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ORIGINAL ARTICLE

Does birthweight predict bone mass in adulthood? A systematic review and meta-analysis

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Abstract
Summary This systematic review and meta-analysis assessed the strength and magnitude of the association between birthweight and adult bone mass. Higher birthweight was associated with higher bone mineral content of the spine and hip in adult men and women at ages between 18 and 80 years across a range of settings.
Introduction The aim of this review was to assess the strength and magnitude of the association between early size and adult bone mass.
Methods Systematic review and meta-analysis of studies that assessed the association between birthweight or weight at 1 year, and bone mineral content (BMC) or bone mineral density (BMD) in adulthood.
Results Fourteen studies met inclusion criteria. Nine assessed the relationship between birthweight and lumbar spine BMC, most showing that higher birthweight was associated with greater adult BMC. Meta-analysis demonstrated that a 1 kg increase in birthweight was associated with a 1.49 g increase in lumbar spine BMC (95% CI 0.77-2.21). Birthweight was not associated with lumbar spine BMD in 11 studies. In six studies, considering the relationship between birthweight and hip BMC, most found that higher birthweight was associated with greater BMC. Meta-analysis demonstrated that a 1 kg increase in birthweight was associated with a 1.41 g increase in hip BMC (95% CI 0.91-1.91). Seven studies considered the relationship between birthweight and hip BMD and, in most, birthweight was not a significant predictor of hip BMD. Three studies assessing the relationship between weight at 1 year and adult bone mass all reported that higher weight at one was associated with greater BMC of the lumbar spine and hip.
Conclusions Higher birthweight is associated with greater BMC of the lumbar spine and hip in adulthood. The consistency of these associations, across a range of settings, provides compelling evidence for the intrauterine programming of skeletal development and tracking of skeletal size from infancy to adulthood.

Keywords Developmental origins · Epidemiology · Osteoporosis · Programming

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Introduction

Bone mass in adulthood depends on the peak bone mass attained during skeletal growth and on the subsequent rate of bone loss. While a number of factors are known to predict risk of osteoporosis including exercise and diet, a substantial proportion of the variance in bone mass within the general population cannot be explained by known genetic and environmental factors [1]. There is growing evidence to suggest that part of the residual variance in bone mass may be explained by pre- and post-natal growth [2]. Studies from around the world have suggested that low birthweight is associated with lower bone mass in later life. However, they have often studied small numbers of subjects, and their results have been inconsistent. We have

carried out a systematic review to assess the strength of evidence in support of an association between early size and adult bone mass, and to explore the magnitude of this relationship.

Methods

We sought studies relating birthweight or weight at 1 year of age to bone mineral content, bone mineral density or osteoporotic fracture in adults aged 18 years and over. We did not impose any limits in relation to study setting, timing or language. We excluded ecological studies and non-human studies but did not impose any other limits on study design.

We searched Medline and Embase from their start dates to June 2009, and handsearched the bibliographies of all included studies. A single reviewer independently assessed each title and abstract for relevance to the review.

We followed the methods recommended by the Centre for Reviews and Dissemination (CRD), University of York [3]. Two reviewers (JB and AK) assessed potentially relevant papers in detail. Disagreements over inclusion were resolved through consensus and, where necessary, following discussion with a third member of the review team.

The quality of included studies was assessed by the two reviewers, using a checklist of questions. The questions used, while based on CRD guidelines, were developed in an iterative process of piloting. A number of aspects of quality were assessed according to whether they posed a low, medium or high risk of bias for study results. Aspects of quality assessed included appropriateness of study design, ascertainment of exposure and outcome, and consideration of the effects of important confounding factors. The effect modifiers and confounding factors we considered important in the relation between early size and later bone mass were physical activity, alcohol intake, smoking, dietary calcium, current medication including oestrogen, and menopausal status. Risk of bias ratings for each aspect of quality were used to produce an overall numerical quality score where scores within a particular range indicated whether the study had low, medium or high risk of bias in relation to the review question. Overall judgment on study quality, as summarised in Table 2, was based on the combination of performance in the checklist and consensus between the two independent reviewers.

In order to combine studies that reported correlation coefficients with studies that used linear regression methods in our meta-analyses, we applied a method of estimation based on the fact that a correlation coefficient is equivalent to a standardised regression coefficient, i.e. the slope of a regression line with both predictor and outcome variables expressed as Z-scores. Therefore, to convert a correlation coefficient into a regression coefficient, we multiplied it by the ratio of the standard deviations of the outcome and predictor variables [4], wherever the baseline data were available. The associated standard errors were obtained using the same method. Meta-analyses were then carried out using the 'metan' command in Stata version 11.0 software [5], to derive pooled estimates of regression coefficients and 95% CIs for the relationships between birthweight and adult BMC or BMD, using fixed effects models (Mantel-Haenszel method [6]). When the heterogeneity test based on the Q statistic yielded a P value <0.1, a new estimate was computed using a random effects model [7]. Forest plots were used to visually assess the results across studies, and a sensitivity analysis was performed to explore the influence of gender on our findings.

Results

Searches identified 4,142 abstracts. Screening of abstracts and reference lists identified 30 studies of potential relevance. Following detailed assessment, 14 studies met review inclusion criteria. All were cohort studies. Eight were set in the UK, three in other European countries, one in the USA, one in New Zealand and one in Japan. All studies considered the relationship between birthweight and adult bone mass at a number of different anatomical sites, with three of the 14 studies also assessing the relationship between weight at 1 year of age and later bone mass (Table 1). Of the 16 excluded studies, most were excluded either because the age at which outcomes were measured was less than 18 years or because the relationship between birthweight and adult bone mass was not reported. Table 2 describes the characteristics of included studies and their main findings.

The association of birthweight with bone mass of the lumbar spine

Thirteen studies assessed the relationship between birthweight and bone mass of the lumbar spine [8–20]. Eight of the studies were set in the UK [8–10, 12–14, 16, 18], one in the USA [11], one in New Zealand [19], one in Japan [17] and two in the Netherlands [15, 20].

Birthweight and lumbar spine BMC

Nine of the 13 studies considered the relationship between birthweight and BMC of the lumbar spine [9–12, 14–17, 19] and all but two reported a statistically significant positive association at ages ranging from 18 to 89 years. Two of the studies related to women only [11, 17] while the remaining seven studies included both men and women.

Table 1 Anatomical sites considered for bone mass outcomes

Outcome—anatomical site	Studies considering relationship with birthweight	Studies considering relationship with weight at 1year
Lumbar spine	Hamed [8], Cooper 1995 [9], Cooper1997 [10] Yarborough [11], Gale [12], McGuigan [13], Antoniades [14], Te Velde [15], Dennison [16], Saito [17], Pearce [18], Dalziel [19], Leunissen [20]	Cooper 1995 [9], Cooper 1997 [10], Dennison [16]
Total hip (proximal femur)	Cooper 1995 [9], Yarborough [11], McGuigan [13], Antoniades [14], Te Velde [15], Dennison [16], Saito [17], Pearce [18], Dalziel [19]	Cooper 1995 [9], Dennison [16]
Femoral neck	Hamed [8], Cooper 1997 [10], Gale [12]; Antoniades [14], Dalziel [19]	Cooper 1997 [10]
Distal radius and/or ulna	Yarborough [11], Antoniades [14], Laitinen [21]	

Two studies failed to show a statistically significant relationship between birthweight and lumbar spine BMC. The first, by Dalziel et al. of 174 adults aged 34 years, reported a positive relationship in univariate analyses, but this was no longer significant following adjustment for current size and other confounding factors. The second was of men and women aged 63–73 years in Hertfordshire, UK [10]. An association between birthweight and lumbar spine BMC of borderline significance was reported in the 189 women but there was no significant trend in the 224 men.

We combined the findings of six of the nine studies that considered the relationship between birthweight and lumbar spine BMC in a meta-analysis [11, 14–17, 19]. The three studies that were not included did not report sufficient data to allow their inclusion. These three studies were all of UK cohorts: two of these, based in Bath and Sheffield [9, 12], reported positive associations between birthweight and BMC while the third, of men and women in Hertfordshire demonstrated a borderline significant association in women but not men [10].

We used both fixed and random effects models to compute the pooled estimate for the relationship between birthweight and lumbar spine BMC in the six studies, because the I-squared statistic suggested that 34% of the variation between studies was due to heterogeneity rather than chance. Both models yielded a positive estimate, and suggested a relatively strong association between birthweight and lumbar spine BMC (Fig. 1). The pooled estimate suggested that an increase in 1 kg birthweight is associated with a lumbar spine BMC increase of 1.49 g (95% CI 0.77, 2.21). Since our meta-analysis included both sex-specific and non-sex-specific measures of association, we carried out a sensitivity analysis to compare results from a meta-analysis comprising studies of women only with those from a meta-analysis combining studies that were not sex-specific (only one study looked at men only). The effect was stronger in women, whereby an increase in 1 kg birthweight was associated with an increase in 2.88 g lumbar spine BMC (95% CI 1.56, 4.21), whilst for studies that did not stratify by sex, the meta-analysis yielded a pooled estimate of only 0.64 g increase in lumbar spine BMC for a 1 kg birthweight increase (95% CI –0.28, 1.56).

Birthweight and lumbar spine BMD

Eleven studies reported the association between birthweight and BMD of the lumbar spine [6, 9, 11–20]. Three of the studies, two based in the UK and one in the USA, stated that there was no significant association between birthweight and BMD but did not report any statistical findings [8, 11, 13]. A fourth study of women aged 21 years in Bath, UK, reported a correlation of 0.05 but did not report significance levels [9]. Increase in BMD across thirds of birthweight was not statistically significant in the Sheffield study of men and women aged 70–75 years [12]. The remaining six studies [14–16, 18–20] also reported that there was no statistically significant relationship between birthweight and lumbar spine BMD, after adjustment for confounding factors. These six studies were combined in a meta-analysis (Fig. 2), which confirmed that there was no association between birthweight and lumbar spine BMD in the studies considered. The pooled estimate was close to zero at 0.002 (95% CI –0.007, 0.010).

The association of birthweight with bone mass of the hip

Nine studies assessed the relationship between birthweight and bone mass of the hip (or proximal femur) [9, 11, 13–19]. Five of the studies were set in the UK [9, 13, 14, 16, 18], one in the Netherlands [15], one in Japan [17], one in New Zealand [19], and the ninth in the USA [11].

Birthweight and hip BMC

Six studies reported the relationship between birthweight and hip BMC and all reported a positive association with higher birthweight associated with greater levels of BMC at ages ranging between 18 and 66 years, in both men and women [9, 11, 15–17, 19]. Combining regression coefficients from five of the six studies in a meta-analysis (Fig. 3) [11, 15–17, 19], the pooled estimate suggested that

Table 2 Summary data extracted from studies included in review

Study details	Participants and setting			Main findings	Risk of bias	Summary of trend
	Number	% Follow up	Mean (SD) bwt and wt at 1 year (kg)			
Hamed [8] 1993 Osteoporosis International	230 women aged 20–23 years UK	Not stated	Mean bwt not reported	*Birthweight (Bwt)* was exposure of interest. 58 participants were low birthweight (LBW) <2.5 kg, 17 were preterm and the rest were small for gestational age. BMD at lumbar spine and femoral neck did not differ significantly in the preterm infants or LBW group as a whole, when compared with the 172 normal bwt infants. In all 230 participants, there was no significant correlation between bwt and BMD at either site: Lumbar spine r=0.08, 95% CI 0.05, 0.21 Femoral neck r=0.10 95% CI 0.03, 0.23.	High	*No association* between bwt and BMD of lumbar spine and femoral neck at age 20–23 years
Cooper [9] 1995 J Bone Min Res	153 women aged 21–22 years Bath UK	47%	Bwt 3.31(0.51) Wt at 1 year 9.81 (0.91)	*Bwt and weight (wt) at 1 year* were exposures of interest. There was no significant association between bwt and BMC at either site. Wt at 1 year was positively associated with BMC of the lumbar spine and proximal femur (hip). Proximal femur BMC r=0.26 p<0.01 Lumbar spine BMC r=0.32 p<0.01	Medium	*Positive* association between wt at 1 year and BMC lumbar spine and hip in women aged 21 years. *No association* between bwt and BMC of the lumbar spine or hip.
Cooper [10] 1997 Ann Rheumatic Disease	413 (189 women, 224 men) aged 63–73 years, born 1920-1930 Hertfordshire, UK	63%	Bwt: Men 3.60 (0.61) Women 3.46 (0.53) Wt at 1 year Men 10.31 (1.25) Women 9.63 (1.07)	*Bwt and wt at 1 year* were exposures of interest. Bwt was not associated with BMC or BMD in either sex. In unadjusted analyses, there was a positive association between wt at 1 year and BMC of lumbar spine and femoral neck in women. Positive association also present in spine, for men but not femoral neck. Men Women Lumbar spine r=0.16 p=0.02 r=0.15, p=0.04 Femoral neck r=0.06 p=0.41 r=0.15, p=0.03	Medium	*Positive* association between wt at 1 year and BMC of the lumbar spine and femoral neck at age 63–73 years. No association between bwt and BMC or BMD.
Yarborough [11] 2000 Osteoporosis	305 women aged 47–89 years USA	80%	3.4 (0.8)	*Bwt* was correlated with age-adjusted BMC at hip, lumbar spine and mid-shaft radius Hip r=0.12 p=0.04 Lumbar spine r=0.18 p=0.002 Midshaft radius r=0.15 p=0.01 Only association between bwt and lumbar spine BMC remained significant after adjustment for confounding factors. Age-adjusted BMD was not significantly correlated with birthweight Hip r=0.05 p=0.43 Lumbar spine r=0.08 p=0.18 Midshaft radius r=0.09 p=0.13	Medium	*Positive* association between bwt and BMC of lumbar spine in post-menopausal women aged 47–89 years
Gale [12] 2001 JECM	143 (102 men and 41 women) aged 70–75 years Sheffield, UK	44%	Men 3.39 (0.52)	*Bwt* was correlated with BMC of the lumbar spine and femoral neck in men and women—paper states that these remain significant after adjustment for confounding—but adjusted findings not reported. Bwt also had positive association with BMD of the lumbar spine and femoral neck in women, although not men.	Medium	*Positive* association between bwt and BMC of lumbar spine and femoral neck in men and women aged 70–75 years

			Women 3.23 (0.44)	BMC (g) and BMD (g/cm$_2$) levels are reported according to thirds of bwt (kg)—see below. No correlation coefficients were presented for bwt, lumbar spine and femoral neck associations. Men BMC: <3.15 / 3.15-3.64 / >3.64 / *p* for trend Lumbar spine: 69.61 / 75.28 / 78.23 / 0.012 Femoral neck: 4.40 / 4.65 / 4.73 / 0.024 Women BMC Lumbar spine: 46.52 / 48.64 / 56.41 / 0.003 Femoral neck: 3.14 / 3.18 / 3.72 / 0.004		
McGuigan [13] 2002 J Bone and Mineral Research	460 (244 men, 216 women) aged 22 years Northern Ireland	45%	Men 3.46 (0.59) Women 3.34 (0.49)	No significant association between *bwt* and BMD of spine or hip. No regression coefficients reported for bwt/BMD relationship. In women, current weight accounted for most variance in spine and hip BMD. In men, physical activity was the most important predictor of BMD at both sites. No statistics presented relating to these associations.	Medium	*No association* between bwt and total hip and spine BMD in men or women aged 22 years
Antoniades [14] 2003 Rheumatology	2,822 (1,411 twin pairs) aged 47.5 years UK	70%	2.39 (0.61)	*Bwt* was exposure of interest. There was an inverse assoc between bwt and BMD (g/cm^2) at lumbar spine, hip and forearm in univariate analyses. However, none of the associations persisted after adjustment for current size. Findings of regression analyses reported below apply to monozygotic and dyzygotic twins together Adjusted analyses for *bwt*, BMD relationship: Lumbar spine: Regr coeff −0.001, 95% CI −0.016, 0.014 Hip (total): −0.001, −0.013, 0.011 Femoral neck: 0.012, −0.001, 0.024 Forearm: −0.001, −0.007, 0.004 Adjusted analyses for bwt, BMC relationship: Lumbar spine: Regression coefficient 0.418, 95% CI −0.751,1.588 Hip (total): No findings, No findings Femoral neck: 0.044, −0.022, 0.109 Forearm: 0.160, −0.024, 0.345	Medium	*No association* between bwt and BMD or BMC of lumbar spine or hip
Te Velde [15] 2004 Osteoporosis International	261 (151 women, 110 men) aged 36 years Netherlands	82%	Men 3.55 (0.46) Women 3.42 (0.52)	*Bwt* was positively associated with BMC in crude regression model, but not after adjustment for adult body wt. Adjusted (for body wt, and lifestyle factors) findings in men and women combined: Lumbar BMC (g): Regression coefficient 1.0, 95% CI −1.83, 3.83 Hip BMC: 0.84, −0.89, 2.54 Lumbar BMD (g/cm^2): −0.014, −0.050, 0.023 Hip BMD: −0.003, −0.033, 0.027	Medium	*Positive* association between bwt and BMC of lumbar spine and hip at age 36 years, did not persist after adjustment for confounding factors

Table 2 (continued)

Study details	Participants and setting			Main findings			Risk of bias	Summary of trend
	Number	% Follow up	Mean (SD) bwt and wt at 1 year (kg)					
Dennison [16] 2005 Paediatric Research	966 (498 men, 468 women) aged 64.8–66.4 years, born 1931-1939 Hertfordshire, UK	65%	Not stated	*Bwt and wt at 1 year* were positively associated with BMC of lumbar spine and proximal femur (hip). Relationships remained significant after adjustment for confounding factors including HRT and timing of menopause in women. Figures in table are correlations coefficients.			Medium	*Positive* association of bwt and wt at 1 year with BMC of lumbar spine and hip at age 65 years
				BMC (g) and bwt	Men	Women		
				Lumbar Spine	0.10, p=0.03	0.11, p=0.03		
				Proximal femur	0.16, p=0.0003	0.16,p=0.0008		
				BMD (g/cm^2) and bwt				
				Lumbar spine	0.05, p=0.26	0.03, p=0.59		
				Proximal femur	0.10, p=0.03	0.02, p=0.62		
				BMC and wt at 1 year				
				Lumbar spine	0.17, p=0.0001	0.13, p=0.01		
				Proximal femur	0.22, p<0.0001	0.14, p=0.002		
				BMD and wt at 1 year				
				Lumbar spine	0.11, p=0.01	0.04, p=0.40		
				Proximal femur	0.08, p=0.09	−0.01, p=0.80		
Saito [17] 2005 J Bone Mineral Metab	86 women aged 18–21 years Japan	40%	3.17 (0.46)	*Bwt* was positively associated with BMC lumbar spine, and BMC of total hip. Bwt was not associated with BMD of femoral neck or total hip.			Medium	*Positive association* between bwt and BMC of lumbar spine and total hip in women aged 18–21 years.
				BMC (g)	Regression coefficient (SE)	*P* value		
				Lumbar spine	3.48 (1.72)	0.0474		
				Hip (total)	2.25 (1.05)	0.0352		
Pearce [18] 2005 JECM	389 (171 men and 218 women) aged 53 years Newcastle, UK	40%	Men 3.42 (0.47) Women 3.38 (0.51)	*Bwt* was not significantly associated with BMD of the hip and lumbar spine after adjustment for confounding factors.			Medium	*No association* between bwt and BMD of total hip and lumbar spine
				Adjusted standardised regression coefficients and 95% CI:				
				BMD	Men	Women		
				Hip (total)	0.00 (−0.02, 0.02)	0.0 (−0.01, 0.02)		
				Lumbar spine	0.01 (−0.01, 0.03)	0.0 (−0.01. 0.02)		
Dalziel [19] 2006 J Bone Mineral Research	174 (88 men and 86 women). Mean age 34 years New Zealand	62%	2.375 (0.788)	*Bwt* was exposure of interest. Mothers of participants had taken part in trial of betamethasone and two thirds of participants were preterm. Analyses were adjusted for betamethasone exposure and for gestational age. Bwt was positively associated with BMC and BMD of the lumbar spine, but these associations did not persist after adjustment for confounding factors including current size. Positive associations of bwt with BMC and BMD of the proximal femur (hip) and femoral neck were not statistically significant (see below), although bwt z-score was significantly associated with BMC and BMD of the proximal femur (hip).			Medium	*No association* of bwt with BMC or BMD of lumar spine, proximal femur or femoral neck *Positive* association of bwt z-score with BMC and BMD of proximal femur

					Regression coeff (SE)	*P* value	
				Lumbar spine BMC	1.01 (0.89)	0.257	
				Lumbar spine BMD	0.01 (0.01)	0.303	
				Proximal Femur BMC	0.87 (0.60)	0.151	
				Proximal Femur BMD	0.01 (0.01)	0.492	
				Femoral neck BMC	0.13 (0.09)	0.152	
				Femoral neck BMD	0.01 (0.01)	0.411	
Leunissen [20] 2008 Clin Endocrinol	121 women and 191 men Aged 18–24 years Netherlands	97%	All 2.76 (0.67), Men 2.75 (0.65), Women2.80 (0.69)	*Birthweight Z-score* was inversely associated with BMD of the lumbar spine, but the association was no longer statistically significant after adjustment for confounding factors.			Medium	*No association* between bwt z-score and BMD of the lumbar spine
Laitinen [21] 2005 Osteoporosis	1,102 (563 men, 539 women) aged 31 years Finland	65%	Men 3.56 (0.54) Women 3.46 (0.49)	*Bwt* was significantly correlated with distal radius BMC in men and women. Correlation analyses of the association between standardised bwt and standardised distal radial BMC:			Low	*Positive association* between bwt and distal radius BMC in men and women aged 31 years
				Men	r=0.17,	p<0.0001		
				Women	r=0.11,	p=0.0095		
				Growth retardation at birth (lowest tertile of ponderal index) was associated with low (sex-specific value <10th centile) distal and ultradistal BMC and low distal BMD of radius.				
				Odds ratios (OR) for growth retardation at birth (yes/no) and 95% CI given below adjusted for BMI at follow up, calcium intake and socio-economic status:				
				Low distal BMC=2.61		1.42, 4.80		
				Low distal BMD=1.92		1.01, 3.66		
				Low ultadistal BMC=2.54		1.40, 4.59		
				Low ultradistal BMD=1.73		0.90, 3.33		

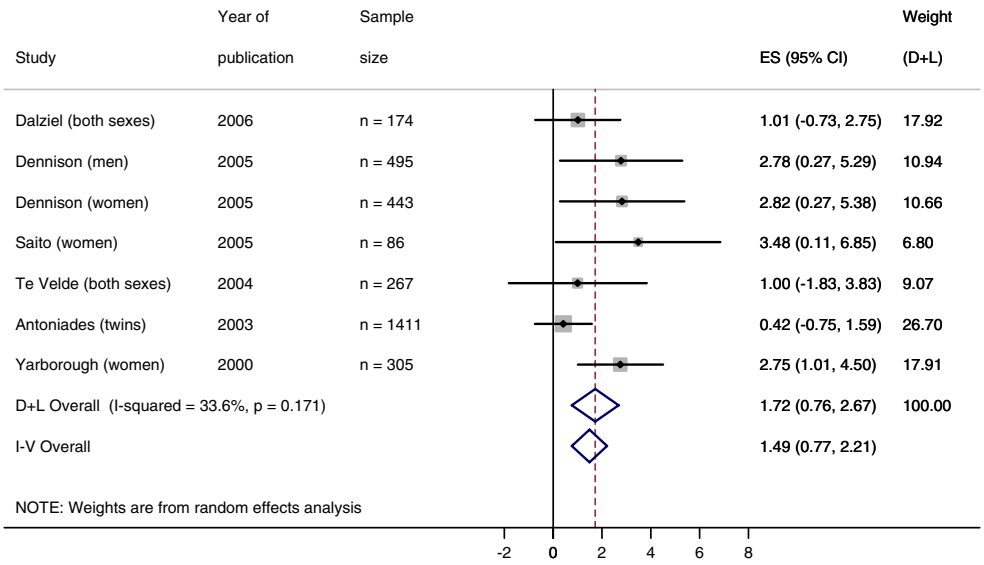

Fig. 1 Forest plot of studies assessing the association between birthweight (kg) and BMC of the lumbar spine in adulthood

Figures are regression coefficients – change in lumbar spine BMC (g) per unit change in birthweight (kg)

an increase in 1-kg birthweight was associated with an increase in hip BMC of 1.41 g (95% CI 0.91, 1.91). The sixth study, of the Bath cohort of women aged 23 years could not be included because regression coefficients could not be estimated from the findings reported [9].

Birthweight and hip BMD

Seven studies reported the relationship between birthweight and hip BMD [9, 13–16, 18, 19]. The study of Hertfordshire adults aged 63 years reported a statistically significant positive association between birthweight and hip BMD in men, but not in women [16]. The study of 21-year-old women in Bath, UK reported a positive correlation between birthweight and BMD but did not report a significance level [9]. The remaining five studies failed to demonstrate a statistically significant association [13–15, 18, 19], and meta-analysis combining four of these with the Hertfordshire study confirmed the lack of an association between birthweight and adult hip BMD (Fig. 4). The

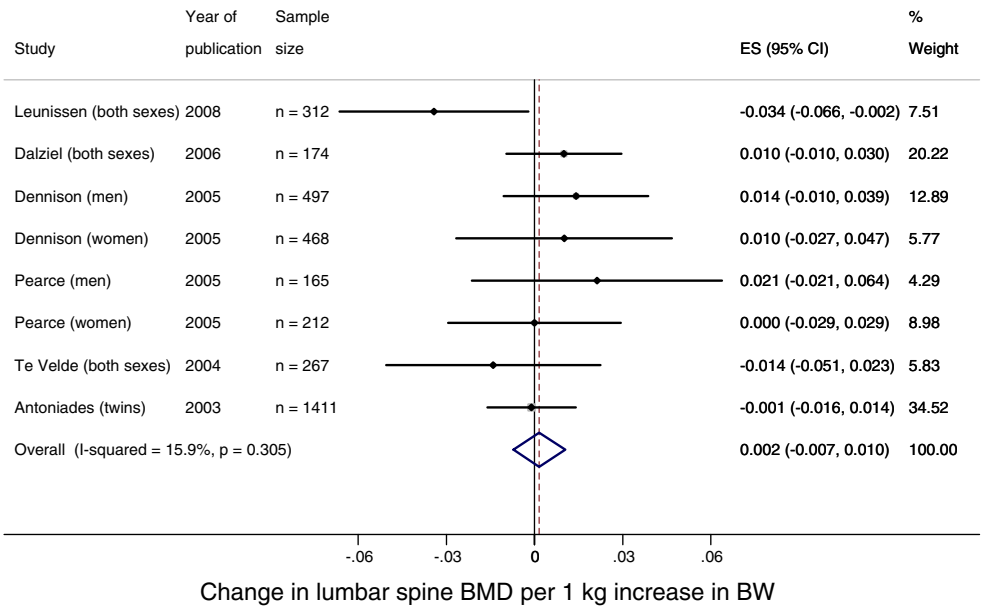

Fig. 2 Forest plot of studies assessing the association between birthweight (kg) and BMD of the lumbar spine in adulthood

Figures are regression coefficients – change in lumbar spine BMD (g/cm^2) per unit change in birthweight (kg)

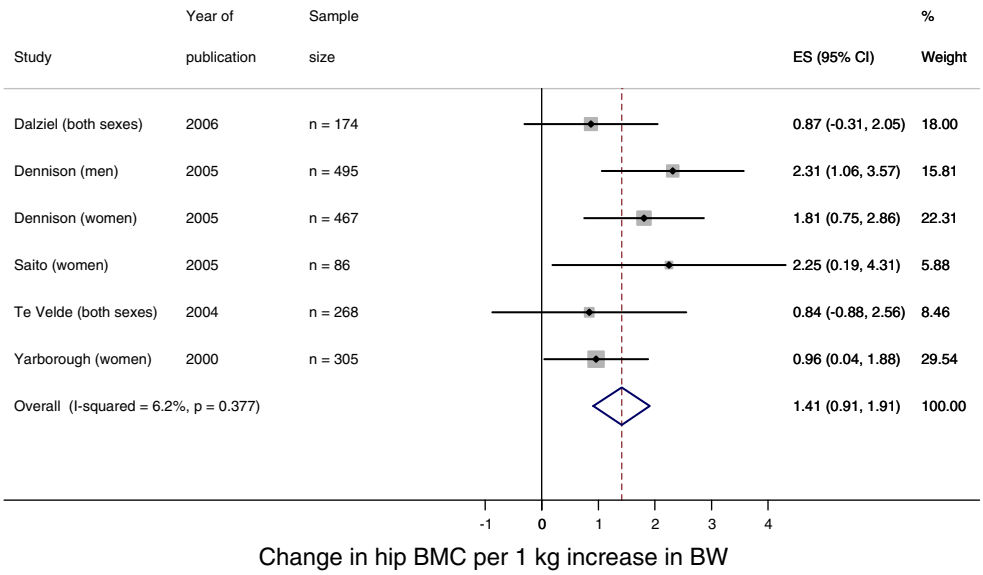

Fig. 3 Forest plot of studies assessing the association between birthweight (kg) and BMC of the hip in adulthood

remaining study of men and women aged 22 years in Northern Ireland stated that birthweight was not a significant predictor of hip BMD but did not report an estimate of effect size and so could not be included in meta-analyses [13].

The association of birthweight with bone mass of the femoral neck

Five studies explored the association between birthweight and bone mass of the femoral neck. Three studies, by Hamed et al. [8], Cooper et al. [10] and Antoniades et al. [14], showed no association between birthweight and BMC or BMD of the femoral neck in either sex. A fourth study explored the association between birthweight and BMC of the femoral neck only, and again showed no association [19]. The final study, of men and women aged 70–75 years in Sheffield, UK reported a trend for increased femoral neck BMC across thirds of birthweight [12]. The trend was statistically significant in both men and women. Meta-analysis of the association between birthweight and femoral neck BMC was not carried out because only three of the studies gave estimates of effect size that could have been used to calculate a pooled estimate.

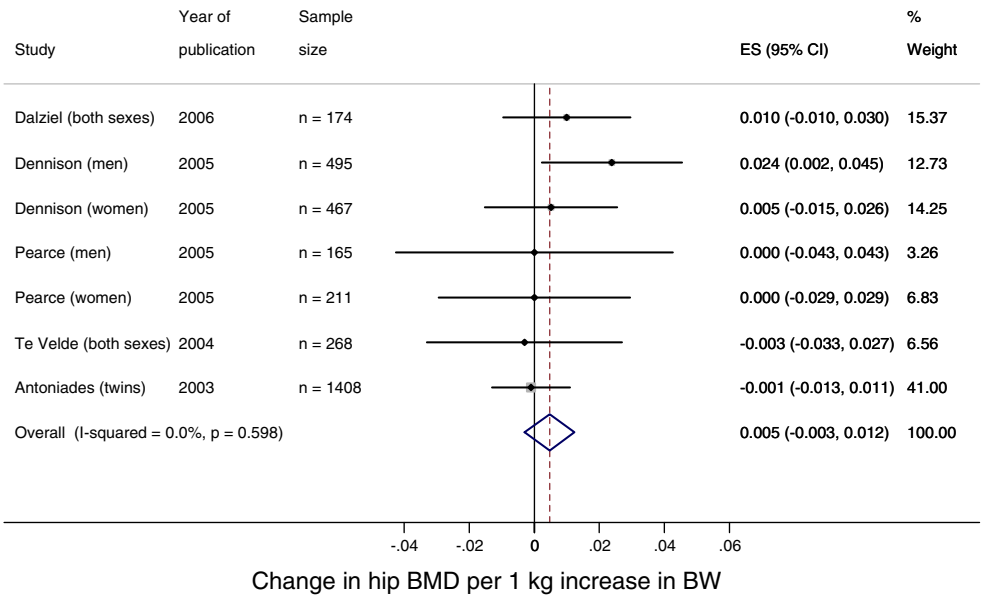

Fig. 4 Forest plot of studies assessing the association between birthweight (kg) and BMD (g/cm2) of the hip in adulthood

The association of birthweight and bone mass of the radius and ulna

Three studies considered the relationship of birthweight with bone mass of the radius and ulna. The study of adults aged 31 years reported a significant positive association between birthweight and distal radius BMC in both men and women [21]. In a US study of post-menopausal women aged 47–89 years, a positive association between birthweight and radial mid-shaft BMC did not persist after adjustment for confounding factors [11]. The UK-based study of adult twins reported no significant association between birthweight and forearm BMC or BMD, but did not state whether the radius, ulna or both sites were assessed [14]. Meta-analysis was not attempted because of the small number of studies assessing the anatomical sites concerned.

The association of weight at 1 year with bone mass of the lumbar spine and hip

Three studies explored the association between weight at 1 year and adult bone mass at different sites [9, 10, 16]. Two were studies of the Hertfordshire cohort. The first study of men and women aged 63–73 years demonstrated a positive association between weight at 1 year and BMC of the lumbar spine and femoral neck in the 189 female participants with correlation coefficients of 0.15 (p=0.04) and 0.15 (p=0.03), respectively [10]. A similar positive correlation was seen in the 224 male participants but this was only statistically significant for the lumbar spine (r= 0.16, p=0.02). Associations between weight at 1 year and BMD of the lumbar spine and femoral neck were not statistically significant. The second Hertfordshire study, based on a larger sample comprising 498 men and 468 women aged 64–66 years who were born later than participants in the first Hertfordshire study, explored the relationship between weight at 1 year and bone mass of the lumbar spine and hip (proximal femur) [16]. Statistically significant associations between weight at 1 year and BMC were reported at the lumbar spine and hip in both men and women. Correlation coefficients for women were 0.11 (p= 0.03) and 0.16 (p=0.0008) at the lumbar spine and hip, respectively. Corresponding correlation coefficients for men were 0.10 (p=0.03) and 0.16 (p=0.0003). Correlations between weight at 1 year and BMD at these sites were not statistically significant. The third study of 153 women aged 21 years in Bath, UK was consistent with findings in the older age groups in demonstrating a positive association between weight at 1 year and BMC of the lumbar spine and hip (proximal femur) [9]. Correlations coefficients were 0.32 (p<0.01) and 0.26 (p<0.01) for the lumbar spine and hip, respectively.

Discussion

This systematic review of the relationship between early size and adult bone mass has demonstrated a consistent positive association between birthweight and adult bone mineral content at the lumbar spine and hip. Higher weight at birth was associated with higher bone mineral content of both the spine and hip in adult men and women at ages between 18 and 80 years across a range of settings. Associations between birthweight and lumbar spine BMC were stronger in women. Birthweight was not a predictor of areal bone mineral density of the lumbar spine and hip.

There was less consistent evidence, from a small number of studies, about the relationship between birthweight and bone mass at other anatomical sites including the neck of femur, radius and ulna. Likewise, few studies had considered the influence of size at 1 year on adult bone mass; only three studies that considered the relationship between weight at 1 year of age and adult bone mass were identified [9, 10, 16]. However, these studies were consistent in suggesting that weight at 1 year bore a positive association with adult bone mass of the lumbar spine and hip, with higher weight at 1 year of age associated with higher levels of bone mineral content in adulthood.

There have to our knowledge been no published meta-analyses of the relationship between early size and later bone mass. Our systematic review is the first to report the magnitude of the association between birthweight and bone mass of the lumbar spine and hip across studies in different populations and settings. For every 1 kg increase in birthweight, the bone mineral content of the adult lumbar spine and hip increase by 1.49 (95% CI 0.77, 2.21) and 1.41 g (95% CI 0.91, 1.91), respectively. A 1.41 g increase in hip BMC, corresponds to a 0.24 SD increase in hip BMC. Extrapolating from the work of Cummings et al. who reported a relative risk for hip fracture of 1.6 (95% CI 1.3, 2.1) per 1 SD decrease in hip BMC in women aged 65 years and over, the effect size we observed is equivalent to a relative risk for hip fracture of 1.12 (1.06, 1.19) per 1 kg decrease in birthweight. Previous studies evaluating the comparative predictive capacity of areal BMD, volumetric BMD and BMC, for future fracture have highlighted the importance of BMC as a predictor of fracture risk and have suggested that these three measures do not differ significantly in their relationship with future fracture [22].

Our review used rigorous and standard methods. We calculated pooled estimates for the relationships between birthweight and bone mass of the lumbar spine and hip. While the included studies were heterogeneous in their settings and target populations, all used DXA to assess bone mass outcomes. We took account of study heterogeneity within our meta-analyses. We identified significant heterogeneity between the studies considering the associa-

tion of birthweight with BMC of the lumbar spine, and so a random effects model was used to derive a pooled estimate. There were a number of other challenges in interpreting the evidence. Most studies had at least a medium risk of bias in relation to the review question—loss to follow-up and insufficient consideration of the effects of important confounding factors on the relationship between early size and adult bone mass were the most common problems leading to elevated risk of bias. However, none of the studies included in meta-analyses had a high risk of bias, and where possible we used adjusted estimates of effect size. Not all studies reported sufficient data to allow their inclusion in meta-analyses, although the directions of association in studies not included in the meta-analyses relating to lumbar spine and hip were consistent with those reported in studies that were included in meta-analyses.

The consistency of the association between birthweight and bone mineral content of the lumbar spine and hip from early adulthood through to old age, across a range of settings, provides compelling evidence for the intrauterine programming of skeletal development and the tracking of skeletal size from infancy to adulthood. Programming is the term used for persisting changes in structure and function caused by environmental stimuli during critical periods of early development. It is thought that the mechanism underlying the association between early growth and later bone mass may be the programming of a range of metabolic and endocrine systems that control the skeletal growth trajectory [2].

The absence of an association with areal or volumetric bone mineral density suggest that this highly conserved aspect of bone structure is largely determined by other postnatal factors (including pubertal timing, and physical activity in childhood), or by fixed genetic variation. Isolated studies using QCT to assess cortical or trabecular density endorse this hypothesis [23], while a single analysis of femoral geometry suggests that poor early growth may also contribute to disproportionate proximal femoral shape and compromised femoral neck compression strength [24].

The associations between birthweight and BMC of the lumbar spine were stronger in women. Three of the seven studies included in the meta-analysis of this association, as reported in Fig. 1, relate to women only and it is possible that we detected a stronger association in women because we had more statistical power in the meta-analysis to detect an effect in that group. However, there are biological reasons that might account for the stronger association observed in women. There are important differences in the intra-uterine experiences of male and female offspring and these may have an influence on the extent to which skeletal development is programmed. The growth of every human foetus is constrained by the limited capacity of the mother and placenta to deliver nutrients to it. The influence of maternal constraint is greater for boys in utero because they grow more rapidly than girls and so are at greater risk of becoming undernourished if maternal diet is compromised [25]. In circumstances where maternal diet is compromised, the programming effects of early size may be masked by the effects of maternal constraint. Programming effects of early growth may therefore be more pronounced in women who have experienced less maternal constraint in utero.

The findings of this review suggest that strategies to optimise maternal nutrition and intra-uterine growth should be a component of public health action to reduce the burden of osteoporotic fracture. A number of important gaps in evidence have been identified by this review. None of the studies identified looked at osteoporotic fracture as an outcome and so there is a gap in our understanding of how the relationship between early growth and later bone health translates into clinical outcomes. Further studies are also needed to explore the influence of post-natal growth—the small number of UK-based studies reviewed here were consistent in suggesting that higher weight at 1 year of age was associated with higher bone mineral content in adulthood. These findings need to be replicated in other settings and populations.

Conflicts of interest None.

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