

Skin Autofluorescence—Indicated Advanced Glycation End Products as Predictors of Cardiovascular and All-Cause Mortality in High-Risk Subjects: A Systematic Review and Meta-analysis

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Background—Chronic deposits of advanced glycation end products produced by enzymatic glycation have been suggested as predictors of atherosclerotic-related disorders. This study aimed to estimate the relationship between advanced glycation end products indicated by skin autofluorescence levels and the risk of cardiovascular and all-cause mortality based on data from observational studies.

Methods and Results—We systematically searched Medline, Embase, the Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews, and the Web of Science databases from their inception until November 2017 for observational studies addressing the association of advanced glycation end products by skin autofluorescence levels with cardiovascular and all-cause mortality. The DerSimonian and Laird random-effects method was used to compute pooled estimates of hazard ratios and their respective 95% confidence intervals for the risk of cardiovascular and all-cause mortality associated with levels of advanced glycation end products by skin autofluorescence. Ten published studies were included in the systematic review and meta-analysis. Higher skin autofluorescence levels were significantly associated with a higher pooled risk estimate for cardiovascular mortality (hazard ratio: 2.06; 95% confidence interval, 1.58–2.67), which might not be important to moderate heterogeneity ($I^2=34.7\%$; $P=0.163$), and for all-cause mortality (hazard ratio: 1.91; 95% confidence interval, 1.42–2.56) with substantial heterogeneity ($I^2=60.8\%$; $P=0.018$).

Conclusions—Our data suggest that skin autofluorescence levels could be considered predictors of all-cause mortality and cardiovascular mortality in patients at high and very high risk. (*J Am Heart Assoc.* 2018;7:e009833. DOI: 10.1161/JAHA.118.009833.)

Key Words: advanced glycation end products • cardiovascular complications • meta-analysis • mortality • skin autofluorescence

Advanced glycation end products (AGEs) are a group of heterogeneous cross-link formations that result from the glycation processes involved in several pathologies including arteriosclerosis and atherosclerosis-related disorders and particularly complications from micro- and macrovascular diabetes mellitus.¹ Several pathophysiological pathways by which AGEs contribute to these conditions have been described, including (1) adduct formations in basement membranes that permanently change the extracellular matrix

proteins, such as collagen or elastin, and (2) interaction with AGE receptors, known as receptors for advanced glycation end products (RAGEs).² These receptors alter intracellular signaling cascades and the release of proinflammatory cytokines and, consequently, stimulate oxidative stress in various cells, such as certain neurons and endothelial or smooth muscle cells; all these alterations contribute to the pathological modifications involved in the start of vascular complications.³

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Accompanying Tables S1 through S4 and Figures S1, S2 are available at <https://www.ahajournals.org/doi/suppl/10.1161/JAHA.118.009833>

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Clinical Perspective

What Is New?

- This systematic review and meta-analysis synthesizes the evidence supporting higher levels of skin autofluorescence indicating advanced glycation end products as a predictor of cardiovascular and all-cause mortality.
- Our data confirm that chronic deposits of skin autofluorescence–indicated advanced glycation end products produced by enzymatic glycation in skin are predictors of cardiovascular and all-cause mortality in patients with diabetes mellitus and cardiovascular and/or renal diseases.

What Are the Clinical Implications?

- Our findings highlight that skin autofluorescence levels may be useful as a biomarker of the risk of mortality assessment in patients with diabetes mellitus and cardiovascular and renal diseases.

From the time of onset of diabetes mellitus, and also for patients with impaired glucose tolerance, high glucose levels are present not only in plasma but also within cells (kidney and retina) and interstitial spaces where the metabolism of glucose is not insulin dependent.^{4,5} These elevated glycemic levels result in increased production of AGEs, fostering the development of the vascular complications of diabetes mellitus and chronic kidney disease.⁶

Conflicting results have been reported from measurement of AGE levels in plasma and concern the ability of AGEs to predict cardiovascular events or cardiovascular mortality, even though most recent works support such a predictive role.⁷ Changes in levels of plasma RAGEs have also been associated indirectly with increased risk of cardiovascular disease (CVD),⁸ namely, heart failure⁹ and coronary heart disease.¹⁰

Although the reference standard for measuring AGE levels in tissues is biochemical determination in skin biopsies, skin autofluorescence (SAF) has emerged as a noninvasive, accurate, and practical method for the analysis of AGE levels in skin.^{11,12} SAF-indicated AGE levels are elevated in diabetes mellitus and end stage renal disease, and some studies suggest that they are associated with CVD independent of known CVD risk factors.^{13–15} In fact, recent reviews have pointed out a role for SAF levels as new biomarkers of CVD and diabetes mellitus complications.^{16,17}

To our knowledge, relatively limited evidence exists on the association of AGE levels measured by SAF with cardiovascular and all-cause mortality, and no meta-analysis has synthesized this relationship. This systematic review and meta-analysis aims to estimate the relationship between SAF levels and the risk of cardiovascular and all-cause mortality based on data from observational studies.

Methods

This study was performed using available data from published literature. The data, analytic methods, and study materials are all available on request by other researchers who want to reproduce the results or replicate the procedures.

This study was reported according to the MOOSE (Meta-analysis of Observational Studies in Epidemiology) statements¹⁸ and followed the recommendations of the Cochrane Collaboration Handbook.¹⁹ This systematic review and meta-analysis was registered through the International Prospective Register of Systematic Reviews (registration no. CRD42017058432).

Search Strategy

We systematically searched Medline (via PubMed), Embase, the Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews, and the Web of Science databases from their inceptions until November 2017. Observational studies addressing the association of SAF levels with cardiovascular and all-cause mortality were eligible. The search expressions are presented in Table S1. The literature search was complemented by screening of references included in the articles that were considered eligible for the systematic review.

Study Selection

Inclusion criteria were as follows: (1) Participants were adults with diabetes mellitus and/or cardiovascular and/or renal disease, (2) study design was longitudinal with prospective data collection, (3) exposure was SAF, and (4) outcome was cardiovascular or/and all-cause mortality. The criteria for excluding studies were as follows: (1) Reports were not written in English or Spanish; (2) studies included individuals aged <18 years; and (3) publication types were not eligible, such as review articles, editorials, comments, guidelines, or case reports.

When >1 study provided data from the same sample, we considered only the one presenting the most detailed results or providing data for the largest sample size; however, data regarding sample characteristics could be extracted from multiple reports to obtain the most complete information.

The literature search was performed independently by 2 reviewers (I.C.-R. and C.A.-B.), and disagreements were solved by consensus or by involving a third researcher (V.M.-V.).

Data Extraction and Quality Assessment

The following data were extracted from the original reports: (1) year of publication, (2) study characteristics (country and

length of follow-up), (3) sample characteristics (type of population; sample size; male sex percentage; age and body mass index distribution; current smoker status percentage; and prevalence of diabetes mellitus, hypertension, and preexisting CVD), (4) SAF levels as the predictor variable, and (5) cardiovascular or all-cause mortality as the outcome variable. In addition, the following covariates included in the studies were extracted: levels of high-sensitivity C-reactive protein (hs-CRP), systolic and diastolic blood pressure, hemoglobin, HbA1c, albumin, creatinine, total cholesterol, LDL (low-density lipoprotein), and triglycerides.

The Quality in Prognosis Studies (QUIPS) tool²⁰ was used to evaluate the risk of bias in 6 domains: study participation (sampling bias), study attrition (attrition bias), prognostic factor measurement, outcome measurement (ascertainment bias), study confounding, and statistical analysis and reporting. Studies were considered to have low risk of bias if they satisfied 5 or all 6 domains, moderate risk of bias if they satisfied 3 or 4 of the 6 domains, or high risk of bias if they satisfied 1 or 2 of the 6 domains.

Data extraction and quality assessment were independently performed by 2 researchers (I.C.-R. and C.A.-B.), and inconsistencies were resolved by consensus or by involving a third researcher (V.M.-V.).

Statistical Analysis

The DerSimonian and Laird random-effects²¹ method was used to compute pooled estimates of hazard ratios (HRs) and respective 95% confidence intervals (95% CIs) for the risk of cardiovascular and all-cause mortality associated with SAF levels. The lowest SAF levels measured as continuous or categorical variables reported from included studies were considered as the reference level to calculate pooled HR estimates. The heterogeneity of results across studies was evaluated using the I^2 statistic and was categorized as *might not be important* (0–40%), *may represent moderate* (30–60%), *may represent substantial* (50–90%), and *considerable* (75–100%) heterogeneity.¹⁸ In addition, the corresponding *P* values were considered.

When a study reported several statistical models, only the one including the largest number of additional covariates was considered. For each HR estimate, the lnHR was calculated by converting it to the natural log scale.

Sensitivity analyses (systematic reanalysis while removing studies one at a time) were conducted to assess the robustness of the summary estimates. Results of the sensitivity analyses were considered meaningful when the resulting estimates were modified beyond the CIs of the original summary estimate. In addition, sensitivity analyses provided insight into whether any particular study accounted for a large proportion of heterogeneity among the correlation

pooled estimations, based on the change in I^2 values (and associated categories reported previously).

Subgroup analyses were performed based on the type of target population used to estimate the risk of mortality associated with SAF levels (diabetes mellitus, cardiovascular, or renal patients). In addition, subgroup analyses were performed based on whether or not patients received hemodialysis. For subgroup analyses, at least 3 studies in each group were needed.

Random-effects metaregression was used to evaluate whether results differed according to the length of follow-up; percentage of male participants; mean age of participants; prevalence of diabetes mellitus; body mass index; percentage of current smokers; prevalence of hypertension and preexisting CVD; and levels of baseline SAF, hs-CRP, systolic and diastolic blood pressure, hemoglobin, HbA1c, albumin, creatinine, total cholesterol, LDL and triglycerides, as these could be considered major sources of heterogeneity.²²

Finally, publication bias was evaluated through visual inspection of funnel plots and by using the method proposed by Egger.²³ The trim-and-fill computation was used to assess the effect of publication bias on the interpretation of results.²⁴ Statistical analyses were performed using StataSE software v14 (StataCorp).

Results

Systematic Review

Of the 56 full-text articles reviewed, only 10 studies^{25–34} met the eligibility criteria (Figure 1). Seven studies^{25,27,28,30,31,33,34} quantified the risk for all-cause mortality, and 8 samples from 7 studies^{25–27,29,32,34} quantified the risk for cardiovascular mortality. The studies were conducted in 4 European countries^{25–28,30–34} and 1 Asian country.²⁹ The reports were published between 2005 and 2015 (Table 1).

The age of the included participants ranged between 45.0 and 67.5 years, with sample sizes ranging from 48 to 1707 participants. The studies included patients with renal disease,^{25,27–29,31,33,34} peripheral artery disease,²⁶ and diabetes mellitus.^{30,32} The percentage of male participants ranged from 39.3% to 73.0%, and the percentage of current smokers ranged from 10.0% to 50.0%. Most studies included a normal weight population,^{25,28,29,31,32} and only 3 included an overweight population.^{26,27,31} The prevalence of hypertension ranged from 18.0% to 91.0%, and the prevalence of preexisting CVD ranged from 29.0% to 50.0%.

Studies that included patients with diseases other than diabetes mellitus (ie, focused on renal and peripheral arterial disease patients) showed a prevalence of diabetes mellitus that ranged from 16.6% to 41.9%. Only 2 studies focused on patients with diabetes mellitus specified the type of diabetes

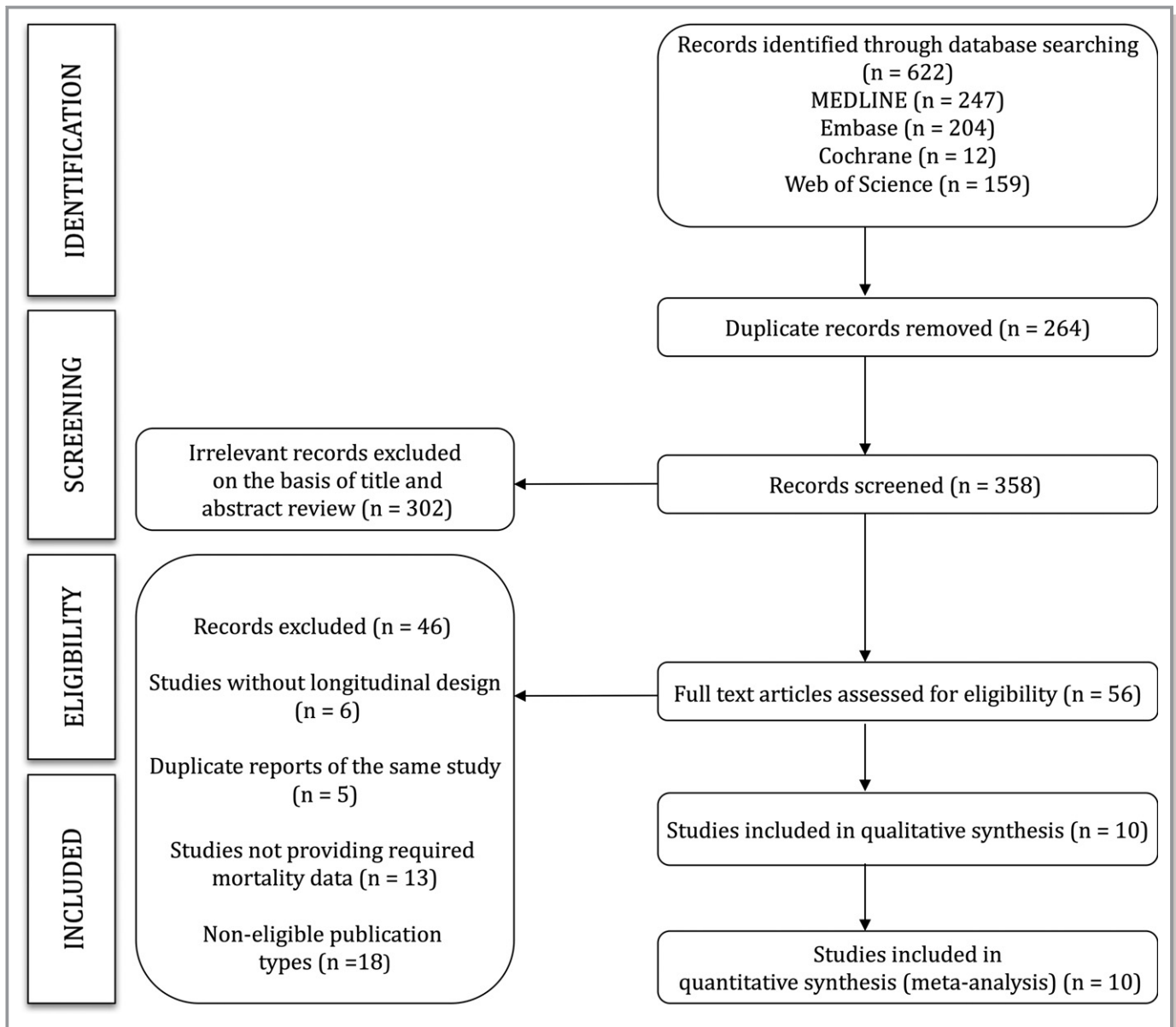


Figure 1. Literature search: CONSORT (Consolidated Standards of Reporting Trials) diagram.

mellitus.^{30,32} On baseline measurements, SAF levels ranged from 1.6 to 3.6 arbitrary units.^{32,34} All studies estimated SAF using an AGE Reader device (DiagnOptics). The biochemical (hs-CRP, hemoglobin, HbA1c, albumin, creatinine, total cholesterol, LDL, and triglycerides) and vascular (systolic and diastolic blood pressure) covariates of the included studies are shown in Table 2. Most studies reported models adjusted for several covariates (Table S2).

Study Quality

As assessed by the QUIPS tool (Table S3), 70% of the studies had a low risk of bias and 30% had a high risk of bias. The

study attrition domain showed a high risk of bias in 90% of the studies. Conversely, 100% of the studies showed a low risk of bias in the statistical analysis and reporting domain, and no study scored a high risk of bias in the study participation, statistical analysis and reporting, and study confounding domains.

Meta-analyses

Higher SAF levels were significantly associated with higher pooled risk estimates for cardiovascular mortality (HR: 2.06; 95% CI, 1.58–2.67) and all-cause mortality (HR: 1.91; 95% CI, 1.42–2.56). Heterogeneity in the HR estimates was not

Table 1. Characteristics of Studies Included in the Systematic Review and Meta-analysis

Study	Study Characteristics		Population Characteristics										Predictor Variable	Outcome
	Country	Length of Follow-up, y	Type of Target Population	n	Male Sex, n (%)	Age, y, Mean±SD	DM, n (%)	BMI, Kg/m ² , Mean±SD	Current Smoker, n (%)	Hypertension, n (%)	Pre-CVD, n (%)	SAF, AU, Mean±SD		
Atsov et al, 2013 ²⁵	Macedonia	3.0	ESRD patients	169	104 (61.0)	56.0±13.0	41 (24.0)	23.2±4.8	17 (10.0)	34 (18.0)	12 (29.0)	3.2±0.9	All-cause: 49 (28.9) Cardiovascular: 32 (18.9)	
de Vos et al, 2014 ²⁶	Netherlands	5.1	PAD patients	252	183 (73.0)	66.0±11.0	74 (29.0)	27.0±4.0	127 (50.0)	229 (91.0)	112 (44.0)	2.8±0.7	Cardiovascular: 62 (24.6)	
Fraser et al, 2014 ²⁷	UK	3.6	Stage 3 CKD patients	1707	671 (39.3)	73.0±9.0	284 (16.6)	29.0±5.1	79 (4.6)	1495 (87.6)	580 (34.0)	2.7±0.7	All-cause: 170 (10.0) Cardiovascular: 69 (4.0)	
Gerrits et al, 2012 ²⁸	Netherlands	4.9	ESRD patients	105	68 (64.8)	65.1±14.6	23 (22.0)	24.9±5.1	15 (14.0)	N/A	53 (50.0)	3.2±0.9	All-cause: 69 (65.7) Cardiovascular: 34 (32.4)	
Kimura et al, 2014 ²⁹	Japan	6.0	ESRD patients	128	59 (46.1)	65.1±11.6	44 (34.3)	22.1±3.3	N/A	N/A	39 (30.5)	2.3±0.9	All-cause: 42 (32.8) Cardiovascular: 19 (14.8)	
Lutgers et al, 2009 ³⁰	Netherlands	3.0	Type 2 DM patients	967	454 (47.0)	66.0±11.0	967 (100.0)	29.0±5.0	184 (19.0)	N/A	377 (39.0)	2.8±0.8	All-cause: 86 (8.9) Cardiovascular: 44 (4.6)	
Meerwaldt et al, 2005 ³¹	Netherlands	3.0	ESRD patients	109	68 (62.4)	57.0±16.0	23 (21.0)	23.9±3.4	N/A	41 (37.6)	N/A	2.4±0.7	All-cause: 42 (38.5) Cardiovascular: 25 (22.9)	
Meerwaldt et al, 2007 ³²	Netherlands	5.0	Type 2 DM patients	69	45 (65.0)	61.0±13.0	69 (100.0)	24.4±1.2	10 (14.5)	33 (47.8)	N/A	2.1±0.3	Cardiovascular: 23 (33.3)	
Nongnuch and Davenport, 2015 ³³	UK	2.5	Type 1 DM patients	48	23 (48.0)	45.0±15.0	48 (100.0)	22.8±1.6	11 (22.9)	15 (31.2)	N/A	1.6±0.5	Cardiovascular: 11 (22.9)	
Siriopol et al, 2015 ³⁴	Romania	2.5	Stage 5 CKD patients	332	213 (64.2)	67.5±18.2	139 (41.9)	N/A	123 (37.0)	205 (61.7)	107 (32.2)	3.3±0.9	All-cause: 74 (22.3)	
			ESRD patients	304	135 (44.4)	56.7±14.4	56 (18.4)	N/A	47 (15.5)	273 (89.8)	104 (34.2)	3.6±0.8	All-cause: 57 (18.8) Cardiovascular: 24 (7.9)	

AU indicates arbitrary units; BMI, body mass index; CKD, chronic kidney disease; DM, diabetes mellitus; ESRD, end-stage renal disease; N/A, not available; PAD, peripheral artery disease; pre-CVD, preexisting cardiovascular disease; SAF, skin autofluorescence (indicating advanced glycation end products).

Table 2. Covariates of Studies Included in the Systematic Review and Meta-analysis

Study	hs-CRP, mg/L, Mean±SD	SBP, mm Hg, Mean±SD	DBP, mm Hg, Mean±SD	Hemoglobin, g/dL, Mean±SD	HbA1c, %, Mean±SD	Albumin, g/L, Mean±SD	Creatinine, mg/dL, Mean±SD	TC, mg/dL, Mean±SD	LDL-C, mg/dL, Mean±SD	Triglycerides, mg/dL, Mean±SD
Arsov et al, 2013 ²⁵	12.6±42.0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
de Vos et al, 2014 ²⁶	N/A	140.0±125.5	80±60.7	N/A	6.8±4.4	N/A	N/A	N/A	N/A	N/A
Fraser et al, 2014 ²⁷	N/A	134.0±18.0	72.0±11.0	13.2±125.5	N/A	N/A	N/A	N/A	N/A	N/A
Gerrits et al, 2012 ²⁸	N/A	146.0±24.0	65.0±20.0	12.6±1.3	N/A	38.0±5.0	9.9±2.7	146.9±34.8	N/A	N/A
Kimura et al, 2014 ²⁹	1.4±1.7	N/A	N/A	10.1±1.6	N/A	37.0±0.4	10.4±3.4	148.3±N/A	81.2±26.6	108.2±61.2
Lutgers et al, 2009 ³⁰	N/A	146±±20.0	81±10.0	N/A	7.0±1.3	N/A	1.1±0.2	201.1±38.7	112.1±34.8	203.7±115.1
Meerwaldt et al, 2005 ³¹	4.8±5.6	N/A	N/A	N/A	N/A	38.3±2.6	11.1±2.7	204.9±N/A	123.7±30.9	212.6±79.7
Meerwaldt et al, 2007 ³²										
Type 2 DM patients	N/A	N/A	N/A	N/A	8.2±0.9	N/A	1.0±0.2	196.1±N/A	123.7±38.7	168.3±70.8
Type 1 DM patients	N/A	N/A	N/A	N/A	7.9±1.0	N/A	1.0±0.1	203.3±N/A	123.7±27.1	146.1±70.8
Nonguch and Davenport, 2015 ³³	15.1±27.2	N/A	N/A	10.9±1.4	11.7±15.0	38.9±4.9	N/A	158.5±42.5	N/A	N/A
Siriopol et al, 2015 ³⁴	4.3±36.5	N/A	N/A	11.3±1.6	N/A	47.6±64.0	N/A	185.0±275.6	N/A	160.0±449.1

DBP indicates diastolic blood pressure; DM, diabetes mellitus; HbA1c, glycated hemoglobin A1c; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; N/A, not available; SBP, systolic blood pressure; TC, total cholesterol.

important to moderate for the risk of cardiovascular mortality ($I^2=34.7\%$; $P=0.163$) and substantial for the risk of all-cause mortality ($I^2=60.8\%$; $P=0.0.18$; Figure 2).

Sensitivity Analysis

The pooled HR estimate was not significantly modified in magnitude or direction when individual study data were removed from the analysis one at a time (eg, HRs of 1.86–2.08 for cardiovascular mortality and 1.74–2.09 for all-cause mortality). Heterogeneity was modified from not important to moderate after removing data from Meerwaldt et al ($I^2=43.5\%$)³² and Fraser et al ($I^2=43.6\%$)²⁷ for cardiovascular mortality. In addition, heterogeneity was modified from substantial to moderate only after removing data from Siriopol et al ($I^2=47.0\%$).³⁴

Subgroup Analysis and Metaregression

When analyses were performed based on the type of target population, there were only enough studies to perform an analysis in renal patients. The risk of mortality associated with higher SAF levels in renal patients was 2.23 (95% CI, 1.31–3.82; $I^2=54.0\%$) for cardiovascular mortality and 1.88 (95% CI, 1.34–2.64; $I^2=65.4\%$) for all-cause-mortality (Figure 3).

For hemodialysis treatment status analysis, the risk of cardiovascular mortality associated with higher SAF levels was 1.97 (95% CI, 1.11–3.49; $I^2=62.4\%$) for hemodialysis patients and 1.95 (95% CI, 1.56–2.45; $I^2=0.0\%$) in non-hemodialysis patients. Nevertheless, for the risk of all-cause mortality, there were only enough studies to perform an analysis in hemodialysis patients (HR: 2.08; 95% CI, 1.41–3.06; Figure 4).

The random-effects metaregression model showed that no covariate was related to the pooled HR estimates (Table S4). For cardiovascular mortality, heterogeneity was modified from not important to moderate when metaregression models were based on levels of albumin ($I^2=42.6\%$), total cholesterol ($I^2=44.2\%$), and triglycerides ($I^2=59.7\%$) and from not important to substantial when models were based on hs-CRP levels ($I^2=6.1.8\%$). Furthermore, for all-cause mortality, heterogeneity was modified from substantial to not important when metaregression models were based on percentage of male participants ($I^2=1.4\%$), body mass index ($I^2=21.8\%$), hypertension prevalence ($I^2=0.0\%$), and levels of hs-CRP ($I^2=26.7\%$), systolic blood pressure ($I^2=0.0\%$), albumin ($I^2=16.8\%$), and triglycerides ($I^2=0.0\%$). heterogeneity for all-cause mortality was modified from substantial to moderate when metaregression models were based on length of follow-up ($I^2=49.4\%$), diabetes mellitus prevalence ($I^2=36.4\%$), percentage of current smokers ($I^2=38.5\%$), preexisting CVD

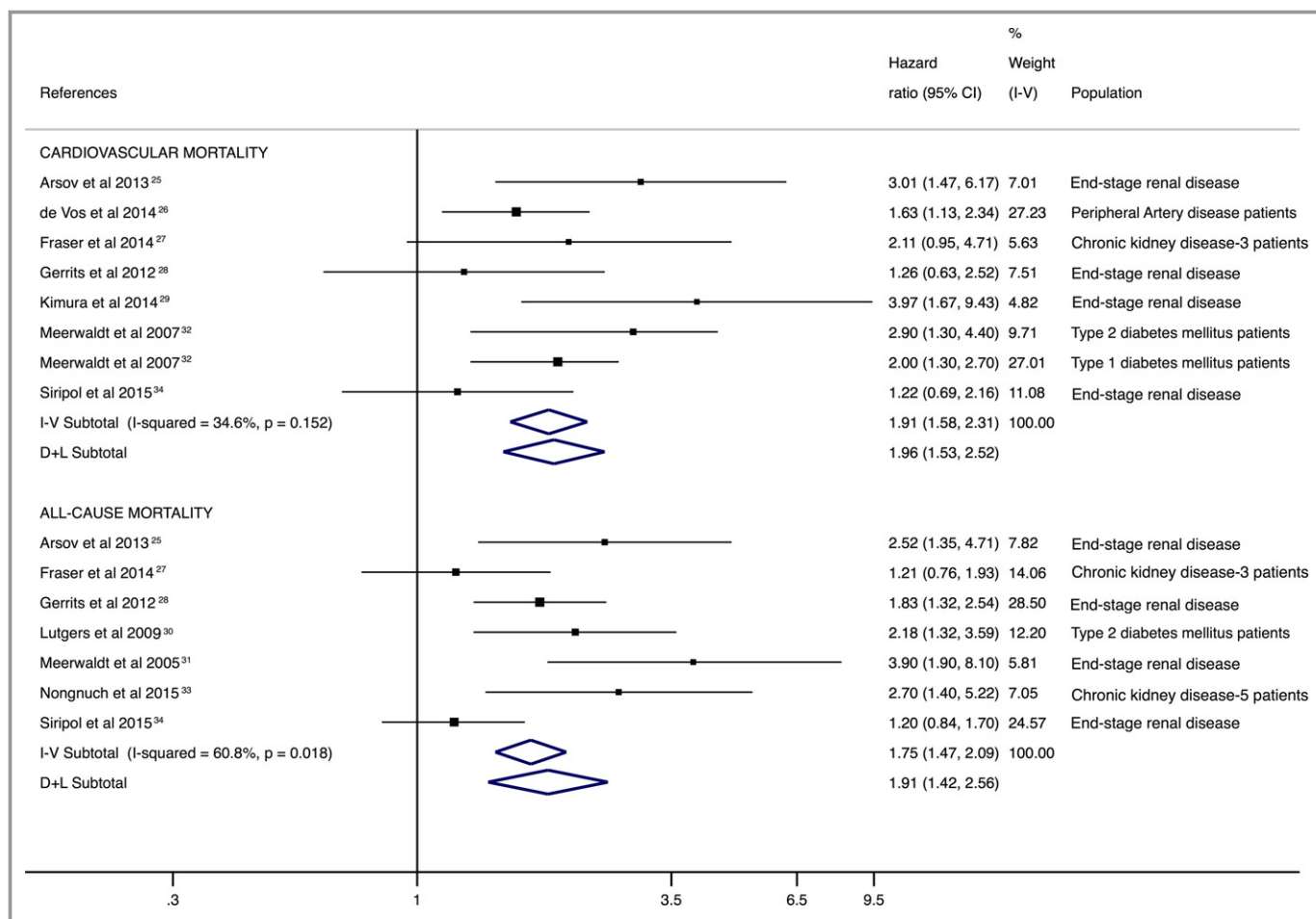


Figure 2. Forest plot including pooled hazard ratios for cardiovascular and all-cause mortality using skin autofluorescence–indicated advanced glycation end products as predictors. CI indicates confidence interval; D+L, DerSimonian and Laird; I-V, inverse variance.

prevalence ($I^2=38.8\%$), baseline SAF levels ($I^2=48.3\%$), and creatinine levels ($I^2=41.4\%$).

Publication Bias

Evidence of publication bias was found by funnel plot asymmetry and the Egger test for the cardiovascular mortality estimate ($P=0.056$) and for the all-cause mortality estimate ($P=0.007$; Figure S1). Moreover, trim-and-fill computation showed that 3 studies were needed to remove publication bias from both cardiovascular mortality ($P=0.909$) and all-cause mortality ($P=0.698$; Figure S2).

Discussion

This systematic review and meta-analysis provides a synthesis of the evidence suggesting that higher SAF levels could be a predictor of cardiovascular and all-cause mortality. Our data confirm the association between chronic deposits of AGEs produced by enzymatic glycation in skin and mortality,

suggesting that SAF may be used as a tissue biomarker of cardiovascular and all-cause mortality risk in patients with diabetes mellitus, CVD, and renal disease.

Previous studies in which AGE levels were estimated in plasma have reported ambiguous results regarding the association between AGE levels and mortality.^{35,36} Conversely, the results of this meta-analysis show that SAF is consistently associated with mortality. This may be due to the levels of AGEs in long-lived proteins placed in skin over time, which is a chronic indicator of AGE levels,³⁷ whereas in blood plasma, we can find AGEs produced in a short period of time, which may not be directly related to chronic outcomes.

The crucial role of chronic hyperglycemia in the development and progression of atherosclerosis and CVD events in patients with diabetes mellitus or renal disease is not debatable.^{38–40} However, the identification of AGEs in the atherosclerotic plaques of nondiabetic patients with coronary artery disease have magnified the importance of AGEs and oxidative stress in accelerating atherosclerosis.⁴¹ AGEs from long-lived proteins such as collagens⁴² predict future

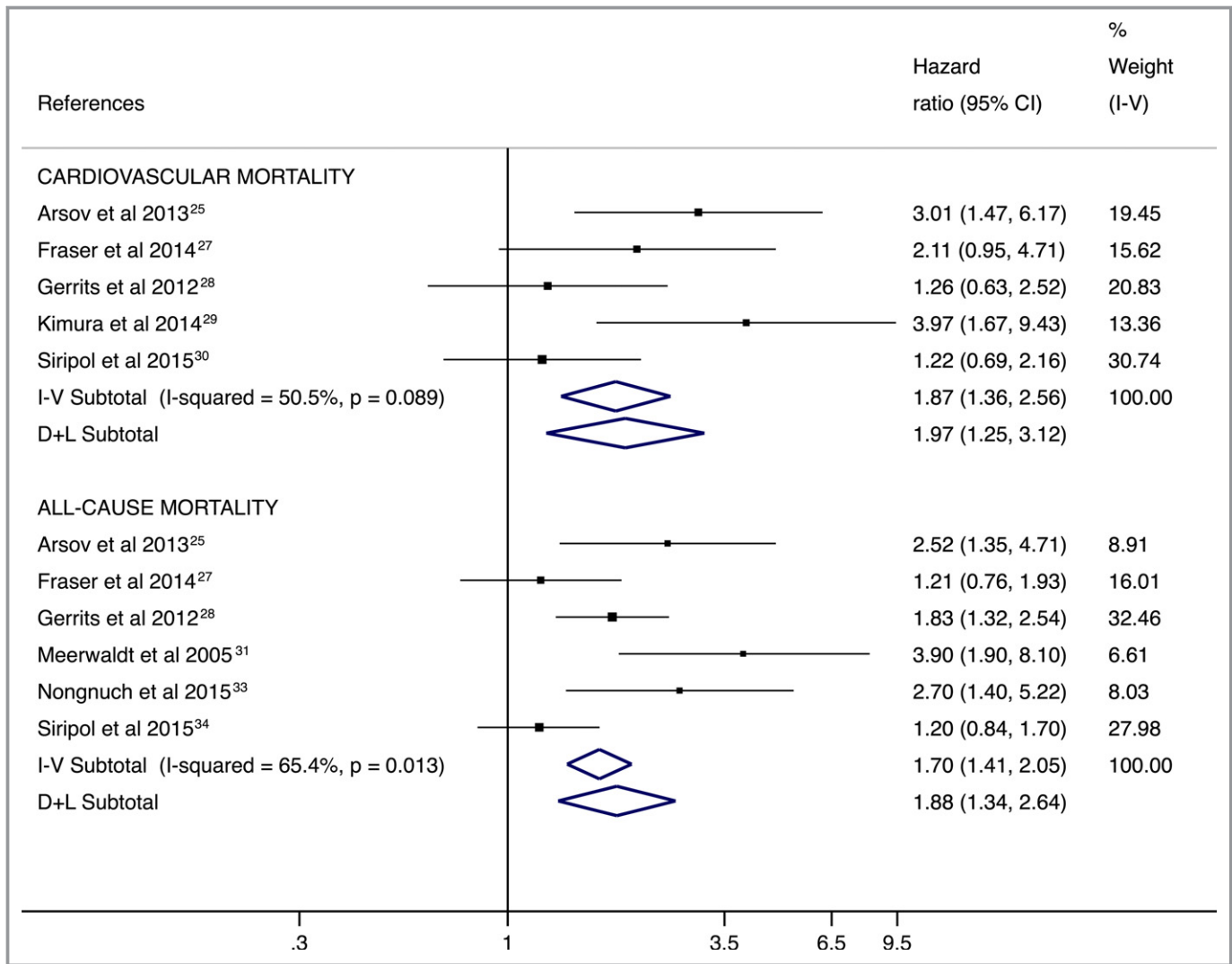


Figure 3. Forest plot including the pooled hazard ratios for cardiovascular and all-cause mortality in renal patients using skin autofluorescence–indicated advanced glycation end products as predictors. CI indicates confidence interval; D+L, DerSimonian and Laird; I-V, inverse variance.

progression of microvascular disease, progression of carotid intima-media thickness, left ventricular mass, and the severity of coronary artery calcium.⁴³ Accordingly, the results of our study demonstrate that levels of SAF are associated with cardiovascular events and cardiovascular mortality. Moreover, the homogeneity in the results of the longitudinal studies included in this meta-analysis argues in favor of the validity of our findings.

Three pathophysiological mechanisms are known by which AGEs may cause cardiovascular events and cardiovascular mortality: (1) AGEs can affect the physiological properties of cardiac proteins in the extracellular matrix by creating cross-links, and excessive cross-linking caused by the accumulation of AGEs weakens the flexibility of the matrix proteins and produces stiffness in vascular walls⁴⁴; (2) they can affect vascular function by influencing both endothelial function and vascular compliance, which occurs because AGEs reduce

nitric oxide vasodilator levels⁴⁵ and favor the production of a potent vasoconstrictor, endothelin-1⁴⁶; and (3) they can cause multiple vascular and myocardial changes through interaction with RAGEs. RAGEs mediate the induction of fibrosis through the increase of TGF- β (transforming growth factor β)⁴⁷ and influence calcium metabolism in cardiac myocytes.⁴⁸ In addition, RAGE interaction may induce atherosclerosis, thrombosis, and vasoconstriction.⁴⁹

Some limitations of this study that could compromise our results should be stated. First, the reasons for death included in the definition of all-cause mortality could vary across the studies included; therefore, misclassification bias could potentially affect our estimates of the associations between SAF levels and the risk of mortality. Second, there was evidence of significant publication bias with the Egger test, and results from studies that are not published could have modified the results of our meta-analysis. Traditionally,

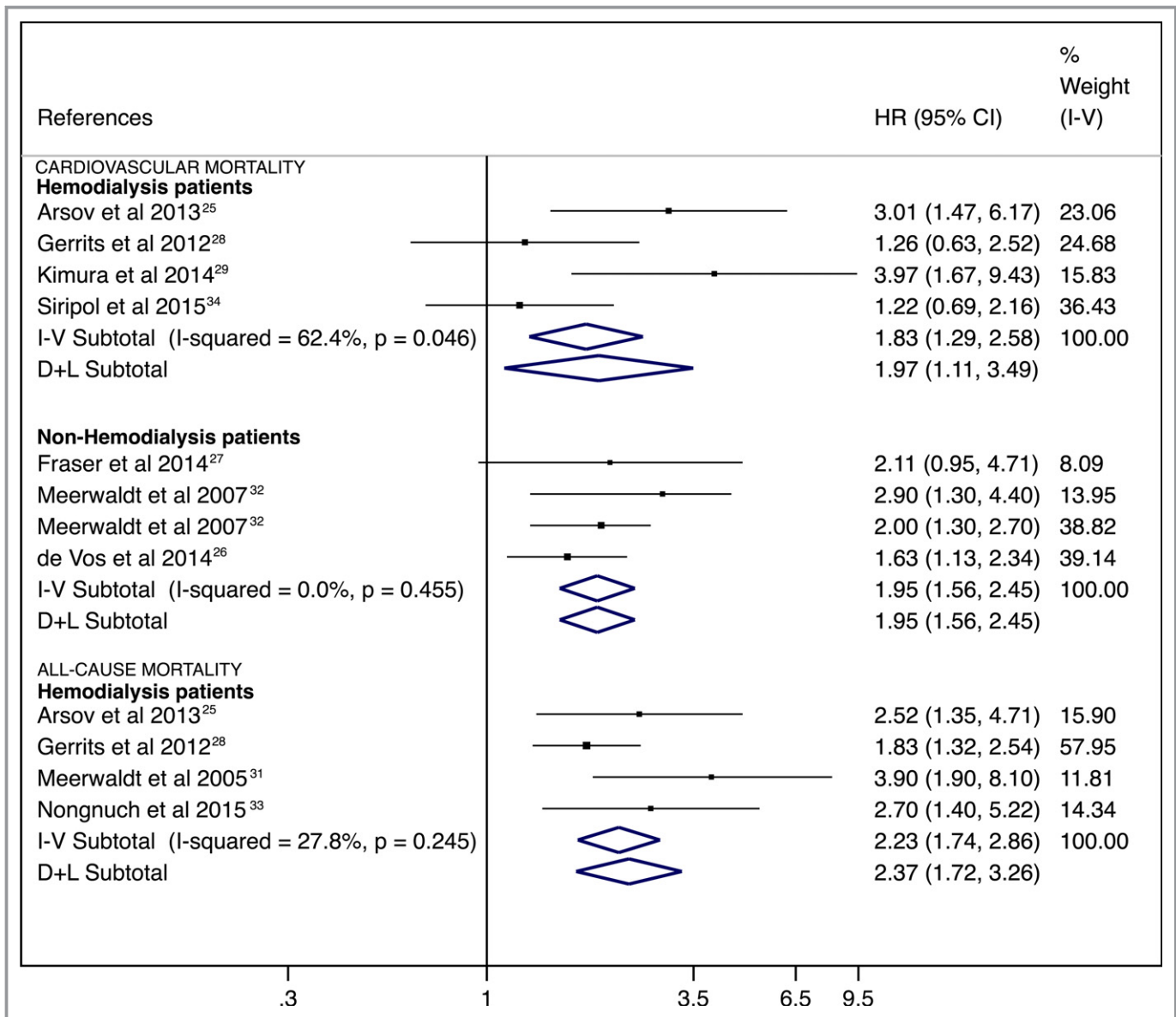


Figure 4. Forest plot including the pooled hazard ratios for cardiovascular and all-cause mortality in hemodialysis and nonhemodialysis patients using skin autofluorescence–indicated advanced glycation end products as predictors. CI indicates confidence interval; D+L, DerSimonian and Laird; HR, hazard ratio; I-V, inverse variance.

publication bias is thought of as the editorial tendency to publish significant results to the detriment of research reporting a nonsignificant relationship between the variables being analyzed. Moreover, in this study, we cannot neglect that SAF measurements have not been included as a cardiovascular risk factor until recently, and this can be a source of publication bias publication. To better understand the effect of publication bias on the interpretation of results, the trim-and-fill computation was used. Finally, although we extracted the most fully adjusted risk estimates, our results might still be threatened by residual confounding. Conversely, this meta-analysis has several strengths: Two searches were performed across several electronic databases to ensure that

all suitable studies were identified. Regarding SAF measurements, all included studies used the same device—the AGE Reader—to perform measurements.

Conclusions

In summary, our data support that SAF levels could be considered predictors of all-cause mortality and cardiovascular mortality in patients at high and very high risk. Although the appropriate use of our results should be understood in each particular clinical context, our data suggest that clinicians should consider the level of SAF when they assess the risk of cardiovascular and all-cause mortality.

Notwithstanding, our data highlighted the need for more research to establish an optimal level of SAF in different populations to evaluate the appropriateness of including this biomarker as a routine assessment for cardiovascular risk in the usual clinical practice of patients at different CVD risk levels.

Future Perspectives

It would be of particular interest to study the clinical performance of SAF for predicting cardiovascular events and mortality risk in patients at moderate risk and in the general population. Furthermore, it would be important to understand the increased value of using SAF levels as predictors of CVD above and beyond the risk estimates that are already in use in clinical practice.^{50–53} The definitive establishment of SAF as a biomarker of CVD and mortality will be well established once all the conventional consensus criteria are fulfilled.^{54,55}

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Disclosures

None.

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SUPPLEMENTAL MATERIAL

Table S1. Search strategy for MEDLINE.

<p>“Skin Autofluorescence”</p> <p>OR</p> <p>Fluorescence</p> <p>OR</p> <p>Autofluorescence</p> <p>OR</p> <p>SAF</p>	<p>AND</p>	<p>"Tissue advanced glycation end products"</p> <p>OR</p> <p>"Advanced Glycosylation End Products"</p> <p>OR</p> <p>"Advanced Glycation End Products"</p>	<p>AND</p>	<p>Cardiovascular</p> <p>OR</p> <p>Mortality</p> <p>OR</p> <p>"all-cause mortality"</p> <p>OR</p> <p>"cardiovascular mortality"</p> <p>OR</p> <p>"cause-specific mortality"</p> <p>OR</p> <p>Death</p> <p>OR</p> <p>"cardiovascular death"</p> <p>OR</p> <p>"overall mortality"</p>
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Table S2. Covariates used for adjusting the data reported by the included studies.

Reference	Covariates
Arsov et al 2013 ¹	Age, sex, pre-CVD, diabetes mellitus, hypertension, HbSAg, dialysis duration, hs-CRP, ICAM-1, SOD, MPO, albumin.
de Vos et al 2014 ²	Age, sex, current smoking, weight status, diabetes mellitus, hypertension, lipid-lowering drugs, eGFR, pre-CVD.
Fraser et al 2014 ³	Age, sex, pre-CVD, diabetes mellitus, hypertension, current smoking, BMI, central obesity, total-to-HDL cholesterol ratio, eGFR, uACR, hemoglobin.
Gerrits et al 2012 ⁴	Age, albumin, diabetes mellitus, pre-CVD, renal replacement therapy, pulse pressure, hematocrit, serum phosphorus, PTH.
Kimura et al 2014 ⁵	Age, sex, dialysis duration, diabetes mellitus, carotid IMT, albumin, pentosidine, hs-CRP, pre-CVD.
Lutgers et al 2008 ⁶	Sex, pre-CVD.
Meerwaldt et al 2005 ⁷	Age, albumin, hs-CRP, diabetes mellitus, dialysis duration, dialysis duration, hemodialysis treatment, triglycerides, LDL, smoking, PTH.
Meerwaldt et al 2007 ⁸	Age, HbA1c, hypertension, hemodialysis treatment, triglycerides, pre-CVD, LDL.
Nongnuch et al 2015 ⁹	Sex, Davies' score, dialysis duration, albumin, cholesterol, phosphate binder, ethnicity, pre-CVD, diabetes mellitus, mode of haemodialysis, Kt/v, dialysis duration, hs-CRP, urine output, β 2 microglobulin.
Siripol et al 2015 ¹⁰	None.

Pre-CVD: preexisting cardiovascular diseases; HbSAg: hepatitis B surface antigen; hs-CRP: high-sensitivity C-reactive protein; ICAM-1: Intercellular Adhesion Molecule 1; SOD: superoxide dismutase; MPO: Myeloperoxidase; eGFR: estimated glomerular filtration rate; HDL: high density lipoprotein; uACR: albumin-to-creatinine ratio; PTH: parathyroid hormone; IMT: intima-media thickness; LDL: low density lipoprotein; HbA1c: glycated haemoglobin.

Table S3. Study quality assessed by QUIPS tool.

Reference	Study Participation	Study Attrition	Prognostic Factor (PF) Measurement	Outcome Measurement	Study Confounding	Statistical Analysis and Reporting	Total
Arsov et al 2013 ¹	●	●	●	●	●	●	●
de Vos et al 2014 ²	●	●	●	●	●	●	●
Fraser et al 2014 ³	●	●	●	●	●	●	●
Gerrits et al 2012 ⁴	●	●	●	●	●	●	●
Kimura et al 2014 ⁵	●	●	●	●	●	●	●
Lutgers et al 2008 ⁶	●	●	●	●	●	●	●
Meerwaldt et al 2005 ⁷	●	●	●	●	●	●	●
Meerwaldt et al 2007 ⁸	●	●	●	●	●	●	●
Nongnuch et al 2015 ⁹	●	●	●	●	●	●	●
Siripol et al 2015 ¹⁰	●	●	●	●	●	●	●

● : Low risk of bias ● : Moderate risk of bias ● : High risk of bias

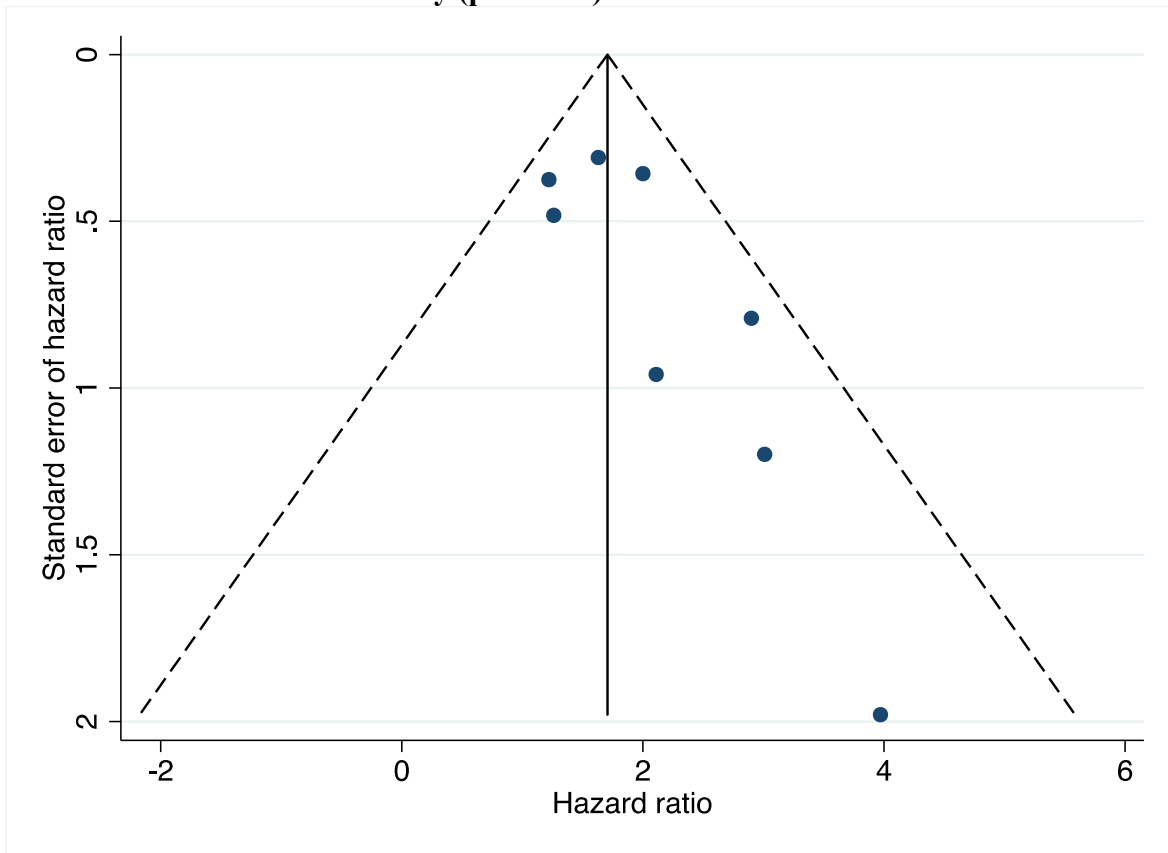
Table S4. Random effect metaregression model.

Covariate	Cardiovascular mortality				All-cause mortality			
	Number of studies	β (SE)	p	I ²	Number of studies	β (SE)	p	I ²
Length of follow up (years)	8	0.18 (0.17)	0.340	14.0	7	-0.01 (0.32)	0.985	49.4
Male sex (%)	8	0.00 (0.02)	0.998	27.0	7	0.03 (0.01)	0.068	1.4
Age (years)	8	-0.01 (0.02)	0.679	23.4	7	-0.02 (0.05)	0.730	52.4
Diabetes mellitus (%)	8	0.01 (0.01)	0.136	0.0	7	0.01 (0.01)	0.284	36.4
BMI (kg/cm ²)	7	-0.10 (0.10)	0.383	3.0	5	-0.14 (0.12)	0.307	21.8
Current smoker (%)	7	-0.00 (0.01)	0.813	27.4	6	0.04 (0.03)	0.273	38.5
Hypertension (%)	6	-0.01 (0.01)	0.160	0.0	5	-0.02 (0.01)	0.104	0.0
Pre-CVD (%)	6	-0.02 (0.03)	0.553	6.0	6	0.01 (0.03)	0.699	38.8
Baseline SAFs (AU)	8	-0.20 (0.38)	0.619	22.8	7	-0.47 (0.77)	0.567	48.3
hs-CRP (mg/L)	3	0.04 (0.25)	0.885	61.8	4	0.14 (0.09)	0.270	26.7
SBP (mmHg)	3	-0.07 (0.08)	0.544	0.0	3	0.06 (0.03)	0.335	0.0
DBP (mmHg)	3	0.02 (0.04)	0.676	0.0	3	0.01 (0.06)	0.827	69.2
Haemoglobin (g/dL)	4	0.02 (0.42)	0.960	20.9	4	-0.10 (0.36)	0.805	58.7
HbA1c (%)	3	0.50 (0.39)	0.419	0.0	N/O	-	-	-
Albumin (g/L)	3	-0.08 (0.17)	0.720	42.6	4	-0.10 (0.08)	0.322	16.8
Creatinine (mg/dL)	4	-0.08 (0.09)	0.454	31.1	3	0.02 (0.15)	0.899	41.4
Total cholesterol (mg/dL)	5	0.01 (0.01)	0.532	44.2	5	0.00 (0.02)	0.875	59.5
LDL cholesterol (mg/dL)	3	-0.04 (0.05)	0.537	7.0	N/O	-	-	-
Triglycerides (mg/dL)	4	-0.02 (0.04)	0.640	59.7	3	0.03 (0.13)	0.285	0.0

SE: standard error; BMI: body mass index; Pre-CVD: preexisting cardiovascular disease; AGES: advanced glycation end products; AU: arbitrary units; hs-CRP: high-sensitivity C-reactive protein; SBP: systolic blood pressure; DBP: diastolic blood pressure; HbA1c: glycated haemoglobin A1c; LDL: low density lipoprotein; N/O: not enough observations.

Figure S1. Assessment of potential publication bias by Egger test.

A Cardiovascular mortality (p = 0.072)



B All-cause mortality (p = 0.007)

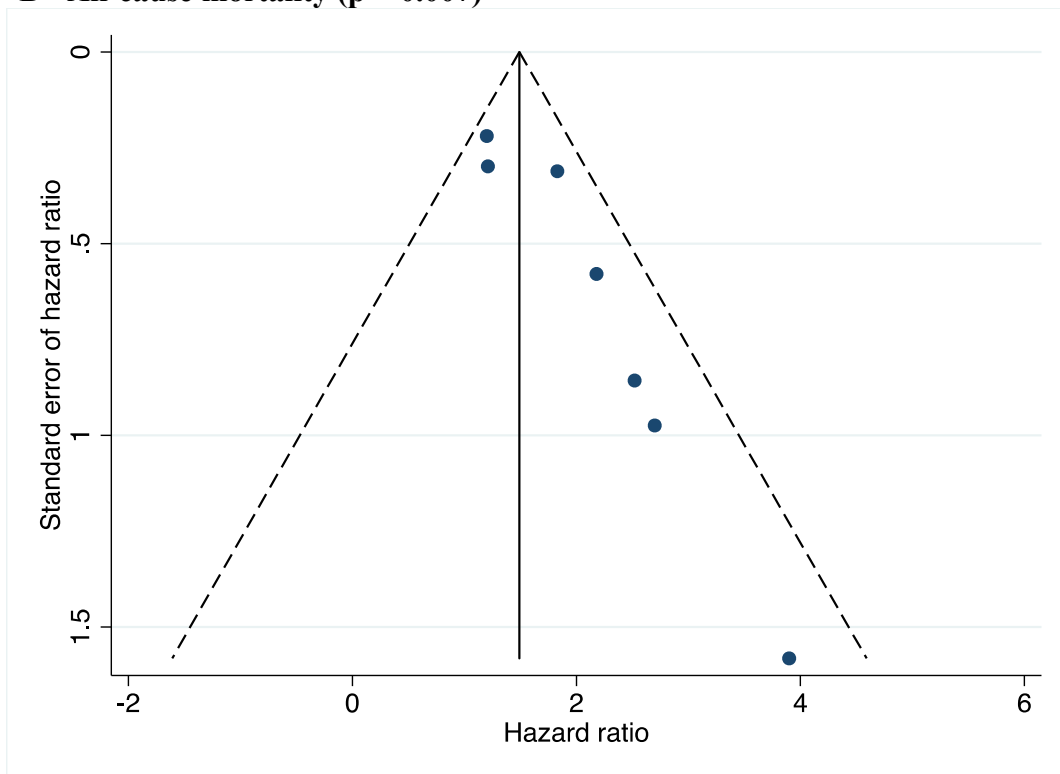
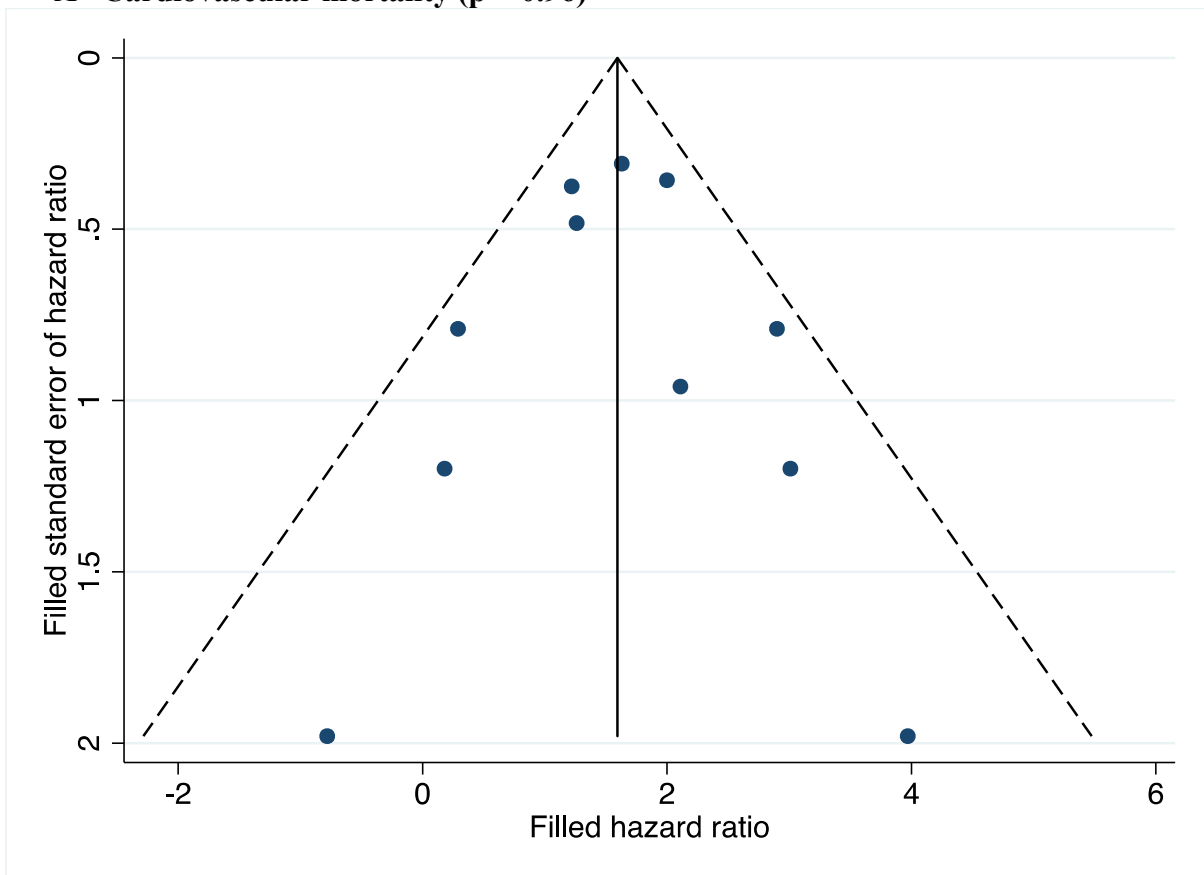
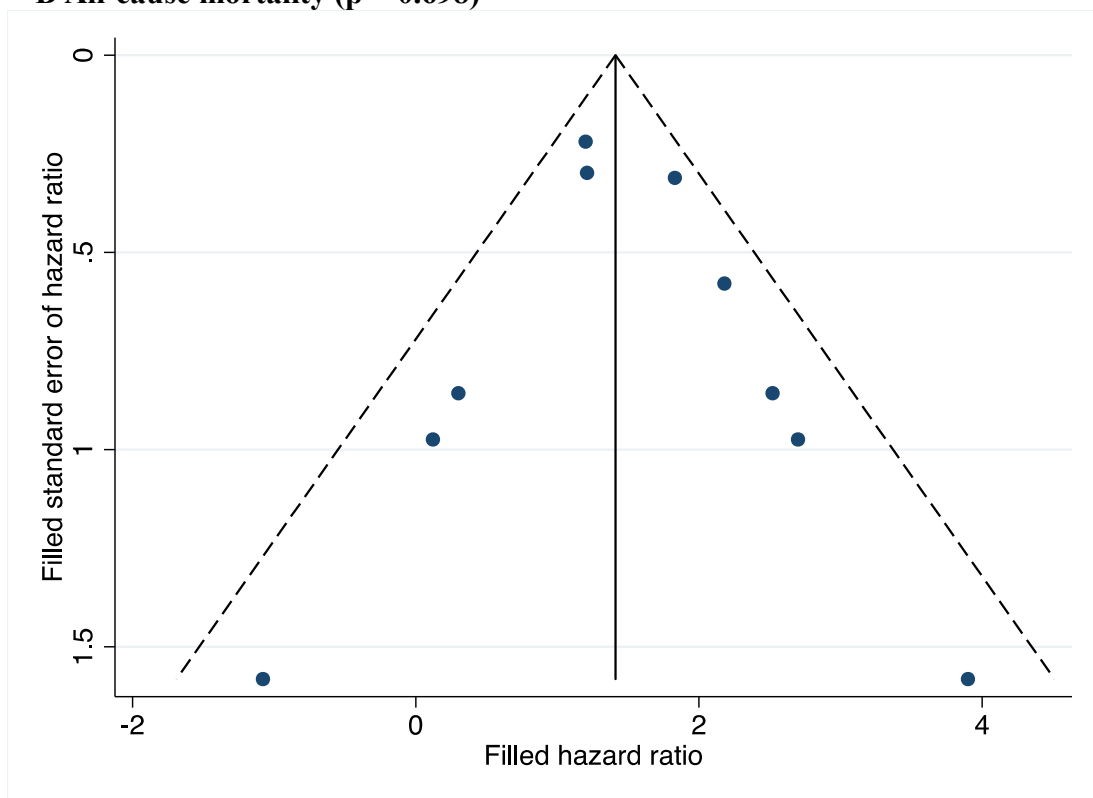


Figure S2. Assessment of potential publication bias by Egger test post Trim and fill.

A Cardiovascular mortality (p = 0.96)



B All-cause mortality (p = 0.698)



Supplemental References:

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