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Meta-analysis: Retinal Vessel Caliber and Risk for Coronary Heart Disease

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Background: Retinal vessel caliber may be a novel marker of coronary heart disease (CHD) risk. However, the sex-specific effect, magnitude of association, and effect independent of traditional CHD disease risk factors remain unclear.

Purpose: To determine the association between retinal vessel caliber and risk for CHD.

Data Sources: Relevant studies in any language identified through MEDLINE (1950 to June 2009) and EMBASE (1950 to June 2009) databases.

Study Selection: Studies were included if they examined a general population, measured retinal vessel caliber from retinal photographs, and documented CHD risk factors and incident CHD events.

Data Extraction: 6 population-based prospective cohort studies provided data for individual participant meta-analysis.

Data Synthesis: Proportional hazards models, adjusted for traditional CHD risk factors, were constructed for retinal vessel caliber and incident CHD in women and men. Among 22 159 participants who were free of CHD and followed for 5 to 14 years, 2219 (10.0%) incident CHD events occurred. Retinal vessel caliber changes (wider venules and narrower arterioles) were each associated with an increased risk for CHD in women (pooled multivariable-adjusted hazard ratios, 1.16 [95% CI, 1.06 to 1.26] per 20-μm increase in venular caliber and 1.17 [CI, 1.07 to 1.28] per 20-μm decrease in arteriolar caliber) but not in men (1.02 [CI, 0.94 to 1.10] per 20-μm increase in venular caliber and 1.02 [CI, 0.95 to 1.10] per 20-μm decrease in arteriolar caliber). Women without hypertension or diabetes had higher hazard ratios.

Limitation: Error in the measurement of retinal vessel caliber and Framingham variables was not taken into account.

Conclusion: Retinal vessel caliber changes were independently associated with an increased risk for CHD events in women.

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Coronary heart disease (CHD) remains the leading cause of death in the United States despite advances in prevention, diagnosis, and therapy. Further improvement in outcomes can be achieved through more accurate identification of persons at risk, enhanced understanding of pathogenesis, novel interventions, and better implementation of existing preventive and therapeutic strategies.

Coronary microvascular dysfunction is increasingly recognized as an important contributor to CHD, particularly among women (1), and interest in noninvasive methods of assessing the coronary microcirculation is considerable (2). The coronary and retinal vessels undergo similar changes (such as sclerosis) in hypertension (3, 4), and assessment of retinal vessels may provide an indication of coronary microvascular damage (5). With the advent of computer-assisted methods for measuring retinal vessel caliber from retinal photographs, retinal vascular imaging has been found to independently predict increased risk for CHD in prospective epidemiologic studies (6–10), which raises the possibility of using retinal vessel assessment as a novel risk marker. However, the results reported thus far have not been consistent. The ARIC (Atherosclerosis Risk in Communities) study (6), the first large epidemiologic study to report associations of retinal vessel caliber with incident CHD, suggested that these associations were only present in middle-age women. Subsequent studies have produced conflicting results. The CHS (Cardiovascular Health Study) (9) reported associations of narrower retinal arterioles and wider venules with incident CHD in both older women and men, but other studies found associations mainly in younger women and men, with weak or no association in older persons (10).

Differences in study populations and inclusion criteria may account for the varying findings. For example, participants with diabetes or prevalent CHD were included in some studies (10) but not others (9, 11), and analytic methods and adjustment for traditional cardiovascular risk factors varied considerably among studies.

To provide robust evidence to address these discrepancies, we conducted a systematic review and an individual-participant meta-analysis of population-based cohort studies, adjusting for traditional risk factors, to determine the associations between retinal vessel caliber and CHD risk. We particularly examined whether the associations differed between women and men.

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METHODS

Data Extraction

We reviewed the literature to identify all studies that measured retinal vessel caliber, documented CHD events, and were conducted in general populations. We conducted a search of MEDLINE and EMBASE of all studies published between 1950 and 4 June 2009. We used the MEDLINE search terms (exp Retinal Diseases/, (retina or retinal).tw., retinopathy.tw., Arteriolar narrowing.tw., Arterio-venous nicking.tw., Arteriovenous nicking.tw., venular dilatation.tw., venular dilation.tw., arterio-venular ratio.tw.) and (Cardiovascular Diseases/, exp Heart Diseases/, exp Vascular Diseases/, cardiovascular.tw., coronary.tw., heart.tw., mortality.tw.) and (incidence/, exp Mortality/, exp epidemiologic studies/, prognos$.tw., Prognosis/, predict$.mp., course.tw., (score or scoring or scored).tw., observ$.mp., risk:.mp., between group:.tw.) and (Photography/, Photomicrography/, photo$.tw., image$.tw.). We then searched the selected papers to identify studies that met our inclusion criteria: carried out in general populations, measured retinal vessel caliber from either photographic film or digital photographs by using computer-assisted methods, and recorded incident CHD events.

We contacted the principal or lead investigators of the chosen studies and obtained individual-participant data from each study to investigate heterogeneity in the published results and, if appropriate, to calculate pooled estimates of the associations between retinal vessel caliber and CHD risk. If the investigators agreed to participate, we then requested original recorded data on individual retinal vessel caliber measurements, fatal and nonfatal CHD events and time to these events, baseline measurements of variables included in the Framingham Risk Score (age, sex, systolic blood pressure, serum total cholesterol and high-density lipoprotein [HDL] cholesterol levels, current smoking status, use of blood pressure–lowering medications, and presence of diabetes), body mass index, diastolic blood pressure, leukocyte count, and previous CHD.

Statistical Analysis

We analyzed the data for women and men separately because our primary hypothesis was that retinal vessel caliber predicts incident CHD more strongly in women than in men (8). In addition, separate Framingham Risk Scores, with different coefficients for the variables in the score, are used for men and women (12).

The standard deviation for the means of arteriolar and venular caliber was approximately 20 μm. We estimated the hazard ratio associated with each 20-μm decrease in arteriolar caliber and each 20-μm increase in venular caliber, which were adjusted for the other retinal vessel caliber, the variables that make up the Framingham Risk Score, and other risk factors associated with CHD and retinal caliber (13, 14). We estimated these separately for each study by using a proportional hazards model. We then combined data from all studies and used a stratified proportional hazards model to test for interaction between the study stratification variable and retinal vessel caliber variables, as well as sex and the CHD risk factors. This tests heterogeneity across studies in associations with retinal vessel caliber. Where no heterogeneity was present, we obtained a pooled hazard ratio adjusted for the CHD risk factors. The stratified proportional hazards model allows the baseline hazard function to differ among the studies but assumes that the effect of the retinal vessel caliber and the other variables are fixed.

We defined nonfatal CHD events as myocardial infarction, coronary artery bypass graft, or coronary angioplasty. For those events that were coded by using International Classification of Diseases, Tenth Edition, codes, we classified fatal events as CHD deaths if the main or underlying cause of death received a code from I21 to I25 or if the study-adjudicated cause of death was CHD.

Within each study, we assessed the appropriate functional form of each of the continuous variables in the models by using fractional polynomials, and we tested the proportional hazards assumption by using plots of the Schoenfeld residuals and by testing for the effect of adding time-dependent covariates (15).

We repeated the main analysis to examine the robustness of our results, this time standardizing the retinal vessel caliber measurements by dividing them by the study-specific standard deviations to allow for different means and standard deviations of the retinal vessel caliber measurements in the different studies (16). We also pooled the study-specific hazard ratios by using a random-effects model (17).

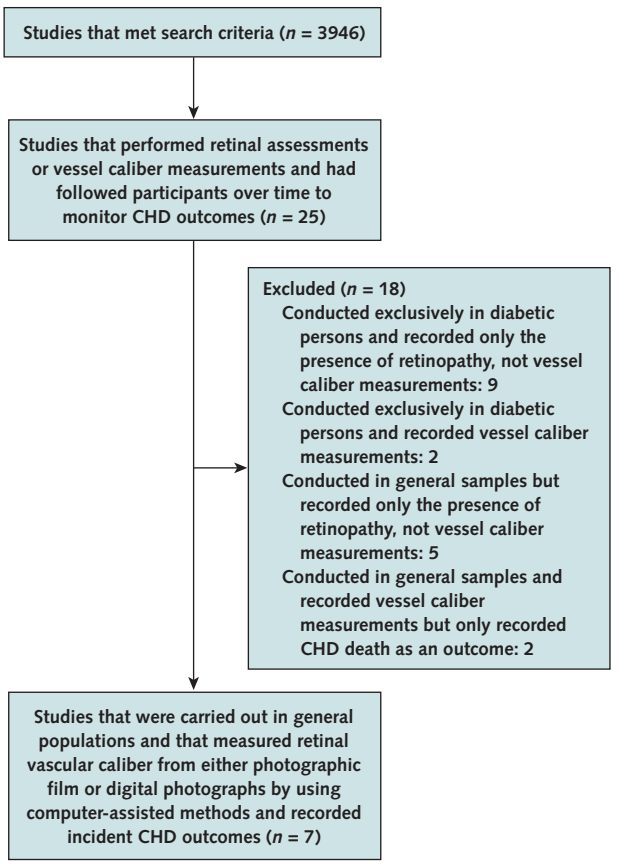
RESULTS

Characteristics of the Studies Identified

We found 3946 studies with our initial search strategy. We then identified 25 studies that had performed retinal assessments or vessel caliber measurements and had followed participants over time to monitor CHD events. Of these, 18 studies (18–35) recorded only the presence of retinopathy and not retinal vessel caliber, were conducted exclusively in persons with diabetes, or recorded only fatal events (**Figure 1**). This left 7 studies that met our inclusion criteria. One study, MESA (Multi-Ethnic Study of Atherosclerosis) (36), had insufficient outcome data available at the time of the analysis. Investigators from the other 6 studies (ARIC, CHS, AusDiab [Australian Diabetes, Obesity and Lifestyle] study, BMES [Blue Mountains Eye Study], BDES [Beaver Dam Eye Study], and RS [Rotterdam Study]) agreed to provide data for the individual-participant meta-analysis.

Table 1 shows the characteristics for 22 159 participants from each of the 6 studies we included. The measurement of retinal vessel caliber was similar in each study with some slight variations (7, 37–41). Briefly, participants in each study had retinal photographs (film or digital)

Figure 1. **Literature search and selection.**



CHD = coronary heart disease.

taken for either a single eye or both eyes, centered on the optic disc and macula. The BDES and BMES both used the Zeiss FF3 camera (Carl Zeiss Meditec, Jena, Germany) and 30° fields (10), ARIC and CHS used the Canon CR6-45NM (Canon, Tokyo, Japan) with 45° fields (37, 41), AusDiab used the Canon CR45UAF (Canon) with 45° fields (38), and RS used the Topcon TRC-SS2 (Topcon, Tokyo, Japan) with 20° fields (11). Trained graders, who were masked to participant characteristics, then viewed the optic disc photographs. The graders measured the diameters of all arterioles and venules that coursed through a zone that surrounded the optic disc, one-half to one-whole disc diameter away from the optic disc margin, by using a computer-assisted software program specifically developed for this purpose (37). The measurement module was custom programmed in Khoros (public domain image-processing software from the University of New Mexico–Albuquerque, Albuquerque, New Mexico) and used the green channel of the digital image to enhance contrast of the retinal vessels against the retinal pigment epithelium.

The ARIC, BDES, and BMES used an earlier version of this software to measure the retinal vessel caliber, whereas AusDiab, CHS, and RS used a later version of the same software. Both versions are available on request from the reviewers or the Wisconsin Fundus Photograph Reading Center, University of Wisconsin–Madison, Madison, Wisconsin. For this meta-analysis, we summarized the individual mean retinal vessel calibers from each study by using the Parr–Hubbard formula (37). Reproducibility statistics were high for these measurements, on the basis of repeated readings of the same retinal photograph, with intra- and intergrader reliability correlation coefficients of 0.73 and 0.72, respectively, for arteriolar caliber measurements and 0.86 and 0.76, respectively, for venular caliber measurements (37, 42).

We identified fatal events in all studies by searches of death registers, supplemented by contact with relatives or local medical providers (43–47). For nonfatal CHD outcomes, AusDiab, BDES, and BMES identified nonfatal CHD events only among patients who returned for subsequent visits (47, 48), who were asked whether they had had a CHD event. Investigators for BMES and AusDiab (but not BDES) verified this by using the patients' medical records (47, 48). The remaining 3 studies (ARIC, CHS, and RS) identified nonfatal events by using a process of continuous monitoring that included regular telephone interviews and contacts with general practitioners and local hospitals (43–45).

Participants in all studies completed baseline questionnaires on medical history, and traditional CHD risk factors were measured. Participants in ARIC, CHS, and RS received a more extensive clinical examination than did participants in the other studies (43–45). All studies used standard methods to measure the traditional CHD risk factors of systolic blood pressure, smoking status, and serum total cholesterol and HDL cholesterol levels. The BMES recorded systolic blood pressure taken from 1 measurement at the baseline visit, whereas all other studies used the average of at least 2 measurements taken at the baseline visit (49). The RS and BDES measured nonfasting cholesterol and HDL cholesterol levels, whereas all other studies measured fasting values (7, 10). In the CHS, cholesterol and HDL cholesterol levels and presence of diabetes were not recorded at the same visit as the retinal caliber measurements. Presence of diabetes was measured 2 years before the retinal caliber measurements and cholesterol, and HDL cholesterol levels were measured 5 years before this visit. We found no other differences among the trials.

Assessment of Heterogeneity of Hazard Ratios Among Studies

The proportional hazards assumption held for all variables in each study. We found no evidence of a nonlinear relationship between any covariate and the log–hazard function in any of the studies. **Table 2** shows the hazard ratios by quintile of retinal vessel caliber for women and men. Among women, the hazard ratio increased as the arteriolar caliber decreased and as the venular caliber increased. No trend was evident among men.

Table 1. **Participant Characteristics***

Characteristic	ARIC (8)	AusDiab (38)	BDES (39)	BMES (40)	CHS (9)	RS (7)
Women						
Participants, *n*	5699	813	1889	1135	844	2718
CHD events, *n*	303	23	220†	33	129	245
Median follow-up, *y*	9.2	5.0	14.5	4.9	8.3	12.1
Mean arteriolar caliber (SD), *μm*‡	163 (17)	179 (24)	201 (21)	195 (20)	166 (20)	183 (18)
Mean venular caliber (SD), *μm*‡	192 (17)	208 (23)	227 (20)	225 (20)	189 (18)	219 (18)
Mean age (SD), *y*	59 (6)	57 (13)	60 (11)	64 (9)	78 (4)	68 (8)
Mean systolic blood pressure (SD), *mm Hg*	123 (19)	134 (20)	130 (21)	147 (21)	132 (20)	139 (23)
Mean serum total cholesterol level (SD)						
mmol/L	5.5 (1.0)	5.8 (1.0)	6.2 (1.2)	6.2 (1.0)	5.5 (1.0)	6.9 (1.2)
mg/dL	212.4 (38.6)	223.9 (38.6)	239.4 (46.3)	239.4 (38.6)	212.4 (38.6)	266.4 (46.3)
Mean body mass index (SD), kg/m^2	29 (6)	29 (6)	28 (6)	26 (5)	27 (5)	27 (4)
Diabetes, *n (%)*	719 (13)	216 (27)	152 (8)	57 (5)	99 (12)	244 (9)
Receiving blood pressure–lowering medication, *n (%)*	1737 (30)	210 (26)	636 (34)	362 (32)	456 (54)	803 (30)
Current smoker, *n (%)*	954 (17)	73 (9)	351 (19)	115 (10)	48 (6)	533 (20)
Men						
Participants, *n*	4153	600	1373	765	479	1691
CHD events, *n*	565	29	225†	60	116	271
Median follow-up, *y*	9.1	5.0	14.4	4.9	8.0	11.8
Mean arteriolar caliber (SD), *μm*‡	161 (17)	172 (24)	202 (20)	191 (21)	164 (19)	181 (18)
Mean venular caliber (SD), *μm*‡	194 (17)	205 (22)	231 (20)	225 (20)	190 (18)	220 (18)
Mean age (SD), *y*	60 (6)	58 (13)	59 (10)	64 (9.0)	79 (4)	67 (8)
Mean systolic blood pressure (SD), *mm Hg*	124 (17)	140 (19)	132 (18)	144 (20)	129 (18)	138 (22)
Mean serum total cholesterol level (SD)						
mmol/L	5.2 (0.9)	5.6 (1.0)	5.9 (1.0)	5.8 (1.0)	4.9 (0.9)	6.3 (1.1)
mg/dL	200.8 (34.7)	216.2 (38.6)	227.8 (38.6)	223.9 (38.6)	189.2 (34.8)	243.2 (42.5)
Mean body mass index (SD), kg/m^2	28 (4)	28 (5)	29 (5)	26 (4)	27 (4)	26 (3)
Diabetes, *n (%)*	607 (15)	210 (35)	114 (8)	61 (8)	74 (16)	134 (8)
Receiving blood pressure–lowering medication, *n (%)*	1103 (27)	152 (25)	386 (28)	184 (24)	234 (49)	350 (21)
Current smoker, *n (%)*	777 (19)	88 (15)	310 (23)	108 (14)	34 (7)	503 (30)

ARIC = Atherosclerosis Risk in Communities; AusDiab = Australian Diabetes, Obesity and Lifestyle; BDES = Beaver Dam Eye Study; BMES = Blue Mountains Eye Study; CHD = coronary heart disease; CHS = Cardiovascular Health Study; RS = Rotterdam Study.
* Excluding participants with diabetes or previous CHD.
† Does not include coronary artery bypass graft or coronary angioplasty because dates for these events are not available from the BDES.
‡ Calculated by using the Parr–Hubbard formula.

Table 3 provides the hazard ratios for CHD event outcomes for each study adjusted for the CHD risk factors of age, systolic blood pressure, diastolic blood pressure, serum cholesterol level, serum HDL cholesterol level, presence of diabetes, smoking status, current use of antihypertensive medication, and body mass index. Among women, both wider venules and narrower arterioles were associated with an increased risk for CHD events in ARIC and CHS. The hazard ratios for retinal vessel caliber measures were not significant for men in any of the studies.

We found no evidence that the associations of retinal vessel caliber with CHD were heterogeneous among studies and among either men or women; we also found no evidence that the effect of any of the Framingham variables varied among studies for men or women, except for age and serum cholesterol and HDL cholesterol levels among women. When we included interactions between study site and these variables in the model, the estimated hazard ratio for the retinal vessel calibers did not change.

Pooled Hazard Ratios for CHD

Among women, both wider venules (pooled hazard ratio, 1.16 [95% CI, 1.06 to 1.26]) and narrower arterioles (pooled hazard ratio, 1.17 [CI, 1.07 to 1.28]) indicated an association between retinal vessel caliber changes and increased risk for CHD (**Table 3**). We found no evidence that retinal vessel caliber was associated with CHD events in men (hazard ratio for venules, 1.02 [CI, 0.94 to 1.10]; hazard ratio for arterioles, 1.02 [CI, 0.95 to 1.10]). **Figure 2** summarizes the study-specific and pooled hazard ratios. Evidence indicates that the hazard ratios for venular and arteriolar caliber differed between women and men ($P = 0.03$ and 0.02, respectively).

Table 4 shows the associations after adjustment for different baseline covariates. Women showed a moderate decrease in the hazard ratio for venular caliber but not arteriolar caliber when we included the traditional CHD risk factors of cholesterol and HDL cholesterol level, smoking status, and diabetes. When we then included systolic blood pressure, the hazard ratio for arteriolar caliber declined more than that for venular caliber. We observed a similar effect among men, although the hazard ratios were smaller.

Table 5 shows the pooled hazard ratios for subgroups of men and women, stratified by age, presence of diabetes, and presence of hypertension. We observed the highest

Table 2. **Pooled Hazard Ratios for Coronary Heart Disease, by Quintile of Retinal Vessel Caliber***

Vessel Caliber	Hazard Ratio (95% CI)
Women	
Venular caliber	
<190 μm	1
190 μm to 199 μm	1.06 (0.85–1.33)
200 μm to 209 μm	1.17 (0.92–1.48)
210 μm to 220 μm	1.21 (0.94–1.57)
≥220 μm	1.50 (1.16–1.94)
Arteriolar caliber	
<160 μm	1.62 (1.25–2.10)
160 μm to 169 μm	1.31 (1.02–1.68)
170 μm to 179 μm	1.21 (0.96–1.53)
180 μm to 189 μm	1.17 (0.94–1.45)
≥190 μm	1
Men	
Venular caliber	
<190 μm	1
190 μm to 199 μm	0.89 (0.74–1.08)
200 μm to 209 μm	0.98 (0.80–1.18)
210 μm to 220 μm	0.98 (0.79–1.22)
≥220 μm	0.96 (0.76–1.21)
Arteriolar caliber	
<160 μm	1.07 (0.85–1.35)
160 μm to 169 μm	0.92 (0.73–1.15)
170 μm to 179 μm	1.05 (0.86–1.30)
180 μm to 189 μm	1.08 (0.88–1.32)
≥190 μm	1

* Hazard ratios are adjusted for age, systolic blood pressure, diastolic blood pressure, presence of diabetes, body mass index, serum cholesterol level, serum high-density lipoprotein cholesterol level, current smoking status, current use of antihypertensive medication, and the other retinal vessel caliber.

hazard ratios among women without hypertension or diabetes.

Additional Analyses

We obtained similar findings when we analyzed the data by standard deviation change in retinal vessel caliber and when we combined the study-specific hazard ratios by using a random-effects model. Excluding the CHS, which did not record some risk factors at the same visit as the retinal vessel caliber, also did not affect our overall results.

Discussion

In this individual-participant meta-analysis of 22 159 participants from 6 population-based studies, we show that variations in retinal vessel caliber (both wider venules and narrower arterioles) were associated with an increased risk for incident CHD in women but not in men. We found no heterogeneity across study results. The risk associated with changes in retinal vessel caliber was higher among women without diabetes or hypertension.

Our findings have several clinical implications. First, we confirm the sex difference in the association of retinal vessel caliber with CHD. This finding provides strong support for our hypothesis that microvascular dysfunction is a greater contributor to CHD pathogenesis in women than in men (50–52), and could explain sex differences in CHD presentation (women with no obstructions on a coronary angiogram have more chest pain) and outcome with revascularization (which is worse in women) (53–56). Women have smaller coronary arteries with more diffuse atherosclerosis than men, as well as more impaired arteriolar vasodilator responses (52). Arteriolar narrowing in response to aging, elevated blood pressure, and endothelial dysfunction may further compromise myocardial perfusion and lead to increased CHD risk in women (6, 51, 56). The pathophysiologic implication that wider retinal venules are associated with an increased CHD risk only in women is less clear but is consistent with the reported associations of this retinal vessel change with inflammatory markers, endothelial dysfunction, and increased aortic and large arterial wall stiff-

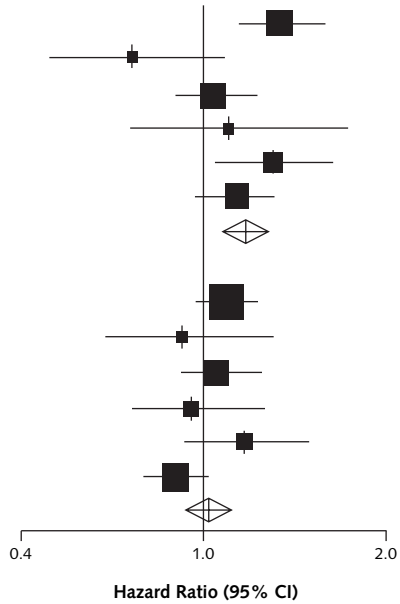
Table 3. **Adjusted Hazard Ratios for CHD, by Retinal Vessel Caliber Variables***

Variable	ARIC (8)	AusDiab (38)	BDES (39)	BMES (40)	CHS (9)	RS (7)	Pooled	*P* Value†
Women								
Participants, *n*‡	5699	813	1889	1135	844	2718	13 098	
CHD events, *n*	303	23	220	33	129	245	953	
Arteriolar caliber§	1.34 (1.14–1.59)	0.70 (0.46–1.09)	1.04 (0.87–1.23)	1.10 (0.69–1.74)	1.31 (1.04–1.65)	1.14 (0.95–1.36)	1.17 (1.07–1.28)	0.38
Venular caliber‖	1.22 (1.04–1.43)	0.79 (0.51–1.22)	1.09 (0.92–1.29)	1.19 (0.80–1.77)	1.32 (1.03–1.70)	1.11 (0.93–1.31)	1.16 (1.06–1.26)	0.92
Men								
Participants, *n*‡	4153	600	1373	765	479	1691	9061	
CHD events, *n*	565	29	225	60	116	271	1266	
Arteriolar caliber§	1.09 (0.96–1.23)	0.90 (0.61–1.31)	1.05 (0.89–1.25)	0.94 (0.70–1.27)	1.17 (0.91–1.51)	0.87 (0.74–1.02)	1.02 (0.94–1.10)	0.31
Venular caliber‖	1.01 (0.89–1.14)	0.71 (0.47–1.08)	1.12 (0.94–1.33)	0.78 (0.58–1.06)	1.24 (0.94–1.62)	0.99 (0.84–1.16)	1.02 (0.95–1.10)	0.17

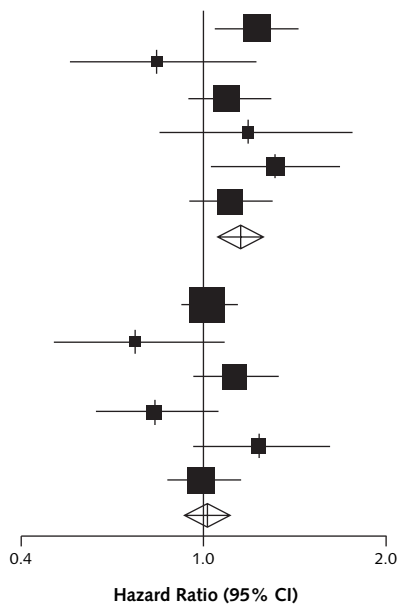
ARIC = Atherosclerosis Risk in Communities; AusDiab = Australian Diabetes, Obesity and Lifestyle; BDES = Beaver Dam Eye Study; BMES = Blue Mountains Eye Study; CHD = coronary heart disease; CHS = Cardiovascular Health Study; RS = Rotterdam Study.
* Hazard ratios are adjusted for age, systolic blood pressure, diastolic blood pressure, presence of diabetes, body mass index, serum cholesterol level, serum high-density lipoprotein cholesterol level, current smoking status, current use of antihypertensive medication, and the other retinal vessel caliber.
† For test of heterogeneity of study-specific hazard ratios.
‡ Excluding people with previous CHD.
§ Per 20-μm decrease in arteriolar caliber.
‖ Per 20-μm increase in venular caliber.

Figure 2. **Forest plots of the adjusted hazard ratios for coronary heart disease events.**

Study (Reference)	Events, *n/n*	Hazard Ratio (95% CI)
Women		
ARIC (8)	303/5699	1.34 (1.14–1.59)
AusDiab (38)	23/813	0.70 (0.46–1.09)
BDES (39)	220/1889	1.04 (0.87–1.23)
BMES (40)	33/1135	1.10 (0.69–1.74)
CHS (9)	129/844	1.31 (1.04–1.65)
RS (7)	245/2718	1.14 (0.95–1.36)
Pooled estimate	953/13 098	1.17 (1.07–1.28)
Men		
ARIC (8)	565/4153	1.09 (0.96–1.23)
AusDiab (38)	29/600	0.90 (0.61–1.31)
BDES (39)	225/1373	1.05 (0.89–1.25)
BMES (40)	60/765	0.94 (0.70–1.27)
CHS (9)	116/479	1.17 (0.91–1.51)
RS (7)	271/1691	0.87 (0.74–1.02)
Pooled estimate	1266/9061	1.02 (0.94–1.10)



Study (Reference)	Events, *n/n*	Hazard Ratio (95% CI)
Women		
ARIC (8)	303/5699	1.22 (1.04–1.43)
AusDiab (38)	23/813	0.79 (0.51–1.22)
BDES (39)	220/1889	1.09 (0.92–1.29)
BMES (40)	33/1135	1.19 (0.80–1.77)
CHS (9)	129/844	1.32 (1.03–1.70)
RS (7)	245/2718	1.11 (0.93–1.31)
Pooled estimate	953/13 098	1.16 (1.06–1.26)
Men		
ARIC (8)	565/4153	1.01 (0.89–1.14)
AusDiab (38)	29/600	0.71 (0.47–1.08)
BDES (39)	225/1373	1.12 (0.94–1.33)
BMES (40)	60/765	0.78 (0.58–1.06)
CHS (9)	116/479	1.24 (0.94–1.62)
RS (7)	271/1691	0.99 (0.84–1.16)
Pooled estimate	1266/9061	1.02 (0.95–1.10)



ARIC = Atherosclerosis Risk in Communities; AusDiab = Australian Diabetes, Obesity and Lifestyle; BDES = Beaver Dam Eye Study; BMES = Blue Mountains Eye Study; CHS = Cardiovascular Health Study; RS = Rotterdam Study.
Plots are adjusted for age, systolic blood pressure, diastolic blood pressure, presence of diabetes, body mass index, serum cholesterol level, serum high-density lipoprotein cholesterol level, current smoking status, current use of antihypertensive medication, and the other retinal vessel caliber. **Top.** Ratios per 20-μm decrease in retinal arteriolar caliber. **Bottom.** Ratios per 20-μm increase in retinal venular caliber.

ness (5, 33, 57, 58). Our findings suggest that an assessment of the pathophysiology of venular dilatation could provide new insights into microvascular CHD pathology.

Second, our findings provide suggestive evidence for the need to evaluate the microvasculature, particularly in women for whom coronary angiography reveals no visible

Table 4. **Pooled Hazard Ratios for Coronary Heart Disease, by Sex and Retinal Vessel Caliber Variables***

Adjusted Variable	Hazard Ratio (95% CI)	
	Arteriolar Caliber†	Venular Caliber‡
Women		
Age	1.18 (1.09–1.29)	1.26 (1.16–1.37)
Plus cholesterol and HDL cholesterol level, smoking status, and diabetes	1.20 (1.10–1.31)	1.17 (1.07–1.27)
Plus body mass index	1.20 (1.10–1.30)	1.16 (1.06–1.26)
Plus systolic blood pressure	1.15 (1.05–1.25)	1.14 (1.05–1.24)
Plus diastolic blood pressure and blood pressure medications	1.17 (1.07–1.28)	1.16 (1.06–1.26)
Plus leukocyte count§	1.20 (1.09–1.31)	1.17 (1.08–1.28)
Men		
Age	1.06 (0.98–1.14)	1.12 (1.04–1.20)
Plus cholesterol and HDL cholesterol level, smoking status, and diabetes	1.06 (0.98–1.14)	1.03 (0.96–1.11)
Plus body mass index	1.05 (0.98–1.13)	1.03 (0.95–1.11)
Plus systolic blood pressure	1.00 (0.94–1.09)	1.02 (0.94–1.10)
Plus diastolic blood pressure and blood pressure medications	1.02 (0.94–1.10)	1.02 (0.95–1.10)
Plus leukocyte count§	1.02 (0.95–1.11)	1.04 (0.96–1.12)

HDL = high-density lipoprotein.
* Stratified by study.
† Per 20-μm decrease in arteriolar caliber.
‡ Per 20-μm increase in venular caliber.
§ We did not include data from the Australian Diabetes, Obesity and Lifestyle study because the investigators did not measure leukocyte count.

obstructions (51, 56). Retinal arteriolar narrowing can be reversed with antihypertensive therapy (59) and is potentially a visible secondary end point of end-organ damage in trials of antihypertensive agents. The retinal component of the ADVANCE (Action in Diabetes and Vascular Disease) trial (33) is investigating whether this translates into a meaningful CHD risk reduction.

The differences between the first and last quintile of retinal arteriolar and venular caliber independently convey a 50% to 62% higher risk for incident CHD in women, respectively. However, whether physicians can reliably estimate such differences in retinal vessel caliber by using fundoscopy in clinical examinations is unclear. Van den Born and colleagues (60), in their meta-analysis, found no studies that assessed the reliability of direct fundoscopy in detecting microvascular changes and found that only hemorrhages and exudates could be reliably assessed from retinal photographs. The software program that the studies in our paper used to measure retinal vessels shows similar levels of reliability (37, 42, 61–63). The value that quantitatively evaluating retinal vessel caliber from retinal photographs adds to CHD risk prediction in women has not been determined, and we cannot yet recommend it for clinical practice.

We observed a moderate decrease in the pooled hazard ratio for venular caliber (but not arteriolar caliber) when we included the traditional CHD risk factors of cholesterol, HDL cholesterol, smoking status, and diabetes, which is consistent with data that indicate venular caliber is influenced by dyslipidemia, inflammation, and hyperglycemia (2, 5, 7). The greater decline in the hazard ratio for arteriolar caliber than that for venular caliber when we included systolic blood pressure is also consistent with reports that narrower arteriolar caliber is associated with elevated blood pressure and may also play a role in maintaining peripheral resistance and blood pressure (2, 5, 7).

The strengths of our meta-analysis include access to the individual-participant data records from all population studies to date that met our entry criteria, which resulted in a large sample of 22 159 individuals and 2219 CHD events, and standardized methods of retinal vessel caliber analysis and covariate adjustment. Because the use of retinal photography to measure retinal vessel caliber is a rela-

Table 5. **Pooled Hazard Ratios for CHD, by Retinal Vessel Caliber Variables, for Participants Categorized by Age and Presence of Hypertension or Diabetes***

Variable	Persons at Risk, *n*†	CHD Events, *n*	Hazard Ratio (95% CI)	
			Arteriolar Caliber‡	Venular Caliber§
Women				
Hypertension				
Yes	6445	654	1.10 (1.00–1.23)	1.10 (0.99–1.22)
No	6653	299	1.31 (1.12–1.54)	1.28 (1.10–1.50)
Age				
<60 y	5396	191	1.16 (0.95–1.43)	1.26 (1.04–1.53)
60–69 y	4783	335	1.22 (1.05–1.42)	1.18 (1.02–1.37)
≥70 y	2919	427	1.10 (0.97–1.25)	1.09 (0.96–1.23)
Diabetes				
Yes	1487	207	1.00 (0.83–1.20)	1.04 (0.87–1.25)
No	11 611	746	1.22 (1.11–1.35)	1.18 (1.08–1.30)
Hypertension or diabetes				
Yes	6884	694	1.09 (0.99–1.21)	1.09 (0.99–1.21)
No	6214	259	1.34 (1.13–1.59)	1.33 (1.12–1.57)
Men				
Hypertension				
Yes	4164	724	1.06 (0.96–1.17)	1.03 (0.93–1.13)
No	4897	542	0.94 (0.84–1.06)	0.98 (0.87–1.11)
Age				
<60 y	3796	372	1.13 (0.98–1.32)	1.11 (0.96–1.28)
60–69 y	3559	557	0.99 (0.88–1.11)	0.98 (0.88–1.10)
≥70 y	1706	337	0.94 (0.82–1.08)	0.98 (0.85–1.14)
Diabetes				
Yes	1200	257	1.05 (0.89–1.24)	0.91 (0.77–1.08)
No	7861	1009	1.01 (0.93–1.10)	1.05 (0.96–1.14)
Hypertension or diabetes				
Yes	4647	825	1.04 (0.95–1.15)	1.01 (0.92–1.10)
No	4414	441	0.95 (0.83–1.08)	1.04 (0.90–1.19)

CHD = coronary heart disease.
* Hazard ratios are adjusted for age, systolic blood pressure, diastolic blood pressure, presence of diabetes, body mass index, serum cholesterol level, serum high-density lipoprotein cholesterol level, current smoking status, current use of antihypertensive medication, and the other retinal vessel caliber.
† Excluding persons with previous CHD.
‡ Per 20-μm decrease in arteriolar caliber.
§ Per 20-μm increase in venular caliber.

tively new technique, we have been able to collaborate with all of the researchers worldwide who have reported using this technology in cohort studies that have recorded CHD events. We have also included data from studies that have yet to publish results on the relationship between retinal vessel caliber and incident CHD. Therefore, we feel that publication bias is highly unlikely.

Our study has limitations. Two of the studies measured nonfasting rather than fasting cholesterol and HDL cholesterol levels. However, normal food intake has a small effect on lipid levels (64) and is unlikely to affect the estimates of the association between retinal caliber and CHD risk. We did not take into account error in the measurement of retinal vessel caliber and Framingham variables, which may have led us to over- or underestimate the true association between retinal vessel caliber and CHD (65). These errors may differ among the studies because of the different photographic procedures and software used. We used the Parr–Hubbard formula to summarize retinal vessel caliber because all 6 studies provided these data (37); a revised formula is available but it is not believed to affect the estimated relationship between retinal vessel caliber and CHD outcomes (66). In 3 of the studies, nonfatal events were recorded only for those who returned for a subsequent visit. The hazard ratios for these 3 studies were lower than those for the 3 studies that used a process of continual monitoring, which may mean we have underestimated the true hazard ratio. We could not include data from MESA; however, this study had fewer events than the smallest included study (the AusDiab study) and inclusion would therefore have had little effect on the results (67).

In summary, our meta-analysis of the individual-patient data records of 22 159 middle-age and older persons confirmed that retinal vascular caliber changes (both wider retinal venules and narrower retinal arterioles) were independently associated with increased risk for CHD events in women but not in men. These findings further emphasize the role, contribution, and importance of the microvasculature in the pathogenesis of CHD in women.

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Note: A full list of principal CHS investigators and institutions can be found at www.chs-nhlbi.org/pi.htm.

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