BMJ Open

Health impact assessment of air pollution in Valladolid, Spain

Mario Cárdaba Arranz,[1] María Fe Muñoz Moreno,[2] Alicia Armentia Medina,[3] Margarita Alonso Capitán,[4] Fernando Carreras Vaquer,[4] Ana Almaraz Gómez[5]

To cite: Cárdaba Arranz M, Muñoz Moreno MF, Armentia Medina A, *et al*. Health impact assessment of air pollution in Valladolid, Spain. *BMJ Open* 2014;**4**:e005999. doi:10.1136/bmjopen-2014-005999

▸ Prepublication history for this paper is available online. To view these files please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2014-005999).

Received 1 July 2014
Revised 3 September 2014
Accepted 23 September 2014

[1]Castilla y León Regional Health Service, Valladolid, Spain
[2]Research Support Unit, University Clinical Hospital, Valladolid, Spain
[3]Allergy Unit, Rio Hortega University Hospital, Valladolid, Spain
[4]Ministry of Health, Social Services and Equality, Madrid, Spain
[5]Medical Faculty, University of Valladolid, Valladolid, Spain

Correspondence to
Dr Mario Cárdaba Arranz; mario00med@yahoo.es

ABSTRACT

Objective: To estimate the attributable and targeted avoidable deaths (ADs; TADs) of outdoor air pollution by ambient particulate matter (PM_{10}), $PM_{2.5}$ and O_3 according to specific WHO methodology.

Design: Health impact assessment.

Setting: City of Valladolid, Spain (around 300 000 residents).

Data sources: Demographics; mortality; pollutant concentrations collected 1999–2008.

Main outcome measures: Attributable fractions; ADs and TADs per year for 1999–2008.

Results: Higher TADs estimates (shown here) were obtained when assuming as 'target' concentrations WHO Air Quality Guidelines instead of Directive 2008/50/EC. ADs are considered relative to pollutant background levels. All-cause mortality associated to PM_{10} (all ages): 52 ADs (95% CI 39 to 64); 31 TADs (95% CI 24 to 39). All-cause mortality associated to PM_{10} (<5 years): 0 ADs (95% CI 0 to 1); 0 TADs (95% CI 0 to 1). All-cause mortality associated to $PM_{2.5}$ (>30 years): 326 ADs (95% CI 217 to 422); 231 TADs (95% CI 153 to 301). Cardiopulmonary and lung cancer mortality associated to $PM_{2.5}$ (>30 years):

- Cardiopulmonary: 186 ADs (95% CI 74 to 280); 94 TADs (95% CI 36 to 148).
- Lung cancer : 51 ADs (95% CI 21 to 73); 27 TADs (95% CI 10 to 41).All-cause, respiratory and cardiovascular mortality associated to O_3 (all ages):
- All-cause: 52ADs (95% CI 25 to 77) ; 31 TADs (95% CI 15 to 45).
- Respiratory: 5ADs (95% CI −2 to 13) ; 3 TADs (95% CI −1 to 8).
- Cardiovascular: 30 ADs (95% CI 8 to 51) ; 17 TADs (95% CI 5 to 30).

Negative estimates which should be read as zero were obtained when pollutant concentrations were below counterfactuals or assumed risk coefficients were below one.

Conclusions: Our estimates suggest a not negligible negative impact on mortality of outdoor air pollution. The implementation of WHO methodology provides critical information to distinguish an improvement range in air pollution control.

Strengths and limitations of this study

- Using ecological data to assume ambient pollutant concentrations as surrogates of individual exposure adds error.
- In addition, pollutant concentrations were not corrected for sub-Saharan dust intrusions.
- CIs only cover statistical uncertainty related to the risk estimates from the concentration-response functions (CRFs), currently under review by the WHO, while further uncertainty is added due to potential errors in assuming the general shape of CRFs, background pollutant levels, selection of health outcomes and structure of monitoring network.
- In sensitivity analysis, we considered different $PM_{2.5}/PM_{10}$ ratios, background concentrations and exposure-response relationships.
- It is difficult to generalise results to other populations as data were obtained from only one city.

INTRODUCTION

Numerous epidemiological studies conducted over the past decades point to adverse health impacts from exposure to outdoor air pollution, attributing the most severe health effects to particulate matter (PM)[1 2] and, to a lesser extent, ozone[3] (O_3). New studies incorporate to the growing body of evidence,[4–6] currently under review by the WHO through projects such as REVIHAAP (Review of evidence on health aspects of air pollution) and HRAPIE (Health risks of air pollution in Europe), confirming that outdoor air pollution is an important risk factor for health.[7 8]

According to the WHO, in the year 2012, ambient air pollution was responsible for 3.7 million deaths, representing 6.7% of the total deaths. Worldwide, ambient air pollution is estimated to cause about 16% of the lung cancer deaths, 11% of chronic obstructive pulmonary disease deaths, more than 20% of ischaemic heart disease and stroke, and about 13% of respiratory infection deaths.[9] Recently, the International Research Agency on Cancer (IARC) classified air pollution mixture and PM as carcinogenic to human beings (Group 1).[10]

It could be expected that the impact caused by a preventable risk factor would decline if the exposure to that risk factor could be

reduced or removed. According to this approach, the proportional reduction in the number of health problems or deaths as a result of reducing the risk factor is known as the attributable fraction (AF).[11]

Estimating the environmental burden of disease associated with exposure to air pollution is critical information for policymakers who can define strategies and prioritise actions by considering the health gains that could be achieved if the exposure to the risk factor were reduced to a 'target' concentration.[1]

We estimated the burden of mortality from exposure to PM_{10}, $PM_{2.5}$ and O_3 at the city of Valladolid, as a health impact assessment (HIA) under various exposure scenarios in order to provide quantitative information of the potential benefits of reducing the exposure to these pollutants.

METHODS

Calculation of burden of mortality

On the basis of the method outlined by the WHO in the Environmental Burden of Disease (EBD) series[1 12] we followed a classical risk assessment approach:

1. Determination of the ambient exposure of the population using data from model estimates or monitoring networks. A 'counterfactual' background or target concentration is also needed to determine the attributable disease or the potential gains of a reduction strategy.
2. Number of people exposed to air pollutants.
3. Baseline incidence of the adverse health outcomes associated with air pollutants (eg, the mortality rate in the population).
4. Concentration-response functions (CRFs) that relate changes in air pollutants concentrations with changes in the incidence of adverse health effects.

Assessment of the ambient exposure of the population

About 300 000 people live in Valladolid, a Spanish city located at an altitude of 698 m in the Inner Plateau, 200 km North to Madrid. The orography of this plateau surrounded by mountains except on the border with Portugal favours winds penetrating from the Atlantic Ocean and on the contrary prevents or greatly reduces air circulation to and from the Bay of Biscay and the Southern Plateau. Notably, the Central System Range isolates Valladolid from the influence of Madrid as a great source of precursors, at least respecting direct transport at surface level. The climate is continental, with cold winters and dry summers. The pollution levels are strongly dependent on the atmospheric synoptic conditions, in this case a long and cold winter, with frequent fog events. The type of surface that surrounds the city is basically rough, bare and dry soil used primarily for agriculture. The urban aerosol corresponds to a lightly industrialised city whose contamination mostly comes from road traffic and domestic heating. Regarding economic activity, automotive sector is an important manufacturing industry. As natural sources of PM affecting occasionally the area, wildfires and wind-blown dust-like Saharan intrusions can be included. Regarding ozone, orography and solar radiation favour ozone formation and accumulation. No municipal emission source inventory has been developed yet.[13–15]

PM_{10} concentrations (annual means) were obtained from the annual reports 1999–2008 published by the Environmental Health Unit (EHU) of the city council responsible for the municipal fixed-site monitoring stations network.[16] O_3 concentrations (daily maximum 8 h means) were provided on request to the EHU.The annual mean concentrations from the operating stations with a minimum data capture of 90% (operating stations with valid data according to regulatory standards)[17–19] for the 10 years of data 1999–2008 were averaged to develop the following annual average estimates for PM_{10} and O_3: 35.41 and 141.38 $\mu g/m^3$, respectively. As there were no direct measures of $PM_{2.5}$, they were estimated by applying the recommended $PM_{2.5}/PM_{10}$ ratio of 0.73 for Europe.[1] Hence, the estimated concentration for $PM_{2.5}$ was 25.85 $\mu g/m^3$. Table 1 provides a scope of our exposure data set.

Population exposed and mortality data

Annual population figures from the municipal register and annual deaths by different causes and age groups (underlying causes of death selected according to WHO[1 8 20] and coded in accordance with the International Classification of Diseases (ICD) 10th version), extracted from the Spanish Statistical Office for 1999–2008,[21] were averaged and rounded off to the nearest whole number to obtain population and mortality figures for different age groups. In doing so, respiratory mortality for children <5 years old resulted zero. Crude mortality rates (in deaths per 100 000 people) for each age group and health outcomes were calculated. Table 2 describes population indicators and mortality rates by age group for the period of analysis.

Concentration-response functions

Epidemiological studies can use regression models that generate relative risk (RR) functions with a β-coefficient that relates the per cent change in the health outcome to a unit change in air pollutant concentration, that is, an increase of the risk per 10 $\mu g/m^3$ PM_{10}. CRFs are equations derived from epidemiological studies that link the change in the number of adverse health effect incidences in a population to a change in pollutant concentration experienced by that population. Existing studies have reported either a β-coefficient or a RR. Additionally, 95% CIs are provided for the β-coefficients and RR estimates in order to obtain upper and lower bounds of the health impacts.[1 8 20]

According to the WHO and depending on data availability, we used the recommended and alternative risk functions summarised in table 3 to calculate the RR for

Table 1 PM_{10} and O_3 concentration data set

Pollutant	Year	Number of operating stations	Operating stations with valid data	Minimum	Maximum	Annual average	SD
PM_{10}	1999	7	2	44	47	45.5	2.121
	2000	7	7	33	47	41.6	5.127
	2001	7	4	38	46	42.7	3.695
	2002	8	4	25	39	33.3	5.909
	2003	6	6	23	39	30.2	6.853
	2004	6	4	33	52	39.5	8.583
	2005	6	6	31	49	36.2	6.911
	2006	6	5	30	41	36.4	4.393
	2007	5	5	20	31	25.6	4.159
	2008	6	4	22	26	23.3	1.893
O_3	1999	4	4	89	134	111.5	19.638
	2000	4	4	101	152	121.3	21.930
	2001	4	2	122	130	126	5.657
	2002*	3	1	126	168.7	147.3	30.169
	2003	4	3	165	174	168.7	4.726
	2004	3	3	142	164	149.7	12.423
	2005	3	3	146	159	154.7	7.506
	2006	3	3	138	151	142.7	7.234
	2007	3	3	137	146	143	5.196
	2008	3	3	138	160	149	11

*In 2002 1 of 3 stations could provide valid data so it was decided to use the average of the years 2001 and 2003.
PM, particulate matter.

the following mortality outcomes associated with exposure to PM_{10}, $PM_{2.5}$ and O_3.[1 8 20] As not all of the listed outcomes can be reliably converted into DALYs (disability-adjusted life years) estimates and owing to data availability, preference was given to mortality instead of morbidity indicators or DALYs estimates as the health effect for this assessment. Short-term estimates should not be added to long-term estimates or estimates for children, since that would involve some double counting of the mortality cases.[1]

1. All-cause (natural) mortality associated with short-term exposure to PM_{10} for all ages.[1] These results should not be added to the other mortality estimates. DALYs cannot be determined for each of these premature deaths but can be used as an alternative to DALYs, and used as a basis for comparing short-term and long-term effects of pollutant exposure.[1]
2. All-cause (natural) and respiratory mortality in infants and children <5 years old related to short-term exposure to PM_{10}.[1] The application of this rate

Table 2 Population data and cause-specific mortality by age group (1999–2008)

All ages			
Population	All-cause (natural) mortality	Respiratory mortality	Cardiovascular mortality
319.482	2.563	267	872
	Mortality rate*		
	802	83	273
>30 years			
Population	All-cause (natural) mortality	Cardiopulmonary mortality	Lung cancer mortality
212.702	2.535	729	142
	Mortality rate*		
	1.192	342	67
<5 years			
Population	All-cause (natural) mortality	Respiratory mortality†	
11.752	12	0	
	Mortality rate*		
	100	2	

International Classification of Diseases 10th version: all-cause (natural) mortality: all except V01-Y89; respiratory mortality: J00-J99; cardiovascular mortality: I00-I99; cardiopulmonary mortality: I00-I02; I10-I15; I20-I49; I51-I52; J00-J99; lung cancer mortality: C33-C34.
*Mortality rate in deaths per 100 000 people.
†There were two cases of death of respiratory mortality for children <5 years in 2003 (period 1999–2008). The annual average of respiratory mortality for 1999–2008, rounded off to the nearest whole number, resulted 0. Hence, the respiratory mortality rate per 100 000 people is 2.

Table 3 Health outcomes and risk functions used to calculate the burden of disease associated to PM_{10}, $PM_{2.5}$ and O_3

Outcome and exposure metric	RR function*	β-coefficient/RR (95% CI)	Age group	ICD-10 codes
All-cause (natural) mortality and short-term exposure to PM_{10}	RR=exp [β (X−X_o)]	0.0008[1] (0.0006 to 0.0010)	All ages	All except V01-Y89
All-cause (natural) and respiratory mortality and short-term exposure to PM_{10}†	RR=exp [β (X−X_o)]	0.00 166[1] (0.00 034 to 0.0030)	<5 years	All except V01-Y89/ J00-J99‡
All cause (natural) mortality and long-term exposure to $PM_{2.5}$	RR=exp [β (X−X_o)]	1.062[8] (1.040 to 1.083)	>30years	All except V01-Y89
Cardiopulmonary mortality and long-term exposure to $PM_{2.5}$ (log-linear exposure)§	RR=[(X+1)/(X_o)+1)]$^{\beta}$	0.15 515[1] (0.0562 to 0.2541)	>30 years	I00-I02 ;I10-I15 ;I20-I49 ;I51-I52 ;J00-J99
Cardiopulmonary mortality and long-term exposure to $PM_{2.5}$ (linear exposure)	RR=exp [β (X−X_o)]	0.00 893[1] (0.00 322–0.01 464)	>30 years	I00-I02 ;I10-I15 ;I20-I49 ;I51-I52 ;J00-J99
Lung cancer and long-term exposure to $PM_{2.5}$ (log-linear exposure)§	RR=[(X+1)/(X_o)+1)]$^{\beta}$	0.23 218[1] (0.08 563 to 0.37 873)	>30 years	C33-C34
Lung cancer and long-term exposure to $PM_{2.5}$ (linear exposure)	RR=exp [β (X−X_o)]	0.01 267[1] (0.00 432 to 0.02 102)	>30 years	C33-C34
All-cause mortality and short-term exposure to O_3	RR=exp [β (X−Xo)]	1.002[20] (1.0005 to 1.0035) 1.0029[8] (1.0014 to 1.0043)	All ages	All except V01-Y89
Respiratory mortality and short-term exposure to O_3	RR=exp [β (X−Xo)]	0.999[20] (0.995 to 1.004) 1.0029[8] (0.9989 to 1.0070)	All ages	J00-J99
Cardiovascular mortality and short-term exposure to O_3	RR=exp [β (X−Xo)]	1. 004[20] (1.003 to 1.005) 1.0049[8] (1.0013 to 1.0085)	All ages	I00-I99

*X=current pollutant concentration (μg/m^3) and X_o=target or threshold pollutant concentration (μg/m^3).
†All-cause mortality for upper bound where applicable.
‡Respiratory mortality.
§Recommended relationship.
ICD-10 codes, International Classification of Diseases 10th version; PM, particulate matter; RR, relative risk.

to all-cause mortality could however represent an upper boundary of disease burden caused by outdoor air pollution, but may result in an overestimate when applied to certain regions.[1]

3. All-cause (natural) mortality associated with long-term exposure to $PM_{2.5}$ for >30 years old.[8] The recommended risk coefficient is based on the meta-analysis of cohort studies published by Hoek *et al*[4] According to the HRAPIE report (2013), preference was given to use of the all-cause function instead of cause-specific indicators.[8]
4. Cardiopulmonary and lung cancer mortality related to long-term exposure to $PM_{2.5}$ for >30 years old.[1] The long-term estimate should not be added to the estimate for short-term exposure, since this would double count a portion, if not all, of the short-term cases.[1]
5. All-cause (natural), respiratory and cardiovascular mortality related to short-term exposure to O_3 for all ages.[8 20] Using two different sets of risk coefficients estimates for the same outcomes (from Anderson *et al* and the HRAPIE report, 2013) enabled the results under these assumptions to be compared. The coefficients summarised by Anderson *et al*[20] were revised for publication bias.

Examining the sensitivity of the results to alternative assumptions is recommended.[1] A sensitivity analysis was conducted using alternative values for these parameters:

- $PM_{2.5}/PM_{10}$ ratio: an alternative ratio of 0.65[1 8] that results in an estimated $PM_{2.5}$ concentration of 23.01 µg/m^3 was examined. This ratio is considered an average for the European population by the HRAPIE report. However, in specific locations the ratio may be in the range 0.4–0.8.[8]
- Background concentrations for $PM_{2.5}$ and O_3[1 3 22]: 7.5 and 50 µg/m^3, respectively.
- Shape of the CRF: for cardiopulmonary and lung cancer mortality associated with $PM_{2.5}$ exposure a linear model was examined as an alternative to the recommended log-linear relationship.[1]

Those RR functions in table 3 compare current measured pollutant concentrations with a counterfactual level (a hypothetical 'natural' background or a 'target' concentration). Therefore, two kinds of calculations can be made[1]:

1. The total number of attributable deaths (ADs) due to current air pollution levels.
2. The number of deaths that could be prevented if the target concentration were achieved (targeted avoidable deaths, TADs).

The only difference between the two calculations is the counterfactual level used in (1) it is the 'natural' background level (ie, the level that would exist without any man-made pollution) and (2) it is a 'target' concentration.[1] Different counterfactual concentrations were selected to reflect different exposure scenarios, as described following.

The counterfactual concentrations used for PM_{10} were:

- 10 µg/m^3: background level scenario.[1]
- 20 µg/m^3: target value scenario from the WHO Air Quality Guidelines (AQG).[23]
- 40 µg/m^3: target value scenario from the Directive 2008/50/EC.[19]

Four counterfactual concentrations were used for $PM_{2.5}$:

- 3 µg/m^3: background level scenario.[1]
- 10 µg/m^3: target value scenario from the WHO AQG.[23]
- 25 µg/m^3: target value scenario from the Directive 2008/50/EC.[19]
- 7.5 µg/m^3: alternative background level for sensitivity analysis.[1 22]

Four counterfactual concentrations were used for O_3:

- 70 µg/m^3: background level scenario from the WHO AQG.[23]
- 100 µg/m^3: target value scenario from the WHO AQG.[23]
- 120 µg/m^3: target value scenario from the Directive 2008/50/EC.[19]
- 50 µg/m^3: alternative background level for sensitivity analysis.[3]

Once the RRs have been computed, the AF is determined in the classic attributable risk calculation[1]:

$$AF = (RR - 1)/RR$$

Regarding O_3 exposure, these RR estimates can be converted into an estimated β using the following equation where ΔO_3 is a specified change in pollutant (ie, for a 10 µg/m^3 increase)[24]:

$$\beta = \mathrm{Ln}(RR)/\Delta O_3$$

Then, the difference between current ozone (8 h mean) and a counterfactual level is used to calculate RR as follows[24]:

$$RR = \exp(\beta \Delta O_3)$$

These RR estimates are subsequently applied to determine the AF as stated before. Ultimately, the expected number of deaths is calculated by[1]:

$$E = AF \times M \times P$$

where M, mortality rate; P, exposed population size.

The previous steps come with a range of assumptions and uncertainties. To reflect these uncertainties results are presented with a point estimate as well as an upper and lower bound given by the 95% CI of the CRF.ADs and TADs estimates were rounded off to the nearest whole number.

RESULTS

Table 4 shows the impact (in terms of mortality) of the estimated current ambient levels of pollutants relative to the assumed background concentrations and the benefit of reducing pollutant concentrations to the levels set as targets by the WHO AQG or the Directive 2008/50/EC. Our estimates point out that compliance with the WHO

AQG target values might result in higher savings, in terms of mortality avoided, than with the Directive 2008/50/EC standards. Morbidity adverse health effects are not included in the assessment.

This table presents the annual number of ADs and TADs (deaths per year) for the period 1999–2008 along with their corresponding AFs (multiplied by 100 to express as percentage).

Table 4 Annual number of deaths (deaths per year) from outdoor air pollution for 1999–2008

All-cause mortality and short-term exposure to PM_{10}: all ages[1]						
Counterfactual concentration	***20 µg/m^3**		**†40 µg/m^3**		**‡10 µg/m^3**	
Indicator	AFs	TADs	AFs	TADs	AFs	ADs
Lower estimate	0.92	24	−0.276	−7	1.513	39
Central estimate	1.225	31	−0.368	−9	2.012	52
Higher estimate	1.529	39	−0.46	−12	2.509	64
All-cause mortality and short-term exposure to PM_{10}: age <5 years*						
Counterfactual concentration	**†20 µg/m^3**		**‡40 µg/m^3**		**‡10 µg/m^3**	
Indicator	AFs	TADs	AFs	TADs	AFs	ADs
Lower estimate	0.523	0	−0.156	0	0.86	0
Central estimate	2.526	0	−0.765	0	4.13	0
Higher estimate	4.518	1	−1.386	0	7.34	1
All-cause mortality and long-term exposure to $PM_{2.5}$: age >30 years[8]						
Counterfactual concentration	***10 µg/m^3**		**†25 µg/m^3**		**‡3 µg/m^3**	
Indicator	AFs	TADs	AFs	TADs	AFs	ADs
Lower estimate	6.027	153	0.333	8	8.572	217
Central estimate	9.094	231	0.510	13	12.842	326
Higher estimate	11.872	301	0.675	17	16.656	422
Cardiopulmonary mortality and long-term exposure to $PM_{2.5}$: age >30 years[1]						
Counterfactual concentration	***10 µg/m^3**		**†25 µg/m^3**		**‡3 µg/m^3**	
Indicator	AFs	TADs	AFs	TADs	AFs	ADs
Lower estimate	4.891	36	0.181	1	10.148	74
Central estimate	12.929	94	0.498	4	25.577	186
Higher estimate	20.288	148	0.814	6	38.356	280
Lung cancer mortality and long-term exposure to $PM_{2.5}$: age >30 years[1]						
Counterfactual concentration	***10 µg/m^3**		**†25 µg/m^3**		**‡3 µg/m^3**	
Indicator	AFs	TADs	AFs	TADs	AFs	ADs
Lower estimate	7. 357	10	0.275	0	15.044	21
Central estimate	18.713	27	0.744	1	35.729	51
Higher estimate	28.678	41	1.211	2	51.378	73
All-cause mortality and short-term exposure to O_3: all ages						
Counterfactual concentration	***100 µg/m^3**		**†120 µg/m^3**		**§70 µg/m^3**	
Indicator	AFs	TADs	AFs	TADs	AFs	ADs
Source of risk estimates: Anderson et al[20]						
Lower estimate	0.207	5	0.107	3	0.356	9
Central estimate	0.823	21	0.426	11	1.416	36
Higher estimate	1.435	37	0.744	19	2.463	63
Source of risk estimates: HRAPIE Project[8]						
Lower estimate	0.577	15	0.299	8	0.994	25
Central estimate	1.191	31	0.617	16	2.046	52
Higher estimate	1.760	45	0.913	23	3.016	77
Respiratory mortality and short-term exposure to O_3: all ages						
Counterfactual concentration	***100 µg/m^3**		**†120 µg/m^3**		**§70 µg/m^3**	
Indicator	AFs	TADs	AFs	TADs	AFs	ADs
Source of risk estimates: Anderson et al[20]						
Lower estimate	−2.096	−6	−1.077	−3	−3.642	−10
Central estimate	−0.415	−1	−0.214	−1	−0.717	−2
Higher estimate	1.638	4	0.85	2	2.809	7

Continued

Table 4 Continued

Respiratory mortality and short-term exposure to O_3: all ages						
Counterfactual concentration	***100 µg/m^3**		**†120 µg/m^3**		**§70 µg/m^3**	
Source of risk estimates: HRAPIE Project[8]						
Lower estimate	−0.456	−1	−0.236	−1	−0.789	−2
Central estimate	1.191	3	0.617	2	2.046	5
Higher estimate	2.845	8	1.480	4	4.857	13
Cardiovascular mortality and short-term exposure to O_3: all ages						
Counterfactual concentration	***100 µg/m^3**		**†120 µg/m^3**		**§70 µg/m^3**	
Indicator	AFs	TADs	AFs	TADs	AFs	ADs
Source of risk estimates: Anderson et al[20]						
Lower estimate	1.232	11	0.638	6	2.115	18
Central estimate	1.638	14	0.85	7	2.809	25
Higher estimate	2.042	18	1.06	9	3.497	31
Source of risk estimates: HRAPIE Project[8]						
Lower estimate	0.536	5	0.277	2	0.923	8
Central estimate	2.002	17	1.039	9	3.429	30
Higher estimate	3.441	30	1.793	16	5.862	51

Counterfactual concentrations:
*Target concentration from WHO.[23]
†Target concentration from Directive 2008/50/EC.[19]
‡Background level from Ostro.[1]
§Background level from WHO.[23]
ADs, attributable deaths; AFs, attributable fractions; HRAPIE, Health risks of air pollution in Europe; PM, particulate matter; TADs, targeted avoidable deaths.

As for the TADs, which estimate the number of deaths that could have been avoided in case of having reduced the air pollutant concentrations to the levels set as a target, the AFs estimate the proportional reduction of the mortality cause that could have been prevented in case of having decreased to the target scenario the exposure to the air pollutant. Regarding the ADs, which estimate the number of deaths due to current air pollution concentrations relative to the assumed background levels, the AFs estimate the proportion of the mortality cause that could have been attributed to those pollutants.

ADs and TADs estimates were rounded off to the nearest whole number. For this reason, zero values for ADs and TADs are calculated for all-cause mortality related to PM_{10} for <5 years and for lung cancer mortality related to $PM_{2.5}$ in >30 years under the Directive 2008/50/EC exposure scenario (25 µg/m^3). Negative estimates, which should be read as zero, were obtained when current pollutant concentrations were below the counterfactual value assumed (Directive 2008/50/EC exposure scenario for all-cause mortality related to exposure to PM_{10}) or assumed risk coefficients were below 1 (for respiratory mortality related to exposure to O_3: the lower and central risk estimates revised for publication bias from Anderson *et al* and the lower risk estimate from HRAPIE project). Likewise, since annual average for 1999–2008 of respiratory mortality for children <5 years old was rounded off to zero, ADs and TADs estimates for respiratory mortality related to PM_{10} exposure for this age group resulted null and are not presented. It bears noting that AFs of respiratory mortality for children <5 years are the same as for all-cause mortality.

When applying the more stringent WHO target values scenarios, higher TADs and AFs estimates than under Directive 2008/50/EC exposure conditions were obtained. Overall, estimates for the mortality related to $PM_{2.5}$ exposure were higher than for PM_{10} and O_3. Specifically, for cardiopulmonary and lung cancer mortality associated to $PM_{2.5}$ exposure, notable AFs were obtained and the CIs show quite a broader range than those for mortality related to PM_{10} and O_3.

Concerning mortality associated to O_3 exposure, central and higher estimates were slightly larger when assuming the risk coefficients derived from the HRAPIE project than those from Anderson *et al*. For respiratory mortality, negative estimates were obtained as described previously. CIs range is narrower than for mortality estimates associated to $PM_{2.5}$. The overall picture from the two sets of coefficients assumed might be considered similar.

Table 5 provides the estimates for the different input parameters evaluated as a sensitivity analysis.

Overall, for long-term effects of $PM_{2.5}$ exposure, the results remained within the range calculated on the basis of the recommended parameters. For the alternative $PM_{2.5}/PM_{10}$ ratio of 0.65, negative TADs estimates were obtained as the counterfactual level of 25 µg/m^3 (Directive 2008/50/EC) was higher than the estimated $PM_{2.5}$ concentration of 23.01 µg/m^3 for the alternative ratio. Broadly, estimates under the recommended ratio

Table 5 Effects of alternative assumptions on annual number of deaths estimates (deaths per year)

All-cause mortality and long-term exposure to $PM_{2.5}$: age >30 years[8]

	$PM_{2.5}/PM_{10}$ ratio: 0.73[1]							
Counterfactual concentration	***10 µg/m^3**		**†25 µg/m^3**		**‡3 µg/m^3**		**‡§7.5 µg/m^3**	
Indicator	AFs	TADs	AFs	TADs	AFs	ADs	AFs	ADs
Lower estimate	6.027	153	0.333	8	8.572	217	6.944	176
Central estimate	9.094	231	0.510	13	12.842	326	10.451	265
Higher estimate	11.872	301	0.675	17	16.656	422	13.611	345
	$PM_{2.5}/PM_{10}$ ratio: 0.65[1 8]							
Lower estimate	4.977	126	−0.781	−20	7.551	191	5.904	150
Central estimate	7.532	191	−1.200	−30	11.344	288	8.912	226
Higher estimate	9.859	250	−1.594	−40	14.752	374	11.638	295

Cardiopulmonary mortality and long-term exposure to $PM_{2.5}$: age >30 years[1]

	Log-linear relationship[1] $PM_{2.5}/PM_{10}$ **ratio: 0.73[1]**							
Counterfactual concentration	***10 µg/m^3**		**†25 g/m^3**		**‡3 µg/m^3**		**‡§7.5 µg/m^3**	
Indicator	AFs	TADs	AFs	TADs	AFs	ADs	AFs	ADs
Lower estimate	4.891	36	0.181	1	10.148	74	6.26	46
Central estimate	12.929	94	0.498	4	25.577	186	16.344	119
Higher estimate	20.288	148	0.814	6	38.356	280	25.343	185
	$PM_{2.5}/PM_{10}$ ratio: 0.65[1 8]							
Lower estimate	4.294	31	−0.447	−3	9.583	70	5.670	41
Central estimate	11.410	83	−1.238	−9	24.278	177	14.884	109
Higher estimate	17.997	131	−2.036	−15	36.585	267	23.198	169

	Linear relationship[1] $PM_{2.5}/PM_{10}$ **ratio: 0.73[1]**							
Counterfactual concentration	***10 µg/m^3**		**†25 µg/m^3**		**‡3 µg/m^3**		**‡§7.5 µg/m^3**	
Indicator	AFs	TADs	AFs	TADs	AFs	ADs	AFs	ADs
Lower estimate	4.976	36	0.273	2	7.094	52	5.738	42
Central estimate	13.198	96	0.756	6	18.458	135	15.114	110
Higher estimate	20.709	151	1.237	9	28.432	207	23.558	172
	$PM_{2.5}/PM_{10}$ ratio: 0.65[1 8]							
Lower estimate	4.105	30	−0.641	−5	6.242	46	4.874	36
Central estimate	10.974	80	−1.786	−13	16.369	119	12.940	94
Higher estimate	17.351	126	−2.945	−21	25.402	185	20.322	148

Lung cancer mortality and long-term exposure to $PM_{2.5}$: age >30 years[1]

	Log-linear relationship[1] $PM_{2.5}/PM_{10}$ **ratio: 0.73[1]**							
Counterfactual concentration	***10 µg/m^3**		**†25 µg/m^3**		**‡3 µg/m^3**		**‡§7.5 µg/m^3**	
Indicator	AFs	TADs	AFs	TADs	AFs	ADs	AFs	ADs
Lower estimate	7.357	10	0.275	0	15.044	21	9.38	13
Central estimate	18.713	27	0.744	1	35.729	51	23.437	33
Higher estimate	28.678	41	1.211	2	51.378	73	35.313	50
	$PM_{2.5}/PM_{10}$ ratio: 0.65[1 8]							
Lower estimate	6.468	9	−0.682	−1	14.229	20	8.510	12
Central estimate	16.582	24	−1.859	−3	34.044	48	21.429	30
Higher estimate	25.602	36	−3.050	−4	49.281	70	32.523	46

	Linear relationship[1] $PM_{2.5}/PM_{10}$ **ratio: 0.73[1]**							
Counterfactual concentration	***10 µg/m^3**		**†25 µg/m^3**		**‡3 µg/m^3**		**‡§7.5 µg/m^3**	
Indicator	AFs	TADs	AFs	TADs	AFs	ADs	AFs	ADs
Lower estimate	6.618	9	0.367	1	9.4	13	7.621	11
Central estimate	18.194	26	1.071	2	25.137	36	20.745	29
Higher estimate	28.335	40	1.771	3	38.141	54	32.004	45

Continued

Table 5 Continued

Counterfactual concentration	Linear relationship[1] $PM_{2.5}/PM_{10}$ ratio: 0.73[1] *10 µg/m³		†25 µg/m³		‡3 µg/m³		‡§7.5 µg/m³	
	$PM_{2.5}/PM_{10}$ ratio: 0.65[1 8]							
Lower estimate	5.468	8	−0.860	−1	8.284	12	6.484	9
Central estimate	15.204	22	−2.544	−4	22.401	32	17.848	25
Higher estimate	23.938	34	−4.256	−6	34.345	49	27.832	40
All-cause mortality and short-term exposure to O_3: all ages								
Counterfactual concentration	***70 µg/m³**				**¶50 µg/m³**			
Indicator	AFs		Ads		AFs		ADs	
Source of risk estimates: Anderson et al[20]								
Lower estimate	0.356		9		0.456		12	
Central estimate	1.416		36		1.809		46	
Higher estimate	2.463		63		3.142		81	
Source of risk estimates: HRAPIE Project[8]								
Lower estimate	0.994		25		1.270		33	
Central estimate	2.046		52		2.611		67	
Higher estimate	3.016		77		3.845		99	
Respiratory mortality and short-term exposure to O_3: all ages								
Counterfactual concentration	***70 µg/m³**				**¶50 µg/m³**			
Indicator	AFs		Ads		AFs		ADs	
Source of risk estimates: Anderson et al[20]								
Lower estimate	−3.642		−10		−4.687		−12	
Central estimate	−0.717		−2		−0.918		−2	
Higher estimate	2.809		7		3.582		10	
Source of risk estimates: HRAPIE Project[8]								
Lower estimate	−0.789		−2		−1.011		−3	
Central estimate	2.046		5		2.611		7	
Higher estimate	4.857		13		6.175		16	
Cardiovascular mortality and short-term exposure to O_3: all ages								
Counterfactual concentration	***70 µg/m³**				**¶50 µg/m³**			
Indicator	AFs		ADs		AFs		ADs	
Source of risk estimates: Anderson et al[20]								
Lower estimate	2.115		18		2.7		24	
Central estimate	2.809		25		3.582		31	
Higher estimate	3.497		31		4.455		39	
Source of risk estimates: HRAPIE Project[8]								
Lower estimate	0.923		8		1.180		10	
Central estimate	3.429		30		4.368		38	
Higher estimate	5.862		51		7.443		65	

Counterfactual concentration:
*Target concentration (background level for mortality and short-term exposure to O_3) from WHO.[23]
†Target concentration from Directive 2008/50/EC.[19]
‡Background level from Ostro.[1]
§Background level from Pope III.[22]
¶Background level from Amann *et al*.[3]
ADs, attributable deaths; AFs, attributable fractions; HRAPIE, Health risks of air pollution in Europe; PM, particulate matter; TADs, targeted avoidable deaths.

of 0.73 were higher than under the alternative assumption of 0.65.

Regarding the shape of the model, slightly higher estimates were obtained under the recommended log-linear model. As for the alternative background level of 7.5 µg/m^3, lower estimates than for the recommended background concentration of 3 µg/m^3 were calculated.

Concerning mortality associated with short-term exposure to O_3, slightly higher ADs estimates than for the suggested background level of 70 µg/m^3 were obtained under the alternative background level of 50 µg/m^3 for both sets of risk coefficients. Negative estimates were also obtained as described before.

DISCUSSION

This HIA study pointed to a detrimental effect on mortality from PM_{10}, $PM_{2.5}$ and O_3 exposure. Our estimates indicated a higher number of avoidable deaths from reducing pollutant concentrations to the WHO AQG levels than from a reduction to the European Union (EU) standards. The impact would have been greater if attainment of the legal standards at the moment had not been achieved.

When negative or null estimates were obtained, no deaths would have been possible to attribute or prevent relative to the exposure scenarios considered.

Comparison with other studies

HIA is an underutilised tool in Spain.[25] To the best of our knowledge, there are no Spanish studies that have followed this EBD series guideline on outdoor air pollution.[1] Estimates of the burden of disease associated to air pollution were calculated in various Spanish cities within the framework of different European[26–28] and Spanish[29–45] projects. A study estimated the health and economic benefits resulting from two scenarios of improved air quality (EU standards and WHO targets) in Barcelona.[46] Two recent studies estimated the number of avoidable deaths associated with reducing $PM_{2.5}$ in Spain.[47 48] The heterogeneity of exposure data and methods used in the studies conducted in Spain do not let compare properly their results with our estimates. However, our estimates follow the trend showed by the literature.

Strengths and weaknesses of this study

This type of analysis has a range of inherent uncertainties and methodological limitations that must be considered when interpreting our estimates. Limitations can affect every step of the method.[1]

CIs only cover statistical uncertainty related to the risk estimates.Our estimates are sensitive to the alternative assumptions for $PM_{2.5}/PM_{10}$ ratio, background concentration and shape of CRF. Although the risk parameters are never completely transferable from one population to another, the methods and CRFs summarised by the WHO applied in our study provide the most appropriate, albeit imperfect, effect estimates. The methodology described in the current EBD series can be adapted both to local and national levels. The updated guidance and risk coefficients arising from the review process coordinated by the WHO would provide more accurate estimates of the impact on health that will be used to revise our results.

Caution must be taken as short-term estimates should not be added to long-term estimates or estimates for children since adding them would involve double count.[1] As mentioned previously, the estimates for all-cause mortality associated with short-term exposure to PM_{10} for <5 years might result in an overestimate.[1] Probably no deaths would have been possible to attribute or prevent in children <5 years old related to short-term exposure to PM_{10}. It should be emphasised that the HRAPIE report indicates that generalisation of the recommended approaches to other regions of the globe or individual countries, or to particular mixtures at the local level, may be not appropriate. Specifically, risk estimates for certain health outcomes exhibit more uncertainty. It bears noting that the background national data on all-cause mortality have greater precision than the cause-specific data. The latter may be affected by misclassification of causes of death in mortality registration.[8]

Our estimates of mortality associated to long-term exposure to $PM_{2.5}$ show quite a large range. Reality is likely to lie in between. Probably differences in mortality rates and the proportion of population in age groups affect our results. Likely a data set including a longer period of analysis would have provided a better scope of the real impact of $PM_{2.5}$.

Regarding the ambient exposure of the population, our results are affected by the ecological fallacy because of using ecological data on exposure to pollutants. We have also underestimated the effect of outdoor air pollution as morbidity adverse health effects, which impose a considerable health burden, are not included in the assessment. Similarly, assuming independence of the effects of pollutants could overestimate our results.

Our data (described in table 1) are based on a network of fixed-site monitors whose location, number and range of pollutants measured have changed over time, decreasing the quality and robustness of our exposure estimates. Equally, the effect on averages of outliers, street canyon effect and hot spot sites can overestimate our results.

Likewise, PM_{10} concentration data corrected for sub-Saharan dust intrusions were not available. In the absence of local data on fine particle matter, $PM_{2.5}$ levels were estimated from the recommended $PM_{2.5}/PM_{10}$ ratio.[1] There is a lack of a municipal emission source inventory and of local data for background levels of the pollutants considered in our study. In addition, the impact of other co-pollutants and seasonal effects (for instance the strong seasonal cycle for O_3, high in summer and low in winter) can influence our estimates. Therefore, although presenting our results with a CI can provide a range for our estimates and set bounds to statistical error, we cannot diminish the uncertainty embodied in our results by the quality of the exposure data and our assumptions to estimate population exposure.

Meaning of the study and directions for future research

The WHO EBD series framework seems to prove useful to apply at local level. Our estimates, although constrained by major uncertainties, should be a quantitative input to local authorities become aware of the magnitude of the problem, help realise the substantial potential health benefits from compliance with WHO AQG target values and prioritise actions on strengthening control of outdoor air pollution.

Local governments, through policies aimed mainly to reduce emissions from urban transport that provide alternatives to private motor vehicle traffic, could achieve considerable health gains. It must be stressed that these strategies, through synergies between policies, may yield other important co-benefits for health in traffic injury prevention, noise reduction, creation of spaces for exercise and recreation, etc.[1] Actions should be taken to provide the population with this kind of information, since their awareness and active participation are basic to reduce air pollution.

As implications for future research, the recommendations and risk coefficients resulting from the current evidence review process led by the WHO will be used to revise and update our estimates. Likewise, the analysis with local measurements of $PM_{2.5}$ to reduce uncertainty of estimates related to this pollutant should also be conducted. Collective efforts for developing the availability of morbidity data are needed in order to improve the evaluation of the burden of disease. Future research on improving the monitoring and description of the urban atmosphere and the background levels of pollutants in our local and regional setting should be developed.

Conclusions

Our study suggests a not negligible impact on mortality of outdoor air pollution by PM_{10}, $PM_{2.5}$ and O_3. The implementation of the EBD series guideline on outdoor air pollution[1] compiled by the WHO provides critical information to distinguish an improvement range in air pollution control.

Our results support a reflection on the opportunities to develop feasible actions in order to adopt the more stringent WHO targets, yielding more benefits than simply attaining the current Directive 2008/50/EC, and to enhance the monitoring of ambient air quality at local level.

In any case, we cannot forget that small reductions in the levels of risk factors may yield a great benefit for the health of the entire population.

Acknowledgements The authors thank Dr Annette Prüss-Üstün and Dr Sophie Bonjour from the WHO for the provision of the spreadsheet and valuable comments on its use, the Environmental Health Unit of the city of Valladolid for the provision of data on air pollution. The authors would also like to thank King Philip III of Spain for moving the capital city of Spain from Valladolid to Madrid in 1606 facilitating unconsciously the future feasibility of long-term air pollution control strategies.

Contributors MCA had the idea for this study from his doctoral thesis, leading the design, exposure assessment, data analysis and drafting of the manuscript. MFMM contributed to the exposure assessment, data analysis and the statistical script. AAM, MAC, FCV and AAG contributed to the exposure assessment and data analysis. All authors contributed to the critical reading of and comments to the manuscript, interpretation of data and approved the final draft. MCA is the guarantor.

Disclaimer The views expressed herein can in no way be taken to reflect the official opinion of the Environmental Health Unit of the city of Valladolid.

Funding This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement Extra data can be accessed via the Dryad data repository at http://datadryad.org/ with the doi:10.5061/dryad.3p4f3.

REFERENCES

1. Ostro B. Outdoor air pollution: assessing the environmental burden of disease at national and local levels. Geneva: World Health Organization. 2004. (WHO. Environmental Burden of Disease Series.No. 5). http://www.who.int/quantifying_ehimpacts/publications/ebd5/en/ (accessed 12 Apr 2014).
2. Amann M, Derwent D, Forsberg B, *et al*. Health risks of particulate matter from long-range transboundary air pollution. Copenhagen: World Health Organization, Regional Office for Europe, 2006. http://www.euro.who.int/en/health-topics/environment-and-health/air-quality/publications/pre2009/health-risks-of-particulate-matter-from-long-range-transboundary-air-pollution (accessed 12 Apr 2014).
3. Amann M, Derwent D, Forsberg B, *et al*. Health risks of ozone from long-range transboundary air pollution. Copenhagen, World Health Organization, Regional Office for Europe, 2008. http://www.euro.who.int/en/publications/abstracts/health-risks-of-ozone-from-long-range-transboundary-air-pollution (accessed 12 Apr 2014).
4. Hoek G, Krishnan RM, Beelen R, *et al*. Long-term air pollution exposure and cardio- respiratory mortality: a review. *Environ Health* 2013;12:43.
5. Beelen R, Raaschou-Nielsen O, Stafoggia M, *et al*. Effects of long-term exposure to air pollution on natural-cause mortality: an analysis of 22 European cohorts within the multicentre ESCAPE project. *Lancet* 2014;383:785–95.
6. Burnett RT, Pope CA III, Ezzati M, *et al*. An integrated risk function for estimating the global burden of disease attributable to ambient fine particulate matter exposure. *Environ Health Perspect* 2014;122:397–403.
7. Review of evidence on health aspects of air pollution—REVIHAAP project. Technical report. World Health Organization 2013. http://www.euro.who.int/en/health-topics/environment-and-health/air-quality/activities/health-aspects-of-air-pollution-and-review-of-eu-policies-the-revihaap-and-hrapie-projects (accessed 12 Apr 2014).
8. Health risks of air pollution in Europe—HRAPIE project. Recommendations for concentration–response functions for cost–benefit analysis of particulate matter, ozone and nitrogen dioxide. World Health Organization. 2013. http://www.euro.who.int/en/health-topics/environment-and-health/air-quality/activities/health-aspects-of-air-pollution-and-review-of-eu-policies-the-revihaap-and-hrapie-projects (accessed 12 Apr 2014).
9. http://www.who.int/gho/phe/outdoor_air_pollution/burden_text/en/ (accessed 12 Apr 2014).
10. http://www.iarc.fr/en/media-centre/iarcnews/pdf/pr221_E.pdf (accessed 12 Apr 2014).
11. Prüss-Üstün A, Corvalán C. Preventing disease through healthy environments. Towards an estimate of the environmental burden of disease. WHO, 2006. http://www.who.int/quantifying_ehimpacts/publications/preventingdisease/en/ (accessed 12 Apr 2014).
12. Prüss-Üstün A, Mathers C, Corvalán C, *et al*. Introduction and methods: assessing the environmental burden of disease at national and local levels. Geneva: World Health Organization, 2003. (WHO Environmental Burden of Disease Series, No.1). http://www.who.int/quantifying_ehimpacts/publications/9241546204/en/ (accessed 12 Apr 2014).
13. Diéguez Rodríguez JJ, Muñoz MM, Padilla Gómez L, *et al*. «Estudio y evaluación de la contaminación atmosférica por ozono troposférico en España ». 2009. Informe final. Ministerio de Medio Ambiente y Medio Rural y Marino. http://www.magrama.gob.es/es/calidad-y-evaluacion-ambiental/temas/atmosfera-y-calidad-del-aire/calidad-del-aire/estudios/ (accessed 6 Aug 2014).
14. Mogo S, Cachorro VE, De Frutos, AM. Morphological, chemical and optical absorbing characterization of aerosols in the urban atmosphere of Valladolid. *Atmos Chem Phys* 2005;5:2739–48.
15. http://www10.ava.es/rccava/03contaminantes2.html (accessed 6 Aug 2014).
16. http://www10.ava.es/rccava/08biblioteca1.html (accessed 14 Dec 2013).
17. Directive1999/30/EC. http://ec.europa.eu/environment/air/quality/legislation/existing_leg.htm (accessed 28 Feb 2014).

18. Directive 2000/69/EC. http://ec.europa.eu/environment/air/quality/legislation/existing_leg.htm (accessed 28 Feb 2014).
19. Directive 2008/50/EC. http://ec.europa.eu/environment/air/quality/standards.htm (accessed 28 Feb 2014).
20. Anderson HR, Atkinson RW, Peacock JL, *et al*. Meta-analysis of time-series studies and panel studies of particulate matter (PM) and ozone (O3). Report of a WHO task group. 2004. http://www.euro.who.int/en/health-topics/environment-and-health/air-quality/publications/pre2009/meta-analysis-of-time-series-and-panel-studies-of-particulate-matter-and-ozone (accessed 12 Apr 2014).
21. http://www.ine.es/en/welcome.shtml (accessed 14 Dec 2013).
22. Pope CA III, Thun MJ, Namboodiri MM, *et al*. Particulate air pollution as a predictor of mortality in a prospective study of US adults. *Am J Respir Crit Care Med*. 1995;151:669–74.
23. WHO Air Quality Guidelines for particulate matter, ozone, nitrogen dioxide and sulfur dioxide. Global update 2005.Summary of risk assessment. WHO. 2006. http://www.who.int/phe/health_topics/outdoorair/outdoorair_aqg/en/ (accessed 12 Apr 2014).
24. California Environmental Protection Agency. Air Resources Board. Review of the California ambient air quality standard for ozone. Volume IV of IV. Appendices B-G.Staff Report. Initial statement of reasons for proposed rulemaking. 27 October 2005. http://www.arb.ca.gov/carbis/research/aaqs/ozone-rs/rev-staff/vol4.pdf (accessed 12 Apr 2014).
25. Boldo E, Aragonés N, Medina S, *et al*. Evaluación de Impacto en Salud: una herramienta infrautilizada en salud pública. Ejemplo Apheis (Air Pollution and Health: a European Information System). *Bol Epidemiol Sem* 2005;13:97–108. http://gesdoc.isciii.es/gesdoccontroller?action=download&id=06/03/2013–9bf3a16ce7 (accessed 12 Apr 2014).
26. Touloumi G, Katsouyanni K, Zmirou D, *et al*. Short-term effects of ambient oxidant exposure on mortality: a combined analysis within the APHEA project. *Am J Epidemiol* 1997;146:177–85.
27. Katsouyanni K, Touloumi G, Samoli E, *et al*. Confounding and effect modification in the short-term effects of ambient particles on total mortality: results from 29 European cities within the APHEA 2 project. *Epidemiology* 2001;12:521–31.
28. Le Tertre A, Medina S, Samoli E, *et al*. Short-term effects of particulate air pollution on cardiovascular diseases in eight European cities. *J Epidemiol Community Health* 2002;56:773–9.
29. Ballester F, Corella D, Pérez-Hoyos S, *et al*. Air pollution and mortality in Valencia, Spain: a study using the APHEA methodology. *J Epidemiol Community Health* 1996;50:527–33.
30. Ballester F, Rodríguez P, Iñíguez C, *et al*. Air pollution and cardiovascular admissions association in Spain: results within the EMECAS project. *J Epidemiol Community Health* 2006;60:328–36.
31. Sunyer J, Antó JM, Murillo C, *et al*. Effects of urban air pollution on emergency room admissions for chronic obstructive pulmonary disease. *Am J Epidemiol* 1991;134:277–86.
32. Sunyer J, Basagaña X. Particles, and not gases, are associated with the risk of death in patients with chronic obstructive pulmonary disease. *Int J Epidemiol* 2001;30:1138–40.
33. Guillén Pérez JJ, Guillén Grima F, Medrano Tortosa J, *et al*. Afluencia inusual por asma y enfermedad pulmonar obstructiva crónica en urgencias hospitalarias y contaminación por SO2 en Cartagena. *Rev Esp Salud Publica* 1995;69:305–14.
34. Tenías JM, Ballester F, Rivera ML. Association between hospital emergency visits for asthma and air pollution in Valencia, Spain. *Occup Environ Med* 1998;55:541–7.
35. Ballester F, Iniguez C, Pérez-Hoyos S, *et al*. Polución atmosférica particulada y salud en Valencia. España. 1994–1996. *Gac Sanit* 2002;16:464–79.
36. Galan I, Tobías A, Banegas JR, *et al*. Short-term effects of air pollution on daily asthma emergency room admissions. *Eur Respir J* 2003;22:802–8.
37. Sunyer J, Castellsagué J, Sáez M, *et al*. Air pollution and mortality in Barcelona. *J Epidemiol Community Health* 1996;50(Suppl 1):s76–80.
38. Tobías A, Sunyer J, Castellsague J, *et al*. Impacto de la contaminación atmosférica sobre la mortalidad y las urgencias por enfermedad pulmonar obstructiva crónica y asma en Barcelona. *Gac Sanit* 1998;12:223–30.
39. Sunyer J, Basagana X, Belmonte J, *et al*. Effect of nitrogen dioxide and ozone on the risk of dying in patients with severe asthma. *Thorax* 2002;57:687–93.
40. Sunyer J, Schwartz J, Tobías A, *et al*. Patients with chronic obstructive pulmonary disease are at increased risk of death associated with urban particle air pollution: a case-crossover analysis. *Am J Epidemiol* 2000;151:50–6.
41. Ballester Diez F, Sáez Zafra M, Alonso Fustel ME, *et al*. El proyecto EMECAM: estudio multicéntrico español sobre la relación entre la contaminación atmosférica y la mortalidad. Antecedentes, participantes, objetivos y métodología. *Rev Esp Salud Pública* 1999;73:165–75.
42. Ballester F, Sáez M, Pérez-Hoyos S, *et al*. The EMECAM project: a multicentre study on air pollution and mortality in Spain: combined results for particulates and for sulfur dioxide. *Occup Environ Med* 2002;59:300–8.
43. Alonso Fustel E, Martínez Rueda T, Cambra Contín K, *et al*. Evaluación en cinco ciudades españolas del impacto en salud de la contaminación atmosférica por partículas. Proyecto europeo APHEIS. *Rev Esp Salud Publica* 2005;79:297–308.
44. Boldo E, Medina S, LeTertre A, *et al*. Apheis: health impact assessment of long-term exposure to PM(2.5) in 23 European cities. *Eur J Epidemiol* 2006;21:449–58.
45. Ballester F, Medina S, Boldo E, *et al*. Reducing ambient levels of fine particulates could substantially improve health: a mortality impact assessment for 26 European cities. *J Epidemiol Community Health* 2008;62:98–105.
46. Pérez L, Sunyer J, Künzli N. Estimating the health and economic benefits associated with reducing air pollution in the Barcelona metropolitan area (Spain). *Gac Sanit* 2009;23:287–94.
47. Boldo E, Linares C, Lumbreras J, *et al*. Health impact assessment of a reduction in ambient $PM_{2,5}$ levels in Spain. *Environ Int* 2011;37:342–8.
48. Boldo E, Linares C, Aragonés N, *et al*. Air quality modeling and mortality impact of fine particles reduction policies in Spain. *Environ Res* 2014;128:15–26.