Heat related mortality in the two largest Belgian urban areas: a time series analysis

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Abstract

Background

Summer temperatures are expected to increase and heat waves will occur more frequently, be longer, and be more intense as a result of global warming. A growing body of evidence indicates that increasing temperature and heatwaves are associated with excess mortality and therefore global heating may become a major public health threat. However, the heat-mortality relationship has been shown to be location-specific and differences could largely be explained by the most frequent temperature. So far, in Belgium there is little known regarding the heat-mortality relationship in the different urban areas.

Objectives

The objective of this study is to assess the heat-mortality relationship in the two largest urban areas in Belgium, i.e. Antwerp and Brussels for the warm seasons from 2002 until 2011 taking into account the effect of air pollution

Methods

The threshold in temperature above which mortality increases was determined using segmented regressions for both urban areas. The relationship between daily temperature and mortality above the threshold was investigated using a generalized estimated equation with Poisson distribution to finally determine the percentage of deaths attributable to the effect of heat.

Results

Although only 50km apart, the heat-mortality curves for the two urban areas are different. More specifically, an increase in mortality occurs above a maximum temperature of 25.2°C in Antwerp and 22.8°C in Brussels. We estimated that above these thresholds, there is an increase in mortality of 4.9% per 1°C in Antwerp and of 3.1% in Brussels. During the study period, 1.5% of the deaths in Antwerp and 3.5% of the deaths in Brussels can be attributed to the effect of heat. The thresholds differed considerably from the most frequent temperature, particularly in Antwerp. Adjustment for air pollution attenuated the effect of temperature on mortality and this attenuation was more pronounced when adjusting for ambient ozone.

Conclusion

Our results show a significant effect of temperature on mortality above a city-specific threshold, both in Antwerp and in Brussels. These findings are important given the ongoing global warming. Recurrent, intense and longer episodes of high temperature and expected changes in air pollutant levels will have an important impact on health in urban areas.

Key words

Funding

1. Introduction

Global warming is undeniable according to the International Panel of Climate Change (IPCC) and has a clear anthropogenic cause (IPCC et al., 2018). Over the past decades, temperature rose approximately 1°C above pre-industrial levels and this evolution is expected to continue. Whether or not global warming will remain below a 1.5°C rise by 2100 will depend on the implementation of mitigation strategies (Allen et al., 2018). Subsequently, heat waves will occur more frequent and will be longer and more intense (Meehl and Tebaldi, 2004).

Climate change will not only lead to higher temperatures, but other regional meteorological factors (e.g. precipitation) will be affected as well. This change in regional meteorology will have an impact on air pollution levels. For example, the amount of particulate matter is influenced by temperature, relative humidity, stability of air masses, boundary layer height, chemistry, precipitation and circulation (Tai et al., 2010), while ground-level ozone is additionally influenced by a photochemical reaction in the presence of sunlight (Sillman, 1999). It is important to mention that especially for the production of ozone, changes in emissions will influence the possibility to produce more or less ozone; a change in the VOC/NOx ratio will have an impact if a city/region is located in a VOC sensitive or NOx sensitive region (Seinfeld and Pandis, 2006). It is therefore expected that with climate change, air pollution levels will also change regionally, as atmospheric chemistry and the transport of pollutants will change (Fiore et al., 2015).

A growing body of evidence suggests a clear rise in mortality with temperature (Baccini et al., 2008; Gasparrini et al., 2015; Hajat and Kosatky, 2010). This happens especially during heat waves and has been described, among others, for the heat waves in Belgium in 1994 (Sartor et al., 1995), in Chicago in 1995 (Kaiser et al., 2007) and in France in 2003 (Fouillet et al., 2006). Also during less extreme weather events a rise in mortality with temperature has been observed (Baccini et al., 2008; Ballester et al., 2016). Conversely, air pollution has a clear effect on mortality (Liu et al., 2019) and it is reported that the effect of temperature on mortality is higher on days with high air pollution (Analitis et al., 2018).

Studies investigating the heat-mortality relationship generally estimate two parameters: the heat threshold, i.e. the temperature above which there is an increase in mortality, and the slope of the heat-mortality relation above this threshold. Differences in both parameters have been observed between different countries and even within countries (Almeida et al., 2010; Baccini et al., 2008; Díaz et al., 2015; Leone et al., 2013). The differences in the thresholds have been reported as correlated with different local temperature statistics, such as the 75th percentile (Guo et al., 2014). Recently, Yin et al. provided evidence that the differences in thresholds between geographical areas can largely be explained by differences in the most frequent temperature (Yin et al., 2019). This finding corresponds to the underlying biological mechanism of heat acclimatization, i.e. people are better adapted to temperatures they are used to (Kregel, 2002). Whether or not the most frequent temperature could also be used to explain differences within countries is currently not clear.

In the recent decades, Europe was subject to a few extremely strong heat waves (Gabriel and Endlicher, 2011) including the heat wave of summer 2003 (Robine et al., 2008). Future climate projections clearly indicate prolonged and more intense heat waves for Europe upon increase of the global temperature

(Füssel et al., 2017; Guerreiro et al., 2018; Jacob et al., 2014). Heat wave changes were recently found to have the biggest impact for the European population when comparing all weather-related hazards (droughts, flooding, windstorms, wildfires) associated to climate change (Forzieri et al., 2017).

For Belgium, due to a projected increase in heat waves in Belgium (Hamdi et al., 2015; Termonia et al., 2018a) and in the Brussels Capital Region (Lauwaet et al., 2016; Termonia et al., 2018b; Verdonck et al., 2019) it is estimated that the heat stress will significantly increase by the end of the century. Martinez et al. (2018) showed one may expect the heat-attributable mortality in Antwerp to increase by a factor of 1.7 and 4.5 in the near and far future, respectively (Martinez et al., 2018). So far, there is limited knowledge about the heat-mortality relationship in the different urban areas. Moreover, Belgium is a densely populated country with the majority of its population living in urban areas (Eurostat, 2016). Due to higher absorption of heat during the day which is released at night, the nocturnal temperatures in urban environments are known to be higher as compared to their city surrounding (Arnfield, 2003; Oke et al., 2017). This is particularly detrimental to health during heat waves, as the large urban population is unable to recover from extreme daytime temperatures (Gabriel and Endlicher, 2011; Laaidi et al., 2012). In addition, Belgium has one of the highest projected increase in ozone-related mortality among all European countries (Orru et al., 2013).

The present study investigates the short-term impact of heat on mortality in the two largest and most populated urban areas in Belgium (i.e. Brussels and Antwerp). First, we assess the shape of the heat-mortality relationship and define urban area-specific thresholds in temperature above which the mortality increases. Second, we explore differences between urban-specific relations in terms of the most frequent temperature. Third, we determine the percentage change in mortality for temperature above these thresholds and the corresponding attributable number of deaths. Finally, we investigate the effect of additional adjustment for air pollution on the percentage change in mortality per 1°C increase in the temperature above the threshold.

2. Materials and methods

2.1. Study area

Antwerp and Brussels are the two largest urban agglomerations in Belgium and counted 0.9 and 1.4 million inhabitants in 2011, respectively (Belgian statistical office). With a population density of 2 437 and 5 348 citizens/km², Antwerp and Brussels are also the most densely populated urban areas in Belgium (Belgian statistical office). The urban agglomeration of Brussels under study consists of 33 municipalities (i.e. towns) whose population density ranges from 480 to 24 354 inhabitants/km². The agglomeration of Antwerp contains 12 municipalities with a population density ranging between 618 and 3 198 inhabitants/km². Antwerp is located in the northern and Brussels in the central part of the country. Both cities are approximately 50 km apart. Antwerp is located at the banks of the Scheldt river at 10 m above sea level and the distance to the North Sea is approximately 60 km. Brussels is located on the central loam plateau of Belgium at 20–130 m above sea level and is approximately 80 km away from the North Sea.

Daily temperatures were estimated using the urban climate model UrbClim (De Ridder et al., 2015). Based on the combination of large-scale meteorological information from the European Centre for Medium-Range Weather Forecasts (ECMWF) ERA-Interim reanalysis (Dee et al., 2011) and a land surface scheme containing urban physics, this model simulates the urban temperature at fine scale (100 m). The model has been validated for several cities in Belgium, including Antwerp and Brussels (Lauwaet et al., 2016, 2015). Further methodological details on the model are described elsewhere (De Ridder et al., 2015). Daily maximum, minimum and mean temperatures were provided at municipality level for the warm seasons (May until September) from 2002 until 2011 for Brussels and Antwerp, the two urban areas under study.

In a sensitivity analysis, we used daily maximum temperatures estimated by the regional climate model ALARO-SURFEX (Berckmans et al., 2019, 2017; Hamdi et al., 2014). Also this model is used to downscale ECMWF ERA-Interim reanalysis (Dee et al., 2011) and includes ALARO model version 0 and the Météo-France SURFace EXternalisée land surface model (SURFEX) version 5 (Berckmans et al., 2017; Masson et al., 2013). Data were available for May until September for the years 2002 until 2010 and at a horizontal spatial resolution of 1 km x 1 km.

A population-density weighted average of all daily temperature variables was calculated to obtain daily temperature for each urban area. To capture the delayed effect of temperature on mortality, we introduced temperature indicators (maximum, minimum and mean) by calculating the average of the daily temperatures of the current day and the 3 days prior to the mortality count (lag 0-3 days).

2.3. Mortality outcome

We obtained mortality register data from the Belgian statistical office. Mortality was identified through the WHO International Classification of Diseases Tenth Revision codes (ICD-10) (World Health Organization, 2004), based on the selection of the primary underlying cause of death recorded on the death certificate. Daily natural cause mortality data (ICD 10 codes A00-R99) were available for each urban area by 5-year age groups, for the warm seasons from 2002 until 2011. The total number of natural deaths was 27 489 for Antwerp and 45 563 for Brussels for the entire study period. We generated time-series of temperature and mortality by linking the daily temperature and mortality data by their exact date. *Statistical analysis*

2.3.1.Heat-mortality relationship

Daily mortality was modelled using a generalized estimated equation with Poisson distribution assuming independence between warm seasons and a first-order autocorrelation structure within the seasons (Liang and Zeger, 1986). The model was adjusted for the following covariates: age (5-year age groups), holiday (binary variable), day of the week and month to take into account that mortality rates could be higher during weekends and public holidays (Bell and Redelmeier, 2001; Wilches-gutiérrez et al., 2012; Wunsch et al., 2004). The relative humidity derived from the UrbClim model was included in the model

because relative humidity affects the apparent (perceived) temperature (Almeida et al., 2010). The year variable was introduced as linear and quadratic terms to control for the yearly time trend.

First, in order to describe the heat-mortality relationship, the temperature indicators (using a lag 0-3 days, see 2.2) were included in the model using natural cubic splines (with 5 knots). Subsequently, the thresholds of temperature below or above which the mortality decreases/increases was determined using the approach proposed by Muggeo (Muggeo, 2003). In short, the method allows the estimation of regression models with piecewise linear relationships and the corresponding break points (i.e. thresholds). Given a threshold T, the model for the daily number of deaths N_i can be written as:

$$N_i \sim Poisson(\theta_i)$$

$$\log(\theta_i) = \alpha + covariates + \beta_l(T_i - T) \times I_{T_i \leq T} + \beta_u(T_i - T) \times I_{T_i > T}$$

T_i is the temperature indicator on day i; $I_{T_i \leq T}$ is an indicator variable equal to 1 if $T_i \leq T$ and 0 otherwise and $I_{T_i > T}$ is an indicator variable equal to 1 if $T_i > T$ and 0 otherwise; β_l and β_u are the linear coefficients expressing on a log scale the effect of 1 degree increase, respectively under (i.e. cold effect) and above (i.e. heat effect) the threshold.

Since this algorithm might converge to a local rather than a global break point (Armstrong, 2006), we used three different starting points to test the robustness of the estimated thresholds. All analyses were performed using R software (version 3.4.0)(R core team, 2019) using the packages segmented, mgvc and geepack.

2.3.2. Attributable deaths

The total number of attributable deaths (AD) for the whole period was calculated as the sum of daily AD. The following formula was used:

$$AD = \sum_i (N_i \times AF_i)$$

where N_i is the number of deaths on day i and AF_i is the corresponding fraction of deaths attributable to the temperature above the threshold for the day i, calculated as follows (with T and β_u obtained from the final model)(Levin, 1953):

$$AF_i = 1 - \exp(-\beta_u (T_i - T) I_{T_i > T})$$

2.3.3. Sensitivity analyses

To assess the impact of air pollution, we included three air pollutants (lag 0-3 days) in the model: particulate matter PM_{10}, nitrogen dioxide NO_2 and ozone O_3. Models were also constructed by including each pollutant one by one. Daily pollution data were obtained from the Belgian Interregional Environment Agency (IRCEL-CELINE) and were estimated with the RIO-IFDM model (Lefebvre et al., 2013). The hypothesized Directed Acyclic Graph (DAG) used as basis for this analysis can be found in supplementary material (figure S1).

In addition, the main analysis was repeated using the daily maximum temperature estimated by ALARO-SURFEX model.

3. Results

3.1. Descriptive statistics

Our study period included 1 530 days. During this time period, 73 052 deaths were recorded in the study area, of which 27 489 lived in Antwerp and 45 563 in Brussels. The maximum temperature was slightly lower in Antwerp than in Brussels (table 1): the median of the daily maximum temperatures over the study period was 20.8°C in Antwerp, while in Brussels it was 21.5°C. Slightly lower minimum and mean temperatures were also observed in Antwerp compared to Brussels (table S1, supplementary materials). The most frequent temperature for both urban areas was 19.5°C.

Table 1: Summary statistics for the daily maximum temperature (in Celsius degrees) derived from the UrbClim model in Antwerp and Brussels, 2002-2011

	Antwerp	**Brussels**
	maximum	
Minimum	8.8°C	9.2°C
Lower quartile	18.2°C	18.7°C
Median	20.8°C	21.5°C
Upper quartile	23.7°C	24.6°C
Maximum	35.4°C	36.7°C
Mode	19.5°C	19.5°C

3.2. Heat-mortality relationship

The relationship between the mortality and the daily maximum temperature for the period 2002-2011 followed different patterns in Antwerp and Brussels (figure 1). For Antwerp, the curve showed almost no relation with temperature until a certain point beyond which mortality increased with temperature. For Brussels, the curve showed a decrease until a certain point, followed by an increase with temperature. The smoothed relationships between mortality and the mean and minimum temperature estimates were similar to the one of maximum temperature (figures S2 and S3, supplementary materials).

Figure 1: Natural cubic splines (and 95% confidence bands) describing the relationship between maximum temperature (lag 0-3) and mortality in Antwerp and Brussels, 2002-2011.
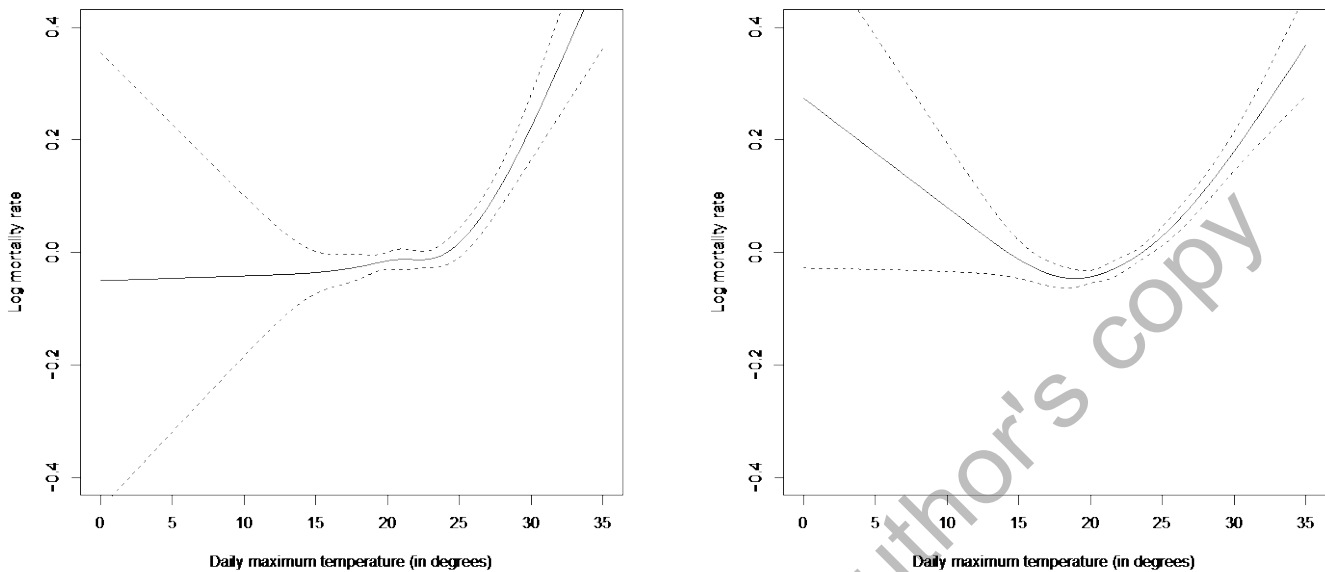

Figure 1a Antwerp   Figure 1b Brussels

For Antwerp, we found an increase in mortality of 4.9% per 1°C when the maximum temperature rose above the threshold of 25.2°C (table 2). During the study period, the maximum temperature exceeded the threshold on 13% (N=201) of the days. In Brussels, the estimated threshold was found to be at 22.8°C. The maximum temperature exceeded the latter on 37% (N= 557) of the days and the corresponding increase in mortality per 1°C increase was 3.1%. The thresholds were robust to the different starting points specified in the Muggeo algorithm. The thresholds for Antwerp and Brussels were different from the most frequent temperature (table 1).

For the mean and the minimum temperature, the estimated thresholds were higher for Antwerp (23.2°C and 18.3°C, respectively) compared to Brussels (19.2°C and 15.2°C respectively) (table S2 in supplementary material). The percentage increase in mortality was as well higher in Antwerp (12.4% and 14.8%, respectively) compared to Brussels (3.5% for both mean and minimum temperature).

Table 2: Heat-mortality relationships for the daily maximum temperatures derived from the UrbClim model in Antwerp and Brussels, 2002-2011

Antwerp (N=27 489)	Brussels (N=45 563)
maximum	maximum
T in °C (95% CI)	
25.2	22.8
(23.9 - 26.6)	(21.8 - 23.9)
Observed number of days above T	
201	557
% increase in mortality (95% CI)	
4.9 (2.5 - 7.3)	3.1 (2.5 - 3.7)
Number of attributable deaths	
411	1 585

N: number of deaths during the study period; T: threshold; The % increase in mortality is expressed as the change in mortality per 1°C increase in temperature when the temperature exceeds T

During the study period, 411 deaths (1.5% of the total number of deaths recorded over the study period) in Antwerp and 1 585 deaths in Brussels (3.5%) can be attributed to a daily maximum temperature exceeding the threshold. The number of deaths attributable to a daily mean and daily minimum temperature above the threshold were 230 and 216 in Antwerp, 1 558 and 1 398 in Brussels respectively (table S2 in supplementary material).

3.3. Sensitivity analysis

The sensitivity analyses, adjusting for PM_{10}, NO_2 and O_3 (lag 0-3 days), resulted in a lower percentage change in mortality per 1°C increase in temperature in both urban areas. For Antwerp, the latter became not significant. When adding the air pollutants one by one in the models, adjustment for ozone turned out to lead to the most pronounced reduction in percentage change in mortality per 1°C increase in temperature (table S3, supplementary materials).

Repeating the main analysis but now with the daily maximum temperature estimated by the ALARO-SURFEX model (summary statistics in table S4, supplementary materials) resulted in similar results for the heat-mortality relationship (figure S4, supplementary materials). As compared to the main analyses, changes were observed with regard to the threshold in Antwerp (27.4°C as compared to 25.2°C in the main analysis) but not for Brussels (22.8°C in both analyses). Slight changes in the percentage change in mortality per 1°C increase in temperature above the threshold were found (6.1% as compared to 4.9% in the main analysis for Antwerp and 2.7% compared to 3.1% in the main analysis) (table S5, supplementary materials).

4. Discussion

The present study investigated the short-term impact of heat on mortality in the two largest and most populated urban areas in Belgium. Our results showed a significant effect of temperature on mortality above an urban area-specific threshold, both in Antwerp and in Brussels. In Antwerp, this threshold was found to be at 25.2°C whereas in Brussels at 22.8°C for daily maximum temperatures. We estimated that per 1°C increase in the temperature above these thresholds, the mortality increases with 4.9% in Antwerp and with 3.1% in Brussels. During our study period, we estimated that 1.5% of the deaths in Antwerp and 3.5% of the deaths in Brussels could be attributed to the effect of heat.

The observed heat-mortality relationship is in line with previous studies where a U-shaped or J-shaped heat-mortality relationship was obtained (Baccini et al., 2008; Leone et al., 2013). In addition, the threshold and slope of the relationship for Antwerp are in line with a recent study in Antwerp(Martinez et al., 2018) that reported a 2.8% (0.8%- 4.9%) increase in mortality per 1°C increase when the maximum temperature exceeded the threshold of 26°C.

Our study has several strengths. It has a long follow-up time and both cities consisted of a large population. Heat-mortality relations are known to vary with time (Michelozzi *et al., 2006*) and the study period here considered (years 2002-2011) was longer and started earlier than the one of Martinez et al (2018a) (years 2009-2013). Likewise, we expanded our study area to Antwerp and (12) surrounding municipalities. As a result, our results are complementary to those described by Martinez et al. In

addition, we were able to investigate the temperature-mortality in Brussels for the first time. This also enabled us to examine in detail the differences in the relationship between heat and mortality in two similar and nearby urban areas.

Although we used the same methodology, study period and data sources for Brussels and Antwerp, the heat-mortality relationships differed between the two cities. We found a markedly lower threshold and a less steep heat-mortality relationship above the threshold in Brussels. Additionally, when using a different model to estimate the maximum temperature indicator (ALARO-SURFEX), results were comparable. Differences in the heat-mortality relation between different cities in the same country have been described previously (Almeida et al., 2013; Díaz et al., 2015; Michelozzi et al., 2006) as well as a positive relation between the heat slope and the heat threshold (Hajat and Kosatky, 2010). Some studies suggested that differences in socio-economic characteristics, Gross Domestic Product (GDP), population density, population size and age distribution (Díaz et al., 2015; Hajat and Kosatky, 2010; Michelozzi et al., 2006) could potentially explain these differences. In Belgium, differences in GDP, socio-economic characteristics and population density between the two urban areas exist (Belgian statistical office) and could as such be possible explanations. Further analyses stratified by vulnerability could potentially confirm this hypothesis. In addition, our temperature estimates were averaged for the entire urban area. Consequently, within-city differences in temperature were smoothed out and, although well represented by the models, the effect of a locally enhanced urban heat island effect might have been averaged out. Differences in thermal comfort between the two urban areas are also plausible. The proximity of the Scheldt estuary (15km) and the North Sea (60km) in the urban area of Antwerp could create a more temperate climate in terms of thermal comfort. The mortality rate for lower temperatures (below the threshold) being almost constant in Antwerp, can suggest that people in Antwerp are more adapted to a wide range of temperatures, which might just as well fit the hypothesis of a more temperate climate. This interpretation should however be done with caution since the mortality rates for low temperature show large uncertainties. The difference between the threshold and the most frequent temperature during the study period, which is larger for Antwerp, can indicate that other meteorological factors contributing to thermal comfort (e.g. wind speed, solar radiation) could play a role in heat acclimatization. Further analyses including more meteorological data could be informative while noting that the choice of the best meteorological variables to be included is important (Heo et al., 2019) and can differ between cities (Zhang et al., 2014). At the moment it is not clear which meteorological variables are important when assessing the heat-mortality relationship and the optimal indicator can differ between cities (Barnett et al., 2010; Zhang et al., 2014). Since the heat index used can significantly change the investigated heat-mortality relationship, it is important to further investigate the effect of inclusion of additional meteorological variables. Some of them, including wind and solar radiation, have a physiological effect on body temperature and can contribute to heat stress (Steadman, 1984).

As temperature indicator, we used the daily maximum temperature for comparison with similar research (Baccini et al., 2008; Martinez et al., 2018). .The maximum temperature was the more sensitive indicator in Antwerp: it classified more days as "hot days" i.e. days, on which excess mortality may occur. The minimum temperature was the most specific one here. In Brussels, on the contrary, the maximum

temperature was the most specific indicator and the minimum temperature the most sensitive. Therefore, the different indicators could be informative in the framework of public health policies.

We used a lag of zero to three days before mortality count to capture the delayed effect of temperature on mortality, as usually reported in the literature (Almeida et al., 2013; Baccini et al., 2008; Martinez et al., 2018, 2016) and to allow comparisons with similar studies (Baccini et al., 2008). When the analysis focuses more on the delayed mortality effect, more sophisticated methods that flexibly describe simultaneously non-linear and delayed effects can be used (Armstrong, 2006; Gasparrini et al., 2010).

To describe the relationship between temperature and mortality, general smooth curves are useful. Nevertheless a simpler quantitative summary such as the temperature threshold above which the temperature increases is also useful, in particular if relationships are to be compared across areas or population subgroups (Armstrong, 2006). In our study, we used the algorithm of Muggeo (Muggeo, 2003) to estimate these thresholds since this simple model is attractive for interpretability. Sensitivity analyses showed robustness of the estimated thresholds.

The need for adjustment for air pollutants is debatable and depends on underlying assumptions about the heat-mortality relationship (Buckley et al., 2014). We included several air pollutants in our models for comparability purposes with other studies. We hypothesize that air pollutants are an intermediate factor in the relation between heat exposure and mortality, but not a confounder. As such, we proposed a model without adjustment for air pollutants since it can best reflect the total effect of temperature on mortality (direct effect and through changes in air pollutant levels). Adjustment for air pollutants reduced the effect of heat on mortality as it has been reported in other similar studies (Martinez et al., 2016). In the models adjusted for air pollutants one by one, the attenuation was most pronounced after adjustment for ozone. In Belgium, with climate change, the projected ozone-related mortality is expected to increase in the future (Orru et al., 2013).

In addition to the above mentioned limitations, we used an ecological design, which entails a risk of ecological fallacy. Health effects of heat observed at individual level may not be observed at aggregated (city) level. More specifically, different groups may have different background risks or different groups may have unequal risk differences. For heat, elderly (Bouchama et al., 2007), socioeconomically deprived persons (Bernhard et al., 2015) and people with pre-existing chronic conditions (Bouchama et al., 2007) belong to vulnerable subpopulations in which such background risks, risk differences or both tend to be higher than in the general population. Translation of the results to an individual level should consequently be taken with caution. Furthermore, we assumed independence between different seasons and did not take into account a possible harvesting effect.

Conclusion

Our results showed a significant effect of temperature on mortality above an urban area-specific threshold, both in Antwerp and in Brussels. The heat-mortality relation differed considerably between the two urban areas and the thresholds differed from the most frequent temperature, particularly in Antwerp. Adjustment for air pollution attenuated the effect and this attenuation was more pronounced

for ozone-adjusted models. These results are important given the ongoing climate emergency and related global warming. Recurrent episodes of high temperature and changes in air pollutant levels will have an important health impact in urban areas.

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Author contributions

Conceptualisation: DP, CD, RA, AVN; Methodology: DP, CD; Software: MB; Formal analysis: KDT, MB; Resources, Data curation: MB, JB; AD, RH, BVS, HH, DL; Writing-original draft: KDT; Supervision: CD, AVN. All authors critically revised and approved the final version of the manuscript.

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