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Heat-related first cardiovascular event incidence in the city of Madrid (Spain): vulnerability assessment by demographic, socioeconomic, and health indicators

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ABSTRACT

While climate change and population ageing are expected to increase the exposure and vulnerability to extreme heat events, there is emerging evidence suggesting that social inequalities would additionally magnify the projected health impacts. However, limited evidence exists on how social determinants modify heat-related cardiovascular morbidity. This study aims to explore the association between heat and the incidence of first acute cardiovascular event (CVE[1]) in adults in Madrid between 2015-2018, and to assess how social context and other individual characteristics modify the estimated association.

We performed a case-crossover study using the individual information collected from electronic medical records of 6514 adults aged 40-75 living in Madrid city that suffered a first CVE during summer (June-September) between 2015-2018. We applied conditional logistic regression with a distributed lag non-linear model to analyse the heat-CVE association. Estimates were expressed as Odds Ratio (OR) for extreme heat (at 97.5th percentile of daily maximum temperature distribution), compared to the minimum risk temperature. We performed stratified analyses by specific diagnosis, sex, age (40-64, 65-75), country of origin, area-level deprivation, and presence of comorbidities.

Overall, the risk of suffering CVE increased by 15.3 % (OR: 1.153 [95%CI 1.010-1.317]) during extreme heat. Males were particularly more affected (1.248, [1.059-1.471]), vs 1.039 [0.810-1.331] in females), and non-Spanish population (1.869 [1.28-2.728]), vs 1.084 [0.940-1.250] in Spanish). Similar estimates were found by age groups. We observed a dose-response pattern across deprivation levels, with larger risks in populations with higher deprivation (1.228 [1.031-1.462]) and almost null association in the lowest deprivation group (1.062 [0.836-1.349]). No clear patterns of larger vulnerability were found by presence of comorbidity.

We found that heat unequally increased the risk of suffering CVE in adults in Madrid, affecting mainly males and deprived populations. Local measures should pay special attention to vulnerable populations.

Keywords: Urban heat, Cardiovascular events, Case-crossover, social inequalities, neighbourhood deprivation, gender assessment

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[1] First acute cardiovascular disease event

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1. INTRODUCTION

Heat is an important environmental and occupational hazard associated with a substantial burden of morbidity and mortality worldwide (Kovats and Hajat, 2008; Watts et al., 2017; Bell et al., 2018; IPCC, 2022). A recent study estimated that between 2000 to 2019 nearly 1% of all annual deaths worldwide could be attributed to heat, corresponding to 7 deaths per 100 thousand population (Zhao et al., 2021). Exposure to heat has been associated with a wide variety of health outcomes such as cardiovascular and respiratory diseases (Lin et al., 2009; Konstantinoudis et al., 2022; Liu et al., 2022), renal failure (Fletcher et al., 2012; Vaidyanathan et al., 2019), mental health disorders (Lee et al., 2018; Nori-Sarma et al., 2022), dementia (Gon et al., 2022), pregnancy complications (Qu et al., 2021), birth outcomes (Sun et al., 2019) and ultimately with premature mortality (Kovats and Hajat, 2009; Gasparrini et al., 2015; Song et al., 2017; Rodrigues et al., 2019; IPCC, 2022).

Among these illnesses associated with heat, cardiovascular disease is the leading cause of mortality worldwide with 32% of the total deaths (WHO, 2021a). Although the impact of heat on cardiovascular mortality has been extensively assessed in the scientific literature, the evidence on heat-related cardiovascular morbidity is scarce and inconsistent between locations and populations (Michelozzi et al., 2009; Turner et al., 2012; Li et al., 2015; Halaharvi et al., 2020; Schulte et al., 2021; Wang et al., 2021; Cicci et al., 2021; Liu et al., 2022). Some studies have compared the effect of high temperatures on mortality and hospital admissions due to cardiovascular conditions showing contrasting patterns. In particular, a strong positive association was found for mortality, while absence of effect or even a negative association was found for morbidity (e.g., Urban et al., 2013; Iñiguez et al., 2021; Schulte et al., 2021). In contrast, a recent review and meta-analysis also indicated a robust positive association between heat and cardiovascular morbidity, including both hospital admissions, emergency visits and ambulance attendances (Liu et al., 2022). Thus, further research addressing existing uncertainties on the effect of heat on morbidity due to cardiovascular conditions is needed to obtain better knowledge on its association.

Vulnerability to heat is highly variable between and within regions and cities due to the heterogeneous distribution of impact drivers and composition of the populations (e.g., Reid et al., 2009; Madrigano et al., 2015). Social determinants of health (conditions in which people born, grow, work, live, and age) have a relevant implication in health inequality (e.g., Haeberer et al., 2020; WHO, 2023) and often mediate heath risks associated with extreme weather events such as extreme heat (WHO, 2021b). For example, older adults, children, pregnant women, outdoor workers, athletes, and people with pre-existing comorbidities are more vulnerable to heat (WHO, 2018; Ebi et al., 2021; EPA, 2022; Daalen et al., 2022; IPCC, 2022). Additionally, emerging evidence suggests that socioeconomic factors are important determinants of health impacts due to climate change. For example, populations with high deprivation and marginal individuals are often disproportionately more affected by climate-related hazards including heat (IPCC, 2022; Romanello et al., 2021; WHO, 2021b). They are more vulnerable to heat due to the lack of preventive resources (e.g., infrastructure) and are usually more exposed since these populations live in areas in cities more affected by the urban heat island effect (Harlan et al., 2006; Rosenthal et al., 2014; Chakraborty et al., 2019; Hsu et al., 2021; EPA, 2022; IPCC, 2022). Disparities between rural and urban environments could also greatly influence the impacts (e.g., higher heat stress exposure related to a higher settlement density and reduced vegetation in urban areas *or* tend to a higher concentration of older, low-income, and isolate populations in rural settings) (Cardona et al., 2012; Hyland, 2016; Li et al., 2017; López-Bueno et al., 2021; Romanello et al., 2021; IPCC, 2022). However, there is still a research gap on how demographic characteristics and social conditions do interact with and influence the risk of heat-related cardiovascular disease events. In this aspect, there are inconsistencies on whether females or males are more at risk (e.g., Halaharvi et al., 2020; Cicci et al., 2022; Liu et al., 2015) as well as on the role of age as a risk factor. Some studies suggest that older adults seem to be more affected than the younger population (e.g., Wang et al., 2021) whereas others show opposite patterns or non-differential effects by age (e.g., Phung et al., 2016; Ponjoan et al., 2017). Additionally, marginalized populations and individuals with low socioeconomic position have been associated with an increased risk of cardiovascular disease incidence (Powell-Wiley et al., 2022) and mortality (Haeberer et al., 2020). However, the role of racial/ethnical and socioeconomic characteristics as potential risk modifiers in heat-related cardiovascular illness remains understudied and unclear (Gronlund, 2014). Recent evidence indicates that Black individuals seem to be more at risk for cardiovascular disease and mortality associated with heat events than White ones (Madrigano et al., 2015; Son et al., 2019; Berberian et al., 2022; Kahatana et al., 2022). However, the influence of race/ethnicity in the relation heat-cardiovascular outcome can vary between cities and countries. Marital status may also play a relevant role as effect modifier of heat-related health effects (e.g., Son et al., 2019). For instance, a recent study conducted in Turin indicated that alone and widower men (among men population) and divorced and separated women (among women) seemed to be more vulnerable to heat (Ellena et al., 2020).

Meanwhile, climate change and its interaction with other societal challenges such as growing urbanization and ageing are expected to exacerbate the exposure and vulnerability of the population to extreme heat conditions, intensifying existing social inequalities and posing a growing threat to society and public health (Rodrigues et al., 2020; Ebi et al., 2021; Romanello et al., 2021; Daalen et al., 2022; IPCC, 2022). Thus, further evidence on the role of social context on heat vulnerability is needed to support the design of public health strategies aimed to reduce inequalities in the health burden of climate change. Thus, this study aims to address uncertainties on the association between heat and a first acute cardiovascular disease event (overall and by specific diagnosis) using a unique dataset with information collected from primary care services in the city of Madrid and contribute knowledge on how social characteristics and underlying comorbidity act as drivers of the effect and associated social inequalities.

BOX 1. Implications of this study in climate epidemiology

Evidence from previous studies	**Additional value of this research**
The effect of heat on cardiovascular mortality is widely known but the effect on cardiovascular morbidity remains unclear. Different methodologies, heat event definition, lags, type of outcome and	We advance knowledge about the impact of high temperatures on the first acute cardiovascular disease event (overall and by specific causes) in the large city of Madrid using advanced methodology and

demographic characteristics may largely influence differences found between studies.	for the first time a unique dataset based on individual medical records collected from primary care services of the city.
Social determinants of health are relevant factors for health inequality but there is a gap in the literature on the role of these factors as modifiers in health-related cardiovascular morbidity risk. Inconsistencies exist between studies.	These results provide valuable information for a better understanding of vulnerability profiles to heat based on demographic, socioeconomic, and health indicators: age, sex, place of origin, area-level deprivation, and underlying comorbidities.
Changes in climatic and socioeconomic conditions are expected to exacerbate pre-existing inequalities in heat-related cardiovascular burden. This constitutes a current pressing challenge in environmental health.	We provide evidence that could be useful for public health polices, enabling the planning of effective measures in health care to reduce climate change-related health inequality and reduce current and future risks associated with extreme heat, particularly among the most vulnerable individuals.

2. MATERIAL AND METHODS

2.1. Study region

The Municipality of Madrid is the capital of Spain with a geographical extension of 604.5 km^2 and a population size of around 3.3 million residents (Madrid city council, 2022a). Madrid is one of the 179 municipalities that constitute the province with the same name, located in the centre of the country (Figure 1). The city of Madrid is currently divided into 21 heterogeneous districts, further divided into 131 neighbourhoods and 2450 administrative units, named census sections (Madrid city council, 2022b). This study population is ideal to address the main objectives of this research for the following reasons: 1) high heat exposure due to its large population (the third largest city in Europe) and warm climate, with very hot summers (Fernández García and Rasilla Álvarez, 2008; Eurostat, 2016; AEMET, 2019), 2) presence of strong social inequalities across the city (Leal and Sorando, 2016) with a decreasing northwest-southeast decreasing gradient relative to socioeconomic status (Gullón et al., 2017).

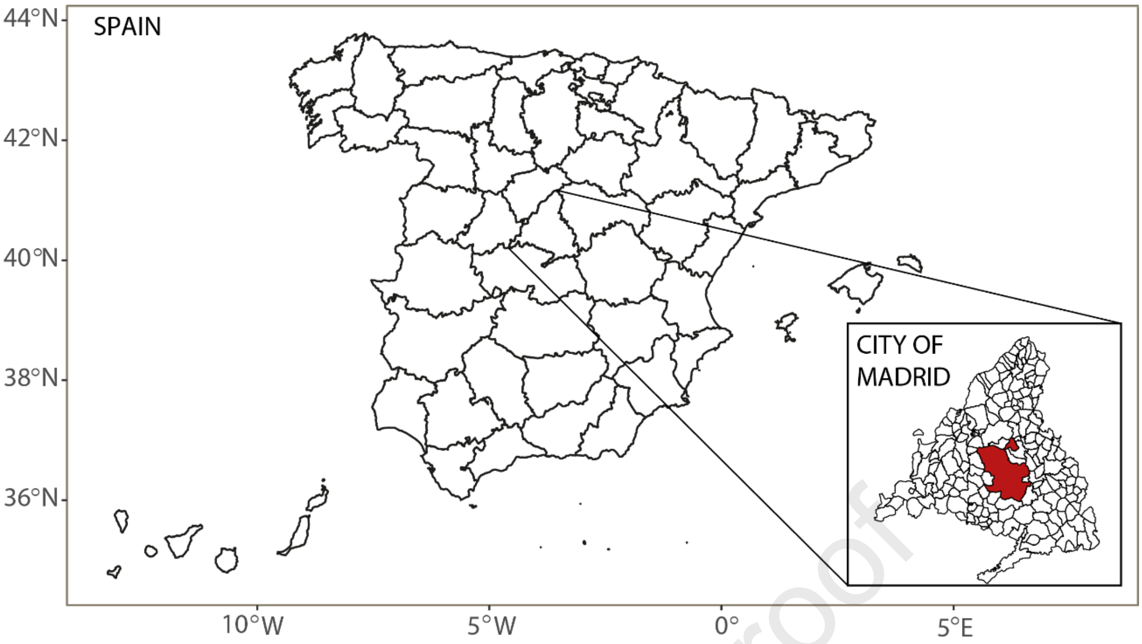

Figure 1. Study region. Map of Spain showing the study region of the city of Madrid (red), located within the Autonomous Community of Madrid (Centre of Spain).

2.2. Study population

We used the dataset collected by the Heart Healthy Hoods (HHH) project (https://www.hhhproject.es/), a study focused on the social and physical urban environments and cardiovascular health and inequalities across the city of Madrid (Franco et al., 2015; Bilal et al., 2016). This dataset was based on primary care data with information from 1,442,840 residents aged 40-75 who were registered in any primary health care centre of the city of Madrid from 2015, corresponding to 91% of the residents of this age group in the municipality. We restricted our study population to individuals that experienced a first acute cardiovascular disease event (CVE) in Madrid during the summer months (June to September) between 2015 and 2018. We considered as outcome of interest the first acute cardiovascular event due to the data availability (the "date" variable in the database corresponded to the date when the subject was diagnosed with a first diagnosis by cardiovascular disease). This in turn resulted in a more uniform and comparable population sample. We included the following groups of cardiovascular diagnoses: ischaemic heart disease with angina (K74 according to the International Classification of Primary Care (https://www.semfyc.es/)), acute myocardial infarction (K75), ischaemic heart disease without angina (K76), heart failure (K77), transient cerebral ischaemia (K89), and stroke and cerebrovascular accident (K90). We excluded the cases with missing information for the district of residence (2.2%) since that information was required to link the high-resolution exposure data.

2.3. Individual data

We included information on sex, age, country of origin, and area-level deprivation. The latter was defined according to the census-section of residence (smallest administrative spatial unit in Spain) and indicated as an index defined in quintiles. The socioeconomic deprivation index was created by the Spanish Epidemiology Society (Sociedad Española de Epidemiología, SEE) by applying Principal Component Analysis using data from the 2011 Spanish census (https://seepidemiologia.es/determinantes-sociales-de-la-salud/). It incorporated six indicators included in the main socioeconomic domains: education (insufficient education overall and in young people aged 16 to 29 years), occupation (manual and temporary workers, unemployment), and dwellings (lack of internet access) (Duque et al., 2021). From the index defined in quintiles, we created three levels of deprivation to account for low deprivation (corresponding to individuals with a deprivation value classified in the first or second quintile), medium deprivation (third quintile), and high deprivation (fourth or fifth quintile). The database also included information about the preexisting diagnosis of a chronic affection, described as risk factors for cardiovascular disease such as hypertension uncomplicated (K86), hypertension with affectation (K87), diabetes type I or insulin-dependent (T89), diabetes type II or non-insulin dependent (T90), and dyslipidaemia (T93) (Upadhyay, 2015; WHO, 2021a; CDC, 2022).

2.4. Environmental data

We used daily maximum temperature (Tmax, in degrees Celsius (°C)) as the main exposure variable for this study. We used daily temperature data on a spatial grid of 5 km resolution covering Spain from 1951 onwards provided by the Meteorological State Agency (Agencia Estatal de Meteorología, AEMET) (AEMET, 2022). The database was generated using information from all AEMET weather stations and the historical analysis of the HIRLAM (High-Resolution Limited Area Modelling) numerical prediction model operated by AEMET. This high-resolution gridded data allowed us to assign the specific temperature exposure in each small area (i.e., district level). We estimated the district-level exposure by averaging the temperature data of all the grid cells that intersected each district. We assigned to each study individual the level of exposure for each case day and control days according to the district of residence.

Additionally, we collected information on other time-varying environmental factors which could potentially act as confounders. In particular, we obtained the daily mean concentrations (µg/m3) of particulate matter with an aerodynamic of less than 10µm (PM_{10}), nitrogen dioxide (NO_2), and ozone (O_3) recorded at the air quality monitoring stations situated in the municipality of Madrid. Datasets are publicly available on the Open data portal of the Madrid city Council (Madrid city council, 2022c). Contrary to temperature data, it was not possible to derive district-specific measurements since monitors were unevenly distributed across the city. Thus, we created a single daily time series of each pollutant at the municipality level across the study period by averaging the daily observations from all stations available in the city of Madrid.

2.5. Study design and statistical analyses

Different methodologies have been used to explore the association between high temperatures and cardiovascular outcomes. The most common of these are case-crossover design and time series analysis combined with distributed lag-nonlinear models to flexibly describe non-linear and delayed associations between heat and cardiovascular events (Rodrigues et al., 2019; Cicci et al., 2021; Alahmad et al., 2023). Linear models have been also considered to assuming a linear association between the exposure and health outcome (Li et al., 2015; López-Bueno et al., 2021). Here, we performed a case-crossover study, where each study subject serves as its own control and all time-invariant confounders are controlled by design (Maclure, 1991; Carracedo-Martínez et al., 2009). We applied a conditional logistic regression model (Method S1 in the supplementary material). In this analysis, we used a time-stratified approach to compare the exposure on each case day (corresponding to the first diagnosis of acute cardiovascular disease) with exposures on control days corresponding to all other days of the same month and year, based on the criteria followed by other authors (e.g., Guo et al., 2011; Lubczynska et al., 2015; Dabrowiecki et al., 2022). We did not included the day of the week in the stratum as in other studies (e.g., Xu et al., 2013; Amstrong et al., 2014; Alahmad et al., 2023) to gain statistical power by increasing the number of controls for each case (e.g., 30 *vs* 4, depending on the year). We controlled for day of the week by including that variable as indicator in the regression model. Similar to Gasparrini (2002), we conducted a more thorough control of the temporal trends by including a natural spline of the day of the year with two degrees of freedom and a quadratic B-spline of time with two degrees of freedom since their inclusion improved the robustness of the model ($p<0.05$ in Likelihood Ratio Test (LRT) and lower AIC, Table S1 in Supplementary Material). We modelled the heat-CVE association with a distributed lag non-linear model (DLNM) (Gasparrini et al., 2010) that flexibly accounts for potential non-linearities and delayed dependencies. We fitted a quadratic B-spline with an internal knot at the 85th percentile of the summer-Tmax distribution to model the exposure-response dimension. We applied an unconstrained lag structure with two days of lags to account for delayed effects and potential harvesting. The “harvesting effect” or also commonly known (mortality) displacement occurs when an environmental stressor (e.g., high temperatures) strongly affects a pool of frail individuals leading to a sudden increase in risk (e.g., CVE) and a strong depletion of frail individuals that eventually translates into a lower or even negative estimate (protective) in the following days (Gasparrini et al., 2010). We performed a series of sensitivity analyses to assess the robustness of the main model (Table S2 in the supplementary material) and the model specifications were selected based on the Akaike Information Criterion (AIC) (Table S2 in the supplementary material). We also explored the effect of heat on CVE accounting for different lags (0, 2, 4, 6 days) (Table S3). Additionally, we assessed the potential confounder effect of air pollution using distributed linear models (DLMs) for each pollutant as an explanatory variable (Table S4 in the supplementary material).

We reported the association estimates as odds ratios (OR) for extreme heat (97.5th percentile of the daily maximum temperature distribution in Madrid), using the minimum risk temperature as reference located between the 25th and 90th percentiles. We conducted stratified analysis by subgroups of diagnosis, sex, age, country of origin, area-level deprivation and presence of comorbidities. We created three main groups relative to comorbidities by grouping individuals diagnosed with any type of hypertension (K86 or/and K87), individuals diagnosed with any type of diabetes (T89 or/and T90), and people with dyslipidaemia (T93). Individuals that were diagnosed on the same day with the first diagnosis of more than one specific cardiovascular cause were considered as independent events in the stratified analysis.

All analyses were performed in R software (version 4.1.3) using *gnm* and *dlnm* packages.

3. RESULTS

3.1. Descriptive statistics

Table 1 shows descriptive statistics of the study population. In total, we examined 6514 individuals who suffered a first CVE during the summer months between 2015 to 2018. Men accounted for 61.1% of the total population, with a mean age of 62 years, whereas women accounted for 38.9% with a mean age of 65 years. According to age groups, 53.2% were younger adults (40-64 years) and 46.81% were older adults (≥65 years). The population was mostly born in Spain, accounting for 89.4% of the total, whereas the rest of individuals were born mostly in South American countries (i.e., Ecuador, Peru, Colombia), Dominican Republic (Greater Antilles) and Morocco (Africa) (Table S5). The spatial distribution of the deprivation level showed that lower deprivation was mostly located in the northern and west-central areas of the city (Figure 2). We did not have information on socioeconomic deprivation for 1.4% of the total cases. We found the highest number of cardiovascular events in the diagnoses of stroke and cerebrovascular accident (22.9%) and acute myocardial infarction (21.7%), while ischaemic heart disease without angina was the least frequent (7.5%). Regarding the presence of comorbidities, we observed a larger prevalence of cases previously diagnosed with dyslipidaemia (46.3%), and uncomplicated hypertension (44.9%) (Table 1).

Table 1. Descriptive statistics of the study population (n= 6514).

Variable	Sub-category	n (%)
Code of cardiovascular diagnosis	Ischemic heart disease with angina (K74)	1105 (17.0)
	Acute myocardial infarction (K75)	1412 (21.7)
	Ischemic heart disease without angina (K76)	490 (7.5)
	Heart failure (K77)	823 (12.6)
	Transient cerebral ischemia (K89)	1219 (18.7)
	Stroke/ cerebrovascular accident (K90)	1493 (22.9)
Sex	Males	3981 (61.1)
	Females	2533 (38.9)
Age	Younger adults (40-64 years)	3465 (53.2)
	Older adults (65-75 years)	3049 (46.8)
Country of origin	Spanish	5823 (89.4)

	Non-Spanish	691 (10.6)
Area-level socioeconomic deprivation index	Low	3072 (47.2)
	Medium	1123 (17.2)
	High	2228 (34.2)
Comorbidities	Dyslipidaemia (T93)	3013 (46.3)
	hypertension uncomplicated (K86)	2926 (44.9)
	hypertension with affectation (K87)	411 (6.3)
	Type I diabetes (T89)	54 (0.8)
	Type II diabetes (T90)	1397 (21.4)

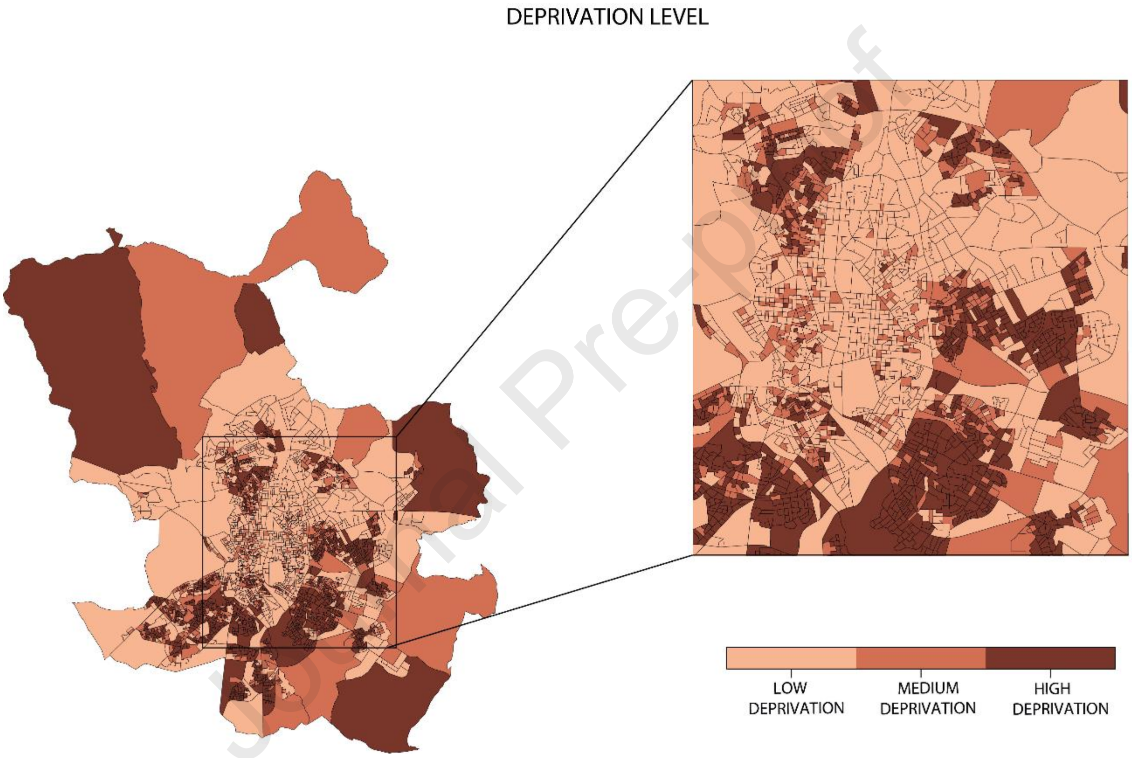

Figure 2. Spatial distribution of the deprivation index for all the census sections of Madrid. The index was originated from the socioeconomic deprivation index created by the Spanish Epidemiology Society using data from 2011 Spanish census (SEE, 2022), defined in quintiles. Three levels of deprivation are showed: low level corresponded to values within the first and second quintile (in light brown colour), medium level included values in the third quintile (in medium brown colour), and high deprivation accounted for values within the fourth and fifth quintile (in dark brown colour).

As shown in Table 2, the average daily Tmax (°C) in Madrid between June-September (2015-2018) was 32.1°C (range 19.3, 40.5°C). We did not find strong differences in Tmax exposure across districts, ranging from an average of 31.1ºC in the districts of Tetuan and Chamberi to 33.3°C in Villa de Vallecas (table S6).The average levels for daily PM_{10}, NO_2, and O_3 (µg/m3) were 23.3 µg/m3 (range 6.3, 93.7 µg/m3), 32.0 µg/m3 (range 9.6, 70.6 µg/m3), and 68.5 µg/m3 (range 25.29, 108.36 µg/m3), respectively.

Environmental variable	mean	range (min, max)
Tmax (ºC)	32.1	(19.3, 40.5)
PM10 (µg/m3)	23.3	(6.3, 93.7)
NO2 (µg/m3)	32.0	(9.6, 70.6)
O3 (µg/m3)	68.5	(25.3, 108.4)

Table 2. Descriptive statistics corresponding to the exposure variable (daily maximum temperature, ºC) and environmental confounders (PM_{10}, NO_2, O_3, µg/m3) in the city of Madrid during the summer months (June-September) between 2015 and 2018.

3.2. Short-term risk of the first cardiovascular event due to extreme heat

Figure 3 depicts the overall cumulative association between daily Tmax and CVE in the study population, expressed as OR (95%CI) (Figures S1-S6 for each subgroup of diagnosis and Figures S7-S18 for each subgroup of population). Figure 4 shows the OR corresponding to extreme heat exposure (97.5th temperature percentile in Madrid, 39.34ºC) for the total population and by subgroups.

We found a positive association between daily Tmax and CVE in adults in Madrid (Figure 3). In particular, we estimated that the risk of suffering a first CVE increases by 15.3 % after an extreme heat day (OR of 1.153 (95%CI: 1.010, 1.317)). According to specific groups of diagnosis, we found a positive (but imprecise) association for all specific cardiovascular causes analysed, except for heart disease without angina with a slightly negative but largely imprecise estimate. The largest effect of extreme heat was found for transient cerebral ischaemia (1.447 [1.028, 2.036]), followed by ischaemic heart disease with angina (1.231 [0.899, 1.687]) and acute myocardial infarction (1.157 [0.88, 1.523]). In contrast, we found a slight reduction in the risk of heart disease without angina during extreme heat conditions (0.936 [0.561, 1.564]). The ORs [95%CI] for heart failure and stroke/cerebrovascular accident associated with extreme heat were 1.114 [0.753, 1.649] and 1.042 [0.784, 1.387], respectively (Figure 4).

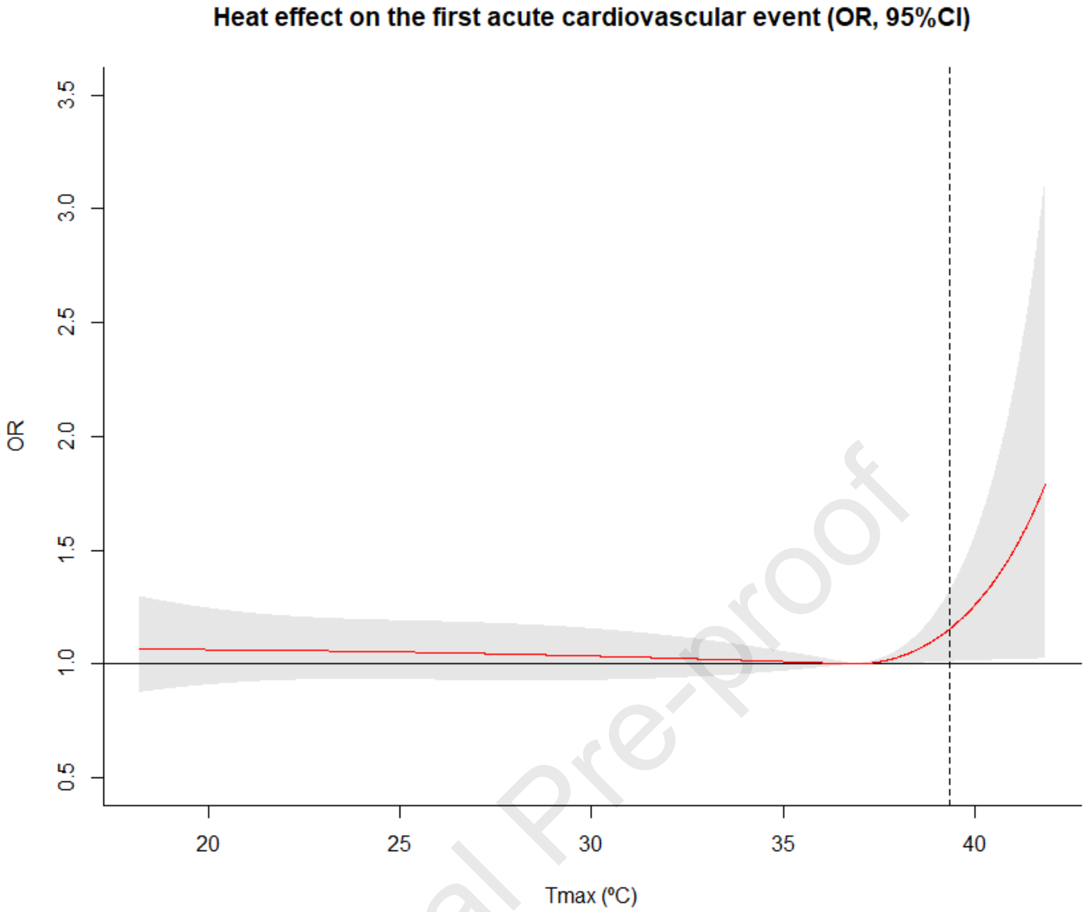

Figure 3. Cumulative short-term association between daily maximum temperature (Tmax, ºC) and first cardiovascular disease event in adults during the summer 1157 months in Madrid (2015-2018). The association was expressed as odds ratio (OR), 1158 together with the 95% confidence interval (CI, grey area). The dashed line indicates the 97.5th 1159 temperature percentile in the municipality of Madrid.

We found differences in the risk of suffering a CVE associated with heat across subgroups. Extreme heat mostly affected males (1.248 [1.059, 1.471] vs 1.039 [0.810, 1.331] in females). Similar risks were found across age groups, with a slightly higher risk in older adults (1.191 [0.978, 1.450] vs 1.126 [0.945, 1.342] in young adults). Substantial differences in the risk were observed between Spanish and non-Spanish residents, being the latter more affected (1.869 [1.280, 2.728] vs. 1.084 [0.940, 1.250]). We also observed a clear dose-response pattern relative to the deprivation condition: the greater level of deprivation the higher risk of suffering a first cardiovascular event (OR ranged from 1.062 [0.836, 1.349] in low deprivation to 1.228 [1.031, 1.462] in high deprivation). The stratified analysis by the presence of comorbidities did not show substantial differences across subgroups and the obtained estimates were imprecise due to the low statistical power (Figure 4).

We also checked the potential confounder effect of atmospheric pollution by including PM_{10}, NO_2, and O_3 in the main model. However, the inclusion of these variables did not improve the fit of the model nor the main association estimate changed substantially

(Table S3 in the supplementary material). Additionally, when extending the lag period to 4 and 6 days, the association estimates were slightly lower and also more imprecise (1.145 [0.957, 1.371] and 1.091 [0.885, 1.347] for 4 and 6 days of lag, respectively).

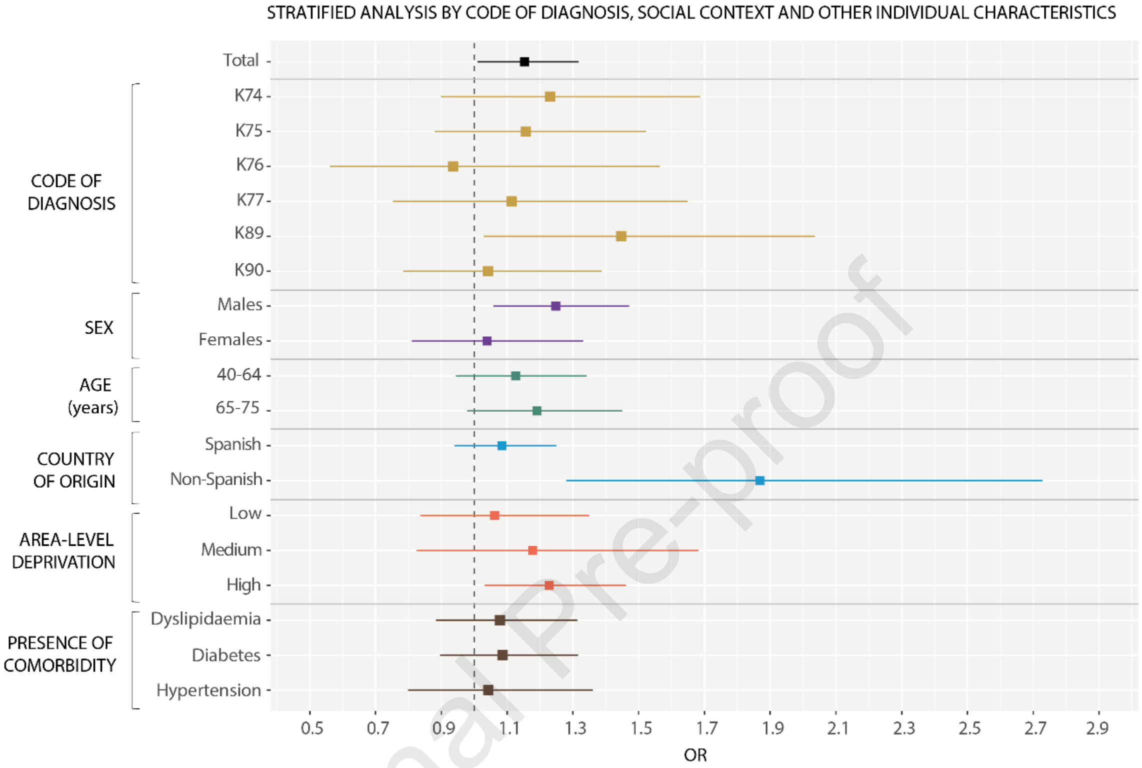

Figure 4. Odds ratio (OR) of first cardiovascular disease event associated with extreme heat (and 95% CI) by diagnosis, categories of social determinants (sex, age, country of origin, area-level deprivation status) and presence of comorbidies. Horizontal bars correspond to the 95% confidence intervals. K74: Ischemic heart disease with angina; K75: Acute myocardial infarction; K76: Ischemic heart disease without angina; K77: Heart failure; K89: Transient cerebral ischemia; K90: Stroke/cerebrovascular accident.

4. DISCUSSION

In this study, we found that exposure to heat increased the risk of suffering a first cardiovascular event in 40-to-75-years-old adults living in the city of Madrid. We used a unique database with information from primary care electronic medical records to comprehensively explore the role of the main social determinants as potential vulnerability factors leading to inequalities in heat-cardiovascular morbidity. Our results suggest that males and non-Spanish residents were at a higher risk, while we did not find differences across age groups. Interestingly, we observed a clear dose-response pattern between area-level of deprivation and heat-morbidity risk with significant higher risks in more deprived populations.

These findings are consistent with previous studies that indicate a positive association between high-temperature exposure and cardiovascular morbidity (Lin et al., 2009; Phung et al., 2016; Aklilu et al., 2020; Halaharvi et al., 2020; Wang et al., 2021). However, the heat-related morbidity risk still remains unclear since other studies found an opposite pattern (Michelozzi et al., 2009; Gronlund et al., 2014; Urban et al., 2014; Schulte et al., 2021) or no substantial effect of heat on cardiovascular disease (Linares and Díaz, 2008; Hanzlíková et al., 2015; Ponjoan et al., 2017; Iñiguez et al., 2021). Differences between study results may be explained by the heterogeneity of the studied populations (e.g., climate area, demographic structure of the population, culture, risk management, healthcare system) as well as by differences in the study design, outcome type, definition of heat events and lags analyzed (Cardona et al., 2012; Li et al., 2015; Dang et al., 2019; Cicci et al., 2022; IPCC, 2022).

The potential pathways linking heat and cardiovascular outcomes have been extensively explored in physiological models. Extreme heat exposure can compromise the capacity of the body to get rid of excess heat (i.e., heat stress) triggering complex physiopathological processes that ultimately lead to cardiovascular impairment (e.g., higher cardiac output and contractility and greater myocardial oxygen consumption, systemic inflammation and changes in the blood rheology, which promotes hypercoagulability and thrombosis) (Keatinge et al., 1986; Liu et al., 2015; Chaseling et al., 2021, Liu et al., 2022). Nawrot et al. 2005 suggested that vascular endothelial function can be reduced in response to increased outdoor temperature (Nawrot et al., 2005; García-Lledó et al., 2020). Thus, exposure to elevated temperature could lead to a higher risk of suffering ischaemia, myocardial infarction and circulatory collapse, particularly in susceptible individuals such as those with impaired cardiovascular health (Ebi et al., 2021).

We found a positive but imprecise association between daily maximum temperature and the CVE risk by subgroups of diagnoses (Figure 4, Figures S1-S6). It should be noted that the low precision of these estimates is due to the low number of cases reported in each subgroup. In particular, we found that extreme heat more largely increased the risk of the first event of transient cerebral ischemia (44.7% [95%CI:2.8, 103.6]), followed by ischaemic heart disease with angina (23.1 % [-10.1, 68.7]) and acute myocardial infarction (15.7% [-12.0, 52.3]). Our results also support a previous study conducted in the Province of Madrid which found a positive (but not robust) association between warm temperatures and SR-segment elevation myocardial infarction (García-Lledó et al., 2020). A similar pattern was also observed in a study in Ontario (Canada), with a strong positive association between high temperature and overall coronary heart diseases, whereas a positive but more uncertain association was found for specific diagnoses, including myocardial infarction, stroke, and ischemic stroke (Bai et al., 2018). Studies conducted in Israel (Vered et al., 2020) and China (Chen et al., 2017) also showed an increased risk of hospital admissions for transient ischemic attack/stroke associated with high ambient temperature. Underlying physiological processes related to heat exposure (haemoconcentration and hyperviscosity) may cause thromboembolism, compromising the blood flow to the brain thereby increasing the risk of cerebral ischemia and stroke (Liu et al., 2015). In contrast to our findings, Lin et al. 2009 suggested a positive association for ischaemic heart disease but a negative association for cerebrovascular disease and heart failure in New York. Thus, further understanding of the mechanisms explaining the association between high temperature and specific cardiovascular diagnosis is needed, especially considering the inconsistent results observed between studies (Cicci et al., 2022).

Furthermore, we found that heat-related cardiovascular risk may be unevenly distributed across subpopulations of adults in Madrid, with a relevant influence of sex, country of origin, and small-area deprivation level as risk modifier factors. First, our findings indicate that males may be particularly more vulnerable to heat, compared to females, as suggested in previous assessments (e.g., Lin et al., 2009; Li et al., 2015; Phung et al., 2016; Halaharvi et al., 2020). However, other studies show an opposite pattern or no relevant implication of sex group as a risk-modifying factor (e.g., Cui et al., 2019; Liu et al., 2022). The biological mechanisms involved in differences in vulnerability to heat between both sex groups are still uncertain (Li et al., 2015). However, differences in living habits and gender behaviours could explain differences in vulnerability to heat between men and women. We hypothesize that men may tend to engage in less preventive behaviours during extreme heat events and be more involved in outdoors jobs and activities than women, resulting in higher exposure and risk, or having a higher prevalence of cardiovascular risk factors (Li et al., 2015; Liu et al., 2015; Wang et al., 2021). For example, a recent study conducted in Spain found a larger prevalence of smoking and obesity in men compared to women (Gullón et al., 2021). However, we could not assess the role of specific cardiovascular risk factors such as smoking due to the large percentage of missing information. Finally, the fact that this study only included adults aged 40 to 75 years may have led to a lower risk in females compared to other studies using adults of older age. Previous studies suggested that this subgroup is at higher risk because their life expectancy longer (e.g., van Steen et al., 2019; Díaz et al., 2022a).

Overall, previous studies showed that age is a strong risk factor of heat-related morbidity and mortality, with people aged 65 years and above being the most vulnerable population (Díaz et al., 2002b; Kenny et al., 2010; Lin Et al., 2009; Romanello et al., 2021; Saucy et al., 2021; Daalen et al., 2022; IPCC, 2022; Khraishah et al., 2022). It is because older adults have decreased ability to maintain body core temperature during heat stress, reduced adaptation to dehydration, increased prevalence of comorbidities, and frequently live alone and isolate, with less resources to cope with extreme heat events (Li et al., 2015; Kenny et al., 2010; CDC, 2017). However, in this study, we did not find substantial differences in heat-CVE morbidity risk by age groups, with a slightly higher risk in older adults compared to young adults (19.1 % [-2.2, 45.0 (%)] *vs* 12.6% [-5.5, 34.2 (%)] associated with extreme heat). This pattern could be explained by the fact that our study population included adults between 40 and 75 years and, thereby, we could not explore the effect in the most susceptible age groups (ie., above 75 years). However, our results may also indicate that heat impact may not only be limited to older adults since a positive (although not robust) association between heat and cardiovascular disease was also observed in younger adults, who are predictably less at risk. This finding is of particular relevance since young adults could be more at risk of recidivism and with larger impacts on labour productivity, which altogether could translate into important socioeconomic effects (Watts et al., 2017; Ebi et al., 2021; Daalen et al., 2022).

Moreover, we found a clear pattern of increasing vulnerability to heat with more deprived populations. We also estimated a higher risk of suffering CVE associated with heat in foreign born populations (mostly born in developing countries) (86.9% [28.0, 172.8 (%)]), which usually live in more deprived areas (Rodriguez et al., 1993; Jaegowsky, 2009; Benassi et al., 2022). This pattern could be explained by the *a priori* higher level of exposure to heat among more deprived and marginalized populations because most of them are outdoor workers or live in areas more affected by urban heat island (Hsu et al., 2021). However, we did not find strong differences in heat exposure by districts, which may be in part explained by the fact that spatial resolution of temperature dataset was not detailed enough to capture them (Table S5). Additionally, lower adaptive behaviour due to cultural issues or low education (e.g., lower access and control of resources, limited ability to get information due to different culture and language, health illiteracy, less awareness of heat-related health risks) and factors related with infrastructure (e.g., less access to cooling mechanisms and health care, living in areas with buildings highly concentrated and with reduced green space accessibility and quality). Finally, higher exposure to chronic stressors (e.g., violence, isolation, food insecurity) (Harlan et al., 2013; Gronlund, 2014; Li et al., 2015; Hoffimann et al., 2017; Saucy et al., 2021; Liu et al., 2022). Evidence indicates that people with low socioeconomic status are more likely to suffer chronic stress, which is associated with proinflammatory processes and atherogenesis, with important implications for cardiovascular health (Power-Wiley et al., 2022). Additionally, socioeconomic status can also influence the prevalence of cardiovascular risk factors such as smoking, physical inactivity, and obesity (Sundquist et al., 1999; Schultz et al., 2018; Gullón et al., 2021). A recent study conducted in the city of Madrid indicates that low socioeconomic areas were linked to lower availability of exercise, which was associated with the prevalence of obesity and type 2 diabetes (Cereijo et al., 2022) and could influence stress levels (Sharma et al., 2006). Other studies show a lower availability and access of stores with healthy foods in low-socioeconomic areas in the cities of Madrid (Spain) (Martínez-García et al., 2020) and Melbourne (Australia) (Ball et al., 2009), compared to middle-and-high-socioeconomic areas. This could increase the consumption of unhealthy food in more disadvantageous regions, increasing the risk of cardiovascular risk factors. However, further research is needed to test these hypothesis on the lifestyle-related mechanisms involved in the association between deprivation level and heat-related cardiovascular risk. On the other hand, it has been described that discrepances in genetic susceptibility and interactions between genetic and environmental factors between migrants and the host population may influence differences in cardiovascular disease prevalence and risk factors in the different populations (Agyemang and van den Born, 2022), however further evidence is required.

Additionally, no clear patterns of increased risk were found in individuals with hypertension, diabetes, and dyslipidaemia, which are considered the major modifiable risk factors for cardiovascular disease (Lu et al., 2019; CDC, 2022). Lavigne et al., 2014 showed that comorbid hypertension did not substantially increase the risk of emergency room visits due to cardiovascular disease associated with extreme temperatures in Toronto, but they also found a stronger association for persons with underlying diabetes compared to persons without diabetes. However, it should be noted that we did not have additional information on whether these individuals were under medical treatment for these chronic diseases, which could influence our results.

The role of air pollution as effect modifier in the association between heat and health remains still debatable. Our results suggest no substantial confounding effect of air pollution in heat-related CVE incidence, similar to other studies that addressed the impact of heat on mortality (e.g., Antonella and Schwartz, 2008; López-Bueno et al., 2020).

This study presents several strengths. Firstly, we conducted for the first time an analysis at individual level using a unique database based on electronic health records from the

Madrid Primary Health Care System. The detailed information on sociodemographic variables and health data allowed us to perform a comprehensive assessment of risk across relevant population subgroups. Second, we used high-resolution dataset of daily maximum temperature (5km of spatial resolution, and daily temporal resolution), which allowed us to get level exposure to a smaller scale than municipal level (i.e., district-level exposure), reducing the potential misclassification of exposure in this analysis. However, the temperature data was not detailed enough to assign a refined exposure to the census track level-the geographical information available for each patient. Nevertheless, we believe that it is likely that the use of a finer resolution would not have substantially influenced the results. For example, a previous study on the effects of temperature on kidney conditions in New York, in where authors using a case-crossover design, showed that the effects did not meaningfully differ when authors compared across different temperature spatial resolutions (Chu et al., 2023). Third, we applied the state-of-the-art method to flexibly assess the non-linear and delayed association between daily maximum temperature and CVE.

We also acknowledge several limitations of our study. Our results represent the risk in the adult population between 40 and 75 years, thereby, we did not consider a relevant and potentially more vulnerable population of above 75 years old. It should be noted that other factors such as house infrastructure, air conditioning, race/ethnicity and follow-up of the medical treatments were not included in the analysis because data was not available. Considering the results obtained by deprivation level, further analysis including additional control of specific variables at small area level (e.g., green areas availability, violence level) could be useful to better understand the mechanisms on the association between deprivation and heat-related risk in the city. Unfortunately, we could not retrieve estimates by sex: age: country of origin strata to assess potential differences among the non-Spanish population across age and sex groups because the number of non-Spanish individuals was too small for a powerful statistical analysis on a such small scale. Thus, we encourage future research addressing this using a larger population sample. Additionally, the exposure to daily maximum temperature was defined at district level of the residence, and do not reflect the level of personal exposure. Regarding the exposure to air pollution, we used an average level for the whole city rather than assigning levels for each census track or district due to the lack of sufficient air pollution monitoring stations available at these levels of disagregation. This limitation is also indicated in López-Bueno et al. (2020). In this study we could not include the control of other weather variables such as humidity due to the lack of suitable data. However, this limitation is also indicated in other studies such as in Schulte et al. (2021), which suggests that the influence of humidity as confounder in heat-related health effects remains debatable. Thus, it is probably that in case of existing an effect it would be small.

5. CONCLUSIONS

Our findings indicate that heat poses a relevant threat to population health after analysing data of the whole city of Madrid. These results are of particular relevance as Madrid is the third largest city in Europe and a densely populated urban area exposed to frequent extreme-high temperature events. Madrid is also characterized by strong social inequalities. We found that high summer temperatures in Madrid increased the risk of having a first cardiovascular event in adults aged 40-75 years. More importantly, the risk of a first cardiovascular event was unevenly distributed across the city socioeconomic gradient, indicating that neighbourhood and individual characteristics have a substantial influence in heat-related health inequalities. Men, residents of foreign origin and those living in high deprivation areas were more vulnerable to heat. This study emphasizes the need of integrating evidence from vulnerability assessments in the planning of public health interventions to reduce heat-related health burden to improve awareness and protection against climate change effects, especially in more susceptible and disadvantaged populations. This is essential considering that climate change is expected to further amplify social inequality and health risks associated with extreme heat in urban areas.

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TABLES CAPTIONS

Table 1. Descriptive statistics of the study population (n= 6514).

Table 2. Descriptive statistics corresponding to the exposure variable (daily maximum temperature, ºC) and environmental confounders (PM_{10}, NO_2, O_3, µg/m3) in the city of Madrid during the summer months (June-September) between 2015 and 2018.

FIGURES CAPTIONS

Figure 1. Study region. Map of Spain showing the study region of the city of Madrid (red), located within the Autonomous Community of Madrid (Centre of Spain).

Figure 2. Spatial distribution of the deprivation index for all the census sections of Madrid. The index was originated from the socioeconomic deprivation index created by the Spanish Epidemiology Society using data from 2011 Spanish census (SEE, 2022), defined in quintiles. Three levels of deprivation are showed: low level corresponded to values within the first and second quintile (in light brown colour), medium level included values in the third quintile (in medium brown colour), and high deprivation accounted for values within the fourth and fifth quintile (in dark brown colour).

Figure 3. Cumulative short-term association between daily maximum temperature (Tmax, ºC) and first cardiovascular disease event in adults during the summer 1157 months in Madrid (2015-2018). The association was expressed as odds ratio (OR), 1158 together with the 95% confidence interval (CI, grey area). The dashed line indicates the 97.5th 1159 temperature percentile in the municipality of Madrid.

Figure 4. Odds ratio (OR) of first cardiovascular disease event associated with extreme heat conditions by diagnosis, categories of social determinants (sex, age, country of origin, area-level deprivation status) and comorbidity variables. Horizontal bars correspond to the 95% confidence intervals. K74: Ischemic heart disease with angina; K75: Acute myocardial infarction; K76: Ischemic heart disease without angina; K77: Heart failure; K89: Transient cerebral ischemia; K90: Stroke/cerebrovascular accident.

HIGHLIGHTS

Extreme heat increased the risk of a first cardiovascular event in adults in Madrid

Extreme heat mostly impacted men, non-Spanish, and deprived populations

The larger deprivation level, the higher heat-related first cardiovascular event risk

No substantial risk differences were found between age groups (40-64; 65-75)

Comorbidity presence did not increase heat-related first cardiovascular event risk

Declaration of interests

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

☐ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: