Original Article

Effect of preterm birth on blood pressure in later life: A systematic review and meta-analysis

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Abstract

Introduction: Preterm birth is linked to various complications in both infancy and adulthood. We assessed the association between preterm birth and hypertension in adulthood. **Materials and Methods:** PubMed, EMBASE, and Cochrane CENTRAL Register were searched for randomized controlled trials (RCT) comparing systolic and diastolic blood pressures in individuals born preterm and those born full-term, from inception till April 11th, 2022. Data were extracted, pooled, and analyzed. Forest plots were created for a visual demonstration. **Results:** Twenty-eight studies were included in our meta-analysis. SBP and DBP across all categories (Mean, Ambulatory, Daytime, and Nighttime) were higher in the preterm group compared to the term group. Mean SBP, mean ambulatory SBP, mean daytime SBP and mean nighttime SBP were 4.26 mmHg [95% CI: 3.09–5.43; $P < 0.00001$], 4.53 mmHg [95% CI: 1.82–7.24; $P = 0.001$], 4.51 mmHg [95% CI: 2.56–6.74; $P < 0.00001$], and 3.06 mmHg [95% CI: 1.32–4.80; $P = 0.0006$] higher in the preterm group, respectively. Mean DBP, mean ambulatory DBP, mean daytime DBP, and mean nighttime DBP were 2.32 mmHg [95% CI: 1.35–3.29; $P < 0.00001$], 1.54 mmHg [95% CI 0.68–2.39; $P = 0.0004$], 1.74 mmHg [95% CI: 0.92–2.56; $P < 0.0001$], and 1.58 mmHg [95% CI: 0.34–2.81; $P = 0.01$] higher in the preterm group, respectively. **Conclusion:** Our observations suggest that individuals who were born preterm may have higher blood pressures as compared to those who were born full-term.

Keywords: Adult, blood pressure, meta-analysis, premature birth

Introduction

Hypertension remains a major cause of cardiovascular mortality globally and is estimated, to affect 1.56 billion people by 2025.[31]

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It also represents a significant economic burden, with Kirkland *et al.*[32] estimating the adjusted annual incremental cost to be US$131 billion higher for the hypertensive adult population than for the nonhypertensive population. Its high prevalence and wide epidemiological spread underscore the importance of risk stratification, early diagnosis, and appropriate management before end-organ damage occurs. Despite heavy investments and numerous studies, a complete understanding of the different characteristics of hypertension is still lacking.[1,2]

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Approximately 15 million babies are born premature annually worldwide.[3] Not only is prematurity the leading cause of death in children younger than 5 years of age,[4] but it can also have long-term complications including hypertension.[5]

The association between low birth weight and hypertension in later life is well established in the literature.[6] However, these studies focused more that lead to impaired fetal growth including smoking and maternal nutrition.[7,8] The association of gestational age due to preterm birth as an independent risk factor of hypertension in later life remains less established. Data from recent studies have found a strong correlation between prematurity and hypertension in adulthood.[9,10]

Hypertension, being widespread, necessitates early detection and management to minimize its long-term complications, and is most optimally detected, managed, and followed up at a primary care level.[11] Primary care is important in the prevention and management of chronic diseases;[12] thus, its involvement with the objective of our meta-analysis is highly relevant. Preterm birth has been linked to high blood pressure later in life,[13,14] and understanding its link to the development of hypertension in adulthood is critical for primary care physicians, since it can help identify individuals who are at a higher risk of developing hypertension early on.

This systematic review and meta-analysis aim to test the hypothesis that individuals who were born preterm have a higher systolic blood pressure (SBP), diastolic blood pressure (DBP), and hypertension prevalence, as compared with those born full term, thereby, providing valuable insights to the primary care providers, allowing early detection and appropriate intervention to enhance patient outcomes.

Materials and Methods

Data sources and search strategy

This meta-analysis was performed according to the preferred reporting items for systematic review and meta-analyses (PRISMA) guidelines.[15] An electronic search of EMBASE, PubMed, and Cochrane CENTRAL Register of Controlled Trials was conducted from their inception to April 11th, 2022, without any language restrictions, using the keywords; "premature birth," "preterm birth," "blood pressure," "hypertension," "cardiovascular outcomes," "cardiovascular disease," "Cardiovascular risk factors," "young adults," "adulthood," "adult," and "later life" A detailed search string is provided in the supplementary material [Table S1]. Furthermore, we manually screened the reference list of retrieved trials, previous meta-analyses, and review articles to identify any relevant studies.

Study selection

The following eligibility criteria were used to select studies: (a) were conducted in human participants, (b) were written in English, (c) had a full-text source available, (e) represent a cohort study, a case–control study, or a cross-sectional study, (f) were published before April 11th, 2022, (g) included gestational age, (h) included adult participants (≥18 years old) born preterm (<37 weeks of gestation) in comparison with adult participants born at term (37–42 weeks of gestation), (i) evaluated components of blood pressure, including SBP or, and (k) had mean and standard deviation (SD) (or the raw data with which to calculate them) for SBP and SB*P* values.

Alternatively, studies in nonhuman participants or those conducted in children and/or adolescents (<18 years old) and genetic studies, systematic reviews/meta-analyses, case reports, and studies published from April 11th, 2022, and onward, were not eligible for this systematic review and meta-analysis; furthermore, studies not reporting gestational age or blood pressure measurement were also excluded.

Data extraction and assessment of study quality

Articles were assessed by two independent reviewers (AS and AK). Any conflicts and confusions regarding the articles were resolved by consulting the third author (RC). Duplicates of articles were removed by using EndNote X8.0 software (Clarivate Analytics, Philadelphia, PA, USA). Articles were first shortlisted based on title then abstract. If the title and the abstract were insufficient to exclude the articles, the full text was referred. From the finalized articles, the following outcomes were extracted: the name of the author, location and the year of publication of the study, study type, mean age, mean gestational age, male percentage, number of preterm and term participants, mean systolic and diastolic blood pressure, mean 24-hour/ambulatory blood pressure monitoring (ABPM) systolic and diastolic blood pressures, mean day/awake and nighttime/asleep systolic and diastolic blood pressures.

The Newcastle–Ottawa scale (NOS)[16] for nonrandomized studies was used for assessing the risk of bias of each individual study [Supplementary Table 3] included in the meta-analysis. The NOS consists of six items with three subscales: selection, comparability, and outcome. The scoring was performed independently by two reviewers (MA, HA). A study could have a maximum score of 9; a score of 7–9 or above was considered high quality, a score of 4–6 was considered medium quality, and a score of 0–4 or below was considered low quality.

Statistical analysis

For those studies in which the term group was divided and analyzed separately as appropriate for gestational age (AGA) term and small for gestational age (SGA) term, we considered the AGA term as our control group. In addition, for those studies having the preterm group analyzed separately as AGA and SGA preterm, or as extremely preterm (EP) and preterm, or as any form of two categories having gestational age less than 37 weeks, we involved both groups to be in the preterm group. The mean blood pressure values along with the SDs of these two groups were combined to give rise to one single preterm group by using

a formula suggested by the Cochrane Handbook for systematic reviews of interventions.[17]

Sample size = $N_1 + N_2$

$$\text{Mean} = \frac{N_1 M_1 + N_2 M_2}{N_1 + N_2}$$

$$\text{SD} = \sqrt{\frac{(N_1 - 1)\text{SD}_1^2 + (N_2 - 1)\text{SD}_2^2 + \frac{N_1 N_2}{N_1 + N_2}(M_1^2 + M_2^2 - 2M_1 M_2)}{N_1 + N_2 - 1}}$$

Where N_1 = sample size of preterm group 1, N_2 = sample size of preterm group 2, M_1 = mean of preterm group 1, M_2 = mean of preterm group 2, SD_1 = standard deviation of preterm group 1, SD_2 = standard deviation of preterm group 2.

Blood pressure data were collected as mean ± standard deviation (SD). Where the data were given in median and interquartile ranges (IQR), we used the quantile method for estimating the mean and SD from the median and IQR, proposed by Wan X. *et al.* in 2014.[18]

$$Mean \approx \frac{q1 + m + q3}{3} \quad SD \approx \frac{q3 - q1}{1.35}$$

Where $q1$ = first quartile, m = median, $q3$ = third quartile.

All the statistical analyses were conducted by using RevMan (version 5.4.1; Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). The results were presented as mean difference (MD) along with their 95% confidence intervals (CIs). The results were pooled using a random effect model. The I^2 statistic was used to assess heterogeneity across studies, with a value of I^2 between 25% and 50% considered mild heterogeneity, between 50% and 75% considered moderate heterogeneity, and greater than 75% considered severe heterogeneity.[19]

To estimate the extent of publication bias, funnel plots were created, and the Egger test was used for those outcomes having 10 or more studies. In the absence of any publication biases, studies were distributed symmetrically on either side of the combined effect size.[20]

Results

Study selection, trial characteristics, and quality assessment

An initial search of the three electronic databases yielded 19,563 potential studies. After exclusions, 28 studies remained for analysis. The PRISMA flowchart [Figure 1] summarizes the results of our literature search. A detailed search strategy using the databases is available in the supplementary file Table S1. All studies included in the analysis were published between 1998 and 2021 [Table 1]. Analysis was performed on 302,004 participants. Among these, 16,928 were preterm subjects and 285,076 term-born subjects. There were three respective studies that included participants from the HAPI (Health of Adults Born Preterm Investigation) project—a cross-sectional observational study, each of which investigated different outcomes and was hence included in the meta-analysis.[9,21,22] One study, Lewandowski AJ *et al.*[23] 2013, reported term birth as a control group in two categories, term-born young adults and term-born adults. The mean B*P* values for both these groups were combined together using the formula suggested by the Cochrane Handbook for systematic reviews of interventions,[17] as mentioned in the methods section of this manuscript.

Baseline characteristics of the total selected studies are presented in Table 1 [as well as in Table S2 in the supplementary file]. The range of gestational age (GA) for preterm infants was 24–36 weeks of gestation. The range of age at follow-up for blood pressure measurement was 18–49 years. Studies evaluated blood pressure in various forms, such as ambulatory blood pressure monitoring (ABPM),[24-29] awake/day blood pressure,[21,24-30] and nighttime/asleep blood pressure.[9,24-30] The overall quality of studies was medium–high with an average of 7.3 out of a maximum of 9 points. The study quality scored 5 in one study, 6 in three studies, 7 in ten studies, and 8 in 14 studies. The results of the quality assessment are available in supplementary Table S3. The summary of all the forest plots included in this meta-analysis is shown in Figure S9 in the online supplementary file.

Funnel plot asymmetry and significant Egger's test were seen for SBP and DBP, suggesting possible publication bias. However, the associations of the pooled result remained significant after the trim and fill method was used to correct for publication bias [Figures S10 and S11 in supplementary file]. The highest heterogeneity was seen in SBP and DBP, but a reduction in the I^2 value was observed in the subsequent sensitivity analyses while the associations of the pooled data remained significant [Figures S12 and S13 in supplementary file].

Systolic blood pressure

The meta-analysis demonstrated that systolic blood pressure across all categories (mean SBP, ambulatory SBP, daytime SBP, and nighttime SBP) was higher in the preterm group compared to the term group.

Mean systolic blood pressure

Out of the total 28 included studies, 22 studies reported the mean SBP. Our pooled analysis demonstrates a significantly higher mean SBP in the preterm group as compared to the term group [MD = 4.26 mmHg; 95% CI: 3.09–5.43; $P < 0.00001$] [Figure 2 or Figure S1].

Mean ambulatory SBP

Out of the total 28 included studies, six studies reported mean ambulatory SBP. Our pooled analysis demonstrates

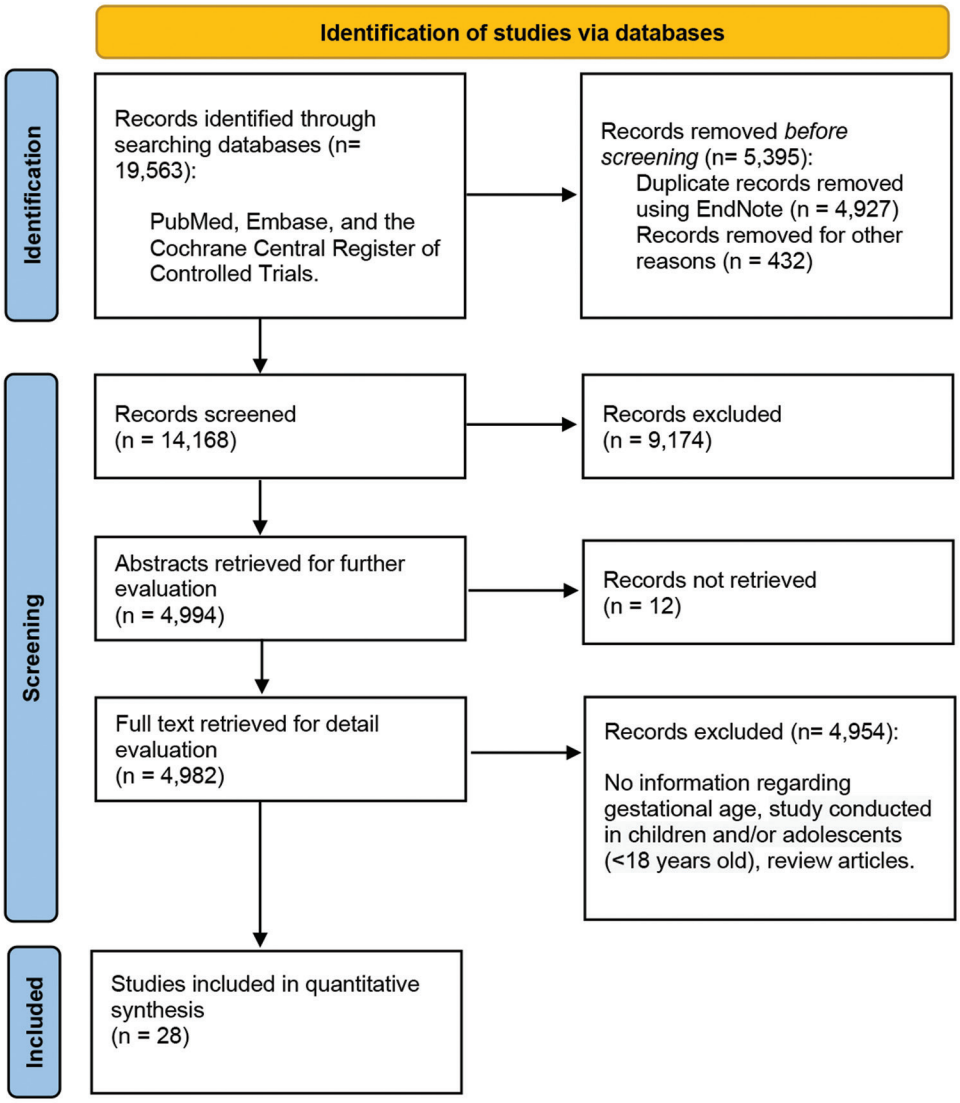

Figure 1: PRISMA flowchart of the literature search

a significantly higher mean ambulatory systolic SBP in the preterm group as compared to the term group [MD = 4.53 mmHg; 95% CI: 1.82–7.24; P = 0.001] [Figure 3 or Figure S2].

Mean daytime SBP

Out of the 28 included studies, eight studies reported mean daytime SBP. Our pooled analysis demonstrates a significantly higher mean daytime SBP in the preterm group as compared to the term group [MD = 4.51 mmHg; 95% CI: 2.56–6.47; P < 0.00001] [Figure 4 or Figure S3].

Mean nighttime SBP

Out of the 28 included studies, eight studies reported mean nighttime SBP. Our pooled analysis demonstrates a significantly higher mean nighttime SBP in the preterm group as compared to the term group [MD = 3.06 mmHg; 95% CI: 1.32–4.80; P = 0.0006] [Figure 5 or Figure S4].

Diastolic blood pressure

Similar to SBP, diastolic blood pressure was also found to be higher across all categories (mean DBP, ambulatory DBP, daytime DBP, and nighttime DBP) in the preterm group compared to the term group.

Mean DBP

Out of the 28 included studies, 22 studies reported mean DBP. Our pooled analysis demonstrates a significantly higher mean DBP in the preterm group as compared to the term group [MD = 2.32 mmHg; 95% CI: 1.35–3.29; P < 0.00001] [Figure 6 or Figure S5].

Mean ambulatory DBP

Out of the 28 included studies, six studies reported mean ambulatory DBP. Our pooled analysis demonstrates a significantly higher mean ambulatory DBP in the preterm group as compared to the term group [MD = 1.54 mmHg; 95% CI: 0.68–2.39; P = 0.0004] [Figure 7 or Figure S6].

Table 1: Baseline characteristics of included studies

Author (Year)	Study design	Location	Male %	Definition of PT in terms of GA (*n*)	Definition of EP in terms of GA (*n*)
Doyle *et al.* 2003	Prospective cohort	Australia	PT: 46.8 FT: 52.6	24–36 weeks (156)	N/A
Evensen *et al.* 2009	Cohort	Norway	PT: 54% FT: 46%	<37 weeks (37)	N/A
Flahault A, CGB *et al.* 2020	Cohort	Canada	PT: 45 FT: 41	≤29 weeks of gestation (101)	N/A
Flahault A, KP *et al.* 2020	Cohort	Canada	PT: 44 FT: 42	<30 weeks (86)	N/A
Hovi *et al.* 2010	Cohort	Finland	VLBW*: 41.5 FT: 40	118	N/A
Hurst *et al.* 2020	Cohort	UK/Ireland	N/A	N/A	<26 weeks (127)
Jarvelin *et al.* 2004	Longitudinal prospective cohort	Finland	PT: 5 FT: 76	<37 weeks (273)	N/A
Johansson *et al.* 2005	Cohort	Sweden	100	29–36 weeks (14,030)	24–28 weeks (162)
Juonala *et al.* 2015	Cohort	Finland	PT AGA: 46.7 PT SGA: 51.9 FT: 48.4	<37 weeks (PT AGA: 87, PT SGA: 39)	N/A
Keijzer-Veen *et al.* 2010	Cohort	Netherlands	PT AGA: 38 PT SGA: 38 FT: 47	<32 weeks (50)	
Kerkhof *et al.* 2012	Cohort	Netherlands	PT: 50.9 FT: 37.86	<36 weeks (163)	N/A
Kistner *et al.* 2000	Cohort	Sweden	0	<32 weeks (15)	N/A
Kowalski *et al.* 2018	Prospective cohort	Australia	PT: 52.6 FT: 38.1	N/A	<28 weeks (76)
Lazdam *et al.* 2010	Cohort	UK	PT: 46.4 FT: 53	<37 weeks (71)	N/A
Lewandowski *et al.* 2013	Cohort	UK	PT: 46.1 FT-born young adults: 46.1 FT-born adults: 46.7	28–31 weeks (102)	N/A
Lewandowski *et al.* 2015	Cohort	UK	50	<37 weeks (30)	N/A
Mathai *et al.* 2015	Cohort	New Zealand	PT: 45 FT: 29	<37 weeks (22)	N/A
Mohamed *et al.* 2021	Cross-sectional cohort	England	PT: 45.5 FT: 50.7	<37 weeks (200)	N/A
Morrison *et al.* 2016	Cohort	Canada	PT: 40 FT: 42	<37 weeks (100)	N/A
Ni *et al.* 2020	Cohort	UK	PT: 47.3 FT: 38.5	N/A	<26 weeks (127)
Paquette *et al.* 2018	Cohort	Canada	44	≤29 weeks (92)	N/A
Roberts *et al.* 2014	Longitudinal prospective cohort	Australia	PT: 52 FT: 43	N/A	<28 weeks (136)
Rotteveel *et al.* 2008	Cohort	Netherlands	PT AGA: 51.7 PT SGA: 46.42 FT: 50	<32 weeks (PT SGA: 28, PT AGA: 29)	N/A
Siewert-Delle *et al.* 1998	Cross-sectional cohort	Sweden	100	<38 weeks (44)	N/A
Skilton *et al.* 2011	Cohort	Finland	PT: 46 FT AGA: 45 FT SGA: 49	<37 weeks (253)	N/A
Sullivan *et al.* 2019	Cohort	USA	47	<37 weeks (135)	N/A
Tauzin *et al.* 2014	Cohort	France	PT: 43.8 FT: 60	<37 weeks (16)	N/A
Thomas *et al.* 2011	Cohort	UK	PT: 56.5 FT: 40	≤33 weeks (23)	N/A

Contd...

Table 1: Contd...

Author (Year)	Definition of FT in terms of GA (*n*)	Variables for matching cases and controls	Age at follow-up, years or mean years (SD)	Mean gestational age in terms of weeks (SD) for preterm/term
Doyle *et al.* 2003	37–42 weeks (38)	N/A	18+	28.8 (2.0)/40 (1.1)
Evensen *et al.* 2009	63	N/A	18	28/40
Flahault A, CGB *et al.* 2020	≥37 weeks (105)	Age	PT: 23.2 (2.2) FT: 23.2 (2.5)	27.1 (1.4)/39.6 (1.1)
Flahault A, KP *et al.* 2020	≥37 weeks (85)	Age and controls recruited among friends and siblings	PT: 23.3 (2.3) FT: 23.2 (2.4)	27.2 (1.6)/38.7 (0.9)
Hovi *et al.* 2010	120	Age, sex, and birth hospital	18–27	29.2 (2.3)/40.1 (1.0)
Hurst *et al.* 2020	64	Age, sex, and controls recruited from classmates	19	N/A
Jarvelin *et al.* 2004	37–41 weeks (4356)	N/A	31	N/A
Johansson *et al.* 2005	37–41 weeks (275,895)	N/A	18	24–28, 29–32, 33–36/37–41
Juonala *et al.* 2015	1630	N/A	3–18 and 34–49	N/A
Keijzer-Veen *et al.* 2010	37–42 weeks (30)	N/A	20	SGA: 30.6 (1.1) AGA: 29.5 (1.4)/40.2 (1.3)
Kerkhof *et al.* 2012	243	N/A	PT: 20.8 FT: 20.9	32.0 (2.2)/39.2 (1.7)
Kistner *et al.* 2000	37–42 weeks (FT SGA: 18, FT AGA: 17)	Age and born in the same hospital	23–30	30.0 (1.0)/41.0 (1.0)
Kowalski *et al.* 2018	42	Sex of the infant and the mother's health insurance status and country of birth	PT: 18.2 (1.3) FT: 18.6 (0.9)	27 (1)/39 (1)
Lazdam *et al.* 2010	38	Age and born of uncomplicated pregnancies	20	30.3 (2.5)/37–42
Lewandowski *et al.* 2013	132	Age and sex	PT: 25.1±1.4 FT-born young adults: 25.0 (2.6) FT-born adults: 35.5 (1.8)	PT: 30.3 (2.5) FT-born young adults: 39.6 (0.9) FT-born adults: 39.8 (0.8)
Lewandowski *et al.* 2015	60	Age and sex	20–30	30.3 (2.5)/39.6 (0.8)
Mathai *et al.* 2015	37–41 weeks (14)	N/A	PT: 35.8 (1.2) FT: 35.6 (1.1)	N/A
Mohamed *et al.* 2021	≥37 weeks (268)	N/A	PT: 25.7 (3.94) FT: 26.5 (4.59)	NT PT: 31.17 (2.99), HT PT: 31.77 (2.99)/NT FT: 39.50 (1.11), HT FT: 39.86 (1.20)
Morrison *et al.* 2016	89	Age, sex, and socioeconomic status	PT: 31.63 (1.66) FT: 31.96 (1.42)	PT: 27.10 (2.45) FT: N/A
Ni *et al.* 2020	≥37 weeks (64)	Age, sex, and ethnicity	19	N/A
Paquette *et al.* 2018	92	Age, sex, and race	PT: 23.2 (2.2) FT: 23.2 (2.3)	27.1 (1.3)/39.5 (1.1)
Roberts *et al.* 2014	120	Age, sex, and social status	18	25.8 (1.1)/39.3 (1.4)
Rotteveel *et al.* 2008	37–42 weeks (30)	N/A	22	AGA: 28.9 (1.4), SGA: 30.7 (1.1)/40.0
Siewert-Delle *et al.* 1998	38–41 weeks (336)	N/A	49	N/A
Skilton *et al.* 2011	FT SGA: 207, FT AGA: 835	N/A	24–45	N/A
Sullivan *et al.* 2019	45	Full-term infants were recruited at the same time as the preterm infants	23	Healthy PT: 31.0 (1.7), Sick PT: 29.7 (2.7)/39.8 (0.86)
Tauzin *et al.* 2014	40 weeks (15)	N/A	21	32/40
Thomas *et al.* 2011	25	N/A	18–27	Men: 29.9 (2.5), women: 28.8 (2.8)/men: 40.5 (2.0), women: 39.9 (1.3)

AGA=Appropriate/average for gestational age, SGA=Small for gestational age, PT=Preterm, FT=Full-term, EP=Extremely preterm, GA=Gestational age, VLBW=Very low birth weight, SD=Standard deviation, N/A=Not applicable, NT=Normotensive, HT=Hypertensive. *All VLBW were preterm

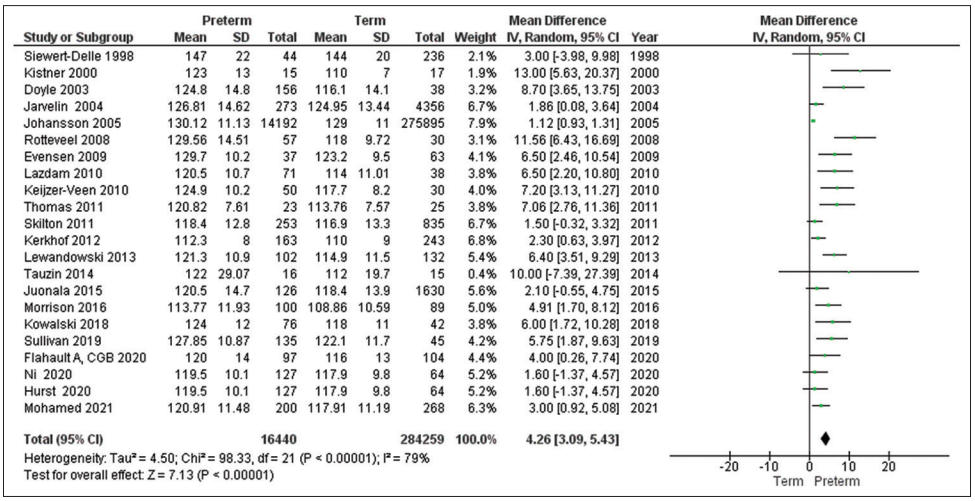

Figure 2: Forest plot comparing mean systolic blood pressure (SBP) between preterm and term groups

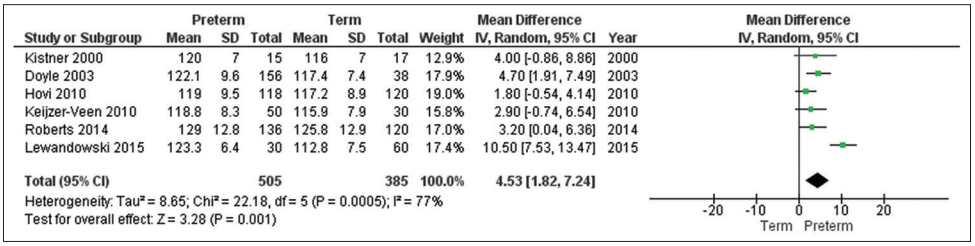

Figure 3: Forest plot comparing mean ambulatory (ABPM) systolic blood pressure (SBP) between preterm and term groups

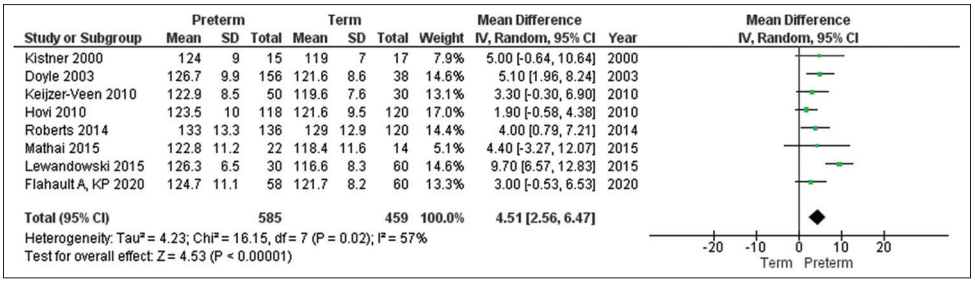

Figure 4: Forest plot comparing mean daytime/awake ambulatory (ABPM) systolic blood pressure (SBP) between preterm and term groups

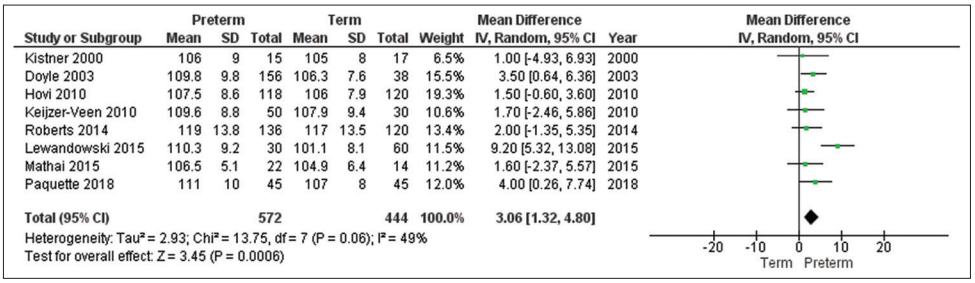

Figure 5: Forest plot comparing mean nighttime/asleep ambulatory (ABPM) systolic blood pressure (SBP) between preterm and term groups

Mean daytime DBP

Out of the 28 included studies, eight studies reported mean daytime DBP. Our pooled analysis demonstrates a significantly higher mean daytime DBP in the preterm group as compared to the term group [MD = 1.74 mmHg; 95% CI: 0.92–2.56; $P < 0.0001$] [Figure 8 or Figure S7].

Mean nighttime DBP

Out of the 28 included studies, eight studies reported mean nighttime DBP. Our pooled analysis demonstrates a significantly higher mean nighttime DBP in the preterm group as compared to the term group [MD = 1.58 mmHg; 95% CI: 0.34–2.81; $P = 0.01$] [Figure 9 or Figure S8].

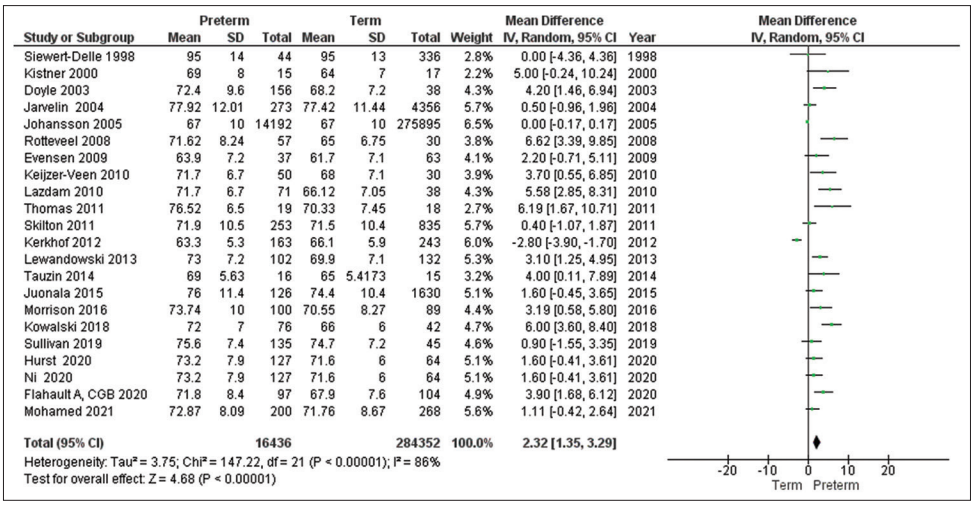

Figure 6: Forest plot comparing mean diastolic blood pressure (DBP) between preterm and term groups

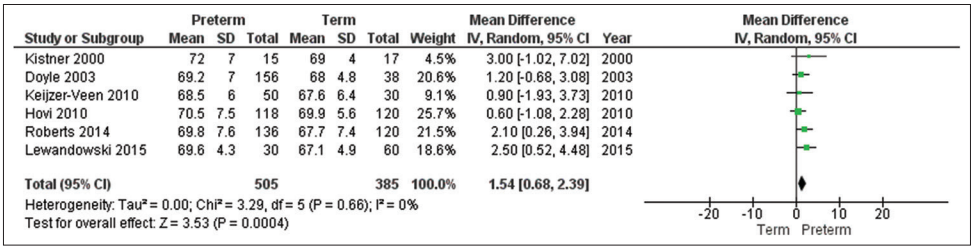

Figure 7: Forest plot comparing mean ambulatory (ABPM) diastolic blood pressure (DBP) between preterm and term groups

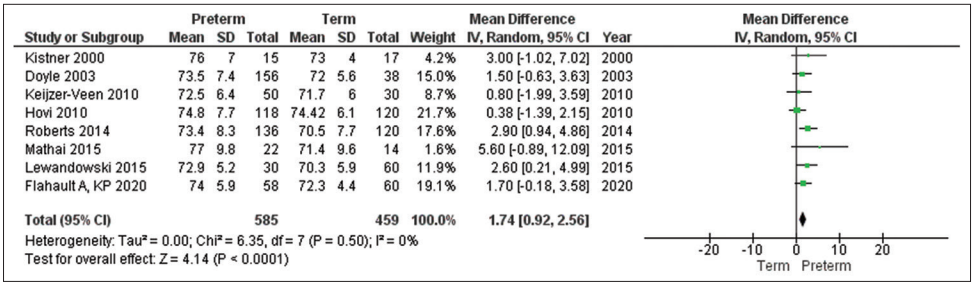

Figure 8: Forest plot comparing mean daytime/awake ambulatory (ABPM) diastolic blood pressure (DBP) between preterm and term groups

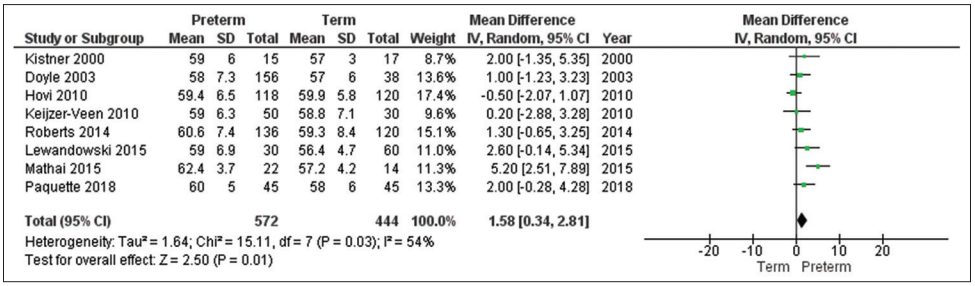

Figure 9: Forest plot comparing mean nighttime/asleep ambulatory (ABPM) diastolic blood pressure (DBP) between preterm and term groups

Discussion

In this systematic review and meta-analysis, an increased risk of hypertension was observed in adults born preterm in comparison with adults born after a full-term pregnancy. This included a significant increase in mean SBP and DBP, ABPM SBP and DBP, daytime SBP and DBP, and nighttime SBP and DBP. The results are in line with those of the previous meta-analysis.[45] The greatest difference between the two groups was observed in 24-hour SBP (4.53 mmHg), and the least was observed in 24-hour DBP (1.54 mmHg).

Many possible explanations have been suggested for the association of hypertension with prematurity. Preterm birth has been shown to alter cardiac geometry and function. Impaired ventricular systolic and diastolic function, increased interventricular septum thickness, and smaller left ventricular cavity have all been observed in preterm infants.[33,34] Increased left ventricle mass has also been observed in adults (aged 20–39) born preterm, with a strong inverse correlation between gestational age and the increase in left ventricle mass.[35] These structural and functional alterations of the heart may play some role in hypertension.

Another noteworthy factor is the presence of a fewer number of nephrons in preterm-born individuals.[36,37] Normally, nephrogenesis ends prenatally at around 34–36 weeks.[38] With approximately 60% of the nephrons being formed in the third trimester of pregnancy, preterm birth imposes a high risk of reduced number of nephrons. Adaptive changes in renal hemodynamics such as an increase in single-nephron glomerular filtration rate (SNGFR) to meet excretory demands and an increase in blood pressure due to the limitation of sodium excretion are seen due to this nephron deficit.[37,39,40] The net effect is the occurrence of glomerular hypertension.

Overactive sympathetic tone, decreased parasympathetic tone, increased ACE (angiotensin-converting enzyme) activity, and greater amounts of oxidative stress in preterm infants may also contribute to hypertension in later life.[41-44] However, more studies are needed to confirm these associations.

Arterial stiffness, endothelial dysfunction, and increase in pulmonary vascular resistance were previously thought to be involved in hypertension in preterm adults. However, Markopoulou *et al*.,[45] in their meta-analyses, found no association between biomarkers of endothelial dysfunction and preterm birth. It should be noted that very few studies were available for their analysis, and more studies should be conducted in the future to shed more light on this topic.

Since the results of our meta-analysis demonstrated a persistent relationship between preterm birth and increased blood pressure later in life, this highlights its importance to primary care physicians, as primary care is frequently the initial point of contact for patients. During routine checkups, primary care physicians can evaluate the BP of preterm infants and children, allowing for prompt treatment and personalized management regimens. A few guidelines do exist, e.g., The 2004 Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents, and the 2008 clinical practice guidelines of the American Academy of Pediatrics (AAP), which recommended BP screening in children <3 years of age who have a history of prematurity during routine healthcare visits.[46,47] Despite these recommendations, pediatricians do not frequently examine BP in preterm children under the age of three.[48] By utilizing this information and the findings of our meta-analysis, primary care physicians can play a critical role in minimizing the long-term effects of high BP in preterm-born individuals by adopting heightened vigilance in monitoring BP and implementing appropriate therapies. Finally, the collaboration of primary care physicians and pediatric specialists is critical in managing these high-risk individuals and delivering a thorough multidisciplinary approach.

We acknowledge the following limitations in this systematic review and meta-analysis. Firstly, as mentioned in our inclusion criteria, the articles published must be in English to be included in this study. As a result of these criteria, this study may have missed important data from studies published in other languages. Secondly, the heterogeneity among studies was also quite high, especially in the analysis done for SBP and DBP. A possible reason for the high heterogeneity is because preterm birth cannot be randomized and hence studies do not report cohorts, case controls, or trials with randomization for both cases and controls. The use of the random effects model, as done in this meta-analysis, could not lower the high heterogeneity. Thirdly, there were a limited number of studies examining 24-hour SBP, 24-hour DBP, daytime/awake SBP, daytime/awake DBP, nighttime/asleep SBP, and nighttime/asleep DBP. This may decrease the validity of the analysis for such outcomes. Furthermore, adults participating in studies included in the meta-analysis were the majority of a young mean adult age; more studies are needed to evaluate blood pressure at an older age (i.e., >30–40 years of age) to determine more precisely the associations between preterm birth and blood pressure. In addition, as mentioned in our study flowchart, some studies were excluded as they lacked accessible raw data. There can also be a possibility of existing cohorts, trials, and case controls that were not accessible. Further subgroup comparisons according to gender and age were not possible due to the limited number of eligible studies.

Conclusion

In conclusion, individuals born preterm had higher SBP and DBP, and their various components as compared to the full-term-born individuals. The development of follow-up programs that aim to monitor such individuals early in life and onwards at a primary care level can be very helpful to reduce hospitalizations caused by complications of high BP. Primary healthcare facilities and primary care physicians should be aware of these findings while managing such patients as they reach adulthood. We believe more studies with greater sample sizes are required to increase scientific understanding of the mechanism and pathophysiology regarding the association of high BP in adulthood among preterm-born patients.

Key take home message

Globally, about 15 million children are born prematurely each year. Preterm birth can lead to immediate as well as delayed complications. Hypertension often referred to as the "silent killer" remains the largest contributor to cardiovascular diseases. Preterm birth has been found to have a significant effect on

the blood pressure of adults born prematurely. Structural and functional changes in the heart, overactive sympathetic tone, and increased vascular resistance are some of the few theories explaining the association between prematurity and hypertension.

List of Abbreviations

Abbreviation	Definition
RCT	Randomized controlled trials
SBP	Systolic blood pressure
DBP	Diastolic blood pressure
ABPM	Ambulatory blood pressure monitoring
NOS	Newcastle–Ottawa scale
AGA	Appropriate for gestational age
SGA	Small for gestational age
EP	Extremely preterm
SD	Standard deviation
IQR	Interquartile range
MD	Mean difference
CI	Confidence interval
HAPI	Health of Adults Born Preterm Investigation
GA	Gestational age
SNGFR	Single-nephron glomerular filtration rate
ACE	Angiotensin-converting enzyme
PT	Preterm
FT	Full term
VLBW	Very low birth weight
NT	Normotensive
HT	Hypertensive
N/A	Not applicable

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Conflicts of interest

There are no conflicts of interest.

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Online Supplementary Appendix

Table S1: Detailed search strategy using databases

Database	Search strategy	Articles retrieved
PUBMED	(“premature birth”[MeSH Terms] OR (“premature”[All Fields] AND “birth”[All Fields]) OR “premature birth”[All Fields] OR (“preterm”[All Fields] AND “birth”[All Fields]) OR “preterm birth”[All Fields])) AND (“blood pressure”[MeSH Terms] OR (“blood”[All Fields] AND “pressure”[All Fields]) OR “blood pressure”[All Fields] OR “blood pressure determination”[MeSH Terms] OR (“blood”[All Fields] AND “pressure”[All Fields] AND “determination”[All Fields]) OR “blood pressure determination”[All Fields] OR (“blood”[All Fields] AND “pressure”[All Fields]) OR “blood pressure”[All Fields] OR “arterial pressure”[MeSH Terms] OR (“arterial”[All Fields] AND “pressure”[All Fields]) OR “arterial pressure”[All Fields] OR (“blood”[All Fields] AND “pressure”[All Fields]) OR (“hypertense”[All Fields] OR “hypertension”[MeSH Terms] OR “hypertension”[All Fields] OR “hypertension s”[All Fields] OR “hypertensions”[All Fields] OR “hypertensive”[All Fields] OR “hypertensive s”[All Fields] OR “hypertensives”[All Fields]) OR ((“cardiovascular system”[MeSH Terms] OR (“cardiovascular”[All Fields] AND “system”[All Fields]) OR “cardiovascular system”[All Fields] OR “cardiovascular”[All Fields] OR “cardiovasculars”[All Fields]) AND (“outcome”[All Fields] OR “outcomes”[All Fields])) OR (“cardiovascular diseases”[MeSH Terms] OR (“cardiovascular”[All Fields] AND “diseases”[All Fields]) OR “cardiovascular diseases”[All Fields] OR (“cardiovascular”[All Fields] AND “disease”[All Fields]) OR “cardiovascular disease”[All Fields]) OR (“heart disease risk factors”[MeSH Terms] OR (“heart”[All Fields] AND “disease”[All Fields] AND “risk”[All Fields] AND “factors”[All Fields]) OR “heart disease risk factors”[All Fields] OR (“cardiovascular”[All Fields] AND “risk”[All Fields] AND “factors”[All Fields]) OR “cardiovascular risk factors”[All Fields])) AND (“young adult”[MeSH Terms] OR (“young”[All Fields] AND “adult”[All Fields]) OR “young adult”[All Fields] OR (“young”[All Fields] AND “adults”[All Fields]) OR “young adults”[All Fields] OR (“adulthood”[All Fields] OR “adulthoods”[All Fields]) OR (“adult”[MeSH Terms] OR “adult”[All Fields] OR “adults”[All Fields] OR “adult s”[All Fields]) OR (“later”[All Fields] AND (“life”[MeSH Terms] OR “life”[All Fields]))))	4,559
EMBASE	(“premature birth”/exp OR “premature birth” OR ((“premature”/exp OR premature) AND (“birth”/exp OR birth)) OR “preterm birth”/exp OR “preterm birth” OR (preterm AND (“birth”/exp OR birth))) AND (“blood pressure”/exp OR “blood pressure” OR ((“blood”/exp OR blood) AND (“pressure”/exp OR pressure)) OR “hypertension”/exp OR hypertension OR “cardiovascular outcomes” OR ((“cardiovascular”/exp OR cardiovascular) AND (“outcomes”/exp OR outcomes)) OR “cardiovascular disease”/exp OR “cardiovascular disease” OR ((“cardiovascular”/exp OR cardiovascular) AND (“disease”/exp OR disease)) OR “cardiovascular risk factors”/exp OR “cardiovascular risk factors” OR ((“cardiovascular”/exp OR cardiovascular) AND (“risk”/exp OR risk) AND factors)) AND (“young adults”/exp OR “young adults” OR (young AND (“adults”/exp OR adults)) OR “adulthood”/exp OR adulthood OR “adult”/exp OR adult OR “later life” OR (later AND (“life”/exp OR life)))	14,593
COCHRANE	(Premature Birth OR Preterm Birth) AND (Blood Pressure OR Hypertension OR cardiovascular outcomes OR cardiovascular disease OR Cardiovascular risk factors) AND (young adults OR adulthood OR adult OR later life)	411 (trials)

Table S2: Baseline characteristics of included studies

Author (Year)	Study design	Location	Male %	Definition of PT in terms of GA (*n*)	Definition of EP in terms of GA (*n*)
Doyle *et al.* 2003	Prospective cohort	Australia	PT: 46.8 FT: 52.6	24–36 weeks (156)	N/A
Evensen *et al.* 2009	Cohort	Norway	PT: 54% FT: 46%	<37 weeks (37)	N/A
Flahault A, CGB *et al.* 2020	Cohort	Canada	PT: 45 FT: 41	≤29 weeks of gestation (101)	N/A
Flahault A, KP *et al.* 2020	Cohort	Canada	PT: 44 FT: 42	<30 weeks (86)	N/A
Hovi *et al.* 2010	Cohort	Finland	VLBW*: 41.5 FT: 40	118	N/A
Hurst *et al.* 2020	Cohort	UK/Ireland	N/A	N/A	<26 weeks (127)
Jarvelin *et al.* 2004	Longitudinal prospective cohort	Finland	PT: 5 FT: 76	<37 weeks (273)	N/A
Johansson *et al.* 2005	Cohort	Sweden	100	29–36 weeks (14,030)	24–28 weeks (162)
Juonala *et al.* 2015	Cohort	Finland	PT AGA: 46.7 PT SGA: 51.9 FT: 48.4	<37 weeks (PT AGA: 87, PT SGA: 39)	N/A
Keijzer-Veen *et al.* 2010	Cohort	Netherlands	PT AGA: 38 PT SGA: 38 FT: 47	<32 weeks (50)	
Kerkhof *et al.* 2012	Cohort	Netherlands	PT: 50.9 FT: 37.86	<36 weeks (163)	N/A
Kistner *et al.* 2000	Cohort	Sweden	0	<32 weeks (15)	N/A
Kowalski *et al.* 2018	Prospective cohort	Australia	PT: 52.6 FT: 38.1	N/A	<28 weeks (76)
Lazdam *et al.* 2010	Cohort	UK	PT: 46.4 FT: 53	<37 weeks (71)	N/A
Lewandowski *et al.* 2013	Cohort	UK	PT: 46.1 FT-born young adults: 46.1 FT-born adults: 46.7	28–31 weeks (102)	N/A
Lewandowski *et al.* 2015	Cohort	UK	50	<37 weeks (30)	N/A
Mathai *et al.* 2015	Cohort	New Zealand	PT: 45 FT: 29	<37 weeks (22)	N/A
Mohamed *et al.* 2021	Cross-sectional cohort	England	PT: 45.5 FT: 50.7	<37 weeks (200)	N/A
Morrison *et al.* 2016	Cohort	Canada	PT: 40 FT: 42	<37 weeks (100)	N/A
Ni *et al.* 2020	Cohort	UK	PT: 47.3 FT: 38.5	N/A	<26 weeks (127)
Paquette *et al.* 2018	Cohort	Canada	44	≤29 weeks (92)	N/A
Roberts *et al.* 2014	Longitudinal prospective cohort	Australia	PT: 52 FT: 43	N/A	<28 weeks (136)
Rotteveel *et al.* 2008	Cohort	Netherlands	PT AGA: 51.7 PT SGA: 46.42 FT: 50	<32 weeks (PT SGA: 28, PT AGA: 29)	N/A
Siewert-Delle *et al.* 1998	Cross-sectional cohort	Sweden	100	<38 weeks (44)	N/A
Skilton *et al.* 2011	Cohort	Finland	PT: 46 FT AGA: 45 FT SGA: 49	<37 weeks (253)	N/A
Sullivan *et al.* 2019	Cohort	USA	47	<37 weeks (135)	N/A
Tauzin *et al.* 2014	Cohort	France	PT: 43.8 FT: 60	<37 weeks (16)	N/A
Thomas *et al.* 2011	Cohort	UK	PT: 56.5 FT: 40	≤33 weeks (23)	N/A

Contd...

Table S2: Contd...

Author (Year)	Definition of FT in terms of GA (*n*)	Variables for matching cases and controls	Age at follow-up, years or mean years (SD)	Mean gestational age in terms of weeks (SD) for cases/control
Doyle *et al.* 2003	37–42 weeks (38)	N/A	18+	28.8 (2.0)/40 (1.1)
Evensen *et al.* 2009	63	N/A	18	28/40
Flahault A, CGB *et al.* 2020	≥37 weeks (105)	Age	PT: 23.2 (2.2) FT: 23.2 (2.5)	27.1 (1.4)/39.6 (1.1)
Flahault A, KP *et al.* 2020	≥37 weeks (85)	Age and controls recruited among friends and siblings	PT: 23.3 (2.3) FT: 23.2 (2.4)	27.2 (1.6)/38.7 (0.9)
Hovi *et al.* 2010	120	Age, sex, and birth hospital	18–27	29.2 (2.3)/40.1 (1.0)
Hurst *et al.* 2020	64	Age, sex, and controls recruited from classmates	19	N/A
Jarvelin *et al.* 2004	37–41 weeks (4356)	N/A	31	N/A
Johansson *et al.* 2005	37–41 weeks (275,895)	N/A	18	24–28, 29–32, 33–36/37–41
Juonala *et al.* 2015	1630	N/A	3–18 and 34–49	N/A
Keijzer-Veen *et al.* 2010	37–42 weeks (30)	N/A	20	SGA: 30.6 (1.1) AGA: 29.5 (1.4)/40.2 (1.3)
Kerkhof *et al.* 2012	243	N/A	PT: 20.8 FT: 20.9	32.0 (2.2)/39.2 (1.7)
Kistner *et al.* 2000	37–42 weeks (FT SGA: 18, FT AGA: 17)	Age and born in the same hospital	23–30	30.0 (1.0)/41.0 (1.0)
Kowalski *et al.* 2018	42	Sex of the infant and the mother's health insurance status and country of birth	PT: 18.2 (1.3) FT: 18.6 (0.9)	27 (1)/39 (1)
Lazdam *et al.* 2010	38	Age and born of uncomplicated pregnancies	20	30.3 (2.5)/37–42
Lewandowski *et al.* 2013	132	Age and sex	PT: 25.1±1.4 FT-born young adults: 25.0 (2.6) FT-born adults: 35.5 (1.8)	PT: 30.3 (2.5) FT-born young adults: 39.6 (0.9) FT-born adults: 39.8 (0.8)
Lewandowski *et al.* 2015	60	Age and sex	20–30	30.3 (2.5)/39.6 (0.8)
Mathai *et al.* 2015	37–41 weeks (14)	N/A	PT: 35.8 (1.2) FT: 35.6 (1.1)	N/A
Mohamed *et al.* 2021	≥37 weeks (268)	N/A	PT: 25.7 (3.94) FT: 26.5 (4.59)	NT PT: 31.17 (2.99), HT PT: 31.77 (2.99)/NT FT: 39.50 (1.11), HT FT: 39.86 (1.20)
Morrison *et al.* 2016	89	Age, sex, and socioeconomic status	PT: 31.63 (1.66) FT: 31.96 (1.42)	PT: 27.10 (2.45) FT: N/A
Ni *et al.* 2020	≥37 weeks (64)	Age, sex, and ethnicity	19	N/A
Paquette *et al.* 2018	92	Age, sex, and race	PT: 23.2 (2.2) FT: 23.2 (2.3)	27.1 (1.3)/39.5 (1.1)
Roberts *et al.* 2014	120	Age, sex, and social status	18	25.8 (1.1)/39.3 (1.4)
Rotteveel *et al.* 2008	37–42 weeks (30)	N/A	22	AGA: 28.9 (1.4), SGA: 30.7 (1.1)/40.0
Siewert-Delle *et al.* 1998	38–41 weeks (336)	N/A	49	N/A
Skilton *et al.* 2011	FT SGA: 207, FT AGA: 835	N/A	24–45	N/A
Sullivan *et al.* 2019	45	Full-term infants were recruited at the same time as the preterm infants	23	Healthy PT: 31.0 (1.7), Sick PT: 29.7 (2.7)/39.8 (0.86)
Tauzin *et al.* 2014	40 weeks (15)	N/A	21	32/40
Thomas *et al.* 2011	25	N/A	18–27	Men: 29.9 (2.5), women: 28.8 (2.8)/men: 40.5 (2.0), women: 39.9 (1.3)

AGA=Appropriate/average for gestational age, SGA=Small for gestational age, PT=Preterm, FT=Full-term, EP=Extremely preterm, GA=Gestational age, VLBW=Very low birth weight, SD=Standard deviation, N/A=Not applicable, NT=Normotensive, HT=Hypertensive, *All VLBW were preterm

Table S3: Quality assessment of published studies included in the meta-analysis

Author	Year	Selection				Comparability	Outcome			Total score
		Representativeness of the exposed cohort	Selection of the nonexposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of the study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow-up of cohorts	
Doyle LW *et al.*	2003	*	*	*	*	*	*	*		7
Evensen KAI *et al.*	2009		*	*	*	*	*	*	*	7
Flahault A, CGB *et al.*	2020	*	*	*	*	*	*	*	*	8
Flahault A, KP *et al.*	2020	*		*	*	*	*	*	*	7
Hovi P *et al.*	2010	*	*	*	*	*	*	*	*	8
Hurst JR *et al.*	2020	*		*	*	*	*	*	*	7
Jarvelin MR *et al.*	2004	*	*	*	*	*	*	*	*	8
Johansson S *et al.*	2005	*		*	*		*	*	*	6
Juonala M *et al.*	2015	*		*	*	*	*	*	*	7
Keijzer-Veen MG *et al.*	2010	*	*	*	*	*	*	*	*	8
Kerkhof GF *et al.*	2012			*	*		*	*	*	5
Kistner A *et al.*	2000	*	*	*	*	*	*	*	*	8
Kowalski RR *et al.*	2018	*	*	*	*	*	*	*	*	8
Lazdam M *et al.*	2010	*	*	*	*	*	*	*	*	8
Lewandowski AJ *et al.*	2013		*	*	*	*	*	*	*	7
Lewandowski AJ *et al.*	2015		*	*	*	*	*	*	*	7
Mathai S *et al.*	2015			*	*	*	*	*	*	6
Mohamed A *et al.*	2021		*	*	*	*	*	*	*	7
Morrison KM *et al.*	2016	*	*	*	*	*	*	*	*	8
Ni Y *et al.*	2020	*	*	*	*	*	*	*	*	8
Paquette K *et al.*	2018	*	*	*	*	*	*	*	*	8
Roberts G *et al.*	2014	*	*	*	*	*	*	*	*	8
Rotteveel J *et al.*	2008			*	*	*	*	*	*	6
Siewert-Delle A *et al.*	1998	*	*	*	*	*	*	*	*	8
Skilton MR *et al.*	2011	*	*	*	*	*	*	*	*	8
Sullivan MC *et al.*	2019	*		*	*	*	*	*	*	7
Tauzin L *et al.*	2014	*		*	*	*	*	*	*	7
Thomas EL *et al.*	2011	*	*	*	*	*	*	*	*	8

Contd...

Supplementary Table 3: Contd...

Author	Outcome			Total score
	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow-up of cohorts	
Rotteveel J *et al.*	*	*	*	6
Siewert-Delle A *et al.*	*	*	*	8
Skilton MR *et al.*	*	*	*	8
Sullivan MC *et al.*	*	*	*	7
Tauzin L *et al.*	*	*	*	7
Thomas EL *et al.*	*	*	*	8

NOS=Newcastle–Ottawa scale, NRS=Nonrandomized study

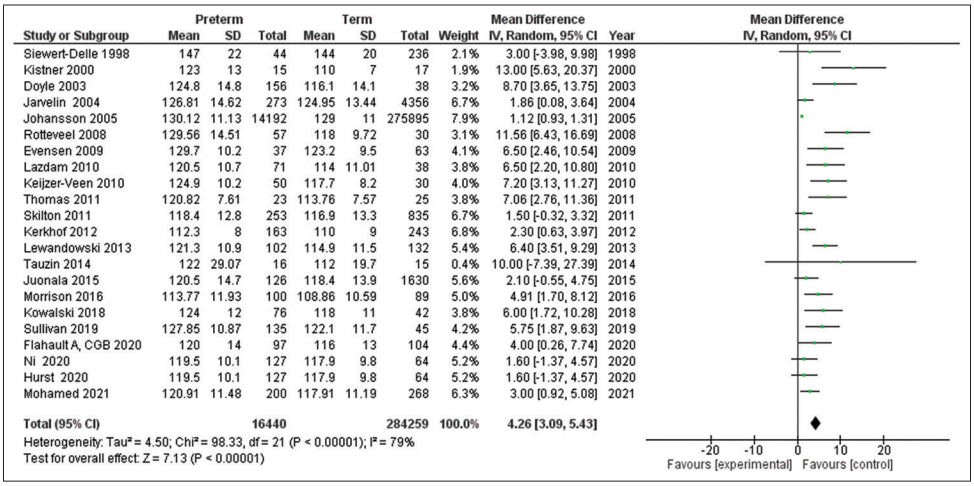

Figure S1: Forest plot comparing mean systolic blood pressure (SBP) between preterm and term groups

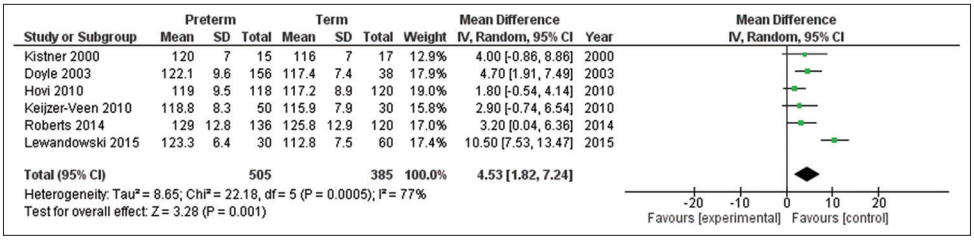

Figure S2: Forest plot comparing mean ambulatory (ABPM) systolic blood pressure (SBP) between preterm and term groups

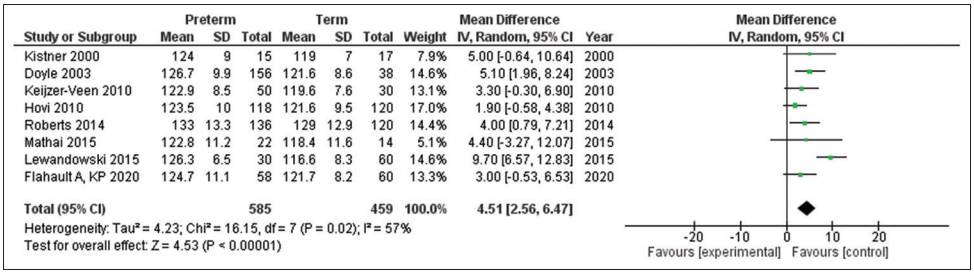

Figure S3: Forest plot comparing mean daytime/awake ambulatory (ABPM) systolic blood pressure (SBP) between preterm and term groups

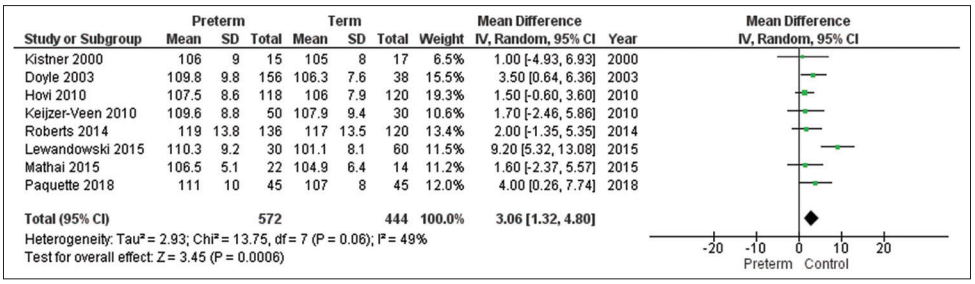

Figure S4: Forest plot comparing mean nighttime/asleep ambulatory (ABPM) systolic blood pressure (SBP) between preterm and term groups

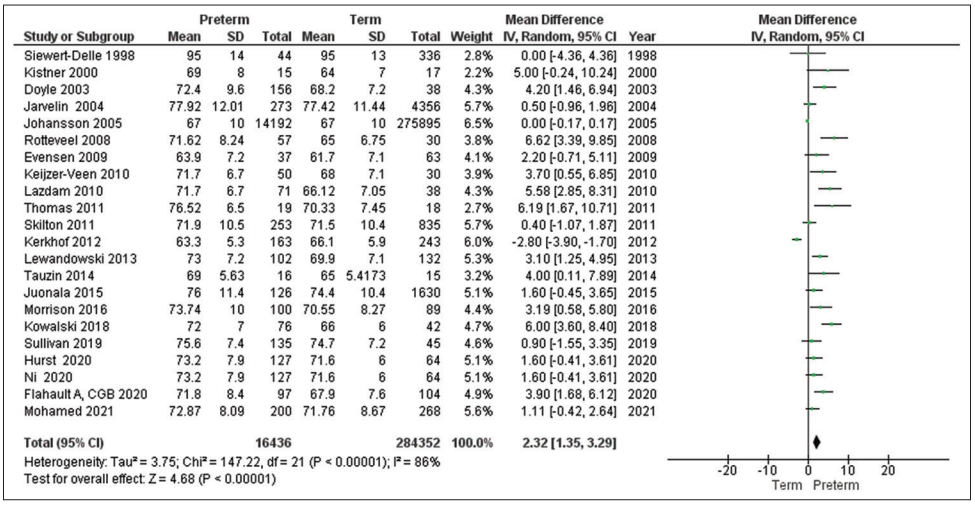

Figure S5: Forest plot comparing mean diastolic blood pressure (DBP) between preterm and term groups

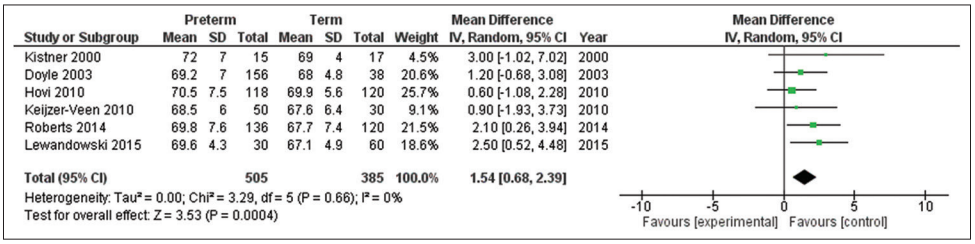

Figure S6: Forest plot comparing mean ambulatory (ABPM) diastolic blood pressure (DBP) between preterm and term groups

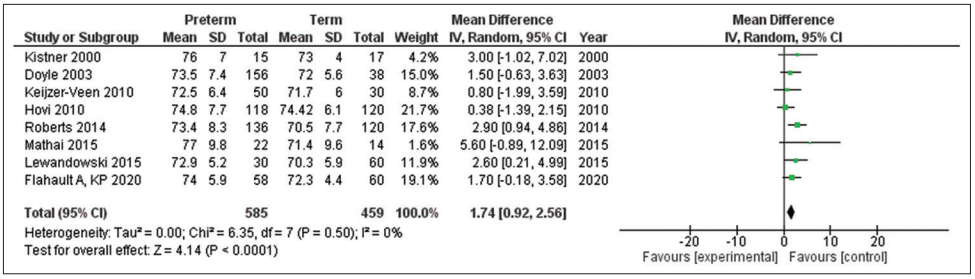

Figure S7: Forest plot comparing mean daytime/awake ambulatory (ABPM) diastolic blood pressure (DBP) between preterm and term groups

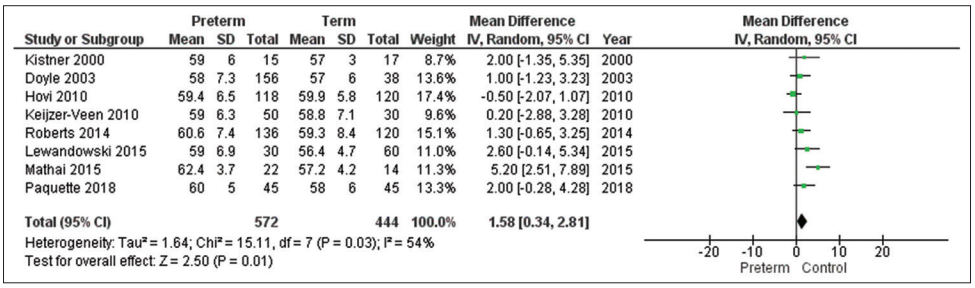

Figure S8: Forest plot comparing mean nighttime/asleep ambulatory (ABPM) diastolic blood pressure (DBP) between preterm and term groups

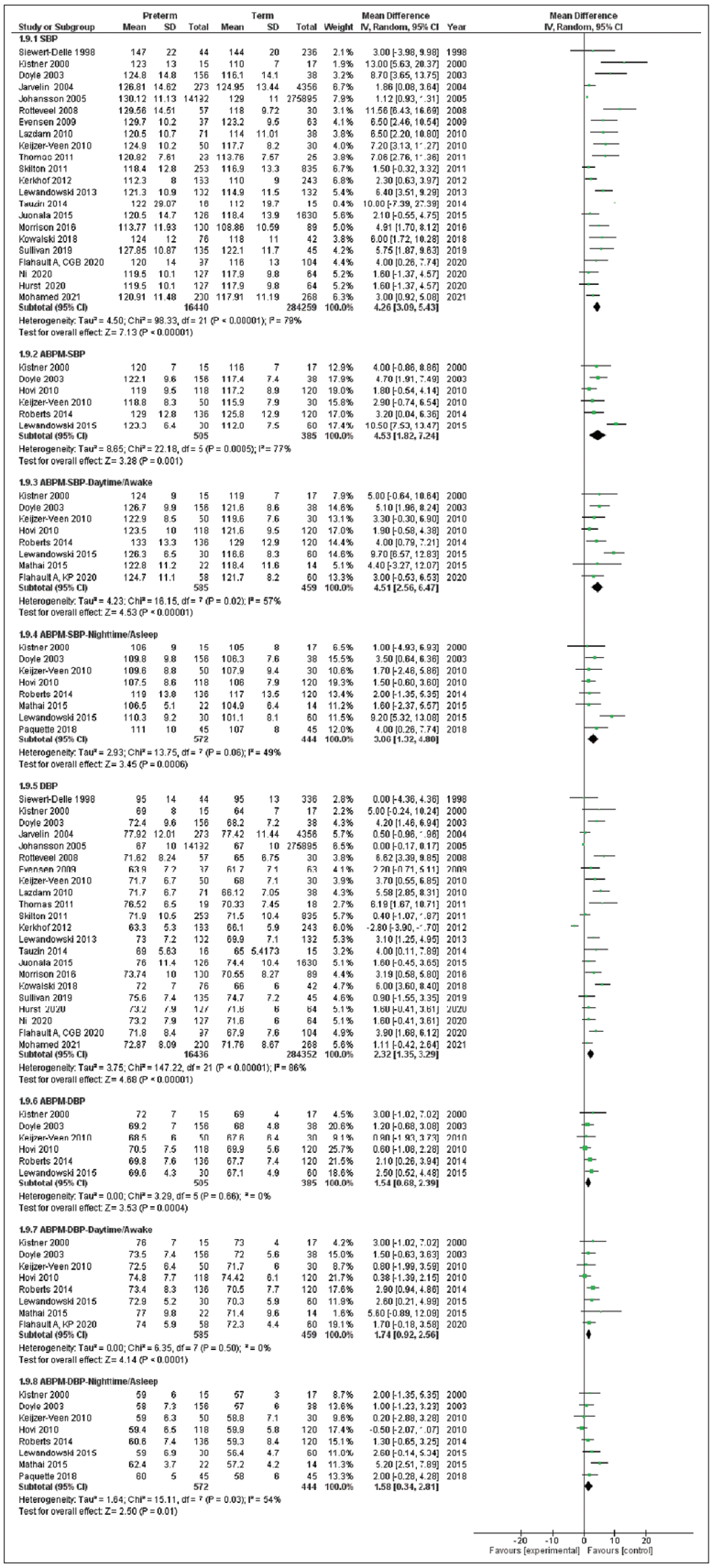

Figure S9: Summary of all the preterm vs term forest plots included in the meta-analysis

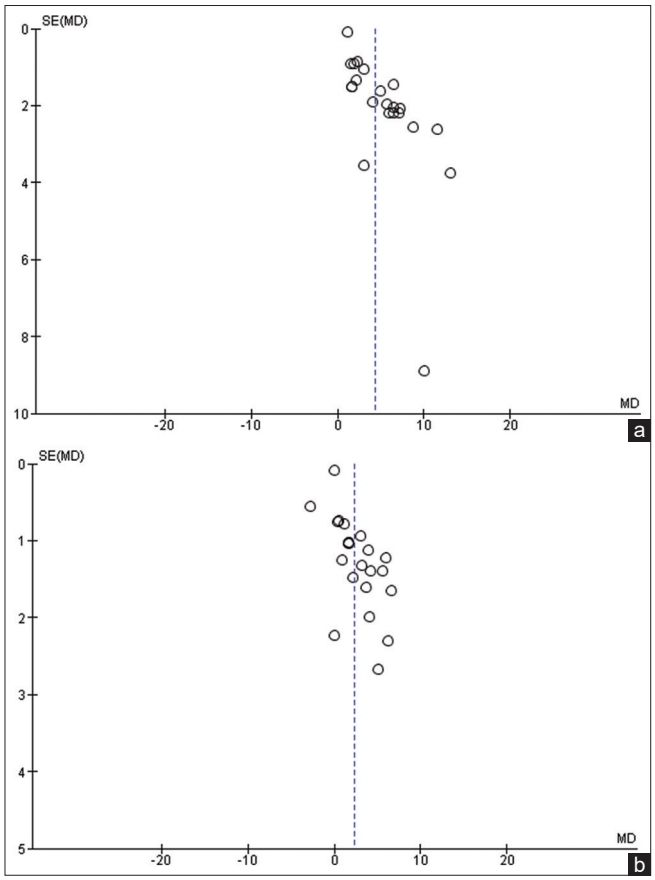

Figure S10: Funnel plots showing the unadjusted pooled association between premature birth and (a) SBP and (b) DBP in adult life. MD = mean difference, SE = standard error

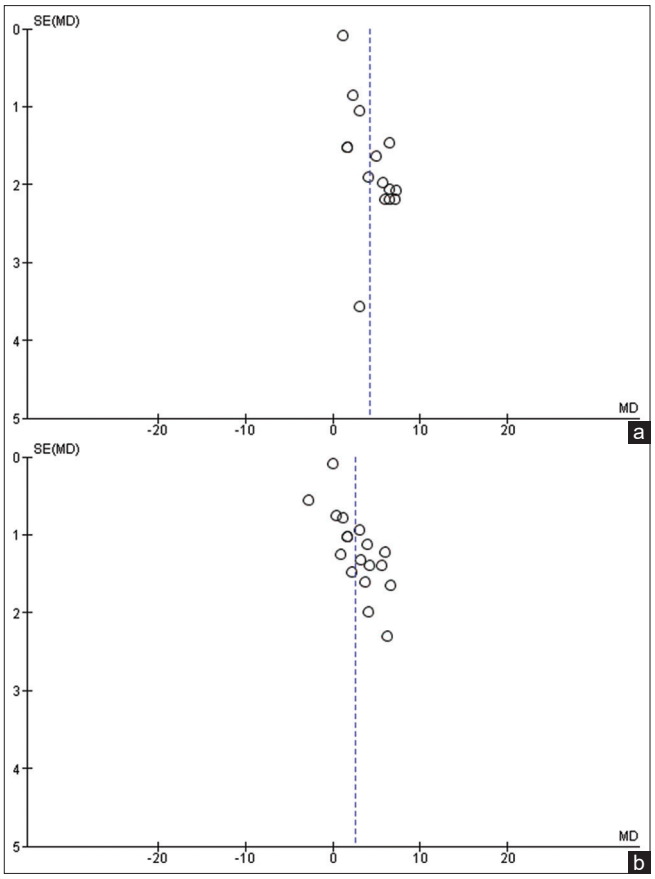

Figure S11: (a) Funnel plot for systolic blood pressure (after excluding studies reporting results with large standard deviations) (b) Funnel plot for diastolic blood pressure (after excluding studies reporting results with large standard deviations)

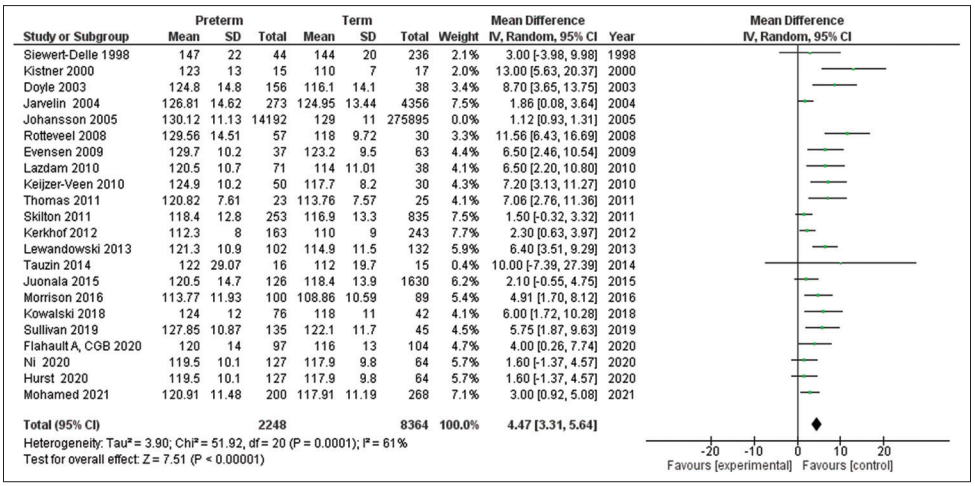

Figure S12: Sensitivity analysis for systolic blood pressure (SBP). By removing Johansson *et al.* 2005, the heterogeneity decreased from 79% to 61%

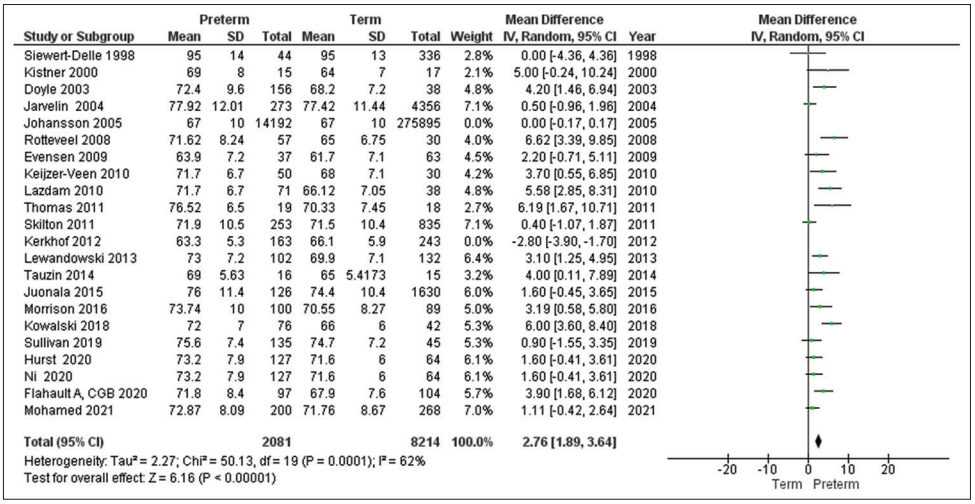

Figure S13: Sensitivity analysis for diastolic blood pressure (DBP). By removing Johansson *et al.* 2005 and Kerkhof *et al.* 2012, the heterogeneity decreased from 86% to 62%