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Health impacts of extreme heat in medically at-risk populations: a space-time stratified case-crossover analysis in Belgium

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Abstract

Background The impact of heat on a vulnerable population, particularly those with pre-existing chronic diseases, is a growing public health concern. However, the risks for those with specific conditions and their variation across geographic, demographic, and socioeconomic (SES) status remain underexplored. This study aimed to investigate the association of extreme heat with morbidity and mortality among individuals with pre-existing chronic diseases in Flanders, Belgium.

Methodology We analysed 14 years (2005–2019) of general practitioners (GPs) data from Flanders, northern Belgium, assessing both morbidity and mortality. Morbidity was defined as GP-recorded general and heat-related illnesses among individuals with pre-existing chronic diseases, while mortality included overall mortality and mortality among people with pre-existing chronic diseases. A space-time-stratified case-crossover design was employed, with a distributed lag non-linear model (DLNM) applied in quasi-Poisson regression. Various subgroup analyses were conducted to identify the most at-risk population. We quantified the relative risk (RR) at the 99th percentile of the daily minimum temperature relative to the minimum morbidity/mortality temperature (MMT).

Results We found a strong association of heat with morbidity and mortality. A substantially increased risk of morbidity was observed among individuals with pre-existing heart failure (RR = 2.79 [95% CI: 1.84–4.24]) and a high risk of mortality was found among those with pre-existing hypertension (RR = 2.01 [95% CI: 1.23–3.30]). We also observed a rise in heat-related morbidity risks for individuals with pre-existing Chronic Obstructive Pulmonary Disease (COPD) (RR = 2.09 [95% CI: 1.53–2.85]), hypertension (RR = 1.37 [95% CI: 1.08–1.74]), chronic kidney disease (CKD) (RR = 1.74 [95% CI: 1.25–2.42]), and chronic mental health disorders (RR = 1.41 [95% CI: 1.06–1.89]). There was an increased risk of overall mortality (RR = 1.29 [95% CI: 1.02–1.62]) and mortality with pre-existing COPD (RR = 1.80 [95% CI: 1.19–2.73]). Urban populations and low-SES groups had increased heat-related risks for some health outcomes, and the highest vulnerability was observed in those aged 85+ for several chronic diseases.

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Conclusion Our findings indicated that chronic diseases are associated with higher vulnerability to adverse health effects due to extreme heat. We observed notable variations across geographic, demographic, and socioeconomic subgroups, emphasizing the need for targeted public health strategies.

Keywords Chronic disease, Environmental exposure, Morbidity, Mortality, Heat exposure

Background

Over the past decade, the Earth has warmed faster than ever before. According to the World Meteorological Organization (WMO), 2014 to 2023 was the warmest period, with average temperatures 1.2 °C higher than the average between 1850 and 1900 [1]. Between 2000 and 2019, approximately 489,000 heat-related deaths occurred, with 36% of these occurring in Europe [2]. In Belgium, extreme heat is systematically monitored through temperature thresholds and public health warnings. In recent years, Belgium has faced several intense and prolonged heat-waves, with record-breaking temperatures, including 41.8 °C recorded in the shade in July 2019 during a severe European heat-wave, and projections indicate a 4.1 °C rise by the 2090s [3, 4].

Several meta-analyses and systematic reviews have examined the association between heat and health outcomes. For example, Bunker et al. (2016) analyzed time-series and case-crossover studies, and found that a 1 °C rise in temperature was associated with increased cardiovascular (3.44% [95% CI: 3.10–3.78]) and respiratory (3.60% [95% CI: 3.18–4.02]) mortality [5], as well as diabetes-specific mortality (RR = 1.139 [95% CI: 1.089–1.192]) [6]. A study involving 854 European cities found that the increase in heat-related deaths outweighed the reduction in cold-related deaths [7]. Evidence from large-scale studies, including another studies in Europe and a multi-country analysis, found a substantial impact of extreme heat on health [8–11]. In addition, increased risk of cardiovascular, respiratory, diabetes, and heat-related morbidity has also been found [5]. This may be because patients with long-term chronic diseases may have reduced ability to deal with heat since their bodies struggle more to regulate temperatures [12, 13].

While extreme temperatures pose a significant health risk to all humans, heat-related health risks are not equally prevalent across population groups. Certain population groups are more vulnerable to heat-related health outcomes due to physiological factors, such as their age and health status, and social determinants of health including housing quality, social network and work conditions. Meta-analyses have identified the elderly, low SES individuals, and those in tropical climates as particularly vulnerable to heat-related morbidity and mortality, regardless of sex, age, climate, or region [14–16].

Despite the growing studies on the impact of heat on health, there remains limited understanding of how individuals with pre-existing chronic diseases respond

to heat. To address this gap, our study provides a broad analysis of morbidity and mortality among individuals with pre-existing chronic diseases, utilizing a space-time stratified case-crossover analysis. By examining a range of chronic conditions, we capture potential differences in vulnerability across disease groups, contributing to a more detailed understanding of heat-related health risks. Furthermore, the use of general practitioner (GP) data enables a more detailed representation by allowing us to identify early-stage and less severe heat-related health effects that might not lead to hospitalization. This broader perspective enhances the generalizability of our findings by capturing a wider spectrum of the population. Additionally, we conducted several subgroup analyses to explore how geographic, demographic, and socioeconomic factors shape the heat-health association for morbidity and mortality. Our study also quantifies the heat-related health burden using the attributable fraction (AF), which represents the proportion of health events attributable to extreme heat, offering a measure of impact beyond relative risks alone. It estimates the excess cases that could be prevented by mitigating extreme heat exposure.

Methods

Study setting and data sources

This study was conducted in the Flanders region of Belgium, using GP data from 2005 to 2019, focusing on the summer season (1st May– 30th September). We obtained the data from the Intego registry, a general practice-based morbidity registry managed by the academic center for general practice at KU Leuven. The Intego registry functions as an administrative cohort, comprising a longitudinal electronic health record system collected from participating general practices across Flanders, Belgium. The Intego registry includes data from GP practices across Flanders, covering 6.23% of the Flemish population. These practices are located in 60 of the 300 municipalities in the region. Meteorological data, including daily minimum temperature (Tmin), daily maximum temperature (Tmax), mean temperature (Tmean), and relative humidity (RH) were measured at the Uccle weather monitoring station, managed by the Royal Meteorological Institute (RMI) of Belgium, and obtained from Intego [17]. We provided detailed information about Intego in our previous study [18].

Pre-existing chronic diseases

Pre-existing chronic diseases were identified using GP data from the Intego registry, with diagnoses retrieved through the International Classification of Primary Care version 2 (ICPC-2) codes, laboratory results extracted from Medidoc codes, and prescription data sourced using Anatomical Therapeutic Chemical (ATC) codes. These conditions included COPD, hypertension, diabetes, heart failure, neurodegenerative diseases, chronic kidney disease (CKD), and chronic mental health disorders. In our study, individuals with CKD were selected based on the estimated glomerular filtration rate (eGFR), particularly those with eGFR less than 45, which corresponds to moderate to severe CKD, including stages 3b, 4, and 5 [19]. This threshold aligns with recent findings by Zhang et al. (2024), that modeled heat-related kidney decline based on a baseline eGFR of 45 [20]. The eGFR value was used based on the most recent lab value available before the occurrence of the health outcome. Chronic mental health disorders were defined by identifying patients diagnosed with specific ICPC-2 codes and prescribed for medication treatment [21]. Detailed codes and descriptions of ICPC-2, Medidoc, and ATC codes can be found in the Appendix (Table S1). The pre-existing chronic diseases are selected based on previous studies [13, 18, 22–25].

Health outcomes

We analyzed both morbidity and mortality. Morbidity was defined as the daily number of diagnoses related to general and heat-related illnesses (ICPC2: A04, A05, A06, A88, K88, N01, N17, T03, T11, U13, S12, S80) among individuals with pre-existing chronic diseases, aggregated per day and stratified by combinations of age group, sex, SES, urbanicity. These codes include conditions typically classified as general illnesses (e.g., A04, A05, N01, T03, U13) as well as those more specifically associated with heat-related symptoms or diagnoses (e.g., A06, A88, K88, N17, T11, S12, S88). Descriptions of those ICPC-2 can be found in the Appendix (Table S1). Because some heat-related conditions can also present as general illnesses in clinical practices, we treated these codes as a single combined morbidity outcome to capture the broader spectrum of health effects potentially related to heat exposure. In this study, we use the terms 'morbidity' and 'general and heat-related illness' interchangeably. Mortality data refer to all-cause deaths during the study period. Overall mortality was defined as all mortality, occurring during the study period. We also specifically examined all-cause mortality among individuals with pre-existing chronic diseases, defined as those who had been diagnosed with a chronic disease before their death. Mortality among individuals with pre-existing chronic diseases was also specifically examined. Mortality data

were primarily sourced from the Belgian Statistical Office (StatBel) and linked to the Intego registry.

Exposure and covariates

The primary exposure in this study was the daily minimum temperature (T_{min}), which was selected based on our previous study showing a stronger association between T_{min} and health outcomes [18].

Covariates and potential confounders are RH, age groups (0–64, 65–84, 85+), sex, urbanicity levels (cities, suburbs, and rural areas), and SES (low, high). We classified urbanicity based on the definition of Eurostat [26]. Among the 300 Flemish municipalities included in the study, 7 were classified as cities, 236 as suburbs and 57 as rural areas. The SES was approximated based on whether patients are entitled to increased healthcare cost reimbursement (increased compensation) in the Belgian health system, with those receiving increased compensation classified as low SES.

Study design

We employed an aggregated space-time-stratified case-crossover design to investigate the associations between heat exposure and health outcomes, among individuals with pre-existing chronic diseases [27]. To account for spatial and temporal heterogeneity, we stratified by space (urbanicity) and time (day of week (DOW) within month and year). It combines space and time into strata, effectively controlling for spatial heterogeneity, seasonality, and long-term trends. For example, each Tuesday, May 2015, within a specific urbanicity level is compared to all other Tuesdays in the same month, year, and within that level [28]. This design removes bias due to failing to account for slowly varying factors, such as changes in diagnostic criteria. Unlike the individual case-crossover analysis, this design is particularly efficient when the number of events per day is low and is less computationally intense due to a lower number of parameters with no influence on the accuracy of the parameter estimate [28, 29].

Statistical analysis

To capture heat exposure's non-linear and delayed effects, we used a distributed lag non-linear model (DLNM) [30]. It allows for the estimation of the exposure-lag-response association by simultaneously modeling the potential nonlinear exposure-response relationship and the time-dependent lag structure of the exposure effect. A maximum lag of 14 days was applied to capture potential delayed and harvesting effects [18, 31]. Within the DLNM framework, we conducted a space-time-stratified analysis using a conditional quasi-Poisson regression model, which accommodates overdispersion and autocorrelation [32]. The exposure-response patterns of

temperature were modeled using a natural cubic spline (NS) with 3 degrees of freedom (df), placing the spline knots at equally spaced quantiles along the temperature range. The lag effect structure was modeled using 2 df, setting the knots at equally-spaced values on the log scale [33]. We also controlled the confounding effect of relative humidity using NS with 3 df, and adjusted for covariates including age groups, sex, and SES.

The heat effects were estimated as relative risks (RRs) [30, 34] with 95% confidence intervals (CIs), quantified at the P99 of the minimum temperatures, compared to the minimum morbidity/mortality temperature (MMT). The term MMT refers to the outcome-specific temperature threshold at which the risk of morbidity or mortality is the lowest. While we use the common term MMT for both morbidity and mortality, its interpretation is always outcome-specific.

We conducted several sensitivity analyses to test the robustness of our findings. First, we repeated our analysis by allowing different maximum lag days, including 3 days, 7 days, and 21 days. Second, we used the maximum temperature and mean temperature instead of the minimum as the main exposure. Finally, we tested alternative df in the spline specification for both the exposure (4 df) and lag (3 df), to assess the influence of model flexibility.

We also performed several subgroup analyses to provide a detailed understanding of the health risks associated with heat, based on the rationale that heat exposure can have different health effects depending on the structure of the population. A separate time-stratified analysis was conducted for urbanicity levels. This analysis was performed for general and heat-related illness of individuals with a history of chronic disease, for overall mortality, and mortality of those with pre-existing chronic disease. In addition, we also carried out a subgroup analysis stratified by age group, sex, and SES, using a space-time stratified framework.

The public health burden of heat was quantified by estimating attributable morbidity and mortality using AF. Specifically, following the method described by Gasparri and Leone (2014) within the DLNM approach, we calculated the AF for extreme heat using a backward method, quantified at minimum temperatures exceeding its P99 [34]. We obtained empirical confidence intervals (eCIs) corresponding to the 2.5th and 97.5th percentiles of the empirical distribution of heat-related morbidity and mortality.

Inclusion and exclusion criteria

For the morbidity analysis, we included individuals with at least one ICD-10 for general and heat-related illness and a documented history of pre-existing chronic disease.

For mortality analysis, we considered two separate analysis of the same outcome (all-cause mortality):

- Overall mortality: Included all individuals who died during the study period (2005–2019), regardless of pre-existing chronic diseases.
- Mortality among individuals with pre-existing chronic diseases: Included only those who died during the study period and had a recorded diagnosis of at least one chronic disease before their death.

Individuals were excluded if they had missing or invalid information of age, sex, SES, residential location or if they reside outside the Flemish region.

All the analyses were performed using R version 4.2.1 [35], and we used the *dlm* package [30] and the *gmm* package [32].

Results

Table 1 presents the distribution of patients with and without pre-existing chronic diseases. Of the total 456,280 patients, among individuals with pre-existing chronic diseases, hypertension was the most prevalent (12.3%), followed by diabetes (5.5%). A higher proportion of patients reside in urban areas (cities and suburbs). For conditions like heart failure and neurodegenerative diseases, we observed that these conditions are more prevalent in older adults (65+ years). Chronic diseases are almost equally distributed between males and females.

The daily minimum temperatures during the study period ranged from 3.49 °C to 24.31 °C, with the 1st and 99th percentiles at 5.4 °C and 22.1 °C, respectively. The lowest and highest daily maximum temperatures were 8.67 °C and 41.10 °C, respectively, while the 1st and 99th percentiles were 12.27 °C and 32.94 °C. Daily mean temperature ranged from 6.9 °C to 30.9 °C. Daily mean RH was found to vary between 30.66% and 100%.

During May–September 2005–2019, a total of 65,691 morbidity events related to general and heat-related illnesses were recorded. Of these, a substantial proportion occurred in individuals with pre-existing chronic diseases (Table 2). Specifically, 27.7% of these cases were among people with pre-existing hypertension, 25.9% with chronic mental health disorders, 11.8% with CKD, and 11.5% with diabetes. Subsequent morbidity analyses in this study were restricted to individuals with chronic diseases. For mortality, among the 5,675 total deaths, 28% occurred in people with pre-existing hypertension, while 25.8% were among those with CKD.

Cumulative RRs (lag 0–14) and 95% CIs, quantified at P99 of minimum temperature (22.1 °C) compared to MMT, are presented in Table 3. The results for morbidity indicate a substantial increase in heat-related risk among individuals with pre-existing chronic diseases. Specifically, an increased risk was observed among those with heart failure (RR = 2.79 [95% CI: 1.84–4.24], COPD (RR = 2.09 [95% CI: 1.53–2.85]), CKD (RR = 1.74 [95%

Table 1 Distribution of patients with and without pre-existing chronic diseases across various covariates

Pre-existing chronic diseases N=456,280									
Covariates		COPD		Hypertension		Diabetes		Heart failure	
		n = 10,925(2.4%) a = 445,355 (97.6%)		n = 56,284(12.3%) a = 399,996(87.7%)		n = 25,294(5.5%) a = 430,986(94.5%)		n = 5,280(1.2%) a = 451,000(98.8%)	
		n(%)	a(%)	n(%)	a(%)	n(%)	a(%)	n(%)	a(%)
Urbanicity	Cities	3,340(30.6)	114,758(25.8)	17,151(30.5)	100,947(25.2)	9,602(38.0)	108,496(25.2)	1,459(27.6)	116,639(25.9)
	Suburbs	6,511(59.6)	232,616(52.2)	33,259(59.1)	205,868(51.5)	13,146(52.0)	225,981(52.4)	3,273(62.0)	235,854(52.3)
	Rural	456(4.2)	20,257(4.5)	3,039(5.4)	17,674(4.4)	1,161(4.6)	19,552(4.5)	307(5.8)	20,406(4.5)
	Missing	618(5.6)	77,900(17.5)	2,835(5.0)	75,507(18.9)	1,385(5.4)	76,957(17.9)	241(4.6)	78,101(17.3)
Age group	0–64	7,694(70.4)	404,964(90.9)	39,392(70.0)	373,266(93.3)	18,097(71.5)	394,561(91.5)	1,542(29.2)	411,116(91.2)
	65–84	2,957(27.1)	35,068(7.9)	15,471(27.5)	22,554(5.6)	6,658(26.3)	31,367(7.3)	3,073(58.2)	34,952(7.7)
	85+	274(2.5)	5,323(1.2)	1,421(2.5)	4,176(1.1)	539(2.1)	5,058(1.2)	665(12.6)	4,932(1.1)
	Missing	-	-	-	-	-	-	-	-
Sex	Male	5,853(53.6)	211,729(47.6)	27,240(48.4)	190,342(47.6)	13,270(52.5)	204,312(47.4)	2,434(46.1)	215,148(47.7)
	Female	5,068(46.4)	232,278(52.3)	29,026(51.6)	209,003(52.3)	12,009(47.5)	226,020(52.4)	2,845(53.9)	235,184(52.1)
	Missing	4(< 0.1)	665(0.1)	18(< 0.1)	651(0.1)	15(< 0.1)	654(0.2)	1(< 0.1)	668(0.2)
SES	Low	3,286(30.1)	52,907(11.9)	11,262(20.0)	44,931(11.2)	6,658(26.3)	49,535(11.5)	1,885(35.7)	54,308(12.1)
	High	6,652(60.9)	286,814(63.0)	40,384(71.7)	253,082(63.3)	16,225(64.1)	277,241(64.3)	2,994(56.7)	290,472(64.4)
	Unclear	174(1.6)	5,448(1.2)	772(1.4)	4,850(1.2)	380(1.5)	5,242(1.2)	70(1.3)	5,552(1.2)
	Missing	813(7.4)	100,186(22.5)	3,866(6.9)	97,133(24.3)	2,031(8.1)	98,968(23.0)	331(6.3)	100,668(22.3)
		Neurodegenerative diseases		CKD		Chronic mental health disorders			
		n = 5,501(1.2%) a = 450,779 (98.8%)		n = 9,972(2.2%) a = 446,308 (97.8%)		n = 28,501(6.2%) a = 427,779 (93.8%)			
		n(%)	a(%)	n(%)	a(%)	n(%)	a(%)		
Urbanicity	Cities	1,682(30.6)	116,416(25.8)	2,641(26.5)	115,457(25.9)	8,357(29.3)	109,741(25.7)		
	Suburbs	3,196(58.1)	235,931(52.4)	6,211(62.3)	232,916(52.2)	17,110(60.0)	222,017(51.9)		
	Rural	253(4.6)	20,460(4.5)	535(5.3)	20,178(4.5)	1,420(5.0)	19,293(4.5)		
	Missing	370(6.7)	77,972(17.3)	585(5.9)	77,757(17.4)	1,614(5.7)	76,728(17.9)		
Age group	0–64	1,260(22.9)	411,398(91.2)	4,600(46.1)	408,058(91.4)	25,304(88.8)	387,354(90.5)		
	65–84	3,503(63.7)	34,522(7.7)	4,231(42.4)	33,794(7.6)	2,962(10.4)	35,063(8.2)		
	85+	738(13.4)	4,859(1.1)	1,141(11.5)	4,456(1.0)	235(0.8)	5,362(1.3)		
	Missing	-	-	-	-	-	-		
Sex	Male	2,213(40.2)	215,369(47.8)	4,200(42.1)	213,382(47.8)	9,329(32.6)	208,253(48.7)		
	Female	3,286(59.7)	234,743(52.1)	5,766(57.8)	232,263(52.0)	19,168(67.3)	218,861(51.2)		
	Missing	2(0.1)	667(0.1)	6(0.1)	663(0.2)	4(0.1)	665(0.1)		
SES	Low	1,922(34.9)	54,271(12.0)	2,934(29.4)	53,259(11.9)	6,062(21.3)	50,131(11.7)		
	High	3,010(54.8)	290,456(64.4)	6,075(60.9)	287,391(64.3)	19,569(68.7)	273,897(64.0)		
	Unclear	77(1.4)	5,545(1.3)	101(1.1)	5,521(1.2)	619(2.1)	5,003(1.2)		
	Missing	492(8.9)	100,507(22.3)	862(8.6)	100,137(22.4)	2,251(7.9)	98,748(23.1)		

N=Total population, n(%)=Number (percentage) of patients with the specified pre-existing chronic disease, a(%)=Number (percentage) of patients without the specified pre-existing chronic disease

CI: 1.25–2.42]), hypertension (RR=1.37 [95% CI: 1.08–1.74]), and chronic mental health disorders (RR=1.41 [95% CI: 1.06–1.89]). In addition, only slight increases, albeit not statistically significant, were found for diabetes (RR=1.10 [95% CI: 0.86, 1.40]) and neurodegenerative diseases (RR=1.16 [95% CI: 0.85, 1.59]).

Furthermore, we found that exposure to heat at P99 (22.1 °C) was strongly associated with mortality (RR=1.29 [95% CI: 1.02, 1.62]), predominantly among individuals with pre-existing hypertension (RR=2.01 [95% CI: 1.23–3.30]) and COPD (RR: 1.80 [95% CI: 1.19–2.73]), as well as among patients with chronic mental health disorders (RR=1.81 [95% CI: 0.72, 4.56]), albeit not statistically significant. A less pronounced association was found among individuals with pre-existing

heart failure (RR=1.04 [95% CI: 0.43, 2.55]), diabetes (RR=1.30 [95% CI: 0.66, 2.55]), neurodegenerative disease (RR=1.41 [95% CI: 0.64, 3.08]) and CKD (RR=1.35 [95% CI: 0.80, 2.27]).

The cumulative RR for maximum temperature and mean temperature relative to the corresponding MMT is presented in Table S2 (see Appendix), showing similar results as for minimum temperature; however, for morbidity outcome, the statistical significance was lost for patients with pre-existing hypertension, but gained for individuals with pre-existing neurodegenerative diseases (RR=1.91 [1.35–2.69]). We also observed that in similar analyses for mortality, the significance was lost for those with pre-existing COPD for both Tmax and Tmean, compared to its minimum temperature counterpart.

Table 2 General and heat-related illness and mortality occurred in individuals with pre-existing chronic diseases during May–September 2005–2019

Pre-existing chronic diseases	Morbidity events <i>n</i> (%) [*]	Total deaths <i>n</i> (%) [*]
All	65,691 (100%)	5675 (100%)
COPD	4,929 (7.5%)	663 (11.7%)
Hypertension	18,190 (27.7%)	1,628 (28.7%)
Diabetes	7,571 (11.5%)	977 (17.2%)
Heart failure	3,343 (5.1%)	543 (9.6%)
Neurodegenerative	3,417 (5.2%)	617 (10.9%)
CKD	7,741 (11.8%)	1,466 (25.8%)
Chronic mental health disorders	17,021 (25.9%)	598 (10.5%)

^{*}total and column percentages. Morbidity events, General and heat-related illnesses

Table 3 Cumulative (lag 0–14) RR and 95% CIs at the 99th percentile of minimum temperature (P99) (22.1 °C), compared to the corresponding minimum morbidity/mortality temperature (MMT). Estimates are presented for the general and heat-related illnesses among individuals with a history of chronic diseases, overall mortality, and mortality among individuals with a history of chronic diseases

Pre-existing chronic diseases	General and heat-related illness RR (95% CI)	All-cause mortality RR (95% CI)
Overall Mortality	-	1.29 (1.02–1.62)
COPD	2.09 (1.53–2.85)	1.80 (1.19–2.73)
Hypertension	1.37 (1.08–1.74)	2.01 (1.23–3.30)
Diabetes	1.10 (0.86–1.40)	1.30 (0.66–2.55)
Heart failure	2.79 (1.84–4.24)	1.04 (0.43–2.55)
Neurodegenerative diseases	1.16 (0.85–1.59)	1.41 (0.64–3.08)
CKD	1.74 (1.25–2.42)	1.35 (0.80–2.27)
Chronic mental health disorders	1.41 (1.06–1.89)	1.81 (0.72–4.56)

We also calculated cumulative RR, estimated for different lag days (lag0–3, lag0–7, and lag0–21) (see Table S3 in the Appendix), with risks remaining consistent with the main findings. The results obtained using 4 df for exposure and 3 for lag effects are presented in Table S4 (Appendix), showing comparable findings with the main analysis, though significance was lost for some outcomes.

We also calculated the cumulative RR over 14 days lag period and 95% CIs for both morbidity and mortality across levels of urbanicity, estimated at P99 (22.1 °C) relative to MMT (Fig. 1).

For morbidity, a strong increased risk was found for individuals with pre-existing heart failure and residing in cities (RR=6.16 [95% CI: 2.18–17.41]), in suburbs (RR=3.99 [95% CI: 1.81–8.79]), and in rural areas (RR=2.47 [95% CI: 1.08–5.67]). In addition, a substantially increased risk was found for those with pre-existing COPD living in cities (RR=2.10 [95% CI: 1.10–4.00]), and suburbs (RR=2.41 [95% CI: 1.44–4.05]), but not in rural areas (RR=3.25 [95% CI: 0.81–12.97]). For

individuals with history of CKD, we observed a substantially increased risk in rural areas (RR=5.66 [95% CI: 1.62–19.83]), suburbs (RR=3.24 [95% CI: 1.87–5.61]) and cities (RR=2.15 [95% CI: 1.06–4.33]), while for people with pre-existing mental health disorders high risk was observed in cities (RR=2.59 [95% CI: 1.12–5.96]) and suburbs (RR=2.14 [95% CI: 1.16–3.96]). Our study did not shows substantial increase across the levels of urbanicity for individuals with pre-existing hypertension and diabetes.

Regarding overall mortality, we observed a substantially increased risk in rural areas (RR=12.91 [95% CI: 3.94–42.22]), and in cities (RR=1.71 [95% CI: 1.07–2.73]), but to a lesser extent in suburbs (RR=1.19 [95% CI: 0.80–1.79]). Specifically for people with pre-existing COPD, mortality risk shows high risk in rural areas (RR=7.43 [95% CI: 1.88–29.37]), but we did not found statistically significant association for those residing in urban areas (RR=1.85 [95% CI: 0.65–5.25]) and suburbs (RR=1.03 [95% CI: 0.39–2.67]). There was a high heat-related mortality risk observed for those living in cities have history of hypertension (RR=2.42 [95% CI: 1.04–5.62]), and CKD (RR=2.52 [95% CI: 0.99, 6.42]), while no strong associations were found for individuals with pre-existing diabetes, heart failure, neurodegenerative, and chronic mental health disorders, regardless of urbanicity level. Potential uncertainty was observed for rural areas due to a small number of events.

We observed acute heat effects, with increased RR during the first few lag days for general and heat-related illnesses among individuals with some of the pre-existing chronic diseases. Additionally, high heat-related risk was found for longer lag periods, particularly among people with pre-existing hypertension, diabetes, neurodegenerative diseases and chronic mental health disorders (Appendix, Figure S1). We also presented the lag-response associations for all-cause mortality (Appendix, Figure S2); however, the lag-specific risk was not very clear.

We also analyzed different morbidity and mortality outcomes depending on age, presented a cumulative RRs and 95% CIs relative to MMT (Fig. 2).

For morbidity, a substantially elevated heat-related risk was observed in the 85+ age group for people with pre-existing CKD (RR=9.54 [95% CI: 4.97–18.30]), mental health disorders (RR=7.01 [95% CI: 3.58–13.72]), heart failure (RR=6.46 [95% CI: 3.91–10.67]), and neurodegenerative diseases (RR=3.28 [95% CI: 1.6–6.72]). Elevated Heat-related morbidity risks were also seen for those with history of COPD (RR=1.69 [95% CI: 1.05–2.73]), hypertension (RR=2.18 [95% CI: 1.42–3.35]), and diabetes (RR=2.02 [95% CI: 1.31–3.12]). In the 65–84 age group, increased risks were observed for COPD (RR=2.81 [95% CI: 1.84–4.29]) and mental health disorders (RR=1.94

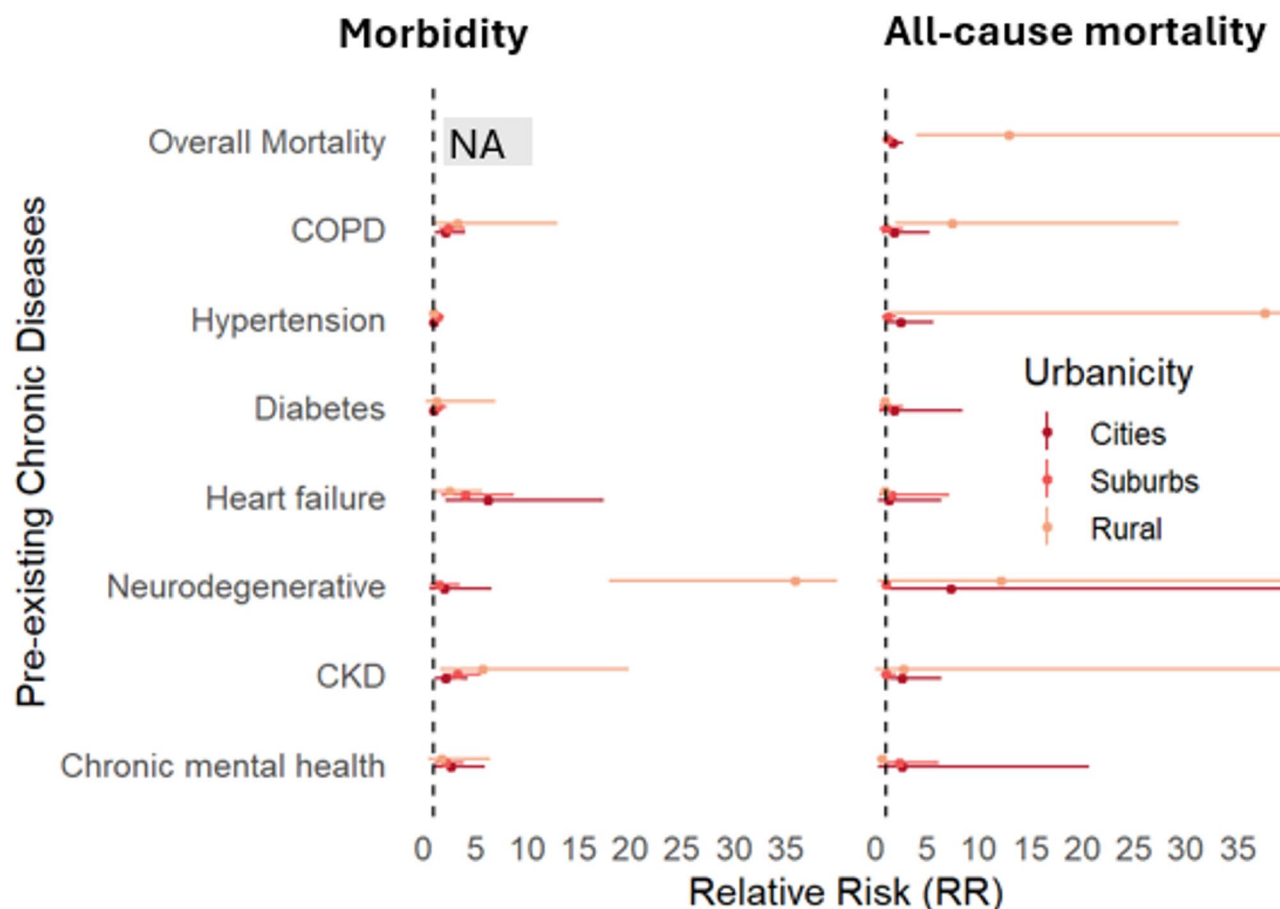


Fig. 1 Cumulative (lag 0–14) RR (dots) and 95% CIs (horizontal lines) at the 99th percentile of minimum temperature (P99) (22.1 °C), compared to the corresponding minimum morbidity/mortality temperature (MMT) across levels of urbanicity. The left panel presents an estimate for morbidity (general and heat-related illnesses) among individuals with chronic diseases, while the right panel is for all-cause mortality (overall mortality and mortality among individuals with chronic diseases)

[95% CI: 1.14–3.30]). Among those aged 0–64, strong associations were found for patients with pre-existing COPD (RR=1.96 [95% CI: 1.35–2.84]) and hypertension (RR=2.18 [95% CI: 1.42–3.35]).

For mortality, we found high heat-related risk in people with 85+ age group (RR=1.82 [95% CI: 1.12–2.97]), particularly among those with history of hypertension (RR=2.41 [95% CI: 1.18–4.96]). In the 85+ group, increased risk was observed for individuals with pre-existing neurodegenerative diseases (RR=2.43 [95% CI: 0.57–10.41]), though this was not statistically significant. There was no strong heat-related mortality risk across age groups for individuals with history of COPD, diabetes, heart failure, CKD, or mental health disorders. No strong heat-overall mortality association was found in the 65–84 (RR=1.12 [95% CI: 0.74–1.70]) or 0–64 (RR=1.75 [95% CI: 0.84–3.63]) groups.

Figure 3 presented the cumulative RRs and 95% CIs estimated for subgroup analysis by sex. For morbidity, males with pre-existing COPD showed a markedly elevated heat-related risk (RR=4.35 [95% CI: 2.88–6.56]),

while the risk was also increased for females (RR=1.53 [9% CI: 1.08–2.16]). Similar patterns were seen in males (RR=2.11 [95% CI: 1.33–3.32]) and females (RR=1.93 [95% CI: 1.34–2.76]) with history of CKD. Heat exposure was associated with an increased risk of morbidity among individuals with pre-existing heart failure in both sexes, higher in females (RR=3.60 [95% CI: 2.19–5.92]) than males (RR=1.84 [95% CI: 1.15–2.95]). For individuals with history of hypertension, heat-related morbidity risk was elevated in females (RR=1.36 [95% CI: 1.01–1.84]) but not in males (RR=1.05 [95% CI: 0.74–1.49]). Heat exposure was linked to increased morbidity risk among males with pre-existing chronic diabetes (RR=1.50 [95% CI: 1.01–2.24]).

For mortality, heat-related risk was observed in males (RR=1.39 [95% CI: 1.01–1.92]) and slightly increased in females (RR=1.30 [95% CI: 0.82–2.08]). Among those with COPD, risk was higher in females (RR=2.02 [95% CI: 1.38–2.98]) than in males (RR=1.11 [95% CI: 0.72–1.72]). The heat-related risk was elevated in females for individuals with pre-existing hypertension (RR=2.24

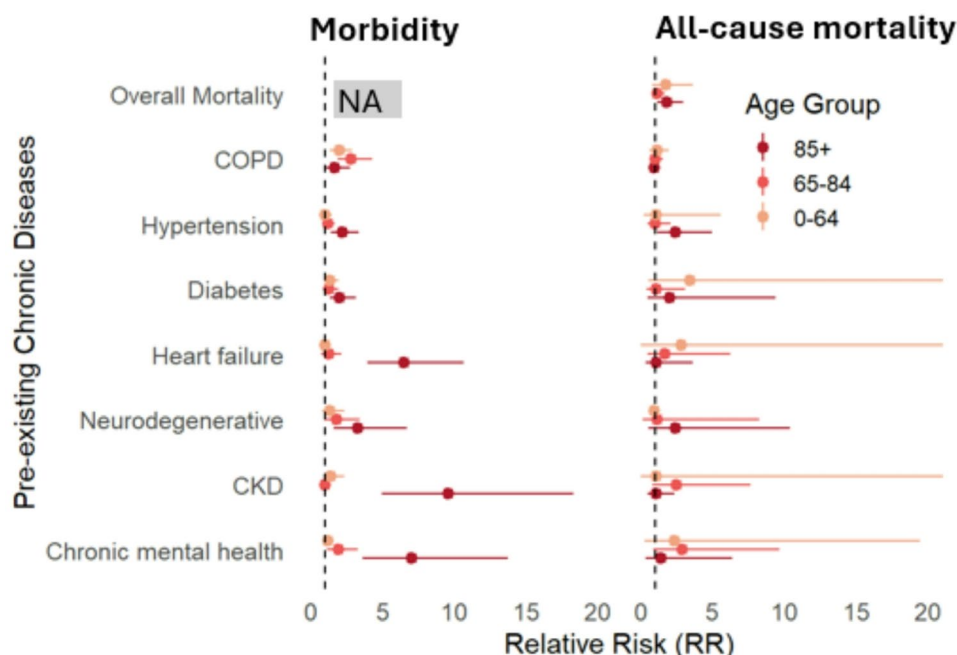


Fig. 2 Cumulative (lag 0–14) RR (dots) and 95% CIs (horizontal lines) at the 99th percentile of minimum temperature (P99) (22.1 °C), compared to the corresponding minimum morbidity/mortality temperature (MMT) across age groups. The left panel presents estimates for morbidity (general and heat-related illnesses) among individuals with chronic diseases, while the right panel is for all-cause mortality (overall mortality and mortality among individuals with chronic diseases)

[95% CI: 1.05–4.77]), but the association was less pronounced in males (RR = 1.65 [95% CI: 0.80–3.38]).

Figure 4 presents the RRs together with 95% CIs compared to MMT, stratified by SES (increased compensation status). For morbidity, individuals with increased compensation (low SES) showed a notable heat-related risk, especially for individuals with pre-existing heart failure (RR = 2.98 [95% CI: 1.73–5.12]), COPD (RR = 2.37 [95% CI: 1.63–3.43]), diabetes (RR = 1.57 [95% CI: 1.05–2.34]), and CKD (RR = 1.47 [95% CI: 1.00–2.14]). Elevated heat-related risks were also seen in high SES among patients with history of COPD (RR = 2.03 [95% CI: 1.40–2.94]), heart failure (RR = 2.15 [95% CI: 1.38–3.33]), and CKD (RR = 2.30 [95% CI: 1.53–3.45]).

For overall mortality, we did not observe a strong association in either low SES (RR = 1.25 [95% CI: 0.79–1.97]) or high SES (RR = 1.07 [95% CI: 0.78–1.48]). Among those with low SES, increased heat-related risk were seen among those with pre-existing mental health disorders (RR = 2.93 [95% CI: 1.09–7.86]) and diabetes (RR = 2.74 [95% CI: 1.07–7.02]). For individuals with high SES, heat-related morbidity risk was elevated for those with history of neurodegenerative diseases (RR = 3.21 [95% CI: 1.67–6.17]).

Finally, we also assessed the attributable fraction, (%) along with its eCIs, quantified for extreme heat, (at P99 of the minimum temperature), (Fig. 5). For morbidity, the highest burden attributable to extreme heat was

observed among individuals with pre-existing heart failure, (AF = 4.66% [95% eCI: 3.17–5.36]), followed by COPD, (2.39% [95% eCI: 0.48–3.31]), CKD, (1.89% [95% eCI: 0.12–3.00]), hypertension, (1.38% [95% eCI: 0.41–2.09]), neurodegenerative diseases, (1.24% [95% eCI: 0.23–1.85]), and mental health disorders, (0.35% [95% eCI: 0.23–0.58]). For mortality, 1.17% [95% eCI: 0.30–1.84] of deaths were attributable to extreme heat. Higher fractions were found for individuals with hypertension, (2.49% [95% eCI: 0.91–3.53]) and COPD, (1.08% [95% eCI: 0.46–1.84])

Discussion

Main findings

Our study highlights the significant impact of extreme heat on morbidity and mortality, particularly among individuals with pre-existing chronic diseases. We found strong associations between heat exposure and general and heat-related illnesses in people with COPD, hypertension, heart failure, CKD, and mental health disorders. An increased heat-related mortality risk was observed among individuals with COPD and hypertension. Urban populations and individuals aged 85+ faced elevated heat-related risks, particularly for morbidity. Sex-specific differences emerged, with males showing a stronger association between heat and overall mortality, and females for COPD and hypertension. Both sexes showed strong heat-related associations with morbidity outcomes across

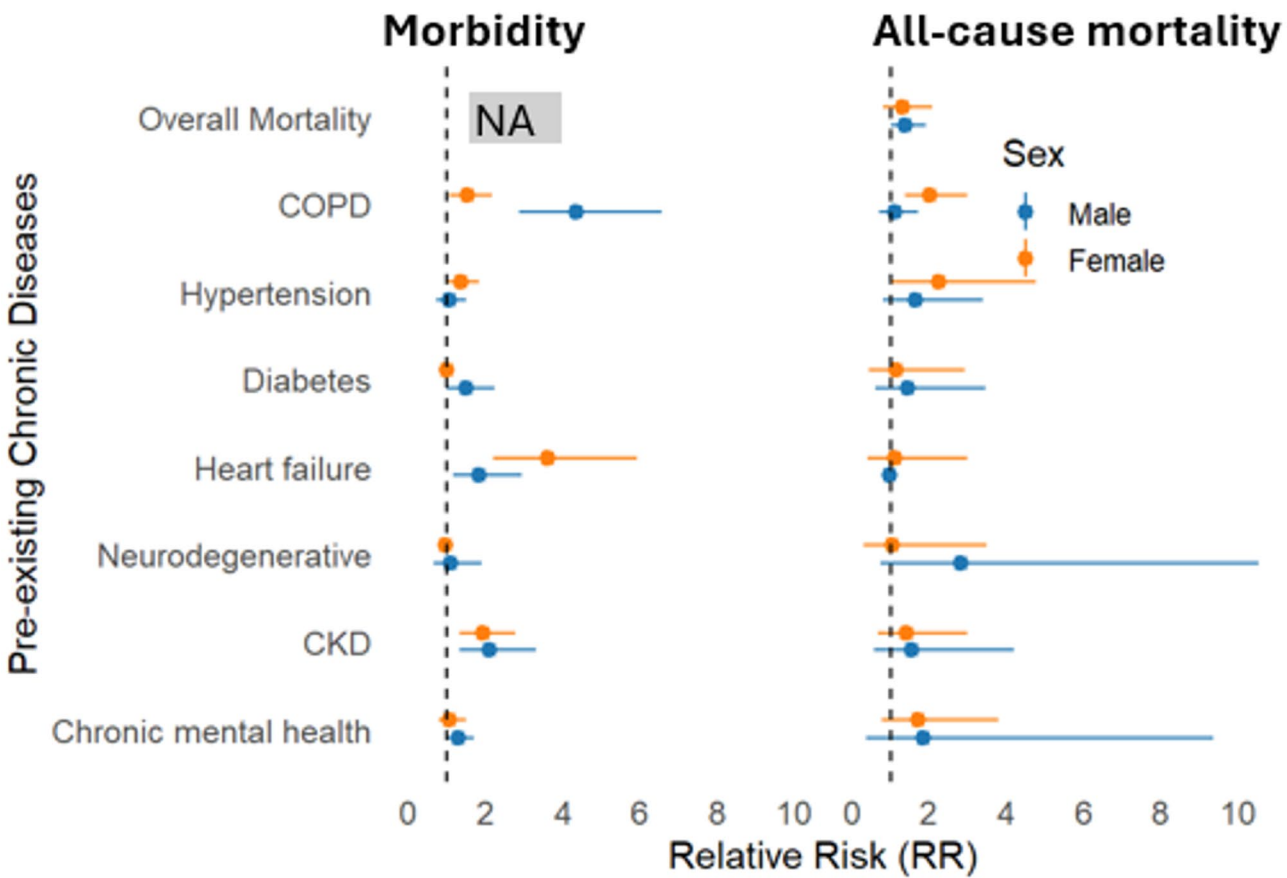


Fig. 3 Cumulative (lag 0–14) RR (dots) and 95% CIs (horizontal lines) at the 99th percentile of minimum temperature (P99) (22.1 °C), compared to the corresponding minimum morbidity/mortality temperature (MMT) across sex. The left panel presents an estimate for morbidity (general and heat-related illnesses) among individuals with chronic diseases, while the right panel is for all-cause mortality (overall mortality and mortality among individuals with chronic diseases)

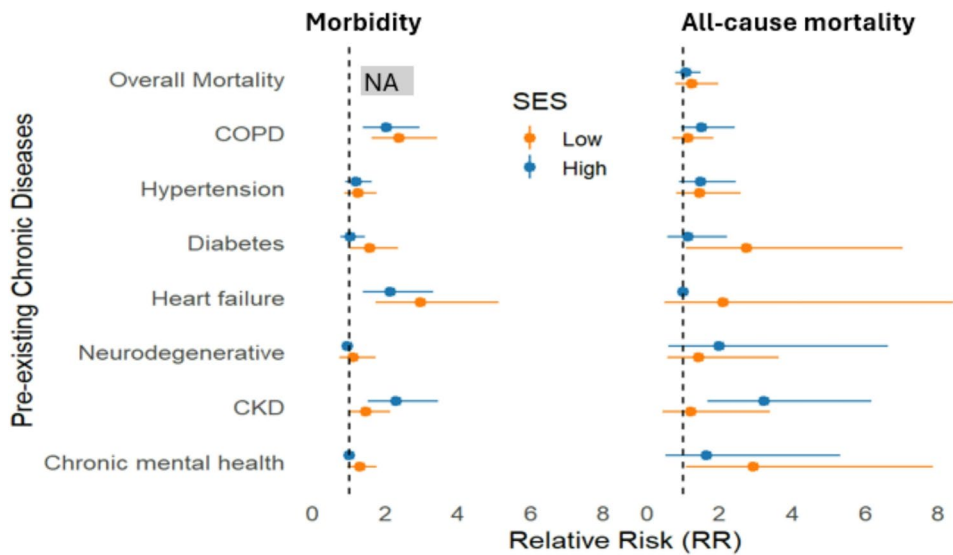


Fig. 4 Cumulative (lag 0–14) RR (dots) and 95% CIs (horizontal lines) at the 99th percentile of minimum temperature (P99) (22.1 °C), compared to the corresponding minimum morbidity/mortality temperature (MMT) across SES (increased compensation status). The left panel presents an estimate for morbidity (general and heat-related illnesses) among individuals with chronic diseases, while the right panel is for all-cause mortality (overall mortality and mortality among individuals with chronic diseases)

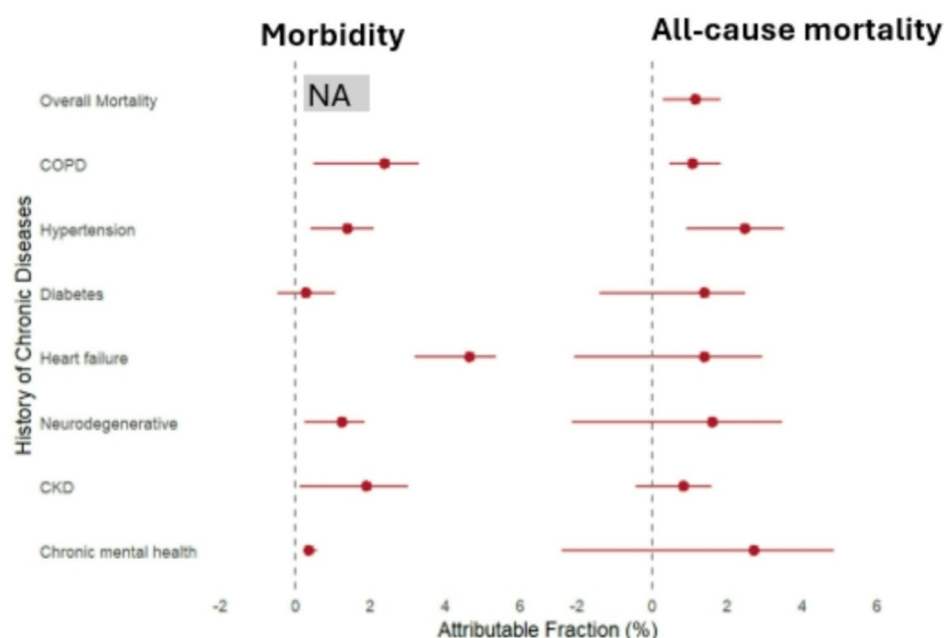


Fig. 5 Attributable fractions (AF, %) with 95% empirical confidence intervals (eCIs) at the 99th percentile of minimum temperature. Left panel: Morbidity (general and heat-related illness) among individuals with pre-existing chronic diseases. Right panel: All-cause mortality (overall mortality and mortality among individuals with pre-existing chronic diseases).

most pre-existing chronic diseases. Socioeconomic disparities were observed, as low SES was associated with higher heat-related risks of illness but not mortality, except for diabetes patients. Our findings suggest that the health effects of nighttime heat exposure extended over several days, supporting the use of a 14-day lag effect to capture the delayed impacts.

Comparison to previous studies

Epidemiological studies have shown that extreme heat is associated with increased morbidity and mortality, particularly among people with pre-existing chronic diseases [13, 36]. The magnitude, source of data, type of pre-existing chronic diseases, and shape of association, however, vary across studies depending on geographical regions, study populations, and methodological approach [13, 37, 38].

Previous studies in the USA analyzed hospitalization and mortality among people with end-stage renal disease (ESRD), using an aggregated time-stratified case-cross-over design [37]. They found that extreme heat was associated with an increased risk of hospital admission and mortality among patients with ESRD. We also obtained a significant association between heat and morbidity among people with pre-existing CKD. A study in Australia on multi-morbidity and emergency hospitalization during extreme temperature used a time-stratified case-crossover design, and found an increased risk of emergency hospitalization of people with pre-existing CKD, asthma/COPD, and mental disorders [13]. Our findings

also showed that there was an increased risk of morbidity among individuals with pre-existing COPD, CKD, and chronic mental health disorders. A meta-analysis based on 30 studies revealed that for every 1 °C increase in temperature, mortality increased by 35% (RR = 1.35, 95%CI: 1.29–1.41) [15]. We also observed an increased risk of overall mortality during extreme heat. The finding was also consistent with previous studies in Belgium [31, 39]. Our study showed a less pronounced association for mortality among most pre-existing chronic diseases. This might be related to the fact that chronic disease patients often receive regular medical care, which may include early interventions by staying hydrated, avoiding outdoor exposure, and monitoring during extreme heat, potentially reducing excess mortality, or due to low numbers for those specific groups, resulting in a lack of statistical power. A meta-analysis by Yang et al., examined heat-related mortality and found that mortality risk increases significantly during extreme temperatures, particularly for those with cardiovascular and respiratory diseases [16]. We also obtained increased mortality risk for individuals with pre-existing COPD.

In our subgroup analysis, we observed that, for people living in cities, there was an increased heat-related risk of general and heat-related illness among individuals with pre-existing COPD, heart failure, CKD, and mental health disorders. According to a meta-analysis on the impact of heat on urban health, a 1 °C increase in temperature was associated with a 2.1% rise in disease-related mortality and a 1.1% increase in morbidity [16].

In our case, this can be explained by the urban heat island (UHI) effect, where cities experience higher temperatures due to limited green spaces, dense infrastructure, and human activities. According to Fastl et al., European people, particularly older people living in urban areas are at a high risk of heat-related disorders due to the urban heat island effect, which can be the combined effect of a lack of vegetation and a high proportion of built-up areas [40]. A study in Belgium looked at heat-related mortality in two large cities in Belgium using data covering the period January 1st, 2010, to December 31st, 2015 [31]. They found that people living in the most built-up municipalities were at higher risk of heat-related disorders. It has also been found in a meta-analysis based on 11 studies that there was a strong association of heat and mortality among people living in rural areas [41]. Our study also found significant associations for some outcomes for people living in rural areas, including overall mortality and morbidity, and mortality among some chronic diseases; however, these estimates have high uncertainties because of the wide CIs. This can be due to small numbers, as Flanders is largely urbanized, with a low percentage of people living in rural areas.

In line with our findings, a previous study found that heat exposure can trigger inflammation and exacerbate COPD, and is highly prevalent in older people [5]. We observed the highest risk of general and heat-related illness among older people with pre-existing CKD, consistent with a nationwide study conducted in China [42]. This can be related to the fact that heat-related dehydration may reduce blood flow to the kidneys, exacerbating existing CKD and potentially accelerating its progression. Older adults, on the other hand, often experience impaired thirst recognition and renal concentrating ability, leading to an increasing risk of dehydration during extreme heat [43]. Delaney et al., found a strong association between ambient temperature and hospitalization for Alzheimer disease and dementia among older people [44]. We also observed an increased risk of morbidity for people with pre-existing mental health disorders in the overall population and for the elderly.

Our finding exhibited a sex-specific difference. For the morbidity outcomes, we observed a strong association for both sexes for most chronic diseases. A meta-analysis has found that heat exposure leads to an elevated risk of cardiovascular exacerbation among females [45]. In the current study, it was also found that females with pre-existing hypertension and heart failure had an increased heat-related morbidity risk. There was a less pronounced association for mortality in both sexes, which could have been explained by the fact that people with chronic disease may receive more medical attention and have better adaptation strategies, such as staying at home or drinking more fluids. It may also be related to small sample sizes

in such specific subgroups. Our findings suggested that for most health outcomes, there were greater risks for individuals entitled to increased compensation (a proxy for lower SES), which is consistent with a previous study [46].

Our study found that minimum temperature showed a stronger association with adverse health outcomes than maximum temperature and mean temperature, indicating the nighttime heat effects. A recent study observed that while urban trees are effective in providing shade and reducing heat stress during the day, open green spaces with low vegetation are more effective for nighttime cooling [47]. Based on this, policies aiming to address nighttime heat stress should prioritize urban green rather than urban trees.

Strength and limitations

Our study has several strengths. First, we included a long period (2005–2019), and data from GPs, allowing for a detailed examination of heat-related health risks. Second, by focusing on individuals with several pre-existing chronic diseases, we provided critical insights into the most at-risk group that is often understudied. Third, we employed a space-time stratified-case-crossover design, which inherently accounts for spatial heterogeneity, seasonal changes, and long-term trends, reducing bias from time-invariant confounders such as changes in healthcare access and diagnostic criteria. Fourth, our analysis provided a comprehensive picture by analyzing morbidity and mortality, allowing us to capture both short-term health impacts leading to GP consultations and long-term health effects resulting in death. Lastly, we performed several subgroup analyses and quantified the public health burden, which helped us identify vulnerable populations for developing targeted public health interventions and adaptation strategies.

We acknowledge several limitations. While we know that individuals had pre-existing diseases, we do not have data on whether their deaths were directly attributable to these chronic diseases. For some subgroup analyses, for example, data from rural areas (which are rare in Flanders) and mortality among pre-existing chronic diseases, we observed a low number of events, leading to less precise estimates with wide confidence intervals. However, the conditional quasi-Poisson regression we used improved estimates when event counts per day were low by leveraging within-strata comparison [48]. Additionally, due to the limited number of cases, we were unable to assess the impact of multimorbidity, which could provide insights into how multiple chronic conditions modify heat-related risks. Our analysis also does not account for individual-level behavioral and physiological adaptations to heat, such as access to cooling measures or medication use. Some acute hospitalizations may not

be captured by GP, which might lead to an underestimation of severe morbidity. However, as the morbidity outcome (general and heat-related illness) is often mild, it is likely expected that patients may first visit their GP. The temperature data was measured at single-station, which might lead to exposure miss-classification. However, we obtained the data from a well-established, centrally located monitoring station with good regional representativeness. Uccle is the most reliable temperature station in Belgium, with one of the longest, high quality continuous temperature time series in the world. Finally, our findings did not fully capture the role of air pollution and other environmental co-exposures, which might modify the association between heat and health outcomes.

In conclusion, our study provides strong evidence that heat exposure may disproportionately affect individuals with pre-existing chronic diseases, with particularly notable association for general and heat-related illnesses. A strong association was observed for population subgroups, including older adults and those residing in urban areas. On top of general heat adaptation strategies and early warning systems, this study highlights the importance of prioritizing specific subgroups of patients at higher risk. These risk groups are identifiable based on their files GP's has of them.

Abbreviations

AF	Attributable Fraction
ATC	Anatomical Therapeutic Chemical
COPD	Chronic Obstructive Pulmonary Disease
CI	Confidence Interval
CKD	Chronic Kidney Disease
DF	Degree of freedom
DOW	Day Of Week
DLNM	Distributed lag Non-Linear Model
eGFR	estimated Glomerular Filtration Rate
ESRD	End-Stage Renal Disease
GP	General Practitioner
ICPC-2	International Classification of Primary Care version 2
MMT	Minimum Morbidity/Mortality Temperature
NS	Natural cubic Spline
RH	Relative Humidity
RMI	Royal Meteorological Institute
RR	Relative Risk
SES	Socioeconomic Status
UHI	Urban Heat Island

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s12889-025-24991-4>.

Supplementary Material 1.

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Authors' contributions

EAA: Writing-original draft, Visualization, Methodology, Formal analysis, Data curation, Software, Conceptualization. RA: Writing-review & editing, Supervision, Conceptualization. BV: Writing-review & editing, Project

administration. CS: Writing-review & editing, Supervision. SGB: Writing-review & editing. KVdV: Writing-review & editing. ED: Writing-review & editing, methodology. GVP: Writing-review & editing, Project administration, Supervision, Resources, Funding acquisition, Conceptualization.

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Data availability

The authors are not allowed to share the data. Requests for aggregated data used for this study and other INTEGO data can be made by sending a reasonable inquiry to dpo.healthdata@sciensano.be.

Declarations

Ethics approval and consent to participate

This study was conducted in accordance with the principles of the Declaration of Helsinki. Ethical approval were received from the ethical review board of the Medical School of the KU Leuven (S70514). INTEGO procedures were also approved by the Belgian Privacy Commission (no. SCSZG/13/079), and the ethical review board of the Medical School of the KU Leuven (no. ML 1723) (Herestraat 49, 3000 Leuven), waived the requirement of informed consent and approved the INTEGO protocol.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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