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Impact of urban environmental exposures on cognitive performance and brain structure of healthy individuals at risk for Alzheimer's dementia

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ABSTRACT

Background: Air quality might contribute to incidence of dementia-related disorders, including Alzheimer's dementia (AD). The aim of our study is to evaluate the effect of urban environmental exposures (including exposure to air pollution, noise and green space) on cognitive performance and brain structure of cognitively unimpaired individuals at risk for AD.

Participants and methods: The ALFA (ALzheimer and FAmilies) study is a prospective cohort of middle-age, cognitively unimpaired subjects, many of them offspring of AD patients. Cognitive performance was measured by the administration of episodic memory and executive function tests (N = 958). Structural brain imaging was performed in a subsample of participants to obtain morphological information of brain areas, specially focused on cortical thickness, known to be affected by AD (N = 228). Land Use Regression models were used to estimate residential exposure to air pollutants. The daily average noise level at the street nearest to each participant's residential address was obtained from noise maps. For each participant residential green exposure indicators, such as surrounding greenness or amount of green, were generated. General linear models were conducted to assess the association between environmental exposures, cognitive performance and brain structure in a cross-sectional analysis.

Results: No significant associations were observed between urban environmental exposures and the cognitive composite ($p > 0.1$). Higher exposure to air pollutants, but not noise, was associated with lower cortical thickness in brain regions known to be affected by AD, especially NO_2 ($\beta = -16.4$; $p = 0.05$) and PM_{10} ($\beta = -5.34$; $p = 0.05$). On the other hand, increasing greenness indicators was associated with greater thickness in these same areas ($\beta = 0.08$; $p = 0.03$).

Conclusion: In cognitively unimpaired adults with increased risk for AD, increased exposure to air pollution was suggested to be associated with greater global atrophy and reduced volume and thickness in specific brain areas known to be affected in AD, thus suggesting a potential link between environmental exposures and cerebral vulnerability to AD. Although more research in the field is needed, air pollution reduction is crucial for decreasing the burden of age-related disorders.

Abbreviations: AD, Alzheimer's dementia; Aβ, Amyloid- β eta; β, β eta coefficient; ALFA, ALzheimer and FAmilies; BMI, Body Mass Index; CI, Confidence Interval; CSF, Cerebrospinal Fluid; MBT, Memory Binding Test; MRI, Magnetic Resonance Imaging; NDVI, Normalized Difference Vegetation Index; NO_2, Nitrogen dioxide; NOx, Nitrogen Oxides; PM, Particulate Matter; ROI, Regions of Interest; SD, Standard Deviation; SE, Standard Error; WAIS, Wechsler Adult Intelligence Scale; TIV, Total Intracraneal Volume

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1. Introduction

Alzheimer's dementia (AD) is the most common cause of dementia and the first cause of neurological disability in the elderly, causing enormous social and economic burden in modern societies (Takizawa et al., 2015). Currently, more than 45 million people suffer from dementia worldwide and this figure is expected to increase to up to 130 million in 2050 as a consequence of the increase in average life expectancy that has occurred in developed countries, and the progressive aging of the population (Alzheimer's Disease International, 2015). Epidemiological studies have identified both modifiable and non-modifiable risk factors associated with an increased incidence of the disease (Barnes and Yaffe, 2011). It has been reported that a third of AD cases could be due to potentially modifiable risk factors (Norton et al., 2014).

Natural history of AD includes an asymptomatic preclinical stage characterized by the presence of brain alterations in the absence of symptoms (Vos et al., 2013). Implementation of AD prevention strategies requires the availability of affordable and non-invasive methods to predict this stage. Given the paucity of evidence for effective disease-modifying treatments, and the recognition that the disease process begins years in advance of symptoms, recent attention has focused on primary prevention, since it could significantly reduce disease estimate future burden. Therefore, to identify potentially modifiable risk factors that influence cognitive performance, brain structure, and consequently AD risk, is of high relevance in order to develop effective public health strategies for disease prevention.

Individuals living in cities often experience exposure to high levels of air pollution and noise, and a lack of natural outdoor environments, which may be detrimental to health (Nieuwenhuijsen, 2016). Long term exposure to air pollution (Beelen et al., 2014; Hoek et al., 2013) and noise (Halonen et al., 2015) and the lack of green space exposure (Gascon et al., 2016) has been associated with premature all-cause mortality (Nieuwenhuijsen et al., 2018), and other health detrimental effects, including mental health (Kioumourtzoglou et al., 2017; Power et al., 2015; Pun et al., 2017).

Urban environmental exposures include air pollution, a mixture of solid particles (including organic components and metals) and gases (such as nitrogen, sulfur oxides and ozone) in the air, which is a well-known environmental hazard, and has been shown to have adverse health effects through mechanism such as inflammation and oxidative stress (Holgate, 2017; Møller et al., 2010). It has been shown that air quality might contribute to incidence of dementia-related disorders, including AD (Chen et al., 2017; Moulton and Yang, 2012; Underwood, 2017). A growing body of epidemiological research suggests that exposure to ambient air pollution has neurological effects, and might have a causal influence via harmful effects on the brain, accelerating cognitive aging, and may even increase the risk of AD and other forms of dementia (Calderón-Garcidueñas et al., 2008; Campbell et al., 2005; Maher et al., 2016). Existing literature on the potential association between exposure to air pollution and cognitive decline has been summarized in several systematic reviews (Clifford et al., 2016; Killin et al., 2016; Peters et al., 2015; Power et al., 2016; Xu et al., 2016). Moreover, a recent publication has evaluated the association between air pollution exposure and cognitive performance in adults indicating small but consistent negative effects (Cullen et al., 2018). Additionally, exposure to fine particles has been related to brain structural and functional alterations in children (Guxens et al., 2018; Pujol et al., 2016). However, evidence on the association between air pollution and neuroimaging hallmarks of AD pathology is inconsistent (Power et al., 2016).

Like air pollution, exposure to noise has been associated with adverse impacts on quality of life and health. However, few epidemiological studies have reported a link between high levels of traffic-related noise, cognitive decline and AD (Oudin et al., 2016; Power et al., 2011; Tzivian et al., 2016; Wellenius et al., 2012; Wilker et al., 2015).

While exposure to air pollutants and noise may negatively influence cognitive decline, an accumulating body of evidence suggests that exposure to other urban exposures, such as urban green spaces, might have health-promoting effects, including improved mental health and reduced morbidity and mortality (Dadvand et al., 2018a; Gascon et al., 2016, 2015; Lee and Maheswaran, 2011). Exposure to green space has been linked to cognitive development in early stages of life, which can have long-term effects in cognitive function in adults and cognitive decline in the elderly (Preuß et al., 2019). However, even though there is a suggestive beneficial effect of exposure to green spaces on cognitive function, the number of studies examining such associations is still very limited. In the review by Keijzer and colleagues (Keijzer et al., 2016), authors conclude that, considering the limited number of available studies, most of poor or fair quality, the existing evidence on the association between green spaces and cognition can be considered as inadequate; however, it is suggestive for beneficial associations between such an exposure and cognitive development in childhood and cognitive function in adulthood. Additionally, in a recent longitudinal study authors report that higher residential surrounding greenness was associated with slower cognitive decline over a 10-y follow-up period (de Keijzer et al., 2018).

The *aim* of our study is to evaluate the association between exposure to urban environmental exposures (including air pollution, noise and green space) and cognitive performance in cognitively unimpaired individuals at risk for AD. Furthermore, we aim to evaluate the association between exposure to air pollution, green spaces and noise, with the morphometry of brain areas known to be affected by AD.

2. Methods

2.1. Study participants

The present is a cross-sectional analysis that was conducted in the context of an existing study, the ALFA (Alzheimer and Families) cohort. The details of the recruitment and participant's characteristics have been extensively described elsewhere (Molinuevo et al., 2016). Briefly, the ALFA study includes a total of 2,743 cognitively unimpaired men and women, aged 45–74, many of them kindred of AD patients (86% had at least one parent with dementia regardless age at onset, 48% of the participants had at least one parent diagnosed with AD before the age of 75). Participants were characterized at their baseline visit in 2013–2014 at multiple levels (sociodemographic, anthropometric, clinical, epidemiological, cognitive, genetic, and neuroimaging). Among ALFA participants, a higher frequency of the *APOE-ε4* allele has been observed compared to general population (19% vs 14% respectively; $P < 0.001$), confirming enrichment for AD risk. Other variables of interest collected at baseline include those related to lifestyle, medication use and cardiovascular risk factors, all of them variables that have been suggested as modifiable risk factors, both in relation to cognitive decline and dementia risk in general. Exclusion criteria included: 1) Cognitive performance falling outside the established cutoffs (Mini-Mental State Examination < 26, or Memory Impairment Screen < 6, or Time-Orientation subtest of the Barcelona Test II < 68, or semantic fluency < 12); 2) Clinical Dementia Rating scale > 0; 3) Major psychiatric disorders (according to DSM-IV-TR) or diseases that could affect cognitive abilities (current major depression or general anxiety disorder, bipolar disorder, schizophrenia, and dementia); 4) Severe auditory and/or visual disorder, neurodevelopmental and/or psychomotor disorder; 5) Significant diseases that could currently interfere with cognition (renal failure on hemodialysis, liver cirrhosis, chronic lung disease with oxygen therapy, solid organ transplantation, fibromyalgia, active cancer in treatment, or any other disease the investigator considered could affect the participant's cognition); 6) Neurological disorders, such as Parkinson's disease, stroke, epilepsy under treatment with frequent seizures (> 1/month) in the past year, multiple sclerosis, or other serious neurological diseases; 7) Brain injury

that could interfere with cognition: history of head trauma with parenchymal lesion or extraaxial macroscopic large vessel ischemic stroke or hemorrhagic stroke, brain surgery, brain tumors, or other causes that could generate acquired brain damage such as cerebral chemotherapy or radiotherapy, and, 8) suspected pattern of family history of autosomal dominant AD: three affected individuals in two different generations with an onset before the age of 60 years.

Following previous analyses on the health effects of air pollution using ALFA data (Vert et al., 2017), due to the heterogeneity of the air pollution and noise measures in the rest of Catalonia, and the small number of participants residing in other parts of Spain (Vert et al., 2017), the present study only includes participants who were living in the city of Barcelona at baseline, and did not change their residence for at least the previous 3 years. A total of 958 ALFA participants, resident in Barcelona, had reliable geocoded data to allow allocating an exposure to them based on the address of residence. All 958 participants had complete information on cognitive performance and were therefore included in the present analysis. Of those, a subset of 228 participants had additional information on brain structure from structural magnetic resonance imaging (MRI).

The local Ethics Committee approved the ALFA study, and all subjects and their accompanying close relative signed an informed consent form.

2.2. Exposure assessment

Residential exposure to air pollutants. Air pollution measurements were collected as a part of the air pollution monitoring campaign of the European Study of Cohorts for Air Pollution Effects (ESCAPE; http://www.escapeproject.eu/) (Beelen et al., 2013; Eeftens et al., 2012). In the city of Barcelona, nitrogen oxides (NO_2 and NO_x) and particulate matter ($PM_{2.5}$[particulate matter with aerodynamic diameter less than 2.5 μm], PM_{10} [less than 10 μm], PM coarse [PM2.5–10, i.e., coarse particulate matter, between 2.5 μm and 10 μm], and $PM_{2.5}$ absorbance [$PM_{2.5}$ light absorption]) were measured in three different seasons (warm, cold, and one intermediate temperature season) to model an annual average for 2009. Following well established protocols (Beelen et al., 2013; Eeftens et al., 2012), we used a Land Use Regression (LUR) model, based on geographical information system (GIS) and statistical methods, to estimate individual levels of air pollution at the participant's residential addresses reported in 2013–2014.

Residential exposure to environmental noise levels. Noise exposure was estimated using Strategic Noise Map of Barcelona (2012–2017; https://sig.gencat.cat/visors/soroll.html) as provided by the city council (one assessment every 5 years under the European Noise Directive). The map was developed with a comprehensive set of standardized noise measurements, according to the Environmental Noise Directive 2002/49/EC (European Commission; http://ec.europa.eu/environment/noise/directive_en.htm), which aims to protect the population from noise pollution. The daily average noise level at the street nearest to each participant's residential address was registered. Total noise level at night (11 pm to 7am), and total noise level based on Lden index (day-evening-night average) were estimated.

Residential exposure to green space. We used different indicators of exposure to residential green spaces within a buffer of 300 m around participant's residence. To assess the amount of green space we used the Map of Land Covers of Catalonia, 2013 (http://www.creaf.uab.es/mcsc/textos/InterpretacioLlegendaMCSC_ANGLES.pdf), which is based on orthophotos with a minimum map unit of 500 m2 (0.5 ha). The map contains a total of 241 simple covers, which can be hierarchically grouped into different levels. To conduct this study, three green spaces categories were created: agricultural green, which included arboreal and herbaceous crops, forest green, which included sclerophyllous, deciduous and conifer forests, and urban green, which included artificial green areas and urban woodland. The categorization of the urban green space comes from an Urban Atlas, which is a database that is normally used for this type of studies. The classifications are standard across Europe. Using residential address of the participants, which was reported by them at recruitment (2013–2014), we calculated the hectares of green space using specific buffers typically used in previous studies (Gascon et al., 2015). To define surrounding greenness, we used the normalized difference vegetation index (NDVI). The NDVI is an indicator of greenness and is based on land surface reflectance of visible (red) and near-infrared parts of the spectrum (Weier and Herring, 2000). The NDVI came from one imagine in the greenest season of the year (May), and provides information on the actual greenness captured by satellite, including small shrubs, grass, etc., independently of the type of land use. Its values range from −1 to 1, with higher positive numbers indicating more greenness (i.e. photosynthetically active vegetation). The index was derived from the Landsat 4–5 TM data at 30 m × 30 m resolution. The Landsat 5 imagery data atmospherically corrected was acquired for 26/07/2009 covering Barcelona city area.

2.3. Outcome assessment

Cognitive performance evaluation. During neuropsychological evaluation at baseline, all participants were administered a cognitive test battery for the detection of early decline in longitudinal follow-up. This battery assesses episodic verbal memory measured by means of the Memory Binding Test (MBT) (Buschke, 2014; Gramunt et al., 2015), as well as executive and reasoning functions assessed by Wechsler Adult Intelligence Scale (WAIS)-IV including psychomotor speed, visual processing, executive function, and non-verbal and verbal reasoning (Coding, Visual Puzzles, Digit Span, Matrix Reasoning, and Similarities) (Wechsler, 2012). A composite to assess cognitive performance was created based on the Preclinical Alzheimer Cognitive Composite (PACC) (Donohue et al., 2014). The original PACC combines tests that assess episodic memory, timed executive function, and global cognition. In our study, we created a modified-PACC (mPACC) composite by averaging the z-scores of the following variables: MBT immediate total paired recall, MBT delayed free recall, WAIS-IV Coding, and semantic fluency. Moreover, we computed two additional cognitive composites to assess global episodic memory and executive function by creating z-scores for the cognitive measures from MBT and from WAIS-IV subtests, respectively. These global measures were calculated by averaging normalized raw scores of all subtests in each domain (Brugulat-Serrat et al., 2018). As with the individual cognitive tests, higher scores in the different composites represent better cognitive performance, while lower scores correspond to worse cognitive performance.

Brain image data acquisition. MRI was conducted in a 3.0-T scanner (GE Discovery MR750 W) at baseline. However, MRI was performed at a later date compared to cognitive assessment. The mean time interval between cognitive assessment and MRI was 11 months. Structural 3D high-resolution T1-weighted images were collected using a fast spoiled gradient-echo sequence implementing the following parameters: voxel size = 1 mm3 isotropic, Repetition Time = 6.16 ms, Echo Time = 2.33 ms, inversion time = 450 ms, matrix size = 256 × 256 × 174, and flip angle = 12°. Cortical thickness and volumes of specific regions of interest (ROI) were determined using FreeSurfer version 6.0, which is a set of software tools for the study of cortical and subcortical anatomy (Fischl, 2012). We determined an AD signature as a composite measure reflecting cortical thickness of specific AD vulnerable regions. The AD signature was calculated by averaging individual cortical thickness regions of the following ROIs (both, right and left areas were included): entorhinal, inferior and middle temporal, fusiform, posterior cingulate, precuneus and supramarginal gyri (Dickerson et al., 2009; Clifford R. Jack et al., 2015; Wirth et al., 2013). In addition, volumes of specific AD-related regions (e.g., hippocampus), as well as regions known to indirectly reflect global (regionally unspecific) brain atrophy (i.e., ventricles) were also measured as additional AD-related outcomes (Dickerson and Wolk, 2012; Schwarz et al., 2016). ROI volume variables were corrected by estimated total intracranial volume (TIV).

2.4. Other variables

Clinical, sociodemographic and epidemiological information was obtained for all study participants at baseline (Molinuevo et al., 2016). Basic sociodemographic data and anthropometric measures were also registered at baseline visits. All participants were asked about their familial and personal medical history, and chronic medication use was recorded. Participants' weight, height, blood pressure, and waist and hip circumference were measured. Their weight and height measurements were used to calculate their body mass index (BMI). Additional epidemiological information was obtained by means of self-reporting questionnaires (e.g., physical activity, dietary habits, alcohol, tobacco, and drug consumption, sleeping habits, among others).

2.5. Statistical analysis

General linear models were conducted to assess the association between urban environmental exposures (air pollution, noise and green spaces) and the two main outcome variables of interest (the cognition composite and the cerebral AD-signature) in a cross-sectional analysis. In addition, we also conducted exploratory analyses against composites of cognitive domains (episodic memory and executive function) and the volume of specific ROIs (hippocampus and ventricles). Both, exposures and outcomes, were included in the models as continuous variables.

Furthermore, we performed mediation analyses (Tingley et al., 2013.) to establish the mediation role of air pollution in the association between exposure to green spaces and our outcomes.

Clinical, sociodemographic and epidemiological factors were considered as potential confounders of the evaluated associations. Models included age (years), gender (female/male) and years of education (years) in the models as potential confounders. Additional multivariable-adjusted stepwise models including BMI (kg/m^2), smoking status at baseline (never/former/current smoker), physical activity (metabolic equivalent, METS, of activity per day), self-reported diabetes status (no/yes), self-reported hypertension (no/yes), self-reported high cholesterol or high blood pressure (no/yes), family history of AD diagnosed before 75 years old (no/yes), and APOE status (non-carrier of the APOE-e4 allele/carrier of the APOE-e4 allele) were performed and confounders were included in the model if they significantly altered the estimates.

Main analysis included a total of 958 ALFA participants, resident in Barcelona, with complete information on cognitive performance. Of those, a subset of 228 participants with additional information on MRI-derived brain structure variables were included in the present analysis.

All reported p values are two sided, and an α level of 0.05 was used to define statistical significance. All analyses were conducted using R statistical software package (version 3.3.3; R Development Core Team).

3. Results

Main characteristics of ALFA study participants and of the subset of participants included in the present analysis are shown in Table 1 (more details in Molinuevo et al., 2016; Vert et al., 2017; Gascon et al., 2018) (Gascon et al., 2018; Molinuevo et al., 2016; Vert et al., 2017). There were no statistically significant differences regarding age, gender and years of education between the whole ALFA study cohort and the 958 participants residing in Barcelona and included in the present analysis. Moreover, no significant differences are seen regarding exposure, nor outcomes distribution (Table 1). A descriptive analysis of the exposures included in the present study are described in Supplementary Table 1. The concentrations of all air pollutants in Barcelona were above the WHO annual guidelines (World Health Organization, 2017).

The correlation coefficients between the main urban environmental exposures evaluated in the present study, and also the main confounders are presented in Supplementary Table 2. Correlation among air pollutants and noise levels ranged between 0.49 and 0.98, while the correlation between these two type of pollutants and surrounding greenness was negative (between −0.38 and −0.59). No correlations

Table 1
Main characteristics of ALFA study participants and of the subset living in Barcelona included in the present analysis.

Descriptive variables	All ALFA Participants N = 2743	ALFA living in Barcelona N = 958	ALFA with MRI N = 228
Age (years)			
Mean (SD)	56.3 (6.8)	57.0 (7.0)	57.7 (7.6)
Gender			
Female	1732 (63.1%)	612 (63.9%)	136 (59.7%)
Male	1011 (36.9%)	346 (36.1%)	92 (40.3%)
Years of education			
Mean (SD)	13.3 (3.5)	14.1 (3.4)	14.0 (3.3)
Smoking status at baseline			
Never	408 (17.5%)	133 (16.0%)	30 (13.7%)
Former	1340 (57.6%)	466 (55.9%)	125 (57.0%)
Current	577 (24.8%)	234 (28.1%)	64 (29.3%)
BMI (kg/m2)			
Mean (SD)	26.9 (4.3)	26.6 (4.2)	26.6 (3.9)
Physical Activity (mets/day)			
Mean (SD)	2817 (3.757)	2797 (3.384)	2807 (3.467)
Hours of sleep			
Mean (SD)	7.0 (0.9)	7.0 (0.8)	7.0 (0.8)
Marital status			
Divorced	294 (10.7%)	115 (12.0%)	27 (11.9%)
Married	2179 (79.5%)	706 (73.8%)	172 (75.4%)
Single	196 (7.2%)	100 (10.5%)	24 (10.5%)
Widow	72 (2.6%)	35 (3.7%)	5 (2.2%)
Living alone			
No	2393 (87.2%)	802 (83.7%)	194 (85.1%)
Yes	350 (12.8%)	156 (16.3%)	34 (11.9%)
Occupational status			
Non-qualified	131 (4.8%)	37 (3.9%)	7 (3.1%)
Manual, qualified	363 (13.2%)	76 (7.9%)	19 (8.3%)
Non-manual, qualified	978 (35.7%)	340 (35.5%)	76 (33.3%)
Professional	944 (34.4%)	403 (42.1%)	48 (43.0%)
Managers	327 (11.9%)	102 (10.6%)	28 (12.3%)
High blood pressure			
No	2212 (80.6%)	777 (81.1%)	178 (80.0%)
Yes	530 (19.4%)	181 (18.9%)	47 (20.0%)
High blood cholesterol			
No	1866 (68.2%)	657 (68.7%)	151 (67.0%)
Yes	872 (31.8%)	299 (31.3%)	74 (33.0%)
Diabetes			
No	2618 (95.5%)	913 (95.4%)	211 (94.2%)
Yes	124 (4.5%)	44 (4.6%)	13 (5.8%)
Family history of AD			
No	337 (12.3%)	147 (15.3%)	30 (13.2%)
Yes	2406 (87.7%)	811 (84.7%)	198 (86.8%)
Carriers of the APOE e4 allele			
No	1743 (65.3%)	632 (67.5%)	115 (50.4%)
Yes	927 (34.7%)	304 (32.5%)	113 (49.6%)
Cognition composite score (PACC)			
Mean (SD)	0.06 (0.72)	0.07 (0.73)	0.05 (0.70)
Episodic memory composite score			
Mean (SD)	0.05 (0.86)	0.05 (0.88)	0.07 (0.82)
Executive function composite score			
Mean (SD)	0.08 (0.63)	0.08 (0.63)	0.08 (0.65)
NO_x(μg/m^3)			
Mean (SD)	–	99.1 (31.6)	99.5 (32.0)
NO_2 (μg/m^3)			
Mean (SD)	–	57.3 (12.4)	57.5 (12.9)
$PM_{2.5}$(μg/m^3)			
Mean (SD)	–	17.2 (2.40)	17.0 (2.33)
PM_{10}(μg/m^3)			
Mean (SD)	–	37.7 (4.21)	37.6 (4.39)
Total noise (decibels)			
Mean (SD)	–	67.3 (5.52)	67.7 (5.77)
NDVI 300m			
Mean (SD)	–	0.22 (0.06)	0.22 (0.06)

are seen between exposures and main confounders (i.e., age and years of education)

3.1. Urban environmental exposures and cognitive performance

Results of the association between urban environmental exposures (including air pollutants, noise, and surrounding greenness indicators) and cognitive performance are presented in Table 2. No associations were found between performance in the PACC composite and the environmental exposures assessed (all p-values > 0.05).

Results on the association between urban environmental exposures and cognition composites are shown in Table 3.Participants exposed to higher levels of air pollutants and noise, present lower performance in the episodic memory composite. However, the effect sizes are small and the results are not statistically significant. In contrast increasing levels of air pollutants and noise, is associated with statistically significant better performance in executive function as measured by the composite. The biggest effect sizes are seen regarding nitrogen oxides (e.g., β coefficient for NO_2 was 1.93, SE = 0.78, p = 0.03), but small effects are seen also for particulate matter (e.g., β coefficient for $PM_{2.5}$ was 0.28, SE = 0.15, p = 0.06). Small but borderline significant effects are seen in relation to noise levels: β coefficient for total nose level at night was 0.63 (SE = 0.36; p = 0.08). Null associations are seen regarding exposure to greenness regarding both episodic memory (β = 0.002; p = 0.33) and executive function composites (β = 0.002; p = 0.33).

3.2. Urban environmental exposures and imaging-related brain structure

Results of the association between urban environmental exposures (including air pollutants, noise, and surrounding greenness indicators) and MRI-based AD signature for cortical thickness are presented in Table 4. Higher exposure to air pollutants showed borderline statistically significant associations in relation to the AD signature composite. Higher levels of nitrogen oxides and particulate matter were associated with overall reduced cortical thickness in the brain areas included in the AD signature: β were −16.4 (SE: 8.39) and −5.34 (SE: 2.85) for NO_2 and PM_{10}, respectively. However, higher exposure to noise levels was not associated with cortical thickness in the AD signature. In contrast, increasing surrounding greenness was associated with greater cortical thickness in the brain areas included in the AD signature (β = 0.08; SE = 0.04, p = 0.03).

Results of the association between urban environmental exposures and volume of specific AD-related ROIs are presented in Table 5. Levels of air pollutants were not statistically significant associated with hippocampal volume (all p-values > 0.05). However, participants exposed to higher levels of PM_{10} and PM coarse showed borderline statistically significant greater ventricular volume reflecting increased global atrophy: β were 77.0 (SE = 46.2) and 52.7 (SE = 25.6) for PM_{10} and PM coarse, respectively.

Exposure to higher noise levels was not associated with brain volumes of specific ROIs. Similarly, no associations with brain volume of specific regions of interest were observed in relation to surrounding greenness (Table 5).

3.3. Additional analysis: Effect modification, multiple exposures and mediation analyses

We also tested whether the potential associations between urban environmental exposures and imaging-based brain structure were modified by *APOE* status. Including *APOE* genotype, nor family history of AD significantly altered the results (Supplementary Table 3). However, when we conducted stratified analysis by *APOE* genotype (Supplementary Table 4C), a significant interaction with *APOE* genotype is suggested: the associations between environmental exposures and the AD signatures are only observed among carriers of the *APOE-ε4* allele (p for interaction is 0.04 for NO_x and PM_{10}).

Additional stratified analysis by gender, age and family history of AD have been also conducted. Supplementary Table 4 presents the associations between environmental exposures and the AD signature for cortical thickness from MRI stratified by gender (A), age (B), *APOE* genotype (C) and family history of AD (D). No significant interactions are observed in relation to age or family history of AD. Even though no significant interactions are shown in the stratified analysis by gender, the associations between urban environmental exposures and the AD signature for cortical thickness are stronger in women than in men. Further studies, with larger sample size are needed to confirm these associations (Supplementary Table 4A). We performed exploratory multiple exposure analyses as well as a mediation analysis in order to evaluate whether air pollutants mediated the effects observed in the AD signature analysis. When conducting additional analysis using two-exposure models, the protective association previously observed between greenness indicators and the AD signature is not significant anymore. However the direction of the estimates remain the same (Supplementary Table 5).

When assessing the percentage of the total effect mediated by air pollutants, our exploratory results show that nitrogen oxides and particulate matter mediated 100% of the total effect between surrounding greenness (300 m buffer) and the AD signature ($p < 0.001$).

4. Discussion

In cognitively unimpaired adults with increased risk for AD dementia, higher exposure to air pollution is suggested to be associated with specific brain structural correlates of AD-related neurodegeneration. Our results show that higher exposure to air pollutants, particularly NO_2 and PM_{10}, was associated with reduced cortical thickness of brain areas known to be affected by AD, while increasing exposure to surrounding greenness was associated with greater cortical thickness in AD vulnerable areas. Additionally, subjects exposed to higher levels of PM_{10} and PM coarse showed greater ventricle volumes indicating greater global brain atrophy. However, no associations between urban environmental exposures and the cognitive composite, episodic

Table 2
Association between urban environmental exposures and global cognitive performance.

Cognitive Performance (N = 958)	Environmental Exposure	β [1]	SE	p-value
Cognition composite (mPACC)	NO_2	0.19	0.63	0.76
	NOx	0.56	1.60	0.73
	$PM_{2.5}$	0.09	1.22	0.48
	PM_{10}	0.15	0.21	0.48
	$PM_{2.5\text{-abs}}$	0.02	0.03	0.61
	PM_{coarse}	0.05	0.12	0.69
	Total noise level at night (11 pm-7am), in decibels	0.11	0.29	0.71
	Noise level based on Lden index (day-evening-night), in decibels	0.10	0.28	0.72
	NDVI in the buffer area of 300m	0.002	0.003	0.58

[1] Adjusted by age, gender and years of education.

Table 3
Association between urban environmental exposures and cognitive performance by using cognition composites.

Cognitive Performance (N = 958)	Environmental Exposure	β [1]	SE	p-value
Episodic memory composite	NO_2	−0.61	0.48	0.20
	NOx	−1.30	1.23	0.29
	$PM_{2.5}$	−0.04	0.09	0.63
	PM_{10}	−0.05	0.16	0.74
	$PM_{2.5\text{-abs}}$	−0.02	0.03	0.45
	PM_{coarse}	0.01	0.09	0.89
	Total noise level at night (11 pm-7 am), in decibels	−0.23	0.22	0.30
	Noise level based on Lden index (day-evening-night), in decibels	−0.22	0.21	0.30
	NDVI in the buffer area of 300m	0.002	0.002	0.33
Executive function composite	NO_2	1.93	0.78	0.03
	NOx	4.33	1.99	0.04
	$PM_{2.5}$	0.28	0.15	0.06
	PM_{10}	0.48	0.26	0.07
	$PM_{2.5\text{-abs}}$	0.08	0.04	0.05
	PM_{coarse}	0.07	0.15	0.63
	Total noise level at night (11 pm-7am), in decibels	0.63	0.36	0.08
	Noise level based on Lden index (day-evening-night), in decibels	0.63	0.35	0.07
	NDVI in the buffer area of 300m	0.002	0.002	0.33

[1] Adjusted by age, gender and years of education.

memory or performance in executive function were shown. No other relevant associations were observed in relation to exposure to noise levels and outdoor green space.

4.1. Urban environmental exposures and cognitive performance

Previous studies have reported associations between exposure to high levels of air pollutants and incidence of dementia, as well as cognitive decline (Clifford et al., 2016; Cullen et al., 2018; Killin et al., 2016; Peters et al., 2015; Power et al., 2016; Xu et al., 2016). Moreover, the latest epidemiological studies support the hypothesis that outdoor air pollution has a negative impact on the neuropsychological development of children (Forns et al., 2016; Suades-González et al., 2015). However, literature on the effects of air pollutants on cognitive performance in old adults is limited and has shown inconclusive results. Clifford et al. systematically reviewed in 2016 the existing evidence on exposure to air pollution and cognitive function across the life course (Clifford et al., 2016). Most of the included studies showed weak relationships between several air pollutants and cognitive function in older adults. Similarly, Power et al (Power et al., 2016) reviewed epidemiological studies on air pollution as a potential contributor to cognitive function. Studies reported associations between exposure to either PMs or NOs and dementia-related outcomes measured through different sets of cognitive tests. Very recently, a cross-sectional and longitudinal analysis on outdoor air pollution and cognitive function was performed in 86,759 middle-to-older-aged adults from the UK biobank general population cohort (Cullen et al., 2018). Unadjusted regression analyses indicated small but consistent negative associations between air pollutant exposure and baseline cognitive performance. However, after adjusting for a range of key confounders, associations

Table 5
Association between urban environmental exposures and volume of specific ROIs from MRI.

Brain region (N = 228)	Environmental exposure	β [1]	SE	p-value
Hippocampal volume (mm^3)	NO_2	−56.8	78.3	0.75
	NOx	−76.1	43.7	0.69
	$PM_{2.5}$	−44.9	32.3	0.89
	PM_{10}	−55.1	60.3	0.52
	$PM_{2.5\text{-abs}}$	−61.9	91.5	0.50
	PM_{coarse}	−28.7	36.2	0.93
	Total noise level at night (11 pm-7am), in decibels	−18.6	82.7	0.91
	Noise level based on Lden index (day-evening-night), in decibels	−18.4	79.9	0.98
	NDVI in the buffer area of 300m	−8.84	8.36	0.29
Ventricles volume (mm^3)	NO_2	34.3	37.1	0.80
	NOx	50.9	37.0	0.88
	$PM_{2.5}$	−4.00	24.9	0.87
	PM_{10}	77.0	46.2	0.06
	$PM_{2.5\text{-abs}}$	1.83	7.05	0.80
	PM_{coarse}	52.7	25.6	0.04
	Total noise level at night (11 pm-7am), in decibels	−38.5	63.6	0.55
	Noise level based on Lden index (day-evening-night), in decibels	−38.3	61.4	0.53
	NDVI in the buffer area of 300m	54.3	64.5	0.93

Brain volume variables are corrected by estimated total intracraneal volume.
[1] Adjusted by age, gender and years of education.

Table 4
Association between urban environmental exposures and AD signature for cortical thickness from MRI.

MRI Outcome (N = 228)	Environmental Exposure	β [1]	SE	p-value
AD signature for cortical thickness	NO_2	−16.4	8.39	0.05
	NOx	−36.8	20.7	0.08
	$PM_{2.5}$	−2.46	1.52	0.11
	PM_{10}	−5.34	2.85	0.05
	$PM_{2.5\text{-abs}}$	−0.65	0.43	0.14
	PM_{coarse}	−3.00	1.57	0.06
	Total noise level at night (11 pm-7am), in decibels	−5.54	3.89	0.16
	Noise level based on Lden index (day-evening-night), in decibels	−4.94	3.75	0.19
	NDVI in the buffer area of 300m	0.08	0.04	0.03

[1] Adjusted by age, gender and years of education.

were inconsistent in direction and of very small magnitude, indicating weak associations between air pollution exposure and cognitive performance in middle age individuals in the largest study performed to date.

In relation to being exposed to high levels of noise, recent evidence suggests an association between living near major roads, and exposure to traffic noise, especially at night time, and incidence of dementia (Carey et al., 2018; Chen et al., 2017). However, studies on the potential adverse effects of ambient noise on cognitive functions are scarce, and findings seem to be inconsistent. Some studies have evaluated the impact of noise exposure on short-term changes in cognitive performance or even the impact of environmental noise on cognitive performance in attention-based tasks, and most of them do not show any significant associations. Recently, Tzivian et al, examined the association between air pollution and traffic noise and cognitive performance in a population-based cohort of 4,086 participants. The authors found that long-term exposure to both, air pollution and traffic noise, was negatively associated with subtests related to memory and executive functions, with little evidence for mutual confounding (Tzivian et al., 2016).

Even though there is a growing body of evidence suggesting that exposure to air pollution and noise are associated with incidence of AD and cognitive decline, we were not able to detect meaningful associations between exposure to air pollutants and noise levels and cognitive performance in a sample of 958 individuals living in the city of Barcelona. It is worth mentioning that our participants are cognitively unimpaired, middle-aged and highly educated. Thus, they displayed high-range scores in most tests, even using challenging cognitive tasks to avoid the ceiling effects observed by such population in regular tests used at memory clinics. This fact, together with the limited sample size, might difficult the detection of weak effects sizes. Follow-up of the ALFA population will be key to elucidate the association between long-term exposure to air pollutants, cognitive decline and AD incidence.

It is worth mention that we found a positive association between exposure to air pollutants (especially nitrogen oxides) and executive function: participants exposed to higher levels of NO_x and NO_2 perform better on the tests included in the executive function composite. This apparent beneficial effect of air pollution on executive function might be due to a selection bias. It is well known that socioeconomic status and welfare are higher in capital city regions in comparison to non-capital regions. Our participants (all living in the city of Barcelona) might have higher socioeconomic status, which is also related to higher education attainment, and consequently better executive function.

Regarding exposure to green spaces, several observational studies have investigated the role of long term green space exposure and cognition across life course (reviewed by Keijzer et al, 2016) (Keijzer et al., 2016). Existing evidence on the association between green spaces and cognition is scarce. However, it is suggestive for beneficial associations between the exposure and cognitive development in childhood and cognitive function in adulthood (Keijzer et al., 2016). The potential underlying mechanisms for a beneficial effect of exposure to green spaces are not fully understood. It has been proposed that they could be related to their ability to restore directed attention after being overused by attentional tasks related to urban life, the opportunity that green spaces offer to develop physical activity, which has been inversely related to cognitive decline, or even the fact that green spaces in residential environments could lead to less loneliness and more social support, which has also been shown to benefit cognitive function (Berman et al., 2008; Maas et al., 2009; Richardson et al., 2013). Furthermore, green spaces have the potential to reduce exposure to air pollution (Dadvand et al., 2012), and consequently its potential adverse effects. However, in our cross-sectional study we did not observe associations between exposure to green spaces and cognitive outcomes. Once again, long-term longitudinal studies, with larger sample size, are relevant to disentangle such associations.

4.2. Urban environmental exposures and brain correlates of AD

Few studies have investigated the effect of air pollution on the structure of the adult brain, recently reviewed by de Prado Bert et al. 2018 (Bert et al., 2018). Some of the reviewed studies integrating environmental epidemiology and neuroimaging suggest that white matter and cortical gray matter could be targets of traffic related air pollutants. However, little is known about the potential effect of air particles and gases on specific brain regions of interest that are hallmarks of the brain atrophy in AD dementia. Our study shows that participants exposed to higher levels of air pollutants show thinner cortices in AD vulnerable areas. Regions included in the AD signature are characteristically atrophied and show hypometabolism in AD dementia, thus suggesting that for cognitively unimpaired individuals with thinner cortices in such areas might be more challenging to cope with the effects of AD pathology in preclinical stages (Fennema-Notestine et al., 2009; Clifford R Jack et al., 2015). Similarly, subjects exposed to higher levels of PM_{10} and PM coarse showed bigger ventricle volumes, which is also related to regionally unspecific brain atrophy.

Even though scientific evidence of a direct impact of exposure to air pollutants on cognitive performance in adults is inconsistent, it appears that specific areas of participant's brains might be altered due to exposure to air pollutants. The fact that these areas are considered hallmarks of AD-related neurodegeneration, indicate that our results might be suggesting that exposure to air pollution increases brain vulnerability to AD.

Although the mechanisms by which air pollutants might affect brain health are unknown, studies including experiments with animals and conducting autopsy of human samples, showed that PMs and diesel exhaust seem to cause oxidative stress and systemic inflammatory responses, disrupt blood-brain barrier, precipitate A β peptides, and activate microglia. Ultrafine particles have also been found in the olfactory bulb and the frontal cortical areas in the brain (Block et al., 2004; Calderón-Garcidueñas et al., 2008). NO_2 has been reported to be associated with inflammatory responses and markers such as increasing systemic serum interleukin IL-6 concentrations (Gruzieva et al., 2017). While diverse environmental factors have been implicated in neuroinflammation, air pollution (including both PMs and NOs) may rank as the most prevalent source of environmentally induced inflammation and oxidative stress (Block and Calderón-Garcidueñas, 2009). Additionally, in vitro and in vivo animal studies focused primarily on the effect of traffic-related air pollution have revealed impaired synaptic functions, alterations in neuron morphology, and neuron death (Davis et al., 2013; Ejaz et al., 2014; Fonken et al., 2011).

Exposure to surrounding greenness has been recently reported to be associated with beneficial structural changes in the developing brain among children (Dadvand et al., 2018a). The study on the association between green space exposure and regional differences in brain volume in schoolchildren suggeted beneficial effects of being raised in greener neighborhoods. However, studies focused on adults are very limited and results are inconclusive. The present study is the first to evaluate the impact of green space exposure on AD-related brain regions in older adults. We observed an association between surrounding greenness and greater thickness in AD vulnerable regions, suggesting a potential beneficial effect of green space exposure on brain hallmarks of AD. However, in our population, the beneficial effect of green spaces on brain structure is suggested to be mediated by the lack of air pollutants in these areas. Further studies, with larger samples sizes and longitudinal follow-up, are needed in order to confirm such associations.

4.3. Limitations of the present study and future studies

Our study is not free of limitations. Participants of our study are included in a well-characterized population, the ALFA cohort, which provides detailed information on the evaluated outcomes, as well as clinical and epidemiological co-variables of adjustment to be included

in the models and in sensitivity analyses. However, the inclusion and exclusion criteria of the study also led to a relatively small study population that might not necessarily be representative of the general population of Barcelona (e.g. over 50% of participants were highly educated, and 88% were among the qualified non-manual, professional or managerial work categories). Therefore, the results of the present study might not be representative of the general population, but we do not think that the selection criterion has an effect on the internal validity of this study, in which we considered education as potential confounder, among other co-variables. Furthermore, and most importantly, our participants are cognitively unimpaired subjects at risk of AD, with high-range scores in most tests, which might difficult the detection of weak effects sizes.

Exposure to air pollution was estimated based on each participant's residential address. However, we did not have access to participants' daily mobility and workplace exposure, which may lead to exposure misclassification, and thereby, we might be underestimating the association between the exposures and the outcomes assessed (Armstrong, 1998; Zeger et al., 2000). However, a number of studies have shown that adding daily mobility does not improve the risk estimates (Nethery et al., 2008). Additionally, it is worth mention that the spatial distribution of air pollution in Barcelona has been fairly consistent over the past 20 years (Cesaroni et al., 2012; Wang et al., 2013). Only some temporal variation with pollutant levels has been seen before and after the crisis. Since the temporal variation affected every area/subject equally, we use the spatial distribution to differentiate the exposure to air pollution in the subjects. Therefore the timing of the assessment is not so critical. Moreover, in the present study we could not distinguish the effects of different green space types because urban green space had a significant weight in the total amount of green space exposure, and surrounding greenness, based on the NDVI, does not distinguish among types of green space. Additionally, we could not distinguish the effects of traffic noise from the effect of other sources of noise since total noise levels in our population essentially came from traffic. It is worth mention that there is a moderate correlation among the assessed exposures and therefore our main results are focused on single exposure analysis. However, exploratory multiple exposure analyses and mediation analyses have been performed to better understand the observed associations. Additionally, the sample size of the present study is limited to focus only on multiple exposure analyses. Thus, the results we present here might be an overlap among different exposures and might limit our ability to distinguish which is the exposure driving the main effects. Despite these limitations, for the first time we were able to evaluate different urban related exposures within the same study population in relation to cognitive and imaging outcomes.

The relatively small sample size might be limiting statistical power to detect potential effects of urban environmental exposures on the outcomes of interest, especially for the imaging-related outcomes. However, this is a very well characterized population, which provides detailed information on the evaluated outcomes, as well as clinical and epidemiological co-variables. Even though we explored multiple environmental exposures, the main analysis included two main outcomes: cognitive performance and an AD signature composites. The AD signature we use in the present analysis has been previously used in the context of similar populations as a gold-standard to predict cognitive change, progression and neurodegeneration in cognitively unimpaired individuals (as discussed by Dickerson et al.., 2009 and Jack et al. 2015, among others). Additionally, since this was an exploratory analysis we did not consider correcting for multiple testing.

Finally, it is crucial to perform studies on the impact of long-term exposure to pollution, as well as longitudinal studies, in order to properly evaluate the effect of air pollution on cognition, especially when including middle age, cognitively unimpaired individuals (i.e., cognitive decline has not occurred yet). The fact that our study participants are cognitively unimpaired might be compromising the observation of potential small effects sizes on cognitive performance; however, the alterations observed in imaging-derived brain structure might be early indicators of faster cognitive decline in the future which makes necessary to follow-up these individuals to confirm such hypothesis. Additionally, different characteristics of the subjects, such as cognitive reserve (Solé-Padullés et al., 2009), could be counteracting the harmful effects of air pollution in a brain that starts showing damage.

In conclusion, in a cohort of cognitively unimpaired adults with increased risk for AD, exposure to air pollution is suggested to be marginally associated with greater global atrophy and reduced volume and thickness in AD vulnerable brain areas, even though there is no impact on cognition yet. Although more research in the field is guaranteed, air pollution reduction might be crucial for decreasing the burden of age-related neurodegenerative disorders, which is especially relevant in a city like Barcelona, where the pollutant levels are high compared to other cities in Europe, particularly for NO_2 and noise, since this is a dense city with a high traffic density.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

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