Birthweight, Vitamin D Receptor Gene Polymorphism, and Risk of Lumbar Spine Osteoarthritis

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ABSTRACT. ***Objective.*** To investigate risk factors for adult lumbar spine osteoarthritis (OA) including polymorphisms of the vitamin D receptor gene (VDR) and birthweight.

Methods. Plain radiographs of the lumbar spine were taken in 392 healthy subjects and graded for osteophytes and disc space narrowing (DSN); demographic data were collected. Details of birthweight and weight at 1 year were retrieved from historical records. VDR gene allelic variation was analyzed in 291 subjects.

Results. The mean age of the cohort was 65.8 years; mean weight was 68.9 kg in women and 80.1 kg and men. Osteophytes of grade ≥ 2 were found in 63.5% of this cohort; DSN ≥ 2 was present in 14.3% of subjects. Increasing osteophyte severity was significantly associated with age, adult weight, and manual social class; DSN was not. Presence and severity of osteophytes were associated with low birthweight and lower weight at 1 year in men, but not in women. No associations were found for DSN. The B allele of the VDR gene was associated with increasing severity of osteophyte. There was a significant interaction between birthweight and VDR gene in determining risk of osteophytosis in men (p for interaction = 0.04). The VDR–birthweight interaction pattern was similar but not statistically significant in women.

Conclusion. Lumbar spine OA was a prevalent finding in this cohort. Both birthweight and polymorphisms in the VDR gene were associated with the presence of lumbar spine osteophytes and a significant interaction was observed between these 2 factors in men. (J Rheumatol 2005;32:678–83)

Key Indexing Terms:
BIRTHWEIGHT LUMBAR SPINE OSTEOARTHRITIS
RISK FACTORS VITAMIN D RECEPTOR GENE

Lumbar spine osteoarthritis (OA) is a common problem, particularly with increasing age[1]. Definitions of what constitutes a radiological diagnosis of lumbar spine OA have varied; early classification utilized a combination of radiological features including disc space narrowing (DSN), sclerosis, and presence of osteophytes[2]. This approach had limitations in both clinical and epidemiological applicability. More recent studies have used individual radiographic features to assess spinal OA[3].

Epidemiological datasets for lumbar spine OA are few. Studies have reported the prevalence of definite osteophytes in subjects with a mean age over 60 years to be 33.7% to 67% in women and 48.5% to 71.4% in men[1,4-7]. Male sex was associated with a higher prevalence of osteophytes in a number of these studies[1,6]. The prevalence of osteophytes also increases with age[1,6,8]. Risk factors associated with lumbar spine OA include heavy physical activity, often occupational[4,6,9,10], and increased weight or body mass index (BMI)[4-6]. Polymorphisms in the vitamin D receptor (VDR) gene have also been reported in association with lumbar spine OA[4]; osteophytes appear to be more strongly associated than DSN[11].

Epidemiological studies suggesting that several chronic disorders may be programmed during early life have emerged. Programming refers to the process whereby a stimulus or insult at a sensitive or critical period of development has lasting or lifelong significance[12,13]. Thereby the nutritional, hormonal, and metabolic environment afforded by the mother may permanently program the structure and physiology of her offspring[14]. Low birthweight has been used as a surrogate epidemiological marker for an adverse intrauterine environment. Epidemiological studies have suggested that adult obesity[15-17], osteoporosis[18,19], coronary artery disease[20,21], and type II diabetes[22] are programmed.

There is currently little information regarding the effects of birthweight on the risk of developing OA in later life, although a recent study found a significant association between low birthweight and hand OA in men but not women[23]. The effects on lumbar spine OA, a common condition in older populations, have never been investigated.

We examined the relationship between birthweight and weight at 1 year, polymorphisms of the VDR gene, and lumbar spine OA in a population based cohort in Hertfordshire,

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UK, in addition to investigating relationships of OA with lifestyle factors and serum vitamin D concentrations.

MATERIALS AND METHODS

In the county of Hertfordshire from 1911 onwards the attending midwife notified all births. The name and address of the infant, date of birth, and information on birthweight, weight at 1 year, and manner of infant feeding were recorded. Using the National Health Service Central Registry at Southport and Hertfordshire Family Health Service Association, we traced men born between 1920 and 1930 and women born between 1923 and 1930 in East Hertfordshire who still lived there. Because of the change of name on marriage, it was difficult to trace women before 1923.

Of those who were traced and still living in Hertfordshire, 285 women and 300 men were invited to participate in a study to examine the association between weight in infancy and bone mass in later life; of these, 173 women (60.7%) and 219 men (73%) agreed to have lumbar spine radiographs[18].

Anteroposterior and lateral thoracolumbar spine radiographs were performed in 173 women and 219 men under standardized conditions. Radiographs were assessed at L1–L4 for DSN and osteophytes at the uncovertebral margins and apophyseal joints, using the method reported by Lane, *et al*[3] as follows: 0, as normal; 1, minimal change; 2, moderate change; and 3, representing severe change. Thus a score could range from 0 to 3. A grade ≥ 2 for either osteophyte score or DSN was defined as radiological OA and these components were analyzed separately. A single trained observer read all radiographs. Thirty radiographs were selected randomly and read twice by the same observer. The equally-weighted kappa score of grading between first and second measurements was 0.614 ($p < 0.0001$) for grading for osteophytes, and 0.660 ($p < 0.0001$) for grading for DSN, showing good agreement.

A trained nurse administered a questionnaire at home and the subjects were also invited to attend a clinic to collect further information. Information was obtained on age, weight, height, social class according to standard occupational classification determined by economic activity status, occupation, status in employment and industry[24], medical and drug history, cigarette smoking (never, ex-smoker, current), alcohol consumption, physical activity, and patient-reported back pain in the past year was assessed by direct enquiry ["Have you had back pain, lasting more than a day, in the region shown (lumbar spine area), in the past year"]. Blood samples were taken for vitamin D (1,25 hydroxycholecalciferol).

Genomic DNA was extracted from whole blood samples according to standard procedures. VDR genotype was determined by polymerase chain reaction (PCR) and restriction fragment length polymorphism (RFLP) analysis, using the restriction endonuclease Bsm-1[25-27]. Presence of the Bsm-I polymorphic site is represented by (b) and absence by (B).

Statistical analysis. Stata statistical software, release 7.0, was used for analyses. Analysis of variance and chi-square tests for linear trend were used to explore the associations between osteophytes or DSN and potential correlates, adjusting for confounders (including age, sex, weight, and social class and diabetes mellitus). Multivariate logistic regression analysis was used, adjusting for confounders, to examine the association between spinal OA, genotype, and early life and adult lifestyle variables.

Full approval was obtained from the Hertfordshire research and ethics committee. Patient consent was obtained according to the Helsinki declaration.

RESULTS

In total, 392 subjects (219 men, 173 women) with a similar mean age had plain radiographs taken (Table 1). Men had a higher mean height and weight than women, as would be expected, and mean BMI was similar. Men were much more likely to have been ex-smokers than women but a similar number were current smokers. Men also drank more alcohol. About two-thirds of men and women were in a manual social class group.

Table 1. Demographic details of study population.

	Women, n = 173	Men, n = 219	All, n = 392
Age, yrs*	65.6 (2.7)	66.0 (3.2)	65.8 (3.0)
Height, cm*	160.0 (5.7)	172.7 (6.5)	167.1 (8.8)
Weight, kg*	68.9 (11.8)	80.1 (11.8)	75.2 (13.0)
BMI, kg/m^2*	26.9 (4.5)	26.8 (3.4)	26.9 (3.9)
Alcohol, units/week**	0 (0, 2)	5 (1, 10)	2 (0, 7)
Smoking, %			
Never	53.8	18.3	34.0
Ex-smoker	32.9	63.0	49.7
Current smoker	13.3	18.7	16.3
Social class, %			
Non-manual (I–IIIA)	36.3	32.6	34.2
Manual (IIIB–V)	63.7	67.4	65.8
Spinal OA disease, %			
Osteophyte grade ≥ 2	59.5	66.7	63.5
DNS grade ≥ 2	12.7	15.6	14.3
Genotype frequency, %	n = 127	n = 164	n = 291
bb	34.6	29.3	31.6
Bb	45.7	49.4	47.8
BB	19.7	21.3	20.6

* Presented as mean (standard deviation). ** Presented as median (interquartile range). BMI: body mass index, DSN: disc space narrowing.

Osteophytes of grade ≥ 2 were found in 66.7% of men and 59.5% of women ($p = 0.33$). DSN of grade ≥ 2 was found in 15.6% of men and 12.7% of women ($p = 0.76$). Severe osteophytes (grade 3) were significantly more common in men (37.4%) than women (23.7%) ($p = 0.008$). Self-reported back pain in the past year was present in 63% of subjects (64.1% of men, 61.7% of women). There were no associations between self-reported back pain and either osteophytes or DSN presence and severity. Twenty-seven subjects (6.9%) were found to have diabetes mellitus (DM). No associations for DM with presence or severity of osteophytes were found ($p = 0.7$ and $p = 0.44$, respectively).

Of these 392 subjects, 291 (74%) agreed to have blood drawn for genotyping; there were 164 men (56%) and 127 women (44%). There were no differences in mean age, weight, height, BMI, or prevalence of osteophytes and DSN of grade ≥ 2 in this subgroup or in subjects who did not agree to have blood drawn as compared with the whole group who had radiographs taken.

Table 2 illustrates the associations identified for men and women combined between spinal osteophytes and lifestyle factors in this cohort. Taking sex differences individually, manual social class ($p = 0.04$) and increasing age ($p = 0.01$) were related to presence and severity of spinal osteophytes in men. In women, increasing weight was highly associated with presence and severity of osteophytes ($p = 0.001$). No associations were found between osteophytes and alcohol consumption or smoking in either sex. No association was

Table 2. Determinants of spinal osteophytes in men and women combined.

	Osteophyte Grade				
	0, n = 38	1, n = 105	2, n = 126	3, n = 123	p
Age, yrs*	65.9	65.2	65.8	66.4	0.02
Weight, kg*	70.7	73.3	73.9	79.4	0.0001
Height, cm*	165.4	167.6	166.3	168.0	0.24
Social class, %					
Non-manual (I–IIIA)	15.8	27.8	33.8	22.6	
Manual (IIIB–V)	6.2	26.6	30.9	36.3	0.003
Smoking, %					
Never	12.8	24.8	31.6	30.8	
Ex-smoker	8.7	30.3	30.7	30.3	
Current smoker	6.3	20.3	37.5	35.9	0.47
Alcohol, units/week†	2 (0, 5)	3 (0, 7)	2 (0, 8)	2 (0, 7)	0.52

* Presented as mean in each osteophyte grade. ** Presented as osteophyte grade percentage distribution by social class or smoking. † Presented as median (interquartile range).

seen between DSN and adult adiposity or any lifestyle factor in either sex.

Severity of osteophyte grade was associated with birthweight and weight at 1 year in men (adjusted p = 0.06 and p = 0.004, respectively; Figure 1); also, presence of osteophytes was significantly more likely in men with low birthweight (adjusted p = 0.07) and low weight at 1 year (adjusted p = 0.02). No association was seen in women and no birthweight or weight at 1 year associations were identified for DSN in either sex.

Presence and severity of osteophytes, but not DSN, were correlated with VDR genotype. Subjects with the BB genotype were significantly more likely to have severe osteophyte scores (p = 0.03; Table 3).

A significant interaction was found between birthweight and VDR genotype as determinants of osteophytes (Figure 2). In the lowest tertile of birthweight, the BB genotype was associated with an increased prevalence of osteophytes, but in the highest tertile, the bb genotype had the highest prevalence. In men this interaction was statistically significant (p = 0.04, adjusting for age, weight, and social class). A similar pattern was seen in women, but was not significant (p = 0.59).

No interactions were found with VDR polymorphisms and serum vitamin D concentrations in determining either lumbar spine osteophytes or DSN. Further, the VDR–birthweight interaction as a determinant of osteophyte presence was independent of vitamin D in this cohort.

DISCUSSION

These results reveal an association between allelic variation in the vitamin D receptor gene and spinal osteophytosis but not disc space narrowing. We also observed a significant interaction between birthweight and the VDR gene as determinants of spinal osteophytes.

Few studies have investigated the association of VDR polymorphisms with lumbar spine OA. However, our results are consistent with other reports, which used the Taq-1 polymorphism of VDR, finding stronger associations with osteophyte presence and severity than for other radiological markers of lumbar spine OA, e.g., disc space narrowing[4,11].

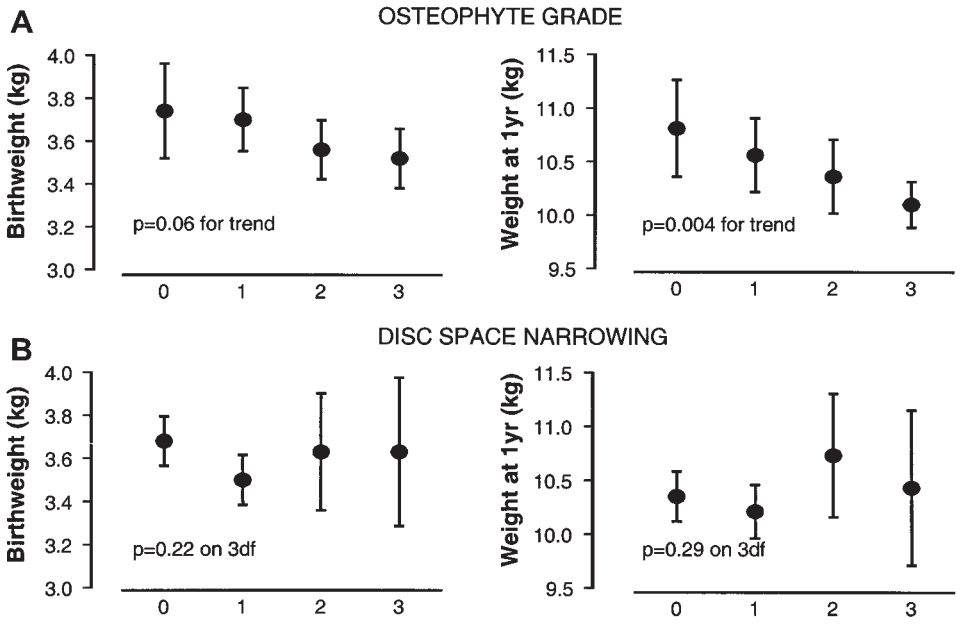

Figure 1. Relationship betyween osteophyte grade (A) and disc space narrowing grade (B) and birthweight and weight at 1 year in men. Mean and 95% CI shown for early weight by OA grading.

Table 3. Osteophyte grade distribution according to VDR genotype.

	Osteophyte Grade, n (%)			
	0	1	2	3
VDR genotype*				
bb	11 (12.0)	23 (25.0)	30 (32.6)	28 (30.4)
Bb	13 (9.4)	48 (34.5)	44 (31.6)	34 (24.5)
BB	6 (10.6)	8 (13.3)	18 (30.0)	28 (46.7)

* Figures presented as n (%) found in each osteophyte grade. p = 0.03 for increasing severity of osteophyte with VDR genotype BB.

Similarly, several studies of knee OA have shown VDR associations with osteophytosis[28-30], rather than joint space narrowing.

Jones, *et al*[4] reported a nonsignificant trend for increasing severity and presence of osteophytes in subjects with the tt genotype; we observed a statistically significant association with the Bsm-1 BB genotype in our cohort. The Bsm-1 and Taq polymorphisms are in strong linkage disequilibrium, with 97% concordance, such that the t allele is linked to the B allele; our results are therefore in agreement with those of Jones, *et al.* They also found a significant association for the presence of DSN and the tt genotype, but not its severity; we found no association between the VDR gene and DSN.

Contrary to this are the findings of Videman, *et al*[11], who found that the Taq polymorphism was significantly associated with lumbar spine osteophytes, but with the direction of effect reversed; there was an increased prevalence of osteophytes in subjects with the TT genotype. No associations with disc height were seen.

One explanation for these contrasting results may be the presence of gene–environment interactions occurring in prenatal life associated with sex-specific patterns of fetal growth, which may influence the presence and severity of lumbar spine OA seen in later life. Males may be more vulnerable because of faster intrauterine growth rates, but the full mechanism for this hypothesis is not yet fully understood. We found a significant interaction between birth-

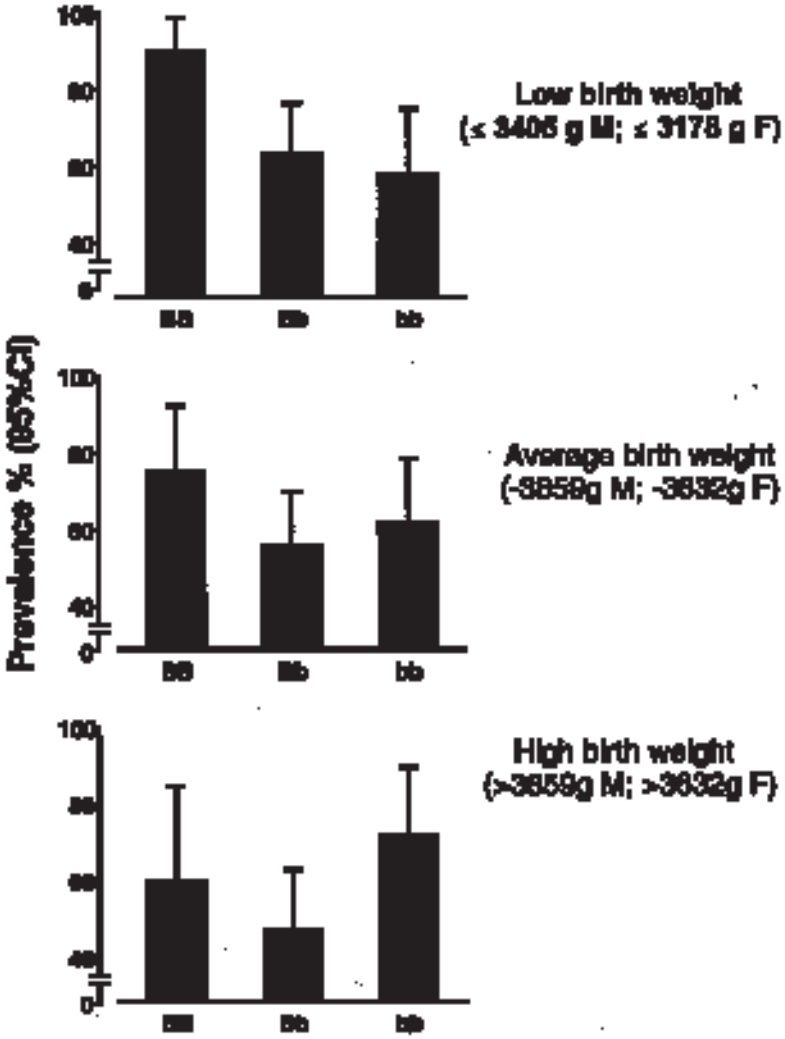

Figure 2. Prevalence of osteophytes (grade ≥ 2) according to birthweight and VDR genotype.

weight and the VDR gene in determining osteophytes in adult men. In the lowest tertile of birthweight, the BB genotype was associated with an increased prevalence of osteophytes, but in the highest tertile the bb genotype had the highest prevalence.

An interaction between birthweight, VDR, and bone mineral density (BMD) has been reported previously in this cohort, showing that the BB genotype in the lowest tertile of birthweight had the highest spine BMD[31], and therefore appears protective for osteoporosis. It has been reported that subjects with OA have increased BMD and an inverse relationship with osteoporosis[32], an association more marked for osteophytes than disc space narrowing. These similar results may represent an interaction between birthweight and the polymorphisms of the VDR on the subjects' tendency to be a "bone-former."

Limitations of our study are its cross-sectional and retrospective approach to examining determinants of spine OA rather than using a prospective cohort. However, we have previously shown that these individuals are representative of the general population regarding body build and other lifestyle factors[33].

We found that age, weight, and being in a manual social class group are associated with the presence and severity of lumbar spine osteophytosis but not disc space narrowing. For social class, this was more marked in men, and may suggest that increased loading on the spine seen in manual occupations can be a risk factor for development of osteophytes. Cumulative occupational exposure to lifting, carrying, and bending have been associated with lumbar spine OA[9], as has heavy lifting, particularly in young adult life[6]. Increasing weight in women had an even greater effect and may act through similar mechanical mechanisms, as generally women would have lighter occupational tasks. These results reflect those seen in a Dutch cohort of women showing that BMI is a predictor of lumbar spine disc degeneration de novo and also a predictor of deterioration[34]; disc degeneration defined in that report was by the Kellgren method of scoring, which amalgamates DSN and osteophytes and in its more severe grades of OA is weighted by severity of osteophytes. We found no association between osteophytosis and age in women in this group. One explanation for this is that the men in the cohort had a wider age distribution than the women; due to the change of name on marriage, it was difficult to trace women before 1923. This lack of variability in age range may reflect the lack of association seen between women, age, and osteophytes.

We found no association between back pain and presence of osteophytes or DSN identified radiologically. This may partially be explained in this cohort in that self-reported back pain was used rather than medically diagnosed disease. However, a recent study in 126 Japanese women also showed a lack of association between lumbar DSN, osteophytes, and back pain[35]; the prevalence of osteophytes seen on plain radiography was similar to that seen in our cohort, but the prevalence of DSN was much higher at 68%, possibly due to their use of magnetic resonance imaging for this measurement.

We have confirmed an association between polymorphisms of the VDR gene and lumbar spine osteophytosis. Further, we observed an interaction between birthweight and the VDR gene, which may explain the discrepancies seen in previous studies. Future research is required to investigate the consequences of gene–environment interactions on the development of osteoarthritis.

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