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Environmental Factors and Risk of Early-Onset Dementia: A Population-Based Case-Control Study

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Air pollution · Benzene · Early-onset dementia · Green spaces · Light at night

Abstract

Introduction: Dementia with symptom onset before the age of 65 is referred to as early-onset dementia (EOD). Many gaps exist regarding EOD etiology, including the role of environmental factors. ***Methods:*** We conducted a population-based case-control study in Modena province, Northern Italy, enrolling and geocoding 326 EOD cases and 1,941 sex- and age-matched controls, to investigate the association of traffic-related benzene, green spaces around the place of residence, and exposure to artificial outdoor light at night (LAN). We used nonlinear modeling to assess the relation between environmental variables and disease risk, overall, and separately for Alzheimer's dementia (AD) and non-AD. ***Results:*** Green spaces generally showed an inverse association with EOD risk that was almost linear for AD and inverted U-shaped for non-AD. We observed a weak positive association between traffic-related benzene exposure and EOD risk that seemed limited to AD, with little change in risk for non-AD. Exposure to LAN showed an inverse linear association with small differences across the two disease subgroups. Analyses stratified by sex and age showed generally stronger (but statistically imprecise) associations in females and older individuals. ***Conclusion:*** Overall, these results are consistent with some environmental influences on EOD risk, particularly with a beneficial effect of green spaces and LAN, as well as a possible adverse role of air pollution, particularly for AD.

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Introduction

Dementia is a neurological syndrome characterized by impairment that is severe enough to interfere with daily functioning [1, 2], including memory deficits and challenges in additional domains such as executive function and language. While typically associated with advanced age, dementia can also affect individuals younger than 65. Age at onset later or earlier than 65 years distinguishes between late-onset dementia (LOD) and early-onset dementia (EOD) [3]. Despite the common features of dementia, whether it is late-onset or early-onset, EOD presents unique and burdensome social and family challenges. Those afflicted are often part of the workforce and caretakers for their family members [4]. They experience a markedly higher mortality compared with same age people without dementia [5, 6]. The prevalence of EOD for those aged 30–64 years is 119 per 100,000 population aged 30–64 years [7, 8], though this value varies geographically [8–10], likely influenced not only by genetic variation and environmental factors but also access to health care. EOD includes different subtypes [9]. The most common include Alzheimer's dementia [11–14], vascular dementia [15–18], and frontotemporal lobar degeneration [19–22].

EOD and LOD have some common and some different risk factors [23], though their effects differ for EOD and LOD. These factors could include mutations in *APP*, *PSEN1*, and *PSEN2* genes [13, 24], Down's syndrome [25], traumatic brain injury [9, 11, 26, 27], lifestyle and dietary factors, exercise, and smoking [23, 28–30], as well as medical conditions such as Parkinson's disease [31], cardiovascular diseases [18, 32–34], and eventually environmental factors, including air pollutants [35].

Neurotoxic air pollutants such as those related to motorized traffic, including heavy metals and other contaminants, have been implicated in EOD etiology based on both human and laboratory evidence [36, 37]. Green spaces (or "greenness") have also been related to dementia risk [38, 39], either beneficially, i.e., thus suggesting a beneficial effect of natural vegetation surrounding homes and workplaces [40], or adversely, attributable to higher pesticide exposure among other factors [41]. Another environmental factor suggested to affect brain health adversely is light at night (LAN), possibly through disruption of circadian rhythms, sleep disturbances, and endocrine disturbances [42–44], though the epidemiologic evidence is still limited [45, 46].

The possible influence of these environmental factors (exposure to air pollution, green spaces, and LAN) remains uncertain, especially since these three factors are highly correlated and therefore may be mutually confounding. In this study, we aimed to investigate the possible association between these environmental factors and EOD in a Northern Italy population, while disentangling the possible independent effect of these factors.

Methods

Study Population

The study area is the province of Modena, located in Northern Italy in Emilia-Romagna Region, and has around 700,000 inhabitants and a surface of 2,688 km^2. We used a population-based case-control study design, following approval by the Ethical Committee of the Emilia-Romagna Region (approval No. AOU 0027399/21, "Area Vasta Emilia Nord" Ethical Committee). We attempted to recruit all patients diagnosed with EOD while residing in the Modena province during the period 1999–2021. To do that, we took advantage of the network of dementia services that covers the entire province and involves its two hospital-based outpatient cognitive neurology clinics (Modena Ospedale Civile di Baggiovara and Carpi Ramazzini hospitals), and eight community-based geriatric memory centers (Centri per i Disturbi Cognitivi e le Demenze [CDCD]). CDCDs serve patients living both at home and in nursing homes and they coordinate care for daytime services and a specialized unit for behavioral disturbances.

All diagnoses of dementia were based on the criteria from the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), which was also used to categorize patients according to dementia subtype as previously described [47], i.e., Alzheimer's dementia (AD) [48], Lewy body dementia [49], and frontotemporal dementia [50]. Diagnosis of each participant was reviewed by the neurologists of the Modena CDCD to ensure consistency of the specific clinical diagnosis and the timing of symptom onset. We excluded patients who were affected by developmental disorders, had chronic major psychiatric disorders, had cognitive impairment due to non-primarily cognitive neurological diseases, were younger than 30 years of age, or who resided outside Modena province.

For each EOD patient ("cases"), we selected 6 randomly chosen controls from the database of National Health Service Directory of Modena residents, matched by sex, year of birth, and calendar year. For the cases, we

obtained the address at the time of diagnosis or for controls at the time of diagnosis for the case to which that control was matched. For some instances, residence information of controls was not available or incomplete (e.g., street number was not reported). Therefore, some cases have 5 matching controls instead of 6.

Exposure Assessment

We geocoded the residential addresses of study subjects at the time of diagnosis by using satellite coordinate databases provided by the province of Modena and the Google Earth software within a Geographic Information System (GIS). We check the accuracy of all coordinates with ARC-GIS software (version 10.8, ESRI, Redlands, CA, USA, 2021).

Traffic-Related Air Pollution

We estimated the average annual outdoor exposure to the traffic-related air pollutant benzene using the California Line Source Dispersion Model version 4 (CALINE4) [51]. CALINE4 is a Gaussian dispersion model that specifies pollutant dispersion from mobile sources along roadways [52], predicting hourly pollutant concentrations at a height of 2 m. We ran the model based on 2006 traffic flow data for the Modena area. Despite traffic-related benzene levels have been modeled from data collected in 2006 due to the availability of validation data collected through ad hoc surveys, so not covering the entire period of diagnosis 1999–2021, and the Padana plain area being known for high levels of air pollutants due to its geomorphology [53, 54], benzene levels in this region have decreased but were stable during the last years, according to measurements at monitoring stations [55]. The model incorporated demographic and occupational information for all residents of the province, and detailed personal mobility information collected by the National Institute of Statistics 2001 Census, validated through ad hoc surveys and automatic vehicle counters in a few major roads. The model allowed to compute a matrix of vehicle movements for each road, on the basis of daily movements estimated for Modena residents taking into account their age, sex, family structure, and occupation [56]. The estimation of benzene levels was not feasible in three subjects (1 case and 2 controls); therefore, we excluded them from the analysis.

Green Space

To investigate green space exposure, we assessed the Normalized Difference Vegetation Index (NDVI) from the Copernicus Global Land Service, a component of the Land Monitoring Core Service of the European flagship program on Earth Observation. NDVI is a satellite-derived index used to quantify and monitor vegetation health and phenology state used as a proxy of green space exposure for epidemiologic purposes because it showed to be effective in capturing neighborhood greenness proximity [57]. NDVI ranges from −1 to +1; the closer the value is to 1, the greater the vegetation density and biomass. We specifically used NDVI data from PROBA-V miniaturized ESA satellite tasked with a full-scale mission to map land cover and vegetation growth across the entire planet. We measured NDVI values during the years 1999–2021, with reference to 5 years before each subject's diagnosis and to the same calendar year for the matched controls, thereby allowing for a 5 year induction period. We estimated individual exposure within 100 m and 200 m radius buffers centered at their residence. We checked the correlation between the estimates using Pearson's coefficient (online suppl. Fig. S1; for all online suppl. material, see https://doi.org/10.1159/000549445) and since we found a high correlation ($r = 0.947$), we selected the smaller buffer in order to compare results with similar investigations in previous studies [58, 59].

Outdoor Artificial Light at Night

We evaluated outdoor artificial light exposure during night hours at the subjects' residence using satellite data of the global nighttime light maps provided by the Earth Observation Group (EOG) of the Colorado School of Mine's Payne Institute. In particular, we used the Visible Infrared Imaging Radiometer Suite (VIIRS) [60], an instrument onboard the Suomi National Polar-Orbiting Partnership (Suomi NPP) spacecraft launched on October 28, 2011, that observes and collects global satellite observations that span the visible and infrared wavelengths across land, ocean, and atmosphere. This instrument also hosts a unique panchromatic day/night band, which is ultra-sensitive in low-light conditions and allows the observation of nighttime lights. For this study, we used annual nighttime radiance maps from the Annual VNL (VIIRS Nighttime Light) V2 dataset expressed in units of $nW/sr/cm^2$ [61].

We also extracted nighttime lights data provided by the Defense Meteorological Satellite Program (DMSP) available since 1992 till 2013 [62] to compare exposure in the investigated subjects. Despite the better temporal resolution of DMSP data over the period of diagnosis of cases, VIIRS data are characterized by higher spatial resolution (5 km for DMSP and 463.83 m for VIIRS in the Modena area). We checked the correlation of DMSP and VIIRS data using Pearson's coefficient (online suppl.

Fig. S2), which showed a moderately strong correlation (r = 0.593).

Since VIIRS data cannot be compared with older systems, especially due to improvements in radiometric resolution, and they have higher spatial resolution, we decided to use VIIRS data for LAN assessment in the overall study population. Finally, we checked the correlation across VIIRS data from 2014 to 2020 and based on the stability over time of this variable in the study area (as shown in online suppl. Table S1 and online suppl. Fig. S3 with Pearson's coefficients ranging from 0.924 to 0.992), we decided to use 2014 levels to attribute exposure to all study participants.

Data Analysis

We conducted the data analysis using a multivariable conditional logistic regression model that took into account the matching by sex, year of birth, and calendar year and mutual adjusting for the three investigated environmental factors. We modeled odds ratios (ORs) for fixed exposure categories as follows: for benzene, we used 0.6 μg/m^3 and 1.2 μg/m^3 as cut points for a trichotomy, based on the distribution of benzene levels in the control population. The lower cut point of 0.6 μg/m^3 is approximately the 66th percentile and corresponds to the proposed limit for benzene in ambient air pollution of 0.2 ppm [63]. The higher cut point was arbitrarily set at double the value of the lower cut point. For the variable representing green spaces, we computed the 25th and the 75th percentiles for the control population, rounding these values into 0.30 NDVI and 0.45 NDVI as was done in previous studies [58]; for LAN exposure, we formed a trichotomy based on information about the distribution from previous studies (using boundaries at 10 and 30 nW/sr/cm^2) [46, 64].

We fit a nonlinear model using restricted cubic splines with three knots at fixed percentiles (10th, 50th, and 90th). We used values of 1.20 μg/m^3, 0.36 (median), and 26 nW/sr/cm^2 (median) as reference points for benzene, greenness, and LAN, respectively. All the models were mutually adjusted for all environmental factors considered in this study.

We used the "mkspline" and "clogit" commands of Stata software (version Stata SE 19.0, Stata Corp., College Station, TX, USA, 2025) for all data analyses comprising the overall population and for those that distinguished between an AD and non-AD diagnosis. We also stratified the analysis according to potential effect-measure-modifiers such as sex and age (<55 and ≥55 years).

Results

The study included 326 EOD patients and 1,941 controls (Table 1). Overall, there were more females than males (53.2 vs. 46.8%). The median age was 60 years (IQR 57–64), with a range from 39 to 65 years, and most subjects being aged ≥55 years.

The most frequent EOD diagnosis was AD (N = 152, 46.63%), followed by frontotemporal dementia (N = 86, 26.38%) (online suppl. Table S2). Characteristics of EOD cases divided into AD and non-AD showed a higher proportion of females and slightly higher age at onset in AD cases (Table 1). Distribution of environmental factors showed substantial comparable exposure for cases and controls, with the partial exception of traffic-related benzene when considering AD and non-AD cases, these latter demonstrating fewer subjects in the highest exposure category.

Risk Analysis by Fixed Categories

In logistic regression analysis, using the lowest exposure category (out of three) as reference, we found that green space exposure was weakly and positively associated with increased risk in the 0.30–0.45 intermediate category (OR = 1.10, 95% CI: 0.83–1.47) but showed a strong inverse association in the highest exposure category (≥0.45 NDVI), with an OR of 0.44 (95% CI: 0.29–0.67) (Table 2). Stratified analysis by dementia diagnosis showed a monotonic decrease in risk with increasing green space exposure for AD diagnosis, whereas a stronger increase risk in the intermediate category can be noted for non-AD diagnosis.

The effect was somewhat stronger among females, who showed an inverse relationship in both categories and for both AD and non-AD diagnosis. Similarly in males, a stronger effect with increased risk was found in the intermediate category for overall EOD and non-AD diagnosis, while decreased risk in both categories was found for AD diagnosis (online suppl. Table S3). Stratified analysis by age at onset showed similar results for subjects with AD diagnosis with decreased risk in both categories, while opposite increased risk in subjects aged <55 years for non-AD diagnosis can be noted (online suppl. Table S4).

We also found weak evidence for a limited increase in EOD risk for exposure to benzene in the highest exposure category (≥1.20 μg/m^3, OR = 1.19, 95% CI: 0.79–1.76), slightly stronger for AD, while for non-AD diagnosis, higher risk was noted also starting from 0.60 μg/m^3 (Table 2). In the stratified analysis by sex, the increased risk was confirmed in females and especially with AD diagnosis, while in males, higher risk was found

Table 1. Characteristics of study population and exposure distribution divided in controls, EOD cases, and separately for AD and non-AD diagnosis

	Controls (*N* = 1,941), *N* (%)	All EOD cases (*N* = 326), *N* (%)	AD cases (*N* = 152), *N* (%)	Non-AD cases (*N* = 174), *N* (%)
Sex				
Females	1,034 (53.2)	174 (53.4)	102 (67.1)	72 (41.1)
Males	907 (46.8)	152 (46.6)	50 (32.9)	102 (58.9)
Age				
Median (IQR)	60 (57–64)	60 (57–64)	61 (58–64)	60 (56–63)
<55 years	310 (16.0)	52 (15.9)	18 (11.8)	34 (19.54)
≥55 years	1,631 (84.0)	274 (84.1)	134 (88.2)	140 (80.5)
Green spaces (NDVI)				
Median (IQR)	0.36 (0.29–0.47)	0.34 (0.29–0.42)	0.34 (0.28–0.42)	0.34 (0.30–0.42)
<0.30	557 (28.7)	90 (27.6)	49 (32.2)	41 (23.6)
≥0.30; <0.45	852 (43.9)	179 (54.9)	76 (50.0)	103 (59.2)
≥0.45	532 (27.4)	57 (17.5)	27 (17.8)	30 (17.2)
Benzene, μg/m^3				
Median (IQR)	0.39 (0.23–0.79)	0.36 (0.18–0.84)	0.38 (0.19–0.92)	0.34 (0.17–0.80)
<0.60	1,318 (67.9)	222 (68.1)	105 (69.1)	117 (67.2)
≥0.60; <1.20	371 (19.1)	59 (18.1)	22 (14.5)	37 (21.3)
≥1.20	252 (13.0)	45 (13.8)	25 (16.4)	20 (11.5)
LAN, nW/sr/cm^2				
Median (IQR)	25.7 (10.2–36.5)	23.1 (9.4–35.7)	24.2 (7.8–35.4)	21.0 (9.8–35.7)
<10	474 (24.4)	88 (27.0)	44 (28.9)	44 (25.3)
≥10; <30	676 (34.8)	113 (34.7)	50 (32.9)	63 (36.2)
≥30	791 (40.8)	125 (38.3)	58 (38.2)	67 (38.5)

AD, Alzheimer's dementia; EOD, early-onset dementia; IQR, interquartile range; LAN, light at night; NDVI, Normalized Difference Vegetation Index.

in subjects with non-AD diagnosis (online suppl. Table S3). Analysis divided by age at onset confirmed the increased risk for AD diagnosis in subjects aged ≥55, while for non-AD, younger subjects appeared to be at increased risk (online suppl. Table S4).

The association between LAN and EOD risk was also inverse and monotonic (≥10; OR = 1.00; <30 nW/sr/cm^2, OR = 0.64, 95% CI: 0.45–0.90; ≥30 nW/sr/cm^2, OR = 0.52, 95% CI: 0.33–0.77), with the results being roughly similar among those with AD and non-AD diagnosis (Table 2) and in males and females (online suppl. Table S3). When stratified by age at onset, subjects aged ≥55 years showed similar results, while in younger (<55 years) subjects, we found decreased risk for AD but increased risk for non-AD in the intermediate category (online suppl. Table S4).

Risk Analysis Using Nonlinear Modeling

Green spaces were associated with little change in risk from low to average levels of NDVI, but risk dropped nearly linearly as green space values approached high values (Fig. 1), with ORs of 1.05 (95% CI: 0.94–1.17), 0.75 (95% CI: 0.66–0.86), and 0.35 (95% CI: 0.22–0.56) at NDVI values, respectively, of 0.30, 0.45, and 0.60. We found a positive association between benzene exposure and EOD risk, increasing almost linearly above 1.2 μg/m^3 with ORs of 0.99 (95% CI: 0.87–1.14), 1.14 (95% CI: 0.95–1.37), 1.30 (95% CI: 0.90–1.86), and 1.48 (95% CI: 0.86–2.55) at benzene levels of 1.2, 1.8, 2.4, and 3.0 μg/m^3. LAN exposure was inversely related with EOD, with risk decreasing steadily throughout the range of LAN exposure with ORs of 1.43 (95% CI: 1.13–1.80), 1.13 (95% CI: 1.05–1.21), 0.93 (95% CI: 0.89–0.98), and 0.81 (95% CI: 0.67–0.98) at LAN exposure of 10, 20, 30, and 40 nW/sr/cm^2. Analysis stratified by AD and non-AD diagnosis showed a nearly linear inverse association between green spaces and AD risk, but an inverted U-shaped association for non-AD (Fig. 2). The association with benzene seemed limited to AD, with little change in risk for non-AD. LAN did not show substantial difference according to diagnosis.

Table 2. OR with 95% CI for EOD associated with green space, benzene, and artificial LAN exposure in overall population and separately for AD and non-AD diagnosis

Overall	Total EOD			AD			Non-AD		
Exposure	C+/C−	OR	95% CI	C+/C−	OR	95% CI	C+/C−	OR	95% CI
Green spaces (NDVI)									
<0.30	98/588	1.00	–	50/588	1.00	–	48/588	1.00	–
≥0.30; <0.45	169/813	1.10	0.83–1.47	75/813	0.83	0.54–1.27	94/813	1.40	0.94–2.09
≥0.45	59/540	0.44	0.29–0.67	27/540	0.27	0.14–0.51	32/540	0.66	0.37–1.19
Benzene, μg/m^3									
<0.60	222/1318	1.00	–	105/1318	1.00	–	117/1318	1.00	–
≥0.60; <1.20	59/371	0.97	0.70–1.36	22/371	0.72	0.43–1.23	37/371	1.24	0.80–1.91
≥1.20	45/252	1.19	0.79–1.76	25/252	1.29	0.73–2.26	20/252	1.10	0.62–1.97
LAN, nW/sr/cm^2									
<10	88/474	1.00	–	44/474	1.00	–	44/474	1.00	–
≥10; <30	113/676	0.64	0.45–0.90	50/676	0.53	0.32–0.86	63/676	0.76	0.47–1.21
≥30	125/791	0.52	0.35–0.77	58/791	0.40	0.22–0.72	67/791	0.64	0.38–1.08

Conditional logistic regression model matched by sex and age and with mutual adjustment of all environmental factors. AD, Alzheimer's dementia; C+, cases; C−, controls; CI, confidence interval; EOD, early-onset dementia; IQR, interquartile range; LAN, light at night; NDVI, Normalized Difference Vegetation Index; OR, odds ratio.

Dose-response analysis stratified by sex and age at onset is reported in online supplementary Figure S4, showing an almost linear relation in females and younger subjects (age <55) but an inverted U-shaped relation in males for green spaces. Further analyses divided by dementia diagnosis showed similar results for AD (online suppl. Fig. S5), while the relation was nonlinear with almost inverted U-shaped association in all subgroups for non-AD (online suppl. Fig. S6). Results for benzene exposure are confirmed in all age and sex subgroups considering overall EOD (online suppl. Fig. S7) and AD diagnosis (online suppl. Fig. S8). Conversely, we found increased risk in males and almost linear decrease in risk in females in the analysis restricted to non-AD diagnosis (online suppl. Fig. S9). Results for LAN exposure are substantially similar in all subgroups, with the exception of the little change in risk from average to high exposure in males and subjects aged ≥55 years for non-AD (online suppl. Fig. S10–S12). Overall, subgroup analyses generally exhibited wide confidence intervals for the risk estimates, indicating a lack of statistical precision as a result of the small size of many subgroups.

Discussion

In this Italian population, we found an indication of beneficial effects of green spaces and LAN near the place of residence for dementia onset occurring at a "young" age and a suggestion of detrimental effects of low-dose traffic-related benzene exposure. These associations differed somewhat in the two disease subtypes, AD and non-AD, and were nonlinear for both greenness and benzene, showing little increase until a threshold level was reached.

For green spaces, we found little evidence of any relation up to intermediate exposure levels, approximately 0.35 of NDVI value. Higher exposure levels clearly indicated a beneficial effect, in line with evidence concerning cognitive function and overall dementia risk [65, 66]. Natural environments play a role in reducing oxidative stress, which may be a cause for neurodegeneration [67]. Greener areas encourage outdoor activities and promote regular exercise, which is linked to improved brain health and a lower risk of cognitive decline [68–72]. Moreover, green spaces contribute to better air quality [70], reducing exposure to pollutants that could damage brain function. However, findings from our study indicate that there may be independent effects of green space and air pollution on brain health and specifically on cognitive function and dementia risk.

These findings are in line with studies showing lower incidence, mortality rates and risk of hospitalization from neurodegenerative diseases and specifically from AD and dementia [73–78] in association with higher green space exposure. Similarly to our findings, Li et al. [66] reported that exposure to green space or tree canopy

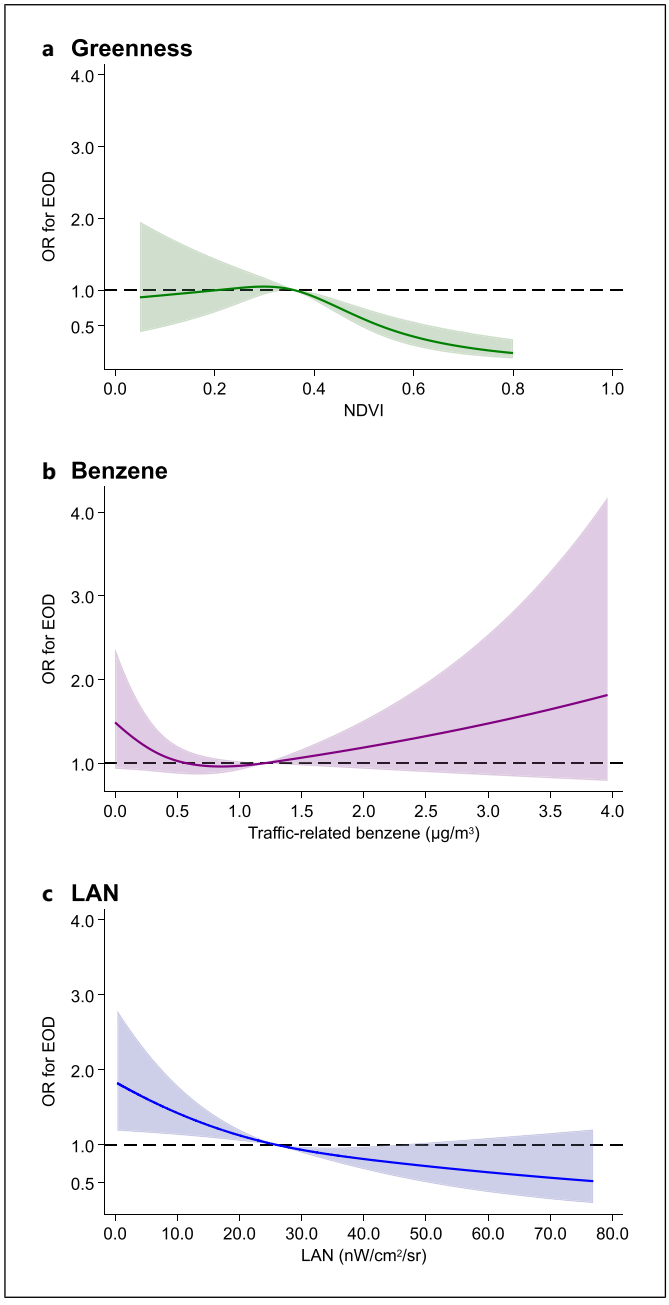

Fig. 1. Odds ratio (OR – solid line) with 95% confidence interval (gray area) for early-onset-dementia (EOD) associated with mean greenness (**a**), benzene (**b**), and light at night (LAN) (**c**) exposure. Conditional logistic regression models are matched by sex and age and mutually adjusted for the environmental factors greenness, benzene, and LAN.

improved cognitive performance. None of these studies addressed EOD in particular, whose etiology has been rarely investigated [28, 79, 80]. We found no excess risk associated with high greenness, i.e., at NDVI levels higher than 0.6–0.8. This result differed from the findings of a dose-response meta-analysis on risk of dementia in relation with green spaces, which showed a U-shaped pattern of association [58].

Results of this study also indicate that exposure to motorized traffic, and benzene in particular, could represent an independent risk factor for EOD and especially for AD, although the effect size is small and imprecise. So far, little is known about the possible effect of benzene on cognitive decline and EOD in particular, a disease subtype for which our knowledge of environmental risk factors is exceedingly limited [79, 80]. While there is growing evidence of an adverse overall effect of air pollution on dementia risk [81–83], little is known about a specific effect of benzene [84], and specifically on its subtype characterized by early onset [35]. Benzene is a contaminant that is thought to reach the brain by crossing the blood-brain barrier, adversely influencing protein expression and enzymatic activity [85, 86]. We note that benzene exposure could also be a proxy for other contaminants that cause EOD, thus simply indicating a general detrimental effect of air pollution on EOD risk [87].

Concerning LAN exposure, we found that probability of developing EOD gradually decreased with increasing LAN exposure. There are preliminary indications that LAN can be positively associated with social activities and interactions, beneficially affecting cognitive health, though the exact extent of such effect still needs to be adequately characterized [88–90]. Our findings differ from those of previous studies that reported inverse associations of cognitive scores and neuropsychiatric symptoms with light pollution [66, 91], but previous investigations did not specifically focus on EOD. LAN can extend both productive hours and the time spent after work in social activities and outdoor, thus encouraging physical activity, mental engagement and social interactions, with beneficial effects on cognitive decline especially in younger subjects. In such cases, LAN would represent a proxy for other relevant exposures for EOD etiology [88, 90, 92, 93]. Our findings about the relation between environmental factors and EOD have to be considered as specific for this early form of cognitive decline and not necessarily relevant for LOD, given some different preliminary results relating to LOD [46, 75] and uncertainties about the etiologies of these two clinical dementia subtypes [94, 95].

One limitation of this study is the low prevalence of high levels of benzene exposure in this population; only a small proportion of the control series had exposure that exceeded 1 µg/m^3. Another limitation is that our exposure modeling was based on data from 2006, a year that is within the period of recruitment of incident cases but may not

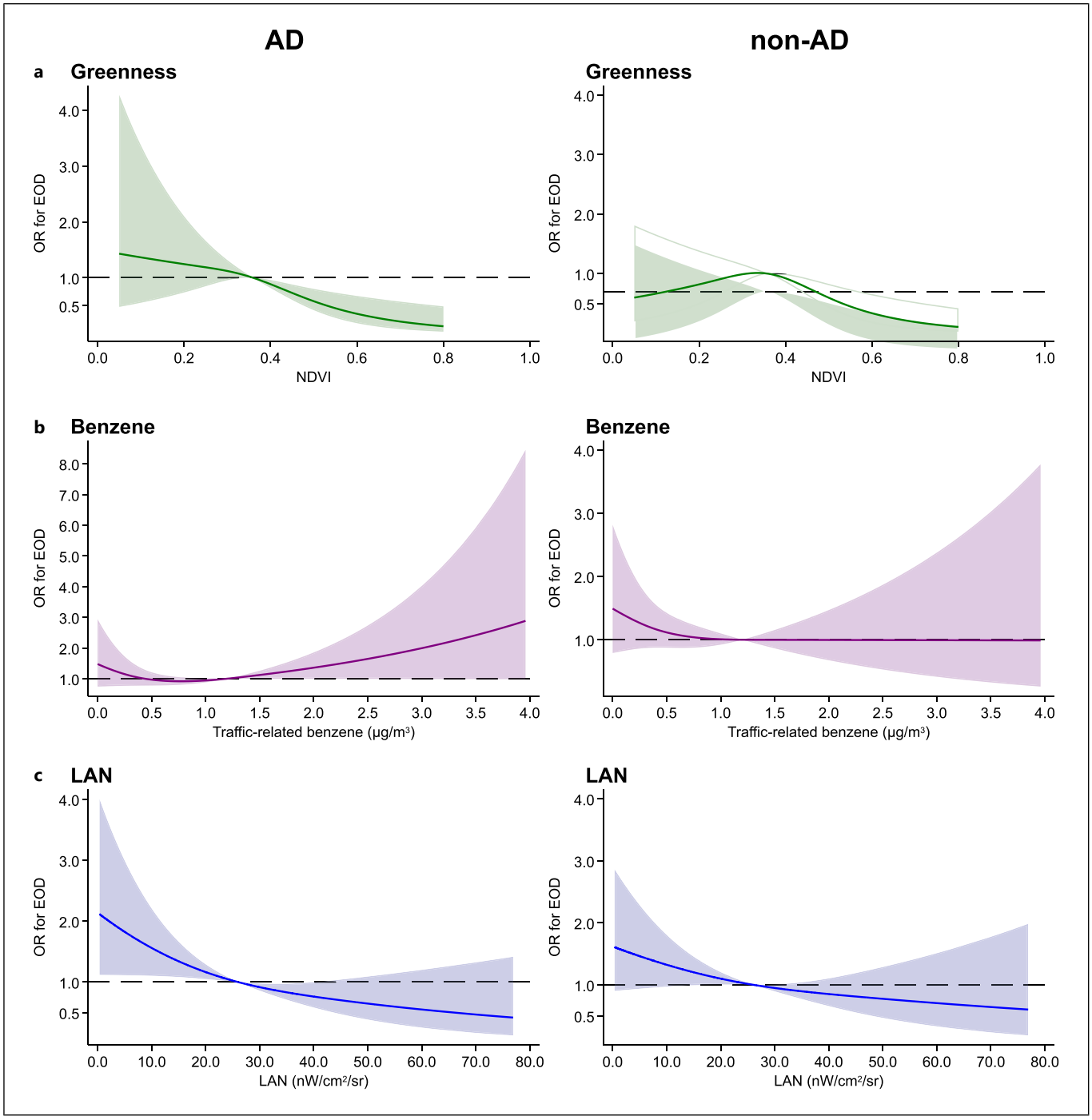

Fig. 2. Odds ratio (OR – solid line) with 95% confidence interval (gray area) for early-onset dementia (EOD) associated with mean greenness (**a**), benzene (**b**), and light at night (LAN) (**c**) exposure divided by diagnosis of Alzheimer's dementia (AD) and non-AD. Conditional logistic regression models are matched by sex and age and mutually adjusted for the environmental factors greenness, benzene, and LAN.

accurately reflect long-term antecedent exposure. If the disease has a long induction time, this limitation could be important [96]. On the other hand, although the induction time between exposure and occurrence of dementia onset, if there is a causal relation, is not known, there was little residential mobility in Modena during the study period,

with a nearly stable population size and vehicle number, as well as stable benzene air concentrations in the last decades. Therefore, we believe that the 2006 values should be reasonably representative of the entire time period of the study [97]. Similar stability over time also applies to LAN exposure [98, 99], mitigating the uncertainty about the disease induction period and of the different time points used in defining exposure status of study participants. Similarly, for green space, analysis of vegetation trends for Europe over the period 1981–2018 showed a modest positive NDVI trend of limited magnitude across about 55% of Europe when considering the full growing season [100]. This observation indicates that, for closely spaced years as in our study, assuming a constant annual NDVI introduces minimal bias, especially in highly urbanized areas where vegetation cover is limited.

Another limitation concerning LAN is lack of collection of indoor LAN exposure, though indoor and outdoor LAN appear to be positively correlated [101]. In addition, we lacked information regarding the subjects' education level, socioeconomic status, lifestyle, and comorbidities such as diabetes and other chronic diseases, all of which could have accounted for some confounding of the results, given that higher educational attainment and economic status could be associated with higher availability of green spaces and lower air pollution levels. Finally, some subgroups of the study population were too small to allow meaningful stratified analyses or to yield statistically precise results, thus hampering our ability to detect heterogeneous and highly specific results across such subgroups.

Strengths of our study include its large size, population-based design and the collection of study data without the need to contact study participants, thus avoiding biases related to self-selection, nonresponse, and information bias. Likewise, the use of residential history to assess exposure avoided recall bias. Case identification was based on a thorough neurological evaluation carried out and updated according to the most recently validated criteria. Finally, the use of spline regression avoided unnecessary assumptions that come with linear or other parametric models, elucidating the pattern in the data rather than imposing a pattern via modeling assumptions.

Statement of Ethics

This study protocol was reviewed and approved by the "Area Vasta Emilia Nord" Ethical Committee of the Emilia-Romagna Region (approval No. AOU 0027399/21). The study has been granted an exemption from requiring written informed consent by same Ethical Committee as it has been conducted using registry data.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Conceptualization: A.Chi., M.V., and T.F.; data curation: C.S., A.Chi., A.Che., N.M., S.C., F.D., G.D.G., and T.F.; formal analysis: C.S. and T.F.; funding acquisition: T.F.; investigation: C.S. and T.F.; methodology: A.Chi., K.J.R., G.M., S.T., T.F., and M.V; resources: A.Chi., N.M., A.Che., S.C., F.D., M.T., G.V., and G.Z.; project administration: M.V. and T.F.; supervision: A.Chi., M.V., and T.F.; writing – original draft: C.S., K.J.R., M.V., and T.F.; and writing – review and editing: all authors.

Data Availability Statement

The data that have been used are confidential and are not publicly available due to restrictions on their containing information that could compromise the privacy of research participants.

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