Published by Oxford University Press on behalf of the International Epidemiological Association
International Journal of Epidemiology 2011;40:647–661
doi:10.1093/ije/dyq267

Birthweight and mortality in adulthood: a systematic review and meta-analysis

Kari R Risnes,[1,2,3]* Lars J Vatten,[1] Jennifer L Baker,[4] Karen Jameson,[5] Ulla Sovio,[6] Eero Kajantie,[7] Merete Osler,[8] Ruth Morley,[9] Markus Jokela,[10] Rebecca C Painter,[11] Valter Sundh,[12] Geir W Jacobsen,[1,3] Johan G Eriksson,[13] Thorkild I A Sørensen[4] and Michael B Bracken[3]

[1]Department of Public Health, Norwegian University of Science and Technology, Trondheim, Norway, [2]Department of Paediatrics, St Olav's Hospital, Trondheim University Hospital, Trondheim, Norway, [3]Center for Perinatal, Pediatric and Environmental Epidemiology, Yale University, New Haven, CT, USA, [4]Institute of Preventive Medicine, Copenhagen University Hospital, Copenhagen, Denmark, [5]Medical Research Council, Lifecourse Epidemiology Unit, Southampton General Hospital, Southampton, UK, [6]Department of Medical Statistics, London School of Hygiene and Tropical Medicine, London, UK, [7]National Institute for Health and Welfare, Helsinki, Finland, [8]Research Centre for Prevention and Health, Glostrup University Hospital, Copenhagen, Denmark, [9]Clinical Epidemiology and Biostatistics Unit, University of Melbourne Department of Paediatrics and Murdoch Childrens Research Institute, Melbourne, Victoria, Australia, [10]Department of Psychology, University of Helsinki, Helsinki, Finland, [11]Department of Gynaecology and Obstetrics, Academic Medical Centre, University of Amsterdam, The Netherlands, [12]Department of Primary Health Care, Goteborg University, Gothenburg, Sweden and [13]National Institute for Health and Welfare, University of Helsinki, Department of General Practice and Primary Health Care, Helsinki University Central Hospital, Unit of General Practice, Folkhalsan Research Centre Helsinki Finland and Vasa Central Hospital, Vasa, Finland

*Corresponding author. Department of Public Health, NTNU, Faculty of Medicine, PB 8905, Medical Research Centre, 7491 TRONDHEIM, Norway. E-mail: kari.risnes@ntnu.no

Accepted 16 December 2010

Background Small birth size may be associated with increased risk of cardiovascular diseases (CVD), whereas large birth size may predict increased risk of obesity and some cancers. The net effect of birth size on long-term mortality has only been assessed in individual studies, with conflicting results.

Methods The Meta-analyses of Observational Studies in Epidemiology (MOOSE) guidelines for conducting and reporting meta-analysis of observational studies were followed. We retrieved 22 studies that assessed the association between birthweight and adult mortality from all causes, CVD or cancer. The studies were systematically reviewed and those reporting hazard ratios (HRs) and 95% confidence intervals (95% CIs) per kilogram (kg) increase in birthweight were included in generic inverse variance meta-analyses.

Results For all-cause mortality, 36 834 deaths were included and the results showed a 6% lower risk (adjusted HR = 0.94, 95% CI: 0.92–0.97) per kg higher birthweight for men and women combined. For cardiovascular mortality, the corresponding inverse association was stronger (HR = 0.88, 95% CI: 0.85–0.91). For cancer mortality, HR per kg higher birthweight was 1.13 (95% CI: 1.07–1.19) for men and 1.04 (95% CI: 0.98–1.10) for women ($P_{\text{interaction}} = 0.03$). Residual confounding could not be eliminated, but is unlikely to account for the main findings.

Conclusion These results show an inverse but moderate association of birthweight with adult mortality from all-causes and a stronger inverse association with cardiovascular mortality. For men, higher

birthweight was strongly associated with increased risk of cancer deaths. The findings suggest that birthweight can be a useful indicator of processes that influence long-term health.

Keywords Birthweight, gestational age, all-cause mortality, cardiovascular mortality, cancer mortality, early origins of health and disease hypothesis

Introduction

Birthweight is an indicator of fetal growth and low birthweight predicts short-term survival of the newborn better than any other characteristic.[1] Small body size at birth also appears to be an important predictor for long-term health. The results of many cohort studies suggest that birthweight is inversely associated with adult morbidity and mortality from cardiovascular diseases (CVD).[2–6] These findings have been interpreted according to the 'developmental origins of health and disease hypothesis', suggesting that fetal undernutrition may increase susceptibility to diseases that occur later in life.[7,8] Evidence from animal studies suggests that the fetus may adapt to an adverse intrauterine environment by slowing down growth and metabolism. This adaptive strategy appears to increase short-term survival, but perhaps with adverse long-term consequences on health.[9] Alternatively, common genetic factors could influence birth size and adult disease[10–12] or a combination of genetic and non-genetic factors could interact throughout the life course to determine disease susceptibility.[13,14]

High birthweight has also been associated with increased risk of adverse adult health outcomes, such as overweight[15] and type 1 diabetes,[16] which are important determinants of adult mortality.[17,18] There is also evidence that high birthweight is associated with higher risk of some adult cancers.[19,20] In particular, birth size has been positively associated with breast cancer risk in many studies.[21–23] In Western countries, birthweights have increased over recent decades[24–26] and it is important to assess whether a high birthweight may be associated with adverse effects on long-term survival.

Birthweight appears to be inversely associated with adult mortality, but there is conflicting evidence related to the importance of potentially confounding factors such as socio-economic status and gestational age. Also, there is conflicting evidence of possible sex differences and in some studies, the results suggest increased adult all-cause mortality for the highest birthweights instead of a linear inverse association across the spectrum of birthweights.

The aim of this systematic review and meta-analysis was to determine whether birthweight, or other measures of birth size, is associated with adult mortality from all-causes, CVD and all cancers.

Methods

The proposal for conducting and reporting meta-analyses of observational studies in epidemiology (MOOSE)[27] was followed.

Study inclusion criteria

Included studies have assessed the association of birthweight with one or more of the following causes of adult mortality; all-causes, CVD or cancer. Historical and prospective cohort studies were eligible, retrospective studies were not. Inclusion was restricted to studies where the majority (>80%) of deaths occurred after 15 years of age. Studies that predominantly included twins were excluded. For studies where information had been published in more than one report, we used data that included the longest follow-up. All-causes of death were defined according to the International Classification of Diseases (ICD); deaths from CVD were defined according to ICD8 and ICD9: 390–458 and ICD10: I00–I99. Mortality from cancer was defined according to ICD8 and ICD9: 140–290 and ICD10: C00–C99.

Search strategy

Searches were conducted through October 2010 using MEDLINE from 1950 (via ISI web of science), PubMed (from 1966), Ovid EMBASE (from 1980) and Google Scholar (www.google.com). The following terms were used as keywords to locate studies: 'birthweight' and 'birth weight', 'birth length', 'head size', 'ponderal index', 'birth size', all separately combined with: 'all-cause mortality', 'adult mortality', 'mortality', 'cohort study', 'etiology', 'cardiovascular mortality' and 'cancer mortality'. We also used an alternative search strategy conducted by a medical librarian with special training in searching the medical literature (details available upon request).

References of studies eligible from full text, including cross references, were searched without restriction by language of publication. Unpublished abstracts were excluded. Searches were performed independently by the lead author and a librarian specialized in medical database searches. Titles identified from searches were first checked for relevance by the lead author. Abstracts of studies regarded as relevant on the basis of the title were assessed for eligibility. The full text of studies regarded as potentially eligible by abstract were assessed to decide whether the studies

should be included. Two reviewers (K.R.R. and G.W.J.) worked independently to search eligible studies for inclusion, data extraction and methodological quality. Data extraction and assessment of quality were performed using a structured form, and differences resolved by consensus and discussion with a third reviewer (M.B.B.).

Methodological quality assessment, including assessment of potential biases, were based on 'The Newcastle–Ottawa quality assessment scale for cohort studies' (http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp), which is evaluated to be one of few useful tools in assessing quality of observational studies.[28] For each study, a maximum of 8 points could be achieved and a priori, high-quality studies had $\geqslant 6$ points and medium- or low-quality studies <6 points.

Measures of exposure

For individual studies, hazard ratios (HRs) with 95% confidence intervals (95% CIs) per unit increase in each birth size measure were cited from the published report. The estimate most completely adjusted for confounders in the original study was used in the meta-analysis. Authors of the studies who did not report estimates that could be used for the meta-analyses were contacted to provide this information. For studies where HRs per kilogram (kg) birthweight could not be provided by one of the authors, the published results were sought to be converted into appropriate estimates.

In one study,[29] results were reported per units of standard deviation (SD) in grams (g) and HRs and CIs could be calculated per kg.[30]

Since many published studies have assessed these associations by sex and some have suggested sex differences, the main analyses were stratified by sex. For the meta-analyses, sex-specific HRs per 1 kg increase in birthweight were calculated for each study. Sex interactions were tested using a chi-squared test between the sex-specific pooled results for each outcome of interest. An additional categorical analysis was performed for all-cause mortality according to the birthweight categories (<3000 g and >4000 g, compared with the referent category 3000–4000 g). For this analysis, each HR from individual studies was adjusted for sex before the combined result for men and women was entered into the meta-analysis. To assess the associations of alternative birth size measurements with mortality, sex-specific HRs per centimetre increase in birth length and per 1 U (kg/m^3) increase in ponderal index were sought. In two studies,[31,32] the association of birth length with adult all-cause mortality was assessed and suggested a possible inverse association of birth length. There were no available data to justify the pooled analysis for birth size measures other than birthweight and any of the outcomes of interest.

Data synthesis

In the analyses, studies were weighted according to the inverse variance of the regression coefficient, and the weighted regression coefficients were combined assuming a fixed effect model. An alternative approach, assuming a random effects model, was evaluated and this revealed the same results. For reports where the variance was not reported, the variance of each study was calculated by deriving the standard error from the reported 95% CI.[30] Separate analyses were performed including the crudest and the most adjusted estimate from each report.

Funnel plots were assessed for symmetry to evaluate the impact of possible publication bias. Given sufficient number of included studies, heterogeneity was assessed using the I^2 statistic.[33] Sensitivity analyses were performed when the I^2 statistic showed evidence of moderate or high heterogeneity, corresponding to values of $>40\%$ or 75%, respectively. We also performed sensitivity analyses to evaluate potential bias due to exclusion of studies where exact results per kg birthweight were not available. In these analyses, approximate HRs calculated from results in the published reports were added to the meta-analyses.[30] All analyses were performed in Review Manager 5 from the Cochrane Collaboration (www.cc-ims.net/revman)

Results

Availability of data

Initial searches retrieved 1522 articles (Figure 1). After screening titles and abstracts, we identified 22 reports that assessed the association of birthweight with adult mortality from one or more of the following causes: all-causes, CVD and total cancer. All these studies were systematically reviewed. Authors of 10 of the studies contributed additional information by clarifying methodology and providing results that could be included in the meta-analyses.[31,32,34–41]

The included studies were all prospective or longitudinal cohort studies and included populations from the UK, Denmark, Sweden, Finland, Norway, The Netherlands, Australia and Israel. The oldest cohort included populations born in the 1850s and the youngest dated from the 1960s and 1970s, with roughly half of all participants born after 1940.

Table 1 shows study characteristics of the 15 reports that assessed the association of birthweight with adult all-cause mortality. Three reports,[42–44] including 781 deaths, were secondary reports from studies that were already included and these were excluded from the analysis. Two eligible studies,[45,46] including 222 deaths (3.6% of total deaths), were excluded from the meta-analysis because risk estimates per kg birthweight were unavailable. In total, the meta-analysis for all-cause mortality (Supplementary Figure S1) included 10 studies; 9 studies[29,31,32,36–38,40,41,47] with

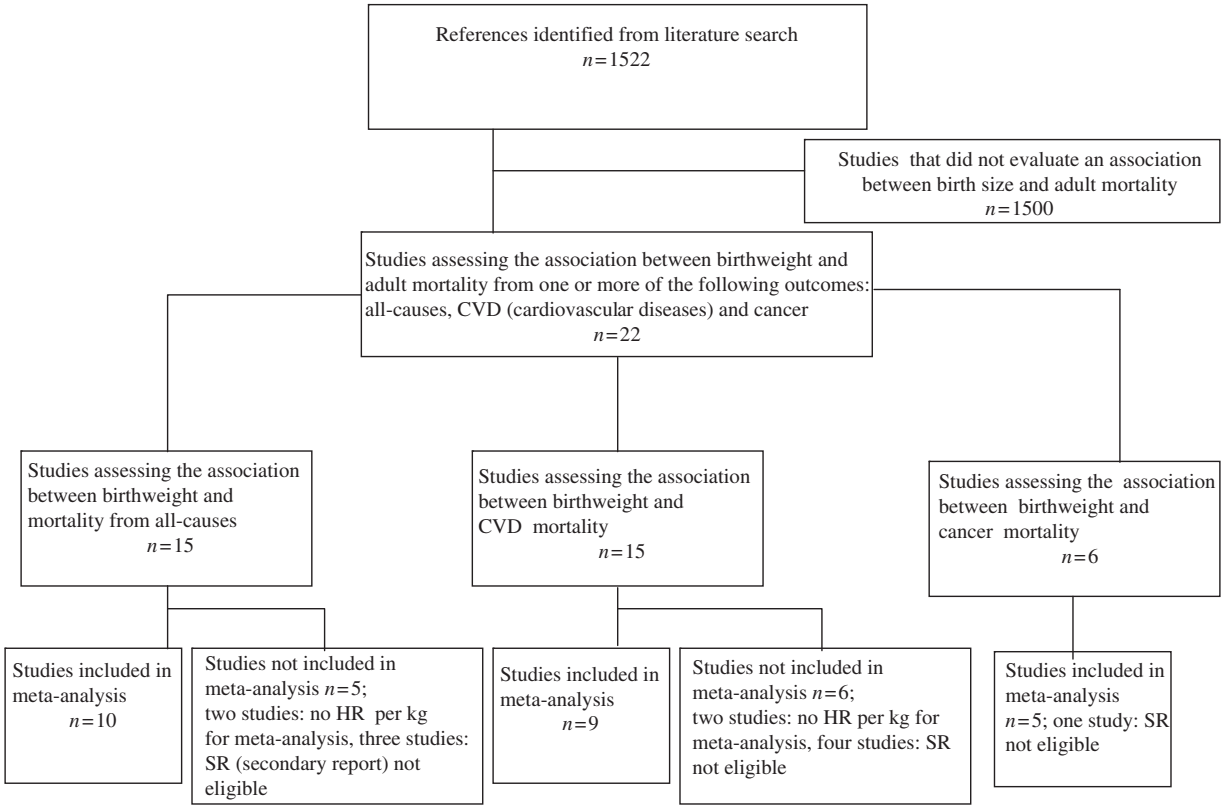


Figure 1 Flow chart for selection of studies in meta-analysis of birth size and adult mortality

23 839 deaths among men and 9 studies[29,32,35–38,40,41,47] including 12 995 deaths among women.

The association of birthweight with cardiovascular mortality was reported in 14 eligible reports (Supplementary Table S1). Four secondary reports were excluded[4,44,48,49] and 2 studies including 372 male deaths[2,45] were excluded from the meta-analysis of deaths from CVD due to unavailability of data. The meta-analysis for cardiovascular deaths (Supplementary Figure S2) included 9 studies[31,32,34,36,38–41,50] with 8570 cardiovascular deaths in men and 2796 cardiovascular deaths in women.

Five studies[32,36,38,40,41] that assessed the association of birthweight with adult cancer mortality are presented in Supplementary Table S2. The meta-analysis included 4208 cancer deaths in women and 4176 cancer deaths in men (Supplementary Figure S3).

Birthweight and all-cause mortality

Of the 12 primary reports reviewed, 4[31,32,38,41] suggested inverse associations of birthweight with adult mortality for men and women. One study suggested an inverse association for men and a positive association in women,[29] whereas inverse associations for women and no associations for men were reported in three studies.[32,37,46] In several studies, the number of deaths was low and could not yield strong evidence for any association. In the cohort from Australia including individuals born before 1900,[47] in a Swedish cohort of women born after 1938,[35] in the Dutch famine study[40] and in a follow-up study of British men,[45] there were no associations with adult mortality. The largest study reported strong evidence for a U-shaped association using five categories of birthweight, whereas there was an over-all inverse association per kg increase in birthweight provided for the present meta-analysis.[36]

The summary results of the meta-analyses are presented in Figure 2. The results show a reduction in the risk of death from all-causes per kg increase in birthweight; the sex-specific HRs were 0.95 (95% CI: 0.92–0.97) for men and 0.93 (95% CI: 0.90–0.96) for women. Funnel plots did not suggest evidence of publication bias for these associations and the I^2 statistics suggest evidence of low heterogeneity: I^2 was 13% for men and 26% for women.

We assessed all-cause mortality related to categories of birthweight using birthweight between 3000 and 4000 g as the reference category. These analyses showed higher mortality for individuals born relatively small (birthweight <3000 g); the sex-adjusted HR was 1.11 (95% CI: 1.08–1.15) for this group (Figure 3A). There was no evidence that relatively high birthweight (>4000 g) was associated with a further reduction or an increase in all-cause mortality

Table 1 Characteristics of studies reporting on the association between birthweight (BW): and adult all-cause mortality in men (M) and women (W)

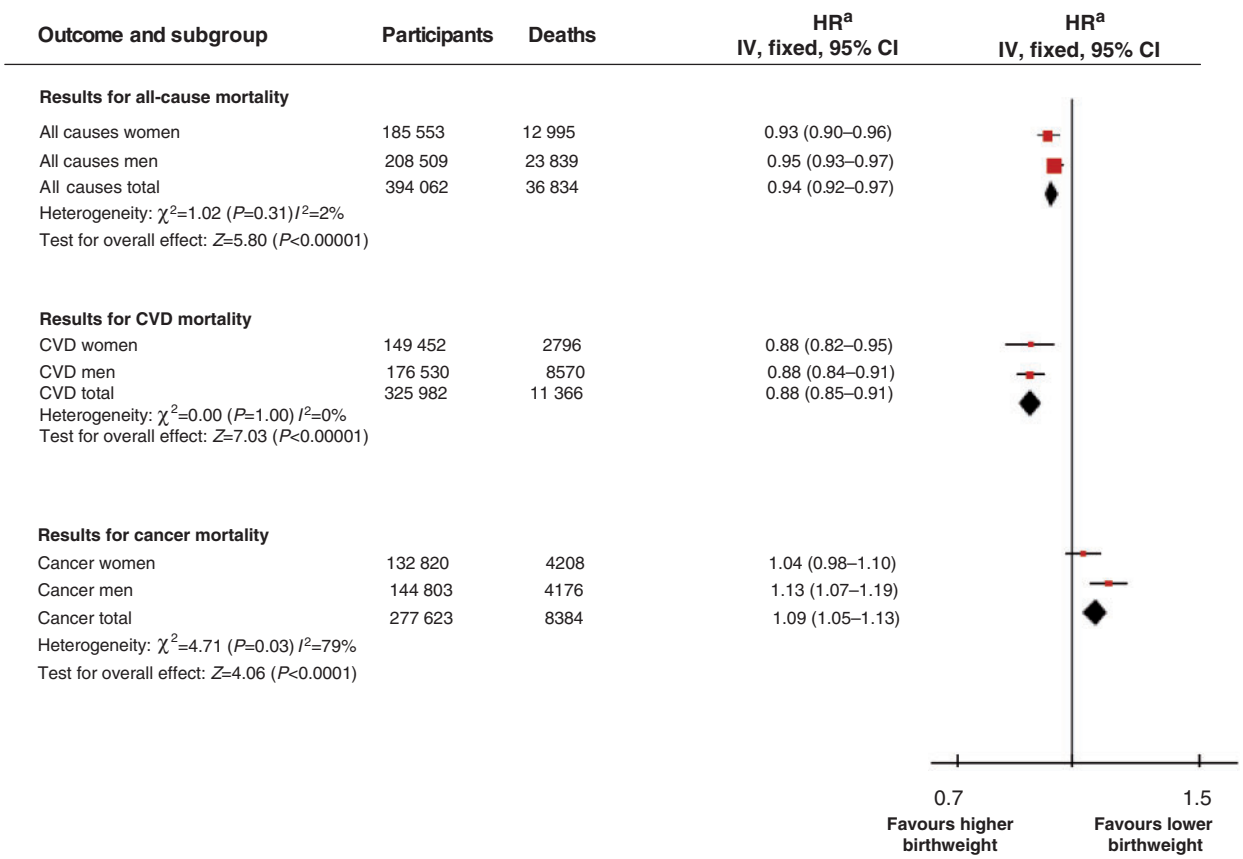
Study	Country and birth year	No of participants	Deaths	Age[a]	Published association for birthweight with 95% CI	HR[b] with 95% CI per kg increase in BW	Adjusted HR[c] with 95% CI per kg increase in BW
Included in meta-analysis							
Leon *et al.*[41]	Sweden 1915–29	6162 M 5675 W	2039 M 1109 W	64 (32–80)	HR per kg increase: M: 0.92 (0.84–1.00) F: 0.95 (0.84–1.07)	M: 0.92 (0.84–1.00) W: 0.96 (0.84–1.07)	M: 0.94 (0.87–1.03)[d] W: 0.95 (0.84–1.07)[d]
Friedlander *et al.*[29]	Israel 1964–74	40 774 M 39 776 W	383 M 179 W	>15	HR per SD score increase M: 0.92 (0.83–1.03) W: 1.08 (0.92–1.27)	M: 0.85 (0.69–1.05)[e] W: 1.15 (0.83–1.58)[e]	M: 0.79 (0.64–0.98)[e,f] W: 1.21 (0.85–1.72)[e,f]
Andersen and Osler[31]	Denmark 1953	10 753 M	810	36.4 (15–49)	HR per 500 g increase: 0.93 (0.87–0.99)[g]	0.83 (0.73–0.97)	0.86 (0.76–0.98)[g]
Kajantie *et al.*[32]	Finland 1924–44	7203 M 6627 W	1668 M 671 W	56 (26–74)	HR per 1 kg decrease: M: 1.08 (0.96–1.19) W: 1.25 (1.04–1.49)	M: 0.96 (0.87–1.06) W: 0.81 (0.68–0.96)	M: 0.93 (0.84–1.04)[h] W: 0.80 (0.67–0.95)[h]
Painter *et al.*[40]	The Netherlands 1943–47	2254 M and W	82 M 53 F	47 (18–57)	HR per kilo decrease in birth weight: 0.98 ($P = 0.95$)	M: 1.03 (0.65–1.62) F: 1.01 (0.56–1.80)	0.97 (0.67–1.40)[i]
Syddal *et al.*[38]	England 1911–39	37 615 M and W	5698 M 2218 W	60 (13–88)	HR per SD score increase. Adjusted for year of birth M: 0.97 (0.94–0.99) W: 0.96 (0.92–1.00)	M: 0.94 (0.90–0.99) W: 0.92 (0.85–1.00)	M: 0.94 (0.90–0.99)[j] W: 0.92 (0.85–1.00)[j]
Baker *et al.*[36]	Denmark 1936–79	110 860 M 105 604 W	11 149 M 6609 W	48 (25–68)	Adjusted for period of birth. U shaped association over five categories. Elevated risk for the lowest and the highest category.	M: 0.95 (0.92–0.99) W: 0.92 (0.88–0.96)	No
Lapidus *et al.*[35]	Sweden 1938–64	786 W	439	38–100	No association. Estimate not published.	1.11 (0.94–1.31)	1.11 (0.94–1.31)[k]
McCalman *et al.*[47]	Australia 1857–1900	3347 M and W	1767 M 1579 W	65 (18–death)	Mean age at death, by four categories of BW: M + W: $P = 0.5$	M: 1.02 (0.94–1.17) F: 0.93 (0.85–1.02)	M: 1.04 (0.94–1.14)[l] F: 0.96 (0.87–1.06)[l]
Jokela *et al.*[37]	Great Britain 1958	8231 M 7804 W	243 M 138 W	35 (23–46)	OR^m per 100 g increase M + W: 0.99 (0.97–1.02)	M: OR^m: 0.96 (0.76–1.22) W: OR^m: 0.76 (0.55–1.05)	M: OR^m: 1.03 (0.80–1.32)[n] W: OR^m: 0.82 (0.59–1.15)[n]

(continued)

Table 1 Continued

Study	Country and birth year	No of participants	Deaths	Age[a]	Published association for birthweight with 95% CI	HR[b] with 95% CI per kg increase in BW	Adjusted HR[c] with 95% CI per kg increase in BW
Not included in meta-analysis							
Frankel *et al.*[45]	England 1920–38	1258 M	130 M	45–69	Mortality percentage over quartiles of birthweight: $P_{trend} = 0.5$, age adjusted	NA	
Power and Li[42]	England 1958	17 000 M and W	143 M 79 W	16–38	Per gestational age and sex-specific SD score: P_{trend} = M: 0.94. F: 0.91	SR	
Roseboom *et al.*[44]	The Netherlands 1943–47	2155 M and W	97	18–50	No association. Mortality percentage over four categories of birth-weight $P > 0.2$	SR	
Osler *et al.*[43]	Denmark 1953	7493 M	541	15–49	Three-level category of birthweight. <2400 g compared with referent >3500 g: HR: 1.69 (1.14–2.59)	SR	
Nilsson *et al.*[46]	Sweden 1964–67	2010 M 1982 W	54 M 38 W	1–38	SMR[o] over six categories of birthweight. Men: P_{trend}:0.65 Women: Inverse: $P_{trend} = 0.0006$	NA	

[a]Age is the age (years) when participants were followed. Mean age at death (range).
[b]The less adjusted estimate, only adjusted for age and period of birth (if applicable). Estimates are provided for meta-analysis.
[c] The most fully adjusted estimate provided from study, provided for meta-analysis.
[d]$n = 11\,486$ (excluded individuals missing information on confounders). Adjusted for: birth cohort (1915–19, 1920–24, 1925–29). Socio-economic group in 1960: manual, non-manual, self-employed, other), level of education in 1960 (elementary vs senior high school to PhD), civil status in 1960 (married, single, widower/divorced).
[e]Calculated from data in original report; HR per birthweight SD score increase(SD score: M; 552 g, W; 520 g).
[f]Adjusted for age, origin and education of mother, SES, pregnancy complication, previous fetal loss.
[g]Adjusted for paternal occupational status, paternal and maternal lifespan, maternal marital status.
[h]Adjusted for gestational age (weeks).
[i]Estimate for men and women combined, adjusted for sex and exposure to famine.
[j]Adjusted for weight at 1 year.
[k]Adjusted for education, social class, adult BMI (quadratic).
[l]Adjusted for birth cohort (1857–70, 1871–80, 1881–90, 1891–00), first child (yes, no), maternal marital status (supported, unsupported), socio-economic status (1–3, based upon paternal occupation), preterm birth (yes, no), residential area at death (four groups).
[m]Analysis using discrete-time survival analysis.
[n]Adjusted for fathers' social class, mother smoking before pregnancy and mothers' age.
[o]Adjusted for maternal smoking, age, parity, placental weight, disparity index.
NA, not available results (HR per kg) for meta-analysis; SMR, standard mortality ratio; SR, secondary report of study included in meta-analysis; report not eligible for meta-analysis.



[a]The most fully adjusted estimate from studies were entered analyses

Figure 2 Forest plots with sex-stratified results of meta-analyses assessing the association between birthweight and adult mortality from all-causes, CVD and cancer. HRs with 95% CIs per kg increase in birthweight

compared with the reference group (sex-adjusted HR = 1.02, 95% CI: 0.99–1.05) (Figure 3B). There was no evidence of heterogeneity among studies for these analyses.

Three of the individual studies that were included had assessed departures from linearity in the associations. The largest study[36] showed strong evidence for non-linearity across five categories of birthweight, with the highest risk in the lowest and highest birthweight groups, using a cut-off of 4250 g for the latter group. Omitting that study from the analysis of birthweight categories did not substantially change the overall results. In the large English cohort study,[38] there was no evidence for non-linearity verified by testing a quadratic term of the continuous birthweight measure, and in two studies[29,32] there were evidence for non-linear associations only for women.

Based on the pre-specified threshold criteria, the quality assessment (Table 2) showed that all included studies except the 19th-century Australian cohort[47] had a score of $\geqslant 6$, indicating high quality.

The two largest studies[36,38] had no information on potential confounders such as socio-economic factors and gestational age, but included adjustment for period of birth. The Danish Metropolitan Study[31] assessed the influence of childhood social indicators (maternal marital status and paternal occupation) and parental lifespan. Although the offspring of unmarried mothers, manual workers and parents with shorter lifespan had relatively higher adult mortality, there was only a marginal attenuation of the association of birthweight with mortality after adjustment for social indicators and parental lifespan. In other studies that included adjustment for indicators of socio-economic status in childhood[41,47] or adulthood,[35] the estimates were not substantially changed after adjustment. In the Israeli study,[29] adjustment for maternal education, social class and pregnancy complications strengthened the observed associations. In the British 1958 cohort, adjustment for paternal social class, maternal smoking and maternal age attenuated the estimated associations.[37] In the Helsinki Birth Cohort Study, adjustment for gestational age in individuals born at term slightly strengthened the associations.[29] Only two studies included information on maternal smoking. One study emphasized this issue[46] and included birthweight and maternal smoking in the same model, suggesting that for men, maternal smoking, but not lower birthweight, may be associated with increased mortality risk in the offspring. In women, however, the results showed that lower birthweight, but not maternal smoking, was

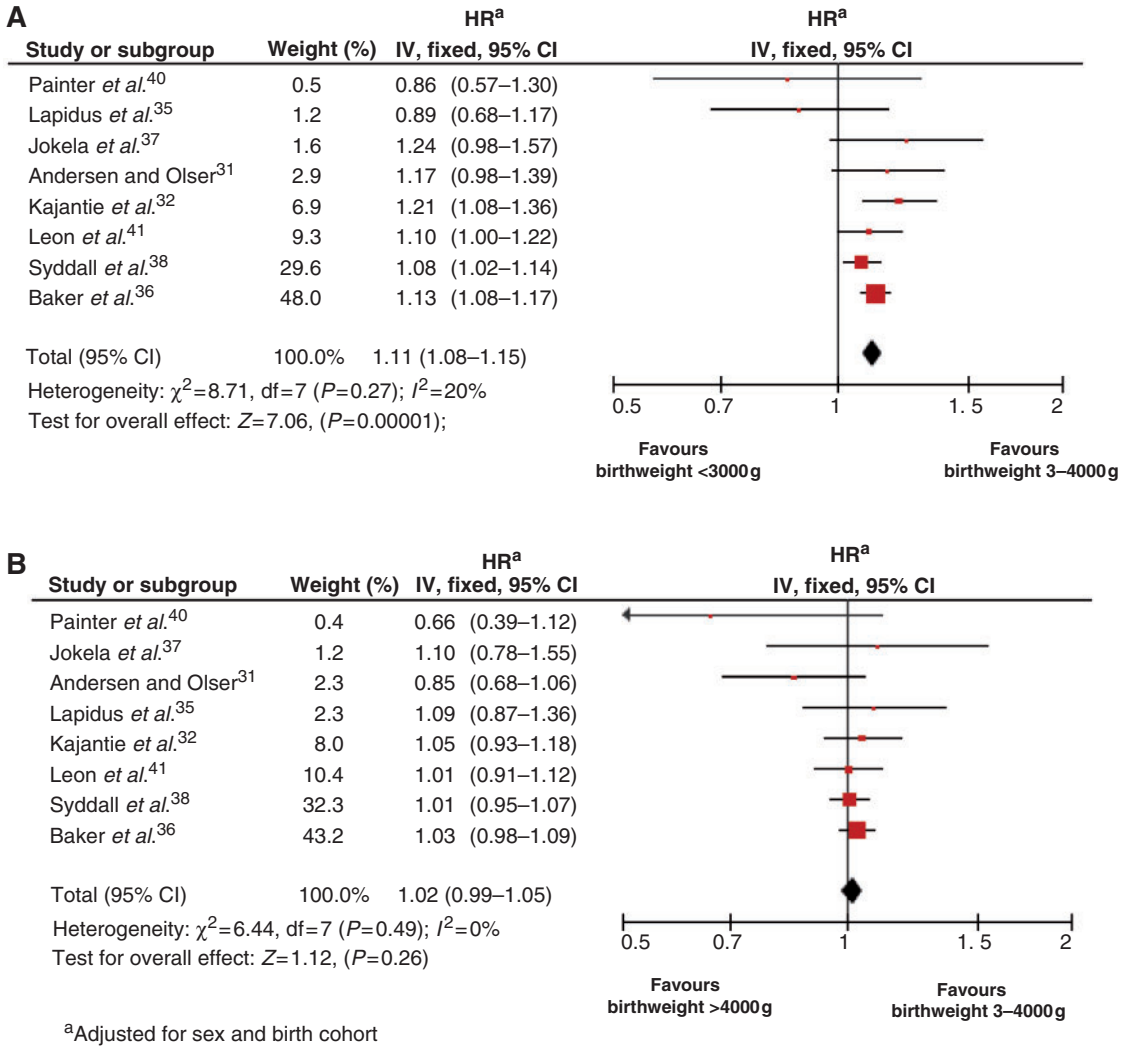


Figure 3 Forest plots presenting the associations between birthweight and all-cause mortality for categories of birth weight. (**A**) HRs with 95% CIs associated with birthweight <3000 g compared with referent with birthweight 3–4000 g. (**B**) HRs with 95% CIs associated with birthweight >4000 g compared with referent with birthweight 3–4000g

associated with higher mortality.[46] Adjustment for maternal smoking did not substantially alter the results in the British cohort of men born in 1958.[37]

In the present study, subgroup analyses were performed to evaluate confounding. Using adjusted or unadjusted estimates from studies that could adjust for potentially confounding factors resulted in nearly identical pooled estimates (data not shown). In a separate analysis, excluding the two large studies that could not adjust for gestational age or socio-economic factors,[38,51] the effect estimate [HR per kg increase in birthweight: 0.95 (95% CI: 0.91–0.99)] remained unchanged.

Birthweight and cardiovascular mortality

Consistent inverse associations between birthweight and cardiovascular disease mortality were found across most studies. Three studies, including data from the Dutch famine,[40] a cohort of British men[45] and a cohort of people born in Australia before 1900,[34] did not find any associations of birthweight with cardiovascular mortality. The meta-analysis of cardiovascular mortality (Supplementary Figure S2) showed a reduction in risk per kg increase in birthweight in both men (HR = 0.88, 95% CI: 0.84–0.91) and women (HR = 0.88, 95% CI: 0.82–0.95). For cardiovascular deaths, the I^2 statistics were 20% for studies in men and 0% for studies in women. Studies that could adjust for potentially confounding factors,[31,32,34,35,39,50] including paternal social class, maternal marital status and gestational age, showed marginal effects of adjustment on the estimated associations.

Birthweight and cancer mortality

The five included studies of birthweight and cancer mortality reported stronger positive associations for men than for women.[32,36,38,40,52] The meta-analysis

Table 2 Quality assessment in studies reporting on associations between birthweight and adult mortality from all-causes, CVD and cancer

Study	Representativity of cohort. >70% followed (0–1 points)	Birth size from birth record (0–1 points)	Outcome not present at time of study (0–1 points)	Adjusted for listed potential confounders (0–2 points)	Mortality from secure record (0–1 points)	Follow-up >80% (0–1 points)	Follow-up >15 years (0–1 points)	Summary quality assessment (0–8 points)
All-causes, CVD and cancer								
Leon *et al.*[41]	Yes	Yes	Yes	Yes. Birth cohort (1 point)	Yes	Yes	Yes	7
Painter *et al.*[40]	Yes	Yes	Yes	Yes. Gestational age, restricted to term births (1 point)	Yes	Yes	Yes	7
Kajantie *et al.*[32]	Yes	Yes	Yes	Yes. Gestational age, restricted to term births (1 point)	Yes	Yes	Yes	7
Syddal *et al.*[38]	Yes	Yes	Yes	Yes. Birth cohort, weight at 1 year (1 point)	Yes	Yes	Yes	7
Baker *et al.*[36]	Yes	No	Yes	Yes. Birth cohort (1 point)	Yes	Yes	Yes	6
All-causes and CVD								
Andersen and Olser[31]	Yes[a]	Yes	Yes	Yes. Maternal marital status, paternal occupation, maternal and paternal lifespan (2 points)	Yes	Yes	Yes	8
All-causes								
Friedlander *et al.*[29]	Yes	Yes	Yes	Yes. Maternal age, parity, previous fetal losses, pregnancy complications (2 points)	Yes	Yes	Yes	8
Lapidus *et al.*[35]	Yes[b]	Yes	Yes	Yes. Education, BMI, SES (1 point)	Yes	Yes	Yes	6
McCalman *et al.*[47]	No	Yes	Yes	Yes. Marital status, maternal age, parity, SES, year of birth (2 points)	No	No	Yes	5
Jokela *et al.*[37]	Yes	Yes	Yes	Yes. Paternal SES (1 point)	Yes	No[c]	Yes	6
CVD								
Eriksson *et al.*[50]	Yes[a]	Yes	Yes	Yes. Adult diabetes and height restricted to term in subpopulation. (2 points)	Yes	Yes	Yes	8
Risnes *et al.*[39]	Yes	Yes	Yes	Yes. Maternal age, parity, SES. Restricted to term (2 points)	Yes	Yes	Yes	8
Studies not included in meta-analysis because hazard ratios per kg birthweight were not available								
Barker *et al.*[7]	No	Yes	Yes	No	Yes	Yes	Yes	5
Frankel *et al.*[45]	Yes[a]	No	Yes	Social class, father social class, smoking, CVD risk factors (2 points)	Yes	Yes	No	6
Nilsson *et al.*[46]	Yes	Yes	Yes	Yes. Smoke in pregnancy, maternal age and parity (2 points)	Yes	Yes	Yes	7

[a]Only men included.
[b]Only women included.
[c]Follow-up not continuous.
BMI, body mass index; SES, socio-economic status.

showed that in men, birthweight was positively associated with cancer mortality; the HR per kg increase in birthweight was 1.13 (95% CI: 1.07–1.19), whereas in women, there was no strong evidence that birthweight was associated with cancer mortality (HR per kg increase in birthweight = 1.04, 95% CI: 0.98–1.10) (Supplementary Figure S3). These results suggest that the associations may differ by sex ($P_{\text{interaction}} = 0.03$). There was no evidence of high heterogeneity among the studies: $I^2 = 20\%$ for men and 0% for women. In the study from Uppsala, Sweden, adjustment for indicators of adult socio-economic circumstances did not alter the estimated associations.[41] In one study,[32] adjustment for gestational age strengthened the positive association among men. In two other studies, year of birth was included as a covariate.[36,38] Non-linearity was assessed in the same two studies, but no evidence of non-linear effects was reported. None of the studies of cancer mortality had adjusted for socio-economic factors in childhood or maternal factors.

Discussion

This systematic review and meta-analysis included data on nearly 40 000 adult deaths among some 400 000 individuals. The results suggest that birthweight is inversely associated with adult mortality from all-causes; more specifically, we found 6% lower mortality per kg higher birthweight in men and women combined. The association appeared to be stronger at relatively low birthweights and levelled off at higher birthweights. We also found that cardiovascular mortality was 12% lower per 1 kg higher birthweight, whereas for cancer mortality, findings differed by sex. For men, the risk of cancer death was 13% higher per kg higher birthweight, but for women, there was little evidence of any association between birthweight and total cancer mortality.

Although the present study demonstrates consistent results across study populations, there are potential concerns about interpretations of the main findings. The major weakness for all study outcomes was heterogeneity in data on potentially confounding factors such as those related to socio-economic circumstances, gestational age and smoking. In the present analysis, adjustments for confounding made in the original studies were incorporated, but the factors that could be taken into account were limited in some studies.

All-cause mortality

Increased risk of CVD associated with lower birthweight is likely to be a main contributor to the inverse association of birthweight with mortality from all-causes. Individual studies with a limited number of cases have reported an association of low birthweight with higher risk of mortality from cirrhosis of the liver[31] and diabetes,[35,38] whereas for diseases of the nervous system, lung diseases and mental disorders,[38,41] the direction of the association has differed between studies. Restricted fetal growth may adversely affect growth and development of specific organs, and may result in reduced function of lungs, kidneys, blood vessels, muscles and brain.[53] Associations with other causes of death are also plausible and need to be examined.

Socio-economic status in childhood is inversely associated with adult mortality, especially from cardiovascular disease, smoking-related cancers, cancer of the stomach and possibly chronic lung disease as well as psychiatric, alcoholic and drug-related deaths.[54,55] Adjustment for parental social class at the time of birth was performed in five studies with no or minimal attenuation of the observed associations. Information on social class was abstracted from records as opposed to self-report, but measures of social class may have been crude, often limited to manual vs non-manual work and the possibility of residual confounding by socio-economic factors cannot be ruled out. Nevertheless, given the minimal change in associations when socio-economic status could be controlled, it seems unlikely that confounding by socio-economic status can account for the main findings of this analysis.

Given the strong relation between length of gestation and birthweight, it is possible that the inverse association of birthweight with all-cause mortality is, at least in part, explained by shorter gestation. Pre-term birth is associated with cognitive[56] and medical disabilities[57] that are associated with increased mortality in adulthood.[58] Adjustment for gestational age in individuals born at term strengthened the association in one study[32] and this may support the interpretation that the higher long-term mortality associated with relatively low birthweight may be attributed to fetal growth restriction. There was, however, no information in the included studies to examine whether the association of birthweight with all-cause mortality could be confounded by premature birth.

The results related to large birth size should be cautiously considered. Women who develop gestational diabetes are more likely to give birth to large babies who are at increased risk of developing diabetes later in life.[16] High birthweight is also associated with increased risk of obesity,[15] which is an important determinant of mortality.[18] Although there was no evidence from the present analyses of an increased mortality risk for individuals born large, the results may be compatible with the results from individual studies suggesting that the association is positive for the highest birthweights when using a higher cut-off for high birthweight than the 4000 g used in our study. The present study did not include appropriate data to test for non-linearity in a meta-regression model, and the use of a standardized meta-regression

approach[59] or an individual patient data meta-analysis would be more appropriate to assess this issue.

Cardiovascular mortality

Many studies report an inverse association of birthweight with adult CVD. An earlier meta-analysis of ischaemic heart disease showed 15–20% risk reduction per kg higher birthweight,[5] with no clear differences between estimates for incidence and mortality. Our findings related to cardiovascular mortality are consistent with that study. The strong inverse association of birthweight with the risk of cardiovascular death is also compatible with studies that have suggested a strong inverse association of birthweight with stroke.[3,6,48,60] It has been suggested that the inverse association of birth size is stronger for haemorrhagic stroke than for ischaemic stroke.[3,61] However, differences between subtypes of stroke were not found in the follow-up of US nurses,[62] nor in a Scottish cohort study.[6] Few cases of haemorrhagic stroke yield imprecise results and further studies are needed.

There is a growing body of evidence that relatively short length of gestation may increase cardiovascular risk later in life.[63,64] Unfortunately, we could not address this issue, since the included studies had not assessed effects of pre-term birth. Studies including incident cases have found that the effect of gestational age may differ between coronary heart disease and stroke. For stroke, lower gestational age may be associated with increased risk,[6,65] but it was recently suggested that the association of birthweight with coronary heart disease may be explained by restricted fetal growth, rather than by low gestational age

Our main findings for CVD mortality were unlikely to be attributed to confounding by socio-economic status early in life. A similar interpretation was made from a previous meta-analysis on birthweight and ischaemic heart disease.[5] This may support an interpretation that the inverse association between birthweight and adult cardiovascular disease is not attributed to confounding by socio-economic status early in life.

Several mechanisms could explain the increased risk of cardiovascular disease associated with being born small. The dominant hypothesis is that intrauterine under-nutrition causes fetal adaptations that are related to adverse cardiovascular risk later in life.[7] This interpretation has been supported by numerous animal studies[9] and may also be supported by studies that found indicators of fetal growth restriction, rather than birthweight itself, to be associated with CVD.[41] However, common genetic factors[45,46] could be associated with both small birth size and cardiovascular risk.[11,12] Also, genetic and non-genetic factors are likely to interact over the life course,[66] possibly through epigenetic mechanisms[67–69] and cause CVD.

Cancer mortality

Higher birthweight was associated with higher risk of cancer in men, but not in women. That the positive association of birthweight was restricted to men may be surprising, since there is strong evidence that birthweight is positively associated with breast cancer risk.[21,70] The result are compatible with main findings of a follow-up study of individuals born in Uppsala, Sweden, between 1915 and 1929.[20] That study included almost 3000 primary cancers and reported a positive association between birthweight and all cancers combined. For men, the adjusted HR for all cancers associated with 1 SD gestational age-adjusted birthweight was 1.08 (95% CI: 1.02–1.14). In women, the corresponding HR for women <50 years was 1.23 (95% CI: 1.06–1.44), whereas for women aged $\geqslant 50$ years no association was observed [HR = 0.98 (95% CI: 0.91–1.05)]. The lack of association in the older age group of women was explained by the lack of any association of birthweight with the risk of post-menopausal breast cancer in that study. Another follow-up study of more than 200 000 Danes born between 1936 and 1975[19] included more than 12 000 cases of invasive cancer and reported a 7% increased total cancer risk per kg increase in birthweight. The main result in this study did not differ by sex and/or by menopausal status.

The individual studies included in the present analysis did not report associations for specific cancer types. Mean age at death from cancer was between 50 and 60 years, indicating that the findings are based on relatively early cancer deaths. The results from studies of cancer incidence show conflicting evidence related to specific cancer types. In the Swedish study,[20] birthweight was positively associated with risks for lymphatic and haematopoietic cancers and for colorectal cancer. In the Danish study,[19] there were positive associations of birthweight with the risk of kidney and lung cancer, multiple myeloma and malignant melanoma. Other studies have suggested positive associations of birthweight with prostate[71] and testicular cancer,[72] but results have not been consistent.[19,73]

The present meta-analysis included all cohort studies reporting associations of birthweight with adult cancer mortality. Consistent findings across studies and a large number of cases limit the possibility that the main findings could be due to chance. The study quality was generally high, there was no evidence of heterogeneity and the estimated associations were homogenous across studies. The individual studies included limited information on potential confounding factors. However, different mechanisms of confounding may apply to the association of birthweight with cancer than with CVD. There is no evidence that adverse socio-economic circumstances in childhood are associated with increased risk of all cancers.[54,55] In the Uppsala cohort,[20,41] adjustment

for socio-economic and maternal factors did not substantially change the estimated associations of birthweight with cancer mortality. However, it is possible that maternal conditions associated with large birth size, such as gestational diabetes or obesity, may influence long-term cancer risk.

The biological mechanisms for the association of pre-natal factors with adult cancer are poorly understood. Birthweight is a marker for different factors related to intrauterine growth, such as maternal factors, growth factors, hormones, epigenetic changes and genetic variations. The positive association of birth size with breast cancer risk observed in many studies has been explained by high levels of hormones that both increase fetal growth and long-term susceptibility to cancer.[74] Factors that promote fetal growth may influence long-term cancer risk by alterations in the number of stem cells or expression of genes that regulate stem cell behaviour.[75] Finally, gene–environment interactions may be an alternative explanation.[69,76] Environmental influences that enhance fetal growth may cause altered gene expression that increase susceptibility to cancers. Such epigenetic mechanisms have been demonstrated in pregnant mice fed with a high-fat diet resulting in increased incidence of tumours in the offspring,[69] whereas poor maternal nutrition has been suggested to increase breast cancer risk.[77]

Studies are needed to identify which cancers are related to large birth size and more research is required to understand prenatal processes that could be important for the pathogenesis of cancer in adulthood.

Study strengths and limitation

Search strategies for observational studies pose a challenge and incomplete identification of studies is a potential source of bias. We sought to reduce this potential bias by completing two different search strategies that selected the studies separately. Despite very high agreement in the searches, we cannot be certain that some studies were not missed.

The large number of deaths is a strong feature of these analyses, and <1% of all reported deaths were excluded from the analyses due to unavailable data. Very modest heterogeneity among studies suggests robust associations of birthweight with mortality across different study populations. However, all studies were from high-income countries, mainly in northern Europe and we cannot generalize results to societies where health-care resources are scarce and nutrition may be less satisfactory. Participants in the included studies were born across a considerable time span, mainly from around the turn of the 20th century up to 1979, but findings were largely consistent across different birth cohorts. We could not evaluate whether associations differed by age at death, but mean age at death varied between 35 and 60 years in the included studies, indicating that birthweight is a predictor of mortality at fairly young to middle adult age. One study[36] reported constant HRs across the life course.

The included studies were of high quality and individual studies depended on assessment of outcomes from official registries. Misclassification of causes of death may still introduce bias, although it is unlikely that this misclassification is related to birth size and would therefore mainly underestimate associations.

Conclusion

This systematic review reveals evidence that lower birthweight is associated with increased all-cause mortality in men and women. The results also show strong evidence of an inverse association of birthweight with cardiovascular mortality that do not differ by sex. For cancer mortality, there was a strong positive association of birthweight with cancer mortality in men, but not in women. The findings suggest that birthweight is an indicator of developmental processes that influence long-term health. However, the available data cannot determine whether social factors, genetic factors, the intrauterine environment or life course exposures are more influential in explaining the observed associations.

Supplementary Data

Supplementary data are available at *IJE* online.

Funding

Liaison Committee between the Central Norway Regional Health Authority (RHA); Norwegian University of Science and Technology (NTNU to K.R.R.).

Acknowledgements

This study is included in the activities of the Danish Obesity Research Centre (DanORC, www.danorc.dk). K.R.R. planned the study, collected and analysed the data, interpreted the results and wrote the paper. L.J.V. interpreted the results and revised the manuscript. J.L.B., K.J., M.O., L.L., U.S., R.M., V.S., R.C.P., M.J., E.K., J.E. and T.I.A.S. provided additional results to the study, as requested from the first author on the basis of the protocol, interpreted the results and reviewed the manuscript. G.W.J. abstracted data, assessed quality of studies and revised the manuscript. M.B.B. planned the study, interpreted the results and revised the paper. M.B.B. is guarantor for this study. Thanks to Solveig Isabel Taylor, Academic Librarian, NTNU Library, Medical Library, who completed the alternative search strategy for relevant studies.

Conflict of interest: The first and second authors were first and last authors of one of the included studies. Assessment of bias for that study was done by the two independent authors (G.W.J. and M.B.B.). There is no conflict of interest related to this work. The lead author has checked references for accuracy and completeness and confirms that this material has not been published previously in a substantially similar form.

References

[1] Wilcox AJ. On the importance–and the unimportance–of birthweight. *Int J Epidemiol* 2001;**30:**1233–41.

[2] Barker DJ, Osmond C, Simmonds SJ, Wield GA. The relation of small head circumference and thinness at birth to death from cardiovascular disease in adult life. *BMJ* 1993;**306:**422–26.

[3] Eriksson JG, Forsen T, Tuomilehto J, Osmond C, Barker DJ. Early growth, adult income, and risk of stroke. *Stroke* 2000;**31:**869–74.

[4] Osmond C, Barker DJ, Winter PD, Fall CH, Simmonds SJ. Early growth and death from cardiovascular disease in women. *BMJ* 1993;**307:**1519–24.

[5] Huxley R, Owen CG, Whincup PH *et al*. Is birth weight a risk factor for ischemic heart disease in later life? *Am J Clin Nutr* 2007;**85:**1244–50.

[6] Lawlor DA, Ronalds G, Clark H, Smith GD, Leon DA. Birth weight is inversely associated with incident coronary heart disease and stroke among individuals born in the 1950s: findings from the Aberdeen Children of the 1950s prospective cohort study. *Circulation* 2005;**112:** 1414–18.

[7] Barker DJ, Gluckman PD, Godfrey KM, Harding JE, Owens JA, Robinson JS. Fetal nutrition and cardiovascular disease in adult life. *Lancet* 1993;**341:**938–41.

[8] Forsdahl A. Are poor living conditions in childhood and adolescence an important risk factor for arteriosclerotic heart disease? *Br J Prev Soc Med* 1977;**31:**91–95.

[9] Bateson P, Barker D, Clutton-Brock T *et al*. Developmental plasticity and human health. *Nature* 2004;**430:**419–21.

[10] Bergvall N, Cnattingius S. Familial (shared environmental and genetic) factors and the foetal origins of cardiovascular diseases and type 2 diabetes: a review of the literature. *J Intern Med* 2008;**264:**205–23.

[11] Hattersley AT, Tooke JE. The fetal insulin hypothesis: an alternative explanation of the association of low birthweight with diabetes and vascular disease. *Lancet* 1999; **353:**1789–92.

[12] Davey Smith G, Hypponen E, Power C, Lawlor DA. Offspring birth weight and parental mortality: prospective observational study and meta-analysis. *Am J Epidemiol* 2007;**166:**160–69.

[13] Ben-Shlomo Y, Kuh D. A life course approach to chronic disease epidemiology: conceptual models, empirical challenges and interdisciplinary perspectives. *Int J Epidemiol* 2002;**31:**285–93.

[14] Gluckman PD, Hanson MA, Cooper C, Thornburg KL. Effect of in utero and early-life conditions on adult health and disease. *N Engl J Med* 2008;**359:**61–73.

[15] Rugholm S, Baker JL, Olsen LW, Schack-Nielsen L, Bua J, Sorensen TI. Stability of the association between birth weight and childhood overweight during the development of the obesity epidemic. *Obes Res* 2005;**13:**2187–94.

[16] Harder T, Roepke K, Diller N, Stechling Y, Dudenhausen JW, Plagemann A. Birth weight, early weight gain, and subsequent risk of type 1 diabetes: systematic review and meta-analysis. *Am J Epidemiol* 2009; **169:**1428–36.

[17] Batty GD, Shipley MJ, Jarrett RJ, Breeze E, Marmot MG, Davey Smith G. Obesity and overweight in relation to disease-specific mortality in men with and without existing coronary heart disease in London: the original Whitehall study. *Heart* 2006;**92:**886–92.

[18] Whitlock G, Lewington S, Sherliker P *et al*. Body-mass index and cause-specific mortality in 900 000 adults: collaborative analyses of 57 prospective studies. *Lancet* 2009; **373:**1083–96.

[19] Ahlgren M, Wohlfahrt J, Olsen LW, Sorensen TI, Melbye M. Birth weight and risk of cancer. *Cancer* 2007; **110:**412–19.

[20] McCormack VA, dos Santos Silva I, Koupil I, Leon DA, Lithell HO. Birth characteristics and adult cancer incidence: Swedish cohort of over 11,000 men and women. *Int J Cancer* 2005;**115:**611–17.

[21] Xue F, Michels KB. Intrauterine factors and risk of breast cancer: a systematic review and meta-analysis of current evidence. *Lancet Oncol* 2007;**8:**1088–100.

[22] Silva Idos S, De Stavola B, McCormack V. Birth size and breast cancer risk: re-analysis of individual participant data from 32 studies. *PLoS Med* 2008;**5:**e193.

[23] Vatten LJ, Maehle BO, Lund Nilsen TI *et al*. Birth weight as a predictor of breast cancer: a case-control study in Norway. *Br J Cancer* 2002;**86:**89–91.

[24] Kramer MS, Morin I, Yang H *et al*. Why are babies getting bigger? Temporal trends in fetal growth and its determinants. *J Pediatr* 2002;**141:**538–42.

[25] Wen SW, Kramer MS, Platt R *et al*. Secular trends of fetal growth in Canada, 1981 to 1997. *Paediatr Perinat Epidemiol* 2003;**17:**347–54.

[26] Schack-Nielsen L, Molgaard C, Sorensen TI, Greisen G, Michaelsen KF. Secular change in size at birth from 1973 to 2003: national data from Denmark. *Obesity* 2006;**14:**1257–63.

[27] Stroup DF, Berlin JA, Morton SC *et al*. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA* 2000;**283:**2008–12.

[28] Deeks JJ, Dinnes J, D'Amico R *et al*. Evaluating non-randomised intervention studies. *Health Technol Assess* 2003;**7:**iii–x, 1–173.

[29] Friedlander Y, Paltiel O, Deutsch L *et al*. Birthweight and relationship with infant, child and adult mortality in the Jerusalem perinatal study. *Paediatr Perinat Epidemiol* 2003; **17:**398–406.

[30] Parmar MK, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. *Stat Med* 1998;**17:**2815–34.

[31] Andersen AM, Osler M. Birth dimensions, parental mortality, and mortality in early adult age: a cohort study of Danish men born in 1953. *Int J Epidemiol* 2004;**33:** 92–99.

[32] Kajantie E, Osmond C, Barker DJ, Forsen T, Phillips DI, Eriksson JG. Size at birth as a predictor of mortality in adulthood: a follow-up of 350 000 person-years. *Int J Epidemiol* 2005;**34:**655–63.

[33] Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002;**21:**1539–58.

[34] Morley R, McCalman J, Carlin JB. Birthweight and coronary heart disease in a cohort born 1857–1900 in Melbourne, Australia. *Int J Epidemiol* 2006;**35:**880–85.

[35] Lapidus L, Andersson SW, Bengtsson C, Bjorkelund C, Rossander-Hulthen L, Lissner L. Weight and length at birth and their relationship to diabetes incidence and all-cause mortality–a 32-year follow-up of the population study of women in Gothenburg, Sweden. *Prim Care Diabetes* 2008;**2:**127–33.

[36] Baker JL, Olsen LW, Sorensen TI. Weight at birth and all-cause mortality in adulthood. *Epidemiology* 2008;**19:** 197–203.

[37] Jokela M, Batty GD, Deary IJ, Gale CR, Kivimaki M. Low Childhood IQ and Early Adult Mortality: The Role of Explanatory Factors in the 1958 British Birth Cohort. *Pediatrics* 2009;**124:**e380–88.

[38] Syddall HE, Sayer AA, Simmonds SJ *et al*. Birth weight, infant weight gain, and cause-specific mortality: the Hertfordshire Cohort Study. *Am J Epidemiol* 2005;**161:** 1074–80.

[39] Risnes KR, Nilsen TI, Romundstad PR, Vatten LJ. Head size at birth and long-term mortality from coronary heart disease. *Int J Epidemiol* 2009;**38:**955–62.

[40] Painter RC, Roseboom TJ, Bossuyt PM, Osmond C, Barker DJ, Bleker OP. Adult mortality at age 57 after prenatal exposure to the Dutch famine. *Eur J Epidemiol* 2005;**20:**673–76.

[41] Leon DA, Lithell HO, Vagero D *et al*. Reduced fetal growth rate and increased risk of death from ischaemic heart disease: cohort study of 15 000 Swedish men and women born 1915–29. *BMJ* 1998;**317:**241–45.

[42] Power C, Li L. Cohort study of birthweight, mortality, and disability. *BMJ* 2000;**320:**840–41.

[43] Osler M, Andersen AM, Due P, Lund R, Damsgaard MT, Holstein BE. Socioeconomic position in early life, birth weight, childhood cognitive function, and adult mortality. A longitudinal study of Danish men born in 1953. *J Epidemiol Community Health* 2003;**57:**681–86.

[44] Roseboom TJ, van der Meulen JH, Osmond C, Barker DJ, Ravelli AC, Bleker OP. Adult survival after prenatal exposure to the Dutch famine 1944–45. *Paediatr Perinat Epidemiol* 2001;**15:**220–25.

[45] Frankel S, Elwood P, Sweetnam P, Yarnell J, Smith GD. Birthweight, adult risk factors and incident coronary heart disease: the Caerphilly Study. *Public Health* 1996; **110:**139–43.

[46] Nilsson PM, Hofvendahl S, Hofvendahl E, Brandt L, Ekbom A. Smoking in pregnancy in relation to gender and adult mortality risk in offspring: the Helsingborg Birth Cohort Study. *Scand J Public Health* 2006;**34:**660–64.

[47] McCalman J, Morley R, Mishra G. A health transition: birth weights, households and survival in an Australian working-class population sample born 1857–1900. *Soc Sci Med* 2008;**66:**1070–83.

[48] Risnes KR, Romundstad PR, Nilsen TI, Eskild A, Vatten LJ. Placental weight relative to birth weight and long-term cardiovascular mortality: findings from a cohort of 31,307 men and women. *Am J Epidemiol* 2009; **170:**622–31.

[49] Koupilova I, Leon DA, McKeigue PM, Lithell HO. Is the effect of low birth weight on cardiovascular mortality mediated through high blood pressure? *J Hypertens* 1999; **17:**19–25.

[50] Eriksson M, Wallander MA, Krakau I, Wedel H, Svardsudd K. The impact of birth weight on coronary heart disease morbidity and mortality in a birth cohort followed up for 85 years: a population-based study of men born in 1913. *J Intern Med* 2004;**256:**472–81.

[51] Baker JL, Olsen LW, Sorensen TI. Childhood body-mass index and the risk of coronary heart disease in adulthood. *N Engl J Med* 2007;**357:**2329–37.

[52] Leon DA, Koupilova I, Lithell HO *et al*. Failure to realise growth potential in utero and adult obesity in relation to blood pressure in 50 year old Swedish men. *BMJ* 1996; **312:**401–6.

[53] de Boo HA, Harding JE. The developmental origins of adult disease (Barker) hypothesis. *Aust N Z J Obstet Gynaecol* 2006;**46:**4–14.

[54] Galobardes B, Lynch JW, Davey Smith G. Childhood socioeconomic circumstances and cause-specific mortality in adulthood: systematic review and interpretation. *Epidemiol Rev* 2004;**26:**07–21.

[55] Lawlor DA, Sterne JA, Tynelius P, Davey Smith G, Rasmussen F. Association of childhood socioeconomic position with cause-specific mortality in a prospective record linkage study of 1,839,384 individuals. *Am J Epidemiol* 2006;**164:**907–15.

[56] Aarnoudse-Moens CS, Weisglas-Kuperus N, van Goudoever JB, Oosterlaan J. Meta-analysis of neurobehavioral outcomes in very preterm and/or very low birth weight children. *Pediatrics* 2009;**124:**717–28.

[57] Moster D, Lie RT, Markestad T. Long-term medical and social consequences of preterm birth. *N Engl J Med* 2008; **359:**262–73.

[58] Hemmingsson T, Melin B, Allebeck P, Lundberg I. The association between cognitive ability measured at ages 18–20 and mortality during 30 years of follow-up–a prospective observational study among Swedish males born 1949–51. *Int J Epidemiol* 2006;**35:**665–70.

[59] Gamborg M, Byberg L, Rasmussen F *et al*. Birth weight and systolic blood pressure in adolescence and adulthood: meta-regression analysis of sex- and age-specific results from 20 Nordic studies. *Am J Epidemiol* 2007;**166:** 634–45.

[60] Kaijser M, Bonamy AK, Akre O *et al*. Perinatal risk factors for ischemic heart disease: disentangling the roles of birth weight and preterm birth. *Circulation* 2008;**117:** 405–10.

[61] Hypponen E, Leon DA, Kenward MG, Lithell H. Prenatal growth and risk of occlusive and haemorrhagic stroke in Swedish men and women born 1915–29: historical cohort study. *BMJ* 2001;**323:**1033–34.

[62] Rich-Edwards JW, Kleinman K, Michels KB *et al*. Longitudinal study of birth weight and adult body mass index in predicting risk of coronary heart disease and stroke in women. *BMJ* 2005;**330:**1115.

[63] Hack M. Adult outcomes of preterm children. *J Dev Behav Pediatr* 2009;**30:**460–70.

[64] Hovi P, Andersson S, Eriksson JG *et al*. Glucose regulation in young adults with very low birth weight. *N Engl J Med* 2007;**356:**2053–63.

[65] Koupil I, Leon DA, Lithell HO. Length of gestation is associated with mortality from cerebrovascular disease. *J Epidemiol Community Health* 2005;**59:**473–74.

[66] Kuh DaB-S Y (ed.). *A Life Course Approach to Chronic Disease Epidemiology*. 2nd edn. Oxford: Oxford University Press, 2004.

[67] Sinclair KD, Lea RG, Rees WD, Young LE. The developmental origins of health and disease: current theories and epigenetic mechanisms. *Soc Reprod Fertil Suppl* 2007;**64:** 425–43.

[68] Burdge GC, Lillycrop KA. Nutrition, epigenetics, and developmental plasticity: implications for understanding human disease. *Annu Rev Nutr* 2010;**30:**315–39.

[69] Aguilera O, Fernandez AF, Munoz A, Fraga MF. Epigenetics and environment: a complex relationship. *J Appl Physiol* 2010;**109:**243–51.

[70] Silva Idos S, De Stavola B, McCormack V, Collaborative Group on Pre-Natal Risk F, Subsequent Risk of Breast C. Birth size and breast cancer risk: re-analysis of individual participant data from 32 studies. *PLoS Med* 2008;**5:**e193.

[71] Eriksson M, Wedel H, Wallander MA *et al*. The impact of birth weight on prostate cancer incidence and mortality in a population-based study of men born in 1913 and followed up from 50 to 85 years of age. *Prostate* 2007; **67:**1247–54.

[72] Ramlau-Hansen CH, Olesen AV, Parner ET, Sorensen HT, Olsen J. Perinatal markers of estrogen exposure and risk of testicular cancer: follow-up of 1,333,873 Danish males born between 1950 and 2002. *Cancer Causes Control* 2009; **20:**1587–92.

[73] Platz EA, Giovannucci E, Rimm EB *et al*. Retrospective analysis of birth weight and prostate cancer in the Health Professionals Follow-up Study. *Am J Epidemiol* 1998;**147:**1140–44.

[74] Trichopoulos D. Hypothesis: does breast cancer originate in utero? *Lancet* 1990;**335:**939–40.

[75] Johnson KJ, Springer NM, Bielinsky AK, Largaespada DA, Ross JA. Developmental origins of cancer. *Cancer Res* 2009;**69:**6375–77.

[76] Burdge GC, Lillycrop KA, Jackson AA. Nutrition in early life, and risk of cancer and metabolic disease: alternative endings in an epigenetic tale? *Br J Nutr* 2009;**101:** 619–30.

[77] Painter RC, De Rooij SR, Bossuyt PM *et al*. A possible link between prenatal exposure to famine and breast cancer: a preliminary study. *Am J Hum Biol* 2006;**18:** 853–56.