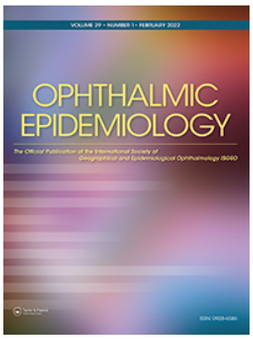

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ARTICLE

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Relationships among visual acuity, risk of acute myocardial infarction, and stroke: a nationwide cohort study in south korea

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ABSTRACT

Purpose: Visual impairment (VI) is highly prevalent in the elderly and is associated with functional decline. Previous research demonstrated an association between VI and cardiovascular events, but investigations have yet to be conducted in general population samples. We evaluated the relationship between visual acuity (VA) and development of cardiovascular diseases (CVD) in a nationwide Korean population.

Methods: This is a nationwide retrospective cohort study. We used the National Health Information Database of the National Health Insurance Service of Korea to identify subjects who participated in the National Health Insurance Service health screening program in 2012. We monitored 5,941,761 subjects for the development of cardiovascular diseases for a period of 5 years.

Results: After adjustments for age, sex, and other covariates, with subjects having a visual acuity better than 20/20 as the reference group, the adjusted hazard ratios (HRs) and 95% confidential intervals (CI) for acute myocardial infarction and stroke were visual acuity between 20/20 and 20/60, 1.073 (95% CI 1.053, 1.094) and 1.151 (95% CI 1.132, 1.171), respectively; for visual acuity between 20/60 and 20/200, 1.236 (95% CI 1.197, 1.277), and 1.336 (95% CI 1.302, 1.371), respectively; and for visual acuity worse than 20/200, 1.325 (95% CI 1.285, 1.366) and 1.383 (95% CI 1.349, 1.418), respectively.

Conclusion: Subjects with lower VA had higher risks of acute myocardial infarction and stroke. These results suggest that low VA is an independent risk factor for CVD.

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visual acuity; cardiovascular diseases; acute myocardial infarction; stroke

Introduction

Visual impairment (VI) is a major public health concern due to the aging of the population. It is highly prevalent in the elderly[1,2] with one-third of the elderly population affected by mild to severe VI.[3] Visual loss is associated with greater functional decline[4] and limits the ability to perform activities of daily living, thereby negatively affecting quality of life.[5–8] VI and eye diseases are also associated with depression[9,10] and reduced mobility.[11] In a British study, disability-free life expectancies were 2 years shorter in men and 3 years shorter in women with VI[12] than in those with normal vision.

Previous reports have identified associations between cardiovascular events and visual acuity (VA). High cardiovascular disease (CVD) mortality was previously reported in subjects with VI caused by diabetic retinopathy.[13] The predicted 10-year risk for a first atherosclerotic cardiovascular disease event is also higher in visually impaired adults.[14] However, direct associations between VA and cardiovascular events have not been demonstrated.

In this study, we investigated the relationships between VA, acute myocardial infarction (AMI), and stroke using the national Korean health insurance database. Among the 10 leading causes of death in 2016 in the US, heart disease and stroke were ranked 1 and 5, and are the top 2 causes of death among CVD patients.[15] An association between ischemic stroke and AMI has been recognized for decades,[16] based on similar pathogenesis (atherosclerosis and thromboemboli)[17] and several shared risk factors (tobacco, diabetes, hypertension, etc.).[18] Therefore, we selected AMI and stroke for

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further examination in the present study. We evaluated the influence of VA on the risk of these diseases while adjusting for relevant confounders.

Materials and methods

Data sources

The data analyzed in this study were derived from the National Health Information Database (NHID) of the National Health Insurance Service (NHIS). All individuals born in South Korea are assigned a unique resident registration number and included in the NHIS system. The NHID is a public database of information about health care utilization, health screening, socio-demographic variables, and mortality for the whole population of South Korea that is maintained by the NHIS.[19] The eligibility database includes information about income-based insurance contributions, demographic variables, and date of death. The database includes over 50 million individuals, comprising 97% of Korean residents. The health care utilization database includes records of inpatient and outpatient usage (diagnosis, length of stay, treatment costs, services received) and prescription records (drug code, days prescribed, daily dosage).[20] The NHIS follows the Korean Classification of Diseases (KCD), which is similar to the International Classification of Diseases (ICD).

NHID is a health screening database derived from the biennial Korean national health screening program, in which the candidates are all National Health Insurance members over 40 years of age. The health screening database includes information on health behaviors based on physician counseling and examinees' questionnaire results, and bio-clinical variables including anthropometric measurements, systolic and diastolic blood pressure (SBP, DBP), VA, hearing, and blood laboratory tests. The rate of participation in health screening was 74.8% in 2014.

Measurements

Definitions of events

Patients with AMI and stroke were identified by searching for diagnostic codes for AMI (acute myocardial infarction, ICD-10 code: I21.x), and stroke (cerebral infarction, ICD-10 code: I63.x). Incident time was defined as the earliest claim related to the AMI or stroke code and hospital admission event.

VA and visual disability

VA was measured at the time of health screening. The visual acuity measurement procedure at the health screening institute follows the KSP ISO 8596, which is the Korean modification of the international standard. The measurement is performed under bright room light (more than 200 lux), using the standard visual acuity chart placed more than 4 m (generally 5 m) from the person being tested. Spectacle-corrected VA was recorded if participants used glasses. Individuals were categorized into four groups according to the better VA (spectacle-corrected if possible) of both eyes: VA greater than or equal to 20/20 was group 1, VA from 20/60 to 20/20 was group 2, VA from 10/100 to 20/60 was group 3, and VA less than 10/100 was group 4. Subjects with visual disability included individuals with certifications of visual disability from the Korean government (Ministry of Health and Welfare), which requires a registration document from a certificated ophthalmologist. Visual disability grade was determined by the criteria outlined in Table 1. In this study, subjects with visual disability were divided into a higher group that included grades 1, 2, and 3, and a lower group that included grades 4, 5, and 6.

Other variables

Blood pressure (BP) was measured while the subject was in a seated position after 5 min of rest during the daytime. Blood samples were collected after an overnight fast and serum levels of glucose, total cholesterol (TC), triglyceride (TG), high-density lipoprotein (HDL), and low-density lipoprotein (LDL) cholesterol were measured.

Subjects were considered to have hypertension, diabetes mellitus, or dyslipidemia if they had health claims for hypertension, diabetes, or dyslipidemia and were on medication to treat those diseases, or if SBP ≥140 mmHg or DBP ≥90 mmHg, fasting blood glucose levels ≥126 mg/dL, or TC ≥240 mg/dL.

Table 1. Criteria used for grading visual disability in South Korea.

Grade 1	Visual acuity of the better eye is less than or equal to 20/1,000
Grade 2	Visual acuity of the better eye is less than or equal to 20/500
Grade 3	Visual acuity of the better eye is less than or equal to 20/300, or the visual field of each eye is less than 5 degrees in any direction
Grade 4	Visual acuity of the better eye is less than or equal to 20/200, or the visual field of each eye is less than 10 degrees in any direction
Grade 5	Visual acuity of the better eye is less than or equal to 20/100, or the sum of visual fields of both eyes is less than 50% of normal
Grade 6	Visual acuity of the worse eye is less than or equal to 20/1,000

Visual acuity is given according to the Snellen visual acuity system.
Visual disability grading is based on documented best-corrected visual acuity.

Subjects with income in the lowest 20th percentile were defined as low income.

The definitions of lifestyle variables were as follows. Smoking status was categorized into three groups: non-smokers, current smokers who had smoked 100 cigarettes or more in their lifetime, and ex-smokers who had smoked in the past but had since quit at least 1 month prior. Alcohol consumption status was categorized into three groups: non-drinker, those who drank less than 30 g a day on average, and those who drank more than 30 g a day. Regular exercise was defined as strenuous physical activity (PA) that was performed for at least 30 min, and subjects were asked if they exercised at least five times per week. Body mass index (BMI) was defined as weight in kilograms divided by the square of height in meters (kg/m^2). Elevated waist circumference (WC) was defined as ≥90 cm for men and ≥85 cm for women according to the Korean Society for the Study of Obesity cut-off point for central or abdominal obesity. Hospitals, where health examinations were performed, were certified by the National Health Insurance Service and subjected to regular quality control audits.

Smoking habit, alcohol consumption habit, physical activity, diabetes, hypertension, and dyslipidemia were included as covariates in the multivariable regression because these are well-known risk factors for CVD.[18] We considered subject residence (place) to be an irrelevant variable. Income, BMI, and waist circumference were also known to be associated with CVD.[21] However, they act as effect modifiers or mediators between other confounders, including DM or HTN with CVD, and were not included as covariates in the multivariable regression model.

Ophthalmologic diseases such as age-related macular degeneration (AMD), glaucoma, and diabetic retinopathy (DR) were defined with diagnostic codes. Patients who had these diagnostic codes before health screening examination were considered to have each disease.

Study population

Identical cohorts were used for AMI and stroke analyses. Inclusion criteria were individuals who were over 40 years of age and received health screening between 1 January 2009 and 31 December 2012. A total of 17,539,992 subjects underwent the health screening program at least once during the study period. Among these subjects, 4,815,596 subjects under 40 years of age, 6,410,544 lacking information about VA, and 183,670 with incomplete data were excluded. We also excluded 153,631 subjects who were previously diagnosed with AMI and stroke. To apply a 1-year lag period, another 34,790 subjects were excluded. Finally, 5,941,761 subjects were included in the analysis. All included subjects were monitored for the development of health events until 31 December 2017. Eligibility criteria are presented in Figure 1.

Study protocol approvals and registrations

The Deliberative Committee of the Health Insurance Review and Assessment service approved the conditional use of the database of this study. The study adhered to the Declaration of Helsinki, and the study protocol was reviewed and approved by the Institutional Review Board of Samsung Medical Center (SMC 2018–02-112).

Statistical analysis

Data are described as mean ± SD and number (%). Kaplan-Meier analysis was used to assess the cumulative incidences of disease in the enrolled population. Multivariable adjusted Cox regression analysis was conducted to examine adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) to evaluate the risk of event occurrence associated with VA, visual disability presence, and visual disability grade. We included these visual factors as independent variables in three adjusted models that were constructed for multivariable adjusted Cox regression analyses (age and sex for model 1; age, sex, smoking habit, alcohol consumption habit, physical activity, diabetes, hypertension, and dyslipidemia for model 2; age, sex, smoking habit, alcohol consumption habit, physical activity, diabetes, hypertension, dyslipidemia, and ophthalmologic diseases for model 3). Differences between disease and non-disease groups were investigated by independent t-tests for continuous data and chi-square tests for categorical data. Statistical Analysis System software version 9.4 (SAS Inc., Cary, NC) was used for all analyses.

Results

Stroke developed in 120,975 subjects (2.03%) and AMI occurred in 79,916 subjects (1.34%). Detailed characteristics of the study subjects are shown in Table 2. The length of follow-up was 6.72 ± 1.04 years for the outcome of stroke and 6.74 ± 0.99 years for the outcome of AMI. According to the result of multivariable Cox regression models (Supplement Table 1), male sex, current smoker, hypertension, diabetes, dyslipidemia, and diabetic retinopathy increased the risk of stroke and AMI. Being an ex-smoker only increased the risk of AMI. Alcohol consumption more than 30 g/day increased the risk of stroke and decreased the risk of AMI.

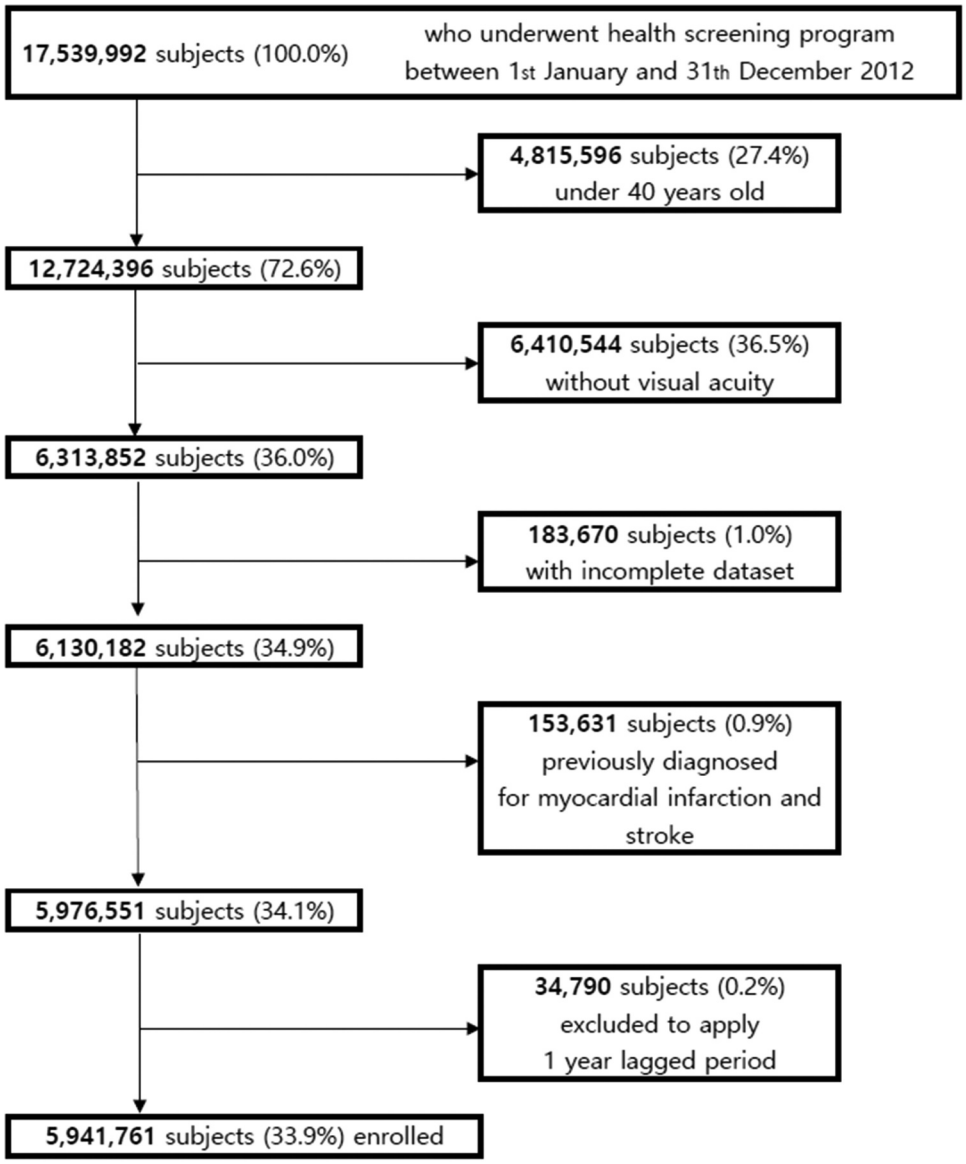

Figure 1. Flow diagram of sample selection for acute myocardial infarction and stroke cohorts.

Lower VA was associated with an increased the risk of stroke in all adjusted models. After adjustments for age, sex, and other covariates (model 3), the adjusted HRs for stroke according to VA, for which group 1 served as the reference group, were 1.151 (95% CI, 1.132–1.171) for group 2, 1.336 (95% CI, 1.302–1.371) for group 3, and 1.383 (95% CI, 1.349–1.417) for group 4. The risk of stroke development was higher for subjects with visual disability. The HR for stroke according to the presence of visual disability, for which subjects with no visual disability served as the reference group, was 1.250 (95% CI, 1.180–1.320) in model 3. In the visual disability group, subjects with higher grade disability developed stroke more frequently. Analyses of the group without visual disability were similar to those for the total population. The risk of stroke development was higher in the lower VA group. Figure 2 shows the cumulative incidence probability of stroke development according to VA and visual disability presence.

Better VA reduced the risk of AMI. The adjusted HRs for AMI development according to VA, for which group 1 served as the reference group, were 1.073 (95% CI, 1.053–1.094) in model 3 for group 2, 1.236 (95% CI, 1.196–1.276) for group 3, and 1.324 (95% CI, 1.284–1.365) for group 4. Subjects with visual disability were more vulnerable to AMI. The HRs for AMI development according to visual disability presence, for which group with no visual disability served as the reference group, were 1.150 (95% CI, 1.060–1.230) in model 2. AMI occurrence was more frequent in the higher visual disability group. Analyses of subjects without visual disability also indicate that better VA reduces the risk of

Table 2. Detailed characteristics of subjects with and without stroke or acute myocardial infarction.

	Stroke		
	Absent (N = 5,820,786)	Developed (N = 120,975)	p-value ‡
Sex (male)	2,849,202 (48.95)	65,922 (54.49)	<.0001
Age (years)	53.93 ± 10.36	64.77 ± 10.72	<.0001
Hypertension	1,881,254 (32.32)	70,757 (58.49)	<.0001
Diabetes	642,334 (11.04)	30,103 (24.88)	<.0001
Dyslipidemia	1,329,112 (22.83)	37,117 (30.68)	<.0001
Regular exercise*	2,941,831 (50.54)	48,316 (39.94)	<.0001
Smoking			<.0001
Non-smoker	3,736,890 (64.2)	74,577 (61.65)	
Ex-smoker	903,721 (15.53)	18,203 (15.05)	
Current smoker	1,180,175 (20.28)	28,195 (23.31)	
Alcohol (%)			<.0001
None	3,414,024 (58.65)	79,214 (65.48)	
Less than 30 g/day	2,053,018 (35.27)	33,959 (28.07)	
More than 30 g/day	353,744 (6.08)	7,802 (6.45)	
Income (low)†	1,510,293 (25.95)	32,673 (27.01)	<.0001
Place (urban)	2,627,052 (45.13)	46,793 (38.68)	<.0001
Body-mass index	23.94 ± 3.04	24.13 ± 3.16	<.0001
Waist circumference	80.99 ± 8.61	83.6 ± 8.47	<.0001
Fasting glucose	99.49 ± 23.98	108.07 ± 35.26	<.0001
Systolic blood pressure	123.83 ± 15.26	130.51 ± 16.7	<.0001
Diastolic blood pressure	77.01 ± 10.09	79.48 ± 10.47	<.0001
High-density lipoprotein	54.85 ± 16.54	52.7 ± 18.94	<.0001
Low-density lipoprotein	117.33 ± 34.06	117.61 ± 36.38	<.0001
Triglyceride	116.99 (116.93–117.04)	131.37 (130.98–131.75)	<.0001
	Acute myocardial infarction		
	Absent (N = 5,861,845)	**Developed (N = 79,916)**	***p*-value***
Sex (male)	2,869,403 (48.95)	45,721 (57.21)	<.0001
Age (years)	54.05 ± 10.42	62.12 ± 11.38	<.0001
Hypertension	1,910,081 (32.58)	41,930 (52.47)	<.0001
Diabetes	654,032 (11.16)	18,405 (23.03)	<.0001
Dyslipidemia	1,339,739 (22.86)	26,490 (33.15)	<.0001
Regular exercise*	2,956,279 (50.43)	33,868 (42.38)	<.0001
Smoking			<.0001
Non-smoker	3,765,563 (64.24)	45,904 (57.44)	
Ex-smoker	909,583 (15.52)	12,341 (15.44)	
Current smoker	1,186,699 (20.24)	21,671 (27.12)	
Alcohol %			<.0001
None	3,441,080 (58.7)	52,158 (65.27)	
Less than 30 g/day	2,064,051 (35.21)	22,926 (28.69)	
More than 30 g/day	356,714 (6.09)	4,832 (6.05)	
Income (low)†	1,521,236 (25.95)	21,730 (27.19)	<.0001
Place (urban)	2,640,303 (45.04)	33,542 (41.97)	<.0001
Body-mass index	23.94 ± 3.04	24.23 ± 3.2	<.0001
Waist circumference	81.01 ± 8.62	83.61 ± 8.43	<.0001
Fasting glucose	99.57 ± 24.12	106.77 ± 33.87	<.0001
Systolic blood pressure	123.9 ± 15.3	128.56 ± 16.21	<.0001
Diastolic blood pressure	77.04 ± 10.1	78.76 ± 10.29	<.0001
High-density lipoprotein	54.84 ± 16.56	52.2 ± 18.59	<.0001
Low-density lipoprotein	117.3 ± 34.06	120.2 ± 37.37	<.0001
Triglyceride	117.05 (116.99–117.1)	134.37 (133.88–134.86)	<.0001

Numerical continuous parameters were described as mean ± standard deviation, and categorical parameters were described as total number (percentage).
*Regular exercise was defined as strenuous physical activity that was performed for at least 30 min at least five times per week.
†Subjects with income less than the lowest 20th percentile were defined as low income.
‡*P*-values were obtained by independent t-tests for continuous data and chi-square tests for categorical data.

AMI development. Figure 3 outlines the cumulative incidence probability of AMI development according to VA and visual disability presence. The results of all multivariable adjusted Cox regression analyses are presented in Table 3.

We performed additional subgroup analyses for the HR of each type of adverse health event according to visual disability. Subjects were grouped by age, sex, smoking status, drinking habit, regular exercise, diabetes, hypertension, and dyslipidemia. The risk of stroke development according to visual disability presence was higher in subjects who were female (HR: 1.175 for male, 1.377 for female, $P = .0043$), aged less than 65 years (HR: 1.321 for age under 65, 1.218 for age over 65, $P = .0307$), and who reported no alcohol intake (HR: 1.313 for no alcohol intake, 1.102 for alcohol intake less than 30 g/

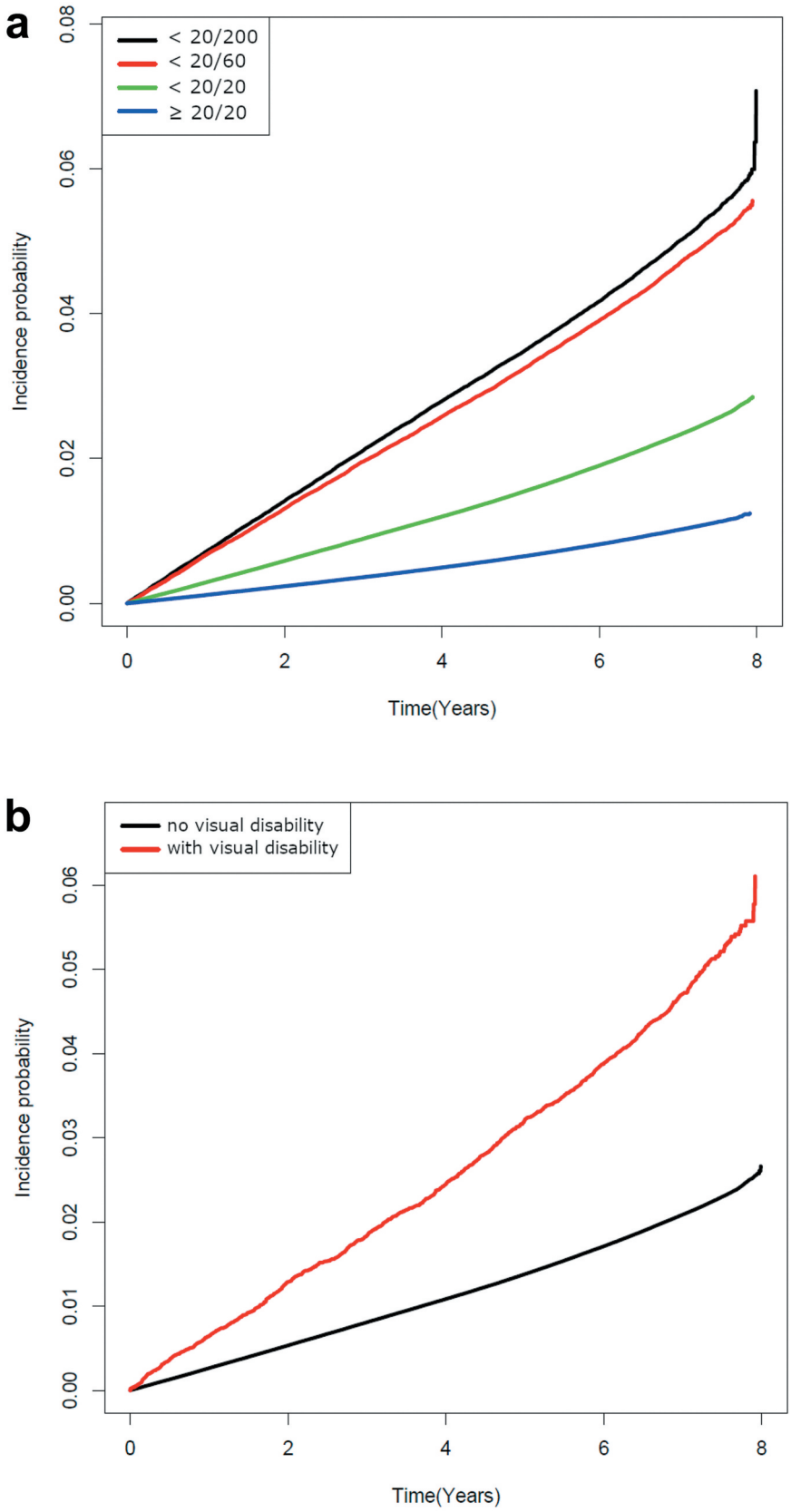

Figure 2. Cumulative incidence probability of stroke development grouped by visual acuity (VA) and visual disability presence. VA is presented using the Snellen VA system. All categories excluded inferior categories. (i.e. category [<20/20] contains individuals with VA more or equal to 20/60 and less than 20/20) Presented graphs are based on the crude regression model.

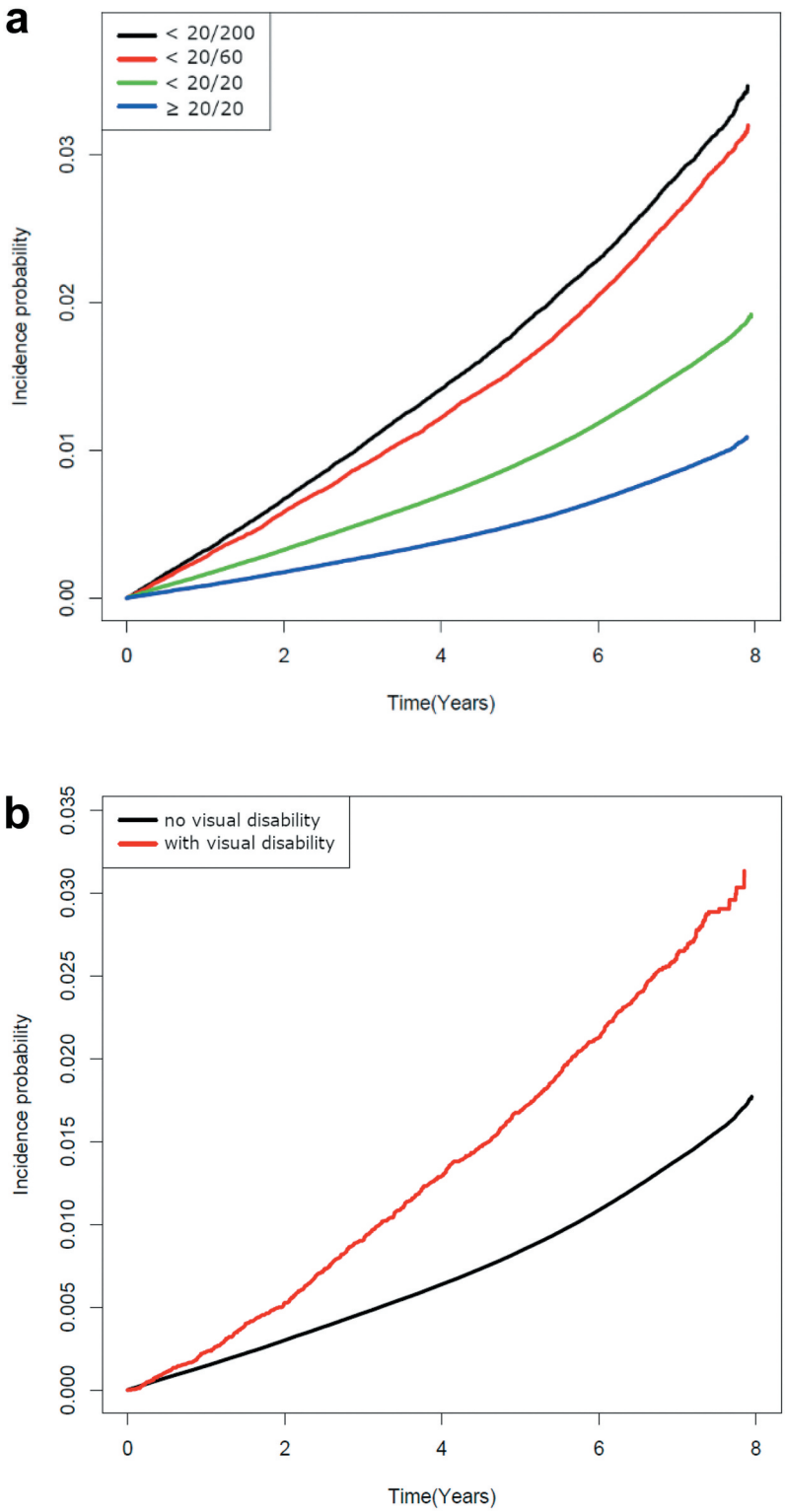

Figure 3. Cumulative incidence probability of acute myocardial infarction development grouped by visual acuity (VA) and visual disability presence. VA is presented using the Snellen VA system. All categories excluded inferior categories. (i.e. category [<20/20] contains individuals with VA more or equal to 20/60 and less than 20/20) Presented graphs are based on the crude regression model.

day, 1.178 for alcohol intake more than 30 g/day, P = .0421). AMI risk increased in subjects who were female (HR: 1.088 for males, 1.265 for females, P = .0051), aged less than 65 years (HR: 1.294 for age under 65, 1.076 for age over 65, P = .0067), non-smokers (HR: 1.23 for non-smoker, 1.02 for ex-smoker, 1.06 for current smoker, P = .0168) and those who had diabetes (HR: 1.073 for non-diabetes subjects, 1.321 for diabetes

Table 3. Cox regression analysis of stroke and myocardial infarction development according to visual acuity and visual disability.

				Hazard ratio (95% confidence interval)		
Stroke		**Total N**	**Number of stroke patients (%)**	**Model 1***	**Model 2†**	**Model 3‡**
Visual acuity						
Greater or equal to 20/20		1,935,310	19,063 (1.0)	1 (Ref.)	1 (Ref.)	1 (Ref.)
Greater or equal to 20/60, less than 20/20		3,512,495	79,237 (2.3)	1.188 (1.168,1.208)	1.151 (1.132,1.171)	1.151 (1.132,1.171)
Greater or equal to 10/100, less than 20/60		233,783	10,402 (4.4)	1.387 (1.352,1.423)	1.336 (1.302,1.371)	1.336 (1.302,1.371)
Less than 10/100		260,173	12,273 (4.7)	1.447 (1.412,1.483)	1.383 (1.349,1.418)	1.383 (1.349,1.417)
Visual disability						
No		5,912,767	119,664 (2.0)	1 (Ref.)	1 (Ref.)	1 (ref)
Yes		28,994	1,311 (4.5)	1.292 (1.224,1.364)	1.253 (1.186,1.323)	1.250 (1.180,1.320)
Visual disability & visual acuity						
No	Greater or equal to 20/20	1,934,080	19,031 (1.0)	1 (Ref.)	1 (Ref.)	1 (Ref.)
	Greater or equal to 20/60, less than 20/20	3,507,953	79,038 (2.3)	1.188 (1.168,1.208)	1.151 (1.132,1.171)	1.151 (1.132, 1.171)
	Greater or equal to 10/100, less than 20/60	232,042	10,334 (4.5)	1.388 (1.353,1.425)	1.338 (1.304,1.373)	1.338 (1.304,1.373)
	Less than 10/100	238,692	11,261 (4.7)	1.439 (1.403,1.476)	1.377 (1.343,1.413)	1.378 (1.343,1.413)
Yes	Lower (4,5,6)	23,130	959 (4.1)	1.468 (1.375,1.567)	1.338 (1.304,1.373)	1.384 (1.296,1.477)
	Higher (1,2,3)	5,864	352 (6.0)	1.861 (1.674,2.069)	1.737 (1.563,1.931)	1.734 (1.560,1.928)
Acute myocardial infarction (AMI)				**Hazard ratio (95% confidence interval)**		
		Total N	**Number of AMI patients (%)**	**Model 1***	**Model 2†**	**Model 3‡**
Visual acuity						
Greater or equal to 20/20		1,935,310	16,012 (0.8)	1 (Ref.)	1 (Ref.)	1 (Ref.)
Greater or equal to 20/60, less than 20/20		3,512,495	51,224 (1.5)	1.105 (1.084,1.126)	1.073 (1.053,1.094)	1.073 (1.053,1.094)
Greater or equal to 10/100, less than 20/60		233,783	5,742 (2.5)	1.277 (1.236,1.319)	1.236 (1.197,1.277)	1.236 (1.196,1.276)
Less than 10/100		260,173	6,938 (2.7)	1.379 (1.338,1.422)	1.325 (1.285,1.366)	1.324 (1.284,1.365)
Visual disability						
No		5,912,767	79,193 (1.3)	1 (Ref.)	1 (Ref.)	1 (Ref.)
Yes		28,994	723 (2.5)	1.184 (1.100,1.274)	1.147 (1.066,1.234)	1.150 (1.060,1.230)
Visual disability & visual acuity						
No	Greater or equal to 20/20	1,934,080	15,997 (0.8)	1 (Ref.)	1 (Ref.)	1 (Ref.)
	Greater or equal to 20/60, less than 20/20	3,507,953	51,126 (1.5)	1.105 (1.084,1.126)	1.073 (1.053,1.093)	1.073 (1.053,1.093)
	Greater or equal to 10/100, less than 20/60	232,042	5,702 (2.5)	1.277 (1.237,1.319)	1.237 (1.197,1.277)	1.236 (1.197,1.277)
	Less than 10/100	238,692	6,368 (2.7)	1.379 (1.337,1.424)	1.328 (1.287,1.37)	1.326 (1.285,1.369)
Yes	Lower (4,5,6)	23,130	546 (2.4)	1.282 (1.176,1.397)	1.215 (1.115,1.324)	1.215 (1.115,1.324)
	Higher (1,2,3)	5,864	177 (3.0)	1.523 (1.313,1.766)	1.415 (1.22,1.641)	1.411 (1.216,1.638)

Hazard ratios (95% CI) were calculated using a Cox proportional hazards model.
*Adjusted for age and sex.
†Adjusted for age, sex, smoking habit, alcohol consumption habit, physical activity, diabetes, hypertension, and dyslipidemia.
‡Adjusted for age, age, sex, smoking habit, alcohol consumption habit, physical activity, diabetes, hypertension, dyslipidemia, age-related macular degeneration, diabetic retinopathy, and glaucoma.

subjects, $P = .0270$). Other subgroups showed no differences. The results of subgroup analysis are presented in Figure 4.

Declaration

This submission has not been published anywhere previously and that it is not simultaneously being considered for any other publication.

Discussion

We conducted a retrospective observational nationwide cohort study in Korea to evaluate the effects of VA on the development of AMI and cerebral stroke. We found that lower VA was independently associated with increased risk of CVD, including AMI and stroke.

The risks of AMI and stroke were higher in subjects who were male and were current smokers. Subjects with diabetes, dyslipidemia, less physical activity, higher WC, higher BMI, higher SBP/DBP, lower HDL, and higher LDL/TG were also more vulnerable to both diseases. These are previously known and validated risk factors for CVD.[18,22–26] Although the supposed associations of each cholesterol subfraction with total stroke have been inconsistent,[18] the findings of several studies were similar to our results.[27–29] Concordance with previous reports constitutes indirect evidence that demonstrates the accuracy of the disease definitions used in this study, which is an important issue in registry research.

The results of this study indicate that lower VA may be an independent risk factor for AMI and stroke development. In a previous report using 1999–2008 National Health and Nutrition Examination Survey data from the US,[14] visually impaired adults had increased odds of being at high risk for a future atherosclerotic cardiovascular disease. Future CVD risk with VI was calculated using the Pooled Cohort Equations developed by the American College of Cardiology/American Heart Association (ACC/AHA).[30] However, the Pooled Cohort Equation includes cholesterol levels, hypertension, diabetes, and smoking as independent variables, so the interpretation of results is limited to the conclusion that low VA is related to increased proportions of individuals with CVD risk factors. After adjusting for all values included in the equation except population origin, since the Korean population is extremely homogeneous in terms of ethnic or population diversity, low VA subjects still showed a higher risk of AMI and stroke in this study.

Physical inactivity is a major risk factor for CVD.[31] Several studies have reported that increased PA decreases CVD risk.[32–34] The AHA and the 2008 US federal guidelines for PA recommend that adults get at least 150 minutes of moderate-intensity or 75 minutes of vigorous-intensity aerobic activity (or an equivalent combination) per week and perform muscle-strengthening activities at least 2 days per week.[35] The amount of PA prescribed in the guidelines is comparable to the definition of regular exercise (strenuous activity more than 30 minutes, 5 times per week) that we used as a covariate in our analysis. But the new 2018 US federal guidelines for individuals not meeting the recommendation for 150 minutes of moderate PA per week state that even small increases in moderate-intensity PA or replacing sedentary time with light-intensity PA could provide health benefits.[36] As adults with poorer vision tend to engage in more sedentary activities,[37] we hypothesized that individuals in this study who were more sedentary and did not engage in regular exercise were more likely to be in the low VA group than the good VA group. However, in a previous meta-analysis, the relationship between sedentary time and risk of CVD became stronger only at very high levels of sedentism (>10 hours/day).[38] This result suggests that low PA is an important risk factor but cannot entirely explain the effect of VA on CVD risk.

In subgroup analyses, female sex, age less than 65 years, being a non-smoker, and having diabetes increased the effect of VA on AMI development, while stroke risk was increased more by VA for females, those aged less than 65 years, and non-drinkers. This suggests that male sex, old age, smoking, and alcohol consumption are strong risk factors for AMI and stroke, and therefore the effect of VA was relatively decreased.

Otherwise, the increased risk of AMI in visual disability subjects was higher in diabetic patients than non-diabetes, although diabetes is also a strong risk factor. Diabetes has complications that deteriorate VA including diabetic retinopathy (DR). DR is known to be associated with an increased risk of CVD.[39–41] In a previous meta-analysis, patients with type 2 diabetes and diabetic macular edema or proliferative DR, which are both vision-threatening complications, had an increased risk of incident CVD.[42] Diabetes was previously found to be most severe in diabetic subjects with VI caused by retinopathy,[13] with CVD risk increased along with VI. Accordingly, the vulnerability of diabetes patients for an increased risk of AMI due to visual disability presented in this study seems to be associated with diabetic retinopathy. Diabetic retinopathy might play the role of mediator between visual disability and AMI.

The exact mechanism underlying the effect of VA on CVD development is not known. Although a previous

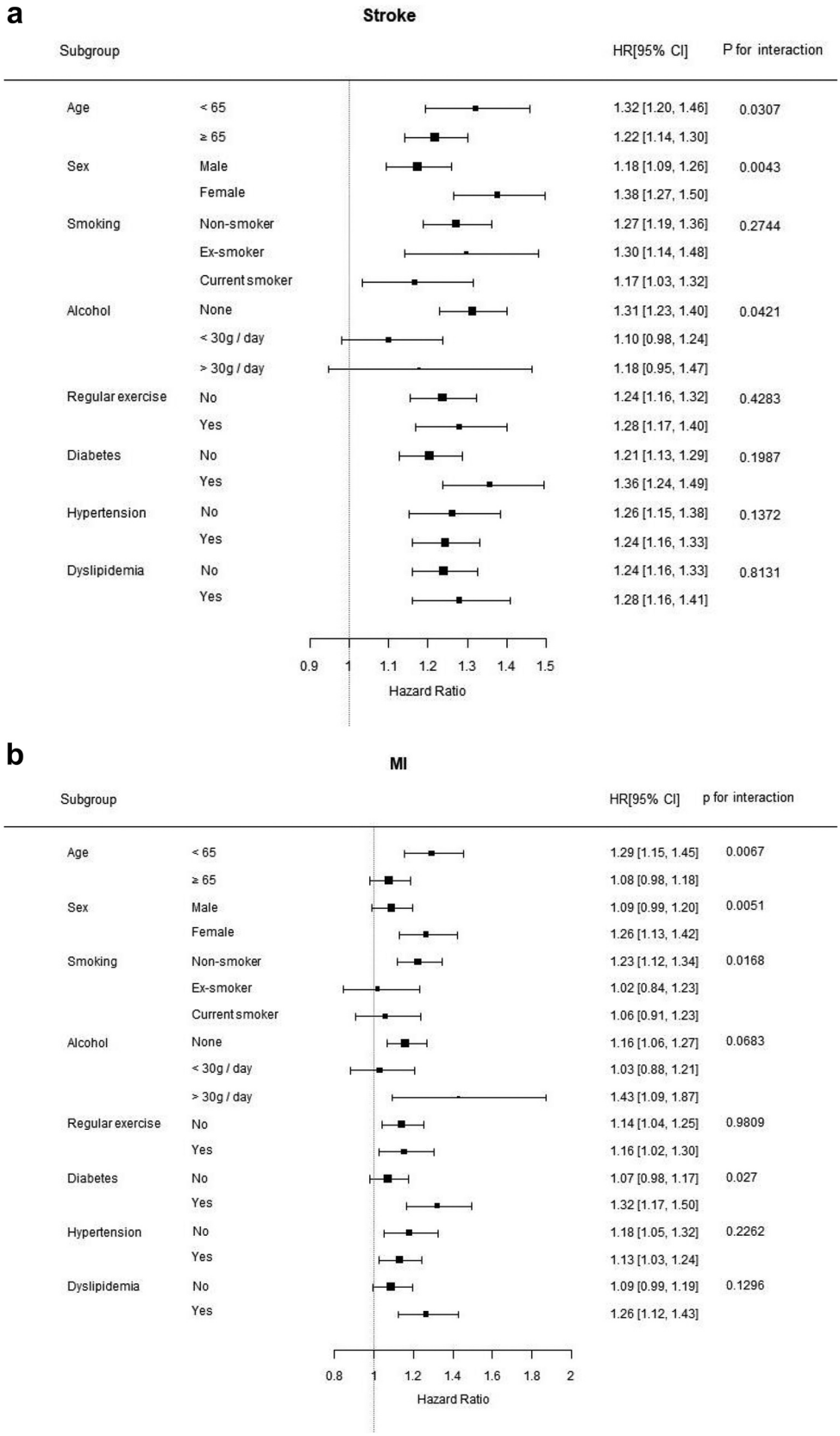

Figure 4. Forest plots of subgroup analysis for stroke and acute myocardial infarction. Hazard ratios and 95% confidential interval presented are calculated with no visual disability group as reference for each category.

report[43] noted that the effects of VI on general health and disability suggest that VI should be considered a key frailty indicator, these results were derived statistically and did not explain how VI influences general health. It can be inferred that the mechanisms are a combination of factors, including physical inactivity. Our result could not reveal whether VI itself was an independent risk factor for CVD or if it acts as a hurdle for daily health care. But the implication that vision care might be effective to control CVD does not differ either way.

This study has several limitations. First, the etiology of low VA could not be determined using information available in the database used for the analyses. VI can be caused by various etiologies such as uncorrected refractive error and cataracts. Any of these conditions might be directly related to our outcome and act as undetected confounders. We tried to overcome this limitation by adjusting for the main causes of visual impairment including several ophthalmologic diseases (AMD, glaucoma, and diabetic retinopathy). Second, 50.4% of subjects were excluded because of lack of visual acuity data. Visual acuity measurement is mandatory in the health screening exam by NHIS, however, the loss of data might have happened during database construction. We had tried to analyze the demographics between subjects with and without visual acuity data to demonstrate the representability of the included population. At this point, further analysis was not possible due to limited access to the database because of COVID-19. However, our previous study that used the same database[44] showed that the demographics between subjects with and without visual acuity were not different, therefore, we can postulate that this study's result would be similar to that study. Third, to our best knowledge, no prospective clinical trials or laboratory experiments support the results of our study. We hope that such studies may be conducted in the future. Finally, our sample comprised only South Korean nationals, so regional or population effects could not be included in the analysis. Therefore, our findings may be generalized to other populations only with careful consideration.

Despite these limitations, there are important strengths in this study, including its large sample size (almost 6 million) and a high representation of the total population due to the mandatory national insurance system in South Korea. While previous studies defined exposure groups only with VI and without VI, the availability of VA data from the Korean health-screening program database enabled us to analyze the dose-dependent effects of VA on CVD.

In conclusion, individuals with low VA have increased risks of AMI and stroke development. The medical costs of CVD are projected to almost double over the next 10 years.[45,46] Therefore, attention to associated risk factors is important in terms of general health. The results of this study suggest that low VA is an independent risk factor for CVD that must be considered when preparing health policies.

Abbreviations

AMI, acute myocardial infarction; BP, blood pressure; BMI, body mass index; CI, confidential interval; CVD, cardiovascular disease; NHID, National Health Information Database; NHIS, National Health Insurance Service; DBP, diastolic blood pressure; HDL, high-density lipoprotein; HR, hazard ratios; CI, confidence interval; ICD, International Classification of Diseases; KCD, Korean Classification of Diseases; LDL, low-density lipoprotein; PA, physical activity; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride; VI, visual impairment; WC, waist circumference.

Authors' contributions

Conception and design: Dong Hui Lim, Kyung-Shun Na
Data acquisition: Dong Hui Lim, Kyung-Shun Na
Data analysis and interpretation: Kyungdo Han
Drafting the manuscript: Gyule Han, Jisang Han
Critique and revision of manuscript: Jisang Han, Dong Hui Lim, Tae-Young Chung
Final approval of manuscript to be published: Dong Hui Lim, Kyung-Shun Na.

Conflicts of interest

None of the following authors have any proprietary interests or conflicts of interest related to this submission.

Data availability

The data used in this study are not available to other researchers because it is secured national data which only researchers who have permission from the Korean government can assess.

* Gyule Han and Jisang Han contributed equally to the article as the first authors.

† Dong Hui Lim and Kyung-Shun Na are co-corresponding authors of this study.

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