



Faber, B. G., Frysz, M., & Tobias, J. H. (2019). Unpicking observational relationships between hip shape and osteoarthritis: hype or hope? *Current Opinion in Rheumatology*.
<https://doi.org/10.1097/BOR.0000000000000673>

Peer reviewed version

Link to published version (if available):
[10.1097/BOR.0000000000000673](https://doi.org/10.1097/BOR.0000000000000673)

[Link to publication record in Explore Bristol Research](#)
PDF-document

This is the author accepted manuscript (AAM). The final published version (version of record) is available online via Lippincott, Williams & Wilkins at https://journals.lww.com/co-rheumatology/Abstract/publishahead/Unpicking_observational_relationships_between_hip.99015.aspx#pdf-link . Please refer to any applicable terms of use of the publisher.

University of Bristol - Explore Bristol Research

General rights

This document is made available in accordance with publisher policies. Please cite only the published version using the reference above. Full terms of use are available:
<http://www.bristol.ac.uk/red/research-policy/pure/user-guides/ebr-terms/>

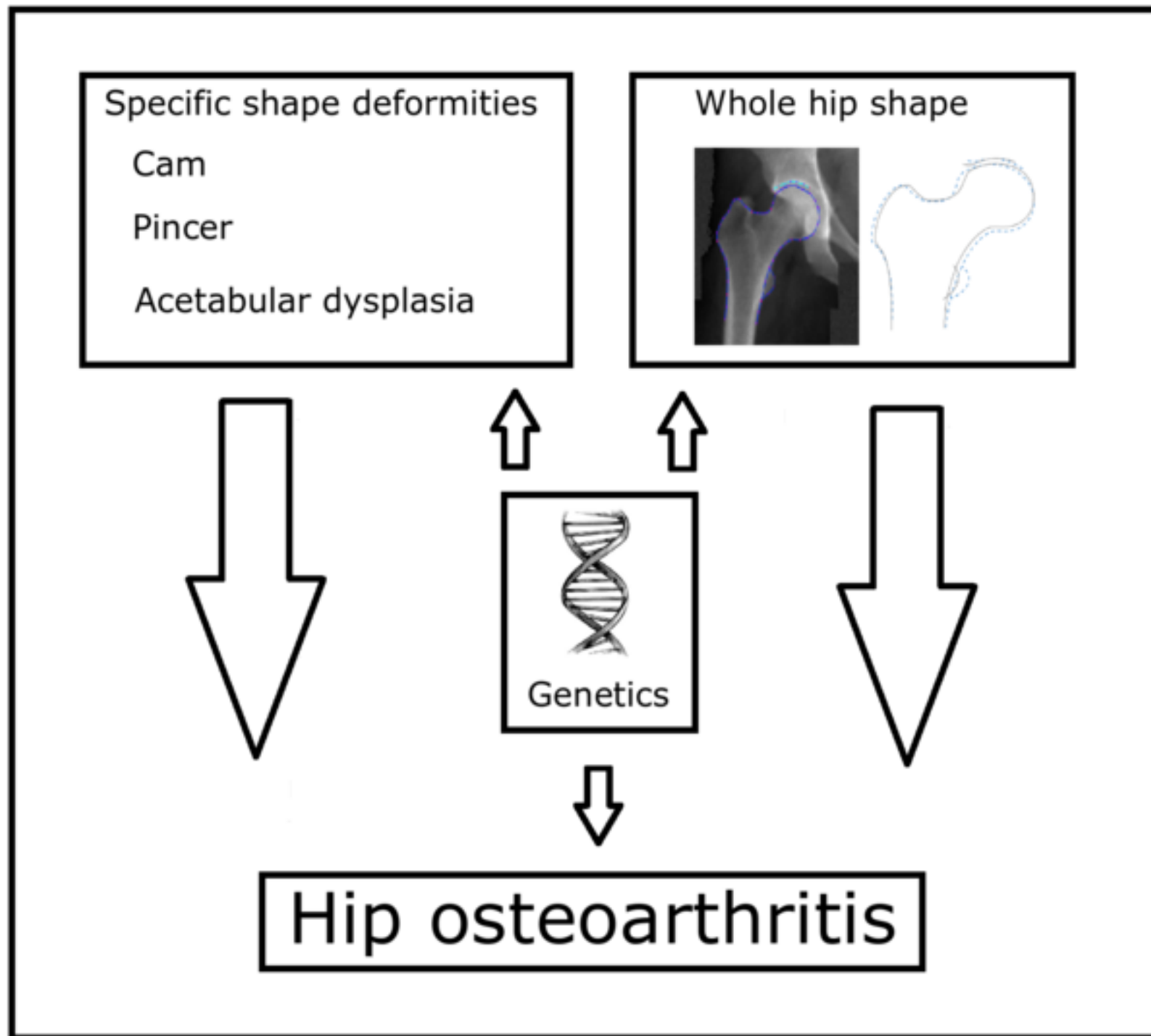
Current Opinion in Rheumatology

Unpicking observational relationships between hip shape and osteoarthritis: hype or hope?

--Manuscript Draft--

Manuscript Number:	BOR320105
Full Title:	Unpicking observational relationships between hip shape and osteoarthritis: hype or hope?
Article Type:	Review Article
Corresponding Author:	Benjamin Faber University of Bristol UNITED KINGDOM
Corresponding Author Secondary Information:	
Corresponding Author's Institution:	University of Bristol
Corresponding Author's Secondary Institution:	
First Author:	Benjamin G Faber
First Author Secondary Information:	
Order of Authors:	Benjamin G Faber Monika Frysz Jon H Tobias
Order of Authors Secondary Information:	

Figure 1



Editorial Manager MS Check Form, Current Opinion

MS Number	BOR320105 Faber
Corresponding Author name (# of authors?)	Ben Faber
No. of Authors	3
Review title	Unpicking observational relationships between hip shape and osteoarthritis: hype or hope?
Section	OSTEPARTHRTIS
Author address on MS?	Y
Author email on MS?	Y

Structured abstract	Y
Key words	Y
Introduction	Y
Headings in text	Y
Conclusion	Y
Key points	Y

Word count: abstract	164
Word count: text	2591

Bullets/annotations	Y
Refs. in sequence?	Y

Conflicts of Interest	Y
-----------------------	---

	Identify	Permissions
Colour figures	y	original
Half tones	0	N/A
Line drawings	0	N/A
Tables	2	original
Figures/Tables cited in text?	Y	
Figure legends and titles?	Y	

Colour online? (Y/N, charge or free)	Y
Colour in print? (Y/N, charge or free)	N

Comments for **copyeditor**:

Editorial Manager MS Check Form, Current Opinion

Supplementary Digital Content	N/A
Cited in text?	N/A

Comments for **copyeditor**:

Unpicking observational relationships between hip shape and osteoarthritis: hype or hope?

BG Faber¹, M Frysz¹, JH Tobias¹

¹Musculoskeletal Research Unit, Bristol Medical School, University of Bristol UK

Corresponding author:

Dr Ben Faber

Musculoskeletal Research Unit

Learning and Research Building

Southmead Hospital

Bristol

BS10 5NB

ben.faber@bristol.ac.uk

+44117 4147840

Work funded by the National Institute for Health Research and Wellcome Trust

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

Purpose of review

To review recent findings concerning the observational relationship between hip shape and hip osteoarthritis (HOA) and their shared genetic influences, and the potential for clinical application.

Recent findings

Recent observational studies have strengthened the evidence that specific shape deformities, such as cam and acetabular dysplasia, are related to HOA. Statistical shape modelling has emerged as a method to measure hip shape holistically, with the added advantage that this can be applied to DXA scan images. This has led to several additional aspects of hip shape variation being identified, such as a wider femoral neck and larger lesser trochanter, in association with HOA. Furthermore, this method has formed the basis of genetic studies identifying novel genetic influences on hip shape, several of which are shared with known genetic risk factors for HOA.

Summary

Shared genetic influences of hip shape and HOA raise the possibility that hip shape plays a casual role in the development of HOA, justifying preventative approaches aiming to combat these adverse consequences.

Key words: Osteoarthritis, hip shape, genetics

Introduction

Osteoarthritis (OA) affects 250 million individuals worldwide, and the number is steadily rising as the population ages (1-3). OA is characterised by cartilage loss, joint space narrowing, bone formation, inflammation, pain and loss of function of the joint (4). Hip OA (HOA) is the third most commonly affected joint, after knees and hands, with prevalence ranging from 2-43% depending on the population and how it is defined (3). Though effective interventions to prevent onset and delay progression are currently lacking, it may be possible to develop these in future, based on greater understanding of the risk factors involved.

As previously reviewed by Baker-LePain and Lane, hip shape appears to be an important risk factor for HOA with subtle changes in hip morphology present in up to 90% of cases with primary HOA (5), possibly reflecting shared genetic influences (6). Here we aim to provide a more up to date perspective on the relationship between hip shape and HOA, in light of methodological advances such as DXA-derived hip shape, and recent large-scale genome wide association studies (GWAS) for HOA and hip shape. (Fig1)

Hip shape and its observational relationship with osteoarthritis

HOA is a complex and phenotypically heterogeneous disease (7). In this review we focus on epidemiological studies of HOA defined as radiographic (based on scoring criteria such as Kellgren-Lawrence (8) or Croft (9)), symptomatic (assessed by questionnaire (10) and/or examination (11)) or total hip replacement (THR) (12). As previously reported, the correlation between radiographic HOA (RHOA) and symptomatic HOA (SHOA) is known to be inconsistent (6, 13). Our review focuses on hip shape derived from two dimensional (2D) imaging; although computed tomography and magnetic resonance imaging have both been used for

1 three dimensional (3D) shape modelling (14, 15), they have yet to feature in large scale
2 epidemiological studies described here.
3

4 5 Specific hip shape deformities 6

7
8
9 Since the Baker-LePain et al review (6), many large epidemiological studies have investigated
10 the relationship between hip shape and OA, as summarised in Table 1. The most recent
11 studies focus on subtler variations in hip shape, in contrast to severe congenital dysplasias
12 such as developmental dysplasia of the hip (DDH) which has well established links with early
13 onset HOA(16-18).
14
15
16
17
18
19
20
21

22 Femoro-acetabular impingement (FAI) is a symptomatic condition characteristic of cam,
23 pincer or mixed (the presence of both) deformity (19), which is thought to increase the risk
24 of developing HOA(20). Cam deformity represents a bulging of the lateral femoral head
25 resulting in a non-spherical head and is most commonly defined by measuring alpha angles
26 on anterior-posterior or lateral radiographs(21). It is thought to develop during adolescence,
27 in particular as a result of high impact activities (21, 22). Previous studies reported
28 associations between cam deformity (defined by alpha angle) and worsening RHOA (23),
29 incident RHOA(24), and end-stage HOA (defined as either incident RHOA or THR) (25, 26) with
30 odds ratios (OR) ranging from 1.05-9.66 (24, 25). For example, the largest study (n=4,438)
31 observed an OR 2.11 for incident RHOA or THR(26). The triangular index is a further measure
32 of cam deformity and has been linked with prevalent RHOA(27) and incident end-stage
33 HOA(28).
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53

54 Another component of FAI, pincer deformity, representing over-coverage of the acetabulum
55 relative to the femoral head, has also been suggested to be a risk factor for HOA (20, 29).
56
57
58
59

1 Consistent with this suggestion, using a CEA cut off of ≥ 45 degrees, Gosvig et al reported an
2 association with prevalent RHOA (RR 2.4 [2.0-2.9]) (27). On the other hand, in the CHECK and
3 Chingford cohorts, pincer deformity, defined as a centre-edge angle (CEA) > 40 degrees, was
4 not associated with an increased risk of incident RHOA or THR (30, 31),
5
6
7
8
9

10 Acetabular dysplasia describes a lack of acetabular coverage of the femoral head, measured
11 with a CEA on pelvic radiographs (range < 20 - 28 degrees) (24-26) and is distinct from FAI.
12 Recent studies have shown a relationship of acetabular dysplasia with incident RHOA and
13 THR, replicating earlier studies and suggesting it represents a further hip joint deformity
14 contributing to the pathogenesis of HOA (24, 26).
15
16
17
18
19
20
21
22
23

24 Global assessment of proximal femur/ hip shape

25
26
27 Statistical shape modelling (SSM) has been developed to describe joint shape as a whole,
28 using principal component analysis to generate hip shape modes (HSMs) describing variation
29 in hip shape in a given data set (typically a subset of HSMs, which explain between 85-95% of
30 variation in hip shape are used in analysis (11, 12, 32)). These HSMs encompass different
31 areas of the joint such as the acetabulum, femoral head and femoral shaft in one
32 measurement. This enables relationships between hip shape and disease outcomes to be
33 examined in a hypothesis-free manner, offering the potential to identify novel aspects of hip
34 shape contributing to HOA. Gregory et al first applied this technique to hip radiographs to
35 investigate the relationship with hip fracture (33) before looking at RHOA(34).
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50

51 In two recent prospective cohorts (CHECK and Chingford), where SSM was applied to hip
52 radiographs, six HSMs predicted THR but only one HSM (describing a flatter femoral neck to
53 head junction, flatter greater trochanter and prominent acetabular wall) was predictive in
54
55
56
57
58
59
60
61
62
63
64
65

1 both cohorts (35). In the Johnston County OA project, three HSMs were associated with
2
3 incident symptomatic radiographic HOA (as a single phenotype); in particular HSM2
4
5 representing a cam-type deformity, and larger greater and lesser trochanters [OR 1.47], and
6
7 HSM3 representing smaller greater trochanter and larger femoral head [OR 1.54] (36). In a
8
9 separate study, the authors also found that smaller femoral head and lesser trochanter was
10
11 associated with RHOA in the small sample of African American women (37).
12
13
14
15

16 DXA-derived hip shape

17
18
19 Whereas the aforementioned studies are based on radiographs, SSM has subsequently been
20
21 extended to hip dual X-ray absorptiometry (DXA) scans (38), for which greater numbers of
22
23 population based cohorts are available. Recently, in the Osteoporotic Fractures in Men Study
24
25 (MrOS), DXA-derived SSM from 4,100 individuals found five HSMs to be associated with
26
27 prevalent RHOA [negative SD shapes OR 0.73-0.83 and positive SD shapes OR 1.23-1.24] and
28
29 of these HSM3 was also associated with hip pain as assessed by pain scores and clinical
30
31 examination [OR 0.88 and 0.83 respectively] (11). In the Tasmanian Older Adult Cohort
32
33 (TASOAC), DXA-derived hip shape showed association with incidence and progression of HOA,
34
35 specifically HSM2 and 4 which predicted THR [OR 1.6 & 0.6 respectively] (39). However,
36
37 whereas HSM2 was positively related to risk of THR, this was negatively related to RHOA.
38
39
40
41
42
43
44
45

46 In both these DXA studies, as well as representing cam or pincer-type deformities, proximal
47
48 femur HSMs found to be associated with HOA were also related to a range of other features
49
50 previously reported to be associated with HOA. These include a larger greater and lesser
51
52 trochanters seen by Nelson et al in their SSM study based on radiographs (36), and a wider
53
54 femoral neck associated with HOA when measured geometrically (Castano-Betancourt et al
55
56 (28) and Javaid et al (40)). A limitation of SSM is that it is difficult to establish which particular
57
58
59
60
61
62
63
64
65

1 feature of hip shape is relevant to HOA and further work is needed to clarify these
2 relationships. Interestingly, in analysis based on a sub-regional shape model limited to the
3 lesser trochanter, and validated against 3D hip shape from CT, lesser trochanter size showed
4 a similar relationship with prevalent RHOA in MrOS, compared to HSMs derived from the
5 whole proximal femur (Faber et al, manuscript in preparation) (41). The reported associations
6 between HSMs representing a pincer-type deformity and RHOA contrast with null
7 relationships reported in radiographic studies that assessed pincer deformity by measuring
8 CEA (30, 31). It may be that the presence of pincer-type deformity is only important in the
9 presence of other variations in shape such as a larger greater and lesser trochanters as seen
10 in HSM1 in MrOS (11) and HSM2 in TASSOAC (39) that are not captured when assessing pincer
11 deformity on its own (30).
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28

29 When comparing results from different studies it is important to note that HSMs are specific
30 to the population being examined, since they are derived from principle components analysis
31 applied to the specific image set in question. Therefore, results cannot be directly compared
32 between studies. However, one way of overcoming this issue is to build an SSM model on
33 multiple cohorts combined, as done in a recent GWAS meta-analysis of hip shape (42).
34 Alternatively, an existing SSM template can be applied as a reference, as exemplified by our
35 recent study in adolescents where we applied a template built from adult images to enable
36 comparison of hip shape between different ages (43).
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

Genetic influences on hip shape and OA

To date, GWASs have identified 86 single nucleotide polymorphisms (SNPs) associated with OA at any site (44), defined as radiographic OA, severe OA (defined by joint replacement) or self-reported OA (44-49). Of these, a number of variants associated with HOA specifically, or HOA and OA at other sites, have also been found to associate with measures of hip shape, as shown in Table 2.

The majority of recently published studies exploring genetics of hip shape used measures quantified with SSM. For example, a longitudinal study of Caucasian women reported associations between two *FRZB* SNPs and proximal femur shape, of which rs288326 was associated with HSM2 which predicted incident RHOA (50). The only GWAS meta-analysis of SSM DXA-derived hip shape identified nine novel variants associated with hip shape. Of those, three were found to associate with HOA in previous GWASs based on arcOGEN and UK Biobank (42). Two of these loci (near *PTHLH* and *RUNX1*), which were associated with HSM1, are known regulators of endochondral bone formation, raising the possibility that altered development of hip shape may have implications for future risk of HOA (42). A further locus, *ASTN2*, associated with HSM2 (42) (a RHOA associated shape in MrOS (Faber et al, manuscript in preparation (41))) was also found to associate with HSM5 in a cohort of subjects with unilateral HOA (51). In contrast to SSM derived hip shape, Zengini et al explored genetic associations with geometric measures of hip shape (defining acetabular dysplasia and cam deformity) using data from UK Biobank and the Rotterdam studies, with largely null findings (52).

1
2
3 In studies performed in older adults it is difficult to distinguish shape changes that are the
4
5 direct result of OA, from those that lead to OA development . For example, rather than pre-
6
7 dating OA, pincer-type deformities may result from osteophytes formed as part of the OA
8
9 process (11). Findings of associations between known OA risk loci and hip shape in younger
10
11 individuals who are likely to be disease free could point towards causal variants for OA
12
13 development. For example, in a look-up study of known OA susceptibility loci in peri-
14
15 menopausal women, *PTHLH* rs10492367 SNP (in high linkage disequilibrium, $r^2=0.74$, with
16
17 rs10743612 SNP reported in the above GWAS meta-analysis of DXA derived hip shape in
18
19 adults and previously found to associate with hip shape in adolescents (43)) was associated
20
21 with a greater height-to-width ratio of upper femur (53), further reinforcing the suggestion
22
23 that altered femoral morphology plays a role in HOA development. In addition, the
24
25 *COL11A1* locus was associated with lateral displacement of the femoral head and previous
26
27 studies reported associations of this locus with hip bone size (54), and altered load-induced
28
29 cartilage damage in *COL11A1* insufficient mice (55). In addition *COL11A1* mutations are
30
31 associated with Stickler's syndrome which causes accelerated HOA (53, 56, 57). This look-up
32
33 study also reported an association between *DOT1L* rs12982744 and superolateral joint space,
34
35 consistent with previous GWAS findings implicating *DOT1L* with joint space width (46, 52).

36
37
38
39
40
41
42
43
44
45
46
47 DDH, characterized by uncovering of the femoral head and in its most severe forms complete
48
49 dislocation of the hip joint (58), is a common cause of premature HOA in young adults (59)
50
51 and has a strong genetic component (60). A recent GWAS identified a robustly replicating
52
53 association between genetic locus at *GDF5* (previously found to be associated with HOA risk
54
55 (45, 52)) and DDH case status (47). In addition, *GDF5* has been shown to affect proximal femur
56
57
58
59

1 development in animal studies (61) consistent with the suggestion that OA development is
2 mediated through joint shape and variants associated with hip morphology are likely to
3
4 mediate this relationship.
5
6

7 8 ***Clinical utility of hip shape HOA relationships*** 9

10
11
12 As discussed above, evidence that certain OA susceptibility loci are associated with hip shape
13
14 in cohorts thought to be free of HOA suggests that at least some of the hip shape variations
15
16 identified precede the development of OA, consistent with a causal role. Identification of
17
18 further genetic influences on hip shape should enable methods such as Mendelian
19
20 randomisation (MR) to be applied to examine the causal relationship between hip shape and
21
22 HOA, by providing instrumental variables for hip shape(62). To the extent that hip shape
23
24 alterations play a causal role in HOA development, this would provide justification for
25
26 developing novel preventative approaches aiming to combat these adverse consequences.
27
28 The latter are presumably mediated by adverse biomechanics associated with hip shape,
29
30 which a number of methods have been developed to model based on finite element analysis
31
32 (63).
33
34
35
36
37
38
39
40

41
42 Whereas conservative methods such as physiotherapy and orthotics could be used to combat
43
44 adverse biomechanical consequences of altered hip shape (64), surgical approaches are also
45
46 feasible, as exemplified by surgical correction of FAI syndrome, with three recent trials
47
48 examining physiotherapy versus arthroscopic intervention in this group (65-67). The two
49
50 largest studies found only a marginal improvement with surgical intervention as compared to
51
52 physiotherapy (65, 67), with the smallest study showing no difference (66). The follow up
53
54 periods were short (<2 years) with no evidence that either intervention is protective for HOA.
55
56
57
58
59
60

1 None of the trials had well defined, objective measures of FAI instead it was at the surgeons
2 discretion reflecting the inconsistent definitions used in epidemiological studies (21). Finally,
3
4 the physiotherapy interventions varied greatly between these studies, highlighting the
5
6 uncertainty regarding the best conservative care (64).
7
8
9

10 Analogous to predictive models for hip fracture risk (68), hip shape measures could also be
11
12 used to develop HOA prediction tools (69). Variables in such a tool do not need to be causal,
13
14 merely predictive of the outcome. Using data from CHECK cohort participants, Hosnijeh et al
15
16 constructed a model to predict incident RHOA. The authors showed that the inclusion of
17
18 radiographic measures of acetabular dysplasia and cam deformity (defined as the presence
19
20 of a CEA<20° and an alpha angle of >60°), greatly improved the discriminative ability of their
21
22 model from AUC 0.60 [95% CI 0.56-0.60] with purely demographic details, to 0.75 [0.72-0.79]
23
24 (70). It would be useful to examine whether the predictive ability of such tools is further
25
26 enhanced by including measures of hip shape derived by SSM.
27
28
29
30
31
32
33
34
35
36
37

38 **Conclusion**

39
40
41
42 There are strong associations between hip shape and HOA, comprising of a spectrum from
43
44 severe DDH, to more subtle variation in hip shape such as FAI and those measured by SSM
45
46 which seem to contribute to HOA risk. However, more work is needed to establish which
47
48 particular aspects of hip shape and in what combinations, contribute to associations with
49
50 HOA. Methodological developments in applying SSM to hip DXA scans in large population
51
52 cohorts have facilitated GWAS of hip shape, which identified novel genetic influences on hip
53
54 shape. Findings to date have highlighted the role of developmental genes involved in
55
56
57
58
59

endochondral bone formation and pointed to an overlap with genetic risk factors for OA. These findings not only point to biological pathways involved in hip shape development but may enable opportunities for examining causal relationships between hip shape and HOA based on the application of MR methods. To the extent that hip shape plays a causal role in the development of HOA this would justify new approaches to prevention based on amelioration of adverse consequences of altered biomechanics.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

Key points

- There is strong observational evidence that hip shape is associated with HOA
- DXA scans can be used to identify hip shape variation enabling large-scale GWASs
- There is increasing evidence of shared genetic influences between hip shape and HOA
- Whether there is a causal relationship between hip shape and HOA remains unclear

Acknowledgements

- 1
 - 2
 - 3
 - 4
 - 5
 - 6
 - 7
 - 8
 - 9
 - 10
 - 11
 - 12
 - 13
 - 14
 - 15
 - 16
 - 17
 - 18
 - 19
 - 20
 - 21
 - 22
 - 23
 - 24
 - 25
 - 26
 - 27
 - 28
 - 29
 - 30
 - 31
 - 32
 - 33
 - 34
 - 35
 - 36
 - 37
 - 38
 - 39
 - 40
 - 41
 - 42
 - 43
 - 44
 - 45
 - 46
 - 47
 - 48
 - 49
 - 50
 - 51
 - 52
 - 53
 - 54
 - 55
 - 56
 - 57
 - 58
 - 59
 - 60
 - 61
 - 62
 - 63
 - 64
 - 65
- 1) BGF receives salary support from the National Institute of Health Research as an academic clinical fellow, and MF is funded by the Wellcome Trust.
 - 2) Conflicts of interest: none.

References and recommended reading

1. Vina ER, Kwok CK. Epidemiology of osteoarthritis: literature update. *Curr Opin Rheumatol*. 2018;30(2):160-7.
2. OARSI. Osteoarthritis: A Serious Disease, Submitted to the U.S. Food and Drug Administration https://www.oarsi.org/sites/default/files/docs/2016/oarsi_white_paper_oa_serious_disease_121416_1.pdf: Osteoarthritis Research Society International; 2016 [
3. Hunter DJ, Bierma-Zeinstra S. Osteoarthritis. *Lancet*. 2019;393(10182):1745-59.
4. OARSI. OARSI Definition of OA 2018 [Available from: <https://www.oarsi.org/research/standardization-osteoarthritis-definitions>.
5. Khanna V, Beaulieu PE. Defining structural abnormalities of the hip joint at risk of degeneration. *J Hip Preserv Surg*. 2014;1(1):12-20.
6. Baker-LePain JC, Lane NE. Relationship between joint shape and the development of osteoarthritis. *Curr Opin Rheumatol*. 2010;22(5):538-43.
7. Kraus VB, Blanco FJ, Englund M, Karsdal MA, Lohmander LS. Call for standardized definitions of osteoarthritis and risk stratification for clinical trials and clinical use. *Osteoarthritis Cartilage*. 2015;23(8):1233-41.
8. Kellgren JH, Lawrence JS. Radiological assessment of osteo-arthrosis. *Ann Rheum Dis*. 1957;16(4):494-502.
9. Croft P, Cooper C, Wickham C, Coggon D. Defining osteoarthritis of the hip for epidemiologic studies. *American Journal of Epidemiology*. 1990;132(3):514-22.
10. Bellamy N, Buchanan WW, Goldsmith CH, Campbell J, Stitt LW. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. *J Rheumatol*. 1988;15(12):1833-40.
11. Faber BG, Baird D, Gregson CL, Gregory JS, Barr RJ, Aspden RM, et al. DXA-derived hip shape is related to osteoarthritis: findings from in the MrOS cohort. *Osteoarthritis Cartilage*. 2017;25(12):2031-8. * Largest SSM hip shape study into OA.
12. Agricola R, Reijman M, Bierma-Zeinstra SMA, Verhaar JAN, Weinans H, Waarsing JH. Total hip replacement but not clinical osteoarthritis can be predicted by the shape of the hip: a prospective cohort study (CHECK). *Osteoarthritis and Cartilage*. 2013;21(4):559-64.
13. Kinds MB, Welsing PM, Vignon EP, Bijlsma JW, Viergever MA, Marijnissen AC, et al. A systematic review of the association between radiographic and clinical osteoarthritis of hip and knee. *Osteoarthritis Cartilage*. 2011;19(7):768-78.
14. Gaffney BMM, Hillen TJ, Nepple JJ, Clohisey JC, Harris MD. Statistical shape modeling of femur shape variability in female patients with hip dysplasia. *J Orthop Res*. 2019.
15. Inamdar G, Pedoia V, Rossi-Devries J, Samaan MA, Link TM, Souza RB, et al. MR study of longitudinal variations in proximal femur 3D morphological shape and associations with cartilage health in hip osteoarthritis. *J Orthop Res*. 2019;37(1):161-70.
16. Murray RO. The Aetiology of Primary Osteoarthritis of the Hip. *The British Journal of Radiology*. 1965;38(455):810-24.
17. Harris WH. Etiology of osteoarthritis of the hip. *Clin Orthop Relat Res*. 1986(213):20-33.
18. Loder RT, Skopelja EN. The epidemiology and demographics of hip dysplasia. *ISRN Orthop*. 2011;2011:238607.
19. Griffin DR, Dickenson EJ, O'Donnell J, Agricola R, Awan T, Beck M, et al. The Warwick Agreement on femoroacetabular impingement syndrome (FAI syndrome): an international consensus statement. *Br J Sports Med*. 2016;50(19):1169-76.
20. Ganz R, Parvizi J, Beck M, Leunig M, Nötzli H, Siebenrock KA. Femoroacetabular Impingement: A Cause for Osteoarthritis of the Hip. *Clinical Orthopaedics and Related Research*. 2003;417:112-20.

21. van Klij P, Heerey J, Waarsing JH, Agricola R. The Prevalence of Cam and Pincer Morphology and Its Association With Development of Hip Osteoarthritis. *J Orthop Sports Phys Ther.* 2018;48(4):230-8.
22. van Klij P, Heijboer MP, Ginai AZ, Verhaar JAN, Waarsing JH, Agricola R. Cam morphology in young male football players mostly develops before proximal femoral growth plate closure: a prospective study with 5-year follow-up. *Br J Sports Med.* 2019;53(9):532-8.
23. Nelson AE, Stiller JL, Shi XA, Leyland KM, Renner JB, Schwartz TA, et al. Measures of hip morphology are related to development of worsening radiographic hip osteoarthritis over 6 to 13 year follow-up: the Johnston County Osteoarthritis Project. *Osteoarthritis Cartilage.* 2016;24(3):443-50.
24. Thomas GE, Palmer AJ, Batra RN, Kiran A, Hart D, Spector T, et al. Subclinical deformities of the hip are significant predictors of radiographic osteoarthritis and joint replacement in women. A 20 year longitudinal cohort study. *Osteoarthritis Cartilage.* 2014;22(10):1504-10.
25. Agricola R, Heijboer MP, Bierma-Zeinstra SMA, Verhaar JAN, Weinans H, Waarsing JH. Cam impingement causes osteoarthritis of the hip: a nationwide prospective cohort study (CHECK). *Annals of the Rheumatic Diseases.* 2013;72(6):918-23.
26. Saberi Hosnijeh F, Zuiderwijk ME, Versteeg M, Smeele HT, Hofman A, Uitterlinden AG, et al. Cam Deformity and Acetabular Dysplasia as Risk Factors for Hip Osteoarthritis. *Arthritis Rheumatol.* 2017;69(1):86-93.
27. Gosvig KK, Jacobsen S, Sonne-Holm S, Palm H, Troelsen A. Prevalence of Malformations of the Hip Joint and Their Relationship to Sex, Groin Pain, and Risk of Osteoarthritis. A Population-Based Survey. 2010;92(5):1162-9.
28. Castano-Betancourt MC, Van Meurs JB, Bierma-Zeinstra S, Rivadeneira F, Hofman A, Weinans H, et al. The contribution of hip geometry to the prediction of hip osteoarthritis. *Osteoarthritis Cartilage.* 2013;21(10):1530-6.
29. Beck M, Kalhor M, Leunig M, Ganz R. Hip morphology influences the pattern of damage to the acetabular cartilage. Femoroacetabular impingement as a cause of early osteoarthritis of the hip. 2005;87-B(7):1012-8.
30. Agricola R, Heijboer MP, Roze RH, Reijman M, Bierma-Zeinstra SMA, Verhaar JAN, et al. Pincer deformity does not lead to osteoarthritis of the hip whereas acetabular dysplasia does: acetabular coverage and development of osteoarthritis in a nationwide prospective cohort study (CHECK). *Osteoarthritis and Cartilage.* 2013;21(10):1514-21.
31. Nicholls AS, Kiran A, Pollard TCB, Hart DJ, Arden CPA, Spector T, et al. The association between hip morphology parameters and nineteen-year risk of end-stage osteoarthritis of the hip: A nested case,ÄöVÑv control study. *Arthritis & Rheumatism.* 2011;63(11):3392-400.
32. Nelson AE, Golightly YM, Renner JB, Schwartz TA, Liu F, Lynch JA, et al. Variations in Hip Shape Are Associated with Radiographic Knee Osteoarthritis: Cross-sectional and Longitudinal Analyses of the Johnston County Osteoarthritis Project. *The Journal of Rheumatology.* 2016;43(2):405-10.
33. Gregory JS, Testi D, Stewart A, Undrill PE, Reid DM, Aspden RM. A method for assessment of the shape of the proximal femur and its relationship to osteoporotic hip fracture. *Osteoporos Int.* 2004;15(1):5-11.
34. Gregory JS, Waarsing JH, Day J, Pols HA, Reijman M, Weinans H, et al. Early identification of radiographic osteoarthritis of the hip using an active shape model to quantify changes in bone morphometric features: Can hip shape tell us anything about the progression of osteoarthritis? *Arthritis & Rheumatism.* 2007;56(11):3634-43.
35. Agricola R, Leyland KM, Bierma-Zeinstra SM, Thomas GE, Emans PJ, Spector TD, et al. Validation of statistical shape modelling to predict hip osteoarthritis in females: data from two prospective cohort studies (Cohort Hip and Cohort Knee and Chingford). *Rheumatology (Oxford).* 2015;54(11):2033-41.
36. Nelson AE, Liu F, Lynch JA, Renner JB, Schwartz TA, Lane NE, et al. Association of Incident Symptomatic Hip Osteoarthritis With Differences in Hip Shape by Active Shape Modeling: The Johnston County Osteoarthritis Project. *Arthritis Care & Research.* 2014;66(1):74-81.

- 1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65
37. An H, Marron J, Schwartz TA, Renner JB, Liu F, Lynch JA, et al. Novel statistical methodology reveals that hip shape is associated with incident radiographic hip osteoarthritis among African American women. *Osteoarthritis and Cartilage*. 2016;24(4):640-6.
 38. Waarsing JH, Rozendaal RM, Verhaar JAN, Bierma-Zeinstra SMA, Weinans H. A statistical model of shape and density of the proximal femur in relation to radiological and clinical OA of the hip. *Osteoarthritis and Cartilage*. 2010;18(6):787-94.
 39. Ahedi HG, Aspden RM, Blizzard LC, Saunders FR, Cicuttini FM, Aitken DA, et al. Hip shape as a predictor of osteoarthritis progression in a prospective population cohort. *Arthritis Care Res (Hoboken)*. 2016.
 40. Javaid MK, Lane NE, Mackey DC, Lui LY, Arden NK, Beck TJ, et al. Changes in proximal femoral mineral geometry precede the onset of radiographic hip osteoarthritis: The study of osteoporotic fractures. *Arthritis Rheum*. 2009;60(7):2028-36.
 41. Faber BG, Bredbenner TL, Baird D, Gregory JS, Saunders FR, Giuraniuc CV, et al. Lesser trochanter size could be a novel risk factor for hip osteoarthritis. *Bone Research Society Conference 2019;Abstract*.
 42. Baird DA, Evans DS, Kamanu FK, Gregory JS, Saunders FR, Giuraniuc CV, et al. Identification of Novel Loci Associated With Hip Shape: A Meta-Analysis of Genomewide Association Studies. *J Bone Miner Res*. 2019;34(2):241-51. * an interesting insight into the genetics of hip shape.
 43. Frysz M, Baird D, Gregory JS, Aspden RM, Tobias JH, Paternoster L. Investigating the influence of adult hip shape genetic variants across the life course: findings from a population-based study in adolescents. *J Bone Miner Res* 2018;32 (Suppl 1).
 44. Tachmazidou I, Hatzikotoulas K, Southam L, Esparza-Gordillo J, Haberland V, Zheng J, et al. Identification of new therapeutic targets for osteoarthritis through genome-wide analyses of UK Biobank data. *Nat Genet*. 2019;51(2):230-6. **the most comprehensive GWAS into OA.
 45. arc OC, arc OC, Zeggini E, Panoutsopoulou K, Southam L, Rayner NW, et al. Identification of new susceptibility loci for osteoarthritis (arcOGEN): a genome-wide association study. *Lancet*. 2012;380(9844):815-23.
 46. Castano-Betancourt MC, Evans DS, Ramos YF, Boer CG, Mestrury S, Liu Y, et al. Novel Genetic Variants for Cartilage Thickness and Hip Osteoarthritis. *PLoS Genet*. 2016;12(10):e1006260.
 47. Hatzikotoulas K, Roposch A, Consortium DDHCC, Shah KM, Clark MJ, Bratherton S, et al. Genome-wide association study of developmental dysplasia of the hip identifies an association with GDF5. *Commun Biol*. 2018;1:56.
 48. Styrkarsdottir U, Helgason H, Sigurdsson A, Norddahl GL, Agustsdottir AB, Reynard LN, et al. Whole-genome sequencing identifies rare genotypes in COMP and CHADL associated with high risk of hip osteoarthritis. *Nat Genet*. 2017;49(5):801-5.
 49. Styrkarsdottir U, Lund SH, Thorleifsson G, Zink F, Stefansson OA, Sigurdsson JK, et al. Meta-analysis of Icelandic and UK data sets identifies missense variants in SMO, IL11, COL11A1 and 13 more new loci associated with osteoarthritis. *Nat Genet*. 2018;50(12):1681-7.
 50. Baker-Lepain JC, Lynch JA, Parimi N, McCulloch CE, Nevitt MC, Corr M, et al. Variant alleles of the Wnt antagonist FRZB are determinants of hip shape and modify the relationship between hip shape and osteoarthritis. *Arthritis Rheum*. 2012;64(5):1457-65.
 51. Lindner C, Thiagarajah S, Wilkinson JM, Panoutsopoulou K, Day-Williams AG, Cootes TF, et al. Investigation of association between hip osteoarthritis susceptibility loci and radiographic proximal femur shape. *Arthritis Rheumatol*. 2015;67(8):2076-84.
 52. Zengini E, Hatzikotoulas K, Tachmazidou I, Steinberg J, Hartwig FP, Southam L, et al. Genome-wide analyses using UK Biobank data provide insights into the genetic architecture of osteoarthritis. *Nat Genet*. 2018;50(4):549-58.
 53. Baird DA, Paternoster L, Gregory JS, Faber BG, Saunders FR, Giuraniuc CV, et al. Investigation of the relationship between susceptibility loci for hip osteoarthritis and DXA-derived hip shape in a population based cohort of peri-menopausal women. *Arthritis Rheumatol*. 2018.

- 1 54. Styrkarsdottir U, Stefansson OA, Gunnarsdottir K, Thorleifsson G, Lund SH, Stefansdottir L, et al. GWAS of bone size yields twelve loci that also affect height, BMD, osteoarthritis or fractures. *Nat Commun*. 2019;10(1):2054.
- 2
- 3 55. Holyoak DT, Otero M, Armar NS, Ziemian SN, Otto A, Cullinane D, et al. Collagen XI mutation lowers susceptibility to load-induced cartilage damage in mice. *J Orthop Res*. 2018;36(2):711-20.
- 4
- 5 56. Rose PS, Ahn NU, Levy HP, Magid D, Davis J, Liberfarb RM, et al. The hip in Stickler syndrome. *J Pediatr Orthop*. 2001;21(5):657-63.
- 6
- 7 57. Acke FR, Malfait F, Vanakker OM, Steyaert W, De Leeneer K, Mortier G, et al. Novel pathogenic COL11A1/COL11A2 variants in Stickler syndrome detected by targeted NGS and exome sequencing. *Mol Genet Metab*. 2014;113(3):230-5.
- 8
- 9 58. Harcke HT. Developmental dysplasia of the hip: a spectrum of abnormality. *Pediatrics*. 1999;103(1):152.
- 10
- 11 59. Furnes O, Lie SA, Espehaug B, Vollset SE, Engesaeter LB, Havelin LI. Hip disease and the prognosis of total hip replacements. A review of 53,698 primary total hip replacements reported to the Norwegian Arthroplasty Register 1987-99. *J Bone Joint Surg Br*. 2001;83(4):579-86.
- 12
- 13 60. Zamborsky R, Kokavec M, Harsanyi S, Attia D, Danisovic L. Developmental Dysplasia of Hip: Perspectives in Genetic Screening. *Med Sci (Basel)*. 2019;7(4).
- 14
- 15 61. Kiapour AM, Cao J, Young M, Capellini TD. The role of Gdf5 regulatory regions in development of hip morphology. *PLoS One*. 2018;13(11):e0202785.
- 16
- 17 62. Davies NM, Holmes MV, Davey Smith G. Reading Mendelian randomisation studies: a guide, glossary, and checklist for clinicians. *BMJ*. 2018;362:k601.
- 18
- 19 63. Ng KC, Lamontagne M, Labrosse MR, Beaulé PE. Hip Joint Stresses Due to Cam-Type Femoroacetabular Impingement: A Systematic Review of Finite Element Simulations. *PLoS One*. 2016;11(1):e0147813.
- 20
- 21 64. Kemp JL, King MG, Barton C, Schache AG, Thorborg K, Roos EM, et al. Is exercise therapy for femoroacetabular impingement in or out of FASHIoN? We need to talk about current best practice for the non-surgical management of FAI syndrome. *Br J Sports Med*. 2019.
- 22
- 23 65. Palmer A, Fernquest S, Gimpel M, Birchall R, Judge A, Broomfield J, et al. Physical activity during adolescence and the development of cam morphology: a cross-sectional cohort study of 210 individuals. *Br J Sports Med*. 2018;52(9):601-10.
- 24
- 25 66. Mansell NS, Rhon DI, Meyer J, Slevin JM, Marchant BG. Arthroscopic Surgery or Physical Therapy for Patients With Femoroacetabular Impingement Syndrome: A Randomized Controlled Trial With 2-Year Follow-up. *Am J Sports Med*. 2018;46(6):1306-14.
- 26
- 27 67. Griffin DR, Dickenson EJ, Wall PDH, Achana F, Donovan JL, Griffin J, et al. Hip arthroscopy versus best conservative care for the treatment of femoroacetabular impingement syndrome (UK FASHIoN): a multicentre randomised controlled trial. *Lancet*. 2018;391(10136):2225-35.
- 28
- 29 68. Kanis JA, Oden A, Johansson H, Borgstrom F, Strom O, McCloskey E. FRAX and its applications to clinical practice. *Bone*. 2009;44(5):734-43.
- 30
- 31 69. Joseph GB, McCulloch CE, Nevitt MC, Neumann J, Gersing AS, Kretzschmar M, et al. Tool for osteoarthritis risk prediction (TOARP) over 8 years using baseline clinical data, X-ray, and MRI: Data from the osteoarthritis initiative. *J Magn Reson Imaging*. 2018;47(6):1517-26.
- 32
- 33 70. Saberi Hosnijeh F, Kavousi M, Boer CG, Uitterlinden AG, Hofman A, Reijman M, et al. Development of a prediction model for future risk of radiographic hip osteoarthritis. *Osteoarthritis Cartilage*. 2018;26(4):540-6.* An interesting early model for predicting OA.
- 34
- 35 71. Rodriguez-Fontenla C, Calaza M, Evangelou E, Valdes AM, Arden N, Blanco FJ, et al. Assessment of osteoarthritis candidate genes in a meta-analysis of nine genome-wide association studies. *Arthritis Rheumatol*. 2014;66(4):940-9.
- 36
- 37 72. Lane NE, Lian K, Nevitt MC, Zmuda JM, Lui L, Li J, et al. Frizzled-related protein variants are risk factors for hip osteoarthritis. *Arthritis Rheum*. 2006;54(4):1246-54.
- 38
- 39 73. Miyamoto Y, Mabuchi A, Shi D, Kubo T, Takatori Y, Saito S, et al. A functional polymorphism in the 5' UTR of GDF5 is associated with susceptibility to osteoarthritis. *Nature Genetics*. 2007;39:529.
- 40
- 41
- 42
- 43
- 44
- 45
- 46
- 47
- 48
- 49
- 50
- 51
- 52
- 53
- 54
- 55
- 56
- 57
- 58
- 59
- 60
- 61
- 62
- 63
- 64
- 65

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

Figure 1: Schematic diagram for the known associations between hip shape, genetics and hip osteoarthritis

The whole hip shape box shows two images one representing a DXA scan marked up for SSM (left) and the other is the output from SSM showing a HSM ± 2 stand deviations (original figure)

16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

Table 1 Summary of hip shape and OA relationships published since 2010 (adjusted results where available) – original table

Abbreviations: KL = Kellgren-Lawrence, THR = Total hip replacement, RHOA = radiographic hip osteoarthritis, SHOA = symptomatic hip osteoarthritis, SRHOA = symptomatic radiographic hip osteoarthritis, OR = odds ratio, RR = risk ratio, AP = anteroposterior, LCEA = lateral centre-edge angle, ACEA = anterior centre-edge angle. *Not all papers reported 95% confidence intervals nor p-values. Available statistics listed. **Authors note that statistical significance is not implied from results and therefore not all measures are reported as smaller associations are not adjusted for multiple testing *** At risk OA shape described for HSM **** Only modes significant in both cohorts is featured. Only geometric measures and statistical shape modelling papers included

Study and date	Study size	Measure of hip shape	Definitions of HOA	Findings (effect size [95% CI] p-value)
Continuous geometric measures from X-ray				
Nicholls et al 2011 (31)	135	Alpha angle	THR	OR 1.05 p 0.006
		LCEA	THR	OR 0.89 p 0.004
		Extrusion index	THR	OR 1.06 p 0.005
Castano-Betancourt et al 2013 (28)	688	Wilberg	Incident RHOA (KL) or THR	OR 0.76 [0.63-0.92] p 0.004
		Neck Width	Incident RHOA (KL) or THR	OR 1.60 [1.24-2.05] p 2.45 x 10 ⁻⁴
		Hip axis length	Incident RHOA (KL) or THR	OR 1.49 [1.18-1.90] p 0.001
		Pelvic width	Incident RHOA (KL) or THR	OR 1.43 [1.16-1.75] p 0.001
		Triangular index	Incident RHOA (KL) or THR	OR 1.93 [1.54-2.43] p < 0.0001
Specific hip shape deformities derived from X-ray				
Gosvig et al 2010 (27)	3620	Deep acetabular socket (aka pincer deformity) (CEA≥45°)	Prevalent RHOA (KL)	RR 2.4 [2.0-2.9]
		Pistol grip deformity (aka cam deformity) (triangular index)	Prevalent RHOA (KL)	RR 2.1 [1.7-2.8]
Agricola et al 2013 (30)	720	Acetabular dysplasia (ACEA < 25°)	Incident RHOA (KL)	OR 2.62 [1.44-4.77] p 0.002
			THR	OR 4.34 [1.99-9.47] p 0.000
		Acetabular dysplasia (LCEA < 25°)	Incident RHOA (KL)	OR 2.83 [1.54-5.20] p 0.001
			THR	OR 3.8 [1.84-7.84] p 0.000
	723	Cam deformity (AP Alpha angle>60°)	Incident end-stage OA (KL ≥ 3 or THR)	OR 3.67 [1.68-8.01]

16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

Agricola et al 2013 (25)		Cam deformity (AP Alpha angle >83°)	Incident end-stage OA (KL ≥ 3 or THR)	OR 9.66 [4.72-19.78]
Thomas et al 2014 (24)	358 – RHOA 726 - THR	Cam deformity (AP alpha angle >65°)	Incident RHOA (KL)	OR 1.05 [1.01-1.09] p 0.007
		Acetabular dysplasia (LCEA ≤28°)	Incident RHOA (KL)	OR 0.87 [0.78-0.96] p 0.008
			THR	OR 0.82 [0.75-0.89] p <0.001
		Extrusion index (per SD)	THR	OR 2.50 [1.78-3.49] p<0.001
		Triangular index height (per unit)	Incident RHOA (KL)	OR 1.14 [1.03-1.26] p 0.026
THR	OR 1.25 [1.10-1.43] p 0.001			
Nelson et al 2016** (23)	120	Cam deformity (AP alpha angle >60°)	Incident RHOA (KL>3)	Men OR 3.57 [1.17 – 10.90] Women OR 4.61 [2.09 – 10.16]
Saber et al 2017 (26)	4,438	Cam deformity (AP alpha angle >60°)	Incident RHOA (KL) or THR	OR 2.11 [1.55-2.87]
		Acetabular dysplasia (LCEA <20°)	Incident RHOA (KL) or THR	OR 2.19 [1.50-3.21]
Statistical shape modelling from X-ray***				
Castano-Betancourt et al 2013 (28)	688	HSM 5 (Less acetabular coverage, wider femoral neck, cam-type bulge, larger lesser trochanter)	Incident RHOA (KL) or THR	OR 0.65 [0.54-0.77] p <0.0001
		HSM 9 (Less acetabular coverage, shorter femoral neck)	Incident RHOA (KL) or THR	OR 1.40 [1.14-1.72] p 0.001
Agricola et al 2013 (12)	723	HSM 7 (Shorter femoral neck, smaller lesser trochanter)	THR	OR 0.54 [0.38-0.78] p 0.001
		HSM 11 (Less acetabular overhang, larger lesser trochanter, less concave femoral head-neck junction)	THR	OR 1.78 [1.28-2.47] p 0.001
		HSM 12 (Greater acetabular overhang, reduced joint space)	THR	OR 2.10 [1.46-3.10] p <0.001

16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

		HSM 15 (Wider femoral neck, flatter femoral head)	THR	OR 1.90 [1.39-2.59] p <0.001
Nelson et al 2014 (36)	342	HSM 2 (Larger femoral head (cam-type bulge), greater trochanter and lesser trochanter)	SRHOA	OR 1.47 [1.03-2.08]
		HSM 3 (Smaller greater trochanter, steeper curve between femoral neck and head)	SRHOA	OR 1.54 [1.09-2.17]
		HSM 11 (not pictured)	SRHOA	OR 1.52 [1.05-2.17]
Agricola et al 2015 **** (35)	664	HSM 17 (flattened femoral head neck junction, flatter greater trochanter, prominent acetabular posterior wall)	THR	OR 0.51 [0.33-0.80] p 0.003 (CHECK cohort) OR 0.41 [0.23-0.82] p 0.01 (Chingford cohort)
Statistical shape modelling from DXA scans***				
Waarsing et al 2010 *** (38)	222	HSM 6 (deep placement of femoral head in acetabulum, pronounced curvature of superior neck)	SHOA (WOMAC)	p 0.0007
		HSM 11 (pronounced curvature of superior neck)	RHOA (KL)	p 0.0015
Ahedi et al 2016 (39)	831	HSM2 (marked acetabular overhang, larger femoral head, greater and lesser trochanter)	Prevalent RHOA (OARSI grading)	OR 0.85 [0.76-95]
		HSM 2 (Less acetabular coverage, smaller trochanters)	THR	OR 1.6 [1.20-2.15]
		HSM 4 (cam-type bulge and larger lesser trochanter)	THR	OR 0.63 [0.50-0.84]
		HSM 6 (greater acetabular overhang and smaller greater trochanter)	RHOA	OR 1.31 [1.01-1.27]
Faber et al 2017 (11)	4,100	HSM 1 (pincer-type deformity, larger femoral head, greater and lesser trochanters)	Prevalent RHOA (Croft score)	OR 1.23 [1.09-1.39] p 8.2 x 10 ⁻⁴

15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

		HSM 3 (cam-type deformity and larger lesser trochanter)	Prevalent RHOA (Croft score)	OR 0.73 [0.65-0.85] p 4.0×10^{-7}
			Prevalent hip pain on walking, examination & WOMAC	OR 0.88 [0.81-0.95], 0.84 [0.76-0.92], 0.87 [0.80-0.93] respectively p <0.005
		HSM 4 (cam-type deformity and lateral displacement of femoral head)	Prevalent RHOA (Croft score)	OR 0.83 [0.73-0.93] p 0.0021
		HSM 8 (pincer-type deformity)	Prevalent RHOA (Croft score)	OR 0.78 [0.69-0.88] p 7.4×10^{-5}
		HSM 10 (cam-type deformity)	Prevalent RHOA (Croft score)	1.24 [1.1-1.41] p 6.1×10^{-4}

16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

Table 2. SNP associations with HOA and various measures of hip shape – original table

* OA risk allele shape described; **proxy SNP Abbreviations: HSM = Hip Shape Mode, FN = femoral neck, DDH = developmental dysplasia of the hip, JSN = joint space narrowing, RHOA = Radiographic hip OA

			Association with hip shape			Association with HOA		
Lead SNP	Gene/locus	EA	Study population	Measure of hip shape*	Effect size (p value)	Study population	Effect size (p value)	Ref
rs10743612	<i>KLHL42/PTHLH</i>	A	GWAS meta-analysis N = 15,934	HSM1 (proximal femur and acetabulum SSM - flattened femoral head, narrower and longer FN)	beta 0.093 (2.91×10^{-12})	Results looked up in arcOGEN GWAS	OR **1.14 (9.6×10^{-5})	(42, 44)
rs73197346	<i>RUNX1</i>	C		HSM1 (proximal femur and acetabulum SSM - curved femoral head, wider and shorter FN)	beta -0.11 (2.52×10^{-10})	Results looked up in UK Biobank GWAS	OR 0.87 (0.006)	
rs1885245	<i>ASTN2</i>	G		HSM2 (proximal femur and acetabulum SSM - narrower FN, smaller femoral head and less acetabular coverage)	beta 0.071 (4.95×10^{-9})	Results looked up in arcOGEN GWAS	OR **1.09 (0.003)	
rs10492367	<i>KLHDC5/PTHLH</i>	T	3,111 ALSPAC mothers	SSM measured proximal femur and acetabulum shape - (greater height-to-width ratio of upper femur)	Canonical correlation 0.11 (0.000014)	7,410 arcOGEN OA cases and 11,009 controls	OR 1.14 (1.48×10^{-8})	(45, 53)

16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

rs4907986	<i>COL11A1</i>	C		Subregional SSM of superior femoral head and acetabulum (superior JSN)	Canonical correlation 0.078 (0.00049)	GWAS meta-analysis 4,349 patients with hip OA and 17,836 European controls	OR 0.89 (1.29×10^{-5})	(53, 71)
rs12982744	<i>DOT1L</i>	G		Subregional SSM of superior femoral head and acetabulum (superior JSN)	Canonical correlation 0.077 (0.0024)	GWAS meta-analysis of 11,277 radiographic and symptomatic HOA cases and 67,473 European controls	OR 0.91 (8.1×10^{-8})	(53, 71)
rs4836732	<i>ASTN2</i>	T	929 subjects with unilateral hip OA	HSM 5 (based on female proximal femur SSM, superior femoral head size)	(0.0016)	arcOGEN Consortium and arcOGEN Collaborators	(6.11×10^{-10})	(45, 51)
rs6976	<i>GLT8D1</i>	T		HSM 7 (based on mixed-sex proximal femur SSM, medial femoral head size)	(0.0003)	arcOGEN Consortium and arcOGEN Collaborators	(7.24×10^{-11})	
rs5009270	<i>IFRD1</i>	A		combination of HSM 3, 4, and 9 of the mixed-sex proximal femur SSM	(0.0004)	11,277 cases of radiographic and symptomatic hip OA and 67,473 controls	OR 1.10 (9.0×10^{-07})	
rs288326	<i>FRZB</i>	T	Cases (n = 451) with incident RHOA during follow-up (mean 8.0 ± 0.4 years). Controls (n = 601)	HSM 2 (proximal femur SSM - smaller femoral head, steeper FN angle and narrower FN)	Beta -0.21 (0.019)	570 female cases with RHOA (of those 130 had femoral osteophyte) and 4,136 female controls	OR 3.18 (0.01) in patients with TT genotype and osteophytosis	(50, 72)
rs7775	<i>FRZB</i>	G		HSM 2 (proximal femur SSM - smaller femoral head, steeper FN angle and narrower FN)	Beta -0.23 (0.019)	570 female cases with RHOA (of those 326 had JSN) and 4,136 female controls	Frequency of the G allele was 0.11 in subjects with severe JSN ($P = 0.04$ versus controls)	(50, 72)

15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

rs143384	<i>GDF5</i>	A	1,129 cases and 4,652 UKHLS controls	idiopathic DDH diagnosed in childhood	OR 1.44 (3.55×10^{-22})	Chinese and Japanese hip OA cases (N=1,000) and controls (N=984)	OR** 1.79 ($p 3.1 \times 10^{-11}$)	(47) (73)
----------	-------------	---	--------------------------------------	---------------------------------------	---------------------------------------	--	--	--------------