A systematic review and participant-level meta-analysis found little association of retinal microvascular caliber and reduced kidney function

Lye, W. K., Paterson, E., Patterson, C. C., Maxwell, A. P., Binte Mohammed Abdul, R. B., Tai, E. S., Cheng, C. Y., Kayama, T., Yamashita, H., Sarnak, M., Shlipak, M., Matsushita, K., Mutlu, U., Ikram, M. A., Klaver, C., Kifley, A., Mitchell, P., Myers, C., Klein, B. E., ... McKay, G. J. (2020). A systematic review and participant-level meta-analysis found little association of retinal microvascular caliber and reduced kidney function. *Kidney International*, *2020*, 1. Advance online publication. https://doi.org/10.1016/j.kint.2020.06.033

Published in:
Kidney International

Document Version:
Peer reviewed version

Queen's University Belfast - Research Portal:
Link to publication record in Queen's University Belfast Research Portal

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Download date:16. Jul. 2024

Title page

Retinal microvascular caliber and chronic kidney disease: a systematic review and participant-level meta-analysis.

Running headline: Retinal microvascular caliber and chronic kidney disease

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Abstract

Previously, variation in retinal vascular caliber has been reported in association with chronic kidney disease (CKD) but findings remain inconsistent. To help clarify this we conducted individual participant data meta-analysis and aggregate data meta-analysis on summary estimates to evaluate cross-sectional associations between retinal vascular caliber and CKD. A systematic review was performed using Medline and EMBASE for articles published until October 2018. The aggregate analysis used a two-stage approach combining summary estimates from eleven studies (n=44,803 participants) while the individual participant analysis used a one-stage approach combining raw data from nine studies (n=33,222 participants). CKD stages 3-5 was defined as an estimated glomerular filtration rate under 60 mL/min/1.73m^2. Retinal arteriolar and venular caliber (central retinal arteriolar and venular equivalent) were assessed from retinal photographs using computer-assisted methods. Logistic regression estimated relative risk (RR) of CKD stages 3-5 associated with a 20 µm decrease (approximately one standard deviation) in central retinal and arteriolar equivalent. Prevalence of CKD stages 3-5 was 11.2 % of 33,222 and 11.3 % of 44,803 patients in the individual participant and aggregate data analysis, respectively. No significant associations were detected in adjusted analyses between central retinal arteriolar and venular equivalent and CKD stages 3-5 in the aggregate analysis for central retinal arteriolar relative risk (0.98, 95% confidence interval 0.94-1.03); venular equivalent (0.99, 0.95- 1.04) or individual participant central retinal arteriolar (0.99, 0.95-1.04) or venular equivalent (1.01, 0.97-1.05). Thus, meta-analysis provided little evidence to suggest that cross sectional direct measurements of retinal vascular caliber was associated with CKD stages 3-5 in the general population. Hence, meta-analyses of longitudinal studies evaluating the association between retinal parameters and CKD stages 3-5 may be warranted.

Keywords: chronic kidney disease, retina, microvasculature, biomarker, caliber

Translational Statement

Estimated glomerular filtration rate and urinary albumin to creatinine ratio are useful for diagnosis of chronic kidney disease (CKD) but have limited use for prediction of progression to end-stage renal disease. Direct examination of clinically relevant tissue may aid CKD risk prediction but renal biopsies are invasive, costly and not appropriate for repeated assessments in at risk individuals. The retinal microvasculature is uniquely amenable to non-invasive, rapid, and repeated imaging, using widely available fundus cameras, commonly used in diabetic eye screening. These retinal images may be sufficiently sensitive to identify early systemic vascular changes related to CKD and aid in risk stratification of CKD progression.

Introduction

With an estimated prevalence of 13% in the US[1] and from 3 to 17% in countries worldwide,[1–6] chronic kidney disease (CKD) is considered a global public health issue. Furthermore, CKD is predicted to become the fifth most common cause of death worldwide by 2040[7]. Clinically, CKD can be defined as persistently elevated urinary albumin excretion (e.g. a urinary albumin to creatinine ratio of at least 30 mg/g) or an estimated glomerular filtration rate (eGFR) of less than 60 mL/min/1.73m^2.[8] CKD is characterized by irreversible reductions in the excretory and homeostatic functions of the kidneys[9–12] that lead to greatly increased risk of several adverse outcomes including cardiovascular mortality.[13]

Early detection of CKD remains challenging because eGFR calculations are less precise when applied to individuals with small reductions in renal function.[14] Reduced eGFR and elevated urinary albumin to creatinine ratio provide predictive value for progressive renal decline and end-stage renal disease but only at levels already associated with increased mortality and cardiovascular disease risk.[15] A variety of risk scores and biochemical[16–18] and genetic markers[19] have been explored to improve prediction algorithms for CKD. Direct examination of a relevant tissue would aid prediction of CKD risk but renal biopsies are costly, invasive, potentially hazardous and not appropriate for repeated assessments in individuals at increased risk of renal disease. Microvascular injury may result in impaired vascular homeostasis and aberrant vascular calcification in response to small reductions in renal function.[11,20]

The retinal microvasculature is uniquely amenable to non-invasive, rapid, and repeatable imaging that may reflect physiological changes in the kidney, given the shared properties between the cells of both renal and ocular microvascular beds.[21] Indeed, previous associations between renal function and retinal microvascular caliber have been reported in several cross-sectional and prospective studies independent of established CKD risk factors, such as diabetes and hypertension. Specifically, narrower arteriolar and venular caliber have been associated with lower eGFR and incident CKD.[22–

[33] However, the findings reported have not always been consistent.[34,35] Therefore, this meta-analysis of cross-sectional studies sought to address the hypothesis that retinal arteriolar and venular calibers are associated with CKD stages 3-5 (eGFR < 60 mL/min/1.73m^2) in the general population.

Results

Study inclusion and characteristics

Following the application of inclusion/exclusion criteria, eleven cohorts (n=44,803) were included in the aggregate data meta-analysis (AD-MA) (ARIC,[32] BDES,[27] BMES,[36] CHS,[37] MESA,[26] Rotterdam,[38] SCES,[39] SiMES,[24] SINDI,[40] SP2,[41] Takahata,[42]), and nine of these cohorts (n=33,222) were included in the individual participant data meta-analysis (IPD-MA) (Figure 1; ARIC,[32] BMES,[36] CHS,[37] MESA,[26] SCES,[39] SiMES,[24] SINDI,[40] SP2,[41] Takahata,[42]). Data from studies included were collected between 1988 and 2011. The majority of studies collected participant data from a variety of ethnicities in the USA[26,27,32,37] and Singapore,[24,39–41] in addition to data collected from the Netherlands [38] and Japan.[42]

Study characteristics are provided in Table 1. Mean study age varied between 49.7 years (standard deviation [SD] 11.4) to 78.3 years (SD 9.1), and age ranged from 24 - 97 years. CKD stages 3-5 was prevalent in 11.2% (n=3,717) of the IPD-MA and 11.3% (n=5,078) of the AD-MA study participants. Hypertension was present in a large proportion of participants ranging from 39.4% (n = 1,254) in the SP2 study to 68.1% (n = 1,934) in the SiMES study. Diabetes prevalence ranged from 7.0% (n = 80) in the Takahata study to 38.9% (n = 1,156) in the SINDI study. Study participant ethnicity was classified as white in 56.7% (n = 25,404), black in 9.1% (n = 4,085), American Indian 2.8% (n = 1,265) or other, including Asian ethnicities 31.4% (n = 14,049).

Aggregate data meta-analysis

Outputs from the random effects AD-MA with relative risks (RR) for CKD stages 3-5 calculated per 20µm decrease in central retinal arteriolar equivalent (CRAE) and central retinal venular equivalent (CRVE) are presented in Tables 2 and 3 respectively. Forest plots for fully adjusted model 3 with CRAE and CRVE as the predictor variable are presented in Figures 2 and 3 respectively. There was little evidence to suggest that CRAE was associated with CKD stages 3-5. Lower CRAE (narrower arterioles) was significantly associated with lower relative risk of CKD stages 3-5 in the minimally adjusted model 1 (pooled RR = 0.95; 95% confidence interval [CI], 0.91, 0.99). However, the association did not remain significant following adjustment in the multivariable model 2 (pooled RR = 0.98; 95% CI, 0.94, 1.01) and model 3 (pooled RR = 0.98; 95% CI, 0.94, 1.03). Similarly, there was little evidence of an association between CRVE and CKD stages 3-5 in the AD-MA (model 1: pooled RR = 0.97; 95% CI, 0.94, 1.01; model 2: pooled RR = 0.98; 95% CI, 0.95, 1.02; model 3: pooled RR = 0.99; 95% CI, 0.95, 1.04). However, in the CRVE analysis between-study heterogeneity was significant (model 1, I^2= 50%, p= 0.03; model 2, I^2= 50%, p= 0.03; model 3, I^2= 47%, p= 0.04). In the minimally adjusted model, two studies (MESA and BDES) both showed a small but significant positive association between wider CRVE and CKD stages 3-5 , and for BDES this remained significant even in the fully adjusted model (Table 3, Figure 3).

Individual participant data meta-analysis

In the IPD-MA, the results did not support an association between CRAE or CRVE and CKD stages 3-5. Narrower retinal arteriolar caliber was not significantly associated with risk of CKD stages 3-5 following adjustment for age, sex and study center (CRAE model 1: pooled RR = 0.97; 95% CI, 0.94, 1.01, Table 4) or further adjustment for potential confounders (model 2: pooled RR = 0.99; 95% CI, 0.96, 1.04; model 3: pooled RR = 0.99, 95% CI, 0.95, 1.04. Similarly, narrower retinal venular caliber was not significantly associated with CKD stages 3-5 in any of the models tested (CRVE model 1:

pooled RR = 1.00; 95% CI, 0.97, 1.03; model 2: pooled RR = 0.98; 95% CI, 0.94, 1.03; model 3: pooled RR = 1.01, 95% CI, 0.97, 1.05).

In subgroup analyses of the IPD-MA (Table 5), lower CRAE was significantly associated with reduced risk of CKD stages 3-5 in those with diabetes (RR = 0.88, 95% CI 0.81, 0.96) and in those of American Indian ethnicity (RR = 0.71, 95% CI 0.52, 0.96) after adjustment for age, sex, ethnicity (if multi-ethnic), current smoking, diabetes, hypertension, body mass index (BMI), total cholesterol and fellow vessel central retinal equivalent. No evidence of association between CKD stages 3-5 and retinal caliber in other subgroups was found. Furthermore, sensitivity analyses, including stratification to allow for variation in CKD prevalence and exclusion of studies such as ARIC with large numbers of controls but few cases, revealed no significant deviation from the main IPD-MA findings.

Discussion

Direct examination of the retinal vasculature provides a non-invasive means of assessing systemic vascular health that may be sensitive to early vascular changes associated with CKD and offer utility in the stratification of CKD progression. Indeed, previous meta-analyses have identified changes in retinal vessel caliber in diabetes and hypertension.[43-44] two important contributors to CKD and its progression. Therefore, we assessed non-invasive measures of retinal vessel caliber, for associations with CKD in cross-sectional AD-MA and IPD-MA.

Pooled estimates from AD-MA from eleven studies including 44,803 participants, and from IPD-MA of nine studies including 33,222 participants did not provide evidence in support of associations between retinal vessel caliber (CRAE or CRVE) and CKD stages 3-5 the general population, independent of the potential confounding variables considered, and only weak associations in models

including fewer covariates. Subgroup analyses showed a weak but significant association between narrower arteriolar caliber and CKD stages 3-5 in those with diabetes (RR = 0.88, 95% CI 0.81, 0.96) and in those of American Indian ethnicity (RR = 0.71, 95% CI 0.52, 0.96). However, the effect size of these associations were small to moderate, and the risk of type 1 error resulting from the number of sub-groups tested suggests independent replication in future studies should be considered.

Several studies included have previously indicated associations between retinal vascular caliber and CKD stages 3-5 that may reflect population variation while highlighting the necessity of adjustment for appropriate confounders. Reported prevalence of CKD stages 3-5 differed markedly between studies. The ARIC study accounted for nearly a quarter of participants included in the AD-MA, but had a very low prevalence of CKD stages 3-5 (3%), while BMES and CHS reported a prevalence of CKD stages 3-5 between 8% and 20% respectively. Estimating equations used to calculate eGFR are less sensitive in individuals at values around and above 60 mL/min/1.73m^2, and the dichotomization of the renal function used in the AD-MA, may have contributed to the lack of associations detected. Likewise, variation in additional potential confounding vascular effects also varied widely between the included studies. Hypertension for example, was almost twice as common in SiMES compared to SP2, while SINDI had a diabetes prevalence more than 5-fold greater than recorded in the Takahata study. Both diabetes and hypertension are associated with variation in the retinal vasculature[43,44] and so direct comparisons between studies can prove challenging.

Genetic and environmental differences between study populations may also contribute to variation in the associations observed. Within MESA, an association between narrower retinal arterioles and CKD stages 3-5 was reported in "whites" only but not in other ethnic/racial groups, with inter-ethnic variation proposed as a potential explanation, possibly as a consequence of multi-ethnic variation in the contrast levels represented by melanin deposition within the retinal pigment epithelium.[26] Lower levels of retinal pigmentation improves the contrast between the retinal vessels and the underlying

fundus, enabling more accurate vascular caliber estimates.[45] However, subgroup analyses in the present study failed to detect associations between retinal vascular caliber and CKD stages 3-5 according to racial subgroup beyond those of American Indian ethnicity.

This study had several strengths. The retinal imaging used to evaluate the clinical utility of retinal caliber as a potentially novel CKD biomarker is widely available. The search strategy included major databases (Medline and EMBASE), minimizing the likelihood of excluding relevant studies, and facilitating the use of IPD-MA through the provision of individual-level data. The large sample size achieved through pooling data in a meta-analysis minimized the risk of type 2 error and the use of population-based studies reduced the potential for selection bias. The study populations included were well-characterized enabling adjustment for potential confounders (study center, age, sex, ethnicity, education, current smoking, diabetes, hypertension, BMI, total cholesterol and fellow vessel caliber). The inclusion of several multi-center studies further reduced the risk of bias given they are less likely to over-estimate effect sizes compared to single center studies alone[46].

The generalizability of the findings was improved by the inclusion of population-based studies from the US, Europe, South East Asia, and Japan, comprising a wide range of ethnicities and age groups (Table 1). Notwithstanding the age and ethnic variation among the studies included, a low level of heterogeneity was observed between studies for CRAE and CRVE in the IPD-MA (Table 4). *A priori* random effects modelling was considered more appropriate, as it does not assume homogeneity of RRs across studies and produces results more suitable for generalisation to other populations. Nevertheless, a sensitivity analysis using fixed effects did not result in any substantive changes in the direction of associations, effect sizes, or statistical significance (data not shown). Furthermore, the funnel plots representing the data included in the meta-analysis suggest a low risk of publication bias (Supplementary Figures S1 and S2). Additionally, the inclusion criteria used were limited to studies that obtained retinal vascular caliber measurements using computer-aided methods. Automated

algorithmic retinal vessel caliber measurement platforms have excellent inter-operator reliability[47] which exceeds that of manual vessel tracing[48,49].

The study undertaken also had several limitations. Although meta-analysis provides an improved level of evidence compared with single observational studies, the cross-sectional nature of our analysis precludes identification of causal relationships and generally provides weaker evidence compared with cohort or case-control study designs in which cause and effect are separated in time. Furthermore, cross-sectional analyses are especially susceptible to survival bias, which is less of an issue in the evaluation of longitudinal data. Indeed, given previously reported associations between conditions such as diabetes, hypertension and cardiovascular disease and retinal caliber, and that the natural history of such retinal microvascular changes are not well defined, longitudinal analyses may prove beneficial. The studies included in the present meta-analyses consist of studies with data collection periods ranging from 1987[32] to 2006[24]. As a result, data collection methods and image acquisition technologies varied between studies. For example, more recent studies acquired photographs using digital cameras, while studies making use of older image sets used digitized images[32,38,50] Digital retinal images are more prone to illumination problems (over/under saturation) and tend to have poorer green channel contrast.[51] Similarly, field of view and image centring varied between studies and as a consequence, study center was adjusted for in all models. These parameters may affect measured (as opposed to actual) vessel caliber. Despite such differences, the studies included reported good reproducibility and the heterogeneity between studies was low to moderate indicating suitability for pooled meta-analysis of data. In addition, the studies included made use of the Knudtson and Parr-Hubbard formulae for caliber estimation. These formulae have shown significant correlation with coefficients exceeding 0.94[52] and were thus considered suitable for pooled analyses. The CRAE and CRVE measurement units used in the studies included rely on an estimation of scale based on the assumption of an average optic disc size (1800 μm). This may lead to unaccounted variability as differences in the physiology of the eye and magnification artefacts may

prove challenging using standard fundus photography.[53] However, in practice, associations of vessel caliber with related outcomes such as blood pressure appear not to be significantly altered by refractive error.[36,54] Relative risks for associations were calculated per 20 μm decrease in CRAE or CRVE and were calculated on the assumption of a linear relationship. It may be that a non-linear model better describes the data. Associations with CKD stages 3-5 have also been reported for retinal pathologies such as retinopathy and for other retinal microvascular parameters such as fractal dimension, tortuosity and branching angle. These were not assessed in the present study and so conclusions relating to these parameters cannot be drawn.

The definition of CKD stages 3-5 applied in this study was based on a single eGFR measurement with a value < 60 mL/min/1.73m^2 and failed to account for variation in renal function or renal damage as indicated by elevated urinary albumin to creatinine ratio. This is common in population-based epidemiological studies but differs from clinical CKD staging which, in the absence of proteinuria, depends on two measures of eGFR < 60 mL/min/1.73m^2 over at least a 3 month period.[8] Single eGFR measures captured through population-based studies are usually stable and mild compared to clinically confirmed cases. As such, population-based studies may not accurately reflect clinically observed eGFR and may give conclusions which are not readily applicable to clinically confirmed CKD. Several studies included were unable to determine eGFR from serum creatinine samples collected on the same day as the retinal imaging, increasing the potential for random error being introduced into the analysis by day-to-day variations in the measurements. The use of an estimating equation to calculate eGFR and define CKD stages 3-5 may result in misclassification as the CKD-EPI equation has been reported to have reduced precision for higher eGFR levels,[14] potentially leading to misclassification and possibly reduced study power compared to direct measurement of GFR. However, direct measurement of GFR, e.g. by inulin clearance, is impractical in large population-based studies. Furthermore, the underlying cause of reduced renal function is important but pathology and prognosis remained largely unaccounted for in most of the studies included and so

could not be considered in the context of this meta-analysis. Proteinuria can occur independently of reduced eGFR and has been reported in association with retinal vascular caliber in several studies.[22,24,32,54,55] Assessment of this association and the potential predictive capacity of proteinuria with retinal vessel caliber was beyond the scope of the present study.

The results of these cross-sectional meta-analyses provided little evidence that direct measurement of retinal microvascular caliber provides a means of assessing systemic vascular health associated with CKD stage 3-5 beyond what can be explained by confounding variables. Further studies are also required to establish longitudinal associations between retinal microvascular caliber and other measures of renal function and damage.

Methods

We conducted two meta-analyses using AD-MA and IPD-MA to evaluate the cross-sectional association between retinal vessel caliber and CKD stages 3-5. AD-MA combines the summary measures reported by each study, whereas IPD-MA relies on the availability of combined individual level data from each participant within the studies.

Literature search, study selection & data extraction

MEDLINE and EMBASE were searched for articles published up to October 2018 using pre-specified search terms for Medline: [exp Microvessels/ or vessel*.mp. or caliber.mp. or calibre.mp. or vein*.mp. or arter*.mp. or vascular.mp.] and [retina*.mp.] and [(kidney or renal or GFR or eGFR or glomerular or CKD).mp.]; and translated for EMBASE: [exp microvasculature/ or vessel*.mp. or caliber.mp. or calibre.mp. or vein*.mp. or arter*.mp. or vascular.mp.] and [retina*.mp.] and [(kidney or renal or GFR or eGFR or glomerular or CKD).mp.]. In addition, reference lists and conference proceedings were screened to identify additional studies. Further studies and unpublished data were

also identified through discussion with collaborators. Studies were independently assessed for suitability for inclusion by study authors (CS and GMK). Any lack of clarity or agreement was resolved through discussion.

Population-based studies in adults, with measurements of renal function and computer-assisted measurements of retinal vascular caliber from digital photographs, or digitized images from 35 mm photographic film originals, published in the English language were eligible for inclusion. Individual participant data were requested from study principal investigators. Requested data points included age, sex, ethnicity, systolic blood pressure, diastolic blood pressure, total cholesterol, diabetes, smoking status, body mass index, cardiovascular disease history, retinal arteriolar and venular caliber measurements and eGFR. Inclusion criteria for participants in the IPD-MA required data to be available for at least eGFR, presence/absence of diabetes, and retinal vascular caliber. For studies meeting inclusion criteria, study quality and risk of bias were assessed using the guidelines published by Hayden et al.[56] The assessment included evaluation of study participation, attrition, measurement of prognostic factors, outcome, confounding factors, and data analysis (Table 6). All eligible studies were considered to have an acceptable risk of bias for inclusion.

Qualitative assessment of studies meeting inclusion criteria indicated suitability for data pooling. Similar methods for retinal vessel caliber measurement were used in all studies, without substantive variation. Retinal vessel caliber measurements were obtained from optic disc centered images and were recorded from participants' right eyes in most cases. CRAE and CRVE were calculated using the Parr-Hubbard formula[57] or revised Knudston formula[52] in all studies using the following software packages: Interactive Vessel Analysis (IVAN, University of Wisconsin, Madison, WI, USA) and Retinal Analysis (Optimate, Madison, WI, USA). All studies used trained image graders that were blinded. Reproducibility for retinal arteriolar and venular caliber was good in studies included, with intra- and inter- grader reliability coefficients ranging from 0.69 to 0.99.

For the meta-analyses, CKD stages 3-5 was defined as an eGFR < 60 mL/min/1.73m^2. eGFR was calculated using the CKD-EPI equation using isotope dilution mass spectrometry (IDMS) calibrated serum creatinine values. In cohorts where standardized creatinine is not available, we used a calibration factor (reduce creatinine levels by 5%) to match it to IDMS.[58] Retinal caliber was expressed as the CRAE and CRVE measured in microns (μm). CRAE and CRVE provide summary scores for vessel caliber accounting for all major arterioles and venules passing through an annular zone around the optic disc, extending from 0.5 to 1.0 optic disc diameters (ODD) from the optic disc margin.

Statistical analysis:

Statistical analyses were performed using Review Manager (RevMan) Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014. Logistic regression models were constructed using study baseline data to estimate RRs and 95% CI of CKD stages 3-5 associated with a 20 μm (approximately 1 standard deviation [SD]) narrower CRAE or CRVE. For AD-MA, pooled estimates were obtained using a two-stage approach. In the first stage, association estimates were calculated separately for each individual study and in the second stage, estimates from different studies were pooled using random effects models. RRs were estimated from odds ratios for the BDES and the Rotterdam Study only by applying the Zhang and Yu approximation.[59] For IPD-MA, pooled analyses were conducted using random effects models with each study center weighted by the inverse of its variance and the data were combined using a one-stage approach. Three models were considered: model 1, adjusted for age, sex and study center; model 2 additionally adjusted for ethnicity (if multi-ethnic), education, current smoking, diabetes, hypertension, BMI and total cholesterol; model 3 additionally adjusted for fellow vessel caliber which provides an adjustment accounting for innate individual differences in vessel caliber. Heterogeneity was assessed using the I^2 statistic. To evaluate the consistency of association in the IPD-MA, subgroup analyses stratified by

pre-specified characteristics including sex, ethnicity, diabetes and hypertension status were undertaken. Furthermore, sensitivity analyses also included stratification to allow for variation in CKD prevalence.

Disclosure

None.

List of supplementary material:

Figure S1: Funnel plots for **s**tudies included in the 11 study, two-stage, aggregate data random effects meta-analysis (model 3) for the association between a 20µm decrease in central retinal arteriolar equivalent (CRAE) and CKD stages 3-5. Abbreviations: RR Relative risk; Standard error (SE).

Figure S2: Funnel plots for studies included in the 11 study, two-stage, aggregate data random effects meta-analysis (model 3) for the association between a 20µm decrease in central retinal venular equivalent (CRVE) and CKD stages 3-5. Abbreviations: RR Relative risk; Standard error (SE).

Supplementary information is available at *Kidney International's* website.

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Acknowledgements

This project was funded by the Medical Research Council UK; grant number MR/K003364/1 (GMK).

The Singapore Epidemiology of Eye Diseases (SEED) study was supported by grants from the Singapore Ministry of Health's National Medical Research Council (NMRC), NMRC/0796/2003, NMRC/STaR/0003/2008, NMRC/1249/2010 and NMRC/OFLCG/001/2017.

The Atherosclerosis Risk in Communities study (ARIC) has been funded in whole or in part with Federal funds from the National Heart, Lung, and Blood Institute, National Institutes of Health, Department of Health and Human Services, under Contract nos. (HHSN268201700001I, HHSN268201700002I, HHSN268201700003I, HHSN268201700005I, HHSN268201700004I). The authors thank the staff and participants of the ARIC study for their important contributions.

The multi-ethnic Study of Atherosclerosis (MESA) was supported by contracts N01-HC-95159 through N01-HC-95165 from the National Heart, Lung and Blood Institute and NIH Intramural Research award Z01EY000403 from the National Eye Institute, USA.

The Cardiovascular Health Study (CHS) was supported by contracts HHSN268201200036C, HHSN268200800007C, HHSN268201800001C, N01HC55222, N01HC85079, N01HC85080, N01HC85081, N01HC85082, N01HC85083, N01HC85086, and grants U01HL080295 and U01HL130114 from the National Heart, Lung, and Blood Institute (NHLBI), with additional contribution from the National Institute of Neurological Disorders and Stroke (NINDS). Additional support was provided by R01AG023629 from the National Institute on Aging (NIA).

BMES was supported by the Australian National Health & Medical Research Council (NHMRC), in the following project grants: 991407, 974159, 350448, 302068, 211069, 153948 and 457349.

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Figure legends:

Table 1. Baseline characteristics of participants in the 11 cohort studies (n = 44,803). Abbreviations: ARIC, Atherosclerosis Risk in Communities Study; BMES, Blue Mountains Eye Study; CHS, Cardiovascular Health Study; MESA, Multi-Ethnic Study of Atherosclerosis; SCES, Singapore Chinese Eye Study; SiMES, Singapore Malay Eye Study; SINDI, Singapore Indian Eye; SP2, Singapore Prospective Study; Standard deviation (SD); Chronic Kidney Disease (CKD); Body Mass Index (BMI); Systolic blood pressure (SBP); Diastolic blood pressure (DBP); central retinal arteriolar equivalent (CRAE); central retinal venular equivalent (CRVE).– Data not available.

Table 2. Association between a 20µm decrease in central retinal arteriolar equivalent and CKD stages 3-5 for each study included in the two-stage aggregate data random effects meta-analysis (11 cohorts, n = 44,803). Abbreviations: RR, Relative risk; 95% CI, 95% confidence interval; ARIC, Atherosclerosis Risk in Communities Study; BDES, Beaver Dam Eye Study; BMES, Blue Mountains Eye Study; CHS, Cardiovascular Health Study; MESA, Multi-Ethnic Study of Atherosclerosis; SCES, Singapore Chinese Eye Study; SiMES, Singapore Malay Eye Study; SINDI, Singapore Indian Eye; SP2, Singapore Prospective Study Programme; Model 1: Adjusted for age, sex. Model 2: As Model 1 plus ethnicity (if multi-ethnic), education, current smoking, diabetes, hypertension, BMI, total cholesterol. Model 3: As Model 2 plus fellow vessel central retinal venular equivalent. †RR were estimated from odds ratios for the BDES and the Rotterdam Study only, by applying the Zhang and Yu approximation.[59] *Multivariable models 2 and 3 did not include education.

Table 3. Association between a 20µm decrease in central retinal venular equivalent (CRVE) and CKD stages 3-5 for each study included in the two-stage aggregate data random effects meta-analysis (11 cohorts, n = 44,803). Abbreviations: RR, Relative risk; 95% CI, 95% confidence interval; ARIC, Atherosclerosis Risk in Communities Study; BDES, Beaver Dam Eye Study; BMES, Blue Mountains Eye Study; CHS, Cardiovascular Health Study; MESA, Multi-Ethnic Study of Atherosclerosis; SCES, Singapore Chinese Eye Study; SiMES, Singapore Malay Eye Study; SINDI, Singapore Indian Eye; SP2, Singapore Prospective Study Programme. Model 1: Adjusted for age and sex. Model 2: As Model 1 plus ethnicity (if multi-ethnic), education, current smoking, diabetes, hypertension, BMI, total cholesterol. Model 3: As Model 2 plus fellow vessel central retinal arteriolar equivalent. †RR were estimated from odds ratios for the BDES and the Rotterdam Study only, by applying the Zhang and Yu approximation.[59] *Multivariable models 2 and 3 did not include education.

Table 4. Association between a 20µm decrease in central retinal arteriolar equivalent (CRAE), central retinal venular equivalent (CRVE) and CKD stages 3-5 in a one-stage individual participant data random effects meta-analysis (9 cohorts, n = 33,222). Model 1: Adjusted for age, sex, study center. Model 2: As Model 1 plus ethnicity (if multi-ethnic), education, current smoking, diabetes, hypertension, body mass index, total cholesterol. Model 3: As Model 2 plus fellow vessel central retinal arteriolar equivalent. Abbreviations: RR, Relative risk; 95% CI, 95% confidence interval.

Table 5. Association between a 20µm decrease in retinal vessel caliber and chronic CKD CKD stages 3-5 by subgroupings for participants included in the two-stage individual participant data random effects meta-analysis (9 cohorts, n=33,222). Subgroup analyses adjusted for adjusted for age, sex, ethnicity (if multi-ethnic), current smoking, diabetes, hypertension, BMI, total cholesterol and fellow vessel central retinal arteriolar equivalent. NA: Not applicable - subgroup analyses for American Indians is derived from the MESA study only and therefore calculation of I^2 values are not appropriate. Abbreviations: Chronic Kidney Disease (CKD); Central retinal arteriolar equivalent (CRAE); central retinal venular equivalent (CRVE); RR, Relative risk; 95% CI, 95% confidence interval.

Table 6. Risk of bias assessment. Abbreviations: ARIC, Atherosclerosis Risk in Communities Study; BMES, Blue Mountains Eye Study; CHS, Cardiovascular Health Study; MESA, Multi-Ethnic Study of Atherosclerosis; SCES, Singapore Chinese Eye Study; SiMES, Singapore Malay Eye Study; SINDI, Singapore Indian Eye; SP2, Singapore Prospective Study.

Figure 1. Study selection and data extraction. Abbreviations: ARIC, Atherosclerosis Risk in Communities Study; BMES, Blue Mountains Eye Study; CHS, Cardiovascular Health Study; MESA,

Multi-Ethnic Study of Atherosclerosis; SCES, Singapore Chinese Eye Study; SiMES, Singapore Malay Eye Study; SINDI, Singapore Indian Eye; SP2, Singapore Prospective Study.

Figure 2. Forest plots showing the association between a 20µm decrease in central retinal arteriolar equivalent (CRAE) and CKD stages 3-5 for studies included in the two-stage aggregate data random effects meta-analysis (Model 3). Model 3: Adjusted for age and sex, ethnicity (if multi-ethnic), education, current smoking, diabetes, hypertension, body mass index, total cholesterol, and fellow vessel central retinal arteriolar equivalent. *Multivariable model did not include education. Abbreviations: RR Relative risk; Standard error (SE); 95% Confidence Intervals (95% CI); ARIC, Atherosclerosis Risk in Communities Study; BDES, Beaver Dam Eye Study; BMES, Blue Mountains Eye Study; CHS, Cardiovascular Health Study; MESA, Multi-Ethnic Study of Atherosclerosis; SCES, Singapore Chinese Eye Study; SiMES, Singapore Malay Eye Study; SINDI, Singapore Indian Eye; SP2, Singapore Prospective Study Programme.

Figure 3. Forest plots showing the association between a 20µm decrease in central retinal venular equivalent (CRVE) and CKD stages 3-5 for studies included in the two-stage aggregate data random effects meta-analysis (model 3). Model 3: Adjusted for age and sex, ethnicity (if multi-ethnic), education, current smoking, diabetes, hypertension, BMI, total cholesterol, and fellow vessel central retinal arteriolar equivalent. *Multivariable model did not include education. Abbreviations: RR Relative risk; Standard error (SE); 95% Confidence Intervals (95% CI); ARIC, Atherosclerosis Risk in Communities Study; BDES, Beaver Dam Eye Study; BMES, Blue Mountains Eye Study; CHS, Cardiovascular Health Study; MESA, Multi-Ethnic Study of Atherosclerosis; SCES, Singapore Chinese Eye Study; SiMES, Singapore Malay Eye Study; SINDI, Singapore Indian Eye; SP2, Singapore Prospective Study Programme.

Table 1.

Characteristics	ARIC[32]	BDES[27]	BMES[54]	CHS[41]	MESA[26]	Rotterdam[42]	SCES[43]	SiMES[24]	SINDI[44]	SP2[45]	Takahata[46]
Sample Size	10725	4724	1698	1884	5700	6857	3085	2842	2969	3181	1138
Year of retinal / renal data collection	1993-95	1988-90	1992-94	1997-98	2002-04	1989–93	2009-11	2004-07	2007-09	2004-07	2004-06
Mean age at baseline (SD), years	60.1 (5.6)	61.7 (11.0)	65.0 (9.1)	78.3 (4.3)	61.5 (10.0)	63.5 (9.4)	59.1 (9.6)	58.3 (10.6)	57.1 (9.7)	49.7 (11.4)	60.5(9.6)
Age range, years	50-73	43-86	45-97	69-95	44-84	45-95	44-86	40-81	42-84	24-95	40-87
Men, n (%)	4765 (44)	2091 (44)	808 (48)	763 (40)	2720 (48)	2802 (41)	1538 (50)	1370 (48)	1521 (51)	1547 (49)	517 (45)
Ethnicity, n (%)											
White	8473 (79)	4697 (99)	1698 (100)	1574 (83)	2269 (40)	6693 (98)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Black	2219 (21)	0 (0)	0 (0)	302 (16)	1503 (26)	61 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Other (including Asian)	23 (0.2)	27 (0.6)	0 (0)	2 (0.1)	679 (11.9)	103 (1.5)	3085 (100)	2842 (100)	2969 (100)	3181 (100)	1138 (100)
American Indian	10 (0.1)	0 (0)	0 (0)	6(0.3)	1249 (21.9)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Current smoker, n (%)	1873 (18)	941 (20)	217 (13)	125 (7)	661 (12)	1756 (26)	403 (13)	585 (21)	450 (15)	379 (12)	168 (15)
Current drinker, n (%)	5780 (54)	113 (2)	1212 (71)	1075 (57)	2939 (52)	5391 (79)	340 (11)	45 (2)	391 (13)	1053 (33)	-
Hypertension, n (%)	4235 (40)	2382 (50)	1038 (61)	933 (50)	2575 (45)	3869 (56)	1841 (60)	1934 (68)	1744 (59)	1254 (39)	571 (50)
Diabetes, n (%)	1413 (13)	431 (9)	126 (7)	265 (14)	874 (15)	531 (8)	535 (17)	913 (32)	1156 (39)	375 (12)	80 (7)
CKD stages 3-5, n (%)	193 (2)	667 (14)	786 (46)	871 (46)	607 (11)	694 (10)	202 (7)	592 (21)	220 (7)	204 (6)	42 (4)
Mean BMI, (SD), kg/m^2	28.4 (5.5)	28.8 (5.4)	26.2 (4.3)	27.1 (4.5)	28.4 (5.4)	26.9 (4.2)	23.7 (3.6)	26.5 (5.1)	26.2 (4.7)	24.2 (5.3)	23.4 (3.2)
Mean SBP (SD), mmHg	124 (19)	132 (20)	145 (21)	131 (20)	124 (21)	136 (21)	136 (19)	146 (23)	135 (20)	132 (21)	133 (16)
Mean DBP (SD), mmHg	72 (10)	77 (11)	83 (10)	67 (11)	70 (10)	77 (12.2)	78 (10)	80 (11)	78 (10)	78 (11)	79 (10)
Mean Plasma glucose (SD), mmol/l	6.1 (2.2)	5.9 (2.2)	0.0 (0.0)	5.7 (1.7)	5.6 (1.7)	6.3 (2.3)	6.4 (2.8)	6.8 (3.7)	7.1 (3.5)	5.2 (1.6)	5.2 (0.8)
Hemoglobin A1c, mean (SD), %	-	4.9 (1.3)	-	-	5.7 (1.0)	-	6.1 (0.9)	6.5 (1.6)	6.4 (1.4)	5.8 (1.1)	5.2 (0.6)
Mean Serum cholesterol (SD), mmol/l	5.4 (1.0)	6.0 (1.1)	6.0 (1.1)	5.2 (1.0)	4.9 (0.9)	6.2 (1.3)	5.5 (1.1)	5.6 (1.2)	5.2 (1.1)	5.3 (1.0)	5.2 (0.8)
CRAE, mean (SD), µm	162 (17)	150 (14)	187 (18)	163 (17)	144 (14)	152 (16)	140 (16)	140 (16)	143 (14)	143 (14)	148 (14)
CRVE, mean (SD), µm	193 (17)	230 (22)	225 (20)	191 (18)	214 (22)	230 (23)	207 (21)	219 (22)	208 (20)	220 (21)	210 (22)

Table 2.

Study	Model 1 RR (95% CI)	Model 2 RR (95% CI)	Model 3 RR (95% CI)
ARIC	0.92 (0.78, 1.09)	1.03 (0.86, 1.23)	1.09 (0.89, 1.35)
†BDES	0.86 (0.77, 0.97)*	0.90 (0.81, 1.01)*	1.07 (0.93, 1.23)*
BMES	0.99 (0.80, 1.22)	0.98 (0.82, 1.16)	0.96 (0.78, 1.18)
CHS	1.01 (0.95, 1.08)	1.02 (0.94, 1.10)	0.98 (0.89, 1.09)
MESA	0.86 (0.79, 0.95)	0.91 (0.83, 1.00)	0.92 (0.82, 1.02)
†Rotterdam Study	0.97 (0.87, 1.08)*	1.01 (0.90, 1.12)*	1.02 (0.89, 1.16)*
SCES	1.02 (0.90, 1.17)	1.03 (0.92, 1.17)	1.03 (0.89, 1.19)
SiMES	0.97 (0.90, 1.05)	0.98 (0.91, 1.07)	0.98 (0.90, 1.08)
SINDI	0.94 (0.79, 1.12)	0.94 (0.80, 1.10)	0.94 (0.78, 1.14)
SP2	0.90 (0.71, 1.13)	0.94 (0.80, 1.10)	0.88 (0.74, 1.06)
*Takahata	1.18 (0.79, 1.74)	1.28 (0.84, 1.95)	1.39 (0.88, 2.18)
Combined	0.95 (0.91, 0.99)	0.98 (0.94, 1.01)	0.98 (0.94, 1.03)
	I^2=29% (p=0.17)	I^2=0% (p=0.52)	I^2=0% (p=0.60)

Table 3.

Study	Model 1 RR (95% CI)	Model 2 RR (95% CI)	Model 3 RR (95% CI)
ARIC	0.93 (0.78, 1.10)	0.93 (0.78, 1.10)	0.88 (0.72, 1.09)
†BDES	0.87 (0.81, 0.93)*	0.86 (0.80, 0.92)*	0.83 (0.76, 0.92)*
BMES	1.02 (0.87, 1.19)	1.01 (0.86, 1.19)	1.03 (0.85, 1.25)
CHS	1.03 (0.94, 1.14)	1.05 (0.97, 1.13)	1.05 (0.96, 1.16)
MESA	0.92 (0.87, 0.98)	0.96 (0.91, 1.03)	1.00 (0.93, 1.08)
†Rotterdam Study	1.02 (0.95, 1.10)*	1.03 (0.95, 1.11)*	1.04 (0.95, 1.13)*
SCES	1.02 (0.92, 1.14)	1.02 (0.92, 1.13)	1.01 (0.89, 1.15)
SiMES	1.01 (0.96, 1.06)	1.00 (0.95, 1.05)	1.00 (0.95, 1.06)
SINDI	0.96 (0.86, 1.08)	0.97 (0.86, 1.09)	0.99 (0.87, 1.12)
SP2	1.02 (0.92, 1.13)	1.03 (0.93, 1.13)	1.08 (0.96, 1.21)
*Takahata	0.94 (0.73, 1.22)	0.96 (0.74, 1.25)	0.88 (0.64, 1.20)
Combined	0.97 (0.94, 1.01)	0.98 (0.95, 1.02)	0.99 (0.95, 1.04)
	I^2=50% (p=0.03)	I^2=50% (p=0.03)	I^2=47% (p=0.04)

Table 4.

	CRAE	CRVE
	Overall RR (95%CI)	Overall RR (95%CI)
Model 1	0.97 (0.94, 1.01)	1.00 (0.97, 1.03)
Model 2	0.99 (0.96, 1.04)	0.98 (0.94, 1.03)
Model 3	0.99 (0.95, 1.04)	1.01 (0.97, 1.05)

Table 5.

			CRAE		CRVE	
Variable	Number at risk	Cases (%)	Overall RR (95%CI)	I^2 (p-value)	Overall RR (95%CI)	I^2 (p-value)
Diabetes						
Yes	5737	909 (15.8)	0.88 (0.81, 0.96)	0% (1.00)	1.01 (0.96, 1.07)	0% (0.50)
No	27485	2808 (10.2)	1.01 (0.95, 1.08)	11% (0.34)	1.01 (0.97, 1.06)	0% (0.94)
Hypertension						
Yes	16125	2657 (16.5)	0.98 (0.92, 1.03)	0% (0.93)	1.01 (0.97, 1.05)	0% (0.97)
No	17097	1060 (6.2)	0.98 (0.89, 1.08)	29% (0.19)	1.00 (0.92, 1.09)	0% (0.47)
Gender						
Male	15549	1932 (12.4)	0.98 (0.92, 1.05)	0% (0.72)	1.00 (0.95, 1.06)	0% (1.00)
Female	17673	1785 (10.1)	0.97 (0.90, 1.04)	0% (0.78)	1.02 (0.96, 1.11)	0% (0.73)
Ethnicity						
White	14014	2014 (14.4)	0.90 (0.75, 1.07)	72% (0.01)	1.02 (0.95, 1.11)	0% (0.97)
Black	4024	269 (6.7)	1.09 (0.93, 1.28)	0% (0.94)	0.91 (0.74, 1.12)	51% (0.13)
Asian	13919	1333 (9.6)	0.98 (0.92, 1.05)	0% (0.53)	1.01 (0.97, 1.05)	0% (0.81)
American Indian	1265	101 (8.0)	0.71 (0.52, 0.96)	NA	0.97 (0.80, 1.17)	NA
Prevalence of CKD stages 3-5						
<10%	21098	861 (4.1)	1.01 (0.92, 1.12)	7% (0.37)	0.99 (0.92, 1.07)	0% (0.57)
≥10%	12124	2856 (23.6)	0.96 (0.91, 1.02)	0% (0.77)	1.00 (0.96, 1.04)	0% (0.82)

Table 6.

Risk of bias item	ARIC	BDES	BMES	CHS	MESA	Rotterdam	SCES	SiMES	SINDI	SP2	Takahata
Study participation The study sample represents the population of interest on key characteristics, sufficient to limit potential bias to the results Yes, Partly, No, Unsure	Partly	Partly	Partly	Partly	Partly	Yes	Yes	Yes	Yes	Yes	Partly
Study attrition Loss to follow-up (from sample to study) is not associated with key characteristics (i.e. the study data adequately represent the sample), sufficient to limit potential bias Yes, Partly, No, Unsure	Unsure	Yes	Yes	Unsure	Unsure	Unsure	Unsure	Yes	Yes	Unsure	Unsure
Prognostic factor measurement The prognostic factor of interest is adequately measured in study participants to sufficiently limit potential bias Yes, Partly, No, Unsure	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Outcome measurement	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

The outcome of interest is adequately measured in study participants to sufficiently limit bias Yes, Partly, No, Unsure											
Confounding measurement and account Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest Yes, Partly, No, Unsure	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Analysis The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid results Yes, Partly, No, Unsure	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Figure 1.

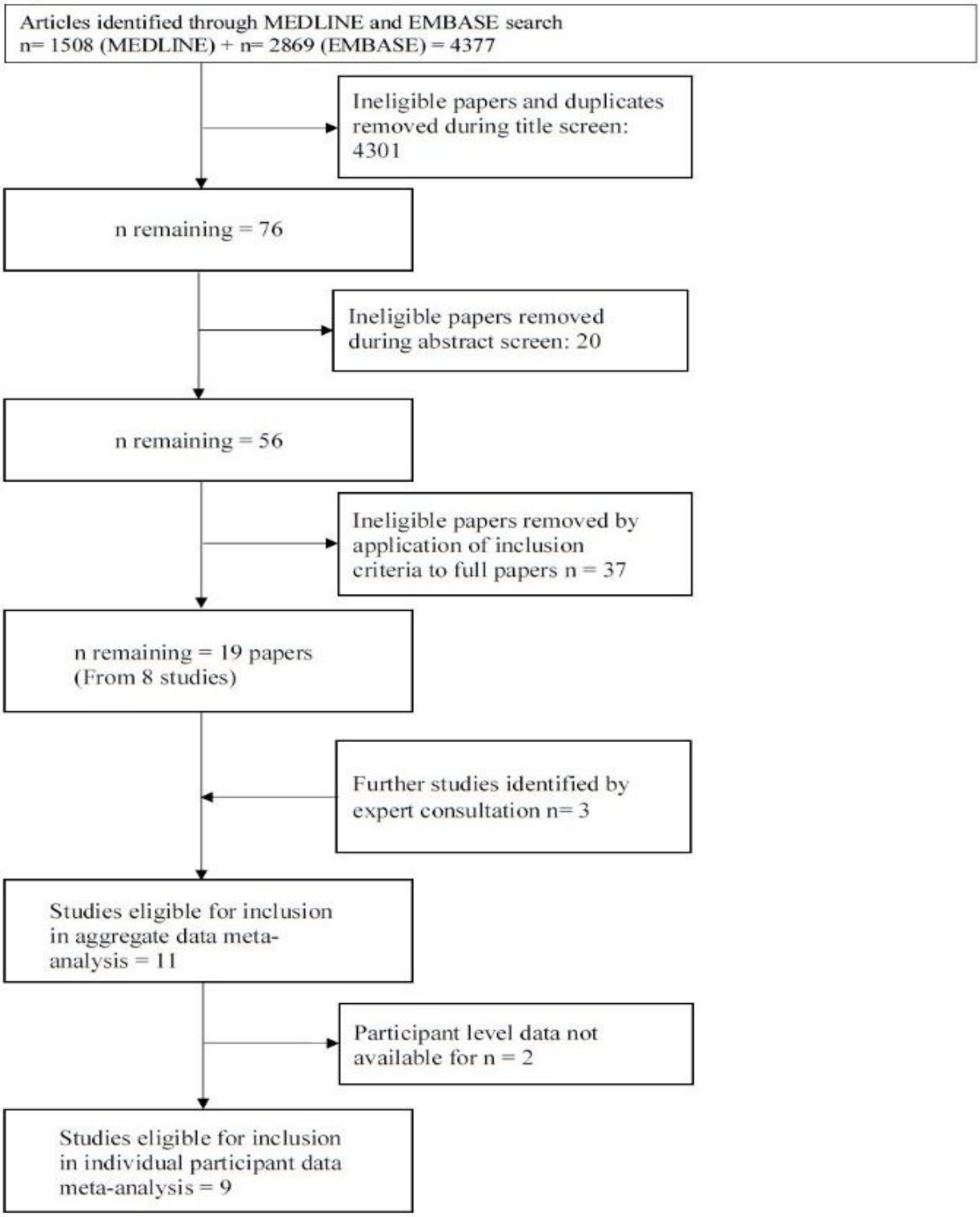

Articles identified through MEDLINE and EMBASE search
n= 1508 (MEDLINE) + n= 2869 (EMBASE) = 4377
Ineligible papers and duplicates removed during title screen: 4301
n remaining = 76
Ineligible papers removed during abstract screen: 20
n remaining = 56
Ineligible papers removed by application of inclusion criteria to full papers n = 37
n remaining = 19 papers (From 8 studies)
Further studies identified by expert consultation n= 3
Studies eligible for inclusion in aggregate data meta-analysis = 11
Participant level data not available for n = 2
Studies eligible for inclusion in individual participant data meta-analysis = 9

Figure 2.

Study	ln [RR]	SE(ln[RR])	RR (95% CI)	Weight
ARIC	0.09	0.11	1.09 (0.89, 1.35)	4.1
BDES	0.07	0.07	1.07 (0.93, 1.23)	9
BMES	-0.04	0.11	0.96 (0.78, 1.18)	4.1
CHS	-0.02	0.05	0.98 (0.89, 1.09)	17.1
MESA	-0.08	0.06	0.92 (0.82, 1.02)	14.8
Rotterdam	0.02	0.07	1.02 (0.89, 1.16)	10.2
SCES	0.03	0.07	1.03 (0.89, 1.19)	8.3
SiMES	-0.02	0.05	0.98 (0.90, 1.08)	21.2
SINDI	-0.06	0.10	0.94 (0.78, 1.14)	4.9
SP2	-0.13	0.09	0.88 (0.74, 1.06)	5.5
Takahata*	0.33	0.23	1.39 (0.88, 2.18)	0.9
Pooled			0.98 (0.94, 1.03)	**100**

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 8.34$, df = 10 (P = 0.60); $I^2 = 0\%$

Test for overall effect: Z = 0.71 (P = 0.48)

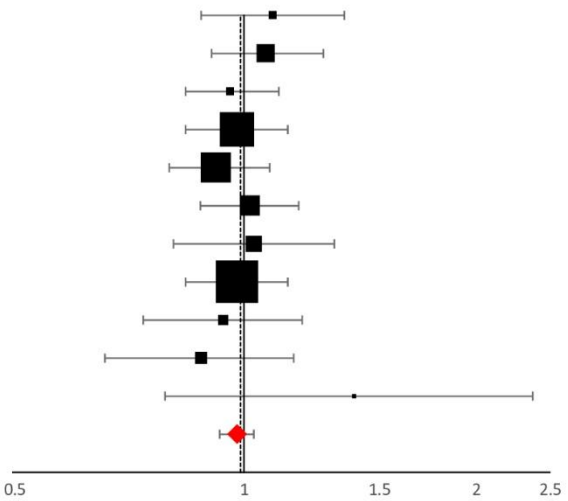
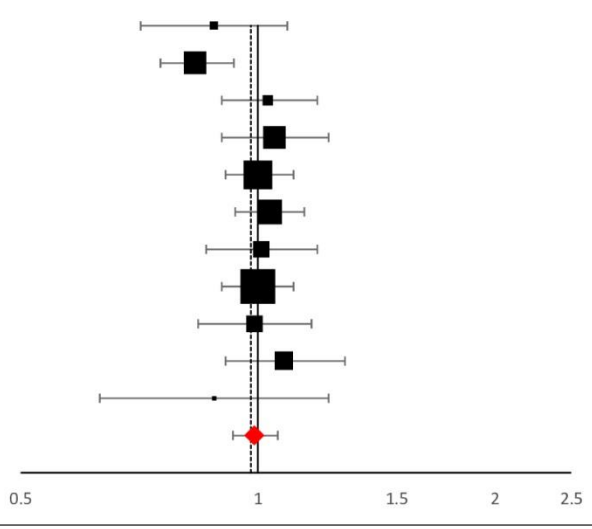


Figure 3.

Study	ln [RR]	SE (ln[RR])	RR (95% CI)	Weight
ARIC	-0.13	0.11	0.88 (0.72, 1.09)	4
BDES	-0.18	0.05	0.83 (0.76, 0.92)	11
BMES	0.03	0.10	1.03 (0.85, 1.25)	4.5
CHS	0.05	0.05	1.05 (0.96, 1.16)	11.3
MESA	0.00	0.04	1.00 (0.93, 1.08)	13.8
Rotterdam	0.04	0.05	1.04 (0.95, 1.13)	11.8
SCES	0.01	0.07	1.01 (0.89, 1.15)	8
SiMES	0.00	0.03	1.00 (0.95, 1.06)	16.6
SINDI	-0.01	0.06	0.99 (0.87, 1.12)	8.2
SP2	0.08	0.06	1.08 (0.96, 1.21)	9.1
Takahata*	-0.13	0.16	0.88 (0.64, 1.20)	1.9
Pooled			0.99 (0.95, 1.04)	**100**

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 19.04$, df = 10 (P = 0.04); $I^2 = 47\%$

Test for overall effect: Z = 0.42 (P = 0.68)



Figure·S1¶

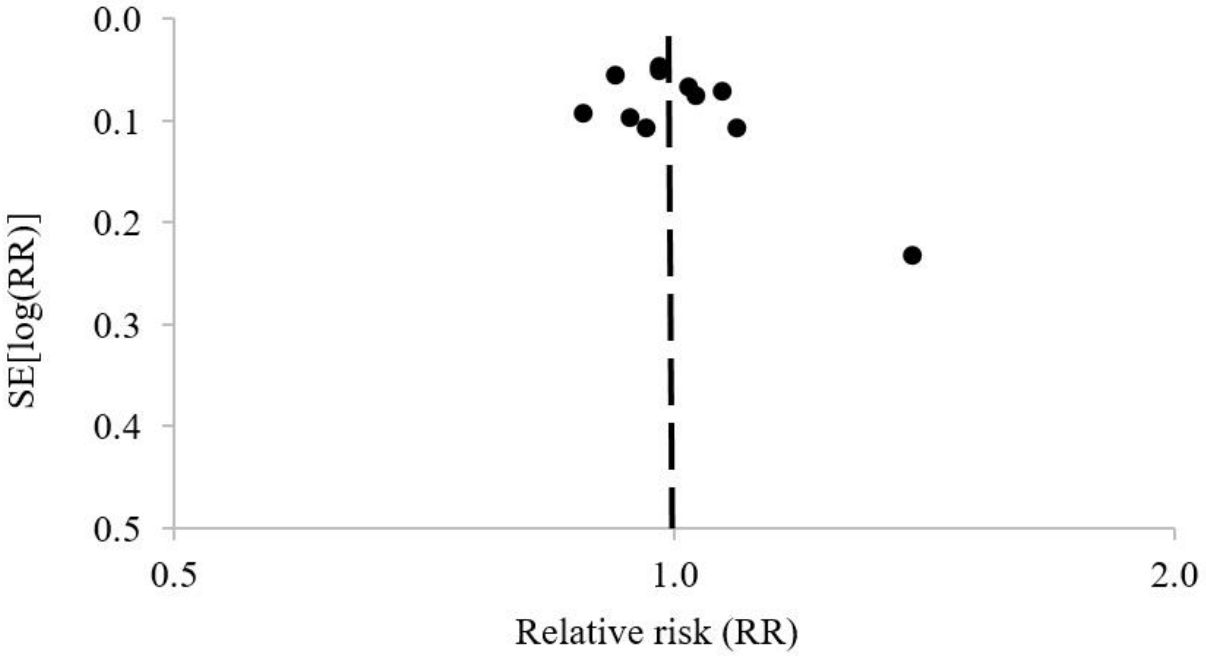


Figure S2