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

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eClinicalMedicine 2022;49: 101498
Published online xxx
https://doi.org/10.1016/j.eclinm.2022.101498

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, I^2=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, I^2=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-SI/0012/2017) of the Singapore Ministry of Health's National Medical Research Council.

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

Introduction

Glaucoma 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

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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.

111.8 million by 2040.[1] Moreover, glaucoma contributes substantially to health burden in terms of disability-adjusted life years (DALYs).[2] Chronic kidney disease (CKD) is another prevalent and progressive disease affecting between 8-16% of the global population,[3] 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.[4] In addition, they involve common pathogenic pathways, such as microvascular damage and ischemia, endothelial dysfunction, inflammation and oxidative stress.[4]

Despite emerging evidence to suggest the relationship between glaucoma and CKD,[5-7] there have also been studies reporting no association between them,[8,9] 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.[10] 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.

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 handsearched 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.[13] 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., intra-ocular 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),[14] assessing bias to be high (<5 stars), moderate (5-7 stars) or low (≥8 stars).

Data analysis

Where ≥2 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,[15] we adopted a hierarchical model.[16] 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 I^2 statistic was ≥50%.[17]

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.[18] 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 both visually and 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 omitted each study in turn from our meta-analyses. To examine the stability and sufficiency of evidence as it accumulated over time, we performed a cumulative meta-analysis ranked by year of publication.

We conducted all analyses using Review Manager (version 5.4.1) and R (version 4.0.3) (Supplemental Methods). Unless otherwise specified, we considered a two-sided p-value of <0.05 as statistically significant.

Two authors (FYCN and HJJMDS) independently evaluated the quality of pooled evidence at the outcome level (Supplemental Table S2) using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework.[19] Any conflict was resolved by mutual consensus. There was no funding source for this study.

This review is registered on PROSPERO (CRD42021262846) and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines.[11,12] Institutional review board approval was not required for this study as it involved the use of data extracted from literature available in the public domain. The requirement for informed consent was waived and all research adhered to the tenets of the Declaration of Helsinki.

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.[5-10,20-27] If studies used the same dataset for analysis, we selected the study with the longest window period of enrolment,[23] or greatest specificity in its reporting of the outcome as measured by the odds ratio.[8,10]

Study characteristics

Of the 14 articles included, 10 analyzed glaucoma as the outcome with CKD as the exposure (Table 1),[5,6,8-10,21,23,24,26,27] while 4 analyzed CKD as the outcome with glaucoma as the exposure (Table 2).[7,20,22,25] 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,[5,7,10,20,22,25] 1 article studied POAG and PACG, and 1 article studied POAG, PACG, normal-tension glaucoma (NTG) and the need for trabeculectomy.[23] Glaucoma was defined according to the International Classification of Diseases Codes (ICD) (5 articles),[6,7,20,21,23] International Society of Geographical and Epidemiological Ophthalmology (ISGEO) guidelines (4 articles),[5,8,10,28] or diagnosed by certified glaucoma specialists (3 articles).[18,25,29] 2 articles reported the mean difference in central corneal thickness (CCT) between participants with and without CKD.[8,24]

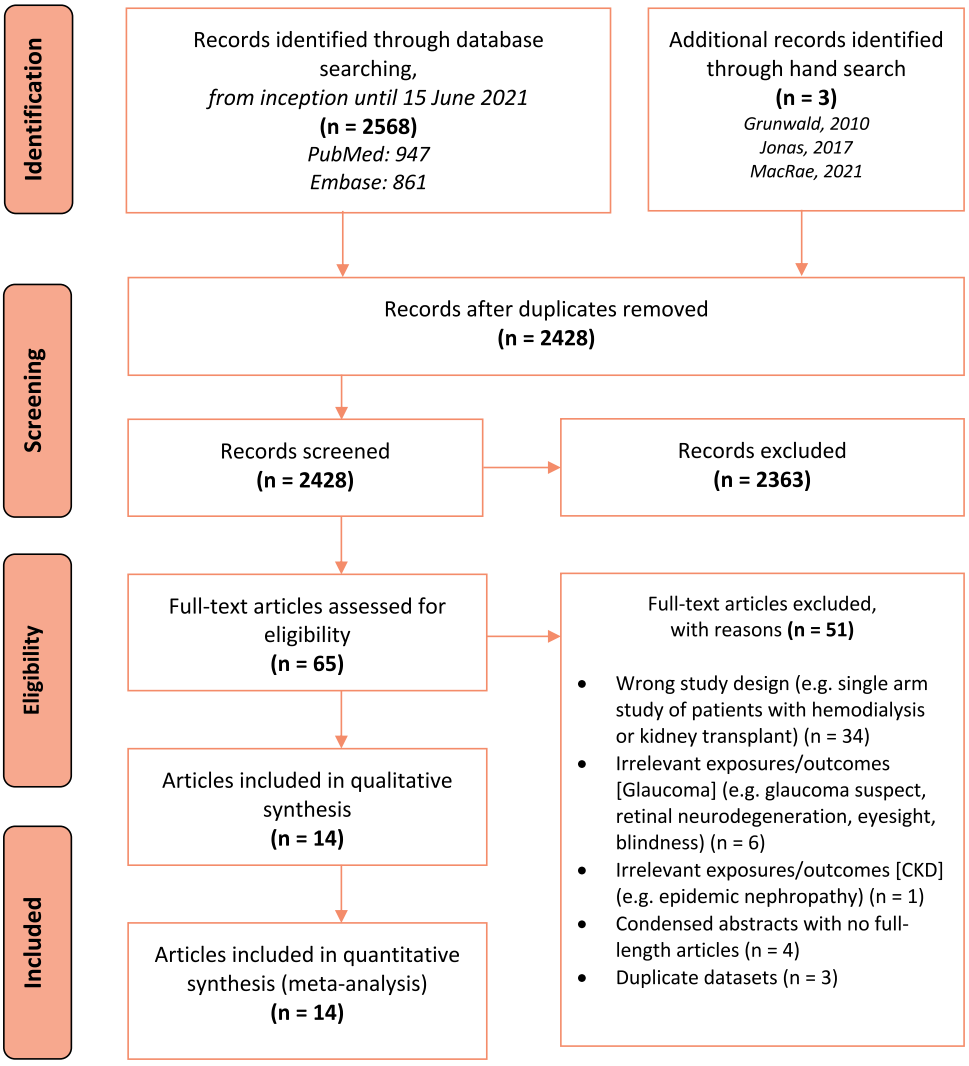

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of the study selection process.

Definitions of CKD and renal parameters

Seven articles studied CKD, defined by an eGFR of less than 60ml/min/1.73m^2.[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, I^2=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).

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 /9
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, NTG, Trabeculectomy	ICD-9 and ICD-10 codes	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 records 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 45.8 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 < 60ml/min/1.73m^2 or UACR ≥ 17mg/g (men) or UACR ≥ 25mg/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 43.6 54.0 N.A.	CKD, Proteinuria	CKD: eGFR < 60ml/min/1.73m^2 Proteinuria: Urine protein > 30mg/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), UEMS (2015-2017)	Cross-sectional	15,190 44.0 56.4 N.A.	CKD	eGFR < 60ml/min/1.73m^2	POAG	ISGEO guidelines	N.A.	Age, gender, hypertension, diabetes, hyperlipidemia, BMI, smoking status and IOP	7

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 /9
Wang, 2012 Taiwan, Asia Taiwan Longitudinal Health Insurance Database 2000	Cross-sectional matched	36,956 55.6 N.S. N.A.	CRF	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 (SINDI) 2007-2009 Singapore Chinese Eye Study (SCES) 2009-2011	Cross-sectional	9,434 49.7 58.7 N.A.	CKD	eGFR < 60ml/min/1.73m^2	N.S.	Presence of glaucomatous 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.	ESRD	Need for hemodialysis	N.A.	N.A.	Corneal hysteresis, Corneal resistance factor, IOP (corneal compensated), IOP (Goldmann-related), CCT	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/1.73m^2	N.S.	Determined by glaucoma specialists based on vertical cup-to-disc ratio, tilting and hemorrhage 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 /9
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, hyperlipidaemia, 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/1.73m^2 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 artery disease, atrial fibrillation) co-medication (anti-hypertensives, antiplatelet, 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/1.73m^2 or both eGFR values < 60ml/min/1.73m^2 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.

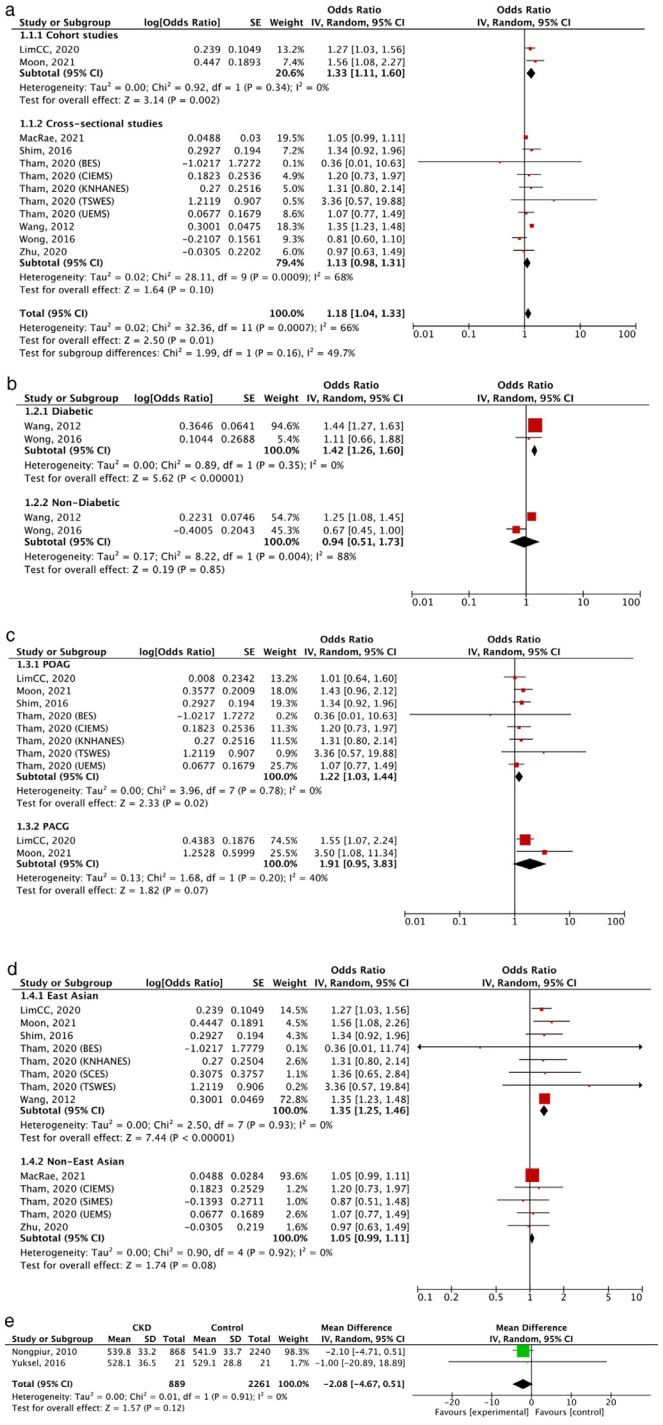

Figure 2. Forest plots showing the odds ratio of glaucoma in participants with chronic kidney disease.

The black diamond at the bottom of each graph is the estimated pooled odds ratio of glaucoma in participants with chronic kidney disease in each 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 (μm) 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, I^2=0%, N=2) but not cross-sectional studies (OR=1.13, 95%CI=0.98-1.31, I^2=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, I^2=0%, N=2), POAG subgroup (OR=1.22, 95%CI=1.03-1.44, I^2=0%, N=8) and East Asian subgroup (OR=1.35, 95%CI=1.25-1.46, I^2=0%, N=8). However, the association became non-significant in participants of the PACG subgroup (OR=1.91, 95%CI=0.95-3.83, I^2=40%, N=2), non-diabetic subgroup (OR=0.94, 95%CI=0.51-1.73, I^2=88%, N=2) and Non-East Asian subgroup (OR=1.05, 95%CI=0.99-1.11, I^2=0%, N=5). The mean CCT of participants with CKD was 2.08µm 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, I^2=75%, N=2). However, this association was not significant in cross-sectional studies (OR=0.83, 95%CI=0.37-1.86, I^2=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.[30-32] Glaucoma has been associated with increased peripheral arterial stiffness and carotid intima-media thickness, along with significantly higher systolic and diastolic blood pressures.[33] Altered perfusion of the optic nerve head is postulated to result in reperfusion injury, causing glaucomatous damage of retinal ganglion cells.[34] In chronic hypertension, retinal blood flow is less able to resist changes in ocular perfusion pressure due to blood flow dysregulation.[35] This results in raised IOP, which deforms and damages the lamina cribrosa, the site of retinal ganglion cell axonal injury in glaucoma.[36] Meanwhile, atherosclerotic events are also known to be risk factors for the progression of renal failure.[37] 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.[38] Ocular RAS is

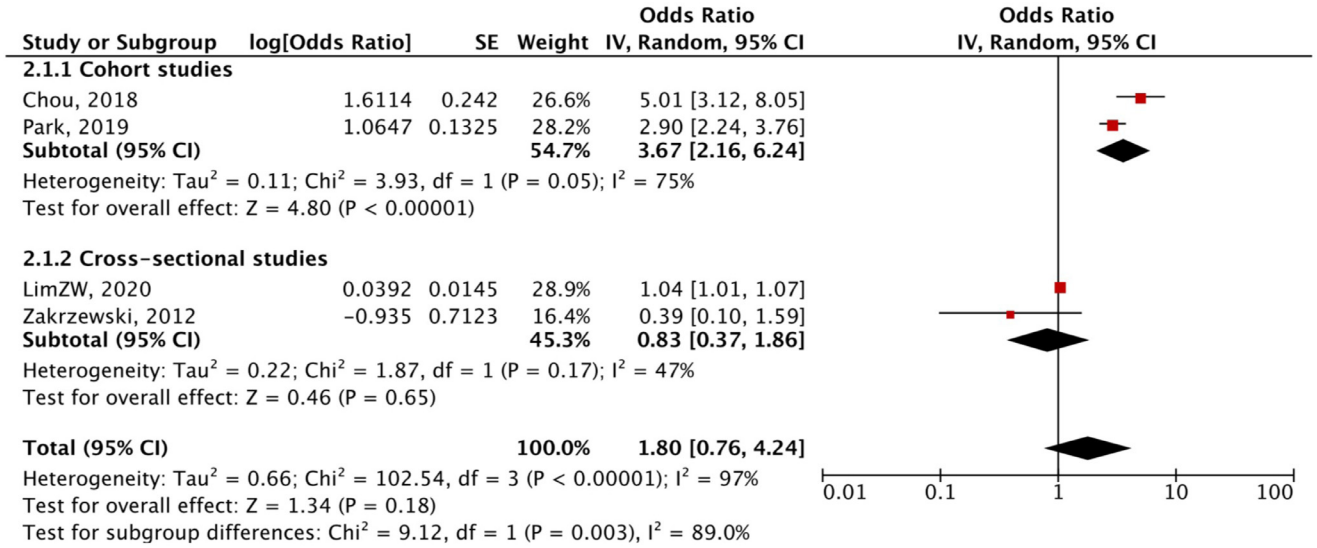

Figure 3. Forest plot showing the odds ratio of chronic kidney disease in participants with glaucoma.

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.

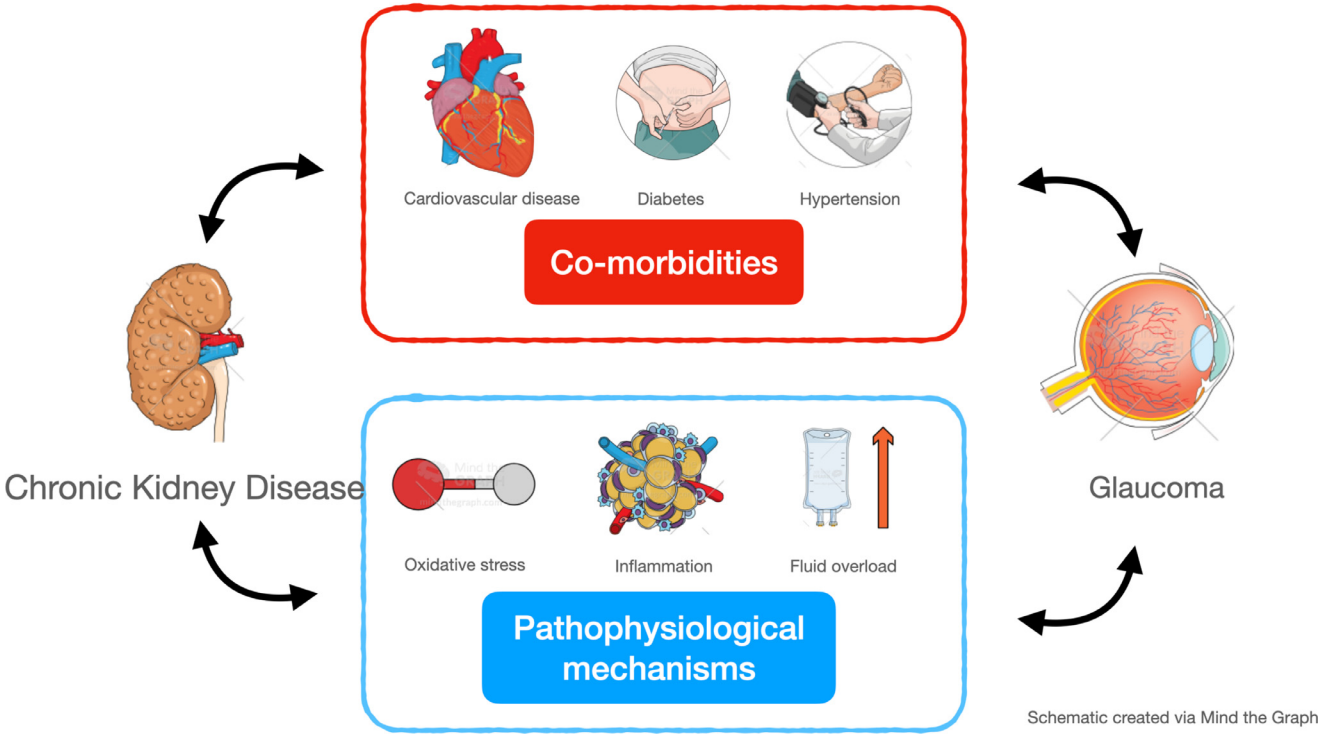

Figure 4. Graphical schematic explaining association between glaucoma and chronic kidney disease.

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.[38] 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.[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.[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.[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,[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 presently been identified.[42] This may explain why some studies in our analysis found CKD to be associated with PACG but not POAG.[15,21]

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 moderator 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 severity of CKD as stratified by eGFR 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 we included may have risk of referral bias. CKD patients with an underlying aetiology 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.

Declaration of interests

All authors declare no competing interests.

Data sharing statement

No additional data was collected for this study.

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.

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