EBioMedicine 5 (2016) 193–197

Contents lists available at ScienceDirect

EBioMedicine

journal homepage: www.ebiomedicine.com

Research Paper

Increased Burden of Vision Impairment and Eye Diseases in Persons with Chronic Kidney Disease — A Population-Based Study

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ARTICLE INFO

Article history:
Received 20 November 2015
Received in revised form 14 January 2016
Accepted 18 January 2016
Available online 19 January 2016

Keywords:
Chronic kidney disease
Visual impairment
Ocular disease
Cataract
Retinopathy

ABSTRACT

Background: Chronic kidney disease (CKD) has been shown to be associated with diabetic retinopathy (DR) and age-related macular degeneration (AMD), leading causes of blindness in elderly adults in previous studies. However, the association of CKD with visual impairment (VI) is not clear. We aimed to examine the association of CKD with VI and other age-related ocular diseases in a population-based sample of Asian adults.

Methods: We analyzed data from 10,033 adults aged 40–80 years who participated in the Singapore Epidemiology of Eye Diseases (SEED, 2004–11) Study. CKD was defined as an estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m^2 from serum creatinine. VI was defined as best-corrected visual acuity <20/40 in the better eye. Cataract, retinopathy, DR, glaucoma and AMD were assessed using standardized ocular examination, retinal photography and visual field assessments. The associations of CKD with VI and ocular conditions were examined using logistic regression models adjusted for age, sex, race, smoking, alcohol intake, education status, body mass index, systolic blood pressure, diabetes mellitus, cholesterol levels and cardiovascular disease.

Findings: The prevalence of VI and ocular disease were significantly higher in participants with CKD (36.1% and 84.7%) than in those without (12.9% and 54.3%, both $p < 0.001$). In multivariable models, CKD was significantly associated with VI (odds ratio [95% confidence interval] = 1.34 [1.14–1.58]), any ocular disease (1.28 [1.03–1.61]), cataract (1.24 [1.01–1.52]), any retinopathy (1.77 [1.45–2.15]), and DR (1.94 [1.47–2.54]).

Interpretation: The burden of VI and eye diseases is high among persons with CKD. Our findings suggest that it may be useful to screen for ocular disease and VI in persons with CKD.

1. Introduction

Chronic kidney disease (CKD) is an emerging public health problem associated with adverse cardiovascular and renal outcomes as well as premature deaths (Chronic Kidney Disease Prognosis C et al., 2010). The prevalence of CKD is expected to rise with the aging of the population worldwide. In the US, the prevalence of CKD in adults 30 years or older is projected to increase from 13.2% currently to 14.4% in 2020 and 16.7% in 2030 (Hoerger et al., 2015). In Singapore, the age, sex-standardized prevalence of CKD was reported to be 12.8% (Sabanayagam et al., 2010).

In addition to adverse cardiovascular and renal outcomes, patients with CKD may also be at a higher risk of age-related ocular diseases (Grunwald et al., 2010). Age-related ocular diseases including cataract, retinopathy, glaucoma and age-related macular degeneration (AMD), are leading causes of blindness in middle aged and elderly adults. As the population ages, the prevalence of these diseases is also expected to rise. Age-related ocular diseases share similar cardiovascular risk factors and pathogenic mechanisms including oxidative stress and inflammation, two of the major pathogenic mechanisms underlying CKD. Previous epidemiological studies conducted in the US have shown CKD to be associated with cataract (Klein et al., 1998), diabetic retinopathy (DR) (Wong et al., 2004) and AMD (Klein et al., 2009; Weiner et al., 2011). In a recent study, Grunwald et al. found nearly half of the participants with CKD to have some form of fundus pathology (Grunwald et al., 2010). Hu et al. observed a rise in intraocular pressure and decrease in ocular perfusion pressure in patients on hemodialysis, both being risk factors for glaucoma development and progression (Hu et al., 2013). Intuitively, the burden of visual impairment (VI) should be higher in persons with CKD but the prevalence of VI and other ocular diseases in persons with CKD are unknown, as previous studies did not conduct a complete ophthalmological examination. Besides worsening

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http://dx.doi.org/10.1016/j.ebiom.2016.01.023

the quality of life (Varma et al., 2006), VI could also contribute to all-cause mortality in persons with CKD, through direct and indirect pathways (Karpa et al., 2009).

In this context, we examined the prevalence and association of CKD with major age-related ocular diseases assessed using a comprehensive eye examination in a population-based sample of Asian adults in Singapore. We hypothesize that persons with CKD would have higher prevalence of ocular diseases and VI than those without CKD.

2. Methods

2.1. Study Population and Design

The data for this study were derived from the Singapore Epidemiology of Eye Diseases (SEED, n = 10,033) Study, comprising of three independent cross-sectional studies encompassing the three major ethnic groups (Chinese, Malays and Indians) in Singapore: the Singapore Malay Eye Study (SiMES, 2004–2006, n = 3280, response rate = 78.7%), the Singapore Indian Eye Study (SINDI, 2007–2009, n = 3400, response rate = 75.6%) and the Singapore Chinese Eye Study (SCES, 2009–2011, n = 3353, response rate = 72.8%). All three studies followed similar protocols and were conducted in the same study clinic (Singapore Eye Research Institute). The detailed methodologies of these studies have been published elsewhere (Foong et al., 2007). In brief, an age-stratified random sampling was used to select ethnic Malays, Chinese and Indians 40 to 80 years of age, who were living in Singapore during each stipulated study period. Each study was conducted in accordance with the Declaration of Helsinki, with written informed consent obtained from all subjects before participation. Ethics approval was obtained from the SingHealth Institutional Review Board. Of the 10,033 study participants, after excluding those with missing information on serum creatinine (n = 434) and other variables (systolic blood pressure, diabetes, cardiovascular disease, total cholesterol, corrected high density lipoprotein, body mass index, smoking status and alcohol intake (n = 165), 9434 were included in the current analysis. In addition, we excluded those with missing values on each of the outcomes separately (AMD: 208 excluded, 9226 included; uncorrected refractive error: 13 excluded, 9421 included; glaucoma: 0 excluded, 9424 included; any retinopathy: 205 excluded, 9229 included; DR: 7251 excluded, 2183 included; cataract: 1581 excluded, 7853 included; VI: 38 excluded, 9396 excluded).

2.2. Study Procedures

Standardized systemic and ocular examinations, interviewer-administered questionnaires, and standard blood investigations were conducted for all participants. Standardized slit-lamp examinations (Haag-Streit model BQ-900; Haag-Streit, Bern, Switzerland) were performed by trained study ophthalmologists after pupil dilatation and the fundus was examined with a 78D lens. A detailed interviewer-administered questionnaire was used to collect relevant demographic data and medical history from all participants. Alcohol drinkers were defined by the consumption of alcohol at least once a week. Cigarette smoking was categorized into current, former and never smoker. Blood pressure was measured with a digital automatic blood pressure monitor (Dinamap model Pro Series DP110X-RW, 100V2; GE Medical Systems Information Technologies, Inc., Milwaukee, WI, USA) after the participants were seated for at least 5 min. The average of the 2 systolic and diastolic blood pressure measurements was used as the systolic and diastolic blood pressure value. Venous blood samples were collected for biochemistry tests, including serum lipids (total cholesterol, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol), glycosylated hemoglobin A1c (HbA1c), creatinine, and random glucose. Diabetes mellitus was defined as random glucose of 11.1 mmol/L (Alberti and Zimmet, 1998) or more, use of diabetic medication, or a physician diagnosis diabetes mellitus. Cardiovascular disease (CVD) was defined as self-reported myocardial infarction, angina or stroke.

2.3. Assessment of CKD

CKD was defined as an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2, using the US National Kidney Foundation Kidney Disease Outcome Quality Initiative (KDOQI) Working Group definition (National Kidney F, 2002). eGFR was estimated from the serum creatinine concentration (eGFR) (Levey et al., 2009) using the CKD Epidemiology Collaboration (CKD-EPI) equation. Severity of CKD was defined by eGFR categories: ≥60 (stage 1 and 2), 30–59 (stage 3), 29–15 (stage 4) and <15 (stage 5)ml/min/1.73 m^2 (National Kidney F, 2002). Creatinine concentrations were measured by the Jaffe method on the Beckman DXC800 analyzer. The creatinine assay was calibrated to the isotope Dilution Mass Spectroscopy (IDMS) method using the National Institute of Standards and Technology (NIST) Reference material.

2.4. Assessment of VI

Presenting visual acuity was monocularly measured by using a logarithm of the minimum angle of resolution (logmar) number chart (Lighthouse International, New York, USA) at a distance of 4 m. Autorefraction, was performed with an autorefractor machine (Canon RK-5 Auto Ref-Keratometer, Canon Inc. Ltd., Japan). Final refraction was determined by subjective refraction by trained and certified study optometrists. Best-corrected visual acuity after subjective refraction was monocularly assessed and recorded in logMAR scores. VI was defined as best-corrected visual acuity worse than 20/40 in the better eye, based on the US definition (Congdon et al., 2004). Under-corrected refractive error was defined as an improvement of at least 0.2 logMAR (2 lines equivalent) in the best-corrected visual acuity compared with the presenting visual acuity in the better eye.

2.5. Cataract

A digital slit-lamp camera (Topcon model DC-1; Topcon, Japan with FD-21 flash attachment) and a Scheimpflug retroillumination camera (Nidek EAS-1000, Nidek, Japan) were used to photograph the lens through the dilated pupil. Cataract was defined as the presence of nuclear, cortical, or posterior subcapsular cataract using the Wisconsin cataract grading system (Klein et al., 1990).

2.6. DR and any retinopathy

Fundus photography was performed using a digital non-mydriatic retinal camera (Canon CRDGi with a 20Diopter SLR backing, Canon, Japan) using Early Treatment for Diabetic Retinopathy Study (ETDRS) standard field 1 (centered on the optic disk) and ETDRS standard field 2 (centered on the fovea). DR was considered present if characteristic lesions as defined by the Early Treatment Diabetic Retinopathy Study were found on retinal photographs (Wong et al., 2006). DR was evaluated following a standard protocol based on retinal photographs which were graded according to a modified scale from the Airlie House classification system by trained graders (Early Treatment Diabetic Retinopathy Study Research Group, 1991).

2.7. Age-related macular degeneration (AMD)

The presence of AMD signs was graded based on fundus photographs according to the Wisconsin Age-Related Maculopathy Grading System (Kawasaki et al., 2008). The presence of AMD was defined as the presence of either early or late AMD.

2.8. Glaucoma

Intraocular pressure was measured with Goldmann applanation tonometry. After pupil dilation, the optic disk was evaluated using a +78-diopter (D) lens at ×16 magnification, with a measuring graticule. Vertical cup–disk ratio exceeding 0.6 or vertical cup–disk ratio asymmetry exceeding 0.2 A 24-2 SITA static, threshold-related visual field examination was performed with near refractive correction prior to dilation using the Humphrey Visual Field Analyzer II (model 750, Carl Zeiss, Switzerland). Test reliability was determined by the instrument's algorithm (fixation losses <20%, false positives <33%, or false negatives <33%). Visual fields test was repeated once if deemed unreliable. Glaucomatous visual field loss was defined as glaucoma hemifield test graded "outside normal limits" and a cluster of three contiguous points at the 5% level on the pattern deviation plot. Glaucoma was defined as the presence of both glaucomatous visual field loss and optic disk changes in one or both eyes (Foster et al., 2002).

2.9. Any ocular disease

Any ocular disease was defined as the presence of any of the major ocular disease including cataract, retinopathy, DR (among those with diabetes), glaucoma and AMD.

2.10. Statistical Analysis

Statistical analysis was performed with SPSS version 20.0 (Texas, USA). A p value of <0.05 was considered statistically significant. We examined the characteristics of the participants with and without CKD using the Chi square test for categorical variables and the independent t test for continuous variables. The associations of CKD with VI and ocular diseases were examined using logistic regression models: first adjusted for age and gender, followed by additional adjustment for potential confounding factors: ethnicity, smoking, alcohol intake, education status, body mass index, systolic blood pressure, diabetes mellitus (duration of diabetes and HbA1c, for the analysis of DR), cholesterol levels and CVD. In separate multivariable models, we also examined the severity of CKD with VI. We performed test for p-trend by modeling CKD stages as an ordinal variable in the corresponding multivariable model. Finally, we repeated the multivariable analysis testing the association of CKD with VI stratified by diabetic status. We tested for interaction by diabetes in the association between CKD and VI by including cross-product interaction terms in the multivariable logistic regression models.

3. Results

Of the 9434 included participants, 1179 (12.5%) had CKD. The mean eGFR in participants with and without CKD were 46 ± 12 mL/min/1.73 m^2 and 89 ± 15 mL/min/1.73 m^2 respectively. Among the 1179 participants with CKD, 1051 (89.1%) had stage 3 CKD, 85 (7.2%) had stage 4 CKD and 43 (3.7%) had stage 5 CKD. 42.6% of those with CKD had diabetes mellitus.

Table 1 shows the baseline characteristics of participants stratified by CKD status. Those with CKD were older, more likely to be men, primary or below educated, less likely to be current smokers, alcohol drinkers, had higher prevalence of diabetes, hypertension, hyperlipidemia and CVD and had higher levels of systolic BP, BMI, triglycerides, glucose and HbA1c levels and lower levels of LDL cholesterol levels (all p < 0.001). Participants with CKD were also more likely to be on anti-hypertensive, diabetic and lipid lowering medications (all p < 0.001).

The prevalence of VI was 15.8% (n = 1481) in the study population. The prevalence of VI was nearly three times higher in persons with CKD than those without (36.1% vs 12.9%, p < 0.001). Fig. 1 shows the prevalence of VI by CKD severity. The prevalence of VI increased with decreasing categories of eGFR (p-trend < 0.001). The prevalence of other major ocular diseases is shown in Table 2. The prevalence of all major ocular diseases including cataract, any retinopathy, AMD, glaucoma, under-corrected refractive error and any ocular disease were significantly higher in persons with CKD than those without. Among those with diabetes, the prevalence of DR was also higher in those with CKD than those without (46.0% vs 31.6%).

Table 1
Characteristics of participants by CKD status.

	CKD absent (n = 8255)	CKD present (n = 1179)	p Value*
Age (years)	57.3 (9.8)	68.3 (8.6)	<0.001
Women, %	4215 (51.1)	532 (45.1)	<0.001
Current smokers, %	1372 (16.6)	144 (12.2)	<0.001
Alcohol drinkers, %	773 (9.4)	35 (3.0)	<0.001
Primary/below educated, %	4702 (57.0)	958 (81.3)	<0.001
Cardiovascular disease, %	719 (8.7)	276 (23.4)	<0.001
Hypertension, %	4710 (57.2)	1044 (88.8)	<0.001
Systolic blood pressure (mm Hg)	138 (21)	152 (24)	<0.001
Diastolic blood pressure (mm Hg)	78 (10)	78 (11)	0.51
BMI (kg/m^2)	25.31 (4.64)	26.15 (4.83)	<0.001
Hyperlipidemia, %	3494 (42.5)	717 (61.2)	<0.001
LDL-cholesterol (mmol/L)	3.40 (0.94)	3.22 (1.08)	<0.001
HDL-cholesterol (mmol/L)	1.24 (0.37)	1.23 (0.35)	0.28
Triglycerides (mmol/L)	1.72 (1.06)	1.98 (1.38)	<0.001
Diabetes mellitus, %	1749 (21.2)	502 (42.6)	<0.001
Blood glucose, mmol/L	6.67 (3.26)	7.71 (4.16)	<0.001
HbA1c, (%)	6.3 (1.3)	6.7 (1.5)	<0.001
Anti-hypertensive medication use, %	2483 (30.2)	735 (62.9)	<0.001
Lipid lowering medication use, %	1800 (21.9)	491 (42)	<0.001
Diabetic medication use, %	1295 (15.8)	388 (33.2)	<0.001
eGFR ($mL/min/1.73m^2$)	89 (15)	46 (12)	<0.001

Abbreviations: BMI, body mass index; LDL, low density lipoprotein; HDL, high density lipoprotein; HbA1c, glycosylated hemoglobin; eGFR, estimated glomerular filtration rate; data presented are number of observations and proportions or mean and standard deviation as appropriate for the variable.

Table 3 shows the associations of CKD with VI and ocular diseases. CKD was significantly associated with VI, any ocular disease, cataract, any retinopathy, and DR. The odds of VI increased with increasing severity of CKD. In models additionally adjusting for anti-hypertensive medication use, the associations of CKD with VI, any ocular disease, any retinopathy and DR remained significant, while the association with cataract lost significance (Supplementary Table). In analysis stratified by eGFR categories, compared to those with eGFR ≥ 60, the odds of VI were 1.24 (1.05–1.48) for eGFR = 30–60, 1.71 (1.05–2.79) for eGFR = 15–30 and 4.99 (2.46–10.13) for eGFR < 15 (data not shown).

When stratified by diabetes status (Table 4), CKD was found to be significantly associated with VI, and any ocular disease in persons with diabetes. CKD was also significantly associated with any retinopathy in persons with and without diabetes. Consistent with the main analysis, the odds of VI increased with the decreasing categories of eGFR among those with diabetes (eGFR = 30–60: OR 1.61 95% CI 1.21–2.15; eGFR = 15–30: OR 2.24 95% CI 1.23–4.09; eGFR < 15: OR 8.43 95% CI 2.67–26.67). However, no significant interaction was

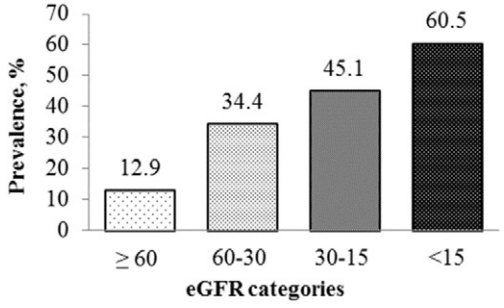

Fig. 1. Prevalence of VI by eGFR categories.

Table 2
Prevalence of ocular disease in persons with or without CKD.

Ocular conditions	CKD absent (n = 8255)	CKD present (n = 1179)	p Value
Visual impairment (VI)	1062 (12.9)	419 (36.1)	<0.001
Any ocular disease	3706 (54.3)	731 (84.7)	<0.001
Any retinopathy	848 (10.4)	265 (23.9)	<0.001
*DR	540 (31.6)	218 (46.0)	<0.001
AMD	500 (6.2)	121 (10.9)	<0.001
Glaucoma	268 (3.2)	68 (5.8)	<0.001
Cataract	2418 (34.9)	693 (74.6)	<0.001
Under-corrected refractive error	1779 (21.6)	293 (25.0)	0.005

Abbreviations: CKD, chronic kidney disease; VI, visual impairment; OR, odds ratio; CI, confidence interval; DR, diabetic retinopathy; AMD, Age related macular degeneration.

found between diabetes and CKD on the association with VI (p-interaction = 0.153). In a supplementary analysis stratified by ethnicity, although the association of CKD with VI was stronger in Indians (OR 1.81 95% CI 1.33–2.48), compared to Chinese (OR 1.01 95% CI 0.78–1.56) and Malays (OR 1.15, 95% CI 0.90–1.46), there was no significant interaction by race–ethnicity (p-interaction = 0.62, data not shown).

4. Discussion

In a population-based sample of multi-ethnic Asian adults, we found the prevalence of VI and major ocular diseases to be significantly increased in persons with CKD compared to those without. CKD was significantly associated with VI, cataract, and any retinopathy independent of potential confounding factors. When stratified by diabetes status, CKD showed significant associations with VI, DR, and any ocular disease among persons with diabetes and with any retinopathy among those without diabetes. The odds of VI were higher with increasing severity of CKD, particularly in persons with diabetes.

Several large epidemiological studies have reported the prevalence of ocular diseases in persons with CKD (Grunwald et al., 2010; Klein et al., 2009; Weiner et al., 2011). Grunwald et al. investigated the prevalence of fundus pathology and glaucoma in a population based cross sectional study of 1936 adults who participated in the Chronic Renal Insufficiency Cohort (CRIC) study. He found that 45% of persons with CKD had ocular pathology requiring follow up examination by an ophthalmologist. Diabetic, hypertensive or other retinopathy was present in 25.3%, 8.9% had signs of glaucoma and 7.6% had signs of AMD. Stage 4 and 5 CKD were associated with increased odds of any fundus pathology (OR 2.12 95% CI 1.62–2.78) and of any retinopathy (OR 2.99 95% CI 2.05–4.06), compared to persons with eGFR ≥ 50 mL/min/1.73 m^2 (Grunwald et al., 2010). In the Third National Health and Nutrition Examination Survey (NHANES III), Weiner et al. conducted a cross sectional nested case control study comparing markers of kidney disease in 7667 persons with and without AMD. He observed an independent association of lower eGFR with late AMD (OR 3.05 95% CI 1.51–6.13) (Weiner et al., 2011). In the Beaver Dam Eye Study, Klein et al. found an association of CKD with the 15-year incidence of early AMD (OR 1.36 95% CI 1.00–1.86) but not with exudative AMD or geographic atrophy (Klein et al., 2009). Although the prevalence and risk of ocular disease has been reported to be high in persons with CKD, none of these studies have examined the burden of VI in those with CKD.

Table 3
Associations of CKD with VI and major ocular diseases.

	Age, sex adjusted OR (95% CI)	p Value	[a]Multivariable adjusted OR (95% CI)	p Value
VI	1.45 (1.24–1.68)	<0.001	1.34 (1.14–1.58)	0.001
Any ocular disease	1.54 (1.24–1.91)	<0.001	1.28 (1.03–1.61)	0.03
Any retinopathy	2.45 (2.06–2.90)	<0.001	1.77 (1.45–2.15)	<0.001
[b]DR	1.99 (1.60–2.48)	<0.001	1.94 (1.47–2.54)	<0.001
AMD	0.85 (0.68–1.07)	0.16	0.93 (0.73–1.17)	0.52
Glaucoma	0.94 (0.70–1.25)	0.66	0.81 (0.60–1.10)	0.18
Cataract	1.46 (1.20–1.78)	<0.001	1.24 (1.01–1.52)	0.041
Under-corrected refractive error	0.98 (0.84–1.14)	0.82	0.98 (0.84–1.15)	0.82

Abbreviations: CKD, chronic kidney disease; VI, visual impairment; DR, diabetic retinopathy; AMD, Age related macular degeneration.
[a] Multivariable model adjusted for age, gender, ethnicity, education status, current smoking, alcohol consumption, diabetes status, systolic blood pressure, body mass index, triglyceride levels, low density lipoprotein cholesterol, and cardiovascular disease.
[b] Multivariable model additionally adjusted for diabetes duration, and HbA1c.

Table 4
Association of CKD with VI and major ocular diseases stratified by diabetes status.

Condition	Diabetes present		Diabetes absent	
	Prevalence, %	[b]Multivariable OR (95% CI)	Prevalence, %	[a]Multivariable OR (95% CI)
VI	23.4	1.80 (1.37–2.36)	13.4	1.11 (0.89–1.38)
Any ocular disease	91.5	1.98 (1.29–3.06)	80.0	1.07 (0.81–1.39
Any retinopathy	34.7	1.94 (1.47–2.55)	5.1	1.45 (1.01–2.07)
AMD	7.9	0.98 (0.64–1.51)	6.4	0.89 (0.66–1.20)
Glaucoma	4.6	1.11 (0.66–1.88)	3.2	0.67 (0.45–1.00)
Cataract	55.0	1.27 (0.90–1.80)	34.9	1.13 (0.87–1.48)
Under-corrected refractive error	22.6	1.01 (0.76–1.34)	21.8	0.96 (0.78–1.17)

Abbreviations: CKD, chronic kidney disease; VI, visual impairment; OR, odds ratio; CI, confidence interval; AMD, Age related macular degeneration.
[a] Multivariable model adjusted for age, gender, ethnicity, education status, current smoking, alcohol consumption, diabetes status, systolic blood pressure, body mass index, triglyceride levels, low density lipoprotein cholesterol, and cardiovascular disease.
[b] Multivariable model additionally adjusted for adjusted for diabetes duration, and HbA1c.

The high burden of ocular disease in CKD can be explained, in part, by the sharing of risk factors common to both kidney and eye diseases such as age, smoking, hypertension, diabetes, raised serum cholesterol and obesity. Ocular diseases may also be directly linked to CKD via common pathogenic pathways, including, atherosclerosis, microangiopathy, inflammation and oxidative stress (Wong et al., 2014). In our study, cataract and retinopathy were independently associated with CKD. Some of the possible pathogenic mechanisms underlying CKD, cataract and retinopathy are as follows: 1. Advanced glycation end products (AGEs) are a group of structures that form under conditions of oxidative stress or hyperglycemia. In the kidney, AGEs bind to receptors on podocytes and endothelial cells, resulting in cellular apoptosis and upregulation of proinflammatory markers (Busch et al., 2010). In the eye, AGEs target lens proteins, causing crosslinking, yellowing of the lens and generation of oxygen free radicals that lead to cataractogenesis (Ortwerth et al., 2003). In DR, AGEs induce apoptosis of retinal pericytes, breakdown of the inner blood retinal barrier and mediates increased expression of proinflammatory cytokines in both retinal vessels and neuroglia (Stitt, 2010). High levels of serum AGEs, such as in patients with CKD, can induce retinopathy similar to that seen in diabetic patients (Canning et al., 2007) 2. Vitamin D deficiency, via dysregulation of the renin–angiotensin system, mediates increased oxidative stress, inflammation and angiogenesis leading to CKD and DR (Payne et al., 2012). 3. Cystatin C, a biomarker of CKD, has been shown to be associated with increased risk of DR, possibly via a direct effect on vascular endothelial growth factor driven angiogenesis (Wong et al., 2015). The higher odds of retinopathy and VI in diabetic persons with CKD are likely to be related to some of these common pathogenic mechanisms that are also present in persons with diabetes. Thus, early intervention to preserve renal function and adequate control of diabetes is key to the reduction of ocular disease prevalence and low vision burden in persons with CKD. The importance of timely and frequent eye screening in persons with both CKD and diabetes cannot be over-emphasized.

Our study demonstrated that cataract and retinopathy were important causes of VI in persons with CKD. With modern cataract surgical techniques, cataract is an easily correctable cause of VI. In the Blue

Mountains Eye Study, Fong et al. found that surgical correction of cataract resulted in significantly lower 15-year mortality risk (hazard ratio 0.54 95% CI 0.41–0.73), compared to persons with VI from cataract that did not undergo surgery (Fong et al., 2013). In the Salisbury Eye Evaluation project, a 53% drop in 6-year mortality risk was observed in participants who had a gain of 2 or more lines in binocular visual acuity 2 years from baseline examination, compared to those without visual improvement (Freeman et al., 2005). VI secondary to DR can be corrected if early sight threatening disease is detected and treated with laser photocoagulation. The high prevalence of ocular disease in persons with CKD with readily correctable causes for VI suggests that eye screening should be performed in all patients with reduced renal function, but there are currently no recommendations for such screening.

In the present study, prevalence of current smoking and alcohol drinking was found to be lower among those with CKD. It is plausible that CKD patients may have changed their lifestyle and quit smoking and alcohol after knowing their condition. Accordingly, when we explored the data by smoking status, 23.4% of those with CKD reported being former smokers compared with 13.1% of those without CKD being former smokers.

The strength of our study lies in the large sample size, population based design, detailed eye examination and information on potential confounders allowing an adequate estimate of the ocular disease burden in persons with CKD. The cross-sectional nature of our study is a limitation and a prospective study would be ideal to assess the incidence and risk of these ocular diseases as well as VI. Second, estimation of GFR from a single measure of serum creatinine could have misclassified CKD status in some participants. Third, information on other filtration markers such as cystatin C was not available in two-thirds of the participants (available only in Indian participants) and hence was not evaluated. Fourth, we did not have information on the etiology of CKD. Therefore, we were unable to determine the association of CKD with ocular diseases by specific cause of CKD.

In conclusion, there is a high burden of major eye diseases in persons with CKD, with nearly one in two suffering from VI. Cataract and retinopathy are potentially reversible causes of VI, especially if treated early. It may be useful to screen for ocular disease and VI in persons with CKD, particularly if they also have diabetes. The results of our study can inform public health initiatives for the prevention of CKD and early eye screening in these high-risk individuals.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ebiom.2016.01.023.

Author Contributions

All authors contributed to the intellectual development of this paper. CS and TYW had the original idea for the study. TYW supervised data collection. CS designed the study and supervised data analysis. CWW performed the analysis and wrote the first draft. EL, CYC, GCC, EST, TYW and CS provided critical corrections to the manuscript and approved the final manuscript.

Funding Sources

This study was funded by Biomedical Research Council (BMRC), 08/1/35/19/550 and National Medical Research Council (NMRC), STaR/0003/2008, Singapore and Ministry of Health -Singapore's National Medical Research Council under its Talent Development Scheme R927/36/2012 (CS). The funding agencies had no role in the conduct or interpretation of the study.

Acknowledgments

The authors also thank Miss. Riswana Banu Binte Mohamed Abdul, Singapore Eye Research Institute, Singapore for her help with formatting the manuscript.

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