

SUPPLEMENTAL MATERIAL

Long-term exposure to ambient air pollution and risk of dementia: results of the prospective Three-City study

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I. Comparison of the characteristics of included and excluded participants.

Table S1. Comparison of the characteristics of included and excluded participants.

	Included		Excluded^a		p-value^b
	N Total	n (%) or median (IQR)	N Total	n (%) or median (IQR)	
Age at baseline, years	7066	73.4 (8.0)	1971	73.8 (8.6)	0.006
Incident cases of dementia	7066	791 (11.2%)	1971	157 (8.0%)	<0.001
Duration of follow-up, years	7066	10.0 (6.9)	1971	4.1 (9.7)	<0.001
Sex, women	7066	4359 (61.7%)	1971	1143 (57.9%)	0.003
Study centre	7066		1971		
Bordeaux		1616 (23.0 %)		408 (21.0%)	<0.001
Dijon		4034 (57.0 %)		7997 (40.0%)	
Montpellier		1416 (20.0%)		764 (39.0%)	
Living alone	7050	2580 (36.6%)	1966	652 (33.2%)	0.005
Education	7066		1967		
≤ 5 years		2323 (32.9 %)		651 (33.1%)	0.095
5 - 9 years		2108 (29.8 %)		629 (32.0%)	
>9 years		2635 (37.3 %)		687 (34.9%)	
Deprivation index	7066	-0.27 (2.02)	1273	-0.15 (2.03)	0.03
APOE ε4 allele carriers	7066	1397 (19.8%)	1392	308 (22.1%)	0.045
Smoking habits	7066		1969		
Never		4374 (61.9%)		1162 (59.0%)	0.020
Past or current		2692 (38.1%)		807 (41.0%)	
Alcohol intake	7066		1827		
None		1438 (20.3%)		406 (22.2%)	<0.001
Moderate		5067 (71.7%)		1232 (67.4%)	
High		561 (8.0%)		189 (10.4%)	

^a 823 participants without any follow-up and 1148 participants with missing data for covariates.

^b Wilcoxon test for quantitative variables, and Chi2 test for qualitative variables.

Abbreviations: APOE, apolipoprotein E; IQR, interquartile range.

High alcohol intake was defined by an intake >36g per day.

II. Adjustment for household income and family history of dementia, vascular risk factors, depressive symptomatology, and physical activity.

Household income and family history of dementia

Household income was considered in euros per month and categorized into four classes: <750, 750-1500, 1500-2300, and >2300 (table SA). There were 416 missing data.

For the family history of dementia, participants were first asked whether one of their parents had had a memory or a language disorder. In the case of positive answer, participants had to specify whether these disorders were the consequence of dementia or Alzheimer's disease. Hence, family history of dementia was considered when at least one of the participants' parents had a language and/or a memory disorder that was associated with dementia or Alzheimer's disease. This information was not available for participants from the Bordeaux centre.

Table SA. Household income and family history of dementia at baseline

	All Participants	All-cause dementia cases over the 12-year follow-up		
	Total, n=6650 ^a	Non-cases, n=5920	Cases, n=730	
	n (%)			P value ^c
Household income (in euros/month)				
<750	341 (5%)	279 (5%)	62 (8%)	<0.001
750-1500	2076 (31%)	1801 (30%)	275 (38%)	
1500-2300	1892 (29%)	1700 (29%)	192 (26%)	
>2300	2341 (35%)	2140 (36%)	201 (28%)	
	Total, n=4471^b	Non-cases, n=4075	Cases, n=396	0.209
Family history of dementia				
Yes	305 (7%)	284 (7%)	21 (5%)	
No	4168 (93%)	3791 (93%)	375 (95%)	

^a There were 416 missing data for household income.

^b There were 2179 missing data for family history of dementia (no data from the Bordeaux centre).

^c Chi2 test.

Vascular risk factors at baseline

Covariates related to vascular risk factors were body mass index (BMI; calculated from height and weight measurements), dyslipidaemia (plasma cholesterol >6.20 mmol/l, or using lipid-lowering drugs), diabetes (glycaemia \geq 7.0 mmol/l, or taking anti-diabetic treatment), hypertension (systolic/diastolic blood pressure \geq 140/ \geq 90mm Hg, or taking antihypertensive drugs), and history of vascular pathology (self-reported history of stroke, angina pectoris, myocardial infarction, coronary surgery, coronary angioplasty, and arterial surgery of the legs for arteritis) (table SB). Model 2 included only covariates selected based on their association with the risk of dementia ($p < 0.20$), i.e. diabetes and history of vascular pathology.

As 44 data were missing for the vascular risk factors at baseline, analyses were carried out in a sample of 7022 participants (table S3).

Respiratory diseases, depressive symptomatology, and physical activity at baseline

History of respiratory pathology was defined as self-reported chronic obstructive pulmonary disease-like symptoms in the 3 months before the baseline visit (cough and mucus production) or asthma-like symptoms in the 12 months before the baseline visit (asthma crisis, or wheezing and shortness of breath).

Depressive symptoms were assessed using the Center for Epidemiologic Studies-Depression Scale (CESD). Participants with CESD score >16 or taking antidepressant treatment (ATC code: N06A) were considered as having depressive symptoms.

Regular physical activity was defined as performing some sport regularly or having at least one hour of leisure or household activity per day. This information was missing for more than 9% of participants.

Table SB. Frequency of vascular risk factors, depressive symptomatology and regular physical activity at baseline in 7022 participants.

	All Participants	All-cause dementia cases over the 12-year follow-up		P value ^b
	Total, n=7022 ^a	Non-cases, n=6237	Cases, n=785	
	n (%)			
Body Mass Index				
Normal (<25 kg.m ⁻²)	3307 (47.4%)	2945 (47.5%)	362 (46.7%)	0.925
Overweight (25-30 kg.m ⁻²)	2744 (39.5%)	2435 (39.2%)	309 (39.9%)	
Obese (>30 kg.m ⁻²)	931 (13.3%)	827 (13.3%)	104 (13.4%)	
Hypertension	5442 (77.5%)	4817 (77.2%)	625 (79.6%)	0.132
Diabetes	652 (9.3%)	538 (8.6%)	114 (14.5%)	<0.001
Dyslipidaemia	4158 (59.4%)	3696 (59.4%)	462 (59.2%)	0.939
History of cardiovascular pathology	2028 (28.9%)	1769 (28.4%)	259 (33.0%)	0.007
History of respiratory pathology	419 (6.0%)	363 (5.8%)	56 (7.1%)	0.143
Depressive symptomatology*	504 (7.3%)	405 (6.6%)	99 (12.7%)	<0.001
Regular physical activity**	2057 (32.1%)	1905 (33.3%)	152 (22.3%)	<0.001

^a There were 44 missing data for vascular risk factors.

^b Chi2 tests.

*n=6955, **n=6405

Hypertension was defined by systolic/diastolic blood pressure ≥ 140 mm Hg/ ≥ 90 mm Hg or use of antihypertensive drugs; diabetes by glycemia >7.0 mmol/l or antidiabetic treatment; dyslipidaemia by plasma cholesterol ≥ 6.20 mmol/L or use of lipid lowering drugs; history of vascular pathology as self-reported history of stroke, angina, pectoris, myocardial infarction, coronary surgery, coronary angioplasty, and arterial surgery of the legs for arteritis; history of respiratory pathology as self-report of chronic obstructive pulmonary disease-like symptoms in the last 3 months (cough and mucus production) or asthma-like symptoms in the last 12 months (asthma crisis or wheezing and shortness of breath); regular physical activity as at least 3 hours of exercise per month; depressive symptomatology by a CESD score >16 or antidepressant treatment (ATC code: N06A).

Table S2. Hazard ratios (95% CI) for the association between air pollutants^a and dementia risk during the 12-year period of follow-up with additional adjustments for household income and family history of dementia

	M1a				M1b			
	N [*] _{total}	N _{cases}	HR (CI 95%)	p	N ^{**} _{total}	N _{cases}	HR (CI 95%)	p
All-cause dementia								
PM _{2.5} ^b	6650	730	1.18 (1.05-1.32)	0.004	4471	396	1.14 (1.09-1.20)	<0.001
BC ^c	6650	730	1.08 (0.84-1.38)	0.545	4471	396	1.03 (0.74-1.43)	0.856
NO ₂ ^b	6650	730	1.00 (0.95-1.06)	0.940	4471	396	1.01 (0.93-1.09)	0.906
Alzheimer's disease								
PM _{2.5} ^b	6414	494	1.15 (1.03-1.28)	0.012	4349	274	1.14 (1.08-1.21)	<0.001
BC ^c	6414	494	0.98 (0.80-1.19)	0.818	4349	274	0.94 (0.79-1.12)	0.484
NO ₂ ^b	6414	494	0.99 (0.96-1.03)	0.675	4349	274	1.01 (0.97-1.05)	0.730
Vascular or mixed dementia								
PM _{2.5} ^b	6066	146	1.35 (1.07 – 1.70)	0.011	4162	87	1.45 (1.25 – 1.69)	<0.001
BC ^c	6066	146	1.42 (0.80 – 2.52)	0.238	4162	87	1.48 (0.63 – 3.50)	0.371
NO ₂ ^b	6066	146	1.01 (0.88 – 1.17)	0.854	4162	87	1.05 (0.82 – 1.34)	0.720

Abbreviations: BC, Black Carbon; CI, Confidence Interval; HR, Hazard Ratio; PM, Particulate Matter.

*There were 416 missing data for household income.

** There were 2179 missing data for family history of dementia (no data from the Bordeaux centre).

^a for each year of follow-up, a 10-year moving window of the mean past exposure to each pollutant was estimated for each subject.

^b for each 5µg/m³ increase

^c for each 10⁻⁵/m increase

^d after exclusion of all incident cases of dementia other than AD

^e after exclusion of all incident cases of dementia other than vascular or mixed dementia

M1a: Cox Proportional Hazards model with delayed entry with age as the basic timescale and birth as the time origin adjusted for sex, centre, education, APOE genotype, deprivation index, alcohol intake, smoking habit, monthly household income (<750, 750- 1500, 1500-2300, and >2300 euros)

M1b: M1a adjusted for familial history of dementia (yes/no)

Table S3. Hazard Ratios (95%CI) for the association between air pollutant exposure^a and dementia risk during the 12-year follow-up with additional adjustments for vascular risk factors, depressive symptomatology, respiratory diseases and physical activity.

	Model 2				Model 3			
	N_{total}	N_{cases}	HR [CI 95%]	p	N_{total}	N_{cases}	HR [CI 95%]	p
All-cause dementia								
PM _{2.5} ^b	7022	785	1.17 (1.06-1.30)	0.002	6344	675	1.16 (1.05-1.27)	0.003
BC ^c	7022	785	1.08 (0.81-1.43)	0.617	6344	675	1.08 (0.86-1.36)	0.119
NO ₂ ^b	7022	785	1.01 (0.94-1.08)	0.857	6344	675	1.01 (0.96-1.06)	0.735
Alzheimer's disease								
PM _{2.5} ^b	6773 ^d	536	1.20 (1.09-1.32)	<0.001	6128 ^d	459	1.18 (1.07-1.30)	<0.001
BC ^c	6773 ^d	536	1.00 (0.80-1.26)	0.981	6128 ^d	459	0.99 (0.81-1.20)	0.898
NO ₂ ^b	6773 ^d	536	1.01 (0.96-1.05)	0.816	6128 ^d	459	1.01 (0.97-1.04)	0.725
Vascular or mixed dementia								
PM _{2.5} ^b	6391 ^e	154	1.21 (0.95-1.54)	0.117	5805 ^e	136	1.28 (1.04-1.56)	0.019
BC ^c	6391 ^e	154	1.34 (0.73-2.47)	0.350	5805 ^e	136	1.41 (0.80-2.48)	0.239
NO ₂ ^b	6391 ^e	154	0.99 (0.85-1.15)	0.863	5805 ^e	136	1.01 (0.89-1.16)	0.838

Abbreviations: BC, Black Carbon; CI, Confidence Interval; HR, Hazard Ratio; PM, Particulate Matter.

^a for each year of follow-up, a 10-year moving window of the mean past exposure to each pollutant was estimated for each participant.

^b for each 5µg/m³ increase

^c for each 10⁻⁵/m increase

^d after exclusion of all incident cases of dementia other than AD

^e after exclusion of all incident cases of dementia other than vascular or mixed dementia

Model 2: adjusted for age, sex, centre, education, APOE genotype, deprivation index, alcohol intake, smoking habits, diabetes, history of vascular pathology.

Model 3: M2 adjusted also for history of respiratory pathology, depressive symptomatology, and physical activity.

III. Analyses in non-mover participants

Table S4. Hazard Ratios (95%CI) for the association between air pollutants^a and all-cause dementia risk during the 12-year follow-up in non-mover participants.

Model 1			
	n	HR [IC 95%]	P
PM 2.5 ^b	5621	1.21 [1.09-1.34]	<0.001
BC ^c	5621	1.09 [0.81-1.48]	0.568
NO2 ^b	5621	1.02 [0.94-1.11]	0.627

Abbreviations: BC, Black Carbon; CI, Confidence Interval; HR, Hazard Ratio; PM, Particulate Matter.

^a for each year of follow-up, a 10-year moving window of the mean past exposure to each pollutant was estimated for each subject.

^b for each 5µg/m³ increase

^c for each 10⁻⁵/m increase

Model 1: adjusted for age, sex, centre, education, APO genotype, deprivation index, alcohol intake, and smoking habits.

IV. Multiple imputation analyses

The covariates that presented missing data in our sample are shown in table S5. The dataset had an arbitrary missing pattern.

Table S5. Missing data

	n missing
Education level	3
APOE genotype	395
Deprivation index	638
Alcohol intake	132
Smoking habits	3

We assumed that data were missing at random. To impute missing values for education level, deprivation index, alcohol intake, and smoking habits, we used the fully conditional specification (FCS) method with the proc MI in SAS (Liu & De, 2015). We did not impute the missing data for the APOE genotype because it is challenging to predict such data with the covariates available in our dataset.

Liu, Y. and De, A. (2015). Multiple Imputation by Fully Conditional Specification for Dealing with Missing Data in a Large Epidemiologic Study. Int J Stat Med Res. 2015 ; 4(3): 287–295.

We selected age, sex, study centre, occupation (housewife, blue collar, white collar, other), monthly household income (<750, 750- 1500, 1500-2300 and >2300 euros), family status (married, divorced/celebrate, widow/widower), and history of cardiovascular pathology (see section II of the supplemental material) as predictive covariates for the multiple imputation process. We built five imputed datasets and then used the proc MIANALYZE to combine the results of the analyses of imputations and generate valid statistical inferences.

Table S6 presents the results from the Cox proportional hazards models with imputed missing data (n=7819, n. event=886). The results are very similar to those shown in the main results.

Table S6. Hazard ratios (95% CI) for the association between air pollutants^a and dementia risk during the 12-year period of follow-up using the multiple imputation procedure

M1c			
	N*_{total}	N_{cases}	HR (CI 95%)
All-cause dementia			
PM _{2.5} ^b	7819	886	1.20 (1.09-1.33)
BC ^c	7819	886	1.07 (0.84-1.36)
NO ₂ ^b	7819	886	1.01 (0.95-1.07)
Alzheimer's disease			
PM _{2.5} ^b	7545	592	1.19 (1.08 -1.30)
BC ^c	7545	592	0.94 (0.81-1.21)
NO ₂ ^b	7545	592	1.00 (0.96 -1.05)
Vascular or mixed dementia			
PM _{2.5} ^b	7124	171	1.37 (1.14- 1.64)
BC ^c	7124	171	1.42 (0.87- 2.31)
NO ₂ ^b	7124	171	1.01 (0.90- 1.14)

Abbreviations: BC, Black Carbon; CI, Confidence Interval; HR, Hazard Ratio; PM, Particulate Matter.

^a for each year of follow-up, a 10-year moving window of the mean past exposure to each pollutant was estimated for each subject.

^b for each 5µg/m³ increase

^c for each 10⁻⁵/m increase

^d after exclusion of all incident cases of dementia other than AD

^e after exclusion of all incident cases of dementia other than vascular or mixed dementia

M1c: Cox Proportional Hazards model with delayed entry with age as the basic timescale and birth as the time origin, adjusted for sex, centre, education, APOE genotype, deprivation index, alcohol intake, and smoking habits.

IV. Inverse probability weighting analyses

In this method, each participant is given a weight that is inversely proportional to their respective attrition probabilities in order to give a proportionally higher weight to individuals who are under-represented and proportionally lower weights to the most represented ones.

All participants who developed dementia during the follow-up period or who were present at the last visit (year 12 after inclusion) were assigned “attrition=0” and the other participants (i.e. death, withdrawal, and lost to follow-up) were assigned “attrition=1”.

Propensity scores were calculated using logistic regression analyses with age at baseline, sex, centre, education level, APOE genotype, deprivation index, alcohol intake, smoking habits, diabetes, history of vascular pathology, history of respiratory pathology as predictors of attrition.

Propensity scores and weights were computed using the SAS proc causaltr tool.

After exclusion of participants with a weight $>99^{\text{th}}$ or $<1^{\text{th}}$, weights ranged from 1.27 to 3.96. Finally, the marginal Cox proportional hazards model included the 6881 remaining participants. Exposure to air pollution was included as a time-varying variable. For each year of follow-up, the 10-year moving average of the past exposure to each pollutant was estimated for each participant.

Table S7. Hazard Ratios (95%CI) for the association between air pollutants^a and all-cause dementia risk for the 12-year follow-up in participants weighted by the inverse of their respective attrition probabilities.

Model 1			
	n	HR [IC 95%]	P
PM 2.5 ^b	6881	1.42 [1.30-1.56]	<0.001
BC ^c	6881	1.32 [0.95-1.83]	0.099
NO2 ^b	6881	1.07 [0.99-1.15]	0.089

N cases=753

Abbreviations: BC, Black Carbon; CI, Confidence Interval; HR, Hazard Ratio; PM, Particulate Matter.

^a for each year of follow-up, a 10-year moving window of the mean past exposure to each pollutant was estimated for each subject.

^b for each 5 $\mu\text{g}/\text{m}^3$ increase

^c for each 10⁻⁵/m increase

Model 1: adjusted for age, sex, centre, education, APOE genotype, deprivation index, alcohol intake, smoking habits.