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Obesity and the Microvasculature: A Systematic Review and Meta-Analysis

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Abstract

Background: Overweight and obesity are thought to significantly influence a person's risk of cardiovascular disease, possibly via its effect on the microvasculature. Retinal vascular caliber is a surrogate marker of microvascular disease and a predictor of cardiovascular events. The aim of this systematic review and meta-analysis was to determine the association between body mass index (BMI) and retinal vascular caliber.

Methods and Findings: Relevant studies were identified by searches of the MEDLINE and EMBASE databases from 1966 to August 2011. Standardized forms were used for data extraction. Among over 44,000 individuals, obese subjects had narrower arteriolar and wider venular calibers when compared with normal weight subjects, independent of conventional cardiovascular risk factors. In adults, a 1 kg/m^2 increase in BMI was associated with a difference of 0.07 μm [95% CI: −0.08; −0.06] in arteriolar caliber and 0.22 μm [95% CI: 0.21; 0.23] in venular caliber. Similar results were found for children.

Conclusions: Higher BMI is associated with narrower retinal arteriolar and wider venular calibers. Further prospective studies are needed to examine whether a causative relationship between BMI and retinal microcirculation exists.

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Introduction

Obesity is estimated by the World Health Organisation to affect 400 million people globally. Overweight/obesity is well recognized to increase a person's risk of cardiovascular disease (CVD) and this is possibly associated with the development of large vessel atherosclerosis in the carotid [1–3] and femoral [3] arterial beds. However, the impact of overweight/obesity on the microcirculation is less well described. Greater body-mass index (BMI) has been shown to result in a reduction in skin capillary density and lower tissue perfusion, one of the earliest detectable alterations in microvascular function in overweight individuals [4,5]. Capillary recruitment is also reduced in obese individuals compared to lean control subjects [6].

The retinal microcirculation is accessible to non-invasive measurement and provides a window to the human microvasculature. Recent developments in retinal imaging techniques using computer-based analysis of retinal photographs allow quantification of retinal vascular caliber in an objective and reproducible way. Studies show that adverse changes in retinal vascular caliber (principally narrower retinal arteriolar caliber and wider venular caliber) are associated with cardiovascular risk factors, [7] the metabolic syndrome, [8] risk of diabetes, [9–10] hypertension, [11] coronary heart disease, [12] and stroke [13–14].

Several studies have reported an association between greater BMI and retinal vascular caliber. However, the consistency and strength of the associations have remained unclear. [15–16] Some studies suggest that greater BMI is associated with wider retinal venular caliber, while others report that greater BMI is associated with both narrower arteriolar and wider venular retinal calibers.

We conducted a systematic review and meta-analysis to determine the association between categories of BMI and retinal arteriolar and venular caliber, in adults and children. We examined whether these associations varied according to age and were independent of conventional cardiovascular risk factors.

Methods

Data sources and Searches

We performed a systematic review and meta-analysis of available literature according to the MOOSE guidelines. [17] To investigate the impact of BMI on retinal vascular parameters in humans (adults and children), relevant articles published in English between 1966 and August 2011 were identified from MEDLINE and EMBASE using a combined text and the following MeSH heading search strategies: (arteriolar narrowing OR retinal arteriolar caliber OR retinal venular caliber OR retinal vasculature OR retinal vascular caliber OR retina/arteriovenous ratio OR retinal microcirculation OR retinal vessels) AND (obesity OR BMI OR body mass index OR waist-to-hip ratio OR waist circumference) (Table S1). References listed in articles of interest were then scrutinised to identify other relevant studies and experts in the field were contacted to find additional relevant studies.

Study selection

Studies were included if they had published quantitative estimates (including variability) of the association between body weight and central retinal arteriolar equivalent (CRAE) and/or central retinal venular equivalent (CRVE). In the case of duplicates, we included the most recent publication. Studies that were not published as full reports, such as conference abstracts or letters to editors, were excluded.

Titles of all articles retrieved from database searches were screened. The abstracts of relevant articles investigating the relationship between BMI and retinal vascular parameters were examined and all studies that could be included were retrieved. References from these studies and previous reviews were also scanned for any other relevant articles. The literature research was conducted by two authors (A.B. and S.C.) without disagreement over study eligibility.

Data extraction and Quality Assessment

Due to the variety of reported outcomes and statistical methods (particularly variety of covariates included in multivariate analysis), authors of relevant studies for the meta-analysis were contacted by e-mail and asked to a complete a standardized data abstraction form regarding participants characteristics, and crude and adjusted retinal vascular parameters according to BMI categories.

Outcome measurement

Retinal vascular diameters were assessed using 45-degree digital camera. Two photographic fields (optic disc and macula) were taken of each eye. Retinal vascular calibers were measured using computer-based programs. The right eye was used for assessment of retinal vascular calibre. If the photographs of the right eye were not gradable, the left eye assessment was used. For each image all arterioles and venules coursing through an area one-half to one disc diameter from the optic disc margin were measured and summarized as the central retinal arteriolar equivalent and the central retinal venular equivalent. Both represent the average diameter of arterioles and venules of the eye, respectively, by using a modification of the Parr-Hubbard formulas [18] as described by Knudtson et al [19].

Data synthesis and analysis

Mean retinal vascular parameters were compared using mean differences (MD) across BMI categories (Underweight: <18.5 kg/m^2, Normal weight: [18.5–24.9] kg/m^2, Overweight: [25.0–29.9] kg/m^2, Obese: ≥ 30 kg/m^2) with [18.5–24.9] kg/m^2 as the reference. Although BMI, age and gender dependent cut-offs exist for children, we chose the same categories for adults and children because we had no access to individual participant data. The inverse variance method with random effects was used. Moreover, crude and maximum adjusted regression coefficients were pooled to assess the continuous associations between retinal parameters and a 1kg/m^2 increase in BMI. Significance was set at $p<0.05$ and 95% confidence intervals (95%CI) calculated. Analyses were conducted for both children and adults, with crude and maximum adjusted values of retinal outcomes (levels of adjustment are described for each included study in Table 1). The percentage of variability across studies attributable to heterogeneity rather than chance was estimated using the I^2 statistic. [20] Publication bias was assessed using Egger's regression test. [21] Because of the number of studies included, we did not conduct subgroup analyses. All analyses were performed using R (R, version 2.12.1, the R Core Development team, 2010), STATA (Release 10; STATA Corporation, College Station, Texas, USA) and Review Manager (RevMan, version 5.0, The Cochrane Collaboration, 2008).

Results

Study characteristics

The search strategy identified a total of 162 titles including 28 duplicates and 51 titles that had no relevance to our primary research question. After reading the abstracts, the authors excluded 65 abstracts. Two additional studies were identified from reference lists. After review of 20 articles, 12 articles were selected and an email was sent to each contact author. [7,9,16,22–30] All contacted authors contributed to the meta-analysis (Figure 1).

Nine studies were identified in adults [7,16,22,23,26–30] and three in children [9,24,25]. Sample sizes ranged from 797 [23] to 10,778 [26], for a total of 38,979 adults and 5,204 children. Study participants were from diverse countries including USA [7,22–23,26,30], Australia [9,25,27], Singapore [24,28–29] and The Netherlands [16] (Table 1). Mean BMI was 25.0 kg/m^2 or higher in seven adult studies [7,16,22,26–27,29–30] In four studies [7,27,29–30] more than one-half of participants had hypertension and one study was conducted in people with type 2 diabetes [7] (Table S2).

Mean differences in CRAE/CRVE across BMI categories

A higher BMI was associated with narrower arteriolar caliber in both adults and children (Figure 2, Table 2). When pooling maximum adjusted data, the mean difference was -0.62 μm [-1.06; -0.18] in overweight adults and -0.95 μm [-1.52; -0.38] in obese adults, when compared to their normal-weight counterparts (Figures 2, 3, 4). Similar results were found with children in crude (Table 2) and adjusted models (Table S3).

In contrast, the pooled summary estimates from studies of adults and children indicated that overweight and obese individuals had

Table 1. Characteristics of studies included in the meta-analysis.

Study Ref	Cohort study	Country	Study size	Age (mean±sd)	Level of adjustment
Cheung N et al., 2007 (24)	Singapore Cohort Study of Risk Factors for Myopia (SCORM)	Singapore	1153	13.7±1.2	Age, gender, race, systolic blood pressure, diastolic blood pressure, eye measurements.
Gopinath B et al., 2011 (25)	Sydney Childhood Eye Study (SCES12yr)	Australia	2353	12.7±0.4	Age, gender, race, hypertension
Hughes A et al., 2009 (30)	Beaver Dam Eye Study cohort (BDES)	USA	4659	61.5±10.9	Age, gender, race, smoking, hypertension, type 2 diabetes mellitus, HDL cholesterol
Ikram M et al., 2004 (16)	Rotterdam Study	The Netherlands	5602	67.9±8.1	Age, gender, mean arterial blood pressure, non-fasting blood glucose, total cholesterol, smoking.
Jeganathan V et al., 2009 (28)	Singapore Prospective Study Program and Singapore Cardiovascular Cohort Study 2 (SPSP/SCCS2)	Singapore	3600	49.4±11.3	Age, gender, race, systolic blood pressure, smoking, cholesterol, HbA1c
Klein R et al., 2003 (23)	The Wisconsin Epidemiologic Study of Diabetic Retinopathy: XVIII (WESDR/T1DM)	USA	797	33.2±12.0	Age, gender, race, smoking, hypertension.
Klein R et al., 2006 (7)	The Wisconsin Epidemiologic Study of Diabetic Retinopathy: XX (WESDR/T2DM)	USA	1362	66.6±11.3	Age, gender, race, smoking, hypertension.
Liew G et al., 2008 (26)	Atherosclerosis Risk in Communities (ARIC)	USA	10778	59.7±5.6	Age, gender, race, diabetes medication, insulin use, glucose level, smoking, HDL, cholesterol, hypertension, medication for hypertension.
Sun C et al., 2008 (29)	Singapore Malay Eye Study (SIMES)	Singapore	3001	57.7±10.6	Age, gender, systolic blood pressure, HbA1c, smoking, cholesterol.
Taylor B et al., 2007 (9)	Sydney Childhood Eye Study (SCES6yr)	Australia	1773	6.7±0.4	Age, gender, race, hypertension.
Wang JJ et al., 2006 (27)	The Blue Mountains Eye Study (BMES)	Australia	3295	65.5±9.4	Age, gender, smoking, hypertension, type 2 diabetes mellitus.
Wong TY et al., 2006 (22)	The Multi-Ethnic Study of Atherosclerosis (MESA)	USA	5885	63.0±9.9	Age, gender, race, family history of type 2 diabetes mellitus, glucose level, insulin use, smoking, HDL, LDL, triglycerides, exercise, hypertension, medication for hypertension.

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wider retinal venular caliber than their normal-weight counterparts (Figure 2, Table 2). After adjustment, overweight adults had a mean 0.88 μm [0.24; 1.52] increase in CRVE and 1.71 μm [1.10; 2.32] for obese adults (Figures 2, 3, 4). We found similar associations in children with a mean 2.20 [1.46; 2.95] increase in CRVE for overweight children and 6.73 μm [1.21; 12.25] for obese children (Table S3).

Testing revealed no evidence of heterogeneity among pooled studies of adults providing adjusted data for CRAE and CRVE in overweight (CRAE: $I^2 = 2\%$; CRVE: $I^2 = 13\%$) and obese (CRAE: $I^2 = 14\%$; CRVE: $I^2 = 0\%$). In contrast significant heterogeneity was observed among pooled studies of children providing adjusted data for CRAE in overweight ($I^2 = 75\%$) and for CRVE in obese ($I^2 = 91\%$).

No publication bias was observed (all p-values above 0.31 in adults and 0.09 in children).

Continuous associations between CRAE/CRVE and BMI

In adults, a 1 kg/m^2 increase in BMI was associated with a significant decrease in CRAE (−0.12 μm [−0.13; −0.11] in the crude model and −0.07 μm [−0.08; −0.06] in the adjusted model). Similar results were observed in children (−0.42 [−0.44; −0.40] in the crude model, and -0.20 [−0.23; −0.18] in the adjusted model).

A 1 kg/m^2 increase in BMI was also associated with a significant increase in CRVE in adults (adjusted model 0.22 μm [0.21; 0.23]) and in children (adjusted model 0.28 μm [0.25; 0.30]).

Discussion

This meta-analysis of over 44,000 individuals found that higher BMI levels were associated with narrower arteriolar and wider venular caliber, independent of conventional cardiovascular risk factors. This association was consistent across regions, ethnicity, age groups and study sample size. In studies of children significant heterogeneity in the pooled data was observed. This is likely to be explained by differences in the age range of the participants (two studies were conducted in children with mean age of 12–13 years [24,25] and the third was conducted in children with mean age 6.7 years [9]), and the different levels of adjustment for confounding covariates.]. In spite of the heterogeneity in the pooled data for children, similar differences in retinal microvasculature were observed in adults and children with retinal arteriolar and wider venular calibres with increasing BMI, suggesting biological mechanisms involved in retinal microcirculation alterations are not age-dependent.

Our study suggests a significant influence of obesity on the human microcirculation. We offer several explanations for our findings. Nitric oxide (NO) is a key endothelium-derived relaxing factor causing vasodilatation and therefore an increase in volume perfusion in response to elevated metabolic demand. In obesity, decreased levels of NO have been observed and could explain impaired dilatation of the vasculature. [31] This endothelium-dependent dysfunction has been proposed to be responsible for the vasoconstriction observed in obese subjects. Moreover, increased levels of vasoconstrictor molecules (endothelin-1, angiotensin-II and other metabolites of arachidonic acid) have been associated

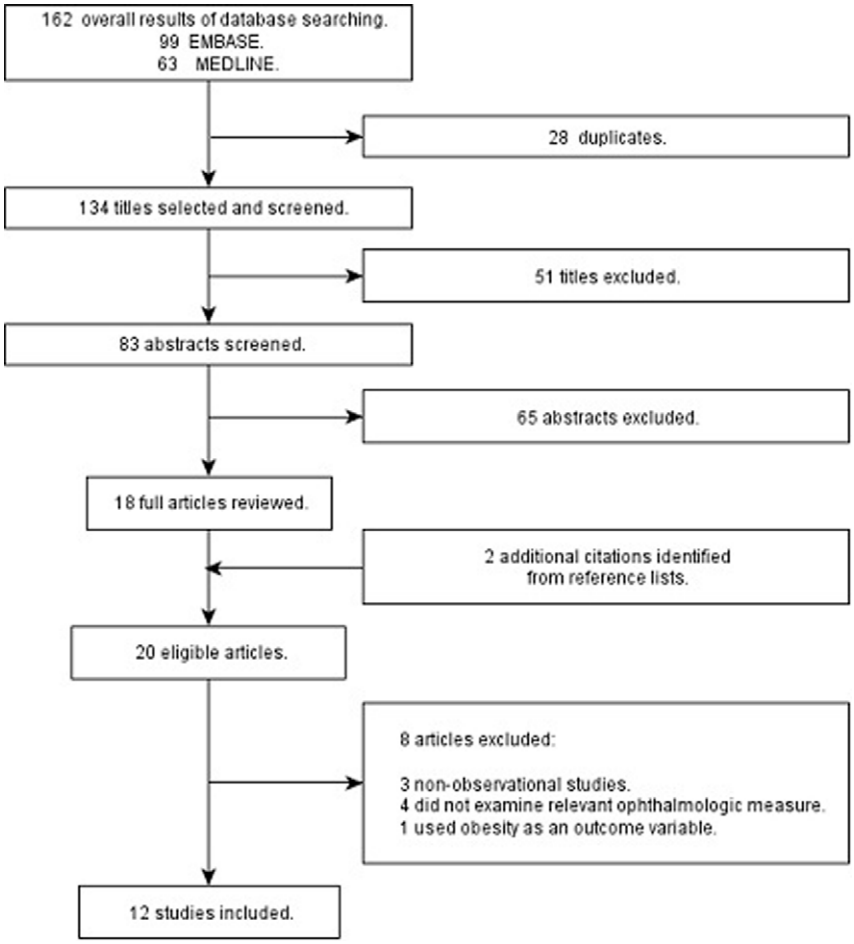


Figure 1. Flow-chart identifying eligible studies.
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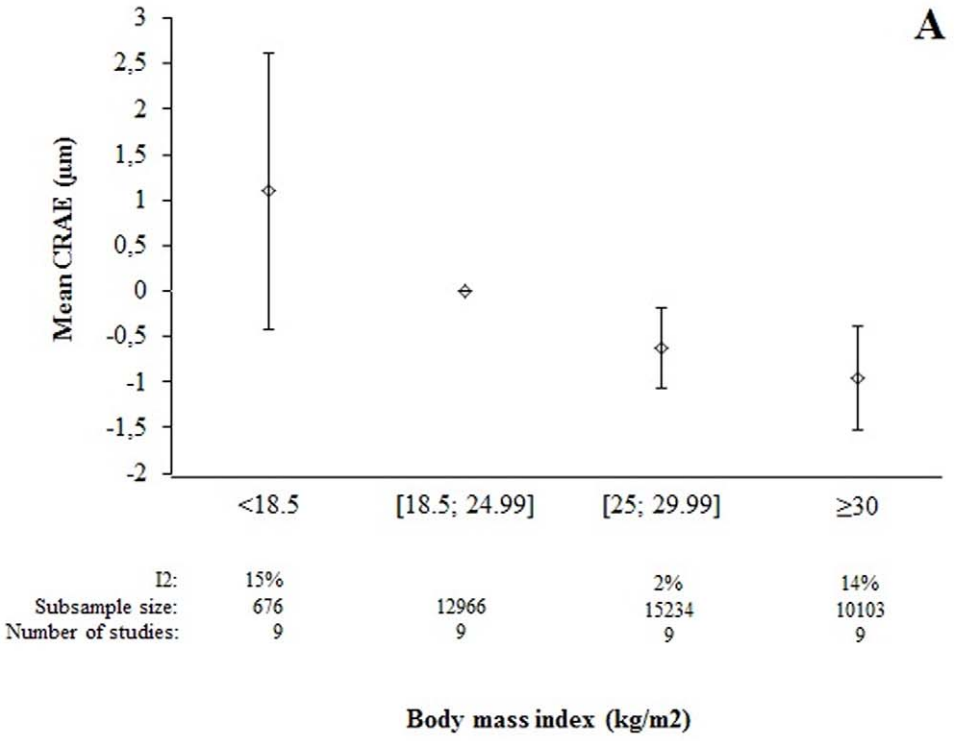
with higher BMI. [32–33] Enhanced myogenic activation, mediated by antagonizism of calcium-activated potassium channels, has also been hypothesized to play a key role in alterations in blood flow in animal models of obesity [34]. In addition, a decrease in microvessel density, that may lead to tissue hypoxia and ischemia has been observed in obese subjects. Moreover, obesity-mediated insulin resistance may result in impaired capillary recruitment via insulin-mediated mechanisms [35].

Alterations in vascular stucture have previously been descibed in both animal and human models of obesity. These have included thickening of basement membranes, an increase in vascular diameter, stiffness of resistance arterioles and a decrease in lumen size. These changes lead to hypertension and increase the risk of ischemia, peripheral vascular disease and aneurysms [36].

Finally, excess release of inflammatory markers in obese subjects has been described and may contribute to vascular dysfunction. For example, TNFα is associated with impaired capillary recruitment and vasodilatation, and angiotensinogen is responsible for the activation of the renin-angiotensin system, resulting in higher production of angiotensin II, which is a powerful vasoconstrictor [37]. Vasoconstrictor and vasodilator mechanism alterations and anatomical changes result in impaired functional hyperemia in response to metabolic demand. Animal and human models have shown a reduced blood flow response to an increase in local metabolic activity in conditions of obesity [38].

An association between obesity and CVD such as coronary heart diseases, [39] stroke, [40] venous thromboembolism, [41] and even cardiovascular mortality [42] has long been described. More recently retinal caliber has also been shown to predict stroke [13] and coronary heart diseases [43]. Based on the results of our meta-analysis, we hypothesize that obesity induces microvascular alterations, reflected here in retinal vessel caliber. The clinical significance of these changes however, remain unclear. In children for example, the absolute differences in arteriolar and venular calibers between overweight and normal weight children were less than 1%, and whether these differences are clinically meaningful requires further study. If found to be clinically important retinal photography could be a useful non-invasive preventive tool to assess long-term microvascular changes as a marker of cardiovascular risk in overweight and obese persons. Review of longer-term inter-relationships between changes in obesity, retinal vessels and outcomes are now needed to determine whether changes are causally related to clinical outcomes.

The strengths of this meta-analysis are its large sample size and also the participation of all authors that were identified and contacted on the basis of the systematic search. Finally, because we were able to collect retinal vascular caliber data per BMI categories from each study, this reduced any heterogeneity in the categorisation of outcomes. This meta-analysis also has a number of limitations. First, an important limitation worth highlighting is the paucity of data on the prospective association



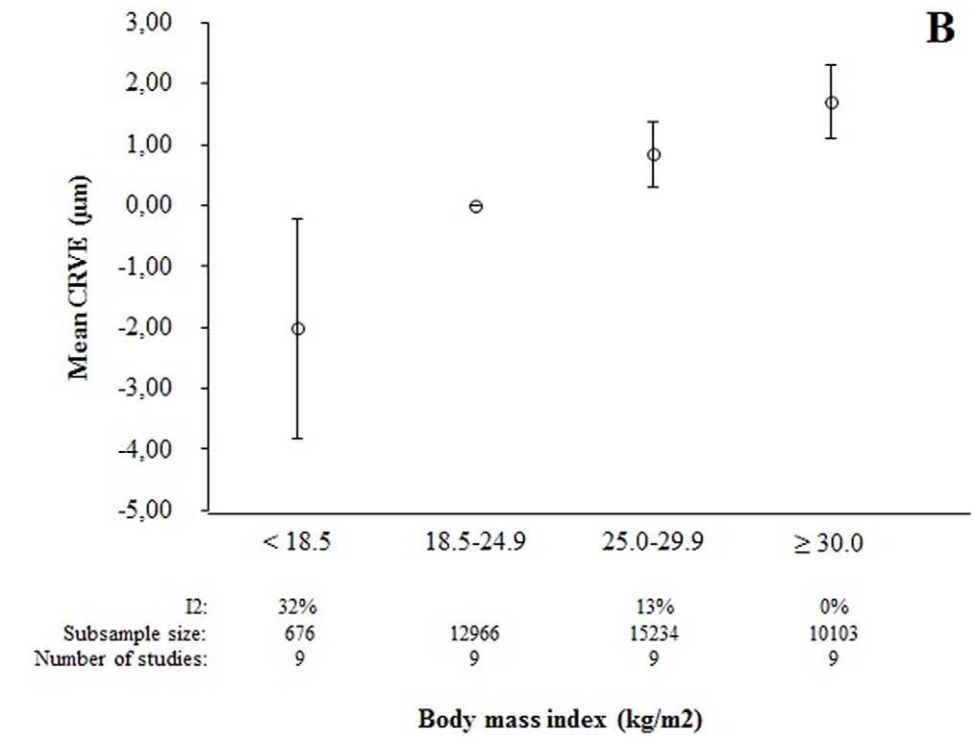


Figure 2. Adjusted adult mean retinal vascular values across BMI categories (maximum level of adjustment. CRAE (A); CRVE (B)).
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Table 2. Crude mean retinal vascular values across BMI categories.

	<18.5 vs [18.5; 24.99]		[18.5; 24.99] vs [25; 29.99]		[18.5; 24.99] vs ≥30	
	Mean difference (95% CI) (μm)	**Heterogeneity (I^2)**	**Mean difference (95% CI) (μm)**	**Heterogeneity (I^2)**	**Mean difference (95% CI) (μm)**	**Heterogeneity (I^2)**
Crude values. Adult studies[(1)]						
CRAE	3.25 [1.70, 4.80]†	22%	−1.04 [−1.62, −0.47]†	53%	−1.35 [−2.42, −0.28]†	82%
CRVE	−0.73 [−3.63, 2.16]	56%	1.54 [0.32, 2.76]†	81%	3.03 [1.04, 5.03]†	90%
Crude values. Children studies.[(2)]						
CRAE	1.89 [−1.13, 4.91]	87%	−1.44 [−2.90, 0.02]	56%	−1.59 [−4.18, 1.00]	63%
CRVE	0.31 [−3.26, 3.89]	82%	2.26 [0.90, 3.61]†	0%	6.54 [3.07, 10.02]†	62%

(1) *: p<0.05. †: p<0.01. <18.5 vs [18.5; 24.99]: n = 13642. [18.5; 24.99] vs [25; 29.99]: n = 28200. [18.5; 24.99] vs ≥30: n = 23069.
(2) *: p<0.05. †: p<0.01. <18.5 vs [18.5; 24.99]: n = 4004. [18.5; 24.99] vs [25; 29.99]: n = 4202. [18.5; 24.99] vs ≥30: n = 3647.
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between BMI and retinal vascular caliber, and also on the relationship between changes in BMI and in retinal vascular caliber over time. Consequently, a causal link cannot be extrapolated from these findings. Second, our study was limited to studies published in English, which results in a potential source of bias limiting the search to published reports. However, authors

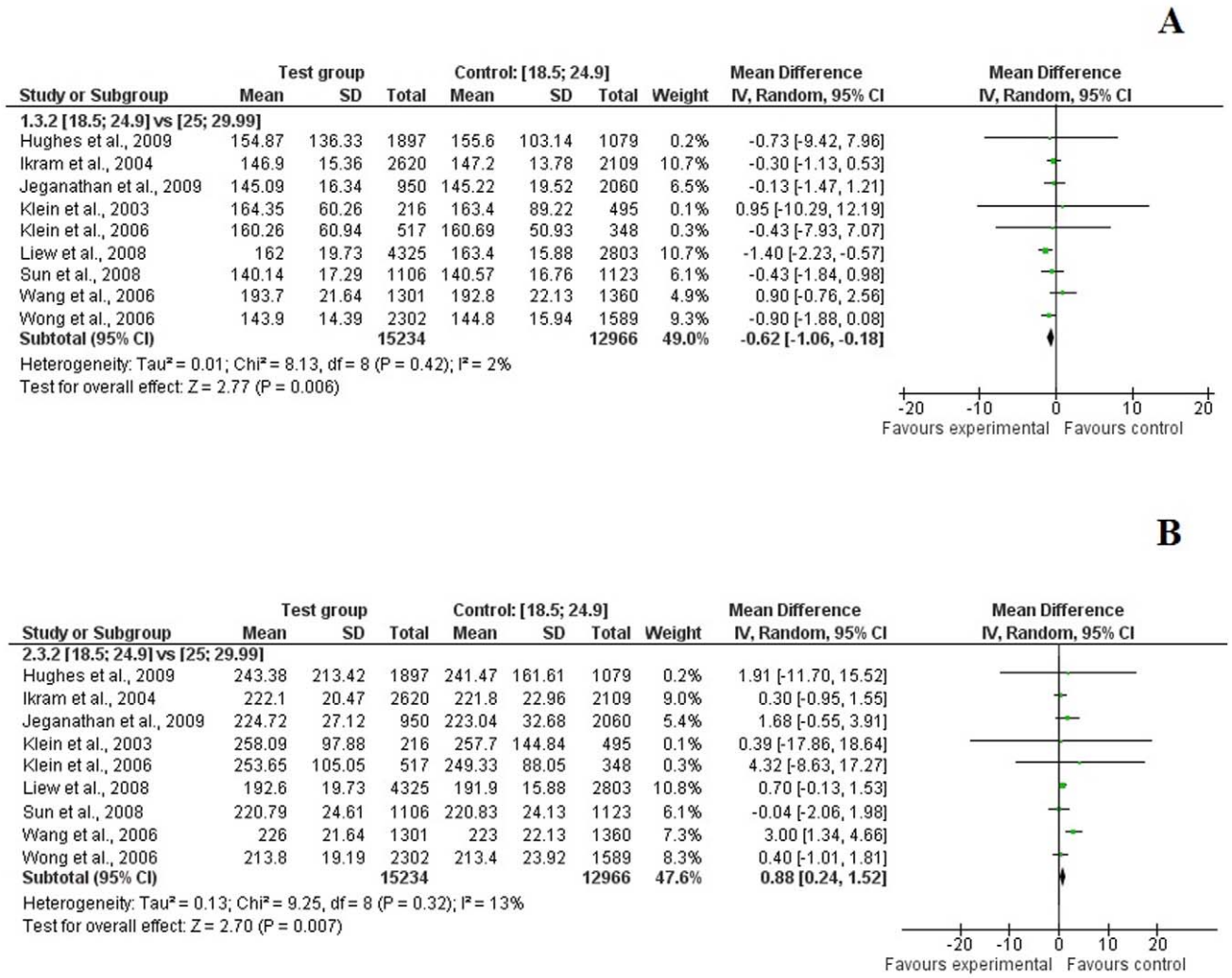


Figure 3. Association between overweight (BMI between 25.0 and 29.9 kg/m^2) and CRAE (*A*), and CRVE (*B*) in adults (maximum level of adjustment).
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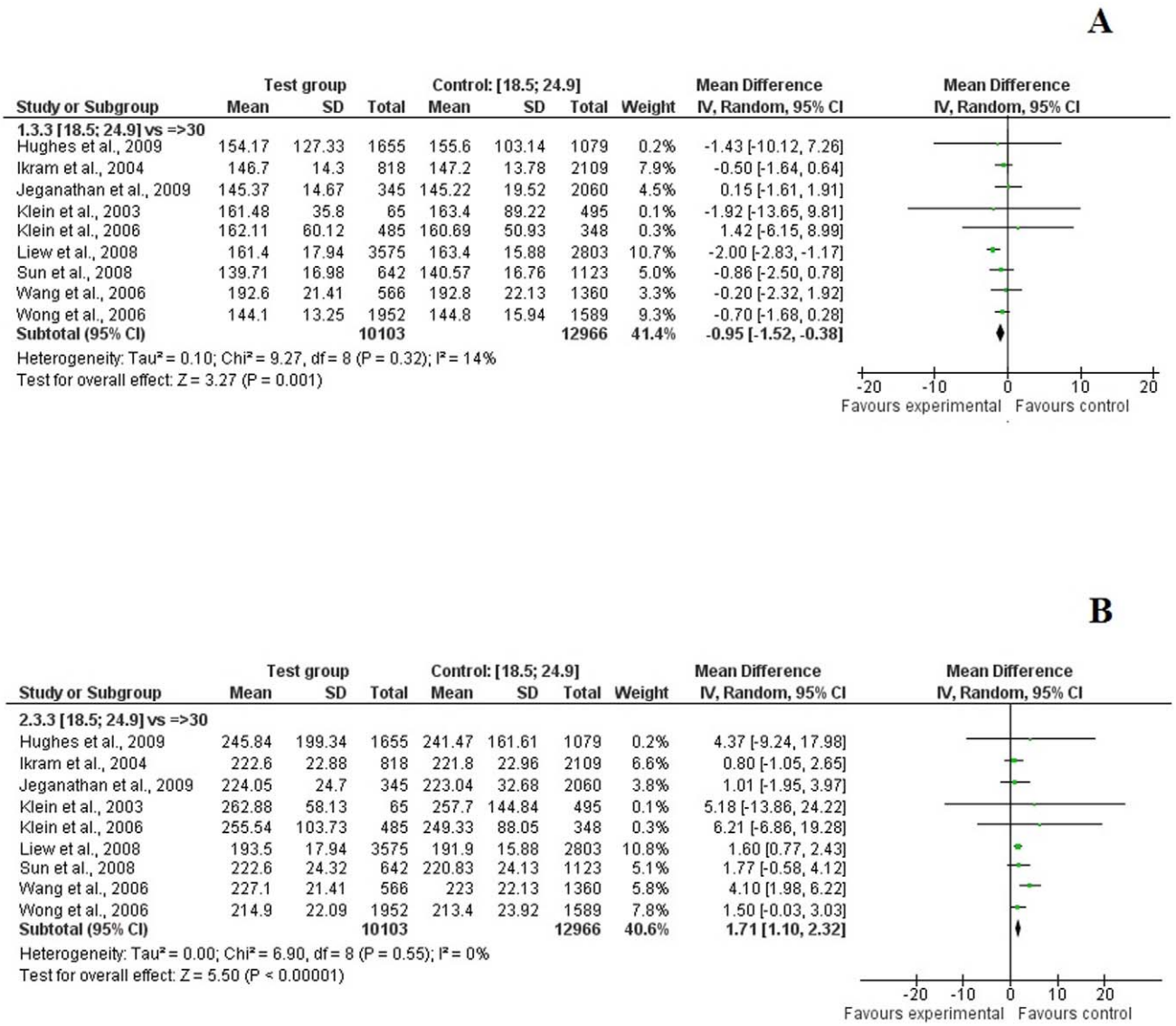


Figure 4. Association between obesity (BMI >30.0 kg/m^2) and CRAE (*A*), and CRVE (*B*) in adults (maximum level of adjustment).
doi:10.1371/journal.pone.0052708.g004

in this field were contacted to enhance the search field to grey litterature. Third, there is potential measurement bias due to different photographic procedures and software used in measuring retinal vascular caliber, resulting in possible overestimation or underestimation of the true association between BMI and retinal vascular calibers. Fourth, we standardized BMI categories according to the WHO classification for Caucasians whereas three studies were conducted in Asians [24,28–29]. Also, both unmeasured and residual confounding, e.g. due to measurement error, may have influenced our findings. However, when regression coefficients were pooled to obtain a summary estimate corresponding to the change in retinal parameters for a 1 kg/m2 increase in BMI, results were still significant and had a similar level of magnitude. Fifth, because we had no access to individual participant data we used the same BMI categories for adults and children.

In conclusion, we observed in a large pooled population a significant association between overweight/obesity and narrower retinal arteriolar and wider venular caliber, while controlling for traditional cardiovascular risk factors (age, smoking, diabetes and hypertension). These findings suggest that obesity is not only linked to macrovascular pathology but also to microvascular changes. Further prospective studies are needed to explore a possible causative association between BMI and retinal microvasculature, which mirrors changes in the systemic microvasculature, including the microcirculation of the heart. If such a relationship is confirmed, examining retinal vascular caliber may provide information about small vessel alterations among individuals with obesity and other cardiovascular risk profiles. Small vessel disease is increasingly being recognized as a contributor to cardiovascular and cerebrovascular diseases, however, there is no widely available tool by which to assess small vessel condition. Retinal imaging and retinal vascular structural assessment may help to fill in this gap.

Supporting Information

Table S1 Sensitive search strategy.
(DOC)

Table S2 Description of studies included in the meta-analysis.
(DOC)

Table S3 Adjusted children mean retinal vascular values across BMI categories (maximum level of adjustment). **: $p<0.05$. †: $p<0.01$. <18.5 vs [18.5; 24.99]: n = 4004. [18.5; 24.99] vs [25; 29.99]: n = 4202. [18.5; 24.99] vs ≥30: n = 3647.*
(DOC)

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Interpretation of data: LF, CI. Collection of data and descriptive analysis: XYL, ER, TJ, KL, CM, PTdJ, JRV, JX, NCT, KOK, TIS, AK, AW.

Author Contributions

Conceived and designed the experiments: AB SZ TYW SC. Performed the experiments: PM RK BK MKI CK JJW BG EST ASN SH LB SMS. Analyzed the data: AB SC. Wrote the paper: AB SC TYW SZ.

References

1. Fortunato G, Rubba P, Panico S, Trono D, Tinto N, et al. (2003) A paraoxonase gene polymorphism, PON 1 (55), as an independent risk factor for increased carotid intima-media thickness in middle-aged women. Atherosclerosis 167: 141–148.
2. Kotsis VT, Stabouli SV, Papamichael CM, Zakopoulos NA (2006) Impact of obesity in intima media thickness of carotid arteries. Obesity (Silver Spring) 14: 1708–1715.
3. Berni A, Giuliani A, Tartaglia F, Tromba L, Sgueglia M, et al. (2011) Effect of vascular risk factors on increase in carotid and femoral intima-media thickness. Identification of a risk scale. Atherosclerosis 216: 109–114.
4. Czernichow S, Greenfield JR, Galan P, Bastard JP, Charnaux N, et al. (2010) Microvascular dysfunction in healthy insulin-sensitive overweight individuals. J Hypertens 28: 325–332.
5. Czernichow S, Greenfield JR, Galan P, Jellouli F, Safar ME, et al. (2010) Macrovascular and microvascular dysfunction in the metabolic syndrome. Hypertens Res 33: 293–297.
6. de Jongh RT, Serne EH, RG IJ, de Vries G, Stehouwer CD (2004) Impaired microvascular function in obesity: implications for obesity-associated microangiopathy, hypertension, and insulin resistance. Circulation 109: 2529–2535.
7. Klein R, Klein BE, Moss SE, Wong TY, Sharrett AR (2006) Retinal vascular caliber in persons with type 2 diabetes: the Wisconsin Epidemiological Study of Diabetic Retinopathy: XX. Ophthalmology 113: 1488–1498.
8. Wong TY, Duncan BB, Golden SH, Klein R, Couper DJ, et al. (2004) Associations between the metabolic syndrome and retinal microvascular signs: the Atherosclerosis Risk In Communities study. Invest Ophthalmol Vis Sci 45: 2949–2954.
9. Taylor B, Rochtchina E, Wang JJ, Wong TY, Heikal S, et al. (2007) Body mass index and its effects on retinal vessel diameter in 6-year-old children. Int J Obes (Lond) 31: 1527–1533.
10. Kato K, Calafat AM, Wong LY, Wanigatunga AA, Caudill SP, et al. (2009) Polyfluoroalkyl compounds in pooled sera from children participating in the National Health and Nutrition Examination Survey 2001–2002. Environ Sci Technol 43: 2641–2647.
11. Wong TY, Shankar A, Klein R, Klein BE, Hubbard LD (2004) Prospective cohort study of retinal vessel diameters and risk of hypertension. BMJ 329: 79.
12. Wong TY, Klein R, Sharrett AR, Duncan BB, Couper DJ, et al. (2002) Retinal arteriolar narrowing and risk of coronary heart disease in men and women. The Atherosclerosis Risk in Communities Study. JAMA 287: 1153–1159.
13. McGeechan K, Liew G, Macaskill P, Irwig L, Klein R, et al. (2009) Prediction of incident stroke events based on retinal vessel caliber: a systematic review and individual-participant meta-analysis. Am J Epidemiol 170: 1323–1332.
14. Wong TY, Klein R, Couper DJ, Cooper LS, Shahar E, et al. (2001) Retinal microvascular abnormalities and incident stroke: the Atherosclerosis Risk in Communities Study. Lancet 358: 1134–1140.
15. Sun C, Wang JJ, Mackey DA, Wong TY (2009) Retinal vascular caliber: systemic, environmental, and genetic associations. Surv Ophthalmol 54: 74–95.
16. Ikram MK, de Jong FJ, Vingerling JR, Witteman JC, Hofman A, et al. (2004) Are retinal arteriolar or venular diameters associated with markers for cardiovascular disorders? The Rotterdam Study. Invest Ophthalmol Vis Sci 45: 2129–2134.
17. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, et al. (2000) Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA 283: 2008–2012.
18. Hubbard LD, Brothers RJ, King WN, Clegg LX, Klein R, et al. (1999) Methods for evaluation of retinal microvascular abnormalities associated with hypertension/sclerosis in the Atherosclerosis Risk in Communities Study. Ophthalmology 106: 2269–2280.
19. Knudtson MD, Lee KE, Hubbard LD, Wong TY, Klein R, et al. (2003) Revised formulas for summarizing retinal vessel diameters. Curr Eye Res 27: 143–149.
20. Higgins JP, Thompson SG, Deeks JJ, Altman DG (2003) Measuring inconsistency in meta-analyses. BMJ 327: 557–560.
21. Egger M, Davey Smith G, Schneider M, Minder C (1997) Bias in meta-analysis detected by a simple, graphical test. BMJ 315: 629–634.
22. Wong TY, Islam FM, Klein R, Klein BE, Cotch MF, et al. (2006) Retinal vascular caliber, cardiovascular risk factors, and inflammation: the multi-ethnic study of atherosclerosis (MESA). Invest Ophthalmol Vis Sci 47: 2341–2350.
23. Klein R, Klein BE, Moss SE, Wong TY, Hubbard L, et al. (2003) Retinal vascular abnormalities in persons with type 1 diabetes: the Wisconsin Epidemiologic Study of Diabetic Retinopathy: XVIII. Ophthalmology 110: 2118–2125.
24. Cheung N, Saw SM, Islam FM, Rogers SL, Shankar A, et al. (2007) BMI and retinal vascular caliber in children. Obesity (Silver Spring) 15: 209–215.
25. Gopinath B, Baur LA, Teber E, Liew G, Wong TY, et al. (2011) Effect of obesity on retinal vascular structure in pre-adolescent children. Int J Pediatr Obes 6: e353–359.
26. Liew G, Sharrett AR, Wang JJ, Klein R, Klein BE, et al. (2008) Relative importance of systemic determinants of retinal arteriolar and venular caliber: the atherosclerosis risk in communities study. Arch Ophthalmol 126: 1404–1410.
27. Wang JJ, Taylor B, Wong TY, Chua B, Rochtchina E, et al. (2006) Retinal vessel diameters and obesity: a population-based study in older persons. Obesity (Silver Spring) 14: 206–214.
28. Jeganathan VS, Sabanayagam C, Tai ES, Lee J, Sun C, et al. (2009) Effect of blood pressure on the retinal vasculature in a multi-ethnic Asian population. Hypertens Res 32: 975–982.
29. Sun C, Liew G, Wang JJ, Mitchell P, Saw SM, et al. (2008) Retinal vascular caliber, blood pressure, and cardiovascular risk factors in an Asian population: the Singapore Malay Eye Study. Invest Ophthalmol Vis Sci 49: 1784–1790.
30. Hughes AD, Wong TY, Witt N, Evans R, Thom SA, et al. (2009) Determinants of retinal microvascular architecture in normal subjects. Microcirculation 16: 159–166.
31. Stapleton PA, James ME, Goodwill AG, Frisbee JC (2008) Obesity and vascular dysfunction. Pathophysiology 15: 79–89.
32. Stepp DW, Boesen EI, Sullivan JC, Mintz JD, Hair CD, et al. (2007) Obesity augments vasoconstrictor reactivity to angiotensin II in the renal circulation of the Zucker rat. Am J Physiol Heart Circ Physiol 293: H2537–2542.
33. Cardillo C, Campia U, Bryant MB, Panza JA (2002) Increased activity of endogenous endothelin in patients with type II diabetes mellitus. Circulation 106: 1783–1787.
34. Frisbee JC, Maier KG, Stepp DW (2002) Oxidant stress-induced increase in myogenic activation of skeletal muscle resistance arteries in obese Zucker rats. Am J Physiol Heart Circ Physiol 283: H2160–2168.
35. Clerk LH, Vincent MA, Jahn LA, Liu Z, Lindner JR, et al. (2006) Obesity blunts insulin-mediated microvascular recruitment in human forearm muscle. Diabetes 55: 1436–1442.
36. Zebekakis PE, Nawrot T, Thijs L, Balkestein EJ, van der Heijden-Spek J, et al. (2005) Obesity is associated with increased arterial stiffness from adolescence until old age. J Hypertens 23: 1839–1846.
37. Knudson JD, Dincer UD, Bratz IN, Sturek M, Dick GM, et al. (2007) Mechanisms of coronary dysfunction in obesity and insulin resistance. Microcirculation 14: 317–338.
38. Hodnett BL, Hester RL (2007) Regulation of muscle blood flow in obesity. Microcirculation 14: 273–288.

39. Bogers RP, Bemelmans WJ, Hoogenveen RT, Boshuizen HC, Woodward M, et al. (2007) Association of overweight with increased risk of coronary heart disease partly independent of blood pressure and cholesterol levels: a meta-analysis of 21 cohort studies including more than 300 000 persons. Arch Intern Med 167: 1720–1728.
40. Strazzullo P, D'Elia L, Cairella G, Garbagnati F, Cappuccio FP, et al. (2010) Excess body weight and incidence of stroke: meta-analysis of prospective studies with 2 million participants. Stroke 41: e418–426.
41. Ageno W, Becattini C, Brighton T, Selby R, Kamphuisen PW (2008) Cardiovascular risk factors and venous thromboembolism: a meta-analysis. Circulation 117: 93–102.
42. Czernichow S, Kengne AP, Stamatakis E, Hamer M, Batty GD (2011) Body mass index, waist circumference and waist-hip ratio: which is the better discriminator of cardiovascular disease mortality risk?: evidence from an individual-participant meta-analysis of 82 864 participants from nine cohort studies. Obes Rev 12(9): 680–7.
43. McGeechan K, Liew G, Macaskill P, Irwig L, Klein R, et al. (2009) Meta-analysis: retinal vessel caliber and risk for coronary heart disease. Ann Intern Med 151: 404–413.