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# Birth Weight and Risk of Type 2 Diabetes Mellitus, Cardiovascular Disease, and Hypertension in Adults: A Meta-Analysis of 7 646 267 Participants From 135 Studies

Marianne Ravn Knop, MSc;* Ting-Ting Geng, MPH;* Alexander Wilhelm Gorny, MBBS, MSc; Renyu Ding, MD; Changwei Li, PhD; Sylvia H. Ley, PhD; Tao Huang, PhD

***Background*—**Low birth weight has been associated with increased risk of type 2 diabetes mellitus, cardiovascular disease, and hypertension, but the risk at high birth weight levels remains uncertain. This systematic review and meta-analysis aimed to clarify the shape of associations between birth weight and aforementioned diseases in adults and assessed sex-specific risks.

***Methods and Results*—**We systematically searched PubMed, EMBASE, and Web of Science for studies published between 1980 and October 2016. Studies of birth weight and type 2 diabetes mellitus (T2DM), cardiovascular disease (CVD), and hypertension were included. Random-effects models were used to derive the summary relative risks and corresponding 95% confidence intervals.We identified 49 studies with 4 053 367 participants assessing the association between birth weight and T2DM, 33 studies with 5 949 477 participants for CVD, and 53 studies with 4 335 149 participants for hypertension and high blood pressure. Sex-specific binary analyses showed that only females had an increased risk of T2DM and CVD at the upper tail of the birth weight distribution. While categorical analyses of 6 birth weight groups and dose-response analyses showed J-shaped associations of birth weight with T2DM and CVD, the association was inverse with hypertension. The lowest risks for T2DM, CVD, and hypertension were observed at 3.5 to 4.0, 4.0 to 4.5, and 4.0 to 4.5 kg, respectively.

***Conclusions*—**These findings indicate that birth weight is associated with risk of T2DM and CVD in a J-shaped manner and that this is more pronounced among females. **(*J Am Heart Assoc*. 2018;7:e008870. DOI: 10.1161/JAHA.118.008870)**

**Key Words:** birth weight • cardiovascular disease • hypertension • type 2 diabetes mellitus

The rising prevalence of chronic diseases such as type 2 diabetes mellitus (T2DM), cardiovascular disease (CVD), and hypertension has been recognized as a public health problem affecting both developed and developing countries.[1] Genes and their interactions with the environment are thought to drive cardiometabolic disease risk. Growing evidence from observational studies has suggested that low birth weight, an indicator of intrauterine environment, increases the risk for T2DM, CVD, and hypertension in adulthood.[2–6] We are less certain of the effect of high birth weight, a consequence of maternal overweight/obesity and gestational diabetes mellitus,[7] on chronic disease risk later in life.

Numerous studies investigating the effect of birth weight on T2DM, CVD, and hypertension risk later in life have reported estimates that varied substantially across studies.[2–4,6,8–17]

Studies have consistently reported a U-shaped association between birth weight and T2DM,[15,18,19] while studies examining birth weight and CVD have been inconsistent, reporting either an inverse[12,13,20,21] or a U-shaped[2,22] association. The inconsistency of these findings might be explained by differences in the definition of high birth weight.[23,24] The association between birth weight and hypertension is reported as inverse in the majority of studies.[3,6,10] Specifically in the case of hypertension, however, the absence of a nadir

*From the Epidemiology Domain, Saw Swee Hock School of Public Health, National University of Singapore (M.R.K., T.-T.G., A.W.G.); Department of Otolaryngology, The First Hospital of China Medical University, Shenyang, China (R.D.); Department of Epidemiology & Biostatistics, College of Public Health, University of Georgia, Athens, GA (C.L.); Department of Nutrition, Harvard School of Public Health, Boston, MA (S.H.L.); Department of Epidemiology and Biostatistics, School of Public Health, Peking University, Beijing, China (T.H.).*

Accompanying Tables S1 through S3 and Figures S1 through S4 are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.118.008870

*Dr Knop and Dr Geng contributed equally to this work.

**Correspondence to:** Tao Huang, PhD, Department of Epidemiology and Biostatistics, School of Public Health, Peking University Health Science Center, 38 Xueyuan Road, Haidian District, Beijing 100191, China. E-mail: huangtao@bjmu.edu.cn

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## Clinical Perspective

### What Is New?

- This meta-analysis shows that birth weight is associated with risk of type 2 diabetes mellitus and cardiovascular disease in a J-shaped manner; however birth weight is inversely associated with risk of hypertension.
- Birth weight associates more strongly with type 2 diabetes mellitus and cardiovascular disease in females than males at the higher end of the birth weight distribution.

### What Are the Clinical Implications?

- In keeping with current recommendations, our study highlights the importance of supporting lifestyle and behavioral changes among pregnant women to control their modifiable risk factors during pregnancy to reduce the number of babies being born with low or high birth weight.

in the association at the higher end of the birth weight distribution might be attributed to sample size.

A great number of studies have been published in recent years, which allow us to perform a more specific and detailed analysis of the strength and shape of the dose-response relationship between birth weight and T2DM, CVD, and hypertension in adulthood. Furthermore, it has been suggested that the shape of association might differ between females[19] and males.[25] This brings into question whether sex-stratified analyses should replace the conventional approach of treating sex as a confounding variable. We undertook to systematically review the literature and conduct meta-analyses, which would examine the shape of the association between birth weight and risks of T2DM, CVD, and hypertension in adulthood. Additional stratified analyses would also shed light on sex-specific risk profiles.

## Methods

Data are available on request from Dr Knop. Alternatively, the reader may consider extracting results from references cited in our meta-analyses.

## Literature Search Strategy

In keeping with the Cochrane methodology, we systematically queried PubMed, EMBASE, and Web of Science for studies published between January 1966 and October 2016. We combined search terms describing the exposure with each outcome of interest. Keywords for birth weight included: "Birth weight," "low birth weight," "high birth weight," "intrauterine growth restriction," "fetal macrosomia," "large for gestational age," "small for gestational age," and "ponderal index." Keywords describing T2DM included: "Diabetes Mellitus type 2," "glucose levels," and "insulin levels." We examined CVD using the keywords: "Cardiovascular disease," "cardiovascular mortality," "coronary heart disease," and "stroke." Finally, we investigated hypertension with the keywords: "Hypertension" and "blood pressure." A search strategy combining MESH terms and full-text options was used. All synonyms were included. The search was limited to studies with human participants that were published in the English language. Two authors (MRK and TG) independently screened titles and abstracts of all articles retrieved, evaluated the eligibility of articles based on a full-text review, and extracted data. Where there were differences in opinion on the eligibility of an article the authors sought to achieve a consensus by means of discussion. Our senior author (TH) was consulted when there were disagreements regarding article eligibility. We adhered to the Meta-analysis of Observational Studies in Epidemiology group's recommendations when reporting our meta-analyses.[26]

## Selection of Articles

Inclusion was restricted to studies that assessed the association between birth weight and T2DM, CVD, or hypertension and studies reporting on systolic blood pressure (SBP) and diastolic blood pressure (DBP) in relationship to birth weight. The reference lists of original articles and reviews were scanned to identify other relevant studies. A study could be excluded on any of the following grounds: (1) Being designed as a review, meta-analysis, or twin-study; (2) having a small sample size (<250); (3) low age (<18 years), unless the mean age of the study population was >18 years; (4) insufficient measures of exposure, such as overlapping and/or unobtainable birth weight ranges or mean and standard deviation for studies reporting birth weight as categorical data; (5) insufficient reporting of outcomes such as graphically illustrated odds ratio (OR) or hazards ratio (HR) presented without risk estimates in writing; (6) describing risk estimates without accompanying standard deviation, standard error, or 95% confidence interval (CI); (7) identical outcomes originating from the same cohort reported in multiple studies, whereby the study with the longest follow-up period or largest sample size was included; (8) the full article was inaccessible. Refer to Figure 1 for the summary of articles collected in our selection process.

## Data Extraction

A standard data extraction form was used by 2 authors (M.K. and T.G.) independently to collect the following information: Article metadata including the name of the first author; study

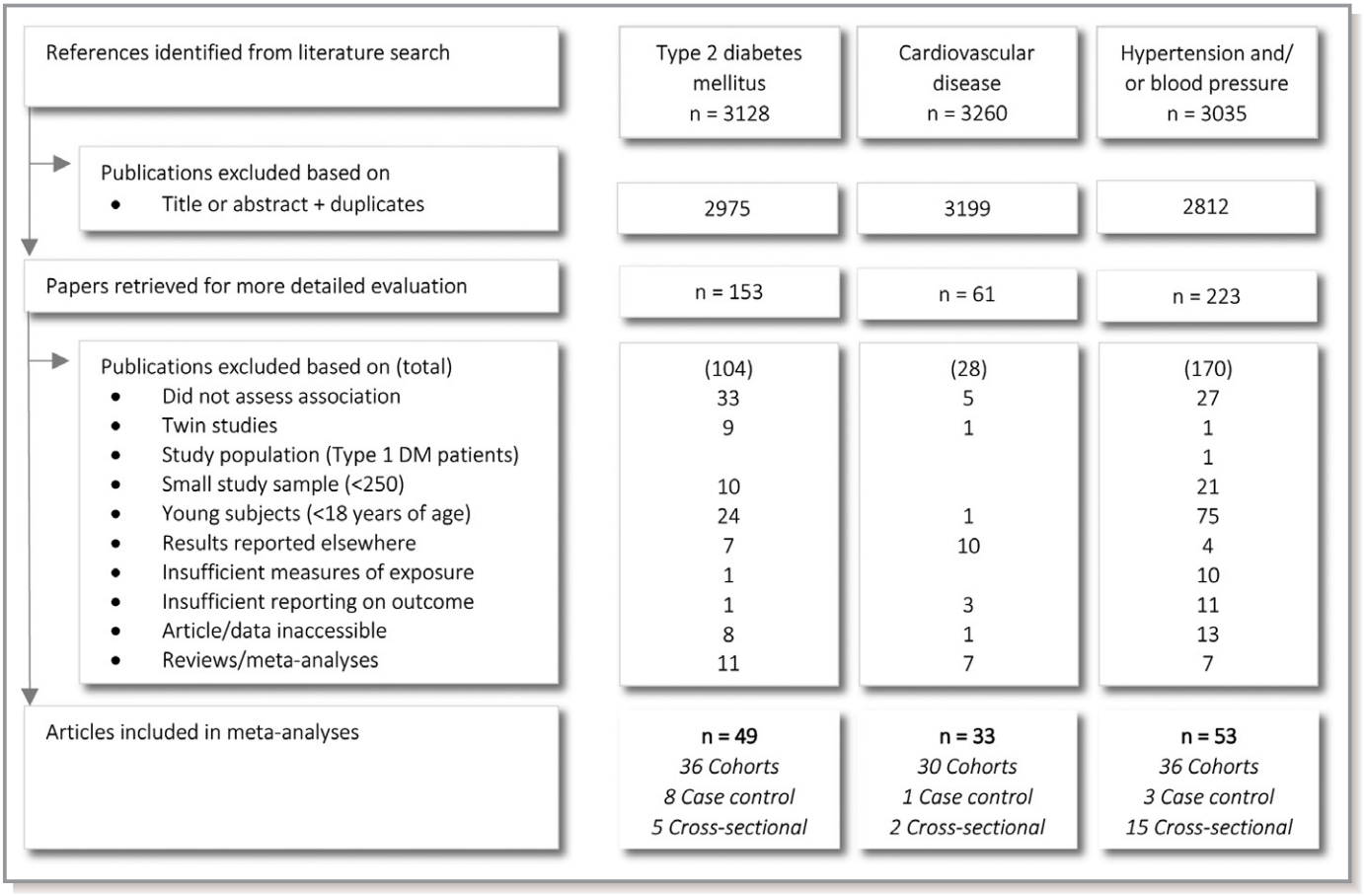


**Figure 1.** Summary of article selection process. DM indicates diabetes mellitus.

metadata including sample size, case number, and risk estimates for T2DM, CVD, and hypertension for defined birth weight groups; ORs or HRs per 1 kg increase in birth weight for T2DM, CVD, and hypertension; β-coefficients for SBP and DBP per 1 kg increase in birth weight; and measures of SBP and DBP or differences in SBP and DBP for defined birth weight groups. Results reported in previous meta-analyses[14,15,27] that were not extractable from the original article were also included. Study characteristics such as location (country and region), age, sex, birth weight ascertainment method, assessment and definition of outcome, and confounding factors were also ascertained. Our senior author (TH) was consulted when there were disagreements regarding data extraction.

## Definition of Outcomes

Definitions of T2DM, CVD, and hypertension varied across studies. The definition of T2DM followed WHO criteria in most studies while a smaller number identified the condition based on *International Classification of Diseases (ICD)*-codes (Table S1). A subset designated the prescription of anti-hyperglycemic drugs as a proxy indicator. The definition of CVD followed *ICD*-codes as shown in Table S2. This meant that coronary heart disease, stroke, and myocardial infarction met the definition of CVD regardless of whether the immediate outcome was fatal. Studies which did not use *ICD*-codes to identify CVD applied a combination of different criteria such as ROSE/WHO chest pain questionnaire, ECG findings, and blood test results. Hypertension was defined as SBP >140 mm Hg and/or DBP >90 mm Hg. A minority of studies, either adopted population-specific definitions of hypertension, used *ICD*-codes or designated the prescription of antihypertensive medication as a proxy indicator (Table S3). A number of studies examined self-reported outcomes.

## Statistical Analyses

We recorded the multivariable model that adjusted for the most covariates whenever >1 model was reported within the same study. Unadjusted estimates were calculated based on the numbers of cases and controls within defined birth weight categories whenever studies did not report risk estimates. Risk estimates were pooled within defined birth weight

categories whenever studies failed to provide case or control numbers. If an individual study gave rise to >1 estimate, the pool-first approach[28] was applied to obtain a single study-specific risk estimate. We did not pool estimates across birth weight groups that did not fit into the chosen categories. Consequently, several published categorical risk estimates were excluded from our analyses. Birth weights reported in pounds were converted to kilograms using a conversion rate of 0.454 kg/lb. Risk estimates reported per unit decrease were converted to estimates per unit increase. All step-wise changes were expressed as change per 1 kg interval. Odds ratio and HR were pooled to estimate risk difference between selected subgroups. The random effects model was employed throughout our analyses using the method described by DerSimonian and Laird.[29]

Sex-neutral and sex-specific dichotomous comparisons were performed using 3 different cut-offs for birth weight: 2.5, 4.0, and 4.5 kg. The majority of studies under review set the threshold for low birth weight at 2.5 kg which was in keeping with the literature.[30] The definition of high birth weight or macrosomic infants varied between studies. Therefore we conducted separate analyses for both the 4.0 and 4.5 kg thresholds for the high birth weight. Equidistant birth weight categories were used to visually inspect the nature of the relationship between birth weight and T2DM, CVD, and hypertension. Based on the Akaike information criterion,[31] a restricted cubic spline regression model with 3 knots was applied to elicit any potential non-linear dose-response relation. Spline variable estimates were subsequently used to derive the generalized least squares trend estimation of pooled dose-response data.[28]

Subsequently, we assessed effect coefficients that predicted the continuous outcomes of SBP and DBP per 1 kg increase in birth weight. Differences in absolute SBP and DBP levels were assessed in repeated binary analyses using 2.5 and 4.0 kg cut-offs for birth weight. We also used binary analyses to examine the differences in BP (blood pressure) comparing either low birth weight (<2.5 kg) or high birth weight (>4.0 kg) with normal birth weight (≥2.5 to ≤4.0 kg).

Cochrane Q-test and associated $I^2$-statistic were calculated to assess the impact of between-study heterogeneity and total variability in the effect estimate.[32] The 95% confidence intervals (95% CI) for the $I^2$–statistic were calculated using the test based method proposed by Higgins et al[33] Initially we estimated the comparative risks for developing T2DM, CVD, and hypertension for each kilogram increase in birth weight. Influence analyses were performed to examine the robustness of this pooled risk estimate and to assess heterogeneity. Subgroup analyses and meta-regression analyses were performed to examine whether study characteristics such as study design, sample size, and region influenced the associations seen or explained heterogeneity across studies.

To assess potential publication bias, we inspected funnel plots. We tested for funnel plot asymmetry in meta-analyses comprising >10 studies using Egger's linear regression test.[34] Trim and fill analysis following the methods outlined by Duval and Tweedie[35] was performed for meta-analyses where funnel plots revealed asymmetry. We set $P<0.05$ as the threshold for statistical significance. All statistical analyses were conducted in STATA, version 11.

## Results

Of the aforementioned 135 publications in total, 49 reported the relationship between birth weight and T2DM. Thirty-three articles described birth weight in relationship to CVD, and a further 53 discussed hypertension and/or BP. Study characteristics are presented in Tables S1 through S3.

## Type 2 Diabetes Mellitus

Thirty-two studies assessed the risk of T2DM per 1 kg increase in birth weight. Of 26 studies[5,19,25,36–58] showing an inverse association, 12[5,19,25,37,41,43,46,51–54,58] reported statistically significant associations. Of the 6 studies[17,18,59–62] showing a positive association, only 1 study[59] reported statistically significant risks. According to our meta-analysis, each kilogram increment in birth weight was associated with a 22% (OR ratio: 0.78, 95% CI: 0.70–0.87) reduction in risk of later developing T2DM.

There was evidence of moderate to highly significant heterogeneity among these 32 studies ($I^2$=72.6%, 95% CI: 62.5–81.1). Influence analysis identified 2 study populations, Saskatchewan Indians and the general population of Saskatchewan[59] that accounted for ≈20% of the overall heterogeneity. When these populations were omitted from our analysis the overall reduction in T2DM risk was amplified to 28% (OR ratio: 0.72, 95% CI: 0.66–0.78). Two other study populations, Pima Indians[18] and nurses,[19] accounted for an additional 15% of overall heterogeneity. Their omission from analyses did not influence the overall risk estimate.

Table shows the subgroup analyses. An asterisk denotes estimates, which exclude the 2 populations from Saskatchewan. When the Saskatchewan studies were omitted, we observed a balancing of $I^2$-statistics and changes in the risk estimates. A meta-regression analysis also revealed that study region strongly influenced the association between birth weight and risk of T2DM ($P<0.0001$).

Binary analyses examining low birth weight indicated that participants with birth weight <2.5 kg experienced a 45% (OR: 1.45, 95% CI: 1.33–1.59) higher risk of T2DM than those with birth weight ≥2.5 kg. The relationship was stronger for females (OR: 1.45, 95% CI: 1.34–1.57) than males (OR:

**Table.** Risk of Type 2 Diabetes Mellitus, Cardiovascular Disease, and Hypertension and Change in Systolic and Diastolic Blood Pressure Per 1 kg Increase in Birth Weight

| | Type 2 Diabetes Mellitus | | Cardiovascular Disease | | Hypertension | | Systolic Blood Pressure | | Diastolic Blood Pressure | |
|---|---|---|---|---|---|---|---|---|---|---|
| | HR (95% CI) | $I^2$ (%) | HR (95% CI) | $I^2$ (%) | HR (95% CI) | $I^2$ (%) | Coeff. (95% CI) | $I^2$ (%) | Coeff. (95% CI) | $I^2$ (%) |
| Unstratified risk | 0.78 (0.70; 0.87) | 72.6 | 0.84 (0.81; 0.86) | 0.0 | 0.77 (0.68; 0.88) | 31.9 | −1.36 (−1.62; −1.09) | 91.3 | −0.33 (−0.54; −0.13) | 66.2 |
| Age, y | | | | | | | | | | |
| ≥40 | 0.70 (0.64; 0.77) | 50.7 | 0.84 (0.81; 0.87) | 13.7 | 0.77 (0.61; 0.97) | 40.7 | −1.38 (−1.91; −0.84) | 60.5 | −0.23 (−0.57; 0.11) | 73.5 |
| <40 | 1.09 (0.85; 1.40) | 77.7 | 0.83 (0.74; 0.92) | 0.00 | 0.74 (0.56; 0.98) | 59.2 | −1.37 (−1.69; −1.05) | 94.5 | −0.51 (−0.93; −0.10) | 43.9 |
| Sex | | | | | | | | | | |
| Female | 1.04 (0.81; 1.33) | 87.5 | 0.81 (0.76; 0.87) | 0.00 | 0.80 (0.70; 0.92) | 13.7 | −1.12 (−1.66; −0.59) | 89.9 | −0.35 (−0.60; −0.10) | 83.2 |
| Female* | 0.83 (0.77; 0.88) | 0.00 | | | | | | | | |
| Male | 0.79 (0.62; 1.01) | 72.5 | 0.86 (0.80; 0.92) | 39.6 | 0.81 (0.59; 1.07) | 57.9 | −1.05 (−1.35; −0.75) | 91.1 | 0.14 (−0.79; 1.06) | 81.1 |
| Male* | 0.70 (0.60; 0.82) | 18.0 | | | | | | | | |
| Combined | 0.78 (0.70; 0.87) | 72.6 | 0.84 (0.81; 0.86) | 0.00 | 0.77 (0.68; 0.88) | 31.9 | −2.26 (−2.87; −1.65) | 41.2 | −0.66 (−1.25; −0.07) | 37.0 |
| Region | | | | | | | | | | |
| N. America | 1.03 (0.85; 1.24) | 83.2 | 0.80 (0.74; 0.86) | | 0.82 (0.74; 0.91) | | −0.61 (−1.13; −0.08) | 95.8 | −0.31 (−0.49; −0.14) | 82.1 |
| N. America* | 0.84 (0.75; 0.94) | 39.9 | | | | | | | | |
| Europe | 0.67 (0.60; 0.74) | 41.5 | 0.85 (0.82; 0.88) | 0.00 | 0.77 (0.61; 0.97) | 40.7 | −1.26 (−1.54; −0.98) | 83.0 | −0.22 (−0.85; 0.40) | 61.0 |
| Asia | 0.79 (0.56; 1.11) | 35.3 | 0.67 (0.47; 0.96) | 0.00 | | | −2.90 (−5.45; −0.35) | | −1.70 (−3.48; 0.08) | |
| Australia | | | 0.93 (0.78–1.12) | | | | −2.33 (−3.68; −0.98) | 73.5 | 0.72 (−0.93; 2.37) | |
| S. America | | | | | 0.60 (0.42; 0.87) | | −3.64 (−5.20; −2.07) | | −1.65 (−2.84; −0.45) | |
| Study design | | | | | | | | | | |
| CH | 0.74 (0.67; 0.82) | 56.0 | 0.84 (0.81; 0.87) | 12.0 | 0.77 (0.68; 0.88) | 31.9 | −1.35 (−1.66; −1.03) | 92.5 | −0.33 (−0.54; −0.13) | 66.2 |
| CC | 0.92 (0.67; 1.26) | 86.5 | | | | | | | | |
| CC* | 0.62 (0.52; 0.73) | 0.00 | | | | | | | | |
| CS | 0.62 (0.47; 0.81) | 0.00 | 0.80 (0.66; 0.96) | 0.00 | | | −1.56 (−2.20; −0.92) | 86.5 | | |
| BW | | | | | | | | | | |
| Self-report | 0.76 (0.70; 0.84) | 32.3 | 0.81 (0.75; 0.86) | 0.00 | 0.82 (0.74; 0.91) | | −0.72 (−1.08; −0.36) | 87.1 | −0.33 (−0.50; −0.16) | 75.9 |
| NR | 0.81 (0.68; 0.95) | 78.5 | 0.85 (0.81; 0.88) | 9.7 | 0.73 (0.60; 0.90) | 39.4 | −1.66 (−1.95; −1.36) | 83.7 | −0.33 (−0.99; 0.33) | 65.2 |
| OC | | | | | | | | | | |
| Self-report | 0.74 (0.66; 0.84) | 44.3 | 0.80 (0.74; 0.85) | 0.00 | 0.82 (0.74; 0.91) | | −0.61 (−1.13; −0.08) | 95.8 | −0.31 (−0.49; −0.14) | 82.1 |
| NR | 0.91 (0.71; 1.17) | 87.8 | 0.85 (0.81; 0.88) | 6.1 | 0.73 (0.60; 0.90) | 39.4 | | | | |
| PE | 0.72 (0.60; 0.87) | 56.2 | 0.89 (0.74; 1.08) | | | | −1.47 (−1.74; −1.21) | 83.8 | −0.39 (−0.98; 0.20) | 62.6 |
| Risk statistics | | | | | | | | | | |
| Odds ratio | 0.79 (0.71; 0.88) | 73.4 | 0.84 (0.78; 0.89) | 0.00 | 0.73 (0.60; 0.90) | 39.4 | | | | |

Continued

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**Table.** Continued

| | Type 2 Diabetes Mellitus | | Cardiovascular Disease | | Hypertension | | Systolic Blood Pressure | | Diastolic Blood Pressure | |
|---|---|---|---|---|---|---|---|---|---|---|
| | HR (95% CI) | $I^2$ (%) | HR (95% CI) | $I^2$ (%) | HR (95% CI) | $I^2$ (%) | Coeff. (95% CI) | $I^2$ (%) | Coeff. (95% CI) | $I^2$ (%) |
| Hazard ratio | 0.62 (0.37; 1.05) | 66.2 | 0.84 (0.80; 0.88) | 24.3 | 0.82 (0.74; 0.91) | | | | | |
| Sample size | | | | | | | | | | |
| <500 | 0.68 (0.45,1.03) | 53.3 | | | 0.67 (0.53; 0.85) | 0.00 | −1.89 (−2.61; −1.18) | 85.7 | 0.06 (−1.17; 1.29) | 52.3 |
| ≥500 to 1000 | 0.86 (0.65; 1.14) | 78.8 | 0.54 (0.31; 0.92) | 0.00 | 0.77 (0.50; 1.17) | 72.3 | −2.08 (−2.92; −1.23) | 36.4 | −0.65 (−2.13; 0.84) | 84.3 |
| ≥1000 | 0.76 (0.68; 0.84) | 69.6 | 0.84 (0.81; 0.86) | 0.00 | 0.82 (0.74; 0.91) | | −1.08 (−1.41; −0.74) | 95.8 | −0.33 (−0.48; −0.18) | 58.9 |
| Diag. | | | | | | | | | | |
| CVD | | | 0.83 (0.77; 0.88) | 38.1 | | | | | | |
| CHD | | | 0.85 (0.81; 0.88) | 0.00 | | | | | | |

BW indicates birth weight ascertainment method; CC, case control; CH, cohort; CHD, coronary heart disease; CI, confidence interval; CS, cross sectional; CVD, cardiovascular disease; Diag., diagnosis; HR, hazard ratio; NR, National Register; OC, outcome assessment method; PE, physical examination.
*Subgroup analysis excludes Saskatchewan populations (T2DM).

1.34, 95% CI: 1.05–1.62). Binary analyses examining high birth weights >4.5 kg showed no significant differences in T2DM risk when compared against the ≤4.5 kg category (OR: 1.08, 95% CI: 0.95–1.23) (Figure 2). However, through sex-stratified analyses, we uncovered a 19% (OR: 1.19, 95% CI: 1.01–1.40) higher risk of T2DM for females with birth weight >4.5 kg.

## Cardiovascular Diseases

Nineteen studies[2,6,8,11,21,63–76] assessed the risk of CVD per 1 kg increase in birth weight. Among them, 10[11,21,65,68,70–73,75,76] reported a statistically significant inverse association. None of the studies reported a positive association. Overall, each kilogram increment in birth weight was associated with a 16.5% (OR: 0.84, 95% CI: 0.81–0.86) reduction in risk of later developing CVD.

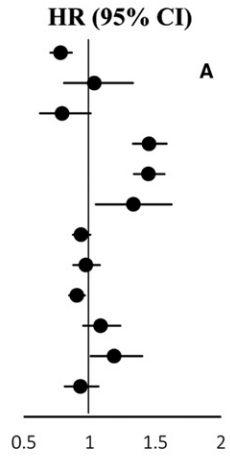
There was little evidence of heterogeneity ($I^2$=0.00, 95% CI: 0–46.1). When the study with the most considerable influence was omitted, the overall risk estimate increased marginally to 17.6% (OR: 0.82, 95% CI: 0.80–0.85) highlighting the robustness of the risk estimate. Meta-regression analysis and stratification by study characteristics did not reveal essential alteration in risk estimates (Table). When studies were stratified by type of diagnosis we observed in similar risk estimates for CVD and coronary heart disease (CHD), 17% (OR: 0.83, 95% CI: 0.77–0.88) and 15% (OR: 0.85, 95% CI: 0.81–0.88), respectively. Binary analyses for CVD illustrated a pattern that was similar to T2DM (Figure 2). Participants with birth weight <2.5 kg experienced 30% (OR: 1.30, 95% CI: 1.01–1.67) higher risk of CVD compared with those with birth weight ≥2.5 kg. Compared with the birth weight ≤4.5 kg category, high birth weight (>4.5 kg) was not associated with any differences in risk. However, when we stratified for sex, we detected an increased risk of CVD in high birth weight females (Figure 2).

## Hypertension

Only 5 studies examining the risks of hypertension per 1 kg increase in birth weight were retrieved.[41,77–80] Of these, 4[41,77,78,80] were statistically significant. Overall, each kilogram increment in birth weight was associated with a 23% (OR: 0.77, 95% CI: 0.68–0.88) reduction in risk. There was some evidence of heterogeneity ($I^2$=32%, 95% CI: 0–74.1) with 1 study[78] accounting for half of the overall point estimate. When this study was omitted, the overall risk estimate declined to 20% (OR: 0.80, 95% CI: 0.72–0.90). Binary analyses did not show differences in sex-specific risk estimates at either tail of the birth weight distribution (Figure 2). Birth weight <2.5 kg was associated with 30% (OR: 1.30, 95% CI: 1.16–1.46) increased risk of hypertension

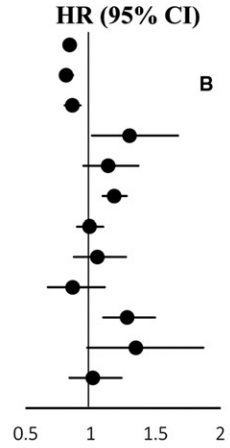
**Type 2 Diabetes**

| Outcome | Estimate (95% CI) | $I^2$ (95%CI) (%) | n |
|---|---|---|---|
| Per 1-kg increase in birth weight (N) | 0.78 (0.70-0.87) | 72.6 (62.5; 81.1) | 32 |
| Per 1-kg increase in birth weight (F) | 1.04 (0.81-1.33) | 87.5 (52.2; 96.7) | 5 |
| Per 1-kg increase in birth weight (M) | 0.79 (0.62-1.01) | 72.5 (40.6; 87.3) | 7 |
| Birth weight < 2.5kg vs > 2.5kg (ref) (N) | 1.45 (1.33-1.59) | 76.1 (42.1; 90.1) | 18 |
| Birth weight < 2.5kg vs > 2.5kg (ref) (F) | 1.45 (1.34-1.57) | 65.1 (31.4; 82.3) | 9 |
| Birth weight < 2.5kg vs > 2.5kg (ref) (M) | 1.34 (1.05-1.62) | 68.7 (39.5; 83.8) | 9 |
| Birth weight > 4.0kg vs < 4.0kg (ref) (N) | 0.94 (0.87-1.01) | 53.2 (21.1; 72.3) | 18 |
| Birth weight > 4.0kg vs < 4.0kg (ref) (F) | 0.97 (0.88-1.08) | 64.1 (29.0; 81.8) | 9 |
| Birth weight > 4.0kg vs < 4.0kg (ref) (M) | 0.90 (0.85-0.96) | 0.00 (0.00; 45.7) | 9 |
| Birth weight > 4.5kg vs < 4.5kg (ref) (N) | 1.08 (0.95-1.23) | 54.5 (0.00; 80.6) | 7 |
| Birth weight > 4.5kg vs < 4.5kg (ref) (F) | 1.19 (1.01-1.40) | 59.7 (21.0; 86.6) | 4 |
| Birth weight > 4.5kg vs < 4.5kg (ref) (M) | 0.93 (0.81-1.07) | 0.00 (0.00; 92.9) | 3 |




**Cardiovascular Disease**

| Outcome | Estimate (95% CI) | $I^2$ (95%CI) (%) | n |
|---|---|---|---|
| Per 1-kg increase in birth weight (N) | 0.84 (0.81-0.86) | 0.00 (0.00; 46.1) | 19 |
| Per 1-kg increase in birth weight (F) | 0.81 (0.76-0.87) | 0.00 (0.00; 69.3) | 5 |
| Per 1-kg increase in birth weight (M) | 0.86 (0.80-0.92) | 39.6 (0.00; 74.7) | 7 |
| Birth weight < 2.5kg vs > 2.5kg (ref) (N) | 1.30 (1.01-1.67) | 95.7 (94.3; 96.8) | 17 |
| Birth weight < 2.5kg vs > 2.5kg (ref) (F) | 1.14 (0.94-1.37) | 69.7 (28.6; 87.1) | 6 |
| Birth weight < 2.5kg vs > 2.5kg (ref) (M) | 1.18 (1.09-1.28) | 0.00 (0.00; 47.6) | 7 |
| Birth weight > 4.0kg vs < 4.0kg (ref) (N) | 0.99 (0.90-1.10) | 80.3 (68.8; 87.6) | 16 |
| Birth weight > 4.0kg vs < 4.0kg (ref) (F) | 1.05 (0.87-1.27) | 78.9 (53.6; 90.4) | 6 |
| Birth weight > 4.0kg vs < 4.0kg (ref) (M) | 0.86 (0.67-1.11) | 89.0 (80.6; 93.7) | 8 |
| Birth weight > 4.5kg vs < 4.5kg (ref) (N) | 1.28 (1.10-1.50) | 49.1 (0.00; 78.9) | 6 |
| Birth weight > 4.5kg vs < 4.5kg (ref) (F) | 1.35 (0.87-1.87) | 58.3 (25.7; 86.2) | 4 |
| Birth weight > 4.5kg vs < 4.5kg (ref) (M) | 1.02 (0.84-1.24) | 0.00 (0.00; 47.4) | 2 |




**Hypertension**

| Outcome | Estimate (95% CI) | $I^2$ (95%CI) (%) | n |
|---|---|---|---|
| Per 1-kg increase in birth weight (N) | 0.77 (0.68-0.88) | 31.9 (0.00; 74.1) | 5 |
| Per 1-kg increase in birth weight (F) | 0.80 (0.70-0.92) | 13.7 (0.00; 50.5) | 2 |
| Per 1-kg increase in birth weight (M) | 0.81 (0.60-1.10) | 57.9 (0.00; 90.0) | 2 |
| Birth weight < 2.5kg vs > 2.5kg (ref) (N) | 1.30 (1.16-1.46) | 85.5 (77.2; 90.8) | 14 |
| Birth weight < 2.5kg vs > 2.5kg (ref) (F) | 1.25 (1.15-1.37) | 61.9 (21.3; 81.6) | 7 |
| Birth weight < 2.5kg vs > 2.5kg (ref) (M) | 1.17 (0.91-1.50) | 36.9 (0.00; 80.1) | 3 |
| Birth weight > 4.0kg vs < 4.0kg (ref) (N) | 0.88 (0.81-0.95) | 82.6 (71.5; 89.4) | 13 |
| Birth weight > 4.0kg vs < 4.0kg (ref) (F) | 0.93 (0.86-1.00) | 62.5 (19.0; 82.6) | 8 |
| Birth weight > 4.0kg vs < 4.0kg (ref) (M) | 0.86 (0.72-1.03) | 62.1 (0.00; 87.3) | 4 |
| Birth weight > 4.5kg vs < 4.5kg (ref) (N) | 1.05 (0.93-1.19) | 84.5 (65.2; 93.1) | 5 |
| Birth weight > 4.5kg vs < 4.5kg (ref) (F) | 1.09 (0.89-1.33) | 79.1 (33.1; 93.5) | 3 |
| Birth weight > 4.5kg vs < 4.5kg (ref) (M) | 1.01 (0.86-1.19) | 87.1 (49.4; 96.7) | 2 |

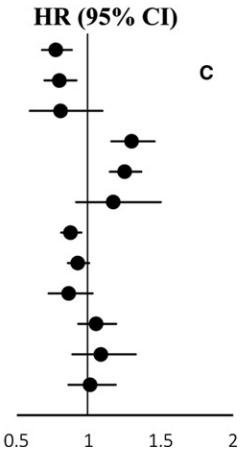



**Figure 2.** Meta-analyses of sex-neutral (N) and sex-specific (M/F) associations between birth weight and type 2 diabetes mellitus, cardiovascular disease, and hypertension. Birth weight is presented as a continuous variable to assess risk per 1 kg increase in birth weight and as a binary variable with 3 different cut-offs (2.5, 4.0, and 4.5 kg). Circles represent the pooled exponentiated log-transformed risk estimates from a random-effects model, horizontal lines their confidence interval, and $I^2$ the heterogeneity detected in each meta-analysis. The "n" is the number of studies contributing to the pooled risk estimate. Several studies only provide sex-neutral estimates. Therefore, the number of studies contributing to sex-specific meta-analyses do not add up to the number of studies for the corresponding sex-neutral meta-analysis. CI indicates confidence interval; M, male; N, neutral; F, female.

compared with birth weight ≥2.5 kg. Unlike T2DM and CVD, there was no increase in the risk of hypertension seen in the birth weight >4.5 kg category.

## Systolic and Diastolic Blood Pressure

Each kilogram increase in birth weight reduced SBP by 1.36 mm Hg (95% CI: −1.62 to −1.09 mm Hg). Similarly, each kilogram increase in birth weight reduced DBP by 0.33 mm Hg (95% CI: −0.54 to −0.13 mm Hg) (Table and Figure S1). We evaluated SBP and DBP for 5 birth weight categories. In support of the inverse association identified for hypertension, an inverse relationship between birth weight and BP was seen in Figure S2, when younger individuals (aged <30 years) were excluded.

## Shape of Association Between Birth Weight and T2DM, CVD, and Hypertension

Assuming a non-linear association, as supported by our binary analyses for T2DM and CVD, we performed categorical analyses using 6 birth weight groups to investigate the nature of the associations further. Sixteen, twelve, and thirteen studies provided 76, 71, and 59 estimates for T2DM, CVD, and hypertension, respectively. The birth weight category 4.0 to 4.5 kg was chosen as the reference group since this combination allowed the largest number of studies to be included. J-shaped associations between birth weight and T2DM (Figures 3A and 4A) and CVD (Figures 3B and 4B) were observed. Participants with birth weight >4.5 kg had a 19% (OR: 1.19, 95% CI: 1.04–1.36) higher risk of T2DM and a 22% (OR: 1.22, 95% CI: 1.08 to1.37) higher risk of CVD compared with those from the reference birth weight group (4.0–4.5 kg). Similar shapes of association were observed in categorical analyses using 3 birth weight groups (Figure S3). Figures 3C and 4C display an inverse association between birth weight and hypertension with the dose-response analysis indicating a non-linear relationship, which may imply a negative exponential association rather than a negative linear. However, binary analyses (Figure 2C) and categorical analyses using 3 groups (Figure S3) provided results which did not support a negative exponential association consistently. The lowest risks for T2DM, CVD, and hypertension were observed at 3.5 to 4.0, 4.0 to 4.5, and 4.0 to 4.5 kg birth weights, respectively.

## Publication Bias

Visual inspection of funnel plot revealed symmetry and Egger's test was not statistically significant ($P$>0.1) for all meta-analyses displayed in Figure S4. Trim and fill analyses had no significant impact on the risk estimates, which overall suggested that there was no publication bias.

# Discussion

In the present comprehensive meta-analyses, we systematically examine the shape of the association between birth weight and risks of T2DM, CVD, and hypertension and further assess sex-specific risks.

We found a 22% reduction in the risk of T2DM per 1 kg increase in birth weight; a 16% reduction in the risk of CVD; and a 23% reduced risk in hypertension per 1 kg increase in birth weight. We also observed that macrosomic infants (>4.5 kg) had 19% higher risk of T2DM in adult life compared with those with a birth weight ranging from 4.0 to 4.5 kg; a 22% increased risk of CVD compared with the reference group in sex-neutral analyses. Our plot of sex-neutral risk estimates in all 6 categories showed a J-shaped association with an increased risk of T2DM and CVD at the upper tail driven by birth weight >4.5 kg. Our results provide robust evidence that birth weight is associated with the risk of T2DM and CVD in a J-shaped manner that is more pronounced among females. Our results were consistent with previous meta-analysis studies examining birth weight and T2DM,[9] CVD,[10,14] and hypertension[12,27,81,82] but includes a much larger number of studies, more detailed dose-response, subgroup and sex-stratified analyses. Harder et al[9] described a U-shaped association where high birth weight (>4.0 kg) and low birth weight (<2.5 kg) categories showed a greater risk of T2DM that was statistically significant when compared with normal birth weight. A subgroup analysis within the same study suggested that the increased risk seen in higher birth weight (>4.0 kg) was mainly driven by participants with birth weight >4.5 kg.[9] Our analyses established that the contradictions over the shapes of association were likely attributable to the authors' preference in the treatment of the exposure variable. To improve the sensitivity of our analyses, we divided birth weight into 6 equidistant categories. Dose-response analysis helped identify which relationships were non-linear. Furthermore, recently published findings from large studies have allowed us to examine sex-neutral T2DM risk in not 1 but 2 high birth weight subcategories.

Two previous meta-analyses found no evidence of sex differences in the inverse association between birth weight and CHD.[10,14] The results from our linear model examining CVD risks suggest likewise. Interestingly our sex-stratified binary analysis demonstrated a higher risk of CVD for females at the upper tail of the birth weight distribution. This difference, however, was not statistically significant. Nevertheless, our sex-neutral dose-response model showed that the highest birth weight category experienced a 22% greater risk of CVD than the reference group. We suspect that the increase in risk in this group might still have been attributable to females from the >4.5 kg birth weight category. In keeping with established literature, the same dose-response model

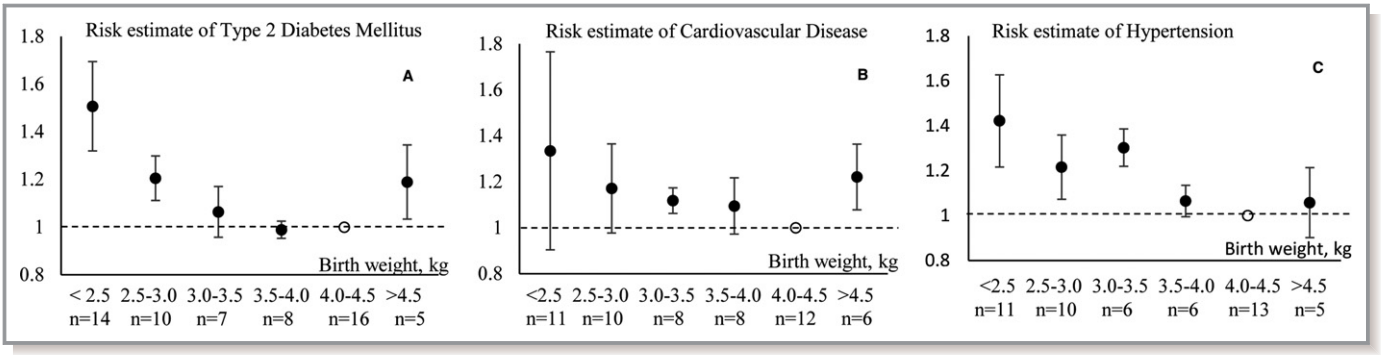



**Figure 3.** Shape of association between birth weight and type 2 diabetes mellitus, cardiovascular disease, and hypertension. The circles represent the exponentiated log-transformed pooled-risk estimate within 6 birth weight groups and the vertical lines their confidence interval. The "n" is the number of studies contributing to the pooled risk estimate within a birth weight group. Risk estimates (95% confidence interval) in (**A**) (risk of type 2 diabetes mellitus): <2.5 kg (1.507 [1.331; 1.706]), 2.5 to 3.0 kg (1.205 [1.115; 1.302]), 3.0 to 3.5 kg (1.064 [0.963; 1.176]), 3.5 to 4.0 kg (0.989 [0.954; 1.026]), 4.0 to 4.5 kg (ref.), >4.5 (1.189 [1.044; 1.355]). Risk estimates (95% confidence interval) in (**B**) (risk of cardiovascular disease): <2.5 kg (1.335 [0.972; 1.834]), 2.5 to 3.0 kg (1.171 [0.993; 1.381]), 3.0 to 3.5 kg (1.118 [1.064; 1.175]), 3.5 to 4.0 kg (1.095 [0.979; 1.224]), 4.0 to 4.5 kg (ref.), >4.5 (1.221 [1.086; 1.372]). Risk estimates (95% confidence interval) in (**C**) (risk of hypertension): <2.5 kg (1.422 [1.231; 1.642]), 2.5 to 3.0 kg (1.216 [1.082; 1.368]), 3.0 to 3.5 kg (1.303 [1.222; 1.389]), 3.5 to 4.0 kg (1.065 [0.998; 1.138]), 4.0 to 4.5 kg (ref.), >4.5 (1.058 [0.914; 1.226]).

demonstrated even greater vulnerability at the lower tail of the birth weight distribution. In addition, we found significant inverse associations between birth weight and BP, particularly SBP, which is consistent with the previous evidence.[12,27,81,82] The plots displayed in Figure S2 showing lower BP estimates in the low birth weight category could be explained by differences in the age of study participants.[83] Two previous meta-analyses offer conflicting findings on the sex-specific patterns of association between birth weight and BP.[81,84] The present study did not identify significant sex-specific relationships.

## Potential Mechanisms

The biological mechanisms underlying our findings are still a matter of debate. The observed associations may have originated in utero where metabolic stress may have led to epigenetic changes, decreased leptin levels, reduced nephron counts, and altered intracellular insulin signaling pathways.[85,86] In keeping with the fetal programming hypothesis, these small yet significant changes would have been amplified in critical periods of fetal growth resulting in delayed or disordered organ maturation which in turn could have resulted in crucial disruptions to endocrine and cardiovascular systems later in life.[86]

Other studies have suggested that malnutrition in the perinatal period might explain the associations between low birth weight and T2DM and long-term CVD risks.[37] In settings where neonatal care is available, it has been postulated that low birth weight babies are highly likely to be overfed, leading to "malprogramming" of neuroendocrine circuits. This is, in turn, thought to lead to excess weight and diabetogenic

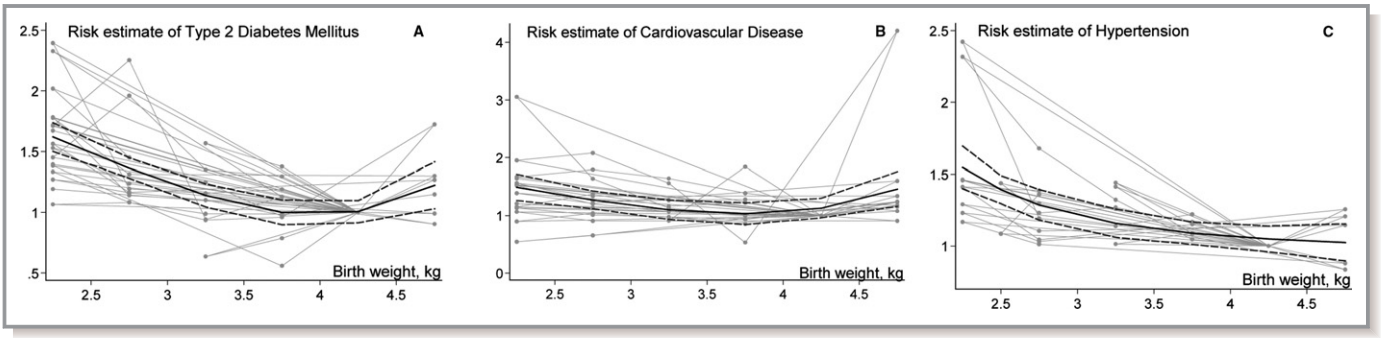



**Figure 4.** Dose-response relationship between birth weight and type 2 diabetes mellitus, cardiovascular disease, and hypertension. The solid regression curves represent point estimates of association, and the dashed lines are the corresponding 95% confidence interval. Grey circles are risk estimates within birth weight groups relative to the reference group (4.0–4.5 kg), which has been connected (grey lines) for the individual studies. A total of 15, 12, and 12 studies provided 73, 71, and 54 estimates of the association between birth weight and type 2 diabetes mellitus (**A**), cardiovascular disease (**B**) and hypertension (**C**), respectively.

disturbances throughout life.[87,88] On the opposite side of the perinatal "malprogramming" spectrum, it has been documented that macrosomic offspring of mothers who suffered diabetes mellitus during pregnancy experienced an increased risk of developing T2DM themselves.[89]

Furthermore, the gene-environment interaction may only account for a part of our findings.[80,90,91] For example, previous evidence from cohort studies suggest that low birth weight and genetic susceptibility to obesity may synergistically affect the risk of T2DM in later life.[92] Combined with unhealthy lifestyles the overall effects of low birth weight on T2DM[91] and hypertension[80] were greater than the sum of risks contributed by individual factors. Naturally, more comprehensive investigations are required to explore the precise mechanism.

It has been shown previously that females were intrinsically less sensitive to insulin than males throughout life. This placed them at particular risk of developing insulin resistance and therefore more susceptible to the development of T2DM.[93] Considering the pivotal role of insulin in lipid metabolism, BP regulation and atherosclerotic disease progression differences in insulin resistance might offer an elegant explanation for the increased risk of CVD seen in high birth weight females.[94] Furthermore, birth weight charts indicate that females tend to be lighter and smaller than males at birth. When sex-neutral cut-offs are applied, we would expect low birth weight to be more prevalent in females and high birth weight more common in males. Therefore, we could speculate that macrosomic female infants, in fact, represent a more extreme manifestation than their male counterparts. In addition to insulin resistance, sexual dimorphism of body composition at birth may also correspond with a more extreme phenotype in girls compared with boys. At birth, males and females may have similar fat mass; however, males are both longer and have greater lean mass.[95] This may imply that sex-identical definitions of high birth weight among females and males may not be appropriate if the intention is to evaluate risk according to birth weight. For epidemiological analyses, this would imply that sex should be treated as an effect modifier in the relationship between high birth weight and chronic disease risk.

## Public Health Implications

Given that the prevalence of both low and high birth weight is increasing,[96] these findings are highly relevant to population health and chronic disease risk estimates. Prenatal events do not fully explain the association between birth weight and chronic disease. Instead, the relationship is influenced by multiple genetic effects and postnatal exposures.[97] For example, rapid catch-up growth and early childhood growth trajectories have been shown to independently influence risk factor development and chronic disease incidence.[98,99] Later in life unhealthy diets, physical inactivity, and unfavorable body composition, play an important part towards chronic disease risk. Birth weight as a risk factor is not modifiable, but when viewed at the population level it offers insight into potentially vulnerable subgroups.[100] Our findings help justify investment in robust maternal and child health services.

## Strengths and Limitations

We have undertaken a comprehensive meta-analysis to clarify the strength and shape between birth weight and risks of T2DM, CVD, and hypertension in adulthood. A major strength of this article is the scope of our systematic review and treatment of the main exposure of interest. Furthermore, we have taken a comprehensive statistical approach that has allowed us to better understand past contradictions over the shape and nature of risk associations between birth weight and chronic disease outcomes. Finally, a large number of studies and larger sample size guaranteed sufficient statistical power for our analyses.

However, several limitations need to be considered. First, our findings might have been affected by reporting bias when we limited our search terms to studies published in English. Citation bias may have also been introduced when we identified additional studies from reference lists of original studies and past systematic reviews. Nevertheless, when we checked the funnel plots, we noted weak evidence of publication bias. Second, the sex-specific risk estimates for binary analyses were drawn from a limited pool of available studies and should be treated with caution. Third, this systematic review and meta-analysis was based on observational studies. This meant that even though we focused on adjusted effect measures the findings were susceptible to residual or unmeasured confounders, such as gestational age, mode of delivery, and gestational diabetes mellitus. The J-shaped association might be considered a recent phenomenon arising in recent birth cohorts where high birth weight because of maternal obesity and gestational diabetes mellitus have become more prevalent. Moreover, potential confounders of chronic disease risk such as physical inactivity, unhealthy diets, and unfavorable body composition were not considered in our analyses. Fourth, we pooled OR and HR to estimate risk difference between selected subgroups. It can be argued that this was inappropriate because of mathematical differences, yet similar meta-analyses did not differentiate between OR and HR.[10,14] When estimates were stratified by comparative risk statistics (OR and HR) in linear and categorical models we found no marked difference in the overall effect size or direction. Fifth, we did not perform

quality assessment of included studies owing to previous observations how subjectivity allowed the same study to be categorized as both low and high quality. Sixth, our meta-analysis included both prospective and retrospective studies which might have introduced recall bias; however, most studies provided recorded birth weights and outcomes.

Lastly, analyses undertaken by other authors that used binary or continuous exposure measures of birth weight might have been inappropriate since we suspected a J-shaped risk of T2DM and CVD across the whole birth weight range. The monotonically decreasing risk was likely to underestimate the true risk in the low (<2.5 kg) and ideal birth weight (≥2.5–4.5 kg) ranges. A cut-off of 2.5 kg in a binary analysis would have underestimated the risk conferred by high birth weights. A cut-off at 4.5 kg in binary analysis consequently neglected the elevated risk in the lowest birth weight groups.

## Conclusion

These findings suggest that birth weight is associated with the risk of T2DM and CVD in a J-shaped manner, and is inversely associated with risk of hypertension in adulthood. Furthermore, birth weight associates more strongly with T2DM and CVD in females than males at the higher end of the birth weight distribution. Future studies assessing the association between birth weight and chronic disease later in life should explicitly investigate potential sex differences. Sex might in fact act as an effect modifier rather than a confounder at the upper tail of the birth weight distribution.

More investigations are required to uncover the true causal pre- and postnatal exposures for the development of strategies for primary prevention.

## Author Contributions

M.R.K. and T.H. designed the study, drafted the study protocol, and planned analyses. M.R.K. wrote the first draft of the article. M.R.K. and T.G. conducted the data collection and combined statistical analysis. A.W.G. contributed to the article structure and language polishing. All of the authors contributed to the design, analysis, interpretation, and drafting of this article. All authors had reviewed and approved the drafts of the article.

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## Disclosures

None.

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# SUPPLEMENTAL MATERIAL

**Table S1. Characteristics of studies included in the meta-analysis for birth weight and type 2 diabetes mellitus.**

| Study, Publica-tion year | Country, City | Study design - Birth year | Sex | Age distribu-tion mean (range) | Sample size | Cases | Birth weight collection method | Assessment and definition of type 2 diabetes Mellitus | Outcome | Confounding factors |
|---|---|---|---|---|---|---|---|---|---|---|
| Anazama et al. 2003. **1** | Japan, Tokyo | CC | M | 49 (40-59) | 2.124 | 301 | BR or SR | SR | OR+CI^<br>OR+CI~<br>(Whincup) | OR+CI~: Age, sex, BMI |
| Barker et al. 2002. **2** | Finland, Helsinki | CH (1924-44) | F/M | 46 (20-73) | 13.517 | 698 | BR | NR<br>T2DM: WHO criteria or ADM | OR+CI~ | Sex, year of birth |
| Bhargava et al. 2004. **3** | India, Delhi | CH (1969-72) | F/M | 29 | 1.364 | 61 | BR | PE<br>T2DM: WHO criteria | OR+CI~<br>(Whincup) | Age, sex, BMI, SES |
| Birgisdot-tir et al. 2002. **4** | Iceland, Reykjavik | CH (1914-35) | F/M | 50 (33-65) | 4.537 | 100 | BR | SR or FBG ≥6.1mmol/l or 90min ≥ 11.1mmol/l | OR+CI~<br>(Whincup) | Age, sex, BMI, SES |

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| Burke et al. 2004. **5** | USA | CC | F/M | 44 | 510 | 170 | BR | NR<br>T2DM: ADM | OR+CI^ | Sex, birth year |
| Carlsson et al. 1999. **6** | Sweden, Stockholm | CS (1938-57) | M | 46 (35-56) | 2.294 | 35 | SR | PE<br>T2DM: WHO criteria | OR+CI^<br>OR+CI~ (Whincup) | OR+CI^ and OR+CI~: Age, BMI, family history of diabetes |
| Class et al. 2013. **7** | Sweden Stockholm | CH (1973-95) | F/M | 23 (12-35) | 3.291.773 | 21.132 | BR | NR<br>T2DM: ICD-codes | OR+CI^ | |
| Curhan et al. 1996. **8** | USA | CH (1911-46) | M | 62 (40-75) | 22.846 | 7248 | SR | SR* | OR+CI^<br>OR+CI~ (Whincup) | OR+CI^: Age, BMI, parental history of diabetes<br>OR+CI~: Age, sex, BMI |
| De Lauzon-Guillain et al. 2010. **9** | France | CH (1925-50) | F | 52 (40-65) | 91.453 | 2.534 | SR | PE<br>T2DM: WHO criteria, SR ADM | HR+CI^ | Year of birth, physical activity, years of education, prematurity, family DM history, smoking status, cholesterol level, hypertension, menopausal status, hormone replacement therapy, oral contraceptive pills, parity and age of first child, age at |

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| De Rooij et al. 2006. **10** | The Netherlands | CH (1943-47) | F/M | 58 | 678 | 58 | BR | PE T2DM: WHO criteria | OR+CI~ (Whincup) | Age, sex, BMI, SES |
| Dyck et al. 2001†. **11** | Canada | CC | F/M | 31 (10-44) | 1.728 | | BR | NR T2DM: ICD-codes | OR+CI^ | Maternal age |
| Dyck et al. 2001‡. **11** | | | | | 2.264 | | | | | Maternal age, maternal parity |
| Dyck et al. 2010†. **12** | Canada | CC | F/M | 31 (10-44) | 1.545 | | BR | NR T2DM: ICD-codes | OR+CI~ | Maternal age, maternal parity |
| Dyck et al. 2010‡. **12** | | | | | 1.984 | | | | | Maternal age, maternal parity |
| Eriksson et al. 2004. **13** | Sweden, Gothenburg | CH (1913) | M | 65 (50-80) | 478 | 54 | BR | SR | RR+CI^ RR+CI~ | RR+CI^ and RR+CI~: Weight at 50 years of age, gestational age, place of birth, parity, maternal diabetes, smoking |
| Fall et al. 1998. **14** | India, Mysore | CH (1934-53) | F/M | 47 (39-60) | 506 | 79 | BR | PE | OR+CI~ (Whincup) | Age, sex, BMI, SES |

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| | | | | | | | | T2DM: WHO criteria | | |
| Forsén et al. 2000. **15** | Finland, Helsinki | CH (1924-33) | F/M | 68 (64-73) | 7044 | 471 | BR | NR<br>DM: WHO criteria or ADM | OR+CI^ | |
| Hales et al. 1991. **16** | England, Hertfordshire | CH (1920-30) | M | 64 (59-70) | 370 | 27 | BR | PE<br>T2DM: WHO criteria | OR+CI^<br>OR+CI~ (Whincup) | OR+CI~: Age, sex, BMI, SES |
| Hjort et al. 2015. **17** | Sweden, Skåne/ Uppsala | CC | F/M | 56 (54-59) | 953 | 350 | SR | NR | OR+CI^<br>OR+CI~ | Age, sex, BMI, family history of DM |
| Hyppönen et al. 2003. **18** | UK | CH (1958) | F/M | 41 | 10.683 | 88 | BR | SR | OR+CI~ (Whincup) | Age, sex, BMI, SES |
| Jeffreys et al. 2006§. **19** | Scotland, Glasgow | CH (1931-44) | F/M | 64 (57-70) | 2.303 | 84 | SR | SR | OR+CI^<br>OR+CI~ (Whincup) | OR+CI~: Age, sex, BMI, SES |

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| Jeffreys et al. 2006‖. **19** | UK | CH (1920-39) | F | 69 (60-79) | 2.251 | 177 | SR | NR | OR+CI^ | |
| Jornayvaz et al. 2016. **20** | Switzerland, Lausanne | CS | F/M | 55 (35-75) | 2.546 | 111 | SR | PE T2DM: ADM or FBG >7.0mmol/l | OR+CI^ | Age, smoking status, physical activity, BMI |
| Kaijser et al. 2009. **21** | Sweden, Stockholm | CH (1935-49) | F/M | 49 (37-62) | 6.425 | 508 | BR | NR T2DM: ICD-codes | HR+CI^ | Calendar period of birth, socioeconomic status, sex |
| Lammi et al 2009. **22** | Finland, Helsinki | CC | F/M | 27 (15-39) | 1.136 | | BR | NR T2DM: ICD-codes or ADM | OR+CI^ | |
| Lawlor et al. 2003. **23** | UK | CS (1920-39) | F | 68 (60-79) | 2431 | 207 | SR | NR | OR+CI~ (Whincup) | Age, sex, BMI, SES |
| Lawlor et al. 2006. **24** | Scotland, Aberdeen | CH (1950-56) | F/M | 47 (44-50) | 5.793 | 113 | BR | SR | OR+CI~ | Sex, year of birth, indicator of childhood SES, pregnancy complications, adult socioeconomic status, adult BMI |

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| Leibson et al. 2005. **25** | USA, MN, Rochester | CC | F/M | 45 (19-72) | 513 | 171 | BR | NR<br>T2DM: WHO criteria or ADM | HR+CI^<br>HR+CI~ | HR+CI^ and HR+CI~: Age, sex, birth year |
| Li et al. 2015¶. **26** | USA | CH | M | 52 (50-55) | 18.305 | 1.603 | SR | SR | RR+CI^ | Ethnicity, family history of diabetes, living alone or with others, marital status, menopausal status and postmenopausal hormone therapy use for women, smoking status, alcohol consumption, physical activity, alternate healthy eating index and BMI |
| Li et al. 2015□. **26** | USA | CH | F | 46 (45-48) | 49.757 | 5.381 | SR | SR | RR+CI^ | |
| Li et al. 2015Δ. **26** | USA | CH | F | 35 (35-36) | 81.732 | 4.725 | SR | SR | RR+CI^ | |
| Lithell et al. 1996. **27** | Sweden Uppsala | CH (1920-24) | M | 60 | 1.093 | 61 | BR | PE<br>T2DM: ** | OR+CI^<br>OR+CI~ (Whincup) | OR+CI~: Age, sex, BMI |
| Martyn et al. 1998. **28** | England, Sheffield | CH (1939-40) | F/M | 52 | 337 | 18 | BR | PE<br>T2DM: WHO criteria | OR+CI~ (Whincup) | Age, sex, BMI, SES |

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| McCance et al. 1994. **29** | USA, Arizona | CH (1940-72) | F/M | 30 (20-39) | 1.179 | 210 | BR | PE T2DM: WHO criteria | OR+CI^ OR+CI~ (Whincup) | OR+CI^: Age, BMI OR+CI~: Age, sex |
| Mi et al. 2000. **30** | China, Beijing | CH (1948-54) | F/M | 45 (41-47) | 627 | 28 | BR | PE T2DM: WHO criteria | OR+CI~ (Whincup) | Age, sex, BMI, SES |
| Mueller et al. 2016. **31** | Brazil | CH | F/M | 54 (35-74) | 12.066 | | SR | SR T2DM: OGTT or $HbA_{1c}$ | PR+CI^ | Age, race, study center, mothers educational level, paternal diabetes, weight at age 20, BMI at baseline |
| Phipps et al. 1993. **32** | England, Preston | CH (1935-43) | F/M | 50 (46-54) | 266 | 11 | BR | PE T2DM: WHO criteria | OR+CI~ (Whincup) | Age, sex, BMI, SES |
| Pilgaard et al. 2010. **33** | Denmark | CH | F/M | 45 (30-60) | 3.972 | | BR | PE T2DM: WHO criteria | OR+CI~ | Age, sex, BMI |
| Rich-Edwards | USA | CH (1921-46) | F | 59 | 68.396 | 1199 | SR | SR[a] | OR+CI~ (Whincup) | Age, sex, BMI, SES |

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| et al. 1999. **34** | | | | | | | | | | |
| Ruiz-Narváez et al. 2014. **35** | USA | CH | F | 39 (37-41) | 21.624 | 2.388 | SR | SR | RR+CI^ | Age, questionnaire cycle, first degree family history of diabetes, being born preterm, activity level, energy intake, SES by neighborhood, education level, BMI |
| Ryckman et al. 2014. **36** | USA | CH | F | 64 (50-79) | 75.993 | 4.002 | SR | SR | OR+CI^ | Age, ethnicity, neighborhood socioeconomic status, BMI, family history of diabetes, physical activity, smoking, alcohol use, hypertension, history of CVD, hysterectomy, and prior postmenopausal hormone therapy, having been breastfed |
| Song et al. 2015. **37** | USA | Nested CC | F | 62 | 3.049 | 1.259 | SR | SR | OR+CI^ | |

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| Suzuki et al. 2000. **38** | Japan, Tochigi | CS | F/M | 25 (19-31) | 299 | | BR | PE<br>T2DM: FBG | OR+CI~ (Whincup) | Age, sex, BMI |
| Tian et al. 2006. **39** | China, Shanghai | CS (1928-84) | F/M | 46 (18-74) | 973 | 114 | BR | PE<br>T2DM: WHO criteria, history of DM or ADM | OR+CI^<br>OR+CI~ (Whincup) | OR+CI^: age, sex, waist circumference, family history of DM, educational background, smoking status and alcohol consumption<br>OR+CI~ :Age, sex, BMI |
| Vanhala et al. 1999. **40** | Finland, Pielsamaki | CH (1947-57) | F/M | 41 (36-46) | 374 | 44 | BR | PE | OR+CI~ (Whincup) | Age, sex, BMI, SES |
| Veena et al. 2009. **41** | India | CH | F/M | 59 (49-70) | 266 | 56 | BR | PE<br>T2DM: WHO criteria | OR+CI^ | |
| Von Bonsdorff et al. 2013. **42** | Iceland, Reykjavik | CH (1914-35) | F/M | 75 (66-90) | 1.682 | 249 | BR | PE<br>T2DM: SR or ADM or FBG >7.0mmol/l | OR+CI~<br>OR+CI^ | OR+CI~: Age, sex, BMI midlife, education, smoking and physical activity |

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| Wadsworth et al. 2005. **43** | UK | CH (1946) | F/M | 42 (31-53) | 3.921 | 78 | BR | SR | HR+CI~ | |
| Xiao et al. 2008. **44** | China, Beijing | CH (1921-54) | F/M | 59 (57-62) | 2.004 | 391 | BR | PE<br>T2DM: WHO criteria, history of DM or ADM | OR+CI^ | |
| Yarbrough et al. 1998. **45** | USA, California | CH (1907-41) | F | 67 (50-84) | 304 | 30 | SR | PE<br>T2DM: WHO criteria or ADM | OR+CI~ (Whincup) | Age, sex, BMI, SES |
| Zimmermann et al. 2015. **46** | Denmark, Copenhagen | CH (1936-83) | F/M | 54 (30-78) | 223.099 | | SR | NR<br>T2DM: ICD-codes | HR+CI^ | Birth cohort |

Cohort (CH), Case-Control (CC), Cross-Sectional (CS), Standard deviation (SD), 95% Confidence interval (CI), Odds ratio (OR), Rate ratio (RR), Prevalence ratio (PR), Birth records or any other secure records (BR), National register or any other secure records (NR), Physical examination (PE), Self- or family-reported (SR), Type 2 diabetes mellitus (T2DM), Impaired Glucose Tolerance (IGT), Oral Glucose Tolerance Test (OGTT), Fasting Blood Glucose (FBG), Anti-diabetic treatment or medication prescription (ADM), Hemoglobin A1c (HbA1c), Socioeconomic status (SES), Body mass index (BMI)

**Age**: as reported in the studies (at outcome, at baseline, at specific time points during follow up) or estimated based on year of birth and follow up period. Age is given as a mean and/or range.

**Outcome:** ~Birth weight is a continuous variable; ^Birth weight is a categorical variable; (Whincup) results transferred directly from Whincup et al. **47**

WHO criteria for diagnosing DM: Fasting blood glucose ≥ 7.0mmol/l or random blood glucose ≥11.1mmol/l. OGTT: IGT = 120min blood glucose > 7.8-11.0mmol/l. DM = 120min blood glucose ≥ 11.0mmol/l

* Confirmation attempted by: 1) one or more classic symptoms and raising fasting (≥ 7.8mmol/l) or random (≥ 11.1mmol/l) plasma glucose concentration; 2) elevated plasma glucose concentrations on at least 2 separate occasions (fasting≥7.8mmol/l; random ≥11.1mmol/l or 2h OGTT ≥ 11.1mmol/l + absence of symptoms: 3) use of ADM

** DM definition: 2 Fasting blood glucose >6.7mmol/l; 120min blood glucose ≥ 10.0Mmol/L + one other blood glucose >10.0mmol/l during the OGTT; use of ADM

**ICD-codes for Type 2 DM**: ICD8 (249,250), ICD9 (250, 362), ICD10 (E11-E14)

†: Native North American population, ‡: General population (predominantly white origin), §: The Glasgow alumni Study, ‖: The British Women's Heart and Health Study, ¶: Health professionals Follow-up Study 1986, □: Nurses' Health Study 1980, Δ: Nurses' Health Study II 1991

**Table S2. Characteristics of studies included in the meta-analysis for birth weight and cardiovascular disease.**

| Study, publica-tion year | Country, City | Study design - Birth year | Sex | Age distribu-tion: mean (range) | Sample size | Cases | Birth weight collection method | Assessment and definition of cardiovascular disease | Outcome | Confounding factors |
|---|---|---|---|---|---|---|---|---|---|---|
| Andersen et al. 2004. **48** | Denmark, Copenhagen | CH (1959) | M | 32 (15-49) | 10.753 | 130 | BR | NR Fatal CVD: ICD-codes | HR+CI~ (Wang) | Maternal marital status, paternal occupation at birth, parental life span |
| Andersen et al. 2010. **49** | Denmark, Copenhagen | CH (1936-76) | F/M | 29 | 200.087 | 8.805 | SR | NR Fatal/non-fatal CHD: ICD-codes | HR+CI^ | |
| | Finland Helsinki | CH (1924-44) | | 34 | 16.684 | | BR | | | |
| Barker et al. 2010. **50** | Finland, Helsinki | CH (1934-44) | F/M | 49 (45-54) | 13.345 | 187 | BR | NR Fatal/non-fatal CHF: ICD-codes | OR+CI^ | |
| Class et al. 2013. **7** | Sweden Stockholm | CH (1973-95) | F/M | 23 (12-35) | 3.291.773 | 8058 | BR | NR | OR+CI^ | |

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|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | CVD, IHD, Stroke: ICD-codes | | |
| Conen et al. 2010. **51** | USA | CH | F | 53 (48-61) | 27.982 | 735 | SR | SR Arterial Fibrillation | HR+CI^ | age, hypercholesterolemia, smoking, exercise, alcohol consumption, education, race, hormone replacement therapy, BMI, SBP, DBP, DM, adult height, max. body weight |
| Eriksson et al. 2000. **52** | Finland, Helsinki | CH (1924-33) | M | 54 (45-64) | 3.639 | 331 | BR | NR Fatal/non-fatal Stroke: ICD-codes | HR+CI^ | Head circumference |
| Eriksson et al. 2004. **53** | Sweden, Gothenburg | CH (1913) | M | 52 (20-85) | 1.209 | | BR | NR Fatal/non-fatal CVD, CHD: ICD-codes | HR+CI^ HR+CI~ | Gestational age |

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|---|---|---|---|---|---|---|---|---|---|---|
| Fall et al. 1995. **54** | England, Hertford-shire | CH (1920-30) | M | 66 | 290 | 42 | BR | Non-fatal CHD* | | |
| Fan et al. 2010. **55** | China, Beijing | CH (1921-54) | F/M | 60 (50-84) | 2.016 | 135 | BR | Non-fatal CHD* | OR+CI^ OR+CI~ (Wang) | OR+CI~: Sex, age, obesity |
| Ferrie et al. 2006. **56** | England, London | CH | F/M | 45 (35-55) | 10.308 | 262 | BR | Non-fatal CHD* | HR+CI~ | Age, Sex, Childhood and adulthood socioeconomic position, smoking habits, alcohol consumption, BMI |
| Frankel et al. 1996. **57** | South Wales, Caerphilly | CH | M | 52 (45-59) | 1.258 | 128 | SR | PE (ECG) and/or NR Fatal/non-fatal CHD: ICD-codes | OR+CI^ OR+CI~ (Wang) | Age |
| Gunnars-dottir et al. 2002. **58** | Iceland, Reykjavik | CH (1914-35) | F/M | 63 | 4.742 | 635 | BR | NR Fatal/non-fatal CHD* | OR+CI^ OR+CI~ (Wang) | Year of birth |

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| Hypponen et al. 2001. **59** | Sweden, Uppsala | CH (1915-29) | F/M | 61 (41-81) | 10.853 | 850 | BR | NR<br>Fatal/non-fatal Stroke: ICD-codes | HR+CI^<br>HR+CI~ | HR+CI~: Sex, period of birth, mothers civil status and social group, offspring social group as adult, car ownership, education, income, head circumference, length at birth |
| Kaijser et al. 2008. **60** | Sweden | CH (1925-49) | F/M | 57 (38-77) | 6.425 | 617 | BR | NR<br>Fatal/non-fatal IHD:<br>ICD codes | HR+CI^ | Gestational duration |
| Kajantie et al. 2005. **61** | Finland, Helsinki | CH (1924-44) | F/M | 56 (26-74) | 13.830 | 833 | BR | NR<br>Fatal CVD:<br>ICD-codes | HR+CI~ | Gestational age |
| Lawlor et al. 2004. **62** | England | CS | F | 69 (60-79) | 1.394 | 204 | SR | NR or SR:<br>Non-fatal CHD | OR+CI^<br>OR+CI~ | OR+CI~: SES factors, age at leaving full education, smoking |
| Lawlor et al. 2005. **63** | Scotland, Aberdeen | CH (1950-56) | F/M | 39 (25-53) | 10.803 | 403 | BR | NR<br>Fatal/non-fatal CHD and | HR+CI~ | Sex, gestational age, social class, childhood height and BMI (z-scores), gravidity, |

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|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | Stroke: ICD-codes | | maternal age, pregnancy induced HT, maternal height, sex and antepartum hemorrhage |
| Leon et al. 1998. **64** | Sweden, Uppsala | CH (1915-29) | F/M | 54 (29-80) | 13.363 | 1.313 | BR | NR<br>Fatal CVD and IHD:<br>ICD-codes | RR+CI~ | Period of birth |
| Martin et al. 2005. **65** | UK | CH | F/M | 71 | 639 | | SR | NR<br>Non-fatal CHD:<br>ICD-codes | OR+CI~ (Wang) | |
| Morley et al. 2006. **66** | Australia, Melbourne | CH (1857-1900) | F/M | > 40 | 2.938 | 486 | BR | NR<br>Fatal CHD** | HR+CI~ | |
| Osler et al. 2009. **67** | Denmark, Copenhagen | CH (1953) | M | 38 (25-52) | 9.143 | 475 | BR | NR<br>Fatal/non-fatal CHD:<br>ICD-codes | HR+CI^ | Father's occupational social class and educational attainment at conscription |

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| Osmond et al. 1993. **68** | England Hertford-shire | CH (1911-30) | F/M | 47 (20-74) | 15.726 | 1.355 | BR | NR Fatal/non-fatal CVD and CHD: ICD-codes | OR+CI^ OR+CI~ (Wang) | |
| Rich-Edwards et al. 1997. **69** | USA | CH | F | 44 (30-55) | 70.297 | 889 | SR | SR Non-fatal CHD (1976-92) | OR+CI^ | age, adult BMI, smoking, hypertension, raised cholesterol, parental history of MI under 60, diabetes, menopausal status + use of hormones |
| Rich-Edwards et al. 2005. **70** | USA | CH | F | 44 (30-55) | 66.111 | 918 (CHD) 1164 (stroke) | SR | SR Fatal/non-fatal CHD (1992-2000) and Stroke (1976-2000) | HR+CI^ HR+CI~ | HR+CI^ and HR+CI~: age, BMI |
| Risnes et al. 2009. **71** | Norway, Trondheim | CH (1920-59) | F/M | 50 (34-67) | 35.846 | 994 | BR | NR Fatal CVD and CHD: | HR+CI^ HR+CI~ | HR+CI^: Sex, year of delivery HR+CI~: Sex, year of delivery, maternal age, birth |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | ICD-codes | | order, maternal marital status, paternal occupation |
| Roseboom et al. 2000. **72** | The Netherlands | CH | F/M | 50 | 736 | | BR | NR<br>Non-fatal CHD* | OR+CI~ (Wang) | Sex |
| Smith et al. 2016. **73** | USA | CH | F | 64 (50-79) | 63.815 | 2457 | SR | SR<br>Fatal/non-fatal "any" CVD | HR+CI^ | |
| Stein et al. 1996. **74** | India, Mysore | CS (1934-54) | F/M | 47 (38-60 | 517 | 57 | BR | Non-fatal CHD * | OR+CI^<br>OR+CI~ (Wang) | OR+CI~: Age and sex |
| Syddall et al. 2005. **75** | England, Hertfordshire | CH (1911-39) | M | 60 (13-88) | 21.632 | | BR | NR<br>Fatal IHD: ICD-codes | HR+CI~ | |
| Tanis et al. 2005. **76** | The Netherlands | CC | F | 50 (25-60) | 720 | 152 | SR | NR<br>Non-fatal MI | OR+CI^ | Age, educational level, BMI, WHR, hypertension, diabetes, hypercholesterolemia, smoking, family history of CVD |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Von Bonsdorff et al. 2013. **42** | Iceland, Reykjavik | CH (1914-35) | F/M | 75 (66-90) | 1.682 | 341 | BR | NR Non-fatal CHD* | OR+CI^ | |
| Yang et al. 2008. **77** | Sweden Uppsala | CH | F | 40 (30-50) | 48.052 | 194 | SR | NR Fatal/non-fatal CHD: ICD-codes | HR+CI^ | Age, smoking, alcohol, years of education, ever use of oral contraceptive, exercise, diabetes, hypertension, BMI |
| Zöller et al. 2015. **78** | Sweden | CH (1973-92) | F/M | 28 (18-38) | 1.970.869 | 668 | BR | NR Fatal/non-fatal IHD: ICD-codes | HR+CI^ HR+CI~ | age, sex, fetal growth, gestational age, multiple birth, maternal marital status, maternal and paternal education, cardiovascular and chromosomal anomalies or syndromes, diabetes, hypertension and parental history of IHD |

Cohort (CH), Case-Control (CC), Cross-Sectional (CS), Standard deviation (SD), 95% Confidence interval (CI), Odds Ratio (OR), Rate Ratio (RR), Hazard ratio (HR), Birth records or any other secure records (BR), National register or any other secure records (NR), Self- or family-reported (SR), cardiovascular disease (CVD), ischemic

heart disease (IHD), coronary heart disease (CHD), myocardial infarction (MI), chronic heart failure (CHF), pulmonary circulation problems (PCP) electrocardiogram (ECG), Socioeconomic status (SES), Body mass index (BMI).

**Age**: as reported in the studies (at outcome, at baseline, at specific time points during follow up) or estimated based on year of birth and follow up period. Age is given as a mean and/or range.

**Outcome:** ~Birth weight is a continuous variable; ^Birth weight is a categorical variable; (Wang) results transferred directly from Wang et al.**79**

* CHD definition: presence of one or more of the following; Typical angina (ROSE/WHO chest pain questionnaire); ECG 1982 Minnesota codes 1-1 or 1-2 (Q and SQ codes); History of coronary artery angioplasty or bypass graft surgery, > 50% coronary artery stenosis on angiography, non-fatal MI based on WHO criteria, cardiac enzymes

** CHD definition: cause of death: ´angina´, ´heart attack´, ´myocardial infarction´, ´cardiac infarction´, ischemic heart disease´, ´myocardial ischemia´, ´coronary thrombosis´, ´coronary occlusion´. **ICD-codes: CVD:** ICD-7 (330-334, 420-468), ICD-8 (390-458), ICD-9 (390-459), ICD-10 (I00-I99); **CVD death**: (ICD-7 (330-468) ICD-8 (390-458) ICD-10 (I00-I52, I60-I99))

**CHD (IHD):** ICD7 (420,422) ICD8 and 9 (410-414), ICD10 (I20-I25). **Stroke**: ICD9 (430-438), ICD10 (I60-I69)

**MI**: ICD9; (410), ICD10 (I21). PCP: 415-417, 426, 450, I26-I28. **CHF**: ICD8 and 9 (428), ICD10 (I50). AF: ICD8 (427.9), ICD9 (427.3), ICD10 (I48)

**Table S3. Characteristics of studies included in the meta-analysis for birth weight and hypertension and blood pressure.**

| Study, Publica-tion year | Country, City | Study design Birth year | Sex | Age distribu-tion: mean (range) | Sample size | Cases | Birth weight collection method | Assessment and definition of hypertension | Outcome | Confounding factors |
|---|---|---|---|---|---|---|---|---|---|---|
| Andersson et al. 2000. **80** | Sweden, Goteborg | CH | F | 60 | 416 | 89 | BR | PE HT: AHM or SBD ≥ 160 and/or DBP ≥ 90 | Mean+SD^ OR+CI^ OR+CI~ | OR+CI~: BMI |
| Barker et al. 2002. **81** | Finland, Helsinki | CH | F/M | 45 (27-63) | 8.760 | 1404 | BR | HT: AHM | OR+CI^ | |
| Bergvall et al. 2005. **82** | Sweden | CH (1973-81) | M | 18 | 330.768 | 65866 | BR | PE HT: SBP ≥ 140mmHg | OR+CI^ | Birth length, gestational age, height at conscription, conscription year, BMI Conscription year, maternal age, maternal parity, household |

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|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | SES, highest education and family structure |
| Bustos et al. 2016. **83** | Chile, Limache | CH (1974-78) | F/M | 35 (32-38) | 796 | | BR | PE HT: AHM or SBD ≥ 140 and/or DBP ≥ 90 | OR+CI~ β+CI~ | Sex, physical activity, BMI |
| Campbell et al. 1996. **84** | Scotland, Aberdeen | CS (1948-54) | F/M | 40 | 253 | | BR | PE | Mean+SD^ β+CI~ (Huxley) | Mean+SD^: Sex, BMI, cuff size, alcohol consumption β+CI~: Sex, cuff size, alcohol consumption |
| Class et al. 2013. **7** | Sweden Stockholm | CH (1973-95) | F/M | 23 (12-35) | 3.291.773 | 6760 | BR | NR HT: ICD-codes | OR+CI^ | |
| Curhan et al. 1996a. **8** | USA | CH | M | 62 (40-75) | 22.846 | 7248 | SR | SR | OR+CI^ β+CI~ | OR+CI^: age, BMI, parental history of HT. β+CI: age, BMI, parental history of HT |

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|---|---|---|---|---|---|---|---|---|---|---|
| Curhan et al. 1996b. **85** | USA | CH | F | 42 (30-55) | 71.100 | 23.873 | SR | SR | OR+CI^<br>β+CI~ | OR+CI^: age, BMI, parental history of HT. β+CI: age, BMI, parental history of HT |
| Curhan et al. 1996c. **85** | USA | CH | F | 32 (25-42) | 92.940 | 6.119 | SR | SR | OR+CI^<br>β+CI~ | OR+CI^: age, BMI, parental history of HT. β+CI: age, BMI, parental history of HT |
| Dalziel et al. 2007. **86** | New Zealand, Auckland | CS | F/M | 30 | 416 | | BR | PE | β+CI~ | Sex, antenatal betamethasone treatment, adult BMI |
| Eriksson et al. 2000. **87** | Finland, Helsinki | CH (1924-33) | F/M | 38+ | 7.086 | 1958 | BR | HT: AHM | OR+CI^ | |
| Eriksson et al. 2004. **13** | Sweden, Gothenburg | CH | M | 65 (50-80) | 478 | | BR | PE<br>HT: AHM | RR+CI^<br>RR+CI~<br>β+CI~ | β+CI~, RR+CI^ and RR+CI~: weight at 50 years, gestational age, place of birth, parity, maternal diabetes and smoking status |

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|---|---|---|---|---|---|---|---|---|---|
| Euser et al. 2010. **88** | Norway, N. Trøndelag | CH | F/M | 24 (20-30) | 7.435 | BR | PE | Mean+SD^ | |
| Fall et al. 1995. **89** | England, Hertford-shire | CH | F | 64 (60-71) | 297 | BR | PE | β+CI~ | BMI |
| Gomes et al. 2013. **90** | Brazil, Sao Paulo | CH | F/M | 26 | 297 | BR | PE | Mean+SD^ | |
| Hack et al. 2005. **91** | USA, Cleveland | CC | F/M | 20 | 403 | BR | PE | Mean+SD^ | |
| Hardy et al. 2003. **92** | UK | CH (1946) | F/M | 53 | 2.890 | BR | PE | Mean+SD^ β+CI~ | β+CI~: Sex |
| Hovi et al. 2007. **93** | Finland, Uusimaa | CC | F/M | 22 (18-27) | 332 | BR | PE | Mean+SD^ | Age, Sex, current lean BM and height, exercise intensity, parental education |

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|---|---|---|---|---|---|---|---|---|---|---|
| Jarvelin et al. 2004. **94** | Finland | CH (1966) | F/M | 31<br>2.858<br>5.960 | 3.102 | 100<br>100<br>200 | BR | PE | Mean+SD^,<br>β+CI~ | β+CI: Sex, gestational age, change in weight SDS score between 0 and 1year, family social class, parity, maternal height and weight pre-pregnancy, maternal age, smoking after second month of pregnancy + adult factors: social class, smoking status, alcohol consumption, BMI |
| Kolacek et al. 1993. **95** | Croatia | CH (1968-69) | F/M | 19 (18-23) | 465 | | SR | PE | β+CI~ (Huxley) | |
| Koupil et al. 2005. **96** | Sweden Uppsala | CH (1920-24) | M | 70 (69-74) | 736 | | BR | PE HT: AHM or SBD ≥ 140 and/or DBP ≥ 90 | Mean+SD^<br>OR+CI^<br>OR+CI~<br>β+CI~ | β+CI~ and OR+CI~: Age, BMI |

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|---|---|---|---|---|---|---|---|---|---|---|
| Kumanran et al. 2000. **97** | India, Mysore | CH (1934-53) | F/M | 49 (40-61) | 435 | 137 | BR | PE HT: AHM or SBD ≥ 140 and/or DBP ≥ 90 | OR+CI^ | |
| Lawlor et al. 2003. **23** | England | CS | F | 69 (60-79) | 1.039 | | SR | PE | β+CI~ | Age, smoking, adult social class, other early life factors (offspring BW, leg length, childhood social class) and adult BMI and WHR |
| Leger et al. 1997. **98** | France, Haguenau | CH | F/M | 20 | 517 | | BR | PE | Mean+SD^ | Sex, BMI, height |
| Leon et al. 2000. **99** | Sweden | CH (1973-76) | M | 18 (17-19) | 165.136 | | BR | PE | β+CI~ | Current weight and height |
| Li et al. 2015. **100** | USA | CH | F | 35 (35-36) | 52.114 | 12.588 | SR | SR | RR+CI^ RR+CI~ | RR+CI^: age, ethnicity, family history of hypertension, oral contraceptive use, smoking status, alcohol consumption, |

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|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | BMI, exercise, DASH score, folic acid supp., use of aspirin RR+CI~: SES |
| Liew et al. 2008a. **101** | USA | CH | F/M | 61 (51-72) | 3.800 | | SR | PE HT: AHM or SBD ≥ 140 and/or DBP ≥ 90 | Means+SD^ OR+CI^ | OR+CI^: Sex, race, center, educational level, BMI, adult height, smoking status, alcohol consumption, total cholesterol, high density lipoprotein cholesterol, triglycerides, fasting Glucose level |
| Liew et al. 2008b. **102** | USA | CH | F/M | 54 (45-64) | 9.730 | 3713 | SR | PE HT: AHM or SBD ≥ 140 and/or DBP ≥ 90 | Means+SD^ OR+CI^ | Mean+SD^: Age, sex |
| Mann et al. 2015. **103** | Australia, Darwin | CH (1987-90) | F/M | 18 (16-20) | 451 | | BR | PE | β+CI~ | |

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|---|---|---|---|---|---|---|---|---|---|
| Martyn et al. 1995. **104** | UK, Sheffield | CS (1939-40) | F/M | 52 (51-53) | 336 | BR | PE | β+CI~ (Huxley) | Sex, alcohol consumption, gestational age |
| Mi et al. 2000. **30** | China, Peking | CH (1948-54) | F/M | 45 (41-47) | 627 | BR | PE | β+CI~ | Sex, BMI |
| Miles et al. 2011. **105** | UK, Wales, Cambridge | CS | F/M | 21 | 1.764 | SR | PE | Mean+SD^ | |
| Moore et al. 1999. **106** | Australia, Adelaide | CH | F/M | 20 | 584 | BR | PE | β+CI~ | Current weight |
| Nilsson et al. 1997. **107** | Sweden | CS | M | 18 | 143.660 | BR | PE | β+CI~ | BMI, Gestational age, mothers age and parity |
| Ramadhani et al. 2006. **108** | The Netherlands, Utrecht | CH (1970-73) | F/M | 28 (26-31) | 744 | BR | PE | Mean+SD^ β+CI~ | β+CI: Sex, adult BMI, education level |
| Rich-Edwards | USA | CH | F | 42 (30-55) | 70.297 | SR | SR | OR+CI^ | |

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|---|---|---|---|---|---|---|---|---|---|---|
| et al. 1997. **69** | | | | | | | | | | |
| Roseboom et al. 1999. **72** | The Netherlands | CH (1943-47) | F/M | 50 | 739 | | BR | PE | β+CI~ | Age, sex |
| Schnatz et al. 2010. **109** | USA, Connecticut | CS | F | 55 | 807 | 291 | SR | SR | OR+CI^ | |
| Singh et al. 2003. **110** | Australia | CS | F/M | 28 (18-43) | 456 | | BR | PE HT: SBD ≥ 140 and/or DBP ≥ 90 | Mean+SD^ OR+CI^ | Age, current BMI |
| Skilton et al. 2011. **111** | Finland | CS | F/M | 31 | 1.042 | | SF | PE | Mean+SD^ | |
| Skogen et al. 2014. **112** | Norway, Bergen | CH (1925-27) | F/M | 72 (72-74) | 480 | | BR | PE | β+CI~ | Age, sex |
| Song et al. | USA | Nested CC | F | 62 | 1.790 | | SR | PE | Mean+SD^ | |

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|---|---|---|---|---|---|---|---|---|---|---|
| 2015. **37** | | | | | | | | | | |
| Sorensen et al. 2000. **113** | Denmark, Ebeltoft | CS | F/M | 41 (30-50) | 905 | | BR | PE | Mean+SD^ | |
| Stocks et al. 1999. **114** | England, Bristol | CS | F/M | 19 (18-25) | 1.358 | | SR | PE | β+CI~ | Age, weight and height |
| Tamakoshi et al. 2006. **115** | Japan | CS | F/M | 50 (35-66) | 3.107 | 757 | SR | PE HT: : AHM or SBD ≥ 140 and/or DBP ≥ 90 | Mean+SD^ OR+CI^ | OR+CI^: sex, age, BMI, paternal and maternal history of hypertension, smoking status, alcohol consumption, exercise |
| Tian et al. 2006. **116** | China, Shanghai | CS | F/M | 46 (18-74) | 973 | 460 | BR | PE HT: AHM or SBD ≥ 140 and/or DBP ≥ 90 | Mean+SD^ OR+CI^ | OR+CI^: age, sex, educational background, smoking status and alcohol consumption |

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| Uiterwall et al. 1997. **117** | Holland, Zoetermeer | CH | F/M | 28 (20-37) | 330 | | SR | PE | β+CI~ | Weight, height, sex, use of alcohol, cigarettes and oral contraception |
| Vestbo et al. 1996. **118** | Denmark | CS | F/M | 48 (41-54) | 620 | | BR | PE | β+CI~ (Huxley) | Age, sex |
| Von Bonsdorff et al. 2013. **42** | Iceland, Reykjavik | CH (1914-35) | F/M | 75 (66-90) | 1.682 | 249 | BR | PE DM: SR or ADM or FGB >7.0mmol/l | OR+CI^ | |
| Wadsworth et al. 1985. **119** | UK | CH (1946) | F/M | 36 | 2.949 | | BR | PE | β+CI~ (Huxley) | |
| Yarbrough et al. 1998. **120** | USA, California | CH | F | 67 (50-84) | 303 | 127 | SR | PE HT: AHM or PD or SBD ≥ 160 and/or DBP ≥ 90 | Mean+SD`^ OR+CI^ | |

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|---|---|---|---|---|---|---|---|---|---|---|
| Yliharsila et al. 2003. **121** | Finland, Helsinki | CH (1924-33) | M | 70 (65-75) | 500 | 213 | BR | PE HT: SR | OR+CI^ β+CI~ | β+CI: age, sex, BMI |
| Zhao et al. 2002. **122** | China, Shanghai | CH | F | 52 (40-70) | 13.467 | 1.433 | SR | SR | OR+CI^ | Age, age$^2$, education level |

**Abbreviations:** Cohort (CH), Case-Control (CC), Cross-Sectional (CS), Standard deviation (SD), 95% Confidence interval (CI), Odds ratio (OR), Rate ratio (RR), Beta-coefficient (β), Birth records or any other secure records (BR), Physical examination (PE), Self- or family-reported (SR), Hypertension (HT), Systolic blood pressure measured in mmHg (SBP), Diastolic blood pressure measured in mmHg (DBP), Antihypertensive medication/treatment or Medication prescription (AHM)

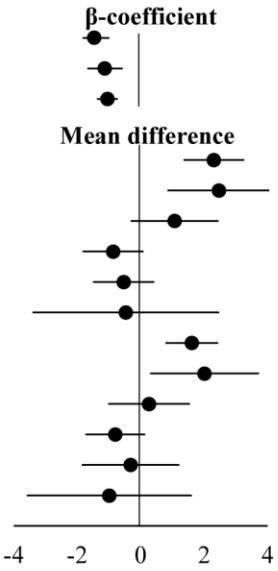
**Age:** as reported in the studies (at outcome, at baseline, at specific time points during follow up) or estimated based on year of birth and follow up period. Age is given as a mean and/or age range.

**Outcome:** ~Birth weight is a continuous variable; ^Birth weight is a categorical variable; (Huxley) results transferred directly from Huxley et al.**123**

**ICD-codes for hypertension:** ICD9 (401-405), ICD10 (I10-I15)

**Systolic Blood Pressure**

| Outcome | Estimate (95% CI) | $I^2$ (95%CI) (%) | n |
|---|---|---|---|
| Per 1-kg increase in BW (N) | -1.36 (-1.62; -1.09) | 91.3 (88.9; 93.2) | 2 |
| Per 1-kg increase in BW (F) | -1.12 (-1.66; 0.59) | 89.9 (83.0; 94.0) | 9 |
| Per 1-kg increase in BW (M) | -1.05 (-1.35; -0.75) | 91.1 (86.2; 94.3) | 1 |
| | | | |
| BW < 2.5kg vs > 2.5kg (ref) (N) | 2.31 (1.38; 3.24) | 51.0 (18.9; 70.3) | 1 |
| BW < 2.5kg vs > 2.5kg (ref) (F) | 2.47 (0.87; 4.06) | 57.5 (6.79; 80.6) | 8 |
| BW < 2.5kg vs > 2.5kg (ref) (M) | 1.07 (-0.29; 2.43) | 20.4 (0.00; 65.0) | 6 |
| BW > 4.0kg vs < 4.0kg (ref) (N) | -0.87 (-1.80; 0.07) | 66.6 (42.5; 80.6) | 1 |
| BW > 4.0kg vs < 4.0kg (ref) (F) | -0.54 (-1.48; 0.41) | 0.00 (0.00; 67.5) | 6 |
| BW > 4.0kg vs < 4.0kg (ref) (M) | -0.47 (-3.39; 2.45) | 86.4 (70.3; 93.8) | 5 |
| BW < 2.5kg vs. 2.5-4.0kg (ref) (N) | 1.61 (0.81; 2.42) | 38.5 (0.00; 65.1) | 1 |
| BW < 2.5kg vs. 2.5-4.0kg (ref) (F) | 2.01 (0.32; 3.71) | 54.6 (0.00; 80.6) | 7 |
| BW < 2.5kg vs. 2.5-4.0kg (ref) (M) | 0.27 (-1.00; 1.53) | 0.00 (0.00; 71.9) | 5 |
| BW > 4.0kg vs. 2.5-4.0kg (ref) (N) | -0.80 (-1.72; 0.12) | 65.0 (38.1; 80.2) | 1 |
| BW > 4.0kg vs. 2.5-4.0kg (ref) (F) | -0.32 (-1.83; 1.20) | 38.3 (0.00; 75.6) | 6 |
| BW > 4.0kg vs 2.5-4.0kg (ref) (M) | -0.99 (-3.57; 1.59) | 81.5 (57.6; 92.0) | 5 |




**Diastolic Blood Pressure**

| Outcome | Estimate (95% CI) | $I^2$ (95%CI) (%) | n |
|---|---|---|---|
| Per 1-kg increase in BW (N) | -0.33 (-0.54; -0.13) | 66.2 (43.6; 83.0) | 12 |
| Per 1-kg increase in BW (F) | -0.35 (-0.60; -0.10) | 83.2 (48.9; 94.5) | 3 |
| Per 1-kg increase in BW (M) | 0.14 (-0.79; 1.06) | 81.1 (40.9; 94.0) | 3 |
| | | | |
| BW < 2.5kg vs > 2.5kg (ref) (N) | 0.83 (0.13; 1.53) | 58.5 (32.6; 74.4) | 15 |
| BW < 2.5kg vs > 2.5kg (ref) (F) | 0.61 (-0.24; 1.46) | 22.7 (0.00; 64.5) | 8 |
| BW < 2.5kg vs > 2.5kg (ref) (M) | 0.32 (-0.94; 1.59) | 42.8 (0.00; 77.4) | 6 |
| BW > 4.0kg vs < 4.0kg (ref) (N) | -0.35 (-0.88; 0.18) | 57.0 (23.4; 75.9) | 11 |
| BW > 4.0kg vs < 4.0kg (ref) (F) | -0.19 (-0.90; 0.52) | 0.00 (0.00; 44.1) | 6 |
| BW > 4.0kg vs < 4.0kg (ref) (M) | -0.08 (-1.44; 1.29) | 76.8 (43.4; 90.5) | 5 |
| BW < 2.5kg vs. 2.5-4.0kg (ref) (N) | 0.40 (-0.07; 0.87) | 21.3 (0.00; 55.4) | 13 |
| BW < 2.5kg vs. 2.5-4.0kg (ref) (F) | 0.45 (-0.41; 1.31) | 16.5 (0.00; 60.5) | 7 |
| BW < 2.5kg vs. 2.5-4.0kg (ref) (M) | -0.16 (-1.32; 1.01) | 24.1 (0.00; 69.2) | 5 |
| BW > 4.0kg vs. 2.5-4.0kg (ref) (N) | -0.39 (-0.85; 0.07) | 40.8 (0.00; 67.9) | 11 |
| BW > 4.0kg vs. 2.5-4.0kg (ref) (F) | -0.14 (-0.89; 0.61) | 0.00 (0.00; 67.4) | 6 |
| BW > 4.0kg vs. 2.5-4.0kg (ref) (M) | -0.22 (-1.24; 0.80) | 56.2 (0.00; 83.8) | 5 |

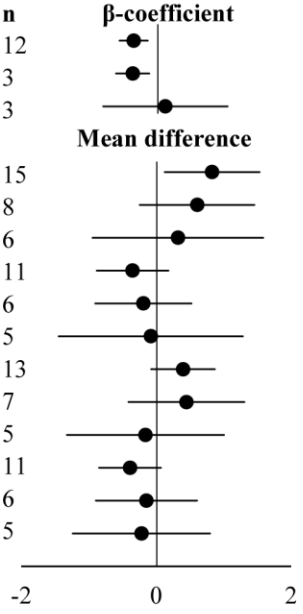



**Figure S1.**

**Sex-neutral (N) and sex-specific (F/M) association between birth weight (BW) and SDB and DBP**

Birth weight (BW) is represented as a continuous variable to assess the change in systolic and diastolic blood pressure per 1kg increase in birth weight and as a binary variable with 2 difference cutoffs for low and high birth weight (2.5kg and 4.0kg). Low and high birth weight are also compared to normal birth weight (2.5kg-4.0kg). Circles represents the pooled β-coefficient or mean difference from a random-effects model, horizontal lines their confidence interval (CI), and $I^2$ the heterogeneity detected in each meta-analysis. n is the number of studies contributing to the pooled estimate. Several studies only provide sex-neutral estimates. Therefore, the number of studies contributing in the sex-specific meta-analysis does not add up to the number of studies.

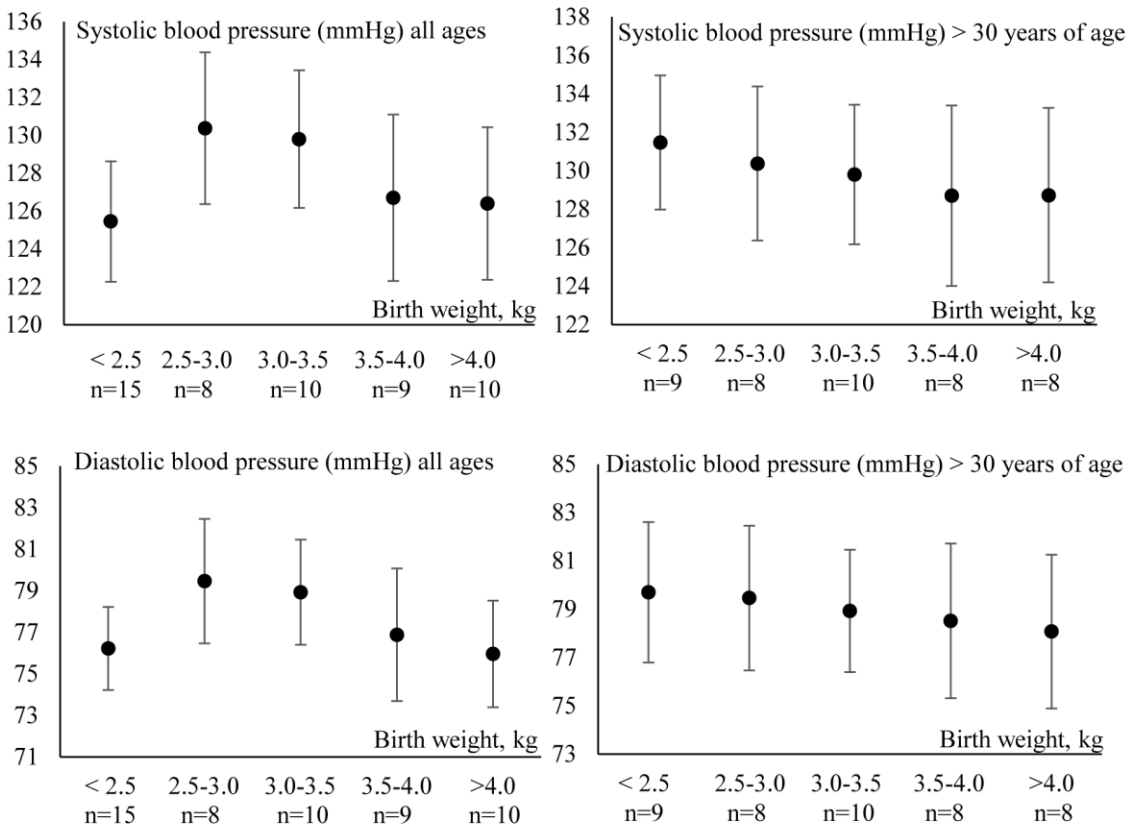



**Figure S2.**

**Mean systolic and diastolic blood pressure for five birth weight groups**

Circles represents the pooled mean for each birth weight group and the vertical lines their confidence interval (CI). Plot A and C includes all studies. Plot B and D includes studies were blood pressure was measured in subjects > 30 years of age. Mean (95%CI) in plot **A**: < 2.5kg (125.45 (122.27;128.63)), 2.5-3.0kg (130.38 (126.37;134.39)), 3.0-3.5kg (129.81 (126.17;133.44)), 3.5-4.0kg (126.70 (122.31;131.10)), > 4.0kg (126.40 (122.37;130.43)). Mean (95%CI) in plot **B**: < 2.5kg (131.47 (127.99;134.95)), 2.5-3.0kg (130.38 (126.37;134.39)), 3.0-3.5kg (129.81 (126.17;133.44)), 3.5-4.0kg (128.70 (123.80;133.19)), > 4.0kg (128.73 (124.19;133.26)). Mean (95%CI) in plot **C**: < 2.5kg (76.22 (74.29;78.29)), 2.5-3.0kg (79.46 (76.46;82.45)), 3.0-3.5kg (78.93 (76.40;81.46)), 3.5-4.0kg (76.88 (73.69;80.08)), > 4.0kg (75.96 (73.39;78.53)). Mean (95%CI) in plot **D**: < 2.5kg (79.70 (76.79;82.61)), 2.5-3.0kg (79.46 (76.46;82.45)), 3.0-3.5kg (78.93 (76.40;81.46)), 3.5-4.0kg (78.52 (75.32;81.72)), > 4.0kg (78.07 (74.89;81.25)).

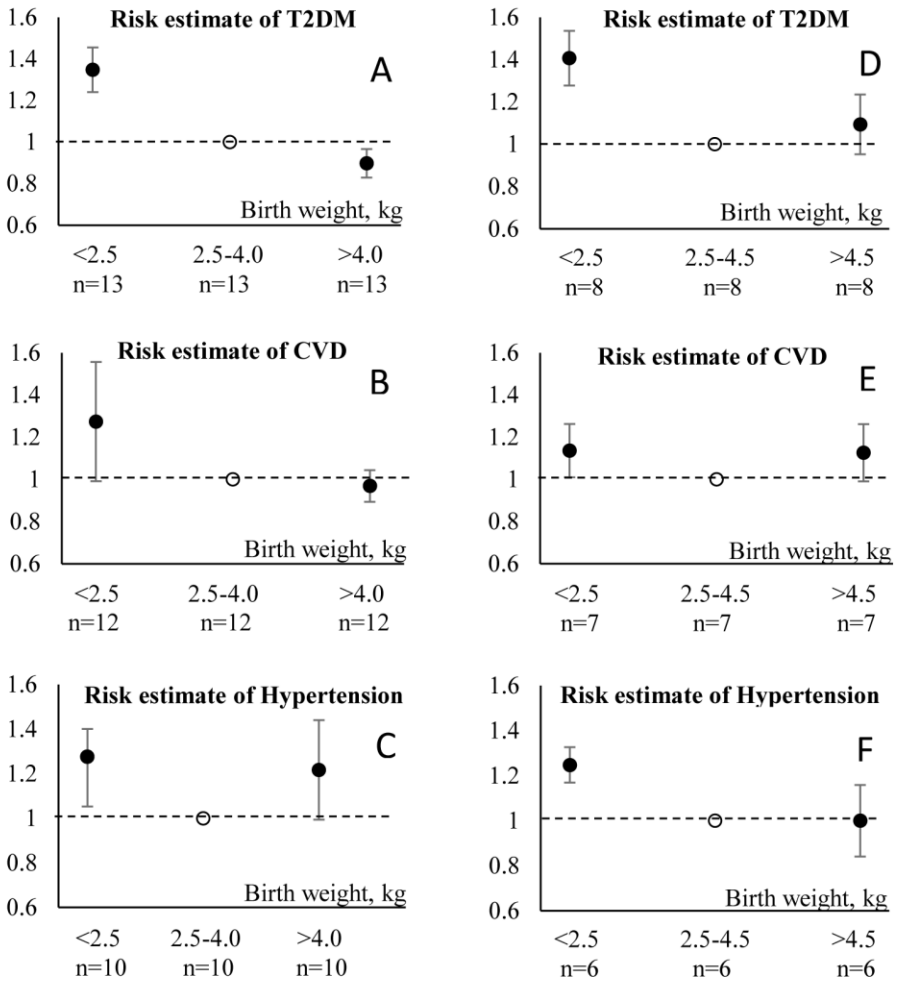
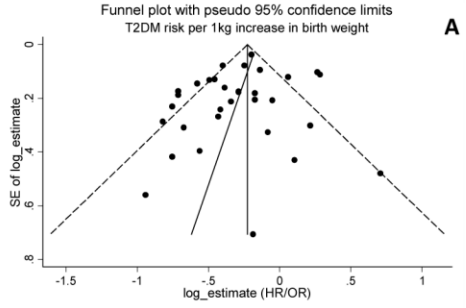



**Figure S3.**

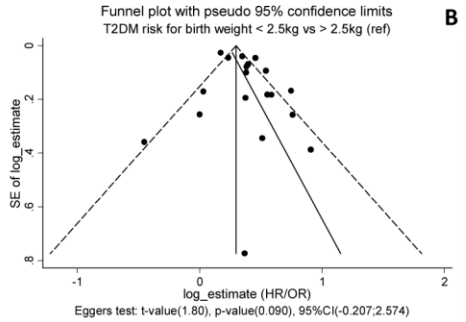
**Shape of association between birth weight and type 2 diabetes mellitus, cardiovascular disease and hypertension**

The circles represent the exponentiated log-transformed pooled risk estimate within two birth weight groups compared to the reference group (hollow circle). Birth weight is categorised as <2.5kg, 2.5-4.0kg, >4.0kg to construct A, B and C, and <2.5kg, 2.5-4.5kg, >4.5kg to construct D, E and F. n is the number of studies contributing to the pooled risk estimate. Risk estimate (95%CI) in plot **A**: <2.5kg (1.348 (1.241;1.457)) >4.0kg (0.898 (0.829;0.967)). Risk estimate (95%CI) in plot **B**: <2.5kg (1.274 (0.991;1.556)) >4.0kg (0.969 (0.894;1.044)). Risk estimate (95%CI) in plot **C**: <2.5kg (1.276 (1.152;1.401)) >4.0kg (1.217 (0.994;1.441)). Risk estimate (95%CI) in plot **D**: <2.5kg (1.407 (1.278;1.536)) >4.5kg (1.094 (0.953;1.235)). Risk estimate (95%CI) in plot **E**: <2.5kg (1.136 (1.009;1.262)) >4.5kg (1.126 (0.991;1.262)). Risk estimate (95%CI) in plot **F**: <2.5kg (1.248 (1.169;1.326)) >4.5kg (1.000 (0.841;1.159)).

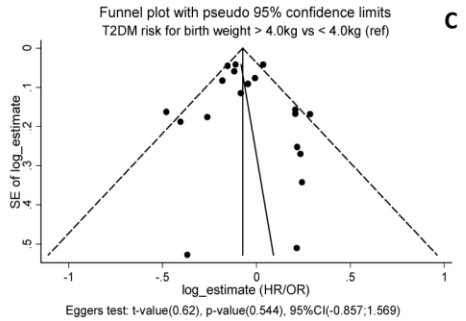
Type 2 diabetes mellitus




Eggers test: t-value(-1.20), p-value(0.239), 95%CI(-1.756;0.455)

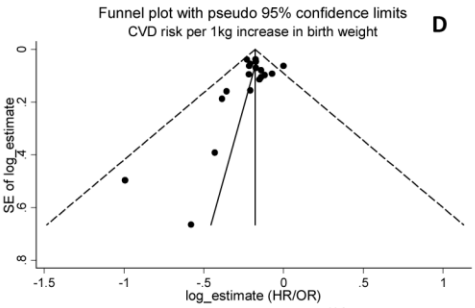



Eggers test: t-value(1.80), p-value(0.090), 95%CI(-0.207;2.574)

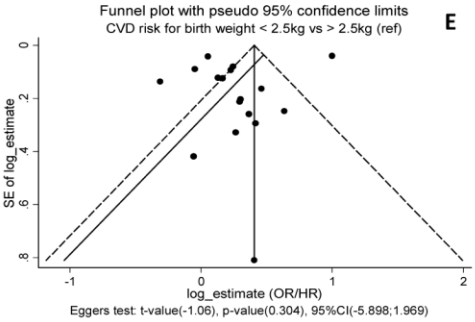



Eggers test: t-value(0.62), p-value(0.544), 95%CI(-0.857;1.569)
Risk_est (original): 0.94(0.87; 1.01), Risk_est (Trim and Fill(2)): 0.92(0.86;0.99)

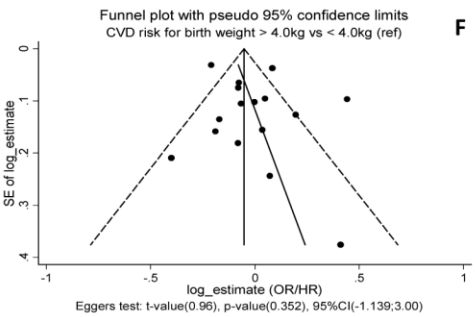
Cardiovascular disease




Eggers test: t-value(-0.459), p-value(0.318), 95%CI(-1.401;0.482)
Risk_est (original): 0.84(0.81; 0.86), Risk_est (Trim and Fill(0)): 0.84(0.81;0.86)

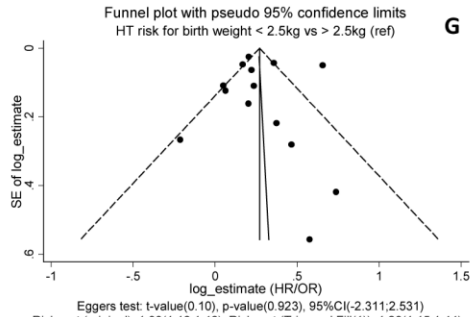



Eggers test: t-value(-1.06), p-value(0.304), 95%CI(-5.898;1.969)

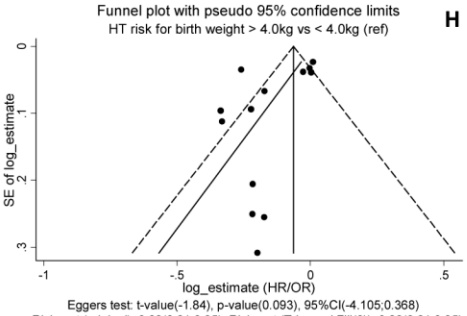



Eggers test: t-value(0.96), p-value(0.352), 95%CI(-1.139;3.00)

Hypertension




Eggers test: t-value(0.10), p-value(0.923), 95%CI(-2.311;2.531)
Risk_est (original): 1.30(1.16;1.46), Risk_est (Trim and Fill(1)): 1.29(1.15;1.44)




Eggers test: t-value(-1.84), p-value(0.093), 95%CI(-4.105;0.368)
Risk_est (original): 0.88(0.81;0.95), Risk_est (Trim and Fill(0)): 0.88(0.81;0.95)

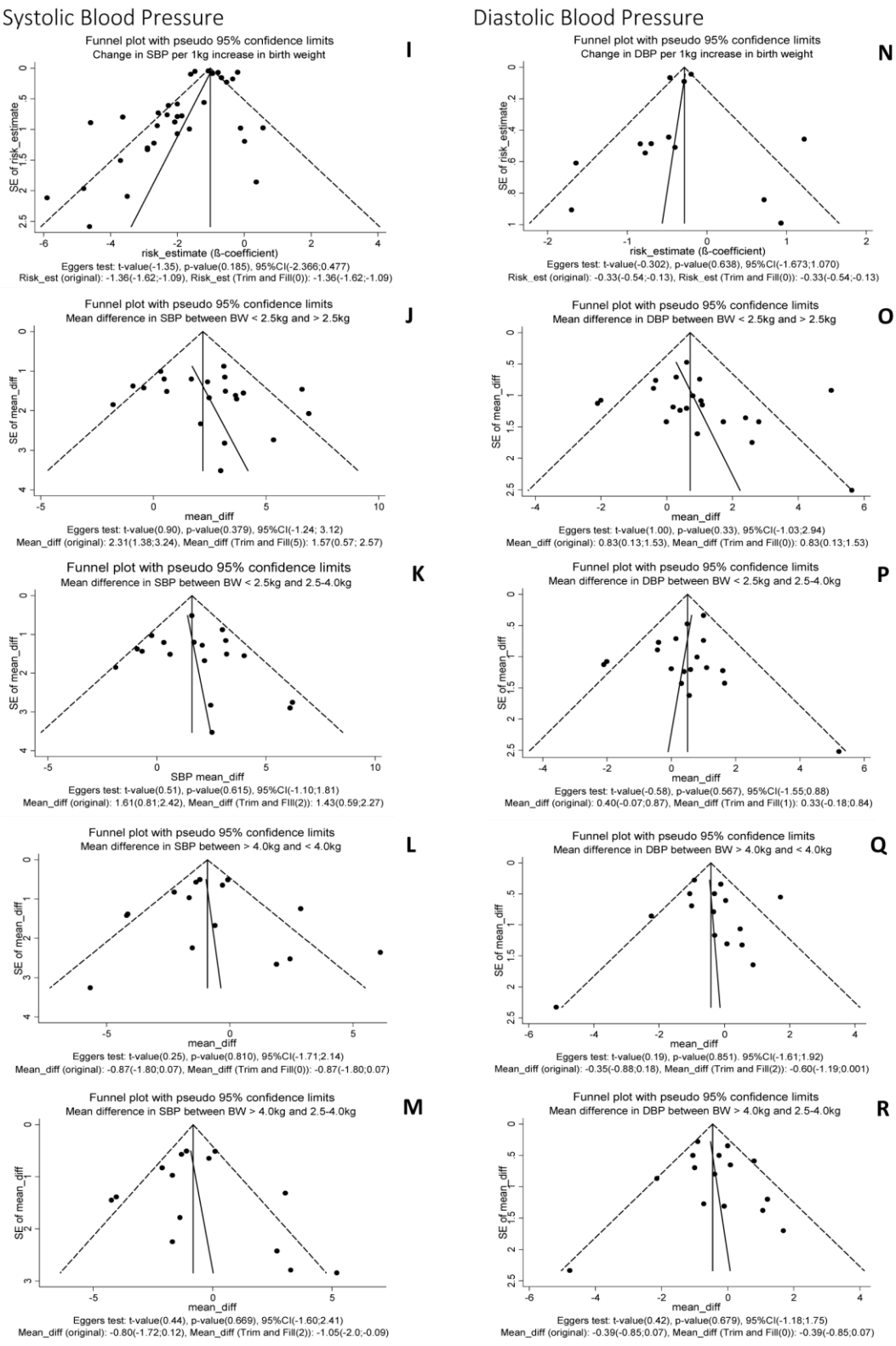



**Figure S4. Funnel Plots**

Funnel plot and Eggers test for all meta-analysis containing more than 10 studies. Fill and Trim estimates are provided for plots that appears asymmetrical regardless of results from eggers test.

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