Stroke

CLINICAL AND POPULATION SCIENCES

Outdoor Light at Night, Air Pollution, and Risk of Cerebrovascular Disease: A Cohort Study in China

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BACKGROUND: We sought to explore the associations of outdoor light at night (LAN) and air pollution with the risk of cerebrovascular disease (CeVD).

METHODS: We included a total of 28 302 participants enrolled in Ningbo, China from 2015 to 2018. Outdoor LAN and air pollution were assessed by Satellite-derived images and land-use regression models. CeVD cases were confirmed by medical records and death certificates and further subdivided into ischemic and hemorrhagic stroke. Cox proportional hazard models were used to estimate hazard ratios and 95% CIs.

RESULTS: A total of 1278 CeVD cases (including 777 ischemic and 133 hemorrhagic stroke cases) were identified during 127 877 person-years of follow-up. In the single-exposure models, the hazard ratios for CeVD were 1.17 (95% CI, 1.06–1.29) for outdoor LAN, 1.25 (1.12–1.39) for particulate matter with an aerodynamic diameter ≤2.5 μm, 1.14 (1.06–1.22) for particulate matter with aerodynamic diameter ≤10 μm, and 1.21 (1.06–1.38) for NO_2 in every interquartile range increase. The results were similar for ischemic stroke, whereas no association was observed for hemorrhagic stroke. In the multiple-exposure models, the associations of outdoor LAN and PM with CeVD persisted but not for ischemic stroke. Furthermore, no interaction was observed between outdoor LAN and air pollution.

CONCLUSIONS: Levels of exposure to outdoor LAN and air pollution were positively associated with the risk of CeVD. Furthermore, the detrimental effects of outdoor LAN and air pollution might be mutually independent.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: cerebrovascular disease ■ cohort study ■ hemorrhagic stroke ■ ischemic stroke ■ risk factors

Cerebrovascular disease (CeVD) refers to a group of diseases caused by pathological changes in the cerebrovascular system leading to brain dysfunction. Stroke, the principal clinical type, is a major cause of disability and death,[1] thus identifying modifiable risk factors is critical to reducing the burden of CeVD. Apart from lifestyle factors, environmental risk factors cannot be ignored.[2]

Outdoor light at night (LAN) is non-natural light used at night to enhance the visual performance and visibility of the environment, thereby improving human safety and comfort. However, the excessive use of artificial light has caused ≈80% of the world's population to live in light-polluted environments.[3] Humans may be directly exposed to artificial light in work, life, rest, and recreation.[4] Currently, artificial light sources mainly include fluorescent, incandescent, and light-emitting diode products.[5] And their spectral power distributions (the radiant power of light in various wavelength bands) are different, for example, LEDs reach

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Nonstandard Abbreviations and Acronyms

CeVD	cerebrovascular disease
HR	hazard ratio
IQR	interquartile range
LAN	light at night
$PM_{2.5}$	particulate matter with an aerodynamic diameter ≤2.5 μm

the peak radiant power in the short-wavelength band (blue light), whereas incandescent lamps are in the long-wavelength light band (red light).[6] The spectral composition of ambient light from these sources can be sensed by the skin or the retina of the eye, triggering regulation of the endocrine or autonomic nervous system to affect the internal clock.[7,8] Moreover, melatonin as the key player is a hormone secreted by the pineal gland during the night to help promote sleep and regulate jet lag and is particularly sensitive to blue light (460–480 nm).[9] Thus, LAN overexposure may suppress melatonin production and impair its circadian rhythm by disrupting sleep patterns and shortening sleep duration, ultimately leading to disease. Accumulating evidence suggested that outdoor LAN may have adverse effects on health outcomes.[10–12] Despite the biological plausibility that circadian rhythm disturbances might cause CeVD,[13] little evidence can be available for the association between outdoor LAN and the risk of CeVD.

Air pollution, including particulate matter and gaseous air pollutants, which are generated directly by combustion processes in vehicles, industry and energy production, and home heating.[14] Exposure to air pollution may lead to an increased risk of cardiovascular disease through mechanisms such as oxidative stress and inflammatory responses.[15] Furthermore, 2 cross-sectional studies showed that the associations of air pollutants with the prevalence of obesity and chronic kidney disease could be modified by night-light index,[16,17] indicating a potential interaction between outdoor LAN and air pollution. However, due to the cross-sectional designs, we should interpret these findings with caution. Moreover, the interaction between outdoor LAN and air pollution on the risk of CeVD remains unclear.

Herein, we investigated the associations of outdoor LAN and air pollution with CeVD based on a prospective cohort. We also examined the multiplicative and additive interactions between outdoor LAN and air pollution.

METHODS

Data Availability

Data was not provided in the article due to protection of participant privacy but could be available from the corresponding authors on reasonable request.

Data Source

The Yinzhou Cohort was established from 2015 to 2018 in Yinzhou District, Ningbo City, China, a developed area located on the eastern coast. The profile of the Yinzhou Cohort has been described elsewhere.[18] Briefly, we recruited 47 516 residents who underwent face-to-face questionnaires and health examinations at baseline.

In our study, we excluded 15 324 subjects who were lost to follow-up due to administrative division adjustments. Furthermore, we excluded 89 subjects with unavailable addresses and error records, 991 subjects with missing covariate data (Table S2), 604 subjects with extreme values of outdoor LAN (above the 99th percentile or below the first percentile), 2206 subjects diagnosed with CeVD at baseline and within 1 year after baseline. In total, a total of 28 302 eligible participants were included in the final analysis (Figure S1). Demographic differences between participants in the final analysis and all participants at baseline were presented in Table S3.

All participants signed informed consent and our study was authorized by the institutional review board of Zhejiang University School of Medicine.

Assessment of Exposures and Covariates

Outdoor LAN and air pollution were assessed based on nighttime light images synthesized by the visible and infrared imaging suite on board the Joint Polar-orbiting Satellite and land-use models (detailed methods in Supplemental Material). At baseline, we collect data on age, sex, annual household income, education, occupation, body mass index, plant-based diet index, smoking, alcohol drinking, physical activity, history of disease, normalized difference vegetation index, gross domestic product and population density (detailed methods in Supplemental Material).

Outcome

We obtained diagnosis records from the Yinzhou Health Information System for all participants, which covered all clinic records from local medical facilities in Yinzhou and allowed us to obtain accurate and timely medical information. In this study, our primary outcome was CeVD (*International Classification of Diseases-Tenth Revision [ICD-10]: I60-I69*), ischemic stroke (*ICD-10: I63* and *I65-I66*), and hemorrhagic stroke (*ICD-10*: *I60-I62*). We defined incident CeVD as the first nonfatal CeVD event or fatal CeVD without a history of CeVD. Nonfatal CeVD cases were obtained from hospital records, and fatal CeVD cases were identified from death certificates in the death registration system. CeVD cases were confirmed by specialized clinicians based on clinical symptoms combined with CT (computed tomography) or magnetic resonance imaging. Each participant was followed up to the death, incident CeVD, or until September 30, 2021, whichever came first.

Statistical Analysis

Distribution of characteristics was presented as median (interquartile range [IQR]), mean±SD, and number (%). Mann-Whitney *U* test or *t* tests for continuous variables, and χ^2 tests for categorical variables were used to compare the differences between participants with and without the incident CeVD. We used the Spearman correlation coefficients to evaluate the correlation between exposures.

Cox proportional hazard models with age as the time scale were performed to estimate hazard ratios (HRs) and 95% CIs for CeVD, ischemic stroke, and hemorrhagic stroke. We used the weighted Schoenfeld residuals to check the proportional hazards assumption (all $P>0.05$). We fitted single-exposure models and multiple-exposure models for the combination of exposures with the correlations <0.70. We used adjusted models including age (time scale), sex, education, occupation, annual household income, body mass index, physical activity, alcohol drinking status, smoking status, plant-based diet index, hypertension, dyslipidemia, diabetes, population density, gross domestic product, and normalized difference vegetation index. All results were presented as HRs and 95% CIs per IQR increase and quartiles with Q1 (lowest) as the reference. Exposure-response curves were explored by restricted cubic spline, and choice of knots was determined by the Akaike information criterion.

We explored the joint effects of outdoor LAN and air pollution on the risk of CeVD. Outdoor LAN and each air pollutant were categorized into 2 groups by median separately, and HRs (95% CIs) were showed with the low level of both outdoor LAN and air pollution as the reference. The multiplicative and additive interactions between outdoor LAN and air pollution were explored by performing likelihood ratio tests between models with and without the interaction term and calculating relative excess risk due to interaction, respectively.

To examine whether the associations of outdoor LAN and air pollution with CeVD differed across subgroups, we investigated effect modifications by age, sex, smoking, drinking, body mass index, and annual household income. Similarly, likelihood ratio tests were used to determine the heterogeneity of HRs across subgroups.

Sensitivity analyses were conducted to assess the robustness of our results. First, we only included individuals who have resided at the baseline address for more than 10 years to reduce misclassification bias of exposure due to moving. Second, the effect of outdoor LAN on night-shift workers may be different. We excluded individuals who were working at baseline due to lack of data on night-shift work. Third, we excluded individuals diagnosed with ischemic heart disease at baseline to minimize the effect of reverse causality. Fourth, we used 2-year average levels of outdoor LAN and air pollution before baseline as the long-term exposure level. Finally, we repeated the main analysis by calculating air pollution score using principal components analysis.

A P value for 2-sided test <0.05 was regarded as statistical significance. Due to the exploratory nature of this study, the P values were not adjusted for multiplicity. All analyses were performed using R software (version: 4.1.2).

RESULTS

A total of 28 302 participants were eligible for our study, 59.4% were women, and the mean age was 61.51±11.02 years (Table 1). During 127 877 person-years of follow-up, we identified 1278 CeVD cases (including 777 ischemic and 133 hemorrhagic stroke). The number of cases in each stroke subtype is presented in Table S4. Participants with incident CeVD tended to be older, men, have lower levels of annual household income and education, higher prevalence of hypertension, dyslipidemia, and diabetes. Outdoor LAN and air pollution showed skewed distribution (Figure S2), and outdoor LAN was positively correlated with air pollution (Table S5).

Table 1. Characteristics of Participants in the Yinzhou Cohort

Characteristics	Overall (N=28 302)	Without CeVD (N=27 024)	With CeVD (N=1278)	*P* value*
Age, y (mean±SD)	61.51±11.02	61.13±10.97	69.53±8.95	<0.001
BMI, kg/m² (mean±SD)	23.68±3.22	23.67±3.22	23.82±3.29	0.103
Women, n (%)	16 825 (59.4)	16 119 (59.6)	706 (55.2)	0.002
Occupation, n (%)				<0.001
Agriculture or industry	11 652 (41.2)	11 133 (41.2)	519 (40.6)	
Public institution or enterprise	1197 (4.2)	1170 (4.3)	27 (2.1)	
Retirement or housework	14 175 (50.1)	13 479 (49.9)	696 (54.5)	
Others	1278 (4.5)	1242 (4.6)	36 (2.8)	
Smoking, n (%)				0.151
Never	22 544 (79.7)	21 552 (79.8)	992 (77.6)	
Former	995 (3.5)	942 (3.5)	53 (4.1)	
Current	4763 (16.8)	4530 (16.8)	233 (18.2)	
Drinking, n (%)				0.364
Never	23 339 (82.5)	22 303 (82.5)	1036 (81.1)	
Former	296 (1.0)	280 (1.0)	16 (1.3)	
Current	4667 (16.5)	4441 (16.4)	226 (17.7)	
Annual household income, n (%)				<0.001
<10 000	1769 (6.3)	1628 (6.0)	141 (11.0)	
≥10 000 and <30 000	9611 (34.0)	8983 (33.2)	628 (49.1)	
≥30 000 and <50 000	8184 (28.9)	7844 (29.0)	340 (26.6)	
≥50 000	8738 (30.9)	8569 (31.7)	169 (13.2)	
Education, n (%)				<0.001
Illiterate	8827 (31.2)	8271 (30.6)	556 (43.5)	
Primary or middle school	17 766 (62.8)	17 077 (63.2)	689 (53.9)	
High school or above	1709 (6.0)	1676 (6.2)	33 (2.6)	
Physical activity, n (%)				0.082
<600 MET-min/wk	7787 (27.5)	7467 (27.6)	320 (25.0)	
600 to 3000 MET-min/wk	17 577 (62.1)	16 766 (62.0)	811 (63.5)	
≥3000 MET-min/wk	2938 (10.4)	2791 (10.3)	147 (11.5)	
PDI (mean±SD)	19.59 (1.74)	19.58 (1.74)	19.78 (1.88)	<0.001
Hypertension, n (%)	17 963 (63.5)	16 991 (62.9)	972 (76.1)	<0.001
Dyslipidemia, n (%)	6674 (23.6)	6301 (23.3)	373 (29.2)	<0.001
Diabetes, n (%)	4925 (17.4)	4611 (17.1)	314 (24.6)	<0.001
NDVI, median (IQR)	0.38 (0.14)	0.38 (0.14)	0.38 (0.17)	0.098
Outdoor LAN (median [IQR], nW/cm²/sr)	6.37 (8.44)	6.37 (8.44)	6.46 (11.08)	0.073
$PM_{2.5}$ (median [IQR], μg/m³)	34.54 (5.38)	34.54 (5.38)	36.45 (5.60)	<0.001
PM_{10} (median [IQR], μg/m³)	52.64 (7.80)	52.64 (8.13)	56.57 (10.77)	<0.001
NO_2 (median [IQR], μg/m³)	26.68 (11.17)	26.68 (11.34)	26.06 (9.33)	<0.001

BMI indicates body mass index; CeVD, cerebrovascular disease; IQR, interquartile range; LAN, light at night; n, number; MET, metabolic equivalents of task; NDVI, normalized difference vegetation index; NO_2, nitrogen dioxide; PDI, plant-based diet index; $PM_{2.5}$, particulate matter with an aerodynamic diameter ≤2.5 μm; and PM_{10}, particulate matter with aerodynamic diameter ≤10 μm.

*P values were estimated using χ^2 test for categorical variables and t test or Mann-Whitney U test for continuous variables.

In the single-exposure models, high levels of exposure to outdoor LAN and air pollution were associated with an elevated risk of CeVD and ischemic stroke (Table 2; Table S6). The unadjusted HRs (95% CIs) per IQR increase were 1.09 (1.03–1.16), 1.25 (1.14–1.38), 1.16 (1.09–1.23), and 1.27 (1.12–1.43) for outdoor LAN, particulate matter with an aerodynamic diameter ≤2.5 μm ($PM_{2.5}$), particulate matter with aerodynamic diameter ≤10 μm, and NO_2, respectively. In the adjusted models, individuals exposed to the highest levels (Q4) of outdoor LAN had a 43% elevated risk of CeVD (HR, 1.43 [95% CI, 1.12–1.83]), compared with those with the lowest levels (Q1) and the HR was 1.17 (95% CI, 1.06–1.29) for per IQR increase. Exposure to higher levels of $PM_{2.5}$ increased the risk of CeVD (Q4 versus Q1: HR, 1.41 [95% CI, 1.18–1.70]; per IQR increase: HR, 1.25 [95% CI, 1.12–1.39]). Particulate matter with aerodynamic diameter ≤10 μm and NO_2 were also positively associated with risk of CeVD. Similar results were observed for ischemic stroke, whereas no significant association was observed for hemorrhagic stroke.

Exposure-response curves of outdoor LAN and $PM_{2.5}$ with risk of CeVD were almost all monotonically increasing and showed the linear relationships (*P* value for nonlinearity >0.05), whereas particulate matter with aerodynamic diameter ≤10 μm and NO_2 were nonlinearly related to risk of CeVD (Figure 1). Similar trends were observed for ischemic stroke (Figure S3). The associations of outdoor LAN and PM with CeVD seemed to be stable in the multiple-exposure models, whereas the association between NO_2 and CeVD was not significant after adjustment for $PM_{2.5}$ (Figure 2). Similar results were observed for ischemic stroke, although the association

Table 2. Associations of Outdoor LAN and Air Pollution With Risk of CeVD (N=28 302)

	Cases/person-years	Unadjusted HRs (95% CIs)	Adjusted HRs (95% CIs)*
Outdoor LAN			
Q1 (0.36–2.75)	318/33 346	1.00 (Ref.)	1.00 (Ref.)
Q2 (2.76–6.37)	319/30 884	1.05 (0.90–1.23)	1.09 (0.92–1.30)
Q3 (6.38–11.19)	252/32 300	0.90 (0.76–1.06)	0.92 (0.75–1.13)
Q4 (11.20–42.28)	389/31 346	1.26 (1.09–1.46)	1.43 (1.12–1.83)
P value for trend		0.014	0.042
Per IQR increase		1.09 (1.03–1.16)	1.17 (1.06–1.29)
$PM_{2.5}$			
Q1 (24.61–32.09)	219/32 645	1.00 (Ref.)	1.00 (Ref.)
Q2 (32.10–34.54)	253/31 532	1.05 (0.87–1.25)	1.05 (0.87–1.27)
Q3 (34.55–37.47)	313/31 266	1.19 (1.00–1.41)	1.21 (1.01–1.46)
Q4 (37.48–48.30)	493/32 434	1.42 (1.20–1.67)	1.41 (1.18–1.70)
P value for trend		<0.001	0.002
Per IQR increase		1.25 (1.14–1.38)	1.25 (1.12–1.39)
PM_{10}			
Q1 (5.03–49.40)	220/32 807	1.00 (Ref.)	1.00 (Ref.)
Q2 (49.41–52.64)	261/31 800	1.08 (0.90–1.29)	1.05 (0.87–1.27)
Q3 (52.65–57.20)	272/29 774	1.15 (0.96–1.38)	1.10 (0.90–1.33)
Q4 (57.21–73.67)	525/33 496	1.52 (1.29–1.78)	1.50 (1.25–1.80)
P value for trend		<0.001	0.007
Per IQR increase		1.16 (1.09–1.23)	1.14 (1.06–1.22)
NO_2			
Q1 (13.66–20.87)	315/35 518	1.00 (Ref.)	1.00 (Ref.)
Q2 (20.88–26.68)	390/32 192	1.47 (1.26–1.70)	1.43 (1.22–1.68)
Q3 (26.69–32.04)	368/31 854	1.45 (1.25–1.69)	1.47 (1.25–1.74)
Q4 (32.05–36.69)	205/28 312	1.37 (1.15–1.64)	1.31 (1.07–1.60)
P value for trend		<0.001	0.002
Per IQR increase		1.27 (1.12–1.43)	1.21 (1.06–1.38)

CeVD indicates cerebrovascular disease; HR, hazard ratio; IQR, interquartile range; LAN, light at night; NO_2, nitrogen dioxide; $PM_{2.5}$, particulate matter with aerodynamic diameter ≤2.5 μm; PM_{10}, particulate matter with aerodynamic diameter ≤10 μm; Q, quartile; and Ref., reference.

*Adjusted for age (timescale), sex, education, occupation, annual household income, BMI, physical activity, alcohol drinking status, smoking status, PDI, hypertension, dyslipidemia, diabetes, gross domestic product, population density, and normalized difference vegetation index.

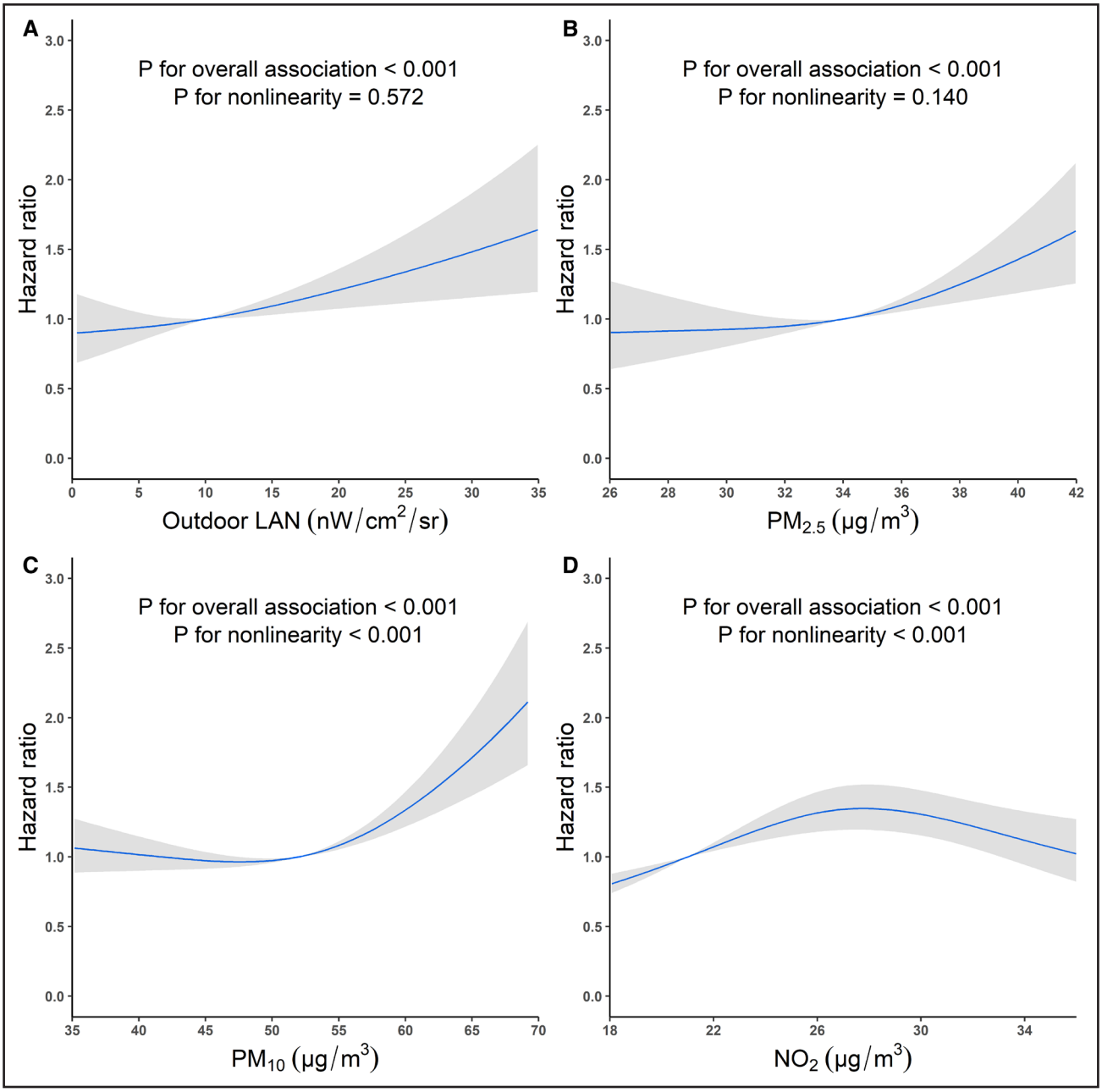

Figure 1. Exposure-response curves of outdoor light at night (LAN) and air pollution with risk of cerebrovascular disease (N=28 302).

Adjusted for age (timescale), sex, education, occupation, annual household income, body mass index, physical activity, alcohol drinking status, smoking status, plant-based diet index, hypertension, dyslipidemia, diabetes, gross domestic product, population density, and normalized difference vegetation index. $PM_{2.5}$ indicates particulate matter with an aerodynamic diameter ≤2.5 μm; and PM_{10}, particulate matter with aerodynamic diameter ≤10 μm.

between outdoor LAN and ischemic stroke was not significant after adjusted for air pollution (Figure S4).

Table S7 illustrates the joint effects of outdoor LAN and air pollution on CeVD. Compared with the reference (low level of both outdoor LAN and $PM_{2.5}$), participants with high level of both outdoor LAN and $PM_{2.5}$ had a 23% elevated risk of CeVD (HR, 1.23 [95% CI, 1.01–1.50]) and HR was 0.91 (95% CI, 0.73–1.14) for high level of outdoor LAN only, 1.21 (95% CI, 1.03–1.43) for high level of $PM_{2.5}$ only. Moreover, no interaction was observed between outdoor LAN and air pollution on both the multiplicative and additive scales (eg, $P_{interaction}$=0.367 and relative excess risk due to interaction [95% CI]=0.111 [−0.138 to 0.360] for outdoor LAN and $PM_{2.5}$). The results remained similar for ischemic stroke (Table S8).

Stratified analyses suggested no difference for the associations of air pollution and outdoor LAN with CeVD and ischemic stroke across subgroups, except for

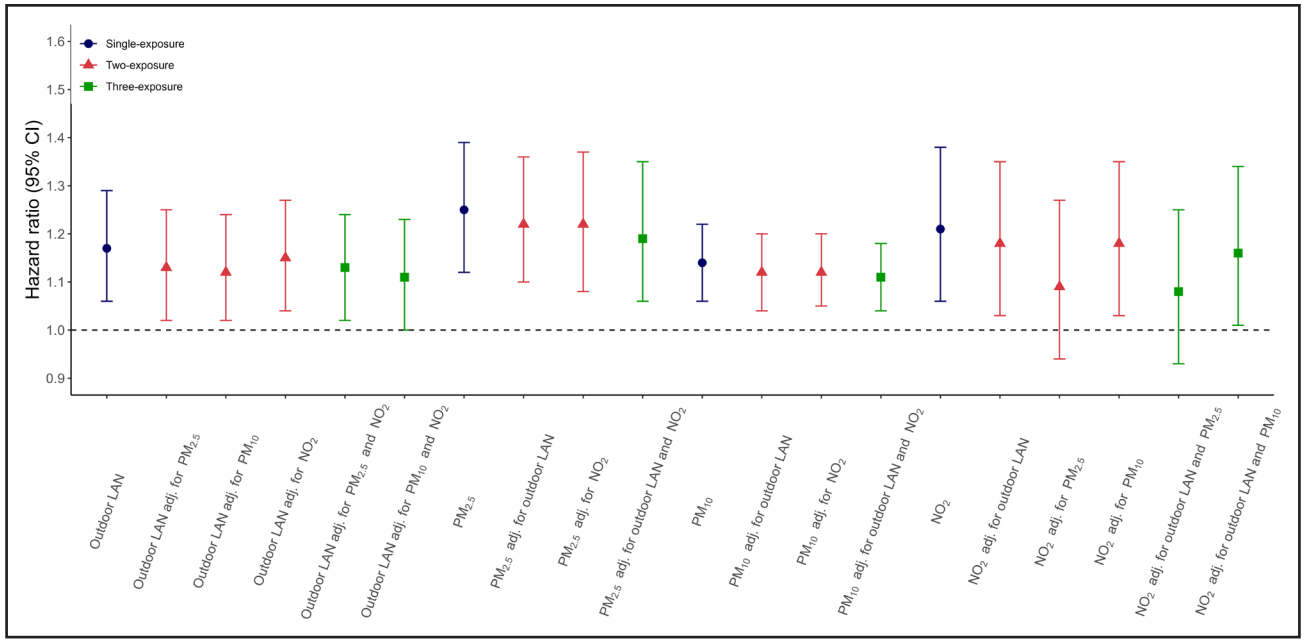

Figure 2. Multiple-exposure models for the associations of outdoor light at night (LAN) and air pollution with risk of cerebrovascular disease (CeVD; N=28 302).

All results were presented as hazard ratios (HRs) and 95% CIs for per interquartile range increase in exposure variables. Adjusted for age (timescale), sex, education, occupation, annual household income, body mass index, physical activity, alcohol drinking status, smoking status, plant-based diet index, hypertension, dyslipidemia, diabetes, gross domestic product, population density, and normalized difference vegetation index. $PM_{2.5}$ indicates particulate matter with an aerodynamic diameter ≤2.5 μm; and PM_{10}, particulate matter with an aerodynamic diameter ≤10 μm.

a stronger association for $PM_{2.5}$ and CeVD in subjects with low annual household income (<3000¥; Figure 3; Figure S5). In the sensitivity analyses, results were not materially changed when including only individuals who had resided at the baseline address for >10 years, using 2-year average levels of outdoor LAN and air pollution before baseline, excluding individuals working at baseline or diagnosed with ischemic heart disease at baseline (Tables S9 through S12). When using air pollution score as the exposure variable, the HRs for CeVD and ischemic stroke were 1.26 (1.14–1.40) and 1.28 (1.12–1.45) for per IQR increase (Table S13).

DISCUSSION

In this prospective cohort study based on the Chinese population, exposure to outdoor LAN and air pollution were positively associated with risk of CeVD, after adjusted for potential covariates. The results from sensitivity analyses were not substantially changed.

To date, our study was the first to examine the association between outdoor LAN and CeVD in a prospective cohort. Growing evidence has indicated potential adverse effects of outdoor LAN.[10–12] In a cohort study based on UK Biobank,[12] every IQR increase in outdoor LAN was associated with a 5% elevated risk of type 2 diabetes and a cohort study from Hong Kong[11] suggested that per IQR increase for outdoor LAN was associated with 11% elevated risk of coronary heart disease hospitalizations. Our findings were consistent with these studies,[11,12] for outdoor LAN in every IQR increase, the HRs were 1.17 (95% CI, 1.06–1.29) for risk of CeVD in the single-exposure models and the associations persisted in the multiple-exposure models. For ischemic stroke, the association was attenuated to null after further adjusted for air pollution, which may be limited by statistical power, so large prospective studies are still needed to explore the association between outdoor LAN and stroke subtypes. Urbanization (eg, regional economic indicators) and environmental exposures (eg, air pollution and greenness) were adjusted in our study. Based on previous studies,[19] these factors may be potential confounders on risk assessment of outdoor LAN and should be considered in future studies. In addition, some LAN sources such as compact fluorescent lamps, metal halide, and white LEDs seem to have a stronger melatonin-suppressive effect due to the peak distribution of short-wavelength light,[20] and it is recommended that light emitted outside at wavelengths ≤540 nm is banned to minimize the adverse effects on humans and animals,[21] but the association between type of LAN sources and CeVD still needs to be explored.

Despite some null studies,[22,23] our results were consistent with most of evidence,[24–26] suggesting exposure to higher level of air pollution elevated risk of CeVD. A meta-analysis of 20 studies reported an association between PM and overall stroke events[23] and a pooled analysis of 6 European cohorts within the ELAPSE (Effects of

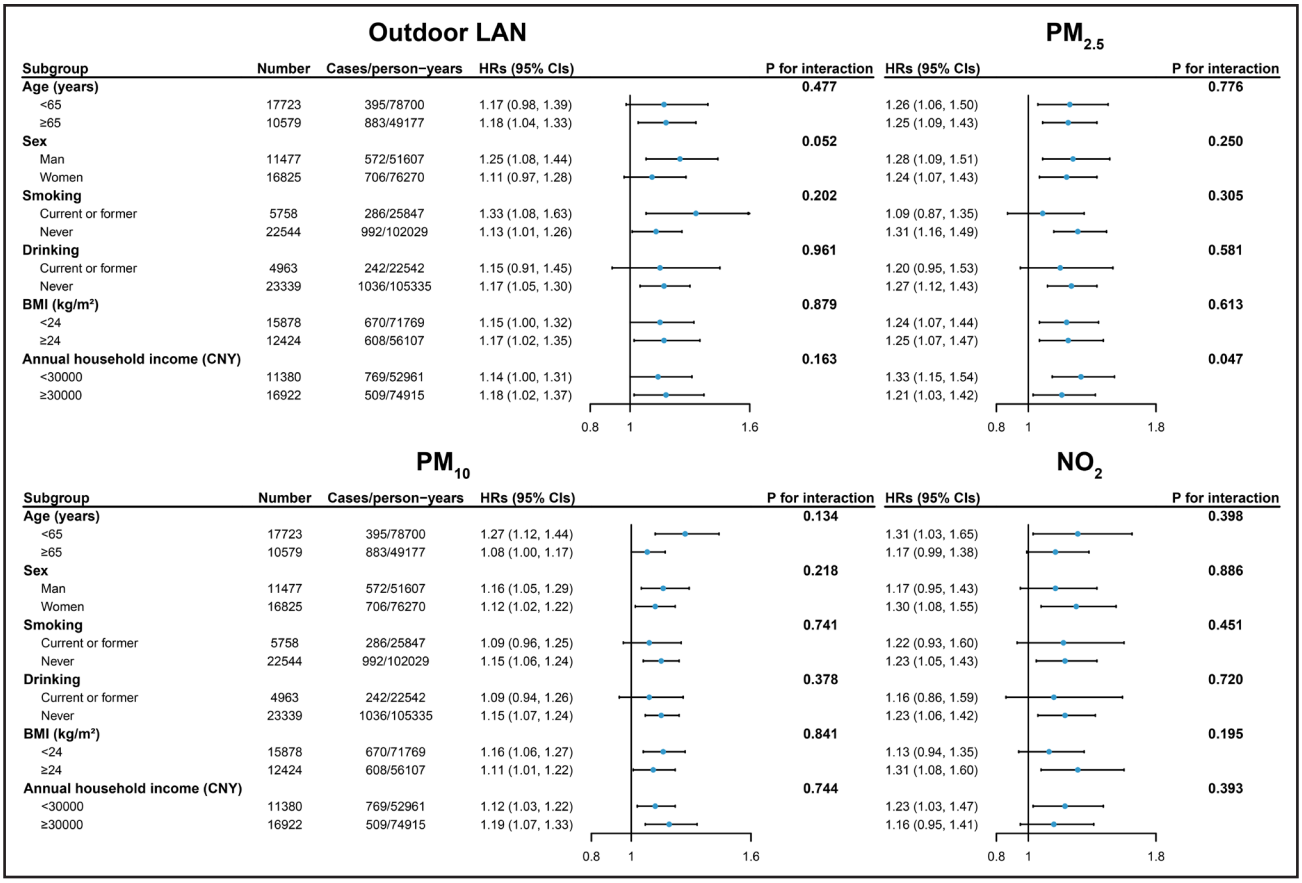

Figure 3. Stratified analyses for the associations of outdoor light at night (LAN) and air pollution with risk of cerebrovascular disease (CeVD).

All results were presented as hazard ratios (HRs) and 95% CIs for per interquartile range increase in exposure variables. Adjusted for age (timescale), sex, education, occupation, annual household income, body mass index (BMI), physical activity, alcohol drinking status, smoking status, plant-based diet index, hypertension, dyslipidemia, diabetes, gross domestic product, population density, and normalized difference vegetation index. $PM_{2.5}$ indicates particulate matter with an aerodynamic diameter ≤2.5 μm; and PM_{10}, particulate matter with an aerodynamic diameter ≤10 μm.

Low-Level Air Pollution: A Study in Europe) project suggested that $PM_{2.5}$ and NO_2 were positively associated with risk of stroke.[27] Recent studies have focused on the impact of air pollution on stroke subtypes and stronger association was observed for ischemic stroke in most studies,[24,26] which was similar to our results. Moreover, our study showed a stronger association between $PM_{2.5}$ and CeVD in low-income populations, in line with the findings of previous studies.[28] The underlying assumption is that higher-income populations have access to more resources to reduce exposure to air pollution.[29]

Limited evidence has demonstrated the combined effects of outdoor LAN and air pollution. Two nationwide cross-sectional studies from China[16,17] suggested that night-light index interacted with $PM_{2.5}$ and NO_2 on the prevalence of obesity and chronic kidney disease, but interpretation of these results required caution due to the cross-sectional designs. Inconsistent with previous studies, we observed no interaction between outdoor LAN and air pollution on risk of CeVD, which may be explained by the differences in sample size, exposure assessment, and primary outcomes besides the study design. Therefore, evidence from large-scale studies is still needed in the future to confirm these findings.

Although our findings are not based on metrics that reflect biologically relevant LAN exposure or photometric responses, there may be several potential mechanisms to support our findings. Exposure to LAN could lead to the body's circadian rhythm by suppressing melatonin secretion,[9] resulting in changes in biological indicators, including elevated triglyceride levels, C-reactive protein, blood pressure, and blood glucose, which are all triggers for the occurrence of CeVD.[13] Moreover, Air pollution could cause ischemic and hemorrhagic strokes by different mechanisms.[30,31] Air pollutants may induce a systemic inflammatory response that could lead to accelerated atherosclerosis, and then raise the risk of ischemic stroke.[32] In contrast, an elevated risk of hemorrhagic stroke may be achieved by provoking arterial vasoconstriction, elevated blood pressure, and increased susceptibility to cerebral vascular rupture by triggering endothelial dysfunction.[33,34] In our study, the effects of outdoor LAN and air pollution were independent of each other, probably because the pathogenic pathways

of outdoor LAN and air pollution are different and do not interfere with each other. However, several studies suggested the biological plausibility of the interaction between outdoor LAN and air pollution, whereby melatonin is effective in alleviating $PM_{2.5}$-induced atherosclerosis,[35] and the inhibition of melatonin secretion by outdoor LAN may amplify the adverse effects of $PM_{2.5}$. Therefore, further studies are necessary to investigate the interaction between outdoor LAN and air pollution.

The strengths of our study include prospective design, large sample size, adjusted for a range of confounders. Our study also has limitations that should be pointed out. First, there may be misclassification bias of exposure due to spatiotemporal variation. We only assessed exposure levels at baseline based on residential address and did not consider the movement of participants and changes in exposure over time especially in China with accelerated urbanization. Second, we did not obtain data on indoor lighting products and shading measures such as blackout curtains used by participants during nighttime; therefore, these results should be interpreted with caution as reflecting the association of CeVD with outdoor LAN rather than with total nighttime light in the bedroom. Third, satellite-based products may provide limited coverage of the spectral power distribution of outdoor LAN sources (500–900 nm) and rarely capture blue light sources (<500 nm), which may lead to an underestimated association between outdoor LAN and CeVD. Fourth, despite adjustment for regional economic and environmental factors, we did not control for effect of nighttime traffic noise as a potential confounder for lack of data. Fifth, due to the relatively short follow-up period, the number of cases in each stroke subtype was small. Considering the limited statistical power, we did not perform the analyses on stroke subtypes. Finally, our study included individuals from 1 district in Ningbo, and generalizability of our results could be limited.

CONCLUSIONS

In a prospective cohort study, we found that exposure to outdoor LAN and air pollution were positively associated with risk of CeVD. These findings could support the existing evidence on the harmful effects of outdoor LAN and air pollution and point out that outdoor LAN might be an emerging risk factor for CeVD.

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Disclosures

None.

Supplemental Material

Supplemental Methods
Tables S1–S13
Figures S1–S5
References 36–40

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