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Cam morphology is strongly and consistently associated with development of radiographic hip osteoarthritis throughout 4 follow-up visits within 10 years

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Objective: To determine the association between cam morphology and the development of radiographic hip osteoarthritis (RHOA) at four time points within 10-year follow-up.
Design: The nationwide prospective Cohort Hip and Cohort Knee study includes 1002 participants aged 45–65 years with 2-, 5-, 8-, and 10-year follow-ups. The associations of cam morphology (alpha angle > 60°) and large cam morphology (alpha angle > 78°) in hips free of osteoarthritis at baseline (Kellgren & Lawrence (KL) grade < 2) with the development of both incident RHOA (KL grade≥2) and end-stage RHOA (KL grade≥3) were estimated using logistic regression with generalized estimating equation at each follow-up and using Cox regression over 10 years, adjusted for age, sex, and body mass index.
Results: Both cam morphology and large cam morphology were associated with the development of incident RHOA at all follow-ups with adjusted Odd Ratios (aORs) ranging from 2.7 (95% Confidence interval 1.8–4.1) to 2.9 (95% CI 2.0–4.4) for cam morphology and ranging from 2.5 (95% CI 1.5–4.3) to 4.2 (95% CI 2.2–8.3) for large cam morphology. For end-stage RHOA, cam morphology resulted in aORs ranging from 4.9 (95% CI 1.8–13.2) to 8.5 (95% CI 1.1–64.4), and aORs for large cam morphology ranged from 6.7 (95% CI 3.1–14.7) to 12.7 (95% CI 1.9–84.4).
Conclusions: Cam morphology poses the hip at 2–13 times increased odds for developing RHOA within a 10-year follow-up. The association was particularly strong for large cam morphology and end-stage RHOA, while the strength of association was consistent over time.

Introduction

Hip osteoarthritis (OA) is one of the most prevalent musculoskeletal conditions affecting the elderly, causing hip pain and functional disability.[1] The social and economic impact of hip OA is steadily rising as the population ages.[2]

In recent years, hip morphology, including hip dysplasia and cam morphology, has been identified as an important risk factor for the development of radiographic hip osteoarthritis (RHOA).[3–7] Cam morphology represents extra cartilage or bone formation at any location around the femoral head-neck junction, which results in a non-spherical femoral head.[8] During hip motion, the cam morphology might impinge against and be forced into the acetabular rim, causing repetitive stress on the acetabular labrum and articular cartilage.[9,10]

The association between cam morphology and RHOA has been shown in some prospective cohort studies.[5,7,11–16] However, there is considerable heterogeneity between those cohorts. Therefore, the strength of association reported varies widely between different cohorts, with odds ratios (OR) varying between 2.11 (95% Confidence interval 1.55–2.87)[7] and 20.6 (95% CI 3.4–34.8).[12] One of the explanations for the variance in the strength of association between cam morphology and RHOA is the different follow-up times used, ranging from 3[14] to over 25 years.[15] It has previously been

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hypothesized that cam morphology can lead to the development of hip OA within a few years of follow-up rather than a gradual development over a decade or more.[11] Other reasons could be the different definitions used for RHOA and different definitions to quantify cam morphology.[5,13,16] To the best of our knowledge, there are no studies showing the strength of association over time within the same cohort. Studying different definitions for both cam morphology and RHOA, as well as their association at multiple follow-up times, can provide a more detailed understanding of the relation between cam morphology and RHOA, which is currently lacking.

The aim of this study was therefore to determine the strength of association of cam morphology and large cam morphology with the development of both incident RHOA and incident end-stage incident RHOA at 2-, 5-, 8-, and 10-year follow-up (T2, T5, T8, and T10).

Methods

Study population

The Cohort Hip and Cohort Knee (CHECK) is a nationwide multicenter prospective cohort study of 1002 individuals. From October 2002 until September 2005, all participants were recruited in the Netherlands through i) invitation by general practitioners (GP), ii) advertisements and articles in local newspapers, and iii) the Dutch Arthritis Foundation website.

Individuals were eligible to participate if they had first onset pain and/or stiffness of the knee or hip, were aged between 45 and 65 years, and had not yet consulted their GPs for these symptoms, or the first consultation was within 6 months before entry. Individuals were excluded from the study if they had any other pathological condition that could explain the symptoms (for hip: previous trauma, fracture, subluxation, rheumatoid arthritis, previous hip surgery, bursitis, tendinitis, previously diagnosed congenital dysplasia, osteochondritis dissecans, septic arthritis or Perthes' disease), any comorbidity precluding physical evaluation and/or follow-up of at least 10 years, malignancy in the past 5 years or inability to understand the Dutch language.[17,18] Radiological data were collected from 11 general and academic hospitals in the Netherlands.

The study was approved by the medical ethics committees of all participating centers, and written informed consent was obtained from all participants.

Radiography

Standardized weight-bearing anteroposterior (AP) radiographs of the pelvis or hip were obtained at baseline and T2, T5, T8, and T10. During acquisition of the AP pelvic radiograph, participants were positioned with the lower extremities parallel and with 15° internal rotation, resulting in the touch of the medial side of the distal part of the first phalanx. The X-ray beam was centered on the proximal edge of the pubic symphysis. The tube to film distance was 100 cm. Only the first 124 participants who entered the CHECK study had an AP hip radiograph of each hip obtained according to the same protocol, but with the X-ray beam centered on the groin.

Radiographic measurements

The alpha angle was used to quantify cam morphology. The alpha angle is constructed by one line from the femoral head center through the middle of the femoral neck and a second line from the femoral head center through a point where the contour of the femoral head-neck junction exceeds the radius of the best-fitting circle of the femoral head[19] (Fig. 1). In this study, the alpha angle was calculated automatically in AP radiographs using Matlab (V.7.1.0) by a set of landmark points.

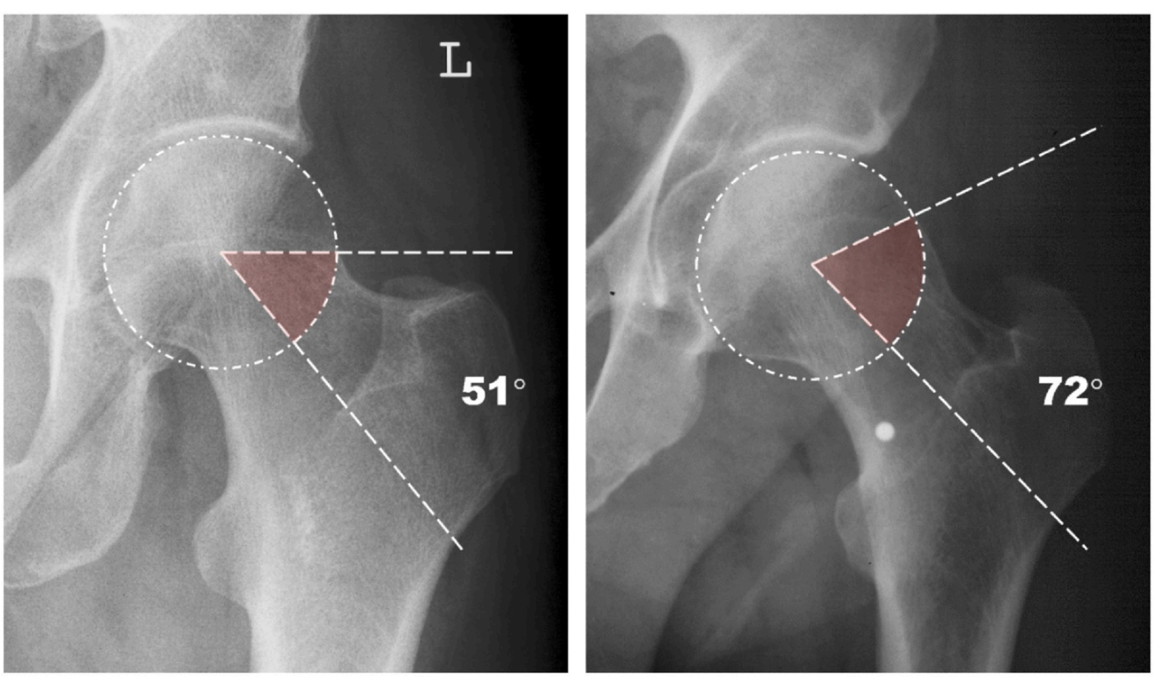

Fig. 1 Osteoarthritis and Cartilage

The measurement of alpha angle on an AP pelvic radiograph. The radiograph on the left shows a normal hip with an alpha angle of 51° whereas the right radiograph shows a hip with cam morphology resulting in an alpha angle of 72°.

We used a previously validated threshold value of > 60° to define the presence of cam morphology.[20] As previous studies[21] showed a higher risk of developing OA with increasing alpha angle, we also used a threshold of > 78° to define a large cam morphology. This threshold previously showed the best discriminative ability between hips that developed and did not develop hip OA.[21]

Outcome measures

At baseline and T2, T5, T8, and T10, the AP pelvic and hip radiographs were scored for OA according to the Kellgren and Lawrence (KL) classification. All available radiographs of each participant were scored simultaneously, so that the information of all images was used for the KL scoring at each time point. This approach has been shown to be more reliable compared to scoring every radiograph independently.[22] From the hips without definite RHOA at baseline (KL grade < 2), the development of incident RHOA was defined by a KL grade equal or greater than two or a total hip replacement (THR) at follow-up and the development of incident end-stage RHOA was defined by a KL grade equal or greater than three, or a THR at follow-up. THR was included because all hips underwent THR due to hip OA and it was assumed that there will be RHOA present in a more advanced stage before this procedure is being performed. This was confirmed by the RHOA grades at the visit prior to the THR procedure, which almost all showed a KL grade > 1.

Statistics

Differences in characteristics between included and excluded hips and between hips with and without cam morphology at baseline were evaluated. We used the Mann-Whitney U test for continuous variables (age and body mass index (BMI) and alpha angle) and the chi-square test for dichotomous variables (sex and baseline KL grade). To study the association between cam morphology and the development of RHOA on a hip level at each follow-up, we used logistic regression with generalized estimating equation, as generalized estimating equation accounted for statistical dependency between two hips within one subject. For each follow-up time point, the inclusion criterion for analysis was the availability of a radiograph both at baseline and at the given follow-up time point. The comparator group for both alpha angle threshold values for cam morphology was hips without cam morphology (alpha angle < 60°). The comparator group for both RHOA outcomes was hips free of definite RHOA (KL grade < 2). Therefore, hips with an alpha angle between 60° and 78° as well as with KL grade equal to two were excluded from the analysis when respectively large cam morphology as predictor or end-stage RHOA as an outcome were used. In addition to quantifying cam morphology as a dichotomous variable, we also present the results of the alpha angle as a continuous variable as supplemental data. Cox proportional hazard regression using the same predictors and outcomes as the logistic regression model was also used to provide better insight in the association between cam morphology and RHOA over time and to allow for incomplete follow-up of participants. The strength of association was expressed in OR or hazard ratios with 95% confidence intervals and adjusted for age, sex, and BMI. Although it is still unsure whether BMI is associated with the development of hip OA, some large cohort studies[23,24] show an association between BMI and hip OA and we therefore adjusted also for BMI. The effect was considered significant at $P < 0.05$. All statistical analyses were performed in IBM SPSS V.26.0 (Windows).

Table 1

Difference in baseline characteristics between included and excluded hips.

Baseline characteristics	CHECK study n = 2004		
	Included hips n = 1514	Excluded hips n = 490	P value
Age in years: mean (± SD)	55.6 (5.2)	56.7 (5.2)	< 0.001
Women, No (%)	1233 (81.4)	347 (70.8)	< 0.001
BMI, kg/m²: mean (± SD)	26.2 (4.1)	26.0 (3.6)	0.183
KL grade 0, No (%)	1121 (74.0)	162 (33.1)	< 0.001
KL grade 1, No (%)	393 (26.0)	88 (18.0)	< 0.001
Alpha angle: mean (± SD)	46.3(12.1)	55.6(18.3)	< 0.001

BMI: body mass index; KL: Kellgren & Lawrence.

Results

Population

Of the 2004 hips from 1002 individuals in the CHECK cohort, 1514 baseline hips were included (Table 1). Of the 490 excluded hips, there were 22 hips that did not have baseline radiographs available, 6 hips did not have baseline BMI values, 244 hips had unavailable alpha angle values due to insufficient quality of radiographs, and 218 hips had a KL score equal or greater than two at baseline. The complete flow of participants (included hips) is provided in the flowchart (Fig. 2).

RHOA

At T2, the prevalence of incident RHOA and incident end-stage RHOA was 5.9% (88 hips) and 0.5% (7 hips), respectively. Over the next eight years, the prevalence increased steadily with respective values of 14.6% (218 hips) and 1.6% (24 hips) at T5, 24.7% (346 hips) and 3.2% (45 hips) at T8, and 43.4% (589 hips) and 5.2% (70 hips) at T10.

Association between cam morphology and RHOA

The baseline prevalence of cam morphology (alpha angle > 60°) was 8.9% (134 hips) and the prevalence of large cam morphology (alpha angle > 78°) was 4.7% (71 hips). Cam morphology was more prevalent in men than in women, see Supplementary Table S1 for all differences in baseline characteristics between hips with and without cam morphology. The absolute risk to develop RHOA in hip with cam morphology ranged from 14.4% at T2 to 69.2% at T10 (Table 2). Cam morphology at baseline was significantly associated with the development of both incident and end-stage RHOA at all follow-up time points (Table 2). The strength of association between cam morphology and incident RHOA ranged between 2.7 (95% CI 1.8–4.1) at T10 and 2.9 (95% CI 2.0–4.3) at T5. For end-stage RHOA, the association ranged between 5.3 (95% CI 2.6–10.6) at T8 and 8.5 (95% CI 1.1–64.4) at T2.

Large cam morphology was also associated with both incident and end-stage RHOA at all follow-up time points (Table 2) and this association seemed to be stronger compared to cam morphology defined by an alpha angle > 60°. The association with development of

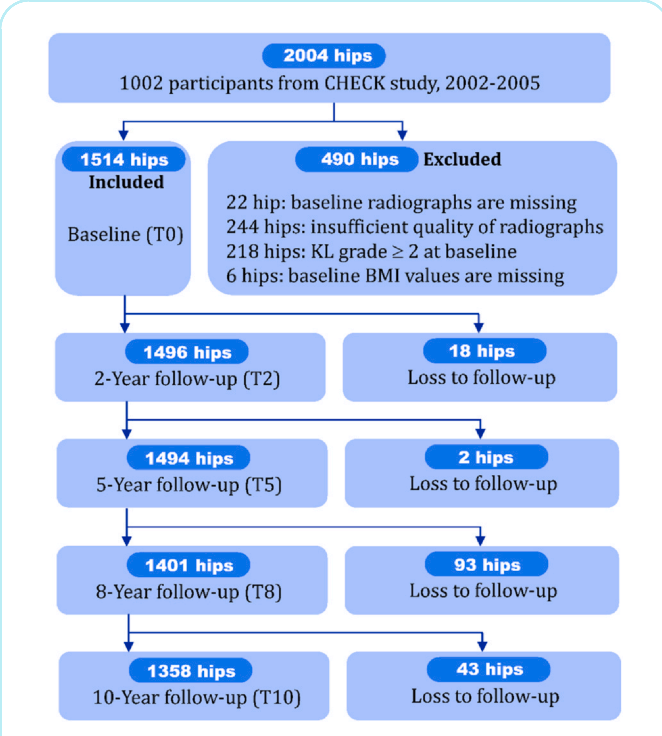

Fig. 2 Osteoarthritis and Cartilage

The flow of subjects (hips) from the beginning of the study to baseline and different follow-up time points.

incident RHOA ranged between 2.5 (95% CI 1.5–4.3, T10) and 4.2 (95% CI 2.0–8.3, T2). For end-stage RHOA the association ranged from 6.7 (95% CI 3.1–14.7) at T10 to 12.7 (95% CI 1.5–84.4) at T2.

At each follow-up visit, the alpha angle as a continuous variable was associated with development of both incident and end-stage RHOA with aORs ranging from 1.02 (95% CI 1.01–1.03) to 1.06 (95% CI 1.02–1.09) for every degree increase in alpha angle (Supplementary Table S2).

Similar results were also found from the Cox regression model as all of predictors (cam morphology, large cam morphology and continuous alpha angle) showed significant association with both incident and end-stage RHOA over 10 years follow-up period (Table 3 and Supplementary Table S3).

Discussion

This prospective cohort study showed a consistent association between cam morphology and the development of RHOA within 10 years follow-up. For large cam morphology (alpha angle > 78°), the association with the development of RHOA seemed to be stronger than cam morphology (alpha angle > 60°). Also, for both cam morphology and large cam morphology, the association was stronger when using end-stage RHOA (KL grade≥3) as an outcome as compared to incident RHOA (KL grade≥2). Considering the wide confidence interval around the OR, further validation on the magnitude of association is required for these findings in future larger studies.

In previously published longitudinal studies on the association between cam morphology and the development of incident RHOA, there seemed to be a trend of weaker associations with a longer follow-up time.[7,11,15] This trend contrasts with our findings which

Table 2 Osteoarthritis and Cartilage

Logistic regression model: association between predictors and the development of incident or end-stage RHOA at four follow-ups over 10 years.

Predictors	Follow-up	Hips with predictor (%)	Outcome: development of incident RHOA						Outcome: development of end-stage RHOA					
			Absolute risk (%)		Crude OR (95% CI)	P value	aOR (95% CI)	P value	Absolute risk (%)		Crude OR (95% CI)	P value	aOR (95% CI)	P value
			In hips with predictor	In hips without predictor					In hips with predictor	In hips without predictor				
Cam morphology (alpha angle > 60°)	T2	132(8.8)	19/132(14.4)	69/1364(5.1)	3.0(1.7–5.1)	<0.001	2.8 (1.6–4.9)	0.001	4/132(3.0)	3/1364(0.2)	15.3(3.4–68.9)	<0.001	8.5(1.1–64.4)	0.037
	T5	132(8.8)	44/132(33.3)	174/1362(12.8)	3.3(2.2–4.8)	<0.001	2.9(2.0–4.4)	<0.001	7/132(5.3)	17/1362(1.2)	5.5(2.3–13.4)	<0.001	4.9(1.8–13.2)	0.002
	T8	121(8.6)	57/121(47.1)	277/1280(21.6)	2.9(2.0–4.1)	<0.001	2.7(1.9–4.0)	<0.001	12/121(9.9)	33/1280(2.6)	5.5(2.9–10.5)	<0.001	5.3(2.6–10.6)	<0.001
	T10	120(8.8)	83/120(69.2)	506/1238(40.9)	2.9(2.0–4.3)	<0.001	2.7(1.8–4.1)	<0.001	18/120(15.0)	52/1238(4.2)	5.7(3.2–10.3)	<0.001	5.4(2.9–10.2)	<0.001
Large cam morphology (alpha angle > 78°)	T2	70(4.7)	14/70(20.0)	69/1364(5.1)	4.5(2.3–8.6)	<0.001	4.2(2.2–8.3)	<0.001	3/70(4.3)	3/1364(0.2)	23.1(4.6–116.1)	<0.001	12.7(1.9–84.4)	0.008
	T5	70(4.7)	28/70(40.0)	174/1362(12.8)	4.5(2.7–7.4)	<0.001	4.1(2.4–6.9)	<0.001	6/70(8.6)	17/1362(1.2)	10.0(3.8–26.2)	<0.001	8.1(2.8–23.5)	<0.001
	T8	64(4.6)	33/64(51.6)	277/1280(21.6)	3.2(2.0–5.1)	<0.001	3.1(1.9–5.1)	<0.001	8/64(12.5)	33/1280(2.6)	7.8(3.5–17.1)	<0.001	6.9(3.0–15.7)	<0.001
	T10	64(4.7)	44/64(68.8)	506/1238(40.9)	2.7(1.6–4.5)	<0.001	2.5(1.5–4.3)	<0.001	13/64(20.3)	52/1238(4.2)	7.8(5.4–22.8)	<0.001	6.7(3.1–14.7)	<0.001

RHOA: radiographic hip osteoarthritis; aOR: adjusted Odds Ratio; T2-T10: 2- to 10-year
Results are adjusted for age, sex and body mass index.

Table 3

Cox regression model: association between predictors and the development of incident or end-stage RHOA over 10 years.

Predictors	Outcome: development of incident RHOA				Outcome: development of end-stage RHOA			
	Crude HR (95% CI)	P value	aHR (95% CI)	P value	Crude HR (95% CI)	P value	aHR (95% CI)	P value
Cam morphology (alpha angle > 60°)	2.2(1.7–2.7)	< 0.001	2.1(1.7–2.6)	< 0.001	4.4(2.7–7.1)	< 0.001	4.1(2.5–6.8)	< 0.001
Large cam morphology (alpha angle > 78°)	2.3(1.7–3.1)	< 0.001	2.1(1.5–2.8)	< 0.001	6.2(3.6–10.7)	< 0.001	5.8(3.4–9.9)	< 0.001

RHOA: radiographic hip osteoarthritis; aHR: adjusted Hazard Ratio.
Results are adjusted for age, sex and body mass index.

showed a consistent strength of association for at least 10 years follow-up. Previously published prospective cohort studies,[5,7,11,13–16] however, only used one follow-up time point and the trend of association over time in those cohorts is therefore unknown. The differences in strength of association between previously published cohorts might therefore also be explained by differences in cohort characteristics and definitions of RHOA and cam morphology which we showed to influence the strength of association. A possibility to overcome this would be to harmonize data from previously published cohort studies which might be a topic of future research.

The alpha angle threshold value for defining cam morphology is still under debate, with a review,[25] reporting threshold values previously used ranging from 50.5° up to 83°. However, a recent systematic review,[20] aiming to identify a threshold value, suggested a 60° cutoff to distinguish between hips with and without cam morphology, but also mentioned that a higher threshold value might increase the risk of developing hip OA. Our findings also supported this, showing a stronger association with RHOA for large cam morphology. We reported the alpha angle with threshold values for its interpretability and because the alpha angle previously showed a clear bimodal distribution in this cohort, thereby having a naturally distinction between hips with and without cam morphology.[21] However, this approach might have some statistical drawbacks (loss of power and incomplete correction for confounding factors[26–28]) which is why we also presented the alpha angle as a continuous measure.

The differences in strength of association between cam morphology and large cam morphology might be explained mechanically. A larger cam morphology might create an earlier premature contact between the cam and acetabulum during hip motion. This earlier premature contact potentially also results in more rapid or extensive cartilage damage.[10] Moreover, during large ranging hip motion, a larger cam morphology could cause higher peak contact pressures on the acetabular cartilage,[6] compared with a smaller size cam morphology.

Our data suggested that the presence of both cam morphology and large cam morphology seemed to have stronger associations with the development of incident end-stage RHOA than incident RHOA at all follow-up time points over 10 years. The pathogenesis of hip OA is heterogeneous and includes mechanical, inflammatory, metabolic, biological and genetic factors amongst others.[29] Cam morphology is a typical mechanical risk factor, known to develop during adolescence. Hip OA is therefore probably the result of a cumulating effect in which the cam is repetitively forced into the acetabulum. It is known that this abnormal contact between cam morphology and the acetabulum can lead to a complete delamination of the cartilage from the subchondral bone, particularly in the anterosuperior region.[30] The mechanism of cam impingement has therefore been suggested to cause end-stage OA within a 2–5-year time frame, which we confirmed with the results of our study. Therefore, more research is urgently needed on how we can reverse this association through primary or secondary prevention.

Our findings may have important clinical implications. In these participants who consulted the GP for the first time with first onset of either hip or knee pain, but without definite signs of RHOA, a simple measurement (alpha angle) on the same AP radiograph can be obtained to assess the risk for developing future RHOA. The risk was 6–13 times increased for a large cam morphology, depending on the follow-up time. The absolute risk of hips with cam morphology developing incident RHOA increased from 14.4% at T2 to 69.2% at T10, with an a priori chance of 5.9% and 43.4% respectively. Identifying such a high-risk subgroup is important to test interventions that might prevent or delay the development of hip OA in these individuals.

The main limitation of this study is the use of AP radiographs, as this view only captures the outline of the femoral head-neck junction in the coronal plane. As cam morphology is a three-dimensional structure mostly located at the anterolateral aspect of the femoral head-neck junction, we may have underestimated the prevalence of cam morphology in this study. Still, quantifying cam morphology only on AP view was highly predictive for the development of hip RHOA. Also, the reader should be aware that participants of CHECK cohort study had first onset symptoms of either hip or knee or both and were aged 45–65 years at baseline. Our findings can therefore not be generalized to individuals without symptoms or younger and athletic individuals. Also, although we excluded hips with definite RHOA at baseline, we cannot rule out that these symptoms were already the first sign of OA. Finally, the reader should bear in mind that the CHECK cohort excluded those with a suspected non-OA pathological condition that could explain the symptoms (such as childhood hip diseases, fracture, bursitis amongst others). However, it is difficult to estimate what the influence of this exclusion criteria on the results is, because the distribution of cam morphology in these groups is unknown.

In conclusion, cam morphology and large cam morphology were consistently associated with the development of incident and end-stage RHOA over 10 years. The association was stronger in hips with large cam morphology than cam morphology and for the development of end-stage RHOA as compared with incident RHOA. Depending on the size of cam morphology and definition of RHOA used, OR ranged from 2 to 13 and the absolute risk ranged from 15% to 69%. Cam morphology can be diagnosed before hip OA is present and might therefore be an interesting target for prevention of RHOA.

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CRediT authorship contribution statement

RA, JR and SBZ contributed to the conception and design of this study. RA and MvB performed data collection; RA, JT, NR and FB contributed to the analysis of data. All authors contributed to the interpretation of data. Article draughts were written by JT and critically revised by all authors. The final version of the article was approved by all authors.

Declaration of Competing Interest

The authors have declared no competing interests.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.joca.2023.08.006.

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