Current Atherosclerosis Reports (2020) 22: 12
https://doi.org/10.1007/s11883-020-0829-z

EVIDENCE-BASED MEDICINE, CLINICAL TRIALS AND THEIR INTERPRETATIONS (L. ROEVER, SECTION EDITOR)

Birth Weight and Risk of Cardiovascular Disease Incidence in Adulthood: a Dose-Response Meta-analysis

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Published online: 23 April 2020

Abstract

Purpose of Review Studies have revealed a relation between birth weight (BW) and later risk of cardiovascular diseases (CVDs). This meta-analysis aimed to report the dose-response relationship between BW and risk of CVDs.

Recent Findings The relation of BW to CVD subtypes was found to be U-shaped as BW below ~ 2500 g and above ~ 4000 g affected positively CVD risk (OR = 1.14 = 95%CI 1.03–1.27 and OR = 1.08; 95%CI 0.99–1.18, respectively). Regarding CVD subtypes, low BW was directly linked to greater risk of CHD (OR = 1.15; 95%CI 1.02–1.29) and stroke (OR = 1.28; 95% CI 1.05–1.55), while high BW was related to increased risk of arterial fibrillation in adulthood. A U-shaped nonlinear relationship was specifically demonstrated between BW and overall CVD and its subtypes.

Summary There is a U-shaped association between BW and all CVD subtypes.

Keywords Birth weight · Cardiovascular diseases · Coronary heart disease · Myocardial infarction · Meta-analysis

Introduction

Prenatal and postnatal life can have profound impacts on the programming of intracellular signals, cell-to-cell interactions, and metabolic pathways [1]. The "developmental origins of adult disease" hypothesis, known as "Barker hypothesis," claims that adverse influences early in development, especially during intrauterine life, could lead to permanent changes in metabolism and physiology, which result in elevated susceptibility to adulthood chronic diseases [2]. A baby's nourishment before birth and during infancy," as manifest in patterns of fetal and infant growth, programs the development of risk factors involving in the pathophysiology of cardiovascular disease [3]. Strong body of evidences had confirmed that undernutrition and subsequent slow growth in utero can change body functions and metabolisms and enhance weight gain during childhood, which leads to an increased risk of CVD in later life [4, 5]. Although there is evidence that

This article is part of the Topical Collection on *Evidence-Based Medicine, Clinical Trials and Their Interpretations*

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excessive energy supply to the fetus or infant, manifested as high birth weight (HBW), also has adverse health consequences [6], prior studies have proposed that birth weight (BW) had an inverse relationship with the risk of myocardial infarction (MI), [7] ischemic heart disease (IHD), [8] CHD, type 2 diabetes mellitus, [9] stroke [10], and coronary artery diseases (CAD) [11] in adulthood. Nonetheless, the findings of some studies revealed that BW is positively linked to relatively greater risk of CAD in males [12]. On the contrary, other reports presented that BW was not significantly associated to the later CHD or CVD mortality and morbidity [13, 14]. Besides, a cohort study on Danish men proposed that abnormal birth weight, whether less or more than normal ranges, contributed to increased risk of CHD [15]. Recently, a meta-analysis of prospective cohort studies reported that there was an remarkable association between risk of CHD and LBW, as 1 kg more birth weight can reduce 10–20% of CHD risk [16••].

As exposure to undernutrition or overnutrition during infancy, manifested by birth weight, results in the susceptibility to metabolic complication in adulthood, some studies have tried to reveal the relation of BW to CVD risk; however, previous studies have yielded inconsistent results. Moreover, the hypothesis of the possibility of nonlinear association between BW and CVD risk has not yet been described. Accordingly, this dose-response meta-analysis of all available observational studies was performed to assess the association between BW and risk of CVD incidence, including CHD, stroke, arterial fibrillation (AF), and myocardial infarction (MI).

Methods

Literature Search Strategy

This meta-analysis was performed and reported according to recommendations of the MOOSE (Meta-analysis of Observational Studies in Epidemiology) group. We undertook a systematic search of EMBASE (http://www.embase.com) and PubMed (http://www.ncbi.nlm.nih.gov/pubmed) through February 2018 for studies related to BW and CVD. The following search terms were entered in the database searches: birth weight, cardiovascular, coronary artery disease, coronary heart disease, ischemic heart disease, myocardial infarction, angina, atrial fibrillation, and stroke. In addition, Reference lists of all relevant articles and identified reviews were inspected to identify pertinent articles that could have been missed in the initial search. The PICOS (Participants, Intervention/exposure, Comparison, Outcomes, Study design) criteria used to define the research question are shown in Table 1.

Study Selection

Studies were included if they met the following criteria: (1) were observational studies, (2) reported diagnosis criteria for CVDs (including CHD, MI, AF, and stroke), and (3) reported relative risk (RR), odds ratio (OR), or hazards ratio (HR) estimates and 95% CIs (or data can be calculated) describing the relationship between BW and risk of CVDs. Incident CVD was primarily defined as a confirmed diagnosis of myocardial infarction, coronary heart disease, and stroke. Of note, atrial fibrillation was also included in the cardiovascular category because the number of studies with this condition was small and we aimed to comprehensively explore the relation of BW to cardiovascular-related outcomes (in case of availability of data) [17]. We excluded (1) no original data (editorials, reviews, meta-analyses), (2) studies that were on twins, (3) studies written in languages other than English, and (4) studies that investigated mortality instead of incidence. In the case of multiple reported papers from the same study, only those with the longest follow-up times or the highest number of cases were included in the meta-analysis.

Data Extraction and Quality Assessment

Two reviewers independently extracted data from the eligible studies using a standard form, which included the first author's name, publication year, geographical location, sample size, mean or range of age, study design, source of cohort, duration of follow-up, source of BW data, cardiovascular outcomes, and covariates adjusted for in analyses. For information that was not reported in the published studies, the corresponding author was directly contacted to get the related data. Finally, we evaluated study quality by using the nine star Newcastle–Ottawa Scale (NOS) for observational studies

Table 1 PICOS criteria for inclusion and exclusion of studies

Parameters	Description
Participants	Adults
Intervention/exposure	Low or high birth weight
Comparison	Subjects with normal birth weight
Outcomes	Risk of cardiovascular disease and its subtypes including coronary heart disease (CHD), atrial fibrillation (AF), myocardial infraction (MI), and stroke
Study design	Cohort and cross-sectional studies

[18]. It allows evaluating methodological quality in three main domains: selection, comparability, and exposure/outcome.

Statistical Analysis

For meta-analysis, risk estimates and 95 confidence intervals (CIs) for dichotomous outcomes from each study were pooled. Initially, we assessed the relation of LBW (BW < 2500 g vs. BW > 2500 g) and HBW (BW > 4000 g vs. BW < 4000) to the risk of CVDs and CVD subtypes. Then, we carried out a dose-response analysis using the nonlinear model. The mean or median BW in each category was assigned to the corresponding dose of the BW. The midpoint of the lower and upper bound was estimated as the dose of each category if the mean or median BW for each category was not provided. When the extreme categories were open-ended, the midpoint of these categories was calculated by assuming the length of the interval was the same as that of the adjacent interval. To assess a potential nonlinear dose-response relationship between BW and the risk of CVD, we used a restricted cubic spline regression analysis with 3 knots at 10%, 50%, and 90% percentiles of the distribution [19]. A *P* value for nonlinearity was obtained by testing against the null hypothesis that the coefficient of the second spline was equal to zero [20].

Heterogeneity among studies was evaluated using the Q statistic (considered significant at $P < 0.10$) and I^2 metric to quantify the extent of statistical heterogeneity. We considered values of I^2 of 50–75% as "moderate heterogeneity" and > 75% as "high heterogeneity" according to Higgins et al.'s proposal [21]. A fixed-effects approach was used to calculate the combined risk estimates in the absence of heterogeneity; otherwise, if there was evidence of significant heterogeneity among studies, a DerSimonian-Laird random effect model was used [22]. Small-study effects, such as publication bias, were evaluated using visual inspection of funnel plots and Egger's and Begg's tests. STATA version 12.0 software (College Station, TX, USA) was used for the analyses. All statistical tests were two sided with a significance level of 0.05.

Results

Studies Characteristics

Figure 1 displays the process of selection of studies. A total of 7034 nonduplicate records were identified through previously mentioned literature search strategy. After excluding 6980 papers on the basis of titles and abstracts, 54 full-text articles were identified for detailed examination. Of the full texts, 30 were excluded, mainly because they were reviews, duplicated reports, or did not reported sufficient data for analysis; a total of 24 articles were finally included in the present meta-analysis. Sixteen studies reported BW only as a categorical variable and seven articles reported BW as both a continuous variable [11, 14, 23–37] and a categorical variable [38–44]. The studies were mainly derived from Europe (*n* = 16) [11, 23, 24, 26–28,

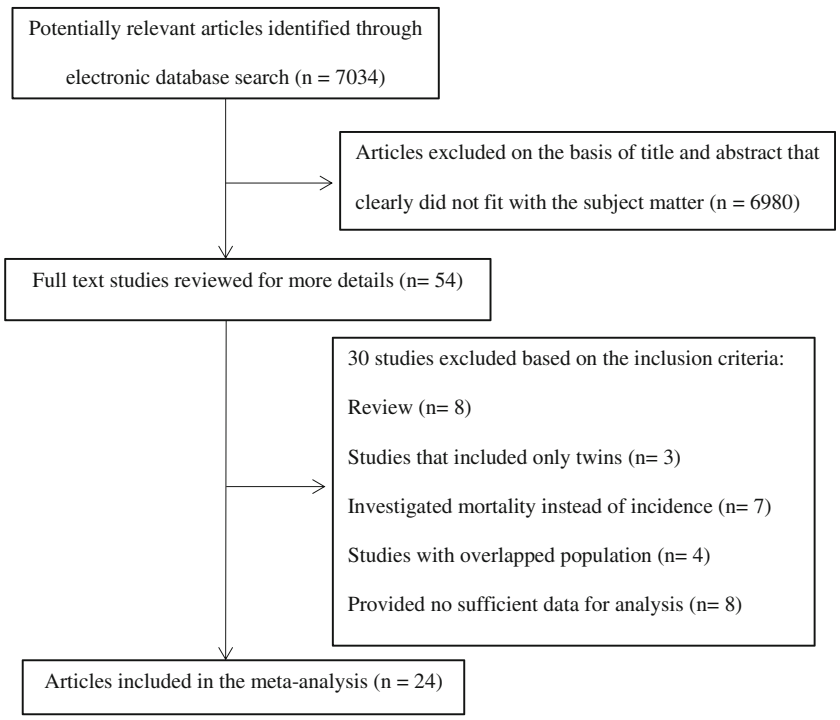

Fig. 1 Literature search for the meta-analysis

29••, 31, 32••, 37–42, 44••], followed by North America (n = 5) [25, 30••, 33, 34••, 43] and Asia (n = 3) [14, 35, 36••]. All included studies ascertained CVD by clinical examination and medical records. According to the Newcastle-Ottawa Quality Assessment Scale, twenty-two studies received scores of 6 or higher and were considered to be of high quality. The study characteristics are summarized in Table 2.

Birth Weight and Cardiovascular Disease Risk

Because sufficient dichotomous data for BW and CVD were not available for 6 articles, these studies could not be included in the meta-analysis [32••, 34••, 38, 40–42]. The remaining 17 articles [11, 14, 23–31, 33, 35, 36••, 37, 39••, 43, 44••] were included in the meta-analysis. Sixteen studies [14, 23–31, 33, 35, 36••, 37, 39••, 43, 44••] analyzed the risk of CVD in subjects with LBW (BW < 2500 g) compared with that of subjects with BW > 2500 g. Results from this analysis indicated a positive association between LBW and total CVD (OR = 1.14; 95% CI 1.03–1.27, P = 0.02). Data from these studies were assessed using the random effects model (I^2 = 59.9%, P < 0.01) (Fig. 2; Table 3). Pooled analysis of 11 studies [11, 23, 25, 26, 28, 29••, 30••, 31, 36, 39••, 44••] showed that HBW (BW > 4000 g), compared with BW < 4000 g, was marginally associated with increased risk of CVD (OR, 1.08; 95% CI 0.99–1.18, P = 0.08), and this effect was observed using the random effects model (I^2 = 62.7%, P < 0.01) (Fig. 3; Table 3).

The relation between BW and total CVD events was found to be U-shaped with the use of a restricted cubic model (P nonlinearity < 0.001) (Fig. 4). At BW below ~2500 g, there was a higher risk of CVD compared with higher BW. BW between ~3000 and 4000 g conferred the lowest risk of CVD. By contrast, at BW above ~4000 g, a higher BW was progressively associated with a higher risk of CVD.

Visual inspection of funnel plots did not reveal substantial asymmetry and Egger's (P = 0.216 for studies comparing BW < 2500 g vs. BW > 2500 g; P = 0.981 for studies comparing BW > 4000 g vs. BW < 4000) and Begg's test (P = 0.51 for studies comparing BW < 2500 g vs. BW > 2500 g; P = 0.93 for studies comparing BW > 4000 g vs. BW < 4000) for publication bias were not statistically significant for studies investigating the relationship between high and low BW with CVD risk.

Birth Weight and Risk of Cardiovascular Disease Subtypes

Table 3 shows the meta-analyses of the association between BW and CVD subtypes, including CHD, AF, MI, and stroke. LBW (BW < 2500 g vs. BW > 2500 g) was associated with an increased risk of CHD (12 studies [14, 23, 24, 27, 28, 31, 33, 35, 37, 39, 43, 44]; OR = 1.15; 95% CI 1.02–1.29, P = 0.02) and stroke (2 studies [26, 43]; OR = 1.28; 95% CI 1.05–1.55, P = 0.01), but not with AF and MI. Furthermore, HBW (BW > 4000 g vs. BW < 4000) was associated with a higher risk of AF (2 studies [29••, 30••]; OR = 1.11; 95% CI 1.03–1.20, P = 0.008), while no significant association was observed with CHD, MI, and stroke (Table 3).

Also, there was a significant evidence of a U-shaped association between BW and all investigated CVD subtypes, including CHD (16 studies [11, 14, 23, 24, 27, 28, 31, 32••, 33, 35, 37, 38, 39••, 41–43]; P nonlinearity < 0.001), AF (3 studies [25, 29••, 30••]; P nonlinearity < 0.001), MI (3 studies [32••, 33, 44••]; P nonlinearity = 0.01), and stroke (3 studies [26, 42, 43]; P nonlinearity = 0.002) in nonlinear dose-response meta-analysis (Fig. 4).

Discussion

Existing empirical and meta-analysis studies have shown that birth weight influences the risk of CVD during adulthood. However, there is no study on the dose-response relationship between birth weight and risk of CVD. Thus, this study was aimed primarily to investigate the dose-response relationship between birth weight and CVD in general as well as its specific forms. We also provided summary estimates on the extent of association of BW with various forms of CVDs. We found that LBW is significantly associated with overall CVD, CHD, and stroke. There were increments of 14%, 15%, and 28% in the odds of overall CVD, CHD, and stroke, respectively, in individuals with a history of LBW, compared with individuals of no history of LBW. HBW was also associated with a higher risk of CVD and AF. There were increments of 8% and 11% in the odds of overall CVDs and AF, respectively. We also observed a nonlinear relationship between BW and overall CVDS. A U-shaped association was specifically demonstrated between BW and all of the conditions assessed, such that the risk of CVD increases as BW decreases further below 2500 g and also increases further above 4000 g. Individuals with BW 3000–4000 g demonstrated the least CVD risk. Our finding that LBW is associated with various CVD conditions is consistent with previous studies. In their meta-analysis, Wang et al. [16••] reported a higher risk of CHD in individuals born with BW of < 2500 g, compared with individuals born with BW > 2500 g. The same findings were also reported by various empirical studies [45, 46]. Our finding of a greater risk of CVD associated with HBW is in concordance with most of the existing evidence [45], though in disagreement with the report of the work by Wang et al. [16••]. They found a lower risk of CHD in HBW individuals, compared with both LBW and NBW individuals. Provided both undernutrition and overnutrition could result in deranged nutritional metabolism, including insulin resistance [47, 48•, 49], we believe our finding is of a plausible biological rationale. The adverse effects of LBW are not limited to cardiovascular outcomes, but have

Table 2 Characteristics of studies included in the meta-analysis

First author	Year	Country	Total number of subjects/ gender	Age (year)		Year of study baseline	Study design	Birth weight ascertainment method	BW reference category (g) for adjusted estimate	Cardiovascular outcomes	CVD ascertainment method	Quality score
Fall	1995	England, Hertfordshire	290 M	Mean 66-.8	1920–30	–	Cohort study	Hospital birth records	2495≤ 2495–2948 2948–3402 3402–3856 3856–4309 > 4309	42 CHD	Clinical examina-tions	6
Stein	1996	India, Mysore	517 M and F	38–60	1934–54	1993	Cross-Sectional	Hospital birth records	2268≤ 2268–2495 2495–2722 2722–2948 2948–3175 > 3175	52 CHD	Clinical examina-tions	6
RichEdwards	1997	USA	70,297 F	30–55	1921–46	1976–92	Cohort study	Recall	2268 < 2268–2495 2495–3175 31,753,856 38,564,536 > 4536	889 CHD 364 Stroke	Medical records	8
Eriksson	2000	Finland, Helsinki University Central Hospital	3639 M	45–64	1924–33	1971–95	Cohort study	Hospital birth records	2500≤ 2501–3000 3001–3500 3501–4000 > 4000	331 Stroke	Medical records	7
Hypponen	2001	Sweden, Uppsala	10,853 M and F	–	191,529	1970–91	Cohort study	Hospital birth records	2750 < 2750–3249 3250–3749 3750–4249 ≥4250	991 Stroke	Medical records	6
Gunnarsdottir	2002	Iceland, Greater Reykjavik	4775 M and F	Mean 5-0 ± 8	1914–35	1967–97	Cohort study	Midwives' birth records	3450≤ 3450–3750 3750–4000 > 4000	574 CAD (MI)	Medical records	8
Lawlor	2004	United Kingdom	1394 F	60–79	–	1999–2001	Cross-Sectional	Recall	1500–3060 3070–3640 3650–4570	199 CHD	Medical records and self-report	5
Eriksson	2004	Sweden, Gothenburg	1319 M	20–85	1913	1969–98	Cohort study	Birth records	3000≤ 3001–4249 ≥4250	859 CVD 502 CHD	Medical records	9
RichEdwards	2005	USA	66,111 F	30–55	1921–46	1976–2000	Cohort study	Recall	2268 < 2268–2495 2495–3175 31,753,856 38,564,536	1504CHD 1164Stroke	Medical records	8

Table 2 (continued)

First author	Year	Country	Total number of subjects/ gender	Age (year)		Year of study baseline	Study design	Birth weight ascertainment method	BW reference category (g) for adjusted estimate	Cardiovascular outcomes	CVD ascertainment method	Quality score
Lawlor	2005	Scotland, Aberdeen	10,803 M and F	–	1950–56	1981–2003	Cohort study	Birth records	> 4536 3250 < 3250–3749 3750–4249 ≥ 4250	296 CHD 107 Stroke	Medical records	9
Kaijser	2008	Sweden	6425 M and F	–	1925–49	1987–2002	Cohort study	Midwives' birth records	1500< 1500–1999 2000–2499 2500–2999 3000–3499 3500–3999 > 4000	617 IHD	Medical records	9
Yang	2008	Sweden	49,259 F	30–50	1941–1961	1991–2003	Cohort study	Recall	2500< 3000–2500 > 3000	256 CHD	Medical records	7
Banci	2009	Italy, Rome	127 cases 395 controls M and F	–	1968–1972	–	Case-Control	–		CAD	Medical records	5
Osler	2009	Denmark, Copenhagen	9143 M	25–52	1953	1978–2005	Cohort study	Birth records	<2500 2500–3999 > 4000	475 CHD	Hospital records	8
Andersen	2010	Nordic (Denmark & Finland)	216,771 M and F	–	Denmark 1936–76 Finland 1924–44	Denmark 1977–2001 Finland 1971–2003	Cohort study	Denmark: Mothers reported Finland: Hospital Birth records	2000–2500 2501–3000 3001–3500 3501–4000 4001–4500 4501–5000 5001–5500	8805 CHD	Medical records	7
Conen	2010	USA	27,982 F	> 45	?	1993–2009	Cohort study	Recall	<2500 2500–3200 3200–3900 3900–4500 ≥4500	735 AF	Medical records	7
Fan	2010	China, Beijing	2033 M and F	50–84	1921–54	2002–04	Cohort study	Birth records	<2500 2500–3000 3000–3500 ≥ 3500	135 CHD	Clinical examina-tions	8
Rajaleid	2011	Sweden, Stockholm	1058 cases 1478 controls M and F	45–70	–	1992–1994	Case-Control	Birth records	<2750 2750–3249 3250–3749 3750–4249 > 4250	MI	Hospital records	7

Table 2 (continued)

First author	Year	Country	Total number of subjects/ gender	Age (year)		Year of study baseline	Study design	Birth weight ascertainment method	BW reference category (g) for adjusted estimate	Cardiovascular outcomes	CVD ascertainment method	Quality score
Heshmati	2014	Sweden, Uppsala	10,503 M and F	–	1915–29	1964–2008	Cohort study	Birth records	≤ 2500 2501–3000 3001–3500 3501–4000 > 4000	3631 IHD	Hospital records	7
Lawani	2014	USA	10,132 M and F	45–64		1996–2008	Cohort study	Recall	<2500 2500–4000 > 4000	882 AF	Medical records	6
Zöller	2014	Sweden	1,970,869 M and F	18–38	1973–92	1973–2010	Cohort study	Birth records	<2500 2500–4000 > 4000	668 IHD	Hospital records	8
Larsson	2015	Sweden, Västmanland and Örebro	29,551 M 23,454 F		1918-52 M 1914-48F	1998–2009	Cohort study	Recall	<1500 1500–2499 2500–3999 4000–4999 ≥5000	(2711 M; 1491 F) AF	Medical records	7
Smith	2016	USA	71,453 F	50–79	–	–	Cohort study	Recall	<2720 2720–3600 3600–4540 ≥4540	970 CVD	Medical records	6
Tian	2017	China	745 M and F	18–76		2002–2014	Cohort study	Birth records	<2500 2500–3999 ≥4000	83 CVD	Medical records	7

F, female; *M*, male; *CHD*, coronary heart disease; *AF*, atrial fibrillation; *MI*, myocardial infarction; *CVD*, cardiovascular disease; *IHD*, ischemic heart disease

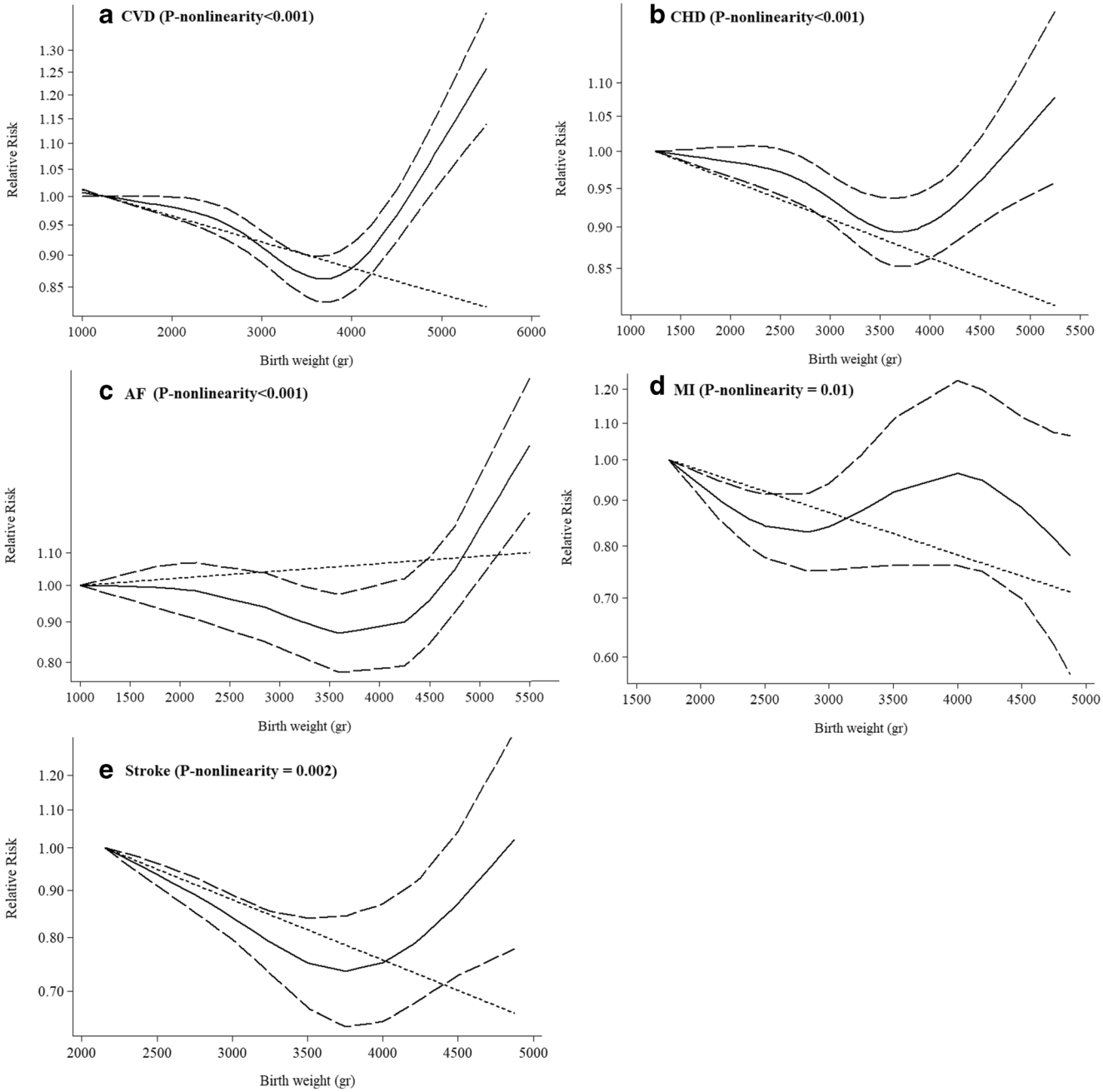

Fig. 2 Pooled analysis of CVD risk in subjects with LBW (BW < 2500 g) compared with subjects with BW > 2500 g

also been linked to a variety of other poor health and nutritional outcomes.

A number of potential mechanisms have been suggested to explain the link of BW with the risk of CVD in adults [48•]. The most widely mentioned and highly likely mechanism is related to the "developmental origins of adult disease" hypothesis which states adverse influences during early stages of life could result in irreversible metabolic, physiologic, and structural changes, some of which become disadvantageous by increasing the risk of negative health outcomes late in life [48•, 50–53]. Permanent alteration of postnatal metabolic and physiologic states of animals has been demonstrated by manipulating maternal diet during pregnancy. In these studies, exposure to global undernutrition or specific nutrient deficiency during early stages of life resulted in impaired glucose tolerance, high blood pressure, and LBW [48•, 54]. Nutritional stress during pregnancy has also been hypothesized to result in excess production of glucocorticoid; the exposure of it has been associated with a permanently reduced number of hypothalamic glucocorticoid receptors and subsequently impairment in hypothalamic–pituitary–adrenal hormonal feedback mechanism [48•]. Impairment in

Table 3 Meta-analysis of the association between birth weight and cardiovascular

	Studies (*n*)		Meta-analysis				Heterogeneity	
			OR	95% CI		P^*	I^2	p^a
CVD								
BW < 2500 vs BW > 2500	16	R	1.14	1.03	1.27	0.02	59.9	< 0.01
BW > 4000 vs BW < 4000	11	R	1.08	0.99	1.18	0.08	62.7	< 0.01
CHD								
BW < 2500 vs BW > 2500	12	R	1.15	1.02	1.29	0.02	46.7%	0.043
BW > 4000 vs BW < 4000	6	F	1.04	0.98	1.10	0.16	37.5%	0.156
AF								
BW < 2500 vs BW > 2500	3	R	1.02	0.77	1.37	0.87	79.8%	0.007
BW > 4000 vs BW < 4000	2	F	1.11	1.03	1.20	0.008	0.0%	0.940
MI								
BW < 2500 vs BW > 2500	2	R	1.59	0.66	3.82	0.30	90.5%	0.001
BW > 4000 vs BW < 4000	1	–	0.83	0.58	1.19	0.31	–	–
Stroke								
BW < 2500 vs BW > 2500	2	F	1.28	1.05	1.55	0.01	0.0%	0.612
BW > 4000 vs BW < 4000	1	–	0.92	0.65	1.31	0.65	–	–

*P**, *p* value for association; P^a, *p* value for heterogeneity; *R*, random effects; *F*, fixed-effects; *CVD*, cardiovascular disease; *CHD*; coronary heart disease; *AF*, atrial fibrillation; *MI*, myocardial infarction

hypothalamic-hormonal feedback mechanism could lead to glucose intolerance as well as other adverse health conditions. Besides these fetal programming and glucocorticoids mechanism, nephrogenic, neurogenic [55], genetic, and epigenetic influences [46, 48•, 49] have also been implicated. Despite the evidence which is not clear on which of the proposed mechanism is largely responsible for the link of BW to CVD, it could, however, be presumed that those born with abnormal

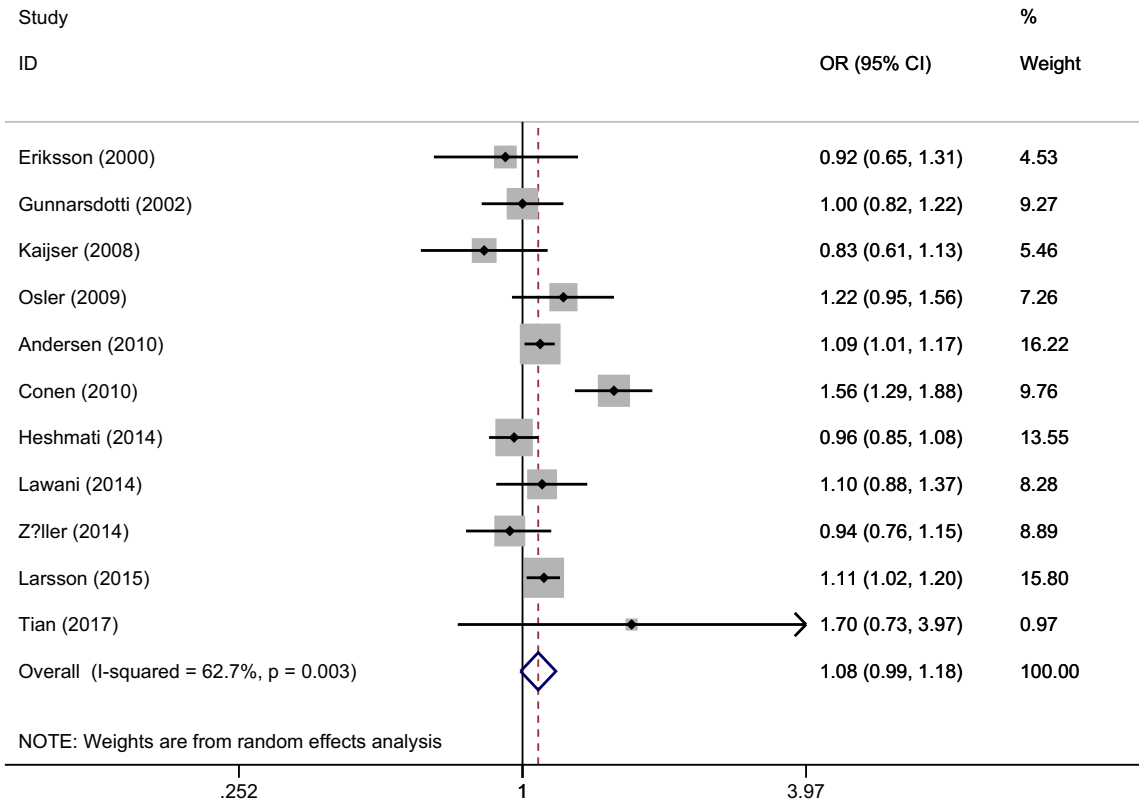

Fig. 3 Pooled analysis of CVD risk in subjects with HBW (BW > 4000 g) compared with subjects with BW < 4000 g

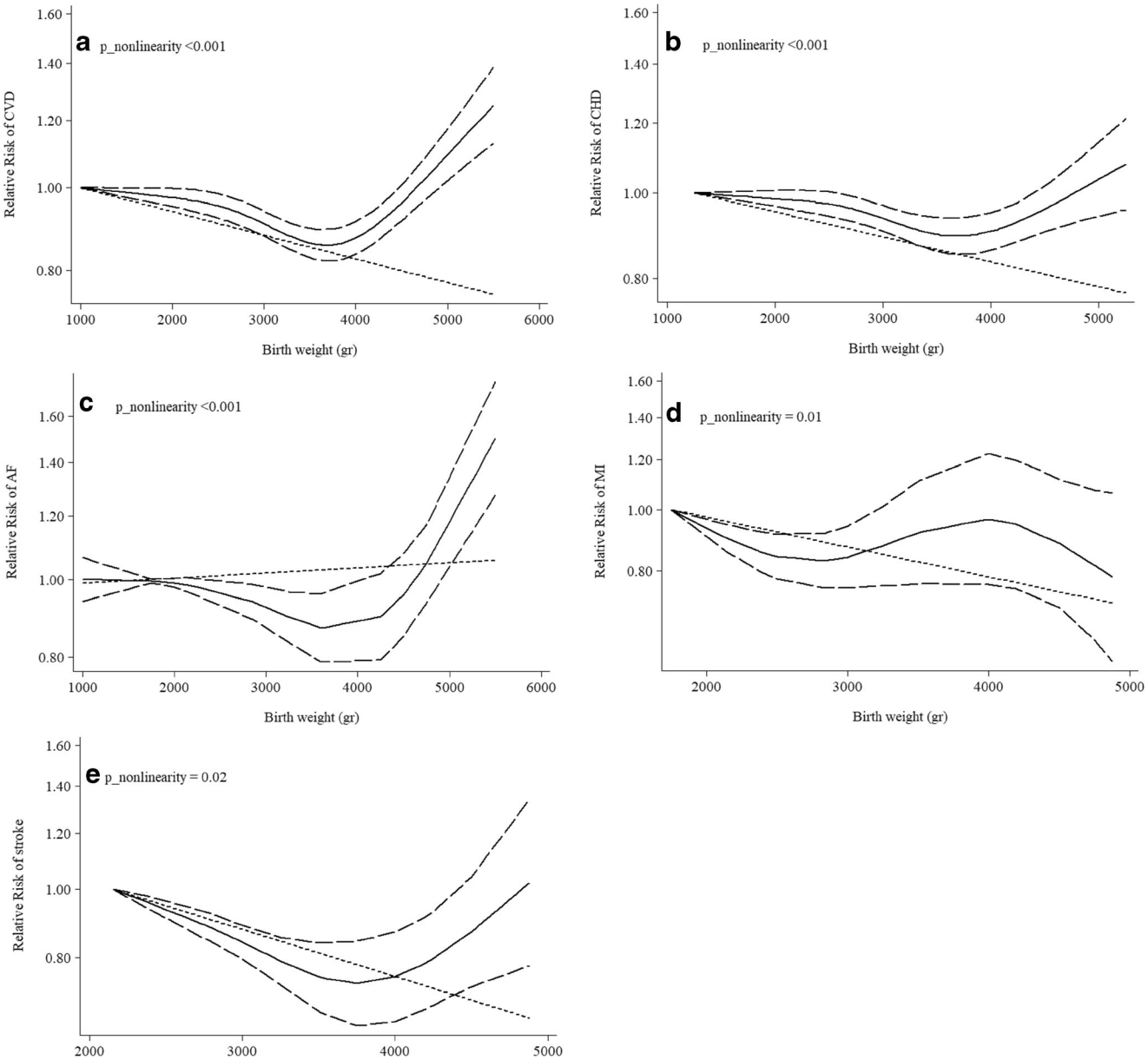

Fig. 4 Nonlinear dose-response association between birth weight and risk of cardiovascular disease (**a**), coronary heart disease (**b**), arterial fibrillation (**c**), myocardial infarction (**d**), and stroke (**e**)

BW would also have impaired metabolism and glucose intolerance and hypertension. These conditions, in turn, will increase the risk of CVD events.

Policy and Research Implications

LBW remains a major public health problem, particularly in developing countries [56]. Evidence shows that children born with LBW have low survival and wellbeing. They have a higher risk for childhood morbidity and mortality and also poor cognitive and motor development [57]. Thus, the World Health Organization has already prioritized LBW as a central global agenda and aimed a 30% reduction in its prevalence over the period 2012–2025 [56]. While LBW by itself poses a significant burden on the health system, its association with a higher risk of CVD is more concerning. CVDs are among the top contributors to health impairment globally, in both developing and developed nations. Like reducing BW, combating CVDs is also a global public health agenda [58]. Thus, the promotion of optimal BW in general and the prevention of LBW, in particular, might have dual benefits, reducing the burden of poor health outcomes during childhood and cardiovascular diseases during adulthood.

Thus, the existing LBW prevention programs might be viewed and emphasized not only to ensure wellbeing during childhood, but also to prevent cardiovascular incidents in adulthood and promote healthy aging.

Studies on the association of LBW with CVD are limited by geographic area. The existing estimates are based on studies conducted mainly in western countries where the prevalence of LBW is low, and child care is better, compared with some regions of Asia and Africa where the burden of LBW is high, and child care practices are still below the acceptable levels. Thus, presuming LBW increases the risk of CVD and other competing risk factors remain the same, it could be presumed that developing countries would bear an extract risk of CVDs. Thus, public health authorities and policymakers of nations with high LBW need to note the extra CVD risks and design mitigation efforts, including health-enhancing lifestyle interventions. Designing a system of early screening CVDs for individuals with a history of LBW would also stand worthy of consideration. However, there is no study on the effectiveness of screening programs in reducing the extra risk of chronic diseases in LBW adults. Thus, further studies are warranted to explore strategies to mitigate the extra CVD risk associated with LBW, including the feasibility of incorporating screening programs into the existing health system.

Strength and Limitations

Strengths of this meta-analysis include the comprehensive analyses of different categories or ranges of BW in relation to various cardiovascular disease outcomes including overall CVD, CHD, AF, MI, and stroke; detailed subgroup analysis, nonlinear dose-response analysis; inclusion of large number of studies covering a large number of individual participants; and the high quality of the studies included. The study also has important limitations worthy of mentioning. First, there was a high level of between studies heterogeneity, most of which could not be avoided even after subgroup analysis. However, our use of random effect meta-analysis models could have reduced the problem of heterogeneity. Second, we compared the risk of HBW in reference to BW < 4000 g. This could be problematic as BW < 4000 includes both NBW and LBW. BW 2500–4000 as a reference of comparison would have provided a better estimate. Third, we cannot exclude that our meta-analysis was underpowered to detect a significant difference in MI risk by BW because of the small number of studies included in the BW-MI subgroup analysis. Fourth, in this study, observational studies were included. Thus, causal inference could not be made on the relation of BW with any of the CVD outcomes assessed.

Conclusion

This meta-analysis revealed that LBW is significantly related to increased risks of CVD, CHD, and stroke, whereas HBW is associated with a higher risk of CVD and AF in adulthood. In nonlinear dose-response analyses, a U-shaped association was identified between BW and CVD, CHD, MI, AF, and stroke, such that the risk increased as BW decreases further below 2500 g and also increases further above 4000 g. In order to reach a robust conclusion, further prospective cohort studies are required to assess the relation of BW to the risk of the incidence of MI, stroke, and AF in adulthood.

Compliance with Ethical Standards

Conflict of Interest Reza Mohseni, Shimels Hussien Mohammed, Maryam Safabakhsh, Fatemeh Mohseni, Zahra Sajedi Monfared, Javad Seyyedi, Zahra Noorani Mejareh, and Shahab Alizadeh each declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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