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Temperature-related effects on respiratory medical prescriptions in Spain

Dominic Royé [a,b,c,*], Aurelio Tobías [d,e], Adolfo Figueiras [b,c,f], Santiago Gestal [f,g], Margarita Taracido [b,c,f], Ana Santurtun [h], Carmen Iñiguez [i,b]

[a] Department of Geography, University of Santiago de Compostela, Santiago de Compostela, Spain
[b] CIBER of Epidemiology and Public Health (CIBERESP), Spain
[c] Health Research Institute of Santiago de Compostela (IDIS), Santiago de Compostela, Spain
[d] Institute of Environmental Assessment and Water Research (IDAEA), Spanish Council for Scientific Research (CSIC), Barcelona, Spain
[e] School of Tropical Medicine and Global Health, Nagasaki University, Nagasaki, Japan
[f] Department of Preventive Medicine and Public Health, University of Santiago de Compostela, Santiago de Compostela, Spain
[g] Hospital of Montecelo, Pontevedra, Spain
[h] Unit of Legal Medicine, Department of Physiology and Pharmacology, University of Cantabria, Santander, Spain
[i] Department of Statistics and Operational Research, University of Valencia, Valencia, Spain

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ABSTRACT

Background: The increased risk of mortality during periods of high and low temperatures has been well established. However, most of the studies used daily counts of deaths or hospitalisations as health outcomes, although they are the ones at the top of the health impact pyramid reflecting only a limited proportion of patients with the most severe cases.
Objectives: This study evaluates the relationship between short-term exposure to the daily mean temperature and medication prescribed for the respiratory system in five Spanish cities.
Methods: We fitted time series regression models to cause-specific medical prescriptions, including different respiratory subgroups and age groups. We included a distributed lag non-linear model with lags up to 14 days for daily mean temperature. City-specific associations were summarised as overall-cumulative exposure-response curves.
Results: We found a positive association between cause-specific medical prescriptions and daily mean temperature with a non-linear inverted J- or V-shaped relationship in most cities. Between 0.3% and 0.6% of all respiratory prescriptions were attributed to cold for Madrid, Zaragoza and Pamplona, while in cities with only cold effects the attributable fractions were estimated as 19.2% for Murcia and 13.5% for Santander. Heat effects in Madrid, Zaragoza and Pamplona showed higher fractions between 8.7% and 17.2%. The estimated costs are in general higher for heat effects, showing annual values ranging between €191,905 and €311,076 for heat per 100,000 persons.
Conclusions: This study provides novel evidence of the effects of the thermal environment on the prescription of medication for respiratory disorders in Spain, showing that low and high temperatures lead to an increase in the number of such prescriptions. The consumption of medication can reflect exposure to the environment with a lesser degree of severity in terms of morbidity.

1. Introduction

The effects of the thermal environment on human health are well known and one of the most critical public health issues related to global climate change. The increase in the risk of mortality and hospital admissions during periods of high and low temperatures has been well established (Gasparrini et al., 2015, 2017; Guo et al., 2017; Iñiguez et al., 2021; Song et al., 2017; Ye et al., 2012). Particularly, respiratory diseases are among the leading causes of death and disability in the world (Ferkol and Schraufnagel, 2014). Additionally, acute respiratory symptoms are among the health effects resulting from exposure to air pollution, and pollen is the largest reported cause of seasonal allergic rhinoconjunctivitis (SAR) (Zhao et al., 2019; Caillaud et al., 2015; Menichini and Mudu, 2010).

* Corresponding author. Faculty of Geography and History, University of Santiago de Compostela, Praza Universidade 1, 15782 Santiago de Compostela, Spain.
E-mail addresses: dominic.roye@use.es, dominic.roye@gmail.com (D. Royé).

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However, most of the studies used daily counts of deaths or hospitalisations as health outcomes, which are the ones at the top of the health impact pyramid and reflect only a limited proportion of patients with the most severe cases. Moreover, these health outcomes are not sufficiently sensitive to detect problems such as discomfort or effects on well-being (Royé et al., 2018; Gestal et al., 2020). Few studies have medical prescriptions as an outcome variable, and most of them are focused on air pollution or antiallergic drug consumption (Caillaud et al., 2015; Menichini and Mudu, 2010; Royé et al., 2018; Fuhrman et al., 2007; Matzarakis et al., 2008; Motreff et al., 2014; Hollingworth et al., 2016).

The use of low-severity morbidity data would reach broader population segments or be a more representative quantification of the morbidity associated with exposure to the environment. Preventive measures at this level could reduce the population's vulnerability to more severe consequences, and become more effective in both the short and the long term. Hence, a deeper knowledge of thermal effects at the lower levels of this pyramid could be extremely useful for public health. It is therefore essential to use other health indicators such as over-the-counter (OTC) drug sales or medical prescriptions (Hollingworth et al., 2016). This kind of health indicator could even potentially identify and anticipate, among others, influenza outbreaks due to a more sensitive degree of the data source (Royé et al., 2018).

This study aims to evaluate the relationship between short-term exposure to daily mean temperature and prescribed medications for the respiratory system in five Spanish cities with different climatic, socioeconomic and populational characteristics. To our knowledge, this approach has never been used before to measure a relationship of this kind with figures for medical prescriptions in Europe.

2. Methods

2.1. Setting

This study was carried out in the cities of Madrid, Murcia, Pamplona, Santander and Zaragoza, with populations that ranged from 3,182,981 inhabitants (Madrid) to 171,951 (Santanderr) in 2017 (Fig. 1). Of the total population, only around 20% are older than 64 years of age. Due to their geographical location, we find different climatic conditions, from a humid oceanic climate in Santander to a Mediterranean coast and inland climate with dry and hot summers in Murcia or Zaragoza.

2.2. Data sources

2.2.1. Meteorological and air pollution data

The meteorological data was obtained from the State Meteorological Agency (AEMET), which was accessed by using the OpenData API. Daily mean temperatures were collected from the weather station closest to each of the cities for the period between the years 2004 and 2018. To control for potential effects of air pollution, in the absence of quality contamination data covering the entire study period, we used the CAMS reanalysis data on atmospheric composition from the European Centre for Medium-Range Weather Forecasts (ECMWF) (Inness et al., 2019). For each city, the nearest reanalysis point (to the centre of the raster cells) of three-hourly PM_{10} concentrations was extracted. Then the average daily concentration was calculated. To prevent the potential influence of model outliers, we cut the daily time series of PM_{10} off at a threshold of 150 g/m^3.

2.2.2. Medical prescription data

Medical prescriptions (both electronic and conventional) of the Anatomical Therapeutic Chemical (ATC) Classification System, group R,

Fig. 1. Locations of the cities studied with population coverage and mean temperature.

were provided by the Spanish Agency for Medicines and Health Products for the study period between the years 2004 and 2018 for the cities of Madrid, Pamplona, Santander and Zaragoza. For the city of Murcia, however, the study period started in 2005 due to lack of availability of data for the previous year. The individual patient registers came from the Database for Pharmacoepidemiological Research in Primary Care (BIFAP) (Salvador Rosa et al., 2002). The BIFAP database currently collects data from seven autonomous communities, although Madrid and Cantabria participate only partially; in both regions data come from primary care physicians who collaborate in the database on a voluntary basis. We included those capitals as being representative of the different climates in Spain (Atlantic, Continental and Mediterranean). The population coverage in the BIFAP database is 94% in Pamplona, 100% in Zaragoza and Murcia, and 21% and 18% in Santander and Madrid, respectively. More specifically, the total daily number of prescriptions for medication for the following ATC groups were collected: main group R01-07 (respiratory system), subgroups R01-02 (nasal and throat preparations), R03 (drugs for obstructive airway diseases), R05 (cough and cold preparations) and R06 (antihistamines for systemic use). In addition, we created three age groups (<15, 15–64, >64) for the age-specific analysis. The subgroup of drugs for obstructive airway diseases (R03) was expected to be less sensitive to daily variations in ambient temperature given that it includes drugs for chronic conditions (such as chronic obstructive pulmonary disease (COPD)), which are routinely dispensed in accordance with a previously fixed schedule. The Spanish National Health System covers practically the entire population. We also obtained the monthly lists of the recommended retail prices of all the medications from the Spanish Ministry of Health so as to be able to estimate the costs attributable to heat and cold.

2.2.3. Other data

The monthly number of affiliates to the Spanish Social Security System (SS) was obtained from the Spanish Ministry of Inclusion, Social Security and Migrations to control for possible socioeconomic effects on medical prescriptions, as the reference population underwent changes particularly during the financial crisis (2008–2012) in Spain (see Figure S1).

2.3. Statistical analysis

We fitted a standard time-series quasi-Poisson regression using distributed lag non-linear models (DLNM) to estimate the associations between daily mean temperature and each respiratory-related prescription (Gasparrinia et al., 2010).

The model included the monthly number of affiliates to the SS as an offset, a natural cubic spline of time with 7 degrees of freedom per year to control for long-term trend and seasonality, dummy variables for day of the week, public holidays and influenza epidemics, the daily PM_{10} level to control for time-varying confounders, and temperature.

Air pollution and mean temperature were modelled by means of a constrained DLNM, using a natural cubic spline with three internal knots placed at equally spaced values in the log scale as a lag-response curve. Seven and 14 days were considered the maximum lag, for PM_{10} and temperature, respectively. The exposure-response curve for PM_{10} was modelled with a natural spline with two internal knots at the 90th and 50th percentiles of the air pollutant distribution in the city. The exposure-response curve for temperature was modelled with a natural spline with internal knots placed at the 10th, 75th and 90th percentiles of city-specific temperature distributions. All of these specifications were widely accepted in the case of temperature. In the case of PM_{10}, the non-linear exposure-response relationship was preferred to the linear specification based on the quasi-likelihood version of the Akaike Information Criterion (AIC).

For each outcome and exposure indicator, the temperature of minimum morbidity (TMM) limited to the range of the 1–99th percentiles effect was calculated. Here this refers to medical prescriptions and is used as a reference to estimate the overall cumulative relative rate of prescription associated with cold and heat, respectively, defined as the risk increment at the 5th and 95th percentiles of the temperature distribution. Effect estimates are reported as Relative Risks (RR), with their 95% confidence intervals (95%CI). The lagged pattern of associations for cold and heat were also examined in all cases. Finally, we calculated the attributable fractions (AF) and the annual attributable costs (AC) per 100,000 inhabitants due to cold and heat from all the days of a temperature below and above the TMM (Gasparrini and Leone, 2014). Statistical analyses were performed in R software (version 4.0.3), using the libraries DLNM 2.4.2.

Some sensitivity and additional analyses were performed: 1) 5 and 10 degrees of freedom for the time trend were also tested; 2) in order to test the possible artefactual of some extreme MMT locations, some ranges narrower than 1–99th centiles were tested; 3) the analysis was repeated without controlling for air pollution and, lastly, 4) the analysis was also performed by age group.

3. Results

The cities included in the study are characterised by different climates and socioeconomic features. Tables 1-2 show summary statistics of the meteorological variables and medical prescriptions. During the study period, there were 30, 332, 610 medical prescriptions attributed to respiratory causes in the five Spanish cities. Figure S2 shows the time trends of the total number of respiratory medications prescribed. A high seasonality and weekly pattern are highlighted, with considerably more prescriptions during winter periods (Figure S3). It is also notable that the number was close to zero at weekends and on holidays because primary care centres were closed, although some medication was still prescribed by emergency services (Figure S4). The magnitude of the main respiratory drug prescriptions ranged between a daily maximum of 129 per 10,000 inhabitants, with 44.2 being the mean value in Santander, and a maximum of 82.8 with a mean value of 31.1 in Pamplona (Table 2).

The distribution of subclasses R01-02 to R06 of each city by month revealed the highest contribution, aside from the observed seasonality in the subclasses, in therapeutic group R03, drugs for obstructive airway diseases (Figure S3). The minimum number of all medical prescriptions is reached in August in all the cities. However, in the summer months the proportion of R03 is the highest. Subgroup R06, antihistamines for systemic use, reached its highest number of prescriptions in May and June, coinciding with the period of the highest pollen concentration. Cough and cold preparations (R05), as expected, showed the largest numbers in the winter months.

Nasal and throat preparations (R01-02), however, showed no seasonal patterns in medical prescriptions. The case distribution by age was highly variable in the respiratory subgroups in and between cites, ranging between 41 years for Murcia in R05 and 68 years for Madrid in R03. However, older patients are distinctly visible in the R03 group compared to the others (Table 2, Figure S5).

The city-specific overall cumulative exposure-response association between total prescriptions and daily mean temperature was in general a non-linear inverted J- or V-shaped increase (Fig. 2). The exposure-response was V-shaped for Madrid, Pamplona and Zaragoza, evidencing clear heat and cold effects. It seems that the exposure-

Table 1
Descriptive statistics of daily mean temperature, 2004–2018.

City	Mean temperature (°C)				
	Max	Mean	Min	P5%	P95%
Madrid	31.7	15.1	−2.7	3.8	27.7
Murcia	34.6	18.9	1.4	8.8	28.9
Pamplona	31.6	13.3	−5.2	2.8	24.7
Santander	28.0	14.9	1.1	7.1	22.0
Zaragoza	33.8	16.1	−4.2	4.4	28.1

Table 2
Daily statistics of medical prescriptions per 10,000 inhabitants with respect to the coverage for the respiratory group and subgroups between 2004 and 2018.

City	ATC	Maximum	Mean	P5%	P95%	Total	Median age
Madrid	R	86.7	25.4	0.6	52.5	7,723,787	59
	R01	13.8	2.7	0.0	6.6	845,024	48
	R03	30.8	10.6	0.1	22.1	3,333,808	68
	R05	35.8	4.5	0.0	18.4	1,407,500	57
	R06	43.0	6.8	0.0	19.3	213,7111	49
Murcia*	R	118.2	33.1	1.9	73.5	7,315,452	50
	R01	12.6	3.4	0.1	8.0	755,608	43
	R03	40.0	11.9	1.1	24.6	2,643,783	62
	R05	66.6	7.8	0.0	32.4	1,719,983	41
	R06	41.5	9.9	0.6	22.9	2,196,077	46
Pamplona	R	82.8	31.1	4.2	56.1	3,146,052	56
	R01	17.1	4.0	0.3	9.2	401,006	46
	R03	31.5	11.6	1.3	20.4	1,176,221	65
	R05	37.2	8.9	0.8	21.5	896,420	56
	R06	38.2	6.6	0.8	16.1	672,111	45
Santander	R	129.0	44.2	1.1	86.7	873,473	57
	R01	18.6	4.5	0.0	10.1	92,133	49
	R03	55.4	19.4	0.0	38.2	396,802	61
	R05	72.4	11.1	0.0	33.7	230,801	58
	R06	29.2	7.5	0.0	16.4	153,737	48
Zaragoza	R	102	31.0	0.3	67.5	11,273,846	56
	R01	18.4	4.0	0.0	10.4	1,454,740	46
	R03	40.0	11.0	0.1	26.9	4,022,448	66
	R05	51.2	8.2	0	26.7	2,997,729	49
	R06	42.5	7.7	0	21.8	2,798,892	50

*period 2005–2018; coverage 100% Zaragoza and Murcia, 94% in Pamplona, 21% Santander and 18% in Madrid; R: respiratory system, R01-02: nasal and throat preparations, R03: drugs for obstructive airway diseases, R05: cough and cold preparations, R06: antihistamines for systemic use.

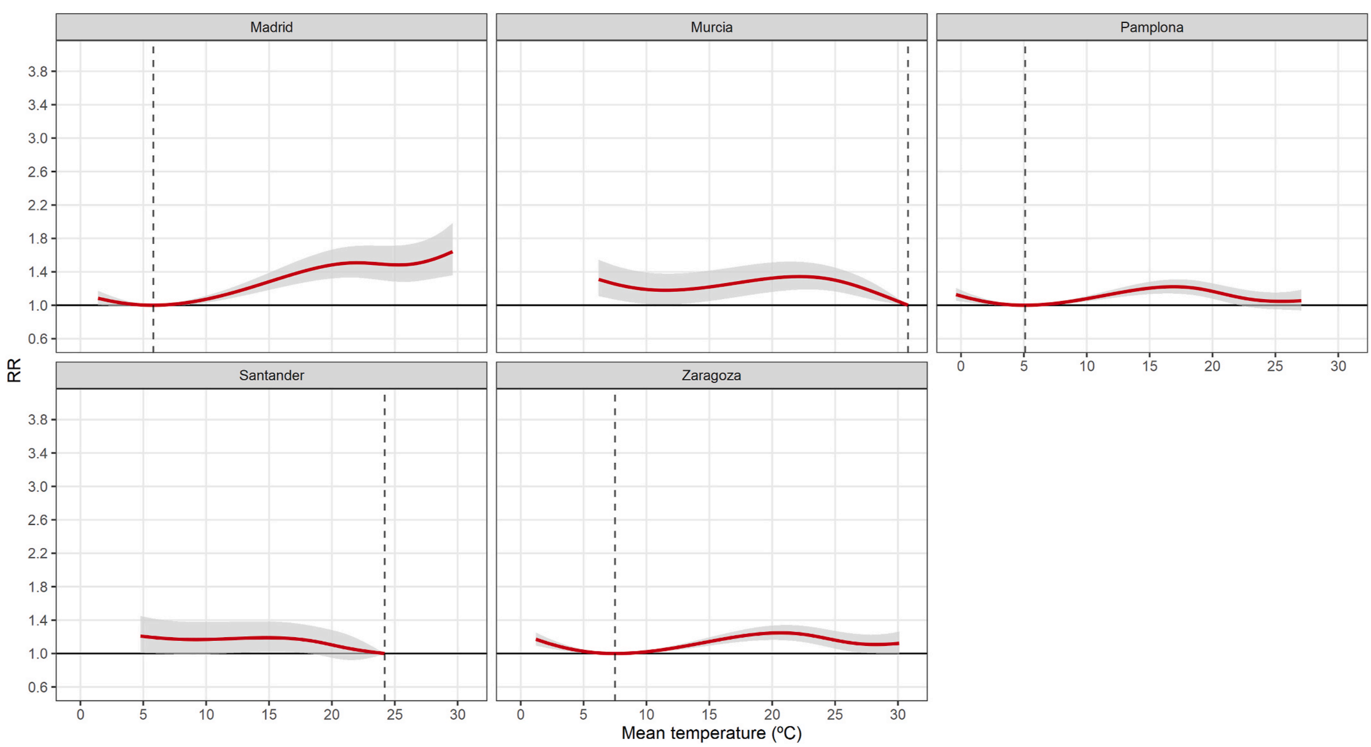

Fig. 2. City-specific overall cumulative exposure-response relationships between mean temperature and respiratory prescriptions. Dashed vertical line is the minimum morbidity temperature.

response curve stabilises as of a certain temperature threshold, for instance, in Madrid at 20 °C. While, for the other two cities, Murcia and Santander, the effect was seen to be limited only to cold.

For nasal and throat preparations (R01-02), we observed cold effects in all cities and also a clear association with high temperatures in Madrid, Pamplona and Zaragoza (Fig. 3). As expected, in the subgroup of drugs for obstructive airway diseases (R03) effects were of lower magnitude but statistically significant for heat in Madrid and Murcia. Cough and cold preparations (R05) showed a similar pattern to R01-02. Finally, the association found in prescriptions of antihistamines for systemic use (R06) was limited to high temperatures, particularly visible in Madrid, Pamplona and Zaragoza. In Pamplona and Zaragoza, a slight effect of cold and some stabilisation at high temperatures were appreciated. Santander, a small coastal city, showed the weakest association

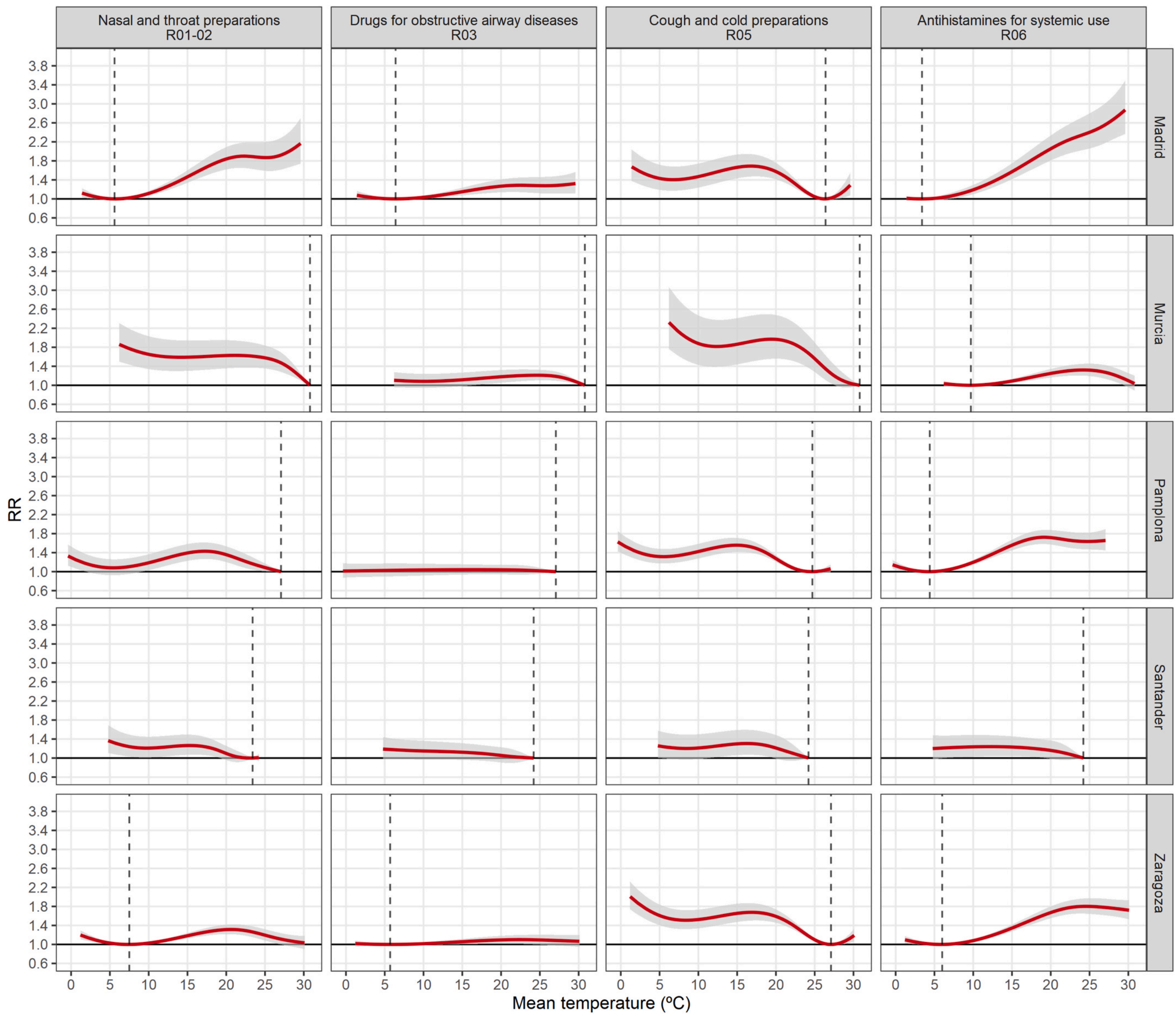

Fig. 3. City-specific overall cumulative exposure-response relationships between mean temperature and subgroups of respiratory prescriptions. Dashed vertical line is the minimum morbidity temperature.

with temperature, only restricted to cold effects for all subgroups.

Regarding sensitivity and additional analyses, our results showed little sensitivity to the changes in the degrees of freedom of the time trend and to stronger restrictions in the range of percentiles allowed for the MMT location. The role of PM_{10} as a potential confounder was also of a small magnitude, in spite of its statistical significance in the model as an explanatory variable in some cases.

The effect analysis by age groups revealed a similar pattern in general (Figure S6-8). However, the greatest risks have been detected in those under 15 years of age with respect to the respiratory subgroups that were analysed (Figure S2). It is particularly remarkable that the oldest group (>64 years) showed the least cold and heat effects. For instance, in Madrid the RR with cold effects in respiratory prescriptions is 1.11 (1.04; 1.19) for <15 years, 1.01 (0.99; 1.03) for 15–64 years and 1.01 (0.98; 1.04) for >64 years. But it could also be observed that the middle age group (15–64) in some cases showed the highest RR; in Zaragoza, for example, the estimated risks are the following: 1.25 (1.14; 1.36) for <15, 1.30 (1.17; 1.44) for 15–64 and 1.06 (0.95; 1.19) for >64 years. Finally, we found an association for the age group below the age of 15 years in the R03 subgroup (drugs for obstructive airway diseases). The MMT (Table S1) ranged between 5.1 °C and 7.5 °C for cities with cold and heat effects (Madrid, Pamplona and Zaragoza), and was estimated with cold only at 24.2 °C and 30.8 °C for Santander and Murcia, respectively. The MMT for the respiratory prescription subgroups showed similar values with some remarkable changes. For instance, in the R06 group (prescriptions of antihistamines for systemic use) for Pamplona and Murcia, we observed a lower MMT of only 4.4 °C and 9.7 °C, respectively. Regarding the patterns found in the age groups, we could only observe that, in general, the MMT seemed to tend to be higher for the youngest age group.

Table 3 shows the excess of medical prescriptions and costs attributable to heat and cold by city and ATC group. Between 0.3% and 0.6% of all respiratory prescriptions were attributed to cold for Madrid, Zaragoza and Pamplona. In cities with effects only due to cold, the attributable fractions (AF) were estimated as 19.2% for Murcia and 13.5% for Santander. Heat effects in Madrid, Zaragoza and Pamplona showed higher AFs of between 8.7% and 17.2%. The estimated attributions were similar in the respiratory subgroups but with apparent singularities in

Table 3
Estimation of fraction and related costs attributable to heat and cold for respiratory prescriptions by city and ATC subgroup.

City	ATC	Attributable Fraction, AF% (95% CI)		Annual attributable Costs per 100,000 person, € (95% CI)	
		Cold	Heat	Cold	Heat
Madrid	R	0.3 (−0.1; 0.7)	17.2 (12.3; 21.5)	5870 (−1506; 12,461)	311,076 (223,274; 389,358)
	R01-02	0.4 (0.0; 0.8)	24.1 (19.7; 28.1)	421 (23; 778)	24,255 (19,745; 28,282)
	R03	0.3 (−0.1; 0.7)	10.9 (6.0; 15.4)	4574 (−1728; 10,723)	161,798 (89,104; 227,815)
	R05	31.1 (20.6; 39.6)	0.3 (0.0; 0.5)	17,051 (11,310; 21,742)	157 (26; 275)
	R06	0.0 (−0.1; 0.1)	33.4 (27.6; 38.4)	38 (−121; 185)	56,788 (47,019; 65,307)
Murcia	R	19.2 (7.9; 28.7)	0.0 (−0.1; 0.0)	379,825 (156,097; 567,041)	−885 (−1660; −195)
	R01-02	37.1 (25.3; 47.1)	−0.1 (−0.1; 0.0)	41,067 (27,989; 52,078)	−97 (−150; −53)
	R03	12.0 (1.9; 20.7)	−0.1 (−0.1; 0.0)	180,821 (28,355; 311,683)	−1027 (−1641; −442)
	R05	44.4 (29.7; 55.5)	0.0 (0.0; 0.0)	43,788 (29,276; 54,794)	−5 (−46; 29)
	R06	0.1 (−0.1; 0.3)	12.7 (8.3; 16.9)	275 (−231; 763)	32,708 (21,243; 43,425)
Pamplona	R	0.5 (0.2; 0.8)	8.7 (5.0; 11.9)	10,878 (3600; 17,747)	195,885 (113,568; 268,389)
	R01-02	18.6 (7.7; 28.3)	0.0 (−0.1; 0.0)	31,320 (12,979; 47,609)	−50 (−121; 14)
	R03	3.3 (−7.3; 12.8)	0.0 (−0.1; 0.0)	59,068 (−132,043; 232,061)	−216 (−1093; 626)
	R05	26.8 (20.3; 32.6)	0.1 (0.0; 0.3)	28,993 (21,989; 35,250)	133 (−45; 295)
	R06	0.3 (0.1; 0.6)	25.2 (21.8; 28.4)	572 (165; 973)	42,305 (36,673; 47,702)
Santander	R	13.5 (0.0; 24.9)	0.0 (−0.1; 0.1)	457,520 (−822; 845,193)	−486 (−3685; 2130)
	R01-02	16.7 (3.6; 28.1)	0.0 (−0.2; 0.2)	29,641 (6443; 49,848)	57 (−302; 339)
	R03	9.8 (−4.1; 21.7)	0.0 (−0.1; 0.1)	282,875 (−118,038; 625,343)	−208 (−3193; 2304)
	R05	19.3 (2.0; 33.1)	0.0 (−0.1; 0.0)	28,500 (3011; 48,877)	−54 (−206; 64)
	R06	16.8 (3.0; 28.8)	−0.1 (−0.2; 0.0)	32,350 (5741; 55,345)	−109 (−342; 86)
Zaragoza	R	0.6 (0.3; 1.0)	9.4 (5.9; 12.7)	13,253 (6192; 19,829)	191,905 (120,421; 259,245)
	R01-02	0.6 (0.3; 1.0)	11.2 (7.4; 14.6)	879 (405; 1341)	15,237 (10,136; 19,927)
	R03	0.0 (−0.2; 0.2)	4.9 (0.4; 9.1)	769 (−2547; 3972)	78,002 (6397; 146,433)
	R05	33.7 (26.8; 39.8)	0.3 (0.1; 0.4)	36,160 (28,773; 42,720)	270 (85; 442)
	R06	0.2 (0.0; 0.4)	25.7 (22.3; 28.6)	388 (37; 719)	50,551 (43,913; 56,415)

R: Respiratory system; R01-02: Nasal and throat preparations; R03: Drugs for obstructive airway diseases; R05: Cough and cold preparations; R06: Antihistamines for systemic use.

coherence with the relationship found for the subgroups. For instance, Madrid had significant high effects in all the subgroups analysed. The estimated costs were in general higher for heat effects, showing annual values ranging between €191,905 and €311,076 for heat and between €5870 and €13,253 per 100,000 persons for cold in Madrid, Pamplona and Zaragoza for the total respiratory group. An important subgroup of respiratory prescriptions is R06, antihistamines for systemic use, where annual costs of between €32,708 and €56,788 per 100,000 persons were estimated.

Table 4 summarises the fraction of medical prescriptions attributable to heat and cold by respiratory subgroup and age group. In coherence with the above, the AFs are higher for those under 15 years of age in all the cities and subgroups analysed. In heat effects, the highest AFs are observed over all age groups in R06 (antihistamines for systemic use) ranging between 7.7% and 42%, with absence of any effect in the case of Santander. Regarding the effect of cold, the pattern is different, showing great AFs in subgroups R05 (Cough and cold preparations) and R01-02 (Nasal and throat preparations).

Figure S9 shows the lag structure of the overall cumulative heat- and cold-related effects of mean temperature on respiratory medical descriptions. Heat effects persisted in a decreasing manner up to a lag of 4–5 days. Longer lagged effects, in general, were observed for low temperatures with lags from 8 days onwards, although in Madrid and Zaragoza there are particularly significant cold effects from the first lag to the third. The lag structure for specific respiratory subgroups and age groups showed a similar pattern (Figures S10-S13).

4. Discussion

The study found evidence that daily medical prescriptions for respiratory use are associated with mean temperature in all the cities analysed. However, there are essential differences in the magnitude, shape and lag structure among cities, age groups and ATC subgroups, which could be related to city-specific climatic, socioeconomic and demographic factors.

In antihistamines for systemic use (R06), the estimated heat effects could be related to the seasonal relationship with the presence of allergens, which could partially explain why the exposure-response curve reaches stability as of a temperature of approximately 20 °C. Pollen is the second most frequent allergen, and the majority of the most allergenic species bloom in spring (e.g. banana trees, olive trees, grasses). But it must be taken into account that house dust mites are the main allergens in Spain. Since citizens tend to spend more time outdoors in summer, this could reduce exposure. In the case of Madrid, the consumption of antihistamines with high temperature could be attributed to other allergens and an extended pollen season or other pollutants (Kanikowska et al., 2018; Damialis et al., 2019).

Although we have not specifically controlled for pollen concentrations, it can be considered that they are partially introduced by the PM_{10} (Anenberg et al., 2020). The explanation of the heat-related effects on antihistamines might lie in an interactive mechanism between hot temperatures and levels of PM_{10} (Analitis et al., 2018). In spite of the

Table 4
Fraction of respiratory prescriptions attributable to heat and cold by city, age group and ATC subgroup.

		Cold			Heat		
City	ATC	<15	15–64	>64	<15	15–64	>64
Madrid	R	1.5 (0.5; 2.5)	0.2 (−0.1; 0.5)	0.2 (−0.2; 0.7)	25.4 (20.7; 29.8)	10.3 (5.1; 14.9)	10 (4.4; 14.8)
	R01-2	1.0 (−0.1; 1.9)	0.3 (0.0; 0.7)	0.5 (−0.1; 1.1)	29.2 (24.6; 33.2)	18.3 (11.1; 24.5)	12.9 (7.4; 17.7)
	R03	14.2 (−10.5; 34.1)	0.4 (03.0; 0.7)	0.2 (−0.2; 0.6)	18.5 (13.8; 22.9)	0.0 (0.0; 0.0)	8.8 (3.5; 13.9)
	R05	45.4 (7.8; 66.8)	32.7 (18.9; 43.5)	27.8 (16.4; 37.1)	0.5 (0.1; 0.7)	0.0 (0.0; 0.0)	0.2 (0; 0.5)
	R06	0.2 (−0.1; 0.4)	0.0 (0.0; 0.0)	0.1 (−0.2; 0.4)	42.0 (33.9; 49.1)	38.3 (33.1; 43.1)	16.5 (11.3; 21.3)
Murcia	R	69.1 (61.2; 75.3)	0.4 (0.1; 0.7)	10.6 (−1.3; 20.5)	8.4 (4.1; 12.5)	−0.2 (−0.3;-0.1)	−0.1 (−0.1; 0.0)
	R01-2	83.3 (77.4; 87.5)	24.9 (9.5; 37.4)	26.8 (11.9; 39.4)	0.0 (−0.1; 0.0)	−0.3 (−0.5;-0.2)	−0.1 (−0.2;-0.1)
	R03	71.8 (63.6; 78.0)	0.0 (−0.1; 0.1)	0 (−0.2; 0.2)	7.7 (2.1; 12.8)	−0.3 (−0.4;-0.2)	7.2 (2.1; 11.8)
	R05	74.0 (65.0; 80.3)	36.8 (24.1; 46.9)	22.9 (6.5; 36)	0.1 (−0.1; 0.2)	−0.1 (−0.2;-0.1)	0.0 (−0.1; 0.1)
	R06	56.2 (46.7; 64.1)	0.0 (0.0; 0.1)	10.7 (−1.7; 21.1)	20.8 (14.8; 26.1)	−0.2 (−0.3;-0.1)	−0.1 (−0.1; 0.0)
Pamplona	R	41.6 (31.0; 50.9)	0.8 (0.5; 1.1)	0.1 (−0.2; 0.4)	16.7 (13.2; 19.8)	−0.1 (−0.2;-0.1)	4.6 (−0.2; 9.1)
	R01-2	51.6 (33.2; 64.5)	0.9 (0.5; 1.3)	21.6 (7.9; 33.4)	16.7 (12.6; 20.6)	−0.2 (−0.2;-0.1)	0.0 (−0.1; 0.0)
	R03	46.4 (35.1; 55.3)	0.2 (−0.2; 0.6)	0.0 (0.0; 0.0)	5.6 (0.4; 10.4)	−0.2 (−0.3;-0.1)	4.2 (−6.5; 13.7)
	R05	60.9 (50.1; 69.3)	32.2 (25.1; 38.5)	17.1 (9.2; 24)	0.4 (0.2; 0.7)	−0.2 (−0.2;-0.1)	0.2 (0.0; 0.4)
	R06	0.2 (−0.2; 0.6)	0.4 (0.2; 0.6)	0.1 (−0.2; 0.5)	31.7 (28.3; 34.9)	26.5 (20.4; 32)	7.7 (2.2; 12.6)
Santander	R	27.3 (11.3; 40.4)	16.6 (2.1; 28.6)	4.9 (−6.3; 14.6)	0.0 (−0.2; 0.0)	0.0 (−0.1; 0.1)	0.0 (−0.3; 0.3)
	R01-2	40.5 (21.5; 53.7)	21.0 (1.1; 36)	12.5 (−16.7; 34.1)	0.0 (−0.2; 0.1)	1.1 (0.1; 1.7)	0.0 (−0.2; 0.1)
	R03	26.9 (15.8; 36.4)	14.9 (−0.7; 28.1)	5.2 (−4.9; 14.2)	−0.1 (−0.2; 0.0)	0.1 (−0.3; 0.5)	0.1 (−0.5; 0.6)
	R05	41.6 (15.7; 59.1)	21.6 (0.2; 37.9)	7.6 (−16.8; 26.4)	0.0 (−0.1; 0.1)	−0.2 (−0.5; 0.0)	0.0 (−0.2; 0.1)
	R06	34.0 (11.1; 50.7)	15.6 (−0.9; 29.2)	−0.1 (−0.1; 0.0)	−0.1 (−0.2; 0.0)	−0.1 (−0.3; 0.1)	14.9 (−0.2; 27.2)
Zaragoza	R	35.2 (24.6; 44.1)	0.7 (0.4; 1.0)	0.3 (0.0; 0.7)	17.6 (14.3; 20.7)	−0.1 (−0.1; 0.0)	6.5 (2.4; 10.2)
	R01-2	39.0 (25.4; 50.1)	0.7 (0.4; 1.0)	13.6 (2.5; 23.4)	17.4 (13.8; 20.7)	−0.1 (−0.1; 0.0)	0.0 (0.0; 0.0)
	R03	40.2 (29.6; 49.0)	0.2 (−0.1; 0.4)	0.0 (−0.2; 0.2)	13.6 (9.4; 17.5)	−0.1 (−0.1;-0.1)	5.3 (0.1; 9.9)
	R05	52.2 (41.9; 60.4)	38.6 (31.9; 44.7)	23.9 (15.7; 31.3)	0.4 (0.2; 0.6)	0.0 (−0.1; 0.0)	0.4 (0.2; 0.6)
	R06	0.1 (−0.2; 0.4)	0.1 (0.0; 0.3)	0.3 (0.0; 0.6)	32.9 (29.5; 36.2)	23.3 (17.7; 28.3)	11.4 (7.5; 15.1)

R: Respiratory system; R01-02: Nasal and throat preparations; R03: Drugs for obstructive airway diseases; R05: Cough and cold preparations; R06: Antihistamines for systemic use.

statistical significance of PM_{10}, in some cases (assessed by the LR test), which proves its role as an outcome predictor, the magnitude of confounding caused by PM_{10} was very small, in fact almost inexistent in most of the cities analysed.

Likewise, exposure to tropospheric ozone has been related to symptoms similar to those produced by allergies (Sheffield et al., 2015; Lee et al., 2013). Furthermore, this compound reaches its maximum levels in spring in coastal regions, but in summer in inland regions (Santurtún et al., 2015), which could also partly explain the results found in Madrid. The geographic location could also explain the lower effects observed in Santander, on the Atlantic coast, where the pollen concentration is usually lower. In this context, the heat effects observed in the case of nasal and throat preparations (R01-02) could be related to the therapeutic use of some medicines, such as decongestants for nasal congestion due to allergies.

The mainly low and constant risks found in the subgroup of drugs for obstructive airway diseases (R03) were expected, as we used it as a control group, and can be explained by the fact that this group is mostly made up of patients with chronic conditions, such as chronic obstructive pulmonary disease (COPD), who have a basal consumption. Potential decompensation of COPD patients is usually associated with infections such as pneumonia treated with other medical therapeutic groups (Restrepo et al., 2018). Nevertheless, it is necessary to emphasise here a positive association with heat and cold effects found in those under the age of 15 years in the case of drugs for obstructive airway diseases, probably related to childhood asthma. In consequence, the effect found in all ages is due to the association in the younger age group.

Many studies have reported U-shaped or J-shaped associations between temperature and mortality and morbidity (Gasparrini et al., 2015, 2017; Guo et al., 2017; Gestal et al., 2020). Likewise, this study confirmed these findings for prescriptions for medication for respiratory conditions with increasing risks at low and high temperatures. Contrasting patterns of temperature-related mortality and morbidity depending on the city were found in previous studies (Iñiguez et al., 2021; Song et al., 2017). For instance, heat was not found to have an impact on hospital admissions, and the estimated fraction of mortality attributable to cold was of greater magnitude in hospitalisations compared to deaths. In contrast to these findings, our results showed effects not only of cold but also of heat.

From a physiological standpoint, the results obtained concerning respiratory prescriptions and mean temperature are coherent with the biological mechanisms put forward to explain how changes in the thermal environment increase respiratory disorders, in turn leading to higher numbers of medical prescriptions. The thermal environment affects the respiratory system through indirect processes and direct physiological processes triggered in the body (D'Amato et al., 2018; Santurtún et al., 2017). Particularly, cold air causes bronchial inflammation, which makes it easier to contract diseases via respiratory viruses (Eccles and Wilkinson, 2015). In the upper respiratory tract, it produces a decrease in the temperature of the respiratory epithelium with associated lower mucociliary clearance, reduced blood flow and a local immune response, which favour respiratory tract infections and cold symptoms (Mourtzoukou and Falagas, 2007).

There are no known direct physiological mechanisms that can explain the effect of heat on the respiratory tract. However, some of our results may be due to indirect mechanisms. Heat has been linked to cardiovascular disorders; high temperatures can damage blood vessels by interfering with nitric oxide synthesis, cytokine production and systemic inflammation, and may promote thrombogenesis (Gostimirovic et al., 2020). Cardiovascular events are related to respiratory diseases. This is why a patient with a basal respiratory disease, exacerbations and greater consumptions of respiratory drugs can be expected to develop cardiovascular diseases (Carter et al., 2019). Moreover, subsequent cardiovascular episodes in some patients are followed by pneumonia, which may be another indirect link between respiratory and cardiovascular responses to high temperatures (Corrales-Medina et al., 2015).

Due to the lack of studies on the relationship between medications and the thermal environment, a comparison with other research results reporting heat or cold effects as relative risks is extremely limited. However, the effect size observed is similar to that noted by Matzarakis et al. (2008), who reported on the thermal environment and pharmaceutical sales (non-prescription medicines for the common cold) for several German cities. In a recent study, Royé et al. (2018) found that low apparent temperatures proved to be associated with increased sales of over-the-counter respiratory drugs in north-western Spain. In contrast to our results, no association with heat was estimated.

The age characteristics found in this study reflect a younger population than is commonly seen from other sources such as hospital admissions or even in mortality. The results obtained by age groups revealed, in general, greater effects in the younger population than in those over 64 years old. This difference is likely to be due, on the one hand, to more chronic conditions and polymedicated elderly patients, who are treated and observed on a regular basis by their general practitioner (Galán-Retamal et al., 2010; Xie et al., 2020). On the other hand, a small decrease in the diameter of the airway in children, due to a stimulus that produces hyperresponsiveness, has a greater impact on the air flow than in adults (Sunyer, 2008; Nhung et al., 2017).

Temperature-related mortality is a premature consequence, although it affects a smaller proportion of the population than the possible effects of morbidity. In this regard, a measure of morbidity based on a lower degree of severity but a larger proportion of a population affected has certain advantages and drawbacks vis-à-vis the measuring of hospital admissions (Royé et al., 2018; Gestal et al., 2020). This assumption is confirmed in our study, since the heat and cold effects observed are found mainly in people under 64 years of age.

We must highlight the advantages of using medical prescriptions, since the population included and affected is younger. Besides, it allows us to analyse the influence of temperature due to pathologies in an indirect way. To our knowledge, this approach has never been used before to measure a relationship of this nature with outcomes for medical prescription in Europe. However, some limitations should also be acknowledged. First, there is the delay in the event with respect to the date of the medical prescription, the dispensing of the drug and its corresponding consumption. However, this limitation was offset by the use of distributed lag models. Another drawback is that they may not correspond to those consumed by self-medication and non-compliance with therapy when using prescribed medicines. However, we do not believe that this biases the study results since both self-medication and therapeutic compliance should not be associated with ambient temperature. Second, the database used does not include over-the-counter drug records, which means that we lose sensitivity with respect to the population affected by exposure to the environment. Another aspect is the database coverage for Madrid and Santander with 18% and 21%, respectively, which are low figures that could influence the statistical power of the model, particularly in Santander. The low coverage can also have impacts on results as the spatial distribution of participating primary care physicians might not be homogeneous.

In conclusion, the results of the first study of the effects of the thermal environment on the prescription of medication for respiratory diseases in Spain from 2004 to 2018 provide new evidence that temperatures lead to increased numbers of such prescriptions. The consumption of medication can reflect exposure to the environment with a lesser degree of severity in terms of morbidity. The exposure-response curves of prescriptions for medication for respiratory ailments can show both heat and cold effects.

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Availability of data and material

Data were obtained from a third party and are not publicly available.

Code availability

Code is available upon reasonable request.

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.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envres.2021.111695.

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