

Association of birth weight with osteoporosis and osteoarthritis in adult twins

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Objectives. Twin studies present a unique opportunity to examine the association of birth weight with adult life phenotypes in a design that naturally accounts for maternal factors and a range of early environmental factors, which might potentially bias the association. In this study, we explored the association of birth weight with osteoporosis (OP) and osteoarthritis (OA), in a large national cohort of female twins.

Methods. Intra-pair differences between the reported birth weight of the twins ($n=4008$) were examined for an association with: (i) intra-pair differences in bone mineral density (BMD) and bone mineral content (BMC) at the lumbar spine, hip and forearm using linear regression; and (ii) osteoarthritis status in pairs discordant for radiographic disease at the hand, hip and knee using matched logistic regression. The confounding influences of height and weight were taken into account.

Results. The mean age of the twins was 47.5 ± 12.3 yr. Intra-pair differences in birth weight were significantly associated with BMD at the spine ($P=0.047$), total hip ($P=0.016$) and femoral neck ($P<0.001$), but not at the forearm ($P=0.245$). These were entirely explained by the birth weight association with height and weight. The associations of intra-pair differences in birth weight and BMC were highly significant ($P<0.001$) at all sites, but were partly explained by adjustment for adult height and weight. We found no clear association between intra-pair birth weight differences and OA in twins discordant for any of the radiographic OA phenotypes at any site.

Conclusions. Bone mass and especially BMC are highly associated with birth weight. These associations are accounted for mainly by environmental factors that are independent of maternal factors such as gestational age, maternal smoking and nutrition, and are largely mediated by skeletal size and particularly adult height. Birth weight does not appear to be a major influence on the later development of radiographic OA in women.

KEY WORDS: Birth weight, Osteoporosis, Osteoarthritis, Twin study.

Low weight and small size at birth have been linked with a predisposition to adverse health outcomes in adulthood, including hypertension, insulin resistance, coronary heart disease [1] and more recently reduced adult bone and muscle mass [2–5]. The reported associations between birth weight and adult disease have been found in different populations around the world, and are supported by animal experiments. Fetal programming has been proposed as a possible mechanism for these

associations. The ‘fetal origins hypothesis’ states that fetal undernutrition in middle to late gestation, which leads to immediate disproportionate fetal growth, can also be translated into pathology and thus determine disease in adult life [1, 6, 7].

With regard to the musculoskeletal system it has been suggested that skeletal growth and adult body composition, particularly bone and mass, might be programmed during fetal life [5]. Studies to date have examined the

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association of birth weight and weight in infancy with adult body composition and they have been interpreted as showing a potential fetal programming of osteoporosis risk. However, these studies were based on small numbers with inconsistent results and were prone to potential selection bias as only a small percentage of the original birth cohort participated in the study [2–5]. If birth weight does indeed have an effect on body composition, it is possible to speculate that an effect may also be seen for osteoarthritis. However, this has not been examined.

Studies showing birth weight influences on adult phenotypes are controversial because of their susceptibility to bias. Environmental or maternal factors represent one of the main confounders of the fetal origin hypothesis, as it is based on the assumption of intrauterine programming due to nutritional constriction at critical periods of fetal development. A purely genetic explanation of the association between birth weight and later phenotypes remains possible.

Twin studies present a unique experimental setting in which the fetal programming hypothesis can be examined [8, 9]. The St Thomas' twin unit has been gathering data on twins since 1993 related to a range of diseases of ageing. We explored the association of birth weight with osteoporosis (OP) and osteoarthritis (OA) in a large national cohort of female twins, using intra-pair differences in birth weight and subsequent adult phenotypes. This study design controls for maternal behavioural and sociodemographic characteristics known to influence birth weight. Potential confounding due to genetic factors is greatly reduced, and among monozygotic twins, eliminated.

Participants and methods

Participants

The analysis used data from the St Thomas' UK Adult Twin Register, which comprises unselected healthy volunteers, recruited through successive national media campaign [10]. Only data from white, female twin pairs were included in the analysis. None of the women were known to suffer from any disease causing secondary OA and OP and were broadly representative of the normal British population [11]. Ethical approval was obtained from St Thomas' Hospital ethical committee and full informed written consent was obtained. The data included anthropometric and lifestyle variables collected through both a standardized nurse-administered questionnaire and clinical examination. Information on recalled birth weight was requested 2 weeks before the twins' visit and they were encouraged to consult their mothers to confirm the answers [12]. Zygosity was determined by a standardized questionnaire and was confirmed when necessary by multiplex DNA fingerprinting.

Bone measurements

Bone mineral density (BMD) and bone mineral content (BMC) were measured at the lumbar spine (L1–L4) in the antero-posterior (AP) projection, the non-dominant hip (femoral neck, total hip) and the non-dominant forearm, using dual energy x-ray absorptiometry (Hologic QDR-2000 DXA scanner—Hologic, Inc. Waltham, MA, USA). Reproducibility has been

assessed by performing duplicate scans of 40 normal volunteers and was between 0.6 and 1.6% depending on the site scanned.

Osteoarthritis measurements

The radiographic features of osteoarthritis (ROA), such as the presence of osteophytes and narrowing of the joint space were examined at three sites.

Hand. Plain posteroanterior (PA) hand radiographs with the hands placed flat, at a tube–film distance of 100 cm were obtained. Fifteen joints were assessed in each hand: five distal interphalangeal joints, four proximal interphalangeal, the first carpometacarpal joint and five metacarpophalangeal joints.

Knee. Anteroposterior weight-bearing and skyline views were obtained at a tube–film distance of 100 cm. Osteophytes and joint space narrowing graded from 0 to 3 were read in the tibiofemoral lateral and medial and patellofemoral compartments.

The summary grade for each joint of the hand and each knee was based on the Kellgren and Lawrence (K&L) grading system (0–4). An individual was considered to have radiographic OA of the hands if at least grade 2 K&L was present in two or more hand joints and ROA of the knee if at least grade 2 K&L was present in either or both knees.

Osteophytes and joint space narrowing were separately evaluated and graded from 0 to 3 for increasing severity with 1+ being considered positive.

Hip. Pelvic radiographs were obtained in supine AP position with a standard tube–film distance of 100 cm and the feet positioned in 15° of internal rotation. We used the Croft grading system (0–5), a modification of the K&L scale specifically developed for hip OA. Cases were defined by a minimum grade of 1 with definite osteophytes [13].

A single observer, who was blind to the zygosity and pairings, assessed the radiographs for each site. If an abnormality was seen, the radiographs were read independently by a second observer, and if there was a discrepancy, the opinion of a third specialist was asked.

Reproducibility. The intra-observer reproducibility for each site was estimated using a weighted kappa statistic and found to be satisfactory ranging from 0.69 to 0.93 for different radiological sites and features.

Confounding variables

Height and weight were considered as potential confounding variables as it is known that birth weight is positively related to adult body size [14] and also has been related to OA and BMD. The effect of other known lifestyle determinants of bone loss including lifetime alcohol consumption (cut-off of 15 units/week), ever smoking, drug use such as steroids and history of heavy physical activity reported during the last 12 months [15] were also considered in the analysis.

Statistical methods

Intra-pair differences in self-reported birth weight were regressed upon intra-pair differences in bone measurements using linear regression for all twins and subsequently stratified by zygosity. Adjustment was made for potential confounding variables, also calculated as intra-pair differences. Significant differences were defined as a *P* value of less than 0.05 using two-tailed tests.

For radiographic features of osteoarthritis, conditional logistic regression analysis for matched case–control groups was used to investigate the relationship with birth weight.

Results

Data from 4008 twins were analysed, consisting of 604 monozygotic (MZ) and 1400 dizygotic (DZ) twin pairs. Table 1 contains anthropometric and lifestyle characteristics and distribution of bone mineral measurements in the twins as a whole and stratified by zygosity. Slight differences between MZ and DZ twin pairs were seen for age, weight, body mass index (BMI) and menopausal status, but this did not influence the intra-pair analysis.

Birth weight and bone mass

A total of 1411 twin pairs provided complete information on self-reported birth weight and bone measurements. The mean birth weight of our twins was 2.39 kg.

Low birth weight (LBW) <2 kg was reported in 26%. These LBW twins had significantly lower BMD at the

hip ($P < 0.01$) and forearm ($P < 0.05$) compared with the heavier twins (birth weight >2 kg). The difference did not reach significant levels at the spine ($P = 0.0947$).

Bone mineral density (BMD). Intra-pair differences in birth weight were significantly associated with intra-pair differences in BMD at the spine ($P = 0.047$), total hip ($P = 0.016$) and femoral neck ($P < 0.001$), but not the forearm.

When MZ twins ($n = 445$) were examined separately, higher regression coefficients were found at all studied sites (spine $P < 0.001$, total hip $P = 0.009$, femoral neck $P < 0.001$, forearm $P < 0.001$), whereas in DZ twins ($n = 966$) the intra-pair differences in birth weight were significantly associated with the intra-pair differences in BMD only at the femoral neck ($P < 0.001$).

However, none of the above associations remained significant after adjustment for intra-pair differences in height and weight (Table 2).

TABLE 1. Twin Characteristics

Variable	ALL			MZ			DZ		
	No	Mean	SD	No	Mean	SD	No	Mean	SD
Age (yr)	4008	47.5	12.3	1208	48.5	13.5	2800	47	11.7
Weight (kg)	3968	65.3	12	1190	63.8	10.6	2778	66	12.5
Height (cm)	3974	162.4	6.1	1193	162.1	6.2	2781	162.5	6.1
BMI (Kg/m ²)	3968	24.7	4.5	1190	24.3	4	2778	25	4.7
Birth Wt (Kg)	3018	2.39	0.61	957	2.32	0.63	2061	2.43	0.6
		%			%			%	
Postmenopausal	3679	51		1107	58		2544	48	
HRT ever	3676	27		1117	25		2559	28	
Alcohol > 15un/w	3627	7		1079	8		2548	7	
Smoking ever	3697	46		1113	44		2584	47	
Vig Phys Act	3584	15		1125	14		2459	15	
Bone Measurements									
Spinal BMD	3944	0.997	0.14	1189	0.973	0.14	2755	1.007	0.14
Spinal BMC	3944	58.957	11.73	1189	57.103	11.45	2755	59.757	11.76
Total Hip BMD	3940	0.921	0.13	1186	0.909	0.13	2754	0.926	0.13
Fem Neck BMD	3940	0.808	0.68	1186	0.793	0.13	2754	0.814	0.13
Fem Neck BMC	3899	3.973	0.68	1164	3.894	0.70	2735	4.006	0.67
Forearm BMD	3909	0.554	0.06	1171	0.546	0.06	2738	0.558	0.06
Forearm BMC	3909	12.148	1.92	1171	11.875	1.86	2738	12.265	1.93

TABLE 2. Associations of intra-pair differences in birth weight with intra-pair differences in bone mineral density

Site	No.	Non-adjusted		Adjusted for weight and height		
		β	CI	β	CI	
Lumbar spine	All	1411	0.015*	0.000–0.030	–0.001	–0.016–0.014
	MZ	445	0.029*	0.012–0.046	0.016	–0.001–0.034
	DZ	966	0.009	–0.011–0.029	–0.008	–0.028–0.012
Hip total	All	1408	0.016*	0.003–0.029	–0.001	–0.013–0.011
	MZ	443	0.021*	0.005–0.037	0.003	–0.013–0.018
	DZ	965	0.014	–0.004–0.032	–0.003	–0.020–0.014
Femoral neck	All	1408	0.028*	0.015–0.041	0.012	–0.001–0.024
	MZ	443	0.031*	0.016–0.046	0.012	–0.004–0.027
	DZ	965	0.027*	0.009–0.044	0.011	–0.006–0.028
Forearm	All	1394	0.003	–0.002–0.009	–0.001	–0.007–0.004
	MZ	439	0.011*	0.004–0.017	0.004	–0.003–0.011
	DZ	955	0.000	–0.007–0.008	–0.005	–0.012–0.003

β , regression coefficients; CI, confidence interval.

*Statistically significant at $P < 0.05$.

TABLE 3. Associations of intra pair differences in birth weight with intra pair differences in bone mineral content

SITE	No	Non Adjusted			Adjusted for weight and height			
		β	CI		β	CI		
Lumbar spine	ALL	1411	3.157*	1.953	4.361	0.418	-0.751	1.588
	MZ	445	3.935*	2.521	5.349	1.681*	0.198	3.164
	DZ	966	2.781*	1.157	4.405	-0.035	-1.601	1.531
Femoral neck	ALL	1385	0.190*	0.121	0.260	0.044	-0.022	0.109
	MZ	432	0.219*	0.130	0.308	0.100*	0.004	0.196
	DZ	953	0.180*	0.088	0.273	0.031	-0.054	0.117
Forearm	ALL	1394	0.633*	0.438	0.828	0.160	-0.024	0.345
	MZ	439	0.723*	0.495	0.951	0.261*	0.018	0.504
	DZ	955	0.593*	0.331	0.856	0.118	-0.128	0.363

Bone mineral content (BMC). The association of intra-pair differences in birth weight with intra-pair differences in BMC were highly significant ($P < 0.001$) at all measured sites: spine, hip (total and femoral neck) and forearm.

When MZ and DZ twins were examined separately, the non-adjusted associations of intra-pair differences in birth weight with intra-pair differences in BMC were highly significant in both groups and at all sites.

Adjustment for intra-pair differences in weight and height removed the significance of the associations in DZs and the group as a whole. Interestingly, the associations remained significant after adjustment for intra-pair differences in height and weight only in MZ twins (spine $P = 0.026$, femoral neck $P = 0.041$, forearm $P = 0.035$) (Table 3).

Additional adjustment for other lifestyle variables, including alcohol consumption, smoking, steroid use and physical activity did not significantly alter the associations.

Birth weight and radiographic osteoarthritis

There were no statistically significant intra-pair differences in birth weight in twins who were discordant for any of the radiographic OA phenotypes examined. These were: overall OA, presence of osteophytes, joint space narrowing at the hands, knees and hips. Similarly, no association was found when MZ and DZ twins were examined separately for all analyses (Table 4).

Discussion

In a large cohort of female twins we have shown that birth weight is associated with adult bone mass and that this association is independent of parental confounding. The association was strongest for BMC and less marked but significant for BMD and appeared to be largely mediated by skeletal size, particularly height. This is the first study to show a clear association independent of maternal factors. No association was found between birth weight and the development of radiographic OA in later life.

The majority of epidemiological studies on fetal programming, including twin studies, have examined birth weight in relation to subsequent development of

TABLE 4. Association of intra-pair differences in birth weight in twins discordant for ROA

ROA	No.	Coefficient	CI	
Hand	OA	222	0.158	-0.714-1.029
	OPH	248	0.111	-0.599-0.819
	JSN	174	-0.193	-1.300-0.913
Hip	OA	168	0.061	-0.740-0.863
	OPH	114	0.200	-0.789-1.189
	JSN	114	0.114	-0.901-1.130
Knee	OA	246	-0.211	-1.043-0.622
	OPH	298	0.382	-0.407-1.171
	JSN	260	-0.592	-1.364-0.180

JSN, Joint space narrowing; OPH, osteophytes.

cardiovascular disease, hypertension and non-insulin-dependent diabetes [16, 17]. Although rickets has served as a paradigm of how undernutrition at a critical stage of early life can lead to persisting structural changes [7], there is a scarcity of studies in the literature exploring the fetal programming of musculoskeletal diseases. This is partly due to practical difficulties of such a study; for instance, seeking out birth records of half a century ago has the inevitable problems of incomplete samples, missing records and follow-up, which can all lead to selection bias and small sample sizes.

Cooper *et al.* [2, 3] have suggested that the trajectory of bone growth might be programmed during fetal and early post-natal life. They have shown weak associations of infant weight with adult bone mineral content that disappeared after correction for bone area, specifically adult height. More recently the same group suggested birth weight to be a predictor of both BMC and BMD even after adjustment for adult height. However, confidence intervals for their estimates were wide, especially for females, as the study was based on data from only 41 women [5].

Our findings were based on a large number of twin pairs, exploiting the advantages of a twin study design and overcoming many of the practical problems of cohort studies. Fetal programming has been considered to be the result of undernutrition and other adverse influences during critical periods of development, many of them attributed to maternal factors [18]. Furthermore, epidemiological studies have shown maternal characteristics

such as maternal birth weight [19], gestational and maternal age, height and body composition, maternal smoking, drug use, nutrition and social class also to be determinants of birth weight [20]. Hence, parental and especially maternal factors play a potentially crucial role on the observed associations of low birth weight with adult disease phenotypes. By investigating intra-pair differences in twins, parental confounding factors, as well as unknown environmental and genetic factors, were controlled for and the significant associations we found were independent of these factors.

Epidemiological studies both in twins [21, 22] and unrelated individuals [23, 24] have shown a consistent association between birth weight and adult skeleton size, particularly height. This is in accordance with our finding of more pronounced associations with BMC, which is the most size-dependent measurement. Furthermore, adjustment for adult weight and height attenuated, and in most instances removed, the effect of birth weight on bone measurements. This indicates the associations were largely mediated by adult skeleton size. Notably, height accounted for most of the association of birth weight with BMC.

The finding of stronger associations in MZ twins, who are entirely matched for genetic factors, is of interest. Poulsen *et al.* [25] reached similar findings when studying the metabolic syndrome in twins. Both observations point to an intrauterine environmental interpretation of the associations. In our twin cohort, MZ twins had greater intra-pair variability in birth weight than DZ. This is a well established observation and has been attributed to the unequal competition for nutrients or placental blood supply between monozygotic MZs (sharing a placenta) [26, 27]. In spite of substantial intra-pair birth weight differences and differences in prenatal environment of monozygotic and dizygotic MZ twins, a recent study of the East Flanders Twin Survey [28] using data on placentation found no difference in intra-pair concordance of adult anthropometry.

Our interest in testing the role of fetal programming in osteoarthritis arose from the following evidence: obesity and osteoarthritis have been consistently linked [29]; skeletal growth and developmental abnormalities have been shown to predispose to premature hip OA [30]; and the presence and severity of osteophytes are strongly related with higher bone mass [13]. There are also potential biological mediators of the examined association. Insulin-like growth factor (IGF)-1 plays a major role in prenatal development [31] and has been suggested as a candidate endocrine system of fetal programming [32]. In addition, synthesis of cartilage components appears to be dependent on a number of growth factors and disruption of the IGF axis might influence disease progression in OA [33, 34]. In contrast to OP phenotypes, we found no intra-pair differences in birth weights in twins discordant for radiographic OA phenotypes.

We had 99.9% power to rule out a 10% difference in birth weight (235 g) between the discordant for ROA twins. Thus our study excludes any major role of birth weight on developing radiographic OA in women,

although a minor association or an effect in men is still possible.

Several potential limitations need to be addressed in our study. Birth weights were self-reported and the validity of recall data has been questioned. However, studies that addressed the problem have found that the validity of the method is acceptable in population settings [35, 36]. In the same cohort of twins, our group confirmed other observations of a birth effect on adult hypertension independent of maternal factors [12]. Moreover, our twin cohort had similar recalled birth weights to other British twin cohorts of the same age range [37]. Another potential concern is representativeness. Although twins have been thought to be ideal for studying fetal programming [38], it has been argued that low birth weight in twins does not have the same implication as low birth weight in singletons [37, 39]. However, as our results mirror earlier results in singletons [5] and mean levels and variance of bone and joint parameters are similar to singletons [11], this is unlikely to be a major concern.

In conclusion, we have shown a clear association between birth weight and bone mass mediated through skeletal size, confirming the importance of fetal programming in skeletal development. The study suggests maternal factors are not responsible, implying that fetal nutrition and placental factors play a key role in the development of the skeleton.

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