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# Long-term exposure to black carbon and mortality: A 28-year follow-up of the GAZEL cohort

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## ABSTRACT

**Background:** The current evidence on health effects of long-term exposure to outdoor airborne black carbon (BC) exposure remains scarce.

**Objectives:** To examine the association between long-term exposure to BC and mortality in a large population-based French cohort, with 28 years of follow-up.

**Methods:** Data from the GAZEL cohort were collected between 1989 and 2017. Land use regression model with temporal extrapolation was used to estimate yearly BC and PM<sub>2.5</sub> exposure at the residential addresses from 1989 until censoring for 19,906 participants. Time-varying Cox models with attained age as time-scale was used to estimate the associations between BC and all-cause and cardiovascular mortality, after adjusting for individual and area-level covariates. To handle confounding by PM<sub>2.5</sub>, we used the residual of BC regressed on PM<sub>2.5</sub> as an alternate exposure variable. For all-cause mortality, we also examined effect modification by sex, smoking status, BMI and fruit/vegetable intake.

**Results:** The median of 20-year moving average of BC exposure was 2.02 10<sup>-5</sup>/m in study population. We found significant associations between BC exposure and all-cause mortality (n = 2357) using both 20-year moving average of BC and residual of BC, with corresponding hazard ratios (HR) of 1.14 (95 %CI: 1.07–1.22) and 1.17 (95 %CI: 1.10–1.24) for an inter-quartile range (IQR) increase (0.86 10<sup>-5</sup>/m for BC and 0.57 10<sup>-5</sup>/m for residual of BC). We found a similar association between BC and cardiovascular mortality (n = 277) with a HR of 1.15 (95 %CI: 0.95–1.38). The dose–response relationship between BC and all-cause mortality was monotonic but nonlinear with a steeper slope at high BC levels. In addition, the effect of BC was higher among never-smokers and among those having fruit/vegetables less than twice a week.

**Conclusions:** There was a positive association between long-term exposure to BC and increased mortality risk, reinforcing the emerging evidence that BC is a harmful component of PM<sub>2.5</sub>.

## 1. Introduction

It is estimated that fine particulate matter (PM<sub>2.5</sub>) was responsible for 2.9 (95 %CI: 2.5–3.4) million premature deaths and 83.0 (95 %CI: 71.4–94.3) million disability-adjusted life-years in 2017 (GBD, 2018). The underlying mechanisms linking particulate matter and various

chronic diseases (such as cardiovascular disease, respiratory disease and diabetes) include increases in systemic inflammation and oxidative stress, endoplasmic reticulum stress, cardiac autonomic nervous system dysfunction, and tumor necrosis factor- $\alpha$  and interleukin-6 (Anderson et al., 2012).

As an ubiquitous component of PM, black carbon (BC) is related to

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incomplete combustion of biomass and fossil fuel and is one of the main components of PM hypothesized to play an important role in the adverse health impacts of PM (Lin et al., 2016; Yang et al., 2020). Recently, studies have specifically focused on the morbidity and mortality risk associated with long-term exposure to BC (Beelen et al., 2008; Chung et al., 2015; Crouse et al., 2016; Hvidtfeldt et al., 2019; Ljungman et al., 2019). However, these investigations reported inconsistent results. For instance, Crouse et al. (2016) found a significant association between long-term exposure to BC and all-cause mortality in 2.4 million adults aged 25 years or older in Canada. Lippmann et al. (2013) and Ostro et al. (2015) identified a significant association of BC with mortality from ischemic heart disease, but not with all-cause mortality. Such discrepancies may be related to differences in study designs, including confounders, methodology and time window, population structure and air pollutant levels. Further investigations are warranted.

In the framework of a French cohort with 28 years of follow-up, we aimed to investigate the associations between long-term exposure to BC and all-cause and cardiovascular mortality, and to identify potential effect modifiers (such as sex, BMI, smoking status and the frequency of vegetable and fruit intake).

## 2. Methods

### 2.1. Study design and population

20,625 participants (15,011 men and 5614 women) in the GAZEL cohort were initially enrolled in 1989 from the French national energy and distribution company: Électricité de France-Gaz de France (EDF-GDF). All participants completed a self-administered comprehensive questionnaire at inclusion, and then a new self-administered questionnaire each year. Follow-up questionnaires administered annually during 1989–2017 achieved response rates greater than 70% and elicited responses regarding many individual variables. Residential addresses were available for every year of follow-up. A more detailed description of GAZEL cohort can be found elsewhere (Goldberg et al., 2007; Goldberg et al., 2015; Zins et al., 2009). The protocol of GAZEL cohort was approved by the French authority for data confidentiality and by the Ethics Evaluation Committee of the “Institut National de la Santé et de la Recherche Médicale” (INSERM) (IRB0000388, FWA00005831).

### 2.2. Outcomes

The data on the vital status of participants between 1989 and 2017 were collected from the EDF-GDF company. Less than 1% of the participants were lost to follow-up. Causes of death were classified by the French national cause-of-death registry based on the international classification of diseases (ICD-9 before 1999 and ICD-10 after 1999). We considered all-cause mortality and cardiovascular disease (ICD-9: 400–440; ICD-10: I00–I99). Due to the time needed to process the classification of death, the cause-specific data were delayed and only available from 1989 up to 2014.

### 2.3. Exposure assessment

For each subject, we assigned BC and PM<sub>2.5</sub> exposure in each year from 1989 to 2015, based on the historic residential addresses linked to the estimates from European 100 m × 100 m land use regression (LUR) models for the year 2010 (de Hoogh et al., 2018). BC and PM<sub>2.5</sub> measurement data were respectively obtained from PM<sub>2.5</sub> absorbance in samples collected in the European Study of Cohorts for Air Pollution Effects (ESCAPE) project (436 sites) (Eeftens et al., 2012), and from AirBase regulatory monitoring data maintained by the European Environment Agency (543 sites) (EEA, 2015). The LUR models were then developed by regressing the concentrations of each measured pollutant against a set of predictor variables (such as land-use variables, road density, altitude, and satellite-derived and chemical transport modelled

pollutant estimates); this was followed by universal kriging to explain spatial autocorrelation in the residuals. Validation explained 51% and 66% of the spatial variation in the measured BC and PM<sub>2.5</sub> concentrations, respectively. Finally, annual estimates for years 1990–2015 were derived using back- and forward-extrapolation of the 2010 estimates, by the populated weighted Danish Eulerian Hemispheric Model (DEHM) calculating concentrations at the NUTS1 level (“Nomenclature of Territorial Units for Statistics” i.e. European-Union-defined administrative regions within countries). The rescaling process was based on annual mean estimates (1990–2015) from the 26 × 26 km DEHM, and down-scaled from the original 50 × 50 km resolution using bilinear interpolation (Brandt et al., 2012). In addition, for this analysis, we further back-extrapolated PM<sub>2.5</sub> and BC exposure to 1989.

### 2.4. Covariates

We controlled for the following covariates *a priori* as potential confounding factors for health effects of long-term exposure to air pollution according to previous investigations (Hvidtfeldt et al., 2019; Lequy et al., 2019; Liang et al., 2020). Time-invariant covariates included age at inception, sex, educational level (9–11 years, 12–13 years, 14–15 years, other secondary education, or other diploma), occupation (blue-collar worker, administrative clerk, foreman/supervisor, or executive/manager), smoking status (smoker or nonsmoker) and deprivation index at the municipality level calculated in 2009 (classified using tertiles as low, middle, and high; and missing values as a category so as not to lose any participant) (Lequy et al., 2019). Time-varying covariates included marital status (single or couple), body mass index (BMI), alcohol use (abstinent, light drinker, moderate drinker, heavy drinker, or unclear pattern), areas of residence (urban, semiurban, or rural), the frequency of fruit and vegetable intake (never or less than once per week, once or twice per week, more than twice per week but not every day, every day or almost every day), and smoking intensity (cumulative pack-years).

### 2.5. Statistical analysis

As the missing rates of some covariates were relatively high (e.g. from 15% to 29% for alcohol consumption and BMI variables during the follow-up period), we used longitudinal multivariate imputations by chained equations with the ‘mice’ and ‘miceadds’ packages (Buuren and Groothuis-Oudshoorn, 2010; Robitzsch et al., 2016) in R to impute covariates with missing data, with participants identifier as a two-level imputation parameter, and a total of 10 complete datasets were generated. All the main analyses were run on the imputed dataset.

The extended Cox model was used to estimate the association between time-varying exposure on attained age as time scale and mortality with adjustment of potential covariates. The proportional hazards assumption was tested using the *cox.zph* function of survival package in R (Therneau and Lumley, 2014). We calculated the hazard ratio (HR) with the corresponding 95% confidence interval (95% CI) associated with an interquartile range (IQR) increase in the long-term exposure to BC on mortality. Since 20-year moving average of BC produced both lowest Akaike information criterion (AIC) and lowest Bayesian information criterion (BIC) in the extended Cox models (Table S1), the main results were estimated using this time window.

Given the high correlation between BC and PM<sub>2.5</sub>, we also assessed the mortality risk associated with the residuals of the linear regression using BC as dependent variable and PM<sub>2.5</sub> level as independent variable (Mostofsky et al., 2012). This technique allows for analyzing the effect of an increase in BC by holding total PM<sub>2.5</sub> constant. The following covariates were considered in the model: age at baseline, sex, areas of residence, BMI, family status, occupation, education level, vegetable and fruit intake, deprivation index, smoking intensity, smoking status, passive smoking and alcohol consumption.

Natural cubic spline functions with two to six degrees of freedom (*df*) were utilized to establish the concentration–response association

between BC and mortality (Crouse et al., 2012; Liang et al., 2020). The final two *dfs* for natural cubic spline function was selected by AIC and BIC. Linearity was evaluated using likelihood ratio  $\chi^2$  test by comparing the goodness of model fit of the linear function versus spline function for BC in the extended Cox model.

Stratified analyses were further performed to identify potential effect modifiers of the association between BC and all-cause mortality by sex, BMI ( $<25 \text{ kg/m}^2$ ,  $25\text{--}30 \text{ kg/m}^2$  and  $\geq 30 \text{ kg/m}^2$ ), smoking status, and the frequency of vegetable and fruit intake. The statistical difference in the effect estimates between two strata (i.e., male and female) was examined using a two-sample Z-test (Altman and Bland, 2003; Yang et al., 2019). The significance level was corrected by the Bonferroni-Holm method (0.05 for two samples and 0.025 for triple-group comparisons) (Aickin and Gensler, 1996).

Sensitivity analyses were conducted to test the robustness of our main findings. We assessed the long-term effects of BC on mortality using exposure at different time windows (three-year, five-year, 10-year, or 15-year moving average of BC). As the cause-specific data were only available for the period 1989–2014 and air pollution for the period 1989–2015, we also performed separated analysis restricting all-cause deaths to 1989–2014 to test the consistency of the results. All the data management and analyses were conducted using R version 3.5.1 (R Foundation for Statistical Computing).

### 3. Results

During the study period (1989–2017), the study population included 19,906 participants (corresponding to 341,402 person-years) for which we could link the geocoded residential addresses with air pollution data and available vital status information. A total of 2357 all-cause deaths were observed, with 277 cardiovascular deaths during the shorter period 1989–2014. In 1989, the study participants were on average 43.8 (SD 3.5) years old, and 14,445 participants (72.6%) were men. The annual mean concentrations of BC and  $\text{PM}_{2.5}$  were  $2.60 \times 10^{-5}/\text{m}$  (SD 0.95) and  $29.76 \mu\text{g}/\text{m}^3$  (SD 5.49), respectively. The baseline characteristics of the participants are presented in Table 1.

Table 2 shows the associations between 20-year moving average of BC and all-cause mortality and cardiovascular mortality. The estimated HRs with an IQR increase ( $0.86 \times 10^{-5}/\text{m}$ ) in BC was 1.14 (95 %CI: 1.07–1.22) for all-cause mortality and 1.15 (95 %CI: 0.95–1.38) for cardiovascular mortality, with the corresponding estimates of 1.17 (95 %CI: 1.10–1.24) and 1.16 (95 %CI: 0.98–1.38) for the residuals of BC (IQR:  $0.57 \times 10^{-5}/\text{m}$ ). Compared to the first quintile, the estimated HRs of BC at second, third, fourth and fifth quintiles on all-cause mortality were 0.98 (95 %CI: 0.86–1.10), 0.87 (95 %CI: 0.76–1.00), 1.09 (95 %CI: 0.94–1.26) and 1.18 (95 %CI: 1.00–1.39).

The exposure–response association between 20-year moving average of BC and all-cause mortality was monotonic but nonlinear (likelihood ratio test:  $\chi^2 = 5.347$ ;  $P = 0.021$ ), with a much steeper slope at high levels of BC, particularly those higher than  $4 \times 10^{-5}/\text{m}$  (the 95th percentile) (Fig. 1). However, the association between residuals of BC and all-cause mortality was monotonic and linear ( $\chi^2 = 0.165$ ;  $P = 0.685$ ) (Fig. S1). Similar associations between BC and residual of BC with cardiovascular mortality were observed in Figs. S2–S3 ( $\chi^2 = 7.692$ ,  $P = 0.006$ ;  $\chi^2 = 2.227$ ,  $P = 0.136$ ).

In the stratified analyses, the association between BC exposure and all-cause mortality was not modified by sex, BMI, or frequency of vegetable and fruit intake (Table 3). However, the estimated HRs were significantly stronger among nonsmokers compared to smokers. Similar trends between subgroups were observed for the residuals of BC, with an additional significant difference between strata of the frequency of vegetable and fruit intake.

In the sensitivity analyses, the results were very similar using 3 to 15-year moving average of exposure, although the associations were slightly attenuated in the models with shorter exposure windows (Table S2). In addition, when using data during 1989–2014 for all-cause

**Table 1**

Socio-demographic characteristics and exposure to air pollution of GAZEL cohort participants at baseline (341,402 person years during the 28-year follow-up).

Variables	Total (n = 19,906)	Alive (n = 17,549)	Dead (n = 2357)	P-value
Age (years)	43.75 (3.50)	43.60 (3.51)	44.83 (3.30)	<0.001
Gender (male)	14,445 (72.6%)	12,465 (71.0%)	1980 (84%)	<0.001
BMI	25.67 (3.63)	25.61 (3.58)	26.11 (4.00)	<0.001
Smoking status				<0.001
Smoker	3951 (19.8%)	3090 (17.6%)	861 (36.5%)	
Nonsmoker	15,955 (80.2%)	14,459 (82.4%)	1496 (63.5%)	
Passive smoking (Yes)	11,535 (57.9%)	10,119 (57.7%)	1416 (60.1%)	0.027
Pack-years among smokers	19.50 (13.87)	25.96 (15.18)	17.56 (12.77)	<0.001
Vegetable intake (per week)				<0.001
Never or less than once	174 (0.9%)	124 (0.7%)	50 (2.1%)	
Once or twice	1593 (8%)	1317 (7.5%)	276 (11.7%)	
More than twice but not every day	4705 (23.6%)	4067 (23.2%)	638 (27.1%)	
Every or almost every day	13,434 (67.5%)	12,041 (68.6%)	1393 (59.1%)	
Alcohol use				<0.001
Abstinent	2196 (11%)	1911 (10.9%)	285 (12.1%)	
Light drinker	8582 (43.1%)	7730 (44.0%)	852 (36.1%)	
Moderate drinker	4544 (22.8%)	4000 (22.8%)	544 (23.1%)	
Heavy drinker	2441 (12.3%)	2053 (11.7%)	388 (16.5%)	
Unclear	2143 (10.8%)	1855 (10.6%)	288 (12.2%)	
Socioeconomic status based on occupation				<0.001
Blue-collar worker	1214 (6.1%)	981 (5.6%)	233 (9.9%)	
Administrative clerk	1487 (7.5%)	1291 (7.4%)	196 (8.3%)	
Foreman or supervisor	11,130 (55.9%)	9818 (55.9%)	1312 (55.7%)	
Executive	6050 (30.4%)	5436 (31%)	614 (26.1%)	
Living in a couple	17,218 (86.5%)	15,255 (86.9%)	1963 (83.3%)	<0.001
Education level				<0.001
9–11 years	14,710 (73.9%)	12,865 (73.3%)	1845 (78.3%)	
12–13 years	1449 (7.3%)	1295 (7.4%)	154 (6.5%)	
14–15 years	1136 (5.7%)	1028 (5.9%)	108 (4.6%)	
Other secondary education	2150 (10.8%)	1956 (11.1%)	194 (8.2%)	
Other diploma	461 (2.3%)	405 (2.3%)	56 (2.4%)	
Deprivation index				0.593
Low	6702 (33.7%)	5894 (33.6%)	808 (34.3%)	
Median	6592 (33.1%)	5833 (33.2%)	759 (32.2%)	
High	6612 (33.2%)	5822 (33.2%)	790 (33.5%)	
Area of residence				0.073
Urban	7433 (37.3%)	6576 (37.5%)	857 (36.4%)	
Semiurban	6723 (33.8%)	5958 (34.0%)	765 (32.5%)	
Rural	5702 (28.6%)	4973 (28.3%)	729 (30.9%)	

(continued on next page)

**Table 1** (continued)

Variables	Total (n = 19,906)	Alive (n = 17,549)	Dead (n = 2357)	P-value
PM <sub>2.5</sub> (μg/m <sup>3</sup> )	29.41 (5.51)	29.46 (5.44)	29.04 (5.97)	0.001
Black carbon (10 <sup>-5</sup> /m)	2.58 (0.99)	2.58 (0.99)	2.57 (1.02)	0.638

Note. The values are mean (sd) for continuous variables and number (percentage) for categorical variables.

**Table 2**

Association between 20-year moving average of black carbon and residuals of black carbon (quintiles and per IQR increase) on all-cause mortality and cardiovascular mortality, as hazard ratios (95 %CI).

Variable	All cause		Cardiovascular disease	
	Black carbon	Residual of black carbon	Black carbon	Residual of black carbon
Quintile 1	Ref	Ref	Ref	Ref
Quintile 2	0.98 (0.86, 1.10)	1.27 (1.09, 1.47)	0.76 (0.53, 1.09)	0.92 (0.61, 1.38)
Quintile 3	0.87 (0.76, 1.00)	1.29 (1.11, 1.50)	<b>0.63 (0.42, 0.95)</b>	1.03 (0.69, 1.55)
Quintile 4	1.09 (0.94, 1.26)	1.30 (1.11, 1.52)	0.67 (0.44, 1.04)	1.16 (0.77, 1.74)
Quintile 5	<b>1.18 (1.00, 1.39)</b>	<b>1.47 (1.25, 1.73)</b>	1.08 (0.69, 1.68)	1.13 (0.73, 1.76)
Per IQR	<b>1.14 (1.07, 1.22)</b>	<b>1.17 (1.10, 1.24)</b>	1.15 (0.95, 1.38)	1.16 (0.98, 1.38)

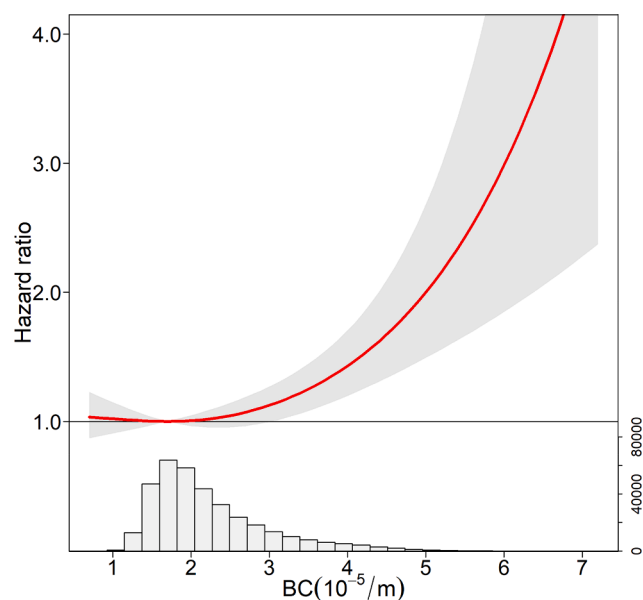
Note. The bolded estimates correspond to  $P$ -value < 0.05. Covariates included age at inception, sex, educational level, occupation, smoking status, smoking intensity, deprivation index, marital status, BMI, alcohol use, areas of residence and frequency of fruit and vegetable intake. Interquartile range (IQR) of BC and residuals of BC was  $0.86 \times 10^{-5}/m$  and  $0.57 \times 10^{-5}/m$ , respectively.

**Table 3**

Hazard ratio (and 95% confidence interval) for the association between black carbon and its residuals (per IQR increase) and mortality, stratified by sex, BMI, smoking status and frequency of vegetable and fruit intake.

Variables	Black carbon	Residuals of black carbon
Sex		
Male	1.08 (1.00,1.16)	1.11(1.04,1.18)
Female	1.22 (1.03,1.45)	1.11(0.95,1.30)
P for difference test	0.200	0.999
BMI (kg/m <sup>2</sup> )		
<25	1.12 (1.02,1.23)	1.14(1.05,1.24)
25–30	1.15 (1.02,1.28)	1.08(0.98,1.19)
≥30	1.01 (0.76,1.32)	1.23(1.00,1.51)
P for difference test (Low vs Median)	0.725	0.407
P for difference test (Obese vs Median)	0.394	0.263
Smoking status		
Smokers	1.01 (0.91,1.12)	1.03(0.94,1.12)
Nonsmokers	1.21 (1.10,1.33)	1.19(1.10,1.30)
P for difference test	<b>0.012</b>	<b>0.019</b>
Vegetable and fruit intake		
Low	1.19 (1.03,1.39)	1.28(1.11,1.47)
High	1.10 (1.02,1.19)	1.09(1.02,1.17)
P for difference test	0.360	<b>0.044</b>

Note. The low level of vegetable and fruit intake denotes twice or less per week; high level denotes more than twice per week; Interquartile range (IQR) of BC and residuals of BC was  $0.86 \times 10^{-5}/m$  and  $0.57 \times 10^{-5}/m$ , respectively.



**Fig. 1.** The dose-response association between 20-year moving average of black carbon and all-cause mortality using a natural cubic spline with two degrees of freedom.

mortality, HRs were 1.19 (95 %CI: 1.12–1.28) and 1.15 (95 %CI: 1.08–1.23) respectively per an IQR increase in BC and residuals of BC (Table S3), which were similar to the main results (Table S3). Another sensitivity analysis based on the complete data set without multiple imputations was also performed. The estimate remained relatively similar after exclusion of the cases with missing values but with wider

confidence interval [HR = 1.29 (95 %CI: 1.14–1.47)].

#### 4. Discussion

Our prospective study investigated the associations between long-term exposure to BC and all-cause, and cardiovascular mortality in a large French cohort, involving 19,906 participants, over a 28-year follow-up period. Increased cumulative exposures to BC were associated with increased risks of all-cause and cardiovascular mortality. The risk was stronger among nonsmokers.

Consistent with previous studies (Aickin and Gensler, 1996; Crouse et al., 2016; Gilmour et al., 2006; Goldberg et al., 2007; Hvidtfeldt et al., 2019; Lipfert et al., 2009; Ostro et al., 2010; Robitzsch et al., 2016), we observed a significant association between long-term exposure to BC and all-cause mortality. This association was reduced when using shorter exposure windows. For example, in this study, the HR was 1.09 (1.01–1.17) per IQR increase using 3-year moving average of BC, compared to HR of 1.14 (1.07–1.22) using a 20-year moving average of BC (Table S2). Consistently, previous studies considering shorter exposure windows of BC also reported relatively smaller effect estimates. For instance, Ostro et al. (2010) reported a HR of 1.10 (95 %CI: 1.03–1.19) per IQR increase of exposure, using the current year exposure to BC, on the all-cause mortality in California Teachers Study. Crouse et al. (2016) observed a mortality risk of 1.04 (1.03–1.05) per  $1 \mu\text{g}/\text{m}^3$  increase in BC exposure at the current year, on all-cause mortality in the Canadian Census Health and Environment Cohort study. In addition, our study revealed a significant nonlinear association between long-term exposure to BC and mortality, with more pronounced effect at higher level of BC. This evidence indicates that alleviation in concentration of BC in high polluted areas (or high polluted period) could lead to considerable reduction in the mortality induced by this pollutant.

There has been very little previous evidence on the effect



modification of the association between long-term exposure to BC and mortality. In the present study, we observed a stronger association between BC and mortality among nonsmokers compared to smokers. Consistently, a study in China reported stronger associations between long-term effect of PM<sub>2.5</sub>, and cardiovascular incidence and mortality among nonsmokers (Liang et al., 2020). It has been hypothesized that smoking and air pollutants may act through similar pathways to induce health risks, including oxidative stress, inflammation and change in circulatory and respiratory functions (Gilmour et al., 2006; Künzli et al., 2005). Among smokers, a large proportion of diseases is attributable to smoking, and therefore proportionately less to air pollutants; by contrast a larger proportion of diseases among nonsmokers is attributable to air pollutants (Künzli et al., 2005).

In addition, females (vs. males) and those consuming vegetable or fruit less (vs. more) than twice a week showed increased risk of mortality associated with BC exposure, although there was considerable overlap in the risk estimates between the subgroups. The difference on sex-specific risk to air pollution may be explained by occupational and physiological differences. Compared with males, females have relatively smaller lungs and narrower airways, favoring cumulative adverse effect of air pollution on health (Yunginger et al., 1992). Regarding dietary intake, vegetables and fruits rich in Vitamins C, E and A and polyphenols may help to detoxify the harmful impact of air pollution through a variety of biological activities, such as anti-tumorigenic, anti-oxidants and antiviral actions (Kampa and Castanas, 2008). In addition, more frequent fruit-vegetable intake may be associated with a healthier lifestyle (Johansson et al., 1999), such as regular leisure physical activities and taking protective behaviors, possibly reducing the harmful effects of air pollution.

There are several important strengths in the present study. First, we conducted a more in-depth analysis on the relationship between BC exposure and mortality compared to previous studies, by analyzing the mortality risks not only of BC but also of its residuals after removing the influence of total PM<sub>2.5</sub> (Mostofsky et al., 2012). Second, this study included a very large number of subjects (>19,000) throughout mainland France over a 28-year follow-up period, with workers from wide-ranging occupations and socio-economic conditions. These characteristics could enhance the generalizability of our results. Third, the data collection from the company and from the subjects themselves allowed us to obtain detailed information on residential histories and a host of other relevant covariates.

Our study has several important public health implications. First, a nonlinear association between BC and mortality was observed in the present study, with more pronounced effects at the higher levels of BC. This result suggests that incremental improvements in air quality will contribute to considerable public health benefits, even in countries like France with relatively low air pollution levels. In order to substantially reduce the burden of disease attributable to traffic-related air pollution, stricter regulation and tighter control policies are still warranted to reduce the source emissions from vehicles, and encourage the use of electric vehicles, but mostly public transport, biking and walking (Faiz et al., 1996). Previous studies have advocated that interventions to reduce concentrations of particulate matter require a concerted action by a host of sectors (environment, transport, energy, health, housing) and cooperation from regional and international levels (Kelly and Fussell, 2015; Sanchez et al., 2020). Personal measures, such as reducing outdoor activities or using air purifier indoor and wearing face mask are recommended for the public during high air pollution episodes (Laumbach et al., 2015).

Several limitations should be noted. First, time-varying covariates were collected annually using a self-reported questionnaire survey of each participant, which might cause potential information bias. However, the resulting bias is likely to be random and non-differential. Second, certain potentially confounding environmental stressors, such as noise, temperature, indoor air pollution, gaseous outdoor air pollutants (e.g., sulfur dioxide and ozone), other particulate matter

constituents (e.g., organic carbon, sulfate and nitrate), and neighborhood characteristics, such as residential greenness, blue space, and access to public health resources (ie, public health service and healthcare) were not available in this study. In addition to the environmental factors, the role of some other factors should not be ignored. For instance, the data on time-activity patterns and social engagement were unavailable in this study. However, we have attempted to adjust for as much as possible personal and contextual factors in the model, including smoking history, passive smoking and detailed fruit or vegetable intake.

Furthermore, since the only place at which outdoor air pollution could be estimated was the GAZEL participants' home addresses, and since people spend a lot of time indoors or at other outdoor locations, our estimates of long-term exposure to BC and PM<sub>2.5</sub> certainly involves misclassification error. However, after reviewing studies available up to 2017, Hoek suggested that exposure characterized at the residential address only presents a modest bias towards the null effect estimates (Hoek, 2017). In addition, the GAZEL cohort study participants were not strictly representative of the general population, with unbalanced sex-ratio (around 70% of men), thus some caution should be taken regarding the generalizability of our findings. As GAZEL is a cohort set in an occupational cohort, a part of the participants may have been exposed to certain specific occupational exposures. However, previous study reported that the profile of mortality and distribution of health determinants among GAZEL population and general population are quite similar (Poncet et al., 2003). Finally, given the differences in socioeconomic profiles, health conditions and/or air pollution exposure between regions of the world, caution should be exercised in generalizing our results to other populations.

The underlying biological mechanisms linking ambient BC exposure and mortality are not fully understood. It has been suggested that exposure to BC may induce reactive oxygen species-mediated DNA damage, cause increase in systemic inflammation, oxidative stress, platelet activation and atherosclerosis, change in heart rate variability, blood pressure and ST-segment depression, and shift in adipose tissue macrophage (Bind et al., 2012; Wilker et al., 2010). These responses induced by the long-term exposure to BC may cause serious chronic health outcomes, such as myocardial infarction, ischemic heart disease, asthma, cancers and other conditions that lead to premature mortality.

## 5. Conclusions

This study in the French GAZEL cohort provides important evidence that long-term exposure to BC is a significant risk factor for mortality, independently of total PM<sub>2.5</sub>. A non-linear association between BC and mortality was observed, with much stronger risk at the higher levels of BC. Our findings contribute to the understanding of the chronic health effect of air pollution in relatively low air pollution environments.

## CRedit authorship contribution statement

**Jun Yang:** Conceptualization, Writing – original draft, Formal analysis. **Mohammad Javad Zare Sakhvidi:** Conceptualization, Writing – review & editing, Formal analysis. **Kees Hoogh:** Resources, Writing – review & editing. **Danielle Vienneau:** Resources, Writing – review & editing. **Jack Siemiatyck:** Resources, Writing – review & editing. **Marie Zins:** Resources, Writing – review & editing. **Marcel Goldberg:** . **Jie Chen:** Resources, Writing – review & editing. **Emeline Lequy:** Conceptualization, Resources, Writing – review & editing. **Bénédicte Jacquemin:** Conceptualization, Writing – review & editing, Funding acquisition, Supervision.

## 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.

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## Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.envint.2021.106805>.

## References

- Aickin, M., Gensler, H., 1996. Adjusting for multiple testing when reporting research results: the Bonferroni vs Holm methods. *Am. J. Publ. Health* 86 (5), 726–728.
- Altman, D.G., Bland, J.M., 2003. Interaction revisited: the difference between two estimates. *BMJ* 326, 219.
- Anderson, J.O., Thundiyil, J.G., Stolbach, A., 2012. Clearing the air: a review of the effects of particulate matter air pollution on human health. *J. Med. Toxicol.: Off. J. Am. College Med. Toxicol.* 8 (2), 166–175.
- Beelen, R., Hoek, G., van den Brandt, P.A., Goldbohm, R.A., Fischer, P., Schouten, L.J., Jerrett, M., Hughes, E., Armstrong, B., Brunekreef, B., 2008. Long-term effects of traffic-related air pollution on mortality in a Dutch cohort (NLCS-AIR study). *Environ. Health Perspect.* 116 (2), 196–202.
- Bind, M.-A., Baccarelli, A., Zanobetti, A., Tarantini, L., Suh, H., Vokonas, P., et al., 2012. Air pollution and markers of coagulation, inflammation and endothelial function: associations and epigenetic-environment interactions in an elderly cohort. *Epidemiol. (Cambridge, Mass.)* 23, 332.
- Brandt, J., Silver, J.D., Frohn, L.M., Geels, C., Gross, A., Hansen, A.B., Hansen, K.M., Hedegaard, G.B., Skjøth, C.A., Villadsen, H., Zare, A., Christensen, J.H., 2012. An integrated model study for Europe and North America using the Danish Eulerian Hemispheric Model with focus on intercontinental transport of air pollution. *Atmos. Environ.* 53, 156–176.
- Buuren, S.v., Groothuis-Oudshoorn, K., 2010. Mice: multivariate imputation by chained equations in R. *J. Stat. Softw.* 1–68.
- Chung, Yeonseung, Dominici, Francesca, Wang, Yun, Coull, Brent A., Bell, Michelle L., 2015. Associations between long-term exposure to chemical constituents of fine particulate matter (PM<sub>2.5</sub>) and mortality in Medicare enrollees in the eastern United States. *Environ. Health Perspect.* 123 (5), 467–474.
- Crouse, Dan L., Peters, Paul A., van Donkelaar, Aaron, Goldberg, Mark S., Villeneuve, Paul J., Brion, Orly, Khan, Saeeda, Atari, Dominic Odwa, Jerrett, Michael, Pope, C. Arden, Brauer, Michael, Brook, Jeffrey R., Martin, Randall V., Stieb, David, Burnett, Richard T., 2012. Risk of nonaccidental and cardiovascular mortality in relation to long-term exposure to low concentrations of fine particulate matter: a Canadian national-level cohort study. *Environ. Health Perspect.* 120 (5), 708–714.
- Crouse, Dan L., Philip, Sajeev, van Donkelaar, Aaron, Martin, Randall V., Jessiman, Barry, Peters, Paul A., Weichenthal, Scott, Brook, Jeffrey R., Hubbell, Bryan, Burnett, Richard T., 2016. A new method to jointly estimate the mortality risk of long-term exposure to fine particulate matter and its components. *Sci. Rep.* 6 (1) <https://doi.org/10.1038/srep18916>.
- de Hoogh, Kees, Chen, Jie, Gulliver, John, Hoffmann, Barbara, Hertel, Ole, Ketzel, Matthias, Bauwelinck, Mariska, van Donkelaar, Aaron, Hvidtfeldt, Ulla A., Katsoyanni, Klea, Klompmaker, Jochem, Martin, Randal V., Samoli, Evangelia, Schwartz, Per E., Stafoggia, Massimo, Bellander, Tom, Strak, Maciej, Wolf, Kathrin, Vienneau, Danielle, Brunekreef, Bert, Hoek, Gerard, 2018. Spatial PM<sub>2.5</sub>, NO<sub>2</sub>, O<sub>3</sub> and BC models for Western Europe – evaluation of spatiotemporal stability. *Environ. Int.* 120, 81–92.
- EEA, 2015. The European Air Quality Database, Version 8.
- Eeftens, Marloes, Tsai, Ming-Yi, Ampe, Christophe, Anwander, Bernhard, Beelen, Rob, Bellander, Tom, Cesaroni, Giulia, Cirach, Marta, Cyrys, Josef, de Hoogh, Kees, De Nazelle, Audrey, de Vocht, Frank, Declercq, Christophe, Dèdèlé, Audrius, Eriksen, Kirsten, Galassi, Claudia, Gražulevičienė, Regina, Grivas, Georgios, Heinrich, Joachim, Hoffmann, Barbara, Iakovides, Minas, Ieichen, Alex, Katsoyanni, Klea, Korek, Michal, Krämer, Ursula, Kuhlbusch, Thomas, Lanki, Timo, Madsen, Christian, Meliefste, Kees, Mölter, Anna, Mosler, Gioia, Nieuwenhuijsen, Mark, Oldenwening, Marieke, Pennanen, Anjo, Probst-Hensch, Nicole, Quass, Ulrich, Raaschou-Nielsen, Ole, Ranzi, Andrea, Stephanou, Euripides, Sugiri, Dorothee, Udvary, Orsolya, Vaskövi, Éva, Weinmayr, Gudrun, Brunekreef, Bert, Hoek, Gerard, 2012. Spatial variation of PM<sub>2.5</sub>, PM<sub>10</sub>, PM<sub>2.5</sub> absorbance and PM<sub>coarse</sub> concentrations between and within 20 European study areas and the relationship with NO<sub>2</sub> – results of the ESCAPE project. *Atmos. Environ.* 62, 303–317.
- Faiz, A., Weaver, C.S., Walsh, M.P., 1996. Air Pollution from Motor Vehicles: Standards and Technologies for Controlling Emissions. World Bank Publications.
- GBD, 2018. Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *The Lancet* 392(392), 1923–1994.
- Gilmour, M. Ian, Jaakkola, Maritta S., London, Stephanie J., Nel, Andre E., Rogers, Christine A., 2006. How exposure to environmental tobacco smoke, outdoor air pollutants, and increased pollen burdens influences the incidence of asthma. *Environ. Health Perspect.* 114 (4), 627–633.
- Goldberg, M., Leclerc, A., Bonenfant, S., Chastang, J.F., Schmaus, A., Kaniewski, N., et al., 2007. Cohort profile: the GAZEL cohort study. *Int. J. Epidemiol.* 36, 32–39.
- Goldberg, M., Leclerc, A., Zins, M., 2015. Cohort profile update: the GAZEL cohort study. *Int. J. Epidemiol.* 44, 77–77g.
- Hoek, Gerard, 2017. Methods for assessing long-term exposures to outdoor air pollutants. *Curr. Environ. Health Rep.* 4 (4), 450–462.
- Hvidtfeldt, Ulla Arthur, Sørensen, Mette, Geels, Camilla, Ketzel, Matthias, Khan, Jibrán, Tjønneland, Anne, Overvad, Kim, Brandt, Jørgen, Raaschou-Nielsen, Ole, 2019. Long-term residential exposure to PM<sub>2.5</sub>, PM<sub>10</sub>, black carbon, NO<sub>2</sub>, and ozone and mortality in a Danish cohort. *Environ. Int.* 123, 265–272.
- Johansson, Lars, Thelle, Dag S., Solvoll, Kari, Bjørneboe, Gunn-Elin A., Drevon, Christian A., 1999. Healthy dietary habits in relation to social determinants and lifestyle factors. *Br. J. Nutr.* 81 (3), 211–220.
- Kampa, Marilena, Castanas, Elias, 2008. Human health effects of air pollution. *Environ. Pollut.* 151 (2), 362–367.
- Kelly, Frank J., Fussell, Julia C., 2015. Air pollution and public health: emerging hazards and improved understanding of risk. *Environ. Geochem. Health* 37 (4), 631–649.
- Künzli, Nino, Jerrett, Michael, Mack, Wendy J., Beckerman, Bernardo, LaBree, Laurie, Gilliland, Frank, Thomas, Duncan, Peters, John, Hodis, Howard N., 2005. Ambient air pollution and atherosclerosis in Los Angeles. *Environ. Health Perspect.* 113 (2), 201–206.
- Laumbach, R., Meng, Q., Kipen, H., 2015. What can individuals do to reduce personal health risks from air pollution? *J. Thoracic Disease* 7, 96–107.
- Lequy, Emeline, Siemiatycki, Jack, Leblond, Sébastien, Meyer, Caroline, Zhivin, Sergey, Vienneau, Danielle, de Hoogh, Kees, Goldberg, Marcel, Zins, Marie, Jacquemin, Bénédicte, 2019. Long-term exposure to atmospheric metals assessed by mosses and mortality in France. *Environ. Int.* 129, 145–153.
- Liang, F., Liu, F., Huang, K., Yang, X., Li, J., Xiao, Q., et al., 2020. Long-term exposure to fine particulate matter and cardiovascular disease in China. *J. Am. Coll. Cardiol.* 75, 707–717.
- Lin, Hualiang, Tao, Jun, Du, Yaodong, Liu, Tao, Qian, Zhengmin, Tian, Linwei, Di, Qian, Rutherford, Shannon, Guo, Lingchuan, Zeng, Weilin, Xiao, Jianpeng, Li, Xing, He, Zhihui, Xu, Yanjun, Ma, Wenjun, 2016. Particle size and chemical constituents of ambient particulate pollution associated with cardiovascular mortality in Guangzhou, China. *Environ. Pollut.* 208, 758–766.
- Lipfert, Frederick W., Wyzga, Ronald E., Baty, Jack D., Miller, J. Philip, 2009. Air pollution and survival within the Washington University–EPRI Veterans cohort: risks based on modeled estimates of ambient levels of hazardous and criteria air pollutants. *J. Air Waste Manag. Assoc.* 59 (4), 473–489.
- Lippmann, M., Chen, L., Gordon, T., Ito, K., Thurston, G., 2013. National Particle Component Toxicity (NPACT) Initiative: integrated epidemiologic and toxicologic studies of the health effects of particulate matter components. *Research report (Health Effects Institute)*, 5–13.
- Ljungman, P.L., Andersson, N., Stockfelt, L., Andersson, E.M., Nilsson Sommar, J., Eneroth, K., et al., 2019. Long-term exposure to particulate air pollution, black carbon, and their source components in relation to ischemic heart disease and stroke. *Environ. Health Perspect.* 127.
- Mostofsky, E., Schwartz, J., Coull, B.A., Koutrakis, P., Wellenius, G.A., Suh, H.H., et al., 2012. Modeling the association between particle constituents of air pollution and health outcomes. *Am. J. Epidemiol.* 176, 317–326.
- Ostro, Bart, Lipsett, Michael, Reynolds, Peggy, Goldberg, Debbie, Hertz, Andrew, Garcia, Cynthia, Henderson, Katherine D., Bernstein, Leslie, 2010. Long-term exposure to constituents of fine particulate air pollution and mortality: results from the California Teachers Study. *Environ. Health Perspect.* 118 (3), 363–369.
- Ostro, B., Hu, J., Goldberg, D., Reynolds, P., Hertz, A., Bernstein, L., Kleeman, M.J., 2015. Associations of mortality with long-term exposures to fine and ultrafine particles, species and sources: results from the California Teachers Study Cohort. *Environ. Health Perspect.* 123, 549.
- Poncet, M., Chevalier, A., Bumsel, F., Lahon, G., 2003. Mortality among active workers at EDG-GDF: social and occupational disparities and evolution. *Rev. Epidemiol. Sante Publique* 51, 481–491.
- Robitzsch, A., Grund, S., Henke, T., 2016. Miceadds: Some additional multiple imputation functions, especially for mice. R package version, vol. 1, pp. 7–8.
- Sanchez, Kristen A., Foster, Margaret, Nieuwenhuijsen, Mark J., May, Anthony D., Ramani, Tara, Zietsman, Joe, Khreis, Haneen, 2020. Urban policy interventions to reduce traffic emissions and traffic-related air pollution: protocol for a systematic evidence map. *Environ. Int.* 142, 105826. <https://doi.org/10.1016/j.envint.2020.105826>.
- Therneau, T.M., Lumley, T., 2014. Package ‘survival’. Survival analysis Published on CRAN, vol. 2, pp. 3.
- Wilker, Elissa H., Baccarelli, Andrea, Suh, Helen, Vokonas, Pantel, Wright, Robert O., Schwartz, Joel, 2010. Black carbon exposures, blood pressure, and interactions with single nucleotide polymorphisms in MicroRNA processing genes. *Environ. Health Perspect.* 118 (7), 943–948.
- Yang, Jun, Yin, Peng, Sun, Jimin, Wang, Boguang, Zhou, Maigeng, Li, Mengmeng, Tong, Shilu, Meng, Bohan, Guo, Yuming, Liu, Qiyong, 2019. Heatwave and mortality in 31 major Chinese cities: Definition, vulnerability and implications. *Sci. Total Environ.* 649, 695–702.
- Yang, Jun, Zhou, Maigeng, Li, Mengmeng, Yin, Peng, Hu, Jianlin, Zhang, Chunlin, Wang, Hao, Liu, Qiyong, Wang, Boguang, 2020. Fine particulate matter constituents

and cause-specific mortality in China: a nationwide modelling study. *Environ. Int.* 143, 105927. <https://doi.org/10.1016/j.envint.2020.105927>.  
Yunginger, J.W., Reed, C.E., O'Connell, E.J., O'Fallon, W.M., Silverstein, M.D., 1992. A community-based study of the epidemiology of asthma. Incidence rates, 1964–1983. *Am. Rev. Resp. Disease* 192 (146), 888–894.

Zins, Marie, Leclerc, Annette, Goldberg, Marcel, 2009. The French GAZEL Cohort Study: 20 years of epidemiologic research. *Adv. Life Course Res.* 14 (4), 135–146.