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Associations of retinal microvascular caliber with intermediate phenotypes of large arterial function and structure: A systematic review and meta-analysis

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Abstract

Objective: Intermediate phenotypes of microcirculation (retinal microvascular caliber) are associated with cardiovascular (CV) risk factors and independently predict CV events. However, the effect of microcirculation variation on the vascular system is unclear. We conducted a systematic review and meta-analysis of observational studies to quantify associations of retinal microvascular caliber (arteriolar, venular caliber, arteriole-to-venule ratio) and preclinical CV measures (large arterial function and structure).

Methods: We identified studies in Medline, Embase and Pubmed (1946 to March 2018) studying (a) general population samples and (b) patients with cardiometabolic disease. Study-specific correlation estimates were combined into meta-analysis where possible.

Results: Of 1,294 studies identified, 26 met inclusion criteria (general population 16, patients 10), of which five studies were included in meta-analysis. Most studied middle-aged adults cross-sectionally, with one childhood study. Large arterial function and structure were predominantly assessed by pulse wave velocity and carotid intima-media thickness, respectively. Only arteriolar caliber was consistently associated with arterial function and structure, with stronger associations observed in cardiometabolic patients. Narrower (worse) arteriolar caliber was associated with faster (poorer) pulse wave velocity (correlation coefficient (r) -0.17, 95% CI -0.25 to -0.10) and greater (poorer) intima-media thickness (r -0.05, 95%CI -0.09 to -0.02) across all adult participants.

Conclusions: Retinal arteriolar, but not venular caliber, was modestly associated with large arterial function and weakly associated with large arterial structure, with stronger evidence in patients with cardiometabolic disease. This suggests that preclinical changes in large arteries and the microcirculation have some shared but mainly unique pathway to associate with cardiovascular disease.

Keywords

Retinal imaging; microcirculation; retinal microvascular caliber; carotid intima-media thickness; pulse wave velocity.

1. INTRODUCTION

Quantifying cardiovascular disease (CVD) risk in asymptomatic individuals largely relies on assessment of traditional risk factors but can be enhanced by non-invasive assessment of vascular phenotypes.[1-4] Vascular phenotypes include measures of large arterial stiffness, most commonly by pulse wave velocity (PWV),[5] and structural changes to the arterial wall indicative of early atherosclerosis, often by carotid intima-media thickness (CIMT).[6, 7] These phenotypes are widely used in population-based studies as they predict adverse CVD events and can be considered 'intermediate' between traditional risk factors and CVD itself. For example, a one unit increase in aortic PWV and a standard deviation unit increase in CIMT (e.g. poorer cardiovascular health) have been shown to be associated with a 14% and 37% increased risk of adverse CVD events respectively.[5, 8]

In addition to these large arterial phenotypes, the microcirculation has increasingly been recognized for its role in CVD pathogenesis.[9, 10] Technological advances now allow non-invasive assessment of the microcirculation in large studies, most commonly by quantification of the retinal microvasculature.[11] Adverse phenotypes of the retinal microcirculation (narrower retinal arteriolar and wider venular caliber) have also been associated with adverse CVD outcomes.[12, 13] For instance, the large Atherosclerosis Risk in Communities Study showed that, over a 16 years follow-up period, generally healthy subjects with narrower arteriolar caliber and wider venular caliber had a higher risk of ischemic stroke in both sexes (hazard ratio 1.10, 95% CI 1.00 to 1.20 and 1.14, 95%CI 1.03 to 1.26, respectively).[12] The arteriole-to-venule ratio (AVR) also predicted CVD events in some earlier studies.[9, 10]

Both large arterial and retinal microvascular intermediate phenotypes are individually recognized as adding value to CVD prediction, yet the extent to which the two are related is largely unknown. Physiologically, they are part of the one circulatory system, sharing elements of pulsatile transmission of pressure and flow,[14] but they capture different profiles of the vascular tree. They are both influenced by traditional CVD risk factors, such as age, hypertension, dyslipidemia and smoking,[11, 15, 16] yet the degree and rate that they impact on one another are unclear. Examining their association could help us understand whether damage to both parts of the vascular tree usually happens in unison or whether variation in each profile occurs at different rates. This knowledge could enhance our understanding of whether assessing both could improve cardiovascular risk prediction. In addition, identifying if and when in the life course they co-vary would inform prediction

1 models and the ages that could benefit most. There may be a certain point in the life course
2 where the two deteriorate in unison.

3 Several studies have examined associations of retinal microvascular caliber with large arterial
4 phenotypes such as PWV[17, 18] and CIMT,[19, 20] but this association has not been
5 comprehensively synthesized across studies or specific populations. We therefore performed
6 a systematic review and meta-analysis to quantify the associations of retinal microvascular
7 caliber with various intermediate large arterial phenotypes.

2. MATERIALS AND METHODS

2.1 Protocol registration

The systematic review conforms to the standards of quality for reporting Meta-analysis of Observational Studies in Epidemiology [21] and the PRISMA checklist.[22] The protocol was prospectively registered with the International Prospective Register of Systematic Reviews (CRD 42017064425) on 5th July 2017.[23]

2.2 Sources and electronic search strategy

We searched Medline, Embase and Pubmed databases in March 2018 for studies reporting the association of retinal microvascular caliber and intermediate phenotypes of large arterial function or structure. The search strategy was developed together with content experts and the institution librarian. MeSH terms, keywords and search limits for the following three topic areas were combined: 1) retinal microvascular caliber, 2) intermediate large arterial phenotypes, and 3) observational studies (Supplementary Table 1S). The search was limited to studies published in English or Chinese between 1946 and 7th March 2018.

2.3 Study selection

All studies identified were uploaded to the web-based systematic review software package 'Covidence' (Veritas Health Innovation, Australia).[24] Two reviewers (ML, YX) independently screened abstracts and titles to identify relevant studies. Each reviewer then independently screened full texts using the pre-defined inclusion criteria. If conflicts arose between the reviewer's decisions, a discussion took place between reviewers to resolve the conflict. However, if a consensus was not reached, then a third independent reviewer (KL) was available to make the final decision. Studies were included if they were observational designs, had retinal microvascular caliber quantified from digital retinal photographs via computer-assisted methods, and intermediate large arterial functional (e.g. PWV, arterial elasticity) or structural phenotypes (e.g. CIMT, calcium scores). Additional studies were sought by hand-searching the reference lists of relevant studies. We excluded conference abstracts and study protocols without original data.

2.4 Data extraction and quality assessment

Data were extracted independently by each reviewer from included full texts into Epidata software (version 3.1). These data included the first author, year of publication, study population, study name, sample size, age of participants, measurement methods, statistical

1 methods, correlation coefficients, main estimates and confidence intervals (CI), and estimates
2 of the association with covariates if applicable. To avoid over-adjustment by potential
3 intermediate variables and to improve comparability between studies, we preferentially
4 extracted minimally adjusted results (e.g. age and sex-adjusted).

5 Each reviewer (ML, YX) also independently assessed the methodological quality of relevant
6 studies to assess risk of bias using a modified version of the Ottawa–Newcastle scale
7 checklist.[25] Briefly, the checklist considers bias arising from three domains: 1) selection of
8 study population; 2) comparability of study groups; and 3) adequacy of outcome assessment.
9 Studies can receive a maximum of 10 stars comprising a total of five for the study group
10 selection, two for comparability between groups, and three for the outcome. The quality of
11 studies is defined as follows: high (9-10 stars), moderate (7-8 stars), low (≤ 6 stars).

12 **2.5 Data synthesis and meta-analysis**

13 Study characteristics and main findings (e.g. magnitude of association and level of statistical
14 evidence) were compiled into tables. In order to conduct a meta-analysis, we aimed to extract
15 correlation coefficients or standardized β from unadjusted or minimally adjusted regression
16 models given that these are directly comparable. When raw regression coefficients were
17 presented, we were able to calculate the standardized β . This meant that we could directly
18 compare associations across studies given that the correlation coefficient and a standardized β
19 from an unadjusted model are equal.[26] This also allowed us to include studies where retinal
20 microvascular caliber was assessed as the outcome, rather than the exposure, given that
21 standardized β avoids the issue of directionality. We then transformed correlation coefficients
22 to Fisher's z scores and pooled estimates using the random-effects model of z-transformed
23 correlations.[27] The 95% confidence intervals of the pooled weighted Fisher's z-scores were
24 calculated, after which all the values were back-transformed to the metric of the correlation
25 coefficients to facilitate interpretation.[27] Statistical heterogeneity was investigated using
26 the I square index (I^2), which measured the percentage of the variation across studies that is
27 likely due to heterogeneity and cannot be explained by chance.[28] The level of heterogeneity
28 were regarded as 'low' (0%-25%), 'moderate' (26-74%) or 'high' ($\geq 75\%$). We used the R
29 software (version 3.4.2), "meta" package to analyze data.

3. RESULTS

3.1 Study selection and characteristics

Figure 1 shows the flow diagram of the review process, according to the PRISMA guidelines.[22] We screened the abstracts and titles of 1,132 non-duplicate studies, of which 33 studies were deemed potentially eligible for full-text screening, and 25 met our inclusion criteria. One further study was identified through hand searching of reference lists. In total, we extracted data from 26 studies.

Table 1 presents the characteristics of the included studies. With the exception of one recent longitudinal study, all were cross-sectional and most were conducted in Europe (11 studies) or the USA (8 studies). Of the 26 studies, 16 were performed in the general populations, most with large sample sizes (median sample size 3715), and 10 were in cardiometabolic patient populations (e.g. hypertension, coronary heart disease, diabetes) with smaller sample sizes (median sample size 181). Only one study was conducted in children (median age six years), and most adult studies were conducted in middle-aged adults (44 to 77 years). Various intermediate large artery phenotypes of function and structure were included, most commonly PWV (9 studies) and CIMT (10 studies); others were arterial elasticity, flow-mediated vasodilatation and carotid plaque. Despite their cross-sectional nature, most studies assessed the association with retinal microvascular caliber as the exposure and arterial function or structure as the outcome.

The risk of bias is summarized in Table 1. Study quality was generally deemed as medium (14 studies) or high (10 studies), with the exception of two studies.[29, 30]

3.2 Synthesis of results

Direct comparison of studies was challenging due to the various measures used to assess large arterial intermediate phenotypes. We therefore conducted a narrative review that focused on the most commonly measured large arterial intermediate phenotypes, PWV and CIMT (Table 2), and then briefly examined all other intermediate phenotypes (Supplementary Table 3S). A meta-analysis also estimated the combined correlation coefficients for PWV and CIMT where possible (Figure 2, Table 3).

3.3 Narrative review

3.3.1 Associations of retinal microvascular caliber with functional intermediate phenotypes

Of the retinal vascular measures, retinal arteriolar caliber was most consistently associated with PWV in adults with cardiometabolic disorders. In these patients, narrower (worse) retinal arteriolar caliber was consistently and modestly correlated with higher (worse) PWV (correlation coefficient (r) range from -0.21 to -0.23, Table 2).[18, 45, 49, 50] This effect was only observed in one of three adult general population studies that compared extreme values using categorical variables.[41] In children who were six years of age, there was little evidence of an association.[17]

Associations between retinal venular caliber and PWV were inconsistent. In children, there was little evidence that venular caliber was associated with PWV ($r = 0.04$).[17] However, two of the three studies of hypertensive adult patients showed that narrower (usually considered to be better) retinal venular caliber was weakly associated with higher PWV ($r = -0.06$ to -0.22).[49, 50] Notably, this finding was in the opposite direction to that expected. Of the four studies examining AVR, two European studies provided some evidence that lower (worse) AVRs were associated with higher PWV (in general population $r = -0.18$, $p < 0.01$ and in hypertensive patients $r = -0.12$, $p = 0.08$).[40, 18]

Of the six studies that examined other large arterial function measures (e.g. arterial elasticity, arterial compliance), all were in the general population (Supplementary Table 2S). Results were largely consistent with the findings for PWV. For example, modest associations were predominantly observed between narrower retinal arteriolar caliber and worse functional intermediate phenotypes,[35, 36, 39] while evidence for associations with retinal venular caliber and AVR were weak and less consistent.[33, 39, 40]

3.3.2 Associations of retinal microvascular caliber with structural intermediate phenotypes

Six studies in the general population reported on associations between retinal arteriolar caliber and CIMT, with inconsistent results. Two studies reported a weak association between narrower arteriolar caliber and higher CIMT (standardized $\beta = -0.06$; Table 2),[32, 42] while the other four studies did not show a significant association. However, in the only study with cardiometabolic patients, this association was not replicated.[20]

Of the four studies examining retinal venular caliber and CIMT in the general population, only one study showed a weak association, with wider (worse) retinal venular caliber associated with higher (worse) CIMT (standardized $\beta = 0.14$).[34] There was weak evidence of a similar association in the only patient study of hypertensive patients ($r = 0.13$).[20] Associations between AVR and CIMT were inconsistent in both general population and cardiometabolic patients.

Four studies reported data on retinal microvascular caliber and other structural intermediate phenotypes (e.g. aortic calcification, coronary artery stenosis; Supplementary table 3S).[29, 32, 38, 48] There was limited evidence of associations between retinal microvascular caliber and coronary artery stenosis,[48] but overall the findings from these studies were inconsistent.

3.4 Meta-analysis

Figure 2, 3 and Table 3 summarize meta-analysis results of retinal microvascular caliber associations with PWV and CIMT in adults. Overall, the level of heterogeneity (I^2) among pooled studies was low to moderate (Table 3). High heterogeneity was observed among pooled studies of venular caliber with CIMT and AVR with CIMT.

3.4.1 Associations of retinal microvascular caliber with PWV

The random effects meta-analysis of all five studies (general population 1, patients 4) showed that narrower retinal arteriolar caliber was modestly correlated with higher PWV across adults ($r = -0.17$, 95% CI -0.25 to -0.10 ; Figure 2(A)). Evidence of an association was stronger for patients (r ranging from -0.21 to -0.23) than the general population ($r = -0.05$, 95% CI -0.18 to 0.08 ; Table 3). The random effects meta-analysis showed little evidence of an association between retinal venular caliber and PWV overall ($r = -0.03$, 95% CI -0.23 to 0.07 ; Figure 2(B)). Of the three studies with sufficient data to perform meta-analysis for AVR (general population 1, patients 2), lower AVR scores were associated with higher PWV ($r = -0.11$, 95% CI -0.21 to 0.00 ; Table 3).

3.4.2 Associations of retinal microvascular caliber with CIMT

In the random effects meta-analysis of five studies (general population 4, patients 1), narrower retinal arteriolar caliber was weakly associated with higher CIMT ($r = -0.05$, 95% CI -0.09 to -0.02 ; Figure 3(A)). There was little evidence of an association between retinal venular caliber and CIMT or AVR and CIMT (Table 3).

4. DISCUSSION

4.1 Main findings

This systematic review and meta-analysis examined 26 studies to determine associations between retinal microvascular caliber and large arterial function and structure in both the general population and patients with cardiometabolic disease. There was little evidence of any associations for retinal venular caliber, but retinal arteriolar caliber was associated with both large arterial function and structure. In the meta-analysis, the strongest associations were observed in the adult patient population for arteriolar caliber and vascular function (PWV; r ranging from -0.21 to -0.23). Although there was little evidence of a similar association in adults within the general population (PWV $r = -0.05$, 95% CI -0.18 to 0.08), the estimate was imprecise, reflecting the limited data of only a single small study on this topic. No associations were seen in children. A similar pattern was observed for vascular structure, although there was a dearth of studies in adult patients (1 small study) and children (no studies) populations, precluding any conclusions in these groups. In the general population, retinal arteriolar caliber showed small associations with large arterial structure (CMT $r = -0.05$, 95% CI -0.09 to -0.02).

4.2 Strengths and limitations

Our study has several strengths. This is the first systematic review and meta-analysis to comprehensively describe and quantify associations between the retinal microvasculature and intermediate phenotypes of large arteries. Studies across a number of large arterial intermediate phenotypes observed similar findings, providing confidence in the results. We investigated both the function and structure of large arteries, as functional changes may precede structural changes in early atherosclerosis.[51] In addition, our meta-analysis findings were consistent with those of our narrative review. We included studies reported in both English and Chinese to address potential language bias. The majority of included studies (92.3%) were of moderate or high quality, indicating that most had attempted to minimize bias. The most common source of bias was the selection of the sample (e.g. unjustified sample size or no description of response rate, supplementary Table 2S), which may limit the generalizability of our conclusions. Future studies warrant more rigorous study design to minimize selection bias.

We acknowledge a number of limitations, many of which were unavoidable. Given that almost all the included studies were cross-sectional, we were unable to explore the temporal directions of the observed associations. The only longitudinal study, which followed an adult population over five years, suggested that narrower retinal arteriolar caliber was an independent predictor of increased PWV.[43] Longitudinal replication in other cohorts is warranted. Participants were mainly middle- or older-aged adults, limiting conclusions that could be drawn for younger stages of the life course. The paucity of data from childhood, when atherosclerosis is first established and interventions may be more effective, remains a significant knowledge gap.[3, 52, 53] In the meta-analysis, we pooled studies reporting unadjusted correlation coefficients and those with minimally adjusted standardized regression coefficients. This may have added bias to the results given that correlation coefficients are equal to unadjusted standardized regression coefficients, not minimally adjusted models, yet one would expect the results to be very similar. Given that we only considered associations based on unadjusted and minimally adjusted models, the combined results may be confounded by factors have not been accounted for, such as demographics and CVD risk factors. This may have biased the results but was unavoidable given the different levels of adjustment in each study. We are not able to report funnel plots to visualize publication bias given the limited number of studies. Publication bias may exist, as there may be null findings that are unpublished studies.

4.3 Interpretation of main findings

The limited data in children make conclusions in this population challenging. The one large study of 6-year-old children (n=4,007) did not suggest retinal microvascular caliber was associated with vascular function intermediate phenotypes [17] and there were no data available for structural intermediate phenotypes. In adults, the narrative review and meta-analysis for retinal arteriolar caliber consistently showed small associations with arterial functional and structural intermediate phenotypes. These associations were most pronounced in the patient groups. This supports the concept that shared pathophysiologic processes may contribute progressively to shared small and large arterial dysfunction, and only later to damage in large arterial structure, as individuals' progress towards disease through the life course.

The small co-variance we observed between retinal arteriolar caliber and large arterial intermediate phenotypes could also suggest that microvascular changes contribute to

1 macrovascular pathology, which aggravates vascular damage. [14, 54, 55] Evidence from
2 animal experiments indicates that decreased vasa vasorum flow in the microcirculation leads
3 to abnormal morphology of elastin and collagen fibers of arterial walls, resulting in increased
4 arterial stiffness.[56] This hypothesis is supported by a longitudinal population-based study
5 indicating that narrower arteriolar caliber was independently associated with increased PWV
6 five years later.[43]. Similarly, damage to the structure and function of large arteries may
7 itself result in adverse changes to the microcirculation.[14]

8 Little evidence on an association was observed between retinal venular caliber and large
9 arterial intermediate phenotypes across both populations. One explanation why we did not
10 observe an association could be that adverse changes of venules may have an adaptive
11 response and emerge when CVD is overt.[60, 61] Our review included three studies
12 performed in patients with different stages of hypertension;[18, 49, 50] all studies showed
13 consistent associations between arteriolar caliber and PWV, but results were inconsistent for
14 venular caliber. In early-stage hypertensive patients, there was little evidence to suggest that
15 retinal venular caliber was associated with PWV, [18] while in never-treated hypertensive
16 patients there was a moderate association in the unexpected direction (e.g. smaller venular
17 caliber and better PWV).[49, 50] This indicates that retinal venules adapt to the hypertensive
18 state with a decrease in caliber,[49, 50] but then there is a tipping point when cardiometabolic
19 disease becomes overt, and this adaption breaks down, leading to an increase in venular
20 caliber.[60, 61] Another explanation for the lack of association observed for venular caliber is
21 different risk factors related to venular changes. Increased retinal venular caliber is associated
22 with inflammatory markers, such as C-reactive protein and leukocyte count, smoking and
23 increased body mass index.[15, 57, 58, 59] Previous studies have shown that retinal venular
24 caliber is an independent predictor of CVD events and mortality.[60, 61] Thus, it is plausible
25 that inflammation and these other factors are a mechanistic link between changes in retinal
26 venular caliber and later CVD events.

27 Results regarding to associations of AVR and large arterial intermediate phenotypes were
28 mixed.[18, 40] This may because AVR fails to capture the different pathophysiological
29 pathways of the retinal arterioles and venules, which is increasingly recognized.[57]

30 **4.4 Implications**

31 Our observations have a number of potential clinical implications. Firstly, the stronger
32 association seen in cardiometabolic patients compared to the general population could

1 suggest a synergistic effect on the variation of small and large vessels, where degradation is
2 escalated once the disease begins. This is consistent with other studies showing that
3 individuals with both type 2 diabetes and hypertension have an increased risk of CVD
4 compared with those with either condition alone.[62] Thus, it highlights the potential
5 importance of the microcirculation in CVD pathogenesis and management, which has largely
6 been overlooked.

7 Secondly, given the association between retinal arterial caliber and large arterial phenotypes
8 was small, each phenotype may contribute to CVD primarily through independent causal
9 pathways. Therefore, combining assessment of both may offer better prediction of CVD. For
10 example, McGeechan et al. found that adding both arteriolar and venular caliber to the
11 Framingham risk score improved prediction of coronary heart disease in individuals without
12 diabetes by 1.7%.[63] In persons with diabetes, Ho et al. showed that the prediction value for
13 CVD was higher (3.0%) when retinal arteriolar, venular caliber and diabetic retinopathy were
14 added to other CVD risk factors.[64] However, it is unclear whether the inclusion of *both*
15 large arterial phenotypes and retinal microvascular caliber adds to clinical risk prediction of
16 CVD and which populations could benefit most. Future studies with clinical outcomes can
17 explore this question by combining both measures from large arteries and microcirculation to
18 inform the optimal use of these measures.

19 Thirdly, the lack of association seen in the only child study could highlight that early in life
20 the micro- and macro-vasculature may operate under different determinants. Over time the
21 micro- and macro-vasculature may gradually come to share pathophysiology and with
22 physiologic dysregulation evident in mid-adulthood. Future studies warrant to examine the
23 potential life course trends of this co-variation.

24 **4.5 Conclusions**

25 Our systematic review and meta-analysis showed that retinal arteriolar but not venular caliber
26 had small associations with large arterial function and modest associations with arterial
27 structure, with stronger evidence in patients with cardiometabolic disease. This suggests that
28 preclinical changes in large arteries and the microcirculation have some shared but mainly
29 unique determinants.

Perspective

The microcirculation is increasingly recognized for its role in the pathogenesis of CVD. We additionally showed that it shares a small amount of co-variation with preclinical cardiovascular phenotypes of large arterial function and structure. This indicates that the contribution of microcirculation to CVD is through some common pathways with the large vessels, but mainly through its own. Given that the small and large vessels do not appear to deteriorate in unison, it is important to understand their unique contribution to CVD across the life course. However, early life and longitudinal data with clinical outcomes are lacking. Such knowledge could inform whether the assessment of both the small and large vessels could improve risk prediction models and when in the life course this could offer the most value.

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Author contributions

Study concept and design: MW, DB, KL, TW, MH, ML

Data selection and extraction: ML, YX

Analysis and interpretation: ML, DB, KL, MW

Drafting of the manuscript: ML

Critical revision of the manuscript: All authors

Study supervision: DB, KL, MW

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TABLES

Table 1. Characteristics of observational studies included in the systematic review.

Table 2. Study-specific associations of retinal microvascular caliber with pulse wave velocity and carotid intima-media thickness.

Table 3. Meta-analysis of correlations of retinal microvascular caliber with pulse wave velocity and carotid intima-media thickness.

FIGURES

Figure 1. PRISMA flow diagram of reviewed and included studies.

Figure 2. Forest plot for associations of retinal microvascular caliber with pulse wave velocity. The hypothesis was that arterioles would show inverse, and venules direct, associations.

Abbreviations: ZCOR, Fisher's z transformation of correlations; P, patient group; G, general population; CI, confidence interval.

Figure 3. Forest plot for associations of retinal microvascular caliber with intima-media thickness. The hypothesis was that arterioles would show inverse, and venules direct, associations.

Abbreviations: ZCOR, Fisher's z transformation of correlations; P, patient group; G, general population; CI, confidence interval.

Table 1. Characteristics of observational studies included in the systematic review.

Lead author; year	Country	Disease conditions	Sample size (women %)	Age (years) mean/median (range)	Exposure/s	Outcome/s	Study quality
General population							
Klein, R; 2000[31]	USA	--	8,524 (56.4)	60 (51-72)	AVR	Carotid plaque	Medium
Wong, TY; 2003[19]	USA	--	1,609 (61.1)	77 (69-97)	CIMT	AVR	High
Ikram, MK; 2004[32]	Netherlands	--	5,674 (59.0)	68 (ng)	CIMT, carotid plaque, aortic calcification	Retinal arteriolar and venular caliber, AVR	High
Liao, D; 2004[33]	USA	--	8,031 (56.0)	56 (45-64)	AVR	Arterial elasticity	High
van Hecke, MV; 2006[34]	Netherlands	--	256 (48.0)	72 (60-85)	Retinal arteriolar and venular caliber, AVR	Flow-mediated vasodilatation, CIMT	Medium
Cheung, N; 2007a[35]	USA	--	2,861 (52.5)	ns (45-84)	Arterial compliance	Retinal arteriolar and venular caliber	High
Cheung, N; 2007b[36]	USA	--	3,425 (54.1)	62 (45-84)	Arterial distensibility	Retinal arteriolar and venular caliber	High
Liew, G; 2008[37]	USA	--	8,794 (54.6)	60 (45-64)	CIMT	Retinal arteriolar and venular caliber	Medium
Wong, TY; 2008[38]	USA	--	6,147 (52.3)	ns (45-84)	Retinal arteriolar and venular caliber	Coronary artery calcification	High
Nguyen, TT; 2010[39]	USA	--	2,851 (49.9)	63 (45-84)	Retinal arteriolar and venular caliber	Flow-mediated vasodilatation	High
Gishti, O; 2015[17]	Netherlands	--	4,007 (ng)	6 (ng)	Retinal arteriolar and venular caliber	PWV	High
Garcia-Ortiz, L; 2015[40]	Spain	--	229 (61.1)	56 (20-80)	Retinal arteriolar and venular caliber, AVR	CIMT, PWV, ankle-brachial index	Medium
Lin, F; 2015[41]	China	--	2,169 (62.6)	52 (ng)	Retinal arteriolar caliber	PWV	High
Agladioglu, K; 2015[29]	Turkey	--	43 (ng)	30 (20-40)	Retinal arteriolar and venular caliber	Internal carotid artery diameter	Low
Yang, JY; 2016[42]	China	--	4,004 (43.0)	60 (>40)	CIMT	Retinal arteriolar and venular caliber	Medium
Kawashima, K; 2018[43]	Japan	--	6,720 (68.5)	52.1 (30-74)	Retinal arteriolar and venular caliber	PWV	Medium

Cardiometabolic patient group

Lead author; year	Country	Disease conditions	Sample size (women %)	Age (years) mean/median (range)	Exposure/s	Outcome/s	Study quality
Masaidi, M; 2009[44]	Italy	Hypertension	386 (55.2)	56 (ng)	AVR	CIMT	Medium
De Silva, DA; 2012[45]	Singapore	Acute stroke	145 (31.7)	62 (ng)	Retinal arteriolar and venular caliber, AVR	PWV	High
Garcia-Ortiz, L; 2012[46]	Spain	Hypertension	205 (42.9)	56 (34-75)	AVR	CIMT, PWV	Medium
Lammert, A; 2012[47]	Germany	Obesity	120 (72.5)	43 (ng)	AVR	CIMT	Medium
Torres, FS; 2013[20]	Brazil	Hypertension	173 (46.0)	58 (18-80)	CIMT	Retinal arteriolar and venular caliber	Medium
Gopinath, B; 2014[48]	Australia	Coronary artery disease	991 (25.4)	60 (ng)	Retinal arteriolar and venular caliber	Coronary artery stenosis	Medium
Triantafyllou, A; 2014[18]	Greece	Hypertension	223 (36.3)	44 (ng)	Retinal arteriolar and venular caliber, AVR	PWV	Medium
Aissopou, EK; 2016[49]	Greece	Hypertension	181 (44.8)	54 (ng)	Retinal arteriolar and venular caliber	PWV	Medium
Li, HY; 2016[30]	China	Carotid artery stenosis	141 (41.1)	62 (ng)	Retinal arteriolar and venular caliber	Carotid artery stenosis	Low
Daien, V; 2017[50]	France	Hypertension	88 (43.2)	54 (32-83)	PWV	Retinal arteriolar and venular caliber	Medium

Abbreviations: ng, not given; USA, United States of America; AVR, arteriole-to-venule ratio; CIMT, carotid intima-media thickness; PWV, pulse wave velocity. Study quality was assessed using the modified Newcastle-Ottawa Quality Assessment Scale for observational studies[25], which defined quality as high (10-9 stars), moderate (7-8 stars) or low (≤ 6 stars).

Table 2. Study-specific associations of retinal microvascular caliber with pulse wave velocity and carotid intima-media thickness.

Lead author; year	Sample	Statistical methods	Retinal arteriolar caliber		Retinal venular caliber		Arteriole-to-venule ratio	
			(↓ = worse)		(↑ = worse)		(↓ = worse)	
			Estimate	p value	Estimate	p value	Estimate	p value
Pulse wave velocity (Children)								
Gishti, O.; 2015[17]	General	Linear regression (standardized β)	0.02 (-0.01, 0.05)	ng ^a	0.04 (0.01, 0.07)	<0.05		
Pulse wave velocity (Adults)								
De Silva, DA; 2012[45]	Patient	Pearson’s correlation	-0.21	<0.01	-0.01	0.89	0.01	0.14
Triantafyllou, A; 2014[18]	Patient	Pearson’s correlation	-0.21	0.002	-0.04	0.56	-0.12	0.08
Garcia-Ortiz, L; 2015[40]	General	Pearson’s correlation	-0.05	ng ^a	0.11	ng ^a	-0.18	<0.01
Aissopou, EK; 2016[49]	Patient	Pearson’s correlation	-0.23	<0.001	-0.06	<0.05		
Daien, V; 2017[50]	Patient	Linear regression (standardized β) ^d	-0.21 (-0.32, -0.11)	0.04	-0.22 (-0.33, -0.11)	0.04		
Garcia-Ortiz, L; 2012[46]	Patient	ANCOVA					ng	0.88
Kawashima, K; 2018[43]	General	ANCOVA	Ng	<0.001	ng	<0.001		
Lin, F; 2015[41]	General	Logistic regression (odds ratio) ^b	3.09 (2.01, 4.76)	<0.001				
Carotid intima-media thickness (all adults)								
Masaidi, M; 2009[44]	Patient	Pearson’s correlation					0.12	0.02
Lammert, A; 2012[47]	Patient	Pearson’s correlation					-0.22	0.02

Lead author; year	Sample	Statistical methods	Retinal arteriolar caliber		Retinal venular caliber		Arteriole-to-venule ratio	
			(↓ = worse)		(↑ = worse)		(↓ = worse)	
			Estimate	p value	Estimate	p value	Estimate	p value
Torres, FS; 2013[20]	Patient	Pearson's correlation	-0.12	0.13	0.13	0.09		
Garcia-Ortiz, L; 2015[40]	General	Pearson's correlation	-0.06	ng ^a	0.12	ng ^a	-0.19	<0.01
Ikram, MK; 2004[32]	General	Linear regression (standardized β) ^d	-0.06 (-0.10, -0.03)	<0.05	-0.01 (-0.04, 0.02)	ng ^a	-0.07 (-0.08, -0.03)	<0.05
van Hecke, MV; 2006[34]	General	Linear regression (standardized β)	0.09 (-0.03, 0.21)	>0.05	0.14 (0.01, 0.25)	<0.05	-0.04 (-0.16, 0.09)	>0.05
Yang, JY; 2016[42]	General	Linear regression (standardized β)	-0.06 (-0.10, -0.03)	0.001				
Wong, TY; 2003[19]	General	Logistic regression (odds ratio) ^c					0.7 (0.5, 1.0)	0.46
Garcia-Ortiz, L; 2012[46]	Patient	ANCOVA					ng	0.46

Abbreviations: P, patient group; G, general population; ng, not given; ANCOVA, analysis of covariance; β , regression coefficient.

^a. p value not given and stated as not significant; ^b. Odds of elevated PWV (e.g. highest quartile versus lowest quartile) by comparing the retinal caliber in highest quartile with the lowest quartile; ^c. Odds of elevated CIMT (e.g. highest quartile versus lowest quartile) by comparing the retinal caliber in highest quartile with the lowest quartile; ^d. The standardized β was transformed by the reviewer from the reported raw β to make the results comparable.

Table 3. Meta-analysis of correlations of retinal microvascular caliber with pulse wave velocity and carotid intima-media thickness.

Classification	Sample	No. of studies	Sample size	Estimate (r)	95% CI	p value ^b	I ² (%)
Pulse wave velocity							
Retinal arteriolar caliber	All	5	866	-0.17	-0.25 to -0.10	<0.0001	13.4
	General	1 ^a	229	-0.05	-0.18 to 0.08	N/A	N/A
	Patient	4	637	-0.22	-0.30 to -0.14	<0.0001	0
Retinal venular caliber	All	5	866	-0.03	-0.23 to 0.07	0.59	49.1
	General	1 ^a	229	0.11	-0.02 to 0.24	N/A	N/A
	Patient	4	637	-0.06	-0.14 to 0.02	0.12	0
Arteriole-to-venule ratio	All	3	597	-0.11	-0.21 to 0.00	0.05	37.4
	General	1 ^a	229	-0.18	-0.30 to -0.05	N/A	N/A
	Patient	2	368	-0.06	-0.19 to 0.06	0.32	28.7
Carotid intima-media thickness							
Retinal arteriolar caliber	All	5	9367	-0.05	-0.09 to -0.02	0.001	35.4
	General	4	9194	-0.05	-0.08 to -0.01	<0.01	46.0
	Patient	1 ^a	173	-0.12	-0.26 to 0.03	N/A	N/A
Retinal venular caliber	All	4	5414	0.08	-0.02 to 0.18	0.10	74.2
	General	3	5241	0.07	-0.04 to 0.19	0.22	77.5
	Patient	1 ^a	173	0.13	-0.02 to 0.27	N/A	N/A
Arteriole-to-venule ratio	All	5	5747	-0.07	-0.17 to 0.03	0.18	80.0
	General	3	5241	-0.09	-0.15 to -0.02	0.01	43.3
	Patient	2	506	-0.04	-0.38 to 0.29	0.81	90.4

^a. As there was only one coefficient estimate no meta-analysis was performed.

^b. p value for the pooled correlation coefficients.

Abbreviations: N/A, not applicable.

*Inclusion criteria: 1) observational designs, 2) had retinal microvascular caliber quantified from digital retinal photographs via computer-assisted methods, and 3) intermediate large arterial phenotypes were measured.

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