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

Yuanyuan Liu, PhD,* Pu Lv, PhD,* Haiqiang Jin, PhD,* Wei Cui, PhD,* Chenguang Niu, PhD,† Mingming Zhao, PhD,† Chenghe Fan, PhD,* Yuming Teng, PhD,* Bing Pan, MD,† Qing Peng, MD,* Jingjing Luo, MD,* Lemin Zheng, PhD,† and Yining Huang, MD*

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.

From the *Department of Neurology, Peking University First Hospital, Beijing, China; and †The Institute of Cardiovascular Sciences and Institute of Systems Biomedicine, School of Basic Medical Sciences, and Key Laboratory of Molecular Cardiovascular Sciences of Ministry of Education, Peking University Health Science Center, Beijing, China.

Received October 15, 2015; revision received November 3, 2015; accepted November 7, 2015.

This study was funded by Grant 2012ZX09303-005-003 from the National S&T Major Project of China.

Authors' contributions: Yuanyuan Liu, Lemin Zheng, and Yining Huang designed the study, analyzed and interpreted the results, and drafted the manuscript. Haiqiang Jin and Pu Lv acquired the data. Yuanyuan Liu, Wei Cui, Chenguang Niu, Mingming Zhao, Chenghe Fan, Yuming Teng, Qing Peng, and Jingjing Luo analyzed and interpreted the data. All authors participated in discussions and interpretation of results and all approved the final version of the manuscript for submission.

Address correspondence to Lemin Zheng, The Institute of Cardiovascular Sciences and Institute of Systems Biomedicine, School of Basic Medical Sciences, and Key Laboratory of Molecular Cardiovascular Sciences of Ministry of Education, Peking University Health Science Center, Beijing 100191, China. E-mail: zhengl@bjmu.edu.cn.;

Address correspondence to Yining Huang, Department of Neurology, Peking University First Hospital, Beijing 100034, China. E-mail: ynhuang@sina.com.

1052-3057/$ - see front matter

http://dx.doi.org/10.1016/j.jstrokecerebrovasdis.2015.11.016

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,