Bidirectional association between glaucoma and chronic kidney disease: A systematic review and meta-analysis

Faye Yu Ci Ng,a Harris Jun Jie Muhammad Danial Song,a Benjamin Kye Jyn Tan,a Chong Boon Teo,a Emmett Tsz Yeung Wong,b Pui Yi Boey,c,e and Ching-Yu Chenga,c,d,e*

aYong Loo Lin School of Medicine, National University of Singapore, Singapore
bDivision of Nephrology, Department of Medicine, National University Hospital, Singapore
cGlaucoma Service, Singapore National Eye Centre, Singapore
dOcular Epidemiology Research Group, Singapore Eye Research Institute, Singapore
eOphthalmology & Visual Sciences Academic Clinical Program (Eye ACP), Duke-NUS Medical School, Singapore

Summary

Background Glaucoma and chronic kidney disease (CKD) are prevalent and debilitating conditions, with common pathogenic pathways like oxidative stress and fluid dysregulation. We evaluated if there is a bidirectional association between them, as previous studies have yielded conflicting results.

Methods In this systematic review and meta-analysis, we searched PubMed, Embase and Cochrane Library from inception until 15 June 2021, including full-length English articles published in peer-reviewed journals reporting on glaucoma and CKD as either exposure or outcome, among participants aged ≥18 years. We pooled overall summary estimates of odds ratios using random-effect meta-analysis and conducted subgroup meta-analyses and univariate meta regression. We assessed risk of bias using the Newcastle-Ottawa Scale (NOS) and quality of evidence using the GRADE framework. Our article is PROSPERO-registered and adherent to both PRISMA and MOOSE guidelines. This review is registered with PROSPERO (CRD42021262846).

Findings We identified 14 articles comprising of 3 retrospective cohort studies and 12 cross-sectional studies from 2,428 records, including 1,978,254 participants. Risk of bias was low to moderate. Participants with CKD at baseline had higher pooled odds of glaucoma (odds ratio[OR]=1.18, 95% confidence interval[CI]=1.04-1.33, I²=66%, N=12) compared to participants without CKD. The association remained significant in subgroups of longitudinal studies, participants with diabetes, East Asian studies and primary open-angle glaucoma. In the reverse direction, participants with glaucoma at baseline had over three-fold higher odds of incident CKD compared to participants without glaucoma after 10-15 years of follow-up in longitudinal studies (OR=3.67, 95% CI=2.16-6.24, I²=75%, N=2). All studies adjusted for age and sex, while most studies adjusted for comorbidities such as diabetes and hypertension. Meta-regression identified ethnicity (East Asians vs Non-East Asians) as a significant effect moderator. Associations were robust to trim-and-fill adjustment for publication bias, single-study influence and cumulative meta-analyses.

Interpretation Our meta-analysis suggests a bidirectional relationship between glaucoma and CKD, particularly among East Asians. Further studies are required to elucidate underlying mechanisms and account for differential association by ethnicity.

Funding Ching-Yu Cheng is supported by Clinician Scientist Award (NMRC/CSA-S1/0012/2017) of the Singapore Ministry of Health’s National Medical Research Council.

Copyright © 2022 The Authors. Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/)

Keywords: Glaucoma; Chronic kidney disease; Systematic review and meta-analysis

Introduction

Glaucma is one of the major causes of irreversible blindness. The number of people with glaucoma has been increasing worldwide, rising rapidly over the previous decade by 27.9%, and is estimated to reach

---

*Corresponding author at: Singapore Eye Research Institute, Singapore National Eye Centre, Singapore, 20 College Road, The Academia, Level 6, Singapore.
E-mail address: chingyu.cheng@duke-nus.edu.sg (C.-Y. Cheng).
Research in context

Evidence before this study

Current evidence reporting the association between glaucoma and chronic kidney disease (CKD) is equivocal and inconclusive. A previous meta-analysis by Tham et al. on participants of the Asian Eye Epidemiology Consortium did not find an association between primary open angle glaucoma (POAG) and CKD, although there was an association between POAG and lower eGFR as well as severe kidney function decline in the subgroup of combined Korean and Chinese participants. Nevertheless, there remains no systematic, evidence-based clarification of the association between glaucoma and CKD globally to date. We searched PubMed, Embase and Cochrane Library from inception until 15 June 2021. We identified 14 articles comprising of 3 retrospective cohort studies and 12 cross-sectional studies reporting on glaucoma and CKD as either exposure or outcome, among participants aged ≥18 years.

Added value of this study

Our study adds value to previous studies by suggesting a bidirectional longitudinal relationship between CKD and glaucoma. Furthermore, our population is not limited to Asian participants, as we include participants from Scotland and the USA, which have not been reported in previous meta-analyses.

Implications of all the available evidence

Our study reminds physicians to keep in mind the potential relationship between glaucoma and CKD when providing holistic care to their patients, such as the recommendation of preventive eye screening for glaucoma in patients with CKD. Future interventional trials are required to investigate the efficacy of eye screening for glaucoma in patients with CKD.

Methods

Search strategy and selection criteria

In this systematic review and meta-analysis, we searched the databases (PubMed, Embase, Cochrane Library) from inception till 15 June 2021, using search terms for “glaucoma” such as “primary glaucoma”, “open-angle glaucoma” and “close-angle glaucoma” and “chronic kidney disease” such as “end stage renal failure”, “permanent kidney damage” and “irreversible kidney dysfunction”. The full list of search terms can be found in our Supplemental Methods. We also hand-searched the bibliographies of included articles and relevant reviews, identifying 3 additional records.

Two authors (FYCN and HJJMDS) independently selected eligible articles (based on title and abstract, followed by full-text article), extracted data and evaluated risk of bias in a blinded manner via the online systematic review platform Rayyan. Conflicts were resolved by a third author (BKJT). We included observational articles, published as full-length articles in peer-reviewed journals, that reported on glaucoma or any measure of its estimate (i.e., intraocular pressure (IOP) or cup-disc ratio), and CKD or any measure of its estimate (i.e., estimated glomerular filtration rate (eGFR) or albuminuria) as either exposure or outcome, among adults aged ≥18 years. A bidirectional relationship was explored, where the association of glaucoma in participants with CKD was assessed in relation to participants without CKD, and the association of CKD in participants with glaucoma was assessed in relation to participants without glaucoma. We excluded case reports, reviews, letters, conference abstracts, other non-full-length articles, and non-English language publications. We extracted key data (Supplemental Methods) from each included article. We evaluated articles for risk of bias using the Newcastle-Ottawa Scale (NOS) at the study level (Supplemental Table S1), assessing bias to be high (<5 stars), moderate (5-7 stars) or low (≥8 stars).

Moreover, glaucoma contributes substantially to health burden in terms of disability-adjusted life years (DALYs). Chronic kidney disease (CKD) is another prevalent and progressive disease affecting between 8-16% of the global population, resulting in significant healthcare costs, morbidity and mortality. CKD has been implicated in multiple ocular diseases, including glaucoma. The two diseases share several risk factors such as diabetes, hypertension, and cardiovascular disease. In addition, they involve common pathogenic pathways, such as microvascular damage and ischemia, endothelial dysfunction, inflammation and oxidative stress.

Despite emerging evidence to suggest the relationship between glaucoma and CKD, there have also been studies reporting no association between them, with existing literature on the subject being inconclusive. Additionally, it remains to be elucidated if demographics, socioeconomic status, and comorbidities are confounders of this relationship. Previously, Tham et al. conducted a pooled-analysis of multiple Asian population-based studies, suggesting association between primary open angle glaucoma (POAG) and CKD in East Asians. However, there is no systematic, evidence-based clarification of the association between glaucoma and CKD globally to date.

Given the increasing public health burden of both glaucoma and CKD, it is timely to elucidate the presence and magnitude of the association between both diseases to improve screening and treatment of patients and to guide preventive health strategies. In this systematic review and meta-analysis, we aim to comprehensively pool the associations of glaucoma and CKD and explore if there is a bidirectional relationship between these conditions.
**Data analysis**

Where 2 or more studies of the same type were available, we carried out our planned meta-analyses. Where studies reported subgroup-level estimates in place of a combined estimate, for example, the individual odds ratios for POAG and primary close angle glaucoma (PACG) respectively, instead of a combined odds ratio for all patients with glaucoma, we adopted a hierarchical model. We first pooled subgroup-level estimates using a fixed effect model to obtain a study-level estimate, and then pooled the study-level estimates using a random-effects model to obtain an overall summary estimate. We assessed and considered between-study heterogeneity as significant if the Q-test p-value was <0.10, or if the I² statistic was ≥50%.

Where ≥10 studies were available, we performed further analyses to identify potential sources of heterogeneity between studies. Subgroup analysis was conducted according to available pre-specified study-level characteristics as potential explanatory variables (Supplemental Methods). Diabetic status was broadly understood to include diabetes of all subtypes, diagnosed according to ICD-9-CM code, or random glucose of 11.1 mmol/L or more, use of diabetic medication, or a physician diagnosis of diabetes mellitus. For ethnicity, we classified studies into East Asian and Non-East Asian subgroups, with East Asian being defined as ethnic groups originating from China, Taiwan, Malaysia, and Korea among included studies. We also performed univariate random-effects meta-regression on study-level characteristics, with significant effect moderators confirmed via permutation testing over 1000 iterations. To assess small-study effects, we evaluated funnel plot asymmetry using Egger’s bias, and imputed potentially missing studies using the trim-and-fill method if publication bias was suspected. To examine the influence of each study on our overall findings, we carried out our planned meta-analyses. Where studies used the same dataset for analysis, we selected the study with the longest window period of enrolment, or greatest specificity in its reporting of the outcome as measured by the odds ratio.

**Role of funding source**

There was no funding source for this study. FYCN and HJJMDS had access to the dataset and CYC had final responsibility for the decision to submit the manuscript for publication.

**Results**

The article selection process is summarized in the PRISMA flowchart in Figure 1. We included 14 articles consisting of 15 studies from 2,428 non-duplicated records after initial selection based on title and abstract, and subsequent selection based on full-text. If studies used the same dataset for analysis, we selected the study with the longest window period of enrolment, or greatest specificity in its reporting of the outcome as measured by the odds ratio.

**Study characteristics**

Of the 14 articles included, 10 analyzed glaucoma as the outcome with CKD as the exposure (Table 1), while 4 analyzed CKD as the outcome with glaucoma as the exposure (Table 2). Four articles had low risk-of-bias and 10 articles had moderate risk-of-bias when assessed using the Newcastle-Ottawa Scale. These 14 articles comprised a total of 15 studies, 3 of which were retrospective cohort studies and 12 were cross-sectional studies, spanning across Asia (10 studies), Europe (3 studies) and North America (2 studies). The mean age of participants ranged from 45 to 73 years.

**Definitions of glaucoma and ocular parameters**

Six articles studied POAG, PACG, normal-tension glaucoma (NTG) and the need for trabeculectomy. Glaucoma was defined according to the International Classification of Diseases Codes (ICD) (5 articles), International Society of Geographical and Epidemiological Ophthalmology (ISGEO) guidelines (4 articles), or diagnosed by certified glaucoma specialists (3 articles). 2 articles reported the mean difference in central corneal thickness (CCT) between participants with and without CKD.
Definitions of CKD and renal parameters

Seven articles studied CKD, defined by an eGFR of less than 60ml/min/1.73m².5-7,10,25,26 Four articles studied end-stage renal disease (ESRD), defined according to ICD codes or the need for dialysis for more than 3 months.20,21,23,24 Two articles studied proteinuria and albuminuria, defined as having urine protein or albumin levels of more than 30mg/dL or 30mg/g respectively.5,22 One article studied the difference in eGFR and urine albumin-to-creatinine ratio (UACR) between participants with and without glaucoma.22

Odds of glaucoma in participants with CKD

Meta-analysis. Our meta-analysis included 12 studies (Figure 2a), with data from the Beijing Eye Study (BES), Central India Eye and Medical Study (CIEMS), Korea National Health and Nutrition Examination Survey (KNHANES), Tin Shui Wai Eye Survey and Biobank (TSWES) as well as Ural Eye and Medical Study (UEMS) being gathered from Tham et al.10 Compared to participants without CKD, those with CKD had a significantly higher pooled odds of glaucoma (odds ratio [OR]=1.18, 95% confidence interval [CI]=1.04-1.33, I²=66%, N=12). All 12 studies adjusted their estimates for potential confounders. These included demographic variables such as sex (12/12), age (12/12), and ethnicity (2/12); socio-economic variables such as income level (4/12) and education (2/12); comorbidities such as diabetes (11/12), hypertension (11/12), dyslipidemia (9/12) and cardiovascular diseases (2/12); and other risk factors such as body mass index (8/12), smoking status (7/12) and alcohol consumption (2/12) (Table 1).
### Table 1 (Continued)

| First author, Year | Country, Continent | Study Name | Study Design | Sample Size | % Male | Mean Age | Median duration of Follow-Up (Years) | Renal impairment studied | Definition of renal impairment | Type of glaucoma | Definition of glaucoma | Ocular parameters studied | Covariates | NOS Score |
|-------------------|--------------------|------------|--------------|-------------|--------|----------|-------------------------------------|--------------------------|-----------------------------|-------------------|--------------------------|---------------------------|------------|-----------|
| Lim CC, 2020      | Taiwan, Asia       | Longitudinal Health Insurance Database (LHID) 1997-2013 | Retrospective matched cohort | 82,929      | 52.6   | N.S.    | 14                                   | ESRF                     | Need for dialysis          | POAG, PACG, NFG | Trabeculectomy           | N.A.                      | Demographic variables (sex, age, urbanization, low income), length of hospital stay, and comorbidities at baseline (hypertension, diabetes, ischemic heart disease, hyperlipidemia, congestive heart failure, cerebrovascular disease, dementia, uveitis, retinal vessel occlusion) | 8 |
| MacRae, 2021      | Scotland, Europe   | Primary Care Clinical Informatics Unit | Cross-sectional | 1,274,374   | 48.9   | 51.2    | NA                                  | CKD                      | Medical record contained code for CKD (not specified if ICD codes were used) | N.S. | N.S. | N.A. | Age, sex and deprivation | 7 |
| Moon, 2021        | Korea, Asia        | National Health Insurance Database of Korea 2007-2015 | Retrospective matched cohort | 32,865      | 59.2   | 46.8    | 9                                    | KT, ESRD                | KT ICD-10 codes for KT or KT-related treatment ESRD ICD-10 codes for CKD diagnosis or History of dialysis for > 3 months | POAG, PACG | ICD-10 codes            | N.A.                      | Age, sex, diabetes, hypertension, dyslipidemia, income and Charlson comorbidity index | 8 |
| Nongpiur, 2010    | Singapore, Asia    | Singapore Malay Eye Study (SMES) 2004-2006 | Cross-sectional | 3,108       | 48.3   | 58.7    | N.A                                  | CKD                      | eGFR < 60 ml/min/1.73 m² or UACR ≥ 17 mg/g (men) or UACR ≥ 25 mg/g (women) | N.S. | ISGEO guidelines        | CCT                       | Age, sex, education, hypertension, diabetes, smoking, alcohol, casual plasma glucose, HBA1c, systolic blood pressure, diastolic blood pressure, BMI, total cholesterol, HDL cholesterol, LDL cholesterol, CRP, CCT | 6 |
| Shim, 2016        | Korea, Asia        | Korea National Health and Nutrition Examination (KNHANES) 2010-2011 | Cross-sectional | 5,971       | 49.6   | 54.0    | N.A                                  | CKD, Proteinuria        | eGFR < 60 ml/min/1.73 m² or Proteinuria: Urine protein > 30 mg/dL, measured via a dipstick test | POAG | ISGEO guidelines        | N.A.                      | Age, sex, low HDL, high glucose, high blood pressure, IOP, high BMI | 7 |
| Tham, 2020        | China, Hong Kong, India, Korea, Russia (Asia/Europe) | BES (2011), CIEMS (2006-2008), KNHANES (2012), TSWES (2016-2018), UMEMS (2015-2017) | Cross-sectional | 11,190     | 44.0   | 56.4    | N.A                                  | CKD                      | eGFR < 60 ml/min/1.73 m² | POAG | ISGEO guidelines        | N.A.                      | Age, gender, hypertension, diabetes, hyperlipidemia, BMI, smoking status and IOP | 7 |
| First author, Year | Country, Continent | Study Name | Study Design | Sample Size | % Male | Mean Age | Median duration of Follow-Up (Years) | Renal impairment studied | Definition of renal impairment | Type of glaucoma | Definition of glaucoma | Ocular parameters studied | Covariates | NOS Score |
|-------------------|-------------------|------------|--------------|-------------|--------|----------|--------------------------------------|--------------------------|-------------------------------|----------------|----------------------|--------------------------|------------|-----------|
| Wang, 2012        | Taiwan, Asia      | Taiwan Longitudinal Health Insurance Database 2000 | Cross-sectional matched | 36,956      | 55.6   | N.S.     | N.A.                                  | CBF                      | ICD-9 code, according to KDIGO guidelines | N.S. | ICD-9 codes         | N.A.                 | Age, sex, diabetes, monthly income, geographic region, level of urbanization of patient’s community, hypertension | 7          |
| Wong, 2016        | Singapore, Asia   | Singapore Malay Eye Study (SMES) 2004-2006 Singapore Indian Eye Study (SINDO) 2007-2009 Singapore Chinese Eye Study (SCES) 2009-2011 | Cross-sectional | 9,434 | 49.7 | 58.7   | N.A.                                  | CKD                      | eGFR < 60ml/min/1.73m² | N.S. | Presence of glaucoma-related visual field loss and optic disk changes in one or both eyes | N.A. | Age, gender, ethnicity, smoking, alcohol intake, education status, BMI, systolic blood pressure, diabetes mellitus (duration of diabetes and HbA1c), cholesterol levels and cardiovascular disease | 7          |
| Yuksel, 2016      | Turkey, Europe/Asia | Cross-sectional matched | 42 | 45.2 | 58.3 | N.A. | N.A. | Corneal hysteresis, Corneal resistance factor, IOP (corneal compensated), IOP (Goldmann-related), CCT | Need for hemodialysis | N.A. | N.A. | Corneal hysteresis, Corneal resistance factor, IOP (corneal compensated), IOP (Goldmann-related), CCT | N.A. | N.A. | 5          |
| Zhu, 2020         | USA, America      | National Health and Nutrition Examination Survey (NHANES) 2005-2008 | Cross-sectional | 5,518 | 47.3 | 56.9 | N.A. | CKD | eGFR < 60ml/min/1.73m² | N.S. | Determined by glaucoma specialists based on vertical cup-to-disc ratio, tilting and hemorrage of the optic disc, relative disc size, neuroretinal rim notching, as well as optic cup excavation | N.A. | Age, gender, race, education, income, marital status, smoking status, alcohol consumption, diabetes, hypertension, high cholesterol, BMI, waist circumference, high C-reactive protein, self-rated health status, history of cardiovascular disease | 7          |

**Table 1: (Summary of included studies, glaucoma as outcome).**

N.S., not stated; N.A., not applicable; CKD, chronic kidney disease; CRF, chronic renal failure; KT, kidney transplant; ESRD, end-stage renal disease; ESRF, end-stage renal failure; eGFR, estimated glomerular filtration rate; UACR, urine albumin-creatinine ratio; POAG, primary open-angle glaucoma; PACG, primary angle-closure glaucoma; NTG, normal-tension glaucoma; IOP, intraocular pressure; CCT, central corneal thickness; ISGEO, International Society of Geographical and Epidemiological Ophthalmology; KDIGO, Kidney Disease: Improving Global Outcomes; BES, Beijing Eye Study; CIEMS, Central Indian Eye and Medical Study; HDES, Handan Eye Study; KNHANES, Korea National Health and Nutritional Examination Survey; TSWES, Tin Shui Wai Eye Survey and Biobank; UEMS, Ural Eye and Medical Study.
| First author, Year Country, Continent Study Name | Study Design | Sample Size | % Male | Mean Age | Median duration of Follow-Up (Years) | Type of glaucoma | Definition of glaucoma | Renal impairment studied | Definition of renal impairment | Renal parameters studied | Covariates | NOS Score |
|------------------------------------------------|-------------|-------------|--------|----------|---------------------------------|----------------|-----------------------|-----------------------|------------------------|-------------------|------------|-----------|
| Chou, 2018 Taiwan, Asia Taiwan Insurance Research Database (NHIRD) 1997-2011 | Retrospective matched cohort | 30,370 | 53.7 | N.S. | 15 | POAG | ICD-9 codes | ESRD | Based on ICD-9 codes and those who received hemodialysis or peritoneal dialysis for > 3 months | N.A. | Age, sex, comorbidities (diabetes mellitus, hypertension, hyperlipidemia), modified Charlson comorbidity index score, anti-hypertensive drugs, drugs for diabetes, antiplatelet drugs | 8 |
| Lim ZW, 2020 Singapore, Asia Singapore Chinese Eye Study (SCES) 2009-2011 | Cross-sectional | 3,009 | 50.0 | 59.1 | N.A. | POAG | ISGEO guidelines | Albuminuria | Urine albumin ≥ 30mg/g | eGFR, UACR | Age, gender, IOP, diabetes mellitus, hyperlipidemia, hypertension, anti-hypertensive medication, history of cardiovascular disease, current smoking status, alcohol intake, BMI and eGFR | 6 |
| Park, 2019 Korea, Asia Korean National Health Insurance Database 2004-2013 | Retrospective matched cohort | 478,303 | 51.3 | N.S. | 10 | POAG | ICD codes | CKD | eGFR < 60ml/min/1.73m² or if patients have markers of kidney damage, or both for at least 3 months’ duration | N.A. | Demographic information (sex, age group at diagnosis, residential area, house income), comorbidities (hypertension, diabetes mellitus, intracerebral hemorrhage, cerebral infarction, ischemic heart disease, congestive heart failure, cancer, tuberculosis, peripheral arterial disease, atrial fibrillation) co-medications (anti-hypertensives, antipatelet, anticoagulant, hypoglycemic) and Charlson Comorbidity Index Score | 9 |
| Zakrzewski, 2012 Canada, America | Cross-sectional | 185 | 53 | 73.1 | N.A. | POAG | Diagnosis by glaucoma specialists | CKD | Initial and follow-up eGFR < 45ml/min/1.73m² or both eGFR values < 60ml/min/1.73m² and UACR > 2.0 | N.A. | Gender, age, hypertension, diabetes | 6 |

**Table 2**: (Summary of included studies, CKD as outcome).

N.S. not stated; N.A. not applicable; POAG, primary open-angle glaucoma; IOP, intraocular pressure; ESRD, end-stage renal disease; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; UACR, urine albumin-to-creatinine ratio; ISGEO, International Society of Geographical and Epidemiological Ophthalmology.
Figure 2. Forest plots showing the odds ratio of glaucoma in participants with chronic kidney disease.

The black diamond at the bottom of each graph is the estimated pooled odds ratio of glaucoma in participants with chronic kidney disease in random-effects meta-analysis. The size of each red/green box reflects the relative weight apportioned to the study in the meta-analysis; the horizontal line running through each red box reflects the 95% confidence interval of the study. a: Odds ratio of glaucoma in participants with chronic kidney disease; b: Odds ratio of glaucoma in participants with chronic kidney disease, stratified by diabetic status; c: Odds ratio of glaucoma in participants with chronic kidney disease, stratified by type of glaucoma: primary open angle glaucoma or primary close angle glaucoma (POAG/PACG); d: Odds ratio of glaucoma in participants with chronic kidney disease, stratified by ethnicity (East Asian vs. Non East-Asian); e: Mean difference in central corneal thickness ($\mu$m) in participants with chronic kidney disease compared with participants without chronic kidney disease.
Subgroup meta-analyses and meta-regression. On subgroup analysis by study design, the association persisted in longitudinal studies (OR=1.33, 95%CI=1.11-1.60, I²=0%, N=2) but not cross-sectional studies (OR=1.13, 95%CI=0.98-1.31, I²=68%, N=10) (Figure 2a). In pre-specified subgroup-analyses by diabetic status (Figure 2b), type of glaucoma (Figure 2c) and ethnicity (Figure 2d), the association remained significant in participants of the diabetic subgroup (OR=1.42, 95%CI=1.26-1.60, I²=0%, N=2), POAG subgroup (OR=1.22, 95%CI=1.03-1.44, I²=0%, N=8) and East Asian subgroup (OR=1.35, 95%CI=1.25-1.46, I²=0%, N=8). However, the association became non-significant in participants of the PACG subgroup (OR=1.91, 95%CI=0.95-3.83, I²=40%, N=2), non-diabetic subgroup (OR=0.94, 95%CI=0.51-1.73, I²=88%, N=2) and Non-East Asian subgroup (OR=1.05, 95%CI=0.99-1.11, I²=0%, N=5). The mean CCT of participants with CKD was 2.08±mm thinner than participants without CKD, but this difference was not significant (p =0.12) (Figure 2e). Univariate meta-regression of 10 continuous variables and 3 categorical variables identified ethnicity (East Asians vs Non-East Asians) as a significant effect moderator (Supplemental Table S3). This was validated on permutation testing.

Publication bias and influence analysis. Funnel plot visual inspection suggested possible asymmetry (Supplemental Figure S1). However, the presence of asymmetry (p=0.54) was not detected on Egger’s test, and the trim-and-fill method imputed no additional articles (Supplemental Figure S2). Leave-one-out and cumulative influence analyses showed a stable pooled effect size (Supplemental Figure S3 and S4).

Odds of CKD in participants with glaucoma
Compared to participants without glaucoma, participants with glaucoma had, on average, more than three times the odds of CKD in longitudinal studies (OR=3.67, 95% CI=2.16-6.24, I²=75%, N=2). However, this association was not significant in cross-sectional studies (OR=0.83, 95%CI=0.37-1.86, I²=47%, N=2) (Figure 3). Due to insufficient studies, we were not able to proceed with further analyses.

GRADE quality of evidence
Using the GRADE framework, we judged the overall quality of evidence for the outcome of glaucoma to be low and the outcome of CKD to be very low (Supplemental Table S4).

Discussion
In this systematic review and meta-analysis of 14 articles comprising a total of 1,978,254 participants, participants with CKD had an overall 18% higher odds of glaucoma compared to participants without CKD, with longitudinal studies showing 33% higher odds of glaucoma among participants with CKD on subgroup analysis by study design. This association was significant after adjusting for covariates including demographic variables, socioeconomic variables, and pre-existing comorbidities, and was robust to influence analysis with no publication bias detected. However, the significant uncertainty surrounding these estimates as evaluated by the GRADE framework should be considered when interpreting these results.

In the reverse direction, participants with glaucoma had more than triple the odds of CKD compared to participants without glaucoma, as observed in longitudinal studies. However, this association should be interpreted with caution due to the low number of studies pooled.

While a previous meta-analysis had studied the relationship between glaucoma and CKD using cross-sectional data on kidney function and POAG of population-based studies from the Asian Eye Epidemiology Consortium,10 we provide additional insight into the bidirectional relationship between the two diseases, investigating the odds of glaucoma in participants with CKD as well as the odds of CKD in participants with glaucoma. We further found the bidirectional association to be significant in longitudinal studies. Our article also included studies from Taiwan, Scotland and the USA, which have not been reported in previous meta-analyses.

Several mechanisms may explain the association between glaucoma and CKD (Figure 4). First, the association could be partially confounded by shared comorbidities, such as diabetes mellitus, hypertension and cardiovascular disease, which are known risk factors for both glaucoma and CKD, by means of microvascular dysfunction and ischemia.10-12 Glaucoma has been associated with increased peripheral arterial stiffness and carotid intima-media thickness, along with significantly higher systolic and diastolic blood pressures.13 Altered perfusion of the optic nerve head is postulated to result in reperfusion injury, causing glaucomatous damage of retinal ganglion cells.14 In chronic hypertension, retinal blood flow is less able to resist changes in ocular perfusion pressure due to blood flow dysregulation.15 This results in raised IOP, which deforms and damages the lamina cribrosa, the site of retinal ganglion cell axonal injury in glaucoma.16 Meanwhile, atherosclerotic events are also known to be risk factors for the progression of renal failure.17 It is hence possible that these comorbidities may have caused both glaucoma and CKD, with either of them manifesting earlier.

Secondly, glaucoma and CKD may share common etiologies and pathophysiological mechanisms. These include renin-angiotensin system (RAS) dysfunction, oxidative stress, and inflammation. RAS regulates blood pressure, fluid and electrolyte balance.18 Ocular RAS is
Figure 3. **Forest plot showing the odds ratio of chronic kidney disease in participants with glaucoma.**

The black diamond at the bottom of each graph is the estimated pooled odds ratio in the random-effects meta-analysis. The size of each red reflects the relative weight apportioned to the study in the meta-analysis; the horizontal line running through each red box reflects the 95% confidence interval of the study.
Figure 4. Graphical schematic explaining association between glaucoma and chronic kidney disease.
postulated to play an important role in IOP regulation via aqueous humor production and the drainage pathway, with localized ocular RAS being present in the trabecular meshwork, aqueous humor, ciliary body, and optic nerve head.\textsuperscript{35} In POAG, retinal ganglion cell death and neurotoxicity via oxidative stress has been demonstrated in several experimental glaucoma models; similarly, in CKD, oxidative stress has been shown to be implicated in renal fibrosis, a common final pathway of ESRD.\textsuperscript{39}

Thirdly, we may consider possible causal mechanisms between glaucoma and CKD. CKD results in derangements in the regulation of body fluids, leading to fluid overload, accumulation of toxic metabolites and a uremic state. Osmotic pressure exerted by increased urea concentration in the aqueous humor may result in fluid overload in the anterior chambers of the eyes, possibly exacerbated by impaired aqueous outflow through the trabecular meshwork due to blockage by accumulated toxic metabolites.\textsuperscript{8} Decreased renal function could also accelerate atherosclerosis by increasing serum concentrations of homocysteine and lipoproteins, contributing to microvascular damage, ischemia and the development of glaucoma.\textsuperscript{40} While our observational meta-analysis provides insufficient evidence for causal conclusions, it does suggest that CKD is a risk factor for glaucoma.

Of note, the pathogenesis of open-angle and angle-closure glaucoma differ. While open-angle glaucoma is related to ganglion cell susceptibility, microcirculatory deficiency at the optic nerve head, or extracellular matrix factors and does not correlate well with elevated IOP,\textsuperscript{41} angle-closure glaucoma is defined by IOP elevation, anatomically narrow angles and shallow anterior chamber depths, resulting in iridotrabecular contact. Asian populations are particularly predisposed to angle-closure glaucoma due to the structure of their eyes. Reports of familial tendency towards the disease and ethnicity differences in risk of PACG imply an underlying genetic basis for the development of PACG. Eight susceptibility genetic loci have been identified.\textsuperscript{44} This may explain why some studies in our analysis found CKD to be associated with PACG but not POAG.\textsuperscript{75–77}

Having demonstrated that CKD is associated with, and may be a risk factor for glaucoma, it is worthwhile for physicians to keep in mind this potential relationship when providing holistic care to their patients. Our findings may provide impetus for the prevention and management of these diseases, such as the recommendation of preventive eye screening for glaucoma in patients with CKD, especially in patients with concomitant diabetes—patients already placed on routine eye screening for diabetic retinopathy may be advised to be adherent to their ophthalmology reviews to facilitate early detection of glaucoma. To this end, future interventional trials are required to investigate the efficacy of eye screening for glaucoma in patients with CKD. It is also worthwhile to assess how the treatment of either glaucoma or CKD affects the morbidity and mortality outcomes of the other.

The strengths of our article lie in our rigorous pre-specified protocol of systematic searching, bias assessment, and quality grading according to international guidelines. None of our 14 included articles had high risk of bias, and we found no outliers or influential cases contributing to the heterogeneity of our data. We extracted and pooled maximally-adjusted effect estimates to account for potential confounders within the limits of existing literature. Heterogeneity was adequately explained by meta-regression, with ethnicity emerging as a significant effect modifier accounting for all reported heterogeneity. Our findings were robust to subgroup, meta-regression, influence, cumulative and small-study analyses. We found no evidence of publication bias.

The results of this article need to be interpreted within the contexts of the following limitations. First, the results of our analysis may possess limited generalizability due to the large proportion of articles originating from Asia. It should also be noted that non-English articles were excluded from our analysis. Further large-scale population-based studies addressing the significance of the association between glaucoma and CKD in Western populations, as well as studies on Japanese, Mongolian, and North Korean populations, should be conducted. Second, not all articles specified the type(s) of glaucoma being investigated. Due to limited data, we were only able to perform subgroup analysis on the association of CKD and primary glaucoma, of which the most common forms were POAG and PACG. The number of patients who had cataract surgery or vitrectomy were not mentioned in the included studies, hence we were unable to account for this in our analysis. Similar, the modalities of treatment of glaucoma were not mentioned in the included studies. Future studies are required to explore if the association between glaucoma and CKD extends to other forms and treatments of glaucoma. In addition, we were unable to proceed with our pre-specified analysis of the association between glaucoma and CKD levels due to insufficient data. Third, a small minority of articles defined glaucoma and CKD according to ICD codes, which are less precise than diagnostic criteria or standardized procedure, such as the ISGEO guidelines or measurement of eGFR of <60ml/min respectively. There was also a study where the diagnosis of glaucoma and CKD were made based on routine electronic clinical data of general practices, without further clarification of how the diagnoses were made. Fourth, as compared to population-based studies, the healthcare databases included may have risk of referral bias. CKD patients with an underlying etiology of diabetes are more likely to be referred to ophthalmology to monitor for complications of diabetic retinopathy, even if they are not known to have glaucoma. Fifth, most of the studies included in our analysis were cross-sectional studies,
which are unable to fully explain the temporal relationship between glaucoma and CKD or suggest there might be a cause-and-effect relationship between them. Sixth, the observational nature of the included studies does not permit causal conclusions as residual confounding cannot be excluded. Of note, dialysis is a possible confounder of the relationship that was not sufficiently accounted for. Our meta-regression of ethnicity as an explanatory variable for our heterogeneity, aggregate/ecological bias and confounding cannot be excluded. Lastly, due to limitations in available literature, the overall quality of evidence for the outcome of glaucoma was judged to be low and the outcome of CKD to be very low.

In conclusion, in this multi-adjusted systematic review and meta-analysis of 14 articles with 1,978,254 participants, participants with CKD at baseline had 18% higher pooled odds of incident glaucoma compared to participants without CKD. The pooled association remained significant in the subgroups of longitudinal studies, participants with diabetes, East Asian studies and primary open-angle glaucoma (POAG). In the reverse direction, participants with glaucoma at baseline had over three-fold higher odds of incident CKD compared to participants without glaucoma after 10-15 years of follow-up in longitudinal studies.

Our meta-analysis demonstrates a bidirectional relationship between glaucoma and CKD in longitudinal studies. It is worthwhile for physicians to be aware of this potential relationship in the holistic care of their patients. This could provide impetus for the prevention and management of these diseases, reducing their burden on public health and obviating their debilitating impact on quality of life.

Contributors
All authors (FYCN, HJJMDS, BKJT, CBT, ETWY, PYB, and CYC) contributed to the conceptualisation and design of the project as well as writing and critical revision of the manuscript.

FYCN and HJJMDS were responsible for the data acquisition, analysis, interpretation, verification as well as statistical analysis of the study.

Data sharing statement
No additional data was collected for this study.

Declaration of interests
All authors declare no competing interests.

Acknowledgements
We thank Dr Marco Yu from the Singapore Eye Research Institute, Singapore (SERI) for his statistical advice.

Funding
Ching-Yu Cheng is supported by Clinician Scientist Award (NMRC/CSA-SI/0012/2017) of the Singapore Ministry of Health’s National Medical Research Council.

Supplementary materials
Supplementary material associated with this article can be found in the online version at doi:10.1016/j. eclinm.2022.101498.

References
1. Tham YC, Li X, Wong TY, Quigley HA, Aung T, Cheng CY. Global prevalence of glaucoma and projections of glaucoma burden through 2040: a systematic review and meta-analysis. *Ophthalmology*. 2014;121(11):2081–2090.
2. Kyu HH, Abate D, Abate KH, et al. Global, regional, and national disability-adjusted life-years (DALYs) for 359 diseases and injuries and healthy life expectancy (HALE) for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet North Am Ed*. 2018;392(10159):1859–1922.
3. Chen TK, Knucley DH, Grams ME. Chronic kidney disease diagnosis and management: a review. *JAMA*. 2019;321(13):1294–1304.
4. Wong CW, Wong TY, Cheng CY, Sabanayagam C. Kidney and eye diseases: common risk factors, etiological mechanisms, and pathways. *Kidney Int*. 2014;85(6):1290–1302.
5. Shim SH, Sung KC, Kim JM, et al. Association between renal function and open-angle glaucoma: the Korea National Health and Nutrition Examination Survey 2010-2011. *Ophthalmology*. 2016;123 (9):1981–1988.
6. Wang TJ, Wu CK, Hu CC, Keller JJ, Lin HC. Increased risk of co-morbid eye disease in patients with chronic renal failure: a population-based study. *Ophthalmic Epidemiol*. 2012;19(1):137–141.
7. Park SJ, Byun SJ, Park JY, Kim M. Primary open-angle glaucoma and increased risk of chronic kidney disease. *J Glaucoma*. 2019;28 (12):1067–1073.
8. Nongpiur ME, Wong TY, Sabanayagam C, Lim SC, Tai ES, Aung T. Chronic kidney disease and intraocular pressure: the Singapore Malay Eye Study. *Ophthalmology*. 2010;117(11):1477–1485.
9. Wong CW, Lamotheux EL, Cheng CY, et al. Increased burden of vision impairment and eye diseases in persons with chronic kidney disease - a population-based study. *EBioMedicine*. 2016;3:193–197.
10. Tham YC, Tao Y, Zhang L, et al. Is kidney function associated with primary open-angle glaucoma? Findings from the Asian Eye Epidemiology Consortium. *Br J Ophthalmol*. 2020;104(9):1290–1293.
11. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:j1771.
12. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis of observational studies in epidemiology (MOOSE) group. *JAMA*. 2000;283(15):2008–2012.
13. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan – a web and mobile app for systematic reviews. *Syst Rev*. 2016:5 (1):210.
14. Wells G, Shea B, O’Connell D, et al. The Newcastle–Ottawa Scale (NOS) for assessing the quality of non-randomized studies in meta-analysis. 2000.
15. Moon JJ, Kim YW, Oh BL, et al. Nationwide Glaucoma incidence in end stage renal disease patients and kidney transplant recipients. *Sci Rep*. 2021;11(1):7418.
16. Higgins JPT ES, Li T (editors). Chapter 25: Including variants on randomized trails. *Cochrane Handbook for Systematic Reviews of Interventions version 6.3 (updated September 2020)*.
17. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med*. 2002;21(11):1539–1558.
18. Wong CW, Lamotheux EL, Cheng CY, et al. Increased burden of vision impairment and eye diseases in persons with chronic kidney disease — a population-based study. *EBioMedicine*. 2016;3:193–197.
19 Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 2008;336(7650):924.

20 Chou CL, Hsieh TC, Chen JS, Fang TC. Risks of all-cause mortality and major kidney events in patients with new-onset primary open-angle glaucoma: a nationwide long-term cohort study in Taiwan. BMJ Open. 2018;8(1):e022720.

21 Lim CC, Lee CY, Huang FC, Huang JY, Hung JH, Yang SF. Risk of glaucoma in patients receiving hemodialysis and peritoneal dialysis: a nationwide population-based cohort study. Int J Environ Res Public Health. 2020;17(18).

22 Lim ZW, Chee ML, Thakur S, et al. Albuminuria and primary open-angle glaucoma: the Singapore Chinese eye study (SCES). Br J Ophthalmol. 2021;105(5):669–673.

23 Moon JJ, Kim YW, Oh BL, et al. Nationwide glaucoma incidence in end-stage renal disease patients and kidney transplant recipients. Sci Rep. 2021;11(1):17418.

24 Yuksel N, Duru N, Uz E, et al. Evaluation of intraocular pressure by ocular response analyzer in patients undergoing hemodialysis. ed. United States. J Glaucoma. 2016;25(4):e355–e358. https://pubmed.ncbi.nlm.nih.gov/26734835/.

25 Zakrzewska iP A, Mackenzie P J, Tsai G, Warner S J, Levin A, Mikkelberg FS. Does an association exist between pseudoexfoliation syndrome and chronic kidney disease? JGlaucoma. 2012;21(8):562–566.

26 Zhu Z, Liao H, Wang W, Scheetz J, Zhang J, He M. Diabetes mellitus as a risk factor for open-angle glaucoma: a systematic review and meta-analysis. PLOS One. 2014;9(8):e102972.

27 Zhou M, Wang W, Huang W, Zhang X. Diabetes mellitus as a risk factor for open-angle glaucoma: a systematic review and meta-analysis. BMJ Open. 2014;4(1):e002415.

28 Zhao D, Cho J, Kim MH, Guallar E. The association of blood pressure and primary open-angle glaucoma: a meta-analysis. Am J Ophthalmol. 2014;158(1):616–627.e9.

29 Chen Y-Y, Hu H-Y, Chu D, Chen H-H, Chang C-K, Chou P. Patients with primary open-angle glaucoma may develop ischemic heart disease more often than those without glaucoma: an 11-year population-based cohort study. PLOS One. 2016;11(9):e0163210.e.

30 Orzalesi N, Rossetti L, Omboni S. Vascular risk factors in glaucoma: the results of a national survey. Graefes Arch Clin Exp Ophthalmol. 2007;245(6):795–802.

31 Tham YC, Lim SH, Gupta P, Aung T, Wong TY, Cheng CY. Interrelationship between ocular perfusion pressure, blood pressure, intraocular pressure profiles and primary open-angle glaucoma: the Singapore Epidemiology of Eye Diseases study. Br J Ophthalmol. 2018;102(10):1402–1406.

32 He Z, Vingrys AJ, Armitage JA, Bui BV. The role of blood pressure in glaucoma. Clin Exp Ophthalmol. 2011;39(2):133–149.

33 Vanholder R, Van Biesen W, Verbeke F, Lameire N. Cardiovascular disease in renal failure: where does it come from, where do we go? Acta Clin Belg. 2006;61(5):205–211.

34 Holappa M, Vapaatalo H, Vaajanen A. Many faces of renin-angiotensin system - focus on eye. Open Ophthalmol J. 2017;11:122–142.

35 Lv W, Booz GW, Fan F, Wang Y, Roman RJ. Oxidative stress and renal fibrosis: recent insights for the development of novel therapeutic strategies. Front Physiol. 2018;9:105.

36 Bostom AG, Sherman D, Lapane KL, et al. Hyperhomocysteinemia, hyperfibrinogenemia, and lipoprotein (a) excess in maintenance dialysis patients: a matched case-control study. Atherosclerosis. 1996;125(1):91–101.

37 Ray K, Mookherjee S. Molecular complexity of primary open angle glaucoma: current concepts. J Genet. 2009;88(4):431–467.

38 Kondkar AA. Updates on genes and genetic mechanisms implicated in primary angle-closure glaucoma. Appl Clin Genet. 2021;14:89–112.