Traffic-related air pollutants increase the risk for age-related macular degeneration

Kuang-Hsi Chang,[1,2,3] Po-Yuan Hsu,[4] Chun-Ju Lin,[5,6] Cheng-Li Lin,[7] Suh-Hang Hank Juo,[3,4,8,9,10] Chung-Ling Liang[10,11,12,13]

► Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/jim-2019-001007).

For numbered affiliations see end of article.

Correspondence to
Professor Suh-Hang Hank Juo; hjuo@mail.cmu.edu.tw and Dr. Chung-Ling Liang; ling0228@gmail.com

Accepted 22 April 2019
Published Online First 19 August 2019

ABSTRACT

The aim of this study was to investigate whether ambient nitrogen dioxide (NO_2) and carbon monoxide (CO) increase the risk for age-related macular degeneration (AMD). This is a longitudinal population-based study using the data on Taiwan National Health Insurance Program between year 2000 and 2010. From the nationwide dataset, we enrolled subjects aged 50 or older and the annually total NO_2 and CO exposure was calculated from 1998 to 2010 for each subject. The Cox proportional hazard regression was used to estimate the HRs with adjustment for other variables. A total of 39,819 AMD-free residents were enrolled, and 1442 participants developed AMD during the 11-year follow-up. Compared with the lowest exposure quartile, the highest quartile of each air pollutant was associated with an increased risk for AMD. The adjusted HR was 1.91 (95% CI 1.64 to 2.23, p<0.001) for the highest NO_2 quartile, and was 1.84 (95% CI 1.5 to 2.15, p<0.001) for the highest CO quartile. In this study, chronic exposure to the highest quartile of ambient NO_2 or CO significantly increases the risk for AMD.

Significance of this study

What is already known about this subject?

- Chronic exposure to air pollution is associated with a high risk for several diseases including respiratory and cardiovascular diseases.
- Previous studies have shown that air pollution increases a risk for conjunctivitis.
- Age-related macular degeneration (AMD) is a late-onset disease characterized by the formation of lipid-rich extracellular deposits, localized inflammation, and ultimately neurodegeneration in the central part of the retina.
- AMD can be caused by interactions between genetic and environmental risk factors.

What are the new findings?

- The adjusted HR was 1.91 (95% CI 1.64 to 2.23, p<0.001) in the highest nitrogen dioxide (NO_2) exposure group compared with lowest NO_2 exposure group.
- The adjusted HR was 1.84 (95% CI 1.57 to 2.15, p<0.001) in the highest carbon monoxide (CO) exposure group compared with lowest CO exposure group.
- The trend tests for increased risk of AMD were significant in both NO_2 and CO exposure.

How might these results change the focus of research or clinical practice?

- This study indicates the air pollution exposure as a risk factor for AMD.
- Further animal studies are necessary to evaluate the association between air pollutants and macular degeneration.

INTRODUCTION

With the rapid industrialization and urbanization in many countries, the air quality problem caused by heavy traffic has become an important issue for public health. Chronic exposure to air pollution is associated with a high risk for several diseases including respiratory and cardiovascular diseases.[1–4] Although the effect of air pollution on eye disorders has been less studied, previous studies have shown that air pollution increases a risk for conjunctivitis and dry eye.[5 6] Because the cornea and conjunctiva are directly exposed to the outdoor air, it is reasonable to conceive that the outer segment of eyes is more susceptible to air pollution. However, recent studies have indicated that air pollution also induces systemic diseases including dementia.[7–9] Therefore, the inner segment of the eye may be also affected by air pollution.

Age-related macular degeneration (AMD) is a late-onset disease characterized by the formation of lipid-rich extracellular deposits, localized inflammation, and ultimately neurodegeneration in the central part of the retina (termed the macula). AMD is one of the major causes of irreversible visual impairment among the elderly in the developed world.[10 11] AMD has increasingly become a global issue and the Asian population over the age of 50 years has high incidence of AMD.[12] As the aging population increases, the prevalence of AMD is expected to increase proportionately. Several risk factors have been proposed for AMD and it is likely that AMD can be caused by interactions between genetic

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To cite: Chang K-H, Hsu P-Y, Lin C-J, *et al*. *J Investig Med* 2019;**67**:1076–1081.

J Investig Med: first published as 10.1136/jim-2019-001007 on 19 August 2019. Downloaded from file:/ on April 27, 2024 by guest. Protected by copyright.

and environmental risk factors.[13] Studies also reveal a link between cardiovascular disease and AMD.[14 15]

Given that air pollution can increase a risk for cardiovascular diseases and neurological diseases, it is biologically plausible to hypothesize that air pollution may also influence AMD development. We specifically focused on two major traffic pollutants (nitrogen dioxide (NO_2) and carbon monoxide (CO)). To test our hypothesis, we analyzed data on a longitudinal cohort study using the Taiwan National Health Insurance data to assess the contribution of traffic-related air pollution to AMD.

METHODS AND MATERIALS

The present study used a nationwide longitudinal cohort to investigate the risk of AMD after chronic exposure to ambient NO_2 and CO.

Data source

The present study used two databases, the Longitudinal Health Insurance Database (LHID) and Taiwan Air Quality Monitoring Database (TAQMD). LHID contained 1 million insurants randomly selected from the original Registry for beneficiaries joining in the Taiwan National Health Insurance Program. This insurance program was set up by the Taiwan Bureau of National Health Insurance since March 1995. At the end of 2009, this insurance covered over 99% Taiwan residents. LHID included all medical records from the start of 1996 to the end of 2010. The identification of insurant was re-coded before the data were released to researchers because of the Personal Information Protection Act. To identify the disease in LHID was according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM).

TAQMD was established by the Taiwan Environmental Protection Administration Executive Yuan in 1998 to record daily concentrations of CO and NO_2 from 74 ambient air quality-monitoring stations over Taiwan Island. However, the $PM_{2.5}$ data were not systematically collected in all 74 stations until 2012. Therefore, we did not analyze $PM_{2.5}$ effects on AMD in the present study. To analyze the effect of air pollution on health, we needed to link the insurant living area to the air quality-monitoring station. Because all traceable codes in the health insurance data were removed, there was no direct way to know the subject's living area. Therefore, we used the follow strategy to predict subject's living area: the living area for an insured person was defined based on his/her sought treatment for acute upper respiratory tract infection (AURTI) (ICD-9-CM code 460).

Study subject, exposure measurement, and comorbidity

We selected people living in areas where there were air quality-monitoring stations. Since AMD is specifically for the aged population, we only analyzed the study subjects aged 50 years or older upon enrollment. The definition of AMD used in the present study was based on the ICD-9 code (362.51 or 362.52) plus at least one of the following four procedures: color photo picture for the fundus (procedure code 23502), optical coherence tomography (OCT) exam (procedure code 23506), fluorescein angiography (procedure code 23505) or intravitreal injection (procedure code 86201). Although the dataset included medical records from the start of 1996, the data in the first few years were incomplete. Accordingly, we only analyzed the longitudinal data between the start of 2000 and the end of 2010. The patients with AMD in the present study had newly diagnosed AMD during this 11-year follow-up. People without AMD development were followed to the date of withdrawal from the program or the end of 2010.

Due to the seasonal variation of air pollution, we first calculated the average daily exposure (total exposure/days of exposure). Then we multiplied the average daily exposure with 365.25 to get the totally annual exposure since 1998 to the end of the observation year. Air pollutant concentrations were grouped into four levels based on quartile: NO_2 concentration (Q1: <6563.2, Q2: 6563.2–8238.2, Q3: 8238.3–9825.5, and Q4: >9825.5 ppb), CO concentration (Q1: <195.7, Q2: 195.7–241.7, Q3: 241.8–297.1, and Q4: >297.1 ppm). Comorbidities analyzed in the present study included diabetes mellitus (DM, ICD-9-CM code 250), ischemic heart disease (IHD, ICD-9-CM codes 410–414), hypertension (ICD-9-CM codes 401–405), chronic obstructive pulmonary disease (COPD, ICD-9-CM codes 490–496), and hyperlipidemia (ICD-9-CM code 272).

Statistical analysis

The χ^2 test was used to test the difference of distribution in sex, insurance fee (<14,400, 14,400–18,300, 18,301–21,000, and >21,000 New Taiwan Dollar), urbanization, and comorbidity among air pollutant quartiles. One-way analysis of variance test was used to test the mean age in each air pollutant quartile. The incidence of AMD (per 10,000 person-years) was counted in different air pollutant quartiles. The Cox proportional hazard regression was used to estimate the HRs and 95% CIs for AMD in Q2–Q4 levels of air pollution compared with AMD in the lowest one (Q1). The multivariable model was used to adjust for age, sex, insurance fee, urbanization, alcoholism, IHD, COPD, DM, hyperlipidemia, and hypertension. Smoking is a risk factor for AMD.[16] Since the dataset did not provide information for the smoking status, alcoholism and COPD were used as surrogates for smoking in the multivariable analysis, which were used in our previous studies.[7 17] The Kaplan-Meier analysis was used to plot the AMD-free rate curve and log-rank test was used to test the difference among air pollution quartiles. All analyses were performed using SAS V.9.3 and the SPSS V.15.1). Data were presented as mean ±SD. All statistical tests were considered statistically significant when two-tailed p values were <0.05.

RESULTS

Demographic data

The present study included the follow-up data on 39,819 residents who were aged 50 or older and did not have AMD upon enrollment (table 1). After the 11-year follow-up, 1442 participants developed AMD. The mean age upon enrollment was 62.33±8.87 years, and men accounted for 47.0% of all participants. The mean follow-up period was 10.77±2.63 years for all of the participants. Most of them lived in either highly (30.1%) or moderately (32.5%) urbanized areas.

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Table 1 Baseline demographics in participants upon enrollment

n=39,819		Mean or n	SD or %
Age	Mean, SD	62.33	8.87
Follow years	Mean, SD	10.77	2.63
Men		18,725	47.0
Insurance fee	Lowest	10,525	26.4
	Second	7101	17.8
	Third	13,000	32.6
	Highest	9193	23.1
Urbanization	Highly urbanized	11,977	30.1
	Moderately urbanized	12,944	32.5
	Boomtown	6168	15.1
	Others	8730	21.9
Alcoholism		2052	5.2
IHD		16,256	40.8
COPD		11,932	30.0
DM		9594	24.1
Hyperlipidemia		17,393	43.7
Hypertension		27,668	69.2

Insurance fee is based on Taiwan dollar.
COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; IHD, ischemic heart disease.

The demographic information separated by the four levels of ambient NO_2 exposure is shown in table 2. The residents in the lowest NO_2 exposure areas were oldest but had the lowest incidence of AMD (2.8%), while the residents in the highest NO_2 exposure areas had the highest incidence AMD (5.4%, table 2).

The demographic data according to the CO exposure levels showed a similar trend (table 3). The highest rate (5.8%) of newly diagnosed AMD was among the people living in the area with the highest CO exposure. The mean of annually total pollution for each quantile and the incidence of AMD over the study years are shown in figure 1.

Multivariable analysis for AMD risk factors

To minimize the confounding effects, we adjusted for age, sex, social status (insurance fee and urbanization), and comorbidities in the multivariable analysis. Compared with the Q1 NO_2 exposure, the highest exposure (Q4) increased the AMD incidence from 25.60 to 51.52 per 10,000 person-years (table 4). Similarly, the Q4 CO level increased the incidence from 28.89 to 56.24 per 10,000 person-years. After adjusting for covariates, the adjusted HR was 1.91 (95% CI 1.64 to 2.23, p<0.001) in the Q4 NO_2 exposure compared with the Q1 group (table 4). The adjusted HRs were not significant for the Q2 or Q3 NO_2 exposure groups: 1.15 (95% CI 0.98 to 1.35, p=0.099) and 1.09 (95% CI 0.93 to 1.29, p=0.300), respectively (see online supplementary table).

Regarding the CO levels, the adjusted HR was 1.84 (95% CI 1.57 to 2.15, p<0.001) in Q4 compared with Q1 (table 4). For the Q2 and Q3 exposure groups, the adjusted HRs were 0.74 (95% CI 0.63 to 0.88, p=0.001) and 1.00 (95% CI 0.85 to 1.17, p=0.999), respectively. The trend tests showed the significant results for both NO_2 and CO (p<0.001).

Furthermore, we pooled Q1, Q2, and Q3 as a single reference group to evaluate the risk of AMD in Q4. The unadjusted HRs (ie, incidence rate ratio) in Q4 compared with the reference group in NO_2 and CO were 1.83 and 2.07, and the adjusted HRs of AMD were 1.77 (95% CI 1.58 to 1.98) and 2.01 (95% CI 1.79 to 2.25), respectively.

Figure 2 and figure 3 show the Kaplan–Meier plots for the AMD-free rate according to pollutant levels. During the follow-up of 12 years, the AMD-free rate in highest level of pollutants decreased faster than Q1, Q2 and Q3 for both NO_2 and CO exposure.

DISCUSSION

This is the first report using the longitudinal human data to indicate that NO_2 and CO possess potential detrimental

Table 2 Baseline characteristics according to quartiles of nitrogen dioxide levels

		Lowest (Q1) (n=10,214)		Second (Q2) (n=9682)		Third (Q3) (n=10,517)		Highest (Q4) (n=9378)		P value
Age	Mean, SD	62.70	8.64	62.56	8.92	61.97	8.84	62.09	9.06	
Men		4802	47.0%	4639	47.9%	4863	46.2%	4406	47.0%	0.128
Insurance fee	Lowest	2175	21.3%	2507	25.9%	3064	29.1%	2769	29.5%	<0.001
	Second	1439	14.1%	1625	16.8%	2089	19.9%	1943	20.7%	
	Third	4622	45.3%	3340	34.5%	2740	26.1%	2288	24.4%	
	Highest	1978	19.4%	2210	22.8%	2624	25.0%	2378	25.4%	
Urbanization	Highly	1762	17.3%	1994	20.6%	3419	32.5%	4794	51.1%	<0.001
	Moderately	2856	28.0%	3702	38.2%	3965	37.7%	2419	25.8%	
	Boomtown	1270	12.4%	1292	13.3%	2115	20.1%	1484	15.8%	
	Others	4326	42.4%	2694	27.8%	1018	9.7%	681	7.3%	
AMD*		287	2.8%	314	3.2%	332	3.2%	506	5.4%	<0.001
Alcoholism		583	5.7%	466	4.8%	576	5.5%	425	4.5%	<0.001
IHD		4350	42.6%	4048	41.8%	4136	39.3%	3712	39.6%	<0.001
COPD		3173	31.1%	3059	31.6%	3097	29.4%	2593	27.6%	<0.001
DM		2511	24.6%	2300	23.8%	2492	23.7%	2284	24.4%	0.360
Hyperlipidemia		4428	43.4%	4057	41.9%	4608	43.8%	4297	45.8%	<0.001
Hypertension		7240	70.9%	6764	69.9%	7173	68.2%	6471	69.0%	<0.001

*Indicating newly diagnosed AMD during follow-up rather than baseline patients with AMD.
AMD, age-related macular degeneration; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; IHD, ischemic heart disease.

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Table 3 Baseline characteristics according to quartiles of CO levels

CO		Lowest (Q1) (n=9475)		Second (Q2) (n=9867)		Third (Q3) (n=11 429)		Highest (Q4) (n=9005)		P value
Age	Mean, SD	62.93	8.68	62.10	8.69	61.96	8.89	62.42	9.19	
Men		4567	48.2%	4502	45.6%	5416	47.4%	4216	46.8%	0.003
Insurance fee	Lowest	1909	20.1%	2455	24.9%	3422	29.9%	2724	30.2%	<0.001
	Second	1276	13.5%	1724	17.5%	2211	19.3%	1883	20.9%	
	Third	4511	47.6%	3345	33.9%	2899	25.4%	2230	24.8%	
	Highest	1779	18.8%	2343	23.7%	2897	25.3%	2168	24.1%	
Urbanization	Highly	1059	11.2%	2380	24.1%	3723	32.6%	4806	53.4%	<0.001
	Moderately	2786	29.4%	3976	40.3%	3823	33.4%	2354	26.1%	
	Boomtown	1277	13.5%	1417	14.4%	2297	20.1%	1168	13.0%	
	Others	4353	45.9%	2094	21.2%	1586	13.9%	677	7.5%	
AMD*		297	3.1%	244	2.5%	373	3.3%	521	5.8%	<0.001
Alcoholism		519	5.5%	527	5.3%	580	5.1%	423	4.7%	0.081
IHD		4068	42.9%	4057	41.1%	4469	39.1%	3644	40.5%	<0.001
COPD		3063	32.3%	3033	30.7%	3266	28.6%	2556	28.4%	<0.001
DM		2335	24.6%	2260	22.9%	2763	24.2%	2226	24.7%	0.011
Hyperlipidemia		4017	42.4%	4238	43.0%	5040	44.1%	4093	45.5%	<0.001
Hypertension		6720	70.9%	6840	69.3%	7847	68.7%	6232	69.2%	0.004

*Indicating newly diagnosed AMD during follow-up rather than baseline patients with AMD.
AMD, age-related macular degeneration; CO, carbon monoxide; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; IHD, ischemic heart disease.

effects on AMD development. In this large population-based study, we found that long-term exposure to the highest quartile of NO_2 significantly increased the risk for AMD by almost twofold even after adjusting for potential confounding factors. Similarly, exposure to the highest quartile of CO also increased the risk for AMD by 84%. NO_2 is one component of reactive nitrogen species (RNS).

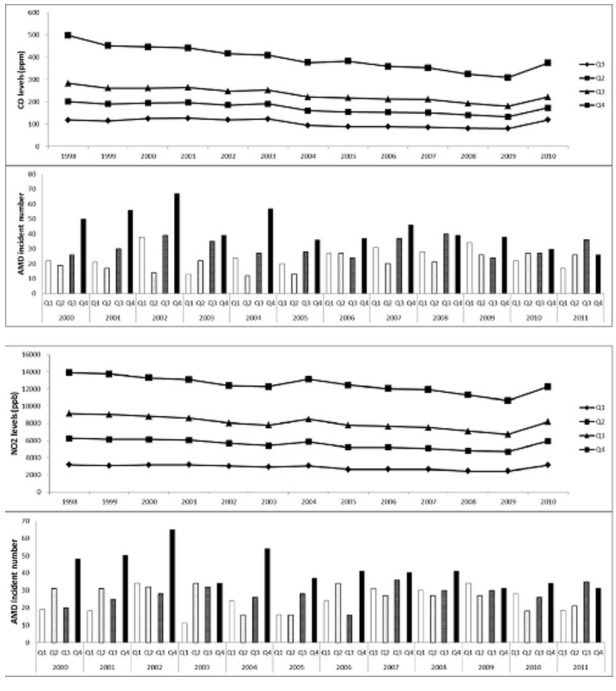

Figure 1 The mean of annually total exposure of air pollutants in each quartile and AMD incidence across study years. AMD, age-related macular degeneration; CO, carbon monoxide; NO_2, nitrogen dioxide.

RNS can act together with reactive oxygen species (ROS) to damage cells. CO has long been known to be toxic for health. However, CO effects on eye diseases have been almost ignored in epidemiological studies.[18] The present study implied the possible harmful consequence to the eyes after exposure to CO and NO_2.

We previously reported that CO and NO_2 were associated with dementia based on the same datasets. Compared with lowest exposure group, the adjusted HR for dementia was 1.5 for the highest quartile of NO_2 exposure, and was 1.61 for the highest quartile of CO exposure. Based on the HRs, our data indicated that these two pollutants have stronger detrimental effects on AMD than dementia. Similar to dementia, AMD is a neurodegenerative disease which is primarily affected in the central region of the retina (ie, macula). The onset of AMD has been linked to several risk factors including chronic oxidative stress and inflammation. The present study further suggests RNS might be a novel factor contributing to AMD development.

In tables 2 and 3, the residents exposed to highest level of pollutants (Q4) had lower prevalence of IHD and COPD than those in Q1. This result may be explained as follows: the residents in Q4 had a higher income than those in Q1 (per cent of highest insurance fees 25.4% in Q4 vs 19.4% in Q1). In addition, the residents in Q4 more likely lived in high urbanization areas. Accordingly to a published report, a higher prevalence of smokers was among the low income Taiwanese.[19] Therefore, lower COPD and IHD rate in Q4 is probably due to a lower smoking rate.

NO_2 is a marker of traffic-related air pollution. After inhalation, NO_2 slowly hydrolyzes to nitrous and nitric acid which causes inflammation resulting from lipid peroxidation and oxidative stress. Due to the inhalation route, NO_2 studies have been mainly focused on the respiratory tract. However, recent studies have linked NO_2 pollution to the cardiovascular and neurological systems.[20] Several studies

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Table 4 Comparisons of AMD incidences and HRs among four levels of air pollutants

	n of AMD	Person- years	IR	IRR	Adj. HR	95% CI		P value	P value for trend
NO_2									
Lowest: Q1	287	112,124	25.60	1.00	1.00				<0.001
Second: Q2	314	104,059	30.18	1.18	1.15	0.98	1.35	0.099	
Third: Q3	332	114,431	29.01	1.13	1.09	0.93	1.29	0.300	
Highest: Q4	506	98,214	51.52	2.01	1.91	1.64	2.23	<0.001	
Q1–Q3	933	330,614	27.19	1.00	1.00				
Q4	506	98,214	51.52	1.83	1.77	1.58	1.98	<0.001	
CO									
Lowest: Q1	297	102,796	28.89	1.00	1.00				<0.001
Second: Q2	244	109,768	22.23	0.77	0.74	0.63	0.88	0.001	
Third: Q3	373	123,586	30.18	1.04	1.00	0.85	1.17	0.999	
Highest: Q4	521	92,634	56.24	1.95	1.84	1.57	2.15	<0.001	
Q1–Q3	914	336,150	28.22	1.00	1.00				
Q4	521	92,634	56.24	2.07	2.01	1.79	2.25	<0.001	

Adj. HR, adjusted HR of a multivariate analysis, after adjustment for age, sex, insurance fee, urbanization, alcoholism, ischemic heart disease, chronic obstructive pulmonary disease , diabetes mellitus, hyperlipidemia, and hypertension; AMD, age-related macular degeneration; CO, carbon monoxide; IR, incidence rate (per 10,000 person-years); IRR, incidence rate ratio; n of AMD, numbers of newly diagnosed patients with AMD; NO_2, nitrogen dioxide.

have reported that high NO_2 is associated with various brain diseases including low cognitive function and a lower functional integration in children, Parkinson disease, stroke, and dementia.[7 21–24] Notably, the retina is also a part of central nervous system which is biologically reasonable to be vulnerable to NO_2 intoxication.

To our knowledge, air pollution has not been reported to be a risk factor for AMD. Our study first ever used a large longitudinal cohort to demonstrate significant association between AMD and high levels of ambient NO_2 and CO. However, certain limitations exist in the present study: (1) the dataset does not contain information for smoking, genetic variants, and inflammatory status which is important risk factors for AMD, (2) the assignment for the residential area was based on the locations of the clinics and hospitals where a participant sought for the treatment of acute upper respiratory infections (AURI). This approach could have underestimated the pollutant risk, because a participant exposed to the lowest level of pollutant may not have any medical record about AURI. If so, we would not be able to include such a participant to the baseline data, which resulted in an increased AMD incidence rate in the lowest exposure group. However, the overall findings are intriguing and warranted for further exploration.

CONCLUSION

In conclusion, we linked the nation health database and air quality database to report NO_2 and CO as risk factors for AMD. Our results indicate the highest quartile of each pollutant could increase the risk of AMD by almost twofold, while the moderate exposure did not contribute to AMD development.

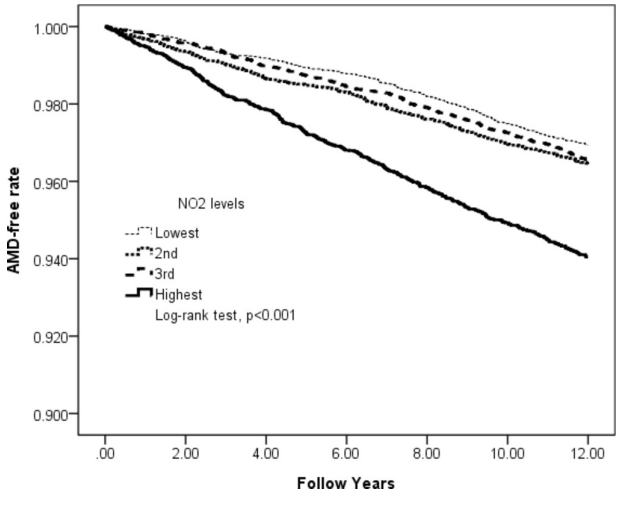

Figure 2 The Kaplan-Meier plot shows the AMD-free rates among quartiles of NO_2 exposure. AMD, age-related macular degeneration; NO_2, nitrogen dioxide.

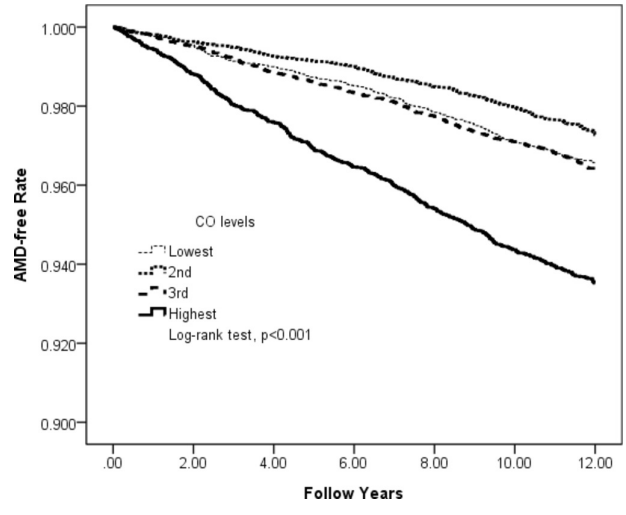

Figure 3 The Kaplan-Meier plot shows the AMD-free rates among quartiles of CO exposure. AMD, age-related macular degeneration; CO, carbon monoxide.

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Author affiliations
[1]Department of Medical Research, Tungs' Taichung Metroharbor Hospital, Taichung, Taiwan
[2]General Education Center, Jen-Teh Junior College of Medicine, Nursing and Management, Miaoli, Taiwan
[3]Graduate Institute of Biomedical Sciences, China Medical University, Taichung, Taiwan
[4]Department of Medical Research, China Medical University Hospital, Taichung, Taiwan
[5]Department of Ophthalmology, China Medical University Hospital, Taichung City, Taiwan
[6]School of Medicine, College of Medicine, China Medical University, Taichung, Taiwan
[7]Management Office for Health Data, China Medical University Hospital, Taichung, Taiwan
[8]Institute of New Drug Development, China Medical University, Taichung, Taiwan
[9]Drug Development Center, China Medical University, Taichung, Taiwan
[10]Center for Myopia and Eye Disease, China Medical University Hospital, Taichung, Taiwan
[11]Department of Ophthalmology, Asia University Hospital, Taichung, Taiwan
[12]Department of Optometry, College of Medical and Health Science, Asia University, Taichung, Taiwan
[13]Bright Eyes Clinic, Kaohsiung, Taiwan

Contributors Conceptualization: K-HC, P-YH, S-HHJ, and C-LL; methodology: K-HC, C-JL, S-HHJ, and C-LL; formal analysis: K-HC and C-LL; investigation: all authors; writing (original draft preparation): K-HC; writing (review and editing): S-HHJ and C-LL; visualization: all authors; supervision: S-HHJ and C-LL; project administration: S-HHJ and C-LL.

Funding This study was supported by the grants from the Asia University-CMU Hospital intramural grant (ASIA-106-CMUH-18), Tungs' Taichung Metroharbor Hospital (TTMHH-108R0029), Taiwan Ministry of Health and Welfare Clinical Trial Center (MOHW108-TDU-B-212-133004), Taiwan Ministry of Science and Technology (MOST 107-2321-B-039-004 and MOST 106-3114-8-039-002), the "Drug Development Center, China Medical University" from The Featured Areas Research Center Program within the framework of the Higher Education Sprout Project by the Ministry of Education in Taiwan.

Competing interests None declared.

Patient consent for publication Not required.

Ethics approval The study was approved by the Ethics Review Board of China Medical University and Hospital, Taiwan (CMUH-104-REC2-115).

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement Data are available from the NHIRD published by Taiwan National Health Insurance Bureau. Due to the 'Personal Information Protection Act', data cannot be made publicly available (http://nhird.nhri.org.tw/en/index.html).

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