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Health impact assessment by the implementation of Madrid City air-quality plan in 2020

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ABSTRACT

Objectives: Air pollutant concentrations in many urban areas are still above the legal and recommended limits that are set to protect the citizens' health. Madrid is one of the cities where traffic causes high NO_2 levels. In this context, Madrid City Council launched the Air Quality and Climate Change Plan for the city of Madrid (Plan A), a local strategy approved by the previous government in 2017. The aim of this study was to conduct a quantitative health impact assessment to evaluate the number of premature deaths that could potentially be prevented by the implementation of Plan A in Madrid in 2020, at both citywide and within-city level. The main purpose was to support decision-making processes in order to maximize the positive health impacts from the implementation of Plan A measures.

Methods: The Regional Statistical Office provided information on population and daily mortality in Madrid. For exposure assessment, we estimated $PM_{2.5}$, NO_2 and O_3 concentration levels for Madrid city in 2012 (baseline air-quality scenario) and 2020 (projected air-quality scenario based on the implementation of Plan A), by means of an Eulerian chemical-transport model with a spatial resolution of 1 km × 1 km and 30 vertical levels. We used the concentration-response functions proposed by two relevant WHO projects to calculate the number of attributable annual deaths corresponding to all non-accidental causes (ICD-10: A00-R99) among all-ages and the adult population (> 30 years old) for each district and for Madrid city overall. This health impact assessment was conducted dependant on health-data availability.

Results: In 2020, the implementation of Plan A would imply a reduction in the Madrid citywide annual mean $PM_{2.5}$ concentration of 0.6 μg/m^3 and 4.0 μg/m^3 for NO_2. In contrast, an increase of 1 μg/m^3 for O_3 would be expected. The annual number of all-cause deaths from long-term exposure (95% CI) that could be postponed in the adult population by the expected air-pollutant concentration reduction was 88 (57–117) for $PM_{2.5}$ and 519 (295–750) for NO_2; short-term exposure accounted for 20 (7–32) for $PM_{2.5}$ and 79 (47–111) for NO_2 in the total population. According to the spatial distribution of air pollutants, the highest mortality change estimations were for the city centre – including Madrid Central and mainly within the M-30 ring road –, as compared to peripheral districts. The positive health impacts from the reductions in $PM_{2.5}$ and NO_2 far exceeded the adverse mortality effects expected from the increase in O_3.

Conclusions: Effective implementation of Plan A measures in Madrid city would bring about an appreciable decline in traffic-related air-pollutant concentrations and, in turn, would lead to significant health-related benefits.

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1. Introduction

Air pollution is considered the world's largest environmental health threat by the World Health Organization (WHO, 2016), with outdoor air pollution estimated to have caused 4.2 million premature deaths worldwide in 2015 (Cohen et al., 2017). Moreover, recent global estimates of mortality attributable to outdoor fine particulate matter ($PM_{2.5}$) air pollution carried out using a Global Exposure Mortality Model were 120% higher than previous estimates, accounting for 8.9 million premature deaths (Burnett et al., 2018). In addition, model projections based on a business-as-usual emission scenario indicated that the contribution of outdoor air pollution to premature mortality could double by 2050 (Lelieveld et al., 2015). Exposure to air pollutants is of particular concern in urban areas because of the highly dense populations exposed to air pollution and the high number of emission sources (Stewart et al., 2017), with emisions from traffic the main contributor (Kumar et al., 2014). Cities currently account for 85% of global economic activity and 55% of the world's population, a share that is expected to grow to 66% by 2050 (United Nations (UN), 2015). This is leading to increases in energy consumption, construction activity, industry, and traffic on a historically unprecedented scale (Landrigan et al., 2018).

Despite recent emission abatement efforts, urban air quality also represents a major public health burden and is of long-standing concern to the citizens in Europe (Pascal et al., 2013). The 2008 Ambient Air Quality Directive (European Commission, 2008) is the cornerstone of the EU's ongoing clean air policy, as it sets air quality standards for major air pollutants. In addition, a new edition of the "Clean Air for Europe" programme (European Commission, 2013) was launched in 2013 to support the European Commission's development of the Thematic Strategy on air pollution, which aims to move closer to the WHO guidelines by 2030. Particular attention has been paid to particulate matter (PM), nitrogen dioxide (NO_2) and ground-level ozone (O_3), which are considered the most significant air pollutants in terms of harm to human health (EEA, 2018). The last European Environment Agency report estimates that exposure to these pollutants in 2015 was responsible for about 483,400 premature deaths in the EU-28 (EEA, 2018). However, a recent study suggests that these health impacts are actually substantially higher than previously assumed, raising the annual excess mortality rate to 659,000 premature deaths in the EU-28 (Lelieveld et al., 2019).

Over the past decade, air quality has slowly improved in many European cities, as a direct result of more robust air-quality policies across various governance levels, the introduction of targeted measures and actions, and technological improvements that have reduced emissions from various sources (EEA, 2019). Nevertheless, many cities and regions still experience regulated limits for air pollutants being exceeded (EEA, 2019). Madrid (Fig. 1a) is one of the European cities where traffic causes high NO_2 levels, exceeding both European Union hourly- and annual-limit values (Borge et al., 2014; EEA, 2019). During the last decade, Madrid City Council has been taking measures to tackle air-pollution issues, including the local strategy, the Air Quality and Climate Change Plan for Madrid City (hereafter Plan A; Ayuntamiento de Madrid AM, 2017), which was approved by the previous government in September 2017. Plan A includes a set of 30 measures organized into four combined lines of action to produce a new urban model: sustainable mobility (21 measures), urban regeneration and low-emission urban management (7 measures), climate-change adaptation (1 measure), and awareness-raising and communication (1 measure). Plan A integrates air-quality and climate-change policies. This public health approach considered two temporal horizons to promote a low-emission city model: 2020 to achieve the air-quality targets (WHO guidelines for $PM_{2.5}$ and NO_2), and 2030 for the necessary energy transition and the consolidation of a low-emission city model (intended to reduced total greenhouse gas emissions by 40% with respect to 1990 levels).

Madrid is the largest city in Spain, as well as its largest built-up urban area, with a population estimated at 3.2 million in 2018. It is well-served by urban motorways (freeways), combining ring roads with radial access roads, which are extensions of national motorways into the city (Fig. 1b) and experiences intense road traffic across the whole metropolitan area. The largest suburbs in the Madrid region are to the south, and in general along the main routes leading out of the city. While activity is concentrated in the capital, residential neighbourhoods and services are located peripherally. This leads to a significant daily flow of people from the suburbs to Madrid city for daily activities, in many cases involving a long-distance commute which is generally only possible using personal vehicles (Picornell et al., 2019). According to the Madrid City Council, on a typical weekday 2.5 million car journeys start or finish in the city of Madrid; along with those of buses, taxis and delivery vehicles, this totals up to 0.9 million journeys. As a result, more than 40 million km are driven on a typical day within Madrid city. Traffic congestion can be severe in the city, and congestion is associated with particularly high emission factors (Borge et al., 2012). This is especially relevant because road traffic is considered the main contributor to NO_2 levels in Madrid city – up to 90% of NO_2 concentrations in the city centre were found to come from this source (Borge et al., 2014). Consequently, measures to abate atmospheric emissions from traffic play a key role in Plan A.

Pollution can no longer be viewed as an isolated environmental issue, since it is a problem that affects the health and wellbeing of entire societies (Landrigan et al., 2018). Quantifying the benefits of air-quality programs is an important step in evaluating the efficacy of regulations, comparing alternative strategies, and communicating to the public the importance of these often costly efforts (Kheirbek et al., 2014). In this

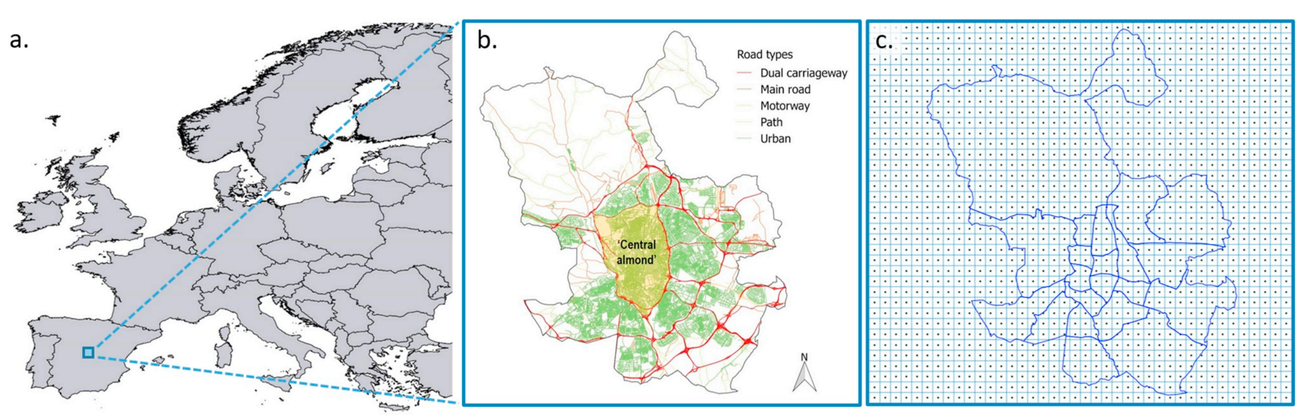

Fig. 1. Study area: (a) Madrid city location; (b) road network map, downtown area of the City (inside M-30 ring road) in yellow and 'Central zero emissions zone' (Madrid Central) in blue; (c) Madrid city districts map, grid cells and centroids of the air-quality Eulerian model. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

context, the aim of this study was to conduct a quantitative health impact assessment (HIA) in relation to the number of premature deaths that could potentially be prevented by the implementation of Plan A in Madrid city in 2020 at citywide and within-city level. These analyses were part of the European H2020 project ICARUS (ICARUS, 2016), whose objective was to support decision-making processes in order to maximize the positive health impacts from the implementation of urban air-quality control measures.

2. Material and methods

2.1. Air-quality scenarios: 2012–2020 (Plan A)

The city of Madrid is a metropolitan area formed by 21 districts (Fig. 1b) located on a continental plateau in the centre of the Iberian Peninsula (Fig. 1a). The expected impact of the implementation of Plan A was simulated through an Eulerian chemical-transport model with a spatial resolution of 1 km × 1 km (Figs. 1c) and 30 vertical levels. Meteorological fields were provided by Weather Research and Forecasting Advanced Research (WRF-ARW) version 3.7.1 (Skamarock and Klemp, 2008), and include BEP (Building Effect Parameterization) (de la Paz et al., 2016; Martilli et al., 2002). Emissions were processed by the Sparse Matrix Operator Kernel Emission (SMOKEV3.6.5) (University of North Carolina at Chapel Hill (UNC), 2015) and come from a very detailed urban emission inventory that includes more than 400 traffic-related emission categories (Borge et al., 2018b; Pérez et al., 2019). This is also consistent with the methodology used for the compilation of Madrid's local official emission inventory (Ayuntamiento de Madrid AM, 2018). Ambient air pollution levels were simulated using Community Multiscale Air Quality (CMAQ) version 5.0.2 (Byun and Schere, 2006; Ching and Byun, 1999).

This modelling system was used to simulate two annual runs (1-h temporal resolution) with identical meteorology and configuration except for emission inputs. On one hand, the baseline air-quality scenario corresponding to 2012 was used to reflect air pollutant levels prior to the implementation of Plan A. On the other, the projected air-quality scenario was designed to simulate air pollution distribution in 2020 in a case where air-quality control measures planned in 2020 will have been successfully implemented. The measures listed in Table S1 are expected to reduce annual NO_X emissions in Madrid by 20% (3011 t) and $PM_{2.5}$ emissions by 27% (222 t). The projected 2020 scenario reflected the most likely future situation, since it included expected outcomes from Plan A in terms of the ambient air concentration of the most relevant pollutants ($PM_{2.5}$, NO_2 and O_3). The modelling results (pollutant concentration change between 2012 and 2020) provided the basis for the health impact assessment (HIA). Each air-quality model grid cell was assigned geographic coordinates corresponding to its centroid, and shapes overlapping Madrid citywide and for its districts were then applied, using GIS software to calculate the daily mean concentration for each pollutant in Madrid citywide and in each district (Fig. 1c). For citywide and district levels which included more than one grid-cell centroid, air-quality data were aggregated to obtain a single value.

Population and mortality data

Population and daily-mortality data – stratified by age, sex and district – were used in this study. Population data for 2012 and the projected 2020 population of 1st January were provided by the Department for Statistics of Madrid City Council according to the official census. The number of deaths corresponding to total non-accidental causes (International Classification of Diseases, 10th revision [ICD-10], codes A00-R99), cardiovascular (CVD; ICD-10, codes I00–I99) and respiratory (ICD-10, codes J00-J99) diseases for 2012 were provided by the Madrid Regional Statistical Office under a specific confidentiality protocol. Population and mortality data for 2012 (Table 1) were used to calculate baseline mortality rates for Madrid city and each district, and also for each specific mortality cause and age group according to applied concentration-response functions (see Subsection 2.4.). These mortality rates for 2012 and projected 2020 population (Table 1) were used to the HIA analysis. The study protocol was approved by the Carlos III Health Institute Ethics Committee (reference: CEI-PI 21_2018).

2.3. Selection of concentration-response functions

Health endpoints were chosen based on available guidelines issued by scientific panels and the Horizon 2020 European project ICARUS. The most appropriate health-effect estimates for our purpose were those provided by the WHO coordinated projects: "Health risks of air pollution in Europe-HRAPIE" (WHO, 2013a) and "Review of evidence on health aspects of air pollution-REVIHAAP" (WHO, 2013b). Nevertheless, the concentration-response functions (CRFs) applied in this study were selected depending on health-data availability (Table 2).

The estimations of the impact of long-term exposure and the 95% confidence intervals (CI) associated with each CRF were calculated by means of: (1) $PM_{2.5}$ annual mean concentrations for all-cause (natural) mortality in adult populations (age > 30)(Hoek et al., 2013); (2) NO_2 annual mean concentrations for all-cause (natural) (Atkinson et al., 2018; Hoek et al., 2013), cardiovascular (Atkinson et al., 2018) and respiratory (Atkinson et al., 2018) mortality in adult populations (age > 30), and (3) O_3 summer months' (April–September) average of daily maximum running 8-h means above a 70 μg/m^3 concentration (cut-off point) for respiratory mortality in adult populations (APHEA-2, 2001; Jerrett et al., 2009)(Table 2). In relation to long-term NO_2 exposure, we conducted a sensitivity analysis using the most up-to-date meta-analysis carried out by Atkinson et al. (2018) following the COMEAP recommendation (COMEAP, 2018). In the case of long-term O_3 exposure, we applied a cut-off point at 70 μg/m^3 according to the HRAPIE expert recommendation. This cut-off point results from the fact that the summer months' mean O_3 concentration exceeded 70 μg/m^3 in most areas included in the American Cancer Society (ACS) analysis, so no information exists on the shape of the CRF below that level (Jerrett et al., 2009).

Table 1
Population for year 2012 and projected 2020-population at 1st January of year, and 2012-baseline mortality corresponding to all non-accidental causes (ICD-codes A00-R99), cardiovascular (ICD-10, codes I00–I99) and respiratory (ICD-10, codes I00–I99) diseases in city of Madrid. Mortality is showed in terms of number of absolute deaths and crude rates per 100000 population.

Age group	Sex	Population		2012-Mortality (deaths in absolute numbers)			2012-Mortality rate (deaths per 100000 population)		
		2012	2020	All-causes	Cardiovascular disease	Respiratory disease	All-causes	Cardiovascular disease	Respiratory disease
All-ages	Total	3247998	3226378	25463	6609	4096	784	203	126
	Man	1518016	1511750	12028	2600	1963	792	171	129
	Woman	1729982	1714628	13435	4009	2133	777	232	123
> 30 years	Total	2436499	2302112	25127	6600	4086	1031	271	168
	Man	1109549	1045399	11849	2596	1959	1068	234	177
	Woman	1326950	1256713	13278	4004	2127	1001	302	160

Table 2
Health outcomes and associated CRFs recommended by the HRAPIE project (WHO, 2013a,b) and COMEAP (2018), expressed as relative risk (RR) per 10 μg/m^3 increase in each pollutant concentration used in the health impact assessment (HIA). The 95% confidence intervals (CI) associated with the recommended CRFs were also included.

Pollutant metric	Range of concentration	Health outcome	ICD-10 codes	Ages	RR (95% CI) per 10 μg/m^3	Reference
Long-term exposure						
$PM_{2.5}$, annual mean	All	Mortality, all-natural causes	A00-R99	> 30 years	1.062 (1.040–1.083)	Hoek et al. (2013)
NO_2, annual mean	All	Mortality, all-natural causes	A00-R99	> 30 years	1.055 (1.031–1.080)	Hoek et al. (2013)
NO_2, annual mean [a]	All	Mortality, all-natural causes	A00-R99	> 30 years	1.020 (1.010–1.030)	Atkinson et al. (2018)
NO_2, annual mean [a]	All	Mortality, cardiovascular diseases	I00–I99	> 30 years	1.030 (1.020–1.050)	Atkinson et al. (2018)
NO_2, annual mean [a]	All	Mortality, respiratory diseases	J00-J99	> 30 years	1.030 (1.010–1.050)	Atkinson et al. (2018)
O_3, summer months (April–September) average of daily maximum 8-h mean	> 70 μg/m^3	Mortality, respiratory diseases	J00-J99	> 30 years	1.014 (1.005–1.024)	Jerrett et al. (2009)
Short-term exposure						
$PM_{2.5}$, daily mean	All	Mortality, all-natural causes	A00-R99	All-ages	1.0123 (1.0045–1.0201)	HRAPIE
NO_2, daily maximum 1-h mean	All	Mortality, all-natural causes	A00-R99	All-ages	1.0027 (1.0016–1.0038)	APHEA-2 study
O_3, daily maximum 8-h mean	All and > 70 μg/m^3	Mortality, all-natural causes	A00-R99	All-ages	1.0029 (1.0014–1.0043)	Katsouyanni et al. (2009)
O_3, daily maximum 8-h mean	All and > 70 μg/m^3	Mortality, cardiovascular diseases	I00–I99	All-ages	1.0049 (1.0013–1.0085)	Katsouyanni et al. (2009)
O_3, daily maximum 8-h mean	All and > 70 μg/m^3	Mortality, respiratory diseases	J00-J99	All-ages	1.0029 (0.9989–1.0070)	Katsouyanni et al. (2009)

[a] Sensitivity analysis for long-term NO_2 exposure was carried out using CRFs provided by Atkinson et al. (2018).

The quantification of the impact of short-term exposure was conducted using: (1) $PM_{2.5}$ daily mean and NO_2 daily maximum 1-h mean concentrations for all-cause (natural) mortality in all-ages population (APHEA-2, 2001; WHO, 2013a) and (2) the daily maximum running 8-h mean for O_3-related mortality comes from all-cause, cardiovascular and respiratory diseases across all ages of the population (Katsouyanni et al., 2009) (Table 2). Regarding short-term O_3 exposure, we conducted the HIA analysis without and with a cut-off point at 70 μg/m^3. In this regard we must point out that the coefficients in the APHENA study (Katsouyanni et al., 2009) were based on the whole range of observed O_3 concentrations; however, HRAPIE experts recommended a cut-off concentration of 70 μg/m^3 to reflect greater confidence in the significant relationship above this threshold (WHO, 2013a). Therefore, the impact of short-term O_3 exposure above 70 μg/m^3 was also estimated in this study.

2.4. Health impact assessment analysis

Standardised HIA methods were used to analyse the expected impact of Plan A by 2020. For Madrid city and each district, data were introduced according to the selected CRF, for both the baseline (mortality rates and estimated air-quality levels in 2012) and projected scenarios (projected 2020 population and estimated air-quality levels in 2020). Assuming that the entire population was exposed to air pollution, potentially avoidable premature deaths were calculated in absolute and relative numbers for Madrid city overall and for each district individually. For each health outcome and pollutant, we calculated a central estimate and related upper and lower 95% confidence intervals (95% CIs) according to the following health impact function (Martenies et al., 2015):

$$\Delta Y = Y_0\,(1\;-e^{-\beta\Delta x})P$$

where ΔY is the change in the mortality based on differences in air-quality model-derived pollutant concentrations between the both scenarios; Y_0, the mortality rate in the reference scenario; β, the coefficient of the CRFs for an increase in air-pollution concentrations of 1 μg/m^3; Δx, the change in the pollutant concentration between the baseline (2012) and projected (2020) air-quality scenarios (μg/m^3); and P, the projected population for year 2020.

In addition to the health impact estimation for the total population (both sexes combined), avoidable premature deaths were also calculated – stratified by sex at city level.

3. Results

Table 1 shows descriptive results for the demographic and mortality variables used in this study. In 2012 the population registered in the city of Madrid was 3.25 million inhabitants, with 2.44 million of these over 30 years of age (our ‘adult age group’). The population is expected to decrease by 2020, accounting for 3.23 total and 2.42 million adult inhabitants. Sex ratio was 0.9 for total population and 0.8 for adults. Moreover, the total baseline-mortality in the all-age group for all-causes accounted for 25,463 deaths, specifically 6609 deaths were from CVDs and 4096 from respiratory diseases, which correspond to the following crude mortality rates for the all-age group: 784 deaths per 100,000 for all-causes, 203 per 100,000 from CVDs and 126 per 100,000 from respiratory diseases. Regarding differences by sex, the population and mortality in terms of absolute numbers showed higher values for women than men, with the CVD figures appearing to be especially notable. In contrast, mortality rates due to all-causes and respiratory diseases were higher for men. Similar patterns were observed in the adult age-group data.

According to our estimates, Madrid city's annual mean concentrations in the baseline air-quality scenario were 7.0 μg/m^3 for $PM_{2.5}$, 17.2 μg/m^3 for NO_2, and 94.0 μg/m^3 for O_3. In 2020, the implementation of Plan A would reduce annual mean $PM_{2.5}$

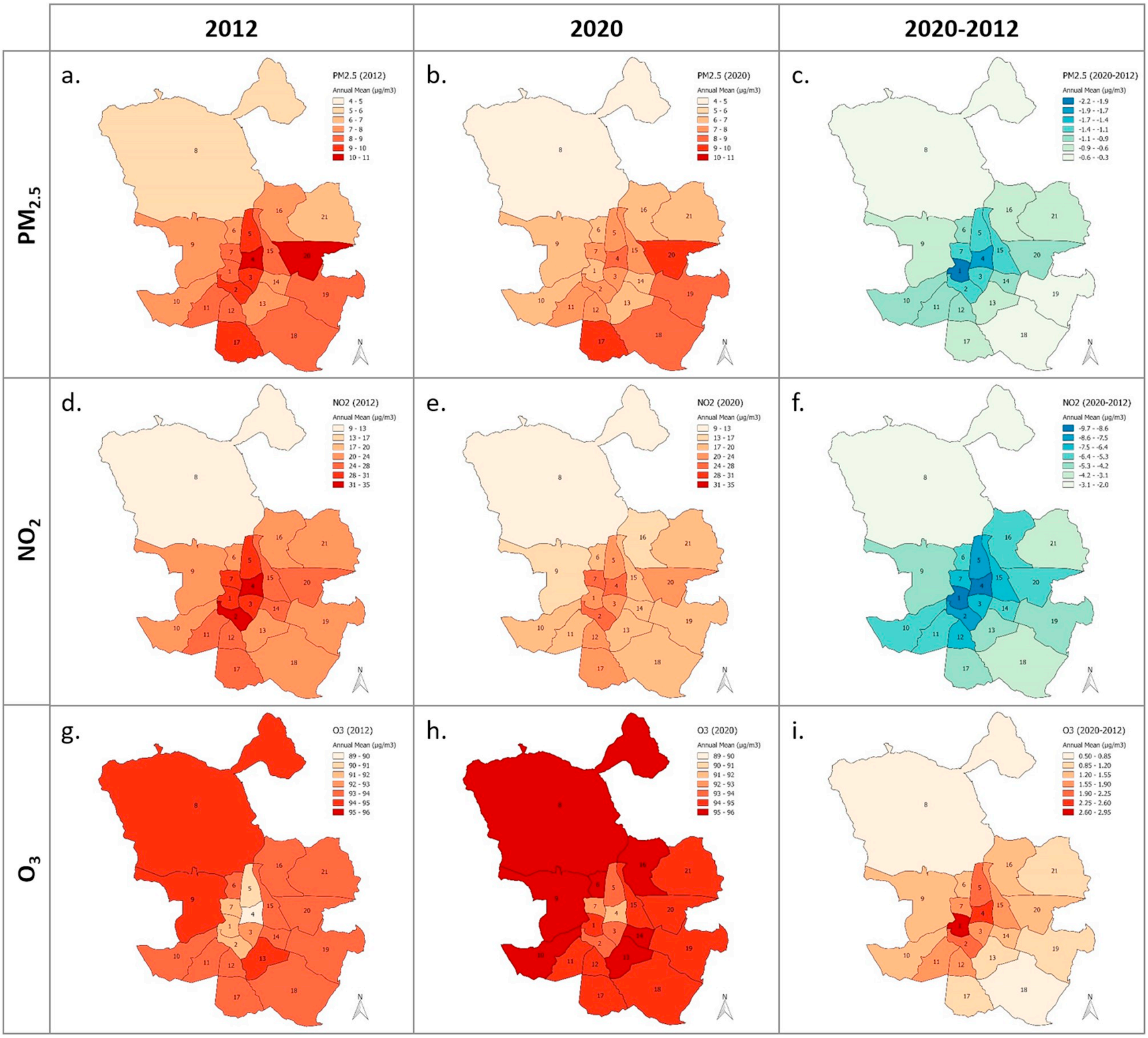

Fig. 2. Annual mean concentrations (µg/m^3) of $PM_{2.5}$ (a–c), NO_2 (d–f) and O_3 (g–i) in the 2012-reference air-quality and 2020-projected air-quality scenarios, and difference between 2020 and 2012 by district in the Madrid city (negative values imply air quality improvements).

concentrations by 0.6 µg/m^3 and NO_2 by 4.0 µg/m^3, but O_3 would increase by 1.0 µg/m^3. It should be noted that O_3 concentrations above 70 µg/m^3 accounted for 91% of the total number of observations in 2012 and 93% in 2020. Fig. 2 illustrates the geographical variations in annual concentrations by pollutant and district for both air-quality scenarios, as well as expected concentration-level changes between 2012 and 2020. The greatest differences between the two scenarios were observed in downtown Madrid (within the M-30 ring road), districts 1 to 7 (Figs. 1b and 2), and were especially notable in districts 1 and 4 (Fig. 2). The predicted concentration reductions in districts in this area (Fig. 1b) ranged between 1.0 and 2.2 µg/m^3 for $PM_{2.5}$ and 5.7–9.6 µg/m^3 for NO_2, whereas O_3 would be expected to increase between 1.5 and 2.9 µg/m^3.

Table 3 summarizes long-term and short-term HIA findings in terms of absolute number deaths and crude rates per 100,000 population which could potentially be prevented by the implementation of Plan A in Madrid city in 2020. Stratified HIA analysis by sex showed a higher health impact for women than for men, although no differences were observed in the mortality-rate results. Using Hoek's estimates, the annual number of all-cause deaths from long-term exposure that could be postponed in the adult population by the expected air-pollutant concentration reduction was 88 (95% CI 57–117) for $PM_{2.5}$ and 519 (95% CI 295–750) for NO_2, which corresponded to a mortality rate of 4 per 100,000 inhabitants for $PM_{2.5}$ (95% CI 2–5) and 23 per 100,000 for NO_2 (95% CI 13–33). A sensitivity analysis using Atkinson's estimates for long-term NO_2 exposure resulted in a lower all-cause mortality-rate impact estimation: 8/100,000 (95% CI 4–12), including 3/100,000 (95% CI 1–5) cardiovascular deaths and 2/100,000 (95% CI 1–3) respiratory deaths. Additionally, the HIA estimated that the short-term improvement in air quality could prevent 20 p.m.$_{2.5}$-related deaths (95% CI 7–32) in the total population and 79 (95% CI 47–111) all-cause premature deaths due to reduced NO_2 concentration levels. These figures corresponded to 1 (95% CI 0–1) deaths per 100,000 population for $PM_{2.5}$ and 2 (95% CI 1–3) for NO_2.

In contrast, an increase in estimated total mortality in absolute numbers was found in relation to the short-term effects associated with expected increases in ground-level O_3 concentration in 2020. In particular, the increase in daily maximum 8-h running mean accounted for a rise of 8 (95% CI 4–12) all-cause attributable deaths (Table 3), 4 (95% CI 1–6) for CVD and 1 (95% CI 1–3) for respiratory diseases. For the O_3

Table 3
Long-term and short-term HIA of changes in air-pollutant levels (µg/m^3) between baseline and projected air-quality scenarios – for all-cause mortality (ICD-10: A00-R99) in Madrid city by sex. Related upper and lower 95% CI bounds are indicated between brackets.

Mortality indicator	Pollution indicator	Sex	Long-term HIA (adult population)			Short-term HIA (all-ages population)		
			Reference	Deaths in absolute numbers [c]	Crude rate of deaths per 100,000 population [c]	Reference	Deaths in absolute numbers [c]	Crude rate of deaths per 100,000 population [c]
All-natural causes	$PM_{2.5}$	Total	Hoek et al. (2013)	−88 (−57, −117)	−4 (−2, −5)	HRAPIE	−20 (−7, −32)	−1 (0, −1)
		Men		−41 (−27, −55)	−4 (−3, −5)		−9 (−3, −15)	−1 (0, −1)
		Women		−47 (−30, −62)	−4 (−2, −5)		−10 (−4, −17)	−1 (0, −1)
All-natural causes	NO_2	Total	Hoek et al. (2013)	−519 (−295, −750)	−23 (−13, −33)	APHEA-2 study	−79 (−47, −111)	−2 (−1, −3)
		Men		−244 (−139, −353)	−23 (−13, −34)		−37 (−22, −53)	−2 (−1, −4)
		Women		−275 (−156, −397)	−22 (−12, −32)		−42 (−25, −59)	−2 (−1, −3)
All-natural causes [a]	NO_2	Total	Atkinson et al. (2018)	−191 (−96, −285)	−8 (−4, −12)			
		Men		−90 (−45, −134)	−9 (−4, −13)			
		Women		−101 (−51, −151)	−8 (−4, −12)			
							No cut-off point/cut-off point at 70 µg/m^3	
All-natural causes [b]	O_3	Total				Katsouyanni et al. (2009)	8 (4, 12)/6 (3, 8)	0 (0, 0)/0 (0, 0)
		Men					4 (2, 5)/3 (1, 4)	0 (0, 0)/0 (0, 0)
		Women					4 (2, 6)/3 (1, 5)	0 (0, 0)/0 (0, 0)
Cardiovascular diseases	NO_2	Total	Atkinson et al. (2018)	−75 (−25, −124)	−3 (−1, −5)			
		Men		−29 (−10, −49)	−3 (−1, −5)			
		Women		−46 (−15, −76)	−4 (−1, −6)			
Cardiovascular diseases [b]	O_3	Total				Katsouyanni et al. (2009)	4 (1, 6)/3 (1, 1)	0 (0, 0)/0 (0, 0)
		Men					1 (0, 2)/1 (0, 0)	0 (0, 0)/0 (0, 0)
		Women					2 (1, 4)/2 (0, 0)	0 (0, 0)/0 (0, 0)
Respiratory diseases	NO_2	Total	Atkinson et al. (2018)	−46 (−16, −77)	−2 (−1, −3)			
		Men		−22 (−7, −37)	−2 (−1, −4)			
		Women		−24 (−8, −40)	−2 (−1, −3)			
Respiratory diseases [b]	O_3	Total	Jerrett et al. (2009)	0 (0, 0)	0 (0, 0)	Katsouyanni et al. (2009)	1 (1, 3)/1 (0, 2)	0 (0, 0)/0 (0, 0)
		Men		0 (0, 0)	0 (0, 0)		1 (0, 1)/0 (0, 1)	0 (0, 0)/0 (0, 0)
		Women		0 (0, 0)	0 (0, 0)		1 (0, 2)/1 (0, 1)	0 (0, 0)/0 (0, 0)

[a] Sensitivity analysis for long-term NO2 exposure was carried out using CRFs provided by Atkinson et al. (2018).
[b] For the short-term O3 HIA, the reported findings consider both no cut-off and a cut-off point at 70 µg/m3. For long-term O3 HIA, the reported findings use a cut-off point at 70 µg/m3.
[c] Negative numbers indicate the number of related deaths postponed by implementation of Plan A. Positive numbers indicate the increase in attributable mortality due to implementation of Plan A.

cut-off point concentration above 70 μg/m^3, the increases in attributable mortality were 6 (95% CI 3–8) for all-cause deaths, 3 (95% CI 1-1) for CVD and 1 (95% CI 0–2) for respiratory diseases. In terms of mortality rate, these figures were very low (almost zero) for any of the analysed causes for short and long-term exposure.

District-specific HIA findings for within-city exposure variations are shown in Figs. 3 and 4. Fig. 3 shows the long-term HIA findings using CRFs provided by Hoek et al. (2013) for $PM_{2.5}$ and NO_2. Our HIA estimated that if long-term concentrations were reduced, the number of preventable adult deaths would range between 1 and 19 for $PM_{2.5}$ and 3–96 for NO_2, corresponding to mortality rates between 1 and 18 per 100,000 for $PM_{2.5}$ and 6–82 per 100,000 for NO_2 (Fig. 3). The total mortality reduction associated with short-term concentration reductions oscillated from less than 1 up to 5 premature deaths for $PM_{2.5}$ and from 1 to 13 for NO_2 (Fig. 4a, c). Regarding absolute numbers, districts 1 and 4 showed the highest health benefits for improvements in $PM_{2.5}$ levels (Figs. 3a and 4a), while for NO_2 these were districts 4, 11 and 15 (Figs. 3c and 4c) for both long- and short-term exposure. In contrast, the increase in total mortality related to the rise in short-term O_3 concentration accounted for less than 2 attributable premature deaths in each district without applying any cut-off point (Fig. 4e).

The greatest estimated health benefits for both long- and short-term effects related to decreases in $PM_{2.5}$ and NO_2 levels were in the districts within the M-30 and some of its surrounding areas (Fig. 3b, d, 4b, d). In particular, three-concentric areas were identified and ranked from highest to lowest avoidable mortality rates: (1) the 'core-area' formed by districts 1 (Madrid Central) and 4; (2) the 'first-ring' area including districts 2, 3, 5 and 7; (3) the 'second-ring' area with a half-moon shape which covers districts 6, 11, 12, 14 and 15 (Fig. 3b and c, 4b,c). Conversely, mortality rates related to short-term O_3 concentrations followed a decreasing spatial gradient across the three-concentric areas; in this case, however, this went from the highest negative effects in the 'core-area' towards the lowest in the 'second-ring' (Fig. 4f).

4. Discussion

This study quantified the potential health gains in terms of the mortality impact due to the air-quality changes that would be achieved by the full implementation of Plan A measures in Madrid city. At a citywide level, the largest positive health impact was attributable to the expected reduction of NO_2 concentration levels. In particular, the estimated reduction of 4.0 μg/m^3 in chronic NO_2 exposure could postpone 519 (2%) all-cause deaths in over 30s yearly by 2020. In parallel, these figures corresponded to 88 (0.4%) all-cause deaths in over 30s in relation to a reduction of 0.6 μg/m^3 in the $PM_{2.5}$ annual mean. It is notable that the NO_2 mortality impact was six times higher than for $PM_{2.5}$. Moreover, stratified HIA analysis by sex showed a greater long-term health impact for women than for men, although no differences were observed in the mortality-rate results. On the other hand, short-term impacts in terms of mortality rates were lower when compared with long-term impacts for any of the analysed mortality causes. This is consistent with the possibility of larger, more persistent cumulative effects from long-term exposures, but both short- and long-term effects are important when implementing air-quality control measures. With regard to the district-specific HIA findings, the estimated reduction in mortality rates for short- and long-term NO_2 and $PM_{2.5}$ concentrations was much larger in districts located in the central area of the city – mainly within the M-30 ring road – compared to peripheral districts.

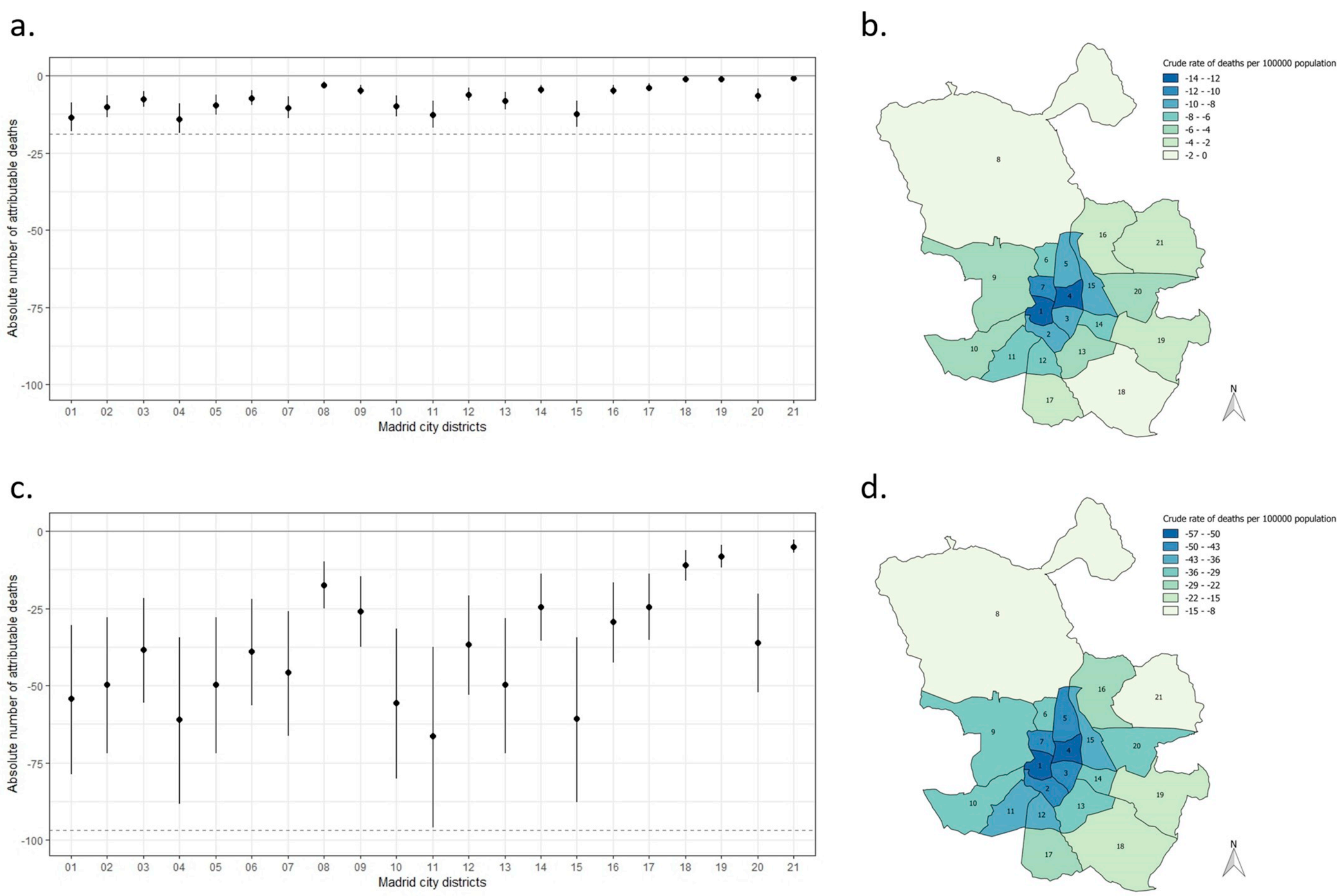

Fig. 3. Long-term HIA related to changes in pollutant levels (μg/m^3) between baseline and projected air-quality scenarios on all-cause adult mortality (ICD-10: A00-R99) in Madrid City districts: a) absolute number of deaths attributable to $PM_{2.5}$; b) crude rate of deaths per 100,000 population attributable to $PM_{2.5}$; c) absolute number of deaths attributable to NO_2; d) crude rate of deaths per 100,000 population attributable to NO_2.

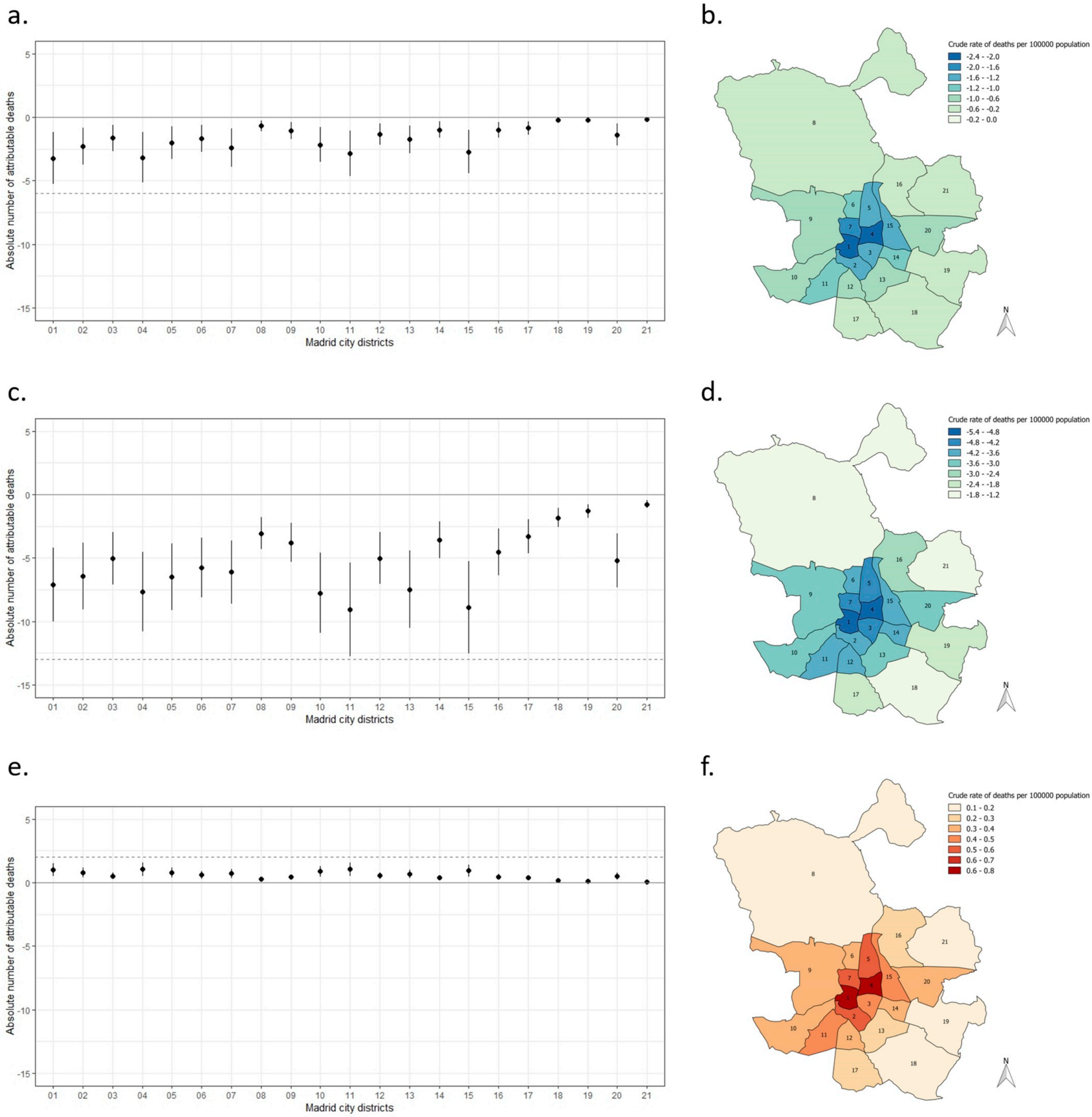

Fig. 4. Short-term HIA related to changes in pollutant levels (μg/m^3) between baseline and projected air-quality scenarios on all-cause all-ages mortality (ICD-10: A00-R99) in Madrid City districts: a) absolute number of deaths attributable to $PM_{2.5}$; b) crude rate of deaths per 100,000 population attributable to $PM_{2.5}$; c) absolute number of deaths attributable to NO_2; d) crude rate of deaths per 100,000 population attributable to NO_2; e) absolute number of deaths attributable to O_3 (no cut-off point); f) crude rate of deaths per 100,000 population attributable to O_3 (no cut-off point).

The same spatial pattern was observed for negative health effects related to the short-term increase in O_3. Finally, it must be emphasized that the positive health impact triggered by the reduction of $PM_{2.5}$ and NO_2 far exceeded the adverse mortality effects expected from the O_3 increase.

All strategies included in Plan A should improve air quality and consequently public health. Several Plan A measures were considered in order to simulate the projected air-quality scenario for 2020. Most of these were focused on sustainable mobility and, hence, were aimed at reducing road-traffic emissions, as this was identified as the most important sector for NO_2, PM_{10} and $PM_{2.5}$ levels in Madrid. In our study, the reduction in air-pollutant concentrations and the subsequent health benefits reported were more significant within the districts affected by traffic-related interventions. Reducing the intensity of private motor vehicle traffic, and promoting public transport and active mobility modes (walking and cycling) is also associated with positive health effects (Gerike et al., 2016; Mueller et al., 2015; Wang et al., 2016). Moreover, these kinds of measures are thought to stimulate social cohesion – with people who commute actively interacting more on the streets (Gerike et al., 2016). Therefore, beyond mortality, other secondary positive consequences associated with the interventions in Plan A could also influence health, e.g. improve physical-activity levels. In addition, a low emission central area (LEZ) has been mapped out, including a set of specific measures which have been designed to act as a catalyst for the necessary transition of the city as a whole towards a low-emission mobility model. More than 200 LEZs have already been implemented in Europe, mainly in major cities, such as Berlin, Amsterdam, London, Lisbon and Rome, which aim to reduce exhaust emissions of PM and NO_x, and studies have indicated that those LEZs have generally improved air quality, particularly in the vicinity of busy roads. Furthermore, of the various traffic-related interventions made, LEZs appear to be the most effective at reducing ambient NO_2 and PM levels (Wang et al., 2016). Other measures included in the projected air-quality scenario affected residential, commercial and institutional sectors, municipal solid-waste management, or cut across a number of sectors. Finally, the plan also includes a measure related to climate-change adaptation. According to the Plan's objectives and the greenhouse gas emissions inventory data, Madrid's total emissions in 2030 should be in the region of 7800 kt CO_2-eq, a reduction of 5200 kt CO_2-eq against 1990 levels (Ayuntamiento de Madrid AM, 2017). These reductions in greenhouse gas emissions will also contribute health benefits elsewhere and other benefits internationally.

Positive associations between long-term concentrations of NO_2 and $PM_{2.5}$ and risk of mortality from a range of diseases have been broadly documented (Atkinson et al., 2018; Burnett et al., 2018). However, less conclusive is the evidence for long-term O_3 effects; reports suggest associations with respiratory mortality, new-onset asthma in children and increased respiratory symptom effects in asthmatics (Nuvolone et al., 2018). A study carried out in Spain estimated that in Madrid city a total of 650 annual all-cause deaths in over 30s were attributable to a 4.3 μg/m^3 reduction in $PM_{2.5}$ due to the implementation of air-quality control measures at national level (Boldo et al., 2014). In relation to short-term exposure, a great number of epidemiological studies have revealed a significant association between $PM_{2.5}$ (Yang et al., 2019), NO_2 (Bazyar et al., 2019), O_3 (Nuvolone et al., 2018) and human health, including mortality. Among them, NO_2 has been identified as the most important risk factor, and $PM_{2.5}$ as the air pollutant most widely reported to be a risk factor (Bazyar et al., 2019).

According to our analyses, the expected increase in O_3-concentration levels in 2020 would lead to an adverse mortality impact. It should be noted that the O_3 HIA scenarios were simulated taking into account measures related with the implementation of Plan A. However, the O_3 dynamics in the western Mediterranean Basin are very complex, and an effective plan for the abatement of O_3 levels is a difficult challenge – one which requires an accurate quantitative knowledge of this pollutant. In recent years, a trend of increasing O_3 concentrations at urban and traffic sites has been observed across the Basin, and in particular in Madrid (Querol et al., 2018, 2016; Saiz-Lopez et al., 2017; Sicard et al., 2016). Part of this O_3 increase may have resulted from the reduction in NO emissions relative to NO_2, and therefore to a lower NO titration effect in VOC-limited regimes (Querol et al., 2018, 2016; Saiz-Lopez et al., 2017). However, the reasons behind the upward trend for urban O_3 are not yet clear due to the variety of sources (local, regional and transboundary), the complexity of the meteorological scenarios which produce O_3 episodes, and the complex VOC–NOx regime (Pay et al., 2019; Querol et al., 2018, 2016; Reche et al., 2018).

Our analyses considered within-city variations in exposure to air pollution, and detected dissimilarities in the potential health benefits achieved across different Madrid districts. Plan A addressed air-pollution-related health inequity by targeting the uneven geographical distribution of pollutant concentration at a geospatial level (Benmarhnia et al., 2014; Wang et al., 2016). According to our estimations, the greatest improvements both in air quality and public health were observed in the innermost area of the city, within the M-30 ring road. It should be highlighted that this area was the most polluted in 2012 and, in addition, includes some of the districts with the highest combined Health, Knowledge and Income Index (e.g. 3, 4, 5 or 7) in Madrid (Ayuntamiento de Madrid AM, 2019). It is notable that the application of short-term measures related to the NO_2 protocol for Madrid city significantly reduced NO_2 concentrations in this area (Borge et al., 2018b, 2018a). In contrast, NO_2 only decreased slightly in the outskirts of the city; this was as a result of traffic redistribution and a border effect. Some of the districts of Madrid with the lowest combined Health, Knowledge and Income Index are found in these outlying districts (e.g. 11, 13 or 17) (Ayuntamiento de Madrid AM, 2019). Therefore, the effectiveness of Plan A in improving health equity in relation to air-pollution exposure should be evaluated in conjunction with these knock-on effects. Further revision to identify options that could achieve significant air-pollutant reductions in the whole metropolitan area would be highly recommended, especially in order to avoid potential environmental health inequalities and disparities in the health achievements of distinct groups (Gouveia, 2016; Tyler et al., 2019). These issues must be taken into account when local authorities commit to implementing air-quality control measures – in order to close the gap between who causes air pollution and who breathes it. Regional planning, especially urban planning, must discourage the use of private vehicles, and encourage larger spaces for the movement and coexistence of citizens. In addition, holistic and integrated measures are needed at both local and regional levels.

Our findings relied on some essential assumptions and inherent uncertainties. Daily mortality data and population information was provided by the Department for Statistics of Madrid City Council, which we have assumed was the most reliable available source. We used all-cause natural mortality as it is a robust health indicator and not subject to misclassification in registration. In addition, this figure is easy to obtain from existing records for all ICARUS participating cities and is, thus, comparable. Furthermore, it has been used previously in HIA models related with transportation (Rojas-Rueda et al., 2013) and urban air pollution (Pascal et al., 2013). Regarding the population, Madrid city had actually nearly reached its present population level by 1970, with 3.1 million residents. By 2012, the city had grown to only 3.2 million. Since 1970, the suburbs (areas in the urban area outside Madrid city) have accounted for nearly 98 percent of the population growth. However, Madrid's population growth has been fairly stable during the last few years, and a slight decrease by 2020 is even expected. Our analyses incorporated these expected changes in population to obtain more accurate HIA findings.

The assessment of human exposure to air pollution is an essential and critical component of the HIA process and for the design of air-pollution control policies in general (Dias and Tchepel, 2018). Despite uncertainties related to population allocation, ambient-pollutant concentrations in this study are provided by an air-quality model. This modelling system has been used and extensively evaluated for several urban air-quality studies undertaken in Madrid (Borge et al., 2018b, 2012; de la Paz et al., 2016; Picornell et al., 2019; Saiz-Lopez et al., 2017), and has also been shown to meet the EU model uncertainty objectives (Borge et al., 2014). For this particular application, the average model mean biases (MB) for urban background locations were -14.8 μg/m^3 for NO_2 and -4.4 μg/m^3 for $PM_{2.5}$, with the aggregated index of agreement (IOA) 0.73 for NO_2 and 0.64 for $PM_{2.5}$. In addition, the largest departures from observed and modelled concentrations are related to the seasons and hours of the day with lowest concentrations. The statistical analysis at air-quality monitoring-station level also shows that the model's performance is better in the city centre, where exposure is more relevant. Despite acceptable performance, it should be noted that the effect of model errors is buffered in the methodology since we focused on the differences between two air-quality scenarios which were presumed to have similar deviations. Therefore, the estimation of concentration changes in absolute values between 2012 and 2020 was deemed to be a more robust approach. The greatest source of uncertainty is probably related to the outcome of Plan A, i.e. to what extent the measures in the plan (Table S1) are actually implemented and the emission projections are accurate. Therefore, the validity of our results would be restricted to a successful enforcement of the local air-quality and climate-change strategy for Madrid city.

Changes in mortality (ΔY) in our HIA were based on changes in concentrations between both annual air-quality scenarios modelled (Δx). The only difference between the 2012 model run (baseline air-quality scenario) and that for 2020 (temporal horizon of Plan A) was the emission dataset considered, which reflect the expected outcome of the full implementation of the measures in Plan A. It could be argued that those emission changes, and therefore Δx and ΔY, may not exactly match those associated with Plan A. A more precise attribution might be based on the comparison of two future scenarios for the year 2020: one considering the implementation of the measures in Plan A and another without such interventions, e.g. a business-as-usual (BAU) scenario used as a counterfactual. That approach may be more consistent conceptually, but it would require the definition of a BAU scenario based on a number of hypotheses and assumptions that could seriously hinder the interpretation of the results, and thus counteract the potential benefits of such an assessment framework. In addition, the effect of most of the measures in Plan A has been assessed without involving any further assumptions about future trends or activity-rate patterns. In other words, the emission abatement potential was assessed by comparing simulations of alternative scenarios based on technological changes, fuel switches, etc. relative to the situation in 2012, which is consistent with the approach followed in our HIA.

It should be also noted that both annual air-quality simulations rely on the same meteorology. This approach prevented us from assessing synergetic effects of pollution and weather, mainly temperature (Chen et al., 2018; Stafoggia et al., 2008). However, interactions between air pollution and temperature are non-linear and very complex to translate into health effects, especially long-term effects (Jhun et al., 2014). Partly for this reason, we have not attempted to characterize the synergetic impacts of air pollution and meteorology on health in Madrid by 2020 in this study. By keeping meteorological conditions fixed, we were able to assess the health impact specifically attributable to the emission abatements associated with the implementation of Plan A, which is the primary aim of this study. This is entirely consistent with the methodology used to assess the change in the pollutant concentration between the baseline (2012) and the projected air-quality scenario (2020) (Δx).

We have to highlight that the process used to derive the summary RRs also needs careful consideration. We were aware that small RRs can translate into substantial consequences for health at the population level due to the ubiquitous nature of ambient air pollution and the very large populations exposed. Hence, small variations in summary RRs can translate into important differences in population impact. In our HIA analyses, most of the selected CRFs were derived from European multi-country and multi-city studies, following the expert recommendations made in the frameworks of the HRAPIE (WHO, 2013a) and REVIHAAP (WHO, 2013b) projects. The coefficients (β) used in this HIA analysis for any given air pollutant were not adjusted for the effects of other air pollutants. This means that mortality estimates attributable for any indicator of traffic pollution (e.g. $PM_{2.5}$) are likely to include effects caused by other correlated pollutants (e.g. NO_2 or other fractions of PM) to some extent. Moreover, it should be noted that some of the long-term NO_2 effects might overlap with effects of long-term $PM_{2.5}$ (up to 33%), and there could also be overlaps between short-term and long-term HIA findings for any pollutants (WHO, 2013a). For this reason, our findings should not be added together to avoid double counting, as both $PM_{2.5}$ and NO_2 are traffic-related pollutants and assuming independence of their health effects could overestimate the final incidence.

For the long-term health effects of $PM_{2.5}$ and NO_2, we chose a meta-analysis of 13 cohort studies conducted in North American and European adult populations (Hoek et al., 2013). We estimated the effects in the adult population (over 30s) as most of the evidence for the CRFs comes from studies that focused on populations around 30 years of age and above. Regarding PM, COMEAP recently recommended the use of the summary effect estimate reported by Hoek et al. (2013) of 1.06 (95% CI: 1.04–1.08) per 10 μg/m^3 for the quantification of all-cause mortality on the basis of $PM_{2.5}$ concentrations (COMEAP, 2018). For NO_2, we conducted a sensitivity analysis using the most up-to-date meta-analysis carried out by Atkinson et al. (2018), whose estimate is substantially lower than that of Hoek et al. (2013). Although using both estimates obviously affected the predicted health benefits, the overall prediction for Plan A's implementation still showed health benefits. It should be highlighted that Atkinson et al. (2018) detected a considerable difference in the summary RRs in their stratified analysis due to the substantial heterogeneity between cohort studies included in the meta-analysis (e.g. age range): 1.02 versus 1.08 per 10 μg/m^3 increment for NO_2, which is actually similar to the 95% CIs provided by Hoek et al. (2013) (1.06; 95%CI 1.03–1.08). Therefore, our HIA estimates using Hoek's CRFs would also fit with the more up-to-date CRF range proposed by Atkinson et al. (2018).

Another key issue is the application of a cut-off point when quantifying mortality effects from long-term NO_2 exposure. According to HRAPIE (WHO, 2013a), NO_2 mortality impact should be calculated for levels above 20 μg/m^3, as mortality has been detected above this level Cesaroni et al. (2013). Our study did not apply this cut-off as the annual average concentrations for this pollutant in Madrid and in many districts were below 20 μg/m^3 in 2012 and 2020, and our objective was to estimate the potential health impacts for both Madrid overall and its different districts. On the other hand, experts from COMEAP (2018) recommended two approaches, either not using a cut-off or using a cut-off of 5 μg/m^3. In our case, the application of a 5 μg/m^3 cut-off would not have made sense because all districts have an annual average above 5 μg/m^3 in both 2012 and 2020 and, therefore, the difference in pollution concentration between 2012 and 2020 (Δx) for the long-term HIA estimations would be the same as without the cut-off. For these reasons, we decided not to apply a NO_2 cut-off in our HIA analyses. Finally, for O_3, we used the risk coefficients for respiratory mortality from the ACS study (Jerrett et al., 2009), and applied the recommended cut-off point as no information was available on the shape of the CRF below 70 μg/m^3. In this case, extrapolating down to zero (no cut-off) for O_3 exposure would have introduced additional uncertainties into the impact estimates, as it would have had to assume that the CRF is linear below the concentrations studied.

In contrast, for short-term impact estimation, we used the $PM_{2.5}$ risk coefficients provided by a meta-analysis conducted within the scope of the HRAPIE project (WHO, 2013a), including 12 single-city time series studies and one multicity study on all-cause mortality for all ages. These CRFs were consistent with other results from European multi-city studies such as the Med-Particles project (Samoli et al., 2013). For NO_2, we considered the results provided by the APHEA-2 project covering 30 European cities (APHEA-2, 2001; Samoli et al., 2006). For O_3, the risk coefficients were based on data from the 32 European cities which were included in the APHENA study (Katsouyanni et al., 2009). These coefficients were based on the whole range of observed O_3 concentrations, including levels below 70 μg/m^3, and consequently our HIA findings were calculated without a cut-off point. However, according to the HRAPIE project (WHO, 2013a), a cut-off point at 70 μg/m^3 should be used to reflect greater confidence in the significant relationship above this concentration. Following this recommendation, we also estimated the health impacts using a cut-off point of 70 μg/m^3 (91% of the total observations in 2012 and 93% in 2020), and findings did not change markedly. In both our air-quality scenarios O_3 concentrations were above 20 μg/m^3, the other cut-off point recommended by HRAPIE (WHO, 2013a) and not applied in this study because it was meaningless, which is the lowest concentration that has been recorded in European monitoring stations.

Many of the human-health impacts of reduced exposure to pollution can be quantified; however, some specific health impacts still remain unquantified. In our study, we have estimated the mortality impact in Madrid attributable to the implementation of Plan A. We are aware that the predicted health benefits from the future implementation Plan A are an underestimation of the total benefits. We did not quantify other health effects (e.g. morbidity, such as hospital admissions and primary care), other endpoints (e.g. low birth-weight, changes in lung function, neurological effects or reduced cancer rates), adverse effects of other air pollutants (e.g. health effects of secondary organic aerosols) or the potential long-term global climatic effects of continued CO_2 release from fossil-fuel combustion (e.g. deaths from, or evacuations made necessary by flooding). Such potential impacts are difficult to quantify in conventional terms, but concerns over such recognized unquantified impacts should be included in decision-making processes to provide a comprehensive overview of the overall air-pollution impact.

5. Conclusions

The effective implementation of Plan A in Madrid city would bring about an appreciable decline in traffic-related air-pollutant emissions, and in turn, would lead to better air quality and remarkable health-related benefits: more than 500 all-cause premature deaths could be postponed annually. However, additional research into O_3 dynamics in Madrid and better management of environmental and health inequalities are needed in order to design improved air-quality control strategies. Plan A is completely aligned with the new urban paradigm, which aims to integrate sustainability criteria and contemporary ways of living with economic progress. Moreover, the local administration should consider the impact of sector-based policies on health, and communicate the economic and social benefits of improving air quality to the population very clearly. Health impact assessments such as this one may also enable local governments and other administrations to pay special attention to the groups most affected, thereby preventing inequality in the face of risk and ensuring a just health-benefit distribution.

Protection of human research subjects

This investigation used aggregated mortality data provided by the Madrid Regional Statistical Office under a specific confidentiality protocol. The study protocol was approved by the Carlos III Health Institute Ethics Committee (reference: CEI-PI 21_2018).

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CRediT authorship contribution statement

Rebeca Izquierdo: Conceptualization, Methodology, Formal analysis, Data curation, Writing - original draft, Writing - review & editing, Visualization. **Saul García Dos Santos:** Resources, Writing - review & editing, Supervision, Project administration, Funding acquisition. **Rafael Borge:** Methodology, Data curation, Formal analysis, Writing - original draft, Writing - review & editing. **David de la Paz:** Methodology, Data curation, Formal analysis, Writing - original draft, Writing - review & editing. **Denis Sarigiannis:** Conceptualization, Funding acquisition, Writing - review & editing, Supervision, Project administration. **Alberto Gotti:** Conceptualization, Funding acquisition, Writing - review & editing, Supervision, Project administration. **Elena Boldo:** Conceptualization, Methodology, Formal analysis, Investigation, Writing - original draft, Writing - review & editing, Supervision, Funding acquisition, Project administration.

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. This article presents independent research. The views expressed are those of the authors and not necessarily those of the Carlos III Institute of Health. None of the funders played any role in conducting research or writing the paper.

Appendix A. Supplementary data

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