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Full length article



## Long-term exposure to air pollution and mortality from dementia, psychiatric disorders, and suicide in a large pooled European cohort: ELAPSE study

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## ABSTRACT

Ambient air pollution is an established risk factor for premature mortality from chronic cardiovascular, respiratory and metabolic diseases, while evidence on neurodegenerative diseases and psychiatric disorders remains limited. We examined the association between long-term exposure to air pollution and mortality from dementia, psychiatric disorders, and suicide in seven European cohorts. Within the multicenter project 'Effects of Low-Level Air Pollution: A Study in Europe' (ELAPSE), we pooled data from seven European cohorts from six countries. Based on the residential addresses, annual mean levels of fine particulate matter (PM<sub>2.5</sub>), nitrogen dioxide (NO<sub>2</sub>), black carbon (BC), ozone (O<sub>3</sub>), and 8 PM<sub>2.5</sub> components were estimated using Europe-wide hybrid land-use regression models. We applied stratified Cox proportional hazard models to investigate the associations between air pollution and mortality from dementia, psychiatric disorders, and suicide. Of 271,720 participants, 900 died from dementia, 241 from psychiatric disorders, and 164 from suicide, during a mean follow-up of 19.7 years. In fully adjusted models, we observed positive associations of NO<sub>2</sub> (hazard ratio [HR] = 1.38; 95 % confidence interval [CI]: 1.13, 1.70 per 10 µg/m<sup>3</sup>), PM<sub>2.5</sub> (HR = 1.29; 95 % CI: 0.98, 1.71 per 5 µg/m<sup>3</sup>), and BC (HR = 1.37; 95 % CI: 1.11, 1.69 per 0.5 × 10<sup>-5</sup>/m) with psychiatric disorders mortality, as well as with suicide (NO<sub>2</sub>: HR = 1.13 [95 % CI: 0.92, 1.38]; PM<sub>2.5</sub>: HR = 1.19 [95 % CI: 0.76, 1.87]; BC: HR = 1.08 [95 % CI: 0.87, 1.35]), and no association with dementia mortality. We did not detect any positive associations of O<sub>3</sub> and 8 PM<sub>2.5</sub> components with any of the three mortality outcomes. Long-term exposure to NO<sub>2</sub>, PM<sub>2.5</sub>, and BC may lead to premature mortality from psychiatric disorders and suicide.

## 1. Introduction

Long-term exposure to ambient air pollution is an established risk factor for premature mortality from cardiovascular and cerebrovascular disease, chronic obstructive pulmonary disease (COPD), lower respiratory infections, lung cancer, and diabetes (Health Effects Institute, 2020; World Health, 2021). Evidence on mortality from other causes, including neurodegenerative diseases and psychiatric disorders, remains limited.

Emerging experimental data show that air pollution has a detrimental impact on brain pathology through neuroinflammation and oxidative stress (Calderon-Garciduenas et al., 2002; Calderón-Garciduenas et al., 2016; Calderón-Garciduenas et al., 2003; Calderón-Garciduenas et al., 2004; Hahad et al., 2020; Jayaraj et al., 2017; Maher et al., 2016) and that these mechanisms can adversely impact cognitive functioning and ultimately lead to the development of dementia (Delgado-Saborit et al., 2021). In line with this, solid epidemiological evidence has linked long-term exposure to air pollution, including particulate matter with diameter <2.5 µm (PM<sub>2.5</sub>) and nitrogen dioxide (NO<sub>2</sub>), to cognitive decline in the elderly (Grande et al., 2021; Kulick et al., 2020; Russ et al., 2021; Tonne et al., 2014; Weuve et al., 2012) and the incidence of dementia (Carey et al., 2018; Chang et al., 2014; Chen et al., 2017; Grande et al., 2021; Ilango et al., 2020; Kioumourtoglou et al., 2016; Mortamais et al., 2021; Oudin et al., 2016; Oudin et al., 2018; Shaffer et al., 2021; Shi et al., 2021; Shi et al., 2020; Smargiassi et al., 2020; Sullivan et al., 2021; Wu et al., 2022). Still, several aspects of the association between air pollution and dementia remain unresolved. Only three studies addressed dementia mortality: two showing an association with PM<sub>2.5</sub>, with one among US veterans (Bowe et al., 2019) and the other in a large administrative Dutch study of 10 million people (Klompaker et al., 2021); meanwhile, another Dutch study based on a national health survey detected no association with dementia mortality, nor with overall and cardiorespiratory mortality (Klompaker et al., 2020). It is not known which pollutants are most relevant for dementia development: only one study to date assessed the impact of black carbon (BC) (Klompaker et al., 2020); only a few provided two- or multi-pollutant models' results, while none have considered specific elemental components or sources of PM.

Air pollution-induced neuroinflammation and oxidative stress are also relevant for mental and emotional health, as shown by studies of air pollution-related depressive responses in mice (Davis et al., 2013;

Fonken et al., 2011). Still, epidemiological evidence on air pollution and mental health is much more limited than that for dementia. Current studies mainly focus on short-term exposures, which show that exposure to air pollution over several days could trigger psychiatric responses, including depressive symptoms and hospital admissions, as well as attempted and completed suicide (Heo et al., 2021; Liu et al., 2021a). The association with long-term exposure to air pollution has been primarily investigated in cross-sectional studies with data on the prevalence of psychiatric disorders, mainly depression and anxiety (Braithwaite et al., 2019). There are only a few studies on the onset of psychiatric disorders (all focusing on depression), while associations with other major psychiatric disorders, including anxiety, substance use, bipolar and psychotic disorder, and eating disorders, remain to be explored. Numerous studies have linked air pollution to depression: a South Korean study linked PM<sub>2.5</sub> to major depressive disorder (Kim et al., 2016); the US Nurses' Health Study linked PM<sub>2.5</sub> and ozone (O<sub>3</sub>) to the onset of depression (Kioumourtoglou et al., 2017); a South Korean Health Insurance record study linked particulate matter with diameter less than 10 µm (PM<sub>10</sub>) and carbon monoxide to the onset of depression (Kim et al., 2021), and another South Korean screening study detected association of PM<sub>10</sub> with depression onset; however, no study has shown an association of PM<sub>2.5</sub> (Zhang et al., 2019). Only one large South Korean study to date examined long-term exposure to air pollution with suicide, reporting strong associations with PM<sub>10</sub> and NO<sub>2</sub> (Min et al., 2018).

The 'Effects of Low-Level Air Pollution: A Study in Europe' (ELAPSE) project recently showed that long-term exposure to low levels of air pollution was associated with increased risks of premature mortality from natural causes, cardiovascular and chronic respiratory diseases, and lung cancer (Stafoggia et al., 2022; Strak et al., 2021), as well as with the increased risk of incidence from cardiovascular diseases (Wolf et al., 2021), adult-onset asthma (Liu et al., 2021b), COPD (Liu et al., 2021c), and lung cancer (Hvidtfeldt et al., 2021). Here, we aimed to examine the association of long-term exposure to PM<sub>2.5</sub>, NO<sub>2</sub>, BC, and O<sub>3</sub> with mortality from dementia, psychiatric disorders, and suicide. In order to elucidate which components and related sources of air pollution may be most relevant for the development of these three outcomes, we also examined associations with eight PM<sub>2.5</sub> components.

## 2. Methods

### 2.1. Study population

The study population was based on seven cohorts from six European countries, which were pooled within the ELAPSE project framework. Cohort and register data were pooled and harmonized in order to control for potential confounders in the pooled cohort. The study population was derived from the following European cohorts: (1) Cardiovascular Effects of Air Pollution and Noise in Stockholm (CEANS) cohort from Sweden, consisting of the following sub-cohorts: Stockholm Diabetes Prevention Program (SDPP) (Eriksson et al., 2008), Stockholm Cohort of 60-year-olds (SIXTY) (Wändell et al., 2007), Stockholm Screening Across the Lifespan Twin study (SALT) (Magnusson et al., 2013), and Swedish National Study on Aging and Care in Kungsholmen (SNAC-K) (Lagergren et al., 2004); (2) Danish Nurse Cohort (DNC) (Hundrup et al., 2012), which consists of two cohort waves with information collected in 1993 and 1999; (3) Etude Epidémiologique auprès de femmes de la Mutuelle Générale de l'Éducation Nationale (E3N) from France (Clavel-Chapelon, 2015); (4) European Prospective Investigation into Cancer and Nutrition-Netherlands (EPIC-NL) cohort from the Netherlands, combining the two sub-cohorts of Morgen (Monitoring Project on Risk Factors and Chronic Diseases in the Netherlands) and Prospect (Beulens et al., 2010); (5) Heinz Nixdorf Recall study (HNR) from Germany (Schmermund et al., 2002); (6) Cooperative Health Research in the Region of Augsburg (KORA) in Germany (Holle et al., 2005), consisting of two sub-cohorts with information collected between 1994 and 1995 and between 1999 and 2001, and; (7) Vorarlberg Health Monitoring and Prevention Programme (VHM&PP) from Austria (Ulmer et al., 2007). Enrollment year and end of follow-up varied by cohorts, ranging from 1985 to 2005 for the enrollment year, and 2011 to 2015 for follow-up (Table S1). All cohorts were approved by the medical ethics committees in their respective countries.

### 2.2. Air pollution exposure assessment

The assessment of exposure to air pollution within ELAPSE has been described in detail elsewhere (de Hoogh et al., 2018). In brief, annual mean concentrations of PM<sub>2.5</sub>, NO<sub>2</sub>, BC, and warm season O<sub>3</sub> for 2010 were estimated at the baseline residential addresses of all individuals in the cohorts. Utilizing monitoring and satellite data, chemical transport model (CTM) estimates, land use, and road variables, as potential predictor variables, standardized Europe-wide hybrid land-use regression (LUR) models (de Hoogh et al., 2018) were developed at a fine spatial scale (100 m × 100 m grids). The LUR models performed well in fivefold hold-out validation, explaining 72 %, 59 %, 54 %, and 69 % of the measured spatial variation for PM<sub>2.5</sub>, NO<sub>2</sub>, BC, and O<sub>3</sub>, respectively. BC was measured by the reflectance of PM<sub>2.5</sub> filters for years 2009 and 2010, and was expressed in absorbance units. O<sub>3</sub> concentrations were estimated as the maximum running 8-hour averages in the warm season (April-September). For the subset of cohorts with available residential address history, a back extrapolation of the air pollution concentrations was applied. We used two different back-extrapolation methods: (1) ratio and (2) difference. The detailed methods can be found in previous publications (Brunekreef et al., 2021; Stafoggia et al., 2022). Briefly, we used the air pollution estimated by the Danish Eulerian Hemispheric Model (DEHM) to extrapolate the annual air pollution level for each individual by comparing the ratio and difference of the year of estimate with the year of 2010. DEHM provides monthly mean concentration estimates at 26 km × 26 km spatial resolution across Europe back to at least 1990. Time-varying annual levels were calculated based on the monthly levels of two different back-extrapolation methods (ratio and difference). Eight components of PM<sub>2.5</sub> were defined in the European Study of Cohorts for Air Pollution Effects (ESCAPE) project and selected to represent major pollution sources: copper (Cu), iron (Fe), and zinc (Zn) as non-tailpipe traffic emissions; sulfur (S) as long-range transport

of secondary inorganic aerosols; nickel (Ni) and vanadium (V) as mixed oil burning/industry; silicon (Si) as crustal material, and; potassium (K) as biomass burning (de Hoogh et al., 2013; Tsai et al., 2015). We estimated exposure to these eight PM<sub>2.5</sub> components at the participants' baseline residential addresses in 2010 using Europe-wide LUR models developed with two algorithms: supervised linear regression (SLR) and random forest (RF) algorithms based on the standardized ESCAPE project monitoring data, with details of the models published elsewhere (Chen et al., 2020). We included large-scale satellite-model and CTM estimates of components to represent background concentrations and land-use, road, population, and industrial point source data to model local spatial variability. Models explained a moderate-to-large fraction of the measured concentration variation at the European scale, ranging from 41 % to 90 % across components (Chen et al., 2020).

### 2.3. Mortality outcome definition

We defined mortality from dementia, psychiatric disorders and suicide based on the underlying cause of death from mortality registers using the following International Classification of Diseases (ICD) 9th version (ICD-9) and 10th version (ICD-10) codes: dementia (ICD-9: 046.1, 290.0–290.4, 294, 331.0, 331.1, 331.5, 331.82; ICD-10: F00-F03, G30, G31.8, G31.9), psychiatric disorders (ICD-9: 290.8–293.9, 295–319; ICD-10: F04-F99) and suicide (ICD-9: E950-E959; ICD-10: X60-X84).

In addition, we considered the following subtypes of dementia and psychiatric disorders only for descriptive analyses, showing number of deaths from different causes but not association analyses: Alzheimer's disease (AD) (ICD-9: 331.0; ICD-10: F00, G30) and vascular dementia (ICD-9: 290.4; ICD-10: F01); as well as psychiatric disorders including mood disorders (ICD-9: 296, 300.4, 311; ICD-10: F30-39), neurotic disorders (ICD-9: 300.0, 300.2, 300.3, 308.3, 309.0, 309.24, 309.28, 309.3, 309.4, 309.8, 309.9; ICD-10: F40-F48), eating disorders (ICD-9: 307.1, 307.51, 307.50; ICD-10: F50), personality disorders (ICD-9: 301.0–301.9; ICD-10: F60), and substance use disorders (ICD-9: 291, 292, 303, 304, 305; ICD-10: F10-F19).

### 2.4. Statistical analysis

Cox proportional hazards models with age as the underlying time-scale were used to examine associations between air pollution and mortality from dementia, psychiatric disorders, and suicide, according to the statistical protocol for the ELAPSE project described in detail elsewhere (Samoli et al., 2021). Cohort participants were followed from the year of enrolment into the cohort (baseline), with the earliest cohort entry in 1985 and the latest in 2005 (both in VHM&PP). Participants were followed until either the occurrence of the outcome of interest, death from other causes, emigration, loss to follow-up, or end of follow-up; whichever came first. We visualized the survival probability of dementia and psychiatric disorders mortality in Kaplan-Meier curves, but not for suicide due to a lack of power. The associations of the four different air pollutants with mortality from dementia, psychiatric disorders, and suicide were all modelled in three steps increasingly controlling for individual and area-level covariates: *Model 1* adjusted for age (time axis), sex (strata), sub-cohort (strata), and year of cohort baseline; *Model 2* additionally adjusted for smoking status (*never, former, current*), smoking duration (*years*) for current smokers, smoking intensity (*linear and squared term; cigarettes/day*) for current smokers, body mass index (BMI, categories: <18.5, 18.5–24.9, 25.0–29.9, and ≥ 30 kg/m<sup>2</sup>), marital status (*married/cohabiting, divorced/separated, single, widowed*), and employment status (*employed/self-employed, other*), and; *Model 3* (main model) additionally adjusted for area-level socioeconomic status (SES) (*mean income at neighborhood or municipality level in 2001*). All models were based on complete case analysis regarding both exposure and covariate information. In addition to single-pollutant models, we estimated the associations in two-pollutant models to identify the most

important pollutants among independent associations after adjusting for other pollutants. When the variance inflation factor (Craney and Surlles, 2002) of the pollutant in the multiple linear regression models was higher than 5, we considered the presence of multicollinearity of the pollutants and did not present the estimates of the pollutants in the two-pollutant models (e.g., NO<sub>2</sub> and BC).

The concentration–response functions of the associations were assessed using natural cubic splines with two degrees of freedom. When we observed that the relationship was not linear, deviations from linearity were evaluated by the likelihood ratio test. Further, associations were evaluated at various cut-off levels of pollutants, from considerably high levels to levels with equal intervals, which can also be comparable to the previous findings in the ELAPSE cohort: 40, 30, and 20 µg/m<sup>3</sup> for NO<sub>2</sub>; 25, 20, and 15 µg/m<sup>3</sup> for PM<sub>2.5</sub>; 3, 2.5 and  $2 \times 10^{-5}$ /m for BC, and; 120, 100, and 80 µg/m<sup>3</sup> for warm season O<sub>3</sub>.

We conducted a Wald test to investigate the potential effect modification by age, sex, overweight, smoking, and employment status on the associations between the air pollutants and the three mortality outcomes.

We performed several sensitivity analyses. First, we compared the effect estimates and model performance assessed by the Akaike Information Criteria (AIC) in Model 3 with alternative models using different approaches for sub-cohort adjustment: (1) without adjustment; (2) using the sub-cohort indicator; (3) including a frailty term, and; (4) including a random intercept in a mixed Cox model. Secondly, we compared the main results with 2010 exposure levels in Model 3 with results of back-extrapolated exposures to cohort baseline year and with results of time-varying annual exposures. Time-varying analyses were performed only in a subset of cohorts with available information on address history (CEANS, EPIC-NL, and VHM&PP), where we included 1-year strata of calendar time to account for time trends in air pollution and mortality. Fourth, we compared the effect estimates in Model 3, excluding one cohort at a time. Fifth, we computed multiple imputation using Fully Conditional Specification (FCS) implemented by the MICE algorithm as described in Van Buuren and Groothuis-Oudshoorn (Van Buuren, 2011), after excluding 57 participants due to a lack of information on the date of the end of follow-up. Sixth, we computed Fine and Gray's sub-distribution hazard ratios (HR) after considering the competing risk of main causes of death, such as cardiovascular and cancer mortality, on outcomes (dementia and psychiatric mortality and suicide) (Austin et al., 2016).

We repeated the same approach for eight components of PM<sub>2.5</sub> to evaluate the risk of mortality associated with PM<sub>2.5</sub> components modelled by two different algorithms separately, SLR and RF. First, we conducted a correlation analysis between PM<sub>2.5</sub> components and PM<sub>2.5</sub> mass and NO<sub>2</sub>. Second, we fit the cox proportional hazard models for each component in single- and two-pollutant models with additional adjustment for PM<sub>2.5</sub> or NO<sub>2</sub>.

The results are presented as HR and 95 % confidence intervals (CI) per unit pre-specified by ELAPSE projects: 10 µg/m<sup>3</sup> increase for NO<sub>2</sub>; 5 µg/m<sup>3</sup> increase for PM<sub>2.5</sub>;  $0.5 \times 10^{-5}$ /m increase for BC; 10 µg/m<sup>3</sup> increase for O<sub>3</sub>, and; interquartile range increase for each of the eight components of PM<sub>2.5</sub>. All statistical analyses were performed in R software (version 3.4.0).

### 3. Results

Of the 324,728 participants among the seven cohorts in six European countries pooled within ELAPSE (Fig. S1), 53,008 had missing data for covariates in Model 3 (Table S1) and were excluded. Of 271,720 participants in the final analyses, 900 died from dementia, 241 from psychiatric disorders, and 164 from suicide, during a mean follow-up of 19.7 years (Table 1). Of 900 dementia deaths, 424 were from AD and 69 from vascular dementia. Of those 241 who died from psychiatric disorders, the majority (n = 200) died from substance use disorders, 23 from mood disorders (including depression), three from eating

disorders, and one from neurotic disorders (including anxiety), and none from personality disorders. Baseline characteristics of participants varied across sub-cohorts (Table S1), justifying the use of strata for sub-cohorts to adjust for differences in baseline hazards. The Austrian VHM&PP was the largest cohort accounting for 53.1 % of the total population. The mean age in the pooled cohort was 47.1 years, ranging from 42.1 years in VHM&PP to 72.9 years in SNAC-K. The majority of participants (69 %) were female, and three cohorts/sub-cohorts included women only (DNC, E3N, and EPIC-NL-Prospect). The proportion of current smokers ranged from 13 % in E3N to 37 % in DNC-1993, and the proportion of overweight individuals from 21 % in E3N to 74 % in HNR (Table 1).

The exposure distributions varied between cohorts, with the lowest concentrations of PM<sub>2.5</sub> and BC in Swedish cohorts (CEANS) and highest in German (HNR, KORA) and Austrian (VHM&PP) cohorts (Fig. 1). Almost all participants were exposed to PM<sub>2.5</sub> and NO<sub>2</sub> levels below the current EU limit values of 25 and 40 µg/m<sup>3</sup>, respectively, and above the new WHO Air Quality Guidelines for PM<sub>2.5</sub> and NO<sub>2</sub> of 5 and 10 µg/m<sup>3</sup>, respectively (World Health Organization 2021). The concentrations of PM<sub>2.5</sub> were substantially higher at the cohorts' baseline years than in year 2010, whereas smaller differences in levels of other pollutants were observed between baseline and year 2010 (Fig. S2). A correlation between NO<sub>2</sub> and BC was high in the majority of cohorts (Pearson correlation coefficient 0.67–0.93) except for SNAC-K, where it was 0.43 (Table S2). PM<sub>2.5</sub> was moderately correlated with BC (0.29–0.76) and NO<sub>2</sub> (0.22–0.81), and O<sub>3</sub> was negatively correlated with the other pollutants in all sub-cohorts (Table S2). Kaplan-Meier curves showed that the survival probabilities of dementia mortality in CEANS and VHM&PP cohorts differed from those in other cohorts (Fig. S3).

We observed linear relationships in the majority of pairs of three health outcomes and four exposure levels; however, we also detected some non-linear associations. For example, the associations of NO<sub>2</sub> with dementia mortality (Fig. S4) and PM<sub>2.5</sub> with psychiatric disorders (Fig. S5) showed an inversed U-shape, which significantly deviated from linearity with positive relationships at low levels of air pollution to which most people were exposed, below 40 µg/m<sup>3</sup> for NO<sub>2</sub> and 17 µg/m<sup>3</sup> for PM<sub>2.5</sub>. However, associations with suicide were linear for all pollutants (Fig. S6).

In overall exposure levels, we detected positive associations between mortality from psychiatric disorders and NO<sub>2</sub> (HR = 1.38; 95 % CI: 1.13, 1.70 per 10 µg/m<sup>3</sup>), PM<sub>2.5</sub> (HR = 1.29; 95 % CI: 0.98, 1.71 per 5 µg/m<sup>3</sup>), and BC (HR = 1.37; 95 % CI: 1.11, 1.69 per  $0.5 \times 10^{-5}$ /m), and a negative association with O<sub>3</sub> (HR = 0.74; 95 % CI: 0.55, 0.99 per 10 µg/m<sup>3</sup>) (Model 3, Table 2). Moreover, the association between PM<sub>2.5</sub> and psychiatric disorders mortality was enhanced below predefined cut-off levels (HR = 1.38; 95 % CI: 1.02, 1.86 per 5 µg/m<sup>3</sup>, below 20 µg/m<sup>3</sup>). For NO<sub>2</sub> and BC, the associations also remained statistically significant below predefined cut-off levels (Table S3), showing no lower thresholds below which air pollution was not harmful (Fig. S5). We also observed positive associations with suicide, although somewhat weaker than those with mortality from psychiatric disorders (HR = 1.19 [95 % CI: 0.76, 1.87] for NO<sub>2</sub>; HR = 1.13 [95 % CI: 0.92, 1.38] for PM<sub>2.5</sub>; HR = 1.08 [95 % CI: 0.87, 1.35] for BC; and, HR = 0.93 [95 % CI: 0.70, 1.24] for O<sub>3</sub>). We did not detect associations between any of the air pollutants with dementia mortality (Table 2).

In two-pollutant models, positive associations of mortality from psychiatric disorders and suicide with NO<sub>2</sub> were robust to adjustment for either PM<sub>2.5</sub> or O<sub>3</sub> (Table 3). Associations of both psychiatric disorders and suicide with PM<sub>2.5</sub> attenuated to null when adjusting for NO<sub>2</sub> or BC. For O<sub>3</sub>, negative associations with psychiatric disorders and dementia decreased or attenuated to unity after adjustment for NO<sub>2</sub>, BC, or PM<sub>2.5</sub>. We observed no effect modification of the association between any air pollutants and psychiatric disorders mortality (Table 4), dementia mortality, and suicide (Table S4) by age, sex, overweight, smoking, or employment status.

The associations for all pollutants were robust in a number of

**Table 1**  
Characteristics of study participants by pooled cohort, cohorts and sub-cohorts at baseline.

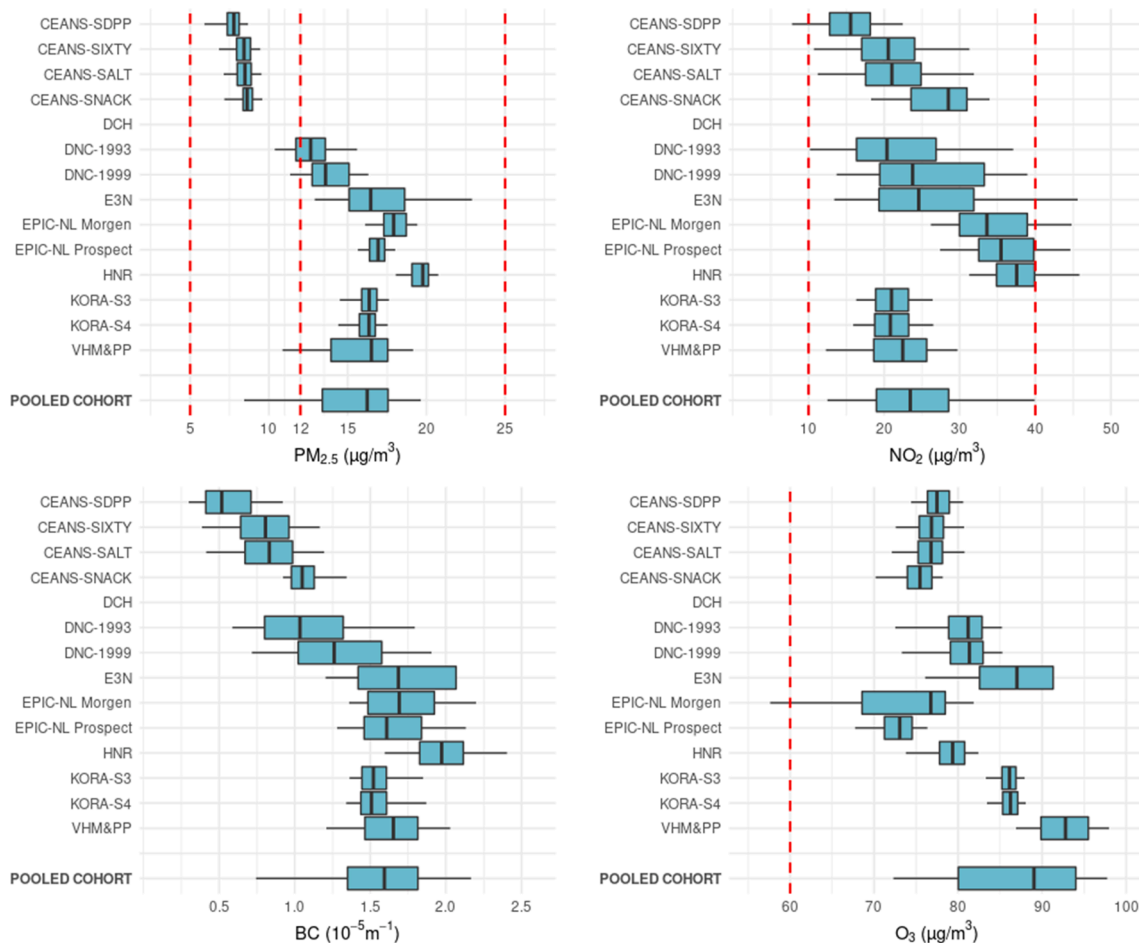
Cohort/sub-cohort	N	Deaths, N			Follow-up time, years	Age, years (mean $\pm$ SD)	Female (%)	Current smokers (%)	Smoking duration, years*	Smoking intensity, n/day*	Over weight (%) <sup>‡</sup>	Married/cohabiting (%)	Employed (%)	Mean income, euro <sup>†</sup>
		Dementia	Psychiatric disorders	Suicide										
<b>Pooled Cohort</b>	271,720	900	241	164	19.7	47.1 $\pm$ 14.0	69	22	21.9 $\pm$ 12.5	14.7 $\pm$ 8.9	41	72	68	20.1 $\pm$ 6.2
<b>CEANS</b>	20,702	159	10	37	13	56.3 $\pm$ 11.4	58	22	33.6 $\pm$ 11.0	13.1 $\pm$ 7.7	51	72	69	25.3 $\pm$ 5.6
SDPP	7,727	4	5	12	15.9	47.1 $\pm$ 4.9	61	26	27.9 $\pm$ 8.6	13.5 $\pm$ 7.4	52	84	91	24.3 $\pm$ 4.2
SIXTY	3,969	7	0	9	15.5	60.0 $\pm$ 0.0	52	21	36.3 $\pm$ 9.9	13.4 $\pm$ 7.6	65	74	68	24.7 $\pm$ 6.9
SALT	6,176	58	2	11	10.4	57.8 $\pm$ 10.6	55	21	37.9 $\pm$ 9.3	12.7 $\pm$ 8.0	40	68	64	25.3 $\pm$ 6.6
SNAC-K	2,830	90	3	5	7.4	72.9 $\pm$ 10.4	62	14	43.3 $\pm$ 13.6	11.7 $\pm$ 8.2	53	46	23	28.7 $\pm$ 2.2
<b>DNC</b>	25,171	187	37	66	17.3	53.5 $\pm$ 8.3	100	35	30.4 $\pm$ 9.5	13.7 $\pm$ 8.0	29	70	78	19.1 $\pm$ 2.5
1993	17,043	180	31	52	18.7	56.2 $\pm$ 8.4	100	37	31.6 $\pm$ 9.9	13.9 $\pm$ 8.2	28	68	70	19.2 $\pm$ 2.6
1999	8,128	7	6	14	14.4	47.9 $\pm$ 4.2	100	29	27.1 $\pm$ 7.1	13.3 $\pm$ 7.3	30	76	95	19.0 $\pm$ 2.4
<b>E3N</b>	39,006	71	18	33	16.7	53.0 $\pm$ 6.8	100	13	28.6 $\pm$ 7.6	11.4 $\pm$ 9.2	21	83	68	11.2 $\pm$ 3.0
<b>EPIC-NL</b>	32,872	111	8	28	16.7	49.5 $\pm$ 11.9	75	29	28.9 $\pm$ 11.2	15.0 $\pm$ 8.7	52	70	61	12.6 $\pm$ 1.6
Morgen	18,302	13	5	18	16.8	42.9 $\pm$ 11.2	55	35	24.8 $\pm$ 10.6	15.7 $\pm$ 8.6	50	65	69	12.2 $\pm$ 1.6
Prospect	14,570	98	3	10	16.4	57.7 $\pm$ 6.1	100	23	36.8 $\pm$ 7.6	13.7 $\pm$ 8.7	55	77	51	13.1 $\pm$ 1.4
<b>HNR</b>	4,733	8	3	0	12	59.7 $\pm$ 7.8	50	24	34.5 $\pm$ 9.4	18.6 $\pm$ 12.0	74	75	40	25.2 $\pm$ 8.2
<b>KORA</b>	4,853	9	8	0	14.3	49.4 $\pm$ 13.9	51	21	24.7 $\pm$ 11.8	16.1 $\pm$ 9.5	68	80	57	37.3 $\pm$ 6.0
S3	2,572	5	6	0	15.6	49.4 $\pm$ 13.9	51	20	25.2 $\pm$ 12.1	16.5 $\pm$ 9.5	67	80	55	36.7 $\pm$ 4.4
S4	2,281	4	2	0	12.9	49.3 $\pm$ 13.8	51	23	24.3 $\pm$ 11.6	15.7 $\pm$ 9.5	69	79	59	38.0 $\pm$ 7.3
<b>VHM&amp;PP</b>	144,383	355	157	0	23.1	42.1 $\pm$ 15.0	56	20	13.4 $\pm$ 8.3	15.6 $\pm$ 8.9	43	69	70	22.9 $\pm$ 1.7

Results of participants' characteristics at baseline are presented as Mean  $\pm$  standard deviation (SD), Number (N), or Percentage (%).

<sup>‡</sup>: Body mass index  $\geq$  25 kg/m<sup>2</sup> indicates overweight according to the World Health Organization (WHO) categories.

<sup>†</sup>: Area-level mean year income in euros  $\times$  1,000 in the year 2001. The spatial scale of an area varied from neighborhoods and city districts (CEANS, E3N, EPIC-NL, and HNR) to municipalities (DNC, KORA, and VHM&PP).

\*: Smoking duration and smoking intensity are only for current smokers. We set these variables to zero for never and former smokers.



**Fig. 1.** Distribution of annual average concentrations of air pollution for the year 2010 by cohorts and sub-cohorts ( $N = 271,720$ ). The bold lines in the middle of the box indicate the median values (the 50th percentile). The lower and upper hinges correspond to the 25th and 75th percentiles. The lower and upper whiskers extend to the 5th and 95th percentiles. Red dotted dash lines represent different limited values in EU, U.S., and WHO guidelines (2021 version). For  $PM_{2.5}$ , they indicate the annual average limited/guideline values of WHO (2021 version;  $5 \mu\text{g}/\text{m}^3$ ), U.S. ( $12 \mu\text{g}/\text{m}^3$ ), and EU ( $25 \mu\text{g}/\text{m}^3$ ). For  $NO_2$ , they indicate the annual average limited/guideline values of WHO (2021 version;  $10 \mu\text{g}/\text{m}^3$ ) and EU ( $40 \mu\text{g}/\text{m}^3$ ). For  $O_3$ , they indicate the annual peak season average limited/guideline values of WHO (2021 version;  $60 \mu\text{g}/\text{m}^3$ ).  $O_3$  was in the warm season from April 1 through September 30. Definition of abbreviation:  $PM_{2.5}$ , particulate matter with aerodynamic diameters of less than  $2.5 \mu\text{m}$ ;  $NO_2$ , nitrogen dioxide; BC, black carbon;  $O_3$ , ozone. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

sensitivity analyses. We found similar effect estimates when comparing alternative methods for adjusting for heterogeneity between sub-cohorts, with somewhat lower HRs with no adjustment and cluster methods (Fig. S7). The best model performance based on AIC was achieved when adjusting for sub-cohorts by including a strata term (Fig. S7). The HRs for all three outcomes were somewhat attenuated when using either ratio or difference methods of back-extrapolated baseline year exposures compared to the main results using 2010 exposure (Table S5). For time-varying exposures, available for a subset of three cohorts ( $N = 132,952$ ) (CEANS, EPIC-NL, and VHM&PP), HRs for suicide were slightly attenuated, whereas HRs for dementia from exposure to BC and  $NO_2$  increased, with  $NO_2$  reaching statistical significance (HR = 1.20; 95 % CI: 1.02, 1.41) (Table S6). For psychiatric disorders and  $NO_2$  and BC, the associations increased more greatly (doubled in effect size) compared to those of the year 2010 exposure. The associations were robust to excluding one cohort at a time (Table S7), multiple imputation (Table S8), and considering death from other causes as competing risk events (Table S9).

Data on  $PM_{2.5}$  components were available in 271,003 participants. Exposure to eight components of  $PM_{2.5}$  was estimated by two different models, SLR and RF, and component correlations with  $PM_{2.5}$  mass and  $NO_2$  can be seen in Supplementary Material (Tables S10–S12, Figs. S8–S9). We detected no significant associations between any of the

eight  $PM_{2.5}$  components and psychiatric disorders and suicide (Figs. S10 and S12), whereas we found negative associations between Ni and V components of  $PM_{2.5}$  and dementia mortality (Fig. S11).

#### 4. Discussion

In this pooled analysis of 271,720 adults from seven European cohorts, we found that long-term exposures to  $NO_2$ ,  $PM_{2.5}$ , and BC were associated with premature mortality from psychiatric disorders and an indicative association with suicide. The associations persisted and were enhanced at low levels of air pollution, well below current EU limit values. We found no associations between long-term exposure to air pollution and dementia-related mortality.

Our results showing no association between long-term exposure to air pollution and dementia mortality, in overall analyses with exposure data from 2010, are generally in contrast to a convincing body of literature on long-term exposure to air pollution and dementia incidence (Carey et al., 2018; Chang et al., 2014; Chen et al., 2017; Ilango et al., 2020; Kioumourtzoglou et al., 2016; Mortamais et al., 2021; Oudin et al., 2016; Oudin et al., 2018; Shaffer et al., 2021; Shi et al., 2021; Shi et al., 2020; Smargiassi et al., 2020; Sullivan et al., 2021; Wu et al., 2022). There are only three studies on long-term exposure to air pollution and dementia mortality. Our results agree with Klompmaker et al.,

**Table 2**

Associations between long-term air pollution exposure and dementia, psychiatric disorders, and suicide mortality (N = 271,720).

	Model 1* HR (95 % CI)	Model 2* HR (95 % CI)	Model 3* HR (95 % CI)
<b>Dementia (900 deaths)</b>			
NO <sub>2</sub>	0.92 (0.83, 1.02)	0.92 (0.83, 1.02)	0.94 (0.85, 1.05)
PM <sub>2.5</sub>	0.93 (0.80, 1.10)	0.94 (0.80, 1.10)	0.96 (0.82, 1.13)
BC	0.89 (0.80, 0.99)	0.89 (0.79, 0.99)	0.91 (0.81, 1.01)
O <sub>3</sub>	1.06 (0.91, 1.24)	1.06 (0.90, 1.23)	1.03 (0.88, 1.20)
<b>Psychiatric disorders (241 deaths)</b>			
NO <sub>2</sub>	1.56 (1.28, 1.89)	1.38 (1.13, 1.68)	1.38 (1.13, 1.70)
PM <sub>2.5</sub>	1.39 (1.05, 1.83)	1.31 (0.99, 1.72)	1.29 (0.98, 1.71)
BC	1.55 (1.27, 1.90)	1.37 (1.12, 1.68)	1.37 (1.11, 1.69)
O <sub>3</sub>	0.61 (0.45, 0.81)	0.73 (0.54, 0.97)	0.74 (0.55, 0.99)
<b>Suicide (164 deaths)</b>			
NO <sub>2</sub>	1.15 (0.95, 1.40)	1.06 (0.87, 1.29)	1.13 (0.92, 1.38)
PM <sub>2.5</sub>	1.18 (0.77, 1.83)	1.08 (0.70, 1.68)	1.19 (0.76, 1.87)
BC	1.12 (0.91, 1.38)	1.02 (0.82, 1.27)	1.08 (0.87, 1.35)
O <sub>3</sub>	0.87 (0.65, 1.17)	0.97 (0.73, 1.30)	0.93 (0.70, 1.24)

Model 1 adjusted for age (time axis), sex (strata), sub-cohort (strata), and calendar year of baseline;

Model 2 additionally adjusted for smoking (status, duration, intensity, and intensity<sup>2</sup>), body mass index (category), marital status, and employment status; Model 3 further adjusted for area-level mean year income.

\*: Results are presented as hazard ratio and 95 % confidence interval [HR (95 % CI)] for the following increases: 10 µg/m<sup>3</sup> for nitrogen dioxide (NO<sub>2</sub>), 5 µg/m<sup>3</sup> for particulate matter with aerodynamic diameters of less than 2.5 µm (PM<sub>2.5</sub>), 0.5 × 10<sup>-5</sup>/m for black carbon (BC), and 10 µg/m<sup>3</sup> for ozone (O<sub>3</sub>).

who in a Dutch national health survey (N = 339,633) found no association between long-term exposure to NO<sub>2</sub>, PM<sub>2.5</sub>, or PM<sub>10</sub> and dementia mortality (de Hoogh et al., 2013; Tsai et al., 2015). On the other hand, Bowe et al., have detected an association between long-term exposure to PM<sub>2.5</sub> and dementia mortality in a large cohort of 4,522,160 US veterans (Bowe et al., 2019); as did Klompmaker et al., in a more recent, large administrative Dutch cohort study of 10 million people (Klompmaker et al., 2021). Notably, our results for dementia were sensitive to which cohorts were included in the analyses based on the availability of historical data on air pollution. We have indeed detected positive associations between PM<sub>2.5</sub>, BC, and NO<sub>2</sub> (HRs: 1.08, 1.09, and 1.20, respectively) and dementia mortality in a subset of three cohorts with available data on time-varying exposure (CEANS, EPIC-NL, and VHM&PP) (Table S6). Although the three cohorts included in the time-varying analyses showed somewhat different survival rates from other cohorts (Fig. S3), the estimates of the associations with air pollution excluding one cohort at a time (Table S7) and estimates of the time-varying cox regression models did not differ much from the overall seven pooled cohorts: they included the cohorts from Northern (CEANS), mid (EPIC-NL), and Southern (VHM&PP) parts of Europe, with a range from lowest (CEANS) to highest (VHM&PP) levels of exposure, with similar mean age, as well as sex and confounder distribution as seen in the entire pooled cohort of seven cohorts (Table 1, and Figs. 1 and S1).

Our lack of association with dementia mortality in main analyses is most likely explained by the limitations related to using mortality data for the dementia definition, such as underestimation of true dementia mortality (Ganguli and Rodriguez, 1999; Rizzuto et al., 2018) and coding of dementia mortality as other diseases, mainly CVDs (Ives et al., 2009).

We present novel results of the association between long-term exposure to air pollution and mortality from psychiatric disorders and suicide. The observed associations, especially with psychiatric disorders, were considerably stronger than those recently reported in this cohort for all-cause mortality, where an increase of 5 µg/m<sup>3</sup> in PM<sub>2.5</sub> and 10 µg/m<sup>3</sup> increase in NO<sub>2</sub> was associated with 13 % (95 % CI: 10.6 %, 15.5 %) and 8.6 % (95 % CI: 7.0 %, 10.2 %) increase in natural deaths, respectively (Strak et al., 2021). Furthermore, detected associations with psychiatric disorders mortality (29 % for PM<sub>2.5</sub> and 38 % for NO<sub>2</sub>) were

**Table 3**

Two-pollutant models for associations between long-term exposure to air pollution and dementia, psychiatric disorders, and suicide mortality based on Model 3 (N = 271,720).

Pollutants	Single-pollutant model HR (95 % CI)	Two-pollutant model (adjusted for pollutants below)			
		NO <sub>2</sub> HR (95 % CI)	PM <sub>2.5</sub> HR (95 % CI)	BC HR (95 % CI)	O <sub>3</sub> HR (95 % CI)
<b>Dementia (900 deaths)</b>					
NO <sub>2</sub>	0.94 (0.85, 1.05)	/	0.93 (0.82, 1.06)	NA	0.92 (0.80, 1.06)
PM <sub>2.5</sub>	0.96 (0.82, 1.13)	1.02 (0.84, 1.25)	/	1.08 (0.88, 1.33)	0.96 (0.80, 1.17)
BC	0.91 (0.81, 1.01)	NA	0.88 (0.76, 1.01)	/	0.87 (0.75, 1.01)
O <sub>3</sub>	1.03 (0.88, 1.20)	0.95 (0.77, 1.17)	1.01 (0.84, 1.21)	0.91 (0.74, 1.12)	/
<b>Psychiatric disorders (241 deaths)</b>					
NO <sub>2</sub>	1.38 (1.13, 1.70)	/	1.39 (1.07, 1.80)	NA	1.38 (1.05, 1.81)
PM <sub>2.5</sub>	1.29 (0.98, 1.71)	0.99 (0.70, 1.41)	/	0.98 (0.67, 1.42)	1.15 (0.83, 1.61)
BC	1.37 (1.11, 1.69)	NA	1.38 (1.04, 1.84)	/	1.34 (1.01, 1.76)
O <sub>3</sub>	0.74 (0.55, 0.99)	0.99 (0.68, 1.45)	0.80 (0.56, 1.14)	0.95 (0.65, 1.38)	/
<b>Suicide (164 deaths)</b>					
NO <sub>2</sub>	1.13 (0.92, 1.38)	/	1.12 (0.86, 1.47)	NA	1.13 (0.90, 1.42)
PM <sub>2.5</sub>	1.19 (0.76, 1.87)	1.01 (0.56, 1.83)	/	1.13 (0.63, 2.03)	1.17 (0.73, 1.87)
BC	1.08 (0.87, 1.35)	NA	1.04 (0.78, 1.39)	/	1.07 (0.85, 1.36)
O <sub>3</sub>	0.93 (0.70, 1.24)	1.00 (0.73, 1.38)	0.96 (0.71, 1.30)	0.96 (0.71, 1.31)	/

NA: not available due to multicollinearity among the two pollutants (variance inflation factor > 5).

Model 3 adjusted for age (time axis), sex (strata), sub-cohort (strata), calendar year of baseline, smoking (status, duration, intensity, and intensity<sup>2</sup>), body mass index (category), marital status, employment status, and area-level mean year income.

Results are presented as hazard ratio and 95 % confidence interval [HR (95 % CI)] for the following increases: 10 µg/m<sup>3</sup> for nitrogen dioxide (NO<sub>2</sub>), 5 µg/m<sup>3</sup> for particulate matter with aerodynamic diameters of less than 2.5 µm (PM<sub>2.5</sub>), 0.5 × 10<sup>-5</sup>/m for black carbon (BC), and 10 µg/m<sup>3</sup> for ozone (O<sub>3</sub>).

stronger, although more uncertain, than those reported for mortality from respiratory disease (5.5 % for PM<sub>2.5</sub> and 10.1 % for NO<sub>2</sub>) or cardiovascular disease (13.5 % for PM<sub>2.5</sub> and 8.9 % for NO<sub>2</sub>), and were comparable to those for diabetes mortality (31.6 % for PM<sub>2.5</sub> and 23.8 % for NO<sub>2</sub>), which is the cause of death for which by far the strongest associations were detected (Strak et al., 2021). As this is the first study on long-term exposure to air pollution and mortality from psychiatric disorders, we can only make comparisons to the existing literature on long-term exposure to air pollution and incidence/onset of psychiatric disorders, which is just emerging, and consist of four studies on depression onset (Braithwaite et al., 2019) showing positive associations with PM<sub>2.5</sub> exposure (Kim et al., 2016; Kim et al., 2021; Kioumourtzoglou et al., 2017; Zhang et al., 2019). Furthermore, we detected an association between long-term exposure to air pollution and suicide, corroborating a



**Table 4**

Effect modification on the association between year 2010 exposure (Model 3) and mortality from psychiatric disorders by baseline characteristics.

Baseline characteristics	N	Deaths, N	HR (95 % CI)				P values*
			NO <sub>2</sub>	PM <sub>2.5</sub>	BC	O <sub>3</sub>	
Age, years							
<65	245,488	218	1.44 (1.16, 1.79)	1.34 (1.01, 1.79)	1.39 (1.12, 1.74)	0.71 (0.52, 0.96)	NO <sub>2</sub> : 0.34;
≥ 65	26,232	23	1.08 (0.62, 1.90)	0.79 (0.33, 1.90)	1.27 (0.74, 2.17)	0.86 (0.44, 1.67)	PM <sub>2.5</sub> : 0.25; BC: 0.73; O <sub>3</sub> : 0.58
Sex							NO <sub>2</sub> : 0.48;
Female	186,766	104	1.32 (1.02, 1.69)	1.30 (0.87, 1.93)	1.30 (1.01, 1.69)	0.76 (0.54, 1.08)	PM <sub>2.5</sub> : 1.00; BC: 0.49; O <sub>3</sub> : 0.70
Male	84,954	137	1.51 (1.10, 2.06)	1.30 (0.92, 1.82)	1.48 (1.09, 2.02)	0.70 (0.48, 1.02)	
Overweight							NO <sub>2</sub> : 0.31;
No	160,976	156	1.31 (1.04, 1.65)	1.32 (0.96, 1.82)	1.36 (1.08, 1.73)	0.76 (0.56, 1.05)	PM <sub>2.5</sub> : 0.77; BC: 0.95; O <sub>3</sub> : 0.48
Yes	110,744	85	1.58 (1.14, 2.19)	1.24 (0.83, 1.85)	1.38 (1.00, 1.91)	0.67 (0.46, 0.98)	
Smoking status							NO <sub>2</sub> : 0.75;
Current smoker	59,125	120	1.43 (1.09, 1.87)	1.38 (0.96, 1.98)	1.42 (1.08, 1.85)	0.71 (0.50, 1.00)	PM <sub>2.5</sub> : 0.84; BC: 0.74; O <sub>3</sub> : 0.81
Former smoker	44,529	23	1.16 (0.69, 1.93)	1.17 (0.61, 2.24)	1.17 (0.74, 1.85)	0.86 (0.48, 1.51)	
Never smoker	168,066	98	1.40 (1.04, 1.88)	1.23 (0.85, 1.78)	1.37 (1.02, 1.83)	0.74 (0.51, 1.08)	
Employment status							NO <sub>2</sub> : 0.53;
Employed	185,768	120	1.30 (0.99, 1.72)	1.25 (0.87, 1.79)	1.19 (0.90, 1.58)	0.70 (0.50, 1.00)	PM <sub>2.5</sub> : 0.75; BC: 0.14; O <sub>3</sub> : 0.67
Others	85,952	121	1.46 (1.12, 1.90)	1.34 (0.93, 1.94)	1.55 (1.18, 2.02)	0.76 (0.54, 1.08)	

Model 3 adjusted for age (time axis), sex (strata), sub-cohort (strata), calendar year of baseline, smoking (status, duration, intensity, and intensity<sup>2</sup>), body mass index (category), marital status, employment status, and area-level mean year income.

Results are presented as hazard ratio and 95 % confidence interval [HR (95 %CI)] for the following increases: 10 µg/m<sup>3</sup> for nitrogen dioxide (NO<sub>2</sub>), 5 µg/m<sup>3</sup> for particulate matter with aerodynamic diameters of less than 2.5 µm (PM<sub>2.5</sub>), 0.5 × 10<sup>-5</sup>/m for black carbon (BC), and 10 µg/m<sup>3</sup> for ozone (O<sub>3</sub>).

Effect modification analyses were conducted based on Model 3 and evaluated by introducing interaction terms. P values for whether there were statistical differences between strata were tested by the Wald test.

\*: A statistically significant P value (at 5% level) for effect modification analyses.

#: Body mass index ≥ 25 kg/m<sup>2</sup> indicates overweight according to WHO categories.

♠: Employed status includes employed and self-employed.

South Korean study, which showed strong associations with long-term exposure to PM<sub>10</sub> and NO<sub>2</sub> but had no data on PM<sub>2.5</sub> (Min et al., 2018). Notably, our findings are in line with a larger body of literature on short-term exposure to air pollution, which showed that exposure to high levels of air pollution over several days could trigger psychiatric responses, including depressive symptoms and hospital admissions, as well as attempted and completed suicide (Heo et al., 2021; Liu et al., 2021a), as well as with experimental data showing that air pollution exposure triggered a depression-like response in mice (Davis et al., 2013; Fonken et al., 2011). Thus, overall, our results agree with the limited evidence suggesting that long-term exposure to air pollution can induce neuroinflammation and oxidative stress and lead to pathology in the brain, which increases the risk of the development of depression (Davis et al., 2013; Fonken et al., 2011) and possibly other psychiatric disorders, including substance use, or suicide.

Two pollutant models showed robust associations with NO<sub>2</sub> and BC after adjustment of PM<sub>2.5</sub>, indicating the relevance of combustion-related pollution for psychiatric disorders and suicide. However, we cannot determine whether NO<sub>2</sub> per se or the associated pollutants, such as ultrafine particles, or other particles or gases from local combustion sources, are responsible for the observed association.

We used two exposure modelling practices (SLR vs RF) for PM<sub>2.5</sub> components in estimating associations with mortality. As noted in a previous ELAPSE publication, the two models performed similarly for within-area variability, while RF out-performed the SLR for between-area variability (Chen et al., 2020). Nevertheless, we did not detect any positive associations of mortality from dementia, psychiatric disorders, and suicide with PM<sub>2.5</sub> components in either SLR or RF models, although some components showed inconsistent correlations (e.g., K in Figs. S8 and S9) and discrepancies in associations with dementia mortality (e.g., K and S in Fig. S11). The inconsistency in the results from the two models may come from the discrepancy in predicted levels of PM<sub>2.5</sub> components by the two methods; RF captures complex non-linear relationships and or interactions between model predictors and pollutants, whereas SLR selects predictors in linear regression models (Chen et al., 2020).

We found null or inverse associations with O<sub>3</sub>, which may be due to the small exposure contrasts within each sub-cohort (Fig. 1), or

generally low levels of O<sub>3</sub> exposure (range: 36–116 µg/m<sup>3</sup>) in our study, as a large US study suggested a possible threshold of 56 ppb (~110 µg/m<sup>3</sup>) for the effect of warm season O<sub>3</sub> on all-cause mortality (Jerrett et al., 2009) or even lower threshold of 35 ppb for dementia incidence (Shi et al., 2021). The inverse relationship between O<sub>3</sub> and psychiatric disorders could also be explained by the strong negative correlations of O<sub>3</sub> with NO<sub>2</sub> and BC in some sub-cohorts (Table S2), which demands caution in interpreting the two-pollutant results for O<sub>3</sub>. Overall, more research on the effects of long-term exposure to low levels of O<sub>3</sub> on psychiatric disorders and dementia-related mortality is needed.

The main strength of our study is the pooled data from seven European cohorts allowing for investigating mortality from several rare outcomes, including dementia, psychiatric disorders, and suicide, as well as detailed and harmonized information on individual- and area-level potential confounders. Another strength of this study is the harmonized exposure data based on the Europe-wide hybrid LUR models at a fine spatial scale.

The main limitation of our study is the use of cause of death register data for mortality from dementia and psychiatric disorders. Dementia mortality data from causes of death is commonly under-reported on death certificates, as people who die with dementia are usually advanced in age and have many other comorbidities. Studies have shown that only 1/4 to 1/3 of the deaths in patients with dementia had dementia listed as the cause of death on death certificates (Ganguli and Rodriguez, 1999; Rizzuto et al., 2018). Dementia cases are often coded as other comorbidities such as pneumonia or CVD (Ives et al., 2009); however, our associations with dementia were robust when considering the competing risk events (CVD and other natural mortality). Furthermore, suicide data are lacking in our largest cohort (VHM&PP) (Table 1). Therefore, the smaller number of cases limited our analyses for the main associations with major pollutants and eight PM<sub>2.5</sub> components and the effect modification by subgroups, resulting in an exploratory and hypothesis-generating study to be confirmed in other studies with larger populations, or preferably with studies on the incidence of psychiatric disorders, which will have a much larger number of outcomes. Another limitation is the use of exposure data for the year 2010 at baseline of the cohorts recruited in 1990 s and early 2000 s, due to a lack of monitoring stations for PM<sub>2.5</sub> in Europe prior to 2010.

However, a previous study reported stable spatial distribution of NO<sub>2</sub> over 10 years in the Netherlands (Eeftens et al., 2011). Similarly, in our study, the predictions from the 2010 model were highly correlated (R<sup>2</sup> > 76 %) with 2000 and 2005 models for NO<sub>2</sub> and O<sub>3</sub>, and 2013 model for PM<sub>2.5</sub> at the European scale (de Hoogh et al., 2018), indicating limited impacts of temporal misalignment by exposures based on the year 2010. In sensitivity analyses, we also observed robust associations using either back-extrapolated baseline year exposures (Table S5) or time-varying exposures for three cohorts with address history information (Table S6). Therefore, we assume that our chosen approach to exposure assessment yields reasonably accurate estimates for the included study regions and pollutants, while acknowledging some degrees of exposure misclassification. The potential for exposure misclassification is inherent when using modelled exposures at the residential address, which does not account for exposures at work, time spent outdoors, activity patterns, commuting to work, and long-term hospitalization; all of which are inevitably not equivalent to personal exposure from outdoor sources. Additionally, we mostly evaluated exposure contrasts within sub-cohorts due to the use of strata for sub-cohorts in analyses, limiting the evaluation of associations with relatively few exposure contrasts. Moreover, we were not able to detect the critical window of exposure to air pollution for these outcomes due to a lack of temporal variation in the exposure. We also lacked information on major life events, data on medication use, and pre-existing diseases at enrollment and during follow-up. Therefore, we cannot rule out residual confounding for the association between air pollution and psychiatric disorders-related mortality. As participants in the study resided in Western Europe, the findings cannot be generalized to populations residing in other parts of the world, which may be exposed to a different mixture of pollutants. Finally, we cannot avoid the risk of false discoveries, as we investigated multiple exposures and health outcomes in a large number of analyses, including main, subset, two-pollutant, and effect-modification models.

Mortality from psychiatric disorders is a rarer outcome than mortality from cardiovascular and respiratory diseases, which have been extensively studied with respect to air pollution. However, we found that psychiatric disorders mortality is of high relevance for public health. In Denmark, psychiatric disease mortality has been steadily increasing in the last 20 years, reflecting increases in psychiatric disorders at all ages. Furthermore, patients with psychiatric disorders have a staggering approximate 20 years shorter life expectancy than the rest of the population, as psychiatric diseases affect much younger populations than cardiorespiratory diseases and mortality from these causes. Similarly, although mortality from psychiatric disorders is still a rare outcome, the prevalence of psychiatric disorders is on the rise in the EU countries, affecting a large portion of populations at some time of their life, and influencing younger adults as much as the elderly, and presenting important public health concerns. Thus, our findings that air pollution can increase the risk of psychiatric disorders, and consequently the risk of dying from these disorders, add valuable knowledge that air pollution is not only affecting the risk of somatic diseases, but also having a major impact on our mental health. This shows that the burden of air pollution is even larger than we thought, adding a good argument for the prevention of diseases and improvements in mental health via reductions in air pollution.

## 5. Conclusion

Our findings from the ELAPSE pooled cohort provide novel, suggestive evidence that long-term exposure to NO<sub>2</sub>, PM<sub>2.5</sub>, and BC may increase the risk of mortality from psychiatric disorder mortality and suicide, even at levels lower than current EU limit values.

## 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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## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.envint.2022.107581>.

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