3704 ± 404	28.9 ± 1.6/40.3 ± 1	N/A	7–12	SBP, DBP, BM
Chan *et al.* 2010[45]	Case control	Australia	≤ 32 weeks (AGA=25, SGA=14))	25 (AGA)	N/A	30/40	N/A	13–14	SBP, DBP, BM
Cheung *et al.* 2004[19]*	Cohort study	China	< 37 weeks (AGA=36, SGA=15)	35 (AGA)	AGA 1381 ± 433, SGA 1245 ± 242/3253 ± 396	AGA 29.4 ± 2.9 SGA 32.3 ± 2.0/39.5 ± 2.1	N/A	7–8	SBP, DBP, BM
Cohen *et al.* 2007[73]	Case control	Sweden	≤ 34 weeks (12)	12	1530/3575	32/40	N/A	1st week	SBP, DBP
Cooper *et al.* 2009[46]	Cohort study	UK	< 37 weeks (279)	7568	N/A/3385 ± 500	N/A/N/A	N/A	44–45	SBP, DBP, BMI, TC, LDL, HDL, TG
Dalziel *et al.* 2007[74]	Cohort study	New Zealand	<37 weeks (311)	147	1958 ± 487/3159 ± 559	34.1/39.6	N/A	30	SBP, TG, BG, insulin
Mathai *et al.* 2013[53]*	Cohort study	New Zealand	< 37 weeks (31)	21	N/A	33.3 ± 2.2/39.7 ± 1.2	N/A	35.7	BMI, TC, LDL, HDL, BG, insulin
Darendeliler *et al.* 2008[57]*	Cohort study	Turkey	< 37 weeks (AGA=63, SGA=30)	44 (AGA)	N/A	SGA32.5 ± 054, AGA 32·6 ± 0·4/39.4 ± 0.2	N/A	3–5	BG, insulin
Doyle *et al.* 2003[20]*	Cohort study	Australia	< 37 weeks (156)	38	1098 ± 235/3493 ± 494	28.8 ± 2.0/40 ± 1.1	N/A	18+	SBP, DBP
Edwards *et al.* 2014[21]*	Cohort study	UK	< 37 weeks (399)	6650	N/A	25–36/37–42	N/A	10.8	SBP, DBP, BMI
Evensen *et al.* 2009[22]*	Case control	Norway	< 37 weeks (37)	63	1245/3700	28/40	N/A	18	SBP, DBP, BMI
Farooqi *et al.* 2006[75]	Case control	Sweden	<26 weeks (83)	83	765 ± 110/3523 ± 606	24.6 ± 0.7/39.2 ± 1.6	Age and gender	10–12	BMI
Fewtreil *et al.* 2004[76]	Case control	UK	< 37 weeks (497)	95	N/A	N/A	Age	8–12	BMI
Lewandowski *et al.* 2011[77]	Case control	UK	< 37 weeks (18)	36	N/A	28.89 ± 2.11/39.87 ± 0.68	Age and gender	23–28	TC, HDL, TG, FG
Singhal *et al.* 2001[71]	Case control	UK	< 31 ± 2.8 (216)	61	N/A	31·0 ± 2·7/40·0 ± 1·2	Age, nonSGA. Cases and control, nonsmokers, clinically well, and no chronic disease or disability	13–16	SBP, DBP, BMI, TC, HDL, FG, insulin
Singhal *et al.* 2003[78]	Case control	UK	< 31 ± 2.8 (216)	61	N/A	31·0 ± 2·7/40·0 ± 1·2	Age, nonSGA. Cases and control, nonsmokers, clinically well, and no chronic disease or disability	13–16	BMI, BG, insulin

(*Continued*)

Table 1. (*Continued*)

Study	Study design	Country	Definition of PTB (n)	Term (n)	Birthweight cases/controls (g)	Gestational age cases/controls (weeks)	Variables for matching cases and controls	Age at follow up (yrs)	Outcome measures reported
Gianni *et al.* 2015[50]*	Cohort study	Italy	<32 weeks (63)	61	1152 ± 282/3250 ± 360	30 ± 2/39 ± 1	Gender, AGA, exclusively breast fed for 6 months, nonsmoking mothers, Caucasian parentage	5	BMI
Goldani *et al.* 2007[79]	Cohort study	Brazil	<37 weeks (59)	879	N/A	N/A	N/A	18	BMI
Gunay *et al.* 2014[80]	Case control	Germany	<37 weeks (65)	65	2521 ± 119/3329 ± 98	35.7 ± 0.4/38.5 ± 0.57	N/A	4–13	SBP, DBP, MAP,
Hack *et al.* 2003[51]	Case control	USA	< 37 weeks (195)	208	1189/3277	29.8/>37	N/A	20	BMI
Hack *et al.* 2005[23]*	Case control	USA	< 37 weeks (195)	208	1189/3278	29.8/>37	N/A	20	SBP, DBP, BMI
Hofman *et al.* 2004[61]*	Case control	New Zealand	< 32 weeks (50)	22	1098 ± 362/3311 ± 417	27.6 ± 2.2/39.3 ± 1.2	N/A	4–10	BG, insulin
Hovi *et al.* 2007[81]	Case control	Finland	VLBW <1500 g (163)	169	1120 ± 221/NA	29.17 ± 2.22/>37	Gender, AGA	18–27	SBP, DBP, BMI, BG, insulin
Hovi *et al.* 2010[24]*	Case control	Finland	VLBW <1500 g (118)	120	1138 ± 224/3623 ± 479	29.2 ± 2.3/401.1 ± 1.0	Gender, AGA	18–27	SBP, DBP
Hovi *et al.* 2011[59]	Case control	Finland	VLBW <1500 g (92)	68	N/A	N/A	Gender, AGA	18–27	SBP, DBP, TC, LDL, HDL, TG, BG, insulin
Kajantie *et al.* 2015[60]*	Case control	Finland	VLBW <1500 g (107)	100	1128 ± 219/3601 ± 484	29.3 ± 2.2/40.1 ± 1.1	Gender, AGA	25	BMI, BG, insulin
Hovi *et al.* 2016[47]	Case control	Finland	VLBW <1500 g or <36.6 weeks (1571)	777	N/A	N/A	N/A	16–24	SBP, DBP
Hui *et al.* 2015[58]	Cohort study	China	Late PTB 34–36 weeks (295)	6872	N/A	35.4/39.2	N/A	14	BMI
Huke *et al.* 2013[52]*	Case control	Germany	<33 weeks (116)	120	1434 ± 470/3486 ± 484	29.8 ± 2.6/39.4 ± 1.2	N/A	5–7	BMI
Irving *et al.* 2000[25]*	Case control	England	VLBW <2000 g (21)	31	1660 ± 220/3130 ± 450	31.9 ± 1.5/39.3 ± 1.90	N/A	24	SBP, DBP, TC, HDL, TG, BG, insulin
Jarvelin *et al.* 2004[26]*	Longitudinal study	Finland (132)	< 37 weeks (132)	2637	N/A	N/A	N/A	31	SBP, DBP
Johanssen *et al.* 2005[27]*	Cohort study	Sweden	< 37 weeks (14,192)	275,895	1192 ± 270 (24–28 weeks), 1825 ± 426 (29–32 weeks), 2745 ± 507 (33–36 weeks)/3590 ± 484 (37–41 weeks)	24–28, 29–32, 33–36/37–41	N/A	18	SBP, DBP, BMI
Joshi *et al.* 2014[28]*	Case control	UK	<32 weeks (32)	30	1500 ± 400/3400 ± 500	30.0 ± 2.0/39.7 ± 1.5	N/A	8–12	SBP, DBP, TC, HDL, TG, BG
Kaijser *et al.* 2009[82]*	Cohort study	Sweden	<37 weeks (2931)	1318	N/A	N/A	N/A	50	HR, BMI, SBP, DBP
Keizer-Veen *et al.* 2010[29]*	Case control	The Netherlands	<32 weeks (50)	30	SGA: 858 ± 132 AGA: 1489 ± 257/3632 ± 489	SGA: 30.6 ± 1.1 AGA: 29.5 ± 1.4/40.2 ± 1.3	N/A	20	SBP, DBP, BMI
Rotteveel *et al.* 2008[83]	Cohort study	The Netherlands	<32 weeks (29 AGA, 28 SGA)	30	AGA: 153 ± 300, SGA: 934 ± 146/3562 ± 465	AGA: 28.9 ± 1.4, SGA: 30.7 ± 1.1/40.0	N/A	22	SBP, DBP, BMI

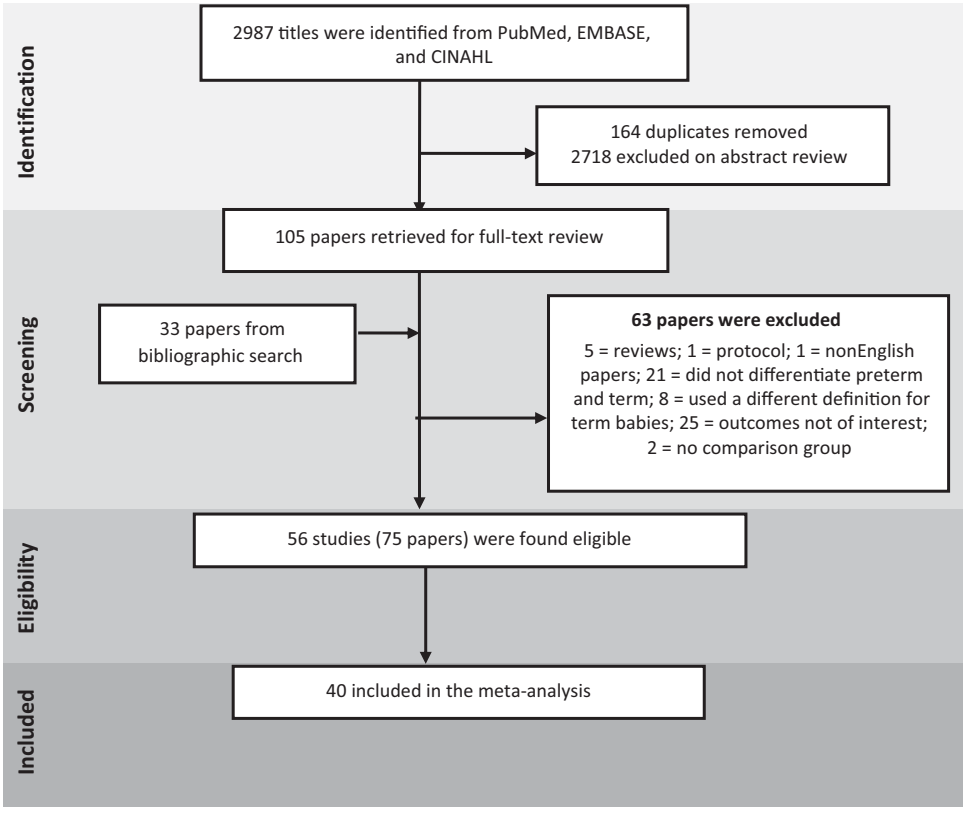
Rotteveel *et al.* 2011[84]	Cohort study	The Netherlands	<32 weeks (17 SGA, 12 AGA)	28 AGA	SGA: 930 ± 127, AGA: 1080 ± 279/AGA: 1497 ± 352	SGA: 31.0 ± 0.7, AGA: 28.7 ± 1.6/AGA: 29.5 ± 1.4	N/A	21	Insulin sensitivity, SBP, DBP
Kistner *et al.* 2000[30]*	Case control	Sweden	<32 weeks (15)	17	1293 ± 283/3720 ± 313	N/A	Age and born in the same hospital	23–30	SBP, DBP, BMI
Kistner *et al.* 2004[85]	Case control	Sweden	<37 weeks (15)	17	1293 ± 283/3720 ± 313	30 ± 1/41 ± 1	Age and born in the same hospital	20–30	BMI, TC, LDL, HDL, TG, BG, insulin
Kowalski *et al.* 2016[31]*	Case control	Australia	< 28 weeks (109)	81	896 ± 169/3398 ± 437	25.7 ± 1/39.1 ± 1	Gender and date of birth	18	SBP, DBP, BMI
Kwinta *et al.* 2011[86]	Case control	Poland	27–29 weeks (78)	38	890 (760–950)/3545 (3409–3820)	27 (26–29)/40 (39–41)	N/A	6–7	SBP, DBP
Lee *et al.* 2014[48]	Case control	Germany	Birthweight <1000 g (GA 26.4 ± 1.9, $n = 54$)	12	753 ± 152/3395 ± 558	26.4 ± 1.9/male: 39.6 ± 1.4, female: 39.2 ± 1.1	N/A	9–14	SBP, DBP, BMI
Lewandowski *et al.* 2015[32]*	Case control	UK	Birthweight <1850 g (102)	102	1295.6 ± 304.5/ 34411 ± 319.0	30.3 ± 2.5/39.6 ± 0.8	Age and gender and born of uncomplicated pregnancies	20–30	SBP, DBP, BMI, TC, LDL, HDL, TG, BG, insulin
Lazdam *et al.* 2010[87]	Case control	UK	<37 weeks (71)	38	N/A	N/A	Age and born of uncomplicated pregnancies	20	SBP, DBP, BMI, TC, LDL, HDL, BG, insulin
McEinery *et al.* 2011[33]*	Case control	UK and Ireland	<25 weeks and 6 d (219)	153	740 ± 120/N/A	24.9 (0.7)/NA	N/A	11	SBP, DBP
Bolton et al 2012[88]	Case control	UK and ROI	< 25 weeks (66)	86	740 ± 130/N/A	24.9 ± 0.8/> 37 weeks	Age and gender	11	HR, SBP, DBP
Bracewell *et al.* 2008[89]	Case control	UK and ROI	< 25 weeks (241)	160	N/A	24 ± 0.7/all 37 weeks + (no S.D)	Age and gender	6	BMI
Mikkola *et al.* 2007[90]	Case control	Finland	27.6 ± 0.8(47)	13	SGA: 821, AGA: 1065 ± 241/3982 ± 425	SGA: 28.5 ± 2.5, AGA: 27.6 ± 0.8/40.4 ± 1.8	Date of birth and from same hospital	5	SBP, DBP
Mohlkert *et al.* 2017[34]*	Case control	Sweden	Extremely preterm (Birthweight 348–1161 g, $n = 176$)	172	787 (165)/3591 (461)	24.9 (1.0)/39.4 (1.2)	Sex, date of birth, hospital, residency, and mothers' country of birth	6.5	SBP, DBP
Bonamy *et al.* 2012[91]	Case control	Sweden	<27 weeks (68)	65	810 ± 164/N/A	25.4 ± 1/term	Birth date, hospital, residency, and mother's country of birth	2.5	SBP, DBP, BMI
Morsing *et al.* 2014[35]*	Case control	Sweden	<24–29 weeks (64)	32	IUGR: 682 ± 158, AGA: 1084 ± 395/3621 ± 395	IUGR:188.9 ± 9.5, 189.5 ± 10.2 /279.3 ± 4.5	Age and gender	7	SBP, DBP, BMI
Oren *et al.* 2003[54]*	Cohort study	The Netherlands	<37 weeks (26)	381	2632 ± 100/3482 ± 26	34.0 ± 0.2/40.0 ± 0.1	N/A	26–30	BMI
Pilgaard *et al.* 2010[92]	Cohort study	Danish	<37 weeks (443)	4055	2555 ± 403/3522 ± 420	N/A	N/A	30–60	BMI, BG, insulin

(*Continued*)

Table 1. (*Continued*)

Study	Study design	Country	Definition of PTB (n)	Term (n)	Birthweight cases/ controls (g)	Gestational age cases/ controls (weeks)	Variables for matching cases and controls	Age at follow up (yrs)	Outcome measures reported
Ramirez-Velez *et al.* 2017[36]*	Cross-sectional study	Columbia	<37 weeks (AGA:843, SGA:249)	1158	N/A	N/A	N/A	9–7.9	SBP, DBP, BMI, TC, LDL, HDL, TG, BG
Rossi *et al.* 2011[93]	Case control	France	<37 weeks (AGA:25, SGA:24)	41	AGA:2202 ± 515, SGA:2552 ± 264/ 3339 ± 341	AGA:34.4 ± 1.8, SGA:38.6 ± 1.6/39.3 ± 1.0	N/A	13–4	BMI, SBP, DBP
Tauzin *et al.* 2014[41]*	Case control	France	<37 weeks (16)	15	1710 (1448, 2404)/ 3430 (3178, 4096)	32 (31, 36)/40 (39, 42)	N/A	21	BMI, SBP, DBP
Saigal *et al.* 2006[55]*	Case control	Canada	Extremely LBW (501–00 g, *n* = 143)	126	841 ± 125/N/A	27.1 ± 2.3/term	Age, sex, and social class	8	BMI
Schubert *et al.* 2013[37]*	Cohort study	Sweden	26–30 weeks	29	66.8 (13.6)/67.5 (13.2)	32.7 (4.6)/31.0 (4.3)	N/A	3 months	SBP, DBP, BMI
Shimizu *et al.* 2014[56]*	Case control	Tokyo	<37 weeks (26)	11	1526 (1282–1819)/ 2948 (2808–3306)	33.4 (31.6–35.3)/ 39.0 (38.0–40.1)	N/A	4–6	BMI
Sipola-Leppanen *et al.* 2014[94]	Cohort study	Finland	<34 weeks (79), 34–36 weeks (238)	6325	Early PTB: 1788 (461), late PTB 2696 (494)/ 3619 (476)	Early PTB <34/late PTB 34–36)/ term >37	N/A	16	SBP, DBP, TC, LDL, TG, BG, insulin
Sipola-Leppanen *et al.* 2014[95]	Cohort study	Finland	< 34 weeks (134), 34–36 (242)	344	Early PTB: 1786 (493), late PTB: 2674 (515)/ 3576 (483)	Early PTB <34/ late PTB 34–36)/ term >37	N/A	23	SBP, DBP, BMI, BG, insulin
Skilton *et al.* 2011[39]*	Case control	Australia	<37 weeks (253)	835	2814 ± 603/3842 ± 193	NA	N/A	24–45	SBP, DBP, BMI, LDL, HDL, TG, BG
Hussain *et al.* 2015[96]	Cohort study	Finland	<37 weeks	N/A	N/A	N/A	N/A	34–49	SBP, DBP, BMI, TC, HDL, TG
Juonala *et al.* 2015[97]	Case control	Finland	37 weeks (SGA:39, AGA:87)	1630	N/A	N/A	N/A	3–18 & 34–49	SBP, DBP, BMI, LDL, HDL, TG, BG, insulin
Steen *et al.* 2015[40]*	Cohort study	Sweden	VLBW (<1500 g), 30 AGA, 19 SGA)	43	Girls AGA 1046 (272), SGA 1054 (332), boys AGA 1104 (265), SGA 1057 (258)/girls 3466 (414), boys 3558 (511)	Girls AGA 27.2 (2.1), SGA 30.6 (3.6), boys AGA 27.4 (2.3), SGA 31.1 (2.3)/girls 39.7 (1.2), boys 39.5 (1.3)	N/A	12–17	BMI, SBP, DBP
Thomas *et al.* 2011[42]*	Cohort study	UK	≤33 weeks (23)	25	Men:1463 ± 500, women:1239 ± 250/ men:3336 ± 500, women:3341 ± 400	Men:29.9 ± 2.5, women:28.8 ± 2.8/ men:40.5 ± 2.0, women:39.9 ± 1.3	N/A	18–27	SBP, DBP, BMI, TC, LDL, HDL, TG, BG, insulin
Toumba *et al.* 2005[98]	Case control	N/A	<37 weeks (SGA:17, LBW:35, VLBW:23)	27	NA	NA	Age	3–8	BMI
Vohr *et al.* 2010[43]*	Case control	USA	VLBW (<1250), 296	95	968 ± 172/NA	27.9 ± 2.0/NA	Age, gender, race, and zip code	16	SBP, DBP, BMI
Willemsen *et al.* 2009[44]	Cohort study	The Netherlands	<36 weeks (169)	136	N/A	N/A	N/A	18 – 24	BMI, BG, insulin
Vollsaeter *et al.* 2018[44]*	Case Control	Norway	<28 weeks (37)	54	918/3701	N/A	N/A	11	SBP, DBP, BMI

AGA, average for gestational age; BG, blood glucose; BMI, body mass index; DBP, diastolic blood pressure; HDL, high density lipoprotein; LBW, low birth weight; LDL, low density lipoprotein; N/A, not available; SBP, systolic blood pressure; SGA, small for gestational age; TC, total cholesterol; TG, triglycerides; VLBW, very low birth weight.
*Included in the meta-analyses.



PRISMA, Preferred Reporting Item for Systematic Reviews and Meta-analysis

Fig. 1. Study selection process.

could not be included in the meta-analysis[14,35,57,58]. Of these, one showed that obesity was more prevalent among those born preterm (Supplementary Table 1)[14].

Total cholesterol

Total cholesterol data were available from 10 studies. Of these, eight were included in the meta-analysis providing data on 2705 individuals, of whom 1265 were born preterm (Supplementary Fig. 2). The meta-analysis demonstrated that there was no difference in total cholesterol between offspring born preterm and at term (SMD, 0.12 [95% CI: −0.05 to 0.30]), (Supplementary Fig. 2)[25,28,32,36,38,42,53,59]. Two studies could not be included in the meta-analysis[14,46]. Of these, one reported that there was no difference in total cholesterol between preterm and term groups[14] while the other reported a reduction in total cholesterol of 0.02 mmol/l for every 1-week increase in gestational age after adjusting for confounders (Supplementary Table 1)[46].

LDL cholesterol

LDL cholesterol data were available from eight studies. Of these, six were included in the meta-analysis providing data on 3437 individuals, of whom 1274 were born preterm (Supplementary Fig. 3). The meta-analysis demonstrated that there was no difference in LDL cholesterol between offspring born preterm and at term (SMD, 0.02 [95% CI: −0.10 to 0.14]), (Supplementary Fig. 3)[32,36,39,42,53,59]. The two studies that were not included in the meta-analysis also reported that there was no difference in LDL between the groups (Supplementary Table 1)[14,46].

HDL cholesterol

HDL cholesterol data were available from 11 studies. Of these, nine were included in the meta-analysis providing data on 3813 individuals, of whom 1538 were born preterm (Supplementary Fig. 4). The meta-analysis demonstrated that there was no difference in HDL cholesterol between offspring born preterm and at term (SMD, 0.00 [95% CI: −0.12 to 0.11]), (Supplementary Fig. 4)[25,28,32,36,38,39,42,53,59]. The two studies that were not included in the meta-analysis also reported that there was no difference in HDL between the groups (Supplementary Table 1)[14,46].

Triglycerides

Triglyceride data were available from nine studies. Of these, seven were included in the meta-analysis providing data on 3475 individuals, of whom 1285 were born preterm (Supplementary Fig. 5). The meta-analysis demonstrated that there was no difference in triglycerides between offspring born preterm and at term (SMD, 0.03 [95% CI: −0.06 to 0.12]), (Supplementary Fig. 5)[25,28,32,36,39,42,59]. The two studies that were not included in the meta-analysis also reported that there was no difference in triglycerides between the groups (Supplementary Table 1)[14,46].

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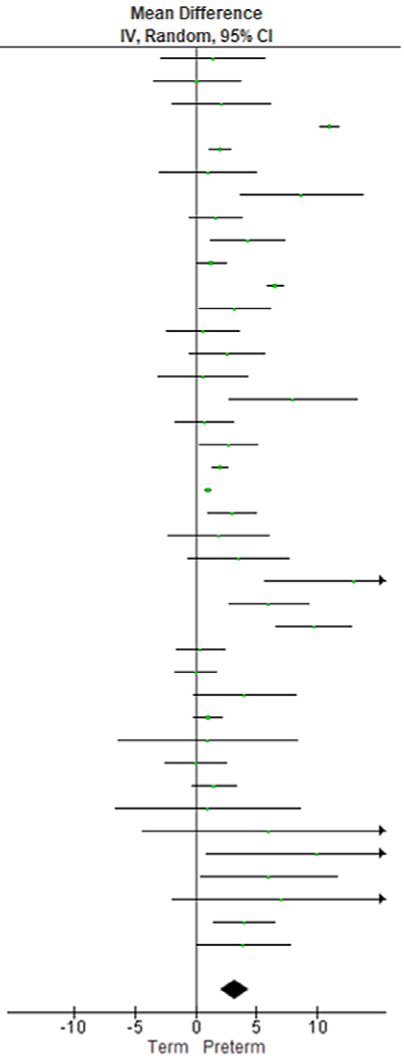
A

Study or Subgroup	Preterm Mean	Preterm SD	Preterm Total	Term Mean	Term SD	Term Total	Weight	Mean Difference IV, Random, 95% CI
Alves 2016 - 10-20 yrs	102.6	12.3	67	101.2	13.2	67	2.3%	1.40 [-2.92, 5.72]
Baross 1999 - 14-15 yrs	114	11.7	44	113.9	11.1	770	2.5%	0.10 [-3.44, 3.64]
Bayrakci 2007 -5-17yrs	108.5	9.3	41	106.4	7.5	27	2.4%	2.10 [-1.91, 6.11]
Bonamy 2005 - 16.5yrs	115	1.5	34	104	1.6	32	3.2%	11.00 [10.25, 11.75]
Bonamy 2007 -7-12yrs	99	1.3	39	97	1.8	21	3.2%	2.00 [1.13, 2.87]
Cheung 2004 -7-8yrs	103	9	36	102	8	35	2.4%	1.00 [-2.96, 4.96]
Doyle 2003 - 18+yrs	124.8	14.8	156	116.1	14.1	38	2.0%	8.70 [3.65, 13.75]
Edwards 2014 - 10.8yrs (1)	105.8	9.26	73	104.12	9.08	2148	3.0%	1.68 [-0.48, 3.84]
Edwards 2014 - 10.8yrs (2)	108.4	12.61	67	104.12	9.08	2148	2.7%	4.28 [1.24, 7.32]
Edwards 2014 - 10.8yrs (3)	105.4	8.99	246	104.12	9.08	2149	3.2%	1.28 [0.09, 2.47]
Evensen 2009 -18 yrs	129.7	1.7	36	123.2	1.2	63	3.2%	6.50 [5.87, 7.13]
Hack 2005 - 20yrs (4)	110.4	9.1	92	107.2	12.1	107	2.7%	3.20 [0.25, 6.15]
Hack 2005 - 20yrs (5)	117.5	10.6	103	116.9	11	101	2.7%	0.60 [-2.37, 3.57]
Hovi 2010 - 18-27yrs (6)	121.2	10.9	69	118.6	7.3	72	2.7%	2.60 [-0.48, 5.68]
Hovi 2010 - 18-27yrs (7)	126.7	7.5	49	126.1	10.7	48	2.5%	0.60 [-3.08, 4.28]
Irving 2001 - 24yrs	123	9	19	115	9	27	2.0%	8.00 [2.72, 13.28]
Jarvelin 2004 - 31yrs (8)	131	13.8	132	130.3	12.5	2114	2.9%	0.70 [-1.71, 3.11]
Jarvelin 2004 - 31yrs (9)	122.6	14.1	141	119.9	12.3	2242	2.9%	2.70 [0.32, 5.08]
Johanssen 2005 - 24-32yrs (10)	131	12	1370	129	11	91965	3.2%	2.00 [1.36, 2.64]
Johanssen 2005 - 24-32yrs (11)	130	11	12660	129	11	91965	3.3%	1.00 [0.80, 1.20]
Johanssen 2005 - 24-32yrs (12)	132	13	162	129	11	91965	3.0%	3.00 [1.00, 5.00]
Joshi 2014 - 8-12yrs	103.6	9.1	32	101.7	7.5	30	2.3%	1.90 [-2.24, 6.04]
Keijzer-veen 2010 - 20 yrs	123.1	8.5	29	119.6	7.6	30	2.3%	3.50 [-0.62, 7.62]
Kistner 2000 - 26yrs	123	13	15	110	7	17	1.4%	13.00 [5.63, 20.37]
Kowalski 2016 - 18yrs	124	13	109	118	10	81	2.6%	6.00 [2.73, 9.27]
Lewandowski 2015 - 20-30yrs	126.3	6.5	30	116.6	8.3	60	2.7%	9.70 [6.57, 12.83]
McEniery 2011 - 11yrs	107.5	9.7	219	107.1	9.2	153	3.0%	0.40 [-1.54, 2.34]
Mohlkert 2017 - 6yrs (13)	98	8	176	98	8	172	3.1%	0.00 [-1.68, 1.68]
Morsing 2014 - 7yrs	106	8	28	102	8	27	2.3%	4.00 [-0.23, 8.23]
Ramirez-Velez 2017 - 9-17yrs	112.4	13.4	843	111.4	12.9	1158	3.2%	1.00 [-0.17, 2.17]
Schubert 2013 - 31-32.7yrs	121	15	21	120	9.9	29	1.4%	1.00 [-6.36, 8.36]
Singhal 2001 - 14-15 yrs	115.8	8.4	216	115.8	8.9	61	2.9%	0.00 [-2.50, 2.50]
Skilton 2011 - 24-45yrs	118.4	12.8	253	116.9	13.3	835	3.0%	1.50 [-0.32, 3.32]
Steen 2015 - 12-17yrs (14)	120	14.3	19	119	9.5	21	1.4%	1.00 [-6.61, 8.61]
Steen 2015 - 12-17yrs (15)	129	14.5	11	123	14.2	22	0.9%	6.00 [-4.42, 16.42]
Tauzin 2014 - 21yrs	122	15.0133	16	112	10.8346	15	1.1%	10.00 [0.83, 19.17]
Thomas 2011 - 18-27yrs (16)	122	5	12	116	7	8	1.9%	6.00 [0.38, 11.62]
Thomas 2011 - 18-27yrs (17)	119	10	7	112	8	10	1.1%	7.00 [-1.91, 15.91]
Vohr 2010 - 16yrs	114	13	296	110	10	95	2.9%	4.00 [1.50, 6.50]
Vollsaeter 2018 - 11 yrs	113	9.45	37	109.1	8.61	54	2.4%	3.90 [0.09, 7.71]
Total (95% CI)			18005			290982	100.0%	3.26 [2.08, 4.44]

Heterogeneity: Tau² = 11.06; Chi² = 925.29, df = 39 (P < 0.00001); I² = 96%
Test for overall effect: Z = 5.42 (P < 0.00001)



Footnotes
(1) GA: 33-34 weeks
(2) GA: 25-32 weeks
(3) GA: 35-36 weeks
(4) Female
(5) Male
(6) Female
(7) Male
(8) Male
(9) Female
(10) GA: 29-32weeks
(11) GA: 33-36 weeks
(12) GA: 24-28 weeks
(13) Extremely preterm
(14) Female
(15) Male
(16) Male
(17) Female

Fig. 2A. MD in SBP between those born preterm and term.

Fasting blood glucose

Fasting blood glucose data were available from 11 studies. Of these, 10 were included in the meta-analysis providing data on 3967 individuals, of whom 1616 were born preterm (Supplementary Fig. 6). The meta-analysis demonstrated that there was no difference in fasting blood glucose between offspring born preterm and at term (SMD, −0.32 [95% CI: −0.70 to 0.07]), (Supplementary Fig. 6)[25,28,32,36,38,39,42,53,57,60]. The study that was not included in the meta-analysis also reported that there was no difference in fasting glucose between the groups. (Supplementary Table 1)[14].

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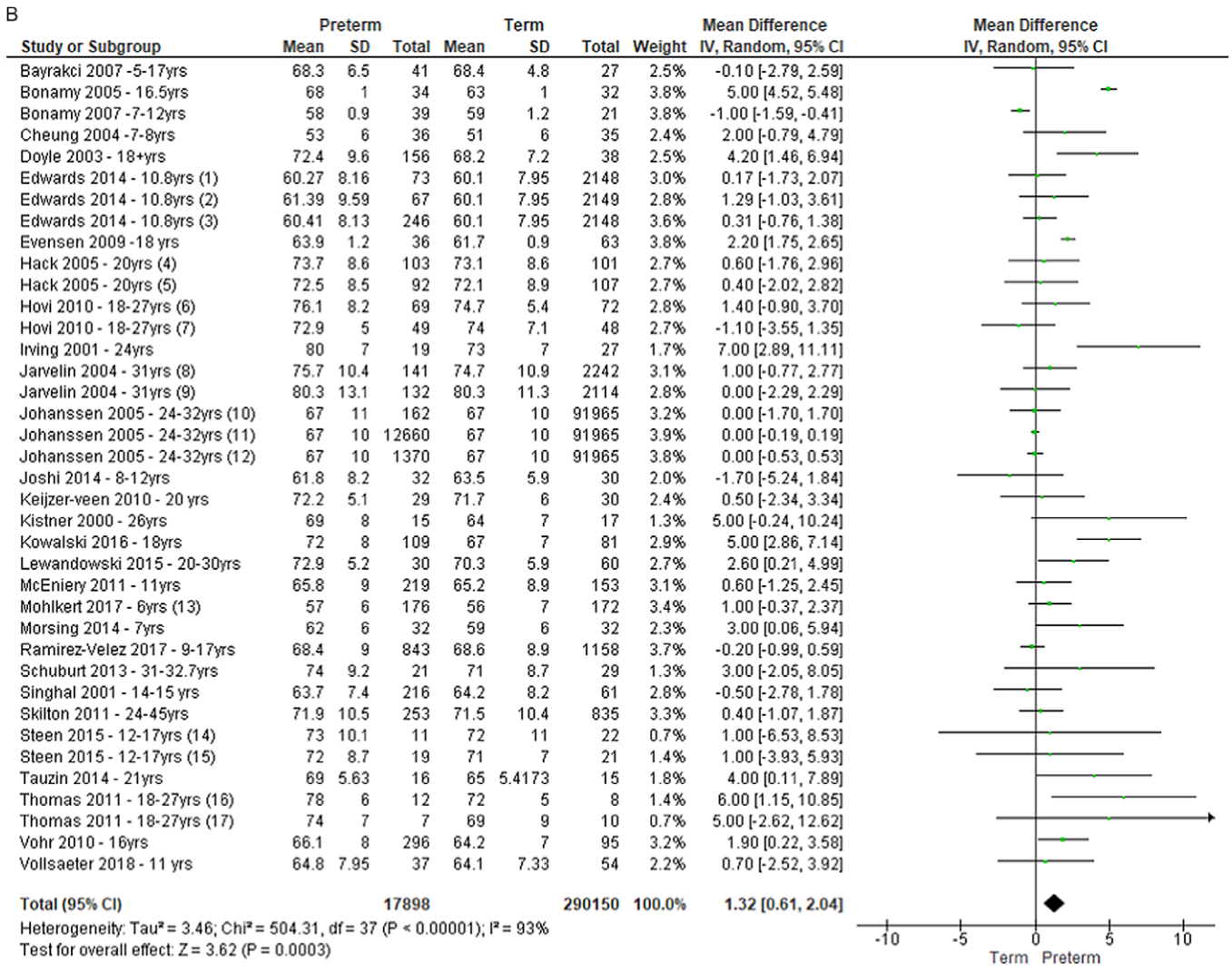

Fig. 2B. MD in DBP between those born preterm and term.

Fasting insulin

Fasting blood glucose data were available from eight studies. Of these, seven were included in the meta-analysis providing data on 602 individuals, of whom 307 were born preterm (Supplementary Fig. 7). The meta-analysis demonstrated that there was no difference in fasting insulin between offspring born preterm and at term (SMD, 0.06 [95% CI: −0.34 to 0.45]), (Supplementary Fig. 7)[25,32,42,53,57,60,61]. The study that was not included in the meta-analysis also reported that there was no difference in fasting insulin between the groups (Supplementary Table 1)[61].

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Table 2. Risk factors profile of preterm born compared to term based on gender and age

	Gender			Age				
Outcome	Combined	Male	Female	Children	Children and adolescents	Adolescents	Young adults	Adults
Systolic blood pressure	**3.47 (2.11 to 4.84)**	1.20 (−0.39 to 2.80)	**2.87 (1.34 to 4.40)**	1.03 (−1.13 to 3.18)	**2.00 (1.17 to 2.83)**	**3.24 (0.90 to 5.57)**	**4.57 (2.25 to 6.89)**	**2.08 (1.12 to 3.04)**
	Chi^2 *p* <0.001; *I*^{2} 97%	Chi^2 *p* 0.40; I^2 1%	**Chi^2 *p* 0.89; *I*^{2} 0%**	Chi^2 *p* 0.22; *I*^{2} 34%	**Chi^2 *p* 1.00; *I*^{2} 0%**	**Chi^2 *p* <0.001; *I*^{2} 96%**	**Chi^2 *p* 0.009; *I*^{2} 68%**	**Chi^2 *p* 0.0002; *I*^{2} 74%**
	26 studies; *n* = 303,607	5 studies; *n* = 2600	**5 studies; *n* = 2780**	3 studies; *n* = 474	**3 studies; *n* = 190**	**12 studies; *n* = 11,339**	**7 studies; *n* = 1052**	**6 studies; *n* = 295,932**
	Preterm, *n* = 17370; term, *n* = 286237	Preterm, *n* = 307; term, *n* = 2293	**Preterm, *n* = 328; term, *n* = 2452**	Preterm, *n* = 240; term, *n* = 234	**Preterm, *n* = 112; term, *n* = 78**	**Preterm, *n* = 2317; term, *n* = 9022**	**Preterm, *n* = 563; term, *n* = 489**	**Preterm, *n* = 14773; term, *n* = 281159**
Diastolic blood pressure	**1.42 (0.59 to 2.24)**	0.59 (−1.23 to2.41)	1.06 (−0.11 to 2.22)	**1.46 (0.33 to 2.60)**	−0.98 (1.54 to −0.41)	1.14 (−0.36 to 2.63)	**2.13 (0.96 to 3.31)**	0.38 (−0.22 to 0.98)
	Chi^2 *p* <0.001; *I*^{2} 95%	Chi^2 *p* 0.15; *I*^{2} 40%	Chi^2 *p* 0.84; *I*^{2} 0%	**Chi^2 *p* 0.44; *I*^{2} 0%**	Chi^2 *p* 0.75; *I*^{2} 0%	Chi^2 *p* <0.001; *I*^{2} 95%	**Chi^2 *p* 0.009; *I*^{2} 56%**	Chi^2 *p* 0.03; *I*^{2} 54%
	29 studies; *n* = 302,668	5 studies; *n* = 2600	5 studies; *n* = 2780	**3 studies; *n* = 483**	3 studies; *n* = 190	8 studies; *n* = 9810	**9 studies; *n* = 1633**	6 studies; *n* = 295,932
	Preterm, *n* = 17263; term, *n* = 285405	Preterm, *n* = 307; term, *n* = 2293	Preterm, *n* = 328; term, *n* = 2452	**Preterm, *n* = 244; term, *n* = 239**	Preterm, *n* = 112; term, *n* = 78	Preterm, *n* = 1801; term, *n* = 8009	**Preterm, *n* = 968; term, *n* = 665**	Preterm, *n* = 14773; term, *n* = 281159
Body mass index	0.07 (−0.24 to 0.38)	**−1.00 (−1.82 to −0.19)**	−0.51 (−1.07 to 0.06)	**−0.70 (−1.13 to −2.28)**	5.20 (−3.82 to 14.21)	−0.25 (−0.76 to 0.26)	−0.64 (−1.29 to 0.00)	−0.04 (−0.14 to 0.05)
	Chi^2 *p* <0.001; *I*^{2} 94%	**Chi^2 *p* 0.03; *I*^{2} 59%**	Chi^2 *p* 0.99; *I*^{2} 0%	**Chi^2 *p* 0.04; *I*^{2} 58%**	Chi^2 *p* <0.001; *I*^{2} 99%	Chi^2 *p* <0.001; *I*^{2} 93%	Chi^2 *p* 0.010; *I*^{2} 56%	Chi^2 *p* 0.34; *I*^{2} 12%
	24 studies; *n* = 309,866	**6 studies; *n* = 547**	6 studies; *n* = 617	**5 studies; *n* = 816**	2 studies; *n* = 128	9 studies; *n* = 17,150	8 studies; *n* = 1211	6 studies; *n* = 291,725
	Preterm, *n* = 17501; term, *n* = 292365	**Preterm, *n* = 275; term, *n* = 272**	Preterm, *n* = 301; term, *n* = 316	Preterm, *n* = 417; term, *n* = 399	Preterm, *n* = 80; term, *n* = 48	Preterm, *n* = 2446; term, *n* = 14704	Preterm, *n* = 590; term, *n* = 621	Preterm, *n* = 14544; term, *n* = 277181
Total cholesterol	0.12 (−0.05 to 0.30)	-	-	-	-	−0.02 (−0.10 to 0.07)	0.31 (−0.10 to 0.71)	0.14 (−0.58 to 0.86)
	Chi^2 *p* 0.07; *I*^{2} 45%	-	-	-	-	Chi^2 *p* 0.54; *I*^{2} 0%	Chi^2 *p* 0.10; *I*^{2} 51%	Chi^2 *p* 0.07; *I*^{2} 70%
	8 studies; *n* = 2705	-	-	-	-	3 studies; *n* = 2311	3 studies; *n* = 287	2 studies; *n* = 107
	Preterm, *n* = 1265; term, *n* = 1440	-	-	-	-	Preterm, *n* = 1068; term, *n* = 1243	Preterm, *n* = 141; term, *n* = 146	Preterm, *n* = 56; term, *n* = 51
High density lipoprotein	−0.00 (−0.12 to 0.11)	-	-	-	-	0.00 (−0.08 to 0.08)	0.20 (−0.12 to 0.51) Chi^2 P 0.26; I^2 25%	−0.26 (−0.67 to 0.16)
	Chi^2 *p* 0.15; *I*^{2} 32%	-	-			Chi^2 *p* 1.00; *I*^{2} 0%		Chi^2 *p* 0.05; *I*^{2} 67%
	9 studies; *n* = 3813	-	-			3 studies; *n* = 2331	3 studies; *n* = 287	3 studies; *n* = 1195
	Preterm, *n* = 1538; term, *n* = 2275	-	-			Preterm, *n* = 1088; term, *n* = 1243	Preterm, *n* = 141; term, *n* = 146	Preterm, *n* = 309; term, *n* = 886
Low density lipoprotein	0.02 (−0.10, 0.14)	-	-	-	-	−0.08 (−0.16, 0.01)	0.17 (−0.07, 0.40)	0.08 (−0.06, 0.22)
	Chi^2 *p* 0.19; *I*^{2} 31%						Chi^2 *p* 0.41; *I*^{2} 0%	Chi^2 *p* 0.39; *I*^{2} 0%
	6 studies; *n* = 3437					1 study; *n* = 2001	3 studies; *n* = 287	2 studies; *n* = 1149
	Preterm, *n* = 1274; term, *n* = 2163					Preterm, *n* = 843; term, *n* = 1158	Preterm, *n* = 141; term, *n* = 146	Preterm, *n* = 290; term, *n* = 859

Triglycerides	0.03 (−0.06, 0.12)	-	-	-	0.02 (−0.11, 0.07)	0.14 (−0.13, 0.42)	0.03 (−0.06, 0.12)
	Chi^2 p 0.35; I^2 10%				Chi^2 p 0.87; I^2 0%	Chi^2 p 0.27; I^2 23%	
	7 studies; n = 3475				2 studies; n = 2054	4 studies, n = 333	1 study; n = 1088
	Preterm, n = 1285; term, n = 2190				Preterm, n = 872; term, n = 1182	Preterm, n = 160; term, n = 173	Preterm, n = 253; term, n = 835
Glucose (fasting)	−0.32 (−0.70, 0.07)	-	-	−5.96 (−6.86, −5.06)	-	−0.12 (−0.35, 0.12)	**0.50 (0.13, 0.87)**	0.03 (−0.09, 0.15)
	Chi^2 p <0.001; I^2 95%					Chi^2 p 0.10; I^2 57%	**Chi^2 p 0.29; I^2 19%**	Chi^2 p 0.71; I^2 0%
	10 studies; n = 3967				1 study; n = 107	3 studies; n = 2331	**3 studies; n = 173**	3 studies; n = 1356
	Preterm, n = 1616; term, n = 2351				Preterm, n = 63; term, n = 44	Preterm, n = 1088; term, n = 1243	Preterm, n = 68; term, n = 105	Preterm, n = 397; term, n = 959
Insulin	0.06 (−0.34, 0.45)	-	-	−0.54 (−1.13, 0.04)	-	-	0.27 (−0.13, 0.68)	0.39 (−0.13, 0.91)
	Chi^2 p <0.001; I^2 80%				Chi^2 p 0.08; I^2 68%		Chi^2 p 0.03; I^2 62%	
	7 studies; n = 602				2 studies; n = 161		4 studies; n = 380	1 study; n = 61
	Preterm, n = 307; term, n = 295				Preterm, n = 95; term, n = 66		Preterm, n = 175; term, n = 205	Preterm, n = 37; term, n = 24

Results are presented in MD or SMD with 95% CIs.
Following outcomes are presented as MD with 95% CI and the rest are in SMD.
Systolic blood pressure, diastolic blood pressure, and body mass index.
Heterogeneity is presented as Chi^2 p value and I^2 percentage.

Risk factor profile based on subgroup analyses

Age

The age groups were classified according to the World Health Organization (WHO) criteria as age <10 years, child; 10–19 years, adolescent; 20–24 years, young adult; and >24 years, adult. Since some studies included a mix of children and adolescents, we classified the groups as, children, children and adolescents, adolescents and adults. SBP was higher among those born preterm compared to term in the subgroups "children and adolescents", adolescents, young adults, and adults (Table 2). No significant difference was seen in SBP between preterm and term groups among children. No trends were seen for any difference in the other risk factors between term and preterm groups based on age (Table 2).

Gender

A total of 635 prematurely born (307 males; 328 females) and 4745 at term born (2293 males; 2452 females) were included in the analyses on SBP and DBP. A total of 576 prematurely born (275 males; 301 females) and 588 at term born (272 males; 316 females) were included in the analysis on BMI. SBP was higher among females born preterm compared to females born at term but not among males born preterm compared to males born at term (Table 2). BMI was lower among males born preterm compared to males born at term but not among females born preterm compared to females born at term (Table 2). Subgroup analyses based on gender could not be performed for the other risk factors as there were no available studies reporting on these outcomes.

PTB based on gestational age at birth

Subgroup meta-analyses were performed based on gestational age at birth (<32 weeks' gestation compared to term and <28 weeks' gestation compared to term) (Table 3). SBP was higher among both study groups compared to the term born group (Table 3). BMI was lower among those born prior to 32 weeks compared to term (Table 3). Subgroup analyses based on gestational age at birth could not be performed for the other risk factors as there were no available studies reporting on these outcomes.

Preterm SGA and AGA

Subgroup meta-analyses were performed on preterm SGA compared to term AGA, preterm AGA compared to term AGA, and preterm SGA compared to preterm AGA (Table 4). Mean DBP was higher among preterm AGA compared to term AGA. SMD of LDL was higher among preterm SGA compared to term AGA and preterm SGA compared to preterm AGA (Table 4). No significant differences were seen between the SGA and AGA preterm groups (Table 4).

Sensitivity analysis based on the evidence of publication bias

The funnel plots on studies reporting on SBP and DBP suggested possible publication bias. Hence, the meta-analyses on the above outcomes were repeated after excluding the studies with high standard deviations. The significant results remained in these secondary analyses (Supplementary Figs. 12–15).

Discussion

This systematic review and meta-analyses demonstrates that those born preterm have higher mean SBP and DBP compared

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Table 3. Risk factor profile of preterm born compared to term based on gestational age at birth

	Preterm	
Outcome	<32 weeks	<28 weeks
Systolic blood pressure	**2.12 (1.25 to 3.00)**	**2.31 (0.27 to 4.36)**
	Chi^2 *p* <0.001; I^2 73%	**Chi^2 *p* 0.004; I^2 74%**
	7 studies; *n* = 202,664	**5 studies; *n* = 93,128**
	Preterm, *n* = 14313; term, *n* = 188351	**Preterm, *n* = 703; term, *n* = 92425**
Diastolic blood pressure	0.45 (−0.22 to 1.12)	0.61 (−0.28 to 1.50)
	Chi^2 *p* <0.001; I^2 76%	Chi^2 *p* 0.85; I^2 0%
	8 studies; *n* = 205,258	4 studies; *n* = 92,938
	Preterm, *n* = 14672; term, *n* = 190586	Preterm, *n* = 594; term, *n* = 92344
Body mass index	**−0.30 (−0.54 to −0.05)**	−0.50 (−1.10 to 0.09)
	Chi^2 *p* 0.002; I^2 77%	Chi^2 *p* 0.002; I^2 76%
	5 studies; *n* = 212,072	5 studies; *n* = 92820
	Preterm, *n* = 14957; term, *n* = 197115	Preterm, *n* = 516; term, *n* = 92304
Total cholesterol	0.00 (−0.77 to 0.77)	-
	1 study; *n* = 33	
	Preterm, *n* = 9; term, *n* = 24	
High density lipoprotein	0.00 (−0.54 to 0.54)	-
	1 study; *n* = 53	
	Preterm, *n* = 29; Term, *n* = 24	
Triglycerides	−0.07 (−0.61 to 0.48)	-
	1 study; *n* = 53	
	Preterm, *n* = 29; term, *n* = 24	
Glucose (fasting)	−0.44 (−0.98 to 0.411)	-
	1 study; *n* = 53	
	Preterm, *n* = 29; term, *n* = 24	

Results are presented in MD or SMD with 95% CIs.
Following outcomes are presented as MD with 95% CI and the rest are in SMD.
Systolic blood pressure, diastolic blood pressure, and body mass index.
Heterogeneity is presented as Chi^2 *p* value and I^2 percentage.

to those born at term. Other conventional CVD risk factors are not significantly different between the two groups. The main findings of the subgroup analyses demonstrate that higher SBP is evident from early adolescence onwards among those born preterm compared to term, higher SBP is only seen among females born preterm, and that the difference in SBP between preterm and term groups is seen both among those born prior to 32 weeks' gestation and prior to 28 weeks' gestation.

The observed SBP difference of 3.5 mmHg and DBP difference of 1.4 mmHg between the preterm and term groups is modest. However, even small differences in BP are important at the population level prevention of CVD since even a 2 mmHg reduction in SBP is associated with 10% lower mortality from stroke and 7% lower mortality from ischemic heart disease in middle age[62]. Both SBP and DBP track from childhood to adulthood with average reported tracking correlation being greater for SBP than for DBP[63]. Therefore, the higher SBP in the preterm group which is evident from early adolescence is an important finding as elevated BP in childhood predicts adult hypertension[63]. Our systematic review was not designed to assess the association between PTB and hypertension in later life. However, a previous systematic review and meta-analysis that comprised 973,458 participants including 76,886 hypertensive cases showed that PTB was associated with increased risk of essential hypertension (defined as BP ≥ 140/90 mmHg, odds ratio 1.31, 95% CI 1.20 to 1.43)[64].

A previous systematic review and meta-analysis comprising 1342 individuals born preterm or with a very low birthweight and 1738 full term participants also showed that those born preterm had 2.5 mmHg higher SBP compared to those born preterm[65]. The above review did not assess DBP or other CVD risk factors. Our meta-analyses on a larger sample demonstrate a stronger association of PTB with higher SBP and a significant association with higher DBP. Markopoulou and colleagues conducted a systematic review and meta-analysis of studies that reported on 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)[7]. The major outcomes assessed in this study were BMI, waist circumference, waist-to-hip ratio, fat mass, SBP, DBP, 24-h SBP, 24-h DBP, endothelium-dependent brachial artery flow-mediated dilation, carotid intima-media thickness, pulse wave

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Table 4. Risk factor profile of preterm born based on size at birth outcomes

	Preterm SGA Vs. term AGA	Preterm AGA Vs. term AGA	Preterm SGA Vs. preterm AGA
Systolic blood pressure	**2.00 (0.21 to 3.78)**	**1.46 (0.13 to 2.79)**	−0.07 (−2.01 to 1.88)
	Chi² *p* 0.19; I^2 30%	**Chi² *p* 0.34; I^2 12%**	Chi² *p* 0.0007; I^2 64%
	7 studies; *n* = 3639	**7 studies; *n* = 3792**	7 studies; *n* = 523
	Preterm, *n* = 185; term, *n* = 3454	**Preterm, *n* = 338; term, *n* = 3454**	Preterm, *n* = 185; term, *n* = 338
Diastolic blood pressure	1.39 (0.00 to 2.78)	**1.22 (0.19 to 2.25)**	0.02 (−1.45 to 1.49)
	Chi² *p* 0.21; I^2 28%	**Chi² *p* 0.92; I^2 0%**	Chi² *p* 0.33; I^2 13%
	7 studies; *n* = 3639	**7 studies; *n* = 3792**	7 studies; *n* = 523
	Preterm, *n* = 185; term, *n* = 3454	**Preterm, *n* = 338; term, *n* = 3454**	Preterm, *n* = 185; term, *n* = 338
Body mass index	−0.38 (−0.98 to 0.22)	0.06 (−0.34 to 0.46)	−0.44 (−1.12 to 0.24)
	Chi² *p* 0.39; I^2 4%	Chi² *p* 0.84; I^2 0%	Chi² *p* 0.88; I^2 0%
	6 studies; *n* = 3537	6 studies; *n* = 3728	6 studies; *n* = 421
	Preterm, *n* = 115; term, *n* = 3422	Preterm, *n* = 306; term, *n* = 3422	Preterm, *n* = 115; term, *n* = 306
Total cholesterol	-	-	-
High density lipoprotein	0.03 (−0.04 to 0.10)	0.01 (−0.04 to 0.07)	0.02 (−0.07 to 0.10)
	Chi² *p* 0.15; I^2 32%	Chi² *p* 0.15; I^2 32%	Chi² *p* 0.90; I^2 0%
	2 studies; *n* = 3338	2 studies; *n* = 3434	2 studies; *n* = 252
	Preterm, *n* = 78; term, *n* = 3260	Preterm, *n* = 174; term, *n* = 3260	Preterm, *n* = 78; term, *n* = 174
Low density lipoprotein	**0.67 (0.38 to 0.97)**	0.13 (−0.03 to 0.29)	**0.30 (0.13 to 0.48)**
	Chi² *p* <0.0001; I^2 98%	Chi² *p* <0.001; I^2 98%	**Chi² *p* 0.60; I^2 0%**
	2 studies; *n* = 3624	2 studies; *n* = 3434	**2 studies; *n* = 538**
	Preterm, *n* = 364; term, *n* = 3260	Preterm, *n* = 174; term, *n* = 3260	**Preterm, *n* = 364; term, *n* = 174**
Triglycerides	−0.00 (−0.07 to 0.06)	−0.04 (−0.09 to 0.02)	0.02 (−0.07 to 0.10)
	Chi² P 0.15; I² 51%	Chi² P 0.34; I² 0%	Chi² P 0.84; I²0%
	2 studies; *n* = 3338	2 studies; *n* = 3434	2 studies; *n* = 252
	Preterm, *n* = 78; term, *n* = 3260	Preterm, *n* = 174; term, *n* = 3260	Preterm, *n* = 78; term, *n* = 174
Glucose (fasting)	**−0.80 (−0.85 to −0.75)**	−0.60 (−0.64 to −0.56)	**−0.20 (−0.24 to −0.16)**
	Not applicable	Not applicable	**Not applicable**
	1 study; *n* = 74	1 study; *n* = 107	**1 study; *n* = 93**
	Preterm, *n* = 30; term, *n* = 44	Preterm, *n* = 63; term, *n* = 44	**Preterm, *n* = 30; term, *n* = 63**
Insulin	−1.65 (−3.39 to 0.10)	−1.07 (−2.29 to 0.15)	0.53 (−0.72 to 1.78)
	Chi² *p* 0.12; I^2 53%	Chi² *p* 0.0006; I^2 69%	Chi² *p* 0.85; I^2 0%
	3 studies; *n* = 1775	3 studies; *n* = 1878	3 studies; *n* = 261
	Preterm, *n* = 79; term, *n* = 1696	Preterm, *n* = 185; term, *n* = 1696	Preterm, *n* = 79; term, *n* = 182

AGA, average for gestational age; SGA, small for gestational age.
Results are presented in MD or SMD with 95% CIs.
Following outcomes are presented as MD with 95% CI and the rest are in SMD.
Systolic blood pressure, diastolic blood pressure, and body mass index.
Heterogeneity is presented as Chi² *p* value and I^2 percentage.

velocity, fasting glucose, insulin, and lipid profiles. The above study included a total of 18,295 preterm and 294, 063 term born adults. Prematurity was associated with significantly higher fat mass ($p = 0.03$), SBP ($p < 0.0001$), DBP ($p < 0.0001$), 24-h SBP ($p < 0.001$), 24-h DBP ($p < 0.001$), fasting glucose ($p = 0.01$), insulin ($p = 0.002$), and total cholesterol levels ($p = 0.05$) in comparison with adults born at term[7]. In our study of children, adolescents, and adults, we found higher SBP and DBP among those born preterm compared to those born at term. Higher SBP was seen in children, adolescents, and young adults born preterm compared to those born at term. We did not find significant differences in fasting blood glucose, insulin, or lipids between preterm and term groups. Our findings extend the findings of Markopoulou and colleagues by demonstrating that higher SBP among those born preterm is seen as early as during childhood and adolescence.

The finding of higher BP among those born preterm compared to term in the absence of differences in any of the other metabolic parameters assessed in this review suggests that an increased BP

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may be a main mechanism that links PTB with CVD. Both prenatal and postnatal factors may underlie the link between PTB and higher BP. The increased BP may be influenced through the process of fetal programming, which involves long-lasting adaptive changes in response to an adverse intrauterine environment during a period of critical development. While most of the initial evidence on fetal programming in response to adverse intrauterine environment focused on intrauterine undernutrition, subsequent epidemiological studies have shown that numerous intrauterine exposures including major pregnancy complications (preeclampsia and gestational diabetes mellitus [GDM]), maternal obesity, and smoking during pregnancy and exposure to environmental chemicals can each trigger propensity for a myriad of cardiovascular and metabolic disorders in the offspring[66]. The adverse intrauterine environment, for example, in the case of maternal preeclampsia, GDM, or intrauterine growth restriction may result in PTB. We recently conducted two systematic reviews and meta-analyses on the association between maternal preeclampsia and GDM and offspring risk for CVD and found that both pregnancy complications were associated with elevated SBP in the offspring[67,68]. These adverse pregnancy outcomes are quite often coexistent and hard to decipher in the context of a systematic review as many studies on PTB do not report on the prevalence of other pregnancy complications in the study cohorts. Therefore, the coexistence of these pregnancy complications may confound the association between PTB and elevated BP. However, being born preterm is one of the most robust clinical surrogates for low nephron number[69]. Human nephrogenesis continues up to about 36 weeks' gestation, and prematurity is associated with a congenital reduction in nephron number. Reduced nephron number is shown to be associated with raised BP (reviewed in reference 69). The preterm infant is also ex-utero during the last weeks of fetal development (PTB to 40 weeks' gestation). Many preterm neonates spend the first few weeks of extra-uterine life in the neonatal intensive care unit and may experience extra-uterine growth restriction which can influence BP through programming mechanisms[70]. Preterm infants are also likely to receive nutrient enriched preterm infant formula that can contribute to rapid early weight gain which may lead to higher BP[71].

Although fetal programming can be considered as the main mechanistic pathway linking PTB with increased BP in later life, genetic, environmental, and lifestyle factors are also likely to play an important role. Understanding the relative contribution of each potential pathway to higher BP is very difficult, due to the possible interactions between these pathways. However, the finding of higher SBP and DBP among those born preterm and especially the higher SBP being evident from early adolescence is of clinical importance.

The finding of higher mean SBP among females born preterm compared to term, but not among males born preterm compared to term, was surprising, especially since most studies included in the meta-analyses were conducted on females in premenopausal age groups. However, a recent very large population-based study from Sweden of 2,141,709 individuals reported that at ages 30–43 years, adjusted hazard ratio for ischemic heart disease (IHD) was 1.53 (95% CI, 1.20 to 1.94) among those born preterm compared to term and that adjusted HR for IHD among women born preterm compared to men born preterm was 1.93 (95% CI, 1.28 to 2.90)[72]. These findings suggest that females born preterm may be at a higher risk of premature CVD and that the finding of higher SBP among females in our study may be an evidence of an increased risk factor profile among women.

We acknowledge the following limitations in this systematic review. We limited our search to articles published in English and may have missed important data from studies published in other languages. Since most studies included in the meta-analyses did not report on the coexistence of other major pregnancy complications including exposure to preeclampsia, gestational diabetes, or intrauterine growth restriction, we could not limit the analyses to a group of spontaneous PTB. Therefore, the results may have been confounded by possible associations between these pregnancy complications and risk for CVD. The heterogeneity among studies was also quite high and the subgroup analyses did not change the I^2 of most analyses. However, most of the included studies (~ 87%) were of moderate quality as assessed by the NOS, and the results of the sensitivity analysis confirmed the previous findings.

Since elevated BP during childhood has been shown to predict the development of hypertension[63], the findings of this study suggest that those born preterm may benefit from routine BP monitoring and targeted interventions when required.

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