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Abbreviations: ECRHS, European Community Respiratory Health Survey; LUR, land use regression; NO_2, nitrogen dioxide; $PM_{2.5}$, particulate matter with aerodynamic diameters smaller than 2.5 µm; PM_{10}, particulate matter with aerodynamic diameters smaller than 10 µm; ELAPSE, Effects of Low-level Air Pollution: A Study in Europe; SD, standard deviation; NDVI, Normalized Difference Vegetation Index; HRQOL, Health-related quality-of-life; PCS, Physical Component Summary; MCS, Mental Component Summary; BMI, Body Mass Index

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ABSTRACT

Background: Associations of long-term exposure to air pollution and greenspace with health-related quality of life (HRQOL) are poorly studied and few studies have accounted for asthma-rhinitis status.

Objective: To assess the associations of air pollution and greenspace with HRQOL and whether asthma and/or rhinitis modify these associations.

Methods: The study was based on the participants in the second (2000-2002, n=6542) and third (2011-2013, n=3686) waves of the European Community Respiratory Health Survey (ECRHS) including 19 centres. The mean follow-up time was 11.3 years. HRQOL was assessed by the SF-36 Physical and Mental Component Summary scores (PCS and MCS). NO_2, $PM_{2.5}$ and PM_{10} annual concentrations were estimated at the residential address from existing land-use regression models. Greenspace around the residential address was estimated by the (i) mean of the Normalized Difference Vegetation Index (NDVI) and by the (ii) presence of green spaces within a 300m buffer. Associations of each exposure variable with PCS and MCS were assessed by mixed linear regression models, accounting for the multicentre design and repeated data, and adjusting for potential confounders. Analyses were stratified by asthma-rhinitis status.

Results: The mean (SD) age of the ECRHS-II and III participants was 43 (7.1) and 54 (7.2) years, respectively, and 48% were men. Higher NO_2, $PM_{2.5}$ and PM_{10} concentrations were associated with lower MCS (regression coefficients [95%CI] for one unit increase in the inter-quartile range of exposures were -0.69 [-1.23; -0.15], -1.79 [-2.88; -0.70], -1.80 [-2.98; -0.62] respectively). Higher NDVI and presence of forests were associated with higher MCS. No consistent associations were observed for PCS. Similar association patterns were observed regardless of asthma-rhinitis status.

Conclusion: European adults who resided at places with higher air pollution and lower greenspace were more likely to have lower mental component of HRQOL. Asthma or rhinitis status did not modify these associations.

Keywords: NO_2, PM, greenness, Well-being, asthma, rhinitis, epidemiology

Introduction

Health-related quality-of-life (HRQOL) is a multidimensional concept, which is not only associated with the presence of diseases, but also with the physical, social and psychological functioning of the individual (Kuyken, 1995). HRQOL goes beyond physical and physiological parameters by assessing how individuals perceive their state of health. There is evidence that in the general population higher HRQOL is associated with lower mortality risk (Phyo et al., 2020). Because HRQOL is a key measure of overall heath, identifying its determinants is of major public health relevance.

It is well established that HRQOL is impaired by chronic diseases, including asthma and rhinitis, in particular, if these chronic diseases are severe or uncontrolled (Boudier et al., 2019; Grassi et al., 2007; Guerra et al., 2017; Leynaert et al., 2000; Matheson et al., 2002; Siroux et al., 2008; Voll-Aanerud et al., 2010). Besides some individual characteristics (age, sex, educational level) (Mulasso et al., 2014) and some lifestyle risk factors (BMI, physical inactivity and smoking status) (Goldenberg et al., 2014), the environmental determinants of HRQOL remain poorly addressed (Shin et al., 2018; Yang et al., 2021).

Although HRQOL was considered as a necessary component of outcomes research in the "*What constitutes an adverse health effect of air pollution*" statement of the American Thoracic Society in 2000 (American Thoracic Society, 2000), studies specifically addressing the effects of ambient air pollution on HRQOL in the general population are still rare. In a large study on the Korean population, increased annual concentrations of particulate matter with aerodynamic diameters smaller than 10µm (PM_{10}) and nitrogen dioxide (NO_2) were associated with poor quality of life, assessed by the Euro Quality of life (AQ-5D) health questionnaire (Shin et al., 2018). A Japanese study showed an association between the "vitality" domain of the SF36 and nitrogen oxides (NOx) concentrations (Yamazaki et al., 2005).

Regarding greenspace, recent reviews and meta-analyses concluded that greenspace benefits a wide range of health outcomes, including good self-reported health, but level of heterogeneity was high (Twohig-Bennett and Jones, 2018; Yang et al., 2021). Several studies showed that living near a greenspace has a positive impact on HRQOL, in particular on its mental component (Bos et al., 2016; Kim et al., 2016; Stigsdotter et al., 2010; Tillmann et al., 2018a), while other studies did not find an association (Bos et al., 2016; Vogt et al., 2015).

The role of asthma and/or rhinitis in the association of air pollution and greenspace with HRQOL deserves specific attention. First, individuals with asthma or rhinitis appear more vulnerable to air pollution (Burte et al., 2018; Jacquemin et al., 2015), suggesting that the impact of air pollution exposure on HRQOL might be modified by asthma and/or rhinitis status. Previous studies have reported acute effects of air pollution exposure on decreased asthma-related quality of life (Bose et al., 2018; Nakao et al., 2016; Scibor et al., 2019; Scibor and Malinowska-Cieślik, 2020; Sommar et al., 2014), but to our knowledge, none have specifically examined whether asthma may modify associations between air pollution and HRQOL in a general population. Secondly, asthma and rhinitis are often allergic diseases, therefore the *a priori* hypothesized positive effect of exposure to greenspace on quality of life might be attenuated in individuals with asthma or rhinitis because greenspaces are also sources of pollen. To the best of our knowledge, this hypothesis has never been tested.

The aim of this study was to assess the association of air pollution and greenspace (including the level of greenness and presence of green spaces) around the home with HRQOL and whether asthma and/or rhinitis modified these associations. We hypothesized that the deleterious effect of air pollution on HRQOL could be exacerbated in individuals with asthma and/or rhinitis, while the beneficial effect of greenspace could be attenuated in individuals with one or both of these chronic diseases.

Material and methods

Participants

The analysis is based on the European Community Respiratory Health Survey (ECRHS) (Burney et al., 1994). The ECRHS is an international population-based study. Participants were 20-44 years of age at the time at recruitment in 1990-95 and were selected through a screening questionnaire sent to the local population of 30 centres in 14 countries. Among responders to the screening questionnaire, two samples were drawn: 1) a “random sample” by randomly selecting 300 participants of each gender and 2) a “symptomatic sample” selecting participants who had reported symptoms of "waking with shortness of breath in the last 12 months", "asthma attack in the last 12 months" or "taking asthma medication" in the screening questionnaire, but who had not been selected in the random sample. Selected participants were invited to a testing centre for a clinical assessment (ECRHS-I, n=18,356 http://www.ecrhs.org/). People who were included in ECRHS-I were recontacted and invited to take part in two new follow-ups, between 2000 and 2002 (ECRHS-II, n=10,933) (Kogevinas et al., 2007; The European Community Respiratory Health Survey II Steering Committee, 2002) and between 2011 and 2013 (ECRHS-III, n=7040). Detailed information on environmental, lifestyle and respiratory health factors was collected at each survey using postal questionnaires and follow-up clinical visits.

The present analysis used data collected at ECRHS-II and ECRHS-III and included participants with data available on HRQOL, air pollution and greenness (Figure 1). The mean follow-up time was 11.3 years. It involved 19 centres in 8 countries (South-Antwerp and Antwerp-City in Belgium, Ipswich and Norwich in England, Grenoble and Paris in France, Pavia, Turin and Verona in Italy, Bergen in Norway, Barcelona, Galdakao, Albacete, Oviedo and Huelva in Spain, Göteborg, Umea, and Uppsala in Sweden, and Basel in Switzerland).

Health-related quality-of-life

The Short Form-36 (SF-36) questionnaire was used to assess HRQOL. The SF-36 is a standardised, widely used and validated tool to assess general HRQOL (Aaronson et al., 1992). It includes 36 questions from which the Physical Component Summary (PCS) and the Mental Component Summary (MCS) scores were computed as described in the SF-36 User Manual (Ware et al., 1994). The physical component comprises physical functioning (PF), bodily pain (BP), role physical (RP) and general health perception (GH). The mental component comprises vitality (VT), social role functioning (SF), role emotional (RE) and mental health perception (MH). The internal consistency for the PCS and MCS were high (overall Cronbach's alpha were >0.75 and >0.82, respectively) indicating that the items within each score measured the same construct. The set of questions covers the current period, over the last 4 weeks. By construction, the PCS and MCS scores have expected means of 50 (range from 0 to 100) and standard deviations of 10 in a general population, with a higher score indicating better HRQOL (Leynaert et al., 2000).

Asthma and rhinitis definition

Asthma and rhinitis were defined by a positive answer to the questions "Have you ever had asthma?" and "Do you have any nasal allergies, including hay fever?" respectively. A combined asthma and/or rhinitis phenotype was generated: no asthma and no rhinitis (A-R-), rhinitis but no asthma (A-R+), asthma but no rhinitis (A+R-), and asthma and rhinitis (A+R+).

Environmental factors

Air pollution exposure

To study air pollution exposure, we used existing land-use regression (LUR) models for Western Europe that were based on satellite- and ground-based measurements from 2010 for NO_2 and $PM_{2.5}$ mass (de Hoogh et al., 2016) from the ELAPSE project (Effects of Low-level Air Pollution: A Study in Europe) and 2007 for PM_{10} mass (Vienneau et al., 2013). These air pollution estimates have been previously used in ECRHS (Fuertes et al., 2018). Briefly, information from >1500 AIRBASE monitoring sites were combined with spatial information on land use characteristics, population density, road lengths, altitude, distance to sea, and satellite-based air pollution measurements to create LUR models that were applied and mapped on 100m grids. An external assessment of the LUR model could not be performed by country as the AIRBASE monitoring sites were used in the training phase. Among ECRHS centres, this was done for $PM_{2.5}$ for Paris (R^2 =0.39) and for NO_2 for a couple of cities in France (R^2 = 0.53). Using these LUR models, we assigned individual-level air pollution estimates to all participants' home addresses at ECRHS-II (2000-02) and ECRHS-III (2011-13). Thus, among individuals who participated at ECRHS-II and ECRHS-III (n=3196), exposure assessments were different at the two time points when participants moved between the two studies (55%), otherwise they were identical. As such, we explicitly assumed the spatial variability in exposures had not changed between the timing of the two follow-ups.

Greenness (i.e. vegetation level)

Greenness surrounding the residential addresses of each ECRHS participant was estimated using the satellite-derived Normalized Difference Vegetation Index (NDVI), as previously used in ECRHS (Triebner et al., 2019). NDVI is calculated based on the knowledge that plants strongly absorb visible red light (Red) for use in photosynthesis while strongly reflecting near-infrared light (NIR) to prevent overheating. The equation for NDVI is based on spectral reflectance measurements acquired in corresponding light wavelengths and reads as NDVI = (NIR – Red) / (NIR + Red). As NIR and Red are ratios of the reflected over absorbed light and their values range from 0 to +1, NDVI values range from −1 to +1, with +1 indicating a highly vegetated area (National Aeronautics and Space Administration, 2018). Landsat 4–5 Thematic Mapper satellite images (30m by 30m resolution), taken during months with the highest vegetation (in general May-September were considered, but the selection depended on the centres: until October for southern countries like Spain and June-August for northern countries like Norway) were used to assess NDVI. The specific images (with the corresponding dates) are listed in the online data supplement (Supplementary Table E1). Residential surrounding greenspace was defined as the mean value of NDVI in a 300m buffer around each participant's residential address at each survey (2000-2002 for ECRHS-II and 2011-2013 for ECRHS-III). The size of the buffer was supported by a study indicating that for Landsat-derived vegetation metrics, metrics became invariant beyond 480 m (Labib et al., 2020).

Green spaces

The presence of green spaces in a circular 300m buffer (according to the recommendations of the World Health Organization (Annerstedt van den Bosch et al., 2016)) around participants' residential addresses was assessed using the Urban Atlas land use data for the year 2006 (http://www.eea.europa.eu/data-and-maps/data/urban-atlas). We considered three binary indicators: presence of urban green spaces (of at least 1 ha), presence of forests (of at least 1 ha) and presence of agricultural land (of at least 1 ha). These data were only available for a subset of the population.

Statistical analysis

Demographic results are given in means ± SD or n (%). For the description of air pollution exposure and greenness, results are given in medians and 25-75th percentiles (Q1 and Q3). The comparison between participants at ECHS-II and ECRHS-III or between excluded and included subjects was performed using Chi-squared tests for categorical variables and Student t-tests for continuous variables.

First, univariate associations between annual air pollution levels, greenspace indicators and HRQL were assessed at ECRHS-II and ECRHS-III separately to address the robustness of the results over time. To do so, mixed linear regression models, with PCS or MCS as outcomes, air pollutant concentrations or the greenspace indicator (greenness and presence of green spaces) as predictors and centre as random effect to account for the correlation of residuals within the same centre, were fitted at both time points separately. The linearity of the associations between air pollutants/NDVI and HRQOL (PCS and MCS) was verified by considering exposure variables categorized into quartiles (unadjusted analysis conducted at ECRHS-II and ECRHS-III separately, to get a clear sense of the data) and by performing splines using likelihood ratio test between the adjusted model with exposure modelled as a natural spline with 5 degrees of freedom and the adjusted linear model

Continuous NO_2, $PM_{2.5}$, PM_{10} and NDVI variables were rescaled by their inter-quartile range (IQR) to provide comparable estimates. Secondly, given that a similar pattern of associations was observed at both time points, longitudinal analyses in the repeated ECRHS-II and ECRHS-III data were conducted using mixed linear regression models to account for the repeated data and the multicentric study design.

Determinants of HRQOL and potential confounders were identified from the existing literature and represented in a Directed Acyclic Graph (Supplementary Figure E1). We considered in the main multiple regression models (M1) age, sex, BMI, active smoking (never, ex or current smokers), second hand smoking, occupational status (manager, technicians, manual and other/missing), educational level (age completed full time education≤16 years, 17-20 years and ≥21 years),season at the time of the HRQOL assessment and a 3-class indicator of urbanicity (the standard European classification of degree of urbanicity at the municipalities level for year 2011 : cities (densely populated areas), towns and suburbs (intermediate density areas) and rural areas (thinly populated areas). Frequency (≤1 a month, 1-3 times a week, ≥4 times a week) and duration (≤30 min, 1-3 hours, ≥4 hours) of physical activity and chronic disease (defined by arthritis, hypertension, varicose veins, heart disease, depression, diabetes, cancer, stroke, asthma, chronic cough or phlegm, chronic bronchitis or answered yes to the question “Do you have any long-term limiting illness”) were added to the models in sensitivity analyses (M2 models), as these could lie on the causal pathway between air pollution/greenspace exposure and HRQOL.

Missing data on confounders (19.75%) were imputed using multiple imputation methods (twenty simulations were performed by using the fully conditional specification method (FCS) (Lee and Carlin, 2010). A complete case analysis was conducted to address the robustness of the results to missing data imputation.

Bi-exposure analyses were performed considering jointly NDVI with each air pollutant (NO_2 or $PM_{2.5}$ or PM_{10}) successively, but air pollutants were not jointly considered given their high levels of correlation (Supplementary Table E2). Then, models including interaction terms between air pollutant and NDVI were performed to address the potential modifying effect of NDVI on the association between air pollutants and HRQOL. Models were further conducted in men and women separately to address a potential gender modifier effect in the exposure-HRQOL associations.

The effect of asthma and/or rhinitis as an effect modifier was assessed by stratifying the analyses into the 4 asthma and/or rhinitis status categories and secondly by inserting a statistical interaction term between each exposure and the asthma and/or rhinitis status categories in the regression models.

Sensitivity analyses

Several sensitivity analyses were conducted: 1) by selecting the minimal sufficient adjustment (MSAS): sex, age, educational level, occupational status and urbanicity in red on the DAG (supplementary figure E1), 2) by stratifying the analyses into the 4 seasons of HRQOL assessment and further testing the modifying effect by season by integrating a statistical interaction term between each exposure and the season categories in the regression models, 3) by testing chronic diseases, then physical activity (≥2 times a week and ≥1 hour) as mediators in single mediation models (R package mediation).

Analyses were done with the SAS 9.4 statistical software (SAS institute, Cary, NC) and with R statistical environment (Version 4.1.2).

Results

Population description

The ECRHS-II participants included in the present analysis (n = 6542) did not differ in terms of sex, age and smoking status, but had a lower educational level (p<0.0001) than those enrolled at ECRHS-II but not included in this analysis because of missing data for HRQOL, air pollution or greenness (n=4391) (Figure 1, supplementary Table E3). No differences between ECRHS-III participants included (n=3686) or excluded (n=3354) were observed.

On average, subjects included in the analysis were 42.8 (SD 7.1) years old in ECRHS-II and 53.9 (7.2) years old in ECRHS-III, and almost half were male at both surveys (Table 1). The majority of the study population. (>60%) never had asthma or rhinitis. Compared to ECRHS-II, at ECRHS-III BMI and frequency of chronic diseases were higher and active and passive smoking lower. Exposures to air pollution and NDVI remained stable between ECRHS-II and ECRHS-III. Mental and physical quality of life scores were close to 50 at ECRHS-II, whereas at ECRHS-III the physical score was slightly lower (47.5) and the mental score slightly higher (51.0) (Table 2). Correlations between air pollutants were positive and strong (from 0.73 to 0.86) and correlations between NDVI and air pollutants were negative and moderate to high (from -0.49 to -0.71) (Supplementary Table E2).

Association between HRQOL and air pollution or greenspace exposures

The unadjusted analysis showed that MCS decreased significantly with higher NO_2, $PM_{2.5}$ and PM_{10} exposures, both at ECRHS-II and ECRHS-III, and results using exposures coded in quartiles were consistent with linear trends (Supplementary Table E4). A positive dose-response association was observed between NDVI and MCS at ECRHS-II, but this association was not found at ECRHS-III. No robust associations were observed for PCS. Linearity was also confirmed in main adjusted model (M1) using splines (Supplementary Figure E2 A and B).

Main models adjusted for age, gender, BMI, active smoking, second hand smoking, occupational status, educational level, season of questionnaire and urbanicity (M1 models) and also models further adjusted for frequency and duration of physical activity and chronic diseases (M2 models) (Figure 2) showed similar results to unadjusted model results. In the adjusted (M1) ECRHS-II and ECRHS-III longitudinal analyses, one IQR increase in NO_2 (13.8 µg/m³), $PM_{2.5}$ (8.3 µg/m³), and PM_{10} (14.6 µg/m³), was associated with lower MCS (betas [95%CIs] were -0.69 [-1.23; -0.15], -1.79 [-2.88; -0.70], -1.80 [-2.98; -0.62], respectively). One IQR increase in NDVI (0.3 unit) was associated with a higher MCS (0.82 [0.22; 1.42]). No association was observed between PCS and NO_2, PM_{10} or NDVI, and only $PM_{2.5}$ was associated with PCS (1.03 [0.30; 1.76]). Analyses stratified by gender showed similar betas of association in men and women, except for associations between NO_2 and MCS showing a stronger association in men than in women (supplementary figure E3).

A secondary analysis for a subset of the population (n=5174) considering the three additional binary green space indicators (all being associated with NDVI, in particular presence of forests and agricultural land, supplementary Table E5) showed that the presence of agricultural lands was associated with higher PCS and that the presence of forests was associated with higher MCS, consistently at ECRHS-II and ECRHS-III (Table 3 and supplementary Table E6). No association was observed with the presence of urban green spaces, except an inverse association with PCS at ECRHS-II which was not observed at ECRHS-III or in the longitudinal analysis.

In jointly adjusted models, all effect estimates for NDVI in relation to MCS were attenuated (Table 4). Changes in the effect estimates were less pronounced for $PM_{2.5}$ and PM_{10} than for NO_2 (18%, 27% and 38% respectively). $PM_{2.5}$ remained associated with lower MCS, but NO_2 and PM_{10} did not. The NDVI effect estimates decreased by 26% after additional adjustment for $PM_{2.5}$ and 41% when additionally adjusting for PM_{10}. NDVI remained associated with higher

MCS only in the model co-adjusted for $PM_{2.5}$ (borderline significant, p=0.05). Regression models including a statistical interaction test between NDVI and each air pollutant on HRQOL scores did not identify statistical interaction (interaction p-values were greater than 0.10) except for the association between NDVI and NO2 in relation to MCS indicating a weak statistical interaction (p=0.06).

Association between HRQOL and air pollution or greenspace exposures, after stratification by the asthma-rhinitis status

The adjusted longitudinal analysis stratified by asthma-rhinitis status showed a strong similarity of the betas across subgroups. The inverse associations between NO_2, $PM_{2.5}$ and PM_{10} exposures and MCS and the positive association between NDVI and MCS were observed in each asthma-rhinitis category, although the associations did not reach the significance threshold in the smaller group of participants with asthma but no rhinitis and for NDVI in those with asthma and rhinitis (Figure 3). The lack of association of NO_2 and NDVI with PCS were observed in each sub-group. None of the asthma-rhinitis exposure interaction tests was statistically significant.

Sensitivity analyses

Results from sensitivity analyses were overall consistent: the MSAS models showed very similar results to those from the unadjusted and main models M1 (supplementary Table E7). The inverse associations between pollutants and MCS and the positive association between NDVI and MCS were observed in each season (Supplementary Figure E4). There was no significant interaction between season and NDVI or any of air pollutants (interaction test p value >0.20). The mediation analyses (Table E8 and E9) showed that among analyses identifying statistically significant total effects, a single one (PM_{10}-MCS association) showed a significant mediating effect of physical activity at both time points, but with a very low proportion mediated (≤5%). The complete case analysis confirmed the robustness of the results to missing data imputation (supplementary Table E10).

Discussion

Key Findings

Using data from a large European population, higher long-term air pollution exposure and lower residential surrounding greenspace were associated with a lower mental HRQOL score while no robust association was observed with the physical HRQOL score. Mutually adjusted models indicated that the NDVI effects on MCS could partially be explained by air pollution. To the best of our knowledge, this study is the first to examine the modifying effect of asthma and/or rhinitis on these associations and showed that the deleterious effect of air pollution and beneficial effect of greenspace on the MCS score were observed regardless of asthma-rhinitis status. Thus, our study, which analysed validated health parameters that refer to an individual's perception of well-being, adds to the knowledge on adverse health effects of air pollution and beneficial health effects of greenspace in the general population.

Comparison with existing literature

Although it is clear that air pollution is a major environmental threat to global public health, mainly through its cardio-respiratory health effects (Thurston et al., 2017), the need for additional research focused on psychological and social aspects has recently been underlined (Dominski et al., 2021). Our results indicating a lower MCS score with higher ambient air pollution exposure extend the literature on the adverse health effect of air pollution. These findings are in accordance with a few previous studies indicating chronic effects of air pollution on objective or perceived mental health outcomes (Gundersen et al., 2013; Hwang et al., 2018; Oudin et al., 2016b, 2016a; Shin et al., 2018; Yamazaki et al., 2005). . Although the mechanisms linking air pollution to mental health are still unknown, neuro-inflammatory process are suspected (Calderón-Garcidueñas et al., 2008).

Regarding the PCS score, our findings did not show any clear association, except an unexpected positive association with $PM_{2.5}$ exposure, also found in men and women separately. Previous studies have also provided conflicting results. Positive associations were reported between SF-12 PCS and traffic density, used as a proxy for air pollutant exposure, in women but not in men in a population-based Norwegian study (Gundersen et al., 2013). No associations were observed however with EQ-5D in a Swedish population enriched with participants with asthma and rhinitis (Sommar et al., 2014) as well as with any domain included in the SF-36 PCS in a population-based Japanese population (Yamazaki et al., 2005). We were unable to identify a plausible explanation to support the unexpected association we observed, but the fact that this association was driven by results at ECRHS-II only (no association observed at ECRHS-III) suggests that this non-robust association could be a spurious relationship. Our results are in agreement with a previous study focused on patients with chronic obstructive pulmonary disease that reported an association between air pollution/greenness levels and mental, but not physical, HRQOL scores (Moitra et al., 2022).

Regarding greenspace, participants with homes with a higher density of vegetation and with forests within 300m had higher mental HRQOL scores, which confirmed findings from previous studies indicating beneficial associations between greenspace and mental health (Cerletti et al., 2021; Coventry et al., 2019; Holt et al., 2019). In contrast to the results of the previous studies, our observed associations do seem to be driven by increased physical activity in participants living close to green areas, as our effect estimates barely changed when physical activity was additionally adjusted for. An interventional study in 45 adults showed that undertaking purposeful activity in public green space had the potential to promote health and prevent mental ill health (Coventry et al., 2019). However, our study did not show any clear pattern of association for PCS and some studies in the literature have found no clear association between distances to green space and an overall quality of life score (Bos et al., 2016; Vogt et al., 2015). Discrepancies in the results between studies on the effect of greenspace exposure on health might be explained by differences in population characteristics (age, sex, socio-economic level etc.) and the type of the environment (rural, suburban, urban), as well as how people interact with the green living environment (accessibility, exposure and engagement (Tillmann et al., 2018b)). Our results based on the NDVI indicator of greenness, that did not account for the different type of vegetation, supported an overall beneficial effect of greenspace on MCS. However, the type of vegetation might be important as suggested by previous studies(Jarvis et al., 2020) and by our results supporting a beneficial impact of exposure to forest while exposures to urban green space and agricultural land were not associated with MCS.

The beneficial effect of greenspace exposure on mental health could be mediated by behavioural factors (e.g. encouraging physical activity), social factors (e.g. fostering social contact), direct mental health effects (e.g. decreasing stress) or correlated environmental factors (e.g. lower air pollution, noise and heat) (Markevych et al., 2017).

Our results did not demonstrate interactions between air pollution and greenness exposures on HRQOL, but when mutually adjusted, the effects of air pollutants and greenness on MCS were all reduced. Interestingly, these results corroborate those of a previous large population-based study in Netherlands showing that in multi-exposure models, associations between higher surrounding green and lower air pollution with poor self-perceived general health were generally attenuated compared with associations in single-exposure models (Klompmaker et al., 2019). These findings are in agreement with the hypothesis the green environment partly influences health by lacking air pollution sources (James et al., 2015; Markevych et al., 2017).

Our results do not support any modifying effect of asthma-rhinitis status on the relationship between air pollution/greenspace exposure and HRQOL, indicating that individuals with asthma and/or rhinitis are not significantly more sensitive to air pollution and greenspace than healthy individuals in regards to HRQOL. There is no other existing study with which we can compare our findings.

Strengths and limitations

The main strength of our study was the large sample studied, recruited from the general European population and by design enriched in participants with asthma, that allowed us to address asthma as a potential effect modifier. The longitudinal study design (ECRHS-II and about 11 years later ECRHS-III) made it possible to assess the robustness of the findings by providing internal replication of the findings over time and also to increase the statistical power and accuracy of the estimates through repeated data analyses. The large ECRHS data collection allowed us to account for a large set of potential confounders. Another methodological strength included annual average air pollution concentrations estimated by validated LUR models based on satellite- and ground-based measurements.

The study has some limitations, some related to exposures. Although health effects of long-term exposure to black carbon and ozone warrant further investigations, these pollutants were not considered in our study. Nevertheless, in the context of this paper focusing on global effects and less on mechanistic effects, $PM_{2.5}$ and NO_2 were good markers of pollution in general and of pollution from traffic. Although the approach used for estimating air pollution levels is the most widely used approach in epidemiological studies, it does not consider time spent at the residential address, indoor exposures and exposures that occur while commuting, which leads to measurement errors. In addition, a limitation of the study relates to the use of exposure models developed for some specific years that did not coincide with the waves of the ECRHS study and differed between the air pollutants (in 2010, i.e. about 10 years after ECRHS-II), green space indicators (in 2006, in-between ECRHS-II and ECRHS-III) and NDVI (mostly assessed concurrent the ECRHS waves). Thus, the non-movers were assigned the same air pollutant exposure and greenspace indicators at ECRHS-II and ECRHS-III. This might have led to exposure measurement errors and to increase differences in measurement errors between exposures, limiting the comparison of their respective effects on HRQOL. However, previous studies showing long-term validity of air pollution land use regression models (Cesaroni et al., 2012; Eeftens et al., 2011; Wang et al., 2013) and stable spatial contrasts of greenness over time (Thiering et al., 2016) support our approach. Regarding unmeasured potential confounders, our study did not account for area-level SES as this indicator was not available for all ECRHS centres, nor for income level that was not collected in ECRHS, but we used education and occupational levels as surrogates.

Perspectives and conclusions

Higher long-term exposure to air pollution and lower greenspace were associated with a lower mental SF-36 HRQOL score in a large European population, while no robust association was observed for the physical SF-36 HRQOL score. Asthma and/or rhinitis did not modify these associations. Given the significance of HRQOL as a public health concern, these novel findings are critical and emphasize the need to reduce air pollution levels and build new or preserve existing green spaces.

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Declaration of competing interest

MJA holds investigator initiated grants for unrelated research from Pfizer, Boehringer-Ingelheim, Sanofi and GSK. He has undertaken an unrelated consultancy for and received assistance with conference attendance from Sanofi. He has also received a speaker's fee from GSK.

Appendix A. Supplementary data

FIGURES

Figure 1. Flow chart

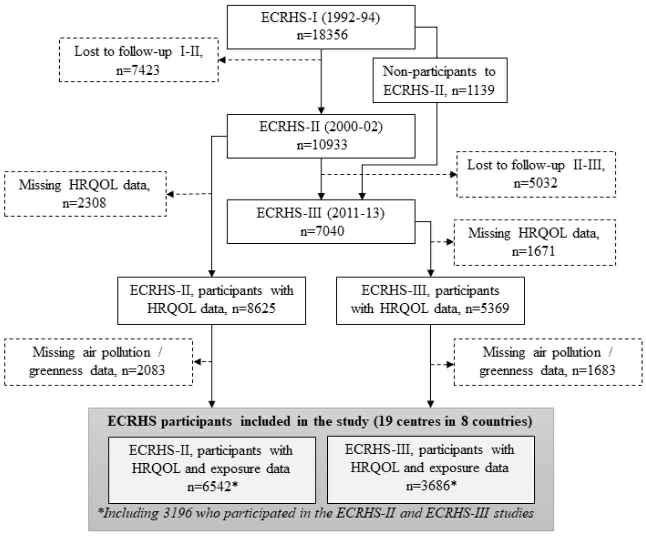

Figure 2. Adjusted associations between exposure to air pollutants, greenness and health-related quality of life.

Figure 2 caption: M1 models were adjusted for age, sex, BMI, active smoking, second hand smoking, occupational status, educational level, season and urbanicity. M2 models were further adjusted for chronic diseases and frequency and duration of physical activity. Beta values were estimated for the increment of one IQR of exposure (NO_2: 13.8 µg/m³; $PM_{2.5}$: 8.3 µg/m³; PM_{10}: 14.6 µg/m³; NDVI: 0.3 unit) from mixed linear regression models to account for the multicentric design (and for the ECRHS-II + ECRHS-III longitudinal analyses to additionally account for the repeated data)

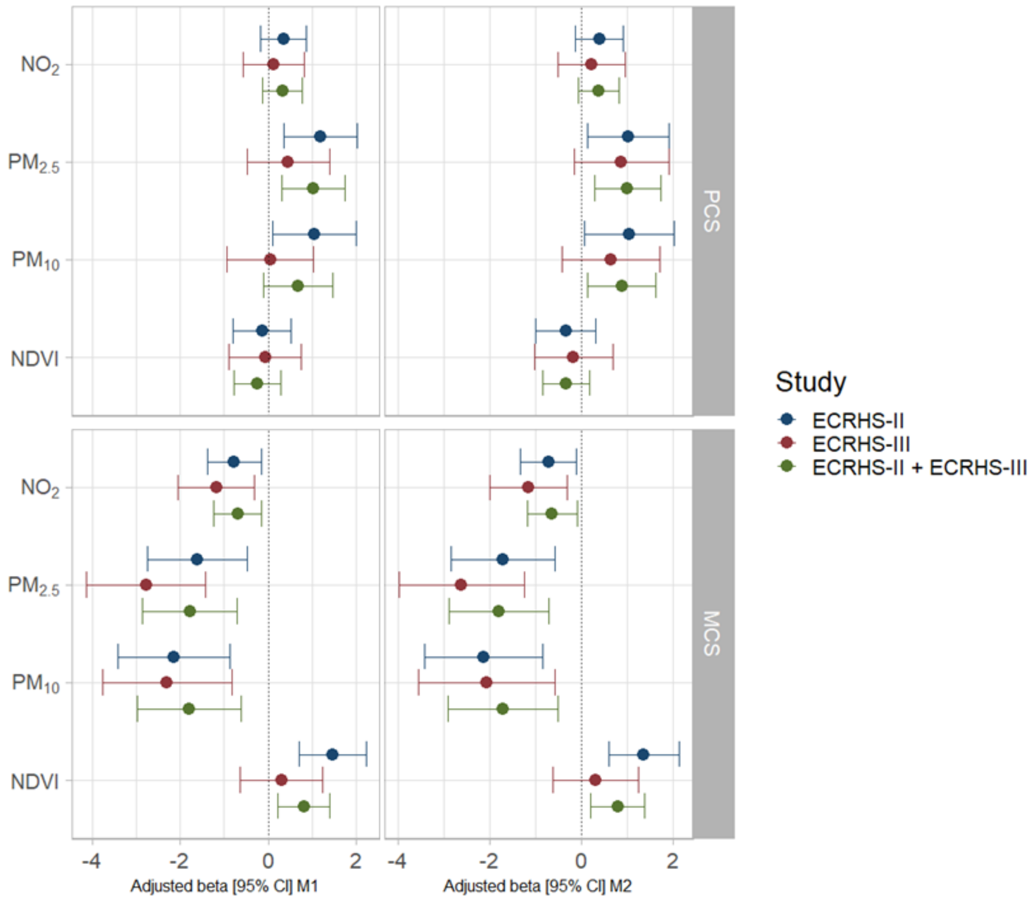

Figure 3. Adjusted associations between exposure to air pollutants, greenness and health-related quality of life stratified on asthma/rhinitis status

Models were adjusted for age, sex, BMI, active smoking, second hand smoking, occupational status, educational level, season and urbanicity (M1 model). Beta values were estimated in the longitudinal ECRHS-II and ECRHS-III data, for an increment of one IQR of exposure (NO_2: 13.8 µg/m³; $PM_{2.5}$: 8.3 µg/m³; PM_{10}: 14.6 µg/m³; NDVI: 0.3 unit) from mixed linear regression models to account for the multicentric design and repeated data.

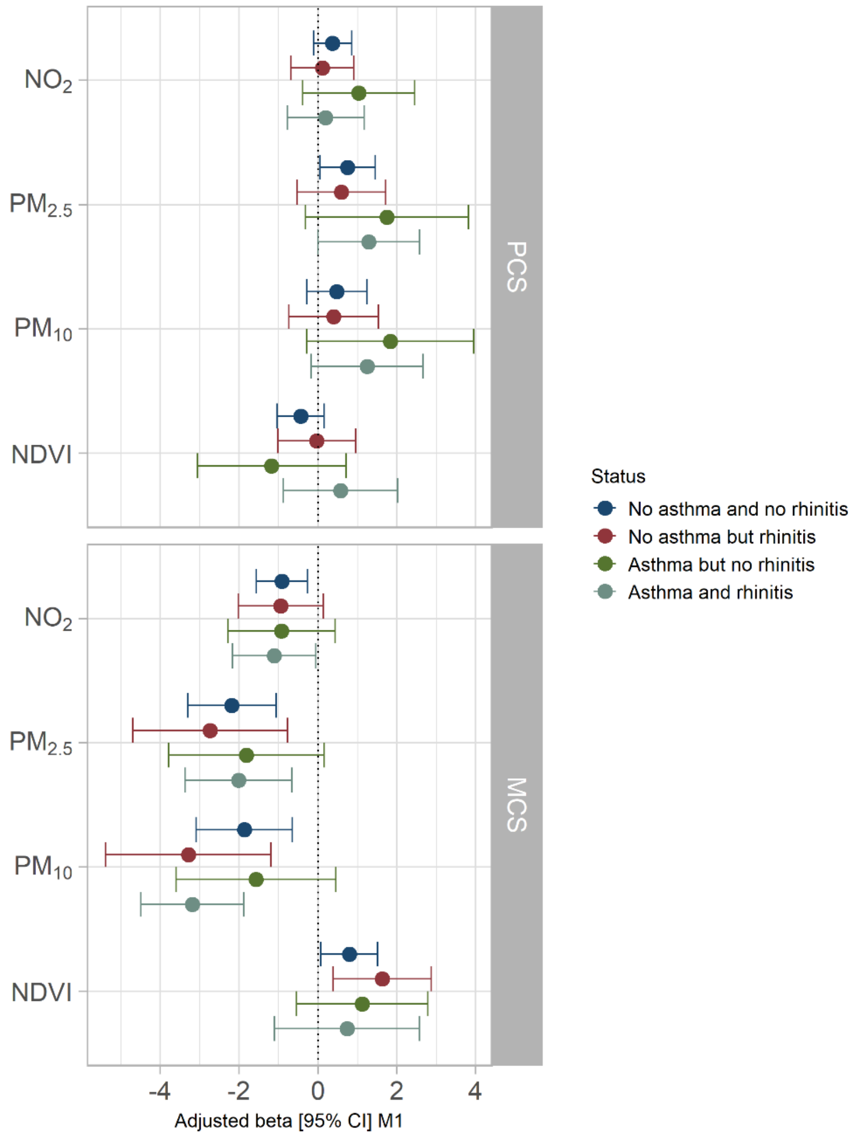

Table 1. Description of the population at ECRHS-II and ECRHS-III

	ECRHS-II (n=6542)		ECRHS-III (n=3686)		P value
	n	**Statistics**	**n**	**Statistics**	
Age years, mean ± sd	6542	42.8 ± 7.1	3686	53.9 ± 7.2	<0.0001
Gender, %					0.84
Men	3107	47.5	1758	47.7	
Women	3435	52.5	1928	52.3	
BMI kg/m^2, mean ± std	5826	25.6 ± 4.3	3529	27.0 ± 4.8	<0.0001
Smoking, %					<0.0001
Never-smokers	2738	42.3	1425	41.3	
Ex-smokers	1803	27.8	1387	40.2	
Smokers	1934	29.9	637	18.5	
Second hand smoking, %					<0.0001
No	3971	61.0	2884	79.1	
Yes	2542	39.0	764	20.9	
Occupational status, %					<0.0001
Manager	1763	26.9	998	27.1	
Technician	2871	43.9	1505	40.8	
Manual	1379	21.2	721	19.6	
Other, missing	529	8.1	462	12.5	
Age completed full-time education, %					0.09
≥21 years	2842	43.9	1606	46.2	
[17-20] years	2127	32.9	1096	31.5	
≤16 years	1501	23.2	773	22.2	
Season at HRQOL questionnaire, %					<0.0001
Jan, Feb, March	1878	28.7	800	21.7	
Apr, May, Jun	1786	27.3	911	24.7	
Jul, Aug, Sep	1226	18.7	954	25.9	
Oct, Nov, Dec	1652	25.3	1021	27.7	
Frequency of physical activity, %					0.003
≤1 a month	2138	33.1	1238	33.9	
1-3 times a week	3398	52.7	1812	49.7	
≥4 times a week	917	14.2	597	16.4	
Duration of physical activity, %					0.001
≤30 min	2722	42.6	1603	44.1	
1-3 hours	2626	41.1	1369	37.6	
≥4 hours	1045	16.3	664	18.3	
Chronic diseases, %					<0.0001
No	2620	44.8	1308	36.2	
Yes	3222	55.2	2300	63.8	
Urbanicity, %					<0.0001
Cities (densely populated areas)	4372	68.4	2272	62.9	
Tows	861	13.5	581	16.1	
Suburbs (intermediate density areas)	1159	18.1	759	21.0	
Ever asthma and/or rhinitis, %					0.04
A-R-, no asthma and no rhinitis	4097	63.0	2216	60.6	
A-R+, no asthma but rhinitis	1315	20.2	763	20.9	
A+R-, asthma but no rhinitis	389	6.0	262	7.2	
A+R+, asthma and rhinitis	703	10.8	417	11.4	

Table 2. Description of HRQOL, air pollution exposure, greenness and green space indicators at residential addresses of ECRHS-II and ECRHS-III participants

	ECRHS-II (n=6542)		**ECRHS-III (n=3686)**	
	n	**Statistics**	**n**	**Statistics**
Air Pollution				
NO_2 (µg/m³), median (q1-q3)	6542	26.2 (19.8-33.2)	3686	25.3 (18.3-32.8)
$PM_{2,5}$ (µg/m³), median (q1-q3)	6542	14.5 (10.9-18.9)	3686	14.3 (10.5-18.7)
PM_{10} (µg/m³), median (q1-q3)	6111	25.2 (15.8-30.7)	3677	25.0 (15.6-29.8)
Greenspace				
NDVI_300, median (q1-q3)	6542	0.26 (0.08-0.38)	3686	0.26 (0.11-0.38)
Presence of urban green spaces, %				
No	1639	50.6	966	50.0
Yes	1602	49.4	967	50.0
Presence of forests, %				
No	2259	69.7	1365	70.6
Yes	982	30.3	568	29.4
Presence of agricultural land, %				
No	2081	64.2	1204	62.3
Yes	1160	35.8	729	37.7
Health-related quality of life				
PCS, mean ± std	6542	49.3 ± 10.1	3686	47.5 ± 10.6
MCS, mean ± std	6542	49.9 ± 10.9	3686	51.0 ± 10.4

NO_2, nitrogen dioxide; $PM_{2.5}$, particulate matter with aerodynamic diameters smaller than 2.5 µm; PM_{10}, particulate matter with aerodynamic diameters smaller than 10 µm; SD, standard deviation; NDVI, Normalized Difference Vegetation Index; HRQOL, Health-related quality-of-life; PCS, Physical Component Summary; MCS, Mental Component Summary

Table 3. Adjusted associations between presence [a] to green space and health-related quality of life

	ECRHS-II			ECRHS-III			ECRHS-II + ECRHS-III		
	n	**Beta (95% CI) [b]**	**P value**	**n**	**Beta (95% CI) [b]**	**P value**	**n**	**Beta (95% CI) [b]**	**P value**
PCS									
Presence of urban green spaces Yes vs. No	3241	-0.80 (-1.50; -0.10)	**0.02**	1933	0.24 (-0.66; 1.13)	0.60	5174	-0.39 (-1.00; 0.18)	0.18
Presence of forests Yes vs. No	3241	0.58 (-0.32; 1.48)	0.21	1933	0.64 (-0.55; 1.82)	0.29	5174	0.59 (-0.16; 1.35)	0.12
Presence of agricultural land Yes vs. No	3241	1.17 (0.37; 1.97)	**0.004**	1933	0.89 (-0.14; 1.93)	0.09	5174	0.90 (0.24; 1.57)	**0.01**
MCS									
Presence of urban green spaces Yes vs. No	3241	0.05 (-0.72; 0.82)	0.89	1933	-0.68 (-1.61; 0.26)	0.16	5174	-0.14 (-0.76; 0.48)	0.66
Presence of forests Yes vs. No	3241	1.12 (0.12; 2.10)	**0.03**	1933	1.35 (0.10; 2.61	**0.03**	5174	0.89 (0.08; 1.70)	**0.03**
Presence of agricultural land Yes vs. No	3241	0.54 (-0.35; 1.43)	0.23	1933	0.89 (-0.21; 1.99)	0.11	5174	0.60 (-0.11; 1.32)	0.10

[a] presence of green spaces (of at least 1 ha) in a circular 300-m buffer around participant's home. [b]Beta were adjusted on age, sex, BMI, smoking, second hand smoking, occupational status, educational level, season and urbanicity (M1 model) from mixed linear regression models to account for the multicentric design (and for the ECRHS-II + ECRHS-III longitudinal analyses to additionally account for the repeated data).

Table 4. Bi-exposure models for associations between exposure to air pollutants and NDVI and health-related quality of life in the longitudinal analysis

	Single-exposure model	Bi-exposure model (adjusted for exposures below)			
		NDVI	NO_2	$PM_{2.5}$	PM_{10}
PCS	**Beta (95% CI) [a]**	**Beta (95% CI) [a]**	**Beta (95% CI) [a]**	**Beta (95% CI) [a]**	**Beta (95% CI) [a]**
NO_2	0.32 (-0.13; 0.78)	0.28 (-0.25; 0.82)	--	--	--
$PM_{2.5}$	1.03 (0.30; 1.76)	1.02 (0.25; 1.79)	--	--	--
PM_{10}	0.69 (-0.11; 1.48)	0.62 (-0.30; 1.56)	--	--	--
NDVI	-0.25 (-0.78; 0.28)	--	-0.08 (-0.70; 0.53)	-0.03 (-0.58; 0.51)	-0.07 (-0.70; 0.55)
MCS	**Beta (95% CI) [a]**	**Beta (95% CI) [a]**	**Beta (95% CI) [a]**	**Beta (95% CI) [a]**	**Beta (95% CI) [a]**
NO_2	-0.69 (-1.23; -0.15)	-0.43 (-1.05; 0.20)	--	--	--
$PM_{2.5}$	-1.79 (-2.88; -0.70)	-1.46 (-2.59; -0.33)	--	--	--
PM_{10}	-1.80 (-2.98; -0.62)	-1.31 (-2.69; 0.07)	--	--	--
NDVI	0.82 (0.22; 1.42)	--	0.59 (-0.10; 1.28)	0.61 (-0.01; 1.23)	0.48 (-0.22; 1.19)

[a] Beta were estimated for the increment of one IQR of exposure (NO_2: 13.8 µg/m³; $PM_{2.5}$: 8.3 µg/m³; PM_{10}: 14.6 µg/m³; NDVI: 0.3 unit) and adjusted on age, sex, BMI, smoking, second hand smoking, occupational status, educational level, season and urbanicity (M1 model) from mixed linear regression models to account for the multicentric design and repeated data)

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Online data supplement

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FIGURE LEGEND

Figure E1. Directed Acyclic Graph (DAG)

Figure E1 caption. The green circle represents the exposure variables. The blue circle (with a I) represents the outcome. The red circles represent the Minimal Sufficient Adjustment Set (MSAS) and the blue circles represents other adjustment variables. The green arrows suggest that variables may stand on the pathway from greenspace to health.

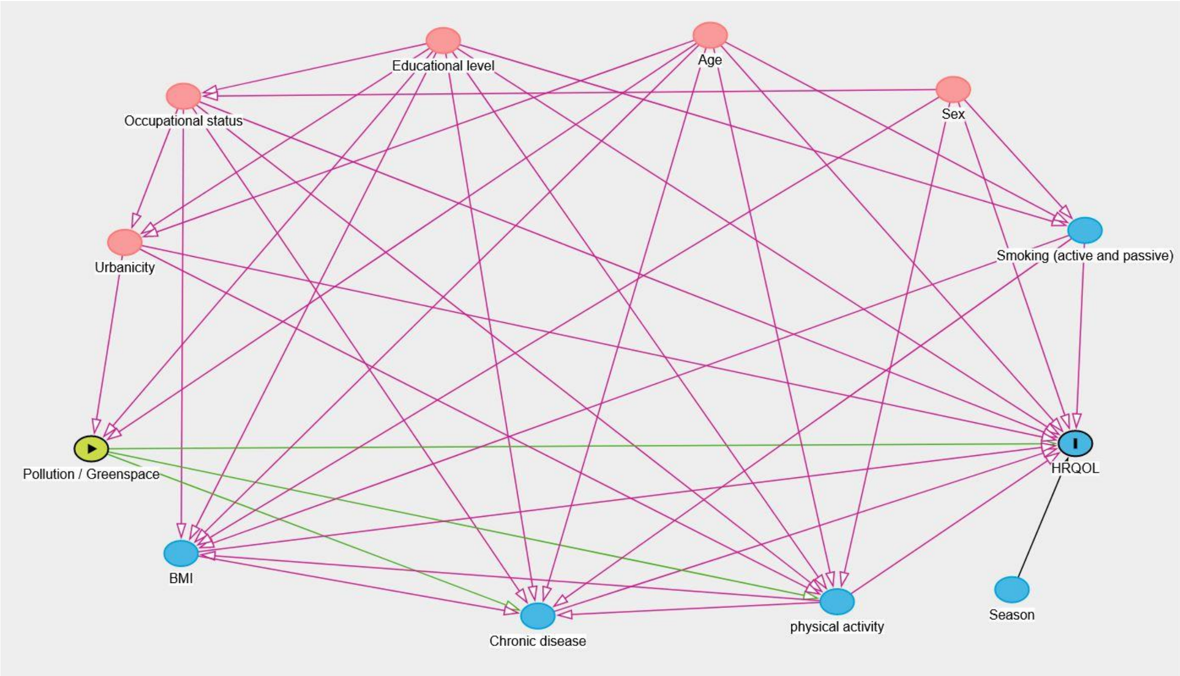
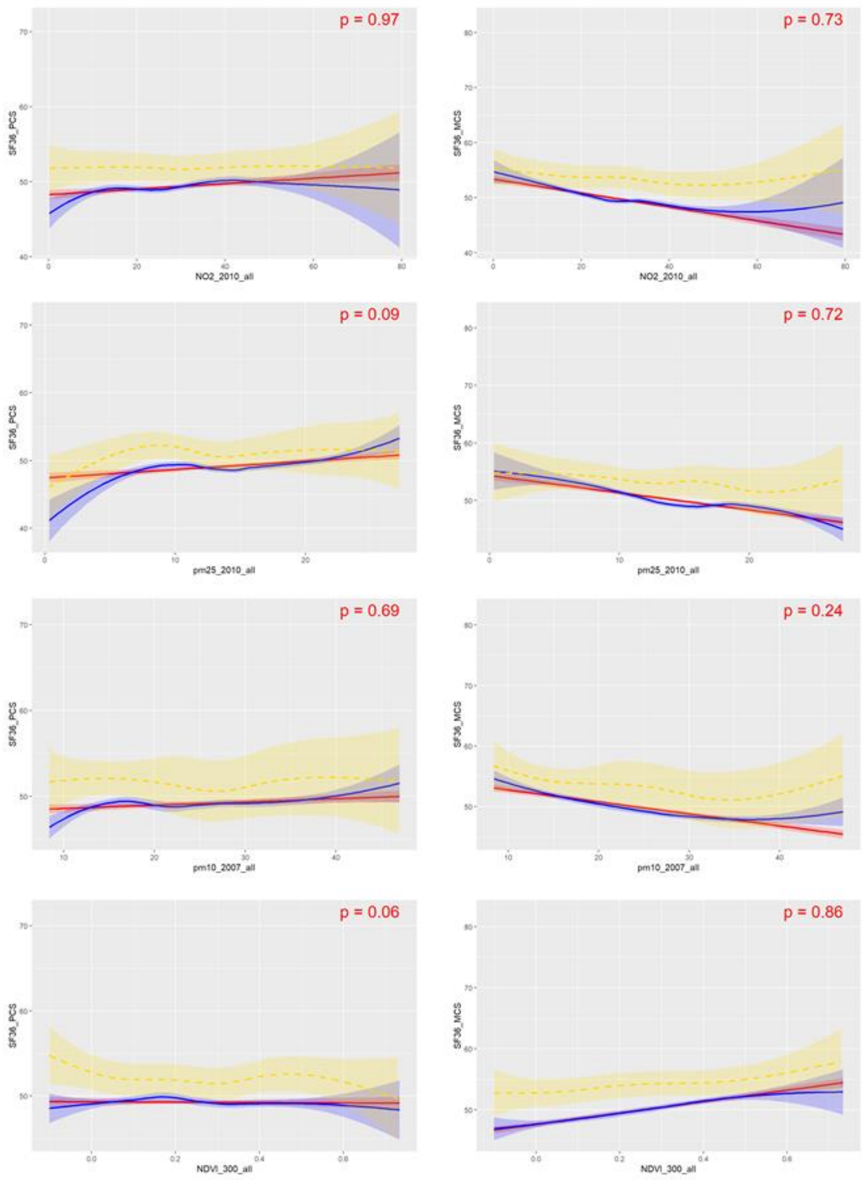


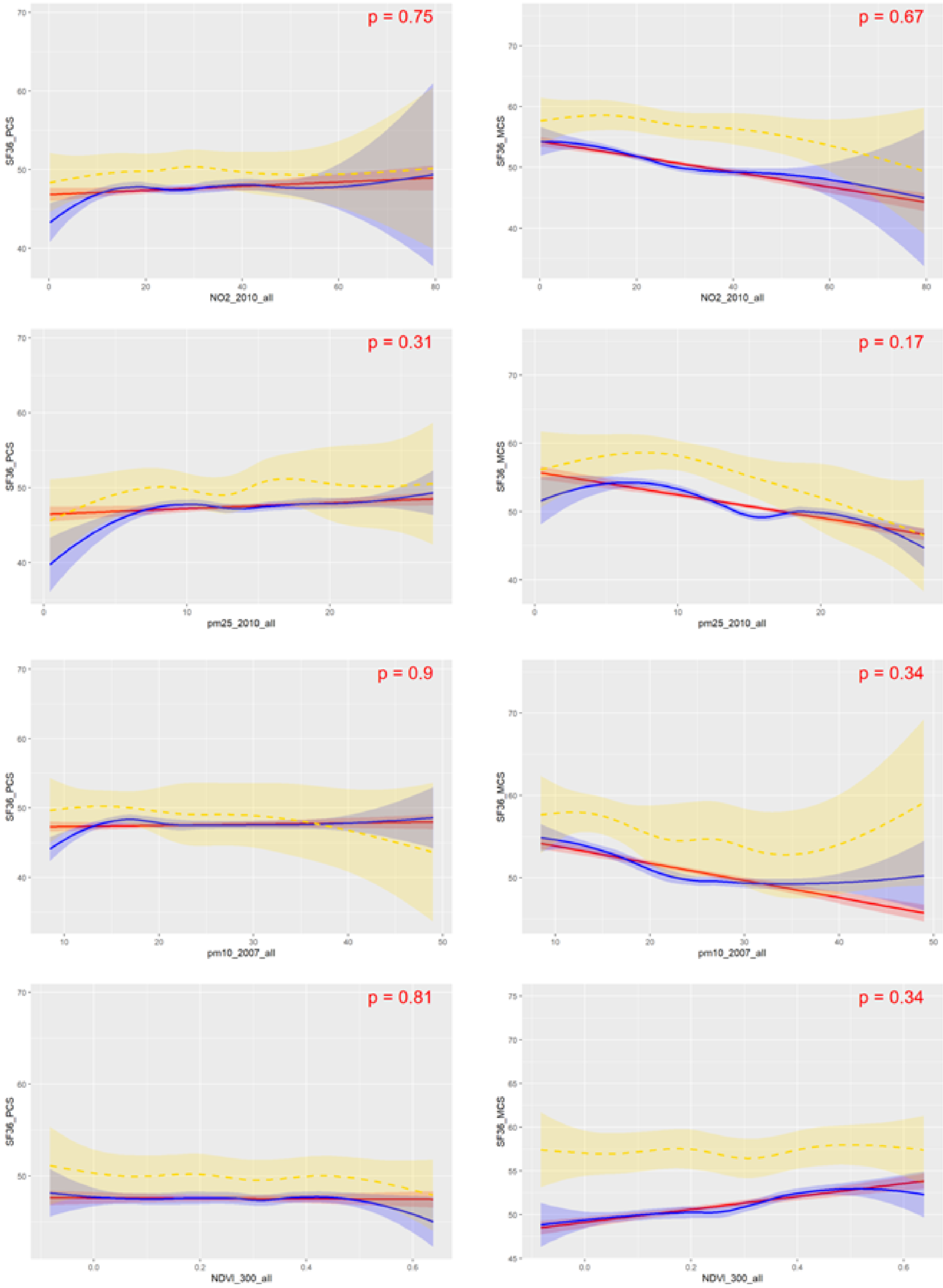
Figure E2. Regression spline plot at A) ECHRS-II and B) ECRHS-III

Figure E2 caption. Models were adjusted for age, BMI, active smoking, second hand smoking, occupational status, educational level, season and urbanicity. Red line represents linear, blue line represent unadjusted LOESS (Locally Weighted Error Sum of Squares regression) and yellow line represent fitted Spline.

A) ECRHS-II



B) ECRHS-III



p = 0.75
SF36_PCS
NO2_2010_all
p = 0.67
SF36_MCS
NO2_2010_all
p = 0.31
SF36_PCS
pm25_2010_all
p = 0.17
SF36_MCS
pm25_2010_all
p = 0.9
SF36_PCS
pm10_2007_all
p = 0.34
SF36_MCS
pm10_2007_all
p = 0.81
SF36_PCS
NDVI_300_all
p = 0.34
SF36_MCS
NDVI_300_all

Figure E3. Adjusted associations between exposure to air pollutants, greenness and health-related quality of life stratified on gender.

Figure E3 caption: Models were adjusted for age, BMI, active smoking, second hand smoking, occupational status, educational level, season and urbanicity. Beta values were estimated in the longitudinal ECRHS-II and ECRHS-III data, for an increment of one IQR (NO_2: 13.8 µg/m³; $PM_{2.5}$: 8.3 µg/m³; PM_{10}: 14.6 µg/m³; NDVI: 0.3 unit) from mixed linear regression models to account for the multicentric design and repeated data

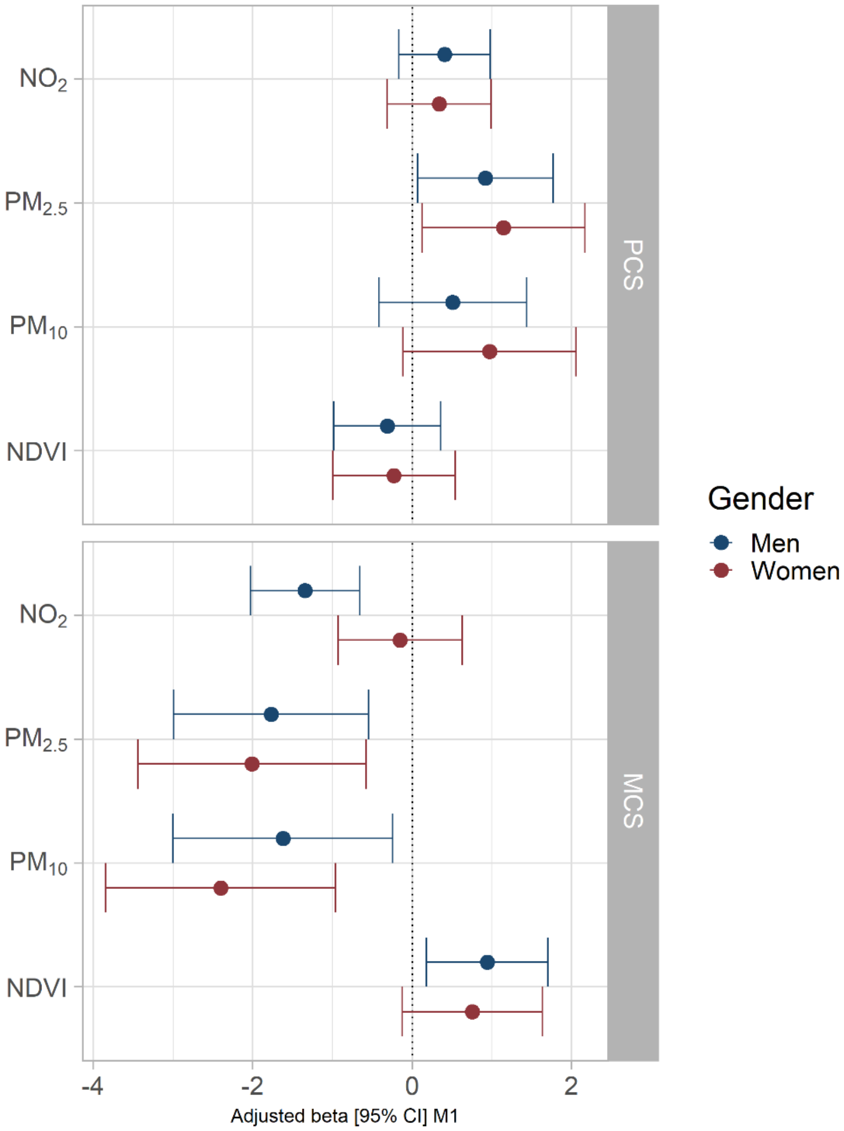


Figure E4. Adjusted associations between exposure to air pollutants, greenness and health-related quality of life stratified on season.

Figure E4 caption: Models were adjusted for sex, age, BMI, active smoking, second hand smoking, occupational status, educational level and urbanicity. Beta values were estimated in the longitudinal ECRHS-II and ECRHS-III data, for an increment of one IQR (NO_2: 13.8 µg/m³; $PM_{2.5}$: 8.3 µg/m³; PM_{10}: 14.6 µg/m³; NDVI: 0.3 unit) from mixed linear regression models to account for the multicentric design and repeated data

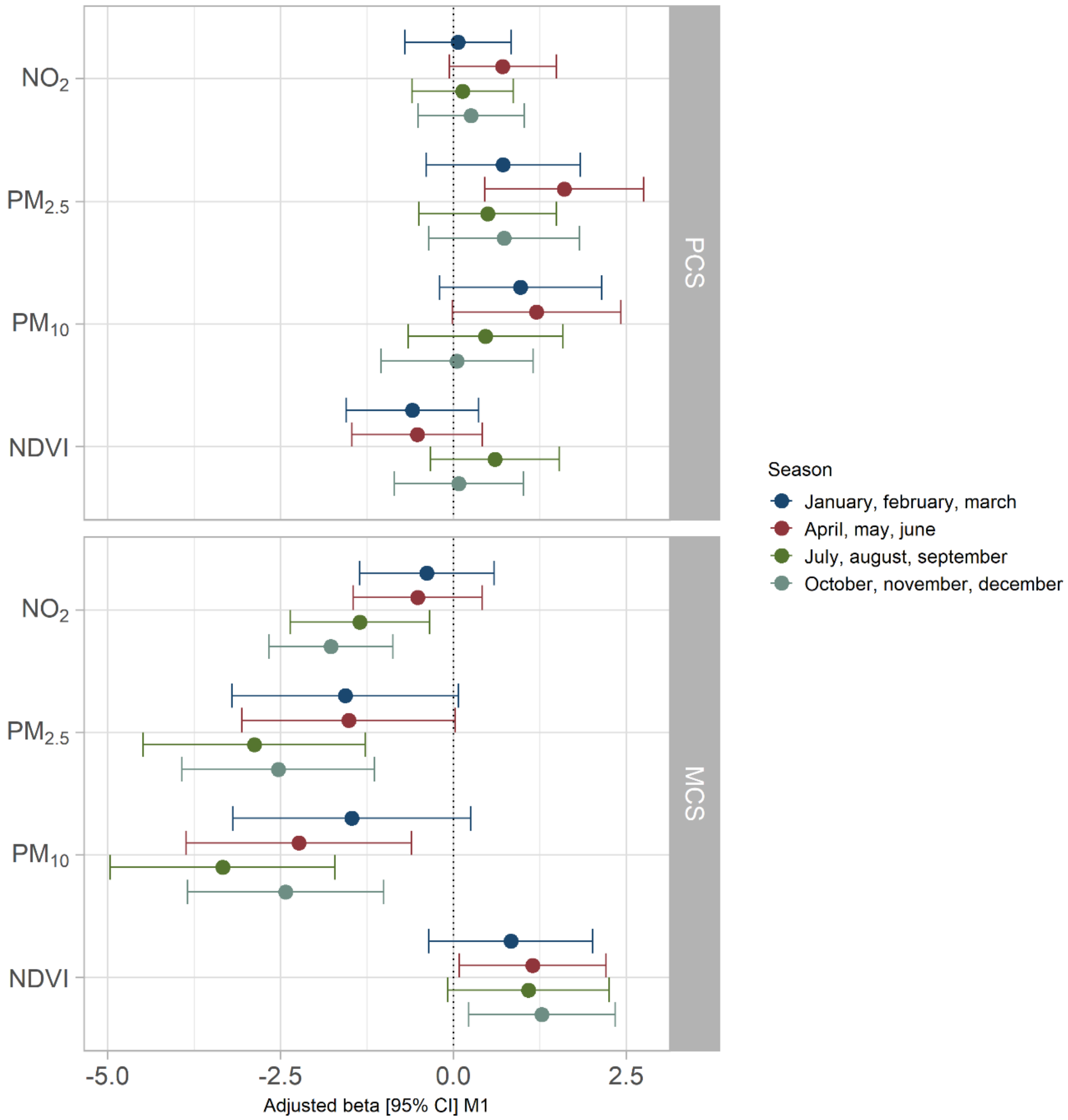


Table E1. Details on Landsat 4-5 TM satellite images used for NDVI calculations

Centre	Landsat 4-5 TM satellite images used (date, path/row)	Centre	Landsat 4-5 TM satellite images used (date, path/row)
Umea	ECRHS2: 30.07.03, 193/15	Gothenburg	ECRHS2: 07.06.02, 195/20
	30.07.03, 193/16		07.06.02, 195/19
	19.07.03, 196/15		14.06.02, 196/19
	23.07.04, 194/15		ECRHS3: 26.06.09, 195/20
	23.07.04, 194/16		26.06.09, 195/19
	ECRHS3: 28.06.09, 193/14		03.07.09, 196/19
	28.06.09, 193/15		
	28.06.09, 193/16	Norwich	ECRHS2: 16.05.02, 201/23
	26.06.09, 195/14		ECRHS3: 26.06.11, 201/23
	26.06.09, 195/15		
	26.06.09, 195/16	Ipswich	ECRHS2: 16.05.02, 201/24
	24.06.09, 197/14		ECRHS3: 05.07.11, 200/24
	24.06.09, 197/15		26.06.11, 201/24
Bergen	ECRHS2: 06.07.03, 201/17	Antwerp city	ECRHS2: 19.09.03, 198/24
	06.07.03, 201/18		19.09.03, 198/25
	15.07.03, 200/19		ECRHS3: 06.09.10, 198/24
	15.07.03, 200/16		06.09.10, 198/25
	ECRHS3: 27.09.10, 201/18		
	27.09.10, 201/17	South Antwerp	ECRHS2: 19.09.03, 198/24
	27.09.10, 201/16		19.09.03, 198/25
	27.09.10, 201/19		ECRHS3: 06.09.10, 198/24
	04.09.10, 200/19		06.09.10, 198/25
	29.09.10, 199/15		
	29.09.10, 199/16	Paris	ECRHS2: 09.08.03, 199/26
	29.09.10, 199/17		ECRHS3: 16.07.06, 199/26
	29.09.10, 199/18		
		Grenoble	ECRHS2: 14.06.02, 196/29
Uppsala	ECRHS2: 11.09.04, 192/18		14.06.02, 196/28
	11.09.04, 192/19		ECRHS3: 09.06.06, 196/29
	11.09.04, 192/20		09.06.06, 196/28
	24.08.04, 194/18		
	ECRHS3: 07.09.03, 194/19	Oviedo	ECRHS2: 05.08.03, 203/30
	28.06.09, 193/18		ECRHS3: 24.06.11, 203/30
	28.06.09, 193/19		
	30.06.09, 191/18	Barcelona	ECRHS2: 20.05.02, 197/31
	30.06.09, 191/19		ECRHS3: 11.10.11, 198/31
			04.10.11, 197/31
		Albacete	ECRHS2: 26.09.03, 199/03
			17.09.03, 200/33
			ECRHS3: 09.10.11, 200/33
		Huelva	ECRHS2: 15.09.03, 202/34
			ECRHS3: 05.09.11, 202/34

Table E2. Correlation between exposure to air pollutants, greenspace and health-related quality of life summary scores at ECRHS-II and ECRHS-III

	Pearson correlation					
	PCS	**MCS**	**NO_2**	**$PM_{2.5}$**	**PM_{10}**	**NDVI**
PCS						
ECRHS-II	1	-0.07	0.04	0.06	0.03	-0.003
ECRHS-III	1	-0.06	0.03	0.04	0.01	-0.003
MCS						
ECRHS-II		1	-0.13	-0.14	-0.16	0.14
ECRHS-III		1	-0.14	-0.17	-0.17	0.11
NO_2						
ECRHS-II			1	0.83	0.73	-0.60
ECRHS-III			1	0.86	0.75	-0.62
$PM_{2.5}$						
ECRHS-II				1	0.83	-0.49
ECRHS-III				1	0.84	-0.50
PM_{10}						
ECRHS-II					1	-0.71
ECRHS-III					1	-0.69
NDVI						
ECRHS-II						1
ECRHS-III						1

Light blue represents weak negative correlations (<0.50), Dark blue represents strong negative correlations (>0.50), light red represents weak positive correlations (<0.50), Dark red represents strong positive correlations (>0.50)

Table E3. Comparison of the included and excluded subjects from the analysis

	Excluded		Included		P Value [a]
	n	Statistic	n	Statistic	
ECRHS-II, n	**4391**		**6542**		
Age, mean ± sd	4391	42.9 ± 7.2	6542	42.8 ± 7.1	0.60
Gender, %					0.10
Men	2016	45.9	3107	47.5	
Women	2375	54.1	3435	52.5	
Smoking, %					0.42
Non-smokers	1850	43.4	2738	42.3	
Ex-smokers	1189	27.9	1803	27.8	
Smokers	1228	28.8	1934	29.9	
Educational level, %					<0.0001
≥21 years	1629	44.7	2842	43.9	
[17-20] years	1366	37.5	2127	32.9	
≤16 years	646	17.7	1501	23.2	
ECRHS-III, n	**3354**		**3686**		
Age, mean ± sd	3354	53.9 ±7.0	3686	53.9 ± 7.2	0.64
Gender, %					0.43
Men	1568	46.7	1758	47.7	
Women	1786	53.3	1928	52.3	
Smoking, %					
Non-smokers	1454	43.6	1657	45.2	0.27
Ex-smokers	1224	36.7	1326	36.2	
Smokers	660	19.8	679	18.5	

[a] Chi-squared tests for categorical variables and student t-tests for continuous variables.

Table E4. Univariate associations between exposure to air pollutants, greenspace and health-related quality of life.

	ECRHS-II			ECRHS-III		
	n	**Beta [b] (95% CI)**	**P value**	**n**	**Beta [b] (95% CI)**	**P value**
PCS						
NO_2	6542			3686		
Continuous (IQR) [a]		0.19 (-0.29; 0.68)	0.43		0.08 (-0.53; 0.69)	0.80
Categorical: <Q1		0			0	
Q1-Q2		-0.23 (-1.04; 0.57)	0.57		0.55 (-0.52; 1.63)	0.31
Q2-Q3		0.004 (-0.88; 0.89)	0.99		0.04 (-1.14; 1.22)	0.95
≥Q3		0.02 (-1.04; 1.08)	0.97		-0.01 (-1.37; 1.35)	0.99
$PM_{2.5}$	6542			3686		
Continuous (IQR) [a]		1.06 (0.21; 1.91)	**0.01**		0.55 (-0.36; 1.45)	0.23
Categorical: <Q1		0			0	
Q1-Q2		0.36 (-0.93; 1.66)	0.58		-0.87 (-2.29; 0.55)	0.23
Q2-Q3		-0.06 (-1.49; 1.36)	0.93		0.36 (-1.19; 1.92)	0.65
≥Q3		1.15 (-0.44; 2.75)	0.16		0.23 (-1.44; 1.91)	0.78
PM_{10}	6111			3677		
Continuous (IQR) [a]		0.60 (-0.40; 1.60)	0.24		-0.03 (-1.01; 0.95)	0.95
Categorical: <Q1		0			0	
Q1-Q2		0.17 (-0.95; 1.28)	0.77		0.53 (-0.84; 1.90)	0.45
Q2-Q3		-0.22 (-1.59; 1.16)	0.76		-0.33 (-1.88; 1.22)	0.68
≥Q3		0.52 (-0.99; 2.02)	0.50		0.11 (-1.49; 1.71)	0.89
NDVI	6542			3686		
Continuous (IQR) [a]		0.12 (-0.55; 0.79)	0.72		0.18 (-0.65; 1.02)	0.67
Categorical: <Q1		0			0	
Q1-Q2		0.02 (-0.86; 0.91)	0.96		0.26 (-0.85; 1.37)	0.65
Q2-Q3		-0.34 (-1.33; 0.66)	0.51		0.13 (-1.06; 1.32)	0.83
≥Q3		0.51 (-0.54; 1.57)	0.34		0.42 (-0.82; 1.66)	0.50
MCS						
NO_2	6542			3686		
Continuous (IQR) [a]		-1.06 (-1.59; -0.52)	**0.0001**		-0.84 (-1.55; -0.13)	**0.02**
Categorical: <Q1		0			0	
Q1-Q2		-0.41 (-1.27; 0.45)	0.35		-0.26 (-1.31; 0.80)	0.63
Q2-Q3		-0.99 (-1.95; -0.04)	**0.04**		-0.41 (-1.61; 0.79)	0.50
≥Q3		-1.42 (-2.59; -0.25)	**0.02**		-1.46 (-2.98; 0.05)	0.06
$PM_{2.5}$	6542			3686		
Continuous (IQR) [a]		-1.93 (-2.97; -0.89)	**0.0003**		-2.24 (-3.44; -1.04)	**0.0002**
Categorical: <Q1		0			0	
Q1-Q2		-1.36 (-2.81; 0.10)	0.07		-0.89 (-2.46; 0.68)	0.27
Q2-Q3		-1.55 (-3.18; 0.08)	0.06		-0.95 (-2.78; 0.89)	0.31

≥Q3		-2.56 (-4.47; -0.65)	**0.01**		-2.61 (-4.86; -0.36)	**0.02**
PM_{10}	6111			3677		
Continuous (IQR) [a]		-2.61 (-3.73; -1.49)	**<.0001**		-1.96 (-3.20; -0.71)	**0.002**
Categorical: <Q1		0			0	
Q1-Q2		-1.33 (-2.52; -0.14)	**0.03**		-2.47 (-3.90; -1.03)	**0.001**
Q2-Q3		-3.11 (-4.58; -1.63)	**<.0001**		-2.87 (-4.56; -1.17)	**0.001**
≥Q3		-3.76 (-5.39; -2.12)	**<.0001**		-3.40 (-5.22; -1.59)	**0.0002**
NDVI	6542			3686		
Continuous (IQR) [a]		1.86 (1.14; 2.58)	**<0.0001**		0.23 (-0.66; 1.11)	0.62
Categorical: <Q1		0			0	
Q1-Q2		1.03 (0.08; 1.98)	**0.03**		0.69 (-0.44; 1.82)	0.23
Q2-Q3		1.85 (0.77; 2.92)	**0.001**		0.05 (-1.20; 1.30)	0.94
≥Q3		2.87 (1.72; 4.01)	**<0.0001**		0.80 (-0.51; 2.10)	0.23

[a] Beta were estimated for an increment of one IQR (NO_2: 13.8 µg/m³; $PM_{2.5}$: 8.3 µg/m³; PM_{10}: 14.6 µg/m³; NDVI: 0.3 unit). [b] Beta from mixed linear regression models to account for the multicentric design.

Tables E5. Associations between NDVI and the presence [a] to green space.

	ECRHS-II			ECRHS-III		
	n	**Median NDVI (q1-q3)**	**P value [b]**	**n**	**Median NDVI (q1-q3)**	**P value [b]**
Presence of urban green spaces	1639	0.21 (0.06-0.36)	<**0.0001**	966	0.22 (0.07-0.41)	**0.03**
No	1602	0.27 (0.12-0.37)		967	0.27 (0.14-0.38)	
Yes						
Presence of forests						
No	2259	0.15 (0.05-0.27)	<**0.0001**	1365	0.16 (0.07-0.29)	<**0.0001**
Yes	982	0.40 (0.32-0.48)		568	0.43 (0.36-0.49)	
Presence of agricultural land						
No	2081	0.14 (0.05-0.30)	<**0.0001**	1204	0.14 (0.06-0.29)	<**0.0001**
Yes	1160	0.34 (0.26-0.45)		729	0.39 (0.29-0.47)	

[a] presence of green spaces (of at least 1 ha) in a circular 300-m buffer around participant's home
[b] student t-tests

Table E6. Univariate associations between presence [a] to green space and health-related quality of life.

	ECRHS II			ECRHS III			ECRHS II + ECRHS III		
	n	**Beta [b] (95% IC)**	**P value**	**n**	**Beta [b] (95% IC)**	**P value**	**n**	**Beta [b] (95% IC)**	**P value**
PCS									
Presence of urban green spaces	3241	-0.86 (-1.58; -0.14)	**0.02**	1933	0.10 (-0.84; 1.04)	0.83	5174	-0.48 (-1.07; 0.12)	0.12
Presence of forests	3241	0.52 (-0.37; 1.42)	0.25	1933	0.78 (-0.39; 1.97)	0.19	5174	0.64 (-0.12; 1.40)	0.10
Presence of agricultural land	3241	0.97 (0.16; 1.77)	**0.02**	1933	0.97 (-0.07; 2.02)	0.07	5174	0.59 (-0.08; 1.26)	**0.08**
MCS									
Presence of urban green spaces	3241	-0.19 (-0.96; 0.59)	0.64	1933	-0.93 (-1.87; 0.01)	0.05	5174	-0.31 (-0.94; 0.31)	0.32
Presence of forests	3241	1.46 (0.48; 2.45)	**0.003**	1933	1.55 (0.33; 2.77)	**0.01**	5174	1.15 (0.35; 1.95)	**0.005**
Presence of agricultural land	32415	0.87 (-0.002; 1.75)	**0.05**	1933	0.99 (-0.08; 2.06)	0.07	5174	1.00 (0.29; 1.70)	**0.006**

[a] presence of green spaces (of at least 1 ha) in a circular 300-m buffer around participant's home. [b] Beta from mixed linear regression models to account for the multicentric design (and for the ECRHS-II + ECRHS-III longitudinal analyses to additionally account for the repeated data).

Table E7. Associations between exposure to air pollutants, greenspace and health-related quality of life adjusted on the minimal sufficient adjustment set (MSAS)

	n	Beta (95% CI) [a]	P value
PCS			
NO_2, continuous (IQR)	10228	0.40 (-0.08; 0.87)	0.19
$PM_{2,5}$, continuous (IQR)	10228	1.30 (0.57; 2.04)	0.0005
PM_{10}, continuous (IQR)	9788	0.72 (-0.13 ; 1.58)	0.10
NDVI, continuous (IQR)	10228	-0.21 (-0.75 ; 0.34)	0.45
MCS			
NO_2, continuous (IQR)	10228	-0.79 (-1.34 ; -0.25)	0.0042
$PM_{2,5}$, continuous (IQR)	10228	-1.90 (-3.00; -0.79)	0.0008
PM_{10}, continuous (IQR)	9788	-2.04 (-3.23; -0.85)	0.0008
NDVI, continuous (IQR)	10228	0.96 (0.36 ; 1.55)	0.002

[a] Beta were adjusted on sex, age, educational level, occupational status and urbanicity from mixed linear regression models to account for the multicentric design and the repeated data.

Table E8. Covariate-adjusted mediation analysis at ECRHS-II

Air pollutants	Mediator	PCS			
		ACME	ADE	TE	PM
NO_2	Chronic diseases	-0.06 (-0.21 ; 0.11)	0.22 (-0.38; 0.80)	0.17 (-0.47; 0.78)	-0.04 (-3.99; 2.59)
	Active	-0.03 (-0.07 ; 0.01)	0.18 (-0.46 ; 0.85)	0.15 (-0.49 ; 0.83)	-0.04 (-1.54 ; 0.93)
$PM_{2,5}$	Chronic diseases	-0.01 (-0.40 ; 0.39)	1.14 (0.09 ; 2.16) *	1.13 (0.06 ; 2.24) *	0.001 (-0.94 ; 0.49)
	Active	-0.07 (-0.15 ; -0.01) *	1.56 (0.37 ; 2.74) *	1.49 (0.28 ; 2.68) *	-0.04 (-0.22 ; 0.00) *
PM_{10}	Chronic diseases	-0.12 (-0.54 ; 0.34)	1.09 (-0.12 ; 2.36)	0.97 (-0.32 ; 2.31)	-0.08 (-2.59 ; 1.88)
	Active	-0.10 (-0.18 ; -0.03) *	1.29 (-0.03 ; 2.72)	1.20 (-0.13 ; 2.63)	-0.07 (-0.60 ; 0.37)
NDVI	Chronic diseases	0.08 (-0.12 ; 0.27)	-0.12 (-0.90 ; 0.65)	0.04 (-0.88 ; 0.75)	0.05 (-4.65 ; 5.10)
	Active	0.08 (0.02 ; 0.15) *	-0.03 (-0.83 ; 0.77)	0.05 (-0.76 ; 0.87)	0.08 (-2.74 ; 0.90)
		MCS			
		ACME	ADE	TE	PM
NO_2	Chronic diseases	-0.04 (-0.14 ; 0.07)	-0.67 (-1.35 ; 0.05)	-0.70 (-1.40 ; 0.01)	0.05 (-0.25 ; 0.38)
	Active	-0.02 (-0.06; 0.01)	-0.66 (-1.33; 0.03)	-0.68 (-1.36; 0.01)	0.02 (-0.04; 0.21)
$PM_{2,5}$	Chronic diseases	-0.004 (-0.25 ; 0.26)	-1.43 (-2.61 ; -0.21) *	-1.43 (-2.66 ; -0.19) *	0.006 (-0.49 ; 0.25)
	Active	-0.05 (-0.11 ; 0.00) *	-1.13 (-2.39 ; 0.09)	-1.18 (-2.44 ; 0.06)	0.03 (-0.16 ; 0.26)
PM_{10}	Chronic diseases	-0.09 (-0.39 ; 0.23)	-1.86 (-3.31 ; -0.43) *	-1.94 (-3.43 ; -0.52) *	0.04 (-0.18 ; 0.29)
	Active	-0.07 (-0.16 ; -0.01) *	-1.70 (-3.10 ; -0.28) *	-1.78 (-3.18 ; -0.36) *	0.04 (0.001 ; 0.19) *
NDVI	Chronic diseases	0.05 (-0.07 ; 0.17)	1.05 (0.18 ; 1.86) *	1.10 (0.20 ; 1.94) *	0.04 (-0.10 ; 0.26)
	Active	0.05 (0.001 ; 0.11) *	1.12 (0.26 ;1.99) *	1.17 (0.31 ;2.04) *	0.04 (0.001 ; 0.17) *

ACME: average causal mediation effect ; ADE: Average direct effect ; TE: Total effect ; PM : proportion mediated. Mixed linear regression models to account for the multicentric design are adjusted for age, sex, BMI, active smoking, second hand smoking, occupational status, educational level, season and urbanicity. Chronic disease (defined by arthritis, hypertension, varicose veins, heart disease, depression, diabetes, cancer, stroke, asthma, chronic cough or phlegm, chronic bronchitis or answered yes to the question "Do you have any long-term limiting illness"). Physical activity represents a combination of variables frequency and duration of physical activity into 2 categories: ≥2 times a week and ≥1 hour are considered active. *represents p value <0.05.

Table E9. Covariate-adjusted mediation analysis at ECRHS-III

Air pollutants	**Mediator**	**PCS**			
		ACME	**ADE**	**TE**	**PM**
NO_2	Chronic diseases	0.06 (-0.13 ; 0.26)	-0.03 (-0.84; 0.73)	0.03 (-0.78; 0.80)	0.07 (-3.18; 2.87)
	Physical activity	-0.05 (-0.15 ; 0.05)	0.14 (-0.64 ; 0.93)	0.10 (-0.69 ; 0.87)	-0.02 (-1.83 ; 2.08)
$PM_{2,5}$	Chronic diseases	0.003 (-0.25 ; 0.24)	0.42 (-0.69 ; 1.54)	0.42 (-0.71 ; 1.58)	0.03 (-2.15 ; 1.93)
	Physical activity	-0.19 (-0.33 ; -0.05) *	0.68 (-0.41 ; 1.80)	0.50 (-0.60 ; 1.61)	-0.24 (-3.59 ; 3.44)
PM_{10}	Chronic diseases	-0.17 (-0.46 ; 0.09)	0.09 (-1.07 ; 1.29)	-0.08 (-1.31 ; 1.20)	0.13 (-5.09 ; 6.39)
	Physical activity	-0.26 (-0.40 ; -0.13) *	0.29 (-0.85 ; 1.46)	0.03 (-1.15 ; 1.20)	-0.16 (-5.74 ; 5.96)
NDVI	Chronic diseases	0.001 (-0.23 ; 0.23)	-0.21 (-1.09 ; 0.71)	-0.21 (-0.12 ; 0.73)	0.05 (-2.53 ; 3.73)
	Physical activity	0.04 (-0.06 ; 0.15)	-0.33 (-1.24 ; 0.60)	-0.29 (-1.20 ; 0.66)	-0.03 (-1.26 ; 1.52)
		MCS			
		ACME	**ADE**	**TE**	**PM**
NO_2	Chronic diseases	0.04 (-0.08 ; 0.15)	-1.31 (-2.20 ; -0.34) *	-1.27 (-2.18 ; -0.29) *	-0.03 (-0.22 ; 0.07)
	Physical activity	-0.03 (-0.10; 0.03)	-1.28 (-2.21; -0.35) *	-1.30 (-2.24; -0.36) *	0.02 (-0.03; 0.11)
$PM_{2,5}$	Chronic diseases	0.003 (-0.15 ; 0.15)	-3.11 (-4.59 ; -1.71) *	-3.11 (-4.60 ; -1.68) *	-0.002 (-0.05 ; 0.05)
	Physical activity	-0.10 (-0.22 ; -0.01) *	-2.99 (-4.42 ; -1.54) *	-3.10 (-4.50 ; -1.63) *	0.03 (0.00 ; 0.09) *
PM_{10}	Chronic diseases	-0.11 (-0.29 ; 0.06)	-2.56 (-4.14 ; -0.91) *	-2.66 (-4.24 ; -0.97) *	0.04 (-0.03 ; 0.14)
	Physical activity	-0.14 (-0.26 ; -0.04) *	-2.50 (-4.11 ; -0.87) *	-2.65 (-4.26 ; -1.02) *	0.05 (0.01 ; 0.16) *
NDVI	Chronic diseases	0.001 (-0.14 ; 0.14)	0.49 (-0.51 ; 1.54)	0.49 (-0.52 ; 1.59)	0.001 (-0.98 ; 1.08)
	Physical activity	0.02 (-0.03 ; 0.09)	0.45 (-0.57 ; 1.51)	0.47 (-0.55 ; 1.52)	0.02 (-0.43 ; 0.67)

ACME: average causal mediation effect ; ADE: Average direct effect ; TE: Total effect ; PM : proportion mediated. Mixed linear regression models to account for the multicentric design are adjusted for age, sex, BMI, active smoking, second hand smoking, occupational status, educational level, season and urbanicity. Chronic disease (defined by arthritis, hypertension, varicose veins, heart disease, depression, diabetes, cancer, stroke, asthma, chronic cough or phlegm, chronic bronchitis or answered yes to the question "Do you have any long-term limiting illness"). Physical activity represents a combination of variables frequency and duration of physical activity into 2 categories: $\geq$2 times a week and $\geq$1 hour are considered active. *represents p value $<$0.05.

Table E10. Associations between exposure to air pollutants, greenspace and health-related quality of life adjusted on complete-case analysis

	n	Beta (95% CI) [a]	P value
PCS			
NO_2, continuous (IQR)	8753	0.24 (-0.26; 0.75)	0.34
$PM_{2,5}$, continuous (IQR)	8753	1.13 (0.32; 1.93)	0.01
PM_{10}, continuous (IQR)	8337	0.77 (-0.15 ; 1.68)	0.10
NDVI, continuous (IQR)	8753	-0.32 (-0.90 ; 0.25)	0.27
MCS			
NO_2, continuous (IQR)	8753	-0.82 (-1.41 ; -0.24)	0.006
$PM_{2,5}$, continuous (IQR)	8753	-2.05 (-3.19; -0.91)	0.0004
PM_{10}, continuous (IQR)	8337	-2.19 (-3.47; -0.90)	0.0009
NDVI, continuous (IQR)	8753	0.90 (0.25 ; 1.54)	0.006

[a] Beta were adjusted on age, sex, BMI, active smoking, second hand smoking, occupational status, educational level, season and urbanicity