**Association between air pollution exposure and handgrip strength as a marker of frailty: findings from the French CONSTANCES study**

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**Supplementary information**

**Study participants**

The CONSTANCES study is a large population-based prospective study on more than 220,000 participants aged 18-69 years, recruited in 21 centers from 20 different administrative divisions of France, covering urban, suburban, isolated cities and rural areas (Goldberg et al., 2017; Zins et al., 2010; Zins & Goldberg, 2015). In this cross-sectional analysis, we used the data from 2012-2017 from the enrollment phase (2012-2020) of the CONSTANCES study (because of air pollution estimates availability). Participants were randomly selected among members of the CNAM health insurance (Caisse Nationale d'Assurance Maladie), which covers 85% of the French population (Zins & Goldberg, 2015). In this study, we used the available data on the participants aged over 45 years old, who were asked to additionally attend physical and cognitive functions examination.

**Handgrip strength measurement**

All the Handgrip strength (HGS) measurements were performed with a portable Hand Dynamometer with 0.1 Kg of precision. Briefly, at first, the experimenter informed the participants about the test aim and procedure (squeezing the Dynamometer handle as hard as the participant could for two seconds, and then relax for one minute). The participants were invited to remove any rings before the test. For each participant, the dynamometer’s handle width was adjusted to the desired spacing to fit comfortably in their hand. The handle resting on the second phalanx of the index finger and the adjacent fingers. After adjustment of the spacing, the standing patient held the dynamometer with the adducted shoulder and neutrally rotated posture, the elbow flexed at 90° and the unsupported forearm in a neutral position. The dorsiflexion of the wrist was between 0 and 30°. The peak-hold reading (in kilograms) was recorded. Any protocol deviations were noted in the patient’s case report form.

**Air pollution exposure assessment**

We used the results of a hybrid land-use regression models developed for western Europe for the air pollution exposures in this study (de Hoogh et al., 2018). Annual mean concentrations of particulate matter with aerodynamic diameters less than 2.5 µm (PM2.5),black carbon (BC), and nitrogen dioxide (NO2) for 2010 were estimated at a fine spatial resolution (100x100 m) using a supervised stepwise linear regression approach. Measured PM2.5 (543 sites),NO2 (2399 sites) and BC (436 sites)concentrations were regressed against a range of predictor variables, including satellite-derived and chemical transport modeled estimates, road density, land-use variables, and altitude. The models explained 72% (PM2.5), 54% (BC) and 59% (NO2) of the spatial variation of the observed pollutants concentrations across Europe.

**Covariates**

Information at individual-level (sociodemographic, anthropometric, health-related behavioral, and clinical risk factors), and at area-level (classification of the commune of residence in term of urbanization, and deprivation index) were included in the models. Individual-level sociodemographic covariates were: age, sex, education (less than 5 years of education, 5-12 years of education, and more than 12 years of education), marital status (unmarried, married or in civil partnership, separated or divorced, widow), smoking status (non-smoker, ex-smoker, current smoker), alcohol drinking habits (based on Alcohol Use Disorders Identification Test (AUDIT) classification in four groups: abstinent, neither abuse nor dependence, abuse, dependence)(Saunders et al., 1993), non-occupational physical activity (based on a questionnaire measuring frequency and intensity of different activities scored from 0 to 6; 0 for inactive people, and six for very physically active people), socio-occupational status (based on current socio-professional category or that which he/she have held for the greatest length of time if not currently in work; in six groups: farmer or craftsman, executive or intellectual profession, middle-level profession, employee, blue-collar worker), geographical origin (France vs. other countries), monthly household income (below 2100 euros/months was defined as a low income). Individual-level anthropometric covariates were: height (in cm), and body mass index (BMI; obtained by dividing weight in kilograms per square of participant height in meter, and categorized into four groups of underweight: BMI<18.5, normal: 18.5≤BMI<25, overweight: 25≤BMI<30, obese: BMI≥30). Individual-level risk factors were: self-assessment of perceived general health (from 1 as "very good" to 8 as "very bad"), self-report diagnosis of cardiovascular diseases (CVDs) (defined as a positive answer to “having angina pectoris, myocardial infarction, arthritis of the lower limbs, or other CVDs?” question), respiratory diseases (defined as a positive answer to “having chronic bronchitis, emphysema, asthma, or other specified respiratory diseases?” question), type-2 diabetes (based on declaration in the questionnaire, or measurements in paraclinical examinations (glycemia > 7 mmoles/l), or treated with antidiabetic medication based on French national system of health data (Système National des Données de Santé (SNDS)), neurological disorders (including stroke and Parkinson's disease), hypercholesterolemia and hypertriglyceridemia. Depressive symptoms as a binary variable was defined based on the Center for Epidemiological Studies-Depression (CES-D) scale score (score ≥16 classified as having depressive symptoms) (Radloff, 1977). Hypertension was defined by data from a) declaration in the medical questionnaires, b) measurements in paraclinical examinations (systolic blood pressure > 140 mm Hg or/and diastolic blood pressure > 90 mm Hg), or c) treated with antihypertensive medication in SNDS). We also constructed a global cognitive score using principal component analysis (PCA) of three cognitive domains (episodic memory, executive functions, and language skills) as described elsewhere (Letellier et al., 2020). Area-level covariates were: classification of participants' commune of residence into four types (urban, suburban, isolated cities, and rural) according to the classification by the INSEE (The National Institute of Statistics and Economic Studies), and the French deprivation index (categorized as tertiles in the models) as a measure of neighborhood deprivation. The French deprivation index is a construct based on four census-derived variables including median household income, percentage of high school graduates, percentage of blue-collar workers, and unemployment rate (Rey et al., 2009).

**Statistical analysis**

We found a high interclass correlation coefficient (ICC) for the three air pollutants across the recruitment centers especially for PM2.5 (ICC=83.81%), indicating high between-clusters variance compared to the within-cluster variances (data not shown). Therefore, we used mixed linear models with a random intercept per center and then reported adjusted regression coefficients (β) and 95% confidence intervals (CIs) for each pollutant separately. Sex difference has been found for hand grip strength values and decline trajectory. Men generally have higher maximum grip strength than women after controlling for body size (based on different variables across the studies, such as height, weight, BMI) (McDowell et al., 2018). Therefore, we ran the models and reported the results separately for men and women. Therefore, we ran the models and reported the results separately for men and women.

Included covariates were selected based on prior knowledge and results of age adjusted models. We defined two different models according to the levels of adjustments. The first model (hereafter *model 1*) was adjusted for variables that were significant in univariate analyses thus is education, height, smoking status, alcohol drinking, marital status, BMI, income, non-occupational physical activity, geographical origin, classification of the commune of residence (urban, suburban, isolated city, or rural), socio-occupational status, and area-level deprivation index. The second model (hereafter *model 2*) was adjusted additionally for health possible mediators including depressive symptoms, hypertension, type-2 diabetes, perceived health status, hypercholesterolemia, hypertriglyceridemia, neurological disorders, respiratory disorders, CVDs~~.~~

**Imputation:**

The percentage of missing values of the selected variables ranged between zero and 8% (income, depressive symptoms and socio-professional status had respectively the highest missing rates, respectively 8.0, 7.5 and 6.5%). We used multiple imputations to construct 5 imputed datasets (with 10 iterations), using mice package in R (Buuren & Groothuis-Oudshoorn, 2010). We included all variables used in the model 2 in the imputation model but also auxiliary variables that were not included in the analysis models, but had the potential to be predictors of missingness and/or the variable with missing data in the imputation model to improve the accuracy of the imputed datasets (i.e. currently has job, weight, suffering from Parkinson’s disease). The density plots of the imputed variables were visually checked to assess the acceptance of the imputation. The models were run on multiple imputed datasets (except specified otherwise), and corresponding parameters estimated in each imputed dataset separately. Estimates were combined using Rubin’s rules and pool function.

**Stratified analyses**

We conducted stratified analyses among subgroups based on the classification of the commune of residence (urban, suburban, isolated city, or rural), age group (65 years old and above, vs. below 65 years old), education (less than 5 years of education, 5-12 years of education, and more than 12 years of education), BMI (below 25, 25-30, above 30), smoking status (smoker, ex-smoker, and non-smoker), CVDs (yes, no), type-2 diabetes (yes, no), respiratory disease (yes, no), depressive symptoms (yes, no), and neurological disorders (yes, no). For these variables, we tested the interaction by including an interaction term between each pollutant and variable of interest, and checked the significance of interaction by the likelihood-ratio test p-value.

**References**

Buuren, S. van, & Groothuis-Oudshoorn, K. (2010). mice: Multivariate imputation by chained equations in R. *Journal of Statistical Software*, 1–68.

de Hoogh, K., Chen, J., Gulliver, J., Hoffmann, B., Hertel, O., Ketzel, M., Bauwelinck, M., van Donkelaar, A., Hvidtfeldt, U. A., & Katsouyanni, K. (2018). Spatial PM2. 5, NO2, O3 and BC models for Western Europe–Evaluation of spatiotemporal stability. *Environment International*, *120*, 81–92.

Goldberg, M., Carton, M., Descatha, A., Leclerc, A., Roquelaure, Y., Santin, G., & Zins, M. (2017). CONSTANCES: a general prospective population-based cohort for occupational and environmental epidemiology: Cohort profile. *Occupational and Environmental Medicine*, *74*(1), 66–71.

Letellier, N., Choron, G., Artaud, F., Descatha, A., Goldberg, M., Zins, M., Elbaz, A., & Berr, C. (2020). Association between occupational solvent exposure and cognitive performance in the French CONSTANCES study. *Occupational and Environmental Medicine*, *77*(4), 223–230.

McDowell, C. P., Gordon, B. R., & Herring, M. P. (2018). Sex-related differences in the association between grip strength and depression: Results from the Irish Longitudinal Study on Ageing. *Experimental Gerontology*, *104*, 147–152.

Radloff, L. S. (1977). The CES-D scale: A self-report depression scale for research in the general population. *Applied Psychological Measurement*, *1*(3), 385–401.

Rey, G., Jougla, E., Fouillet, A., & Hémon, D. (2009). Ecological association between a deprivation index and mortality in France over the period 1997 – 2001: Variations with spatial scale, degree of urbanicity, age, gender and cause of death. *BMC Public Health*, *9*(33). https://doi.org/10.1186/1471-2458-9-33

Saunders, J. B., Aasland, O. G., Babor, T. F., De la Fuente, J. R., & Grant, M. (1993). Development of the alcohol use disorders identification test (AUDIT): WHO collaborative project on early detection of persons with harmful alcohol consumption‐II. *Addiction*, *88*(6), 791–804.

Zins, M., Bonenfant, S., Carton, M., Coeuret-Pellicer, M., Guéguen, A., Gourmelen, J., Nachtigal, M., Ozguler, A., Quesnot, A., & Ribet, C. (2010). The CONSTANCES cohort: An open epidemiological laboratory. *BMC Public Health*, *10*(1), 1–9.

Zins, M., & Goldberg, M. (2015). The French CONSTANCES population-based cohort: Design, inclusion and follow-up. *European Journal of Epidemiology*, *30*(12), 1317–1328.

**List of table sand figures**

**Tables:**

**Table S1.** Sociodemographic characteristics, handgrip strength, and exposure to air pollution among men and women in the French CONSTANCES study (N=51845).

**Figures:**

**Figure S1**. Association between exposure to air pollution and maximum handgrip strength in the French CONSTANCES study participants (N=51845) in different residential areas.

**Table S1.** Characteristics of the French CONSTANCES study participants in this study (n=51845).a

|  |  |  |  |
| --- | --- | --- | --- |
| **Variable** | **Men (N=25753)** | **Women (N=26092)** | **All (N=51845)** |
| Age (year) | 57.72 (7.19) | 57.03 (7.14) | 57.38 (7.17) |
| Missing (%) | 0.0 | 0.0 | 0.0 |
| Height (cm) | 174.69 (6.56) | 161.95 (6.16) | 168.28 (9.01) |
| Missing (%) | 1.9 | 1.9 | 1.9 |
| Body mass index (kg/m2) | 26.41 (3.80) | 24.87 (4.68) | 25.63 (4.33) |
| Missing (%) | 3.3 | 3.5 | 3.4 |
| Years of education |  |  |  |
| Less than 5 years | 828 (3.3%) | 719 (2.8%) | 1547 (3.1%) |
| 5-12 years | 12480 (49.7%) | 11777 (46.1%) | 24257 (47.9%) |
| More than 12 years | 11785 (47.0%) | 13028 (50.9%) | 24813 (49.0%) |
| Missing (%) | 2.6 | 2.2 | 2.4 |
| Smoking status |  |  |  |
| Non-smoker | 9366 (38.3%) | 12827 (51.7%) | 22193 (45.1%) |
| Ex-smoker | 3313 (13.6%) | 3234 (13.0%) | 6547 (13.3%) |
| Smoker | 11769 (48.1%) | 8744 (35.3%) | 20513 (41.6%) |
| Missing (%) | 5.1 | 4.9 | 5.0 |
| Smoking intensity (pack/year) | 9.54 (14.43) | 5.14 (9.85) | 7.34 (12.55) |
| Missing (%) | 10.3 | 11.6 | 11.0 |
| Alcohol drinking |  |  |  |
| Abstinent | 601 (2.5%) | 1279 (5.3%) | 1880 (3.9%) |
| No abuse or dependent | 18208 (75.1%) | 19975 (82.3%) | 38183 (78.7%) |
| Abuse | 4172 (17.2%) | 2519 (10.4%) | 6691 (13.8%) |
| Dependent | 1261 (5.2%) | 488 (2.0%) | 1749 (3.6%) |
| Missing (%) | 0 | 0 | 0 |
| Non-occupational physical activity*b* | 4.65 (1.57) | 4.79 (1.52) | 4.72 (1.55) |
| Missing (%) | 5.9 | 7.0 | 6.4 |
| Marital status |  |  |  |
| Unmarried | 3052 (12.2%) | 3424 (13.5%) | 6476 (12.8%) |
| Married or in a partnership | 18288 (73.1%) | 16504 (64.8%) | 34792 (68.9%) |
| Separated or divorced | 3264 (13.0%) | 4338 (17.0%) | 7602 (15.1%) |
| Widow | 415 (1.7%) | 1188 (4.7%) | 1603 (3.2%) |
| Missing (%) | 2.9 | 2.4 | 2.6 |
| Country of origin (not France) | 2377 (9.4%) | 2129 (8.3%) | 4506 (8.9%) |
| Missing (%) | 2.0 | 2.2 | 2.1 |
| Household income (below 2100 euros/ month) | 4335 (16.8%) | 5654 (21.7%) | 9028 (18.9%) |
| Missing (%) | 6.8 | 9.1 | 8.0 |
| Socio-occupational status |  |  |  |
| Farmer or craftsman | 791 (2.9%) | 398 (1.6%) | 1089 (2.2%) |
| Executive, intellectual profession | 9242 (38.4%) | 5538 (22.7%) | 14780 (30.5%) |
| Middle-level profession | 6978 (29.0%) | 8314 (34.1%) | 15292 (31.6%) |
| Employee | 6321 (26.3%) | 9041 (37.1%) | 15362 (31.7%) |
| Blue-collar worker | 840 (3.5%) | 1100 (4.5%) | 1940 (4.0%) |
| Missing (%) | 6.5 | 6.5 | 6.5 |
| Classification of the commune of residence |  |  |  |
| Urban | 9630 (37.4%) | 9768 (37.4%) | 19398 (37.4%) |
| Suburban | 9571 (37.2%) | 10164 (39.0%) | 19735 (38.1%) |
| Isolated city | 1935 (7.5%) | 1836 (7.0%) | 3771 (7.3%) |
| Rural | 4617 (17.9%) | 4322 (16.6%) | 8939 (17.2%) |
| Missing (%) | 0.0 | 0.0 | 0.0 |
| Perceived health status*c* | 2.88 (1.21) | 2.87 (1.22) | 2.87 (1.21) |
| Missing (%) | 5.3 | 4.8 | 5.1 |
| Deprivation |  |  |  |
| First tertile (lowest) | 8850 (34.4%) | 9484 (36.4%) | 18334 (35.4%) |
| Second tertile | 9090 (35.3%) | 9141 (35.0%) | 18231 (35.2%) |
| Third tertile (highest) | 7805 (30.3%) | 7462 (28.6%) | 15267 (29.5%) |
| Missing (%) | 0.0 | 0.0 | 0.0 |
| Depressive symptoms (yes) | 3452 (14.4%) | 6045 (25.2%) | 9497 (19.8%) |
| Missing (%) | 7.0 | 8.1 | 7.5 |
| Respiratory diseases (yes) | 2284 (9.0%) | 2275 (8.8%) | 4559 (8.9%) |
| Missing (%) | 1.4 | 1.3 | 1.3 |
| Type-2 diabetes (yes) | 2185 (8.5%) | 930 (3.6%) | 3115 (6.0%) |
| Missing (%) | 0.0 | 0.0 | 0.0 |
| Cardiovascular diseases (yes) | 3030 (12.0%) | 1939 (7.6%) | 4969 (9.7%) |
| Missing (%) | 1.6 | 1.6 | 1.6 |
| Hypercholesterolemia (yes) | 4455 (17.6%) | 2457 (9.6%) | 6912 (13.6%) |
| Missing (%) | 1.7 | 2.2 | 2.0 |
| Hypertriglyceridemia (yes) | 801 (3.2%) | 292 (1.2%) | 1093 (2.2%) |
| Missing (%) | 2.6 | 2.9 | 2.7 |
| Hypertension (yes) | 13501 (52.4%) | 8579 (32.9%) | 22080 (42.6%) |
| Missing (%) | 0.0 | 0.0 | 0.0 |
| Neurological disorders*d* (yes) | 966 (3.9%) | 998 (3.9%) | 1964 (3.9%) |
| Missing (%) | 2.7 | 3.8 | 2.9 |
| Global cognitive score*e* | -0.03 (1.69) | -0.05 (1.65) | -0.04 (1.67) |
| Missing (%) | 4.1 | 2.9 | 3.5 |
| PM2.5 (µg/m3) | 16.71 (3.08) | 16.87 (3.16) | 16.79 (3.12) |
| Missing (%) | 0.0 | 0.0 | 0.0 |
| Black carbon (10-5/m) | 1.75 (0.53) | 1.78 (0.55) | 1.76 (0.54) |
| Missing (%) | 0.0 | 0.0 | 0.0 |
| NO2 (µg/m3) | 24.76 (11.41) | 25.41 (11.68) | 25.09 (11.55) |
| Missing (%) | 0.0 | 0.0 | 0.0 |
| Average hand grip strength (kg) | 42.04 (8.58) | 25.53 (5.70) | 33.73 (11.00) |
| Missing (%) | 0.0 | 0.0 | 0.0 |
| Maximum hand grip strength (kg) | 44.09 (8.72) | 27.01 (5.85) | 35.49 (11.31) |
| Missing (%) | 0.0 | 0.0 | 0.0 |

*a*: Table is based on one of the imputed data sets. For the continuous variables, the values are mean (standard deviation). For the categorical variables, the values are n (%).

*b*: Scored 0-6. Higher values represent higher non-occupational physical activity.

*c*: Scored 1-8. Higher values represent poorer perceived health status.

*d*: Including Parkinson’s disease and stroke.

*e*: Higher scores represent better cognitive performance.

**Figure S1**. Association between exposure to air pollution and maximum handgrip strength in the French CONSTANCES study participants (N=51845) in different residential areas.

