Wang Wei (Orcid ID: 0000-0002-5273-3332)
He Mingguang (Orcid ID: 0000-0002-6912-2810)

Original Article – Clinical Science

Use of antihypertensive medications and the risk of glaucoma onset: Findings from the 45 and Up Study

Yixiong Yuan MD,[1] Wei Wang MD, PhD,[1] Xianwen Shang PhD,[2] Ruilin Xiong MD,[1] Jason Ha MBBS(Hons),[3] Lei Zhang PhD,[3,4,5,6] Zhuoting Zhu MD, PhD[2] and Mingguang He MD, PhD[1,2,3,7]

1. State Key Laboratory of Ophthalmology, Zhongshan Ophthalmic Center, Sun Yat-sen University, Guangzhou, China
2. Guangdong Eye Institute, Department of Ophthalmology, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, Guangzhou, China
3. Centre for Eye Research Australia, Ophthalmology, Department of Surgery, University of Melbourne, Melbourne, Australia
4. Artificial Intelligence and Modelling in Epidemiology Program, Melbourne Sexual Health Centre, Alfred Health, Melbourne, Australia
5. Central Clinical School, Faculty of Medicine, Monash University, Melbourne, Australia
6. Department of Epidemiology and Biostatistics, College of Public Health, Zhengzhou University, Zhengzhou 450001, Henan, China
7. Ophthalmology, Department of Surgery, University of Melbourne, Melbourne, Australia

Correspondence: Prof. Mingguang He, Centre for Eye Research Australia, Royal Victorian Eye and Ear Hospital, Melbourne, Australia
mingguang.he@unimelb.edu.au

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Dr. Zhuoting Zhu, Guangdong Eye Institute, Department of Ophthalmology, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, Guangzhou, China
zhuoting_zhu@hotmail.com

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ABSTRACT

Background: Abnormal blood pressure is a potential risk factor for glaucoma. However, the role of antihypertensive medications on glaucoma pathogenesis is controversial. This study aims to investigate the association between use of antihypertensive medications and glaucoma onset.

Methods: This nested case-control study, based on a large-scale longitudinal cohort in Australia, retrieved participants' claims records on drugs and Medicare services from national health databases. Participants with three or more claims records of anti-glaucoma medications from 2009 to 2016 were classified as glaucoma patients; those with none were classified as controls. Claims records of antihypertensive medications were identified within the five years before glaucoma onset and contemporary periods in matched controls without glaucoma. The association between the use of antihypertensive medications and glaucoma onset was assessed by multivariable logistic regression models.

Results: A total of 6748 cases and 13496 controls were analyzed. Compared with controls, the proportion of users of antihypertensive medications was slightly higher in glaucoma patients (46.9% vs 46.0%, $p>0.05$). After adjustments for demographics, health-related factors and medical history, the association between the use of antihypertensive medications and glaucoma onset was nonsignificant (OR 0.95, 95% CI=0.89-1.02). As for specific subtypes, only beta-blocking agents (BBA) (OR 0.82, 95% CI=0.75-0.90) and diuretics (OR 0.85, 95% CI=0.77-0.95) were significantly associated with reduced risks of glaucoma onset.

Conclusions: This study indicated that the use of antihypertensive medications was not associated with glaucoma onset. Decreased risks of glaucoma onset in users of BBA and diuretics requires further validation.

Keywords: Glaucoma, Epidemiology, Antihypertensive medications

1. INTRODUCTION

Glaucoma is the second leading global cause of blindness in individuals aged over 50 years old.[1] Elevated intraocular pressure (IOP) is the main risk factor for the onset and progression of glaucoma, and is the primary therapeutic target for almost all glaucoma therapies.[2,3] However, glaucoma is characterized by multiple phenotypes, with a complex pathogenesis that is still not fully understood. Numerous additional risk factors for glaucoma have been identified up to date, including ageing, family history,[4] refractive error[5] and blood pressure (BP).[6]

Hypertension is a common chronic disease among older adults and one of the strongest risk factors for various cardiovascular disorders.[7] Epidemiological evidence reveals that patients with hypertension are more likely to suffer from glaucoma than healthy individuals.[8,9] The combination of both increased IOP and compromised microvasculature secondary to hypertension has been postulated to be responsible for the increased risk of glaucoma.[6] In contrast, several cross-sectional studies suggest that vascular dysregulation and retinal ischemia secondary to excessive hypotension also contribute to the onset of glaucoma.[10,11] The potential bimodal effect of BP on glaucoma risk[12] has raised concerns regarding the association between glaucoma and antihypertensive medications, which regulate the BP level and affect systemic hemodynamics.[13] Further exploration of this association will greatly improve a mechanistic understanding of BP in glaucoma development, and may yield novel insights into glaucoma prevention and treatment.

Previous studies focusing on specific antihypertensive medications have demonstrated conflicting findings, with both increased and decreased risks of glaucoma development demonstrated in users of different antihypertensives.[14-17] Apart from design limitations, including small study populations and the short follow-up periods, earlier studies were

also limited by potential recall bias given the heavy reliance on self-reported data on the use of antihypertensive medications.

Using real-world claims records provided by the Australian Pharmaceutical Benefits Scheme (PBS), a nation-wide prescriptions database, this study aimed to assess the association between the use of antihypertensive medications and glaucoma onset in a large-scale cohort study in Australia.

2. METHODS

2.1 Study population

The study population consisted of participants of the Sax Institute's 45 and Up Study. The 45 and Up Study is a prospective large-scale cohort study of residents aged over 45 years old residing in New South Wales (NSW), Australia. A total of 123,775 males and 143,378 females were included until 2020. All participants were randomly sampled from the general population via the Department of Human Services (DHS, formerly Medicare Australia) enrollment database and recruited in this cohort from 1st February 2006 to 30th April 2009. Information about demographics, lifestyles, finance and health was collected at baseline via self-reported questionnaires (Sample questionnaires are available online at https://www.saxinstitute.org.au/our-work/45-up-study/questionnaire). The participants also provided consent for longitudinal follow-up and linkage to routine health databases including the Pharmaceutical Benefits Scheme (PBS) and Medicare Benefits Schedule (MBS). The PBS mainly collects information regarding prescriptions dispensed in community pharmacies, and subsidized in part by the Australian Government. The MBS collects data involving Medicare service claims by Australian residents for diagnostic tests and treatments. Services Australia deidentified participant data and assigned identification numbers to 45 and Up Study participants at recruitment. Using the unique identifiers, the Sax

Institute deterministically matched survey data to anonymous claim records in both the PBS and the MBS databases. Detailed methods of the 45 and Up Study have been outlined in previous research.[18]

Claims records in the PBS and the MBS were available from 2004 to 2016. Participants who did not have any claims records of anti-glaucoma medications before 2009 were included in this study. Considering a five-year look-back period without any anti-glaucoma prescriptions, we assumed that these participants did not have diagnosed glaucoma before the follow-up (2009-2016). Participants who only had one or two claims records of anti-glaucoma medications after 2009 were excluded since anti-glaucoma medications could also be temporarily used in postoperative IOP prophylaxis practice. A previous survey found that 37.4% ophthalmic surgeons routinely prescribed IOP-lowering eye drops to prevent postoperative IOP rise after uncomplicated cataract surgeries.[19] The remaining participants were defined as eligible participants in the current analysis.

Ethics approval for the 45 and Up Study was granted by the University of New South Wales Human Research Ethics Committee (HREC 05035/HREC 10186).[20] Data utilization in this study was approved by the Royal Victorian Eye and Ear Hospital Human Research Ethics Committee.

2.2 Case definition

Participants who had three or more claims records of anti-glaucoma medications (listed in Table S1) after 2009 were identified as glaucoma cases, irrespective of the number and types of anti-glaucoma medications they had used. At least three claims records were required to preclude short-term uncertain exposure and prevent the misidentification of postoperative IOP prophylaxis practice, which was consistent with previous studies.[17,21] The onset of glaucoma was indexed as the year during which

anti-glaucoma medications were first prescribed within the follow-up period.

2.3 Control definition

The control group included all participants who did not have any claims records of anti-glaucoma medications from 2004 to 2016. Considering that medical treatments are widely used for the management of glaucoma,[22] those without any anti-glaucoma medications prescribed during the twelve years were unlikely to be glaucoma patients with glaucoma. In order to control major confounding factors and improve statistical efficiency, every participant with glaucoma onset was matched with two randomly selected controls by age (±one year), gender and self-reported cardiovascular diseases (CVD) at baseline. To avoid over-representation due to excess repeated matching, a larger case-to-control ratio (1:3 or 1:4) was not used in the current study. All matched controls shared the same index years with their corresponding cases. In the case of glaucoma patients with only one matched control, this non-glaucoma control was allowed to be matched repeatedly. Glaucoma patients who could not be matched with any non-glaucoma controls by age, gender and CVD were considered unsuitable for analyses and further excluded.

2.4 Drug exposure definition

All claims records of anti-glaucoma medications and systemic antihypertensive medications in the PBS database were identified by the Anatomical Therapeutic Chemical (ATC) system recommended by the World Health Organization (listed in Table S1).[23] In the ATC system, drugs are classified based on the main indication of the main active ingredient, and each route of administration is assigned to a unique code. All claims records of anti-glaucoma medications and systemic antihypertensive medications in the PBS database were identified by ATC codes and retrieved for measurement of medication exposure. According to pharmaceutical properties, antihypertensive medications were divided into five groups including beta-blocking

agents (BBA), calcium channel blockers (CCB), angiotensin-converting enzyme inhibitor (ACEI), angiotensin receptor blockers (ARB) and diuretics. In light of varying ingredients and dosages, antihypertensive medications could also be divided into fixed-dose combination (FDC) products and non-FDC products. FDC products refer to some medications which combine several ingredients with different pharmaceutical properties into a single pill. Since FDC products reduce pill burden, they are usually prescribed for patients whose BP is not adequately controlled.

Participants with at least three claims records of a specific drug during the identification period (one to five years before glaucoma onset) were deemed to have been exposed to this drug. Participants using several medications within the identification period were deemed to have exposure to all these medications. Participants who had used antihypertensive medications for more than three years before the index year were identified as long-term users.

2.5 Covariates

Demographic factors, health-related factors and comorbidities at baseline were adjusted in multivariable analyses to control potential confounding bias. All these covariates were derived from the baseline questionnaire. Demographic factors included age, gender, educational attainment and household income. Health factors comprised body mass index (BMI), smoking, alcohol consumption and physical activity measured in minutes per week. In the baseline questionnaire, participants were asked about their past medical history and family history. Hypercholesterolemia, CVD (including heart disease, stroke and blood clotting disorder), hypertension, family history of diabetes at baseline and the duration of diabetes were investigated as comorbidities based on participant responses in the questionnaire. Additionally, data involving the frequency of consultations with ophthalmologists and optometrists within the identification period were also retrieved from the MBS database. Given the

high likelihood of increased consultations in the case group, it was further adjusted in the final model.

2.6 Statistical analysis

Statistical analysis was performed using SAS 9.4 (SAS Institute, Cary, North Carolina). The comparison of categorical and continuous variables between cases and controls was conducted using χ^2 tests and Student's t-tests, respectively. Association between the use of antihypertensive medications and glaucoma onset was investigated with conditional logistic regression models adjusting for confounding factors at baseline and the frequency of eye-related consultations within the identification period. Risks of glaucoma onset were further compared in participants using FDC and specific antihypertensive medications. The association between long-term use of antihypertensive therapies with glaucoma onset was also analyzed. The odds ratios (*OR*s) and 95% confidence intervals (*CI*s) were calculated. All *p* values were two-sided in this study. A *p*-value of <0.05 was considered statistically significant.

3. RESULTS

Among 252,545 participants who met the eligibility criteria, a total of 6,748 glaucoma cases were identified and matched with 13,496 controls with no claims record of anti-glaucoma medications by age, gender and CVD at baseline. As for glaucoma cases who had only one matched control, these glaucoma patients were repeatedly matched to their corresponding controls (about 2.5% of the control group). Comparison of covariates between the case and the control group were demonstrated in Table 1. The proportion of non-smokers was significantly higher in the case group than that in the control group (54.2% and 51.5%; $p<0.01$). No significant difference was found in other demographic and health-related factors between the two groups. Most comorbidities had similar proportions between cases

and controls, except for family history of diabetes: the proportion was significantly higher in the case group (22.8% and 21.6%; p=0.05). Although no difference was found in the proportion of participants using antihypertensive medications between the case and the control group (46.9% and 46.0%; p=0.24), the proportion of CCB users in the case group was significantly higher compared with that in the control group (18.8% and 17.5%; p=0.02). Additionally, participants in the case group sought consultations with ophthalmologists or optometrists more frequently than those in the control group (19.7 times and 13.1 times; p<0.01) within the identification period.

A total of 3164 cases and 6210 controls were classified as users of antihypertensive medications during the identification period. The proportion of participants using FDC of antihypertensive medications was 14.6% and 13.6% in the case and the control groups, respectively (corresponding to 985 and 1,840 participants). Compared with the control group, the case group had more participants using antihypertensive medications for more than three years within the identification period (33.3% and 30.5%). The association between use of antihypertensive medications and glaucoma onset was presented in Table 2. In the conditional logistic regression model, use of antihypertensive medications was not significantly associated with glaucoma onset (OR=1.01, 95%CI=0.94-1.08) after adjustments for demographic factors, health-related factors and baseline comorbidities in Model 1. With further adjustments for the frequency of consultations with ophthalmologists or optometrists in Model 2, this association remained non-significant (OR=0.95, 95%CI= 0.89-1.02). Similar to the overall use of antihypertensive medications, no significant association between the use of FDC and glaucoma onset was found in both Models 1 and 2 (OR=1.07 and 1.01, respectively). As for long-term use of antihypertensive medications, no significant association with glaucoma onset was found in both two multivariable models.

Association between use of specific antihypertensive medications and glaucoma onset was shown in Table 3. In the case group, ARB and ACEI were the first and the second most used antihypertensives (24.1% and 20.5%), followed by CCB (18.8%) and BBA (14.4%). Diuretics were the least commonly used antihypertensive medications, used in only 9.7% of participants. Similar rankings were also observed in the control group. After adjustment for demographic factors, health-related factors and baseline comorbidities, use of BBA (OR 0.91, 95%CI= 0.83-0.99) was associated with a reduced risk of glaucoma onset. On the contrary, a higher risk of glaucoma onset was found in CCB users compared with those who did not use CCB within the identification period (OR 1.08, 95%CI=1.00-1.18). In Model 2 which further adjusted for the frequency of consultations with ophthalmologists or optometrists, the significantly reduced risk of glaucoma onset in BBA users persisted (OR 0.82, 95%CI=0.75-0.90), while the increased risk in CCB users did not (OR 1.00; 95%CI=0.92-1.09). In addition to BBA, use of diuretics was also associated with a reduced risk of glaucoma onset after further adjustments (OR 0.85, 95%CI= 0.77-0.95) in Model 2. No significant association between the use of ACEI or ARB with glaucoma onset was found in both multivariable models.

4. DISCUSSION

Based on a large-scale cohort of the Australian population, this nested case-control study found that the use of antihypertensive medications was not associated with glaucoma onset in older adults. Current findings did not support the potential effects of pharmacological BP-lowering on the risk of glaucoma. For specific types of antihypertensive medications, reduced risks of glaucoma onset were found in users of BBA and diuretics, respectively. Non-statistically significant associations were observed for other types of antihypertensive medications.

The non-significant association between the use of antihypertensive medications and glaucoma onset found in the current study was consistent with a prospective cohort study in patients with ocular hypertension.[24] Miglior et al. found that there was no significant difference in the risk of open-angle glaucoma (OAG) onset between patients who used antihypertensives and patients who did not. Their study also suggested that combined use of antihypertensive medications was also not associated with OAG onset, except for the combinations of diuretics and other medications. However, a recent population-based study by Horwitz et al. suggested that prescriptions of antihypertensive medications led to a remarkable reduction in the risk of glaucoma.[25] A possible explanation for this discrepancy was that Horwitz et al. adopted a broader definition of glaucoma onset, which required only one claim record of anti-glaucoma medications. Compared with the current study, their identification of glaucoma patients was less rigorous and at higher risk of misclassification, especially in patients receiving one-off IOP-lowering treatments after intraocular surgeries.

The association between the use of antihypertensive medications and glaucoma onset should be interpreted with caution since existing evidence suggests that abnormal BP levels were significant risk factors for glaucoma.[6] Apart from its association with the increased IOP[9,17], hypertension also injures retinal arterioles, which could induce retinal ischemia and glaucomatous damage. In addition, it should be noted that the balance between BP and IOP is responsible for the maintenance of ocular perfusion pressure and retinal microcirculation. For example, some population-based studies found that glaucoma was more prevalent in those with low BP levels. [26,27] Considering that the background risk of glaucoma was higher in those who need to control BP, we have provided a cautious inference that the use of antihypertensive medications was unlikely to be associated with an increased risk of

glaucoma onset. Furthermore, sensitivity analyses demonstrated that intense BP control by FDC and long-term use of antihypertensive medications were not associated with glaucoma onset. However, caution must be applied in the interpretation of the secondary findings with relatively small sample sizes, as these non-significant results might be attributed to insufficient statistical efficiency. It should be noted that the current study were insufficient to preclude the protective effect of antihypertensive medications on glaucoma risk. Despite the adjustment for hypertension in the multivariable model, this association might still be confounded by other factors like disease severity and actual BP levels. More studies are needed to corroborate our findings.

In terms of specific antihypertensive medications, conflicting results were observed, which implied that there may be alternative mechanisms other than BP for these associations. The reduced risk of glaucoma onset in BBA users was supported by many previous studies. Langman et al. found that oral BBA appeared to reduce the risk of glaucoma by about 23% in a case-control study using general practitioner databases.[15] In another case-control study, Owen et al. revealed that BBA, especially β1 receptor antagonists, was associated with a 20% reduced risk of glaucoma onset in the United Kingdom.[28] Two recent large-scale studies based on a national medical claims database also suggested that the risk of glaucoma onset was reduced in BBA users.[17,25] Clinical trials and cross-sectional observations found that orally administrated BBA may significantly reduce IOP in both glaucoma patients and healthy individuals.[29-31] Similar to topical BBA eye drops, systemic BBA may also be implicated in the reduction of aqueous humor production, which reduced the IOP. Although current guidelines did not recommend the use of concurrent topical and systemic BBA, [32] the protective effect of systemic BBA may provide additional therapeutic options for glaucoma patients with intolerance, allergy, or suboptimal adherence to BBA eye drops. With respect to use of diuretics, its association with a

reduced risk of glaucoma corroborated earlier findings of Horwitz et al.[25] However, this result should be interpreted with caution since several studies from 2005 to 2010 suggested that use of diuretics might increase the risk of OAG.[15,24] Compared with those studies focusing on OAG, both OAG and angle-closure glaucoma (ACG) were investigated in the current study. Since previous case reports warned that sulphonamide-derived diuretics might induce anterior choroidal effusion and acute ACG, clinicians may be less likely to prescribe diuretics for patients with narrow angles or shallow anterior chamber in practice.[33] The avoidance of prescriptions in patients at risk of ACG may contribute to the reduced use of diuretics before glaucoma onset. As for other antihypertensive medications, previous findings about associations between use of ACEI, ARB and CCB with glaucoma onset were also controversial. Several pilot trials about normal-tension glaucoma (NTG) in 1990s suggested that CCB might improve hemodynamics of retrobulbar vessels and postpone visual field defects,[34,35] whereas the heterogeneity of this protective effect was remarkable among NTG patients.[35] In contrast, recent longitudinal studies in real world indicated that use of CCB was associated with an increased risk of glaucoma onset, with effect sizes ranging from 1.20 to 1.80.[16,17] Similarly, the favorable effect of ACEI on the visual field found in previous studies[36,37] was also challenged by evidence from population-based studies.[17,28] Considering the important role of ACEI, ARB and CCB in BP control, existing evidence was far from enough to affect the treatment pattern in patients with hypertension who were at risk of glaucoma.

This study has provided a deeper insight into the association between the use of antihypertensives and glaucoma onset. The large-scale study cohort comprising the general population and an extended 10-year follow-up also resulted in high statistical efficacy, and more closely reflected the real-world association between antihypertensive medications and glaucoma measured over a long follow-up period. The major limitation of this study was the lack of glaucoma-related examinations

including IOP, visual field and slit-lamp biomicroscopy, which may have resulted in the misclassification of undiagnosed or subclinical glaucoma and contributed to the non-significance of our findings. However, as part of our study design, we required all controls to have no claims records of anti-glaucoma medications during 2004-2016. Considering that medications served as the first-line therapy of glaucoma treatment, we anticipated that the risk of misclassification might be trivial. In addition, all glaucoma cases in the current study had at least three claims records of anti-glaucoma medications, which partially avoided the misidentification of ocular hypertension and the temporary IOP-lowering after ocular surgeries. Another limitation was the lack of death registration and some important measurements like BP, although the reasonable matching design could partly mitigate this bias. One further weakness was that most covariates including lifestyles and comorbidities used in the current study were derived from the self-reported questionnaire at baseline, and were not objectively compared with medical data. Of note, previous studies suggested that the agreements between self-reported questionnaires and objective records varied from good to fair for BMI and comorbidities in the 45 and UP Study,[38,39] the accuracy of many factors such as smoking was still unknown. The restricted validity of self-reported covariates might lead to recall or confounding biases. Furthermore, claims records in the PBS database may not be a true representation of actual medication use by participants, as participants may have purchased medications off-label or in schemes not subsidized by the PBS. However, the strict definition of drug exposure in this study maximized the chances of capturing patient adherence to pharmacotherapy. Last but not least, the proportions of participants aged 45-54 years, BBA users and diuretics users were relatively low in the current study, which made these results less generalizable to the general population.

In conclusion, this nested case-control study indicated that overall use of antihypertensive medications was not associated with the onset of glaucoma in

Australians aged over 45 years old. In terms of specific antihypertensive medications, reduced risks of glaucoma onset were only found in users of BBA and diuretics. No significant association was found between use of other antihypertensive medications with glaucoma onset. In order to determine this association, quantitative studies with longitudinal BP levels controlled are warranted to provide further definitive evidence.

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TABLES

Table 1: Use of antihypertensive medications and covariates compared between the case and the control groups at baseline and within the identification period.

	Total* (N=20244)	Case group* (N=6748)	Control group* (N=13496)	P value**
Baseline characteristics				
Age group				
45-54	2199(10.9)	730(10.8)	1469(10.8)	
55-64	5934(29.3)	1986(29.4)	3948(29.3)	0.97
65-74	6964(34.4)	2315(34.3)	4649(34.4)	
75+	5147(25.4)	1717(25.4)	3430(25.4)	
Gender				
Female	10053(49.7)	3351(49.7)	6702(49.7)	1.00
Male	10191(50.3)	3397(50.3)	6794(50.3)	
Household income (AUD/y)				
<20000	5076(25.1)	1685(25.0)	3391(25.1)	
20000-40000	3943(19.5)	1340(19.9)	2603(19.3)	
40000-70000	3133(15.5)	1024(15.2)	2109(15.6)	1.00
>70000	3244(16.0)	1077(16.0)	2167(16.1)	
Unknown	4848(23.9)	1622(24.0)	3226(23.9)	
Education levels				
No qualification	2848(14.1)	931(13.8)	1917(14.2)	
Certificate/ diploma/trade	12949(64.0)	4297(63.7)	8652(64.1)	0.16
University	4037(19.9)	1383(20.5)	2654(19.7)	
Unknown	410(2.0)	137(2.0)	273(2.0)	
Body mass index				
Underweight	271(1.3)	81(1.2)	190(1.4)	
Healthy weight	6762(33.4)	2248(33.3)	4514(33.4)	
Overweight	7568(37.4)	2594(38.4)	4974(36.9)	0.57
Obese	4326(21.4)	1394(20.7)	2932(21.7)	
Unknown	1317(6.5)	431(6.4)	886(6.6)	
Smoking history				
Non-smoker	10605(52.4)	3655(54.2)	6950(51.5)	
Current smoker	1099(5.4)	299(4.4)	800(5.9)	<0.01
Ex-smoker	8539(42.2)	2794(41.4)	5745(42.6)	

Alcohol Consumption (times/weeks)				
0	6984(34.5)	2305(34.2)	4679(34.7)	0.61
1-4	3751(18.5)	1300(19.3)	2451(18.2)	
5-7	2970(14.7)	994(14.7)	1976(14.6)	
8-14	3326(16.4)	1117(16.6)	2209(16.4)	
15+	2794(13.8)	901(13.4)	1893(14.0)	
Unknown	419(2.1)	131(1.9)	288(2.1)	
MVPA (min/weeks)				
≥300	3845(19.0)	1256(18.6)	2589(19.2)	0.16
150-300	10961(54.1)	3652(54.1)	7309(54.2)	
≤150	4584(22.6)	1563(23.2)	3021(22.4)	
Unknown	854(4.2)	277(4.1)	577(4.3)	
Hypercholesterolemia	3786(18.7)	1262(18.7)	2524(18.7)	1.00
CVD	3555(17.6)	1185(17.6)	2370(17.6)	1.00
Hypertension	8664(42.8)	2888(42.8)	5776(42.8)	1.00
Family history of diabetes	4459(22.0)	1541(22.8)	2918(21.6)	0.05
Diabetes duration (y)				
0-5	1491(7.4)	475(7.0)	1016(7.5)	0.66
6-9	618(3.1)	214(3.2)	404(3.0)	
10-19	173(0.9)	64(0.9)	109(0.8)	
20+	116(0.6)	39(0.6)	77(0.6)	
Within five years before the index year				
Users of antihypertensive medications	9374(46.3)	3164(46.9)	6210(46.0)	0.24
Beta blocking agents	3035(15.0)	975(14.4)	2060(15.3)	0.13
CCB	3628(17.9)	1268(18.8)	2360(17.5)	0.02
ACEI	4125(20.4)	1385(20.5)	2740(20.3)	0.69
ARB	4772(23.6)	1626(24.1)	3146(23.3)	0.22
Diuretics	1988(9.8)	657(9.7)	1331(9.9)	0.77
Users of FDC	2825(14.0)	985(14.6)	1840(13.6)	0.05
Frequency of consultations with ophthalmologists or optometrists				
	15.3(16.9)	19.7(18.2)	13.1(15.7)	<0.01

* All data presented as n (%), except the frequency of consultations which was presented as mean (standard deviation).

** All P values derived from chi-square tests, except the frequency of consultations which was derived from Student's t-tests.

*** AUD = Australian dollars; MVPA = moderate to vigorous physical activity; CVD = Cardiovascular diseases; FDC = Fixed-dose combinations; CCB = Calcium channel

blocker; ACEI = Angiotensin-converting enzyme inhibitor; ARB = Angiotensin Receptor Blocker

Table 2: Association between use of antihypertensive medications and glaucoma onset using conditional logistic regression models.

	Case group N (%)	**Control group N (%)**	**OR* (95% CI)**	**OR** (95% CI)**
Non-antihypertensive medications users	3584 (53.1)	7286 (54.0)	reference	reference
Antihypertensive medications users	3164 (46.9)	6210 (46.0)	1.01 (0.94-1.08)	0.95 (0.89-1.02)
FDC users	985 (14.6)	1840 (13.6)	1.07 (0.97-1.18)	1.01 (0.92-1.12)
Long-term users	2249 (33.3)	4121 (30.5)	1.11 (1.03-1.20)	1.05 (0.97-1.13)

* Model 1: Adjusted for age, gender, education level, body mass index, smoking, alcohol consumption, exercise habits, hyperlipidemia, hypertension, CVD and diabetes at baseline;

** Model 2: Model 1 with additional adjustments for the frequency of consultations with ophthalmologists or optometrists during the follow-up period.

OR = odds ratio; CI = confidence intervals; FDC = Fixed-dose combinations

Table 3: Associations between the use of specific antihypertensive medications and glaucoma onset evaluated by conditional logistic regression models

	Case group N (%)	Control group N (%)	OR* (95% CI)	OR** (95% CI)
Beta blocking agents	975(14.4)	2060(15.3)	0.91 (0.83-0.99)	0.82 (0.75-0.90)
CCB	1268(18.8)	2360(17.5)	1.08 (1.00-1.18)	1.00 (0.92-1.09)
ACEI	1385(20.5)	2740(20.3)	0.99 (0.92-1.07)	0.99 (0.91-1.07)
ARB	1626(24.1)	3146(23.3)	1.03 (0.96-1.11)	0.97 (0.90-1.05)
Diuretics	657(9.7)	1331(9.9)	0.98 (0.88-1.08)	0.85 (0.77-0.95)

* Model 1: Adjusted for age, gender, education level, body mass index, smoking, alcohol consumption, exercise habits, hyperlipidemia, hypertension, CVD and diabetes at baseline;

** Model 2: Model 1 with additional adjustments for frequency of consultations with ophthalmologists or optometrists during the follow-up period.

OR = odds ratio; CI = confidence intervals; CCB = Calcium channel blocker; ACEI = Angiotensin-converting enzyme inhibitor; ARB = Angiotensin Receptor Blocker

Table S1: Claims records of anti-glaucoma medications and systemic antihypertensive medications in the Pharmaceutical Benefits Scheme.

Anti-glaucoma medications

Categories	Medication name	ATC codes
Sympathomimetics in glaucoma therapy	Apraclonidine	S01EA03
	Brimonidine	S01EA05
	Dipivefrine	S01EA02
Parasympathomimetics	Carbachol	S01EB02
	Pilocarpine	S01EB01
Carbonic anhydrase inhibitors	Acetazolamide	S01EC01
	Brinzolamide	S01EC04
	Dorzolamide	S01EC03
	Brinzolamide and Brimonidine	S01EC54
	Brinzolamide and Timolol	S01EC54
	Dorzolamide and Timolol	S01ED51
Beta blocking agents	Betaxolol	S01ED02
	Levobunolol	S01ED03
	Timolol	S01ED01
	Brinzolamide and Timolol	S01EC54
	Dorzolamide and Timolol	S01ED51
	Bimatoprost and Timolol	S01ED51
	Latanoprost and Timolol	S01ED51
	Travoprost and Timolol	S01ED51
Prostaglandin analogues	Bimatoprost	S01EE03
	Latanoprost	S01EE01
	Travoprost	S01EE04
	Tafluprost	S01EE05
	Bimatoprost and Timolol	S01ED51
	Latanoprost and Timolol	S01ED51
	Travoprost and Timolol	S01ED51

Systemic antihypertensive medications

Categories	Medication name	ATC codes
Diuretics	Hydrochlorothiazide	C03AA03
	Chlortalidone	C03BA04
	Indapamide	C03BA11
	Furosemide	C03CA01
	Etacrynic acid	C03CC01
	Eplerenone	C03DA04
	Spironolactone	C03DA01

	Amiloride and Hydrochlorothiazide	C03EA01
	Tolvaptan	C03XA01
	Enalapril and Hydrochlorothiazide	C09BA02
	Perindopril and Indapamide	C09BA04
	Quinapril and Hydrochlorothiazide	C09BA06
	Fosinopril and Hydrochlorothiazide	C09BA09
	Eprosartan and Hydrochlorothiazide	C09DA02
	Valsartan and Hydrochlorothiazide	C09DA03
	Irbesartan and Hydrochlorothiazide	C09DA04
	Candesartan and Hydrochlorothiazide	C09DA06
	Telmisartan and Hydrochlorothiazide	C09DA07
	Olmesartan medoxomil and Hydrochlorothiazide	C09DA08
	Valsartan, amlodipine and hydrochlorothiazide	C09DX01
	Olmesartan medoxomil, amlodipine and hydrochlorothiazide	C09DX03
	Oxprenolol	C07AA02
	Pindolol	C07AA03
	Propranolol	C07AA05
	Atenolol	C07AB03
Beta blocking agents	Bisoprolol	C07AB07
	Metoprolol	C07AB02
	Nebivolol	C07AB12
	Labetalol	C07AG01
	Carvedilol	C07AG02
	Amlodipine	C08CA01
	Felodipine	C08CA02
	Lercanidipine	C08CA13
	Nifedipine	C08CA05
	Verapamil	C08DA01
	Diltiazem	C08DB01
	Lisinopril and amlodipine	C09BB03
Calcium channel blockers	Perindopril and amlodipine	C09BB04
	Ramipril and felodipine	C09BB05
	Trandolapril and verapamil	C09BB10
	Valsartan and amlodipine	C09DB01
	Olmesartan medoxomil and amlodipine	C09DB02
	Telmisartan and amlodipine	C09DB04
	Valsartan, amlodipine and	C09DX01

	hydrochlorothiazide	
	Olmesartan medoxomil, amlodipine and hydrochlorothiazide	C09DX03
	Atorvastatin and amlodipine	C10BX03
	Captopril	C09AA01
	Enalapril	C09AA02
	Lisinopril	C09AA03
	Perindopril	C09AA04
	Ramipril	C09AA05
	Quinapril	C09AA06
	Fosinopril	C09AA09
Angiotensin-converting enzyme inhibitor	Trandolapril	C09AA10
	Enalapril and Hydrochlorothiazide	C09BA02
	Perindopril and Indapamide	C09BA04
	Quinapril and Hydrochlorothiazide	C09BA06
	Fosinopril and Hydrochlorothiazide	C09BA09
	Lisinopril and amlodipine	C09BB03
	Perindopril and amlodipine	C09BB04
	Ramipril and felodipine	C09BB05
	Trandolapril and verapamil	C09BB10
	Losartan	C09CA01
	Eprosartan	C09CA02
	Valsartan	C09CA03
	Irbesartan	C09CA04
	Candesartan	C09CA06
	Telmisartan	C09CA07
	Olmesartan medoxomil	C09CA08
	Eprosartan and Hydrochlorothiazide	C09DA02
	Valsartan and Hydrochlorothiazide	C09DA03
	Irbesartan and Hydrochlorothiazide	C09DA04
Angiotensin receptor blockers	Candesartan and Hydrochlorothiazide	C09DA06
	Telmisartan and Hydrochlorothiazide	C09DA07
	Olmesartan medoxomil and Hydrochlorothiazide	C09DA08
	Valsartan and amlodipine	C09DB01
	Olmesartan medoxomil and amlodipine	C09DB02
	Telmisartan and amlodipine	C09DB04
	Valsartan, amlodipine and hydrochlorothiazide	C09DX01
	Olmesartan medoxomil, amlodipine	C09DX03

	and hydrochlorothiazide	
	Valsartan and sacubitril	C09DX04
	Quinapril and Hydrochlorothiazide	C09BA06
	Fosinopril and Hydrochlorothiazide	C09BA09
	Eprosartan and Hydrochlorothiazide	C09DA02
	Valsartan and Hydrochlorothiazide	C09DA03
	Irbesartan and Hydrochlorothiazide	C09DA04
	Candesartan and Hydrochlorothiazide	C09DA06
	Telmisartan and Hydrochlorothiazide	C09DA07
	Olmesartan medoxomil and Hydrochlorothiazide	C09DA08
	Valsartan, amlodipine and hydrochlorothiazide	C09DX01
	Olmesartan medoxomil, amlodipine and hydrochlorothiazide	C09DX03
Fixed-dose combination	Lisinopril and amlodipine	C09BB03
	Perindopril and amlodipine	C09BB04
	Ramipril and felodipine	C09BB05
	Trandolapril and verapamil	C09BB10
	Valsartan and amlodipine	C09DB01
	Olmesartan medoxomil and amlodipine	C09DB02
	Telmisartan and amlodipine	C09DB04
	Valsartan, amlodipine and hydrochlorothiazide	C09DX01
	Olmesartan medoxomil, amlodipine and hydrochlorothiazide	C09DX03
	Atorvastatin and amlodipine	C10BX03
	Valsartan and sacubitril	C09DX04