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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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1 2	Heat-related first cardiovascular event incidence in the city of Madrid (Spain): vulnerability assessment by demographic, socioeconomic, and health indicators
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44 ABSTRACT

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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 (CVE¹) 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 53 electronic medical records of 6514 adults aged 40-75 living in Madrid city that suffered 54 a first CVE during summer (June-September) between 2015-2018. We applied 55 conditional logistic regression with a distributed lag non-linear model to analyse the heat-56 CVE association. Estimates were expressed as Odds Ratio (OR) for extreme heat (at 57 97.5th percentile of daily maximum temperature distribution), compared to the minimum 58 risk temperature. We performed stratified analyses by specific diagnosis, sex, age (40-64, 59 65-75), country of origin, area-level deprivation, and presence of comorbidities. 60

Overall, the risk of suffering CVE increased by 15.3 % (OR: 1.153 [95% CI 1.010-1.317]) 61 during extreme heat. Males were particularly more affected (1.248, [1.059-1.471]), vs 62 1.039 [0.810-1.331] in females), and non-Spanish population (1.869 [1.28-2.728]), vs 63 1.084 [0.940-1.250] in Spanish). Similar estimates were found by age groups. We 64 observed a dose-response pattern across deprivation levels, with larger risks in 65 populations with higher deprivation (1.228 [1.031-1.462]) and almost null association in 66 67 the lowest deprivation group (1.062 [0.836-1.349]). No clear patterns of larger vulnerability were found by presence of comorbidity. 68

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.

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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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135 **1. INTRODUCTION**

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Heat is an important environmental and occupational hazard associated with a substantial 137 burden of morbidity and mortality worldwide (Kovats and Hajat, 2008; Watts et al., 2017; 138 Bell et al., 2018; IPCC, 2022). A recent study estimated that between 2000 to 2019 nearly 139 1% of all annual deaths worldwide could be attributed to heat, corresponding to 7 deaths 140 per 100 thousand population (Zhao et al., 2021). Exposure to heat has been associated 141 with a wide variety of health outcomes such as cardiovascular and respiratory diseases 142 (Lin et al., 2009; Konstantinoudis et al., 2022; Liu et al., 2022), renal failure (Fletcher et 143 al., 2012; Vaidyanathan et al., 2019), mental health disorders (Lee et al., 2018; Nori-144 Sarma et al., 2022), dementia (Gon et al., 2022), pregnancy complications (Qu et al., 145 2021), birth outcomes (Sun et al., 2019) and ultimately with premature mortality (Kovats 146 and Hajat, 2009; Gasparrini et al., 2015; Song et al., 2017; Rodrigues et al., 2019; IPCC, 147 2022). 148

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Among these illnesses associated with heat, cardiovascular disease is the leading cause 150 of mortality worldwide with 32% of the total deaths (WHO, 2021a). Although the impact 151 of heat on cardiovascular mortality has been extensively assessed in the scientific 152 literature, the evidence on heat-related cardiovascular morbidity is scarce and inconsistent 153 between locations and populations (Michelozzi et al., 2009; Turner et al., 2012; Li et al., 154 2015; Halaharvi et al., 2020; Schulte et al., 2021; Wang et al., 2021; Cicci et al., 2021; 155 Liu et al., 2022). Some studies have compared the effect of high temperatures on mortality 156 and hospital admissions due to cardiovascular conditions showing contrasting patterns. 157 In particular, a strong positive association was found for mortality, while absence of 158 effect or even a negative association was found for morbidity (e.g., Urban et al., 2013; 159 Iñiguez et al., 2021; Schulte et al., 2021). In contrast, a recent review and meta-analysis 160 also indicated a robust positive association between heat and cardiovascular morbidity, 161 including both hospital admissions, emergency visits and ambulance attendances (Liu et 162 al., 2022). Thus, further research addressing existing uncertainties on the effect of heat 163 on morbidity due to cardiovascular conditions is needed to obtain better knowledge on its 164 association. 165

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Vulnerability to heat is highly variable between and within regions and cities due to the 167 heterogeneous distribution of impact drivers and composition of the populations (e.g., 168 Reid et al., 2009; Madrigano et al., 2015). Social determinants of health (conditions in 169 which people born, grow, work, live, and age) have a relevant implication in health 170 inequality (e.g., Haeberer et al., 2020; WHO, 2023) and often mediate heath risks 171 associated with extreme weather events such as extreme heat (WHO, 2021b). For 172 example, older adults, children, pregnant women, outdoor workers, athletes, and people 173 with pre-existing comorbidities are more vulnerable to heat (WHO, 2018; Ebi et al., 2021; 174 EPA, 2022; Daalen et al., 2022; IPCC, 2022). Additionally, emerging evidence suggests 175 that socioeconomic factors are important determinants of health impacts due to climate 176 change. For example, populations with high deprivation and marginal individuals are 177 often disproportionately more affected by climate-related hazards including heat (IPCC, 178 2022; Romanello et al., 2021; WHO, 2021b). They are more vulnerable to heat due to the 179 lack of preventive resources (e.g., infrastructure) and are usually more exposed since 180 these populations live in areas in cities more affected by the urban heat island effect 181 (Harlan et al., 2006; Rosenthal et al., 2014; Chakraborty et al., 2019; Hsu et al., 2021; 182 EPA, 2022; IPCC, 2022). Disparities between rural and urban environments could also 183 greatly influence the impacts (e.g., higher heat stress exposure related to a higher 184

185 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; 186 Hyland, 2016; Li et al., 2017; López-Bueno et al., 2021; Romanello et al., 2021; IPCC, 187 2022). However, there is still a research gap on how demographic characteristics and 188 social conditions do interact with and influence the risk of heat-related cardiovascular 189 disease events. In this aspect, there are inconsistencies on whether females or males are 190 more at risk (e.g., Halaharvi et al., 2020; Cicci et al., 2022; Liu et al., 2015) as well as on 191 the role of age as a risk factor. Some studies suggest that older adults seem to be more 192 affected than the younger population (e.g., Wang et al., 2021) whereas others show 193 opposite patterns or non-differential effects by age (e.g., Phung et al., 2016; Ponjoan et 194 2017). Additionally, marginalized populations and individuals with low al., 195 socioeconomic position have been associated with an increased risk of cardiovascular 196 disease incidence (Powell-Wiley et al., 2022) and mortality (Haeberer et al., 2020). 197 However, the role of racial/ethnical and socioeconomic characteristics as potential risk 198 modifiers in heat-related cardiovascular illness remains understudied and unclear 199 (Gronlund, 2014). Recent evidence indicates that Black individuals seem to be more at 200 risk for cardiovascular disease and mortality associated with heat events than White ones 201 (Madrigano et al., 2015; Son et al., 2019; Berberian et al., 2022; Kahatana et al., 2022). 202 However, the influence of race/ethnicity in the relation heat-cardiovascular outcome can 203 vary between cities and countries. Marital status may also play a relevant role as effect 204 modifier of heat-related health effects (e.g., Son et al., 2019). For instance, a recent study 205 conducted in Turin indicated that alone and widower men (among men population) and 206 divorced and separated women (among women) seemed to be more vulnerable to heat 207 (Ellena et al., 2020). 208

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Meanwhile, climate change and its interaction with other societal challenges such as 210 growing urbanization and ageing are expected to exacerbate the exposure and 211 vulnerability of the population to extreme heat conditions, intensifying existing social 212 inequalities and posing a growing threat to society and public health (Rodrigues et al., 213 2020; Ebi et al., 2021; Romanello et al., 2021; Daalen et al., 2022; IPCC, 2022). Thus, 214 further evidence on the role of social context on heat vulnerability is needed to support 215 216 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 217 heat and a first acute cardiovascular disease event (overall and by specific diagnosis) 218 using a unique dataset with information collected from primary care services in the city 219 of Madrid and contribute knowledge on how social characteristics and underlying 220 comorbidity act as drivers of the effect and associated social inequalities. 221

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BOX 1. Implications of this study in clim	nate 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	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
event definition, lags, type of outcome and	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 km² 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).



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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).

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256 **2.2. Study population**

We used the dataset collected by the Heart Healthy Hoods (HHH) project 258 259 (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 260 et al., 2015; Bilal et al., 2016). This dataset was based on primary care data with 261 information from 1,442,840 residents aged 40-75 who were registered in any primary 262 health care centre of the city of Madrid from 2015, corresponding to 91% of the residents 263 of this age group in the municipality. We restricted our study population to individuals 264 that experienced a first acute cardiovascular disease event (CVE) in Madrid during the 265 summer months (June to September) between 2015 and 2018. We considered as outcome 266 of interest the first acute cardiovascular event due to the data availability (the "date" 267 variable in the database corresponded to the date when the subject was diagnosed with a 268 first diagnosis by cardiovascular disease). This in turn resulted in a more uniform and 269 comparable population sample. We included the following groups of cardiovascular 270 diagnoses: ischaemic heart disease with angina (K74 according to the International 271 Classification of Primary Care (https://www.semfyc.es/)), acute myocardial infarction 272 (K75), ischaemic heart disease without angina (K76), heart failure (K77), transient 273 cerebral ischaemia (K89), and stroke and cerebrovascular accident (K90). We excluded 274 the cases with missing information for the district of residence (2.2%) since that 275 information was required to link the high-resolution exposure data. 276

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278 **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 283 de Epidemiología, SEE) by applying Principal Component Analysis using data from the 284 2011 Spanish census (https://seepidemiologia.es/determinantes-sociales-de-la-salud/). It 285 incorporated six indicators included in the main socioeconomic domains: education 286 (insufficient education overall and in young people aged 16 to 29 years), occupation 287 (manual and temporary workers, unemployment), and dwellings (lack of internet access) 288 (Duque et al., 2021). From the index defined in quintiles, we created three levels of 289 deprivation to account for low deprivation (corresponding to individuals with a 290 deprivation value classified in the first or second quintile), medium deprivation (third 291 quintile), and high deprivation (fourth or fifth quintile). The database also included 292 information about the preexisting diagnosis of a chronic affection, described as risk 293 factors for cardiovascular disease such as hypertension uncomplicated (K86), 294 hypertension with affectation (K87), diabetes type I or insulin-dependent (T89), diabetes 295 type II or non-insulin dependent (T90), and dyslipidaemia (T93) (Upadhyay, 2015; WHO, 296 2021a; CDC, 2022). 297

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301 **2.4. Environmental data**

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We used daily maximum temperature (Tmax, in degrees Celsius (°C)) as the main 303 exposure variable for this study. We used daily temperature data on a spatial grid of 5 km 304 resolution covering Spain from 1951 onwards provided by the Meteorological State 305 Agency (Agencia Estatal de Meteorología, AEMET) (AEMET, 2022). The database was 306 generated using information from all AEMET weather stations and the historical analysis 307 of the HIRLAM (High-Resolution Limited Area Modelling) numerical prediction model 308 operated by AEMET. This high-resolution gridded data allowed us to assign the specific 309 temperature exposure in each small area (i.e., district level). We estimated the district-310 level exposure by averaging the temperature data of all the grid cells that intersected each 311 district. We assigned to each study individual the level of exposure for each case day and 312 control days according to the district of residence. 313

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Additionally, we collected information on other time-varying environmental factors 315 which could potentially act as confounders. In particular, we obtained the daily mean 316 concentrations (μ g/m3) of particulate matter with an aerodynamic of less than 10 μ m 317 (PM_{10}) , nitrogen dioxide (NO_2) , and ozone (O_3) recorded at the air quality monitoring 318 stations situated in the municipality of Madrid. Datasets are publicly available on the 319 Open data portal of the Madrid city Council (Madrid city council, 2022c). Contrary to 320 temperature data, it was not possible to derive district-specific measurements since 321 monitors were unevenly distributed across the city. Thus, we created a single daily time 322 series of each pollutant at the municipality level across the study period by averaging the 323 daily observations from all stations available in the city of Madrid. 324

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326 **2.5. Study design and statistical analyses**

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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

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332 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 333 have been also considered to assuming a linear association between the exposure and 334 health outcome (Li et al., 2015; López-Bueno et al., 2021). Here, we performed a case-335 crossover study, where each study subject serves as its own control and all time-invariant 336 337 confounders are controlled by design (Maclure, 1991; Carracedo-Martínez et al., 2009). We applied a conditional logistic regression model (Method S1 in the supplementary 338 material). In this analysis, we used a time-stratified approach to compare the exposure on 339 each case day (corresponding to the first diagnosis of acute cardiovascular disease) with 340 exposures on control days corresponding to all other days of the same month and year, 341 based on the criteria followed by other authors (e.g., Guo et al., 2011; Lubczynska et al., 342 2015; Dabrowiecki et al., 2022). We did not included the day of the week in the stratum 343 as in other studies (e.g., Xu et al., 2013; Amstrong et al., 2014; Alahmad et al., 2023) to 344 gain statistical power by increasing the number of controls for each case (e.g., 30 vs 4, 345 depending on the year). We controlled for day of the week by including that variable as 346 indicator in the regression model. Similar to Gasparrini (2002), we conducted a more 347 thorough control of the temporal trends by including a natural spline of the day of the 348 year with two degrees of freedom and a quadratic B-spline of time with two degrees of 349 freedom since their inclusion improved the robustness of the model (p<0.05 in Likelihood 350 Ratio Test (LRT) and lower AIC, Table S1 in Supplementary Material). We modelled the 351 heat-CVE association with a distributed lag non-linear model (DLNM) (Gasparrini et al., 352 2010) that flexibly accounts for potential non-linearities and delayed dependencies. We 353 fitted a quadratic B-spline with an internal knot at the 85th percentile of the summer-354 Tmax distribution to model the exposure-response dimension. We applied an 355 unconstrained lag structure with two days of lags to account for delayed effects and 356 potential harvesting. The "harvesting effect" or also commonly known (mortality) 357 displacement occurs when an environmental stressor (e.g., high temperatures) strongly 358 affects a pool of frail individuals leading to a sudden increase in risk (e.g., CVE) and a 359 strong depletion of frail individuals that eventually translates into a lower or even negative 360 estimate (protective) in the following days (Gasparrini et al., 2010). We performed a 361 series of sensitivity analyses to assess the robustness of the main model (Table S2 in the 362 supplementary material) and the model specifications were selected based on the Akaike 363 Information Criterion (AIC) (Table S2 in the supplementary material). We also explored 364 the effect of heat on CVE accounting for different lags (0, 2, 4, 6 days) (Table S3). 365 Additionally, we assessed the potential confounder effect of air pollution using distributed 366 367 linear models (DLMs) for each pollutant as an explanatory variable (Table S4 in the supplementary material). 368

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.

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

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382 **3. RESULTS**

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384 3.1. Descriptive statistics

Table 1 shows descriptive statistics of the study population. In total, we examined 6514 385 individuals who suffered a first CVE during the summer months between 2015 to 2018. 386 Men accounted for 61.1% of the total population, with a mean age of 62 years, whereas 387 women accounted for 38.9% with a mean age of 65 years. According to age groups, 388 53.2% were younger adults (40-64 years) and 46.81% were older adults (\geq 65 years). The 389 population was mostly born in Spain, accounting for 89.4% of the total, whereas the rest 390 of individuals were born mostly in South American countries (i.e., Ecuador, Peru, 391 Colombia), Dominican Republic (Greater Antilles) and Morocco (Africa) (Table S5). The 392 spatial distribution of the deprivation level showed that lower deprivation was mostly 393 located in the northern and west-central areas of the city (Figure 2). We did not have 394 information on socioeconomic deprivation for 1.4% of the total cases. We found the 395 highest number of cardiovascular events in the diagnoses of stroke and cerebrovascular 396 accident (22.9%) and acute myocardial infarction (21.7%), while ischaemic heart disease 397 without angina was the least frequent (7.5%). Regarding the presence of comorbidities, 398 we observed a larger prevalence of cases previously diagnosed with dyslipidaemia 399 (46.3%), and uncomplicated hypertension (44.9%) (Table 1). 400

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

Variable	Sub-category	n (%)
Code of	Ischemic heart disease with angina (K74)	1105 (17.0)
cardiovascular	Acute myocardial infarction (K75)	1412 (21.7)
diagnosis	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)

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	Non-Spanish	691 (10.6)
Area-level	Low	3072 (47.2)
socioeconomic	Medium	1123 (17.2)
deprivation index	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)

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DEPRIVATION LEVEL



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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).

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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 31.1°C in the districts of Tetuan and Chamberi to 33.3°C in Villa de Vallecas (table S6).The average levels for daily PM₁₀, NO₂, and O₃ (μ g/m3) were 23.3 μ g/m3 (range 6.3, 93.7 μ g/m3), 32.0 μ g/m3 (range 9.6, 70.6 μ g/m3), and 68.5 μ g/m3 (range 25.29, 108.36 μ g/m3), respectively.

Environmental variable	mean	range (min, max)
Tmax (°C)	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)

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Table 2. Descriptive statistics corresponding to the exposure variable (daily maximum temperature, °C) and environmental confounders (PM₁₀, NO₂, O₃, μ g/m3) in the city of Madrid during the summer months (June-September) between 2015 and 2018.

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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,
39.34°C) for the total population and by subgroups.

438

439 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 % 440 after an extreme heat day (OR of 1.153 (95%CI: 1.010, 1.317)). According to specific 441 groups of diagnosis, we found a positive (but imprecise) association for all specific 442 cardiovascular causes analysed, except for heart disease without angina with a slightly 443 negative but largely imprecise estimate. The largest effect of extreme heat was found for 444 transient cerebral ischaemia (1.447 [1.028, 2.036]), followed by ischaemic heart disease 445 with angina (1.231 [0.899, 1.687]) and acute myocardial infarction (1.157 [0.88, 1.523]). 446 In contrast, we found a slight reduction in the risk of heart disease without angina during 447 extreme heat conditions (0.936 [0.561, 1.564]). The ORs [95%CI] for heart failure and 448 stroke/cerebrovascular accident associated with extreme heat were 1.114 [0.753, 1.649] 449 450 and 1.042 [0.784, 1.387], respectively (Figure 4).

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Heat effect on the first acute cardiovascular event (OR, 95%CI)

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Figure 3. Cumulative short-term association between daily maximum temperature (Tmax, °C) 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 462 subgroups. Extreme heat mostly affected males (1.248 [1.059, 1.471] vs 1.039 [0.810, 463 1.331] in females). Similar risks were found across age groups, with a slightly higher risk 464 in older adults (1.191 [0.978, 1.450] vs 1.126 [0.945, 1.342] in young adults). Substantial 465 differences in the risk were observed between Spanish and non-Spanish residents, being 466 the latter more affected (1.869 [1.280, 2.728] vs. 1.084 [0.940, 1.250]). We also observed 467 a clear dose-response pattern relative to the deprivation condition: the greater level of 468 deprivation the higher risk of suffering a first cardiovascular event (OR ranged from 1.062 469 [0.836, 1.349] in low deprivation to 1.228 [1.031, 1.462] in high deprivation). The 470 stratified analysis by the presence of comorbidities did not show substantial differences 471 across subgroups and the obtained estimates were imprecise due to the low statistical 472 473 power (Figure 4).

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475 We also checked the potential confounder effect of atmospheric pollution by including 476 PM_{10} , NO_2 , and O_3 in the main model. However, the inclusion of these variables did not 477 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.

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These findings are consistent with previous studies that indicate a positive association 507 between high-temperature exposure and cardiovascular morbidity (Lin et al., 2009; Phung 508 et al., 2016; Aklilu et al., 2020; Halaharvi et al., 2020; Wang et al., 2021). However, the 509 heat-related morbidity risk still remains unclear since other studies found an opposite 510 pattern (Michelozzi et al., 2009; Gronlund et al., 2014; Urban et al., 2014; Schulte et al., 511 2021) or no substantial effect of heat on cardiovascular disease (Linares and Díaz, 2008; 512 Hanzlíková et al., 2015; Ponjoan et al., 2017; Iñiguez et al., 2021). Differences between 513 study results may be explained by the heterogeneity of the studied populations (e.g., 514 climate area, demographic structure of the population, culture, risk management, 515 healthcare system) as well as by differences in the study design, outcome type, definition 516 of heat events and lags analyzed (Cardona et al., 2012; Li et al., 2015; Dang et al., 2019; 517 Cicci et al., 2022; IPCC, 2022). 518

519

The potential pathways linking heat and cardiovascular outcomes have been extensively 520 explored in physiological models. Extreme heat exposure can compromise the capacity 521 of the body to get rid of excess heat (i.e., heat stress) triggering complex 522 physiopathological processes that ultimately lead to cardiovascular impairment (e.g., 523 higher cardiac output and contractility and greater myocardial oxygen consumption, 524 systemic inflammation and changes in the blood rheology, which promotes 525 hypercoagulability and thrombosis) (Keatinge et al., 1986; Liu et al., 2015; Chaseling et 526 al., 2021, Liu et al., 2022). Nawrot et al. 2005 suggested that vascular endothelial function 527 can be reduced in response to increased outdoor temperature (Nawrot et al., 2005; García-528 Lledó et al., 2020). Thus, exposure to elevated temperature could lead to a higher risk of 529 suffering ischaemia, myocardial infarction and circulatory collapse, particularly in 530 susceptible individuals such as those with impaired cardiovascular health (Ebi et al., 531 2021). 532

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We found a positive but imprecise association between daily maximum temperature and 534 the CVE risk by subgroups of diagnoses (Figure 4, Figures S1-S6). It should be noted that 535 the low precision of these estimates is due to the low number of cases reported in each 536 subgroup. In particular, we found that extreme heat more largely increased the risk of the 537 538 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 539 infarction (15.7% [-12.0, 52.3]). Our results also support a previous study conducted in 540 the Province of Madrid which found a positive (but not robust) association between warm 541 temperatures and SR-segment elevation myocardial infarction (García-Lledó et al., 2020). 542 A similar pattern was also observed in a study in Ontario (Canada), with a strong positive 543 association between high temperature and overall coronary heart diseases, whereas a 544 positive but more uncertain association was found for specific diagnoses, including 545 myocardial infarction, stroke, and ischemic stroke (Bai et al., 2018). Studies conducted 546 547 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 548 Underlying physiological temperature. processes related to heat exposure 549 550 (haemoconcentration and hyperviscosity) may cause thromboembolism, compromising the blood flow to the brain thereby increasing the risk of cerebral ischemia and stroke 551 (Liu et al., 2015). In contrast to our findings, Lin et al. 2009 suggested a positive 552 association for ischaemic heart disease but a negative association for cerebrovascular 553 disease and heart failure in New York. Thus, further understanding of the mechanisms 554 explaining the association between high temperature and specific cardiovascular 555

diagnosis is needed, especially considering the inconsistent results observed betweenstudies (Cicci et al., 2022).

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Furthermore, we found that heat-related cardiovascular risk may be unevenly distributed 559 across subpopulations of adults in Madrid, with a relevant influence of sex, country of 560 origin, and small-area deprivation level as risk modifier factors. First, our findings 561 indicate that males may be particularly more vulnerable to heat, compared to females, as 562 suggested in previous assessments (e.g., Lin et al., 2009; Li et al., 2015; Phung et al., 563 2016; Halaharvi et al., 2020). However, other studies show an opposite pattern or no 564 relevant implication of sex group as a risk-modifying factor (e.g., Cui et al., 2019; Liu et 565 al., 2022). The biological mechanisms involved in differences in vulnerability to heat 566 between both sex groups are still uncertain (Li et al., 2015). However, differences in 567 living habits and gender behaviours could explain differences in vulnerability to heat 568 between men and women. We hypothesize that men may tend to engage in less preventive 569 behaviours during extreme heat events and be more involved in outdoors jobs and 570 activities than women, resulting in higher exposure and risk, or having a higher 571 prevalence of cardiovascular risk factors (Li et al., 2015; Liu et al., 2015; Wang et al., 572 2021). For example, a recent study conducted in Spain found a larger prevalence of 573 574 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 575 the large percentage of missing information. Finally, the fact that this study only included 576 adults aged 40 to 75 years may have led to a lower risk in females compared to other 577 studies using adults of older age. Previous studies suggested that this subgroup is at higher 578 risk because their life expectancy longer (e.g., van Steen et al., 2019; Díaz et al., 2022a). 579 580

Overall, previous studies showed that age is a strong risk factor of heat-related morbidity 581 and mortality, with people aged 65 years and above being the most vulnerable population 582 (Díaz et al., 2002b; Kenny et al., 2010; Lin Et al., 2009; Romanello et al., 2021; Saucy et 583 al., 2021; Daalen et al., 2022; IPCC, 2022; Khraishah et al., 2022). It is because older 584 adults have decreased ability to maintain body core temperature during heat stress, 585 reduced adaptation to dehydration, increased prevalence of comorbidities, and frequently 586 587 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 588 differences in heat-CVE morbidity risk by age groups, with a slightly higher risk in older 589 adults compared to young adults (19.1 % [-2.2, 45.0 (%)] vs 12.6% [-5.5, 34.2 (%)] 590 associated with extreme heat). This pattern could be explained by the fact that our study 591 population included adults between 40 and 75 years and, thereby, we could not explore 592 the effect in the most susceptible age groups (ie., above 75 years). However, our results 593 may also indicate that heat impact may not only be limited to older adults since a positive 594 (although not robust) association between heat and cardiovascular disease was also 595 observed in younger adults, who are predictably less at risk. This finding is of particular 596 relevance since young adults could be more at risk of recidivism and with larger impacts 597 on labour productivity, which altogether could translate into important socioeconomic 598 599 effects (Watts et al., 2017; Ebi et al., 2021; Daalen et al., 2022).

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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 606 them are outdoor workers or live in areas more affected by urban heat island (Hsu et al., 607 2021). However, we did not find strong differences in heat exposure by districts, which 608 may be in part explained by the fact that spatial resolution of temperature dataset was not 609 detailed enough to capture them (Table S5). Additionally, lower adaptive behaviour due 610 to cultural issues or low education (e.g., lower access and control of resources, limited 611 ability to get information due to different culture and language, health illiteracy, less 612 awareness of heat-related health risks) and factors related with infrastructure (e.g., less 613 access to cooling mechanisms and health care, living in areas with buildings highly 614 concentrated and with reduced green space accessibility and quality). Finally, higher 615 exposure to chronic stressors (e.g., violence, isolation, food insecurity) (Harlan et al., 616 2013; Gronlund, 2014; Li et al., 2015; Hoffimann et al., 2017; Saucy et al., 2021; Liu et 617 al., 2022). Evidence indicates that people with low socioeconomic status are more likely 618 to suffer chronic stress, which is associated with proinflammatory processes and 619 atherogenesis, with important implications for cardiovascular health (Power-Wiley et al., 620 2022). Additionally, socioeconomic status can also influence the prevalence of 621 cardiovascular risk factors such as smoking, physical inactivity, and obesity (Sundquist 622 et al., 1999; Schultz et al., 2018; Gullón et al., 2021). A recent study conducted in the city 623 624 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 625 et al., 2022) and could influence stress levels (Sharma et al., 2006). Other studies show a 626 lower availability and access of stores with healthy foods in low-socioeconomic areas in 627 the cities of Madrid (Spain) (Martínez-García et al., 2020) and Melbourne (Australia) 628 (Ball et al., 2009), compared to middle-and-high-socioeconomic areas. This could 629 increase the consumption of unhealthy food in more disadvantageous regions, increasing 630 the risk of cardiovascular risk factors. However, further research is needed to test these 631 hypothesis on the lifestyle-related mechanisms involved in the association between 632 deprivation level and heat-related cardiovascular risk. On the other hand, it has been 633 described that discrepances in genetic susceptibility and interactions between genetic and 634 environmental factors between migrants and the host population may influence 635 differences in cardiovascular disease prevalence and risk factors in the different 636 populations (Agyemang and van den Born, 2022), however further evidence is required. 637

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Additionally, no clear patterns of increased risk were found in individuals with 639 hypertension, diabetes, and dyslipidaemia, which are considered the major modifiable 640 risk factors for cardiovascular disease (Lu et al., 2019; CDC, 2022). Lavigne et al., 2014 641 showed that comorbid hypertension did not substantially increase the risk of emergency 642 room visits due to cardiovascular disease associated with extreme temperatures in 643 Toronto, but they also found a stronger association for persons with underlying diabetes 644 compared to persons without diabetes. However, it should be noted that we did not have 645 646 additional information on whether these individuals were under medical treatment for these chronic diseases, which could influence our results. 647

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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).

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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

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Madrid Primary Health Care System. The detailed information on sociodemographic 656 variables and health data allowed us to perform a comprehensive assessment of risk across 657 relevant population subgroups. Second, we used high-resolution dataset of daily 658 maximum temperature (5km of spatial resolution, and daily temporal resolution), which 659 allowed us to get level exposure to a smaller scale than municipal level (i.e., district-level 660 exposure), reducing the potential misclassification of exposure in this analysis. However, 661 the temperature data was not detailed enough to assign a refined exposure to the census 662 track level-the geographical information available for each patient. Nevertheless, we 663 believe that it is likely that the use of a finer resolution would not have substantially 664 influenced the results. For example, a previous study on the effects of temperature on 665 kidney conditions in New York, in where authors using a case-crossover design, showed 666 that the effects did not meaningfully differ when authors compared across different 667 temperature spatial resolutions (Chu et al., 2023). Third, we applied the state-of-the-art 668 method to flexibly assess the non-linear and delayed association between daily maximum 669 temperature and CVE. 670

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We also acknowledge several limitations of our study. Our results represent the risk in 672 the adult population between 40 and 75 years, thereby, we did not consider a relevant and 673 674 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 675 medical treatments were not included in the analysis because data was not available. 676 Considering the results obtained by deprivation level, further analysis including 677 additional control of specific variables at small area level (e.g., green areas availability, 678 violence level) could be useful to better understand the mechanisms on the association 679 between deprivation and heat-related risk in the city. Unfortunately, we could not retrieve 680 estimates by sex: age: country of origin strata to assess potential differences among the 681 non-Spanish population across age and sex groups because the number of non-Spanish 682 individuals was too small for a powerful statistical analysis on a such small scale. Thus, 683 we encourage future research addressing this using a larger population sample. 684 Additionally, the exposure to daily maximum temperature was defined at district level of 685 the residence, and do not reflect the level of personal exposure. Regarding the exposure 686 to air pollution, we used an average level for the whole city rather than assigning levels 687 for each census track or district due to the lack of sufficient air pollution monitoring 688 stations available at these levels of disagregation. This limitation is also indicated in 689 López-Bueno et al. (2020). In this study we could not include the control of other weather 690 variables such as humidity due to the lack of suitable data. However, this limitation is 691 also indicated in other studies such as in Schulte et al. (2021), which suggests that the 692 influence of humidity as confounder in heat-related health effects remains debatable. 693 Thus, it is probably that in case of existing an effect it would be small. 694

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698 **5. CONCLUSIONS**

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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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1366 TABLES CAPTIONS

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

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

- 1372
- 1373 FIGURES CAPTIONS

1374

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).

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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, °C) 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

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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:

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