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Exploring age and gender sensitivity to high-temperature days: impacts on respiratory, cardiovascular, and all-cause mortality in summer in Flanders

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Abstract

Background With global warming escalating and extreme weather events rising in frequency, the impact of temperature on human health, particularly mortality, has become a critical public health concern. Responses to heat exposure exhibit considerable variability among individuals, influenced by factors such as age and gender. Acknowledging and addressing these differences among population groups is essential for the effective planning of prevention measures. In this context, the present study investigates the age and gender sensitivity to heat in the region of Flanders.

Methods This study employs the distributed lag non-linear model (DLNM) to quantify the non-linear relationship between minimum and average daily temperatures and all-cause mortality, as well as cause-specific cardiovascular and respiratory mortality in Flanders over the period 2000-2019. We focus on the summer period from May 15 to September 30 to assess the impact of extreme temperatures in low-mortality months. While many studies have shown that there is an increasing impact of temperature on mortality, we explore whether the impact of heat is different across different age- and gender groups by incorporating an interaction term between the exposure–lag–response structure and the age–gender categories.

Results Our findings show a noteworthy increase in overall mortality at elevated mean daily temperatures, with a slightly higher relative risk for females compared to males. The elderly, particularly those aged 85 and above, face the longest-lasting effects of heat, followed by the 65-84 age group. The youngest age group experiences the shortest duration of the impact. While the risk of mortality by cardiovascular disease decreases sharply after a heat day, the risk of mortality by respiratory disease remains elevated for several days following the heat exposure.

Conclusion The effect modification by age and gender revealed differences in heat-related mortality across age-gender groups in Flanders, highlighting the importance of considering such interactions to accurately characterize these relationships and inform targeted prevention measures.

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Keywords Heat, Mortality, Distributed lag non-linear models, Effect modification, Age and gender differences

Text box 1. Contributions to the literature

- This study contributes to the understanding of age- and gender-specific responses to heat exposures in Flanders, Belgium.
- Applies a DLNM framework to evaluate lagged exposure effects, incorporating effect modification by age and gender.
- Reveals high heat vulnerability among women and the elderly, and that individuals under 65 years old exposed to excessive heat are at an increased risk of respiratory mortality.
- Highlights the importance of considering population subgroups in studies on heat effects to inform and optimize group-target heat prevention strategies.

Introduction

According to the Intergovernmental Panel on Climate Change (IPCC) Sixth Assessment Report [1] and the most recent 2025 Lancet Countdown on Health and Climate Change report [2], the frequency, duration, and intensity of high temperatures and heat extremes have increased markedly over the past decades. These trends pose substantial public health challenges as prolonged exposure to elevated temperatures is a well-established driver of heat-related illness and mortality.

Numerous global studies [3–5] have highlighted heat and heat waves as pressing global health concerns. Exposure to high temperatures is known to affect mortality patterns worldwide, with studies demonstrating this relationship in a wide range of countries [6–8]. Evidence from Belgium similarly reinforces this association. Using time series analysis, [9] showed that elevated temperatures significantly affect mortality in Belgium's two largest urban centers, Antwerp and Brussels. [10] further confirmed a heightened heat-related mortality risk across nine urban agglomerations in Belgium based on short-term exposure to extreme temperatures. More recently, [11] reported consistent findings in the Flanders region, demonstrating the substantial health impact of extreme heat using General Practitioner surveillance data.

While the association between heat and increased mortality is generally reported, the nuances of these patterns have been observed to vary across subgroups, such as sex and age [11–18]. Moreover, despite the recommendation to adopt standardized metrics to improve comparability across studies assessing heat stress [19–21], findings remain consistent in showing that elevated temperatures can exacerbate pre-existing conditions, amplifying the risk of mortality associated with cardiovascular and respiratory diseases [4, 11, 16, 17, 22].

The documented differences in heat-related risk across specific population subgroups underscore the importance of explicitly considering these subgroups to identify vulnerable groups and support the development of targeted preventive interventions to reduce the mortality burden of extreme temperatures. To promote this awareness among researchers and policymakers, systematic reviews and meta-analyses such as [5, 23, 24], and most recently [3, 25, 26] have provided epidemiological evidence of these associations.

It is well-established that the effects of exposure to environmental stressors, such as extreme temperature, are time-delayed [3, 27–30]. In this sense, studies of the exposure-response relationship, involving these types of stressors, have sought to incorporate the time structure of the effect to capture the sequence of outcomes that occur over a period following the exposure event. A widely accepted methodology to deal with this is the distributed lag model (DLM), which quantifies the overall effect of the exposure with possible delayed effects, though it assumes a linear relationship between exposure and health outcome. In contrast, the distributed lag non-linear model (DLNM, [31]) relaxes the linear assumption by introducing flexible modeling techniques that allow for a more accurate representation of non-linear relationships.

Our study focuses on investigating the effect of temperature on overall and cause-specific mortality in Flanders during the period 2000-2019, with specific emphasis on the summer period from May 15 to September 30. In particular, we wish to understand how the risk of death varies by age and gender, aiming to identify potential temperature thresholds associated with an upsurge in deaths within these distinct demographic groups. Daily temperature and daily counts of deaths were available at the municipality level, which also serves as a model unit, leading to a more accurate representation of the local temperature-mortality relationship. To capture both the temporal dynamics and age-gender-specific variations in temperature-related mortality, we applied a DLNM with an interaction term. Unlike traditional stratified analyses, the effects are estimated within the same model, thereby leveraging information from the entire dataset and avoiding potential loss of statistical power.

So far, little research has examined heat-related mortality specifically in the Flanders region. While [18, 32] rely on the same data, they address different primary research questions. [11] presents a comprehensive analysis of the health impacts of extreme heat; however, their study applies a different design and focuses on a subset of the Flanders population based on general practitioner records, distinguishing it from our broader analysis. By analyzing data from the entire region at the municipality level over a long time frame, assessing effect modification, our research contributes to a deeper understanding of the health effects of rising temperatures on distinct population groups in the whole region of Flanders, providing essential insights for targeted public health interventions.

Methods

Flanders, the northern region of Belgium, is the focal point of our study on the impact of temperature on mortality. Flanders encompasses 300 municipalities covering a total area of 13,626 km^2, with a diverse population distribution and exhibiting an aging population trend. In 2020, the region counted 6,629,143 inhabitants, of whom 20% aged 65 years and older. Within this age group, women represented 55% and men 45%. Flanders experiences a temperate maritime climate characterized by mild temperatures, relatively high humidity, and moderate seasonal variations. Summers in Flanders are marked by occasional heat waves, where temperatures can rise significantly.

The mortality data used in this study include daily records of deaths between 2000 and 2019 in each Flemish municipality, categorized by age, gender, and cause of death. Age groups were classified into four categories: 0–64 years old; 65–74 years old; 75–84 years old, and 85 years old and over. In addition to the information on mortality from all causes, we have information on mortality from specific causes such as respiratory diseases and cardiovascular diseases. This data was provided by the Department of Care of the Flemish Government.

To characterize the available mortality data, Fig. 1 shows the distributions of the number of deaths over the period in the study and by age and gender groups. The temporal evolution in the number of deaths across the study period is presented in panel (a). Cardiovascular mortality exhibits a clear decreasing trend over the years, with curves following similar patterns. Respiratory mortality also shows a decreasing trend, although it is less pronounced, and recent years display occasional peaks. In contrast, all-cause mortality shows an increasing trend in recent years, with individual curves exhibiting more variable patterns. The trends in the proportion of deaths attributed to specific causes over the years are presented in panel (b). The plot highlights the significance of cardiovascular and respiratory mortality as the main causes of death in Flanders. Respiratory mortality accounts for an average 10% of all-cause mortality. Although the proportion of cardiovascular mortality has decreased over time, it still constitutes an average of 30% of the all-cause mortality, representing a relatively high proportion. The map in panel (c) shows the average yearly mortality rate per 1000 inhabitants for each municipality over the twenty-year study period. In the map, a distinct spatial gradient in mortality is observed, increasing from west to east, with a concentration of higher mortality in the northeastern part of the study area. Nevertheless, according to Statistics Flanders (Statistiek Vlaanderen), this region is characterized by an older population structure. Panels (d) and (e) show the total number of deaths by age group and gender for all causes, as well as specific causes, cardiovascular and respiratory diseases. These plots show a clear increase in mortality across age groups and similar patterns for males and females, although cardiovascular mortality appears somewhat more common in males as compared to females. Population numbers in the different age and gender groups per municipality and year were provided by Statistics Belgium.

Along with the information on daily mortality, the data set also includes information on daily temperature for each municipality. The daily minimum and mean temperature data at the municipality level were calculated from model simulations with the urban climate model UrbClim [33], in the framework of a project commissioned by the Flemish Environmental Agency. The UrbClim model was applied to simulate hourly temperatures for all warm periods (April-September) of the years 2000-2019 with a horizontal resolution of 100m. These simulations were driven by ERA5 reanalysis data and used a detailed local land use map [34] as input to downscale the ERA5 air temperatures. The model results have been validated against 12 measurement stations across Flanders, yielding excellent error statistics. Daily minimum and mean temperature data at the municipality level were obtained by spatially (area weighted) averaging the 100 m hourly model results for each municipal unit, and thereafter calculating the daily minimum and mean values. The maps in panels (a) and (b) of Fig. 2 present the spatial distribution of the average daily minimum and mean temperatures across the municipalities over the study period. Average daily minimum temperatures show minimal spatial variability among municipalities, predominantly remaining below 14 °C, except for the municipality of Antwerp. The map of average daily mean temperatures reveals a spatial gradient, with municipalities in the central region and northeast exhibiting higher values, in contrast to the lower values observed in other municipalities.

The DLNM framework [31, 35] was developed to flexibly model associations between an outcome and an exposure where the effect persists after the exposure period. These types of dependencies are defined by [35] as *exposure-lag-response* associations. The idea underpinning the DLNM methodology is the definition of bi-dimensional smooth functions s_j to define the *exposure-lag-response* association. This is achieved using a tensor product to combine the basis functions independently chosen, to represent the nonlinear *exposure-response* curve and the *lag-response* curve. This structure integrated over the lag dimension introduces the concept of *cross-basis* and allows to model simultaneously the exposure-response over the exposure dimension and the lag-response curve

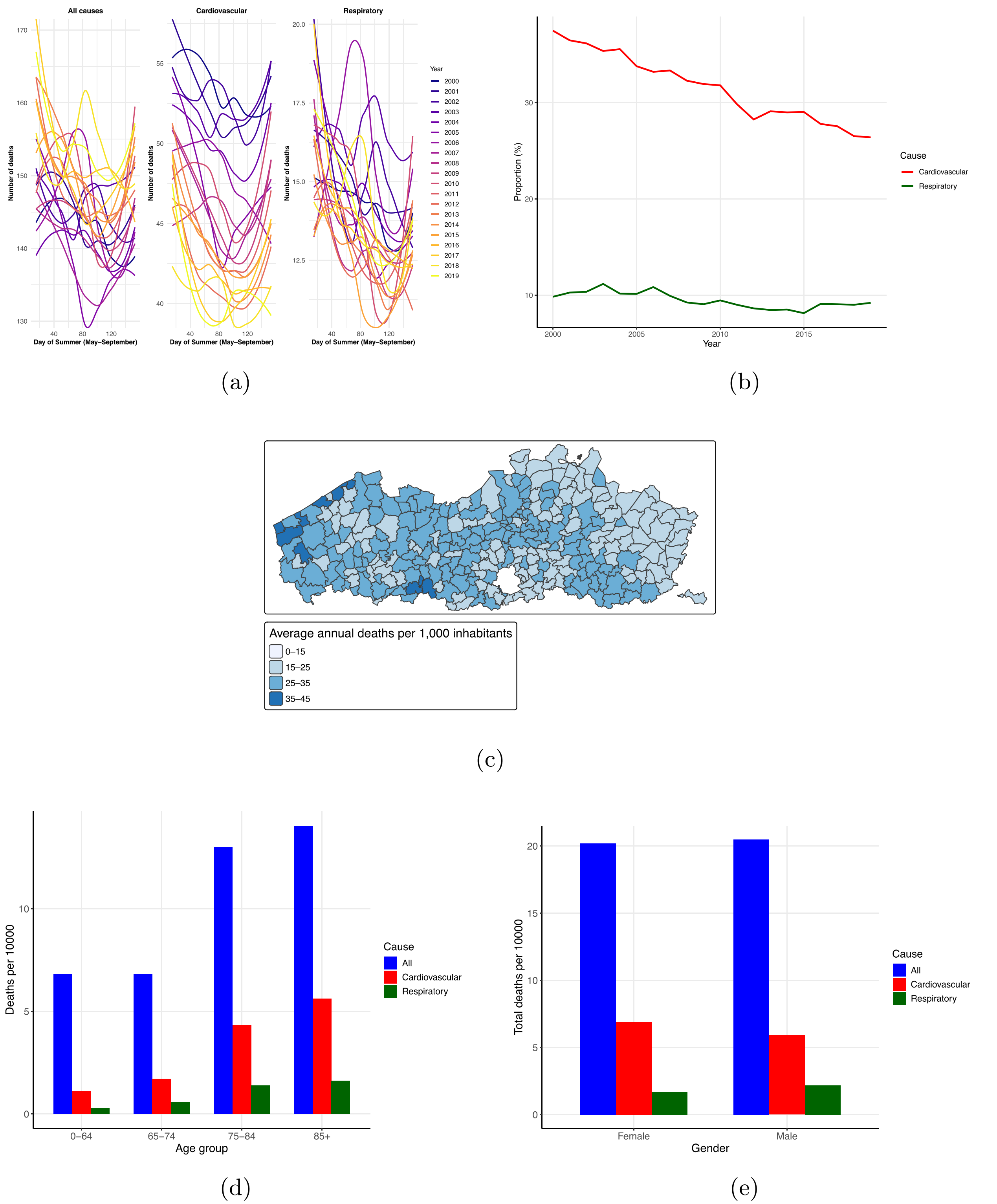
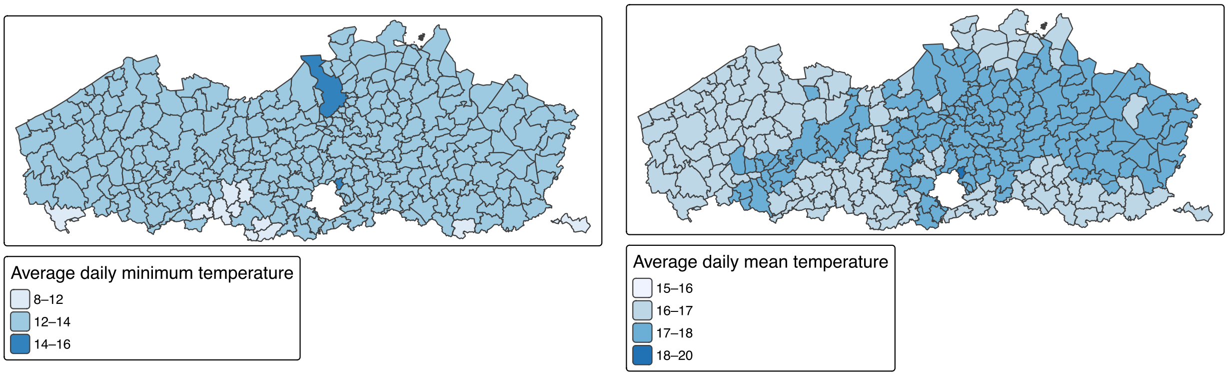


Fig. 1 Distribution of the number of deaths: **a** Smoothed trends in the daily number of deaths across years; **b** Proportion of specific causes of death over the years; **c** Distribution of cumulative deaths across Flanders over 2000–2019; **d** Distribution of deaths by age group; **e** Distribution of deaths by gender



(a) (b)

Fig. 2 Average daily temperatures per municipality (2000–2019): **a** Average daily minimum temperature; **b** Average daily mean temperature

along the lag domain, resulting in a *exposure-lag-response* surface. For more details on the DLNM methodology refer to [31, 35].

Our study focuses on age- and gender-specific associations between temperature and mortality. Both temperature and mortality are measured on a daily basis in each municipality. The time series Y_{tig} represents the number of deaths per day $t = 1, \ldots, 2780$, municipality $i = 1, \ldots, 300$, and age-gender group $g = 1, \ldots, 8$. Each group corresponds to the following combinations: Male - 0 to 64; Female - 0 to 64; Male - 65 to 74; Female - 65 to 74; Male - 75 to 84; Female - 75 to 84; Male - 85 and over; Female - 85 and over. We assume a Poisson regression

$$Y_{itg} \sim Poisson(\mu_{itg} N_{itg}),$$

with N_{itg} the population size and the expected mortality rate μ_{itg} modeled using two components: the baseline component, measuring how mortality depends on several key baseline factors, and the temperature component, measuring how temperature might impact the mortality on a particular day and the days after it:

$$log(\mu_{itg}) = \eta_{itg}^{baseline} + \eta_{itg}^{temperature} \quad (1)$$

The baseline component contains several control variables and is defined as:

$$\begin{aligned}\eta_{itg}^{baseline} =& \alpha + s(\text{year}_t, 2) + s(\text{month}_t, 3) + \sum_{k=1}^{6} \beta_{1_k} I(\text{dayofweek}_t = k) \\ &+ \beta_2 \text{winterrate}_t + \sum_{k=1}^{3} \beta_{3_k} I(\text{age}_g = k) + \beta_4 \text{gender}_g \\ &+ \sum_{k=1}^{3} \beta_{5_k} \text{gender}_g * I(\text{age}_g = k)\end{aligned} \quad (2)$$

This component includes the following variables:

- *year* and *month* modeled using natural cubic splines to describe long-time trends and seasonality;
- indicator variable for the day of the week (*dayofweek*);
- linear term for the mortality rate (*winterrate*) in the preceding winter period (January 1-April 30) in the municipality to account for the influence that the winter months may have on the expected number of deaths during the summer.
- *age* as main effect - four different age groups: 0–64 years old; 65–74 years old; 75–84 years old and 85 years old and above.
- *gender* as main effect - female and male.
- the interaction of *age* and *gender*

The temperature component measures the direct temperature-mortality relationship and is modeled as

$$\eta_{itg}^{temperature} = \sum_{k=1}^{4} \gamma_{1_k} \text{w}_{t,l}^{T} I(\text{age}_g = k) + \gamma_2 \text{w}_{t,l}^{T} I(\text{gender}_g) \quad (3)$$

In this equation, the term $\text{w}_{t,l}^{T}$ represents the matrix obtained by applying the tensor product to the temperature and the lag structure. We use a flexible model with natural cubic splines to describe the relationship in each dimension. The knots describing the temperature relationship are placed at equally spaced values in the temperature range to allow enough flexibility in the tails. The knots describing the relationship of lags are placed at equal intervals on the logarithmic scale of lags to allow more flexibility in the first part of the distributed lag curve, where more variability is expected. We conducted a sensitivity analysis, comparing models using two and three knots (Appendix 3). Since the estimates were largely consistent, we selected the specification with two knots to reduce model complexity. Although heat-related effects on mortality are typically short-lived and many influential studies adopt maximum lag periods of up to 10 days, we opted for a 14-day lag window to capture potential delayed responses, assess short-term mortality displacement, and avoid artificial truncation of the lag structure. This choice was further supported empirically, as the model with a 14-day lag yielded a lower AIC compared to shorter lag specifications (Appendix 3).

Note that to account for age and gender specific heat mortality effects, different age- and gender-specific heat-mortality trends are assumed. Indeed, age has been identified as a factor influencing heat-related mortality in [5, 16, 36]. Recent studies such as [16, 37–39] show a high vulnerability to heat among females.

To explore whether the temperature-mortality relationships are indeed different for different age- and gender-groups, we compare the above model with simpler models in which it is assumed that there is a common temperature-mortality relationship among all age-groups, among all gender-groups, and specific age-groups. Models are compared using AIC (Akaike Information Criterion). The AIC scores from the model-building approach are presented in Appendix 2.

There is an ongoing debate about the optimal temperature measure for assessing the association of temperature with mortality. While a high daily mean temperature typically corresponds to both a high day and night temperature, a high minimum temperature indicates a lack of cooling time over the night, which may impact mortality. Consequently, based on the assumption that mean and minimum temperatures may best represent the heat in assessing its impact on mortality, the model described in (1) was performed twice, with each temperature metric serving as the exposure variable in turn. The two models serve to complement each other in providing insights into the heat-mortality relationship.

Statistical analyses were conducted using R version 4.4.0, R Core Team, Vienna, Austria. The threshold for statistical significance was set at $\alpha = 0.05$.

Results

Baseline variables

Figure 3 shows the risk associated with each baseline variable across different mortality causes. The raw data for the figure is provided in Appendix 1. The winter mortality rate has a small but significant positive effect on summer mortality. Day-of-week shows mild variation, with Friday showing the highest risk. Compared with males aged 85+, mortality is lower in younger age groups and increases with age for both sexes. Females generally exhibit a lower mortality risk than males, however this gender difference becomes less pronounced in the oldest age group.

Time effects are also evident, as shown in Fig. 4. Over the years, the number of deaths from all causes has fallen considerably (an overall reduction of around 30% from 2000 to 2019). The risk of all-cause death is lowest in the

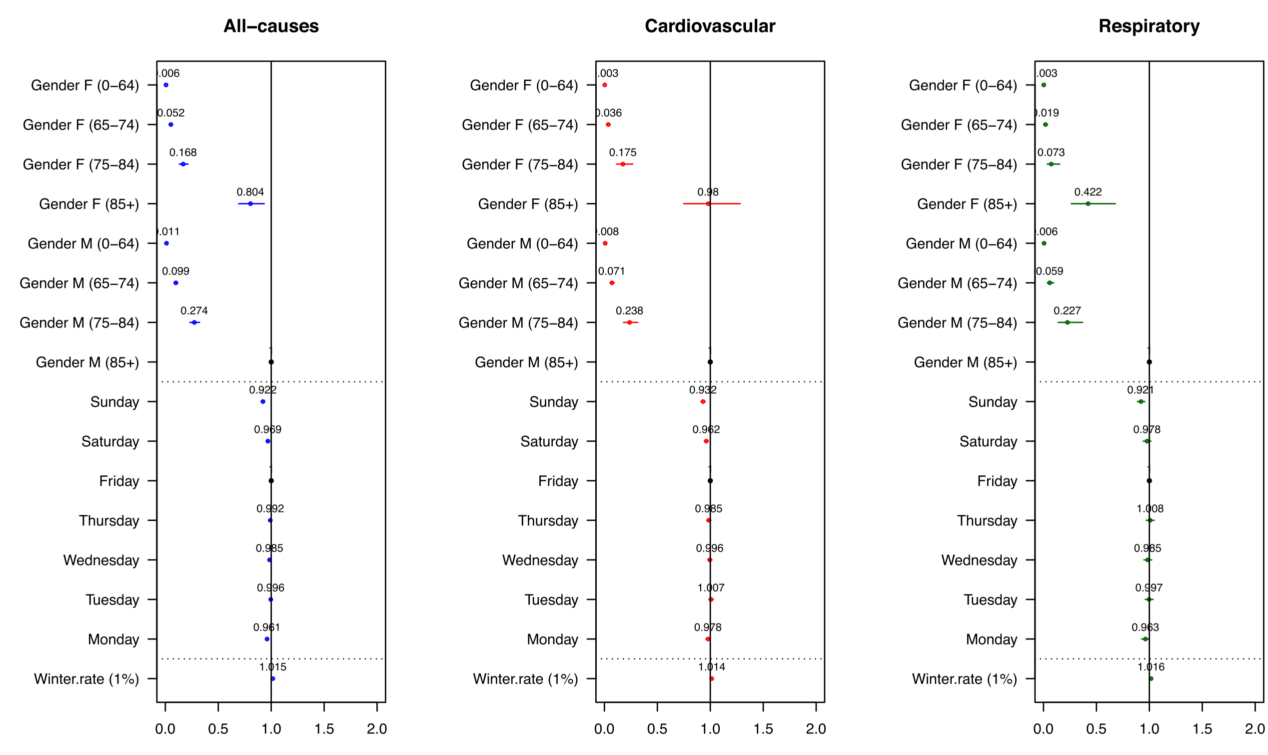


Fig. 3 Relative risk of death associated with the baseline variables, with 95% CI (horizontal bars) - Results related to the daily mean temperature

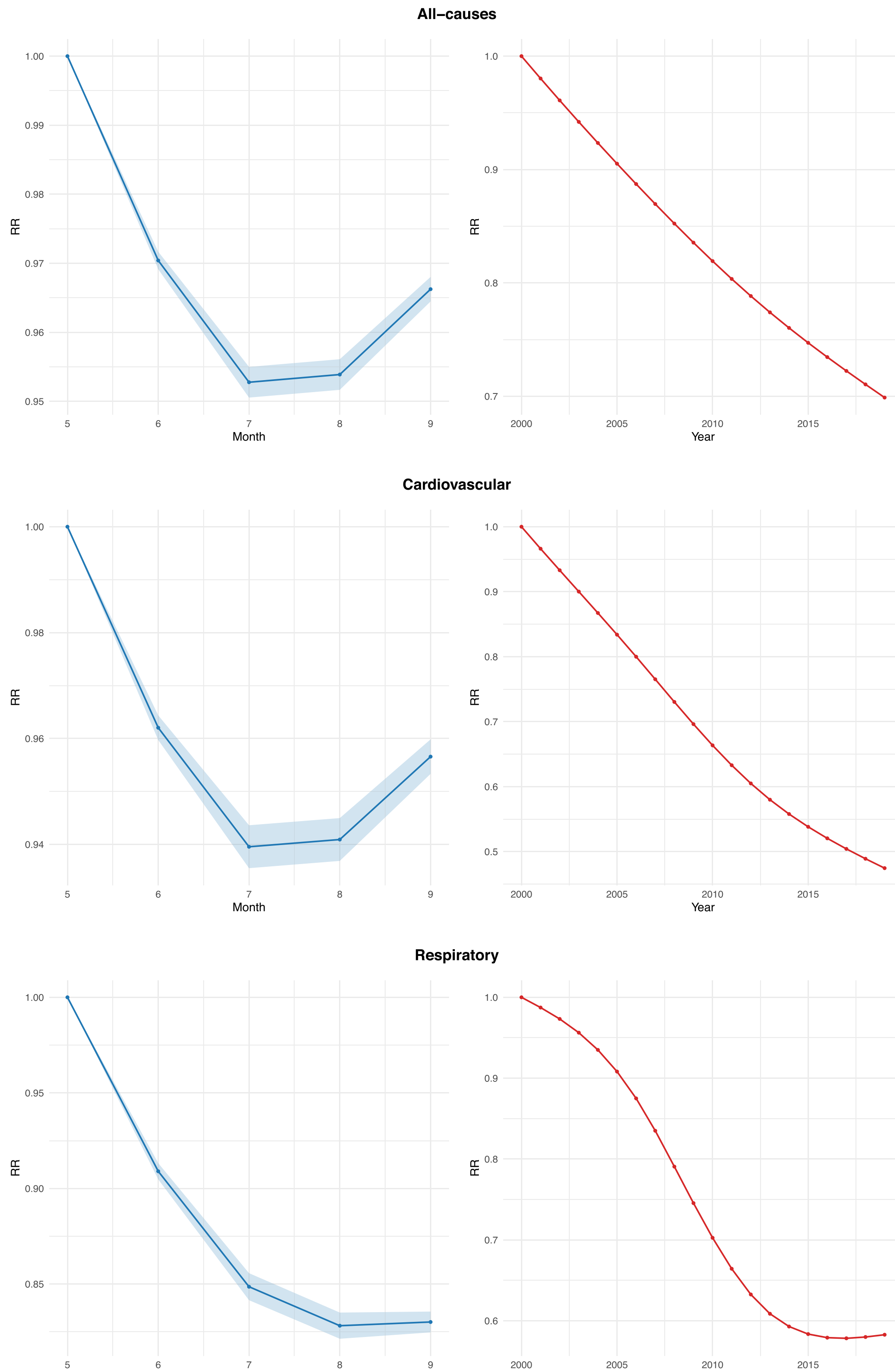


Fig. 4 Effect of the year and the month on the mortality

summer months (5% lower risk in July and August as compared to May), and slightly fewer deaths are observed at weekends (about 9%) lower on Sundays as compared to Fridays. These trends align closely with those observed for the risk of death due to cardiovascular disease. However, respiratory deaths exhibit a distinct pattern, with a sharp decline between 2005 and 2017, followed by a slight increase. Furthermore, the risk of dying from respiratory diseases is lowest in August and September. Even though the mortality is generally lower in July and August, the mortality might spike on days after extreme temperatures in this period.

Temperature-mortality relationship

We first examined the age- and sex-specific associations between temperature and mortality by running the model (1), which includes 4 age groups in the temperature component, corresponding to the same age categories in the baseline. Since the mortality risk trends were the same for those aged 65 to 74 and 74 to 85, it was decided to combine both categories into one (65 to 84) to reduce the complexity of the model. The AIC was then used to evaluate whether this simplification effectively preserves the goodness of fit. For the AIC scores, refer to Appendix 2. Figure 5 summarizes the cumulative effect of daily mean temperature over lag 0 to 14 days, relative to a daily mean temperature of 18 °C, for the six age-gender groups used in the final model. The reference temperature of 18 °C corresponds to the temperature of minimal mortality derived from the overall cumulative association. Details are provided in Appendix 4. The blue curve represents the effect on all-cause mortality, the red curve represents the effect on mortality due to cardiovascular diseases and the green curve represents the effect on respiratory diseases. Regardless of the cause of death, elevated daily mean temperatures exhibit a strong increase in mortality among those aged 65 and above, with somewhat higher relative risks in females compared to males. The impact is stronger in individuals aged 85 and above, followed by the 65–84 age group.

A similar analysis can be seen in Fig. 6, which shows the cumulative effect of minimum temperature relative to a minimum temperature of 14°C. The same approach employed for the selection of the daily mean temperature reference was applied for the selection of the minimum reference temperature (Appendix 4). The risk of death in the older age groups markedly increased when the minimum temperature exceeds 20 degrees, and the increase is more pronounced for mortality related to respiratory diseases.

To delve into the impact of extremely warm days, Table 1 illustrates the variation of the risk of mortality associated with high values of daily mean temperatures as compared to a day with a daily mean temperature of 18°C. Notably, among females aged 85 and over, a day with an average temperature of 28 °C is associated with two to four times the risk of respiratory mortality compared with 18°C. This elevated risk is also evident among 65–84-year-old females, for whom the risk of respiratory-related mortality associated with exposure to high temperatures, relative to 18 °C, is comparable in magnitude to that observed in the older age group. In contrast, this pattern does not emerge for other causes of death under similar thermal conditions.

Examining the impact of a hot night Table 2 shows the relative risk for a set of values of high minimum temperatures compared to a reference temperature of 14°C. The effect of a minimum temperature of 22 °C is strongest among females, with the risk of dying from respiratory disease doubling for females aged 65 and over.

Lagged effects

As mentioned earlier, mortality exhibits observable patterns in the days following exposure to high temperatures. Considering the typical summer temperature range in Flanders, a daily mean temperature of 28 °C and a minimum temperature of 22 °C might indicate an extremely hot day. Figures 7 and 8 illustrate the delayed effects on mortality. These effects correspond to the risk of exposure to the chosen values of mean and minimum temperatures respectively, at different lag times.

Considering the prolonged effects due to high daily mean temperatures reaching up to 28 °C, the oldest age group consistently shows a larger increase in deaths from all causes and cardiovascular-related mortality. This effect is noticeable both on the day of extreme heat and in the week following.

Regardless of age group, all-cause mortality among females is higher than among males at the onset of temperature exposure. The effect of heat is most prolonged for individuals aged 85 and over, followed by those aged 65 to 84, particularly among women, for whom the effects are even more extended. A delayed effect of up to 8 days is observed for a high daily mean temperature for males and up to 12 days for women. An effect of extreme heat on all-cause mortality in the 0–64 age group is also observed but only with an immediate effect of heat on the day of heat and the following day.

While it has been established that women have a higher risk of all-cause mortality compared to men, this finding does not hold when examining cardiovascular-specific mortality. In fact, during the first day of exposure, men exhibit a higher risk of death from cardiovascular causes, but this risk decreases sharply relative to that of women over the next two days.

Unlike the pattern seen in all-cause and cardiovascular mortality, the youngest group (0–64 years old) shows a higher risk of mortality due to respiratory complications

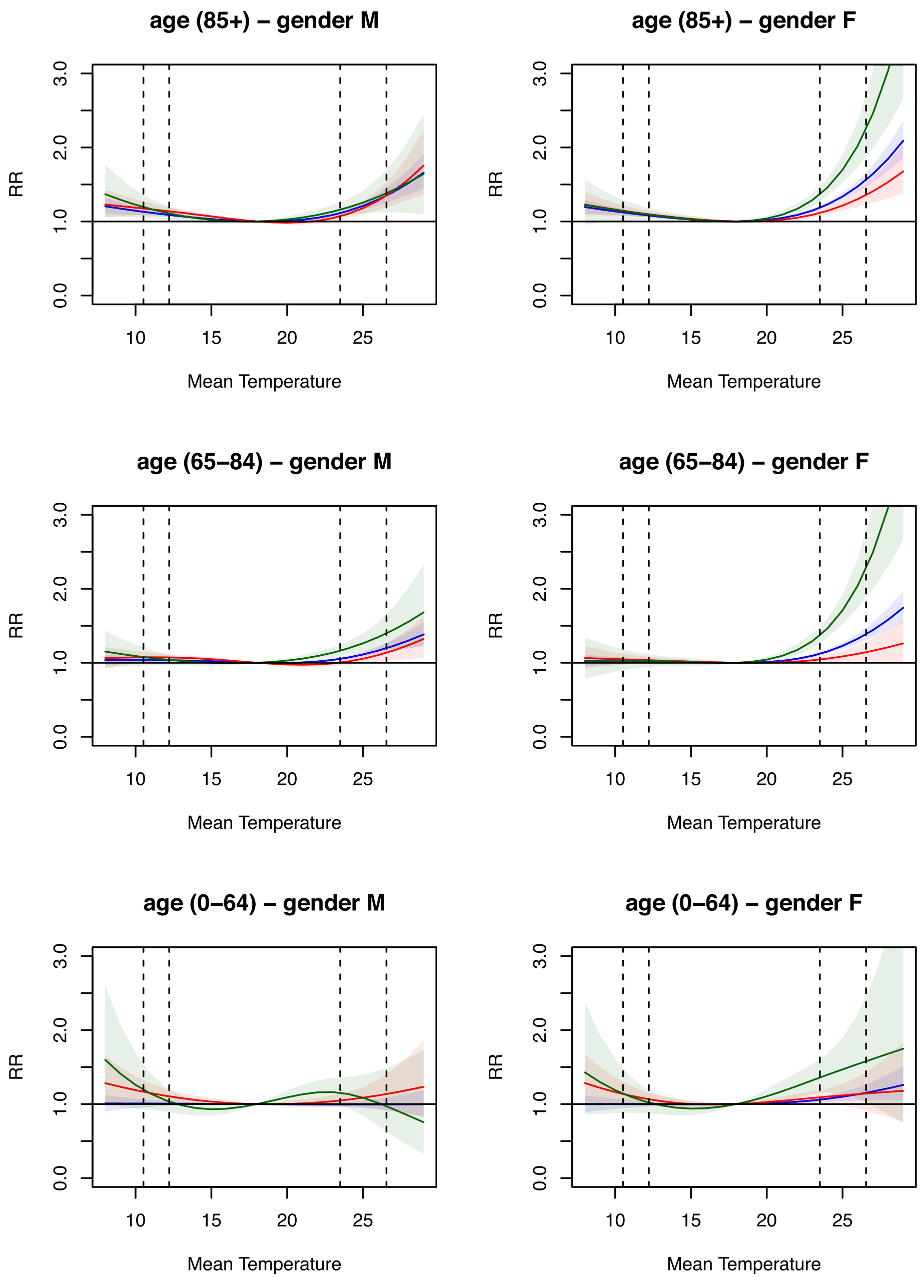


Fig. 5 Cumulative effect of daily mean temperature. Blue: All-causes mortality; Red: Mortality related to cardiovascular diseases; Green: Mortality related to respiratory diseases. The dashed vertical lines represent the 1%, 5%, 95%, and 99% daily mean temperature percentiles. Shaded areas around the curves represent 95% confidence intervals

on the day of exposure to a high daily mean temperature and the elevated risk compared to the older groups remains for two days. Additionally, the risk is higher in the female group - after exposure to extreme daily mean temperatures, the risk persists over 12 days among the oldest individuals in this group, whereas in the male group, it lasts for 6 days.

When evaluating the effect of the extremely warm nights in Fig. 8, we observe patterns that closely mirror those seen in the outputs regarding the high daily mean temperature, irrespective of the mortality cause. Although the effects of a high minimum temperature are similar in form to those related to a high daily mean temperature, maintaining consistent trends across the lagged period, a notable difference is the upward shift of the relative risk on the day of exposure. Moreover, the delayed effect of an extremely warm night is slightly shorter for all-cause mortality across all groups and for respiratory-related causes among the youngest females.

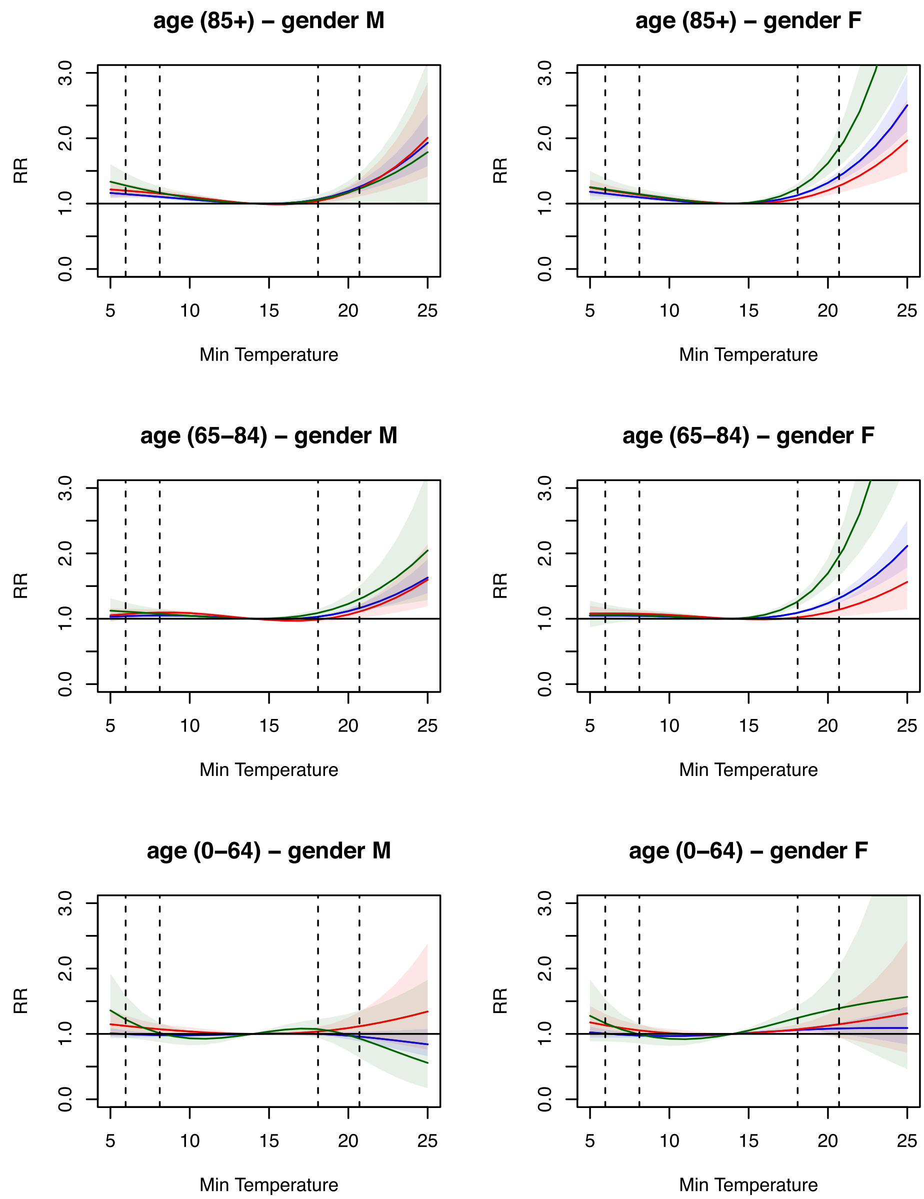


Fig. 6 Cumulative effect of minimum temperature. Red: All-causes mortality; Blue: Mortality related to cardiovascular diseases; Green: Mortality related to respiratory diseases. The dashed vertical lines represent the 1%, 5%, 95% and 99% minimum temperature percentiles. Shaded areas around the curves represent 95% confidence intervals

Discussion

In this study, we investigated the effect of heat stratified by age and gender on all-cause mortality and the specific causes of mortality due to respiratory and cardiovascular diseases in Flanders. Although the mortality and temperature data are available at the municipality level, we did not implement the widely used geographically varying DLNM because most municipalities are relatively small and report low daily mortality counts, which would hinder reliable second-stage meta-regression or produce meaningful pooled estimates. Therefore, the estimation was performed for the entire Flanders region, using municipality-specific time series while assuming a common temperature–mortality association across all municipalities. This approach allows us to capture local spatial variability in exposure and risk, while estimating one single model across all municipality avoids instability arising from sparse case counts in individual municipalities.

Overall, the results show that people in the older age groups are at greater risk of mortality associated with high temperatures. Beyond this well-established

Table 1 Variation of the cumulative risk associated with high values of daily mean temperatures as compared to a day with a daily mean temperature of 18

		85+ Male			85+ Female			65–84 Male			65–84 Female		
	Temp	**RR**	**95% IC**		**RR**	**95% IC**		**RR**	**95% IC**		**RR**	**95% IC**	
All-causes	25	1.21	1.16	1.26	1.34	1.29	1.39	1.11	1.08	1.15	1.23	1.18	1.27
	26	1.30	1.22	1.38	1.47	1.40	1.55	1.16	1.11	1.22	1.32	1.26	1.39
	27	1.40	1.29	1.52	1.64	1.53	1.76	1.23	1.15	1.31	1.44	1.34	1.55
	28	1.52	1.36	1.70	1.85	1.68	2.03	1.30	1.19	1.42	1.58	1.44	1.74
	29	1.66	1.44	1.91	2.09	1.85	2.36	1.38	1.24	1.55	1.74	1.55	1.97
Cardivascular	25	1.18	1.10	1.27	1.21	1.14	1.29	1.05	0.99	1.12	1.09	1.02	1.16
	26	1.28	1.15	1.42	1.30	1.20	1.42	1.10	1.01	1.21	1.12	1.02	1.23
	27	1.41	1.22	1.63	1.41	1.25	1.58	1.16	1.03	1.32	1.16	1.02	1.32
	28	1.57	1.29	1.90	1.53	1.31	1.79	1.24	1.05	1.46	1.21	1.02	1.44
	29	1.75	1.37	2.24	1.68	1.38	2.04	1.32	1.07	1.63	1.26	1.01	1.57
Respiratory	25	1.25	1.11	1.42	1.70	1.52	1.89	1.26	1.14	1.39	1.71	1.52	1.92
	26	1.33	1.12	1.58	2.02	1.74	2.36	1.35	1.17	1.55	2.04	1.74	2.40
	27	1.42	1.12	1.80	2.46	1.99	3.04	1.44	1.19	1.75	2.49	1.99	3.11
	28	1.53	1.11	2.09	3.04	2.29	4.02	1.55	1.20	2.01	3.09	2.30	4.16
	29	1.64	1.10	2.45	3.80	2.65	5.44	1.68	1.21	2.33	3.89	2.66	5.68

pattern, our findings indicate that the strongest temperature–mortality responses are linked to minimum (nighttime) temperatures. This finding is consistent with those observed in Flanders [11], Switzerland [40], and in global multi-country analyses [41], all of which report pronounced associations with daily minimum temperatures. A study conducted in London [42], similarly reported that elevated night-time temperatures substantially increase mortality risk, even after adjusting for daytime exposure. Taken together, these findings reinforce the growing evidence that nighttime heat is a crucial driver of the overall mortality burden associated with high temperatures. Furthermore, our results reveal the longest-lasting effect in individuals aged 85 and above. Although heat-related lag effects are typically short, they are slightly prolonged among older populations [43–46]. This is an important observation as the elderly are the most vulnerable to heat events. Variations across studies may arise from methodological differences, including the choice of heat indicators, reference thresholds, and modeling frameworks.

The increased longevity observed in women may partly explain why women generally experience worse health outcomes when exposed to high temperatures. Therefore, to ensure more accurate comparisons, it is recommended to investigate the gender differences in temperature-related mortality while accounting for age adjustments [37]. Our findings after adjusting for age indicate that females generally exhibit a slightly higher relative risk than males at high mean and minimum temperatures, remaining consistent with existing evidence [38, 39].

Regarding the effects of extreme temperatures on specific causes of mortality, our results indicate a larger effect of high temperatures on mortality from respiratory causes than on mortality from cardiovascular complications. Additionally, the gender-specific effects are more pronounced in females, indicating a heightened susceptibility in this group. Although these findings point in the same direction as previous research [28, 47–50], they depend to some extent on the number and placement of knots used in the model specification. Therefore, for future analyses, we do recommend using a larger number of knots and the addition of a penalization on the spline to remove possible sensitivity to the knot choice. The work of [51] makes such an approach computationally more efficient.

Looking at the lag structure, the risk of mortality by cardiovascular disease decreases sharply after a heat day. In contrast, the risk of mortality by respiratory disease remains high for some days after the heat day. Curiously, in the first two days after exposure to extreme heat, we observed people under 64 years old at higher risk of death by respiratory disease. This could be related to

Table 2 Variation of the cumulative risk associated with high values of minimum temperatures as compared to a day with a minimum temperature of 14

	Temp	85+ Male			85+ Female			65–84 Male			65–84 Female		
		RR	95% IC		RR	95% IC		RR	95% IC		RR	95% IC	
All-causes	21	1.29	1.20	1.38	1.47	1.38	1.56	1.19	1.12	1.25	1.35	1.27	1.43
	22	1.41	1.27	1.55	1.65	1.52	1.80	1.27	1.18	1.37	1.49	1.37	1.62
	23	1.55	1.36	1.77	1.88	1.69	2.10	1.37	1.24	1.52	1.66	1.49	1.86
Cardivascular	21	1.27	1.12	1.44	1.30	1.18	1.44	1.13	1.02	1.25	1.16	1.04	1.29
	22	1.40	1.18	1.67	1.43	1.25	1.63	1.22	1.05	1.40	1.24	1.06	1.44
	23	1.57	1.25	1.97	1.58	1.32	1.89	1.32	1.09	1.60	1.33	1.09	1.62
Respiratory	21	1.25	1.02	1.54	1.95	1.63	2.33	1.33	1.13	1.57	2.07	1.72	2.50
	22	1.36	1.02	1.80	2.41	1.88	3.09	1.47	1.17	1.84	2.61	2.01	3.37
	23	1.48	1.02	2.15	3.04	2.18	4.22	1.63	1.21	2.20	3.34	2.38	4.70

variations in heat tolerance and adaptation mechanisms among age groups. Whether due to a warm day with a high average temperature or a hot night, the effect is more prolonged in women than in men, irrespective of the cause of mortality. The observed differences in coping with high temperatures between the two groups may be attributed to the hormonal differences between males and females, underscoring the importance of sex-specific research.

While this research provides valuable insights, it has some limitations. We assessed the impact of heat based on the daily average temperature and the minimum temperature. The choice of these metrics was empirical, as we believe that the daily average temperature (Tmean) captures the range of values experienced throughout the day. The effect on the body of a high-temperature peak felt at a certain time of day can easily be mitigated by low temperatures that may occur on the same day (cooling effect). Therefore, a high daily average temperature corresponds to periods of high temperature throughout the day without the possibility of effective cooling. The minimum temperature was used as a proxy for the hot nights measure. The optimal metric to be used when modeling heat-related mortality was discussed in [19]. Although the authors have concluded that there is no generic exposure metric to assess the relationship between heat and mortality, they suggested using apparent temperature (AT) to model heat-related mortality in the warm season in Northern and Eastern Europe. We could not extend our study to investigate heat-related mortality using apparent temperature as the heat stress metric since our data did not include information on relative humidity or wind speed to calculate this indicator. Another aspect worthy of consideration is that the "younger" age group consists of individuals aged 0 to 64 years, representing a relatively broad range. Consequently, the relative risk associated with this group may be influenced by the youngest portion of the population, limiting direct comparisons between the elderly (age groups 65 and older) and the subgroups derived from the disaggregation of the younger age category. While such comparisons could reveal potential associations relevant to the younger groups, the present study focused primarily on the older population segment, given their greater vulnerability due to age-related factors, which may call for distinct heat protection measures. Additionally, the study lacks socioeconomic factors such as housing conditions, access to cooling facilities, and societal position, which might influence the vulnerability of individuals to heat, with an impact on the results. These variables can be explored in further analysis if data is made available.

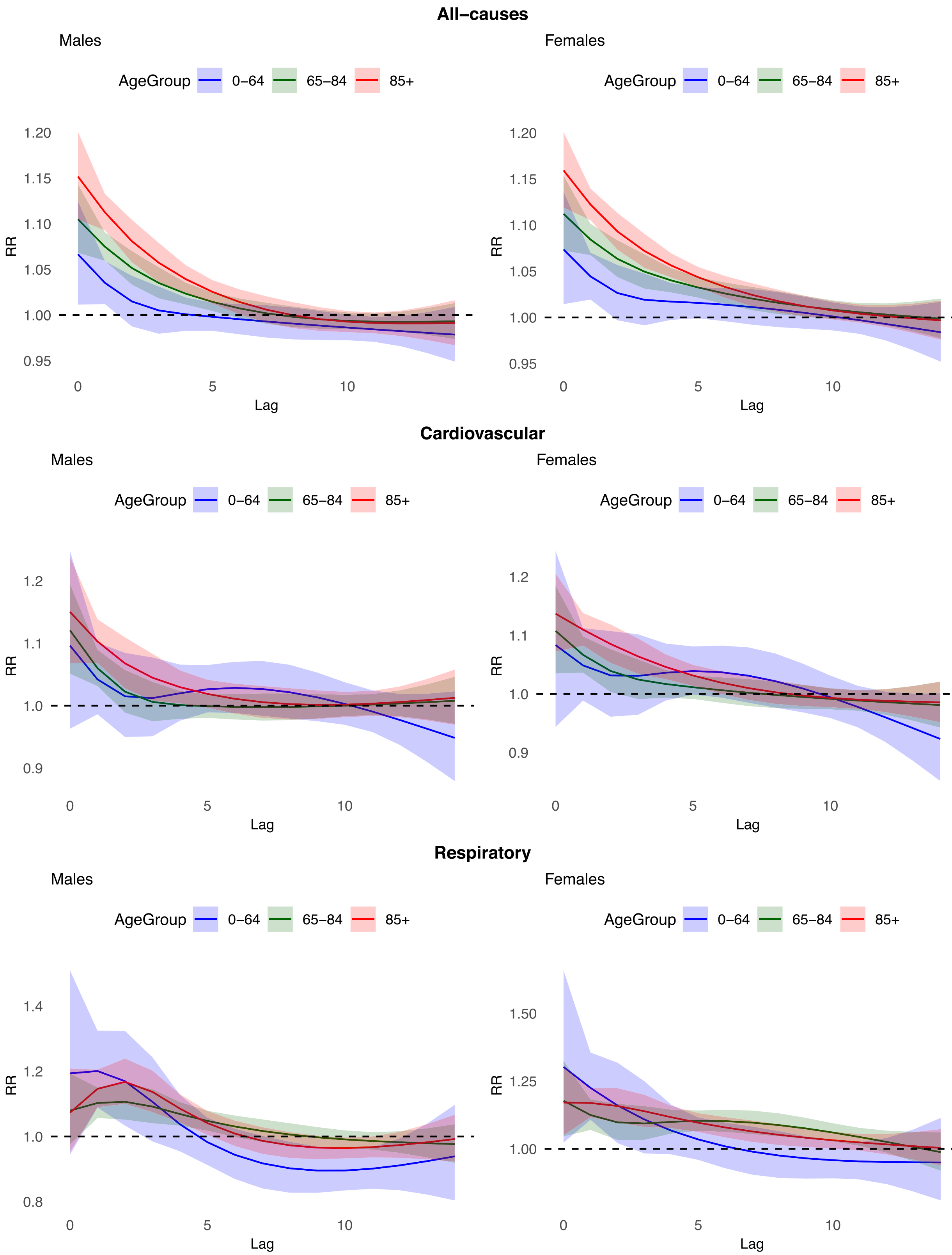


Fig. 7 Risk of mortality associated with exposure to daily mean temperatures of 28 °C, relative to 18 °C, over a 14-day lag period, with 95% CI

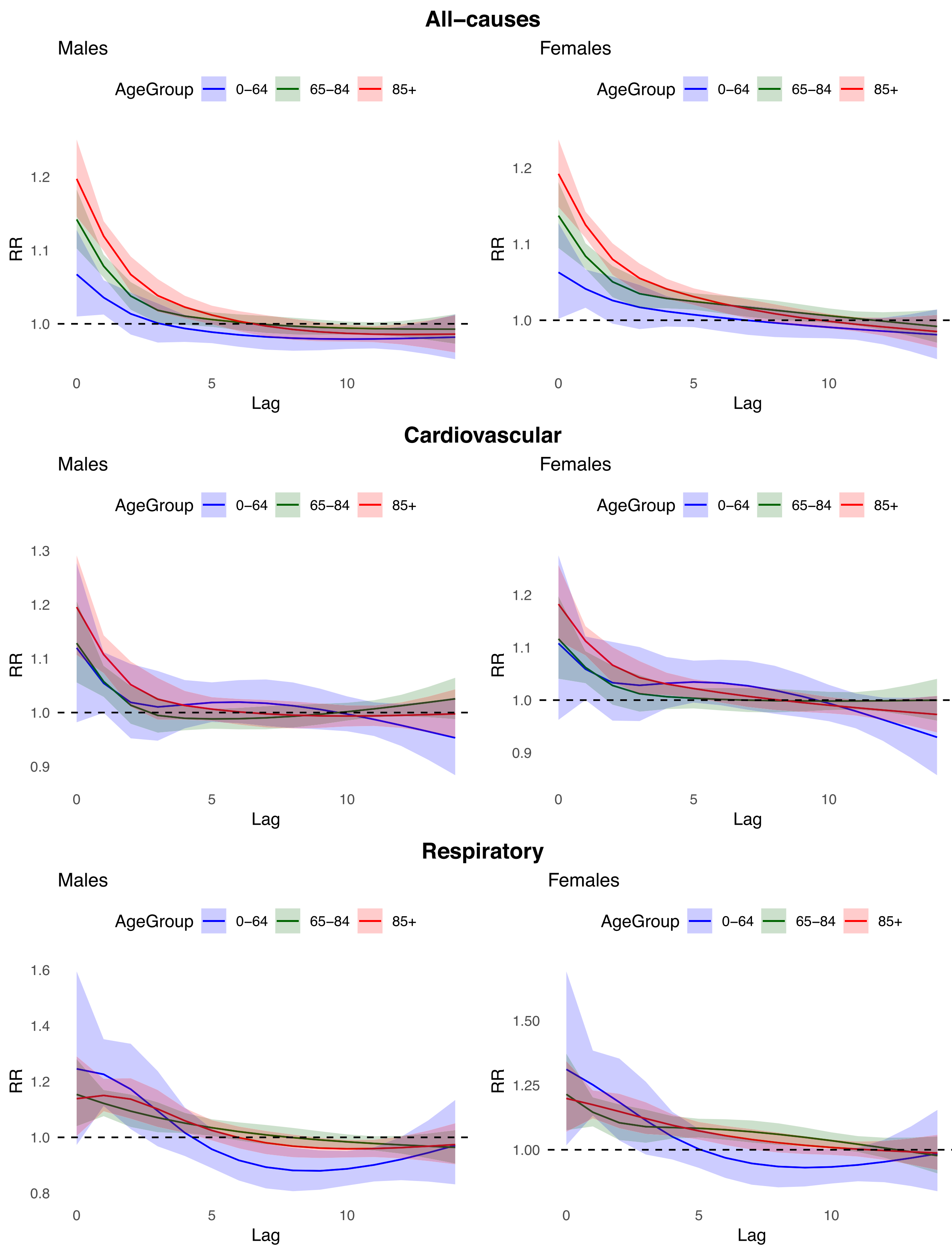


Fig. 8 Risk of mortality associated with exposure to minimum temperatures of 22 °C, relative to 14 °C, over a 14-day lag period, with 95% CI

High values of the maximum temperature on a day may indicate an extremely hot day if no period of minimum temperatures allows it to cool down. Therefore, it would be interesting to understand the combined effect of the minimum and maximum temperatures and their delayed effect on mortality. While additional models exploring this joint effect could be included in the analysis, they were not covered in the current study [32]. Our primary goal was to understand the basic temperature-lag-mortality relationship across the age and gender groups, before addressing the complexities inherent to the inclusion of multiple exposure-response terms, whether additively or through interactions. We recognize the importance of this approach and recommend that it be considered in future research to further understand the effect of the interaction of these two temperature metrics on mortality.

Conclusion

In this study, we investigated the modified effect of heat by age and gender on all-cause mortality and the specific causes of mortality due to respiratory and cardiovascular diseases in Flanders. To our knowledge, this is the first study assessing temperature-related mortality for the whole of Flanders, leveraging municipality-level daily data across a long time frame. By applying a DLNM with interaction terms, we captured both temporal dynamics and age- and gender-specific variations within a single model, allowing for a more precise characterization of local temperature-mortality relationships while preserving statistical power. The results show that subgroup-specific differences in heat-mortality associations within the Flemish population may serve as a valuable framework for informing and enhancing preventive measures against the adverse effects of heat in this region.

Appendix A

1 Risk Estimates for Baseline Variables

Table 3 Risk estimates represent the relative risk (RR) of all-cause mortality associated with each baseline variable. The reference categories are Friday for the day of the week and Males aged 85 and over for the age-gender. For the winter rate, RR represents a 1% increase

Baseline Variable	RR	95% CI
Winter rate (1%)	1.014	(1.013, 1.017)
Monday	0.961	(0.950, 0.972)
Tuesday	0.996	(0.985, 1.007)
Wednesday	0.985	(0.974, 0.996)
Thursday	0.992	(0.980, 1.003)
Saturday	0.969	(0.958, 0.980)
Sunday	0.922	(0.911, 0.933)
Males (0-64)	0.011	(0.009, 0.014)
Males (65-74)	0.099	(0.084, 0.117)
Males (75-84)	0.273	(0.232, 0.323)
Females (0-64)	0.006	(0.005, 0.009)
Females (65-74)	0.052	(0.041, 0.067)
Females (75-84)	0.168	(0.132, 0.214)
Females (85+)	0.804	(0.692, 0.934)

Table 4 Risk estimates represent the relative risk (RR) of the **cardiovascular-specific cause of mortality** associated with each baseline variable. The reference categories are Friday for the day of the week and Males aged 85 and over for the age-gender. For the winter rate, RR represents a 1% increase

Baseline Variable	RR	95% CI
Winter rate (1%)	1.014	(1.010, 1.017)
Monday	0.978	(0.959, 0.999)
Tuesday	1.007	(0.987, 1.028)
Wednesday	0.996	(0.977, 1.016)
Thursday	0.985	(0.966, 1.006)
Saturday	0.962	(0.943, 0.982)
Sunday	0.932	(0.913, 0.951)
Males (0-64)	0.008	(0.005, 0.013)
Males (65-74)	0.071	(0.054, 0.094)
Males (75-84)	0.238	(0.180, 0.314)
Females (0-64)	0.003	(0.002, 0.006)
Females (65-74)	0.036	(0.024, 0.056)
Females (75-84)	0.175	(0.114, 0.268)
Females (85+)	0.980	(0.749, 1.282)

Table 5 Risk estimates represent the relative risk (RR) of the respiratory-specific cause of mortality associated with each baseline variable. The reference categories are Friday for the day of the week and Males aged 85 and over for the age-gender. For the winter rate, RR represents a 1% increase

Baseline Variable	RR	95% CI
Winter rate (1%)	1.016	(1.009, 1.023)
Monday	0.963	(0.928, 1)
Tuesday	0.997	(0.961, 1.035)
Wednesday	0.985	(0.949, 1.022)
Thursday	1.008	(0.971, 1.045)
Saturday	0.978	(0.942, 1.015)
Sunday	0.921	(0.887, 0.957)
Males (0-64)	0.006	(0.002, 0.014)
Males (65-74)	0.059	(0.036, 0.096)
Males (75-84)	0.227	(0.139, 0.370)
Females (0-64)	0.003	(0.001, 0.008)
Females (65-74)	0.019	(0.009, 0.040)
Females (75-84)	0.073	(0.035, 0.154)
Females (85+)	0.422	(0.262, 0.679)

2 AIC results from Model Building Approach

Table 6 Model comparison overview from all-cause mortality. Baseline represents the model component defined in Eq. 2; TDLNM represents the cross-basis structure modeling the *exposure-lag-response* association. Interaction terms in the models are indicated by the colon (:)

	AIC	
Model	**Tmean**	**Tmin**
Baseline + TDLNM	2678460	2678469
Baseline + TDLNM:gender	2678425	2678435
Baseline + TDLNM:age (4groups)	2678387	2678391
Baseline + TDLNM:age (3groups)	2678378	2678378
Baseline + TDLNM:age (4groups) + TDLNM:gender	2678371	2678373
Baseline + TDLNM:age (3groups) + TDLNM:gender	2678360	2678359

Table 7 Model comparison overview from cardiovascular mortality. Baseline represents the model component defined in Eq. 2; TDLNM represents the cross-basis structure modeling the *exposure-lag-response* association. Interaction terms in the models are indicated by the colon (:)

	AIC	
Model	**Tmean**	**Tmin**
Baseline + TDLNM	1093510	1093517
Baseline + TDLNM:gender	1093508	1093526
Baseline + TDLNM:age (4groups)	1093517	1093518
Baseline + TDLNM:age (3groups)	1093508	1093512
Baseline + TDLNM:age (4groups) + TDLNM:gender	1093515	1093527
Baseline + TDLNM:age (3groups) + TDLNM:gender	1093506	1093522

Table 8 Model comparison overview from cardiovascular mortality. Baseline represents the model component defined in Eq. 2; TDLNM represents the cross-basis structure modeling the *exposure-lag-response* association. Interaction terms in the models are indicated by the colon (:)

	AIC	
Model	**Tmean**	**Tmin**
Baseline + TDLNM	419848	419866
Baseline + TDLNM:gender	419836	419854
Baseline + TDLNM:age (4groups)	419880	419893
Baseline + TDLNM:age (3groups)	419868	419880
Baseline + TDLNM:age (4groups) + TDLNM:gender	419868	419881
Baseline + TDLNM:age (3groups) + TDLNM:gender	419856	419867

3 Sensitivity Analyses on Lag and Knot Specifications

Table 9 Results of sensitivity analyses comparing 2- and 3-knot specifications for exposure and lag dimensions in the DLNM *cross-basis* (maximum lag = 14 days), for daily mean (Tmean) and minimum (Tmin) temperatures

	AIC			
	Tmean		**Tmin**	
Model	**2 knots**	**3 knots**	**2 knots**	**3 knots**
All-cause	2678360	2678352	2678359	2678373
Cardiovascular	1093470	1093492	1093463	1093498
Respiratory	419856	419867	419867	419888

Table 10 Results of sensitivity analyses comparing DLNM models with maximum lag windows of 7 vs 14 days, for daily mean (Tmean) and minimum (Tmin) temperatures

	AIC			
	Tmean		**Tmin**	
Model	**Lag 7**	**Lag 14**	**Lag 7**	**Lag 14**
All-cause	2678422	2678360	2678452	2678359
Cardiovascular	1093506	1093470	1093522	1093463
Respiratory	419874	419856	419914	419867

4 Estimation of the Minimum Mortality Temperature (MMT)

The temperature for which minimal mortality is observed was investigated using the algorithm proposed by [52]. The next plot shows the estimated temperature of minimal mortality (and corresponding confidence intervals). The blue lines correspond to the daily mean temperature, and the green lines correspond to the minimum daily temperature. These calculations were done for all gender and age groups together, as well as for the age and gender groups separately (see vertical axes). Based on these results, we selected 18 °C for the daily mean temperature and 14 °C for the daily minimum temperature as MMTs. These values were closest to the majority of model estimates and associated with the narrowest confidence intervals, representing the most consistent and reliable estimate across models. These selected values were then used in subsequent analyses.

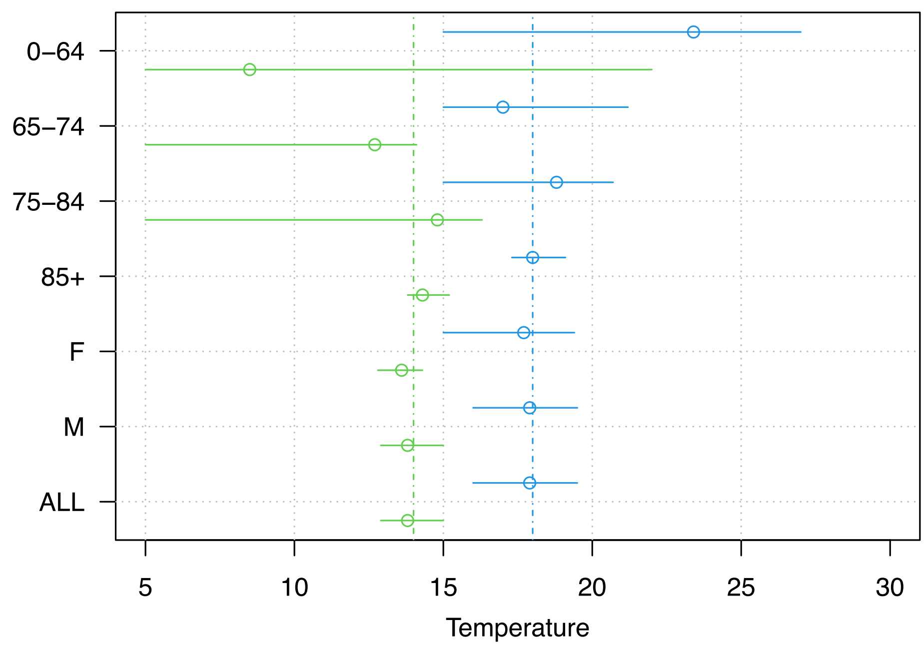


Fig. 9 Estimated minimum mortality temperatures (MMTs) for each model. Points indicate MMT estimates and the horizontal lines their 95% confidence intervals. The blue color represents the daily mean temperature, and the green color the daily minimum temperature. The MMT reference values are indicated by the coloured dashed vertical lines in the figure

Abbreviations

AIC	Akaike Information Criterion
AT	Apparent temperature
CI	Confidence interval
DLM	Distributed lag model
DLNM	Distributed lag non-linear model
ERA5	European Centre for Medium-range Weather Forecasts (ECMWF) Reanalysis version 5
RR	Relative risk
TDLNM	Cross-basis structure modeling the exposure-lag-response association
Temp	Temperature
Tmean	Daily average temperature
Tmin	Daily minimum temperature

Authors' contributions
All authors contributed to the study's conception and design. K.T, E.V, D. L. and M.R. are responsible for the Data Collection and Material preparation. The Statistical Methodology and Analysis were carried out by E.D. and C.F.. The first draft of the manuscript was written by E.D., and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Data availability
The data that support the findings of this study are not openly available due to reasons of sensitivity and are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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