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Hand and knee osteoarthritis are associated with reduced diameters in retinal vessels: the AGES-Reykjavik study

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Abstract

To investigate the association between osteoarthritis (OA) and microvascular pathology, we examined the relationship between retinal microvascular caliber and osteoarthritis of the hand and knee in an elderly population. The AGES-Reykjavik is a population-based, multidisciplinary longitudinal cohort study of aging. Retinal vessel caliber, hand osteoarthritis and total knee joint replacements due to OA were examined in 4757 individuals (mean age 76 ± 5 years; 57% female). Incident knee joint replacements during 5-year follow-up ($n = 2961$, mean age 75 ± 5 years; 58% female) were also assessed. Logistic regression analysis, adjusting for age, sex, and body mass index, showed an association between narrow arteriolar caliber and hand OA, as well as knee replacement. After adjustment for other covariates, including statin therapy, this association was significant for both hand OA in men and women [OR 1.10(1.03–1.17), $p < 0.01$] (per unit standard deviation decrease in CRAE) and TKR prevalence [OR 1.15 (1.01–1.32), $p = 0.04$], especially for men [OR 1.22 (1.00–1.51) $p = 0.04$] and also for incident TKRs in men [OR 1.50 (1.07–2.10), $p = 0.04$]. Narrow venular caliber was associated with hand OA in women [OR 1.10 (1.01–1.21), $p = 0.03$]. Retinal arterial narrowing in hand and knee OA is present in males as well as females. Venular narrowing in hand OA in women was an unexpected finding and is in contrast with the venular widening usually observed in cardiovascular diseases.

Keywords Osteoarthritis · Retinal vessel diameters

Introduction

There is evidence of an association between osteoarthritis (OA) and vascular pathology. We have shown earlier that macrovascular pathology manifest as increased coronary calcium and carotid plaque, as well as cerebral white matter lesions in women with hand OA compared to those without hand OA [1]. These findings were further reinforced when stratifying by joint replacement operations due to OA [2]. There have also been other reports of an association between hand OA and atherosclerosis [3, 4].

Examination of retinal vessels is a standard, non-invasive way of assessing vascular pathology. Digital photography and standardized reading of retinal arterial and venule

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calibers allows for the investigation of microvascular pathology for many health outcomes [5]. Both retinal arteriolar narrowing and retinal venular widening have been associated with reduced arterial compliance and increased risk of hypertension and coronary heart disease [6–8]. Among 1838 participants of the AusDiab Study, the 77 individuals who went on to have knee joint replacements (TKRs) for OA were more likely to have narrower retinal arteriolar caliber compared to those without TKR, but their retinal venule calibers did not differ [9].

The AGES-Reykjavik study is a large population-based study of elderly Icelanders, aged 66 years and older. Given its longitudinal, multidisciplinary design, the study provides a unique opportunity to investigate the relationship between microvascular pathology in retinal vessel calibers and the prevalence of osteoarthritis of the hand and total knee joint replacements due to OA (TKRs), as well as the incidence of TKRs over a 5-year follow-up period [10].

Methods

The AGES-Reykjavik (AGES I) is a longitudinal study of 5764 surviving participants enrolled between 2002 and 2006 from the population-based Reykjavik study cohort established in 1967 [10]. Between 2007 and 2011, 71% returned for a 5-year follow-up visit (AGES II). The participants underwent extensive functional testing, questionnaires, laboratory and imaging investigations. Written informed consent was obtained from all participants. The detailed information gathered from all AGES participants has been described in the study's baseline paper [10].

Retinal vessel imaging

After pharmacological dilation, a Canon non-mydriatic camera (US Canon Inc, Lake Success, NY) captured two 45° digital images of each retina, one centered on the optic disc and the other on the fovea using a standardized protocol [11]. Central retinal artery equivalent (CRAE) and central retinal vein equivalent (CRVE) were derived from the measurements of the six largest arterioles (for CRAE) and six largest venules (for CRVE) within ½ to 1 disc diameter from the optic disc margin using EyeQ Lite image processing software (Digital Healthcare Inc., Cambridge, UK) [12]. Unless one eye had ungradable images, CRAE and CRVE represent the mean from both eyes.

Osteoarthritis diagnosis

The presence and severity of HOA was determined from high quality digital photographs taken during AGES I and graded on a 0–4 scale. Hand OA was defined as no evidence of OA = 0, doubtful OA = 1, mild definite = 2, moderate = 3 and severe = 4, later dichotomized to either absent (0,1) or present (2–4) [1, 13]. Knee joint replacements (TKRs) due to OA were recorded from computed tomography (CT) anterior scout scans at AGES I and AGES II, as previously described, excluding those with evidence of inflammatory arthritis and fractures as causes of TKR [14]. TKR was defined as prevalent at AGES I or AGES II, and incident TKR refers to TKR occurring within the 5-year interval after the AGES I exam.

Exclusion criteria

From 5764 participants, individuals with evidence of inflammatory arthritis and incomplete imaging were excluded leaving a total of 5170 participants (90%) having data on both hand and knee osteoarthritis. Of those, retinal vasculature data were available in 4757 participants (2043 men and 2716 women, mean age 76 ± 5 years), providing the study sample for this analysis.

Statistics

Descriptive statistics are presented for participants with and without hand OA, TKR, or incident TKR. Differences between groups, adjusting for age, were tested using analysis of covariance (ANCOVA) and logistic regression. Multiple logistic regression analyses with hand OA or TKR as the outcome and retinal vessel caliber (CRAE or CRVE) as the explanatory variable were performed. Models were adjusted for age, sex, body mass index (BMI), physical activity, HbA1c level, systolic blood pressure, hypertension, cholesterol, statin use, NSAID use, any antihypertensive medication use, and microalbuminuria based on the variable's significance in preliminary analyses or the relevant literature. Analyses were also stratified by sex. To evaluate the sex-specific relationship between retinal vessels and hand OA, BMI was categorized as normal or underweight (BMI < 25 kg/m^2), overweight (25–29 kg/m^2), or obese (30 + kg/m^2). Odds ratios with 95% confidence intervals, presenting the odds of hand OA or TKR per unit standard deviation decrease in CRAE or CRVE, and p-values were reported. All analyses, conducted using SAS version 9.4 (SAS Institute, Cary, North Carolina, USA), were two sided at the 95% confidence level.

Results

Data on retinal vessels and osteoarthritis were available from 4757 participants (mean age 76 ± 5 years; 57% female); of whom, 2961 individuals had 5-year follow-up data to assess incident TKR. At AGES I, hand OA was apparent in 886 of 2043 men (43%) and 1306 of 2714 women (48%). By AGES II, 111 (5.4%) men and 181 (6.7%) women had a knee joint

replacement due to OA; of which, 37 in 1243 men (3.0%) and 67 in 1718 women (3.9%) had occurred in the participants of AGES II during the 5-year follow-up since AGES I. Baseline characteristics of the study population, shown by OA status appear in Table 1. Men and women with hand osteoarthritis tended to be older and have lower BMI, whereas those with TKRs had higher BMI and were more likely to use NSAIDs or any antihypertensive medication. Both arterial and venular calibers were smaller in females with hand OA; males with TKRs had smaller arteriolar caliber. Figure 1 graphically depicts retinal vessel caliber by BMI category and by the presence of hand OA in men and women. There was no relationship between retinal arteriole caliber and BMI in women with hand OA, although overweight and obese women without HOA had wider arterioles. In contrast, overweight and obese men tended to have narrower arterioles with the narrowest arterioles observed in men who were obese and had hand OA. Retinal venules were widest in obese men and women compared to lean individuals, although this was somewhat less pronounced in those with hand OA.

Table 2 shows the results of logistic regression analyses examining the relationship between retinal vessel diameters and OA of the hand or TKR. Adjusting only for age, sex, and BMI, there was a statistically significant association, for men and women combined, between narrow retinal arteriolar caliber and hand OA [OR 1.08(1.02–1.15) $p=0.007$] per unit standard deviation decrease in CRAE. The significance of this association persisted in this combined group and in women after adjustment for all other covariates [OR 1.10(1.03–1.17) $p=0.007$] and [OR 1.11 (1.02–1.21) $p=0.020$], respectively) but was attenuated for men. The association between narrow retinal arterioles and TKR remained significant after adjustment for covariates in the combined group, driven by the strong association in men. Although odds ratios were elevated in women, they were not statistically significant. Men had a 22% increase in odds of a TKR for each standard deviation decrease in retinal arteriolar caliber.

After full model adjustment, there was an association between narrow retinal venular caliber and hand OA in women, [OR 1.10(1.01–1.21), $p=0.031$] per unit standard deviation decrease in CRVE, but not in men. Women thus had 10% higher odds of hand OA for each standard deviation of reduced venular caliber after adjusting for covariates. There was no association between retinal venule caliber and TKR for men or for women.

Discussion

In this large population-based study of elderly people, we found an inverse association between retinal vessel diameters and both hand OA and knee joint replacement due to OA. For men and women combined, reduced arteriolar diameters were associated with hand OA and knee joint replacement, while interestingly, reduced venular diameters were also associated with hand OA in women.

The odds ratios for incident TKR in all participants were highly similar to those reported in the study by Hussain, with an approximately 25% increase in odds for each standard deviation decrease in retinal arterial caliber. This finding was more marked in men in the current study, but the Australian study did not report sex-specific results [9].

Our findings are in direct contrast to those from 289 asymptomatic individuals aged 50–79 years reporting, independent of age, sex, and BMI, wider retinal venular caliber in individuals with a bone marrow lesion and wider retinal arteriolar caliber in individuals with early signs of decreased knee cartilage [15]. The difference in the two studies may be explained by differences in osteoarthritis definition. In addition, longitudinal studies provide evidence that retinal vascular changes may be dynamic, suggesting considerable remodeling in the retinal vasculature [16].

We found inverse relationships between retinal arteriolar and venular calibers and HOA, but only in women. In women, HOA and atherosclerosis was also noted in the Rotterdam study [3] and our previous work [1]. The association between HOA and decreased retinal venular caliber is novel, but retinal venular caliber is known to decrease with age [17] and statin use [18].

Unlike previous studies, we considered the impact of statin use in our adjusted models because results from a randomized, controlled clinical prospective trial have shown statins to, over time, significantly increase retinal arteriolar caliber and modestly decrease retinal venular caliber allegedly by improving endothelial function and decreasing inflammation [18]. Nevertheless, including statin use as a covariate in our models had only a modest impact on the estimates of odds ratios or their significance.

The evidence for widespread vascular pathology in osteoarthritis is growing, indicating common etiological pathways, but the question whether osteoarthritis itself is an independent risk factor for cardiovascular events is still open. Increased cardiovascular risk has been reported in a number of observational studies, but the relationship is complex due to the associations between OA and a number of other risk factors such as obesity, age, pain, NSAID use and even the gut microbiome [19–22]. Our previous studies did not find any association between hand OA and cardiovascular events [1, 2] and while TJR's are generally considered to be a robust indicator of severe knee and hip OA, there has been some reluctance to calculate cardiovascular risk due to the possibility of confounding (i.e. that cardiovascular status may influence the feasibility of performing TJR's) [19].

The exact mechanisms for this relationship are still unclear. Inflammation itself is atherogenic, and several

Table 1 Characteristics of the study population by hand osteoarthritis and knee replacement prevalence and 5-year incidence

	Hand osteoarthritis			Knee joint replacements (TKR) due to osteoarthritis					
				Prevalent at AGES II			5-Year incidence		
	No Hand OA ($n=1157$)	Hand OA ($n=886$)	p value	No TKR ($n=1932$)	TKR ($n=111$)	p value	No TKR ($n=1206$)	TKR ($n=37$)	p value
Men									
Age at baseline (years)	76.0 ± 5.3	77.0 ± 5.3	**< 0.01**	76.4 ± 5.3	76.1 ± 5.1	0.47	74.9 ± 4.6	74.5 ± 4.0	0.64
BMI (kg/m^2)	27.1 ± 3.7	26.4 ± 3.7	**< 0.01**	26.7 ± 3.7	28.7 ± 3.8	**< 0.01**	26.9 ± 3.6	29.0 ± 3.4	**< 0.01**
Physical activity			0.51			0.56			0.57
Never	224 (20.3)	170 (20.8)		376 (20.7)	18 (17.1)		221 (19.4)	6 (17.1)	
Rarely or occasionally	484 (43.8)	342 (41.8)		779 (42.9)	47 (44.8)		490 (42.9)	14 (40.0)	
Moderate or more	396 (35.9)	306 (37.4)		662 (36.4)	40 (38.1)		431 (37.7)	15 (42.9)	
HbA1c (%)	5.7 ± 0.6	5.7 ± 0.5	0.46	5.7 ± 0.6	5.7 ± 0.6	0.43	5.7 ± 0.5	5.6 ± 0.4	0.78
Systolic blood pressure (mmHg)	143.0 ± 20.2	143.3 ± 19.7	0.93	143.0 ± 20.0	145.1 ± 19.3	0.27	142.8 ± 19.7	143.0 ± 15.8	0.90
Hypertension	929 (80.3)	712 (80.4)	0.75	1546 (80.0)	95 (85.6)	0.14	942 (75.8)	31 (83.8)	0.39
Total cholesterol (mmol/L)	5.2 ± 1.1	5.2 ± 1.1	0.99	5.2 ± 1.1	5.0 ± 1.0	0.13	5.2 ± 1.0	5.1 ± 1.1	0.71
Microalbumin (g/L)	41.1 ± 2.6	41.3 ± 2.8	0.11	41.2 ± 2.7	40.8 ± 2.2	0.28	41.3 ± 2.5	41.2 ± 2.3	0.80
History of angina by self-report	213 (18.8)	154 (17.6)	0.50	353 (18.6)	14 (12.7)	0.06	208 (17.5)	2 (5.4)	0.07
History of cardiovascular disease by self-report	382 (33.0)	290 (32.8)	0.86	640 (33.2)	32 (28.8)	0.35	363 (30.2)	15 (40.5)	0.17
Record of clinical cardiovascular event	303 (26.4)	219 (24.8)	0.46	497 (25.9)	25 (22.7)	0.45	300 (25.0)	12 (33.3)	0.26
Statin use	345 (29.8)	249 (28.1)	0.65	561 (29.0)	33 (29.7)	0.93	370 (30.7)	14 (37.8)	0.36
Aspirin use	503 (43.5)	379 (42.8)	0.74	842 (43.6)	40 (36.0)	0.12	535 (44.4)	17 (46.0)	0.83
NSAID use	76 (7.3)	68 (8.6)	0.31	125 (7.3)	19 (18.3)	**< 0.01**	78 (7.4)	9 (25.7)	**< 0.01**
Any antihypertensive medication use	734 (63.4)	537 (60.6)	0.14	1197 (62.0)	74 (66.7)	0.31	728 (60.4)	22 (59.5)	0.92
Retinal arteriolar caliber (μm)	138.5 ± 13.2	137.3 ± 13.5	0.09	138.1 ± 13.4	134.8 ± 12.7	**0.01**	138.4 ± 13.5	134.1 ± 14.5	0.05
Retinal venular caliber (μm)	202.8 ± 19.5	200.8 ± 18.5	0.14	201.8 ± 19.1	203.7 ± 19.0	0.36	202.8 ± 18.8	203.4 ± 16.9	0.92
	Hand osteoarthritis			Knee joint replacements (TKR) due to osteoarthritis					
				Prevalent at AGES II			5-Year incidence		
	No Hand OA ($n=1408$)	Hand OA ($n=1306$)	p value	No TKR ($n=2533$)	TKR ($n=181$)	p value	No TKR ($n=1651$)	TKR ($n=67$)	p value
Women									
Age at baseline (years)	75.6 ± 5.4	76.8 ± 5.7	**< 0.01**	76.2 ± 5.6	75.9 ± 5.1	0.50	74.8 ± 5.0	73.3 ± 3.9	**< 0.01**

Table 1 (continued)

	Hand osteoarthritis			Knee joint replacements (TKR) due to osteoarthritis					
				Prevalent at AGES II			5-Year incidence		
	No Hand OA ($n=1408$)	Hand OA ($n=1306$)	p value	No TKR ($n=2533$)	TKR ($n=181$)	p value	No TKR ($n=1651$)	TKR ($n=67$)	p value
BMI (kg/m^2)	27.6 ± 4.8	26.8 ± 4.7	**< 0.01**	27.0 ± 4.7	30.1 ± 5.0	**< 0.01**	27.4 ± 4.4	31.5 ± 5.0	**< 0.01**
Physical activity			0.20			0.90			0.68
Never	288 (21.9)	282 (23.7)		537 (23.0)	33 (19.5)		297 (19.5)	11 (17.2)	
Rarely or occasionally	657 (50.0)	538 (45.2)		1106 (47.4)	89 (52.7)		737 (48.4)	34 (53.1)	
Moderate or more	368 (28.0)	370 (31.1)		691 (29.6)	47 (27.8)		490 (32.2)	19 (27.0)	
HbA1c (%)	5.7 ± 0.5	5.7 ± 0.5	0.24	5.7 ± 0.5	5.7 ± 0.4	0.62	5.7 ± 0.5	5.8 ± 0.5	**0.03**
Systolic blood pressure (mmHg)	141.2 ± 20.3	142.8 ± 20.5	0.25	142.1 ± 20.5	140.8 ± 19.6	0.49	140.5 ± 19.9	140.3 ± 16.1	0.70
Hypertension	1138 (80.8)	1067 (81.8)	0.73	2049 (80.9)	156 (86.2)	0.07	1290 (78.2)	59 (88.1)	**0.03**
Total cholesterol (mmol/L)	6.0 ± 1.1	6.0 ± 1.1	0.69	6.0 ± 1.1	5.9 ± 1.1	0.37	6.0 ± 1.1	5.8 ± 1.0	0.17
Microalbumin (g/L)	40.9 ± 2.4	40.9 ± 2.6	0.64	40.9 ± 2.5	40.9 ± 2.9	0.90	41.1 ± 2.5	41.2 ± 2.1	0.96
History of angina by self-report	171 (12.3)	135 (10.6)	0.10	285 (11.4)	21 (11.8)	0.86	164 (10.1)	5 (7.6)	0.55
History of cardiovascular disease by self-report	237 (16.9)	200 (15.3)	0.09	409 (16.2)	28 (15.5)	0.87	219 (13.3)	8 (11.9)	0.98
Record of clinical cardiovascular event	112 (8.1)	98 (7.6)	0.41	197 (7.9)	13 (7.3)	0.82	109 (6.7)	5 (7.6)	0.60
Statin use	261 (18.5)	246 (18.8)	0.71	474 (18.7)	33 (18.2)	0.86	320 (19.4)	15 (22.4)	0.54
Aspirin use	401 (28.5)	372 (28.5)	0.45	721 (28.5)	52 (28.7)	0.85	417 (25.3)	21 (31.3)	0.15
NSAID use	158 (12.3)	156 (12.8)	0.39	282 (12.1)	32 (18.3)	**0.02**	199 (13.3)	16 (24.2)	**0.03**
Any antihypertensive medication use	904 (64.2)	851 (65.2)	0.75	1617 (63.8)	138 (76.2)	**< 0.01**	1006 (60.9)	52 (77.6)	**< 0.01**
Retinal arteriolar caliber (μm)	141.8 ± 12.9	140.3 ± 13.2	**0.03**	141.2 ± 13.0	140.0 ± 12.8	0.21	141.2 ± 12.8	140.5 ± 12.4	0.50
Retinal venular caliber (μm)	203.3 ± 20.1	200.7 ± 20.1	**0.01**	202.1 ± 20.1	201.6 ± 20.3	0.64	202.8 ± 19.6	203.4 ± 19.1	0.98

Hand OA is defined as NO Hand OA (no or doubtful OA) or Hand OA (definite: mild, moderate, severe) at AGES I exam. Data presented as mean ± SD or N (%). P value result of comparison between no hand OA or TKR vs. hand OA or TKR, respectively, adjusted for age. Bolded p vales present statistically significant ($p < 0.05$) results

theories have been proposed, some of them implicating the metabolic syndrome, blood lipids, adipokines and vascular growth factors [23–25]. The possibility of genetic factors must also be considered. A recent discovery identified a common genetic variation in the ALD1H2 gene which confers a major risk for severe hand OA. The risk allele is highly prevalent and leads to reduced expression of retinoic acid in human cells and seems to reduce the bioavailability of retinoic acid in tissues [26]. Retinoic acid has a hormone-like function on genetic expression in the body, and animal studies have shown that reduced bioavailability of retinoic acid leads to increased murine atherosclerosis [27].

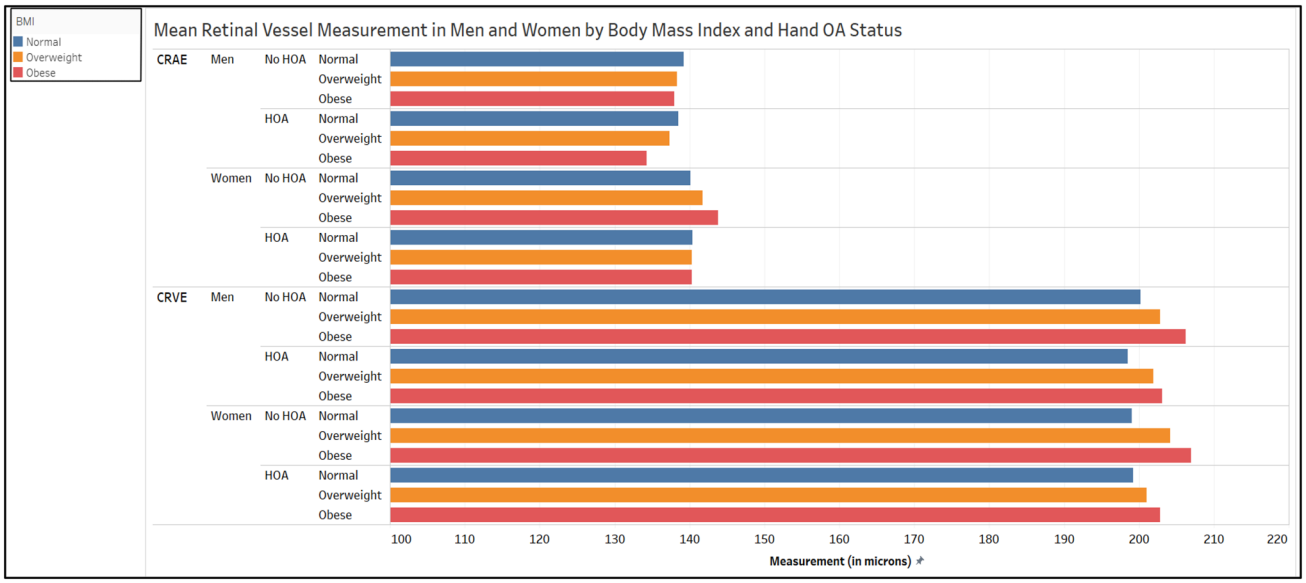

Fig. 1 Mean Retinal Vessel Measurements in Men and Women by Body Mass Index and Hand OA Status

Among the possible caveats of this study are the methods used for diagnosing hand osteoarthritis with photography and using TKR's after exclusion of other causes such as inflammatory arthritis or fractures as a marker of severe knee OA. The photographic method for diagnosing hand OA has been validated in other populations [28], and TKR's are considered as a sensitive marker of severe knee OA, mainly limited by unequal access to operation in different populations. In Iceland, the health care system is socialized and previous Icelandic studies have not found any association between the prevalence of TKR's and education or occupational classes, indicating equal access [14, 29].

The older age of the study population may also be of importance as individuals with severe atherosclerosis may not have reached the study age, indicating a survival bias. On the other hand, the AGES-Reykjavik study with its large number of elderly participants and extensive high quality information is ideal for multidisciplinary clinical studies. The AGES II prospective 5-year follow-up also allows for incidence analysis.

The current study confirms and extends previously published studies of the association between osteoarthritis and vascular pathology. The findings of male microvascular pathology in osteoarthritis and venular pathology in women with hand OA are both novel findings. Unfortunately, the study does little to solve the puzzle regarding the pathogenetic pathways involved, but the curious finding of narrower retinal venular caliber with osteoarthritis, instead of wider venular caliber historically associated with cardiovascular diseases and the metabolic syndrome, needs to be corroborated to determine whether it may indicate a difference in the pathogenic pathways involved in OA-related vascular pathology compared with these conditions.

Table 2 Logistic regression models for retinal vascular caliber by osteoarthritis in the hand or knee joint replacement

	Hand osteoarthritis				Knee joint replacements (TKR) due to osteoarthritis							
					Prevalent at AGES II				5-Year incidence			
	Model 1		Model 2		Model 1		Model 2		Model 1		Model 2	
	Odds ratio (95% CI)	*p* value	Odds ratio (95% CI)	*p* value	Odds ratio (95% CI)	*p* value	Odds ratio (95% CI)	*p* value	Odds ratio (95% CI)	*p* value	Odds ratio (95% CI)	*p* value
Retinal arteriolar caliber												
All participants	1.08 (1.02, 1.15)	**< 0.01**	1.10 (1.03, 1.17)	**< 0.01**	1.21 (1.07, 1.37)	**< 0.01**	1.15 (1.01, 1.32)	**0.04**	1.24 (1.01, 1.52)	**0.04**	1.26 (1.01, 1.57)	**0.04**
Men	1.09 (0.99, 1.20)	0.05	1.08 (0.98, 1.20)	0.14	1.26 (1.04, 1.53)	**0.02**	1.22 (1.00, 1.51)	**0.04**	1.35 (0.98, 1.87)	0.07	1.50 (1.07, 2.10)	**0.02**
Women	1.08 (1.00, 1.17)	**0.04**	1.11 (1.02, 1.21)	**0.02**	1.17 (1.00, 1.37)	0.05	1.10 (0.92, 1.31)	0.28	1.18 (0.91, 1.53)	0.21	1.10 (0.83, 1.46)	0.52
Retinal venular caliber												
All participants	1.08 (1.02, 1.14)	**0.02**	1.07 (1.00, 1.14)	0.05	1.05 (0.93, 1.19)	0.45	0.99 (0.86, 1.13)	0.84	1.08 (0.88, 1.33)	0.46	1.05 (0.84, 1.32)	0.66
Men	1.06 (0.97, 1.16)	0.21	1.02 (0.92, 1.13)	0.70	0.95 (0.77, 1.15)	0.58	0.90 (0.72, 1.12)	0.35	1.04 (0.74, 1.47)	0.82	1.13 (0.78, 1.63)	0.51
Women	1.09 (1.01, 1.18)	**0.03**	1.10 (1.01, 1.21)	**0.03**	1.12 (0.95, 1.31)	0.17	1.04 (0.87, 1.24)	0.67	1.10 (0.85, 1.43)	0.46	1.02 (0.77, 1.35)	0.90

Odds ratio represents the odds of hand OA per one standard deviation **decrease** in CRAE or CRVE, respectively. Bolded *p* values present statistically significant ($p<0.05$) results. Model 1 adjusts for age, sex, and body mass index. Model 2 adjusts for variables in model 1 and physical activity, HbA1c, systolic blood pressure, hypertension, total cholesterol, microalbuminuria, statin use, NSAID use, and any antihypertensive medication use. Age, sex, BMI, physical activity, and NSAID use were the statistically significant covariates in CRAE and CRVE models for all participants. Age, BMI, and NSAID use were the statistically significant covariates in CRAE and CRVE models for men and women

CI Confidence interval

Author contributions All authors have: (1) made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; (2) been involved in drafting the manuscript or revising it critically for important intellectual content; (3) given final approval of the version to be published; and (4) agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Compliance with ethical standards

Conflict of interest The authors have no proprietary or commercial interest in any materials discussed in this article.

Ethical standards All procedures performed were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments. Both studies were approved by the Icelandic National Bioethics Committee, (VSN: 00-063, and VSN 09_098_S1) and the Data Protection Authority.

Ethical approval Both studies were approved by the Icelandic National Bioethics Committee, (VSN: 00–063, and VSN 09_098_S1) and the Data Protection Authority.

Informed consent All participants signed an informed consent declaration.

Consent to publish The study is approved by the AGES-Reykjavik steering committee.

Data availability All data are from the AGES-Reykjavik study and can be obtained upon application.

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