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Ambient air pollution exposure and depressive symptoms: Findings from the French CONSTANCES cohort

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ABSTRACT

Background and Aim: Few studies have reported the association between air pollution exposure with different dimensions of depression. We aimed to explore this association across different dimensions of depressive symptoms in a large population.

Methods: Data from the enrollment phase of the French CONSTANCES cohort (2012–2020) were analyzed cross-sectionally. Annual concentrations of particulate matter with a diameter < 2.5 μm ($PM_{2.5}$), black carbon (BC), and nitrogen dioxide (NO_2) from the land-use regression models were assigned to the residential addresses of participants. Total depressive symptoms and its four dimensions (depressed affect, disturbed interpersonal relations, low positive affect, somatic complaints) were measured using Centre of Epidemiologic Studies Depression questionnaire (CES-D). We reported results of negative binomial regression models (reported as Incidence Rate Ratio (IRR) and 95 % confidence interval (CI) for an interquartile range (IQR) increase in exposure), for each pollutant separately. Stratified analyses were performed by sex, income, family status, education, and neighborhood deprivation.

Results: The study included 123,754 participants (mean age, 46.50 ± 13.61 years; 52.4 % women). The mean concentration of $PM_{2.5}$, BC and NO_2 were 17.14 μg/m^3 (IQR = 4.89), 1.82 10^{-5}/m (IQR = 0.88) and 26.58 μg/m^3 (IQR = 17.41) respectively. Exposures to $PM_{2.5}$, BC and NO_2 were significantly associated with a higher CES-D total (IRR = 1.022; 95 % CI = 1.002: 1.042, IRR = 1.027; 95 % CI = 1.013: 1.040, and IRR = 1.029; 95 % CI = 1.015: 1.042 respectively), and with depressed affect, and somatic complaints. For all pollutants, a higher estimate was observed for depressed affect. We found stronger adverse associations for men, lower-income participants, low and middle education groups, those living in highly deprived areas, and single participants.

Conclusion: Our finding could assist the exploration of the etiological pathway of air pollution on depression and also considering primary prevention strategies in the areas with air pollution.

1. Introduction

Mental illnesses are a leading cause of morbidity worldwide, accounting for 32.4 % of the total years lived with disability (Vigo et al. 2016). Major depression, as the leading cause of mental illness burden, is associated with huge direct and indirect costs including increased risk of cardiovascular disease (Hare et al. 2014), stroke (Williams 2005), diabetes (Knol et al. 2006), obesity (Blasco et al. 2020), premature mortality (Meng et al. 2020), impaired quality of life (Cho et al. 2019) and loss of human capital (Herrman et al. 2019; Hu 2004; Penninx et al.

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2013). Depressive symptoms include low mood and loss of pleasure in everyday activities beyond typical negative emotions of an individual, but also somatic complaints such as fatigue or loss of appetite, which could be manifesting as clinical depression (Ayuso-Mateos et al. 2010; Fergusson et al. 2005). A wide range of social, emotional, familial, biological, and environmental factors are thought to contribute to the onset of depressive symptomatology and depression (van den Bosch and Meyer-Lindenberg 2019).

Environmental exposures including air pollution have been suggested to be associated with brain aging and mental health, particularly both depressive symptoms and depressive disorders- henceforth referred to as depression (Braithwaite et al. 2019; Fan et al. 2020; Rautio et al. 2018; Russ et al. 2015; van den Bosch and Meyer-Lindenberg 2019). Yet the relationships between depression and air pollutants remain unclear. A *meta*-analysis reported a statistically significant elevated risk of depression associated with long-term exposure to particulate matter with an aerodynamic diameter<2.5 μm ($PM_{2.5}$) (Braithwaite et al. 2019). However, another *meta*-analysis found a significant increase in the risk of depression associated with exposure to nitrogen dioxide (NO_2), but not to $PM_{2.5}$ (Fan et al. 2020).

In addition to the inconsistencies between different pollutants, some studies conducted at different locations failed to replicate the findings for the same pollutant (Zijlema et al. 2016). For example, in two general population-based European cohorts, contradictory estimated associations were found between ambient NO_2 and depressed mood (*i.e.* odds ratio: 1.34; 95 % Confidence Interval [CI]: 1.17, 1.53 per 10 $\mu g/m^3$ in Lifeline cohort, versus odds ratio: 0.79; 95 % CI: 0.66, 0.94 per 10 $\mu g/m^3$ in the HUNT cohort). Furthermore, depression encompasses various dimensions of symptoms (e.g. low mood, cognitive complaints, somatic symptoms) that may differently relate to air pollution exposure, but to the best of our knowledge, nearly all of the available studies reported associations of air pollution exposure with total depressive symptoms, and rarely with the different dimensions of the depression (Lim et al. 2012). Moreover, some evidence shows that different dimensions of depression might originate from different causes (Smith et al. 2008) and that some particular symptom dimensions might predict poor outcomes with antidepressant treatments (Uher et al. 2012). Therefore, considering multidimensionality in the assessment of the association between air pollution exposure and depression could assist the exploration of the etiological pathway of air pollution on depression and also choosing better pharmacological and/or psychological treatment approaches in the areas with air pollution (Smith et al. 2008).

More than half of the world population is currently living in urban areas and it is projected that by 2050, this will increase to almost two-thirds (de Keijzer et al. 2016). Urban areas are characterized by a network of non-natural built-up infrastructures with modern transportation systems, traffic, and higher air pollution which has been considered a risk factor for depression (Shanahan et al. 2014). In the context of the CONSTANCES, a large cohort of adults living in metropolitan France, we aimed to: a) replicate the previous findings on the association between air pollution exposure and depressive symptoms; b) if such an association is confirmed, assess which dimensions of depression are particularly concerned, and c) test the robustness of the findings according to different residential area and populations.

2. Materials and methods

2.1. Study population

The French CONSTANCES cohort is a large general population-based study launched in 2012 in 22 health screening centers located in 20 "départements" of France (hereafter referred to as recruitment centers). Between 2012 and 2020, the cohort enrolled a sample of 220,000 adults aged 18–69 randomly selected from those 20 recruitment centers, distributed over a large area of metropolitan France with various environments, from highly urban to mostly rural areas (Zins et al. 2010; Zins and Goldberg 2015). At enrollment, a wide range of data such as demographic, socioeconomic, life events, occupational factors, and anthropometric data were collected using questionnaires and a comprehensive health examination. We removed participants with a missing value in any one of the domain scores (n = 35,428). Additionally, from 167,246 remaining participants, the geocoding was not available at the time of this study for 43,492 participants who were consequently removed from the study. Therefore, we finally included 123,754 participants with available data at the time of the analyses on depressive symptoms and air pollution exposure assigned at a residential address (Fig. 1).

Data collection within CONSTANCES obtained authorization from the French National Commission for Information Technology and Liberties (CNIL) and the institutional review board of the National Institute for Medical Research (Inserm). All participants have given written consent for the use of their data for scientific research.

2.2. Outcomes

Depressive symptoms were evaluated with the self-administered Centre of Epidemiologic Studies Depression questionnaire (CES-D). The CES-D is a 20-item scale developed by Radloff in 1977 and evaluates the frequency of depressive symptoms such as restless sleep, poor appetite, and feeling lonely during the previous week (each item with four options scoring from 0 to 3; 0 = rarely or none of the time, 1 = some or little of the time, 2 = moderately or much of the time, 3 = most or almost all of the time) (Radloff 1977). Various scores were derived: (i) a CES-D total score with a maximum value of 60, (ii) dimension-specific scores for each of the four dimensions including depressed affect (e.g., sadness, loneliness), disturbed interpersonal relationships, low positive affect, and somatic complaints (e.g., fatigue, loss of appetite, restless sleep) (Hays et al. 1998). Higher CES-D total or dimension-specific scores indicate a higher risk of major depression. The CES-D has a very good internal consistency ($\alpha = 0.90$ in the CONSTANCES cohort) (Hoven et al. 2019). In this study, we used CES-D total and dimensions scores measured at enrollment time as the main outcome. Additionally, we used CES-D total score ≥ 19 as a validated threshold for the definition of elevated depressive symptoms (according to the validated cut-off for the French version) to identify individuals at risk for clinical depression (sensitivity/specificity: 0.85/0.86) (Morin et al. 2011).

2.3. Air pollution exposure

For air pollution exposures assessment, we used the results of the ELAPSE models (hybrid land-use regression models developed for western Europe) (de Hoogh et al. 2018). The models were developed using different data sources including monitoring data, satellite remote sensing data, results of chemical transport model, and land traffic data. Annual average concentrations of air pollutants including PM2.5 (543 sites), black carbon (BC; 436 sites measured in Escape project (Eeftens et al. 2012)), and NO2 (2399 sites) in 2010 were modeled at 100 × 100 m spatial resolution by a supervised stepwise linear regression method. BC concentration was measured as the absorbance measurement of the PM2.5 samples filters. Annual average PM2.5 dataset at ~ 10 km resolution for 2010 was produced using satellite remote sensing data of MODIS Aerosol Optical Depth, MISR (Multi-angle Imaging Spectroradiometer), and SeaWiFS instruments. Considering no satellite product for BC, and because BC is a component of PM2.5, PM2.5 satellite data were used for BC. For NO2, Aura satellite data were used. Annual average concentrations of the pollutants were also calculated by long-range chemical transport models (MACC-II ENSEMBLE model for PM2.5, NO2; and Danish Eulerian Hemispheric Model for PM2.5, NO2, and BC). The exposure modeling team also extracted land use, roads, and population data by the Geographic Information System (GIS) for 2011 and entered into the model. Finally, a two-stage statistical procedure was applied (first: standard land use regression models using

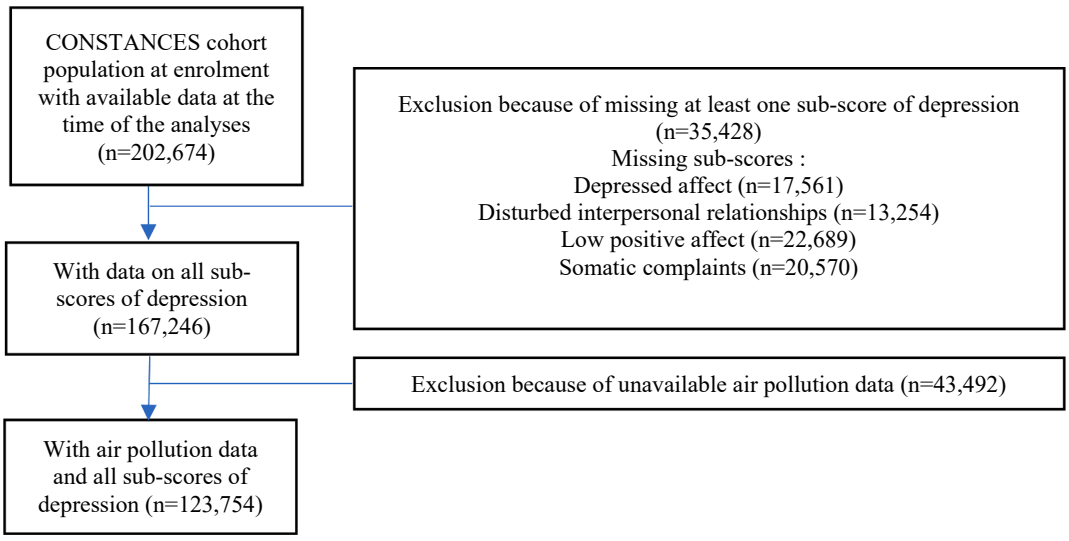

Fig. 1. Study participants selection flowchart.

supervised stepwise linear regression based on all measurements for each pollutant to explain the spatial variation; second: exploring remaining broad-scale variation in the residuals using only the urban and rural background sites). The final models were mapped at a 100 × 100 m resolution across the study area. The models explained 66.4 % (PM2.5), 51.4 % (BC), and 57.5 % (NO2) of the spatial variation (based on hold-out validation R^2) of the pollutant's concentrations across Europe. The estimated concentrations for 2010 were assigned to each participant's residential address recorded at the year of enrollment into the study. If the participant had several recorded addresses at that year, concentrations were averaged from each location.

2.4. Covariables

Variables at the individual-level (sociodemographic, anthropometric, health-related behavioral, and clinical risk factors, temporal variables related to the timing of the assessments), and area-level (contextual variables such as neighborhood deprivation, classification of the commune of residence, and recruitment center) were included in the models or used for stratified and sensitivity analyses. Covariables in the models were selected based on prior knowledge, considering risk factors of depressive symptoms including demographic and life achievement, health behaviors, comorbid chronic diseases, and perceived health status (George 1996; Hays et al. 1998). Individual-level sociodemographic covariables include age, sex, education (<5 years of education, 5–12 years of education, or more than 12 years of education), family status (married or in a civil partnership, widow, separated, or unmarried) and monthly household income (high/low income, with a cut-off at 2100 euros per month).

Body mass index (BMI; obtained by dividing weight in kilograms per the squared height of participant in meters, and categorized into four groups of underweight: BMI $<$ 18.5, normal: 18.5 $\leq$ BMI $<$ 25, overweight: 25 $\leq$ BMI $<$ 30, obese: BMI $\geq$ 30) was included as an individual-level anthropometric covariable.

Smoking status (non-smoker, ex-smoker, or current smoker), alcohol drinking habits (based on Alcohol Use Disorders Identification Test (AUDIT) classification in four groups: abstinent, neither abuse nor dependence, abuse, or dependence) (Saunders et al. 1993), and non-occupational physical activity (based on a questionnaire measuring frequency and intensity of different activities scored from 0 to 6; zero indicates physically inactive people, and six indicates highly physically active people) were considered as health-related behavioral variables.

Individual-level clinical risk factors include self-report diagnosis of cardiovascular diseases (CVDs; defined as a positive answer to the question "having angina pectoris, myocardial infarction, arthritis of the lower limbs, or other CVDs?"), history of diagnosed, or medically traded type-2 diabetes (including a positive answer to self-reported medical diagnosis of type-2 diabetes, or blood glucose level above 110 mg/dL), hypertension (defined based on a: the self-reported medical diagnosis of hypertension, b: measurements in paraclinical examinations [systolic blood pressure greater than 140 mmHg or/and diastolic blood pressure greater than 90 mmHg], or c: treated with antihypertensive medication according to the French national health data system [SNDS]), and perceived health status (scored 1–8, the higher values represent poorer perceived health status).

Temporal variables were the month (to account for the association between season and depression), and the day of the week of completion of the questionnaire by the participants.

Area-level covariables include participants' classification of their commune of residence (classified into four groups of urban, suburban, isolated cities, and rural) based on the continuity of the building and the number of inhabitants, provided by the INSEE (the French National Institute of Statistics and Economic Studies), and the French deprivation index as a measure of neighborhood deprivation (entered as a continuous variable in the models). The French deprivation index is a community-level construct based on census-derived median household income, percentage of high school graduates, percentage of blue-collar workers, and unemployment rate (Temam et al. 2017).

2.5. Statistical approach

The percentage of missing values of the selected covariables ranged between zero and 6.6 %, with the highest for income (6.6 %), alcohol drinking habits (5.9 %), and smoking status (3.3 %). We used multiple imputations to construct five imputed datasets (with five iterations), using the mice package in R (van Buuren and Groothuis-Oudshoorn 2010). In addition to the covariables used in the models, to improve the accuracy of the imputed datasets we also included auxiliary variables (family status, hypertriglyceridemia, and hypertension) that were not included in the models, but had the potential to be predictors of missingness and/or the variable with missing data in the imputation model. The density plots of the imputed variables were visually checked to assess the acceptance of the imputation.

We performed negative binomial models and reported the adjusted regression incidence rate ratios (IRR) and 95 % CIs for each pollutant separately. The associations were expressed as one unit change in the CES-D total and dimensions scores per an interquartile range (IQR) increase in exposure to air pollution. We constructed a Directed Acyclic

Graph (DAG) according to the available literature, and defined three different models according to the level of adjustment (**Figure S1**). The parsimonious model (hereafter *model 1*) was adjusted for age, sex, and recruitment centers. The second model (hereafter *model 2*) was additionally adjusted for income, education, alcohol drinking habits, smoking status, area-level deprivation, the month, and the day of the week of completion of the questionnaires. The third model (hereafter *model 3*) was adjusted additionally for possible mediators specifically BMI, non-occupational physical activity, perceived health status, CVDs, and type-2 diabetes.

To estimate the shape of the exposure–response association between exposure to each air pollutant and CES-D total and dimensions scores, we did exposure–response analyses using regressions with restricted cubic spline functions (Desquilbet and Mariotti 2010). We tested the assumption of linearity of the associations by the likelihood ratio test on the difference between models with linear versus spline terms.

The models for the main analysis were run on the multiple imputed datasets, and model parameters were estimated in each imputed dataset separately. Estimates were combined using Rubin's rules and pool function.

2.6. Stratified analyses

Different personal and contextual variables may modify the association between air pollution exposure and depression (Fan et al. 2020). We performed stratified analyses to identify effect modifiers for the following variables: classification of the commune of residence, sex, education (recategorized into: less than or equal to 12 years of education defined as low and middle education, or more than 12 years of education defined as high education), family status, smoking status, alcohol drinking habits, income, neighborhood deprivation (categorized in three groups based on the tertiles of French deprivation index), CVDs, and type-2 diabetes. To reduce the number of reported analyses, we only displayed stratified analyses when the p-value of the interaction (based on a likelihood ratio test) was below 0.1.

2.7. Sensitivity and additional analyses

To check the robustness of our findings we did several sensitivity analyses. As we found a high interclass correlation for pollutants across the recruitment centers (data are not shown), we applied a multilevel modeling approach by including a random effect for the recruitment centers. We did additional analyses using a complete case dataset (dataset without imputation), and excluding participants living in Paris (because of higher exposure to air pollution, and also higher education compared to the rest of the participants). As the air pollution models in this study were for 2010, and outcome measurements were done between 2012 and 2020, in another sensitivity analysis, we included the enrollment year as a covariate in model 2 (enrollment year was used as a categorical variable, and 2012 was considered as a reference), and additionally tested for an interaction term between air pollution and enrollment year with a likelihood ratio test. In another sensitivity analysis, we also restricted the population to those who did not report any history of depression requiring a treatment, or did suicide attempt.

3. Results

The study population in this analysis included 123,754 of CONSTANCES cohort participants (mean age at enrollment ± standard deviation [SD]: 46.50 ± 13.61 years), of whom 52.4 % (n = 64,804) were women (Table 1). There was no difference between included participants in this study and the whole CONSTANCES cohort participants (**Table S1**). Most of the included participants had more than 12 years of education (59.2 %), and were residents of urban and suburban areas (75.4 %). The average exposure to $PM_{2.5}$, BC, and NO_2 was 17.14 μg/m^3 (IQR = 4.89), 1.82 10^{-5}/m (IQR = 0.88), and 26.58 μg/m^3 (IQR = 17.41) respectively. Strong and significant positive correlations were found between $PM_{2.5}$, BC, and NO_2 (Pearson's correlation coefficient ranged from 0.85 to 0.95), with the highest observed correlation between NO_2 and BC (Pearson's correlation coefficient: 0.95). The median CES-D total score (IQR) was 9 (10) (7 (9) in men and 10 (11) in women). The prevalence of elevated depressive symptoms (based on CES-D score ≥ 19 as a cut-off) was 21.9 %, which was higher in women than in men (26.7 % vs 16.7 %). Additionally, women's scores in all dimensions of depressive symptoms were significantly higher than men's (Table 1). Among the selected comorbidities, hypertension and CVDs were the most frequent (prevalence of 28.9 % and 6.8 % respectively).

3.1. Main findings

Findings for parsimonious models were suggestive for increased risk especially for BC and NO_2(Table 2). With additional adjustment (model 2), the findings for BC and NO_2 were suggestive of an association for CES-D total, depressed affect, and somatic complaints scores (the estimates were similar for BC and NO_2), with the largest associate estimates observed for depressed affect. In model 2, the results of $PM_{2.5}$ were only significant for CES-D total and depressed affect (IRR = 1.022; 95 % CI: 1.002: 1.042; IRR = 1.061; 95 % CI: 1.024: 1.100). After additional adjustment for potential mediators (model 3), again the findings for all three pollutants were significantly associated with worse CES-D total, depressed affect, and somatic complaints scores.

Using the total CES-D score as a binary variable based on a validated threshold, we also found a significant increase in odds of having depressive symptoms with an IQR increase in exposure to all pollutants in the parsimonious models and the adjusted models (for example in model 2: OR: 1.082; 95 % CI: 1.018: 1.150 for $PM_{2.5}$, OR: 1.080; 95 % CI: 1.038: 1.123 for BC, and OR: 1.078; 95 % CI: 1.036: 1.121 for NO_2).

Exposure-response analyses (with cubic spline function) showed a non-linear association only for depressed affect with exposure to BC and NO_2 but not for $PM_{2.5}$ (Fig. 2) (p-value = 0.153 for $PM_{2.5}$; p-value = 0.011 for BC; p-value = 0.013 for NO_2). For the highest third of concentrations of air pollution, the exposure–response association between depressed affect and all air pollutants showed a plateau pattern. However, the number of observations in this region was limited (are shown as rugs in Fig. 2), and the estimations have wide confidence intervals.

3.2. Stratified analyses

Interaction p-values for urbanicity were above 0.1 so no stratification was done on it. We found a significantly stronger adverse association between exposure to different air pollutants in men, those with low and middle education, low income, higher neighborhood deprivation, and those who were not married or in partnership (Fig. 3).

3.3. Sensitivity analyses

Considering recruitment centers as a clustering variable, the results of multilevel models were relatively similar (IRR of ~ 1.02–1.03 vs ~ 1.03–1.04 for multilevel models) (Table 3). Using a complete case dataset or excluding participants from the two Paris centers gave similar associations to those of the main analyses. After inclusion of the enrollment year as a covariate in model 2, we found similar results compared to model 2 without the enrollment year (Table 3, **Table S2**). Additionally, all interaction terms with air pollution had p-values above 0.05 except for somatic complaints (p-values = 0.046 and 0.041 for PM2.5 and NO2 respectively) (**Table S3**). Taking the year 2012 as reference, the associations were weaker for participants who were enrolled in 2014 and 2017. However, no decreasing trend was observed according to the enrollment year. Restricting the population to the participants who did not report any history of depression requiring a treatment or suicide attempt (n = 102,146), we found similar results (**Table S4**).

Table 1
Characteristics of the French CONSTANCES cohort participants included in this study (n = 123,754).

Variable	Men (N = 58,950)	Women (N = 64,804)	Total (N = 123,754)	p value
Age (years)	47.36 (13.53)	45.70 (13.64)	46.50 (13.61)	< 0.001
Missing	*0.0 %*	*0.0 %*	*0.0 %*	
Years of education				< 0.001
<5 years	1752 (3.0 %)	1392 (2.2 %)	3144 (2.6 %)	
5–12 years	23,852 (40.9 %)	22,953 (35.8 %)	46,805 (38.2 %)	
13 and more years	32,682 (56.1 %)	39,840 (62.1 %)	72,522 (59.2 %)	
Missing	*1.1 %*	*1.0 %*	*1.0 %*	
Family status				< 0.001
Unmarried	16,220 (27.9 %)	19,168 (29.9 %)	35,388 (29.0 %)	
Partnership or married	36,114 (62.1 %)	36,032 (56.2 %)	72,146 (59.0 %)	
Separated or divorced	5268 (9.1 %)	7318 (11.4 %)	12,586 (10.3 %)	
Widow	537 (0.9 %)	1547 (2.4 %)	2084 (1.7 %)	
Missing	*1.4 %*	*1.1 %*	*1.3 %*	
Country of origin (not France)	5592 (9.6 %)	5611 (8.8 %)	11,203 (9.2 %)	< 0.001
Missing	*1.3 %*	*1.6 %*	*1.4 %*	
BMI† (kg/m^2)	25.57 (3.96)	24.32 (4.74)	24.91 (4.43)	< 0.001
Missing	*2.0 %*	*1.8 %*	*1.9 %*	
Income (<2100 euro/month)	11,245 (20.2 %)	14,904 (24.8 %)	26,149 (22.6 %)	< 0.001
Missing	*5.8 %*	*7.4 %*	*6.6 %*	
Alcohol drinking habits				< 0.001
Abstinent	1445 (2.6 %)	2938 (4.9 %)	4383 (3.8 %)	
No abuse or dependence	38,650 (68.9 %)	46,634 (77.3 %)	85,284 (73.3 %)	
Abuse	11,696 (20.8 %)	8854 (14.7 %)	20,550 (17.7 %)	
Dependent	4326 (7.7 %)	1885 (3.1 %)	6211 (5.3 %)	
Missing	*4.8 %*	*6.9 %*	*5.9 %*	
Smoking status				< 0.001
No-smoker	23,919 (42.0 %)	32,322 (51.6 %)	56,241 (47.0 %)	
Smoker	11,507 (20.2 %)	11,576 (18.5 %)	23,083 (19.3 %)	
Former smoker	21,553 (37.8 %)	18,748 (29.9 %)	40,301 (33.7 %)	
Missing	*3.3 %*	*3.3 %*	*3.3 %*	
Non-occupational physical activity††	3.45 (1.54)	3.49 (1.49)	3.47 (1.51)	< 0.001
Missing	*1.9 %*	*2.5 %*	*2.2 %*	
Hypertension (yes)	22,259 (37.8 %)	13,429 (20.7 %)	35,688 (28.9 %)	< 0.001
Missing	*0.1 %*	*0.1 %*	*0.1 %*	
Self-reported CVDs† (yes)	4593 (8.0 %)	3646 (5.8 %)	8239 (6.8 %)	< 0.001
Missing	*2.6 %*	*2.6 %*	*2.6 %*	
Type-2 diabetes (yes)	3036 (5.2 %)	1636 (2.5 %)	4672 (3.8 %)	< 0.001
Missing	*0.1 %*	*0.1 %*	*0.1 %*	
Perceived health status†††	2.76 (1.20)	2.76 (1.22)	2.76 (1.21)	0.688
Missing	*3.1 %*	*3.2 %*	*3.3 %*	
Neighborhood deprivation				0.098
Low	19,765 (33.5 %)	21,899 (33.8 %)	41,664 (33.7 %)	
Middle	19,391 (32.9 %)	21,437 (33.1 %)	40,828 (33.0 %)	
High	19,786 (33.6 %)	21,463 (33.1 %)	41,249 (33.3 %)	
Missing	*0.0 %*	*0.0 %*	*0.0 %*	
Classification of the commune of residence				0.225
Urban	25,491 (43.2 %)	28,024 (43.2 %)	53,515 (43.2 %)	
Suburban	18,903 (32.1 %)	20,900 (32.3 %)	39,803 (32.2 %)	
Isolated city	4021 (6.8 %)	4261 (6.6 %)	8282 (6.7 %)	
Rural	10,535 (17.9 %)	11,618 (17.9 %)	22,153 (17.9 %)	
Missing	*0.0 %*	*0.0 %*	*0.0 %*	
CES-D† total score	9.35 (8.01)	11.79 (9.32)	10.63 (8.80)	< 0.001
Depressed affect	1.86 (3.00)	3.00 (3.76)	2.46 (3.47)	< 0.001
Disturbed interpersonal relationships	0.36 (0.83)	0.47 (0.95)	0.42 (0.90)	< 0.001
Low positive affect	3.95 (3.16)	4.19 (3.11)	4.08 (3.14)	< 0.001
Somatic complaints	3.18 (3.10)	4.13 (3.45)	3.68 (3.32)	< 0.001
Having depressive symptoms (CES-D ≥ 19)	9838 (16.7 %)	17,294 (26.7 %)	27,132 (21.9 %)	< 0.001
$PM_{2.5}$ ($\mu g/m^3$)	17.13 (3.35)	17.14 (3.35)	17.14 (3.35)	0.568
Black carbon ($10^{-5}/ m^3$)	1.82 (0.59)	1.82 (0.59)	1.82 (0.59)	0.370
NO_2 ($\mu g/m^3$)	26.56 (12.34)	26.60 (12.34)	26.58 (12.34)	0.297

Note:
For the continuous variables, the values are mean (standard deviation).
For the categorical variables, the values are n (%).
For CESD, CESD dimensions and air pollutants inclusion criteria were no missing data, therefore, there was no missing for these variables.
†: BMI: Body Mass Index; CVDs: Cardiovascular Diseases; CES-D: Center for Epidemiologic Studies Depression Scale.
††: Non-occupational physical activity: scored 0–6. Higher values represent higher non-occupational physical activity.
†††: Perceived health status: scored 1–8; Higher values represent poorer perceived health status.

Table 2
Results of negative binomial regression for the association between exposure to air pollution and depressive symptoms (based on CES-D total score and its four dimensions) (n = 123,754). All results are based on an interquartile range (IQR) increase in the exposure to air pollution ($PM_{2.5}$ IQR = 4.89 μg/m^3, black carbon IQR = 0.8810^{-5}/m, and NO_2 IQR = 17.41 μg/ m^3).*

Outcome	Model	$PM_{2.5}$	Black carbon	NO_2
CES-D total score				
	Model 1	**1.053 (1.033: 1.075)**	**1.062 (1.049: 1.076)**	**1.065 (1.051: 1.079)**
	Model 2	**1.022 (1.002: 1.042)**	**1.027 (1.013: 1.040)**	**1.029 (1.015: 1.042)**
	Model 3	**1.024 (1.005: 1.043)**	**1.026 (1.013: 1.038)**	**1.028 (1.015: 1.040)**
Depressed affect				
	Model 1	**1.134 (1.094: 1.175)**	**1.154 (1.128: 1.181)**	**1.156 (1.130: 1.183)**
	Model 2	**1.061 (1.024: 1.100)**	**1.078 (1.054: 1.103)**	**1.080 (1.055: 1.105)**
	Model 3	**1.066 (1.031: 1.103)**	**1.077 (1.054: 1.102)**	**1.080 (1.056: 1.104)**
Disturbed interpersonal relationships				
	Model 1	1.038 (0.983: 1.096)	**1.058 (1.022: 1.095)**	**1.074 (1.037: 1.112)**
	Model 2	1.008 (0.955: 1.064)	1.016 (0.980: 1.053)	1.032 (0.996: 1.070)
	Model 3	1.013 (0.961: 1.069)	1.015 (0.980: 1.051)	1.030 (0.994: 1.066)
Low positive affect				
	Model 1	1.018 (0.998: 1.039)	**1.027 (1.013: 1.040)**	**1.029 (1.015: 1.042)**
	Model 2	1.005 (0.985: 1.025)	1.012 (0.998: 1.025)	1.012 (0.999: 1.026)
	Model 3	1.005 (0.086: 1.024)	1.012 (0.999: 1.025)	1.012 (0.999: 1.025)
Somatic complaints				
	Model 1	**1.047 (1.025: 1.071)**	**1.049 (1.034: 1.064)**	**1.050 (1.035: 1.065)**
	Model 2	1.022 (0.999: 1.044)	**1.016 (1.002: 1.031)**	**1.019 (1.004: 1.033)**
	Model 3	**1.022 (1.002: 1.044)**	**1.014 (1.001: 1.028)**	**1.016 (1.003: 1.030)**
Dichotomous CES-D				
	Model 1	**1.162 (1.095: 1.232)**	**1.174 (1.132: 1.219)**	**1.171 (1.128: 1.216)**
	Model 2	**1.082 (1.018: 1.150)**	**1.080 (1.038: 1.123)**	**1.078 (1.036: 1.121)**
	Model 3	**1.089 (1.021: 1.160)**	**1.083 (1.040: 1.129)**	**1.078 (1.034: 1.124)**

Note:
Bold estimates are significant at 0.05 level.
*: All the associations are presented as the incidence rate ratio in negative binomial regression (IRR and 95 % confidence interval), except for dichotomous CES-D section which are the odds ratio (OR) (95 % confidence interval) from logistic regression. CES-D total score ≥ 19 was considered as a validated threshold for the definition of dichotomous depressive symptoms.
Model 1: adjusted for age, sex and center of recruitment.
Model 2: adjusted for age, sex, education, income, alcohol drinking habits, smoking status, neighborhood deprivation, the month of completion of the questionnaire, day of the week of completion of the questionnaire, and recruitment center.
Model 3: in addition to the variables in model 2, is adjusted for body mass index, non-occupational physical activity, perceived health status, self-reported cardiovascular diseases, and type-2 diabetes.

4. Discussion

In this study on the French adult population, we found significantly higher depressive symptoms - according to the widely-used CES-D total score - associated with exposure to $PM_{2.5}$, BC, and NO_2. Examining this association within different dimensions of depressive symptoms, we found a robust association between exposure to air pollution and depressed affect and somatic complaints (for $PM_{2.5}$, BC, and NO_2). However, for the two other dimensions (disturbed interpersonal relationships, and low positive affect) our findings were only significant for the parsimonious model for BC and NO_2 but not with other models. We found stronger associations between air pollution exposure and depressive symptoms in men, those with low income, lower education, and those who were not married nor in a civil partnership.

Major depression is associated with impaired productivity (Bodden et al. 2018), increased risk of diseases (Hare et al. 2014; Herrman et al. 2019; Meng et al. 2020; Zhang et al. 2018), and elevated mortality rate (Gilman et al. 2017). Both short and long-term exposures to air pollution have been reported to be associated with depressive symptoms (Braithwaite et al. 2019; Wang et al. 2014). Overall, our findings on three major air pollutants are in line with accumulating body of evidence on the significant association between air pollution exposure and depressive symptoms (Lim et al. 2012; Vert et al. 2017; Wang et al. 2020). Our study provided additional evidence on this association with long-term exposure, in a large sample size of adults with robust exposure assessment, especially for BC, in which the available evidence is quite small. We found the most robust associations for BC and NO_2, and not $PM_{2.5}$. The discrepancy between the associations (based on the type of pollutant) already has been reported in previous studies (Lim et al. 2012; Pun et al. 2017). Possible explanations for $PM_{2.5}$ compared to other pollutants (weaker associations in terms of wider confidence intervals and non-persistent findings across different levels of adjustment) could be related to the relatively small exposure contrast ($PM_{2.5}$ IQR: 4.89 vs NO_2 IQR: 17.41) or exposure misclassification because of the different chemical composition and source of the particulate matter in different regions (Weber et al. 2018). Particulate matter with similar mass concentration, but emitted by different sources would include different components with different toxicological properties (Adams et al. 2015). BC and NO_2 are mainly from the common sources of outdoor air pollution such as traffic and combustion-related sources. However, for $PM_{2.5}$, other sources such as sea salt, or soil dust resuspension including Saharan dust, can introduce heterogeneity in the chemical composition of the particles.

In this study, we separately reported results for the CES-D total score and its dimensions, which is novel compared to previous studies. Our results showed that exposure to air pollution is associated with different

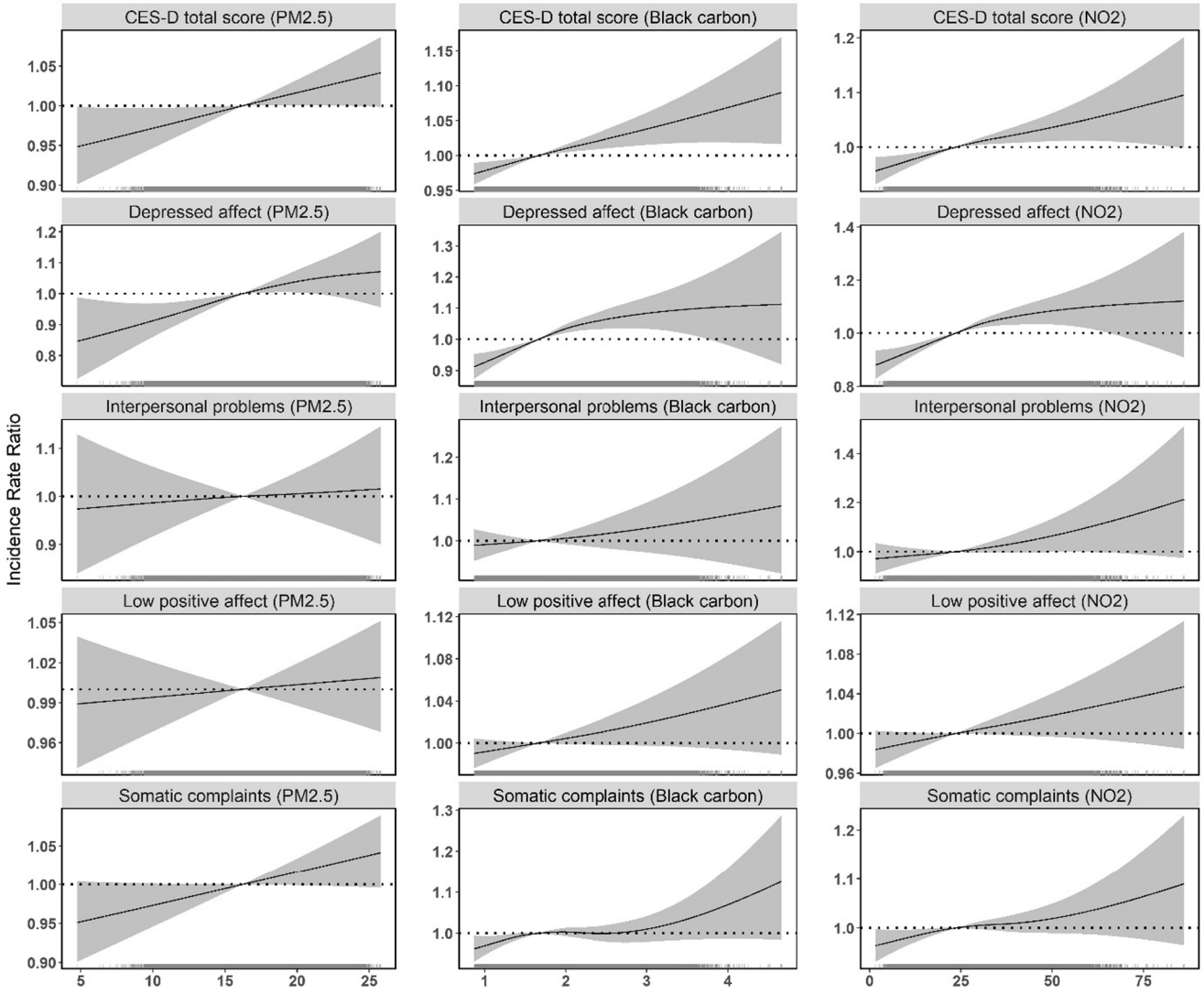

Fig. 2. Exposure-response association between exposure to air pollution and CES-D total score and its four dimensions (n = 123,754). All the associations are based on model 2 (adjusted for age, sex, income, education, alcohol drinking habits, smoking status, area-level deprivation, the month, and the day of the week of completion of the questionnaires and recruitment center) applied to one imputed dataset. The X-axis in all plots is pollutant concentration (for $PM_{2.5}$ and NO_2 in μg/m^3; and for black carbon in 10 $^{-5}$/m). Y-axis in all plots is a negative binomial regression coefficient (adjusted β) for one unit increase in value of the outcomes (for $PM_{2.5}$ and NO_2 is 1 μg/m^3; and for black carbon is 1 10 $^{-5}$/m).

dimensions of depressive symptoms, especially depressed affect, and somatic complaints in addition to total depressive symptoms. A similar study on the Korean population found that negative emotions were more likely to be associated with air pollution exposure than somatic complaints or negative thoughts (Lim et al. 2012). In general, somatic complaints of depression describe physiological symptoms such as fatigue, loss of appetite, and restless sleep (Radloff 1977). Importantly, depressed affect is more specific to depression than somatic complaints that may be shared with other non-psychiatric conditions (Radloff 1977). Therefore, our results suggest that the association between air pollution and depressive symptoms is not explained solely by somatic symptoms. We did not find a similar study on comparable population or outcome measurement for our finding on somatic complaints, however available evidence on the association between exposure to air pollution and poor sleep quality (Zanobetti et al. 2010) and general health perception (Klompmaker et al. 2019) could partly support our findings.

Our findings on the stronger association in men, participants with low and middle education (compared to those with high education), lower income, living in highly deprived areas, and participants not married nor in a civil relationship have been reported in other studies (Kim et al. 2020; Pun et al. 2017). While several biological mechanisms, including hormone-related ones have been suggested to explain differences between men and women in regards to air pollution health effects (Costa et al. 2014; Giordano et al. 2013; Thilakaratne et al. 2020), they are still not conclusive as some suggest greater effects in men and other in women (Kim et al. 2020; Pun et al. 2017; Li et al. 2022; Szyszkowicz 2007). Few other studies also reported no gender difference (Wei et al. 2020). Discrepancies in the literature could also be explained by differences in behavioral or socioeconomic factors that could influence exposure precisions.

Generally, depression could affect more deprived groups. Living in more deprived areas has been reported to be associated with a higher

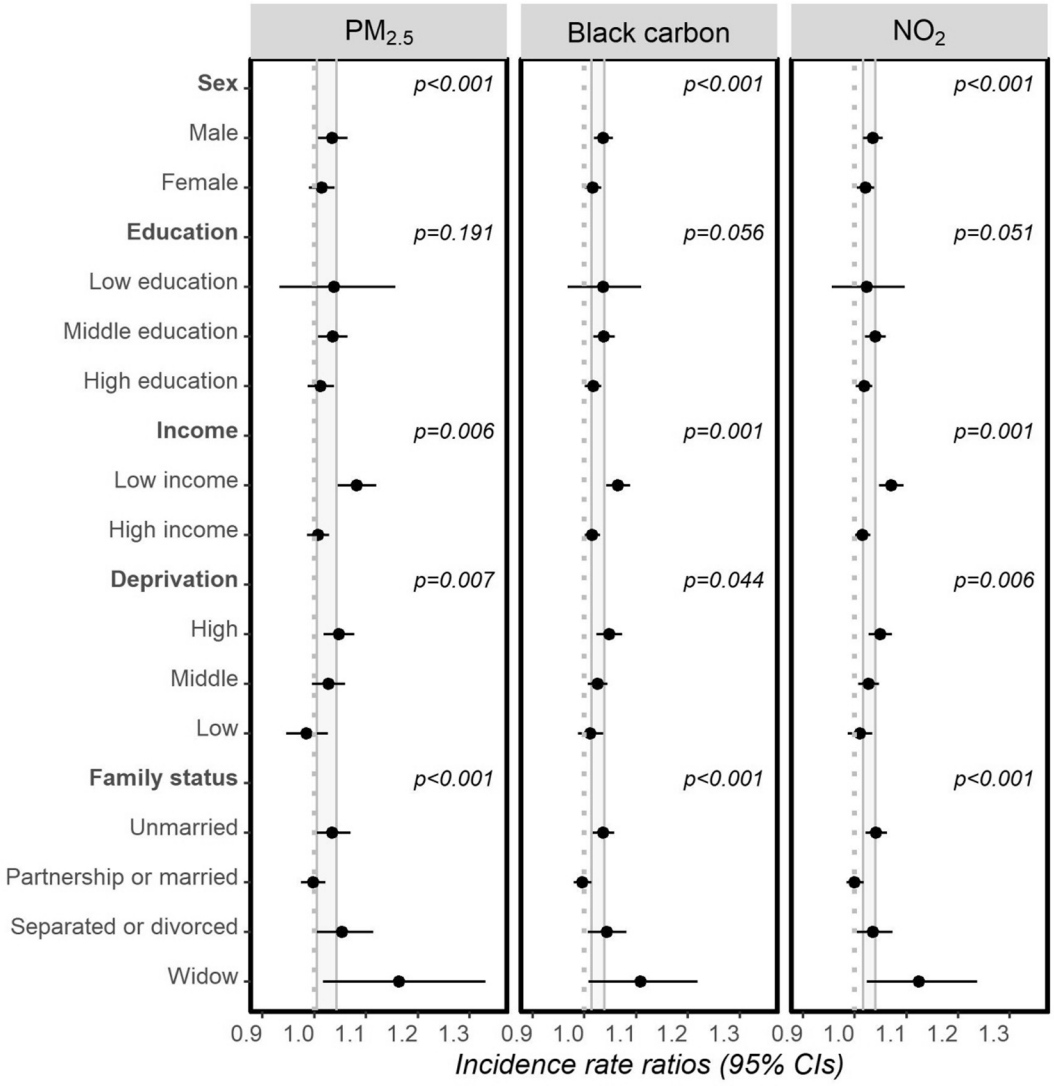

Fig. 3. Incident rate ratios (IRRs) (95% confidence intervals are depicted as bars) for the associations between an interquartile range increase in exposure to air pollution and CES-D total score with p-values for interaction. All the associations are based on the model adjusted for age, sex, education, income, alcohol drinking habits, smoking status, and deprivation index, the month of completion of the questionnaire, day of the week of completion of the questionnaire, and recruitment center, body mass index, non-occupational physical activity, perceived health status, self-reported cardiovascular diseases, and type-2 diabetes, applied to one imputed dataset. For the computation of the p-value of interaction for family status, the model without interaction was also adjusted by family status since it wasn't in the original adjustment. Confidence intervals of the main results for the fully adjusted model are displayed as grey strips.

Table 3
Association between exposure to air pollution and depressive symptoms (CES-D total score) in the French CONSTANCES cohort participants; *a*) results of multilevel negative binomial regression model, *b)* analyses with the complete dataset; *c*) excluding participants from two Paris centers; *d)* additional adjustment of model 2 with "enrollment year"; and *e*) excluding those with self-reported depression with treatment or self-reported history of suicide attempt.

Sensitivity analysis	$PM_{2.5}$	Black carbon	NO_2
Multilevel model (n = 123,754)	**1.035 (1.018: 1.053)**	**1.031 (1.019: 1.044)**	**1.033 (1.021: 1.046)**
Complete cases (n = 104,333)	**1.025 (1.003: 1.047)**	**1.020 (1.006: 1.034)**	**1.021 (1.007: 1.036)**
Excluding Paris centers (n = 102,306)	**1.025 (1.005: 1.046)**	**1.026 (1.012: 1.040)**	**1.028 (1.015: 1.043)**
Additional adjustment of model 2 with "enrollment year" (n = 123,754)	**1.022 (1.002: 1.042)**	**1.026 (1.013: 1.040)**	**1.028 (1.015: 1.042)**
Those without self-reported depression with treatment or self-reported history of suicide attempt (n = 102,146)	**1.024 (1.002: 1.046)**	**1.030 (1.016: 1.044)**	**1.029 (1.015: 1.044)**

All results are based on an interquartile range (IQR) increase in the exposure to air pollution ($PM_{2.5}$ IQR = 4.89 μg/m^3, black carbon IQR = 0.88 10^{-5}/m, and NO_2 IQR = 17.41 μg/ m^3).
All the associations are presented as the incidence rate ratio in negative binomial regression (IRR) (95% confidence interval), except for sex-specific cut-off results that are the odds ratio (95% confidence interval).
All the results are based on Model 2 (adjusted for age, sex, education, income, alcohol drinking habits, smoking status, neighborhood deprivation, the month of completion of the questionnaire, day of the week of completion of the questionnaire, and recruitment center).

prevalence of depression, even after controlling individual-level covariables (Dowdall et al. 2017). For clinical risk factors, there was no significant interaction for CVDs or type-2 diabetes. Such a finding has also been observed elsewhere (Lim et al. 2012). These findings would be of utmost importance to target interventions to the people more vulnerable to the negative effects of air pollution.

From a mechanistic point of view, human and animal studies suggest that air pollution exposure can induce oxidative stress and neuroinflammation (Mehta et al. 2015), which are reported among the hypothesized biological pathways of mental disorders (Black et al. 2015; Maes et al. 2011). Some other biological mechanisms such as the direct neurotoxic effect of air pollutants because of direct translocation to the brain through the olfactory bulb, and subsequent structural brain changes, and stress hormone production are proposed as the possible underlying pathways (Power et al. 2015). In a laboratory setting, treating microglia with diesel exhaust particles resulted in microglia activation and induced neurotoxicity (Block et al. 2004; Lim et al. 2012). Decreased oxygen saturation and hypoxemia following inhalation of air pollutants (DeMeo et al. 2004) can also increase dopamine and tyrosine hydroxylase (Ray et al. 2011), and decrease serotonin levels in the brain (Pandey 2013), which has been implicated in the neurobiology of mental outcomes. Importantly, our results suggest that the association between air pollution and depression is not restricted to a specific dimension of depressive symptoms. Therefore, possible involved causal mechanisms are more likely to be general.

4.1. Strengths and limitations

The observational and cross-sectional nature of the study limited us to draw a cause-effect association. Data on "participant's residential history and mobility before their enrollment" was not available at the time of this study, therefore we used single-year exposure values (in this study for 2010). As the probability of residential mobility might have been similar for most of the participants, this misclassification should mainly be non-differential, and push the effect estimates closer to the null values. Additionally, we used 2010 annual mean concentrations to represent long-term exposure, assuming spatial contrasts of air pollution are stable over the years, which was supported by de Hoogh et al. (2018). As air pollution concentrations decreased in recent years, applying 2010 exposure models to baseline addresses (*i.e.* 2012–2020) may have overestimated the exposure contrasts and thus lead to the underestimation of effect estimates associated with a fixed exposure increase. Additionally, since the enrollment into the study has taken place in different years, and considering temporal variation in the exposure, the "lag time" between enrollment year and exposure modeling could introduce exposure misclassification bias to the results. As air pollution concentrations decreased in recent years, applying exposure models before baseline (*i.e.* 2010) may have overestimated the exposure contrasts and thus lead to the underestimation of effect estimates associated with a fixed exposure increase. However, we found no indication of such potential bias in the findings as the results of the sensitivity analyses by introducing "enrollment year" and its interaction with exposure variables in the models. Moreover, if the overall spatial contrast did not change over this period, the effect estimates associated with "per IQR increase" should not be affected. Additionally, despite widely reported long-term effects of air pollution on mental outcomes, short-term effects of environmental factors including air pollution and temperature on human mental health have been reported but have not been considered in our study. Regarding the outcome, we had around 17 % of missing data due to incomplete score, however, we found no difference in the general characteristics and exposure profile of the participants with those excluded ones.

Our study benefits from several strengths. It is one of the largest studies on the association between air pollution exposure and depressive symptoms on a study population of more than 123,000 participants randomly sampled from the French general population. Additionally, the association between air pollution and different dimensions of depressive symptoms has rarely been reported in other studies. In this study, we defined three models according to the levels of adjustment considering different precursors of mood impairments including demographical (age, sex), life achievement (education, income), and vulnerability (non-occupational physical activity, neighborhood deprivation, BMI, alcohol drinking, smoking status, cardiovascular disease). We used DAG to identify which set of variables should be necessary to be included in model 2 (as model 1 was the parsimonious model). Model 2 was adjusted with the main variables and those identified in the DAG. Model 3 additionally included potential mediators. The results of both models were similar. Additionally, our findings were robust after different levels of adjustments and sensitivity analyses. We also used the results of the CES-D, which is a globally accepted instrument for the assessment of depressive symptoms in the community, increasing the comparability of our findings to other studies. However, reliance on the CES-D did not allow for the diagnosis of "major depression". We also used the modeled exposure to air pollution for the year 2010, applied at the individual level residential address obtained at enrollment. As the CES-D asks the frequency of depressive symptoms in the week before completion of the questionnaire, our findings are linked to long-term exposure to air pollution rather than short-term exposure.

5. Conclusion

In this study, we found that exposure to air pollution, especially BC and NO_2, known as traffic-related air pollutants, has been associated with worse depressive symptoms in general and across different dimensions of CES-D. Depression is ranked as the leading cause of morbidity worldwide, with high social and economic costs. With the increasing trend of urbanization, which is also associated with higher exposure to air pollution, our findings would be of high importance for public health sectors, and policymakers. Reduction of population exposure to air pollutants, and embracing the new WHO guideline (World Health Organization., 2021) remains an important measure to reduce the burden of mental health illnesses on society.

6. Role of the funding source

The study funders did not contribute to the study design, data collection, data analysis, data interpretation, or writing of this manuscript. The corresponding author had full access to all the data used in this study and had final responsibility for the decision to submit it for publication. CL reports personal fees and non-financial support from Lundbeck and Otsuka Pharmaceutical, outside the submitted work. The other authors declare no competing interest.

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Declaration of Competing Interest

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

Data availability

The authors do not have permission to share data.

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