JT [2]2

Bony Phenotype: Worthwhile as a Therapeutic Target?

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Slide 1

JT [2]2 I'd like to thank the organisers for inviting me to talk about our research into the bony phenotype of OA

JH Tobias, 4/30/2015

Disclosure statement

Speaker/consultancy fees from Amgen and Lilly

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JT [2]3

Cross-sectional studies: higher bone mineral density (BMD) is associated with a greater risk of OA SA Hardcastle et al BoneKEy Article 624 (2015)

Reference	Population	Joint site (OA)	OA definition	Site of BMD measurement	Conclusions
Hart et. al. 1994	Women from the UK Chingford study (n=979 hands and knees, n=579 lumbar spine)	Knee, hand (1st CMCJ, DIPJs), lumbar spine	Radiographic (K&L grade ≥2)	Femoral neck and lumbar spine (L1-L4)	Lumbar spine BMD higher in OA cases vs. controls (all joint sites). Femoral neck BMD higher in OA cases vs. controls at CMC joint, knee, lumbar spine. Associations persisted on adjusting for spinal osteophytes.
Nevitt et. al. 1995	4090 Caucasian women from the US Study of Osteoporotic fractures, mean age 71y	Hip	Radiographic (definite osteophytes or narrowing, plus cysts or sclerosis)	Hip (femoral neck, Ward's triangle, trochanter, intertrochanteric), lumbar spine	Increased BMD at all sites in subjects with moderate-severe OA of either hip, increased BMD at femoral neck and lumbar spine in subjects with milder hip OA. Associations persisted on adjusting for vertebral body osteophytes / subchondral sclerosis. OA hips with osteophytes, but not isolated JSN, associated with increased BMD.
Marcelli et. al. 1995	300 women from the French EPIDOS study of hip fracture, mean age 80y	Hand (5 selected joints on each side)	Radiographic (combined score based on summing IRFs)	Femoral neck, Ward's triangle, total body	BMD at all sites positively associated with hand osteophytosis score; spine and total body BMD associated with overall hand OA score. No significant association between hand JSN score and BMD.
Peel et. al. 1995	375 women aged 40-85y from a UK primary care population	Spine	Radiographic (K&L grade ≥2)	Lumbar spine, femoral neck and total body	BMD increased at all sites in OA group.
Burger et. al. 1996	2745 men and women from the Rotterdam Study (Netherlands), mean age 69y	Knee and hip	Radiographic (K&L grade ≥2)	Femoral neck	BMD 3-8% higher in group with OA (not significant for knee OA in men, p=0.07). In general, BMD increased according to number of joint sites affected and increasing OA severity (K&L grade).
Sowers et. al. 1996	573 Caucasian women from the Michigan bone health study, aged 24-45y	Hand and knee	Radiographic (K&L grade ≥2)	Proximal femur, lumbar spine and total body	Total body BMD positively associated with highest OA grade at both hand and knee. Total body BMD associated with knee OA (K&L grade ≥2).
Chaganti et. al. 2010	3929 men from the US MrOS study	Hip	Radiographic (summary grade 0-4, OA defined as grade ≥2)	Lumbar spine, total hip, femoral neck, trochanteric	Higher DXA BMD at all sites in moderate / severe OA group vs. mild / no OA. Volumetric BMD elevated at hip and L1 vertebra in severe OA group.

Slide 3

JT [2]3 Alot of the work I'm going to discuss was carried out by my graduate student Sarah Hardcastle as part of her PhD, who also had this nice review published recently about the link between bone mineral density and OA

JH Tobias, 4/30/2015

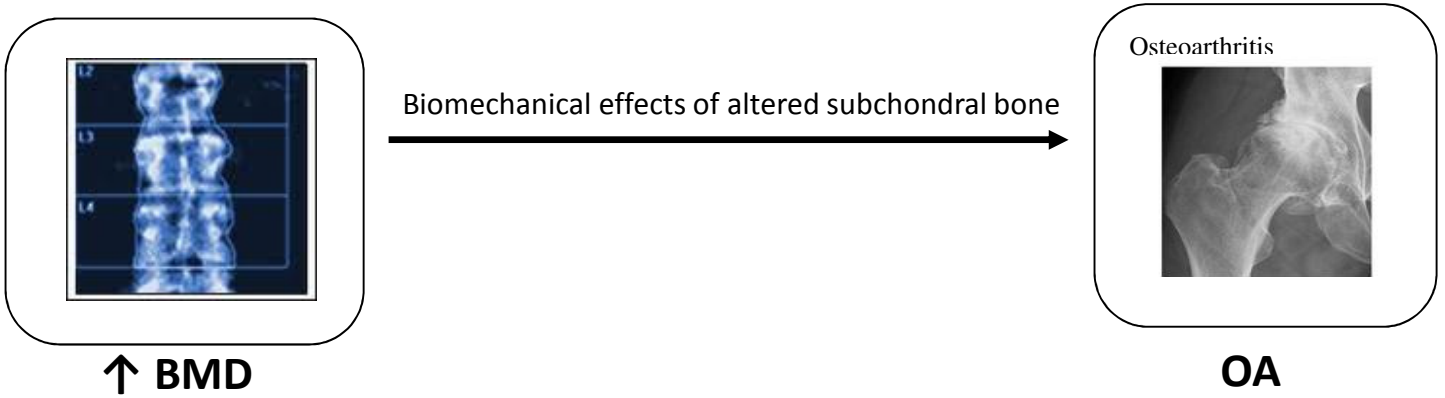
Longitudinal studies: higher BMD increases the risk of developing OA

SA Hardcastle et al BoneKEy Reports 4, Article 624 (2015)

Reference	Population	Follow-up period	Joint site (OA)	Incident OA definition	Site of BMD measurement	Conclusions
Sowers et. al. 1999	482 women from the US Michigan Bone Health study, mean age 37.4y	3 years	Knee and hand	Radiographic (K&L grade ≥2, from <2 at baseline)	Femoral neck, lumbar spine and total body	BMD (Z-scores) greater at all 3 sites in women with incident knee OA, no differences in baseline BMD in women with incident hand OA vs. controls.
Zhang et. al. 2000	473 women from the Framingham study, mean age 71y	8 years	Knee	Radiographic (K&L grade ≥2, from <2 at baseline)	Femoral neck	Trend towards increased incidence knee OA with increasing BMD, mainly via increased osteophytes. Inverse association between baseline BMD and knee OA progression, mainly via reduced risk of progressive JSN.
Hart et. al. 2002	830 women from the Chingford cohort, mean age 54y	48 months	Knee	Radiographic (grade ≥1 osteophytes or JSN, from grade 0 at baseline)	Lumbar spine and femoral neck	BMD significantly higher at both sites in group with incident osteophytes, and suggestion that higher in group with incident JSN. Weak trend towards lower hip BMD in group with progressive osteophytes / JSN.
Hochberg et. al. 2004	5242 women from the Study of Osteoporotic Fractures, mean age 71y	8 years	Hip	Radiographic (minimum JSW ≤1.5mm, definite osteophyte or summary grade ≥2, where feature absent at baseline)	Forearm and total hip	Dose-response relationship between quartile of baseline BMD and and incidence of radiographic hip OA (defined by osteophyte or Croft grade ≥2). No association between BMD and incident hip OA defined by JSN alone.
Bergink et. al. 2005	1403 men and women from the Rotterdam study, aged >55y	6 years	Knee	Radiographic (K&L grade ≥2 in either knee, vs. <2 at baseline)	Femoral neck and lumbar spine	Odds of incident knee OA significantly higher in highest vs. lowest quartiles of both femoral neck and lumbar spine BMD. Trend towards increased odds of knee OA progression with higher lumbar but not femoral BMD.
Nevitt et. al. 2010	1754 men and women from the Multicentre osteoarthritis study (MOST), mean age 63y	30 months	Knee	Radiographic (K&L grade ≥2, from 0-1 at baseline)	Femoral neck and total body	Risk of incident knee OA increased with higher BMD in both genders. Higher femoral neck / total body BMD associated with increased risk of incident JSN and osteophytosis. No association between BMD and OA progression and BMD observed.

Potential Mechanisms Underlying the Association Between BMD and OA

SA Hardcastle et al BoneKEy Reports 4, 2015



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Does high BMD protect against OA Progression?

- Higher BMD was associated with reduced risk of progression in those with pre-existing knee OA in Framingham
  - Y Zhang et al J Rheumatol 2000 27:1032-1037
- Higher bone resorption markers (inversely related to BMD) were associated with greater progression of knee OA in Chingford
  - Arthritis and Rheumatism 2002 46:3178-3184
- Drugs which prevent bone loss have been studied as a possible treatment for OA, though with limited success

JT [2]4

Summary

- High BMD is a risk factor for incident OA but may protect against subsequent progression
- Studies of patients with High Bone Mass indicate that increased BMD has a causal role in the development of hypertrophic forms of OA
- Strategies for targeting the bony phenotype in hypertrophic OA

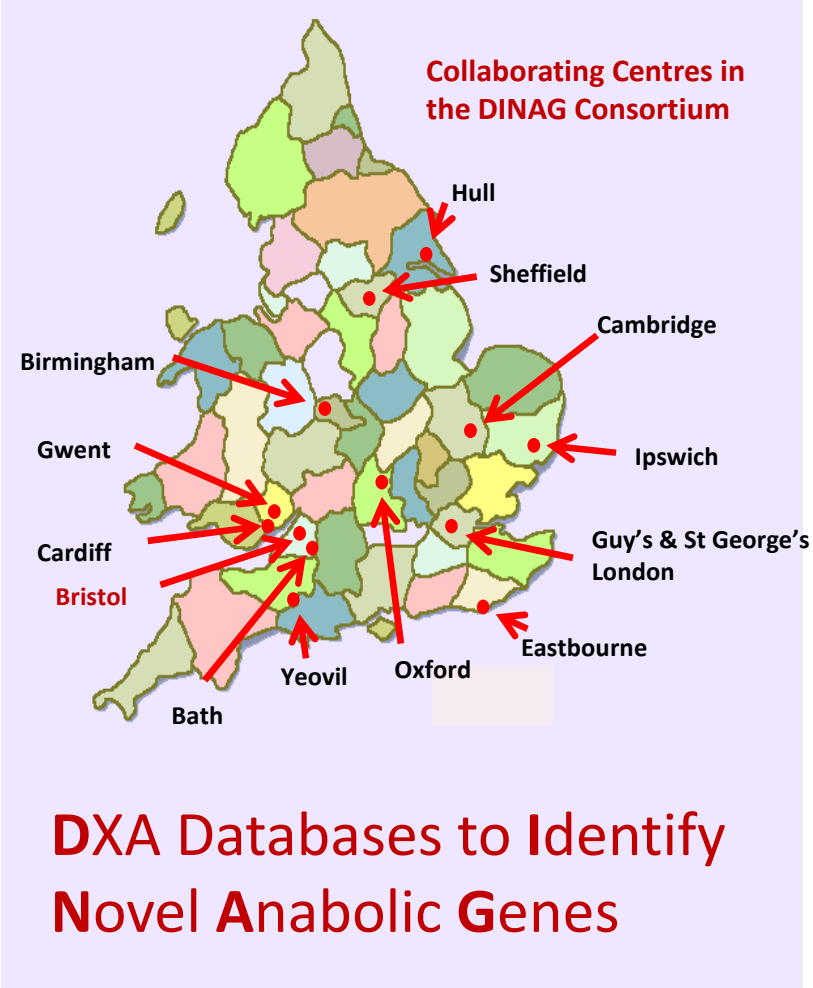
Slide 7

JT [2]4 To tease out this complexity of the relationship between BMD and OA, we characterised the OA phenotype in our cohort of individuals with high bne mass. I'm going to spend most of the presentation describing describing these results, which suggest that increased BMD has a causal role in the development of hypertrophic forms of OA, and then go on to discuss possible implications for therapeutic strategies

JH Tobias, 5/1/2015

The High Bone Mass Study

- A nationwide, multi-centre population of individuals with HBM
- 15 participating centres (England and Wales)
- 335,115 DXA scans screened to identify potential cases (T and / or Z score >+4); scans visually inspected to exclude artefactual BMD elevation
- Index cases recruited to study; family members and spouses screened and recruited as cases / controls
- Clinical phenotype assessed; X-rays performed of pelvis, lumbar spine, knees and dominant hand



Gregson *et. al.* 2011 'Sink or swim': an evaluation of the clinical characteristics of individuals with high bone mass. *Osteoporosis Int* 23(2): 643-54

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JT6

BMD in High Bone Mass cases and family controls

	HBM mean (SD) N=204	Control mean (SD) N=126	Mean difference (95%CI)	p value
Lumbar spine BMD (L1) (g/cm^2)	1.40 (0.16)	1.07 (0.16)	0.33 (0.29, 0.36)	<0.001
Total Hip sBMD (g/cm^2)	1.25 (0.18)	0.99 (0.14)	0.25 (0.21, 0.28)	<0.001
Total body BMD (g/cm^2)	1.36 (0.13)	1.24 (0.12)	0.12 (0.09, 0.15)	<0.001
Total body BMC (kg)	3.48 (0.69)	3.16 (0.65)	0.32 (0.17, 0.46)	<0.001

CL Gregson et al JCEM 2013, 98:818

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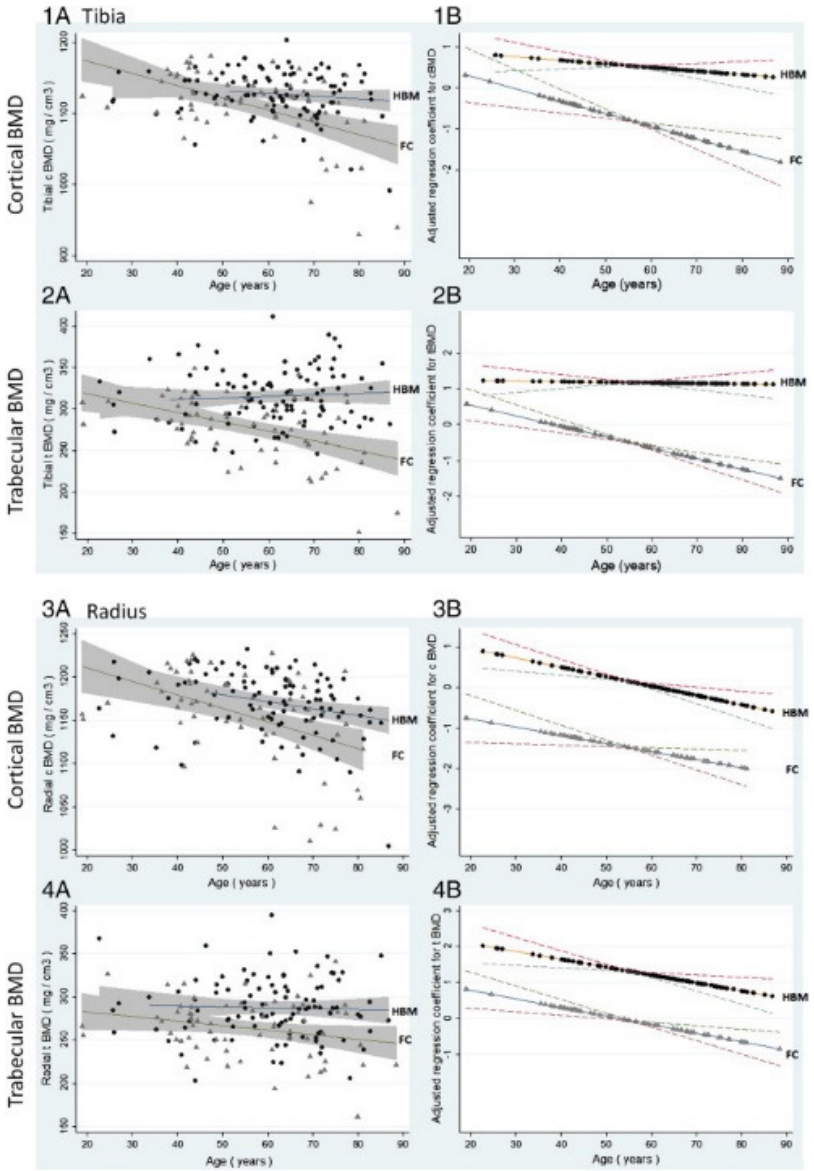
JT6 Because increased weight is an important risk factor for OA, need to adjust subsequent analyses for weight

JH Tobias, 2/16/2015

JT5

Tibial and Radial pQCT parameters in HBM cases versus controls according to Age, CL Gregson et al Bone 2013, 52: 380



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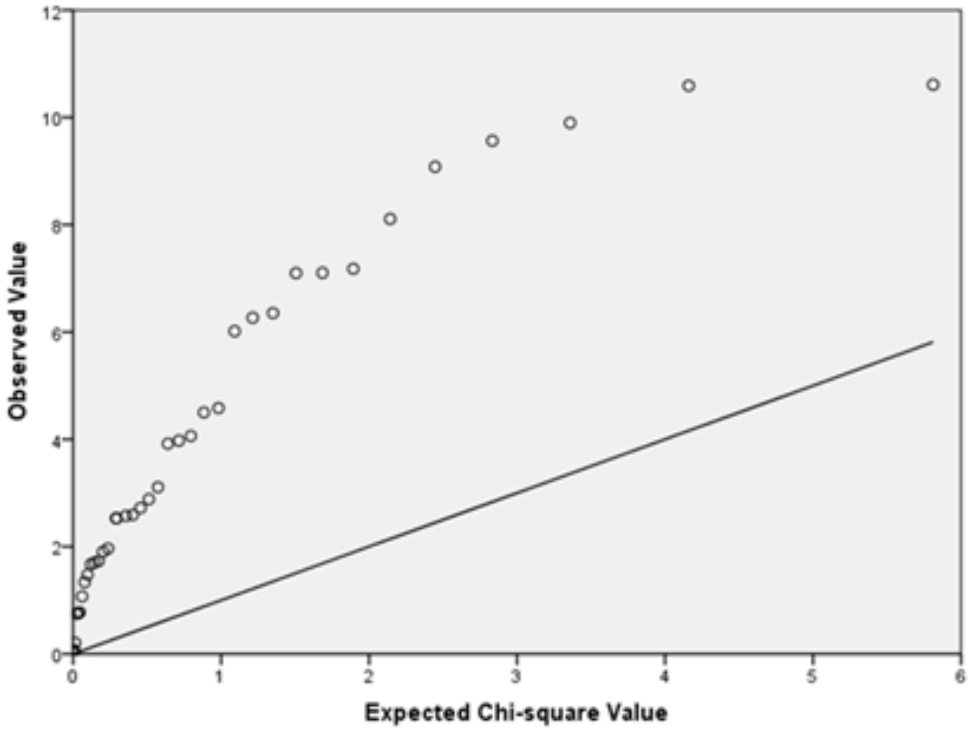
Slide 10

JT5 ie increased BMD occurs relatively early in life and likely to preceed any subsequent OA that might occur
JH Tobias, 2/16/2015

Chi-Square Q-Q plot for 56 BMD loci in 258 HBM cases vs. AOGC low BMD controls (n=900)



Results show over-representation of associations with BMD loci in extreme HBM cases

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DXA measured body composition in High Bone Mass cases and family controls

	HBM mean (SD) N=204	Control mean (SD) N=126	Mean difference (95%CI)	p value
Lean mass (kg)	47.0 (10.3)	51.4 (11.4)	-4.34 (-6.7, -1.9)	<0.001
Fat mass (kg)	35.6 (12.6)	29.8 (11.3)	5.83 (3.35, 8.32)	<0.001
% lean mass	55.3 (8.9)	61.8 (8.7)	-6.5 (-8.4, -4.6)	<0.001
% fat mass	40.7 (9.3)	34.5 (9.1)	6.2 (4.2, 8.2)	<0.001
Android (kg)	3.45 (1.40)	3.01 (1.26)	0.44 (0.16, 0.71)	0.002
Gynoid (kg)	5.70 (1.85)	4.98 (1.82)	0.72 (0.33, 1.10)	<0.001
Android:Gynoid ratio	0.60 (0.18)	0.59 (0.20)	0.00 (-0.04, 0.04)	0.906
Trunk (kg)	19.5 (6.74)	16.7 (6.23)	2.84 (1.51, 4.17)	<0.001
Trunk:Peripheral ratio	1.18 (0.59)	1.28 (0.62)	-0.11 (-0.21, 0.00)	0.046

CL Gregson et al JCEM 2013, 98:818

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Slide 12

JT6 Because increased weight is an important risk factor for OA, need to adjust subsequent analyses for weight

JH Tobias, 2/16/2015

HBM and OA

- Is HBM associated with an increased risk of radiographic hip or knee OA?
- Is HBM associated with a generalised tendency towards bone formation as reflected by enthesophytes?
- Is HBM associated with an increased risk of clinical OA, including progression to more severe disease as reflected by joint replacement?

Study Population

- **HBM cases:**

L1 Z-score ≥ +3.2 and total hip Z score ≥ +1.2, or

total hip Z-score ≥ +3.2 and L1 Z-score ≥ +1.2

- **Controls – 3 groups:**
  1. HBM study family controls (unaffected)
  2. Chingford 1000-women study controls*
  3. Hertfordshire cohort study controls*

- All pelvic radiographs from cases / controls pooled and relabelled for blinded assessment

*Selected using age and gender stratified random sampling in 2:1 ratio with cases

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Radiographic Assessments

All radiographs were assessed for:

- **Individual features of OA**

  - osteophytes (0-3)

  - joint space narrowing (JSN) (0-3) (grade≥2)

  - subchondral sclerosis (0-1)

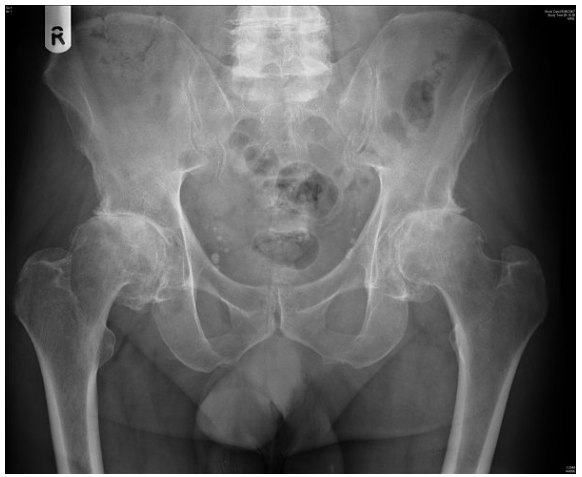
  - cysts (0-1)

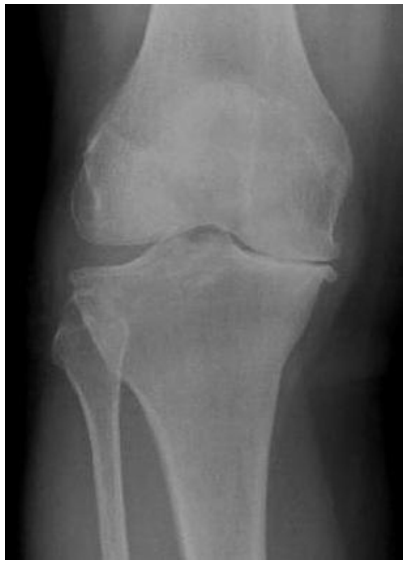
  - chondrocalcinosis (0-1)

- **Global OA grade**

  - Hips: Croft score (0-5); ≥3 defining OA

  -Knees: KL score (0-4); ≥2 and ≥3 cut-offs





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All radiographs were assessed for:

- **Individual features of OA**

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  - cysts (0-1)

  - chondrocalcinosis (0-1)

- **Global OA grade**

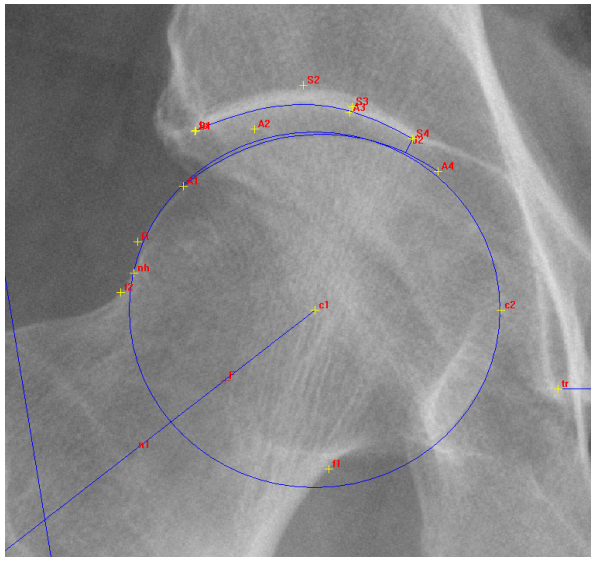
  - Hips: Croft score (0-5); ≥3 defining OA

  -Knees: KL score (0-4); ≥2 and ≥3 cut-offs

- **Minimum joint space width (JSW)**

  measured using purpose-built software package “HipMorf”

  (Nicholls AS *et. al. Arthritis Rheum* 2011 63(11):3392-400)



(Image shown courtesy of team at Botnar research centre, Oxford)

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Demographics of Study Population

	HBM cases (n=272)	Family controls (n=137)	Chingford controls (n=553)	Hertfordshire controls (n=173)	Combined controls (n=863)
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Age (years)	63 (11.5)	59.9 (12.7)	62.8 (9.8)	75.2 (2.7)	64.8 (10.8)
BMI (kg/m^2)	30.5 (5.7)	28.1 (4.9)	27.0 (4.6)	27.7 (4.3)	27.3 (4.6)
BMD total hip (g/cm^2)	1.3 (0.2)	1.0 (0.1)	0.90 (0.1)	1.0 (0.1)	0.9 (0.1)
BMD lumbar spine (g/cm^2)	1.6 (0.2)	1.2 (0.2)	1.0 (0.2)	1.1 (0.2)	1.1 (0.2)
	N (%)	N (%)	N (%)	N (%)	N (%)
Females	202 (74.3)	61 (44.5)	553 (100.0)	114 (65.9)	728 (84.4)

SA Hardcastle et al Osteoarthritis and Cartilage 2014 Aug;22(8):1120-8

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SA Hardcastle et al Osteoarthritis and Cartilage 2014 Aug;22(8):1120-8

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Radiographic hip OA variables in HBM cases *vs* combined controls
(logistic regression, age, gender and BMI adjustment)

Outcome	OR HBM cases *vs.* controls	95% CI	p
Croft score ≥3	1.52	(1.09, 2.11)	0.013
Osteophyte, any site (≥grade 2)	2.39	(1.72, 3.33)	<0.001
Femoral osteophyte (≥grade 1)	1.60	(1.18, 2.17)	0.003
JSN (≥grade 2)	1.48	(0.82, 2.69)	0.196
Cysts	0.34	(0.08, 1.42)	0.139
Subchondral sclerosis	2.78	(1.49, 5.18)	0.001
Chondrocalcinosis	2.08	(1.07, 4.03)	0.030
Outcome	**Mean difference**	**95% CI**	**p**
Measured JSW (mm)	0.04	(-0.05, 0.13)	0.387

SA Hardcastle et al Osteoarthritis and Cartilage 2014 Aug;22(8):1120-8

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SA Hardcastle et al Osteoarthritis and Cartilage 2014 Aug;22(8):1120-8

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Radiographic knee OA variables in HBM cases *vs* combined controls
(logistic regression, age and gender adjustment)

Outcome	OR (95% CI) in HBM cases vs. controls	p value
Knee OA (KL≥2)	2.38 (1.81, 3.14)	<0.001
Knee OA (KL ≥3)	1.98 (1.39, 2.82)	<0.001
Any osteophyte (≥grade 1)	2.38 (1.80, 3.13)	<0.001
Osteophyte (≥grade 2)	2.40 (1.69, 3.41)	<0.001
JSN (≥grade 2)	1.95 (1.20, 3.18)	0.007
Subchondral sclerosis	1.66 (0.89, 3.11)	0.112
Chondrocalcinosis	1.65 (1.02, 2.66)	0.042

SA Hardcastle et al Bone 2015: 71: 171-9

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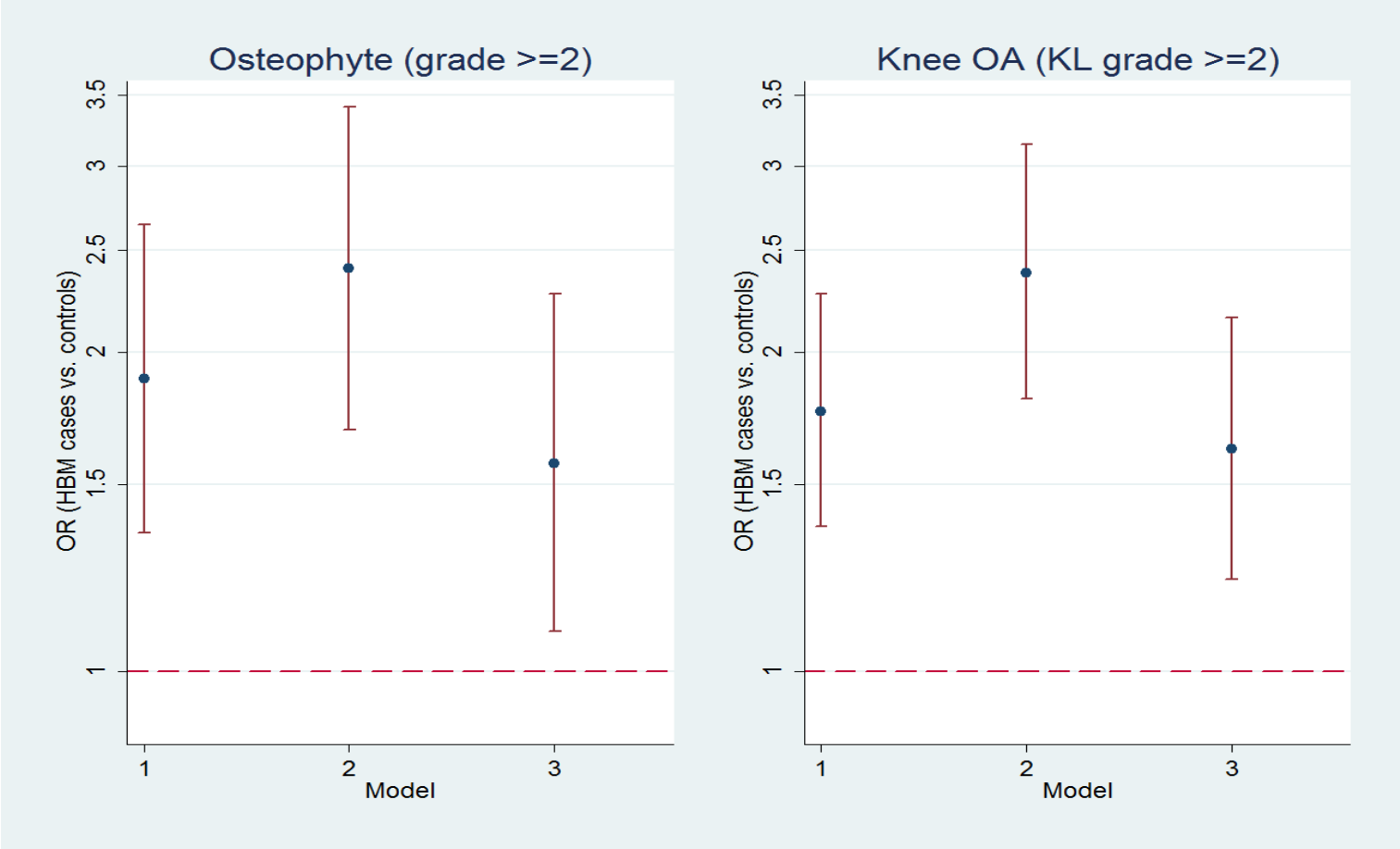
Radiographic knee OA variables in HBM cases *vs* combined controls: effect of further adjustment for BMI



SA Hardcastle et al Bone 2015: 71: 171-9

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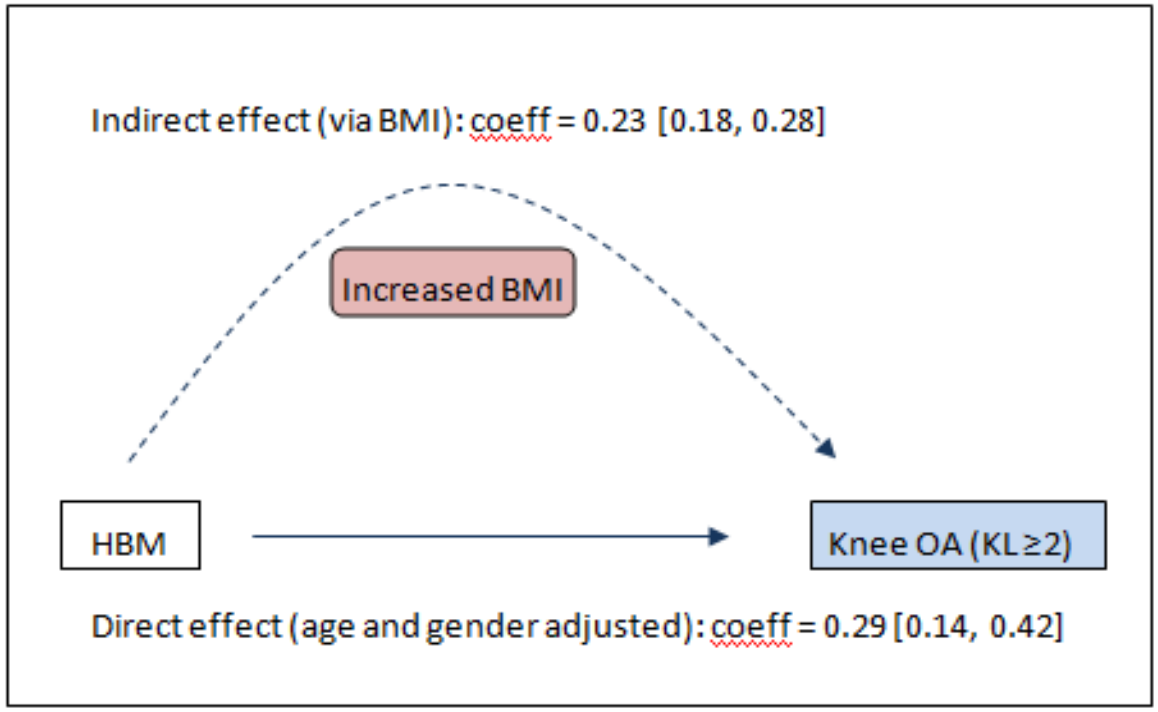
Mediation analysis examining direct and indirect associations of HBM with radiographic knee OA



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Interim Conclusions

- Our findings support a positive association between HBM and risk of radiographic hip and knee OA
- This association was strongest for osteophytes, suggesting a general predisposition to a subtype of OA characterised by increased bone formation in HBM individuals
- In the case of knee OA, the association was in part mediated by increased BMI

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HBM and OA

- Is HBM associated with an increased risk of radiographic hip or knee OA?
- Is HBM associated with a generalised tendency towards bone formation as reflected by enthesophytes?
- Is HBM associated with an increased risk of clinical OA, including progression to more severe disease as reflected by joint replacement?

Radiographic Outcomes

- Osteophytes (acetabular, medial femoral, lateral femoral) graded 0-3 using an atlas[1]

- Enthesophytes graded 0-3 (absent, mild, moderate, florid) based on entire radiograph; an atlas of example images was compiled at baseline for reference

- Key outcomes:
  - Enthesophytes (any *vs.* none, moderate (≥grade 2) *vs.* grade 0-1)
  - Osteophytes (any *vs.* none, moderate (≥grade 2) *vs.* grade 0-1)

- Incomplete X-rays excluded

[1]Burnett *et. al.* A Radiographic Atlas of Osteoarthritis 2004

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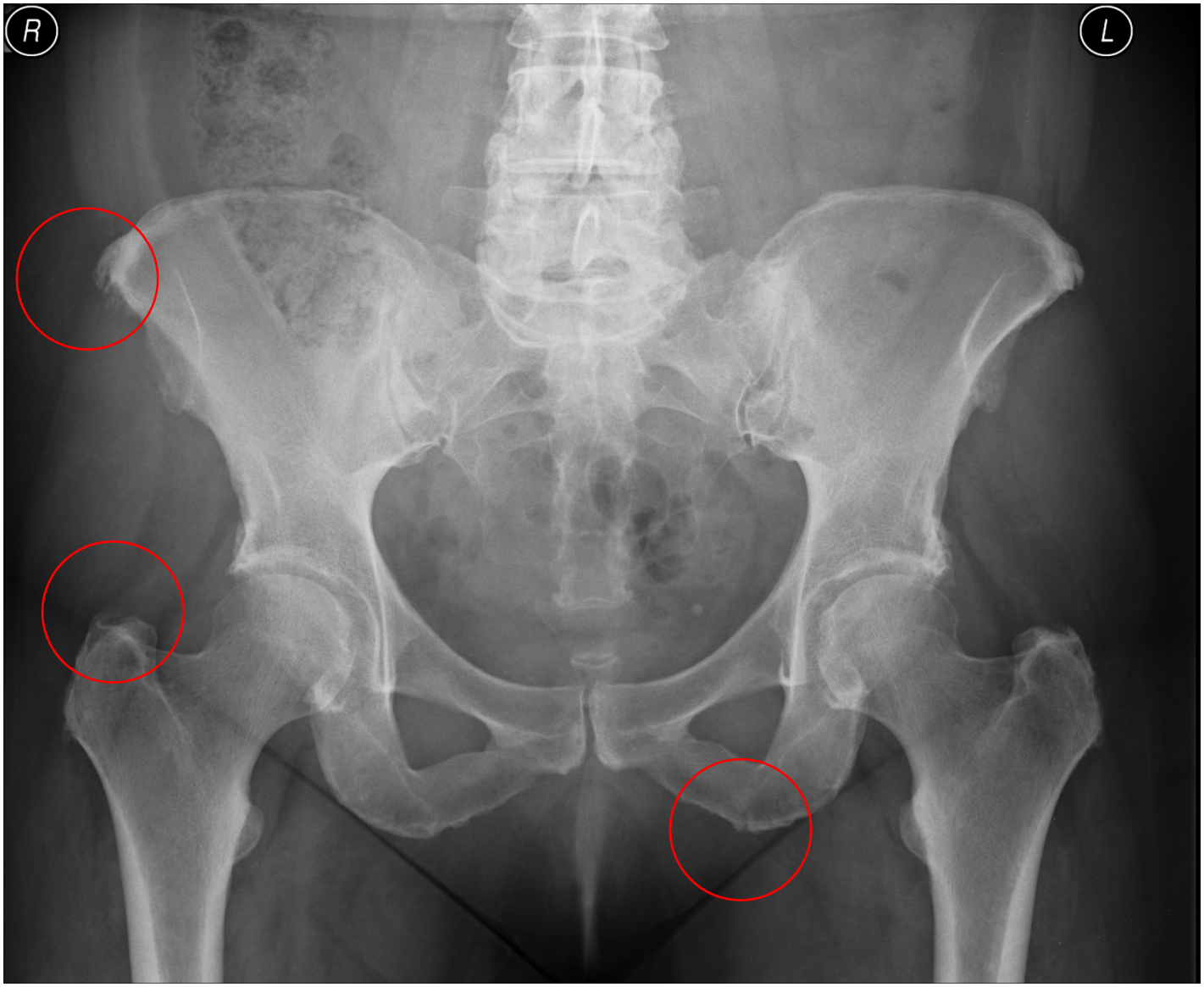

Moderate enthesophytes (grade 2)

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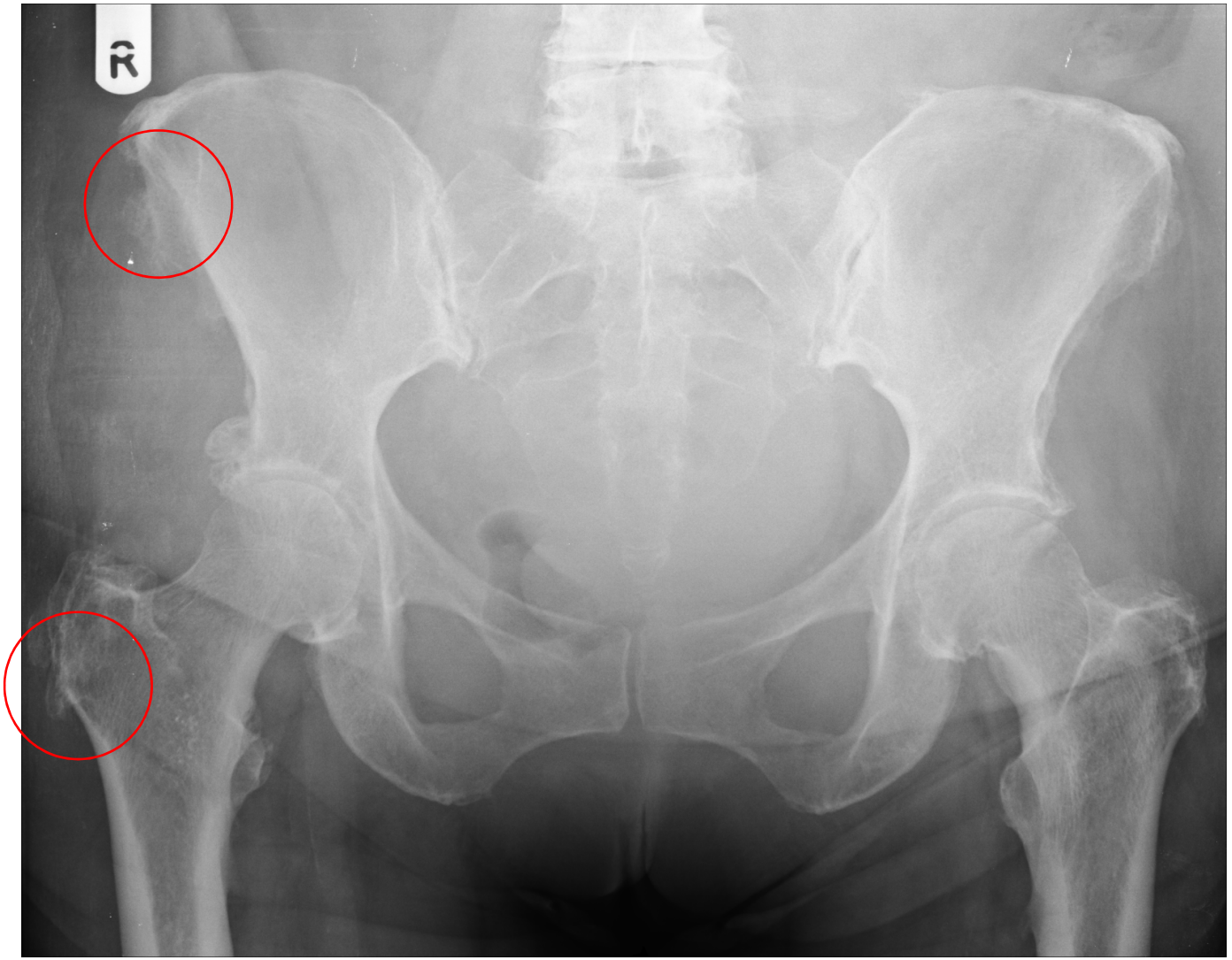

Florid enthesophytes (grade 3)

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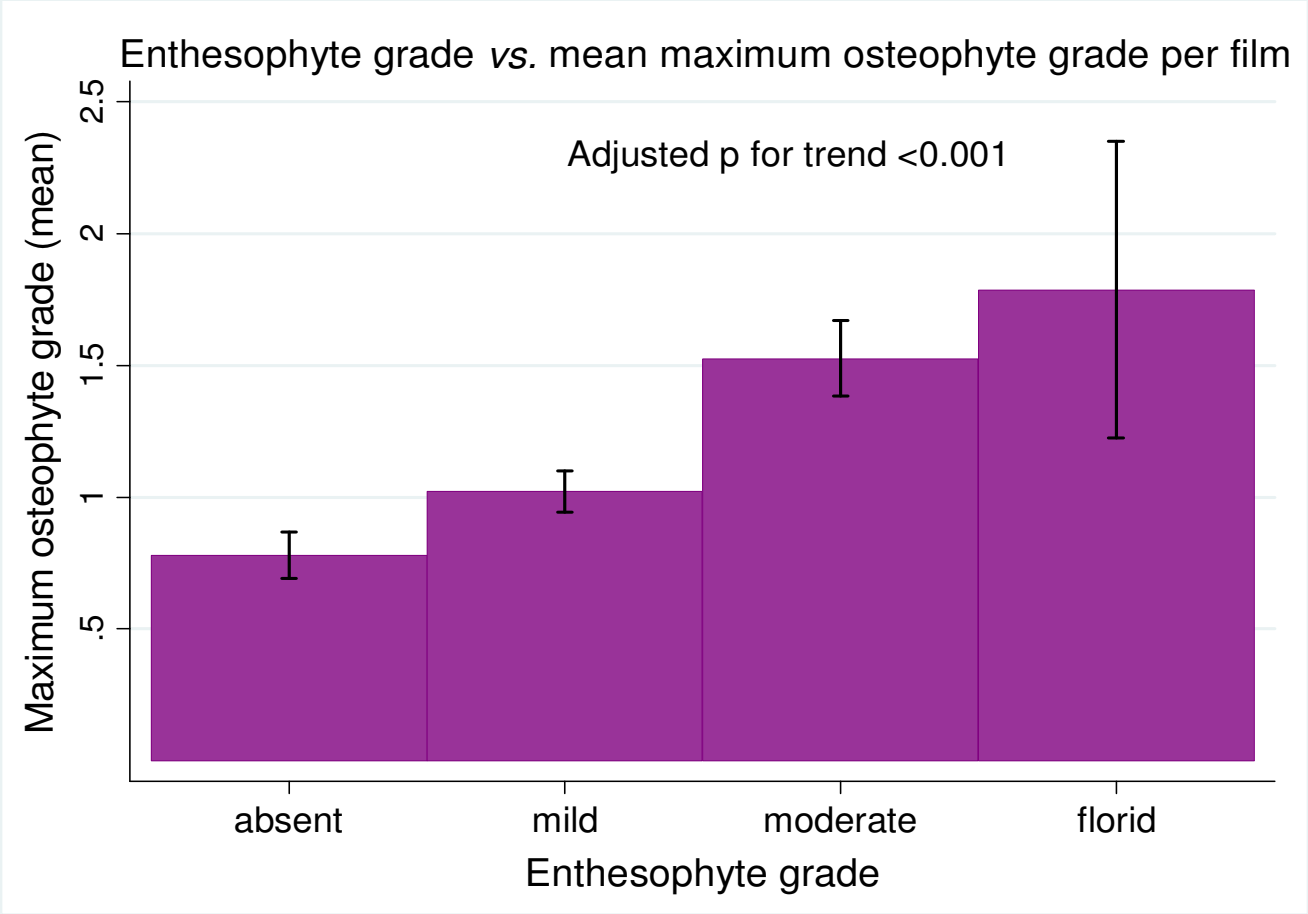
Increased odds of pelvic enthesophytes and hip osteophytes in HBM cases vs combined controls

Outcome	OR in HBM cases *vs.* controls (95% CI)	p value
Enthesophyte (any)	3.00 (1.96, 4.58)	<0.001
Enthesophytes (≥grade 2)	4.33 (2.67, 7.02)	<0.001
Osteophyte (any)	2.24 (1.44, 3.49)	<0.001
Osteophyte (≥grade 2)	2.32 (1.55, 3.49)	<0.001
Femoral osteophyte (any)	1.67 (1.13, 2.47)	0.011

N=226 HBM cases, 437 controls. Adjusted for age, gender and BMI

SA Hardcastle et al Arthritis and Rheumatology 2014 Sep;66(9):2429-39

Positive association between enthesophytes and osteophytes
(HBM cases and all control groups combined)



Error bars represent mean and 95% CI

SA Hardcastle et al Arthritis and Rheumatology 2014 Sep;66(9):2429-39

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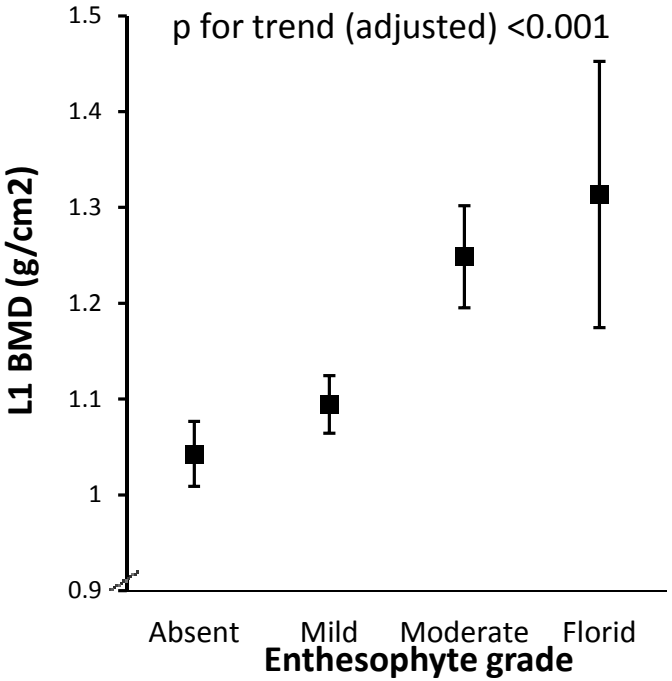
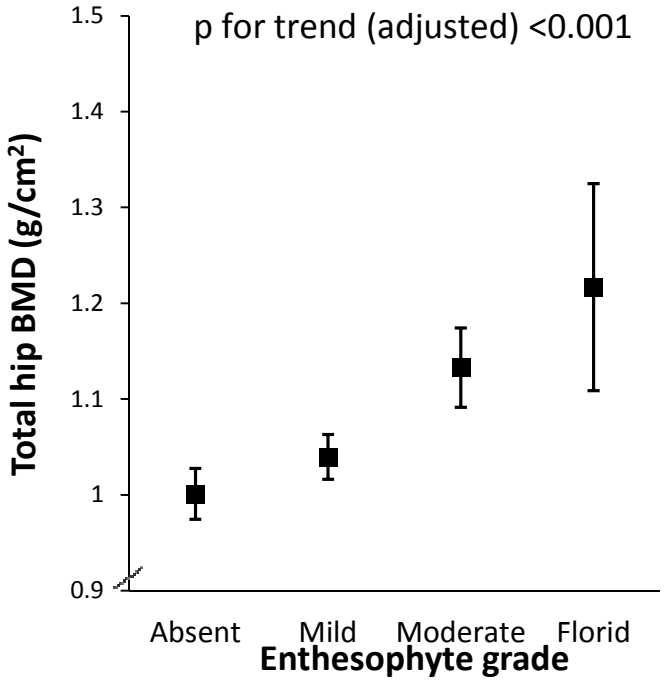
Positive associations between enthesophyte grade and L1/hip BMD

(HBM cases and all control groups combined)



N=217 (HBM), 426 (controls)



N=218 (HBM), 423 (controls)

Bars show mean and 95% CI. P for trend adjusted for age, gender and BMI

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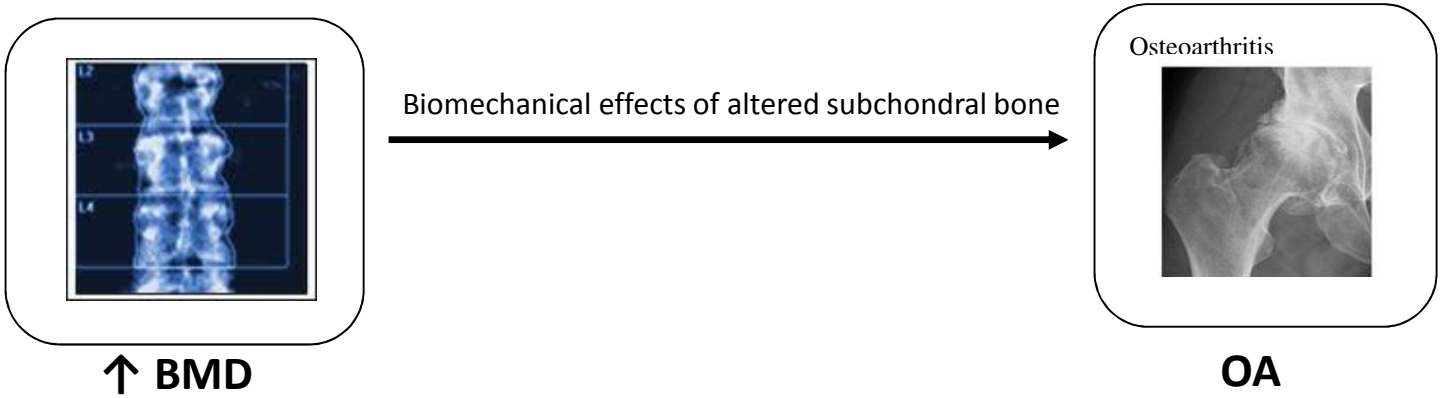
Potential Mechanisms Underlying the Association Between BMD and OA

SA Hardcastle et al BoneKEy Reports 4, 2015



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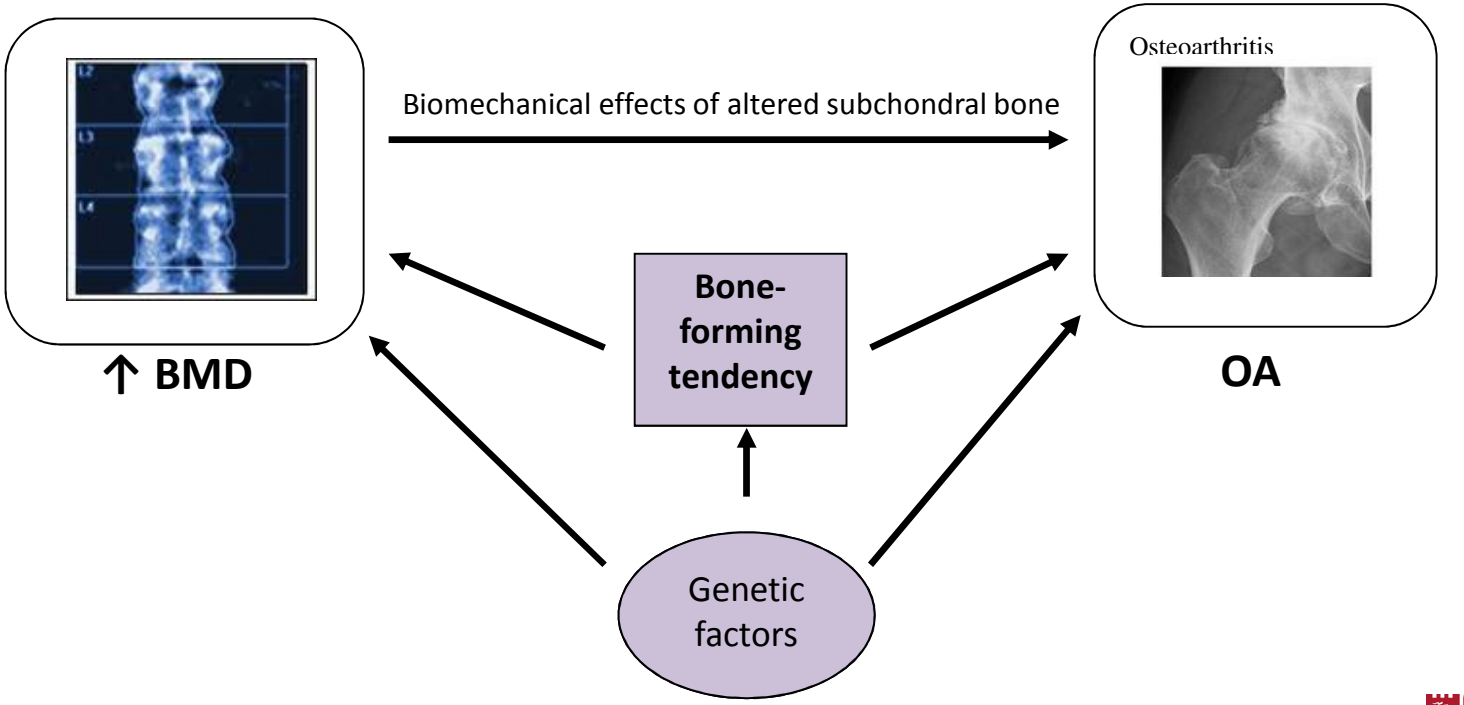

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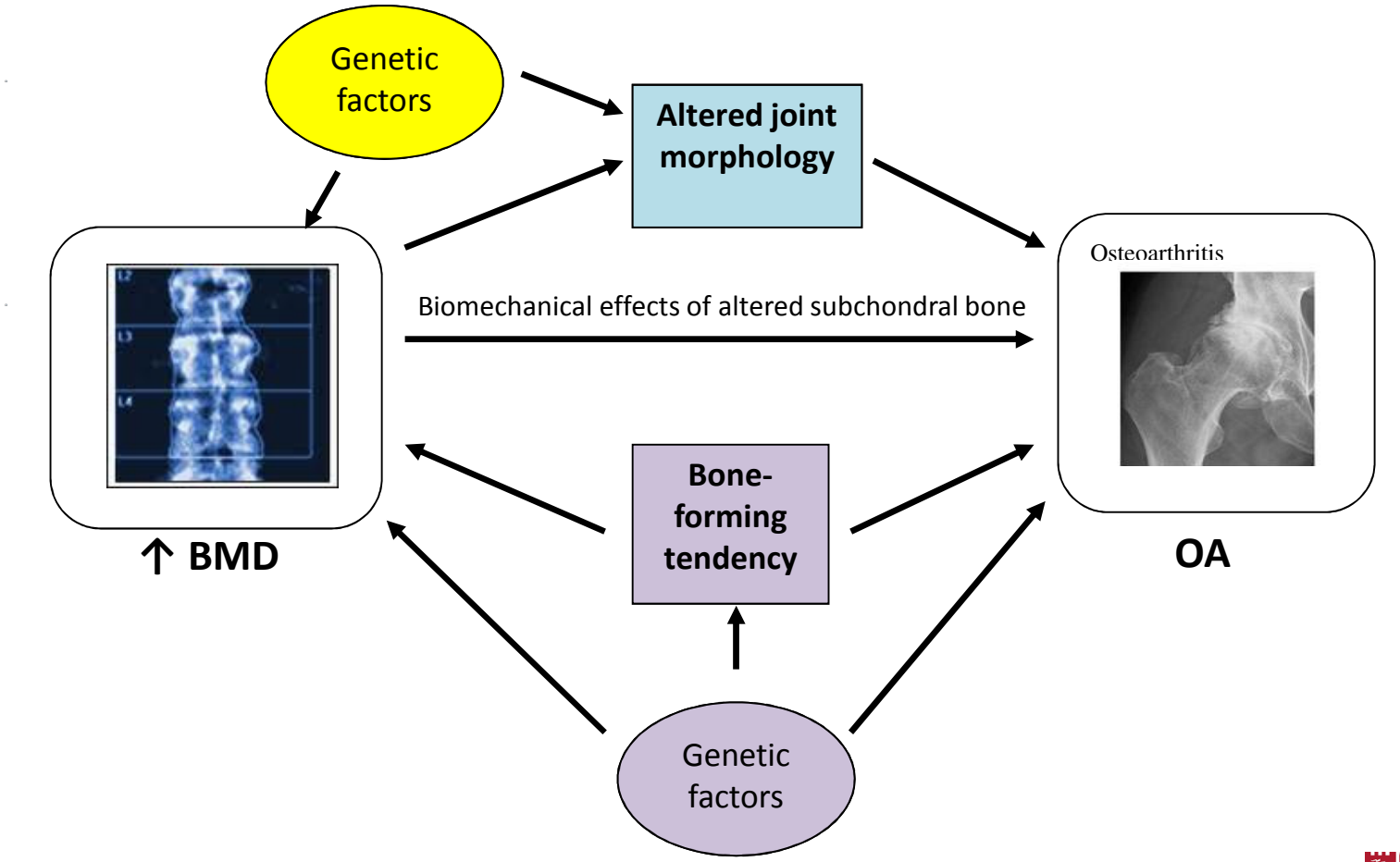

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HBM and OA

- Is HBM associated with an increased risk of radiographic hip or knee OA?
- Is HBM associated with a generalised tendency towards bone formation as reflected by enthesophytes?
- Is HBM associated with an increased risk of clinical OA, including progression to more severe disease as reflected by joint replacement?

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Osteophytes are a stronger predictor of knee pain than joint space narrowing

FM Cicuttini et al Osteoarthritis and Cartilage 1996 4:143

Table II.

Odds ratios for ever having had knee pain (episode lasting 15 or more days) in those with radiological abnormalities vs no radiological abnormality

	Number (%) with radiological features among those with pain ($N=41$) and no pain ($N=459$)	Odds ratio (95% CI)
All radiological disease*:		
Anteroposterior	15 (36.6) 58 (12.6)	3.99 (2.00–7.97)
Lateral	15 (36.6) 82 (17.9)	2.69 (1.36–5.30)
Skyline	21 (51.2) 70 (15.3)	5.84 (3.01–11.33)
Osteophytes:		
Anteroposterior	13 (31.7) 39 (8.5)	5.00 (2.40–10.43)
Lateral	13 (31.7) 64 (15.9)	2.87 (1.41–5.82)
Skyline	21 (51.2) 56 (12.2)	7.56 (3.85–14.81)
Joint space narrowing:		
Anteroposterior	5 (12.2) 28 (6.1)	2.13 (0.78–5.87)
Lateral	5 (12.2) 39 (8.5)	1.54 (0.57–4.14)
Skyline	5 (12.2) 41 (8.9)	1.42 (0.53–3.82)

*Osteophytes or joint space narrowing or both osteophytes and joint space narrowing.

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Clinical OA variables in HBM cases vs family controls (logistic regression)

Outcome	Exposure	Model*	OR	95% CI		p	N
Joint pain	HBM	1	1.80	(1.13 ,	2.88)	0.01	536
(ever, any site)		2	1.08	(0.64 ,	1.84)	0.77	536
		3	0.98	(0.57 ,	1.68)	0.94	536
NSAID use (current)	HBM	1	2.79	(1.49 ,	5.24)	0.00	549
		2	2.50	(1.28 ,	4.87)	0.01	549
		3	2.17	(1.10 ,	4.28)	0.03	549
Knee crepitus (moderate/ severe)	HBM	1	2.26	(1.50 ,	3.42)	0.00	408
		2	1.36	(0.85 ,	2.20)	0.20	408
		3	1.15	(0.70 ,	1.89)	0.57	408

*Model 1 – crude
Model 2 – adjusted for age and gender
Model 3 – adjusted for age, gender and BMI

SA Hardcastle et al British Journal of Rheumatology 2013: 52: 1042-51

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SA Hardcastle et al British Journal of Rheumatology 2013: 52: 1042-51

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Hip/knee joint replacements in HBM cases vs family controls (logistic regression)

Outcome	Exposure	Model*	OR	95% CI		p
Any joint replacement	HBM	1	3.54	(1.64 ,	7.66)	0.00
		2	2.60	(1.15 ,	5.90)	0.02
		3	2.42	(1.06 ,	5.56)	0.04
Hip replacement	HBM	1	6.48	(1.51 ,	27.86)	0.01
		2	4.56	(1.02 ,	20.30)	0.05
		3	4.79	(1.07 ,	21.51)	0.04
Knee replacement	HBM	1	1.98	(0.84 ,	4.68)	0.12
		2	1.48	(0.59 ,	3.72)	0.40
		3	1.23	(0.48 ,	3.16)	0.67

* Model 1 – crude
Model 2 – adjusted for age and gender
Model 3 – adjusted for age, gender and BMI

N=550

SA Hardcastle et al British Journal of Rheumatology 2013: 52: 1042-51

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Hip/knee joint replacements in HBM cases vs family controls (logistic regression)

Outcome	Exposure	Model*	OR	95% CI		p
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* Model 1 – crude
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N=550

SA Hardcastle et al British Journal of Rheumatology 2013: 52: 1042-51

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Health Survey for England (HSE)

- Series of annual surveys about the health of people living in England
- 2005 survey focussed on the health of older people
- 4269 individuals >65y living in private households interviewed
- Questions included joint replacement (ever), site (hips, knees, other joint), and indication (hip replacement)

- Joint replacement prevalence in HBM cases and controls aged >65 years* compared with HSE

*N=201, 37%

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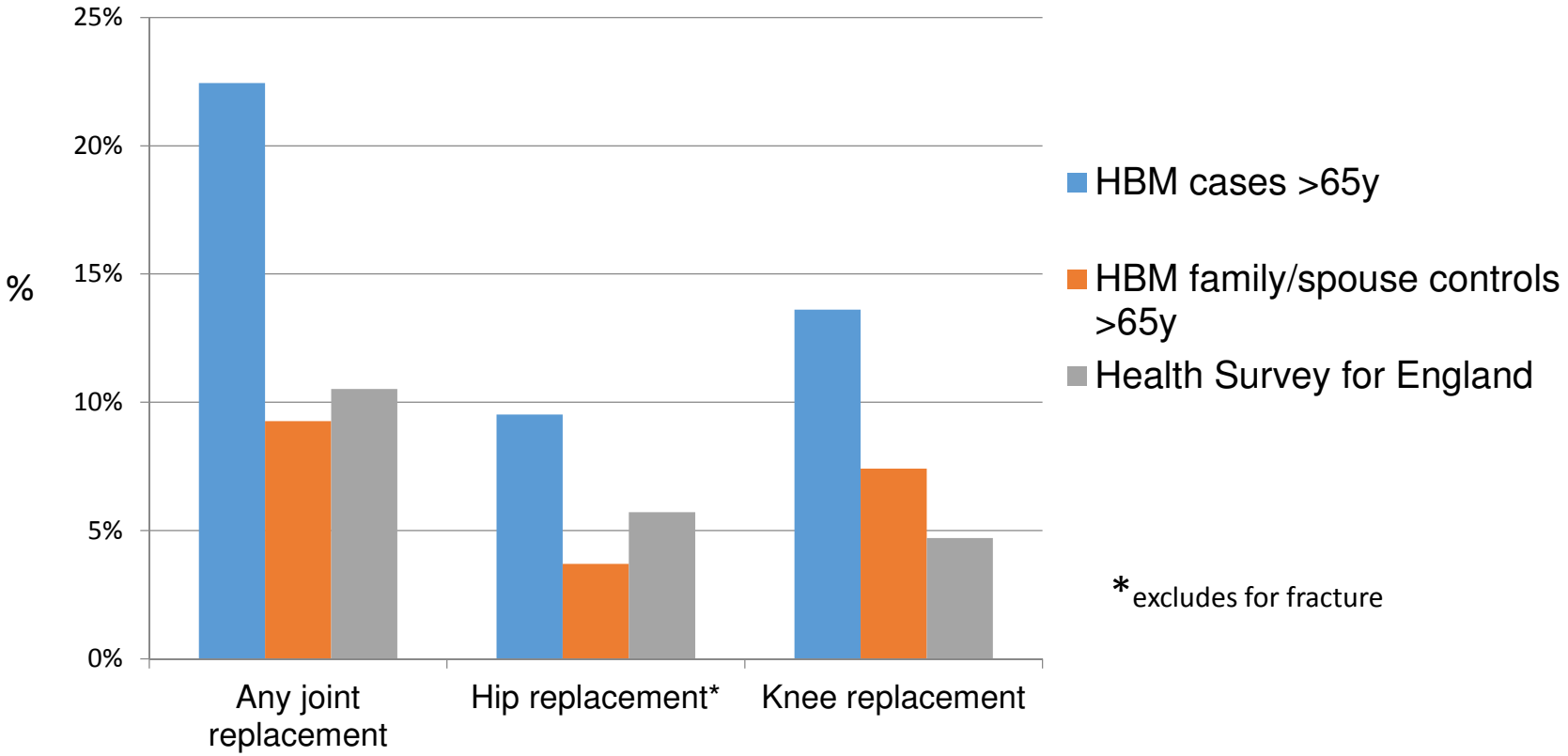
Comparison of joint replacement prevalence in older HBM cases *vs* Health Survey for England 2005



	HSE 2005	HBM cases
Age (mean, range)	74.5 (65-100)	73.8 (65.1-89.8)
Female (%)	55.6	63.4

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Summary

- There is conflicting evidence that bone mineral density (BMD) is a risk factor for osteoarthritis (OA)
- Studies of patients with High Bone Mass indicate that increased BMD has a causal role in the development of hypertrophic forms of OA
- Strategies for targeting the bony phenotype in hypertrophic OA

Targeting the Bone Phenotype in Hypertrophic OA

- Biomechanical inputs
- Osteophyte growth
- Nociceptive pathways

Targeting the Bone Phenotype in Hypertrophic OA

- Biomechanical inputs
- Osteophyte growth
- Nociceptive pathways

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JT2

Local malalignment predicts osteophyte formation in knee X-rays

Y Nagaosa et al 2002 Ann Rheum Dis 61:319

Table 3 Odds ratio (OR) and 95% confidence intervals (CI) for factors associated with grade 2 or 3 osteophyte at each site: multivariate analysis

Site of grade 2 or 3 osteophyte	Associated factor	OR	95% CI
Lateral femoral osteophyte	Attrition of TFJ	4.24	1.38 to 13.0
	Chondrocalcinosis	5.10	1.64 to 15.9
Lateral tibial osteophyte	Female	8.52	1.57 to 46.3
	Attrition of TFJ	5.21	1.69 to 16.1
	Chondrocalcinosis	6.55	2.09 to 20.5
Medial femoral osteophyte	Female	5.09	1.14 to 22.8
	Attrition of TFJ	23.0	7.03 to 75.0
	Femorotibial angle*	1.13	1.04 to 1.23
	Sum osteophyte score‡	11.6	1.96 to 68.6
Medial tibial osteophyte	Age	1.16	1.03 to 1.19
	Chondrocalcinosis	6.68	1.40 to 31.8
	Femorotibial angle*	1.27	1.08 to 1.48
Lateral patellar osteophyte	Body mass index	1.10	1.02 to 1.19
	Attrition of PFJ	17.6	5.38 to 57.7
	Patellar lateral subluxation†	11.8	3.85 to 36.4
Lateral trochlear osteophyte	Femorotibial angle*	0.90	0.83 to 0.98
	Patellar lateral subluxation†	3.69	1.27 to 10.7
	JSN of lateral PFJ†	3.19	1.05 to 9.69
Medial patellar osteophyte	Femorotibial angle*	1.70	1.22 to 2.36
Medial trochlear osteophyte	Body mass index*	1.11	1.01 to 1.22
	JSN of medial TFJ†	7.40	1.50 to 36.4
	Sum osteophyte score‡	7.28	1.85 to 28.7

TFJ, tibiofemoral joint; PFJ, patellofemoral joint; JSN, joint space narrowing; Sum osteophyte score, summated osteophyte score for other three compartments (that is, total osteophyte score – osteophyte score for compartment of interest).
*Continuous variable; †dichotomised at 0–1 *v* 2–3; ‡dichotomised at 0–8 *v* 9–18.

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JT2 May be a case for selectively targeting hypertrophic OA for interventions acting via altered biomechanical inputs eg foot orthoses, muscle strengtening exercises

JH Tobias, 2/16/2015

Targeting the Bone Phenotype in Hypertrophic OA

- Biomechanical inputs
- Osteophyte growth
- Nociceptive pathways

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Can osteophyte growth be targeted?

Osteophyte

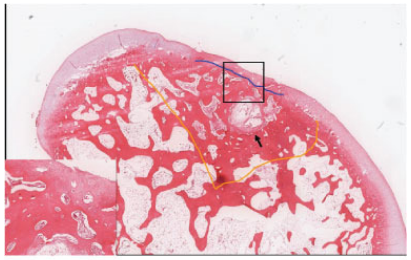
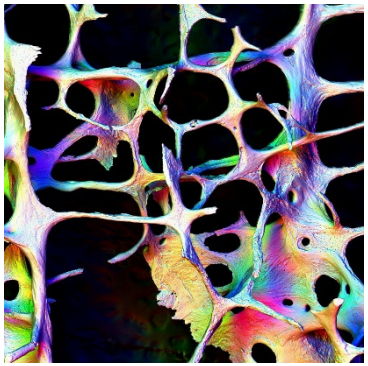


Figure 4 - Group B specimen. Image shows a continuous surface and erosion of the regenerated hyaline cartilage (insert) in the central zone of the original defect area (area within the orange line). A cystic space (arrow) that was filled with granulation tissue in the subchondral area (blue line) with sclerosing change is shown (H & E stain).

Osteoporosis



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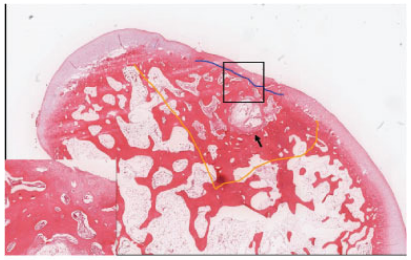
Can osteophyte growth be targeted?

Osteophyte



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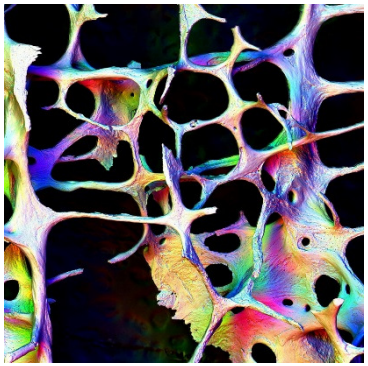
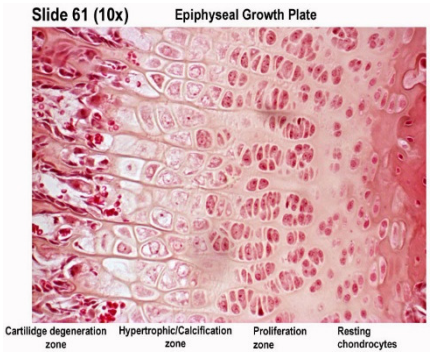
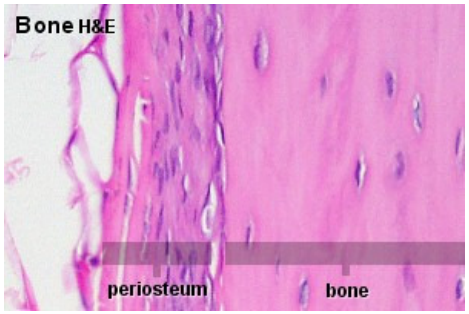


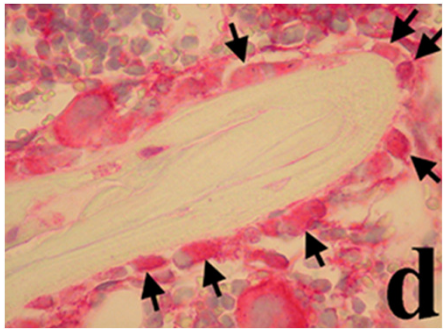
Endochondral Bone Formation

Periosteal Bone Formation

Trabecular Bone Formation







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JT3

Can osteophyte growth be targeted?

Osteophyte

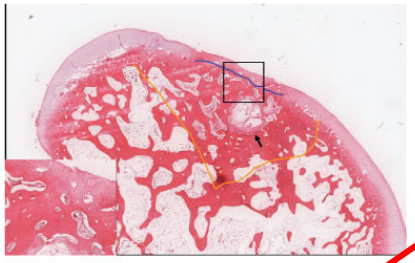
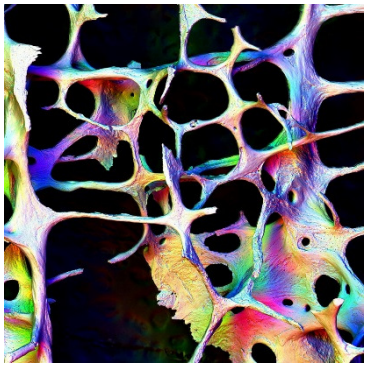


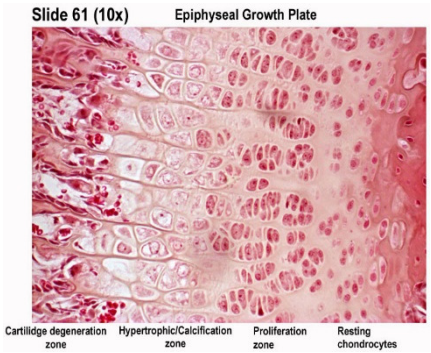
Figure 4 - Group B specimen. Image shows a continuous surface and erosion of the regenerated hyaline cartilage (inset) in the central zone of the original defect area (area within the orange line). A cystic space (arrow) that was filled with granulation tissue in the subchondral area (blue line) with sclerosing change is shown (H & E stain).

Osteoporosis

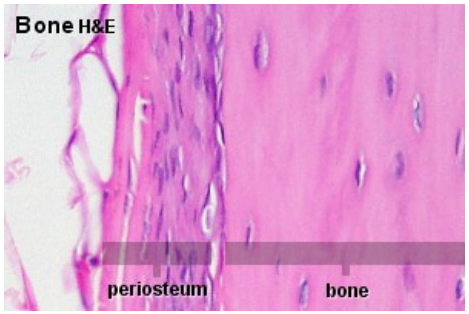


Estrogen

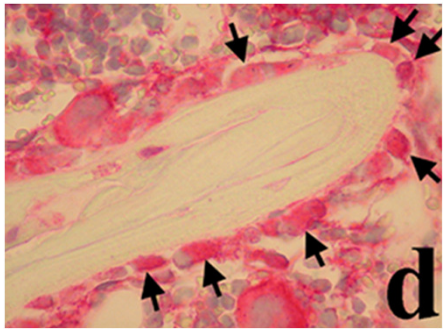
Endochondral Bone Formation



Periosteal Bone Formation



Trabecular Bone Formation



JT3 Fits with observations that accelerated incidence of OA in women after the menopause, and results from several studies suggesting HRT is broadly protective against OA

JH Tobias, 2/16/2015

JT4

Use of Genetic Studies to identify molecular pathways involved in osteophyte growth?

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< Previous Article Volume 380, No. 9844, p815–823, 1 September 2012 Next Article >

Articles

Identification of new susceptibility loci for osteoarthritis (arcOGEN): a genome-wide association study

arcOGEN Consortium and arcOGEN Collaborators

† Members listed at end of paper

Ann Rheum Dis 2014;**73**:2130-2136 doi:10.1136/annrheumdis-2012-203114

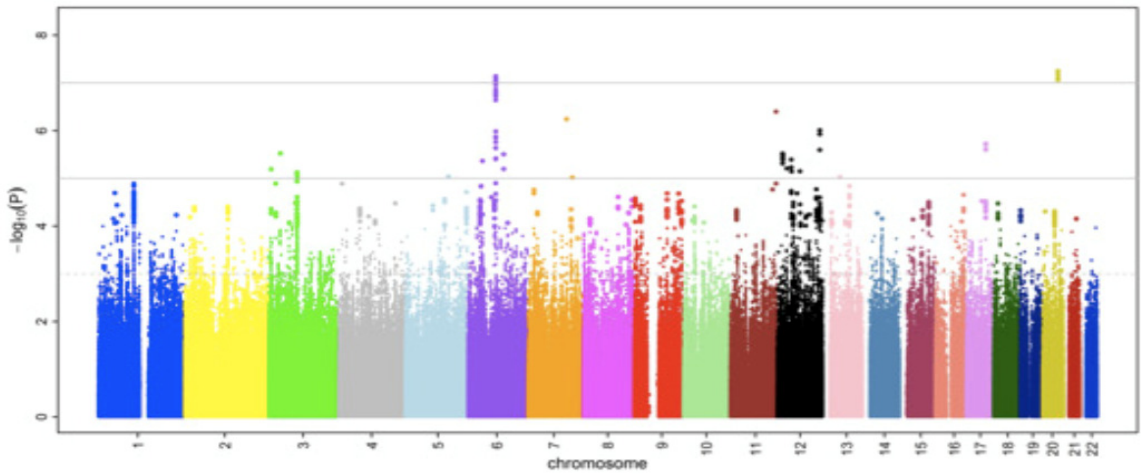
Clinical and epidemiological research

Extended report

A meta-analysis of genome-wide association studies identifies novel variants associated with osteoarthritis of the hip

OPEN ACCESS

Evangelos Evangelou[1,2], Hanneke J Kerkhof[3], Unnur Styrkarsdottir[4], Evangelia E Ntzani[1], Steffan D Bos[5,6], Tonu Esko[7,8], Daniel S Evans[9],



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Slide 51

JT4 It may be possible to refine this approach by looking at endophenotypes related to hypertrophic OA - one or two abstracts have come out looking at this eg arcogen group at OARSI 2014

JH Tobias, 2/16/2015

Targeting the Bone Phenotype in Hypertrophic OA

- Biomechanical inputs
- Osteophyte growth
- Nociceptive pathways

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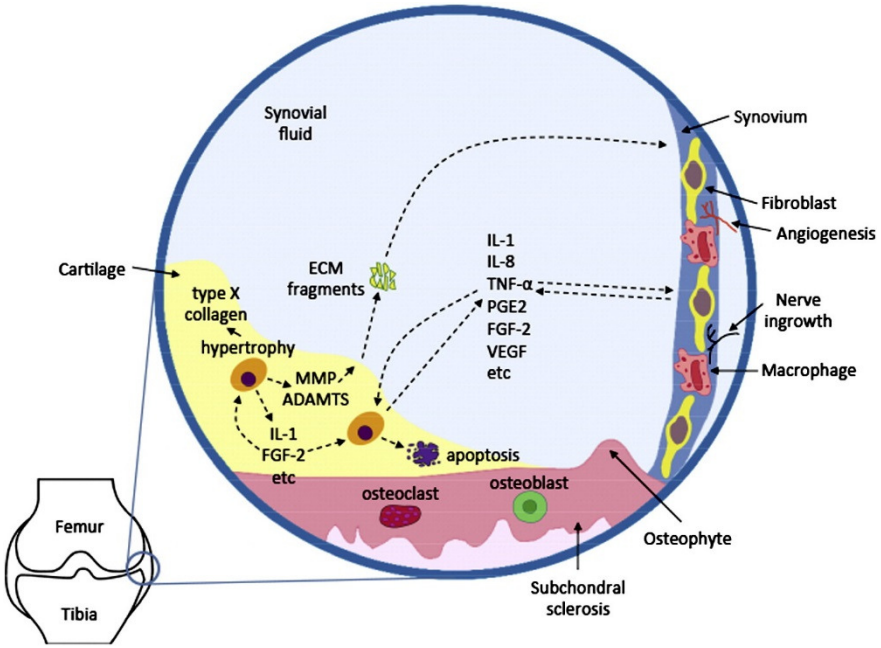
Pain in OA: role of inflammatory mediators produced by cartilage?

A Lee et al, Gene 2013 527: 440-447



Inflammatory mediators	Signaling Mediators	Proteases
• TNF	• NFκB	• MMP-1
• IL-1β	• ERK1/2	• MMP-3
• IL-6	• p38	• MMP-9
• IL-8	• JNK	• MMP-13
• IL-15	• PKCδ	• ADAMTS-4
• IL-17	• TLRs	• ADAMTS-5
• IL-21	• β-catenin	• TACE
• PGE2	• Gli1	
• Substance P	• Ptch	
• NGF	• HHIP	
• EGF	• HIF-2α	
• VEGF	• iNOS	
• FGF-2	• RUNX2	

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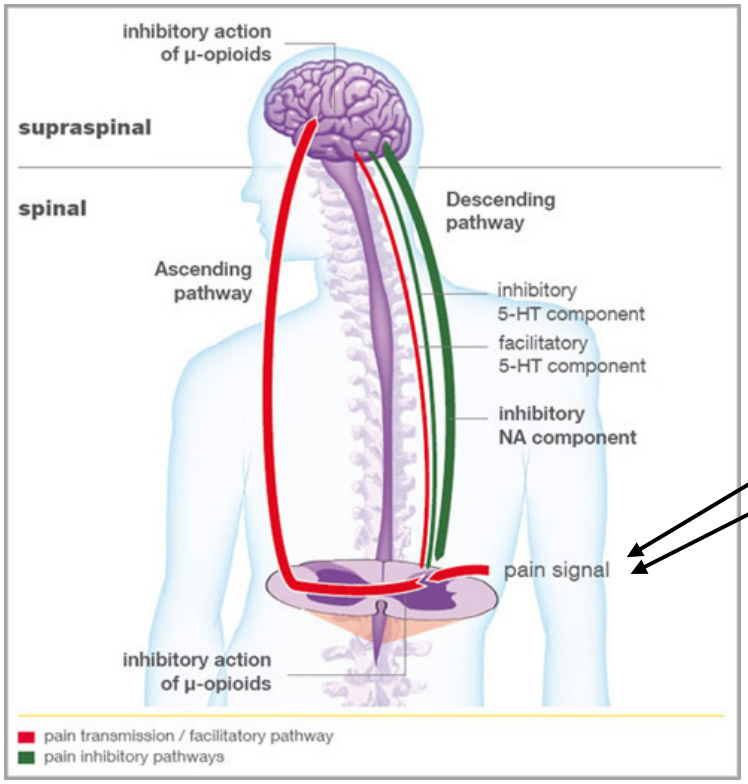
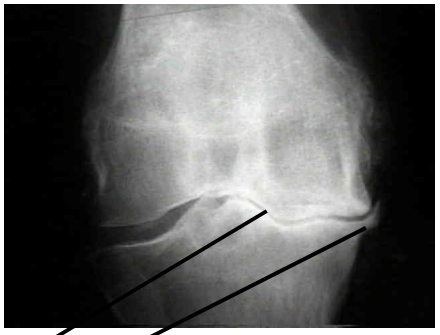
JT7

Pain in hypertrophic OA: afferent pathways from subchondral bone and osteophytes as a therapeutic target





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JT7 Novel nociceptive inhibitors are in development including those acting at level of DRG eg galanin receptor agonists, which may prove helpful in treating pain from hypertrophic OA

JH Tobias, 2/16/2015

Conclusions

- Studies of patients with high bone mass suggest that increased bone mineral density plays a causal role in the development of hypertrophic forms of OA.
- Targeting the bone phenotype in hypertrophic OA may represent a useful therapeutic strategy, for example by suppressing osteophyte growth, or targeting bone-derived nociceptive pain pathways.

Acknowledgements

High Bone Mass

Sarah Hardcastle

Celia Gregson

Paul Dieppe

Martin Williams

George Davey Smith

Chingford

Nigel Arden

Deborah Hart

Tim Spector

Hertfordshire Cohort Study

Elaine Dennison

Mark Edwards

Cyrus Cooper

University of BRISTOL

Study Population

- **HBM cases:**

  Σ L1 Z-score + total hip Z-score ≥+3.2

  n=226

- **Controls – 3 groups:**

  1. HBM study family controls (unaffected), n=124
  2. Chingford 1000-women study controls*, n=193
  3. Hertfordshire cohort study controls*, n=120

- All pelvic radiographs from cases / controls pooled and relabelled for blinded assessment

*Selected using age and gender stratified random sampling in 2:1 ratio with cases

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Hypothesis

- HBM is associated with an increased risk of hypertrophic OA phenotypes as assessed radiologically, which translates into an increased risk of symptomatic OA.

Summary

- HBM is associated with an increased prevalence of joint replacement, compared with unaffected family / spouse controls

- In fully adjusted analyses, HBM was related to hip replacement (OR 4.79, 95% CI 1.1, 21.5) more strongly than to knee replacement (OR 1.23, 95% CI 0.5, 3.2)

- Comparison with population data (HSE 2005) provided further evidence that the prevalence of joint replacement is increased in HBM

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Aims

To quantify and characterise radiographic hip OA in a HBM population by determining

i) Whether the prevalence of radiographic hip OA is increased in HBM compared with family and general population controls

ii) Whether hip OA in this group has a particular phenotype based on individual radiographic features of OA

Is HBM associated with knee OA?

This study aimed to determine whether:

(i) HBM is also associated with an increased risk of knee OA

(ii) Any HBM OA knee phenotype is similar to that seen at the hip

(iii) BMI plays a role in mediating any association which we find

Hypothesis

- HBM is associated with an increased risk of hypertrophic OA phenotypes as assessed radiologically, which translates into an increased risk of symptomatic OA.

Aims

1. To compare the prevalence of clinical variables associated with OA in HBM cases, with unaffected family and spouse controls
2. To compare the prevalence of joint replacement in HBM with that in the wider population

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Aims

To establish whether:-

(i) HBM is associated with an increased risk of enthesophytes on pelvic X-rays

(ii) Pelvic enthesophytes are associated with an increased risk of hip osteophytes irrespective of HBM case status

(iii) Pelvic enthesophytes are associated with increased BMD irrespective of HBM case status

Summary

- HBM was associated with an increased risk of enthesophytes as well as osteophytes
- Enthesophytes and osteophytes were positively associated in analyses based on pooled HBM cases and controls, suggesting a similar relationship exists in the wider population
- Enthesophyte grade was positively associated with L1 and total hip BMD in combined analyses, suggesting a general association also exists between enthesophytes and BMD