Master of Public Health

(European Public Health Master)

Master de Santé Publique

Association between Greenspace and Cognitive Performance: French CONSTANCES cohort.

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EPH - M2, 2019-2021

Location of the practicum:

IRSET – Institut de recherche en santé, environnement et travail / Irset- Inserm, UMR_S 1085

Équipe 9 : Évaluation des expositions et recherche épidémiologique sur l'environnement, la reproduction et le développement

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Acknowledgements

A very special thanks to Team 9 at Irset for all their feedback, advice, and encouragement. I especially want to thank my thesis supervisors, Bénédicte Jacquemin and Mohammad Javad Zare Sakhvidi for their constant guidance, patience, support and broadening my interest in environmental health research.

I am also thankful to the European Commission and the European Public Health Master (Europubhealth) Consortium for giving me this opportunity and their constant support even after all these hard times.

I am also very grateful for The University of Sheffield (United Kingdom) and their staff for showing amazing support throughout these two years, a special thanks to Richard Cooper for being constantly guiding us in the right direction and my tutor Liz Croot for being a great listener. To the École des Hautes Études en Santé Publique (France) for all the interesting courses, with a special thanks to Aurore GELY-PERNOT for her patience and encouragement.

To all my family in Honduras for all their unconditional care and support.

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List of Acronyms

AD	Alzheimer’s disease
CI	Confidence Interval
CONSTANCES	Cohorte des consultants des Centres d’examens de sante
DAG	Directed acyclic graph
DSST	Digit-symbol substitution test
FCSRT	Free and Cued Selective Reminding Test
HSC	Health Screening Centre
LRT	Likelihood ratio test
NDVI	Normalized Difference Vegetation Index
NOE	Natural Outdoor Environments
PCA	Principal Component Analysis
RFT	Fast Free Recall score of FCSRT
RTT	Fast Recall Total score of FCSRT
RFD	Delayed Free Recall score of FCSRT
RTD	Delayed Recall Total score of FCSRT
SES	Socioeconomic status
TMT-A	Trial Making Test part A
TMT-B	Trial Making Test part B
VFT	Verbal fluency tasks

Abstract

Background: Dementia refers to cognitive decline that impairs at least one cognitive domain. Association between greenspace and cognition in adult population have been scarcely studied, and most studies only reported results on general cognition. This cross-sectional analysis studied the association between different domains of cognition and greenspace exposure. We further explored the potential effect modification by the commune of residence (an urban/rural classification).

Methods: The study population included 65316 participants (aged 45-69 years) from the enrolment phase of the French CONSTANCES cohort. Cognitive outcomes included three cognitive domains: episodic memory, language skills, and executive functions. A global score was created as a composite of these cognitive domains to assess general cognition. Greenspace exposure indicator was residential surrounding greenness as Normalized Difference Vegetation Index (NDVI) at different buffer sizes (100m, 300m, 500m, and 1000m). To test the association, multiple linear regressions were performed on the z-scores of the cognitive test and at different levels of adjustment, with the main model adjusted for age, sex, education, health screening centre, commune of residence, physical activity, and air pollution ($PM_{2.5}$). To test the potential effect of a modification of the commune of residence, a likelihood ratio test and stratification was applied.

Results: On the main model, significant protective associations were found mainly on language skills, executive functions, episodic memory, and general cognition at all buffer sizes (e.g. at 300 m buffer, semantic fluency z -score 0.043, 95%CI: 0.024 to 0.063). In stratified analyses by commune of residence we found higher effect of greenspace on executive function (TMT-A; z-score -0.054, 95% CI: -0.084 to -0.025) in suburban areas and on language skills (lexical verbal fluency; z-score 0.054, 0.020 to 0.087) in urban areas compared with other areas.

Conclusion: Exposure to greenspace was associated with improved cognitive performance for all explored cognitive domains, and on the global score. Living on urban and suburban areas could modify the effect of greenspace on cognitive performance.

Résumé

Contexte : La démence désigne un déclin cognitif qui affecte au moins un domaine cognitif. L'association entre les espaces verts et la cognition chez la population adulte a été à peine étudiée, et la plupart des études n'ont rapporté que des résultats sur la cognition générale. Cette analyse transversale a étudié l'association entre différents domaines de la cognition et de l'exposition aux espaces verts. Nous avons également étudié la modification de l'effet potentiel par la commune de résidence (classification urbaine/rurale).

Méthodes : La population de l'étude comprenait 65 316 participants (âgés de 45 à 69 ans) de la phase d'inscription de la cohorte française CONSTANCES. Les résultats cognitifs comprenaient trois domaines cognitifs: la mémoire épisodique, les compétences linguistiques et les fonctions exécutives. Un score global a été créé en tant que composite de ces domaines cognitifs pour évaluer la cognition générale. L'indicateur d'exposition aux espaces verts était la verdure environnante résidentielle comme l'indice de végétation par différence normalisée (NDVI) à différentes tailles de tampons (100m, 300m, 500m et 1000m). Pour vérifier l'association, on a effectué des régressions linéaires multiples sur les scores z du test cognitif et à différents niveaux d'ajustement, le modèle principal étant ajusté en fonction de l'âge, du sexe, du niveau de scolarité, du centre de dépistage médical, de la commune de résidence, de l'activité physique et de la pollution atmosphérique ($PM_{2,5}$). Pour tester l'effet potentiel d'une modification de la commune de résidence, un test du rapport de probabilité et une stratification ont été appliqués.

Résultats : Dans le modèle principal, des associations importantes de protection ont été trouvées principalement sur les compétences linguistiques, les fonctions exécutives, la mémoire épisodique et la cognition générale à toutes les tailles de tampons (par exemple, à 300 m tampon, fluence sémantique z -score 0,043, 95% IC: 0,024 à 0,063) . Dans des analyses stratifiées par commune de résidence, nous avons trouvé un effet plus élevé de l'espace vert sur la fonction exécutive (TMT-A; Z-score -0,054, IC 95%: -0,084 à -0,025) en banlieue et sur les compétences linguistiques (couramment lexical verbal; score z 0,054, 0,020 à 0,087) en milieu urbain par rapport à d'autres domaines.

Conclusion : L'exposition à aux l'espace vert a été associée à l'amélioration des performances cognitives pour tous les domaines cognitifs explorés, et sur le score global. Vivre dans les zones urbaines et suburbaines pourrait modifier l'effet des espaces verts sur la performance cognitive.

1. Introduction

1.1 Cognition in adults

Dementia encompasses several diseases, that are chronic, progressive, and that impairs at least one cognitive domain. One of its most common form has been Alzheimer's disease (AD), a neurodegenerative disease with age related cognitive decline, that may contribute up to 60-70% of cases worldwide. Other major forms include vascular dementia, dementia with Lewy bodies, and diseases that affect frontotemporal dementia. Dementia affects memory, behaviour, orientation, learning capacity, judgement and interferes with a person's ability in social or occupational functioning in daily lives' activities (Fiest *et al.*, 2016; WHO, 2017c, 2020). By 2030, it was projected that around 74.7 million people will be living with dementia, this represents a 60% increase in number cases from 2015 to 2030, and cases will be tripled in the next 30 years (Alzheimer's Disease International, 2018). In 2015, the global economic burden for dementia was estimated to 26 billion US$ (Ru *et al.*, 2021). In France, more than one million people are affected with AD with 225,000 new cases each year (Fondation Vaincre Alzheimer, 2019; Santé Publique France, 2019).

It has been important to identify risk factors, -especially modifiable ones- before clinical manifestation of AD in order to modify exposure to them and to detect at risk population (Baumgart *et al.*, 2015; Lipnicki *et al.*, 2019). Recently it was published (Livingston *et al.*, 2020) that the risk of AD and dementia can be lowered by up to 40% by controlling these modifiable risk factors such as education, lifestyle risks (smoking, physical activity), cardio vascular risks factors (diabetes, hypertension), hearing loss, traumatic brain injury and air pollution exposure.

Air pollution (Gatto *et al.*, 2009; Ailshire, Karraker and Clarke, 2017) has been reported as responsible for 2.3% of population attributed fraction (PAF) for dementia (Livingston *et al.*, 2020). In addition to air pollution, evidence has been accumulating on the role of other environmental factors on cognition such as noise (Tzivian *et al.*, 2017; Carey *et al.*, 2018), artificial light at night (Lee, Cho and Lee, 2020) distance to roads (Chen *et al.*, 2017). Cognitive performance can be affected by distance to natural outdoor environments (NOE) (de Keijzer *et al.*, 2016), where a 100 m increase in residential distance to NOE was associated with a longer time to complete a cognitive function test by 1.50% (95% CI 0.13, 2.89). (Zijlema *et al.*, 2017).

1.2 Greenspaces and health

NOE are defined as natural places with “green” and “blue” elements, such as parks or forests and sea or rivers. Natural outdoor environments have been associated with better health and perceived general wellbeing, especially residents living in urban environments (Maas *et al.*, 2006; Zijlema *et al.*, 2017). Greenspace usually refers to vegetated land or green areas where human control and activities are not intensive (van den Bosch, 2016), these could be gardens, parks, agricultural landscapes, and forests.

Markevych *et al.*, 2017 and Dzhambov *et al.*, 2020 have proposed several, intertwined, biopsychosocial pathways, to explain the health benefits of greenspace on health: mitigation, restoration and instoration. Mitigation, or reducing harm, refers to the effect of greenspace by reducing exposure to air pollution (Crous-Bou *et al.*, 2020), to heat by reduction of heat island effect (Morais *et al.*, 2016), and to noise through green barriers (Vos *et al.*, 2013). Psychological restoration capacities of greenspace referred to greenspace as a resource of relaxation, improved sleep, and reduced in psychological stress (Pun, Manjourides and Suh, 2018; Mavoa *et al.*, 2019). Instoration, or capacity building of greenspace, included the creation of environments with enhanced physical activity (Richardson *et al.*, 2013) and with improved social capital by facilitating social cohesion (van den Bosch, 2016; Zaheed *et al.*, 2019).

Health benefits of greenspace are context dependent, for example greenspace was important in explaining health differences between rural urban areas, and an important factor to consider for spatial planning (Maas *et al.*, 2006) . Therefore, it was important to examine the possible association of greenspace and health, considering factors of urban-rural classifications.

1.3 Greenspace and cognition

The beneficial association has been reported between exposure to greenspace and cognitive development in childhood and cognitive performance in adulthood (de Keijzer *et al.*, 2016). Lower rate of mental disorder has been reported in older population more exposed to greenspace (Wu, Prina, A. Jones, *et al.*, 2015). Several cross-sectional studies on greenspace and cognition have concluded that there was some indication of beneficial role of proximity to greenspace and cognitive performance (Wu, Prina, A. P. Jones, *et al.*, 2015; Zijlema *et al.*, 2017; Dzhambov *et al.*, 2019). However, the type of greenspace may be also important to explore, considering that urban greenspace in urban areas can have a significant weight in total amount of greenspace exposure (Crous-Bou *et al.*, 2020), it was important to consider the possible effect modification of urban rural status (Wheeler *et al.*, 2015).

In view of increasing urbanization (WHO, 2017b), population aging and subsequent increased prevalence of dementia (Fiest *et al.*, 2016), and limited number of research on greenspace and neurodegenerative disorders (de Keijzer *et al.*, 2016), further research on the link between greenspace and cognition was necessary. The CONSTANCES cohort ("Cohorte des consultants des Centres d'examens de santé"), launched in 2012, was the largest population based prospective study in France. One of the objectives of the CONSTANCES was to develop epidemiological research on environmental exposures and cognition (Zins and Goldberg, 2015). This objective aligns with the World Health Organization's (WHO) global strategy on aging and health (WHO, 2017a), where research on healthy ageing and developing of adequate environments for aging was encouraged.

1.4 Research aim and objectives

With continued urbanization, and a longer life expectancy, and high prevalence of dementia (Livingston *et al.*, 2020) or cognitive impairment due to age (Wu, Prina, A. P. Jones, *et al.*, 2015), it was necessary to focus on potential protective factors of cognition, including environmental ones. The aim of this thesis was "to study of the association between exposure to greenspace and cognitive performance in the French CONSTANCES cohort". Considering the potential protective role of greenspace on cognition, we hypothesize that greenspace exposure was associated with better cognitive performance.

The specific objectives of this study were:

a) Determining whether the exposure to greenspace in adults aged 45-69 years is associated with some specific domains of cognitive performance (episodic verbal memory, executive functions, language skills).
b) To examine whether the exposure to greenspace in adults aged 45-69 years is associated with better cognitive performance as a global cognitive score.
c) To explore the potential effect modification of the association between greenspace and cognitive performance by classification of commune of residence (i.e., urban-rural).

2. Methods

2.1 Study design and population

This cross-sectional analysis was conducted using the data from the enrolment phase of the French CONSTANCES cohort, a large population-based prospective study. The CONSTANCES cohort had a partnership with ‘‘Caisse Nationale d'Assurance Maladie des travailleurs salaries’’ (CNAMTS), covering more than 85% of the French population. The cohort, started in 2012 and finalized its recruitment in September 2020. It was composed of randomly selected, French adults aged 18-69 years and includes 220,000 participants (Zins and Goldberg, 2015).

At inclusion participants filled several questionnaires (e.g., socioeconomic, demographic, behavioural). For those aged 45 years of age and older, additional clinical examination and comprehensive cognitive tests were applied. The clinical examination was done in 21 Health Screening Centres (HSCs), located in 19 regions in metropolitan France, and with two HSCs located in Paris (Figure 1). Inclusion criteria of the study population contained all CONSTANCES' participants aged 45 years and more (n=109981) with cognitive assessment data and geocoded residential address for residential greenness data. Exclusion criteria were participants who do not speak French, participants whose tests were made in paper format, those without at least one completed test, participants with Parkinson's disease, and those without greenspace data. After applying this criterion, 40.6% (n=44665) participants were excluded, and 65316 remained as a final study population (Annex 1).

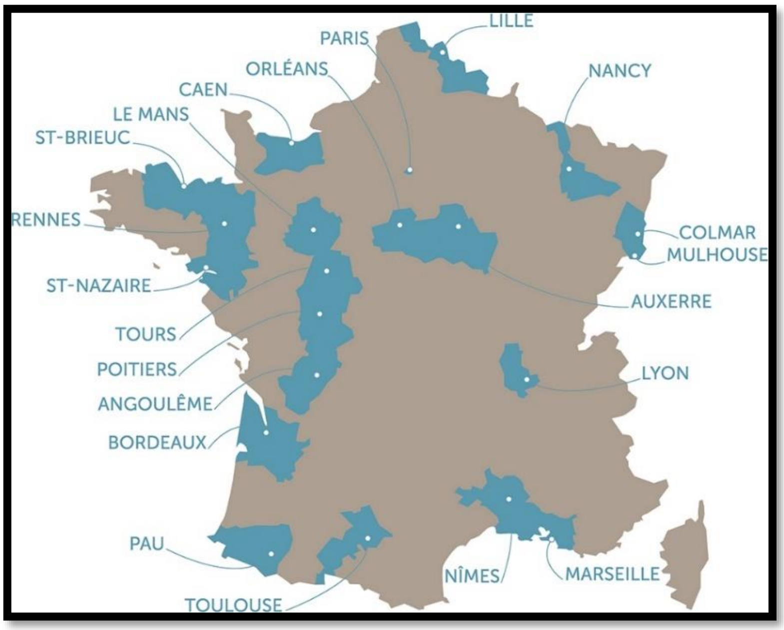


Image source: the CONSTANCES cohort biobank (Henny *et al.*, 2020)

Figure 1. Location of health screening centres for recruitment of the French CONSTANCES cohort, with two centres located in Paris.

2.2 Variables

2.2.1 Outcome variables

The CONSTANCES cohort included a battery of cognitive functioning tests, performed by trained neuropsychologist on the recruitment HSCs. These cognitive tests can be classified in three cognitive domains: verbal episodic memory, executive functions and language skills (Zins and Goldberg, 2015). Episodic memory domain of cognition allows recollections to have interpretations of the past (Mahr and Csibra, 2018) and its progressive loss was often manifested on AD(Silva *et al.*, 2019). Executive function domain is a process that guides behaviour or its flexible readjustment towards a goal and allows the identification of the abilities to live independently (Banich, 2009). Language skills, such as verbal fluency, refers to the flow of spoken language (Mueller *et al.*, 2018) and are predictive of cognitive impairment (Sutin, Stephan and Terracciano, 2019), and its decline has an early presence in most types of dementia (Krein *et al.*, 2019). For this study, a total of six cognitive tests were analysed as continuous outcomes of cognitive performance and a global score was created from the composite of the tests from the different cognitive domains.

Episodic memory domain was assessed with the Free and Cued Selective Reminding Test (FCSRT), which was usually used as screening test for dementia in the elderly (Grober *et al.*, 1988) and a proven tool for diagnosing AD (Teichmann *et al.*, 2017). The FCSRT, consisted of memorizing 16 words from 16 semantic categories, and recalling as many words as possible in two minutes. After repeating this for three times, different sub scores can be taken: the free-fast recall (RFT), which was the sum of the number of words retrieved at the three free recall trials and has a maximum attainable score of 48; the total-fast recall (RTT), was the sum of the number of words retrieved at the three free and cued recall trials and has a maximum attainable score of 48; the free-delayed recall (RFD), was the number of free retrieved words during the delayed phase and has a maximum score of 16; and the total delayed recall (RTD), was the number of free and cued retrieved words during the delayed phase, and has a maximum score of 16 (Grober *et al.*, 1988). For this study, FCSRT was represented by the sub-scores of the cognitive test RTT and RFT.

The executive function domain contains several skills, of which different tests provides different facets of this domain. The trail making test (TMT), currently used as a screening instrument of neuropsychological impairment (Bowie and Harvey, 2006). TMT includes two parts: part A (TMT-A) and part B (TMT-B), where part A was related to measures of visual scanning, graphomotor speed and visuomotor processing speed (Llinàs-Reglà *et al.*, 2017) and part B was related to working memory, inhibition control (Llinàs-Reglà *et al.*, 2017), and cognitive flexibility of the executive functions (Bowie and Harvey, 2006). TMT-A and TMT-B scores are measured by test completion time, the shorter the time correspond to a better performance (Reitan, 1958). Also, for executive functions, the digit symbol substitution test (DSST) was used considering it a sensitive indicator of changes in cognitive dysfunction and cognitive function (Jaeger, 2018). DSST includes nine digit-symbol pairs, paired (or matched) to a list of numerical digits. Under each digit, the participant must write the corresponding symbol as fast as possible in 90 seconds, and the number of correct assignments in 90s considered as a DSST score (Wechsler, 1981).

Language skills includes lexical and semantic verbal fluency tasks (VFT). Semantic verbal fluency relates to semantic memory, and an early indicator of AD while lexical verbal fluency goes along overall language abilities(Mueller *et al.*, 2018; Krein *et al.*, 2019). The semantic task was scored as the number of words belonging to the 'animals' category named in 1 minute. Lexical fluency task was scored as the number of the words starting with the letter R named in 1 minute (Borkowski, Benton and Spreen, 1967).

In addition to the continuous cognitive scores, for each cognitive test, we constructed dichotomous cognitive variables based on the published norms from the CONSTANCES cohort according to age, sex and education (Ouvrard et al., 2019). The defined dichotomous cognitive variables (classified as 0 for good performance and 1 as low performance) were based on the cognitive scores below or equal to the 25^{th} percentile of the published norms (for TMT higher than or equal to 75^{th} percentile, considering it was a measure of time) (Ouvrard *et al.*, 2019; Letellier *et al.*, 2020).

2.2.2 Exposure variables

Residential greenspace (hereafter residential greenness) in environmental epidemiology has been commonly reported as the Normalized Difference Vegetation Index (NDVI) (Markevych *et al.*, 2017; Besser, 2021) due to its data availability, applicability on different buffers and replicability of studies (Rhew *et al.*, 2011). The NDVI was derived from satellite imagery data and it determines the density of vegetation from the visible red (RED) and near-infrared light (NIR) reflected on land, with a range of -1 to +1, with increasing greenness on higher values (NASA, 2000). On geographic information systems (GIS), buffer tools can be used to measure greenness within a specified circular buffer diameters (Browning and Lee, 2017).

Similar to Crous-Bou et al. 2020, to increase the exposure contrast and also reduce the problem by cloud coverage, we used the NDVI values for May- July as the greenest time of year in France. The NDVI for this study includes all of France's provinces and the data was derived from the satellite imagery data Landsat 8 TM satellites, obtained from public sources, between the periods of 2012 to 2020 at 30m x 30m resolution(Zare Sakhvidi *et al.*, 2020). The average NDVI was obtained at different buffer sizes of 100, 300, 500, and 1000 meters. These buffers aim to explore the consistency of the study results at its different sizes, and were chosen based on known literature of exposure to residential surrounding greenness using NDVI (Dadvand Payam *et al.*, 2012; Dzhambov *et al.*, 2019; Asta *et al.*, 2020). Geographic data preparation was conducted on QGIS 3.10.14 LTR (QGIS, 2021) and Google Earth (*Google Earth*, 2021) previous to this study.

2.2.3 Covariates

Potential covariates were chosen based on a) other studies that includes determinants of association between natural environment and cognition (Markevych *et al.*, 2017; Zijlema *et al.*, 2017; Dzhambov *et al.*, 2019; Crous-Bou *et al.*, 2020; Livingston *et al.*, 2020), b) known risk factors of cognitive decline (Livingston *et al.*, 2020), and c) that are also modifiable risk factors of cognition (Livingston *et al.*, 2020) which are available at enrolment phase of the CONSTANCES cohort. These variables are age at inclusion, education (based on years of study and classified as less than five years, five to twelve years and twelve and more years); classification of commune of residence (classified as urban, suburban, isolated city, and rural); deprivation level based on tertiles of the French deprivation index (Rey *et al.*, 2009) (first tertile as low, second tertiles as moderate, and third tertile as high); health screening centres (include 21 centres, Paris includes two centres); non-occupational physical activity (classified from a scale of physical effort as 1-3 as low; 4-5 as medium, and 6-7 as high), and air pollution as annual mean concentration of particulate matter with aerodynamic diameters less than 2.5 micrometres ($PM_{2.5}$).

A directed acyclic graph (DAG) (Annex 3) was used to determine the covariates to adjust the main model, by examining the relationships of covariates, greenspace exposure and cognition outcomes using a web-based application Dagitty (Textor *et al.*, 2016). The variables introduced in the DAG were as follows:

a) Age was included in the DAG, as a known risk factor of dementia, considering that development of neurodegenerative disorders occurs on older population, and its role on age related cognitive decline (Juan and Adlard, 2019); we also consider its variations of potential uses of greenspace due to age, such as physical activity (Kaczynski *et al.*, 2009) or socialization (Markevych *et al.*, 2017).
b) According to literature, sex and education has been used as a confounders on different relevant associations on cognition and greenspace (Dzhambov *et al.*, 2019), greenspace and cognitive development (Asta *et al.*, 2020) and greenspace and stress, anxiety, depression,(Pun, Manjourides and Suh, 2018).

c) Health screening centres (HSCs) were included for potential information bias during the conduction of cognitive tests by different neuropsychologists. Additionally, considering they are in different regions of France there may be proxys of area-level covariates such variation in population sizes and greenspace types and exposure.
d) The type and amount of greenspace varies at different classification of commune of residence (different level of urbanity)(Maas *et al.*, 2006) Depending on the urban-rural status, it may vary on the greenspace accessibility, adverse influences of greenspace on health (i.e. crime potential, allergies, home of disease vectors), the type of air pollution (i.e. less traffic-related air pollution in rural areas), and type of physical activity and mobility of the people that live in it (Markevych *et al.*, 2017).
e) Area-level deprivation, a socioeconomic indicator of health inequality, was used on the DAG considering that due to health inequalities the distribution of greenspace was higher on less deprived areas (Mitchell and Popham, 2008; Astell-Burt *et al.*, 2014) . There was also a potential of residual confounding of area-level socioeconomic status, since health benefits of greenspace exposure, may be due to better neighbourhoods with better socioeconomic status (Markevych *et al.*, 2017).
f) Physical activity has been affected by availability of greenspace and neighbourhood environment, through greenspace and its capacity building that promotes physical activity. There may be unconditional confounding if it was not included (Wu, Prina, A. P. Jones, *et al.*, 2015). Greenspace was also associated with Type 2 diabetes as a protective factor (Astell-Burt, Feng and Kolt, 2014), but similar as other chronic disease such as CVD, that affect cognition (Livingston *et al.*, 2020). Greenspace exposure has reduced the incidence of these diseases (Chen *et al.*, 2020), but chronic diseases were on an indirect pathway, where they cannot predict greenspace exposure.
g) Air pollution might contribute to incidence of dementia-related disorders, and its exposure was associated with poor cognitive performance (Crous-Bou *et al.*, 2020). Greenspace may lead to an attenuating concentrations of air pollution and studies on association of greenspace and health. Studies have commonly used air pollution as a confounding factor, since improvements in health due to greenspace may be due to lower concentrations of air pollution (Markevych *et al.*, 2017).

2.3 Statistical methods

2.3.1 Descriptive statistics analysis

Descriptive statistics were performed on the outcomes, exposures, and main covariates. Descriptive statistics of cognitive outcomes and exposure variables by commune of residence classification was also performed the cognitive outcomes and greenspace exposure was also performed. Additionally, study population characteristics was performed considering sociodemographic, comorbidities and chronic disease variables (Annex 5) and a comparison of study population characteristics of complete case data and imputed data (Annex 6). Considering we have at most was a 4.3% missing data from the physical activity variable, there were negligible differences when comparing complete case and imputed datasets characteristics.

Correlation plots were created to test correlation of outcomes based on commune of residence (Annex 7), and correlation of exposure and outcomes (Annex 8) and using a Pearson correlation coefficients, which measures the strength of linear relationships on a scale from -1 and +1 , where +1 represents a perfect positive relationship (Profillidis and Botzoris, 2019).

2.3.2 Global cognitive score

A global cognitive score was calculated from the cognitive scores, determined with an unsupervised analysis such as the principal component analysis (PCA) on male and female population separately. The score was a composite of all cognitive domain's tests (FCSRT, TMT, DDST, and VFT) and was defined by the first dimension of the PCA, selected based on the bend of the scree plot (Annex 4). The firs dimension explains 46.4% of the variance of the cognitive tests on the male population and 43.6 % on the female population. The global cognitive score was composed of positive scores with higher contribution, and correlations on the first dimension for FCSRT, semantic verbal fluency, lexical verbal fluency (Annex 4).

2.3.3 Regression analyses

To test associations between each cognitive test and each of the exposure variables, we did a crude analysis of the data (not shown) followed by multiple linear regression with different levels of adjustment. First, the Parsimonious model included adjustment on the a priori chosen variables: age, sex, and education and health screening centres (HSCs). Then, a main model, was adjusted on age, sex, education HSCs, non-occupational physical activity, classification of commune of residence, area-level deprivation, and air pollution as $PM_{2.5.}$ The covariates of the main model were chosen based on the minimal sufficient adjustment sets for estimating the total effect of greenspace exposure on cognition considering potential confounders on the DAG (Annex 3). All models were done on the imputed data (5 datasets and 10 iterations), to account missing values.

Linear regression analyses of continuous outcomes are sensitive to outliers (Lunt, 2015), to account for this, the z-score of each cognitive tests' results were used, transformed based on the mean and standard deviation (SD) of tests scores, this standardized measure also facilitates the comparison of the results of different tests. Residential greenness was taken as a continuous exposure and linear regressions estimates were expressed as one interquartile range (IQR) increase in mean NDVI at each buffer (Asta *et al.*, 2020).

Urbanity plays a potential effect-modifier role on the pathway of greenspace effect and health (Markevych *et al.*, 2017), considering variation of findings between health outcomes on rural and urban areas (Maas *et al.*, 2006). Because of this, we tested interactions terms for cognitive outcomes and greenspace exposure as NDVI at 300 m buffer and used a regression likelihood ratio test (LRT) for the interaction terms to assess overall significance for the interaction (Edwards *et al.*, 2010). Finally, we performed a stratified analysis (Annex 9), to explore variation in the associations, and plotted stratification of only significant likelihood ratio test interaction (Wheeler *et al.*, 2015). All data analysis was executed using R version 3.5.

2.3.4 Sensitivity analyses

Several sensitivity analyses were employed on specific cognitive outcomes to test the robustness of the results. For each of the sensitivity analyses models, we selected at least one cognitive outcome of each cognitive domain and general cognition. Exposure to greenspace (NDVI) was set at 300 m buffer, an indicator of minimum access to greenspace (Toftager *et al.*, 2011; van den Bosch, 2016) . The sensitivity analyses models performed were:

a) To consider the possible role of HSC as a clustering variable, a multilevel linear analysis (Annex 11) was performed adjusted on the main model (Wu, Prina, A. Jones, *et al.*, 2015; Letellier *et al.*, 2020).
b) Another sensitivity analysis was to consider the peculiar characteristics of Paris HSCs, since there might be higher participation, urbanity, and air pollution. So, we excluded these centres and adjusted on the main model (Annex 12).
c) Another sensitivity analysis considering HSC, was a meta-analysis (Annex 14), with a fixed effect model, where we assume that the only variation between estimates was due to random error (Borenstein *et al.*, 2010), that includes the pooled results and

heterogeneity, or variation between the centres. Supplementary to the analysis of cognitive test results (as a continuous variable), we performed a sensitivity analysis to assess the association between dichotomized cognitive outcomes and exposure to greenspace with a logistic regression model.

d) Other sensitivity analysis were multiple linear regressions adjusted on the main model, with complete case data.
e) Further sensitivity analysis for potential effect modifiers besides commune of residence, was a stratified analysis, adjusted on the main model, for area level deprivation and sex (Annex 10).
f) Finally, a sensitivity analysis with a further adjusted model (Annex 15), considering most variables that affect cognition (Livingston *et al.*, 2020), these covariates include health behaviours, further socio-demographic characteristics, comorbidities, and chronic diseases and can be found on Annex 5.

2.4 Ethical Considerations

The current study involves secondary data analysis of the French CONSTANCES cohort, and access to its database was granted by the Institut de recherche en santé, environnement et travail / Research Institute for Environmental and Occupational Health (IRSET) through the professional advisor Bénédicte Jacquemin. Included on Annex 2 was the student declaration on form, as part of graduation project Ethics Review of the University of Sheffield's School of Health and Related Research (ScHARR).

3. Results
3.1 Descriptive

Descriptive statistics by sex for covariates and outcomes are shown in Table 1 on the study population (n=65316). On Table 2 the characteristics of greenspace exposure and cognitive outcomes are shown by the classification of commune of residence. The study population aged 57 (SD: 7.2) years old, highly educated with 50% (33069) of them having 12 years or more education, and most of them living in urban (37%, 24146) or suburban areas (37.1%, 24213). The mean (SD) exposure of air pollution ($PM_{2.5}$) concentration was of 16.7 (3.0), and 43 % (28313) exert moderate non-occupational physical activity. Further study population characteristics, on Annex 5, shows that 82% (53611) have high household income (>2100 euro/month), with 30.3% (19776) on high intellect professions, 31.9% (20807) on intermediate profession such as teachers or nurses, and 31.7% (20686) as employees or manual workers. Differences on comorbidities lie with women having 11.3% (1480) more depressive symptoms than men, and men having 18.7% (5180) higher prevalence of hypertension and 8.6% (2325) higher prevalence of dyslipidaemia than women.

Furthermore, descriptive statistics of outcomes and exposures by classification of commune of residence are shown on Table 2. We can observe on the descriptive statistics of greenspace exposure (NDVI) that for all buffer sizes, the further away from urban areas 0.5 (0.2), the higher the mean residential greenness, 0.7(0.1) on rural areas. Mean cognitive scores decrease from urban to rural areas, on episodic memory, DSST, VFT on semantic and lexical, and the global score. On TMT, on which lower scores signify better cognitive performance, it varied between its parts. TMT part B scores increased from urban to rural areas. However, as TMT part A scores decreased between urban 33.6(11.5) and suburban 32.9 (11.3), it increased again on isolated city 33.8 (11.5) and decrease on rural areas 33.4 (11.4), with very marginal differences from urban-rural areas. Which might imply a potential association of urbanity with cognitive scores.

Cognitive outcomes were moderately correlated with each other, and with marginal variation of their correlation coefficients on the different commune of residence (Annex 7). The global score was highly correlated with all outcomes, considering it was a composite of the different cognitive domains. Cognitive tests in similar domains were highly correlated with each other such as the executive function outcomes, DSST, TMT-A and TMT-B. While cognitive outcomes had almost no correlation with exposure measures (Annex8).

Table 1. Characteristics of study population from the French CONSTANCES cohort participants by sex (n=65316)

Variables		Male	Female	Total
Age (years)		57.71 (7.23)	57.41 (7.19)	57.55 (7.21)
Education (years)				
Less than 5 years		844 (2.77)	865 (2.48)	1709 (2.62)
5-12 Years		14702 (48.20)	15836 (45.48)	30538 (46.75)
12 and more years		14953 (49.03)	18116 (52.03)	33069 (50.63)
Classification of commune of residence				
Urban		10963 (35.95)	13183 (37.86)	24146 (36.97)
Suburban		11498 (37.70)	12715 (36.52)	24213 (37.07)
Isolated city		2354 (7.72)	2577 (7.40)	4931 (7.55)
Rural		5684 (18.64)	6342 (18.22)	12026 (18.41)
*Deprivation level**				
Low		10037 (32.91)	11823 (33.96)	21860 (33.47)
Moderate		10179 (33.38)	11588 (33.28)	21767 (33.33)
High		10278 (33.70)	11404 (32.76)	21682 (33.20)
*Physical activity***				
Low		7652 (25.09)	7343 (21.09)	14995 (22.96)
Medium		13165 (43.17)	15148 (43.51)	28313 (43.35)
High		9682 (31.75)	12326 (35.40)	22008 (33.69)
Air Pollution (PM2.5)		16.63 (2.92)	16.75 (3.02)	16.70 (2.97)
Cognitive Tests	**Score description**			
*FCSRT(RFT)****	*0-16*	12.24 (2.23)	13.29 (1.93)	12.80 (2.14)
*FCSCRT(RTT)****	*0-16*	12.24 (2.23)	13.29 (1.93)	12.80 (2.14)
Verbal Semantic Fluency	*Number of words provided in 1 min*	22.16 (4.61)	22.36 (4.55)	22.27 (4.58)
Verbal Lexical Fluency	*Number of words provided in 1 min*	14.71 (4.74)	15.74 (4.76)	15.26 (4.78)
*DSST****	*Number of symbols correctly completed in 90s*	63.89 (14.06)	69.12 (13.88)	66.68 (14.21)
*TMT-A****	*Time (seconds)*	33.77 (11.83)	32.96 (11.06)	33.34 (11.43)
*TMT-B****	*Time (seconds)*	67.70 (29.69)	64.53 (26.79)	66.01 (28.23)
Global Score	*zero centered*	-0.00 (1.67)	-0.00 (1.62)	-0.00 (1.64)

Note: Values expressed as mean (Standard Deviation) for continuous variables and frequency (%) for categorical variables
*Classified based on tertiles of the French deprivation index (first tertile as low, second tertiles as moderate, and third tertile as high)
**Classified based on a scale of non-occupational physical activity 1 -7 (1-3 as low; 4-5 as medium, and 6-7 as high).

***RFT: Fast free recall score of FCSRT (Free and Cued Selective Reminding Test); RTT: Fast recall total score of FCSRT; DSST: digit-symbol substitution test; TMT-A: Trial making test part A; TMT-B: Trial making test part B.

Table 2. Characteristics of greenspace exposure and cognitive outcomes by commune of residence.

	Commune of Residence				
	Urban	**Suburban**	**Isolated city**	**Rural**	**Total**
Exposures					
NDVI					
Buffer at 100 m	0.49 (0.17)	0.63 (0.12)	0.66 (0.12)	0.73 (0.10)	0.60 (0.16)
Buffer at 300m	0.51 (0.17)	0.67 (0.12)	0.71 (0.11)	0.81 (0.08)	0.64 (0.17)
Buffer at 500m	0.52 (0.17)	0.69 (0.12)	0.74 (0.10)	0.83 (0.06)	0.66 (0.17)
Buffer at 1000m	0.54 (0.17)	0.71 (0.11)	0.78 (0.09)	0.86 (0.06)	0.68 (0.18)
Outcomes **					
RSCRT(RFT)*	12.96 (2.12)	12.73 (2.14)	12.65 (2.20)	12.67 (2.14)	12.80 (2.14)
RSCRT(RTT)*	12.96 (2.12)	12.73 (2.14)	12.65 (2.20)	12.67 (2.14)	12.80 (2.14)
DSST*	67.43 (14.48)	66.73 (13.94)	65.86 (13.97)	65.42 (14.15)	66.68 (14.21)
TMT-A*	33.59 (11.54)	32.96 (11.29)	33.79 (11.51)	33.39 (11.45)	33.34 (11.43)
TMT-B*	65.46 (27.83)	65.48 (28.02)	67.33 (28.23)	67.66 (29.33)	66.01 (28.23)
Verbal Semantic Fluency	22.36 (4.58)	22.25 (4.56)	22.12 (4.63)	22.17 (4.59)	22.27 (4.58)
Verbal Lexical Fluency	15.66 (4.77)	15.22 (4.73)	14.97 (4.81)	14.64 (4.80)	15.26 (4.78)
Global Score	0.08 (1.65)	0.02 (1.62)	-0.13 (1.65)	-0.14 (1.65)	-0.00 (1.64)

Note: Values expressed as mean (Standard Deviation) for continuous variables and frequency (%) for categorical variables
*RFT: Fast free recall score of FCSRT (Free and Cued Selective Reminding Test); RTT: Fast recall total score of FCSRT; DSST: digit-symbol substitution test; TMT-A: Trial making test part A; TMT-B: Trial making test part B.
**Test scores described as: FCSRT: 0-16; Semantic fluency: number of words provided in 1 min; Lexical fluency: number of words provided in 1 min; DSST: number of symbols correctly completed in 90s; TMT-A: Time (seconds); TMT-B: Time (seconds); Global Score: zero centered

3.2 Regression analyses

3.2.1 Associations of greenspace and cognitive performance

Results on the association of exposure to greenspace and cognitive performance for Parsimonious model (adjusted for age, sex, education, and HSCs) and the main model are shown on Table 3. Results on Parsimonious model showed significant better cognitive performance on all cognitive domains and the global score at higher values of NDVI at different buffers. At 500m buffer size, greenspace exposure had significant associations (negative for TMT) for most cognitive outcomes. Verbal lexical fluency and RFT sub scores of FCSRT was statistically significant but with negative associations at 500 m and 1000 m buffers.

The main model on (Table 3), had improved cognitive performance (a significant change in z-scores for one IQR increase in exposure) on at least one cognitive test of each cognitive domain at different buffer sizes of greenspace exposure. While the global score increased significantly with greenspace exposure on all buffer sizes. Furthermore, results of cognitive performance on the main model, TMT-B and semantic verbal fluency remained statistically significant with positive (negative for TMT-B) association on residential greenness for all buffer sizes. RTT remained significant and with positive association at buffers of 300 m, 500 m and 1000m.

Adjusting on the main model, an increase in greenspace at 300 m buffer, was significantly associated with improved cognitive performance on RTT (z -score 0.030, 95%CI: 0.012 to 0.048), DSST (z -score 0.020, 95%CI: 0.003 to 0.037), TMT-A (z -score -0.021, 95% CI: -0.039 to -0.003), TMT-B (z -score -0.038, 95% CI: -0.055 to -0.020), semantic verbal fluency (z -score 0.043, 95%CI: 0.024 to 0.063) and the global cognitive score (z-score 0.026, 95% CI: 0.008 to 0.044).

3.2.2 Effect modification

The results of the likelihood ratio test (LTR) and a detailed table of stratification by commune of residence for all outcomes was provided on Annex 9. The results of the stratified analyses by commune of residence (Figure 2), includes the cognitive tests of TMT-A and lexical verbal fluency, which were cognitive outcomes with significant interaction terms and significant LTR.

Stratified analyses revealed that commune of residence modify the effect of greenspace exposure on cognitive performance on specific domains. On executive function (TMT-A), the only significant result was on suburban areas (z-score -0.054, 95% CI: -0.084 to -0.025) which we can observe had higher scores than the main model. Meanwhile, isolated cities and rural areas exhibited non-significant but with an unexpected direction (positive coefficient) results from exposure to residential greenness.

The role of commune of residence on cognitive outcomes in this study will be clearer when we compared the main model results and the estimates of stratified results (Figure 2). On the main model, lexical verbal fluency was non-significant with negative associations, an unexpected direction. Similarly, after stratification, urban areas have also a significant negative association (z-score 0.054, 95% CI: 0.020 to 0.087). Whereas, though not significant, scores from other classifications of residence are showing the expected direction of the results. Population sizes are small on participants that reside in isolated city and rural areas, which could explain how some associations did not achieve statistical significance on these outcomes.

Table 3. Results of association between exposure to greenspace and cognitive performance of the French CONSTANCES cohort participants (n=65316).

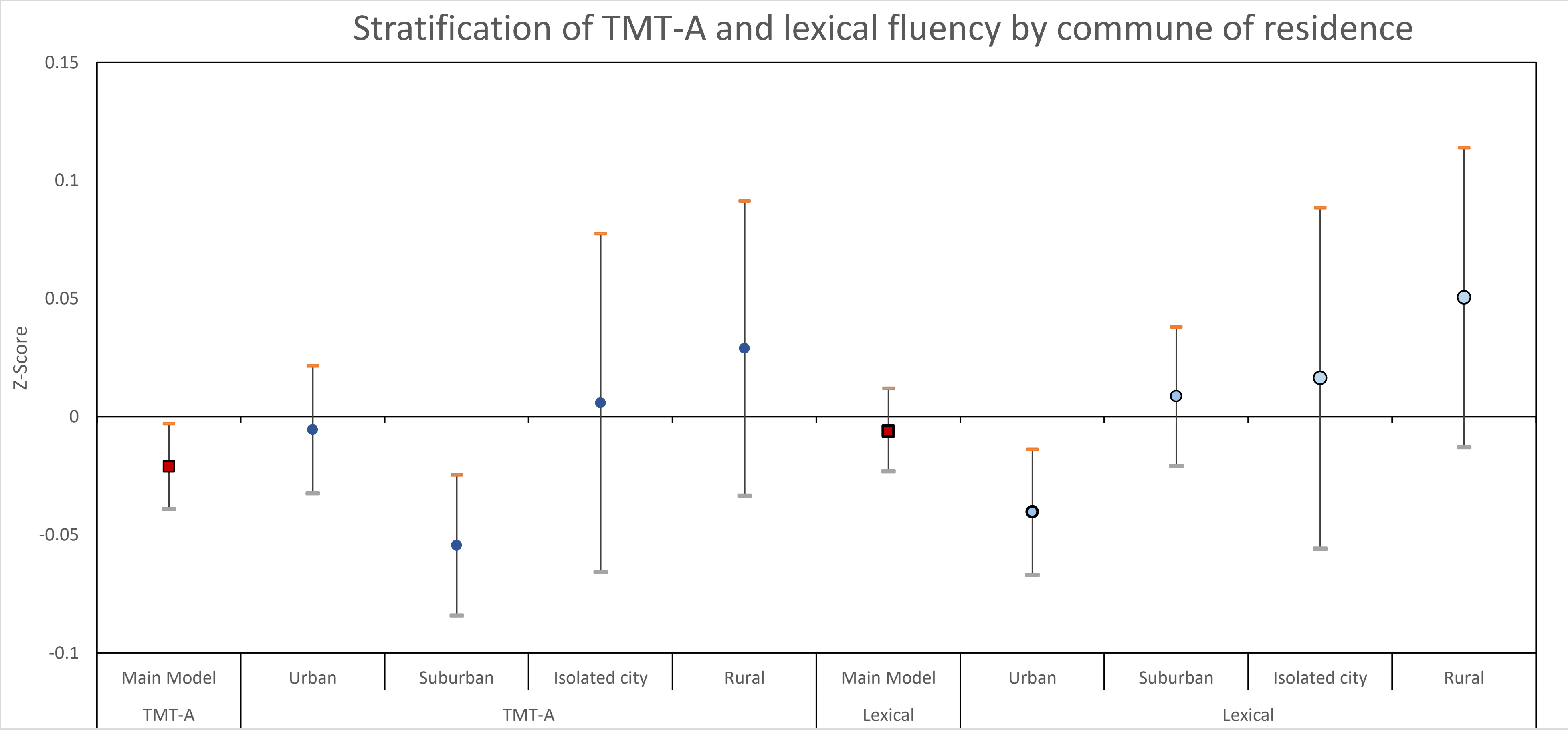
	Cognitive Domains, β (95% CI)							
	Episodic Memory		Executive functions			Language skills		General Cognition
NDVI	RFT*	RTT*	DSST*	TMT-A*	TMT-B*	Lexical fluency	Semantic fluency	Global Score
At 100 m buffer								
Parsimonious**	-0.010 (-0.023: 0.002)	**0.015 (0.002: 0.028)**	**0.014 (0.001: 0.026)**	**-0.023 (-0.036: -0.010)**	**-0.031 (-0.044: -0.019)**	-0.006 (-0.019: 0.007)	**0.034 (0.019: 0.049)**	**0.022 (0.009: 0.035)**
Main Model***	-0.003 (-0.018: 0.011)	0.014 (-0.001: 0.029)	**0.017 (0.004: 0.031)**	**-0.017 (-0.032: -0.002)**	**-0.023 (-0.038: -0.009)**	0.002 (-0.013: 0.017)	**0.021 (0.005: 0.037)**	**0.018 (0.004: 0.033)**
At 300 m buffer								
Parsimonious	**-0.016 (-0.030: -0.002)**	**0.026 (0.011: 0.041)**	0.012 (-0.001: 0.026)	**-0.028 (-0.042: -0.013)**	**-0.044 (-0.058: -0.029)**	-0.014 (-0.029: 0.000)	**0.054 (0.037: 0.070)**	**0.028 (0.013: 0.043)**
Main Model	-0.007 (-0.024: 0.010)	**0.030 (0.012: 0.048)**	**0.020 (0.003: 0.037)**	**-0.021 (-0.039: -0.003)**	**-0.038 (-0.055: -0.020)**	-0.006 (-0.023: 0.012)	**0.043 (0.024: 0.063)**	**0.026 (0.008: 0.044)**
At 500 m buffer								
Parsimonious	**-0.022 (-0.037: -0.007)**	**0.023 (0.008: 0.039)**	**0.016 (0.002: 0.031)**	**-0.035 (-0.051: -0.020)**	**-0.047 (-0.062: -0.032)**	**-0.020 (-0.035: -0.004)**	**0.056 (0.038: 0.073)**	**0.030 (0.014: 0.045)**
Main Model	-0.014 (-0.032: 0.005)	**0.026 (0.007: 0.046)**	**0.027 (0.008: 0.045)**	**-0.031 (-0.051: -0.012)**	**-0.041 (-0.060: -0.022)**	-0.012 (-0.031: 0.007)	**0.045 (0.024: 0.067)**	**0.029 (0.009: 0.048)**
At 1000 m buffer								
Parsimonious	**-0.026 (-0.042: -0.010)**	**0.026 (0.010: 0.043)**	0.015 (-0.000: 0.030)	**-0.043 (-0.059: -0.027)**	**-0.052 (-0.068: -0.036)**	**-0.025 (-0.041: -0.009)**	**0.052 (0.034: 0.070)**	**0.032 (0.015: 0.048)**
Main Model	-0.018 (-0.037: 0.002)	**0.032 (0.011: 0.052)**	**0.025 (0.005: 0.044)**	**-0.042 (-0.063: -0.022)**	**-0.047 (-0.067: -0.027)**	-0.020 (-0.041: 0.000)	**0.039 (0.016: 0.062)**	**0.031 (0.010: 0.051)**

Note: Regression coefficients and 95% confidence intervals; all estimates are based on change in cognitive performance (change in z-scores) and one interquartile range increase in exposure. IQR of NDVI at 100m= 0.2181755, IQR of NDVI at 300m=0.2458683; IQR of NDVI at 500m=0.2593613; IQR of NDVI at 1000m=0.2668411

*RFT: Fast free recall score of FCSRT (Free and Cued Selective Reminding Test); RTT: Fast recall total score of FCSRT; DSST: digit-symbol substitution test; TMT-A: Trial making test part A; TMT-B: Trial making test part B.

** Parsimonious: adjusted for age, education, sex, and health screening centre (HSC).

***Main model: adjusted for age, sex, education, HSC, commune of residence, physical activity, French deprivation, and air pollution exposure ($PM_{2.5}$).



Note: Regression coefficients and 95% confidence intervals; all estimates are based on change in cognitive performance (change in z-scores) and one interquartile range increase in exposure. Main model: adjusted for age, sex, education, HSC, commune of residence, physical activity, French deprivation, and air pollution exposure as $PM_{2.5}$.; TMT-A: Trial making test part A

Figure 2. Results of stratification by commune of residence and the association between exposure to NDVI at 300 m buffer and cognitive performance of the French CONSTANCES cohort participants.

3.3 Sensitivity analyses

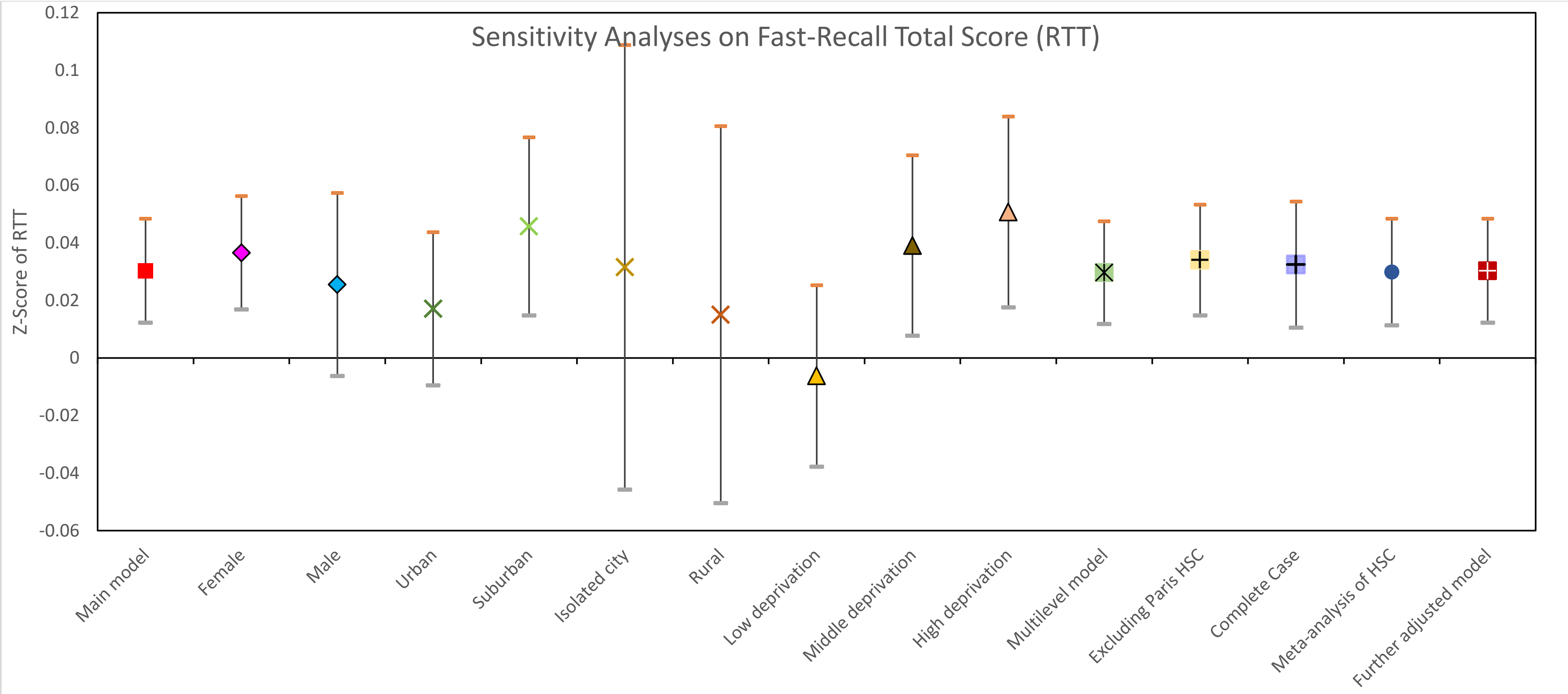
Sensitivity analyses were performed for testing the robustness of the associations found on the main model, with NDVI at 300 m buffer, on the different cognitive domains. These analyses are summarized in figures for episodic memory as RTT (Figure 3) and selected since it contains the sum of the free and cued tests of FCSRT, a more complete representation of this domain than RFT (Teichmann *et al.*, 2017). Executive functions is represented as TMT-B (Figure 4), since it was a good measure of executive functions that do not require a motor component and a represents of cognitive flexibility (Bowie and Harvey, 2006). Language skills is shown as semantic verbal fluency (Figure 5), selected for being consistent on all buffers and a good indicator of cognitive decline (Mueller *et al.*, 2018). The global score was used to represents general cognition (Figure 6). Tables of the individual sensitivity analyses results can be found on Annexes 10 to 16.

Overall sensitivity analyses showed robust findings of improved cognitive performance for RTT, TMT-B and semantic verbal fluency in association with exposure to greenspace. These analyses include findings on female population, suburban areas residents, those living at middle and high deprivation levels, multilevel modelling by considering HSCs as a clustering variable, a model excluding the Paris HSCs participants, a further adjusted model and the pooled meta- analysis of the HSCs with heterogeneity (between-centre variation). The meta-analysis had moderate, significant heterogeneity (I^2= 44.3 % , p-value: 0.016 on RRT; I^2= 47.5 % , p-value: 0.0.009 on semantic fluency) for RTT (z-score 0.026, 95%CI: 0.008: 0.045) and semantic verbal fluency (z-score 0.042, 95% CI: 0.022: 0.063) and low non-significant heterogeneity (I^2= 4.4 % , p-value: 0.40) on TMT-B (z-score -0.033, 95% CI:-0.050: -0.016). Results also showed that participants living in middle and high deprivation levels areas benefit the most from greenspace exposure. Though improved cognitive performance occurs on rural and isolated city, their small sample size, represented by their large confidence intervals, showed non-significant results on most outcomes, except for isolated city on TMT-B.

The global score, as general cognition (Figure 6) was positively associated with greenspace, on female population, suburban areas, multilevel model with HSCs as clustering variable, main model excluding Paris HSCs, and the pooled result of the meta-analysis by HSCs with moderate and significant heterogeneity.

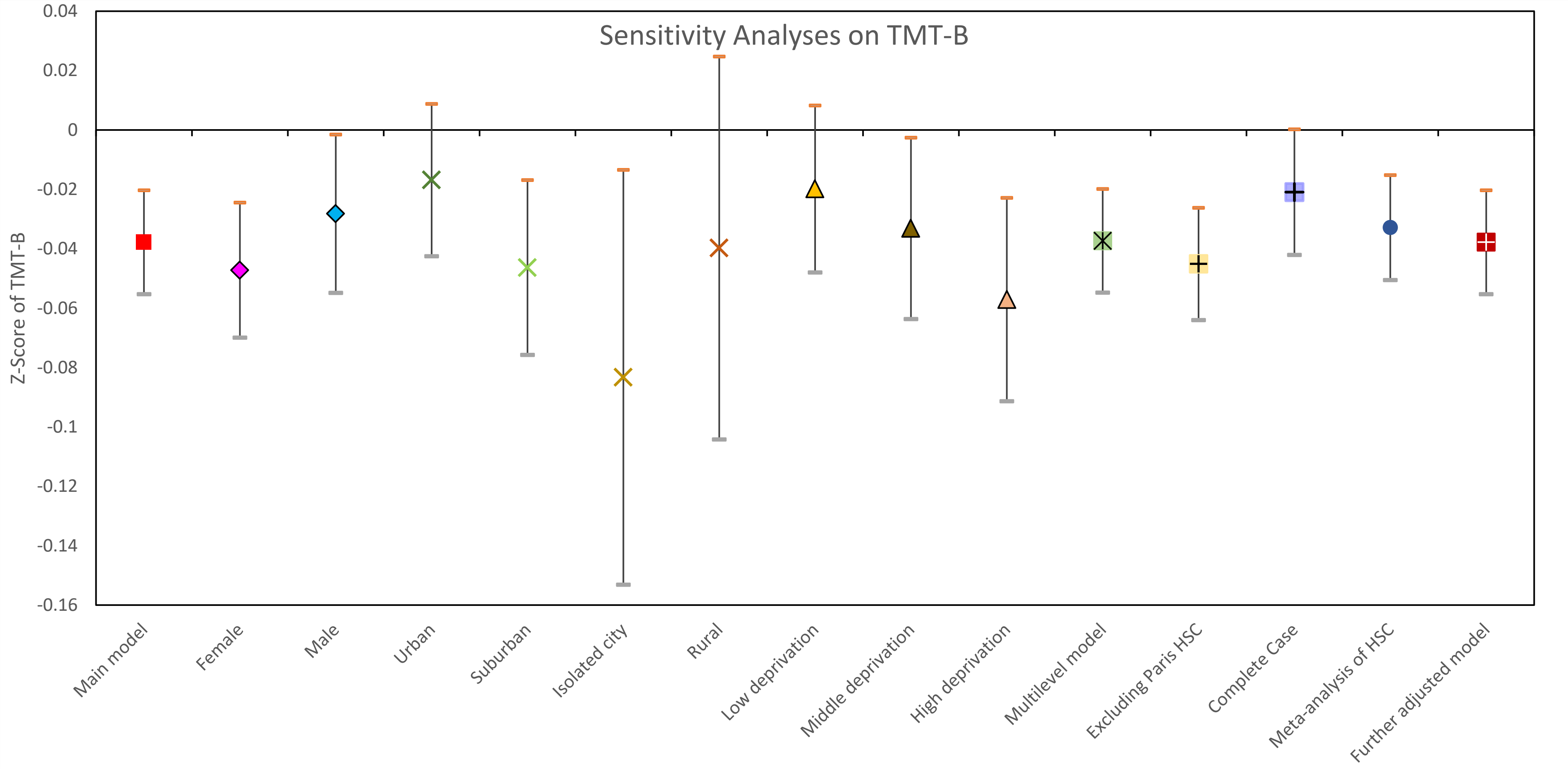
Finally, a sensitivity analysis not included as a figure, was the logistic regression model based on the dichotomous cognitive outcomes based on the norms (Annex 16). These outcomes are presented as odds ratio (95% CI) and show the likelihood of bad cognitive performance. For

RTT, TMT-B and semantic verbal fluency, an increase in greenspace exposure was associated with a decrease in the odds of a participant having a bad performance.



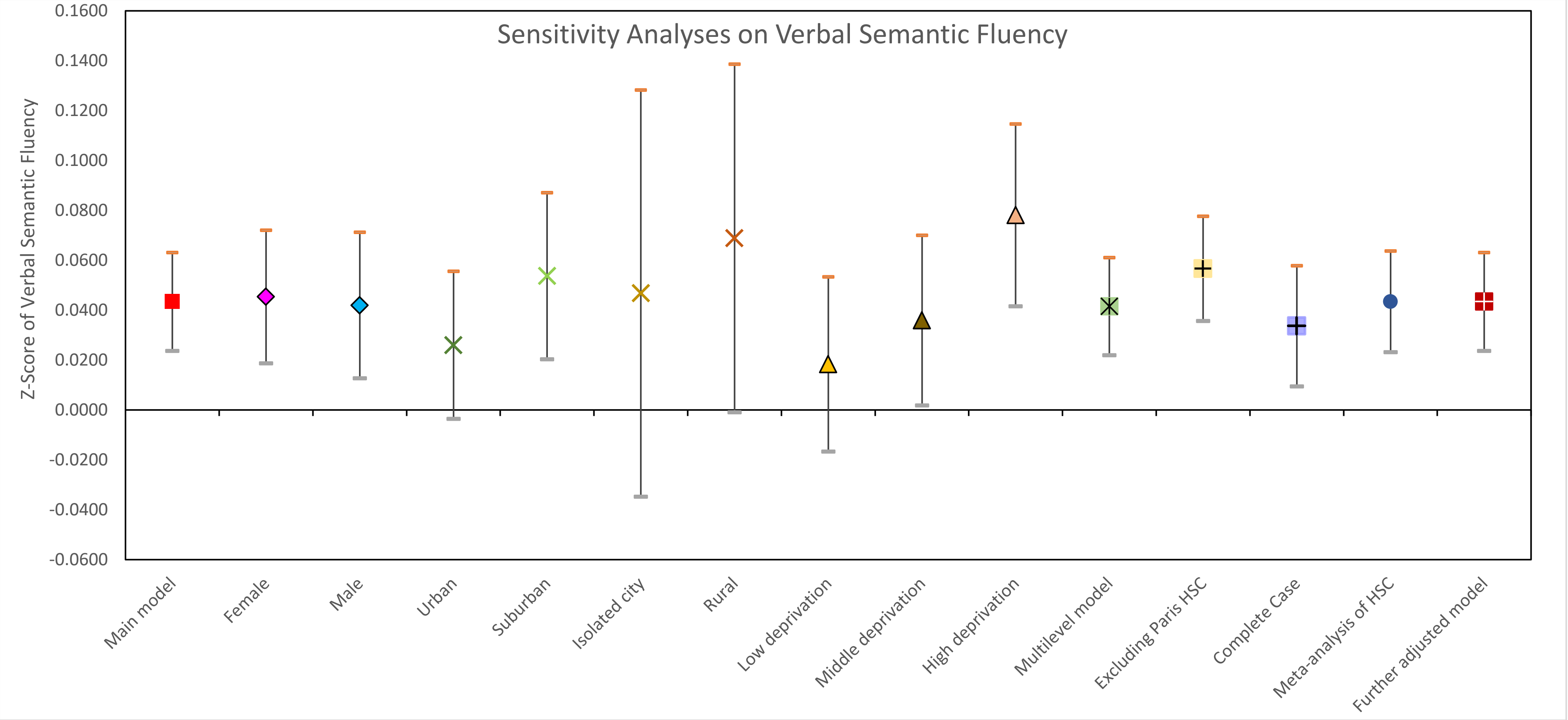
Note: Regression coefficients and 95% confidence intervals; all estimates are based on change in cognitive performance (change in z-scores) and one interquartile range increase in exposure. Main model: adjusted for age, sex, education, HSC, commune of residence, physical activity, French deprivation, and air pollution exposure as $PM_{2.5}$.

Figure 3. Sensitivity analyses of exposure to NDVI at 300 m buffer on the performance of episodic memory as fast recall total score (RTT).



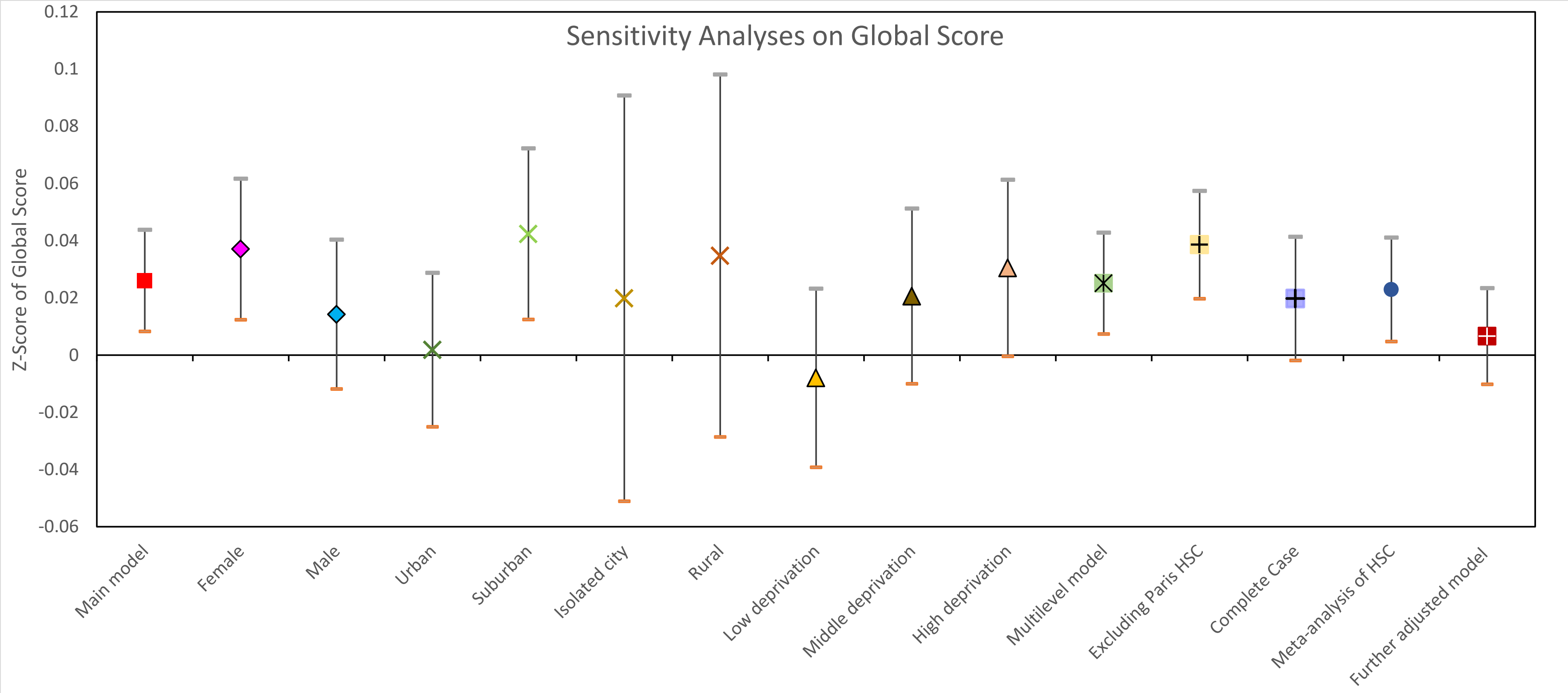
Note: Regression coefficients and 95% confidence intervals; all estimates are based on change in cognitive performance (change in z-scores) and one interquartile range increase in exposure. Main model: adjusted for age, sex, education, HSC, commune of residence, physical activity, French deprivation, and air pollution exposure as $PM_{2.5}$.

Figure 4. Sensitivity analyses of exposure to NDVI at 300 m buffer on the performance of executive function as trial-making test part B (TMT-B).



Note: Regression coefficients and 95% confidence intervals; all estimates are based on change in cognitive performance (change in z-scores) and one interquartile range increase in exposure. Main model: adjusted for age, sex, education, HSC, commune of residence, physical activity, French deprivation, and air pollution exposure as $PM_{2.5}$.

Figure 5. Sensitivity analyses of exposure to NDVI at 300 m buffer on the performance of language skills semantic fluency.



Note: Regression coefficients and 95% confidence intervals; all estimates are based on change in cognitive performance (change in z-scores) and one interquartile range increase in exposure. Main model: adjusted for age, sex, education, HSC, commune of residence, physical activity, French deprivation, and air pollution exposure as $PM_{2.5}$.

Figure 6. Sensitivity analyses of exposure to NDVI at 300 m buffer on the performance of general cognition as global score.

4. Discussion

4.1 General findings

In this study we examined the associations between exposure to greenspace as residential greenness and cognitive performance, on three cognitive domains and general cognition, in a large study population (n=65316) of middle-aged and older participants (45 to 69 years old) from the French CONSTANCES cohort. After adjustment for covariates, we found evidence that more greenspace exposure was associated with improved performance on episodic memory (RTT), language skills (semantic verbal fluency), executive functions (DSST, TMT-A and TMT-B), and on general cognition (global score).

There was a protective association on general cognition, however, given that it only represents <50% of variance of the cognitive tests, it was complementary to the results obtained from the different cognitive domains. Improved general cognition has been reported to be associated with greenspace exposure with similar observational studies (Dzhambov *et al.*, 2019; Asta *et al.*, 2020; Crous-Bou *et al.*, 2020). The global score was a good tool to simplify and present a summary of all cognitive domains, since they are all highly correlated. However, it was not recommended to use it as a sole indicator of cognitive performance since its composition was based on the contribution of variance represented on each cognitive domain and inconsistencies may be found for other studies. A combination of specific cognitive domains and a global score was suggested.

Episodic memory decline has been an essential trait of amnesic AD and low scores of free total recall (RTT), the sum of cued and free recall of FCSRT, can be found for other neurodegenerative diseases, linked to cognitive changes in language, poor executive functions, or episodic amnesia (Teichmann *et al.*, 2017). Reported associations on cortical thickness, brain volume and amygdala integrity with greenspace exposure, highlights the probable importance of improved greenspace exposure on reducing the risk of AD (Kramer *et al.*, 2004; Dadvand Payam *et al.*, 2012; Dzhambov *et al.*, 2019; Besser, 2021). Greenspace restorative capacities (Markevych *et al.*, 2017; Dzhambov *et al.*, 2020), such as stress reduction, can aid episodic memory due to its association with physical disorder, stressors from negative neighbourhood characteristics (Zaheed *et al.*, 2019).

On executive function domain, the trail making test (TMT) was responsive to concentration deterioration, vigilance and visuo-spatial ability due to aging (Bowie and Harvey, 2006) and as such was an early indicator of cognitive impairment or dementia. TMT-A contributes mainly to visuo-perceptual abilities, while TMT-B reflects working memory and task switching abilities, very important on demonstrating executive function (Sánchez-Cubillo *et al.*, 2009). A good performance with DSST correlates with the participants abilities to accomplish everyday tasks (Jaeger, 2018) and its association with greenspace as a protective factor of age related cognitive decline. Greenspace exposure can improve abilities of participants to live independently through, by providing better mobility (Poranen-Clark *et al.*, 2018) with its capacity building and through and improved attention due to its restorative abilities (Gamble, Howard and Howard, 2014).

On language skills, there were very strong associations between semantic verbal fluency and greenspace exposure, no matter the residential greenness buffer size. A deficit in semantic memory was prominently associated with AD, and was a reflection of degradation in the integrity of the semantic knowledge (Henry, Crawford and Phillips, 2004). Identifying language difficulties early on the development of AD was important considering that was highly correlated with challenging behaviours of AD (Mueller *et al.*, 2018). Greenspace exposure through its capacity building (Markevych *et al.*, 2017; Dzhambov *et al.*, 2020) of places where people can meet is favourable for language skills since semantic verbal fluency was associated with social cohesion (Zaheed *et al.*, 2019). Additionally, the interlaced relationship of language and memory on cognitive decline may explain strong associations on these domains (Mueller *et al.*, 2018).

To better understand potential greenspace pathways of improved cognitive performance and to reduce the risk of dementia, we need to consider some of its relationship with other known modifiable risk factors, such as air pollution and protective factors, such as social contact and physical activity.

An important environmental risk factor of dementia was air pollution. On 2015, ambient air pollution as $PM_{2.5}$, contributed to 0.6 Million (95% CI: 0.4 M to 0.8 M) deaths worldwide and around 15% of premature deaths (Ru *et al.*, 2021). Air pollution was also associated with poor cognitive performance, especially on language skills(Zhang, Chen and Zhang, 2018). Language skills as semantic verbal fluency was consistently positively associated with greenspace in our study after adjusting for air pollution as confounding factor, this makes our findings on the association between greenspace and semantic fluency was not due to reduced air pollution in areas with more greenness. However, air pollution can also be considered as a potential mediator, due to a its strong spatial correlation with greenspace (Dzhambov *et al.*, 2020, p. 20).

Physical activity had a dynamic relationship with greenspace exposure and its capacity building (Markevych *et al.*, 2017). Physical activity was associated with the accessibility to greenspace, the more accessible greenspace, the more exercise will be done. Additionally, physical activity was the reason for which people visit greenspace to exercise. Physical activity was also a lifestyle intervention that improves executive function and reduces cardiovascular risk factors (Ngandu *et al.*, 2015), another important modifiable risk factor of dementia.(Baumgart *et al.*, 2015)

Social contact was considered a protective factor of dementia (Livingston *et al.*, 2020), as frequent social contact allows an increase in cognitive reserve, which was a concept on how lifetime exposures makes a brain more resilient to neuropathology (Stern and Barulli, 2019). The relationship between social interaction and greenspaces was reciprocal. Greenspace contains instoration capacities, that generate spaces of enhanced social interactions (Markevych *et al.*, 2017) and creates a strong sense of community and identity of people that live nearby (Maas *et al.*, 2009). Similar to our findings, environmental neuroscientists (Berman, Stier and Akcelik, 2019) have demonstrated that interaction with greenspace improves neurocognitive functioning (Berman, Jonides and Kaplan, 2008), which consequently augments social interactions. Another way view it, was that when cognitive decline occurs, it may deter access to the social spaces created by greenspace which in turn may further accelerate cognitive decline (Poranen-Clark *et al.*, 2018). Social networks can benefit memory and executive function, by improving attention and processing speed, however, there are no detailed studies on the association of social contact and different cognitive domains (Kelly *et al.*, 2017).

We also must consider the potential role of socioeconomic status and the access to greenspace. Those with low socioeconomic standing have more health benefits from greenspace exposure (Dadvand *et al.*, 2014) and there is also evidence that deprivation level is associated with cognitive impairment (Basta *et al.*, 2008; Letellier *et al.*, 2020) . However, those that lived in in areas with better socioeconomical status (SES) may have better access to greenspace(Astell-Burt *et al.*, 2014) and its benefits, such as better social cohesion(Maas *et al.*, 2009) . In our study we adjusted by area level SES, so that the beneficial associations from greenspace do not reflect those that reside in affluent much greener areas. However, we recommend to further explore this relationship, using area level SES as a potential effect modification (van den Berg *et al.*, 2015).

4.2 Effect Modification

This study also explored the effect modification of the commune of residence on the association of greenspace and cognitive performance. Language skills on lexical verbal fluency and executive functions on TMT-A findings were found to have been modified by the different classification of commune of residence, having statistical significance on urban-suburban areas. Population sizes are small on participants that reside in isolated city and rural areas, which could explain some effects did not achieve statistical significance. Similar to our findings on the associations of greenspace exposure, one study shows (Wu *et al.*, 2017) a 30% of reduced odds of cognitive impairment on high conurbation (cities and towns with high density of population).

4.3 Strengths and limitations

A major strength of this study was its large population size (n=65316) that includes all metropolitan regions of France, and with varying types of residence (urban/rural). Additionally, the comprehensive cognitive tests of the CONSTANCES cohort, and inclusion of population of middle age and older participants, which aids in studying role of greenspace on cognitive function of early aging population. This study also applied wide range of sensitivity analyses that consider location (commune of residence and health screening centres), which showed the robustness of main models' findings.

Considering that association of greenspace and cognitive performance has mostly been studied as general cognition (Lee and Maheswaran, 2011; Dzhambov *et al.*, 2019; Asta *et al.*, 2020; Crous-Bou *et al.*, 2020), this study provides preliminary evidence of individual-level association of greenspace exposure on different cognitive domains. This gives a valuable overview of the potential pathways of protection on the development of neurodegenerative diseases and cognitive impairment. Another strength of our study was the proper selection of greenspace exposure index which may have discrepancies among other greenspace studies. Our study used NDVI, a very common exposure measure that increases the comparability of results across studies.

As this was an observational study, with cross-sectional analysis of cognitive performance, it was difficult to infer causality and there was a possibility of residual confounding. Greenspace exposure studies have limitations with spatio-temporal variation of exposure assessments, in our case we used residential address at the time of enrolment, and we did not include their mobility. Estimates of greenspace may be relevant by the type of greenspace (i.e., different types of vegetation), accessibility to greenspace, spatial autocorrelation, perceived amount of greenspace (Zijlema *et al.*, 2017) and temporal associations (Besser, 2021). There was also a limitation on the use of NDVI as greenspace as indicator, since it is only a measure of overall greenness, and there may be better quality satellite imagery data available through other vegetation indexes (Markevych *et al.*, 2017).

5. Conclusions and recommendations

Significant protective associations were found between exposure to greenspaces and some domains of cognition, mainly on language skills (semantic verbal fluency), executive functions (TMT), episodic memory (RTT), and on general cognition. Greenspace benefits on cognition are domain specific with strong association on semantic verbal fluency and executive. Performing several sensitivity analyses, we found robust results for the three cognitive domains.

Effect modification by commune of residence shows that suburban communes may benefit the most from exposure to greenspace on executive function (TMT-A). While on urban communes, increased exposure of greenspace was associated with poor cognitive performance on language skills (lexical verbal fluency).

Considering the association of greenspace with better cognitive performance found on this study and the limited number of studies on the role environmental protective factors of cognition, it was recommended that future research should address the mediated pathways between greenspace, cognition, and cognitive-related health outcomes. Additionally, further research should be done on other potential effect-modifiers, such as area-level deprivation and sex; these were partially observed in on some sensitivity analyses, but it was not part the objectives of this study. Although NDVI was a common greenspace indicator, other types of exposure measures could be used that may enhance the evidence for causal associations (Besser, 2021).

Finally, promoting greenspace exposure on urban planification for sustainable cities can help further achieve the goals of climate neutrality of the European Green Deal (European Commission, 2021), and at the same time improve healthy aging and reduce the risk of cognitive decline.

6. References

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List of annexes

Annex 1. Study population flowchart with exclusion and inclusion criteria.

Annex 2. The University of Sheffield-ScHARR ethics form.

Department of Economics/ScHARR

Research Ethics Review
for Undergraduate and Postgraduate-Taught Students

Form 1C: Student Declaration

To be included in Appendices of dissertation

→ **Research Project Title:** Association between Greenspace and Cognitive Performance: French CONSTANCES cohort.

→ **Name of dataset to be used: CONSTANCES**

Owner of dataset: INSERM/IRSET

Total number of datasets to be used: 1
If more than one, then fill in a separate declaration for each dataset.

State the case that applies to your research project: Case 2

Case 1: Your proposed project will only involve anonymised/aggregated data that any member of the public is legitimately free to access and use without having to obtain permission from anyone else. E.g., macroeconomic statistics provided by legitimate sources such as government departments and international organisations; anonymised secondary data on individuals or firms provided by legitimate sources such as government departments and which do not require any form of registration or statement of purpose to allow access.

Case 2: Your proposed project will involve anonymised secondary data for which you need to obtain permission from the owner (e.g., you need to satisfy some condition before being permitted to download the data, such as a declaration of intended educational purpose. Downloading the BHPS from the Data Archive falls in this category.)

Case 3: None of the above cases. Note that the department does not allow undergraduate or postgraduate taught students to use primary data, or secondary data that may include personal data, unless specific training is undertaken by the student.

→ If your proposed project falls within Case 1, then simply print your name, date and sign below.
If your proposed project falls within Case 2, then you need to append to this form evidence that you have legitimately obtained access to these data. E.g., confirmation email, and statement of purpose if one was required. Then print your name, date and sign below.
If your proposed project falls within Case 3, then contact your supervisor or supervisory team as soon as possible. You may not be able to use the proposed data.

Department of Economics, / ScHARR July 2011.

→ **Name of student: Ana Carolina Ramos Velasquez**

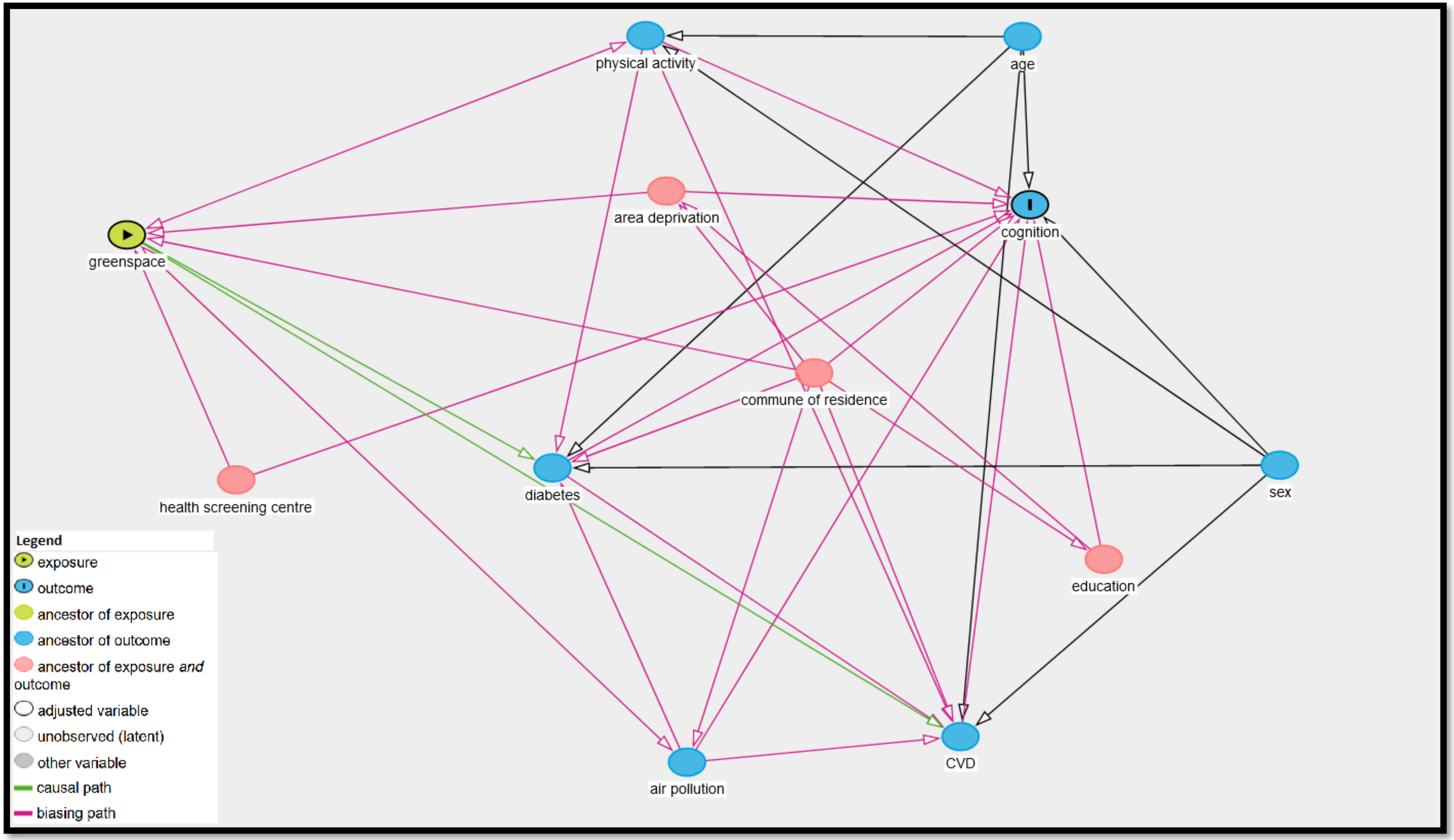
→ **Signature of student:** **Date: 29/04/2021**

→ **Name of supervisor: Bénédicte Jacquemin**

→ **Signature of Supervisor:** **Date: 10/05/2021**

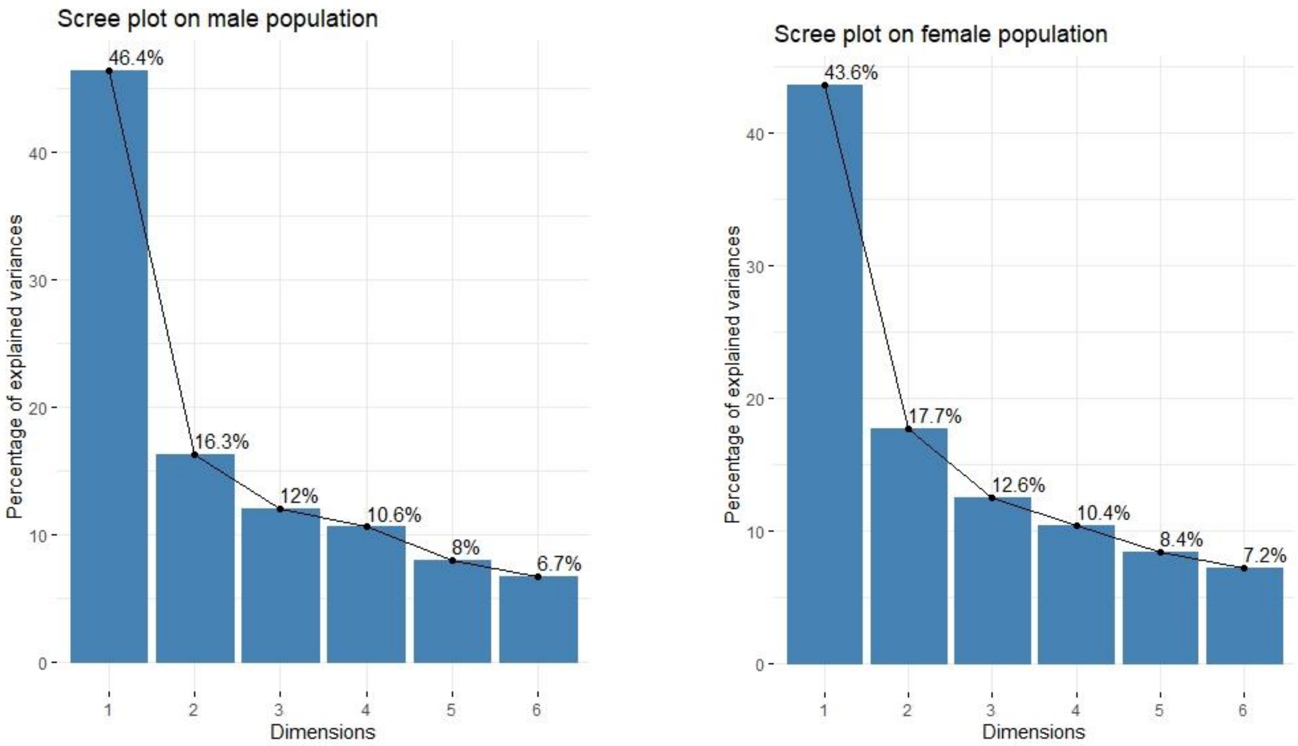
Department of Economics, / ScHARR July 2011.

Annex 3. Directed acyclic graph (DAG) used to estimate the total effect of greenspace exposure on cognition outcomes.

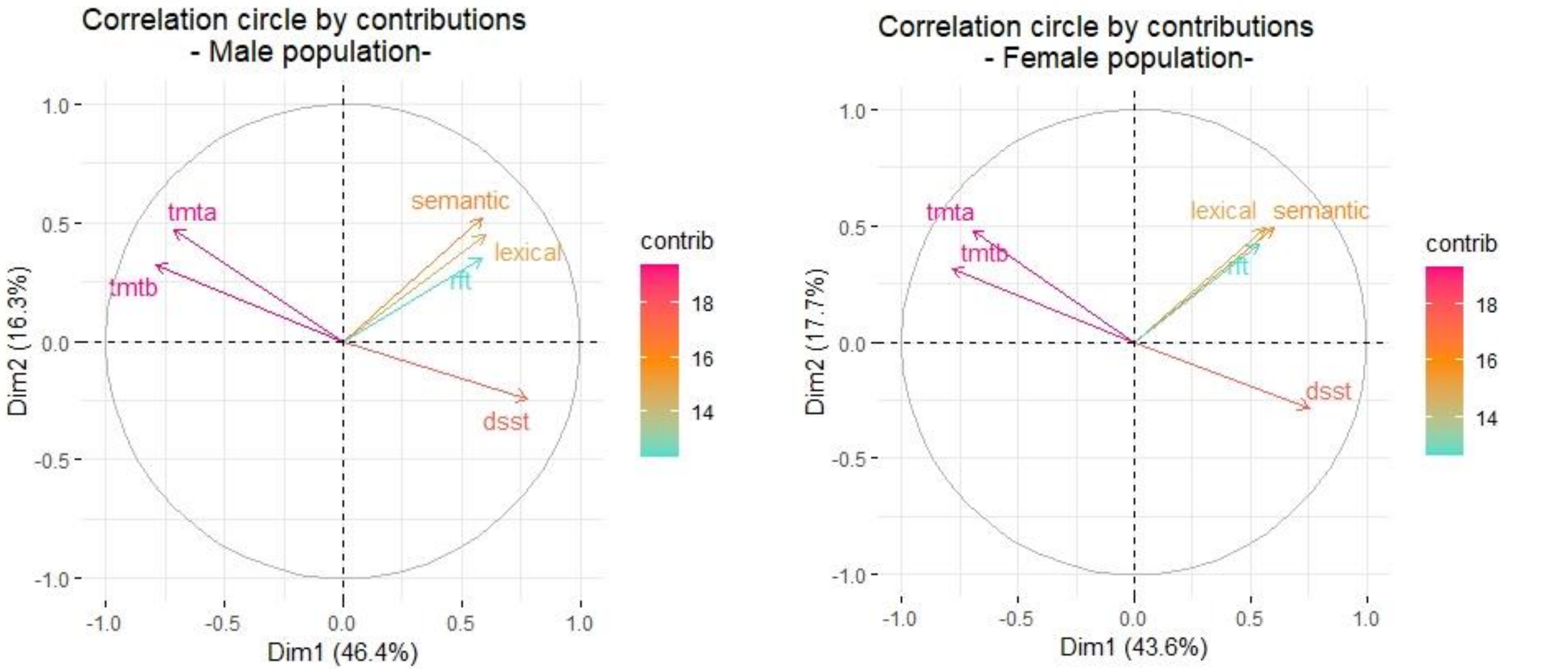


Note: Minimal sufficient adjustment sets for estimating the total effect of greenspace on cognition include: age, air pollution, area deprivation, commune of residence, health screening centre, physical activity, and sex.

Annex 4. Principal component analysis (PCA) plots for the creation of a global score.



Scree-plot of variance explained by different dimensions of the PCA.



Correlation circles by contribution of variance from the cognitive tests.

Annex 5. Overall population characteristics of the French CONSTANCES cohort participants (n=65316).

Variables	Male	Female	Total
Sociodemographic			
Age (years)	57.71 (7.23)	57.41 (7.19)	57.55 (7.21)
Education (years)			
Less than 5 years	844 (2.77)	865 (2.48)	1709 (2.62)
5-12 Years	14702 (48.20)	15836 (45.48)	30538 (46.75)
12 and more years	14953 (49.03)	18116 (52.03)	33069 (50.63)
Classification of commune of residence			
Urban	10963 (35.95)	13183 (37.86)	24146 (36.97)
Suburban	11498 (37.70)	12715 (36.52)	24213 (37.07)
Isolated city	2354 (7.72)	2577 (7.40)	4931 (7.55)
Rural	5684 (18.64)	6342 (18.22)	12026 (18.41)
Country of origin			
France	28233 (92.57)	32403 (93.07)	60636 (92.83)
Outside France	2266 (7.43)	2414 (6.93)	4680 (7.17)
Familial status			
Unmarried	3593 (11.78)	4636 (13.32)	8229 (12.60)
Married or in relation	22418 (73.50)	22635 (65.01)	45053 (68.98)
Divorced or separated	3977 (13.04)	5908 (16.97)	9885 (15.13)
Widow	511 (1.68)	1638 (4.70)	2149 (3.29)
Household Income (euro/month)			
Less than 2100	4530 (14.85)	7175 (20.61)	11705 (17.92)
More than 2100	25969 (85.15)	27642 (79.39)	53611 (82.08)
Socio-occupational status			
Farmer, shopkeeper, or business owner	953 (3.12)	627 (1.80)	1580 (2.42)
High intellect profession	11884 (38.97)	7892 (22.67)	19776 (30.28)
Intermediate profession	8895 (29.16)	11912 (34.21)	20807 (31.86)
Employee or manual Worker	7774 (25.49)	12912 (37.09)	20686 (31.67)
Never worked or other	993 (3.26)	1474 (4.23)	2467 (3.78)
*Deprivation level**			
Low	10037 (32.91)	11823 (33.96)	21860 (33.47)
Moderate	10179 (33.38)	11588 (33.28)	21767 (33.33)
High	10278 (33.70)	11404 (32.76)	21682 (33.20)
Comorbidities			
Occupational solvent exposure			
No	23323 (76.47)	31887 (91.58)	55210 (84.53)
Yes	7176 (23.53)	2930 (8.42)	10106 (15.47)
Parental history of Alzheimer's disease			

Variables	Male	Female	Total
No	28035 (91.92)	31775 (91.26)	59810 (91.57)
Yes	2464 (8.08)	3042 (8.74)	5506 (8.43)
*Perceived health status***	2.87 (1.20)	2.88 (1.21)	2.87 (1.20)
BMI (kg/m²)	26.43 (3.85)	24.94 (4.70)	25.64 (4.39)
*Hearing loss****			
Acceptable	22097 (72.45)	27637 (79.38)	49734 (76.14)
Moderate	7263 (23.81)	6394 (18.36)	13657 (20.91)
High	1139 (3.73)	786 (2.26)	1925 (2.95)
Depressive symptoms			
No	26218 (85.96)	26003 (74.68)	52221 (79.95)
Yes	4281 (14.04)	8814 (25.32)	13095 (20.05)
Smoking status			
No-smoker	11665 (38.25)	17861 (51.30)	29526 (45.20)
Smoker	4003 (13.13)	4387 (12.60)	8390 (12.85)
Former smoker	14831 (48.63)	12569 (36.10)	27400 (41.95)
Alcohol drinking			
Abstinent	601 (1.97)	1686 (4.84)	2287 (3.50)
Nondependent or not abuse	23030 (75.51)	28808 (82.74)	51838 (79.36)
Abuse or dependent	6868 (22.52)	4323 (12.42)	11191 (17.13)
*Physical activity*****			
Low	7652 (25.09)	7343 (21.09)	14995 (22.96)
Medium	13165 (43.17)	15148 (43.51)	28313 (43.35)
High	9682 (31.75)	12326 (35.40)	22008 (33.69)
Sleeping (hrs)	5.91 (2.03)	5.91 (2.11)	5.91 (2.07)
Loneliness (living with others or not)			
No	5250 (17.21)	9609 (27.60)	14859 (22.75)
Yes	25249 (82.79)	25208 (72.40)	50457 (77.25)
Comorbidities/Chronic Diseases as *n*			
Cardiovascular diseases			
Yes	3626 (11.89)	2753 (7.91)	6379 (9.77)
Hypercholesterolemia			
Yes	5143 (16.86)	3425 (9.84)	8568 (13.12)
Hypertriglyceridemia			
Yes	993 (3.26)	435 (1.25)	1428 (2.19)
Hypertension			
Yes	15984 (52.42)	11717 (33.65)	27701 (42.42)
Type II Diabetes			
Yes	2451 (8.04)	1252 (3.60)	3703 (5.67)
Dyslipidemia			
Yes	14016 (45.96)	13020 (37.40)	27036 (41.40)

Note: Values expressed as mean (Standard Deviation) for continuous variables and frequency (%) for categorical variables
*Classified based on tertiles of the French deprivation index (first tertile as low, second tertiles as moderate, and third tertile as high)
**Perceived health from a scale (1=very good to 8= very poor)
***Hearing loss (HL) classified from hearing loss at different frequencies: HL at 500-1000 Hz as acceptable, 2000-4000 Hz as moderate, 8000Hz as high
****Classified based on a scale of non-occupational physical activity 1 -7 (1-3 as low; 4-5 as medium, and 6-7 as high).

Annex 6. Population characteristics with imputed data and complete case data

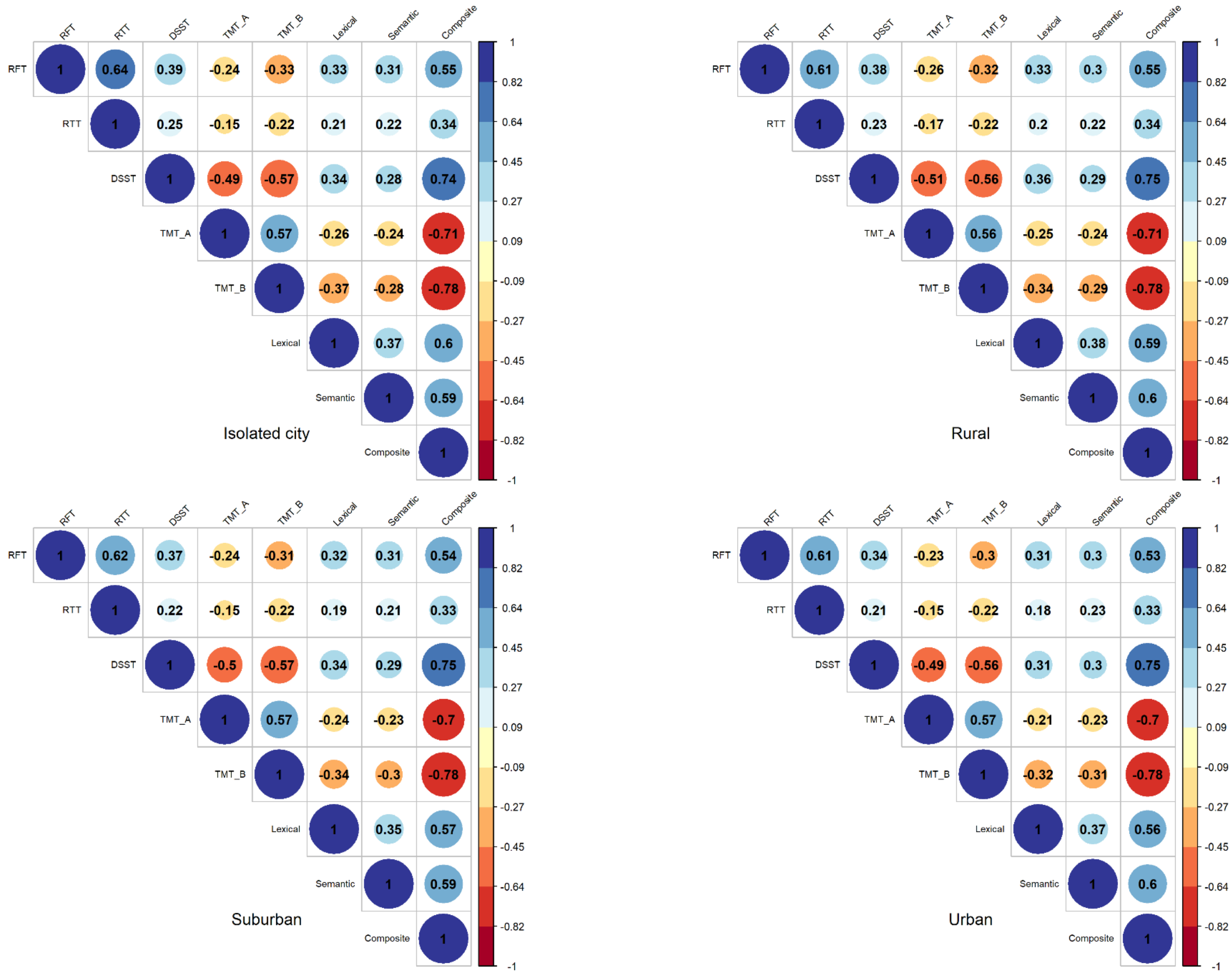
Variables	Complete case data	Imputed data	Total
Sociodemographic			
Age	57.55 (7.20)	57.55 (7.20)	57.55 (7.20)
Sex			
Male	31222 (46.52)	31222 (46.52)	62444 (46.52)
Female	35898 (53.48)	35898 (53.48)	71796 (53.48)
Education			
Less than 5 years	1715 (2.60)	1759 (2.62)	3474 (2.61)
5-12 Years	30800 (46.74)	31425 (46.82)	62225 (46.78)
12 and more years	33384 (50.66)	33936 (50.56)	67320 (50.61)
Classification of commune of residence			
Urban	24771 (36.91)	24772 (36.91)	49543 (36.91)
Suburban	24800 (36.95)	24800 (36.95)	49600 (36.95)
Isolated city	5066 (7.55)	5067 (7.55)	10133 (7.55)
Rural	12481 (18.60)	12481 (18.60)	24962 (18.60)
Country of origin			
France	61466 (92.88)	62318 (92.85)	123784 (92.86)
Outside France	4711 (7.12)	4802 (7.15)	9513 (7.14)
Familial status			
Unmarried	8275 (12.59)	8473 (12.62)	16748 (12.61)
Married or in relation	45347 (69.01)	46216 (68.86)	91563 (68.93)
Divorced or separated	9936 (15.12)	10210 (15.21)	20146 (15.17)
Widow	2155 (3.28)	2221 (3.31)	4376 (3.29)
Sociodemographic			
Household income (euro/month)			
Less than 2100	11240 (18.09)	12138 (18.08)	23378 (18.08)
More than 2100	50908 (81.91)	54982 (81.92)	105890 (81.92)
Socio-occupational status			
Farmer, shopkeeper, or business owner	1503 (2.39)	1622 (2.42)	3125 (2.41)
High intellect profession	19176 (30.53)	20265 (30.19)	39441 (30.36)
Intermediate profession	20169 (32.11)	21369 (31.84)	41538 (31.97)
Employee or manual worker	19589 (31.19)	21315 (31.76)	40904 (31.48)
Never worked or other	2371 (3.77)	2549 (3.80)	4920 (3.79)
*Deprivation level**			
Low	22373 (33.34)	22374 (33.34)	44747 (33.34)

Variables	Complete case data	Imputed data	Total
Moderate	22392 (33.37)	22392 (33.36)	44784 (33.37)
High	22343 (33.29)	22347 (33.30)	44690 (33.30)
Comorbidities			
Occupational solvent exposure			
No	56208 (84.50)	56728 (84.52)	112936 (84.51)
Yes	10311 (15.50)	10392 (15.48)	20703 (15.49)
Parental history of Alzheimer's disease			
No	61535 (91.68)	61535 (91.68)	123070 (91.68)
Yes	5585 (8.32)	5585 (8.32)	11170 (8.32)
*Perceived health status***	2.88 (1.21)	2.88 (1.21)	2.88 (1.21)
BMI (kg/m2)	25.64 (4.39)	25.64 (4.39)	25.64 (4.39)
*Hearing loss****			
Acceptable	46445 (76.19)	51104 (76.14)	97549 (76.16)
Moderate	12739 (20.90)	14029 (20.90)	26768 (20.90)
High	1777 (2.91)	1987 (2.96)	3764 (2.94)
Depressive symptoms			
No	50109 (79.94)	53482 (79.68)	103591 (79.80)
Yes	12577 (20.06)	13638 (20.32)	26215 (20.20)
Smoking status			
No-smoker	28983 (45.07)	30286 (45.12)	59269 (45.10)
Smoker	8293 (12.90)	8667 (12.91)	16960 (12.91)
Former smoker	27024 (42.03)	28167 (41.97)	55191 (42.00)
Alcohol drinking			
Abstinent	2135 (3.39)	2348 (3.50)	4483 (3.44)
Nondependent or not abuse	50096 (79.43)	53259 (79.35)	103355 (79.39)
Abuse or dependent	10838 (17.18)	11513 (17.15)	22351 (17.17)
*Physical activity*****			
Low	14800 (23.01)	15432 (22.99)	30232 (23.00)
Medium	27892 (43.37)	29047 (43.28)	56939 (43.32)
High	21624 (33.62)	22641 (33.73)	44265 (33.68)
Sleeping (hrs)	5.91 (2.08)	5.91 (2.07)	5.91 (2.08)
Loneliness (living with others or not)			
No	14976 (22.75)	15371 (22.90)	30347 (22.82)
Yes	50866 (77.25)	51749 (77.10)	102615 (77.18)
Air pollution exposure (PM2.5)	16.71 (3.06)	16.68 (2.97)	16.69 (3.01)
Comorbidities/Chronic Diseases as *n* (%)			
Cardiovascular diseases			
Yes	6437 (9.75)	6559 (9.77)	12996 (9.76)
Hypercholesterolemia			

Variables	Complete case data	Imputed data	Total
Yes	8630 (13.12)	8822 (13.14)	17452 (13.13)
Hypertriglyceridemia			
Yes	1393 (2.13)	1487 (2.22)	2880 (2.17)
Hypertension			
Yes	28393 (42.33)	28393 (42.33)	56786 (42.33)
Type II Diabetes			
Yes	3807 (5.68)	3807 (5.68)	7614 (5.68)
Dyslipidemia			
Yes	27871 (41.55)	27871 (41.55)	55742 (41.55)
Cognitive Tests[a]			
RSCRT(RFT)[b]	12.80 (2.14)	12.80 (2.14)	12.80 (2.14)
RSCRT(RTT)[b]	12.80 (2.14)	12.80 (2.14)	12.80 (2.14)
Verbal semantic fluency	22.27 (4.58)	22.27 (4.58)	22.27 (4.58)
Verbal lexical fluency	15.26 (4.78)	15.26 (4.78)	15.26 (4.78)
DSST[b]	66.66 (14.21)	66.66 (14.21)	66.66 (14.21)
TMT-A[b]	33.35 (11.44)	33.35 (11.44)	33.35 (11.44)
TMT-B[b]	66.05 (28.22)	66.05 (28.22)	66.05 (28.22)
Global Score	-0.00 (1.64)	-0.00 (1.64)	-0.00 (1.64)

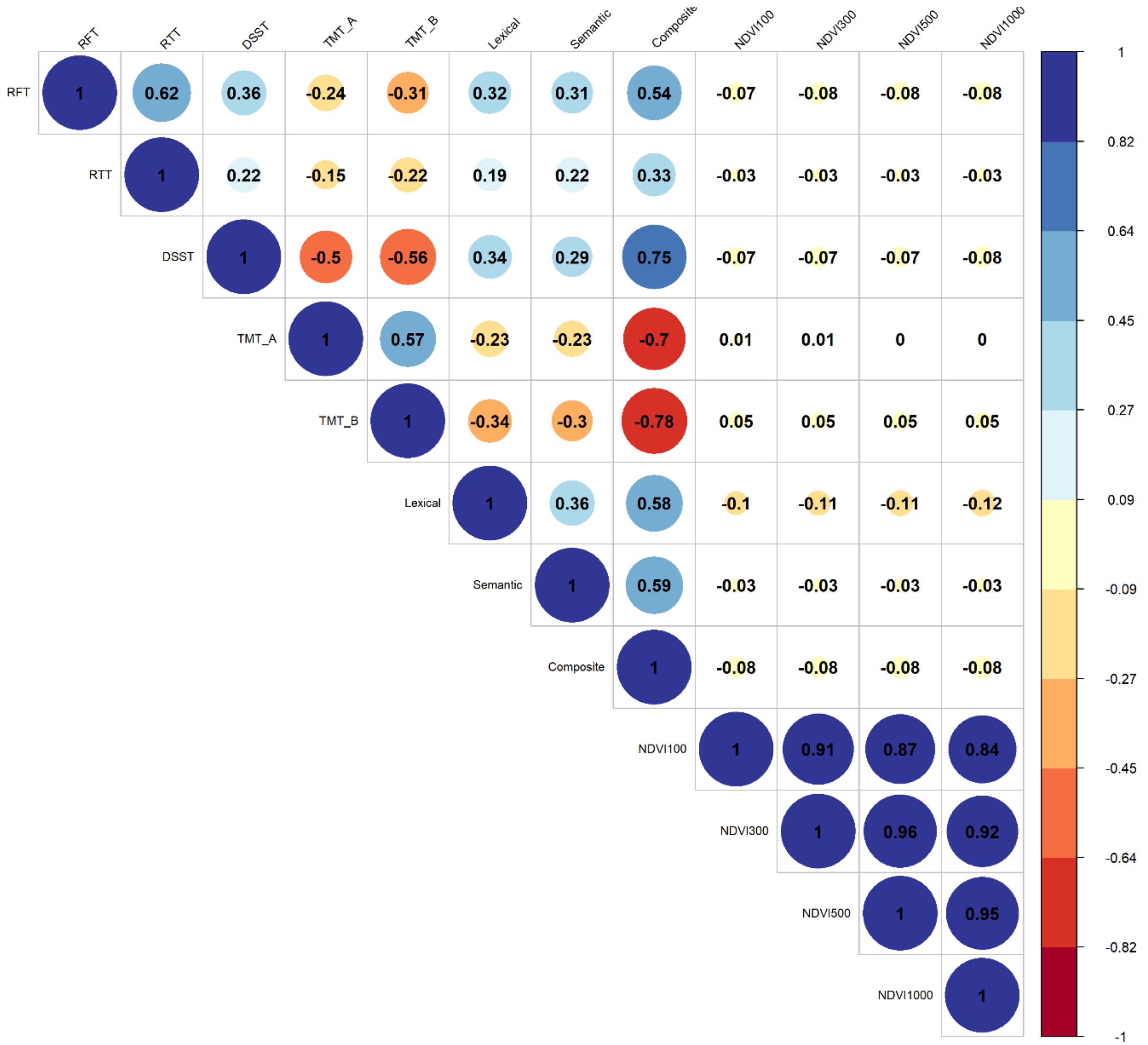
Note: Values expressed as mean (Standard Deviation) for continuous variables and frequency (%) for categorical variables
*Classified based on tertiles of the French deprivation index (first tertile as low, second tertiles as moderate, and third tertile as high)
**Perceived health from a scale (1=very good to 8= very poor)
***Hearing loss (HL) classified from hearing loss at different frequencies: HL at 500-1000 Hz as acceptable, 2000-4000 Hz as moderate, 8000Hz as high.
****Classified based on a scale of non-occupational physical activity 1 -7 (1-3 as low; 4-5 as medium, and 6-7 as high).
[a] RFT: Fast free recall score of FCSRT (Free and Cued Selective Reminding Test); RTT: Fast recall total score of FCSRT; DSST: digit-symbol substitution test; TMT-A: Trial making test part A; TMT-B: Trial making test part B.
[b] Test scores described as: FCSRT: 0-16; Semantic fluency: number of words provided in 1 min; Lexical fluency: number of words provided in 1 min; DSST: number of symbols correctly completed in 90s; TMT-A: Time (seconds);
TMT-B: Time (seconds); Global Score:0 centered

Annex 7. Plot of correlation coefficients between cognitive outcomes by commune of residence.



Note: Pearson correlation coefficient (scale from −1 and +1), with +1 as a perfect positive relationship.

Annex 8. Plot of correlation coefficients between cognitive outcomes and NDVI exposure.



Note: Pearson correlation coefficient (scale from −1 and +1), with +1 as a perfect positive relationship.

Annex 9. Table of the effect modification of commune of residence on the association between exposure to NDVI at 300 m buffer and cognitive performance adjusted on the main model.

Classification of commune of residence	Cognitive Outcomes, β (95% CI)							
	RFT*	**RTT***	**DSST***	**TMT-A***	**TMT-B***	**Lexical Fluency**	**Semantic Fluency**	**Global Score**
LRT**	0.059	0.366	0.210	**0.006**	0.347	**0.050**	0.536	0.246
Urban	**-0.027**	0.017	0.006	-0.005	-0.017	-0.040	**0.026**	0.002
	(-0.052: -0.001)	(-0.009: 0.044)	(-0.020: 0.032)	(-0.032: 0.022)	(-0.043: 0.009)	(-0.067: -0.014)	**(-0.004: 0.056)**	(-0.025: 0.029)
Suburban	0.004	**0.046**	**0.031**	**-0.054**	**-0.046**	0.009	**0.054**	**0.042**
	(-0.025: 0.033)	**(0.015: 0.077)**	**(0.003: 0.060)**	**(-0.084: -0.025)** [a]	**(-0.076: -0.017)**	(-0.021: 0.038)	**(0.020: 0.087)**	**(0.012: 0.072)** [a]
Isolated city	0.029	0.032	0.034	0.006	**-0.083**	0.016	0.047	0.020
	(-0.043: 0.100) [a]	(-0.046: 0.109)	(-0.031: 0.098)	(-0.066: 0.078)	**(-0.153: -0.013)**	(-0.056: 0.089)	(-0.035: 0.128)	(-0.051: 0.091)
Rural	0.006	0.015	-0.002	0.029	**-0.040**	0.051	0.069	0.035
	(-0.054: 0.066)	(-0.050: 0.081)	(-0.059: 0.056)	(-0.033: 0.091) [a]	**(-0.104: 0.025)**	(-0.013: 0.114) [a]	(-0.001: 0.139)	(-0.029: 0.098)

Note: Regression coefficients and 95% confidence intervals; all estimates are based on change in cognitive performance (change in z-scores) and one interquartile range increase in exposure. IQR of NDVI at 300m=0.2458683
Main model: adjusted for age, sex, education, HSC, commune of residence, physical activity, French deprivation, and air pollution exposure as $PM_{2.5}$.
*RFT: Fast free recall score of FCSRT (Free and Cued Selective Reminding Test); RTT: Fast recall total score of FCSRT; DSST: digit-symbol substitution test; TMT-A: Trial making test part A; TMT-B: Trial making test part B.
**LRT: likelihood ratio test, with p-value significance <0.05.
[a] Significant interaction term on the classification of commune of residence

Annex 10. Sensitivity analysis: Table of stratified analyses adjusted on the main model with greenspace exposure of NDVI at 300m buffer on the selected cognitive outcomes.

	Cognitive Outcomes, β (95% CI)			
Covariate	**RTT***	**TMT-B***	**Semantic Fluency**	**Global Score**
Sex				
Female	**0.037 (0.017: 0.056)**	**-0.047 (-0.070: -0.024)**	**0.045 (0.019: 0.072)**	**0.037 (0.012: 0.062)**
Male	0.026 (-0.006: 0.057)	**-0.028 (-0.055: -0.002)**	**0.042 (0.013: 0.071)**	0.014 (-0.012: 0.040)
Classification of commune of residence				
Urban	0.017 (-0.009: 0.044)	-0.017 (-0.043: 0.009)	**0.026 (-0.004: 0.056)**	0.002 (-0.025: 0.029)
Suburban	**0.046 (0.015: 0.077)**	**-0.046 (-0.076: -0.017)**	**0.054 (0.020: 0.087)**	**0.042 (0.012: 0.072)**
Isolated city	0.032 (-0.046: 0.109)	**-0.083 (-0.153: -0.013)**	0.047 (-0.035: 0.128)	0.020 (-0.051: 0.091)
Rural	0.015 (-0.050: 0.081)	**-0.040 (-0.104: 0.025)**	0.069 (-0.001: 0.139)	0.035 (-0.029: 0.098)
Deprivation level				
Low	-0.006 (-0.038: 0.025)	-0.020 (-0.048: 0.008)	0.018 (-0.017: 0.053)	-0.008 (-0.039: 0.023)
Moderate	**0.039 (0.008: 0.070)**	**-0.033 (-0.064: -0.003)**	**0.036 (0.002: 0.070)**	0.021 (-0.010: 0.051)
High	**0.051 (0.018: 0.084)**	**-0.057 (-0.091: -0.023)**	**0.078 (0.042: 0.115)**	0.030 (-0.000: 0.061)

Note: Regression coefficients and 95% confidence intervals; all estimates are based on change in cognitive performance (change in z-scores) and one interquartile range increase in exposure. IQR of NDVI at 300m=0.2458683

Main model: adjusted for age, sex, education, HSC, commune of residence, physical activity, French deprivation, and air pollution exposure as $PM_{2.5}$.

*RTT: Fast recall total score of FCSRT (Free and Cued Selective Reminding Test); TMT-B: Trial making test part B.

Annex 11. Sensitivity analysis: Table of multilevel model results of exposure to different NDVI buffers on selected cognitive outcomes.

	Cognitive Outcomes, β (95% CI)			
NDVI	**RTT***	**TMT-B***	**Semantic fluency**	**Global Score**
At 100 m buffer				
Main Model**	0.014 (-0.001: 0.029)	**-0.023 (-0.037: -0.008)**	**0.020 (0.003: 0.036)**	**0.018 (0.003: 0.032)**
At 300 m buffer				
Main Model	**0.030 (0.012: 0.047)**	**-0.037 (-0.055: -0.020)**	**0.042 (0.022: 0.061)**	**0.025 (0.007: 0.043)**
At 500 m buffer				
Main Model	**0.026 (0.006: 0.045)**	**-0.041 (-0.060: -0.022)**	**0.043 (0.022: 0.065)**	**0.028 (0.008: 0.047)**
At 1000 m buffer				
Main Model	**0.031 (0.010: 0.051)**	**-0.046 (-0.067: -0.026)**	**0.037 (0.014: 0.059)**	**0.029 (0.009: 0.050)**

Note: Regression coefficients and 95% confidence intervals; all estimates are based on change in cognitive performance (change in z-scores) and one interquartile rangeincrease in exposure. IQR of NDVI at 100m= 0.2181755, IQR of NDVI at 300m=0.2458683; IQR of NDVI at 500m=0.2593613; IQR of NDVI at 1000m=0.2668411
*RTT: Fast recall total score of FCSRT (Free and Cued Selective Reminding Test); TMT-B: Trial making test part B.
**Main model: adjusted for age, sex, education, HSC, commune of residence, physical activity, French deprivation, and air pollution exposure as $PM_{2.5}$.

Annex 12. Sensitivity analysis: Table of regression analyses of exposure to NDVI at different buffers on selected cognitive outcomes excluding Paris' health screening centres.

	Cognitive outcomes, β (95% CI)			
NDVI	**RTT***	**TMT-B***	**Semantic fluency**	**Global Score**
At 100 m buffer				
Main Model**	0.014 (-0.002: 0.030)	**-0.032 (-0.048: -0.016)**	**0.036 (0.018: 0.054)**	**0.031 (0.015: 0.047)**
At 300 m buffer				
Main Model	**0.033 (0.011: 0.054)**	-0.021 (-0.042: 0.000)	**0.034 (0.009: 0.058)**	**0.039 (0.020: 0.057)**
At 500 m buffer				
Main Model	0.023 (-0.001: 0.046)	-0.018 (-0.041: 0.005)	**0.030 (0.003: 0.056)**	**0.041 (0.021: 0.061)**
At 1000 m buffer				
Main Model	**0.030 (0.005: 0.054)**	**-0.026 (-0.050: -0.002)**	0.024 (-0.003: 0.052)	**0.041 (0.019: 0.062)**

Note: Regression coefficients and 95% confidence intervals; all estimates are based on change in cognitive performance (change in z-scores) and one interquartile range increase in exposure. IQR of NDVI at 100m= 0.2181755, IQR of NDVI at 300m=0.2458683; IQR of NDVI at 500m=0.2593613; IQR of NDVI at 1000m=0.2668411
*RTT: Fast recall total score of FCSRT (Free and Cued Selective Reminding Test); TMT-B: Trial making test part B.

**Main model: adjusted for age, sex, education, HSC, commune of residence, physical activity, French deprivation, and air pollution exposure as $PM_{2.5}$.

Annex 13. Sensitivity analysis: Table of complete case data regression analyses results of exposure to NDVI at different buffers on selected cognitive outcomes.

	Cognitive outcomes, β (95% CI)			
NDVI	**RTT**	**TMT-B**	**Semantic fluency**	**Global Score**
At 100 m buffer				
Main Model	0.010 (-0.008: 0.028)	-0.011 (-0.028: 0.007)	0.007 (-0.013: 0.027)	**0.033 (0.011: 0.054)**
At 300 m buffer				
Main Model	**0.033 (0.011: 0.054)**	-0.021 (-0.042: 0.000)	**0.034 (0.009: 0.058)**	-0.021 (-0.042: 0.000)
At 500 m buffer				
Main Model	0.023 (-0.001: 0.046)	-0.018 (-0.041: 0.005)	**0.030 (0.003: 0.056)**	**0.034 (0.009: 0.058)**
At 1000 m buffer				
Main Model	**0.030 (0.005: 0.054)**	**-0.026 (-0.050: -0.002)**	0.024 (-0.003: 0.052)	0.020 (-0.002: 0.041)

Note: Regression coefficients and 95% confidence intervals; all estimates are based on change in cognitive performance (change in z-scores) and one interquartile range increase in exposure. IQR of NDVI at 100m= 0.2181755, IQR of NDVI at 300m=0.2458683; IQR of NDVI at 500m=0.2593613; IQR of NDVI at 1000m=0.2668411

*RTT: Fast recall total score of FCSRT (Free and Cued Selective Reminding Test); TMT-B: Trial making test part B.

**Main model: adjusted for age, sex, education, HSC, commune of residence, physical activity, French deprivation, and air pollution exposure as $PM_{2.5}$.

Annex 14. Sensitivity analysis: Table of pooled results from the meta-analysis of health screening centres from exposure of NDVI at 300m buffer on selected cognitive outcomes.

	NDVI at 300 m buffer	
Cognitive Outcome	**β (95% CI)** **	**Heterogeneity(p-value)** ***
RTT*	**0.026 (0.008: 0.045)**	44.3 % (0.016)
TMT-B*	**-0.033 (-0.050: -0.016)**	4..4% (0.40)
Semantic fluency	**0.042 (0.022: 0.063)**	47.5% (0.009)
Global Score	**0.023 (0.005: 0.041)**	51% (<0.001)

Note: Fixed effects model adjusted for age, sex, education, HSC, commune of residence, physical activity, French deprivation, and air pollution exposure as $PM_{2.5}$.
*RTT: Fast recall total score of FCSRT; TMT-B: Trial making test part B.
** Regression coefficients and 95% confidence intervals; all estimates are based on change in cognitive performance (change in z-scores) and one interquartile range increase in exposure. IQR of NDVI at 300m=0.2458683
***Heterogeneity interpretation as: 0% ≤ I^2 ≤ 100%; Low ≈ 25%, Moderate ≈ 50%, High ≈ 75% and p-value significance <0.05.

Annex 15. Sensitivity analysis: Table of regression analyses results on the further adjusted model.

Exposures	Cognitive Domains, β (95% CI)							
	Episodic Memory		**Executive functions**			**Language skills**		**General cognition**
	RFT*	**RTT***	**DSST***	**TMT-A***	**TMT-B***	**Lexical fluency**	**Semantic fluency**	**Global score**
At 100 m buffer								
Further adjusted**	-0.008 (-0.022: 0.006)	0.008 (-0.007: 0.023)	-0.001 (-0.014: 0.012)	-0.006 (-0.020: 0.008)	-0.008 (-0.021: 0.006)	-0.004 (-0.019: 0.010)	**0.017 (0.001: 0.033)**	0.001 (-0.013: 0.015)
At 300 m buffer								
Further adjusted	-0.010 (-0.027: 0.007)	**0.022 (0.005: 0.040)**	-0.001 (-0.017: 0.015)	-0.007 (-0.024: 0.010)	**-0.019 (-0.035: -0.002)**	-0.011 (-0.028: 0.006)	**0.038 (0.019: 0.057)**	0.007 (-0.010: 0.023)
At 500 m buffer								
Further adjusted	-0.016 (-0.034: 0.002)	0.018 (-0.001: 0.037)	0.005 (-0.012: 0.022)	-0.015 (-0.034: 0.004)	**-0.021 (-0.039: -0.003)**	-0.016 (-0.035: 0.002)	**0.039 (0.018: 0.060)**	0.008 (-0.011: 0.026)
At 1000 m buffer								
Further adjusted	-0.019 (-0.038: 0.001)	**0.023 (0.002: 0.043)**	0.003 (-0.016: 0.021)	**-0.025 (-0.045: -0.005)**	**-0.026 (-0.045: -0.006)**	**-0.024 (-0.043: -0.004)**	**0.031 (0.009: 0.054)**	0.009 (-0.011: 0.029)

Note: Regression coefficients and 95% confidence intervals; all estimates are based on change in cognitive performance (change in z-scores) and one interquartile range increase in exposure. IQR of NDVI at 100m= 0.2181755, IQR of NDVI at 300m=0.2458683; IQR of NDVI at 500m=0.2593613; IQR of NDVI at 1000m=0.2668411

*RFT: Fast free recall score of FCSRT (Free and Cued Selective Reminding Test); RTT: Fast recall total score of FCSRT; DSST: digit-symbol substitution test; TMT-A: Trial making test part A; TMT-B: Trial making test part B.

** Further Adjusted model: adjusted for variables in the parsimonious model and smoking status, alcohol drinking, familial situation, sleep time, income, body mass index, history of Alzheimer's disease in parents, non-occupational physical activity, loneliness, country of origin, depression symptoms, hypertension, type-2 diabetes, cardiovascular diseases, hearing loss, income, living area (urban, sub-urban, isolated city or rural) and French deprivation.

Annex 16. Sensitivity analysis: Table of logistic regression analyses results on exposure of NDVI at 300m buffer on selected cognitive outcomes.

	Cognitive Outcomes, OR (95% CI)			
NDVI	**RTT**	**TMT-B**	**Semantic fluency**	**Global Score**
At 100 m buffer				
Main Model	0.973 (0.940: 1.006)	**0.942 (0.907: 0.979)**	0.973 (0.937: 1.010)	0.976 (0.935: 1.019)
At 300 m buffer				
Main Model	**0.946 (0.907: 0.985)**	**0.921 (0.880: 0.965)**	**0.934 (0.893: 0.978)**	0.971 (0.922: 1.023)
At 500 m buffer				
Main Model	**0.950 (0.908: 0.994)**	**0.904 (0.859: 0.951)**	**0.926 (0.882: 0.973)**	0.980 (0.926: 1.037)
At 1000 m buffer				
Main Model	**0.950 (0.906: 0.997)**	**0.886 (0.840: 0.936)**	0.949 (0.900: 1.000)	0.983 (0.926: 1.044)

Note: Odds Ratio and 95% confidence intervals; all estimates are based on change in cognitive performance (0= good performance, 1= bad performance) and one interquartile range increase in exposure. IQR of NDVI at 100m= 0.2181755, IQR of NDVI at 300m=0.2458683; IQR of NDVI at 500m=0.2593613; IQR of NDVI at 1000m=0.2668411

*RTT: Fast recall total score of FCSRT (Free and Cued Selective Reminding Test); TMT-B: Trial making test part B.

**Main model: adjusted for age, sex, education, HSC, commune of residence, physical activity, French deprivation, and air pollution exposure as $PM_{2.5}$.