Available online at www.sciencedirect.com

ScienceDirect

Journal of the Chinese Medical Association 80 (2017) 44–49

www.jcma-online.com

Original Article

Relationship between birth weight and total cholesterol concentration in adulthood: A meta-analysis

Lian-Hui Chen [a,b], Shan-Shan Chen [c], Li Liang [a,*], Chun-Lin Wang [a], Caroline Fall [d], Clive Osmond [d], Sargoor R. Veena [e], Alexandra Bretani [f]

[a] *Department of Pediatrics, The First Affiliated Hospital of College of Medicine, Zhejiang University, Hangzhou, China*
[b] *Department of Pediatrics, The Second Affiliated Hospital of Fujian Medical University, Quanzhou, China*
[c] *Department of Intensive Care Unit, The First Hospital of Quanzhou Affiliated to Fujian Medical University, Quanzhou, China*
[d] *Medical Research Council Lifecourse Epidemiology Unit, University of Southampton, Southampton, UK*
[e] *Epidemiology Research Unit, CSI Holdsworth Memorial Hospital, Mysore, India*
[f] *Department of Pediatrics, Faculdade de Medicina da Universidade de Sao Paulo, Sao Paulo, Brazil*

Received July 8, 2015; accepted June 24, 2016

Abstract

Background: Although a substantial number of studies have investigated the relationship between birth weight and serum cholesterol later in life, the results vary extensively. The aim of this study was to explore the relationship between birth weight and total cholesterol concentration in adulthood.
Methods: We considered the results of several published observational studies that reported the association between birth weight and total cholesterol concentration in adulthood. The associations were assessed by linear regression coefficients. Summary regression coefficients with 95% confidence intervals (CI) were computed using random-effects models. Subgroup and sensitivity analyses were also conducted to explore possible explanations for heterogeneity among the studies.
Results: A total of 20 studies with 26,122 participants were identified. After adjustment for adult body mass index, the summary regression coefficient for an increment in birth weight of 1 kg was −0.09 mmol/L (95% CI: −0.13, −0.05) for men without heterogeneity ($I^2 = 17.2\%$) and −0.08 mmol/L (95% CI: −0.13, −0.03) for women with low heterogeneity ($I^2 = 34.0\%$). Stratified and sensitivity analyses generally confirmed the robustness of the findings in men. However, subgroup analyses by age indicated that the association of birth weight with total cholesterol was statistically significant only in women aged <50 years. There was no evidence of publication bias in these studies.
Conclusion: Based on our results, lower birth weight was found to be associated with higher concentrations of total cholesterol in men aged >18 years and in women aged <50 years.

Keywords: birth weight; cardiovascular diseases; cholesterol; meta-analysis

1. Introduction

Hypercholesteremia in adulthood is commonly known as an important risk factor for cardiovascular disease. To explore the origin of hypercholesteremia, numerous studies have investigated the effects of birth weight on serum cholesterol in later life, and some meta-analyses have been conducted to explore the association; however, the results are pronouncedly varied. Some studies reported that the association between birth

Conflicts of interest: The authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

* Corresponding author. Professor Li Liang, Department of Pediatrics, The First Affiliated Hospital of College of Medicine, Zhejiang University, 79, Qingchun Road, Hangzhou 310003, China.
E-mail address: pediatricschen@gmail.com (L. Liang).

http://dx.doi.org/10.1016/j.jcma.2016.08.001

weight and total cholesterol only existed in men or women,[1–3] whereas other studies suggested that the association was the same in both the sexes.[4] Additionally, the effect of age on this association should be considered.[5] However, none of the published meta-analyses studies focused on adult serum cholesterol; instead, they assessed the association across various age groups. Additionally, since the last meta-analysis was published, many new studies focusing on adults have been reported.[6–8] Therefore, a new meta-analysis of the relationship between birth weight and total cholesterol in adulthood is justified.

2. Methods

This meta-analysis was reported following the recommendations proposed by the Meta-analysis of Observational Studies in Epidemiology and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) groups.

2.1. Search strategy

We performed a literature search on the electronic databases PubMed (1966 to December 2013), Embase (1966 to December 2013), Web of Science (1972 to December 2013), Scopus (1971 to December 2013), BIOSIS Citation Index (1994 to December 2013), and LWW (Lippincott Williams & Wilkins, 1971 to December 2013). The search strategy consisted of title, abstract words, and subject headings related to birth weight and cholesterol. The search strategy was limited to humans, but not to study design. Additionally, references from relevant articles were reviewed to identify potential relevant studies.

2.2. Study selection

Two independent reviewers, Lianhui Chen (CLH) and Shanshan Chen (CSS), screened papers based on the following inclusion criteria: (1) observational studies; (2) there were no additional manipulations or complications during pregnancy; (3) participants were aged >18 years; (4) birth weight was the exposure of interest; (5) birth weight was not self-reported; and (6) total cholesterol was the outcome of interest. Discrepancies in the selection process were independently resolved by a third reviewer Li Liang (LL). The study selection process is summarized in the PRISMA flow diagram.

2.3. Data extraction and quality assessment

CLH extracted data using a standard form, which was checked by LL and CSS. The following were extracted from each included study: the year of publication, first author's name, study location, sample size, participants' sex, age at examination, regression coefficients between birth weight and total cholesterol, and adjustment for confounders. We thoroughly reviewed those studies without regression coefficients by sex and dispersion measures.[6–14]

We used the Newcastle–Ottawa Scale to quantitatively evaluate the methodological quality of the studies. Two reviewers (CLH and CSS) independently assessed all the eligible studies, and disagreements were resolved by a third reviewer (LL). Those studies with a score ≥7 were included in the final meta-analysis.

2.4. Statistical analyses

All statistical analyses were performed using STATA software (version 12.1; StataCorp, College Station, TX, USA). Heterogeneity among the studies was assessed using Q and I^2 statistics. A p value < 0.1 was considered to be statistically significant for the Q statistic. Heterogeneity was considered low, moderate, and high using I^2 values of 25%, 50%, and 75%, respectively. Linear regression coefficients were derived using random-effects models, because, unlike fixed-effect models, these account for sampling errors and possible heterogeneity between the studies. For studies that did not provide standard errors of regression coefficients, these were estimated from the p value or 95% CI.[3,4,10,15–18]

To explore the potential sources of heterogeneity and the effect of age on the associations, we performed stratified analyses according to participants' age. Additionally, studies were stratified by national income levels according to the World Bank classification. To test the influence of a single study on the summary regression coefficient, sensitivity analyses were performed by omitting each study in turn while pooling results from the remainders. Potential publication bias was examined by Egger's regression asymmetry test.

3. Results

3.1. Study characteristics

The course of the systematic review is illustrated in Fig. 1. In summary, a total of 20 studies were included in the meta-analysis. These studies were published between 1993 and 2013, and included a total of 13,358 male and 12,764 female participants.

Of the 20 studies, 16 were conducted in high-income, two in upper-middle-income, and the remaining studies in lower-middle-income countries. Eight of the studies involved participants aged 50–76 years, and the other studies involved participants aged 18–50 years. The majority of studies included both sexes (85%) and presented a sample size below 1000 participants (65%).

3.2. Quality assessment

After the quality assessment was completed, two studies were considered to be of low methodological quality (scores ≤ 6) and excluded from the final meta-analysis. Since we excluded the studies that had birth weight self-reported in the selection process, most of the studies (82%) received a full score in the selection scale, which was based on the representativeness of subjects and ascertainment of exposure. In the

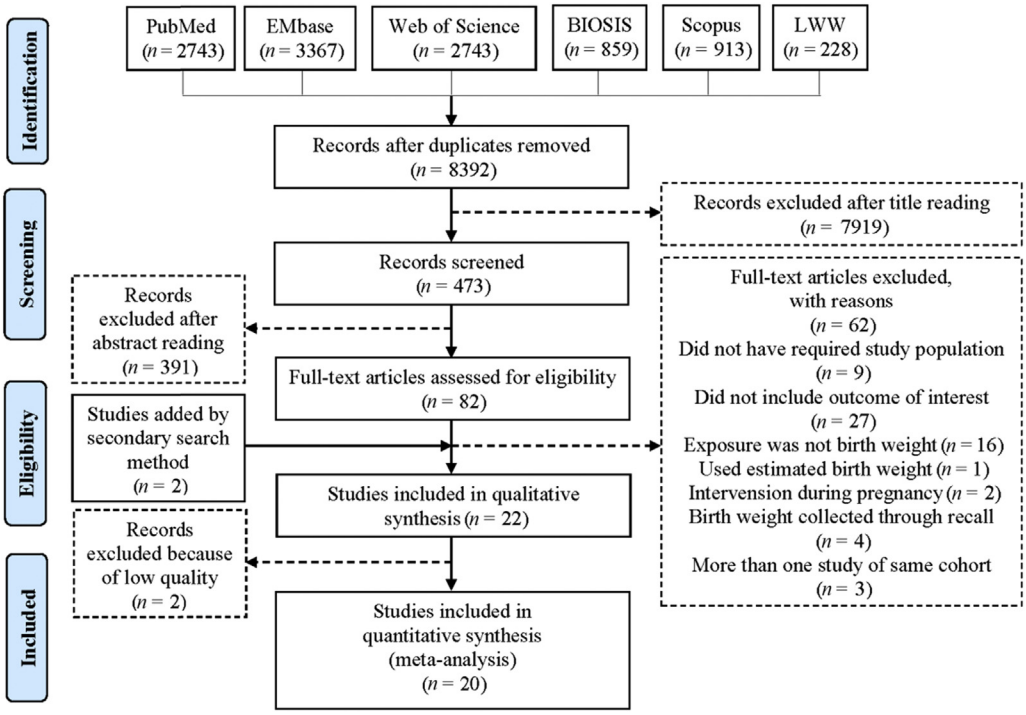

Fig. 1. Course of the systematic review. LWW = Lippincott Williams & Wilkins.

comparability scale, two studies did not adjust for adult body mass index (BMI), and one study only reported crude coefficients. The majority of studies did not receive adequate points for follow-up of cohorts, primarily due to low follow-up rates.

3.3. Main analysis

Among men, 20 studies were included in the meta-analysis of linear regression coefficients.[1,3,4,6–22] The summary regression coefficient of total cholesterol for an increment in birth weight of 1 kg was −0.09 mmol/L (95% CI: −0.13, −0.05), without heterogeneity ($p = 0.239$, $I^2 = 17.2\%$). There was no evidence of publication bias ($p = 0.226$).

Among women, 17 studies were included in the meta-analysis.[1,3,4,6–9,11–14,16,18–22] The pooled regression coefficient for an increment in birth weight of 1 kg was −0.08 mmol/L (95% CI: −0.13, −0.03), with a low level of heterogeneity among the studies ($p = 0.085$, $I^2 = 34.0\%$). Also, there was no evidence of publication bias ($p = 0.613$).

3.4. Stratified and sensitivity analyses

We repeated our statistical analyses on subgroups of the data using 50 years as the stratifying age. The results were generally similar to the results from the full dataset in men; however, it showed a different effect of birth weight on total cholesterol in women (see Table 1). The pooled regression coefficient for an increment in birth weight of 1 kg was 0.10 mmol/L (95% CI: −0.16, −0.04) in women aged <50 years, whereas the coefficient was 0.02 mmol/L (95% CI: −0.10, 0.06) in women aged >50 years. All the subgroup analyses by age had no or low heterogeneity among the studies.

Additionally, we conducted stratified analyses by national income levels as noted in the World Bank report. The results of analyses of high-income countries were generally similar to the results from the full dataset in both sexes. However, in middle-income countries, including lower-middle-income and upper-middle-income countries, the analyses showed no effect of birth weight on total cholesterol (see Table 1). All the subgroup analyses by income levels showed low heterogeneity among the studies, except the analysis of women in middle-income countries, which showed moderate heterogeneity.

In the sensitivity analyses without incorporating the Cooper and Power[1] study, the pooled regression coefficient for men ranged from −0.12 mmol/L (95% CI: −0.15, −0.08) to −0.07 mmol/L (95% CI: −0.11, −0.03) when the study by Miura et al[16] was excluded. The pooled regression coefficient for women ranged from −0.10 mmol/L (95% CI: −0.15, −0.05), when the study by Skidmore[18] was omitted, to −0.07 mmol/L (95% CI: −0.13, −0.02) when the study by Cooper and Power[1] was excluded.

We also repeated all the statistical analyses on the data without adjustment for adult BMI (see Table 1). The summary regression coefficient of total cholesterol for an increment in birth weight of 1 kg in men was −0.06 mmol/L (95% CI: −0.10, −0.03), without heterogeneity ($p = 0.346$, $I^2 = 8.8\%$), whereas that in women was −0.06 mmol/L (95% CI: −0.12, −0.01), with low heterogeneity among the studies ($p = 0.037$, $I^2 = 41.7\%$). The results of the stratified analyses were generally similar to the results from the data adjusted for adult BMI.

Table 1
Pooled estimates of effect size and 95% CIs for the effects of birth weight (kg) on total cholesterol (mmol/L) by sex, age, and national income levels.

Subgroups			No. of studies	Participants (*n*)	Summary regression coefficient	95% CI	I^2 (%)
After adjustment for confounders	Men	Age ≥ 50 y	8	4400	−0.095	−0.156 to −0.033	0
		Age ≤ 50 y	12	8958	−0.095	−0.152 to −0.038	37.0
	Women	Age ≥ 50 y	6	3452	−0.018	−0.100 to 0.064	0
		Age ≤ 50 y	11	9312	−0.105	−0.164 to −0.045	37.6
	Men	High-income countries	16	12,528	−0.093	−0.138 to −0.048	30.7
		Middle-income countries	4	830	−0.092	−0.226 to 0.042	0
	Women	High-income countries	13	11,809	−0.092	−0.139 to −0.046	18.3
		Middle-income countries	4	955	−0.082	−0.296 to 0.132	66.7
Before adjustment for confounders	Men	Age ≥ 50 y	8	4400	−0.091	−0.147 to −0.035	0
		Age ≤ 50 y	12	8958	−0.048	−0.093 to −0.003	9.3
	Women	Age ≥ 50 y	6	3452	−0.017	−0.096 to 0.062	0
		Age ≤ 50 y	11	9312	−0.078	−0.144 to −0.012	53.9
	Men	High-income countries	16	12,528	−0.063	−0.101 to −0.024	13.7
		Middle-income countries	4	830	−0.083	−0.228 to 0.061	10.1
	Women	High-income countries	13	11,809	−0.077	−0.116 to −0.037	8.3
		Middle-income countries	4	955	−0.062	−0.320 to 0.196	77.6

In conclusion, the current meta-analysis ascertained that lower birth weight is associated with higher concentrations of total cholesterol in adult men and women before or after adjustment for adult BMI. This association is consistently observed in men in the subgroup and sensitivity analyses, but the effect was only observed in women aged <50 years. In the stratified analyses by income levels, the association only exists in high-income countries, but not in middle-income countries. Furthermore, the association after adjustment for adult BMI is similar to the results before adjustment, indicating that the observed adjusted association is unlikely to be an artifact due to the positive association between birth weight and adult BMI.

4. Discussion

Lower birth weight is associated with an increased risk of adult coronary heart disease and stroke.[23] However, the mechanisms underlying this association are still elusive. Because elevated serum cholesterol is a strong risk factor for cardiovascular disease, many researchers have tried to clarify the relationship between birth weight and total cholesterol. A most recent meta-analysis published in 2006 showed a slight inverse association (−0.04 mmol/L, 95% CI: −0.07 to approx. −0.02) between birth weight and total cholesterol after adjustment for age and current BMI.[24] The other two meta-analyses both showed a similar inverse association (−0.048 mmol/L, 95% CI: −0.078 to approx. −0.018 and −0.036 mmol/L, 95% CI: −0.047 to approx. −0.025).[5,25] The associations in these studies were similar, yet weaker than those in our study. All these studies assessed the association across all age groups. In the study by Owen et al,[25] the differences in the associations among three age groups were explored using the meta-regression method; however, no consistent difference was found among the three age groups. Furthermore, their research included 12 adult studies, which was considerably less than those included in our study. Additionally, their definition of adulthood was different; they defined adult as age >16 years, whereas we defined it as age >18 years in our study. Hence, we excluded a large study conducted by Davies et al.[2] However, when we included this study, the results were similar (the effect was −0.09 mmol/L, 95% CI: −0.13 to approx. −0.06 for men and −0.07 mmol/L, 95% CI: −0.13 to approx. −0.01 for women). Therefore, the difference between the study by Owen et al[25] and our study may result from the different age groups of participants and the addition of new studies. Moreover, due to regression dilution bias, errors in the assessment of birth weight would tend to produce underestimation of the true strength of any association with subsequent outcome. Hence, the exclusion of studies whose birth weight was reported by recall would produce more precise and greater impact. Additionally, the effect may be underestimated because birth weight was a crude indicator of intrauterine undernutrition. It has been reported that a 0.5 mmol/L increase in total cholesterol concentration results in an increase in coronary heart disease mortality risk of 17%.[26] Thus, the association we describe between birth weight and adult total cholesterol is modest but significant in public health terms.

In the subgroup analyses by age, we found a sex difference in the birth weight−total cholesterol association, which was of no statistical significance in women aged >50 years. The sex differences were also reported by other researchers, although in different forms.[1,3,16] The statistically significant association was only found in men in Ziegler et al's study[3] and in women in Cooper and Power's study,[1] whereas it was found in both sexes in Miura's study. However, our study is the first study analyzing sex difference by age groups in adults. The sex difference may be due to the differences in cholesterol metabolism in men and women, especially after menopause in women.[27] Postmenopausal women had significantly higher concentration of total cholesterol, which may mask a birth weight effect. Additionally, in the review by Aiken and Ozanne,[28] they suggested that the sex differences in

developmental programming models were due to the differential ability of the male and female fetus to respond to a particular stress, and this differential response may lead to different cholesterol levels in men and women, respectively. Moreover, there were 9312 women aged <5 0 years in this meta-analysis compared with only 3452 women aged >50 years. Thus, this phenomenon may result from a much smaller sample size in women aged >50 years. Future cohort studies with larger sample size of postmenopausal females are needed to clarify the association.

A recent study showed that total cholesterol concentration was significantly associated with national income levels in both 1980 and 2008.[29] Thus, the postnatal environment may modify the association between total cholesterol and birth weight. However, it is not feasible to evaluate the association in different countries in one single study. Furthermore, none of the published meta-analyses have assessed the association by national income levels. In the current study, we found a significant association in high-income countries for both sexes, but not in the middle-income countries. This result may be due to the different life styles in different income level countries. Another possible explanation is the much smaller sample size of studies from the middle-income countries ($n = 1785$) compared with high-income countries ($n = 24{,}337$).

It has been suggested that the observed inverse association of birth weight with adult cardiovascular risk factors after adjusting for adult BMI may be based on its positive association with current size.[30] However, in our data, the association was similar before and after adjustment for adult BMI.

In contrast to other studies, we did not find statistically significant heterogeneity in the current study ($p = 0.239$ for men and $p = 0.085$ for women). The heterogeneity was accounted for by differences between men and women in the study by Lawlor et al[24] and by smaller studies and studies focusing on infants like the study by Huxley et al.[5] Therefore, the loss of heterogeneity in our study may be due to a larger sample size of adults, analysis of data by sexes, and only including adults in the current study.

The current meta-analysis presents several strengths. First, the possibility of recall bias, which was often a concern in cohort studies, was eliminated by the restriction to studies which reliably ascertained size at birth. Second, the final meta-analysis excluded low methodological quality studies, so that the results were more reliable. Finally, no publication bias was found, and the sensitivity analyses consolidated our results.

The limitations in our analyses should also be considered. In general, low birth weight is referred to as birth weight lower than 2500 g. In the current study, we did not analyze the data by birth weight category. Therefore, it was impossible to report the range of birth weight that has the strongest effect on total cholesterol. Rich-Edwards et al[23] found that the association between birth weight and nonfatal cardiovascular diseases was driven by participants born at the extremes of birth weight (<2495 g). Whether the situation is the same in the birth weight−total cholesterol association is still unknown, and needs to be evaluated in future studies. Additionally, all the included studies were observational, therefore problems with residual confounding were not addressed. Finally, although we researched the studies without language limitation, there were no non-English papers that met our inclusion criteria. However, we did not find any publication bias in the analyses.

In conclusion, the results of this meta-analysis suggest that lower birth weight, independent of adult adiposity, is associated with higher levels of serum total cholesterol in men aged >18 years and women aged <50 years.

Acknowledgments

This research was supported by the National Natural Science Foundation of China (Grant No. 81170733) and the National Key Technology R&D Program of China (Grant No. 2012BAI02B03).

References

1. Cooper R, Power C. Sex differences in the associations between birthweight and lipid levels in middle-age: findings from the 1958 British birth cohort. *Atherosclerosis* 2008;**200**:141−9.
2. Davies AA, Smith GD, Ben-Shlomo Y, Litchfield P. Low birth weight is associated with higher adult total cholesterol concentration in men: findings from an occupational cohort of 25,843 employees. *Circulation* 2004;**110**:1258−62.
3. Ziegler B, Johnsen SP, Thulstrup AM, Engberg M, Lauritzen T, Sorensen HT. Inverse association between birth weight, birth length and serum total cholesterol in adulthood. *Scand Cardiovasc J* 2000;**34**:584−8.
4. Libby G, McEwan SR, Morris AD, Belch JJF. No difference in the association between birth weight and total cholesterol for males and females. A sharp (Scottish heart and arterial disease risk prevention) study. *Vasc Med* 2008;**13**:271−4.
5. Huxley R, Owen CG, Whincup PH, Cook DG, Colman S, Collins R. Birth weight and subsequent cholesterol levels: exploration of the "fetal origins" hypothesis. *JAMA* 2004;**292**:2755−64.
6. Gomes FM, Subramanian SV, Escobar AMU, Valente MH, Grisi SJFE, Brentani A, et al. No association between low birth weight and cardiovascular risk factors in early adulthood: evidence from Sao Paulo, Brazil. *PLoS One* 2013;**8**:e66554.
7. Harville EW, Srinivasan S, Chen W, Berenson GS. Is the metabolic syndrome a "small baby" syndrome?: the Bogalusa Heart Study. *Metab Syndr Relat Disord* 2012;**10**:413−21.
8. Kerkhof GF, Leunissen RWJ, Hokken-Koelega ACS. Early origins of the metabolic syndrome: role of small size at birth, early postnatal weight gain, and adult IGF-I. *J Clin Endocrinol Metab* 2012;**97**:2637−43.
9. Fall CHD, Osmond C, Barker DJP, Clark PMS, Hales CN, Stirling Y, et al. Fetal and infant growth and cardiovascular risk factors in women. *BMJ* 1995;**310**:428−32.
10. Fagerberg B, Bondjers L, Nilsson P. Low birth weight in combination with catch-up growth predicts the occurrence of the metabolic syndrome in men at late middle age: the atherosclerosis and insulin resistance study. *J Intern Med* 2004;**256**:254−9.
11. Veena SR, Geetha S, Leary SD, Saperia J, Fisher DJ, Kumaran K, et al. Relationships of maternal and paternal birthweights to features of the metabolic syndrome in adult offspring: an inter-generational study in South India. *Diabetologia* 2007;**50**:43−54.
12. Kajantie E, Barker DJP, Osmond C, Forsén T, Eriksson JG. Growth before 2 years of age and serum lipids 60 years later: the Helsinki Birth Cohort study. *Int J Epidemiol* 2008;**37**:280−9.
13. Robinson SM, Batelaan SF, Syddall HE, Sayer AA, Dennison EM, Martin HJ, et al. Combined effects of dietary fat and birth weight on serum cholesterol concentrations: the Hertfordshire cohort study. *Am J Clin Nutr* 2006;**84**:237−44.

14. Valdez R, Athens MA, Thompson GH, Bradshaw BS, Stern MP. Birthweight and adult health outcomes in a biethnic population in the USA. *Diabetologia* 1994;**37**:624−31.
15. Suzuki T, Minami J, Ohrui M, Ishimitsu T, Matsuoka H. Relationship between birth weight and cardiovascular risk factors in Japanese young adults. *Am J Hypertens* 2000;**13**:907−13.
16. Miura K, Nakagawa H, Tabata M, Morikawa Y, Nishijo M, Kagamimori S. Birth weight, childhood growth, and cardiovascular disease risk factors in Japanese aged 20 years. *Am J Epidemiol* 2001;**153**:783−9.
17. Eriksson M, Wallander MA, Krakau I, Wedel H, Svardsudd K. Birth weight and cardiovascular risk factors in a cohort followed until 80 years of age: the study of men born in 1913. *J Intern Med* 2004;**255**:236−46.
18. Skidmore PML, Hardy RJ, Kuh DJ, Langenberg C, Wadsworth MEJ. Birth weight and lipids in a national birth cohort study. *Arterioscler Thromb Vasc Biol* 2004;**24**:588−94.
19. Barker DJP, Martyn CN, Osmond C, Hales CN, Fall CHD. Growth in utero and serum cholesterol concentrations in adult life. *BMJ* 1993;**307**:1524−7.
20. Mi J, Law C, Zhang KL, Osmond C, Stein C, Barker D. Effects of infant birthweight and maternal body mass index in pregnancy on components of the insulin resistance syndrome in China. *Ann Intern Med* 2000;**132**:253−60.
21. Eriksson JG, Forsen T, Tuomilehto J, Jaddoe VWV, Osmond C, Barker DJP. Effects of size at birth and childhood growth on the insulin resistance syndrome in elderly individuals. *Diabetologia* 2002;**45**:342−8.
22. Stein AD, Conlisk A, Torun B, Schroeder DG, Grajeda R, Martorell R. Cardiovascular disease risk factors are related to adult adiposity but not birth weight in young Guatemalan adults. *J Nutr* 2002;**132**:2208−14.
23. Rich-Edwards JW, Stampfer MJ, Manson JE, Rosner B, Hankinson SE, Colditz GA, et al. Birth weight and risk of cardiovascular disease in a cohort of women followed up since 1976. *BMJ* 1997;**315**:396−400.
24. Lawlor DA, Owen CG, Davies AA, Whincup PH, Ebrahim S, Cook DG, et al. Sex differences in the association between birth weight and total cholesterol. A meta-analysis. *Ann Epidemiol* 2006;**16**:19−25.
25. Owen CG, Whincup PH, Odoki K, Gilg JA, Cook DG. Birth weight and blood cholesterol level: a study in adolescents and systematic review. *Pediatrics* 2003;**111**:1081−9.
26. Verschuren WM, Jacobs DR, Bloemberg BP, Kromhout D, Menotti A, Aravanis C, et al. Serum total cholesterol and long-term coronary heart disease mortality in different cultures. Twenty-five-year follow-up of the seven countries study. *JAMA* 1995;**274**:131−6.
27. Stevenson JC, Crook D, Godsland IF. Influence of age and menopause on serum lipids and lipoproteins in healthy women. *Atherosclerosis* 1993;**98**:83−90.
28. Aiken CE, Ozanne SE. Sex differences in developmental programming models. *Reproduction* 2013;**145**:R1−13.
29. Danaei G, Singh GM, Paciorek CJ, Lin JK, Cowan MJ, Finucane MM, et al. The global cardiovascular risk transition: associations of four metabolic risk factors with national income, urbanization, and western diet in 1980 and 2008. *Circulation* 2013;**127**:1493−502.
30. Lucas A, Fewtrell MS, Cole TJ. Fetal origins of adult disease-the hypothesis revisited. *BMJ* 1999;**319**:245−9.