Association between Low Estimated Glomerular Filtration Rate and Risk of Cerebral Small-Vessel Diseases: A Meta-Analysis

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Background: Although chronic kidney disease has been linked to cerebral small-vessel disease (CSVD), a definite relationship between them has not been established. This study assessed whether low estimated glomerular filtration is associated with risk of different subtypes of CSVDs. *Methods:* Electronic databases were systematically searched for studies reporting an odds ratio of the association between low estimated glomerular filtration and CSVD risk. Sixteen studies, including 10,534 participants, were identified. A fix effects model was applied and odds ratios (ORs) with 95% confidence intervals were presented. *Results:* Overall, risk of CSVDs was greater in individuals with low estimated glomerular filtration (OR = 2.20). Stratified analyses consistently showed significant associations across different subtypes, with pooled OR being greatest in subjects with silent cerebral infarction (SCI) (OR = 2.71) and cerebral microbleed (OR = 2.70). A pooled estimate of studies showing OR as a continuous variable showed results consistent with the former analysis (OR = .98 per standard deviation decrease) in low estimated glomerular filtration. *Conclusions:* This study revealed that low estimated glomerular filtration was significantly associated with risk of CSVDs. Low estimated glomerular filtration was most strongly associated with SCI (OR = 2.71) among subtypes of CSVDs. **Key Words:** Cerebral small-vessel diseases—estimated glomerular filtration rate—chronic kidney impairment—meta-analysis.

Introduction

Cerebral small-vessel disease (CSVD), defined as various disorders of the small arteries, arterioles, venules, and capillaries of the brain, is a frequent cause of ischemic stroke and vascular dementia. Age, hypertension, and amyloid angiopathy are the leading causes of CSVD.[1] CSVD is usually diagnosed by the presence, on brain magnetic resonance imaging, of lacunae, white matter lesions (WMLs), and cerebral microbleeds (CMBs).[2] Silent cerebral infarction (SCI), defined as a cerebral ischemic event evident on brain imaging without any clinical symptoms, is regarded as a marker of disorders of the small arteries.[3]

Chronic kidney disease (CKD) is characterized by a decreased estimated glomerular filtration rate (eGFR) below 60 mL/minute/1.73 m^2 or albuminuria as a marker of increased glomerular permeability.[4] CKD has been increasingly associated with cardiovascular diseases, including risk of stroke.[5] The similar hemodynamics and pathological features of stroke and CSVD suggest that CKD may also be linked to CSVD,[5-8] but a definite relationship between them has not been established, especially with regard to subtypes of CSVD. This systematic review and meta-analysis therefore investigated the impact of low eGFR on risk of CSVD.

Methods

Literature Search and Selection Criteria

The search strategy conformed to the recommendations of the Meta-analysis of Observational Studies in Epidemiology.[8] Databases searched included PubMed (from 1966 to November 2014), EMBASE (from 1974 to November 26, 2014), MEDLINE (from 1947 to November 2014), and the Cochrane Library. The systematic search with terms that included "chronic kidney disease," "nephropathy," or "renal insufficiency," and "stroke," "cerebrovascular disease," "lacunar infarction," "cerebral microbleed," "silent cerebral infarction," or "white matter lesions." Studies in any language that met the following criteria were selected: (1) case–control or cross-sectional studies in humans, (2) quantitative estimates using odds ratio (OR) and 95% confidence interval (CI), (3) clear information on adjustments for confounding factors, (4) exclusion of patients with inherited or genetic small-vessel diseases, and (5) patient sample size greater than 100.

Data Extraction

Information recorded for each study included country, population size, demographic data, subtype of CSVD analyzed, definition of kidney dysfunction, and adjusted variables.

Statistical Analysis

The incidence of CSVD in patients with low eGFR was calculated. OR and 95% CI were determined by converting these values to their natural logarithms, as were standard errors and their corresponding 95% CIs. The inverse variance approach was used to combine log OR and standard errors and data pooled across studies using the fix effects model. Heterogeneity was assessed by probability value of χ^2 statistics and I^2. The Cochrane Collaboration Review Manager Software Package (RevMan 5) was used for the meta-analysis (Cochrane's Informatics & Knowledge Management Department, download from http://tech.cochrane.org for free). I^2 of 40% was defined as "heterogeneity might not be important" and I^2 of 75% as "considerable heterogeneity" based on the *Cochrane Handbook for Systemic Reviews of Interventions*. All reported *P* values were 2-sided, and those less than 0.05 were considered statistically significant. Funnel plots were used to evaluate potential systematic bias in studies. Subsequent subgroup analyses were performed based on subtypes of CSVD.

Results

Study Characteristics and Quality

The initial search identified 285 abstracts (Fig 1). Detailed review determined that 16 studies, involving 10,534 participants, were eligible. Fourteen of these studies were from Asian populations and two from European and American populations. The number of participants ranged from 105 to 2106. The characteristics of these 16 studies are shown in Table 1. Determination of study quality was based on guidelines developed by the Newcastle–Ottawa Scale and modified according to a previous study,[6] and study quality details were provided in the supplementary data.

Association between Low eGFR and CSVD

Overall, CSVD risk was greater for patients with low eGFR, after adjustment for established cardiovascular risk factors (pooled OR = 2.22). Further analysis, in which participants were stratified by subtype of CSVD, showed that low eGFR was most strongly associated with SCI (OR = 2.71), followed by CMB (OR = 2.70), WML (OR = 2.03), and lacunar infarction (OR = 1.77) (Fig 2). There was no evidence of significant heterogeneity in the magnitude of the association across studies ($P = .43$, $I^2 = 2\%$). An analysis of studies that determined OR as a continuous variable found similar results (overall OR = .98 per standard deviation decrease in eGFR) (Fig 3).

Publication Bias

No publication bias for the association between low eGFR and CSVD was identified by funnel plot from RevMan 5 (Fig 4).

Discussion

This meta-analysis of 16 observational studies showed that occurrence of low eGFR increased the risk of CSVD,
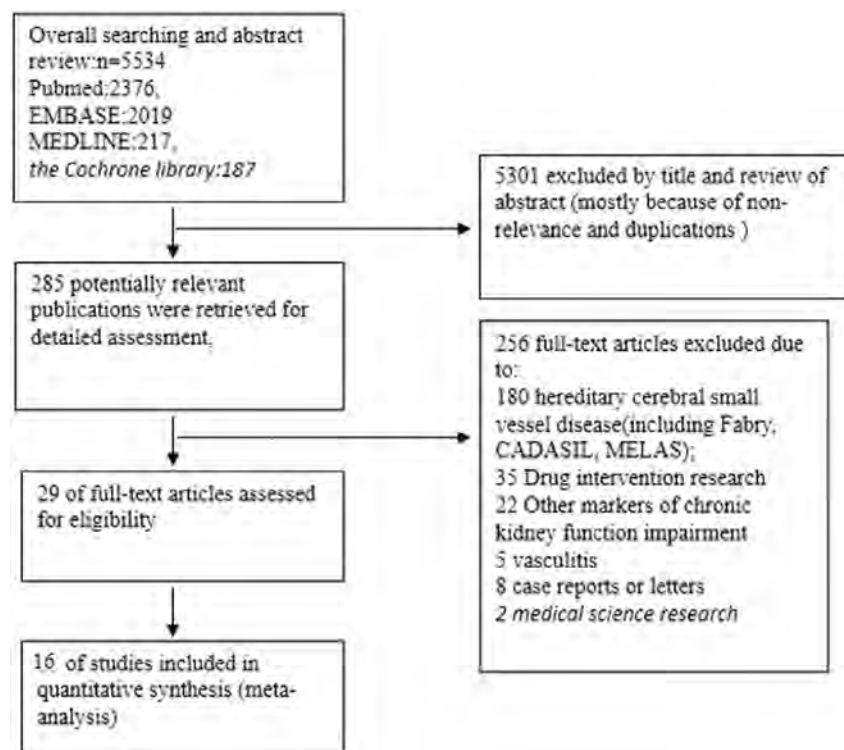
Figure 1. *Study flow diagram. Abbreviations: CADASIL, cerebral autosomal-dominant arteriopathy with subcortical infarcts and leuko-encephalopathy; MELAS, mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes.*

with this relationship consistent across all subtypes of CSVD examined. It may be due to traditional cardiovascular risk factors, which lead to arteriosclerotic insults. However, increasing evidence has shown that CKD is an independent risk factor for CSVD.[5,7] In the present study, the pooled estimates suggest that low eGFR had a significant impact on the risk of CMB (OR = 2.70), in agreement with previous findings.[8] Two reasons should be considered. First, endothelial dysfunction may be common pathophysiologically to both kidney dysfunction and CSVD, characterized by excess leakage to urine and erythrocytes in brain parenchyma.[25] Second, platelet dysfunction may be induced by kidney dysfunction. Patients with severe CKD show prolonged bleeding time, suggesting that blood coagulation disorders may be the link between kidney dysfunction and cerebral microbleeding.[26] A recent study found an increased risk of renal impairment in patients with than without CSVD, in agreement with our findings.[27]

We also found that the pooled OR for low eGFR was greater in patients with SCI and WML, without significant heterogeneity. SCI is asymptomatic, but is important as a predictor of stroke and dementia. The prevalence of WML is also significantly related to the risks of stroke, cognitive decline, and dementia.[28] The features of kidney function impairment are similar to those of small-artery diseases, including glomerular endothelial dysfunction and lipohyalinosis.[29] Thus, chronic impairment in kidney function may be linked to endothelial dysfunction involved in the disruption of the integrity of cerebral small vessels

and the blood–brain barrier. Increased concentration of homocysteine was found to trigger vascular injury by exacerbating oxidative stress reactions.[30] Cerebral and renal small-vessel diseases may progress concomitantly with the inflammatory process, leading to CMB, SCI, WML, and CKD.

Because our study was based on observational studies, we cannot establish causality. Rather, these 2 chronic diseases more likely have common hemodynamic and pathophysiological similarities. Evidence has suggested that protection of the kidneys can reduce the incidence of stroke and that reducing blood pressure can protect against kidney dysfunction. Modulators of the renin–angiotensin system have been shown to effectively reduce stroke incidence,[31] suggesting that these modulators, as well as statins, may be candidate treatments for patients with CSVD.[32,33]

The present study had several limitations. First, meta-analyses can be constrained by search strategy, the criteria for study inclusion, and publication bias, especially when the meta-analysis involves observational studies rather than randomized controlled trials. Second, the studies varied with respect to the characteristics of the participants, the research purposes, and the adjusted variables. Third, although funnel plots showed no major asymmetries, there may be a publication bias, in that studies showing a positive relationship tend to be published.

As we know, risk factors for cardiovascular diseases were different between population of Asian and European.[34]

Table 1. *Study characteristics*

Study ID	Study design	Population	Country	No. of participants (% female)	Age (SD), year	Definition of chronic kidney impairment (mL/min/1.73 m^2)	CSVD subtypes	Adjusted variable
Oh et al[9]	Case–control	Patients with acute stroke	Korea	494 (72.3)	65.7 (12.4)	Highest versus lowest quartiles of eGFR	CMB	Age, gender, total cholesterol, diabetes, hypertension, dyslipidemia, previous heart disease, smoking, previous antithrombotic or anticoagulant use
Chou et al[10]	Cross-sectional	General population	China	1312 (41.7)	52.5 (10)	30 < eGFR < 60	SCI	Age, gender, hypertension, diabetes, moderate carotid plaque
Ikram et al[11]	Cross-sectional	General population	The Netherlands	484 (51)	73.4 (7.8)	eGFR < 60	Lacunar infarcts	Age, gender
Kobayashi et al[12]	Case–control	CKD or CKD risk population	Japan	375 (39.7)	63.5 (14)	eGFR < 60	SCI	Age, hypertension, diabetes mellitus, hyperlipidemia
Bouchi et al[13]	Case–control	Type 2 diabetes mellitus(T2DM)	Japan	786 (42.9)	65 (11)		SCI	Age, gender, total cholesterol, diabetes, hypertension, dyslipidemia, previous heart disease, smoking
Otani et al[14]	Cross-sectional	General population	Japan	1008 (71.5)	66.4 (5.7)	eGFR < 60	Lacunar infarcts	24-h systolic BP, gender, age, BMI, ever smoker, ever drinker, antihypertensive drug, hypercholesterolemia, diabetes, history of heart disease
Shimoyama et al[15]	Case–control	Patients with acute ischemic stroke	Japan	105 (32.4)	70 (4.2)	eGFR < 60	CMB	Gender, age, hypertension, previous stroke, atrial fibrillation, CAVI
Song et al[16]	Case–control	Patients with acute ischemic stroke	Korea	1669 (39)	66 (12)	eGFR < 60	CMB	Age, gender, history of hypertension, coronary artery disease
Takahashi et al[17]	Case–control	General population	Japan	2106 (35)	56 (10)	eGFR < 60	SCI, WML	Age, gender, blood pressure
Wada et al[18]	Cross-sectional	General population	Japan	449 (44.8)	67.7 (4.9)	eGFR < 60	Lacunar infarction, moderate WML	Age, gender, hypertension, TC/HDL cholesterol ratio, diabetes mellitus, current smoker, maximum IMT
Yao et al[19]	Cross-sectional	General population	Japan	675 (59.9)	69.9 (9.3)	eGFR < 60	SCI	Age, gender, hypertension, diabetes, alcohol, smoking
Cho et al[20]	Case–control	Patients with acute ischemic stroke	Korea	152 (39.5)	66.7 (11.7)	eGFR < 60	CMB	Age, hypertension, hyperlipidemia, smoking
Shima et al[21]	Case–control	CKD patients and normal subjects	Japan	186 (43.0)	59.7 (5.8)	eGFR < 60	CMB	Age, gender, pulse pressure
Shima et al[22]	Case–control	General population	Japan	384 (71.3)	56.7 (12)	eGFR < 60	SCI, WML	Age, gender, diabetes, anticoagulation or antiplatelet therapy, LDL cholesterol, hemoglobin, pulse pressure
Sato et al[23]	Case–control	Patients with ischemic stroke	Japan	152 (34)	69	Lowest and middle tertiles versus highest tertile of eGFR < 60	CMB	Age, gender, systolic BP, white matter disease, antihypertensive drug use, diabetes mellitus
Ovbiagele et al[24]	Case–control	Patients with ischemic stroke	United States	197 (48)	59		CMB	Age, sex, systolic BP, white matter disease, antihypertensive drug use, diabetes mellitus

Abbreviations: BMI, body mass index; BP, blood pressure; CAVI, cardio-ankle vascular index; CKD, chronic kidney disease; CMB, cerebral microbleed; CSVD, cerebral small-vessel disease; HDL, high-density lipoprotein; ID, identification; IMT, intima–media thickness; LDL, low-density lipoprotein; SCI, silent cerebral infarction; SD, standard deviation; TC, total cholesterol; WML, white matter lesion.
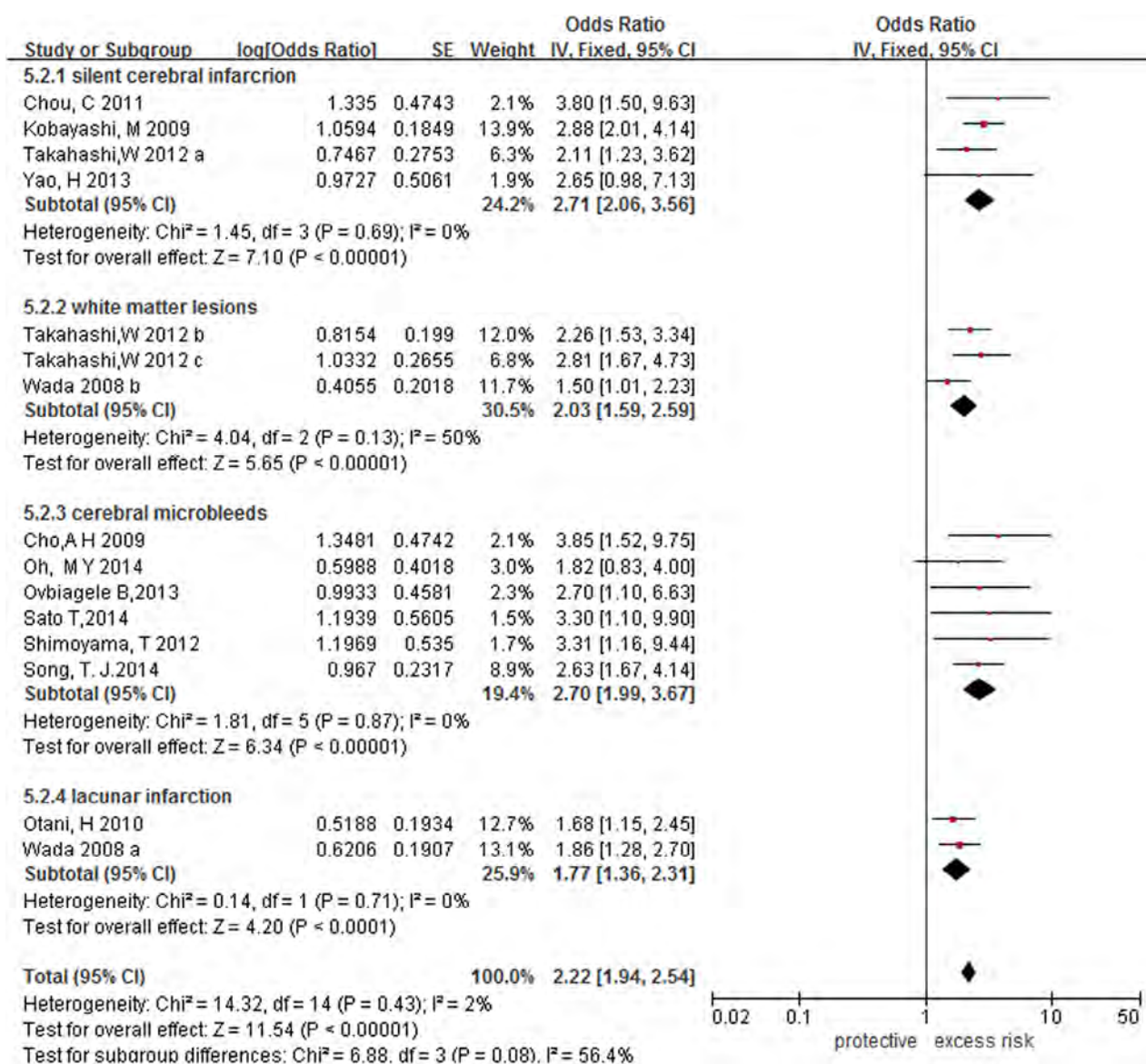
Figure 2. *Overall and stratified OR for the association between chronic kidney function impairment and risk of cerebral small-vessel disease (low versus normal eGFR). Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; IV, inverse variance; OR, odds ratio; SE, standard error.*

Hypertension was the most important risk factor among Asians, more than cholesterol and cigarette smoking. Moreover, Asian people were likely to develop hypertension at earlier ages than other races.[35] It suggested that patients from Asian populations with a longer history of hypertension would suffer more serious damage of small vessels both in kidney and brain, thus leading to a higher event rate of lacunar and hemorrhagic stroke, as well as CKDs.[36] So most studies focusing on the relationship between chronic renal function impairment and CSVDs were conducted in Asian populations, which contributed to the regional difference in the studies included in our analysis. And indeed, investigators found that Asian people with low eGFR were at higher risk of future stroke.[7] It suggested that the higher incidence of cerebral infarct

caused by small vessels and hemorrhagic stroke may partly explain the different effect of low eGFR on stroke between Oriental and Western people.

In conclusion, our meta-analysis found a significant and strong association between chronic kidney impairment and incidence of CSVD. Low eGFR was most strong associated with SCI and CMB among subtypes of CSVDs. However, additional studies are needed to determine whether low eGFR is just a risk marker or a potentially modifiable risk factor for CSVD.

Appendix: Supplementary Material

Supplementary data to this article can be found online at doi:10.1016/j.jstrokecerebrovasdis.2015.11.016.
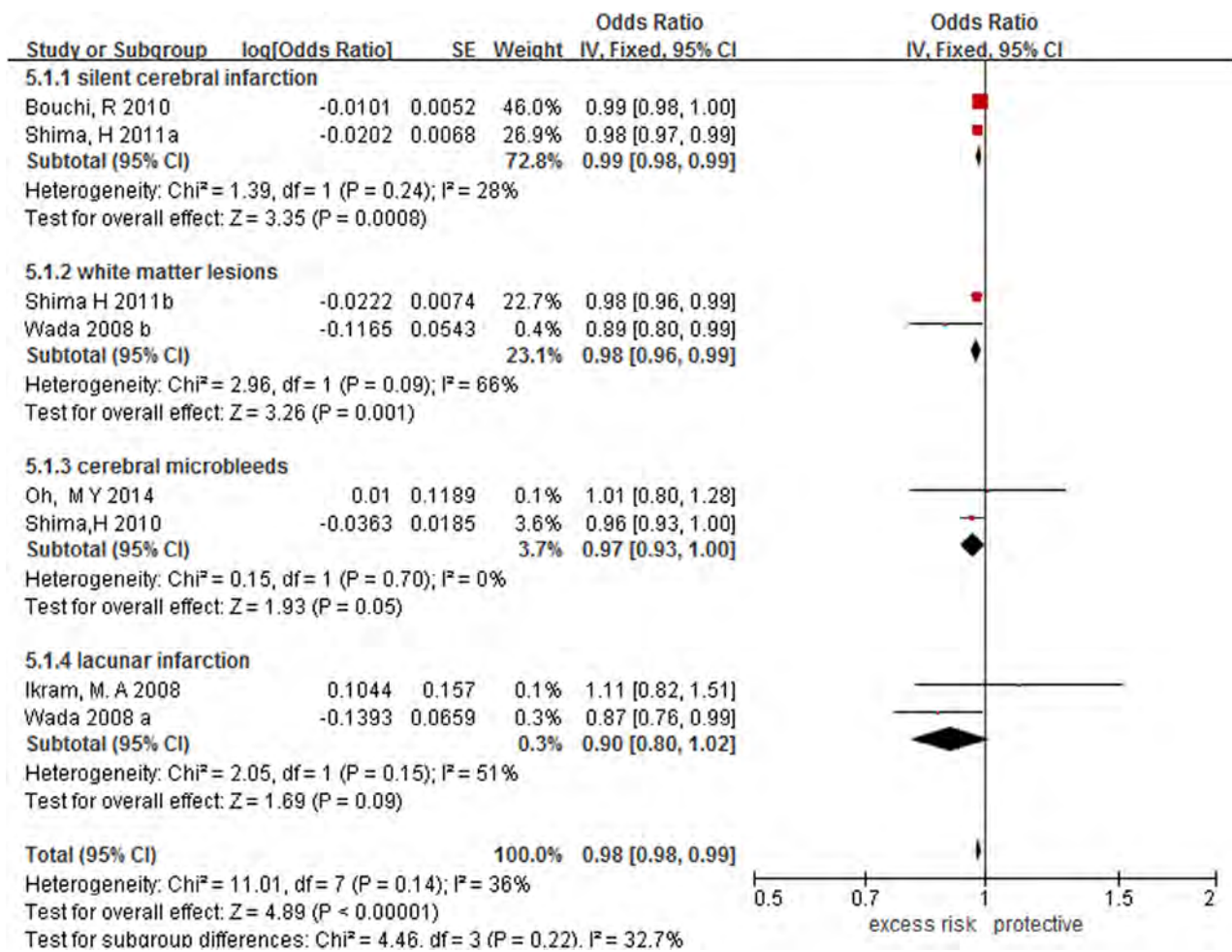
Figure 3. *Overall and stratified OR for the association between chronic kidney function impairment and risk of cerebral small-vessel disease (eGFR analyzed as a continuous variable). Abbreviations: eGFR, estimated glomerular filtration rate; OR, odds ratio; SE, standard error.*

Figure 4. *Funnel plot of included studies. Abbreviations: CI, confidence interval; IV, intravenous; SE, standard error.*
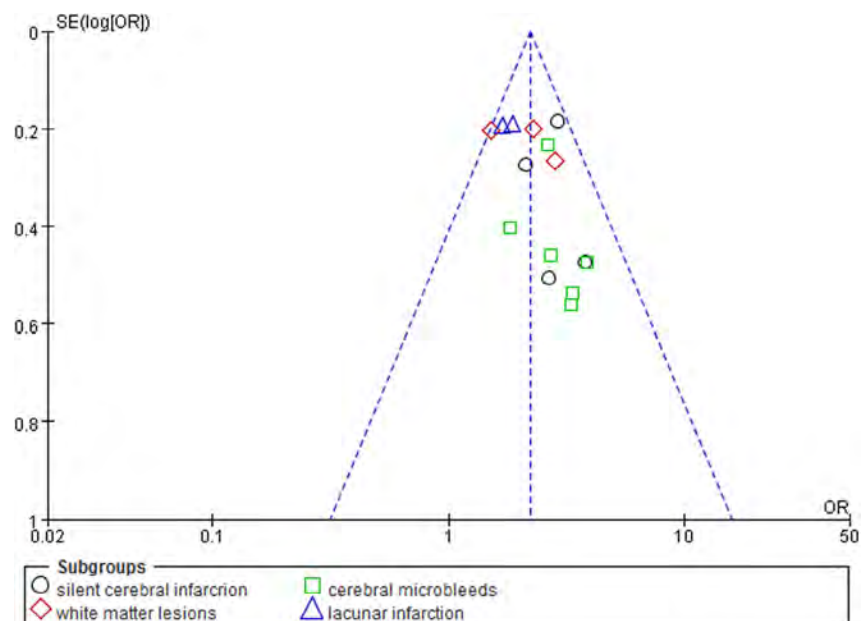
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