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Association between temperature and natural mortality in Belgium: Effect modification by individual characteristics and residential environment

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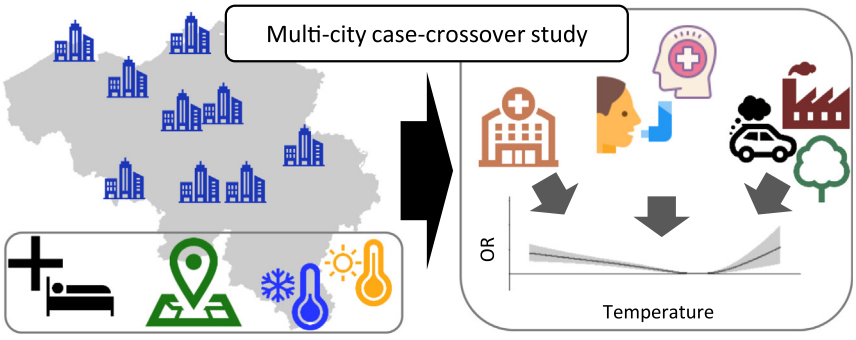
HIGHLIGHTS

- Extreme temperatures increase mortality, from respiratory causes in particular.
- Temperature vulnerability is lower after long or frequent hospital stays.
- People with asthma are more vulnerable to cold.
- Higher heat effects were observed for people with psychoses.
- There was effect modification by air pollutants ($PM_{2.5}$, NO_2, O_3 and black carbon).

GRAPHICAL ABSTRACT



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ABSTRACT

Background: There is strong evidence of mortality being associated to extreme temperatures but the extent to which individual or residential factors modulate this temperature vulnerability is less clear.
Methods: We conducted a multi-city study with a time-stratified case-crossover design and used conditional logistic regression to examine the association between extreme temperatures and overall natural and cause-specific mortality. City-specific estimates were pooled using a random-effect meta-analysis to describe the global association. Cold and heat effects were assessed by comparing the mortality risks corresponding to the 2.5th and 97.5th percentiles of the daily temperature, respectively, with the minimum mortality temperature. For cold, we cumulated the risk over lags of 0 to 28 days before death and 0 to 7 days for heat. We carried out stratified analyses and assessed effect modification by individual characteristics, preexisting chronic health conditions and residential environment (population density, built-up area and air pollutants: $PM_{2.5}$, NO_2, O_3 and black carbon) to identify more vulnerable population subgroups.
Results: Based on 307,859 deaths from natural causes, we found significant cold effect (OR = 1.42, 95%CI: 1.30–1.57) and heat effect (OR = 1.17, 95%CI: 1.12–1.21) for overall natural mortality and for respiratory causes in particular.

Abbreviations: AIC, Akaike Information Criterion; ATC, anatomical therapeutic chemicals; COPD, chronic obstructive pulmonary diseases; CVD, cardiovascular diseases; DDD, Defined Daily Dose; DLNM, distributed lag non-linear models; IHD, ischemic heart diseases; IMA, InterMutualistic Agency; MMT, minimum mortality temperature; NO_2, nitrogen dioxide; OR, odds ratio; O_3, ozone; $PM_{2.5}$, particulate matter with aerodynamic diameter no larger than 2.5 μm; 95%CI, 95 % confidence interval.

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There were significant effects modifications for some health conditions: people with asthma were at higher risk for cold, and people with psychoses for heat. In addition, people with long or frequent hospital admissions in the year preceding death were at lower risk. Despite large uncertainties, there was suggestion of effect modification by air pollutants: the effect of heat was higher on more polluted days of O_3 and black carbon, and a higher cold effect was observed on more polluted days of $PM_{2.5}$ and NO_2 while for O_3, the effect was lower.
Conclusions: These findings allow for targeted planning of public-health measures aiming to prevent the effects of extreme temperatures.

1. Introduction

The excess mortality associated with high temperatures is now well established with very high confidence (Guo et al., 2017; Ma et al., 2015; Cissé et al., 2022) and an increasing number of studies reported cold-related deaths (Almendra et al., 2019; Ma et al., 2021; Lei et al., 2022) worldwide (Gasparrini et al., 2015; Zhao et al., 2021) including in Europe (Leone et al., 2013).

Numerous studies have identified population subgroups vulnerable to cold or heat (Son et al., 2019) such as older people (Chen et al., 2018b; Achebak et al., 2019; Saucy et al., 2021). However, few works go beyond basic characteristics such as age, sex or socioeconomic status (Benmarhnia et al., 2015) and it remains largely unclear to what extent other individual characteristics may impact cold or heat vulnerability. Some studies indicate that medical preexisting conditions such as diabetes (Sun et al., 2016) or dementia (Zanobetti et al., 2013) lead to higher frailty. In light of the ongoing and future global warming, it is important to identify specific populations at risk, especially with respect to heat, in order to underpin targeted prevention strategies.

Ambient air pollution was shown to have strong associations with mortality over Europe (Strak et al., 2021; Stafoggia et al., 2022) but also worldwide (WHO, 2021a) and may raise or, at least, modify the effects of cold and heat on mortality. Yet, little is known about the potential effect modification of the temperature-mortality association by air pollution (Hu et al., 2022). In the last decade, few studies assessed the temperature-related mortality by air pollutant levels with inconsistent results (Hu et al., 2022). In a study covering eight European urban areas, Chen et al. (2018b) reported higher cold and heat effects on highly-polluted days compared to less-polluted days for particulate matter with diameter below 2.5 μm ($PM_{2.5}$) and ozone (O_3), although effect modification was not significant for cold (Chen et al., 2018a). In the US, on the other hand, Choi et al. (2021) found a higher cold effect on days of high $PM_{2.5}$ but no differences for heat nor by levels of O_3, although the cold effect was higher for low levels of O_3 (Choi et al., 2021).

Studies over Belgium so far investigated the association between natural mortality and long-term air pollution exposure (Bauwelinck et al., 2022) or residential greenness (Rodriguez Loureiro et al., 2022), or focused on accidental mortality (Casas et al., 2022). The excess mortality from natural causes associated with extreme temperatures has barely been investigated and the counts of deaths and exposure were always estimated at aggregated levels (De Troeyer et al., 2020; Demoury et al., 2022; Martinez et al., 2018) so that the studies were more prone to misclassification bias (Beale et al., 2008).

In this study, we conducted a case-crossover analysis at individual level to examine the association between extreme temperatures and natural, overall and cause-specific mortality in nine Belgian agglomerations. By means of stratified analyses, we investigated the effect modification of this association by individual characteristics such as age, sex and chronic preexisting health conditions and by levels of population density, built-up area and air pollutants in the residential environment.

2. Materials and methods

2.1. Data collection

We gathered individual information on people of all ages who died from natural causes between January 1st, 2010 and December 31st, 2015 and residing in the nine largest Belgian municipalities and their agglomerations (Van Hecke et al., 2009), i.e. 218 municipalities with an averaged area of 38.2 km^2 over 589 municipalities in Belgium (total surface area of 30,688 km^2) (Fig. A1). These municipalities include 52.9 % of the total Belgian population (11,209,044 inhabitants in 2015). Data of individuals was linked using the Belgian national register number.

Information on the date of death, sex, age (5-year age groups) and cause of death was provided by Statbel, the Belgian statistical office. We used the International Classification of Diseases, 10th revision to define natural, overall (A00-R99) and cause-specific mortality from cardiovascular (I10-I70) and respiratory (J00-J99) diseases. Within the latter two groups, we further identified three specific disease groups: ischemic heart diseases (IHD) (I20-I25), cerebrovascular diseases (I60-I69), and chronic obstructive pulmonary diseases (COPD) (J40-J44, J47).

Meteorological data on daily maximum temperatures and relative humidity, obtained from the spatial interpolation of station observations over Belgium onto a 1-km resolution gridded dataset (Delvaux et al., 2019), were provided by the Royal Meteorological Institute of Belgium and linked to the geographical coordinates of the residence at the time of death.

For further subgroup analyses, we also collected daily mean concentrations (in $\mu g/m^3$) of $PM_{2.5}$, nitrogen dioxide (NO_2), O_3 and black carbon from the Belgian Interregional Environment Agency (RIO-IFDM model, 100 m spatial resolution) (Lefebvre et al., 2013). The population density of the census tract (the smallest Belgian administrative spatial unit, with an average surface area of 1.5 km^2) of residence was also provided by Statbel. The percentage of non-vegetated surface resulting from global training data derived using high-resolution imagery (MODIS/Terra Vegetation Continuous Fields, 250 m spatial resolution) (DiMiceli et al., 2015) was calculated for a 1-km buffer around the residence, as an indicator of built-up area.

Additionally, we used data from the InterMutualistic Agency (IMA) which gathers data collected by the Belgian health insurance companies each year, for all their members. It represents 98 % to 99 % of Belgians since health insurance is mandatory in Belgium. The databases contain information on reimbursed medication dispensed in pharmacies (except those dispensed in hospital settings) to the members of the insurance companies ("Pharmanet"). Based upon these, we constructed indicators of "pseudopathologies" for chronic preexisting diseases (thrombosis, cardiovascular diseases (CVD), COPD, asthma, diabetes, psychoses and thyroid affections). The indicators were developed by experts upon request of the Belgian National Institute for Health and Disability Insurance ("EPS"). People were assigned to a certain pseudopathology if they had received prescriptions corresponding to at least 90 defined daily doses (DDD) of drugs belonging to specific anatomical therapeutic chemicals (ATC) categories during the 12 months preceding death (WHO Collaborating Centre for Drug Statistics Methodology). Since DDD are defined for adults, we only considered subjects older than 20 years. For two pseudopathologies (COPD and asthma), however, an additional condition relies on the age of the patient (Table A.1). Additional information on the employment status (yes/no) at the end of the calendar year preceding death and hospitalization (cumulative total above 120 days in the past 12 months preceding death) was also provided by the IMA.

2.2. Statistical analyses

2.2.1. Temperature-mortality association

We used a time-stratified case-crossover design to assess the association between temperature and mortality. Such a design is suitable to examine

acute adverse health effects resulting from a transient exposure (Maclure, 1991). According to this method, each individual serves as his/her own control: his/her date of death corresponds to the case day, and following a time-stratified approach, three or four control days corresponding to the same day of the week are selected from the same month and year as the date of death (Levy et al., 2001), controlling for seasonality and time trends. Potential confounders such as sex, age or socioeconomic status are adjusted by design because they do not vary for a given person between case and control days.

We followed a two-stage approach: we first estimated the association in the nine agglomerations with conditional logistic regression, and then pooled the agglomeration-specific estimates using a random-effect meta-analysis (Gasparrini and Armstrong, 2013) to describe the global association between temperature and mortality.

In the first stage, we used distributed lag non-linear models (DLNM) (Gasparrini et al., 2010) to describe the non-linear and lagged temperature–mortality relationships. In DLNM models, these relationships are defined by a (three-dimensional) crossbasis function which combines the (two-dimensional) non-linear temperature–mortality and lag–mortality relationships. The crossbasis function is then reduced to obtain an overall cumulative temperature–mortality association by cumulating the risks over the lags considered (Gasparrini and Armstrong, 2013). In line with literature (Saucy et al., 2021; Zhao et al., 2021) and based on previous findings using a similar dataset (Demoury et al., 2022), we considered lag periods of 0–7, 0–21 and 0–28 days preceding death. The lag-mortality dimension was modeled using a natural cubic spline with an intercept and two internal knots at equally-spaced values in the log scale. For each lag period, we defined a list of model candidates by varying the definition of the temperature-mortality relationship in the agglomeration-specific crossbasis functions (Vicedo-Cabrera et al., 2018). More specifically, we tested cubic natural splines and quadratic B-splines with two or three internal knots placed in specific percentiles of the temperature distribution (5^{th}, 10^{th}, 25^{th}, 50^{th}, 75^{th}, 90^{th} and 95^{th}). The selected model was taken as the one featuring the minimal summed Akaike Information Criterion (AIC), over all nine agglomerations (Gasparrini et al., 2012). The conditional logistic models were adjusted for public holidays (binary variable) and relative humidity (natural cubic spline function with 3 degrees of freedom). In case-crossover analyses, temporal confounders such as day of the week, seasonality, and time trends as well as time-invariant confounders such as age or sex, are controlled for by design.

We finally derived the minimum mortality temperature (MMT) from the pooled overall cumulative association obtained by pooling the agglomeration-specific estimates with a random-effect meta-analysis and restricted maximum likelihood estimation (second stage). We tested residual heterogeneity using the Cochran Q test and I^2 statistic. We used the MMT as the reference for calculating the odds ratio (OR) for temperatures corresponding to the 2.5^{th} percentile (cold effect) and 97.5^{th} percentile (heat effect) of the temperature distribution. Based on previous findings (Demoury et al., 2022), we reported the cold effect using a lag period before death of 0 to 28 days, and of 0 to 7 days for the heat effect. We performed sensitivity analyses by cumulating the risk over lags of 0 to 21 days before death for cold and heat effects.

All analyses were performed in R (R Foundation for Statistical Computing, Vienna, Austria) using the packages survival, dlnm, and mvmeta.

2.2.2. Subgroups analyses and effect modification

We first conducted stratified analyses by cause of death. Then, to identify potential risk differences among population subgroups, we performed stratified analysis by replicating the aforementioned two-stage approach in subgroups defined by their individual characteristics (sex, age, employment status), hospitalization, pseudopathologies, population density or built-up area, and using the same temperature-mortality and lag-mortality functions as the main analysis. For population density and built-up area, low and high categories include 25 % of the people living in the least and most populated or built-up areas.

We assessed effect modification using the Z-test and comparing Z to the standard normal distribution (Altman and Bland, 2003):

$$Z = \frac{\beta_1 - \beta_2}{\sqrt{SE(\beta_1)^2 + SE(\beta_2)^2}}$$

where β_1 and β_2 are the effect estimates in two subgroups, SE(β_1) and SE (β_2) their respective standard errors.

To assess effect modification by air-pollutants level ($PM_{2.5}$, NO_2, O_3 and black carbon), we divided the population into two subgroups using the median of the pollutant distribution (lag 0-1 moving average). Based on AIC minimization, we defined pollutant-specific temperature-mortality functions because the temperature distribution varied by air pollutant levels (Table 1). We used Pearson correlation to examine the level of correlation between temperature and air pollutants. In sensitivity analysis, we additionally divided the population into three subgroups using the tertiles of the pollutant distribution.

3. Results

Between 2010 and 2015, 307,859 natural deaths were registered in the study area of which 307,490 geocoding of the address were possible, and IMA information was available for 302,148 people. The daily maximum temperature ranged between −8.3 °C and 38.3 °C with an average of 14.5 °C (Table 1) and the nine agglomerations showed overlapping temperature ranges (Table A.2). The details of the final DLNM models minimizing the AIC and the agglomeration-specific temperature-mortality relationships can be found in Appendix (Table A.3, Figs. A2–A3). Overall, we observed a significant cold effect with an OR of 1.42 (95%CI: 1.30–1.57) for $p_{2.5\%}$ (−1,3 °C) vs MMT (23.7 °C) and a significant heat effect with an OR of 1.17, (95%CI: 1.12–1.21) for $p_{97.5\%}$ (28.6 °C) vs MMT (21.1 °C) (Table 2) and we found very little residual heterogeneity with I^2 of 1 % (Table A.4).

Stratified analyses by cause of death indicated higher cold effects for respiratory causes, and more strongly for COPD (Table 2). The highest effect

Table 1
Summary statistics for maximum daily temperature (in Celsius degrees), 2010–2015.

Temperature	N	Mean (sd)	Min	$p_{2.5}$	IQR	$p_{97.5}$	Max
All	307,490	14.5 (7.6)	−8.3	−0.3	8.9–20.0	28.6	38.3
By air pollutants							
$PM_{2.5}$ ($\rho = -0{,}32$, $p < 0.001$)							
Low	153,745	16.1 (6.3)	−2.3	5.0	11.0–20.4	28.4	38.3
High	153,745	12.8 (8.4)	−8.3	−1.5	6.4–19.4	29.0	36.9
NO_2 ($\rho = -0{,}30$, $p < 0.001$)							
Low	153,745	16.5 (6.6)	−5.4	3.9	11.4–21.0	28.9	38.3
High	153,745	12.5 (8.0)	−8.3	−1.4	6.5–18.5	28.2	38.1
O_3 ($\rho = 0{,}53$, $p < 0.001$)							
Low	153,745	11.4 (7.0)	−8.3	−1.4	6.3–17.1	24.3	33.2
High	153,745	17.5 (6.9)	−4.4	4.5	12.1–22.5	30.6	38.3
Black carbon ($\rho = -0{,}16$, $p < 0.001$)							
Low	153,745	15.5 (6.6)	−5.3	2.6	10.4–20.2	28.0	37.6
High	153,745	13.5 (8.3)	−8.3	−1.3	7.2–19.7	29.2	38.3

N: number of subjects; sd: standard error; min: minimum; $p_{2.5}$ and $p_{97.5}$: percentiles of the temperature distribution; max: maximum; IQR: interquartile range; ρ: Pearson correlation between temperature and the air pollutants and *p*-value for the test of the null hypothesis $\rho = 0$; $PM_{2.5}$: particulate matter with aerodynamic diameter no larger than 2.5 μm; NO_2: nitrogen dioxide; O_3: ozone.
Temperature is estimated at the address of the residence the day of death.
Low and high levels of air pollutants are defined according the median of their distribution: $PM_{2.5}$ (18.2 μg/m^3), NO_2 (23.9 μg/m^3), O_3 (39.3 μg/m^3) and black carbon (1.4 μg/m^3).

Table 2
Cold and heat effects on mortality by subgroups of population, 2010–2015.

		n(%)	Cold effect		Heat effect	
			OR (95%CI)	p[c]	OR (95%CI)	p[c]
All		307,490 (100)	1.42 (1.30–1.57)		1.17 (1.12–1.21)	
Causes of death						
Cardiovascular		91,312 (29.7)	1.38 (1.14–1.68)	0.82	1.17 (1.11–1.23)	0.90
IHD		26,128 (8.5)	1.49 (1.09–2.04)	0.55	1.19 (1.07–1.33)	0.66
Cerebrovascular		21,717 (7.1)	1.35 (1.01–1.78)	0.99	1.20 (1.08–1.33)	0.61
Respiratory		34,487 (11.2)	2.04 (1.64–2.53)	**<0.001**	1.24 (1.09–1.40)	0.35
COPD		13,935 (4.5)	2.52 (1.61–3.94)	**0.01**	1.27 (1.09–1.48)	0.27
Other natural		181,691 (59.1)	1.35 (1.19–1.52)	*ref*	1.16 (1.11–1.21)	*ref*
Individual characteristics						
Sex	Women	161,606 (52.7)	1.49 (1.30–1.70)	0.25	1.20 (1.15–1.26)	***0.07***
	Men	145,884 (47.4)	1.34 (1.20–1.50)		1.12 (1.06–1.19)	
Age	0–64 years	43,702 (14.2)	1.28 (1.00–1.65)	0.80	1.14 (1.06–1.23)	0.62
	65–74 years	45,162 (14.7)	1.23 (0.98–1.54)	*ref*	1.11 (1.03–1.20)	*ref*
	75–84 years	92,231 (30.0)	1.38 (1.20–1.60)	0.38	1.17 (1.10–1.24)	0.31
	85 + years	126,395 (41.1)	1.57 (1.37–1.80)	***0.06***	1.19 (1.11–1.28)	***0.19***
Employment	Yes	35,477 (11.5)	1.31 (1.04–1.66)	0.59	1.12 (1.03–1.22)	0.76
	No	6937 (2.3)	1.09 (0.58–2.07)		1.16 (0.96–1.40)	
Hospitalization > 120 days[a]	Yes	60,153 (19.6)	1.20 (0.96–1.50)	***0.10***	1.06 (1.00–1.13)	**<0.01**
	No	242,995 (79.0)	1.48 (1.33–1.64)		1.19 (1.14–1.24)	
Pseudopathologies[b]						
Thrombosis	Yes	148,744 (48.4)	1.39 (1.24–1.55)	0.74	1.17 (1.12–1.22)	0.96
	No	153,315 (49.9)	1.43 (1.24–1.66)		1.17 (1.10–1.24)	
CVD	Yes	69,185 (22.5)	1.42 (1.20–1.69)	0.91	1.17 (1.10–1.24)	0.91
	No	232,874 (75.7)	1.41 (1.27–1.56)		1.16 (1.11–1.22)	
COPD	Yes	54,847 (17.8)	1.63 (1.34–1.97)	***0.11***	1.21 (1.13–1.31)	0.29
	No	247,212 (80.4)	1.36 (1.24–1.50)		1.16 (1.12–1.21)	
Asthma	Yes	4692 (1.5)	2.98 (1.45–6.11)	**0.04**	1.30 (1.02–1.66)	0.38
	No	297,367 (96.7)	1.40 (1.28–1.54)		1.16 (1.12–1.21)	
Diabetes	Yes	49,727 (16.2)	1.29 (1.03–1.62)	0.37	1.20 (1.07–1.34)	0.51
	No	252,332 (82.1)	1.44 (1.31–1.60)		1.15 (1.10–1.21)	
Psychoses	Yes	19,441 (6.3)	1.56 (1.07–2.25)	0.60	1.33 (1.19–1.49)	**0.02**
	No	282,618 (91.9)	1.40 (1.28–1.54)		1.15 (1.11–1.20)	
Thyroid affections	Yes	25,732 (8.4)	1.69 (1.15–2.49)	0.35	1.22 (1.08–1.38)	0.44
	No	276,327 (89.9)	1.40 (1.27–1.54)		1.16 (1.11–1.21)	
Residential environment						
Population density	Low	76,535 (25.0)	1.45 (1.30–1.63)	0.71	1.13 (1.08–1.18)	***0.10***
	High	77,224 (25.2)	1.41 (1.22–1.62)		1.20 (1.13–1.27)	
Built-up area	Low	67,880 (22.1)	1.56 (1.29–1.88)	***0.13***	1.15 (1.07–1.23)	0.65
	High	78,127 (25.4)	1.29 (1.09–1.51)		1.18 (1.09–1.26)	

[a] In the past 12 months preceding death; [b] in people >20 years (n = 302,059); [c] effect modification, p-value for Z-test which examined the statistical significance of the effect differences between different subgroups; Bold: significant effect modification ($p < 0.05$); bold italic: suggestion of effect modification (p between 0.05 and 0.20) (Faustini et al., 2011).
Cold effect (odds ratio for $p_{2.5\%}$: −1,3 °C vs minimum mortality temperature: 23.7 °C, 88.8th percentile of the temperature distribution): odds ratio are cumulated over 0–28 days, and heat effect (odds ratio for $p_{97.5\%}$: 28.6 °C vs minimum mortality temperature: 21.1 °C, 79.7th percentile of the temperature distribution): odds ratio are cumulated over 0–7 days.
OR (95%CI): odds ratio and their 95 % confidence intervals; IHD: ischemic heart diseases; CVD: cardiovascular diseases; COPD: chronic obstructive pulmonary diseases; *ref*: reference category, for variables containing more than two categories, p was calculated by comparing the estimate of the specified category with the reference category (Knol and VanderWeele, 2012).

of heat was also found in these groups albeit not statistically different from the risk observed for the other natural causes.

With regard to effect modification by individual characteristics and pseudopathologies (Table 2), stratified analyses showed significantly higher cold effects for people suffering from an asthma pseudopathology (p = 0.04). We also encountered suggestions of effect modification by age (higher cold effect observed in people aged >85 years old, p = 0.06), by hospitalization status, COPD pseudopathology and levels of built-up

area in the neighborhood. More specifically, people hospitalized for a long time or repeatedly (cumulative total > 120 days in the past 12 months before death) were at lower risk while people with COPD pseudopathology and people living in lowly built-up areas were at higher risk ($p = 0.10$, $p = 0.11$ and $p = 0.13$, respectively). Significant differences in heat effect were also observed: people with long or frequent hospital stays were at lower risk ($p < 0.01$) as well as people characterized by a psychoses pseudopathology ($p = 0.02$). For heat, there was also suggestion of effect modification by sex ($p = 0.07$), age ($p = 0.19$) and population density ($p = 0.10$): women and people older than 85 years old or residing in the most populated areas were at higher risk. In sensitivity analyses cumulating the risk over 0–21 days, we observed differences in the level of significance of effects modifications but not in terms of contributing factors (Table S5). It is noteworthy that a higher risk was observed for high temperatures in people with thyroid infections ($p = 0.03$).

With regard to air pollution, the maximum daily temperature distribution differed between less and more polluted days. For days with the lowest concentrations of $PM_{2.5}$, NO_2 and black carbon, the temperature was on average higher compared to days with the highest concentrations (Table 1). We observed higher temperatures on more polluted days of O_3 and we found a higher correlation between temperature and O_3 (Pearson correlation = 0.53) than for the other pollutants (Pearson correlations = −0.32, −0.30 and −0.16 for $PM_{2.5}$, NO_2 and black carbon, respectively). Fig. 1 describes the temperature-mortality relationships by air pollutants levels. Despite high uncertainties for very extreme temperatures, a higher cold effect was suggested on more polluted days of $PM_{2.5}$ and NO_2 while for O_3, the effect was lower (*p*-values for effect modification <0.001, Table A.6). These results were confirmed when we cumulated the risk of death over a period of 0–21 days (Fig. A4, Table A.5). Heat effects were higher on more polluted days of $PM_{2.5}$, NO_2, O_3 and black carbon as compared to days with less pollution (p-values for effect modification <0.001, Table S6) but these results were not confirmed for $PM_{2.5}$ ($p = 0.29$) and NO_2 ($p = 0.14$) when cumulating the risk of death over a period of 0–21 days. Sensitivity analyses for low, medium and high levels of

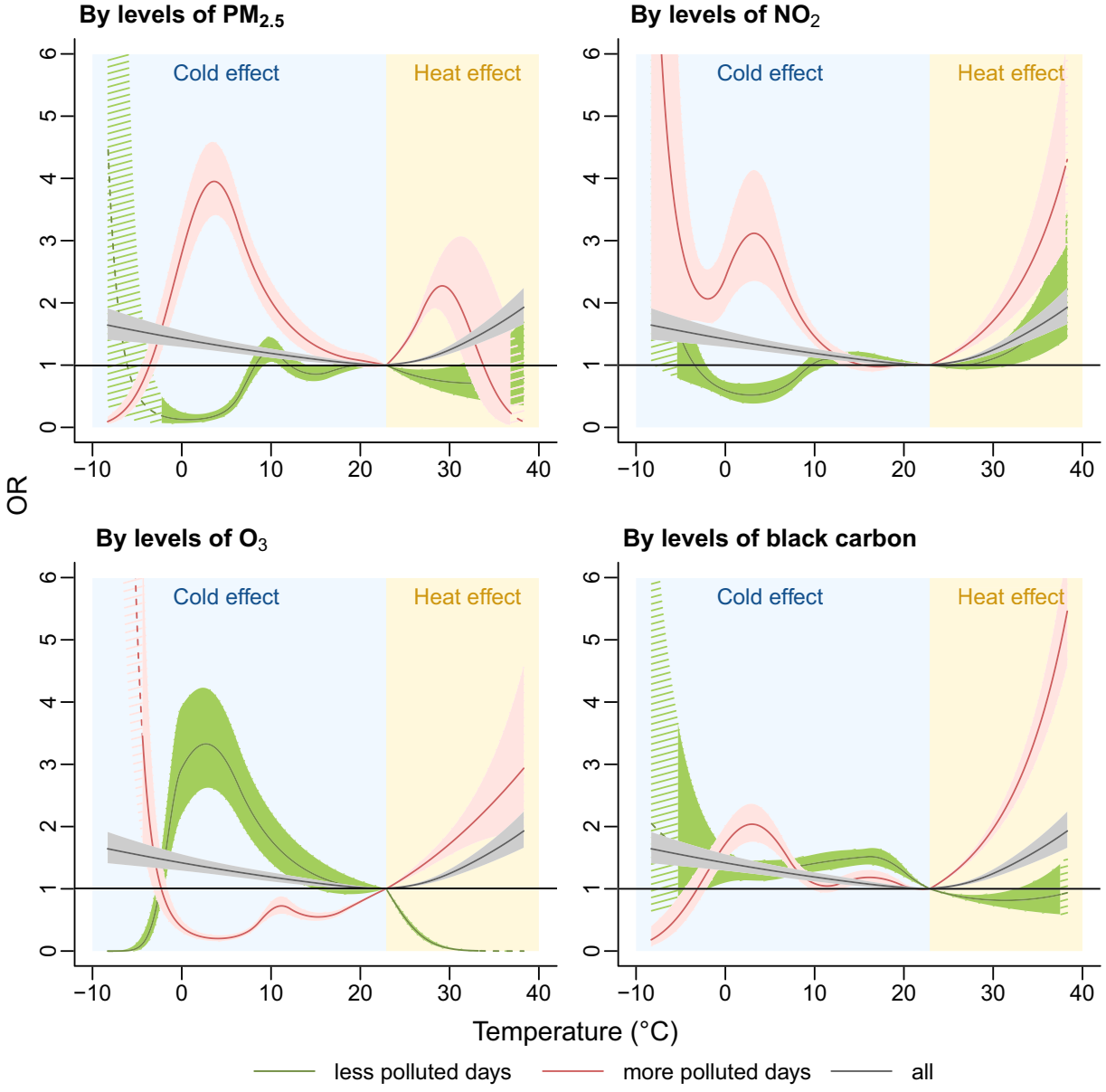

Fig. 1. Temperature-mortality relationships, cumulated over lags of 0–28 days (cold effect) and 0–7 days (heat effect), by levels of air pollutants, 2010–2015. Dashed lines indicate extrapolations beyond the observed temperatures. For graphical visualization, all curves were arbitrarily centered on 22.9 °C (corresponding to the minimum mortality temperature of the non-stratified analysis when the risk is cumulated over 0 to 21 days).

pollutants confirmed effect modification by $PM_{2.5}$, NO_2 and O_3 for low temperatures and by O_3 and black carbon for high temperatures with a gradient from low to high for most of the pollutants (Fig. A5).

4. Discussion

4.1. Principal findings

In this investigation, we observed significant cold and heat effects for overall natural mortality, and we found the highest associations between temperature and mortality for respiratory causes, in particular COPD. We also identified populations who are more vulnerable to heat or cold: women, the elderly, people with preexisting COPD, asthma and psychoses. In addition, we found less vulnerability for people with long or frequent hospital admissions in the year preceding death. Our results also suggest modification by levels of population density, built-up area and air pollutants ($PM_{2.5}$, NO_2, O_3 and black carbon).

4.2. Principal findings and interpretations

Case-crossover designs allow capturing an outcome resulting from a transient exposure. Here, we quantified the impact of a short-term exposure to extreme temperatures on the risk of natural death, in particular deaths from cardiovascular and respiratory diseases. More specifically, we found the COPD to be an underlying cause for increased risk of death due to cold. During extreme cold days, people might die from COPD because of bronchoconstriction or increased mucus production (Koskela, 2007), which may aggravate breathing difficulties.

With analyses accounting for chronic preexisting conditions, we captured the person's frailty on the long-term (Künzli et al., 2001) and we showed that some underlying preexisting conditions, which might be caused by a cumulative or long-term exposure to other environmental exposures, increase the vulnerability to a short-term exposure to extreme temperatures. The stratified analyses revealed a significant effect modification in the association between low temperatures and mortality for asthma and a suggested effect modification for COPD, with higher associations among asthma and COPD patients, meaning that these patients are more vulnerable to cold and have a higher risk of dying (from any cause) at extremely cold temperatures. These elevated risks may arise due to the increased oxygen need for thermoregulation (Morrison and Nakamura, 2019) and are in line with some studies that indicate an excess mortality due to asthma and COPD patients during winter months or in relation to extreme cold (Schwartz, 2005; Donaldson and Wedzicha, 2014; Shrestha et al., 2018). However, literature findings are inconsistent as other studies find, for instance, that people with COPD are susceptible to increased risk of mortality when exposed to high temperatures, but not to low temperatures (Sun et al., 2016). It is worth noting that the real effect modification is probably larger than the effect observed in our study since health insurance data underestimate the number of patients suffering from asthma and COPD (Berete et al., 2020).

We found a significantly higher association between heat effect and mortality for people with psychoses as compared to those without. Note that misclassification cannot be excluded for people with psychoses that do not take their medication. Our finding is in line with a study in the UK that also covered other mental illnesses such as dementia and substance use (Page et al., 2012). Recent studies reported that high temperatures enhance suicide mortality (Liu et al., 2021) as in Japan (Pan et al., 2022) and in Brussels, Belgium (Casas et al., 2022). The underlying mechanisms are not completely clear (Chong and Castle, 2004) but possible explanations include toxic effects of the medication due to inadequate medication doses during extreme heat conditions, thermoregulation impaired by schizophrenia itself or by neuroleptic drug use or more frequent isolation among people with schizophrenia and psychosis.

We observed a lower mortality risk due to extreme temperatures for people with long or frequent hospital admissions before death. This may be related to an isolated lifestyle as this is often reported to increase the probability of death due to temperatures (WHO, 2021b). It is, for example, more difficult to monitor these people's hydration level or body temperature because they are less carefully followed medically. Findings in literature, however, are inconsistent in this regard. For instance, a recent Finnish study reported a higher vulnerability to heat for the elderly in institutional care compared to homes (Kollanus et al., 2021). The prevalence of air conditioners in hospitals could explain differences between countries. Finally, our finding suggesting that women and elderly are more vulnerable to temperature extremes is in line with most of the literature findings (Benmarhnia et al., 2015; Son et al., 2019).

Regarding air pollution, we found differences in the temperature-mortality association when comparing more and less polluted days for cold ($PM_{2.5}$, NO_2, O_3) and heat (O_3 and black carbon), suggesting effect modification by air pollutants. A recent meta-analysis reported effect modification of the temperature-mortality association by air pollution, but only for the heat effect and for particulate matter with diameter below 10 μm (PM_{10}) and O_3 (Hu et al., 2022). Black carbon was not considered separately. Regarding $PM_{2.5}$ and NO_2, there are still few studies investigating their association with temperature (Hu et al., 2022) and results are mostly inconsistent (Analitis et al., 2018; Chen et al., 2018a; Lee et al., 2019; Choi et al., 2021; Saucy et al., 2021). In our stratified analyses by air pollutants level, we found wide uncertainties in temperature-mortality curves making it difficult to conclude effect modification in the association for each temperature level. For some temperature ranges, even a lower probability of dying was found as smaller compared to the probability at the optimal temperature of 22.9 °C. Meteorological factors that determine ambient temperature (wind, sunlight, rainfall, clouds) also affect air pollutant levels. For example, ground-level ozone is formed after a photochemical reaction of nitrogen oxides or volatile organic compounds in the presence of sunlight (Sillman, 1999). As a consequence, some combinations of ambient temperature and air pollutant levels (e.g. low levels of ozone and high temperatures, or, high levels of ozone and low temperatures) are rare, which can explain the uncertainty in extreme temperatures for some curves. With higher cold and heat effects observed on polluted days, our results suggest that multiple exposures can lead to higher adverse effects.

This study can be situated within the framework of the concept of exposome, defined as the totality of environmental exposures from the prenatal period onwards of individuals (Wild, 2005), and more specifically of external exposome, which focuses on the external environment (climate, the urban–rural environment and environmental pollutants) (Wild, 2012; Zhang et al., 2021). Disentangling the effects of temperature and air pollution on health is challenging and there is a need for more exposome research including a better characterization of the overall effect of multiple exposures and their correlation as well as the identification of subgroups of the population carrying a larger environmental burden.

4.3. Strengths and limitations

There are numerous studies on the association between temperature and mortality but the exposure was estimated at the individual level in very few of them (Murage et al., 2020; Saucy et al., 2021; Fu et al., 2018); for the others, counts of deaths and exposure were often aggregated at city- or country-level at the risk of missing local phenomena. Thanks to the estimation of the temperature and other environmental exposures (built-up, air pollution) at the exact geographical coordinates, combined with high-resolution exposure models, we substantially reduce exposure misclassification in this analysis (Beale et al., 2008). We performed a large number of subgroups analyses according to individual and environmental characteristics, putting this study among the few investigating pre-existing chronic health conditions as well as the potential effect modification of the temperature-mortality association by levels of air pollutants (Hu et al., 2022).

This study has, however, some limitations. Individual information on lifestyle characteristics such as the use of air conditioning was lacking. The exact location of the place of death was not available in databases. Instead we assessed exposure at the address of residence at the time of

death, which can differ from the actual place of death (in the hospital for example). There are also limitations to assess the association between temperature and mortality by chronic disease. More specifically, a clear definition of chronic conditions lacks, making it difficult to identify all persons concerned in Belgium (Maertens de Noordhout Charline et al., 2022). Second, the ability to retrace the exact chronic disease status based on reimbursed medication data from the health insurance is limited because this is only possible when the type and volume of medication used is specific enough to identify the disease or disease group of interest. Therefore, the number of chronic diseases for which effect modification could be assessed here, was limited. However, for some important diseases or disease groups (cardiovascular diseases, diabetes, thyroid disorders) it has been shown that the pseudodiagnosis used in this study is an acceptable alternative to identify cases (Berete et al., 2020).

4.4. Conclusions

In this study, women, older people, and people with specific preexisting health conditions were identified as specific population groups at risk. Public-health measures should consider these particular populations when establishing strategies to prevent the effects of extreme temperatures. Our study also suggests that reducing the levels of air pollution could contribute to the reduction of the short-term effects of temperatures on mortality. This is of utmost importance in the context of climate change and global warming.

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CRediT authorship contribution statement

Claire Demoury: Conceptualization, Methodology, Software, Writing - Original Draft Katrien De Troeyer: Conceptualization, Methodology, Writing - Original Draft, Writing - Review & Editing Finaba Berete: Conceptualization, Writing - Review & Editing Raf Aerts: Conceptualization, Writing - Review & Editing Bert Van Schaeybroeck: Conceptualization, Writing - Review & Editing Johan Van der Heyden: Conceptualization, Writing - Original Draft, Writing - Review & Editing Eva M. De Clercq: Conceptualization, Methodology, Writing - Review & Editing, Supervision.

Data availability

The authors do not have permission to share data.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.scitotenv.2022.158336.

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