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Effects of air pollution on dementia over Europe for present and future climate change scenarios

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ABSTRACT

The scientific literature is scarce when referring to the influence of atmospheric pollutants on neurodegenerative diseases for present and future climate change scenarios. In this sense, this contribution evaluates the incidence of dementia (Alzheimer's disease, AD, and dementia from unspecified cause, DU) occurring in Europe associated with the exposure to air pollution (essentially NO_2 and PM2.5) for the present climatic period (1991–2010) and for a future climate change scenario (RCP8.5, 2031–2050). The GEMM methodology has been applied to air pollution simulations using the chemistry/climate regional model WRF-Chem. Present population data were obtained from NASA's Center for Socioeconomic Data and Applications (SEDAC); while future population projections for the year 2050 were derived from the United Nations (UN) Department of Economic and Social Affairs-Population Dynamics. Overall, the estimated incidence rate (cases per year) of AD and DU associated with exposure to air pollution over Europe is 498,000 [95% confidence interval (95% CI) 348,600–647,400] and 314,000 (95% CI 257,500-401,900), respectively. An important increase in the future incidence rate is projected (around 72% for both types of dementia) when considering the effect of climate change together with the foreseen changes in the future population, because of the expected aging of European population. The climate penalty (impacts of future climate change alone on air quality) has a limited effect on the total changes of dementia (approx. 0.5%), because the large increase in the incidence rate over southern Europe is offset by its decrease over more northern countries, favored by an improvement of air pollution caused by the projected enhancement of rainfall.

1. Introduction

Air pollution is one of the main environmental problems facing humanity today, due in large part to the risk it poses to human health (Kampa and Castanas, 2008; Moulton and Yang, 2012; Pozzer et al., 2012; Silva et al., 2013; Lelieveld et al., 2015). Furthermore, this problem will be aggravated in the future, since air quality will worsen under the action of climate change (the so-called "climate penalty" effect) (e.g. Colette et al., (2012); Jiménez-Guerrero et al., (2013a); Liu et al., (2016); Fu and Tian (2019), among others). In fact, according to Tarín-Carrasco et al., (2019), a significant increase in the number of cases of premature death, as well as diseases such as lung cancer or congestive heart failure, is forecasted for 2071–2100 (future scenario RCP8.5) in Europe.

Despite the fact that many studies show the association of poor air quality with different diseases, especially with a respiratory and cardiovascular origin (e.g. Brook et al., (2010); Pope et al., (2011); Hamra et al., (2014); Tarín-Carrasco et al., (2019); Brook et al., (2010); Pope et al., (2011); Hamra et al., (2014); Tarín-Carrasco et al., (2019)), only recently have neurodegenerative diseases linked to air pollution (e.g. Costa et al., (2020); Costa et al., (2020)). Neurodegenerative diseases are of great interest, since life expectancy has been lengthened as a consequence of the improvement in health services. Therefore, there has been a marked increase in the incidence of neurodegenerative diseases, being dementia a great example of this increasing trend (Gorlé et al., 2016; Magalingam et al., 2018; Cummings, 2020).

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Dementia has a multifactorial etiology and its origin is not yet well known, except that there are genetic and environmental factors contributing to its development (Chin-Chan et al., 2015). In fact, Alzheimer's disease represents the fifth cause of death in the world (Nichols et al., 2019) and the sixth leading cause of death in the United States (Alzheimer's Association, 2020). It is expected that by 2060 a third of the population of the European Union will be over 65 years old and therefore the number of people with different dementias over this area will be doubled (Maresova et al., 2016).

Emerging evidence has shown that air pollution is associated with impaired cognitive function, accelerated cognitive decline, Parkinson's disease, Alzheimer's disease (AD) and dementia from unknown origin (DU) (Weuve et al., 2012; Levesque et al., 2013; Ailshire and Crimmins, 2014; Chang et al., 2014; Ailshire and Clarke, 2015; Kioumourtzoglou et al., 2016; Power et al., 2016; Shi et al., 2020), being the two latter the diseases included in this contribution.

With respect to Alzheimer's disease, several contributions based on prospective cohort studies found a positive association between long-term exposure to high concentrations of particulate matter (both coarse particles, PM10, and fine particles, PM2.5), nitrogen oxides (NOx $= NO_2 + NO$) and tropospheric ozone (O_3) pollution and this pathology (Jung et al., 2015; Wu et al., 2015; Oudin et al., 2016; Carey et al., 2018; Oudin et al., 2019). As an example, Carey et al., (2018) found that exposure to NO_2 and PM2.5 (the pollutants considered in this contribution) were related to an increased risk of AD (hazard ratio, HR, of 1.50 and 1.42, for concentrations of NO_2 and PM2.5 $> 41.5\ \mu g\ m^{-3}$ and 16.3 $\mu g\ m^{-3}$ of PM2.5, respectively). Based on a different methodology (increase in hospital admissions for AD), Zanobetti et al., (2014); Kioumourtzoglou et al., (2016); Culqui et al., (2017) and Lee et al., (2019) determined a positive correlation between the increase in hospitalizations in the United States and Europe and the short or long-term exposure to PM2.5. Calderón-Garcidueñas et al., (2018) showed that chronic exposure to high levels of contamination is associated with a high risk of suffering from neurodegenerative diseases, such as AD and Parkinson. Finally, Shi et al., (2020) found that for each 5 $\mu g\ m^{-3}$ increase in annual concentrations of particulate matter, the HR was 1.13 (95% CI 1.12–1.14) for hospital admissions for AD and related dementias.

Focusing on dementia, Chang et al., (2014) conducted a retrospective cohort study in Taiwan, finding that the exposure to elevated levels of NO_2 and carbon monoxide (CO) in the air substantially increased the risk of suffering from dementia. Moreover, two large cohort studies (Chen et al., 2017a,b) conducted in Canada (with a population sample of more than two million people aged between 55 and 85 years) established an association between the risk of dementia, the exposure to PM2.5 and NO_2 and the proximity to a main road, so those who lived closer to a main street had a 7% higher risk of dementia. Carey et al., (2018) showed an association between the increased risk of dementia and NO_2 and PM2.5, obtaining an HR of 1.13 and 1.06, for an increase of 7.5 $\mu g\ m^{-3}$ of NO_2 and 0.9 $\mu g\ m^{-3}$ of PM2.5, respectively. Similarly, Andersson et al., (2018) established an association between high levels of NO_x exposure and an increased risk of dementia (they also found no significant evidence that noise was associated with dementia, either independently or in combination with the pollutant). Finally, Kioumourtzoglou et al., (2016) and Lee et al., (2019) used data from hospital admissions for dementia, establishing a clear association between PM2.5 and the disease (HR of 1.08 per 1 $\mu g\ m^{-3}$ increase and 1.05 per 1 $\mu g\ m^{-3}$ increase, respectively).

From all the aforementioned scientific literature, it becomes clear that only a number of local contributions cover through limited cohort studies the relationship of air pollution with dementia. None of them evaluates what the impact of climate change might be on neurodegenerative diseases, as climate change can modify the concentrations and dynamics of air pollutants.

Therefore, the objective of this study is to quantify the incidence rate (that is, cases per year) of dementia (distinguishing between AD and DU) associated with air pollution over a target domain covering Europe (see Fig. 1 for further details). The incidence rate of dementia is specifically associated with the exposure to NO_2 and PM2.5, both for present climate conditions (present reference period 1991–2010) and the future (2031–2050). This future scenario takes into account the action of climate change penalty (RCP8.5 scenario) and the change in population dynamics projected for 2050. Hence, for the future, two experiments are carried out: (1) keeping the population similar in each cell of the model grid with respect to the reference period (so that climate-change impacts can be isolated); and (2) considering the population projections of the United Nations (UN) for the year 2050, so the effects of population increase and aging can be estimated.

2. Methodology and methods

The methodology used in this study is based on Burnett et al., (2018) in order to estimate the incidence rate of dementia due to exposure to air pollution in the European continent. Specifically, the effects of NO_2 and PM2.5 are taken into account in this contribution. For this, the GEMM (Global Exposure Mortality Model) methodology was applied. Two types of dementia are included, according to the International Classification of Diseases 11th Edition (ICD-11) (Khoury et al., 2017; World Health Organization, 2020): (1) Dementia due to Alzheimer's disease, onset unknown or unspecified (6D80.Z) (AD); and (2) Dementia, unknown or unspecified cause (6D8Z) (DU).

The methodology estimates the incidence rate of these two types of dementia by using non-linear exposure-response functions. Despite the full description can be found in Burnett et al., (2018), a summary of this methodology is presented throughout this section, together with the rest of the methodological aspects.

2.1. *Methodology for the estimation of the incidence by exposure-response functions*

Starting from data compiled from the literature available on cohort

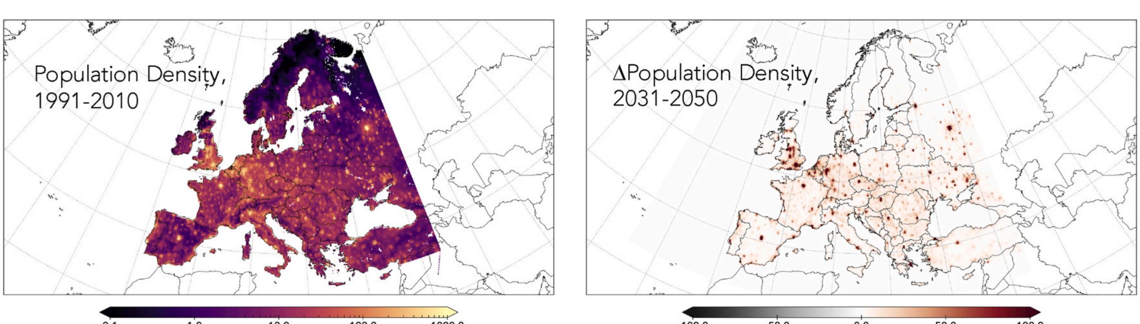

Fig. 1. (Left) Population density in the range 55–80+ years used for the present-day estimation of pathologies. (Right) Differences with 55–80+ years population projected for the 2050s. All units are pop. km^{-1}.

studies (see Appendix A, Table A1 and Table A2), the HRs were adjusted to the function established in Equation (1):

$$HR(z) = exp\left(\frac{\theta log\left(\frac{z}{\alpha}+1\right)}{\left(1+exp\left(\frac{-(z-\mu)}{\nu}\right)\right)}\right) \quad (1)$$

where the *HR* depends on four adjustment parameters (θ, α, μ and ν). In the methodology applied, these parameters define a shape of the dementia-pollutant association. The estimation method is based on a routine that selects multiple values of the parameters (α, μ, ν) and given these values, estimates of θ and its standard error are obtained using standard computer software (*R* statistical computer software has been used in this contribution). These parameters are kept constant for present and future estimations, but not the concentration of pollutants (z) in each climate scenario, so *HR* varies in each cell of the modelling domain and is modified between the future and the present. The concentration corresponding to the lowest quartile of exposure has been selected as the counterfactual level for which no risk is estimated (4.5 μg m^{-3} for NO_2 and 2.4 μg m^{-3} for PM2.5). Further information on the estimation of hazard ratios can be found in the Supplementary Information of Burnett et al., (2018). The statistical adjustment conducted leads to the values of the parameters shown in Table 1 for NO_2 and PM2.5.

From the HRs obtained in Equation (1), the incidence of AD and DU is estimated using Equation (2):

$$\Delta Cases = y_0 \cdot \frac{HR-1}{HR} \cdot Pop \quad (2)$$

where Δ*Cases* is the incidence of the disease for each pathology (AD and DU); *HR*: hazard ratio; *Pop*: exposed population; y_0 is the baseline or incidence ratio, which is calculated from the data provided by the reviewed cohort studies. Since y_0 is grouped together in the literature for all types of dementia, here we assumed that approximately 54% of the cases were associated with AD and 46% to DU, as stated in the literature aforementioned. So, a baseline by age group and disease is shown in Table 2. In this contribution, the population affected by dementia is considered to be over 55 years old, dividing the information in different age ranges (55–59, 60–64, 65–69, 70–74, 75–79 and 80+) (Table 2). Uncertainty ranges are expressed as the 95% confidence intervals (95% CIs). It should be emphasized that the 95% CI refers to statistical uncertainty associated with the epidemiological data, and not methodological uncertainty, including unaccounted confounding factors, assumptions about counterfactuals or limited representativeness of the hazard ratio functions (Lelieveld et al., 2020).

2.2. Population data

Population density data for Europe has been taken from the gridded dataset of NASA SocioEconomic Data and Applications Center (SEDAC) (http://sedac.ciesin.columbia.edu) Basic Demographic Characteristics, v4.11 (2010). These data provide the population density by age and sex for the year 2010 consistent with national censuses and population registers with a resolution of 5 km^2. Population data were interpolated to the working grid to make it consistent with the grid of air pollution (Fig. 1). Future population for the year 2050 has been estimated extrapolating the Population Prospects from United Nations Organization (UN) Department of Economic and Social Affairs Population Dynamics (https://population.un.org/wpp/). The relative variation of the population from this dataset between 2010 and 2050 (Fig. 2) for each European country and age range is calculated in order to obtain the gridded population for the future scenario (2050) in this study. This percentage has been applied to NASA SEDAC 2010 data grid. As commented before, the population affected by dementia is considered to be over 55 years old, and hence Fig. 1 refers only to the population density in the range 55–80+ years old.

Table 1
Parameters obtained after adjusting the HR data from the literature review to fit Equation (1) by Burnett et al., (2018).

AD		DU	
NO_2	PM2.5	NO_2	PM2.5
θ: 0.233	θ: 0.122	θ: 0.222	θ: 0.143
α: 0.465	α: 0.255	α: 0.521	α: 0.267
μ: 9.126	μ: 9.124	μ: 15.991	μ: 10.123
ν: 1.732	ν: 2.123	ν: 5.656	ν: 2.712

Table 2
Baseline values (y_0) for AD and DU by age range.

Age	y_0 AD	y_0 DU
55–59	21.66	18.45
60–64	54.61	46.52
65–69	135.94	115.80
70–74	323.42	275.51
75–79	668.37	569.35
80+	1481.49	1262.01

2.3. Pollution data

One of the main problems when conducting studies on the impacts of air pollution on human health lies in the availability of air quality data. The network of stations for measuring air pollutants is usually insufficient for health due to their spatial misalignment and low coverage (Vedal et al., 2017). In order to solve this problem, air quality model data is often used (Tarín-Carrasco et al., 2019).

Hence, here modeled air pollution is used to verify possible changes in pathologies and diseases between current and future climate change scenarios. The simulations used to assess air quality in this work cover the periods 1991–2010, as the current reference period, and 2031–2050 (RCP8.5 scenario), as a future climate change scenario. This scenario is at the top of the radiative forcing scenarios among all the IPCC alternatives, and projects the largest changes in climate variables. Therefore, the RCP8.5 scenario supposes an upper limit to climate impacts (Moss et al., 2010). The differences between these two model runs (present and RCP8.5) will provide changes in future air quality.

Specifically, the air quality data has been generated using the WRF-Chem model (Grell et al., 2005) under the REPAIR initiative (Palacios-Peña et al., 2020). A bias-correction technique (Borrego et al., 2011) was applied to raw data from REPAIR. The improvements in the error after the bias-correction was in the range of 40% with respect to the original data, in agreement with the results of Monteiro et al., (2013) for particulate matter. The spatial model configuration comprises a domain covering Europe and is presented in a 0.11° grid accomplishing the EURO-CORDEX requeriments (Jacob et al., 2020). The description of the physico-chemical parameterizations of the model has been widely presented and validated in Tarín-Carrasco et al., (2019), Jerez et al., (2020) or Palacios-Peña et al., (2020), among others.

In order to isolate the possible effects of climate change on pathologies only due to changes in atmospheric pollutants (the so-called climate penalty), constant anthropogenic emissions are assumed and taken from the ACCMIP database (Lamarque et al., 2010). This allows possible impacts to be anticipated if mitigation strategies for regulatory pollutants are not carried out and characterizes the climatic penalty in air quality levels.

3. Results

3.1. Present levels and projected variation of NO_2 and PM2.5 concentrations

For the description of the different pollutants, the average annual

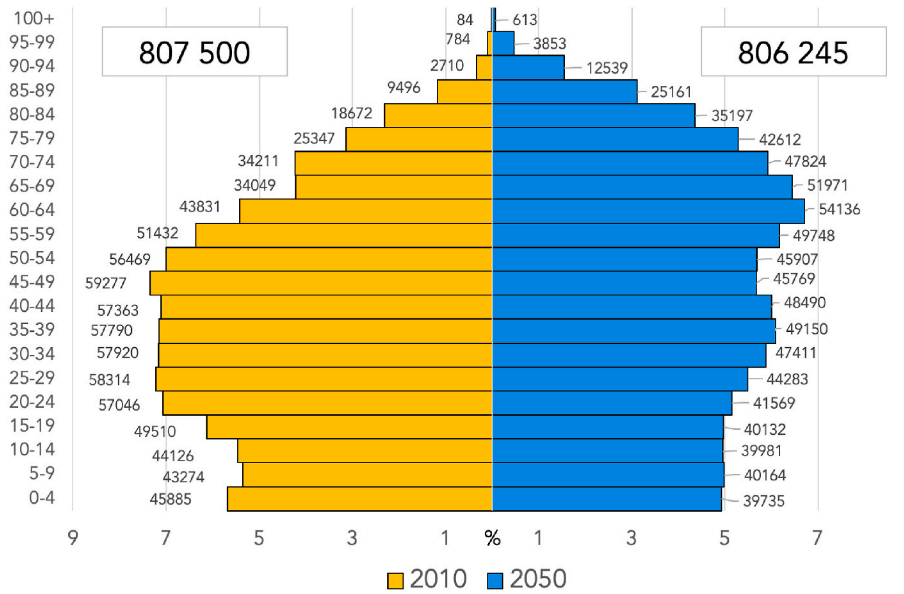

Fig. 2. Population pyramid by age range for the year 2010 (orange, left) and 2050 (blue, right). Population data for each range are in thousands. x-axis represents the relative contribution of each age range to the total population. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

concentrations in Europe for the period 1991–2010 have been used for a present scenario, while projected ground-level NO_2 and PM2.5 are simulated with the model for the years 2031–2050 (RCP8.5 scenario). This future scenario provides information about the magnitude of the climate penalty.

3.1.1. *Nitrogen dioxide (NO_2)*

As shown in Fig. 3,left, for the present period the NO_2 concentration is not distributed homogeneously throughout Europe. The spatial pattern of NO_2 has its maximum concentration in central Europe (with average concentrations above 40 $\mu g\ m^{-3}$ over the Ruhr-Rhine area in Germany) and southern Europe, where levels can reach 30 $\mu g\ m^{-3}$ as annual mean over the Po Valley in Italy, threshold value established by the European Directive 2008/50/EC of May 21, 2008 on ambient air quality and a cleaner atmosphere in Europe. NO_2 is closely related to emissions produced by energy generation and vehicles; therefore the trend of this pollutant depends considerably on the consumption of fossil fuels associated with on-road traffic, especially over large cities (e.g. (Jiménez et al., 2005; Minguillón et al., 2012; Zhang and Batterman, 2013; Harrison, 2018; Kamińska, 2019), among many others).

On the other hand, Fig. 3,right shows that for the future period (2031–2050) and under the effect of climate penalty (RCP8.5 forcing scenario, anthropogenic NOx emissions kept at the 1991–2010 levels in the simulations), NO_2 levels are expected to decrease in central and northern Europe around 0.6 $\mu g\ m^{-3}$, while in southern and southeastern Europe NO_2 will increase by 1.0 $\mu g\ m^{-3}$. This increase in NO_2 levels over southern Europe is associated with the increasing North Atlantic Oscillation (NAO) phenomena under climate change scenarios. Under future climate change scenarios, an eastward extension of Azores high pressure towards the Mediterranean during NAO + regimes is projected (Ullmann et al., 2014), and more positive NAO phases facilitate the accumulation (dispersion) of primary pollutants over southern(northern) Europe (Christoudias et al., 2012; Jerez et al., 2013; Jiménez-Guerrero and Ratola, 2021), thus impacting the dispersion of pollutants and enhancing their accumulation over southern European regions (Jacob and Winner, 2009; Cerro et al., 2015).

3.1.2. *Particulate matter (PM2.5)*

In the case of particulate matter (PM2.5), for the present period, Fig. 4,left shows lower and more homogeneous values than in the case for NO_2. The European Directive 2008/50/EC establishes the limit value for the protection of human health at 25 $\mu g\ m^{-3}$. The maximum levels of PM2.5 in Europe exceed this threshold in large cities of central Europe as Paris, or industrial areas of Poland, Ukraine and northern Italy. The lowest average values of PM2.5 are found over the Scandinavian peninsula and Spain, with mean annual concentrations under 7.5 $\mu g\ m^{-3}$. Hence, the spatial pattern shows important differences with

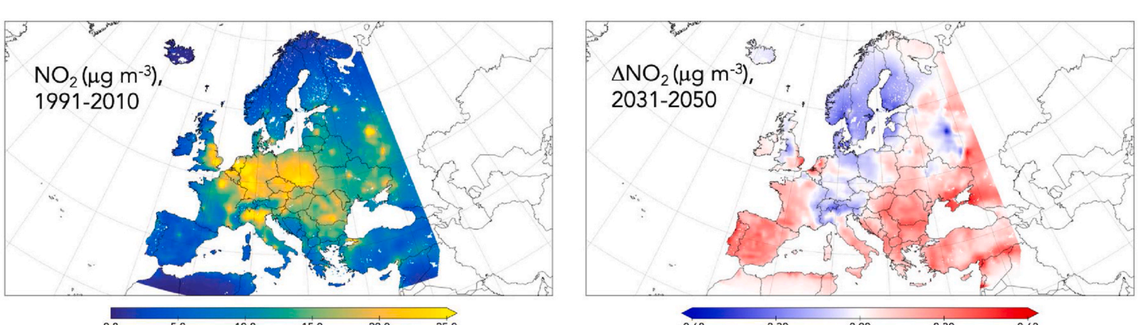

Fig. 3. (Left) Mean annual concentration of NO_2 ($\mu g\ m^{-3}$) in Europe for present climate conditions (1991–2010). (Right) Difference in NO_2 mean annual concentrations ($\mu g\ m^{-3}$) between the future scenario (RCP8.5, 2031–2050) and the present.

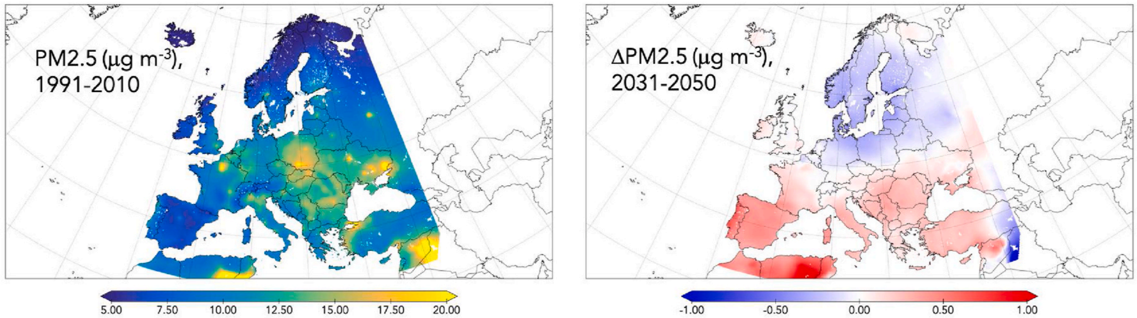

Fig. 4. (Left) Mean annual concentration of PM25 ($\mu g\ m^{-3}$) in Europe for present climate conditions (1991–2010). (Right) Difference in PM25 mean annual concentrations ($\mu g\ m^{-3}$) between the future scenario (RCP8.5, 2031–2050) and the present.

respect to NO_2, being PM2.5 annual concentrations low in some areas as the Netherlands, England or the Ruhr-Rhine area in Germany.

Fig. 4,right corresponds to the difference between the future period (2031–2050, RCP8.5) and the present concentrations of PM2.5. A clear increase in the concentration of fine particles is projected over southern Europe (above 2 $\mu g\ m^{-3}$), particularly over the Iberian Peninsula, as previously commented for NO_2 with respect to the NAO index. PM2.5 increases in southeastern Europe, decreasing or remaining constant in the rest of the areas. These changes are partiality due to the increased loads and episodes towards southern Europe related to Saharan dust outbreaks, enhanced -especially for PM10-under future climate change scenarios (Jiménez-Guerrero et al., 2013b; Kok et al., 2018; Tsikerdekis et al., 2019). Moreover, the variations in the distribution of PM2.5 in Europe, considering a future RCP8.5 scenario, are mainly due to changes in precipitation. The decrease in rainfall in southern Europe (e.g. Jiménez-Guerrero et al., (2012); Domínguez-Morueco et al., (2019); Jiménez-Guerrero et al., (2012); Domínguez-Morueco et al., (2019)) and the increase in rainfall in northern and central Europe projected for this scenario (e.g. Jiménez-Guerrero et al., (2013a); Jacob et al., (2018); Jiménez-Guerrero et al., (2013a); Jacob et al., (2018)) affect the wet scavenging of particles, the fundamental process for the removal of particles from the atmosphere (e.g. Ohata et al., (2016); de Bruine et al., (2018); Hou et al., (2018); Ohata et al., (2016); de Bruine et al., (2018); Hou et al., (2018)).

3.2. *Present and future scenario for dementia*

The following section shows the estimated dementia incidence rate due to air pollution over Europe for both the present period (1991–2010) and the future climate penalty scenario (RCP8.5, 2031–2050, anthropogenic emissions corresponding to the 1991–2010 period). In order to isolate the effects that climate change has on human health, in addition to invariable emissions, in a first case the population has been kept at 2010 levels (population density and spatial distribution) for the future period (2031–2050). A second future case has also been considered where both the effects of climate change and changes in the population projected for the year 2050 are considered.

As aforementioned, the HRs have been obtained from the GEMM methodology, following Equation (1) (Fig. 5). The highest risk of suffering from AD is related to the exposure to NO_2 levels (HR = 1.40 for AD for each 10 $\mu g\ m^{-3}$ increase in annual concentrations, 95% CI 1.27–1.44 both in the present and the future scenario.). This HR is similar to that found by Carey et al., (2018) (1.50 when focusing on AD-NO_2). Average HR is 1.10 for DU for each 10 $\mu g\ m^{-3}$ increase, 95% CI (1.04–1.12). Average HRs for PM2.5 are 1.18 for AD for each 10 $\mu g\ m^{-3}$ increase (95% CI 1.14 and 1.19–1.23) and 1.17 for DU (95% CI for a concentration of 13.6 1.15–1.22) for each 10 $\mu g\ m^{-3}$ increase in annual concentrations. These average values are rather constant for both present and future scenarios, and changing only in those cells of the domain where the modification of future pollution is larger. The HR value found in this contribution for the impacts on DU associated with PM2.5 are slightly lower than those of Jung et al., (2015) (HR 1.38) and Carey et al., (2018) (HR 1.42).

From these HRs and the use of the exposure-response function, the present and future results for the incidence rate of dementia are presented in Table 3 and Fig. 6. As previously commented, the incidence rate has been estimated both keeping the population constant (corresponding to the population of the year 2010) and using the 2050-UN projected population.

For 1991–2010 (Table 3,left) an incidence rate of 498,000 (95% CI 348,600–647,400) is estimated for AD and 314,000 (95% CI 257,500-401,900) for DU (62/100,000 pop. and 39/100,000 pop., respectively), while in the future -when isolating the climate penalty by keeping the population constant-the incidence rate due to air pollution barely increases to 501,000 (95% CI 350,400–651,400) for AD and 315,000 (95% CI 258.300–403,400) for DU (63/100,000 pop. and 40/

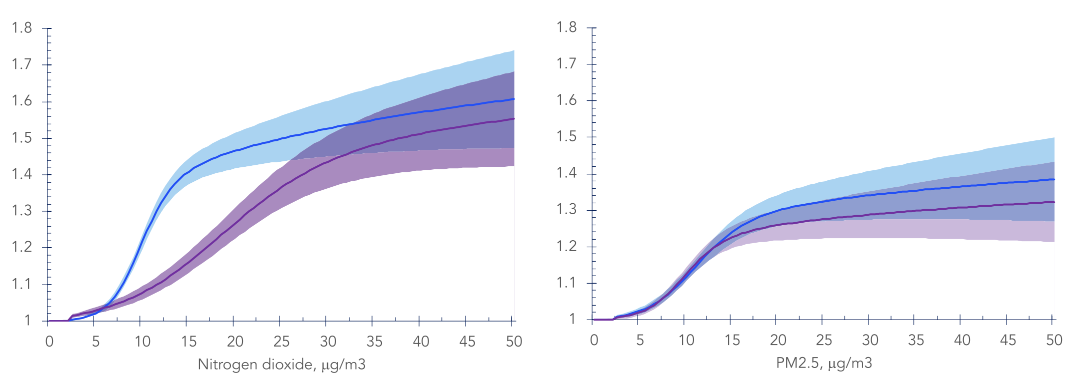

Fig. 5. GEMM hazard ratio predictions over NO_2 (left) and PM2.5 (right) exposure range for AD and DU, with 95% confidence interval (shaded area).

Table 3
Estimated incidence rate of AD and DU from exposure to NO_2 and PM2.5 in the present (1991–2010) and future (RCP8.5, 2031–2050) (both keeping the population constant and with the UN future population projection). Number in parenthesis represent the 95% CI. ΔIncid. indicates the increase (%) of the incidence rate of dementia in the future.

Age range	Present		Future (Pres pop.)		Future (Fut pop.)	
	AD	DU	AD	DU	AD	DU
55–59	21 (14.6–27.2)	13 (10.6–16.6)	21 (14.6–27.2)	13 (10.6–16.6)	21 (14.6–27.2)	13 (10.6–16.6)
60–64	47 (32.7–60.2)	30 (24.5–38.4)	47 (32.7–60.8)	30 (24.5–38.4)	59 (41.1–76.3)	37 (30.3–47.4)
65–69	81 (56.4–104.8)	52 (42.5–66.6)	81 (56.4–104.8)	52 (42.5–66.6)	124 (86.4–160.4)	80 (65.4–102.4)
70–74	114 (79.4–147.4)	71 (58.1–90.9)	115 (80.1–148.7)	72 (58.9–92.2)	159 (110.7–205.7)	99 (80.9–126.8)
75–79	105 (73.1–135.8)	66 (54.0–84.5)	106 (73.8–137.1)	66 (54.0–84.5)	178 (124.0–230.2)	111 (90.8–142.1)
80+	130 (90.5–168.1)	82 (67.0–105.0)	131 (91.2–169.4)	82 (67.0–105.0)	319 (222.2–412.6)	201 (164.3–257.3)
TOTAL	**498** **(348.6–647.4)**	**314** **(257.5–401.9)**	**501** **(350.4–651.4)**	**315** **(258.3–403.4)**	**860** **(600.8–1118.6)**	**541** **(443.6–692.8)**
ΔIncid. (%)	–	–	0.51	0.57	72.43	72.12

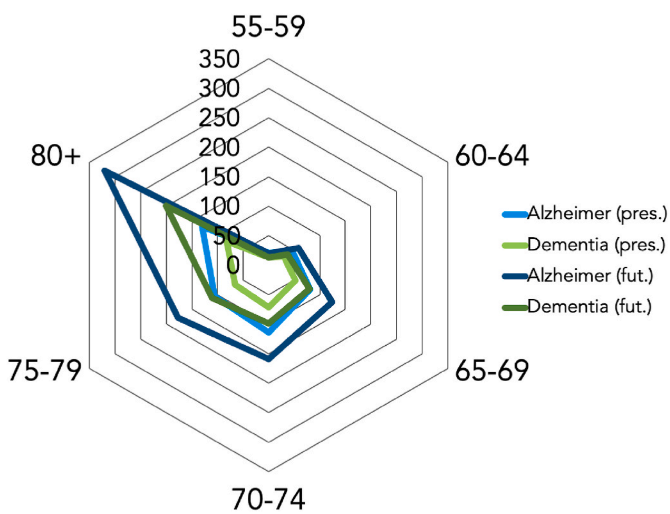

Fig. 6. Estimated incidence rate of AD and DU (both in thousands) for the present (1991–2010) and the future RCP8.5 scenario (2031–2050), considering UN projected population for 2050.

100,000 pop, in that order).

Analogously, if changes in future population are taken into account, the methodology used estimates an increase in the incidence rate of dementia associated with air pollution: 860,000 (95% CI 600,800-1,118,600) and 541,000 (95% CI 443,600–692,800) for AD and DU, in that order; that is, 107/100,000 pop. and 68/100,000 pop. This represents an increase (Table 3,right) in the future of 0.51% and 0.57% for AD and DU, respectively, due to the climate penalty; and of 72.43% and 72.12% for AD and DU, with the future population changing according to the estimates of the United Nations. These numbers indicate that the aging of population stands for the leading factor when estimating future pathologies, since air pollution impacts show an important positive relationship with the hazard ratios.

3.3. Impacts of air pollution on Alzheimer's disease

Focusing on AD, the incidence rate associated with NO_2 and PM2.5 in the current period (1991–2010) is 353,000 (95% CI 224,800-427,200) and 148,000 (95% CI 125,600-207,700) (44/100,000 pop. and 19/100,000 pop.), respectively (see Fig. 7 and Appendix Table A3 for details on the age distribution). As shown in Fig. 8,left, the present distribution of the incidence rate associated with NO_2 in Europe is rather heterogeneous, with central Europe being the most affected area, especially Germany, Belgium, the Netherlands and England. The spatial pattern for PM2.5 is identical (Fig. 9,left), because the population in the present period is mainly concentrated in these areas, as previously seen in Fig. 1.

Regarding the differences expected in the future period (2031–2050, RCP8.5 scenario), if the population is kept similar to the 2010 distribution and density, Fig. 8,right-top depicts that the climate penalty would bring a slight reduction in the incidence rate related to NO_2 in central- and northern-European countries like Switzerland, Germany, England or Scandinavian countries. Conversely, countries in southern Europe (Spain, Portugal, Greece or the Balkan countries) undergo an increase in AD. The reason for this different behaviour has to be sought in the modifications of future gas-phase air pollution over Europe. Jiménez-Guerrero et al., (2013b) found a strong north-south dipole in the variations of NO_2 levels over Europe (large increases/decreases over southern/northern Europe) for future climate change scenarios, under the hypothesis that anthropogenic emissions are kept constant (that is, isolating the impacts of climate change). The spatial pattern of this dipole in independent of the climate change scenario considered, and only varies in intensity depending on the forcing.

In contrast, Fig. 9,right-top shows a more pronounced increase in the incidence rate associated with PM2.5 across southern Europe, including France. Conversely, there are areas where the incidence rate of AD decreases, despite this reduction is milder, especially over central Europe (e.g. Germany). The expected increase, hence, in AD incidence rate associated with NO_2 and PM2.5 for the future period (RCP8.5) is 0.44% and 0.66% (Appendix Table A4), respectively. Overall, this represents an increase of +4000 (95% CI 2800-5100) in the incidence rate of AD over Europe associated with air pollution caused by climate penalty. This limited number is due to the fact that the concentration of pollutants in central and northern Europe will decrease in the future, offsetting the increase of concentrations in the south, therefore showing a very disimilar pattern of variation in AD due to climate change alone.

On the other hand, considering changes in 2050 population, globally the incidence rate associated with air pollution increases throughout Europe for both pollutants (Fig. 8,right-bottom and Fig. 9,right-top), especially in France, Germany and England. The future incidence rate is 605,000 (95% CI 385,400–732,200) and 255,000 (95% CI 216,400-357,900) associated with NO_2 and PM2.5; that is, an average increase in the incidence rate over Europe by NO_2 and PM2.5 pollutants of +252,000 (+72.27%, +32/100,000 pop.) and +108,000 (+72.79%, +14/100,000 pop.), respectively (Appendix Table A5). Although the concentration of both pollutants decreases in these areas of central Europe, it is expected that in the future the sensitive population

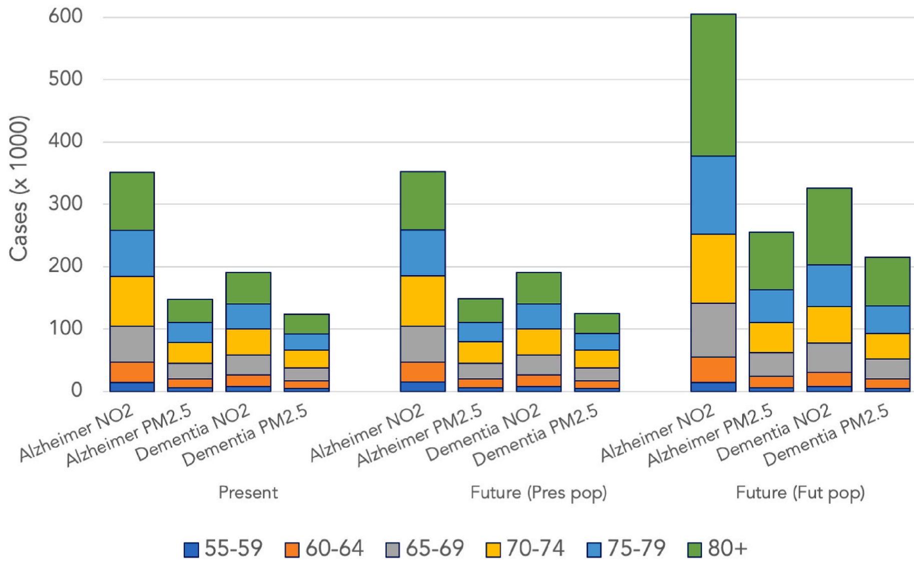

Fig. 7. Incidence rate (in thousands) for each age range related to each neurodegenerative disease (AD and DU) by NO_2 and PM2.5. Left: present incidence; center: future RCP8.5 scenario, present 2010 population (climate penalty); right: future RCP8.5 scenario, UN 2050 population.

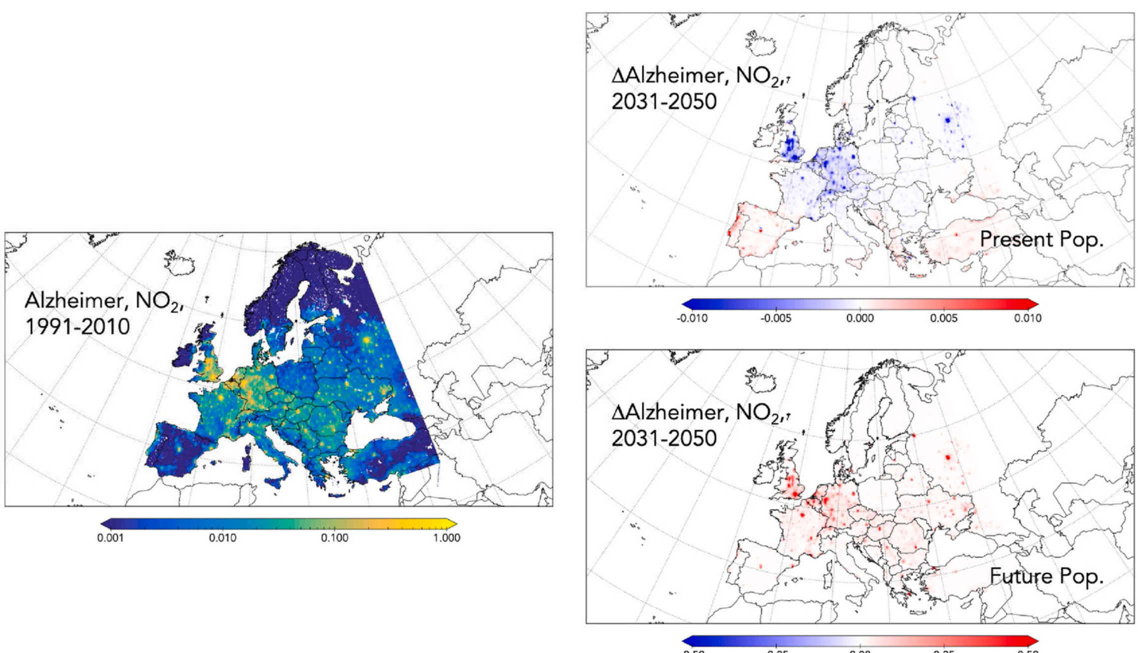

Fig. 8. (Left) Present (1991–2010) incidence rate of AD associated with exposure to NO_2. (Right, top) Differences with 2031–2050 under the RCP8.5 scenario, keeping population constant. (Right, bottom) Id. but with population projected for the 2050s. All units are incidence rate km^{-2} per year.

(principally >65 years) will increase especially over those target regions.

Hence, the increase in the incidence rate makes such a noticeable difference compared to the scenario isolating the climate penalty. In the case when the population is kept invariant, the increase is only produced by modifications in air pollution (which, as previously commented, differs between northern and southern Europe in a marked dipole of differences). The increase in pollution in some areas is offset by the improvement in air quality in others (Fig. 3,right and Fig. 4,right), so modifications in the incidence rate is strongly local and decreases in northern countries compensates the increases in more southern regions. On the contrary, when the future variation of population is considered for the future (2050), the aging of European population becomes a very important factor, having the largest influence on neurodegenerative diseases, since they affect principally the older population (Carey et al., 2018). This is well reflected in Fig. 6, which shows how the increase in the future incidence rate occurs mainly for the age group >80 years (which will importantly increase in the projected population for 2050, Fig. 2) for both types of dementia.

3.4. Impacts of air pollution on dementia, unknown or unspecified cause

Focusing on DU, Fig. 10,left and Fig. 11,left depict a very similar distribution for the air pollutants included in this contribution with respect to the incidence rate for the current period. The incidence rate is 190,000 (95% CI 154,800-257,300; exposure to NO_2, 24/100,000 pop.) and 124,000 (95% CI 105,200-153,100; exposure to PM2.5, 16/100,000 pop.) (Appendix Table A3).

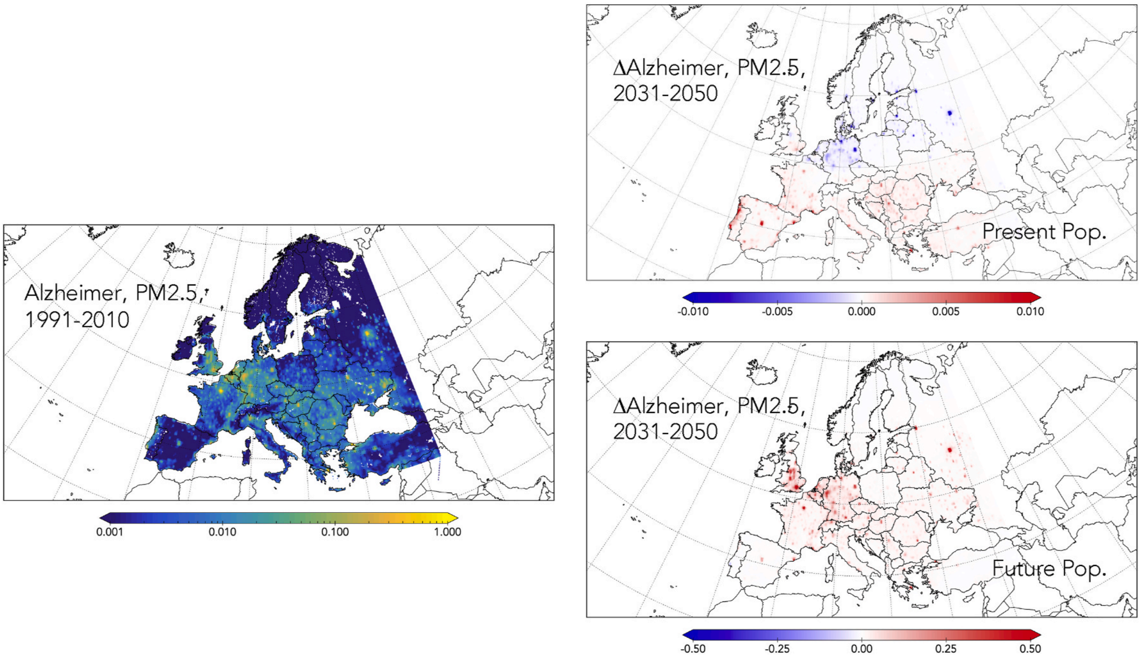

Fig. 9. (Left) Present (1991–2010) incidence rate of AD associated with exposure to PM2.5. (Right, top) Differences with 2031–2050 under the RCP8.5 scenario, keeping population constant. (Right, bottom) Id. but with population projected for the 2050s. All units are incidence rate km^{-2} per year.

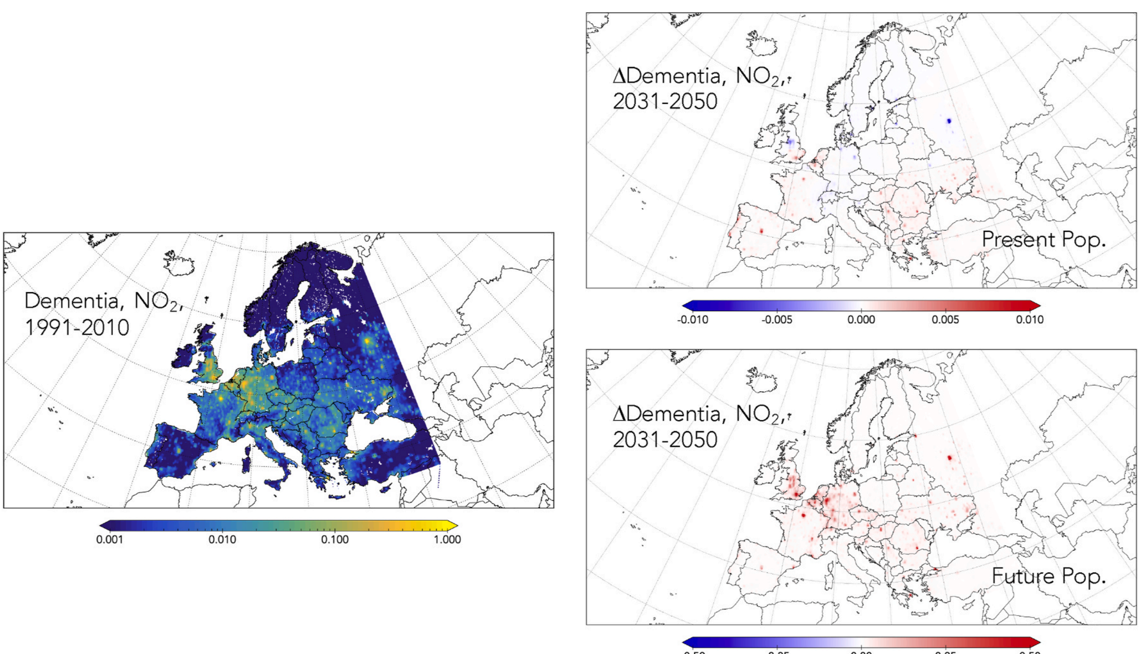

Fig. 10. (Left) Present (1991–2010) incidence of DU to NO_2 exposure. (Right, top) Differences with 2031–2050 under the RCP8.5 scenario, isolating the climate penalty. (Right, bottom) Id. but with population projected for the 2050s. All units are incidence rate km^{-2} per year.

Regarding the future period, the climate penalty alone (Fig. 10,right-top) would lead to an increase in the incidence rate throughout Europe, except for a slight decrease in countries like England. Regarding the incidence rate associated with PM2.5, a decrease is projected in countries such as Germany, while the increase, as for NO_2, is more general and intense. In fact, the total increase in the incidence rate caused by PM2.5 is just 0.75% and 0.46% for NO_2 (Appendix Table A4).

Considering the changes in future population (Fig. 10,right-bottom and Fig. 11,right-bottom), an increase in the incidence rate over central Europe is found. The most affected countries for both pollutants are England and Germany. The increase in the incidence rate as a consequence of changes in NO_2 is +136,000 (95% CI 110,700-184,300) (+71.5%, +17/100,000 pop.) and +91,000 (95% CI 77,200-112,400) (+73.05%, +12/100,000 pop.) for PM2.5 (Appendix Table A5). The reasons for this increase have beed widely discussed in the section devoted to analyzing and discussing the results for AD.

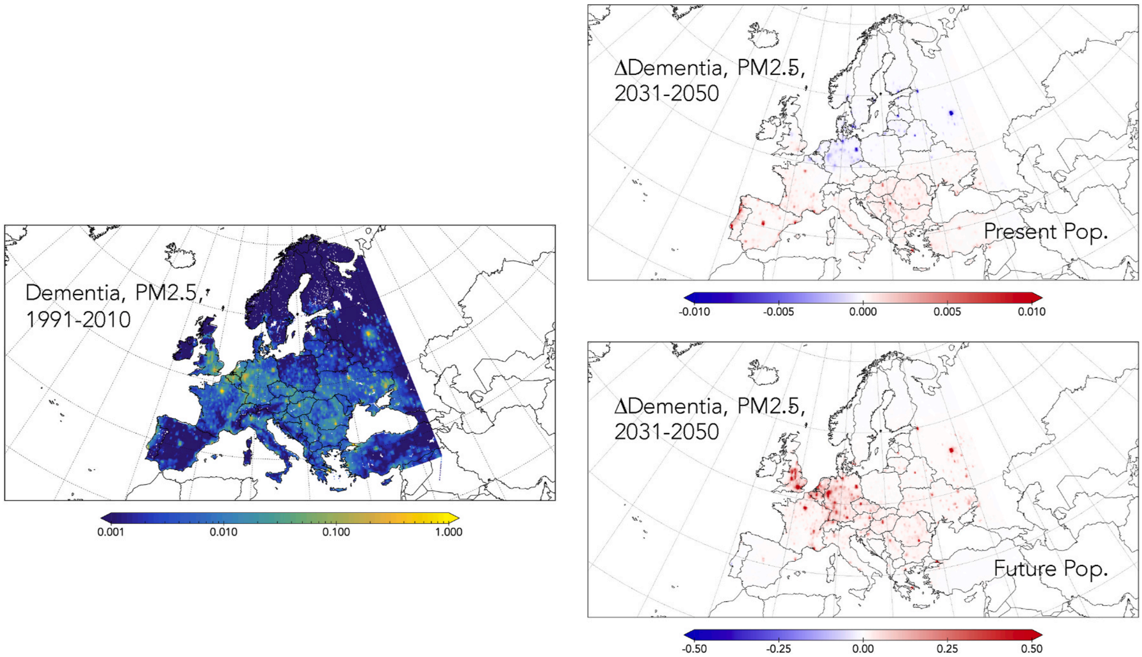

Fig. 11. (Left) Present (1991–2010) annual incidence of DU associated with exposure to PM2.5. (Right, top) Differences with 2031–2050 under the RCP8.5 scenario, isolating the climate penalty. (Right, bottom) Id. but with population projected for the 2050s. All units are incidence rate km^{-2} per year.

4. Discussion and conclusions

This contribution estimates the impacts of air pollution (NO_2 and PM2.5) on dementia over Europe for present and future climate scenarios. Both AD and DU have a larger sensitivity to the exposure to NO_2 than to PM2.5, being NO_2 associated with a higher incidence rate due to air pollution. Overall, the incidence rates of dementia associated with air pollution are estimated at 498,000 (95% CI 348,600–647,400) (62/100,000 pop.) and 314,000 (95% CI 257,500-401,900) (39/100,000 pop.) for AD and DU, respectively.

In the future (2031–2050), under the RCP8.5 scenario, the incidence rate will increase to 860,000 (95% CI 600,800-1,118,600) for AD and 541,000 (95% CI 443,600–692,800) for DU (107/100,000 pop. and 68/100,000 pop., in that order) due to the action of climate change and the projections of UN for population in the year 2050. This represents an increase of 72% compared to the present pathologies. If considering that the total incidence rate of AD in Europe is 11.08 per 1000 person-years (Niu et al., 2017), and the total population included in the target domain is 807.5 million for 2010 and 806.2 million projected for 2050 (Fig. 2), the results of this contribution indicate that 4.8% of the total incidence rate of AD in the present and 9.7% in the future might be attributable to the exposure to air pollution. This range of results is in a good agreement with those of Chen et al., (2017a), who estimate that 6.1% of total cases could have been avoided if the exposure to air pollution would have been that corresponding to the lowest quartile concentration of PM2.5 and NO_2 (7.9 $\mu g\ m^{-3}$ and 8.7 ppb, respectively).

Spatially, the main hotspots are located in several parts of central and western Europe (countries such as Germany, the Netherlands, France and England), coincident with the areas with high levels of NO_2 and PM2.5 concentration in the atmosphere for the present period, but also with a very high density of population. On the other hand, although in the future the hotspots are analogous spatially, the increase under future scenarios are mainly caused by the increment in the sensitive population (aged dwellers) in these areas.

Therefore, not only the levels of pollutants are related to the incidence rate, but also the changes in projected population influence the increase in the neurodegenerative diseases included in this contribution. In the future, despite total population barely changes (even decreases) for the year 2050, the percentage of elderly population in Europe is expected to rise. For this reason, a higher incidence rate of dementia associated with air pollution is expected in areas such as central Europe, despite the fact that the levels of pollutants are reduced as a consequence of the increase of precipitation modeled under the RCP8.5 scenario for northern and central Europe. This hypothesis is ratified by the fact that, if population is kept constant for the future, and only the climate penalty is considered, the total pathologies over the entire Europe would increase by less than 1%, depending on the changes (improvement or worsening) of air pollution over different areas of Europe. For example, the decrease of the incidence rate over central Europe offsets its large increase over southern European countries due to the climate penalty.

Our findings regarding associations between air pollution and dementia are consistent with previous research, both in terms of direction and magnitude. For instance, Shi et al., (2020) recently estimate higher hazard ratios for AD than for other types of dementia. In addition to the results presented here, we must bear in mind that the incidence of dementia does not only depend on the levels of pollution, but is also tied to variables depending on the country's economy or the health system, as well as the projection of the future population.

It should be noticed that the results presented here rely on a very reduced number of studies per outcome (four studies per endpoint), which is limited when compared to the bibliography included in Burnett et al., (2018) regarding global estimates of mortality. This reduced number is also conditioned because different studies cover different types of Alzheimer and other dementia, hampering the election of comparable hazard ratios representing the same endpoint. Still, the results presented here can help shedding some light on the influence of anthropogenic pollution of the atmosphere on the incidence rate of AD and DU, and how climate change and the dynamics of population might modify the number of dwellers affected by dementia. In this sense, the noticeable impacts of air pollution on global health need of policies and protocols between countries that help mitigating the levels of atmospheric pollutants.

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

Table A1
Data selected from the available scientific literature for AD.

Reference	Incidence	Population	y_0	HR	Age	Pollutant	Mean concentration
Oudin et al., (2016)	39	1806	215.95	1.15	55–85	NO_2	13.0 $\mu g\ m^{-3}$
	52	1806	287.93	1.51	55–85	NO_2	21.5 $\mu g\ m^{-3}$
	52	1806	287.93	1.38	55–85	NO_2	26.0 $\mu g\ m^{-3}$
Oudin et al., (2019)	43	1567	274.41	1.25	55–85	NO_2	13.0 $\mu g\ m^{-3}$
	59	1567	376.52	1.72	55–85	NO_2	21.5 $\mu g\ m^{-3}$
	57	1567	363.75	1.53	55–85	NO_2	26.0 $\mu g\ m^{-3}$
Carey et al., (2018)	848	130,978	64.74	1.55	50–79	NO_2	39.5 $\mu g\ m^{-3}$
	848	130,978	64.74	1.50	50–79	NO_2	41.5 $\mu g\ m^{-3}$
	848	130,978	64.74	1.01	50–79	PM2.5	15.3 $\mu g\ m^{-3}$
	848	130,978	64.74	1.13	50–79	PM2.5	15.6 $\mu g\ m^{-3}$
Shi et al., (2020)	3,425,102	473,696,618	72.31	1.13	>65	PM2.5	9.7 $\mu g\ m^{-3}$

Table A2
Data selected from the available scientific literature for DU.

Reference	Incidence	Population	y_0	HR	Age	Pollutant	Mean concentration
Chang et al., (2014)	425	29,547	143.84	1.10	>50	NO_2	39.9 $\mu g\ m^{-3}$
	374	29,547	126.58	1.01	>50	NO_2	48.3 $\mu g\ m^{-3}$
	515	29,547	174.30	1.54	>50	NO_2	52.2 $\mu g\ m^{-3}$
Chen et al., (2017b)	257,816	2,066,639	1247.51	1.06	>65	PM2.5	10.4 $\mu g\ m^{-3}$
	257,816	2,066,639	1247.51	1.14	>65	NO_2	16.2 $\mu g\ m^{-3}$
Carey et al., (2018)	747	130,978	57.03	1.55	50–79	NO_2	41.5 $\mu g\ m^{-3}$
	747	130.978	57.03	1.13	50–79	PM2.5	15.6 $\mu g\ m^{-3}$
	747	130.978	57.03	1.33	50–79	PM2.5	16.3 $\mu g\ m^{-3}$
Shi et al., (2020)	3,425,102	473,696,618	72.31	1.13	>65	PM2.5	9.7 $\mu g\ m^{-3}$

Table A3
Incidence rate of AD and DU associated with NO_2 and PM2.5 under present climate conditions (1991–2010) by each age range considered. Numbers in parenthesis represent the 95% CI.

Present ($\times 10^3$)				
Age range	AD (NO_2)	AD (PM2.5)	DU (NO_2)	DU (PM2.5)
55–59	15 (9.6–18.2)	6 (5.0–8.4)	8 (6.5–10.8)	5 (4.2–6.2)
60–64	33 (21.1–40.0)	14 (11.8–19.6)	18 (14.6–24.4)	12 (10.2–14.8)
65–69	57 (36.4–69.0)	24 (20.3–33.6)	32 (26.0–43.3)	20 (16.9–24.7)
70–74	80 (51.2–96.8)	34 (28.8–47.6)	42 (34.2–56.9)	29 (24.6–35.8)
75–79	74 (47.3–89.5)	31 (26.3–43.4)	40 (32.6–54.2)	26 (22.0–32.1)
80+	93 (59.5–112.5)	38 (32.2–53.2)	50 (40.7–67.7)	32 (27.1–39.5)
All	352 (225.2–426.0)	147 (124.8–205.8)	190 (154.8–257.3)	124 (105.2–153.1)
Total	**AD: 498**	**(348.6–647.4)**	**DU: 314**	**(257.5–401.9)**

Table A4
Incidence rate of AD and DU associated with NO_2 and PM2.5 under a climate penalty scenario (2031–2050) by each age range considered. Numbers in parenthesis represent the 95% CI.

Future ($\times 10^3$), pop. 2010				
Age range	AD (NO_2)	AD (PM2.5)	DU (NO_2)	DU (PM2.5)
55–59	15 (9.6–18.2)	6 (5.1–8.4)	8 (6.5–10.8)	6 (5.0–7.2)
60–64	33 (21.0–39.9)	14 (11.9–19.6)	18 (14.7–24.4)	12 (10.2–14.8)
65–69	57 (36.3–69.0)	24 (20.4–33.7)	32 (26.1–43.4)	20 (17.0–24.7)
70–74	80 (51.0–96.8)	35 (29.7–49.1)	42 (34.2–56.9)	29 (24.6–35.8)
75–79	75 (47.8–90.8)	31 (26.3–43.5)	40 (32.6–54.2)	26 (22.1–32.1).
80+	93 (59.2–112.5)	38 (32.3–53.3)	50 (40.7–67.7)	32 (27.2–39.5)
All	353 (224.8–427.2)	148 (125.6–207.7)	190 (154.8–257.4)	125 (105.2–153.2)
Total	**AD: 501**	**(350.4–651.4)**	**DU: 315**	**(258.3–403.4)**

Table A5
Incidence rate of Alzheimer's disease and dementia (unknown or unspecified cause) associated with NO_2 and PM2.5 under a climate penalty scenario (2031–2050) considering also the UN changes in the population for the year 2050. Results are shown by each age range considered. Numbers in parenthesis represent the 95% CI.

Future ($\times 10^3$), pop. 2050				
Age range	AD (NO_2)	AD (PM2.5)	DU (NO_2)	DU (PM2.5)
55–59	14 (8.9–16.9)	6 (5.0–8.4)	8 (6.5–10.9)	5 (4.2–6.3)
60–64	41 (26.1–49.6)	18 (15.2–25.3)	22 (17.9–29.8)	15 (12.7–18.5)
65–69	86 (54.8–104.1)	38 (32.3–53.3)	48 (39.1–65.0)	32 (27.2–39.5)
70–74	111 (70.7–134.3)	48 (40.7–67.4)	58 (47.2–78.6)	41 (34.8–50.6)
75–79	125 (79.6–151.3)	53 (45.0–74.4)	67 (54.6–90.8)	44 (37.3–54.4)
80+	228 (145.2–275.9)	92 (78.1–129.1)	123 (100.2–166.6)	78 (66.2–96.4)
All	605 (385.4–732.2)	255 (216.4–357.9)	326 (265.5–441.7)	215 (182.5–265.6)
Total	**AD: 860**	**(600.8–1118.6)**	**DU: 541**	**(443.6–692.8)**

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