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# Ambient Air Pollution and the Risk of Central Retinal Artery Occlusion

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***Purpose:*** To investigate whether daily changes in ambient air pollution were associated with an increased risk of central retinal artery occlusion (CRAO).

***Design:*** Retrospective population-based cohort study.

***Participants:*** We identified patients newly diagnosed with CRAO between 2001 and 2013 in a representative database of 1 000 000 patients that were randomly selected from all registered beneficiaries of the National Health Insurance program in Taiwan. We identified air pollutant monitoring stations located near these patients' residences in different administrative areas in Taiwan to determine the recorded concentrations of particulate matter $\leq$2.5 μm ($PM_{2.5}$), particulate matter $\leq$10 μm ($PM_{10}$), nitrogen dioxide ($NO_2$), sulfur dioxide ($SO_2$), and ozone ($O_3$). Patients without corresponding monitoring stations were excluded.

***Methods:*** We used a time-stratified case-crossover study design and conditional logistic regression analysis to assess associations between the risk of CRAO and the air pollutant levels in the days preceding each event.

***Main Outcome Measures:*** Odds ratios (ORs) and 95% confidence intervals (CIs).

***Results:*** We enrolled 96 patients with CRAO in this study. The mean age was 65.6 years (standard deviation, 12.7 years) and 67.7% of patients were male. The risk of CRAO onset was significantly increased (OR, 1.09; 95% CI, 1.01−1.17; $P = 0.03$) during a 5-day period following a 1 part per billion increase in $NO_2$ levels. After multipollutant adjustment, the increase in risk was most prominent after 4 days (OR, 1.40; 95% CI, 1.05−1.87; $P = 0.02$) to 5 days (OR, 2.16; 95% CI, 1.10−4.23; $P = 0.03$) of elevated $NO_2$ levels in diabetic patients. The risk of CRAO onset also significantly increased in patients with hypertension and in patients $\geq$65 years old, after 1 day of elevated $SO_2$ levels (OR, 1.88; 95% CI, 1.07−3.29; $P = 0.03$ and OR, 1.90; 95% CI, 1.13−3.21; $P = 0.02$, respectively). The transient concentration of the other air pollutants, including $PM_{2.5}$, $PM_{10}$, and $O_3$, did not significantly affect the occurrence of CRAO in this study.

***Conclusions:*** These results demonstrated a positive association between air pollution and CRAO onset, particularly in patients with diabetes or hypertension and those older than 65 years. *Ophthalmology 2016;■:1−7 © 2016 by the American Academy of Ophthalmology*

*Supplementary material is available at www.aaojournal.org.*

Central retinal artery occlusion (CRAO) is one of the leading causes of acute permanent loss of vision, with an incidence of approximately 1 per 100 000 people.[1,2] Despite its rarity, the visual outcome of CRAO is typically dire. In addition, these patients had shorter life spans, higher risk of stroke, and more cardiovascular risk factors compared with controls.[3−6] Similar to ischemic cerebral stroke, CRAO is caused by thrombotic or embolic occlusion of the central retinal artery, which leads to ischemia of the retina and optic nerve head with profound loss of vision.[7,8] In addition, CRAO and ischemic stroke have similar risk factors.[6,9] Moreover, the risk of ischemic stroke was significantly increased both before and after the occurrence of CRAO.[10]

Growing evidence has indicated that gaseous and particulate air pollutants were markedly temporally associated with hospital admissions for stroke and stroke-related mortality.[11,12] It has been shown that the risk of stroke was significantly associated with daily increases in both particulate matter (PM), measured in terms of particles $\leq$2.5 μm or $\leq$10 μm in diameter ($PM_{2.5}$ and $PM_{10}$, respectively), and gaseous air pollutants, including carbon monoxide, sulfur dioxide ($SO_2$), and nitrogen dioxide ($NO_2$), but not ozone ($O_3$).[11,12] These associations were stronger in patients with recurrent ischemic stroke, a history of stroke, diabetes mellitus (DM), and $\geq$1 cardiovascular risk factor.[12] Short-term exposure to these air pollutants may also trigger a myocardial infarction, which is also a thromboembolic event.[13] Given the similarities in the pathophysiology of CRAO, ischemic stroke, and myocardial infarction, it is plausible that air pollution may be an important, modifiable risk factor for CRAO.

This study aimed to investigate whether daily changes in the level of ambient air pollution were associated with an increased risk of CRAO.

## Methods

This retrospective, population-based cohort study was based on data retrieved from January 1, 2000, to December 31, 2013, using the Taiwan National Health Insurance Research Database



http://dx.doi.org/10.1016/j.ophtha.2016.08.046
ISSN 0161-6420/16

(NHIRD). We included patients newly diagnosed with CRAO between 2001 and 2013. Patients aged <20 years or those with antecedent CRAO were excluded. CRAO was defined according to the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) diagnostic code 362.31. We defined the onset of CRAO as the first date that the diagnostic code was recorded. The patient's area of residence was defined as the location of the corresponding clinic/hospital in Taiwan, assuming that patients sought medical help at the closest clinic/hospital. We collected data on the patient's comorbidities, including DM, hypertension (HTN), coronary artery disease, hyperlipidemia, cerebral infarction, arrhythmia, heart failure, carotid artery stenosis, rheumatic heart disease, and glaucoma, except for normal tension glaucoma. Each patient's comorbidities were identified using the claims 1 year before the date of incident CRAO (the index date). The study protocol adhered to the tenets of the Declaration of Helsinki, and the study was approved by the institutional review board of the hospital.

The National Health Insurance (NHI) program in Taiwan is a mandatory general health insurance that covers up to 99% of Taiwan residents.[14] It covers emergency, inpatient, and outpatient care. The NHIRD contains encrypted data to prevent identification of individual patients; these data are maintained and released by the National Health Research Institutes for scientific research. In this study, we analyzed data in a representative database of 1 000 000 patients that were randomly selected from the registered beneficiaries of the NHI program. This selected patient group was termed the Longitudinal Health Insurance Database of the NHIRD.

The ambient concentrations of $PM_{2.5}$, $PM_{10}$, $NO_2$, $SO_2$, and $O_3$ were measured hourly and averaged from 78 local monitoring stations operated by the Environmental Protection Administration Executive Yuan of Taiwan (Fig 1, available at http://www.aaojournal.org). We obtained averaged hourly meteorological data, including temperature, from 603 local monitoring sites operated by the Central Weather Bureau of Taiwan. The patients were paired with monitoring stations located in the same administrative division as their area of residence (taken as the hospital location). The individualized exposure to ambient air pollution was then defined according to the date of CRAO onset and the patient's residential location. We excluded subjects that lived in areas that had no monitoring station in the same administrative division.

We used a time-stratified case-crossover study design[15] to assess the association between the risk of CRAO onset and the concentration of each kind of air pollution in the days preceding the event. In brief, each patient's exposure before a case-defining event (case period) was compared with the patient's exposure during a control period, when the patient did not experience a case-defining event. The control period was selected from other days of the same month, on the same day of the week, as the case period. The control period was selected from days both before and after the event, because individual events were not expected to impact the distribution of exposure (Fig 2, available at http://www.aaojournal.org).[16,17] Because the case and control periods were on the same day of the week in the same calendar month for a given individual, this study design controlled for seasonality, effect of the day of the week, time trends, and slowly varying potential confounders.[15,17] Moreover, the personal factors such as lifestyle, activity pattern, working area, and comorbidity were also controlled because the patients themselves were their own control.

## Statistical Analysis

We used conditional logistic regression to analyze associations between CRAO events and air pollution factors. These results are expressed as estimated odds ratios (ORs) and corresponding 95% confidence intervals (CIs).

Exposure to each air pollution factor was assessed relative to the time of CRAO onset. We first examined the risk of CRAO onset for each pollutant based on 1-day interval (single-day lag analysis). The risk of CRAO onset for each air pollutant was then identified based on average levels in the 0 to 2 days, 0 to 4 days, and 0 to 6 days preceding onset to check if there is an effect of increment of air pollution (multiday lag analysis). Additionally, we also stratified the pollutant levels into <25th, 25th to 75th, and >75th percentile of mean daily pollutant levels to examine the effect of high levels or low levels of pollution. At the end of this section, we used a multivariable conditional logistic regression model, adjusted for all pollutants and daily temperatures, to examine our results (multipollutant model).

On the second part, we conducted sensitivity analyses to test the stability of the overall analyses. Because each air pollutant had a different basal concentration, we used the mean pollutant levels of all of the control days in the same patient as his or her baseline. Each value in the case and control period was then divided by the baseline value and entered the subsequent conditional logistic regression analysis. We also set another model with longer buffer periods between the case period and control periods to check the stability of our results. In addition, studies have shown that temperature affects the occurrence of stroke significantly.[18] Therefore, we built another model with ±1° C daily temperature-matched control days in the same month to examine our results.

In the final section of analyses, we performed risk-stratified analyses according to relevant comorbidities, age, and gender to identify effect modification. A multivariable conditional logistic regression model, adjusted for all pollutants and daily temperatures (multipollutant model), was used in this analysis.

Data extraction, processing, and sampling were performed with Microsoft SQL Server 2012 (Microsoft Corporation, Redmond, WA). We used STATA version 12.1 (StataCorp LP, College Station, TX) for statistical analyses. All reported $P$ values were based on 2-sided tests; $P$ values <0.05 were considered statistically significant.

## Results

We identified 266 patients newly diagnosed with CRAO. Of these, 170 were excluded owing to the absence of an air monitoring station in the corresponding residential area or owing to incomplete pollutant or meteorological data. Thus, the study included a total of 96 patients newly diagnosed with CRAO. The mean age of all study subjects was 65.6 years (standard deviation, 12.7 years; range, 30−100 years), and 67.7% of the subjects were male. All eligible patients lived within 20 km of the monitoring stations. The major comorbidity was HTN, followed by DM and hyperlipidemia (Table 1). The distributions of mean daily pollutant and temperature levels in Taiwan are shown in Table 2 (available at http://www.aaojournal.org). The changes of air pollutant levels in Taiwan during the 13-year study period are shown in Figure 3 (available at http://www.aaojournal.org).

In the single-day lag analyses, $NO_2$ levels on the fifth day before CRAO onset (OR, 1.09; 95% CI, 1.01−1.17; $P = 0.03$) and daily temperature on the second day before CRAO onset (OR, 1.23; 95% CI, 1.03−1.47; $P = 0.02$) showed significant impacts on the occurrence of CRAO (Fig 4). In the multiday lag analyses, $NO_2$ levels (OR, 1.13; 95% CI, 0.99−1.28; $P = 0.06$; 0−6 days before CRAO onset), $SO_2$ levels (OR, 1.31; 95% CI, 1.00−1.72; $P = 0.05$; 0−2 days before onset), and daily temperature (OR, 1.21; 95% CI, 1.00−1.47; $P = 0.05$ 0−2 days before onset and OR, 1.25; 95% CI, 1.00−1.56; $P = 0.05$ 0−4 days before onset)

Table 1. Characteristics of 96 Patients Residing in Taiwan with Acute Central Retinal Artery Occlusion in 2001 to 2013

| Characteristic | Patients* |
|---|---|
| Age, mean (SD), years | 65.6 (12.7) |
| Male | 65 (67.7%) |
| Medical history | |
| Hypertension | 48 (50.0%) |
| Diabetes mellitus | 28 (29.2%) |
| Hyperlipidemia | 27 (28.1%) |
| Cerebral infarction | 24 (25.0%) |
| Coronary artery disease | 18 (18.8%) |
| Glaucoma except for NTG | 13 (13.5%) |
| Arrhythmia | 9 (9.4%) |
| Heart failure | 4 (4.2%) |
| Carotid artery stenosis | 1 (1.0%) |
| Rheumatic heart disease | 1 (1.0%) |

NTG = normal tension glaucoma; SD = standard deviation.
*Unless otherwise indicated, values represent the number (percentage) of patients.

showed borderline significance for the CRAO onset (Fig 5, available at http://www.aaojournal.org). In stratification of the pollutant levels into <25th, 25th to 75th, and >75th percentile of mean daily pollutant levels, only $NO_2$ showed a dose−response relationship to the onset of CRAO (OR, 2.5; 95% CI, 0.49−12.89; $P = 0.27$ in 25th−75th vs. <25th percentile; OR, 4.2; 95% CI, 0.47−36.74; $P = 0.20$ in >75th vs. <25th percentile) (Fig 6).

In the multivariable conditional logistic regression model adjusted for $PM_{2.5}$, $NO_2$, $SO_2$, $O_3$, and daily temperature, $SO_2$ levels 1 day before CRAO onset (OR, 1.36; 95% CI, 1.03−1.81; $P = 0.03$) and daily temperature on the second day before CRAO onset (OR, 1.23; 95% CI, 1.03−1.46; $P = 0.03$) showed significant impacts on the occurrence of CRAO (Fig 7, available at http://www.aaojournal.org). The effect of $NO_2$ levels on the fifth day before CRAO onset (OR, 1.09; 95% CI, 0.98−1.22; $P = 0.09$) became borderline significant. The $PM_{10}$ level was not adjusted for separately, because it was highly correlated with $PM_{2.5}$ (correlation coefficient = 0.88).

When adjusted for each pollutant's baseline level in the multiday lag analysis, the results became significant for $NO_2$ (OR, 1.03; 95% CI, 1.01−1.05; $P = 0.01$ 0−6 days before CRAO onset) and $SO_2$ (OR, 1.01; 95% CI, 1.00−1.02; $P = 0.03$ 0−2 days before CRAO onset), but not daily temperature (Fig 8, available at http://www.aaojournal.org). In this analysis, we had processed the number and the OR represented the increase in likelihood from 1% increase of pollutant levels from baseline. For example, each 1% increase of $NO_2$ levels from baseline was associated with a 1.03-fold increase in likelihood of CRAO onset (OR, 1.03; 95% CI, 1.01−1.05; $P = 0.01$ 0−6 days before CRAO onset).

If we used another model with longer buffer periods between the case period and control periods, the impact of $NO_2$ levels on the fifth day before CRAO onset (OR, 1.10; 95% CI, 1.02−1.19; $P = 0.01$) remained robust, but not daily temperature (Fig 9, available at http://www.aaojournal.org). The result of the multiday lag analysis was also similar to the original analysis. In addition, the results of single-day lag and multiday lag analyses were also similar in the model with daily temperature−matched controls in the same month (Fig 10, available at http://www.aaojournal.org).

For the risk-stratified analyses, we studied the effect of age, gender, DM, HTN, hyperlipidemia, and cerebral infarction. The other comorbidities were not analyzed because of the small number of cases. We focused on the influences of $NO_2$ and $SO_2$ because in the previous analyses these 2 air pollutants were the most relevant factors for CRAO onset. In these multivariable conditional logistic regression analyses, we found significant impacts of $NO_2$ levels on CRAO onset on the fourth and fifth days before CRAO onset in patients with DM (OR, 1.40; 95% CI, 1.05−1.87; $P = 0.02$ and OR, 2.16; 95% CI, 1.10−4.23; $P = 0.03$ on fourth and fifth days, respectively), $SO_2$ levels 1 day before CRAO onset in patients with HTN (OR, 1.88; 95% CI, 1.07−3.29; $P = 0.03$), and $SO_2$ levels 1 day before CRAO onset in patients ≥65 years old (OR, 1.90; 95% CI, 1.13−3.21; $P = 0.02$) (Fig 11; Fig 12, available at http://www.aaojournal.org). Borderline significance was noted in $NO_2$ levels on the fifth day before CRAO onset in patients with hyperlipidemia (OR, 1.85; 95% CI, 1.00−3.41; $P = 0.05$) and in patients ≥65 years old (OR, 1.21; 95% CI, 1.00−1.46; $P = 0.05$) (Fig 11).

## Discussion

This retrospective, nationwide, population-based cohort study, based on the NHIRD combined with air pollution data, revealed that short-term exposure to gaseous air pollutants might be positively associated with CRAO onset, particularly in patients with cardiovascular risk factors. After adjusting for multiple pollutants, we found that CRAO risk was significantly impacted by increases in $NO_2$ levels 4 to 5 days before CRAO onset in patients with DM, and by increases in $SO_2$ levels 1 day before CRAO onset in patients with HTN and in patients ≥65 years old. Elevated $NO_2$ levels also increased the risk of CRAO in patients with hyperlipidemia and in patients ≥65 years old, but these effects were borderline significant.

$NO_2$ is a product of combustion, emitted from both stationary sources (e.g., incineration) and motor vehicles, and it may induce oxidative damage in humans.[19,20] $SO_2$ is a major product of fossil fuel combustion processes. It is highly soluble in water, and it is mostly absorbed in the upper airways.[19] Hydration of $SO_2$ in the mucous layer yields significant hydrogen ($H^+$), reactive species ($HSO_3^-$), and sulfite ions ($SO^{2-}$), which may induce general inflammation and oxidative damage and may act directly on smooth muscle.[19]

Several possible mechanisms have been proposed for the association between air pollution and thromboembolic events. The first possible mechanism was inflammation; this mechanism was supported by findings of elevated C-reactive protein levels after air pollution exposure in humans and by evidence from animal models that were exposed to $NO_2$ and $SO_2$.[19−23] The second possible mechanism was a disturbance in the cardiac autonomic system, evidenced by an increase in heart rate and altered heart rate variability in response to air pollution exposure.[24,25] The third potential mechanism was hypercoagulability induced by air pollution; the effects included increased plasma viscosity, a shorter prothrombin time, and increases in von Willebrand factor and fibrinogen levels, which promote thrombus formation.[23,26−28] The fourth potential mechanism was the induction of vasospasms by pollutants, evidenced by increased endothelin levels and reduced nitric oxide bioavailability in the vessel wall.[29−32] Also, air pollutants

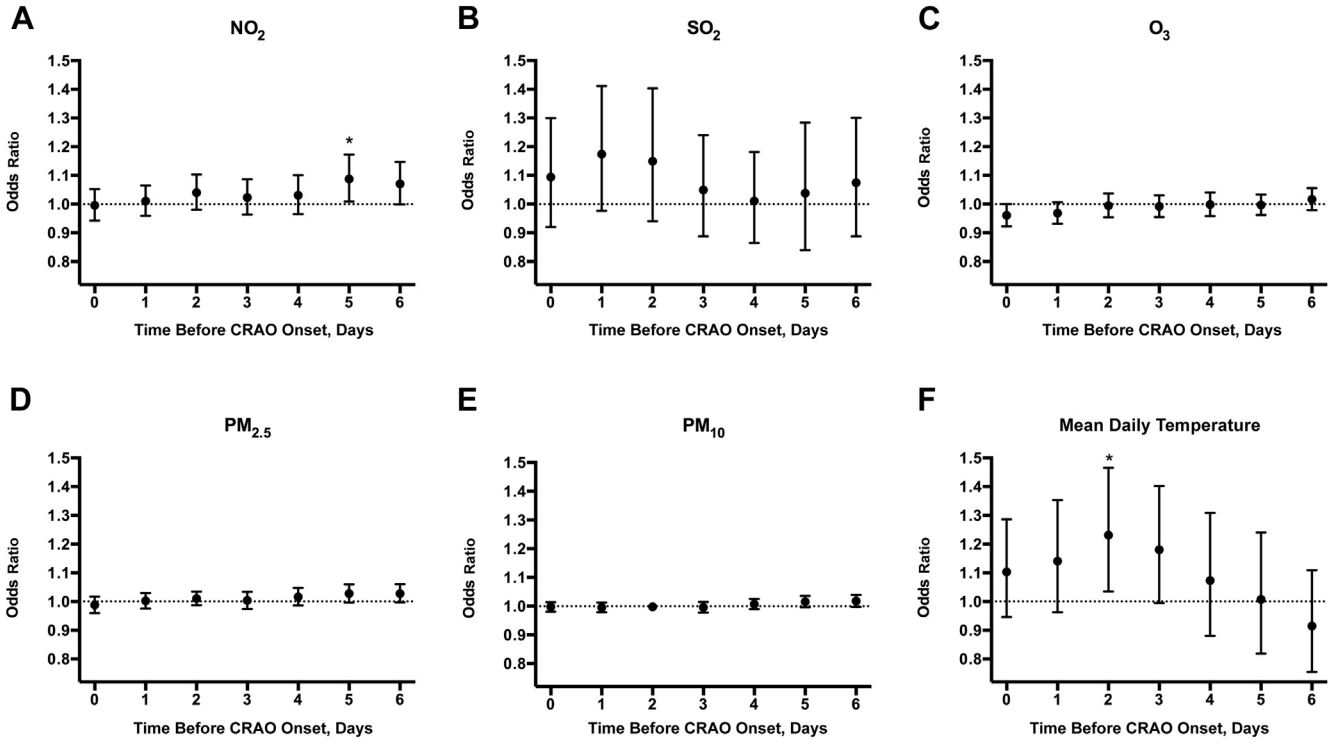


**Figure 4.** Single-day lag analyses of association between central retinal artery occlusion (CRAO) and increased (per 1 unit) ambient air pollutants/daily temperature in the days preceding CRAO onset. The odds ratio peaks showed significant impact of elevated nitrogen dioxide ($NO_2$) levels at 5 days before CRAO onset and elevated daily temperature at 2 days before CRAO onset on the occurrence of CRAO. (**A**) $NO_2$, (**B**) Sulfur dioxide ($SO_2$), (**C**) Ozone ($O_3$), (**D**) Particulate matter ≤2.5 μm in diameter ($PM_{2.5}$), (**E**) Particulate matter ≤10 μm in diameter ($PM_{10}$), and (**F**) Mean daily temperature. Unit: $\mu g/m^3$ for $PM_{10}$ and $PM_{2.5}$; parts per billion for $NO_2$, $SO_2$, and $O_3$; °C for temperature. Error bars indicate 95% confidence intervals. *$P < 0.05$.

may induce arrhythmias, promote HTN, and destabilize atherosclerotic plaques.[24,33] These findings support the biological plausibility that exposure to air pollution might affect the risk of CRAO via multiple mechanisms.

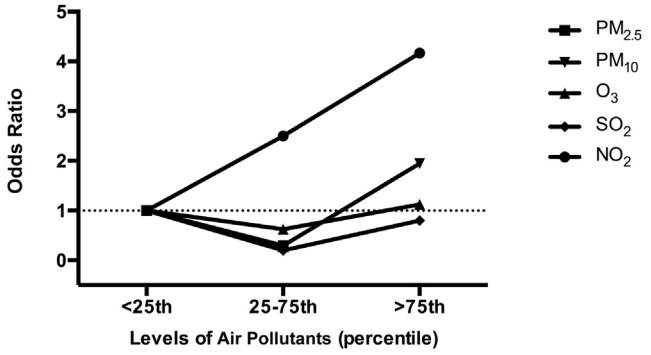


**Figure 6.** Odds ratio of central retinal artery occlusion (CRAO) onset for mean ambient air pollutant levels in the 6 days preceding CRAO, stratified by <25th, 25th to 75th, and >75th percentile. While stratified by <25th, 25th to 75th, and >75th percentile of mean pollutant levels, only $NO_2$ showed a dose–response relationship to the onset of CRAO (odds ratio [OR], 2.5; 95% confidence interval [CI], 0.49–12.89; $P = 0.27$ in 25th to 75th vs. <25th percentile; OR, 4.2; 95% CI, 0.47–36.74; $P = 0.20$ in >75th vs. <25th percentile). The analysis of >75th percentile of $PM_{2.5}$ was not performed because both case and control periods of these patients were within the subgroup of >75th percentile. $NO_2$ = nitrogen dioxide; $O_3$ = ozone; $PM_{2.5}$ = particulate matter ≤2.5 μm in diameter; $PM_{10}$ = particulate matter ≤10 μm in diameter; $SO_2$ = sulfur dioxide.

Here, we found that DM, HTN, hyperlipidemia, and older age made patients more susceptible to the impact of air pollution on the occurrence of CRAO. A similar concept was previously proposed in several animal and clinical studies. Takano et al demonstrated that daily exposure to ambient levels of $NO_2$ enhanced atherogenic lipid metabolism in obese rats, but not in nonobese rats.[34] Chiusolo et al showed that patients with DM and cardiovascular conditions were highly susceptible to air pollution effects on natural, cardiac, and respiratory mortality.[35] Villeneuve et al found that patients with DM, heart disease, and history of stroke were more vulnerable to ischemic stroke associated with short-term elevations in $NO_2$.[36] These findings indicated that, potentially, we might be able to reduce the risk of major cardiovascular events and vision-devastating CRAO by altering activity patterns on high pollution days and promoting efforts to reduce traffic density or fossil fuel combustion.

We also found that daily temperature on the second day before CRAO onset had significant impact on the occurrence of CRAO in both of the univariate and multivariable regression analyses, with each 1°C increase of daily temperature associated with a 1.23-fold increase in likelihood of CRAO onset. Studies had shown that short-term changes of both low and high temperature had significant impact on major adverse cerebrovascular events.[18] In addition, hot temperature acted as a risk factor for ischemic stroke but not hemorrhagic stroke.[18] The potential mechanisms have

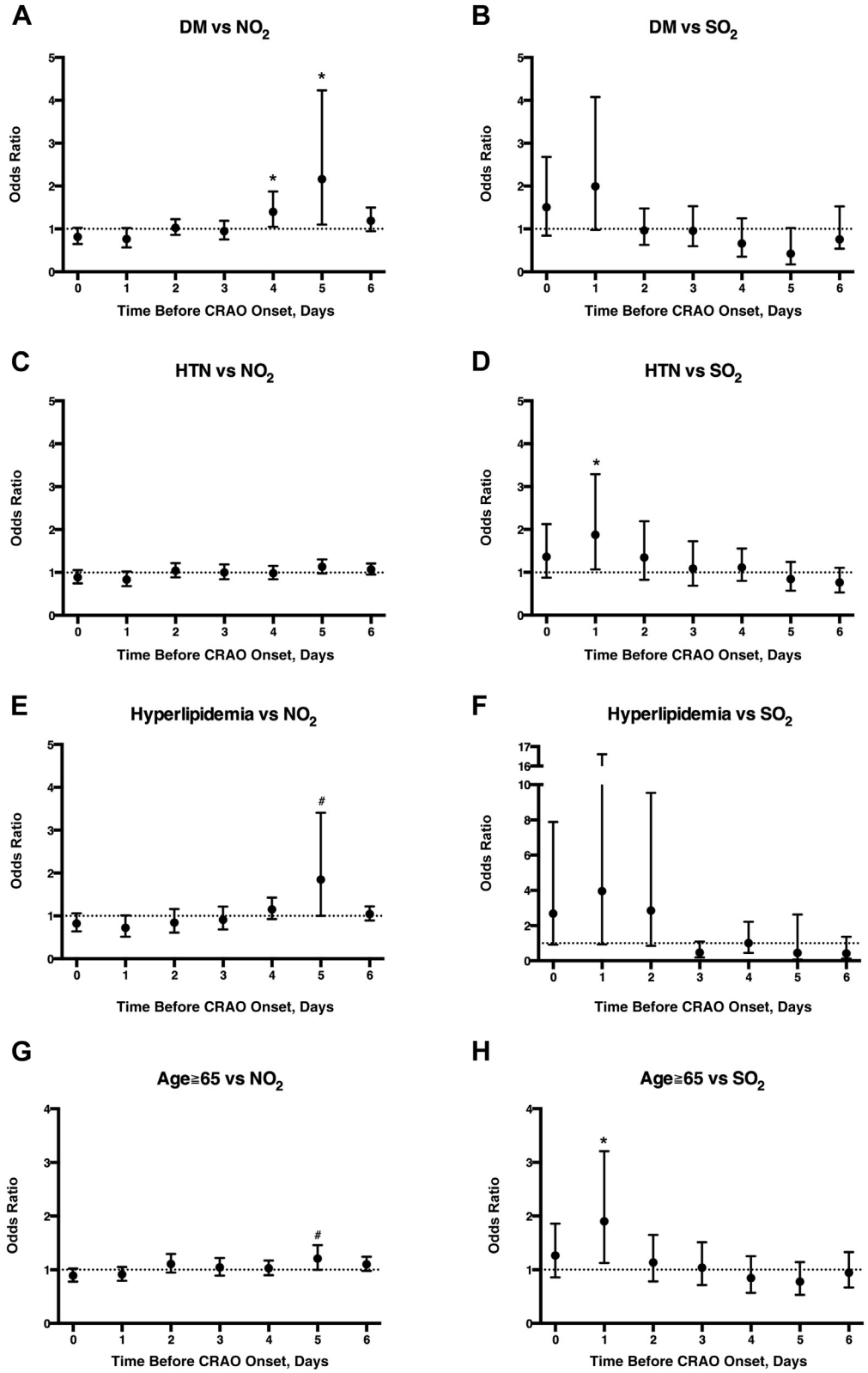


**Figure 11.** Results of risk-stratified analyses for the occurrence of central retinal artery occlusion (CRAO) with multivariable conditional logistic regression model adjusted for all pollutants and daily temperatures. The results showed significant impacts of nitrogen dioxide ($NO_2$) levels on CRAO risk on the fourth and fifth days before CRAO onset in patients with diabetes mellitus (DM), sulfur dioxide ($SO_2$) levels 1 day before CRAO onset in patients with hypertension (HTN), and $SO_2$ levels 1 day before CRAO onset in patients ≥65 years old. (**A**) $NO_2$ levels in DM patients, (**B**) $SO_2$ levels in DM patients, (**C**) $NO_2$ levels in HTN patients, (**D**) $SO_2$ levels in HTN patients, (**E**) $NO_2$ levels in hyperlipidemic patients, (**F**) $SO_2$ levels in hyperlipidemic patients, (**G**) $NO_2$ levels in patients ≥65 years old, (**H**) $SO_2$ levels in patients ≥65 years old. Error bars indicate 95% confidence intervals. $^{*}P < 0.05$, $^{\#}P = 0.05$.

not been well understood but may be attributed to higher temperature–related hemoconcentration and impairment of peripheral vascular endothelial function.[18,37] In our study, short-term change of temperature was a risk factor of CRAO. More studies may be needed to validate our results.

Our study had several strengths. We extended the scope of air pollution on cardiovascular and cerebrovascular diseases to an important, vision-threatening disease, CRAO. We used a nationwide database to identify our subjects, and we correlated exposure levels to data from local monitoring stations, with the strict criterion that every eligible patient lived within 20 km of a station. Also, the time-stratified case-crossover study design eliminated the impacts of seasonality, time trends, and confounders attributable to individual differences. In addition to the 1-pollutant model, we also adjusted for multiple pollutants to verify the stability and reliability of our results.

Our study findings should be interpreted in light of the following limitations. First, the sample size was relatively small, owing to the restriction that patients had to reside in an area that monitored air pollution. Second, the onset of CRAO was defined as the first date that the CRAO diagnostic code was recorded in NHIRD, but we could not rule out time lags between disease onset and visiting the medical facility because we could not directly review the medical records of these patients. However, CRAO typically presents with acute, painless, devastating vision loss; thus, patients typically seek immediate medical help. Moreover, the diagnosis of CRAO is straightforward after a fundus examination; thus, most ophthalmologists can make the diagnosis on site. Therefore, we believe that the first date of recording the CRAO diagnostic code reflected the CRAO onset fairly accurately. Third, the patient's area of residence was defined as the location of the corresponding clinic/hospital but not the patients' addresses. The addresses recorded in the NHI in Taiwan are the insured units, which are usually the addresses of headquarters of the company but not the addresses of residency. In addition, the ophthalmology clinics are widespread and easily accessible in the community. Therefore, we believed that defining the corresponding clinic/hospital was a better way in this circumstance, assuming that patients sought medical help at the closest clinic/hospital. Fourth, cigarette smoking, which is one of the risk factors of CRAO, was not recorded in NHIRD and we could not adjust for this factor. However, the patients themselves were their own controls in the time-stratified case-crossover design and we supposed the lifestyle in the same month of the same person should be the same. Therefore, this confounder had been controlled internally. Fifth, the levels of air pollutants varied over the 13-year study period in Taiwan (Fig 3, available at http://www.aaojournal.org). Because of the small sample size and pollutant variations in different areas in Taiwan, we did not address the issue of long-term effect of air pollution on CRAO. Instead, we focused on the individual-matched local monitoring station and the effect of short-term variation of air pollution. Finally, although we collected data from the monitoring stations nearest to the residences of patients, the data did not reflect exposure at an individual level, and indoor pollutants may have been neglected. In future, a personal monitoring method may provide more individualized air pollution levels.

In conclusion, the present study demonstrated a positive association between air pollution and CRAO onset, particularly in older patients, patients with diabetes, patients with HTN, and, possibly, patients with hyperlipidemia. Altering activity patterns on high pollution days, reducing traffic density, or reducing fossil fuel combustion may reduce the risk of vision-devastating CRAO. A prospective cohort study with ambulatory personal air pollution monitors may be needed to verify our results and guide the public policy in the future.

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## Footnotes and Financial Disclosures

Originally received: May 15, 2016.
Final revision: August 3, 2016.
Accepted: August 29, 2016.
Available online: ■■■. Manuscript no. 2016-1028.

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Presented at the Annual Meeting of the Association for Research in Vision and Ophthalmology (ARVO), May 1-5, 2016, Seattle, Washington.

*Ren-Hao Pan and Huan-Jui Yeh contributed equally to the study. Chien-Lung Chan and An-Guor Wang contributed equally to the study. These two groups of authors contributed differently.

Financial Disclosure(s):
The authors have no proprietary or commercial interests in any materials discussed in this article.

Supported in part by grants from the Ministry of Science and Technology (MOST-104-3115-E-155-002, MOST-104-2218-E-155-004, MOST-104-2410-H-155-024) Taipei, Taiwan. No funding organizations played a role in the design or conduct of this research.

Author Contributions:

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Obtained funding: none

Overall responsibility: Cheng, Pan, Yeh, Lai, Yen, Chan, Wang

Abbreviations and Acronyms:
**CI** = confidence interval; **CRAO** = central retinal artery occlusion; **DM** = diabetes mellitus; **HTN** = hypertension; **NHI** = National Health Insurance; **NHIRD** = National Health Insurance Research Database; **$NO_2$** = nitrogen dioxide; **OR** = odds ratio; **$O_3$** = ozone; **$PM_{2.5}$** = particulate matter ≤2.5 μm in diameter; **$PM_{10}$** = particulate matter ≤10 μm in diameter; **$SO_2$** = sulfur dioxide.

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