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Retinal Vessel Caliber and Risk for Coronary Heart Disease: A Systematic Review and Meta-Analysis

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Abstract

Background—Retinal vessel caliber may be a novel risk marker of coronary heart disease (CHD) risk. However, the gender 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 of CHD.

Data sources—Relevant studies were identified through MEDLINE (1950 to June 2009) and EMBASE (1950 to June 2009) databases.

Study Selection—Studies were included if derived from a general population, retinal vessel caliber was measured from retinal photographs and incident CHD events were documented.

Data Extraction—Six population-based prospective cohort studies were identified and provided data for individual participant meta-analysis.

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Data Synthesis—Proportional hazards models were constructed for retinal vessel caliber and incident CHD in women and men, while adjusting for traditional CHD risk factors. 2,219 (10.0%) incident CHD events were recorded from 22,159 individuals (mean age 62 years) free of CHD followed for 5–14 years. Retinal vessel caliber changes (wider retinal venules and narrower arterioles) were each associated with an increased risk of CHD in women but not men, with pooled multivariable-adjusted hazard ratios of 1.16 (95% confidence interval, CI, 1.06 to 1.26) per 20μm increase in venular caliber, and 1.17 (95% CI, 1.07 to 1.28) per 20μm decrease in arteriolar caliber in women, and 1.02 (95% CI, 0.94 to 1.10) per 20μm increase in venular caliber and 1.02 (95% CI, 0.95, 1.10) per 20μm decrease in arteriolar caliber in men. Higher hazard ratios were found amongst women without hypertension or diabetes.

Limitations—Error in the measurement of retinal vessel caliber and Framingham variables was not taken into account, and may over or underestimate the true association between retinal vessel caliber and CHD.

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

INTRODUCTION

Coronary heart disease (CHD) remains the leading cause of mortality 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 in women,(1) and there is considerable interest in noninvasive methods of assessing the coronary microcirculation.(2) The coronary vessels and retinal vessels undergo similar changes in hypertension (e.g. sclerosis)(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 of CHD in prospective epidemiological studies,(6–10) raising the possibility of retinal vessel assessment as a novel risk marker. However, the results reported thus far have not been consistent. The Atherosclerosis Risk in Communities (ARIC) study, the first large epidemiological study to report associations of retinal vessel caliber with incident CHD, suggested that these associations were only present in middle-aged women.(6) Subsequent studies have produced conflicting results. The Cardiovascular Health Study (CHS) reported associations of narrower retinal arterioles and wider venules with incident CHD in both older women and men,(9) but other studies found associations mainly in younger women and men, with weak or no association in older people.(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,(10) but not other studies,(9,11) while analytic methods and adjustment for traditional cardiovascular risk factors varied considerably between 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 to determine the associations of retinal vessel caliber and CHD risk, while adjusting for traditional risk factors. We particularly examined if there were differences in associations between women and men.

METHODS

Data extraction

We reviewed the literature to identify all studies conducted in general populations that measured retinal vessel caliber and documented CHD events. A MEDLINE and EMBASE search was conducted of all studies published between 1950 and 4th June 2009. The MEDLINE search terms used were (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 the inclusion criteria: that they were carried out in general populations, had measured retinal vessel caliber from either photographic film or digital photographs using computer assisted methods and had recorded incident CHD events.

We contacted the principal or lead investigators of the chosen studies and obtained individual participant data from each of the studies to allow investigation of heterogeneity in published results, and, if appropriate, to calculate pooled estimates of the associations between retinal vessel caliber and CHD risk. Study investigators who agreed to participate in this collaborative project were then requested to provide original recorded data on the following variables – individual retinal vessel caliber measurements, fatal and non-fatal 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, high density lipoprotein, current smoking status, use of blood pressure lowering medications, presence of diabetes) plus body mass index, diastolic blood pressure, white blood cell count and previous CHD.

Statistical analysis

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

The standard deviation for the means of arteriolar and venular caliber was approximately 20 μm. We estimated the hazard ratio associated with per 20μm decrease in arteriolar caliber and per 20μm increase in venular caliber, each adjusted for the other retinal vessel caliber, and adjusted for the variables that comprise the Framingham Risk Score and other risk factors associated with CHD and retinal caliber.(13,14) These were estimated separately for each study using a proportional hazards model. Data were then combined for all studies and a stratified proportional hazard model was used to test for interaction between the study stratification variable and retinal vessel caliber variables, as well as with gender 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 between the studies but assumes that the effect of the retinal vessel caliber and the other variables are fixed.

Non-fatal CHD events were defined as myocardial infarction, coronary artery bypass graft or coronary angioplasty. Fatal events coded using ICD-10 were classified as CHD deaths if the main or underlying cause of death was coded ICD-10 I21 to I25.

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

In order to examine the robustness of these results, we repeated the main analysis by standardizing the retinal vessel caliber measurements by dividing them by the study specific standard deviations to allow for different mean and standard deviation of the retinal vessel caliber measurements in the different studies.(16) Also, we pooled the study specific hazard ratios using a random effects model.(17)

RESULTS

Characteristics of the studies identified

Our initial search strategy found 3946 papers. Twenty-five studies were then identified that had performed retinal assessments or vessel caliber measurements and had followed participants over time to monitor CHD events. Eighteen of these studies recorded only the presence of retinopathy and not retinal vessel caliber, or were conducted exclusively in people with diabetes or recorded only fatal events (Figure 1).(18–35) This left seven studies that met our inclusion criteria. One study, the Multi-Ethnic Study of Atherosclerosis (MESA), did not have sufficient outcome data available at the time of the analysis.(36) Investigators from all six of the other studies agreed to provide data for the individual participant meta-analysis. These six studies were the ARIC, the CHS, the Australian Diabetes, Obesity and Lifestyle (AusDiab) study, the Blue Mountains Eye Study (BMES), the Beaver Dam Eye Study (BDES), and the Rotterdam Study (RS). Table 1 shows the characteristics for 21,428 participants from each of the six studies included in the analysis. The measurement of retinal vessel caliber was similar in each study with some slight variations.(7,37–41) Briefly, for participants of each study retinal photographs (film or digital) for a single, or both, eyes, centred on the optic disc and macula, were taken. The BDES and BMES both used the Zeis FF3 camera and 30° fields, (10) the ARIC and CHS used the Canon CR6-45NM with 45° fields,(37,41) AusDiab used the Canon CR45UAF with 45° fields (38) and RS the Topcon TRC-SS2 with 20° fields.(11) Optic disc photographs were then viewed by trained graders masked to participant characteristics. Graders measured the diameters of all arterioles and venules coursing through a zone surrounding the optic disc, one half to one disc diameter away from the optic disc margin, 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) and utilized the green channel of the digital image to enhance contrast of the retinal vessels against the retinal pigment epithelium. The ARIC, BDES and BMES employed an earlier version of this software to measure the retinal vessel caliber, while the AusDiab, CHS and RS used a later version of the same software. Both versions are available on request from the authors or the Wisconsin Fundus Photograph Reading Center, University of Wisconsin-Madison. The individual mean retinal vessel calibers provided by each study were summarized for the present meta-analysis using the Parr-Hubbard formula.(37) Reproducibility statistics, based on repeat readings of the same retinal photograph, for these measurements were high with intra- and inter-grader reliability correlation coefficients of 0.73 and 0.72 for arteriolar caliber measurements, 0.86 and 0.76 for venular caliber measurements respectively. (37,42)

Fatal events in all studies were identified from searches of death registers, and were supplemented with contact with relatives and/or local medical providers in all studies.(43–47) For non-fatal CHD outcomes, the AusDiab, BDES and BMES identified non-fatal CHD events only among those who returned at subsequent visits.(47,48) These participants were asked whether they had a CHD event. In BMES and AusDiab this was then verified from their

medical records, but not in BDES. (47,48) The remaining three studies – the ARIC, CHS and RS – identified non-fatal events using a process of continuous monitoring which included regular phone interviews and contacts with general practitioners and local hospitals.(43–45)

Participants in all studies completed baseline questionnaires on previous medical history and traditional CHD risk factors were measured. The ARIC, CHS and RS participants underwent a more extensive clinical examination than 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, serum total cholesterol and high density lipoprotein. The only differences between studies were that BMES recorded systolic blood pressure taken from one measurement at the baseline visit, whereas all other studies used the average of at least two measurements taken at the baseline visit.(49) Also, the RS and BDES measured non-fasting cholesterol and HDL levels, while all other studies measured fasting values.(7,10) In the CHS cholesterol, HDL 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 were measured 5 years before this visit.

Assessment of heterogeneity of hazard ratios between studies

The proportional hazards assumption held for all variables in each study. No evidence of a non-linear relationship was found in any of the studies between any covariates and the log-hazard function. Table 2 shows the hazard ratios by quintile of retinal vessel caliber for women and men. Among women as the arteriolar caliber decreased the hazard ratio increased. Also, as the venular caliber increased the hazard ratio increased. No trend was evident amongst men.

Table 3 provides 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, serum HDL, presence of diabetes, smoking status, current use of anti-hypertensive medication and body mass index. Among women, wider venules and narrower arterioles were both associated with an increased risk of CHD events in the ARIC, CHS and RS. The hazard ratios for retinal vessel caliber measures were significant for men only in the CHS.

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

Pooled hazard ratios for CHD

Among women there was evidence that retinal vessel caliber changes (both wider venules, pooled hazard ratio 1.16, 95% confidence interval [CI] 1.06, 1.26, and narrower arterioles, pooled hazard ratio 1.17, 95% CI 1.07, 1.28) were associated with an increased risk of CHD (Table 3). There was no evidence that retinal vessel caliber was associated with CHD events in men (venules hazard ratio 1.02, 95% CI 0.94, 1.10; arterioles hazard ratio 1.02, 95% CI 0.95, 1.10). Study specific and pooled hazard ratios are summarized in Figures 2A and 2B. There was evidence that the hazard ratios for venular caliber and arteriolar caliber differed between women and men (p=0.03 and 0.02, respectively).

Table 4 shows the associations after adjusting for different baseline covariates. Among women there was a moderate decrease in the hazard ratio for venular caliber but not arteriolar caliber when the traditional CHD risk factors of cholesterol, HDL, smoking status and diabetes are included. When systolic blood pressure was then included, the hazard ratio for arteriolar caliber

declined more than that for venular caliber. Among men a similar effect was observed although the hazard ratios were smaller.

Table 5 shows, separately for men and women, the pooled hazard ratios for subgroups stratified by age, presence of diabetes and presence of hypertension status. The highest hazard ratios were observed amongst women without hypertension or diabetes.

Additional analyses

Findings were similar when the data were analyzed per standard deviation change in retinal vessel caliber and also when the study specific hazard ratios were combined 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 the overall results.

DISCUSSION

In this individual participant level meta-analysis of 22,159 participants from six population-based studies, we show that variations in retinal vessel caliber (both wider retinal venules and narrower retinal arterioles) were associated with an increased risk of incident CHD in women, but not in men. There was no apparent 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 gender difference in the associations 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 men,(50–52) and could explain gender differences in CHD presentation (women with nonobstructive coronary angiograms have more chest pain) and outcome with revascularization (this is worse in women).(53–56) As compared to men, women have smaller coronary arteries with more diffuse atherosclerosis, and more impaired arteriolar vasodilator responses.(52). Arteriolar narrowing in response to ageing, elevated blood pressure and endothelial dysfunction may further compromise myocardial perfusion leading to increased CHD risk in women.(6,51,56) The pathophysiological implications that wider retinal venules are associated with an increased CHD risk only in women is less clear but is consistent with reported associations of this retinal vessel change with inflammatory markers, endothelial dysfunction and increased aortic and large arterial wall stiffness.(5,33,57,58) Our findings suggest that an assessment of the pathophysiology of venular dilation could provide new insights into microvascular CHD pathology.

Second, our findings provide suggestive evidence for the need to evaluate the microvasculature particularly in women with nonobstructive coronary angiograms.(51,56) Retinal arteriolar narrowing can be reversed with antihypertensive therapy,(59) and has potential as a visible secondary endpoint of end-organ damage in trials of antihypertensive agents. Nonetheless, whether this translates into a meaningful CHD risk reduction is unknown at present and is being investigated in the retinal component of the Action in Diabetes and Vascular Disease (ADVANCE) trial.(33)

Differences between the first and last quintile of retinal arteriolar and venular caliber independently convey 50–62% higher risk of incident CHD in women. However whether such differences in retinal vessel caliber can be reliably estimated using fundoscopy in clinical examinations is unclear. A meta-analysis found no studies that assessed the reliability of direct fundoscopy in detecting microvascular changes and that only hemorrhages and exudates could be reliably assessed from retinal photographs.(60) The measurement of retinal vessels using the computer-assisted software program utilized by the studies in our paper show similar levels

of reliability.(37,42,61–63) Whether the quantitative evaluation of retinal vessel caliber from retinal photographs adds value to CHD risk prediction in women remains to be determined and cannot yet be recommended for clinical practice.

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

The strengths of this meta-analysis include access to the individual participant data records from all population studies to date which met our entry criteria, resulting in a large sample of 21,159 individuals and 2,219 CHD events, and standardized methods of retinal vessel caliber analysis and covariate adjustment. As the measurement of the retinal vessel caliber using retinal photography is a relatively 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. We thus feel that publication bias is highly unlikely to be present in our review and meta-analysis.

A number of limitations deserve mention. Two of the studies measured non-fasting rather than fasting cholesterol and HDL-cholesterol levels. However, the effect of normal food intake on lipid levels is small(64), and hence unlikely to affect the estimates of the association between retinal caliber and CHD risk. Error in the measurement of retinal vessel caliber and Framingham variables was not taken into account, and may have led to an over or underestimate of the true association between retinal vessel caliber and CHD.(65) These errors may differ between the studies due to the different photographic procedures and software used. We summarized retinal vessel caliber using the Parr-Hubbard formula because all six studies provided these data;(37) a revised formula is available although it is not believed to affect the estimated relationship between retinal vessel caliber and CHD outcomes.(66) In three of the studies non-fatal events were only recorded among those who returned for a subsequent visit. The hazard ratios for these three studies were lower than for the three studies that used a process of continual monitoring. This may mean we have underestimated the true hazard ratio. We were not able to include data from the MESA study, however the number of events in this study is smaller than in the smallest included study, the AusDiab study and so inclusion would have little impact on the results.(67)

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

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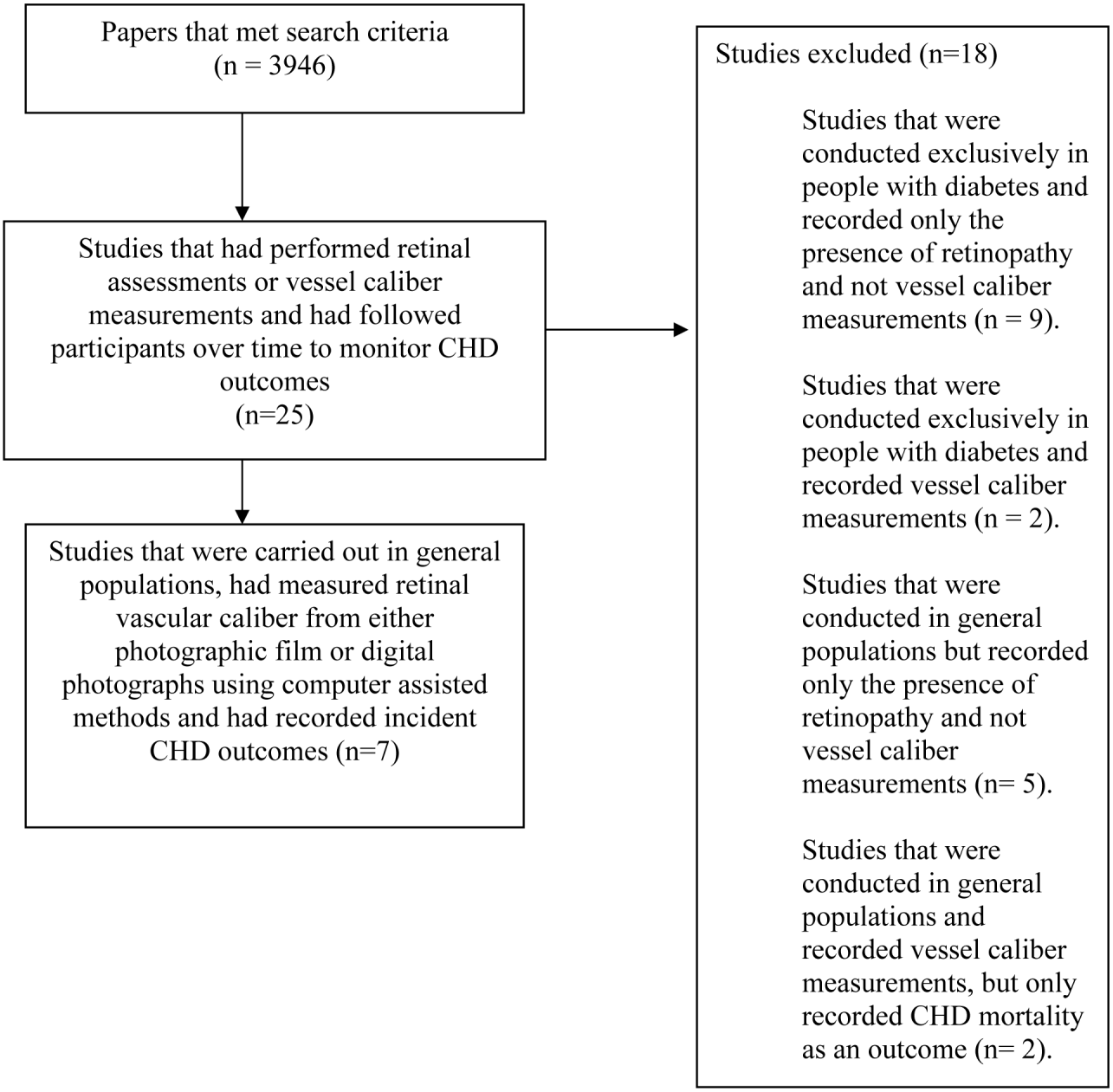
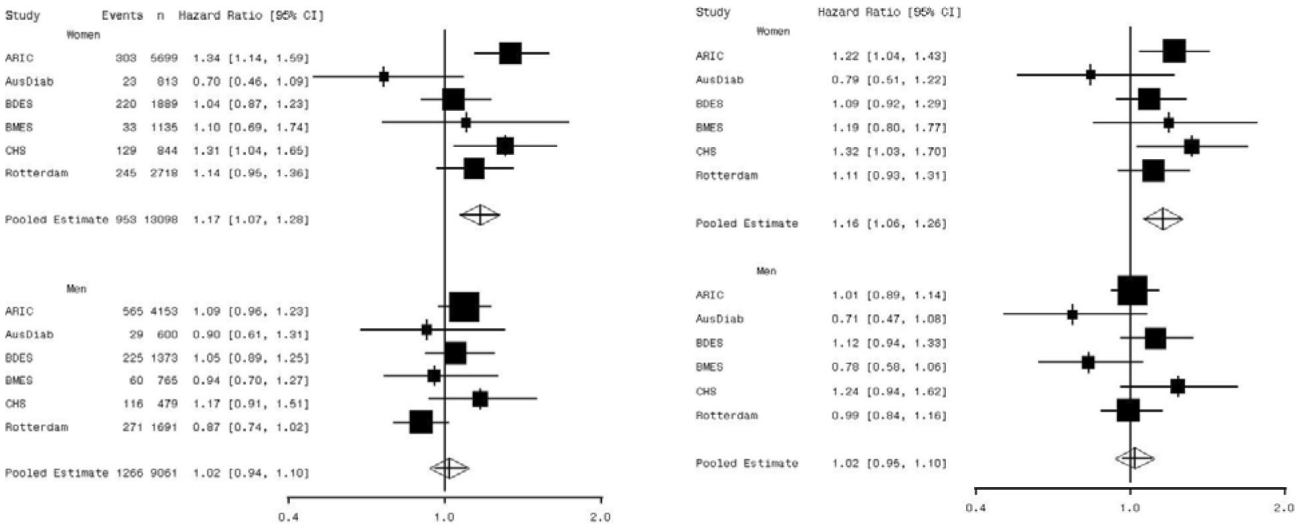


Figure 1.
Flow chart of study selection



A B

Figure 2.

Forest plots of the adjusted* hazard ratios for CHD events per 20μm decrease in retinal arteriolar caliber (A) and per 20μm increase in retinal venular caliber (B).

* adjusted for age, systolic blood pressure, use of anti-hypertensives, total cholesterol, HDL-cholesterol, current smoking status, diastolic blood pressure, presence of diabetes, body mass index and the other retinal caliber. ARIC refers to Atherosclerosis Risk in Communities study; AusDiab to the Australian Diabetes, Obesity and Lifestyle Study; BDES to the Beaver Dam Eye Study; BMES to the Blue Mountains Eye Study; CHS to the Cardiovascular Health Study.

Table 1

Characteristics of study participants included in meta-analysis[a]

					Mean (standard deviation)						Number (%)		
	Study	Participants included in meta-analysis	Number of CHD events	Median follow-up, years	Arteriolar caliber[b], μm	Venular caliber[b], μm	Age years	Systolic blood pressure, mm/ Hg	Serum Total Cholesterol, mmol/L	Body mass Index, kg/m^2	Diabetes	Taking blood pressure lowering medication	Current smoker
Women													
	ARIC[c]	5699	303	9.2	163 (17)	192 (17)	59 (6)	123 (19)	5.5 (1.0)	29 (6)	719 (13%)	1737 (30%)	954 (17%)
	AusDiab[d]	813	23	5.0	179 (24)	208 (23)	57 (13)	134 (20)	5.8 (1.0)	29 (6)	216 (27%)	210 (26%)	73 (9%)
	BDES[e]	1889	220	14.5	201 (21)	227 (20)	60 (11)	130 (21)	6.2 (1.2)	28 (6)	152 (8%)	636 (34%)	351 (19%)
	BMES[f]	1135	33	4.9	195 (20)	225 (20)	64 (8.7)	147 (21)	6.2 (1.0)	26 (5)	57 (5%)	362 (32%)	115 (10%)
	CHS[g]	844	129	8.3	166 (20)	189 (18)	78 (4)	132 (20)	5.5 (1.0)	27 (5)	99 (12%)	456 (54%)	48 (6%)
	Rotterdam	2718	245	12.1	183 (18)	219 (18)	68 (8)	139 (23)	6.9 (1.2)	27 (4)	244 (9%)	803 (30%)	533 (20%)
Men													
	ARIC	4153	565	9.1	161 (17)	194 (17)	60 (6)	124 (17)	5.2 (0.9)	28 (4)	607 (15%)	1103 (27%)	777 (19%)
	AusDiab	600	29	5.0	172 (24)	205 (22)	58 (13)	140 (19)	5.6 (1.0)	28 (5)	210 (35%)	152 (25%)	88 (15%)
	BDES	1373	225	14.4	202 (20)	231 (20)	59 (10)	132 (18)	5.9 (1.0)	29 (5)	114 (8%)	386 (28%)	310 (23%)
	BMES	765	60	4.9	191 (21)	225 (20)	64 (9.0)	144 (20)	5.8 (1.0)	26 (4)	61 (8%)	184 (24%)	108 14%)
	CHS	479	116	8.0	164 (19)	190 (18)	79 (4)	129 (18)	4.9 (0.9)	27 (4)	74 (16%)	234 (49%)	34 (7%)
	Rotterdam	1691	271	11.8	181 (18)	220 (18)	67 (8)	138 (22)	6.3 (1.1)	26 (3)	134 (8%)	350 (21%)	503 (30%)

[a] Excluding people with diabetes or previous CVD

[b] Calculated using the Parr-Hubbard formula

[c] Atherosclerosis Risk in Communities Study

[d] Australian Diabetes, Obesity and Lifestyle Study

[e] Beaver Dam Eye Study

[f] Blue Mountains Eye Study

[g] Cardiovascular Health Study

Table 2

Pooled hazard ratios[a] and 95% confidence interval for CHD according to quintile of retinal vessel caliber

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

b. Excluding people with previous CHD.

[a]The hazard ratios are adjusted for age, systolic blood pressure, diastolic blood pressure, presence of diabetes, body mass index, serum cholesterol, serum HDL, current smoking status and current use of anti-hypertensive medication. The hazard ratios are also adjusted for the other retinal vessel caliber.

Table 3

Adjusted[a] hazard ratios and 95% confidence interval for CHD, according to retinal vessel caliber variables

	Study	Participants[b] included in CHD events meta-analysis	CHD events	Arteriolar caliber[c]	Venular caliber[d]
Women					
	ARIC[e]	5699	303	1.34 (1.14, 1.59)	1.22 (1.04, 1.43)
	AusDiab[f]	813	23	0.70 (0.46, 1.09)	0.79 (0.51, 1.22)
	BDES[g]	1889	220	1.04 (0.87, 1.23)	1.09 (0.92, 1.29)
	BMES[h]	1135	33	1.10 (0.69, 1.74)	1.19 (0.80, 1.77)
	CHS[i]	844	129	1.31 (1.04, 1.65)	1.32 (1.03, 1.70)
	Rotterdam	2718	245	1.14 (0.95, 1.36)	1.11 (0.93, 1.31)
	Pooled	**13098**	**953**	**1.17 (1.07, 1.28)**	**1.16 (1.06, 1.26)**
	P-value for test of heterogeneity of study specific hazard ratios			**0.38**	**0.92**
Men					
	ARIC[e]	4153	565	1.09 (0.96, 1.23)	1.01 (0.89, 1.14)
	AusDiab[f]	600	29	0.90 (0.61, 1.31)	0.71 (0.47, 1.08)
	BDES[g]	1373	225	1.05 (0.89, 1.25)	1.12 (0.94, 1.33)
	BMES[h]	765	60	0.94 (0.70, 1.27)	0.78 (0.58, 1.06)
	CHS[i]	479	116	1.17 (0.91, 1.51)	1.24 (0.94, 1.62)
	Rotterdam	1691	271	0.87 (0.74, 1.02)	0.99 (0.84, 1.16)
	Pooled	**9061**	**1266**	**1.02 (0.94, 1.10)**	**1.02 (0.95, 1.10)**
	P-value for test of heterogeneity of study specific hazard ratios			**0.31**	**0.17**

[a] The hazard ratios are adjusted for age, systolic blood pressure, diastolic blood pressure, presence of diabetes, body mass index, serum cholesterol, serum HDL, current smoking status and current use of anti-hypertensive medication. The hazard ratios are also adjusted for the other retinal vessel caliber.

[b] Excluding people previous CHD.

[c] Per 20μm decrease in arteriolar caliber.

[d] Per 20μm increase in venular caliber.

[e] Atherosclerosis Risk in Communities Study

[f] Australian Diabetes, Obesity and Lifestyle Study

[g] Beaver Dam Eye Study

[h] Blue Mountains Eye Study

[i] Cardiovascular Health Study

Table 4

Pooled hazard ratios[a,b] and 95% confidence interval for CHD, according to retinal vessel caliber variables

	Arteriolar caliber[c]	Venular caliber[d]
Women Adjusted for		
Age	1.18 (1.09, 1.29)	1.26 (1.16, 1.37)
Age, cholesterol, HDL, smoking status, diabetes	1.22 (1.10, 1.31)	1.17 (1.07, 1.27)
Age, cholesterol, HDL, smoking status, diabetes, BMI	1.20 (1.10, 1.30)	1.16 (1.06, 1.26)
Age, cholesterol, HDL, smoking status, diabetes, BMI, SBP	1.15 (1.05, 1.25)	1.14 (1.05, 1.24)
Age, cholesterol, HDL, smoking status, diabetes, BMI, SBP, DBP, BP meds	1.17 (1.07, 1.28)	1.16 (1.06, 1.26)
Age, cholesterol, HDL, smoking status, diabetes, BMI, SBP, DBP, BP meds, WBC[e]	1.20 (1.09, 1.31)	1.17 (1.08, 1.28)
Men Adjusted for		
Age	1.06 (0.98, 1.14)	1.12 (1.04, 1.20)
Age, cholesterol, HDL, smoking status, diabetes	1.06 (0.98, 1.14)	1.03 (0.96, 1.11)
Age, cholesterol, HDL, smoking status, diabetes, BMI	1.05 (0.98, 1.13)	1.03 (0.95, 1.11)
Age, cholesterol, HDL, smoking status, diabetes, BMI, SBP	1.00 (0.94, 1.09)	1.02 (0.94, 1.10)
Age, cholesterol, HDL, smoking status, diabetes, BMI, SBP, DBP, BP meds	1.02 (0.94, 1.10)	1.02 (0.95, 1.10)
Age, cholesterol, HDL, smoking status, diabetes, BMI, SBP, DBP, BP meds, WBC[e]	1.02 (0.95, 1.11)	1.04 (0.96, 1.12)

[a] Stratified by study.

[b] Excluding people previous CHD.

[c] Per 20μm decrease in arteriolar caliber.

[d] Per 20μm increase in venular caliber.

[e] The AusDiab data were not included in these estimates as white blood cell count was not measured in the AusDiab study.

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Table 5

Pooled hazard ratios[a] and 95% confidence interval for CHD, according to retinal vessel caliber variables, for participants categorised by age, presence of hypertension and diabetes

	Number at risk[b]	CHD Events	Arteriolar caliber[c]	Venular caliber[d]
Women				
Hypertension	6445	654	1.10 (1.00, 1.23)	1.10 (0.99, 1.22)
No hypertension	6653	299	1.31 (1.12, 1.54)	1.28 (1.10, 1.50)
Age < 60	5396	191	1.16 (0.95, 1.43)	1.26 (1.04, 1.53)
60–69	4783	335	1.22 (1.05, 1.42)	1.18 (1.02, 1.37)
≥70	2919	427	1.10 (0.97, 1.25)	1.09 (0.96, 1.23)
Diabetes	1487	207	1.00 (0.83, 1.20)	1.04 (0.87, 1.25)
No Diabetes	11611	746	1.22 (1.11, 1.35)	1.18 (1.08, 1.30)
Hypertension or diabetes	6884	694	1.09 (0.99, 1.21)	1.09 (0.99, 1.21)
No hypertension or diabetes	6214	259	1.34 (1.13, 1.59)	1.33 (1.12, 1.57)
Men				
Hypertension	4164	724	1.06 (0.96, 1.17)	1.03 (0.93, 1.13)
No hypertension	4897	542	0.94 (0.84, 1.06)	0.98 (0.87, 1.11)
Age < 60	3796	372	1.13 (.098, 1.32)	1.11 (0.96, 1.28)
60–69	3559	557	0.99 (0.88, 1.11)	0.98 (0.88, 1.10)
≥70	1706	337	0.94 (0.82, 1.08)	0.98 (0.85, 1.14)
Diabetes	1200	257	1.05 (0.89, 1.24)	0.91 (0.77, 1.08)
No Diabetes	7861	1009	1.01 (0.93, 1.10)	1.05 (0.96, 1.14)
Hypertension or diabetes	4647	825	1.04 (0.95, 1.15)	1.01 (0.92, 1.10)
No hypertension or diabetes	4414	441	0.95 (0.83, 1.08)	1.04 (0.90, 1.19)

[a]The hazard ratios are adjusted for age, systolic blood pressure, diastolic blood pressure, presence of diabetes, body mass index, serum cholesterol, serum HDL, current smoking status and current use of anti-hypertensive medication. The hazard ratios are also adjusted for the other retinal vessel caliber.