Effects of ambient temperatures and extreme weather events on circulatory mortality in a high population density area: Exploring mortality data from Malta

Shafkat Jahan [a,*], John Paul Cauchi [a], Charles Galdies [b], Darren Wraith [a]

[a] School of Public Health and Social Work, Faculty of Health, Queensland University, of Technology, Brisbane, QLD 4059, Australia
[b] Institute of Earth Systems, University of Malta, Msida MSD 2080, Malta

A B S T R A C T

Background: Temperature-related circulatory mortality has gained consistent public health importance worldwide due to changes in inter-annual average temperatures and the increased frequency of extreme events over time. This study investigates the association between temperature and circulatory deaths in one of the highest population densities in the world (Malta) with a Mediterranean climate.

Methods: Daily deaths relating to circulatory mortality (32,847 deaths) were obtained from January 1992 to December 2017. A distributed lag non-linear model (DLNM) with a Poisson distribution was utilized to estimate effects of ambient temperatures and heatwaves or cold spells (2–4 consecutive days). Effects were also explored for the specific cause of death, different age groups, gender and time periods.

Results: The study observed a U-shaped cumulative exposure–response curve with a greater mortality risk due to cooler temperatures (8–15°C) after adjusting for harvesting effects (0–27 days). Colder temperatures (<8.9°C) were strongly related to both ischemic heart disease (IHD) (RR, 1.85, 95% CI, 1.24–2.77) and cerebrovascular disease (RR, 3.80,95% CI, 1.57–9.17). While heat effects were short-term (0–5 lag days), the cold effects were long-term (0–27 days) and consistent across different lag days. Cooler temperatures (8.99–12.6°C) were also related to IHD mortality in males (RR, 1.94, 95% CI, 1.05–3.59) and females (RR, 1.95, 95% CI, 1.2–3.59) and cerebrovascular mortality in females (RR, 8.32, 95% CI, 2.58–26.80). Elderly females (over 65 years) had a higher risk of death relating to IHD (RR, 1.33, 95% CI, 1.19–3.18) and cerebro-vascular diseases (RR, 8.84, 95% CI, 2.64–29.61). Interestingly, colder temperatures (<8.9°C) were highly related to cerebrovascular deaths in the earliest time period (1992–2000) and IHD deaths in the most recent time period (2000–2017). While the effect of heatwaves was unclear across the time periods, there was some visible cold-spell effects for cerebrovascular mortality (RR, 1.03, 95% CI, 1.01–1.06).

Conclusion: This study used a long time series of mortality data from a high population density area to explore the impact of ambient temperature and extreme events on circulatory deaths. The results of the study will help to improve preventive and adaptive strategies to mitigate climatic health impacts.

* Corresponding author at: School of Public Health and Social Work, Faculty of Health, Queensland University of Technology, Victoria Park Rd, Kelvin Grove, QLD 4059, Australia.
  E-mail address: s1.jahan@qut.edu.au (S. Jahan).

1. Introduction

Climate change is directly or indirectly linked to human health outcomes, thus could influence or exacerbate cold and heat related mortality (McMichael et al., 2006; Mitchel et al., 2016; Gasparrini et al., 2017; Vicedo-Cabrera et al., 2021). Due to the projected consequences of global warming, the effect of ambient temperatures and extreme weather events on circulatory mortality, particularly cardiovascular mortality, has gained significant public health importance and has been a topic of interest for many decades (Atsumi et al., 2013; Dang et al., 2019; Kouis et al., 2019; Silveira et al., 2019; Yu et al., 2011; Zhou et al., 2017).

In spite of remarkable modifications to treatment and management plans, circulatory diseases, specifically cardiovascular disease (CVD), are the leading cause of deaths, contributing 31% of global mortality in 2016 (WHO, 2016). With economic development and rapid unplanned urbanisation and higher population density the risk for circulatory mortality is increasing in low- and middle-income countries (Bowry et al., 2015; Roth et al., 2015; Teo & Dokainish, 2017). Although the risk for cardiovascular death is declining in higher-income countries, the trend is changing due to socio-economic inequality (Roth et al., 2020).

Along with a wide range of individual modifiable and non-modifiable risk factors (i.e., family history, age, gender, diabetes, high blood pressure, high cholesterol level, physical inactivity, tobacco, unbalanced diet) environmental factors such as ambient temperature and in/outdoor air pollution could advance the disease process and increase mortality risk by augmenting/exaggerating the pathophysiological process related with circulatory diseases (Cosselman et al., 2015; Baumgartner et al., 2011). Extreme temperatures affect the autonomic nervous system, blood pressure, thermogenesis, inflammatory response, thrombogenesis and oxidative stress (Cai et al., 2016, Hintsala et al., 2014; Stewart et al., 2017) and increase the risk of initiation and potential complications of circulatory diseases.

A number of studies from Europe have investigated the impact of temperature variability and extreme weather events exacerbating the risk for cardiovascular mortality in different populations and reported a U (or V) or J shaped exposure–response association (Analitis et al., 2008; Baccini et al., 2008; Chen et al; 2018; D'Ippoliti et al., 2010; Huynen et al., 2001; Iñiguez et al., 2021; Linares et al., 2015; Kouis et al., 2019). While a majority of these studies examined the entire temperature range and reported a higher risk for either hot temperatures (Kouis et al., 2019) or cold temperatures (Iñiguez et al., 2021; Rocklöv et al., 2009; Kendrovski, 2006), other studies restricted the temperature effects by particular season (warm or cold season) and reported heat (Baccini et al., 2008; D'Ippoliti et al., 2010) and cold related (Analitis et al., 2008) excess cardiac mortality.

Malta is an archipelago situated to the south of Sicily (southern Europe) and shares a Mediterranean climate. Galdies et al., (2016) reported a local warming trend in the annual maximum temperature by 0.09°C per annum for the period 1967–2013, accompanied by a positive trend of + 0.2°C per decade in the mean annual air temperature for the period 1951–2010; Galdies, 2011). Malta is expected to experience a moderate effect of climate change with a projected rise in annual average temperature in the range 0.53–1.32°C by 2030 (Climate Change Adaptation Committee for Malta, 2010) with negative impacts on a number of important sectors (Galdies & Vella, 2019).

In contrast to other countries in Europe, Malta is a small, highly urbanised, and densely populated country with a typical Mediterranean climate with a very hot summer and mild winter (Healy, 2003). Inter-annual variability of winter temperature could play an important role in winter mortality in countries with a milder winter compared to countries with consistent year to year winter temperatures due to human thermoregulatory systems or behaviour and adaptation strategies (i.e., protective clothing, insulated housing) which may be less developed (Fowler et al., 2015; Eng & Mercer, 2000).

The Maltese population could be at a higher risk of climate change due to the frequency and severity of extreme weather events. Whilst for the last decade there has been a marked emphasis given to adaptation and mitigation strategies (such as the use of air conditioning), under projected consequences of global warming the Maltese population (particularly vulnerable groups) are still at significant risk for circulatory related morbidity and mortality.

To the best of the authors' knowledge, only one study (England et al., 2010) extensively examined the relationship between ambient temperature and all-cause mortality in Malta and reported that the daily mortality rate was higher during winter (18.07/100,000) at 11.57°C compared to summer (12.46/100,000) at 29.93°C during 1992–2005. However, the results were not specific to the cause of mortality, so the adverse effect of temperature on circulatory mortality is unclear. Moreover, the delayed effect of temperature on all-cause mortality was not clearly examined or discussed. Improved statistical evidence on cause specific mortality particularly for circulatory deaths is required to inform policymakers and improve current adaption and mitigation strategies.

The current study explored the adverse impact of ambient temperature, as well as heatwaves and cold spells, on circulatory related mortality in Malta from 1992 to 2017. The study utilised time-series regression analysis to examine short term and delayed impacts of hot and cold temperatures on circulatory deaths stratified by different cause of mortality i.e., ischemic heart disease and cerebrovascular disease (stroke) and across different socio-demographic groups (i.e., age group and gender). The added effect of the observed heatwaves or cold spells during the study period were also investigated to find the mortality risk related to these extreme events and for a better understanding of the association between extreme temperatures and circulatory related deaths.

2. Methods

2.1. Study settings

Malta is a small island country in the Central Mediterranean, lying at approximately 35°N and 14°E and consists of two main islands - Malta and Gozo. With a small land area (316 km²) and large population (440,433 in 2016) (NSO Malta, 2017), the population density of Malta reached 1,393 persons/km². As a result, Malta is one of the most densely populated places in the world, and the most densely

populated country in the European Union (World Bank, 2018). The local population has a high life expectancy of 79.7 years for males and 83.7 for females (WHO, 2015).

Like other countries in the Mediterranean basin, Maltese people are exposed to a semi-arid Mediterranean climate (hot, dry summers and mild, wet winters). The Islands have a consistent temperature with an annual mean of 23°C and monthly averages ranging from 9°C in January-February to 32°C in July-August. July-September (Summer) are Malta's hottest months with daytime temperatures usually above 30°C, low humidity and minimal rain (Galdies, 2011).

2.2. Mortality data

Daily mortality data (n = 32,847) due to circulatory diseases was obtained from Malta's mortality register for the years 1992 – 2017, with permission from the Directorate for Health Information and Research in Malta (Ministry of Health, Malta, 2017). The data included the cause of death, age at death, sex and was limited to only residents of the country. The supplied data was in aggregated form with cause of death categorized under broad groups (i.e., circulatory disease) and subgroups (i.e., ischemic heart disease, cerebrovascular disease). In this study, age was categorized into three groups of 0 to < 15 years, 15 to < 65 and 65 years+, respectively.

2.3. Meteorological data

Weather data collected from Malta's only weather station situated at Luqa were obtained from the global surface archives of WeatherGraphics.com in the form of 3-hourly machine-coded SYNOP data (WMO FM 14). The decoded dataset consisted of weather information such as air temperature and relative humidity. Weather data was obtained for the period 1992 to 2017 including almost 175,000 weather observations. Daily mean temperature is defined as the average of the maximum and minimum temperature recorded for each day. Daily mean temperature was selected as the exposure variable as it has been reported to be a more suitable temperature indicator compared to minimum or maximum temperatures (Guo et al., 2017; Gasparrini et al., 2015; Armstrong, 2006).

There was no missing data for the mortality and meteorological data collected in this study.

2.4. Statistical analysis

2.4.1. Effects of ambient temperature

A time-series regression analysis was applied to examine the association between daily mean temperature and daily circulatory mortality. The analysis was carried out using a distributed lag non-linear model (DLNM) with a quasi-Poisson distribution (Gasparrini et al., 2010).

In this study, we estimated cold and heat effects on circulatory mortality at different temperature percentiles (i.e., 1st, 5th and 10th percentiles for cold effects; 90th, 95th and 99th percentiles for heat effects) to examine a range of plausible associations between temperature extremes and circulatory related deaths using Minimum mortality temperature (MMT) as the reference temperature. Subgroup analysis was conducted to examine the effect of cold and hot temperatures across different demographic groups (i.e., age group and gender) and time periods (i.e., 1992–2000, 2001–2009, 2010–2017).

To examine the nonlinear lag response relationship between ambient temperature and circulatory deaths, we applied a natural cubic spline (ns) with 4 degrees of freedom for the daily mean temperature with knots fixed by default at equally-spaced values in the place of the predicting variable and a natural cubic spline with 3 internal knots at equally-spaced values in the log scale of lag days (Gasparrini et al., 2010). These will allow more flexibility to capture temperature effects at two extreme values and short-term lag effects respectively.

Models were adjusted for the seasonal and long-term trends (7-df/year), days of the week (as dummy variable), holidays (as a binary variable, a holiday such as public holidays were coded 1) and population. This is similar to the approach adopted in previous studies (Bhaskaran et al., 2013; Guo et al., 2014; Phung et al., 2016).

We used a maximum lag of 27 days between exposure and deaths to assess long term delayed effects and allow for any harvesting effect (Qiao et al., 2015; Hajat et al., 2006). The harvesting effect refers to a short term forward shifting of mortality, when extreme temperature causes a sudden increase in the number of deaths for the first few days from exposure but then a decrease in the expected number of deaths for the next few days. The relationship to temperature was also investigated for different lag periods up to 27 days (0–7,0–14, 0–20, 0–27). The DLNM model with quasi-Poisson distribution can be outlined as follows,

$$\text{Log} (Y_t) = \alpha + \beta\, \text{Temp} + \text{ns} (\text{RH},4\text{df}) + \text{ns} (\text{Time},7\text{df}) + \text{DOW} + \text{HO} + \text{log} (\text{Pop}) \tag{1}$$

where t refers to the day of the observation; Y_t is the observed daily number of deaths due to cardiovascular on day t; β denotes the vector of coefficients for Temp; Temp is a cross basis matrix created by DLNM for daily mean temperature on day t for different lag days l (0–27 days); ns denotes the natural cubic spline functions; RH is the average humidity; Time is a categorical variable of year and calendar month to control the long-term trend and seasonality; DOW is the day of the week; HO is public holidays; and Pop represents the population (on the log scale) to allow for changes in the population over time.

The lowest AIC estimates for the quasi-Poisson model were used to choose the degree of freedom for temperature and lag period (Gasparrini et al., 2010; Phung et al., 2016).

2.4.2. Calculation of MMT

The reference value or MMT was defined as the specific temperature percentile associated with the lowest risk of circulatory mortality. MMT was obtained from the lowest point in the cumulative exposure response curve by using a simple DLNM model fitted with cross basis term of daily mean temperature only.

The estimated reference temperature (MMT) for total circulatory deaths, IHD deaths and Cerebrovascular deaths for the study period were 20.7°C (2.5[th] percentile:15.4 to 97.5[th] percentile:35.8), 18.8 °C (2.5[th] percentile:14.3 to 97.5[th] percentile:35.8) and 26.3 °C (2.5[th] percentile:18.9 to 97.5[th] percentile:35.8) respectively.

2.4.3. Heatwave and cold spell definitions

Various definitions of heatwaves and cold spells can be found from previous studies in the literature (Gasparrini & Armstrong, 2011; Tong et al., 2014; Carmona et al., 2016; Song et al., 2018). In this study, we defined heat waves and cold spells combining both temperature threshold and duration. For heatwaves a daily mean temperature exceeding the temperature threshold (95th, 96th, 97th, 98th, and 99th percentiles of the yearly distribution) for 2 to 4 consecutive days. For cold spells a daily mean temperature under the temperature threshold (1st, 2nd, 3rd, 4th and 5th percentiles) for 2 to 4 consecutive days (Gasparrini & Armstrong, 2011; Tong et al., 2014; Guo et al., 2017).

2.4.4. The added effect of heatwaves and cold spells

We used a distributed lag non-linear model (DLNM) with a quasi-Poisson distribution to explore the added effect of heat waves/cold spells on circulatory mortality (Gasparrini & Armstrong, 2011). We estimated the RRs of cause specific mortality by comparing the heat wave days to non-heatwaves days and cold spells days to non-cold spells days (Bhaskaran et al., 2013). Based on previous studies, heatwave effects were examined using a lag period of 0–10 days to evaluate the immediate effects (Yin et al., 2017; Chen et al; 2015) and cold-spells effects were explored over 0–27 lag days to capture persistent long-term effects (Gasparrini et al., 2015; Guo et al., 2014).

To investigate the added effects of heatwaves/cold spells, the daily mean temperature was included in the DLNM model with a 4-df natural cubic spline for temperature effects and the same lag space as heatwaves/cold spells (Gasparrini & Armstrong, 2011).

The model was also adjusted for other covariates including long-term and seasonal trends, day of the week (DOW), mean relative humidity and public holidays. The model structure is as follows:

$$\text{Log} (Y_t) = \alpha + \gamma \text{ HW/CS} + \beta \text{ Temp} + \text{ns(RH,4df,)} + \text{ns(time,7df)} + \text{DOW} + \text{HO} + \text{log (Pop)} \tag{2}$$

where Y_t is the expected number of deaths on day t with a quasi-Poisson distribution; α is the model intercept; HW/CS has binary values, which is 1 for heat wave/cold spells day and 0 for non-heat wave/non-cold spells day; Temp is the daily mean temperature; HW/CS and Temp is the cross basis matrix created by the DLNM model on day t and for a lag day of l (0–10 days for heatwaves; 0–27 days for cold spells); β and γ are the coefficients for HW/CS and Temp; ns is the natural cubic spline functions; RH is the relative humidity; DOW represents the categorical variables for the day of the week; ns(time) is for the adjustment of long-term and seasonality with 7 degrees of freedom (df); HO denotes public holidays (binary variable). Pop indicates population on log scale.

2.4.5. Sensitivity analysis

Sensitivity analyses were conducted with varying degrees of freedom adjusted for daily mean temperature (3-5df), different knot placements (at 10th, 75th and 90th percentile of temperature), different lag periods (i.e.,0–7, 0–14), variations for long term trends by smoothing the calendar time and using a time stratified case-crossover analysis with quasi-Poisson distribution (e.g., strata as a categorical variable of the year and calendar month to control for trends and seasonality) (Guo et al., 2011).

A natural cubic spline double threshold model considering reference temperatures at cold and hot points was also used to examine the consistency of estimates (Guo et al., 2011). We visually identified the two temperature thresholds (cold and hot temperature) from plots and examined the exposure–response relationship to confirm the observed cold effects below the cold threshold and heat effects above the hot threshold.

All statistical analyses were conducted using the R statistical software package (3.2.5) with the 'dlnm' package to fit regression models (Gasparrini et al., 2010).

3. Results

During the study period, a total of 32,847 people died due to circulatory disease (ischemic heart disease: 54.15%, Cerebrovascular disease: 23.63%, Unspecified cause: 22.22%). While more males (53.46%) died due to ischemic heart disease compared to females (46.65%), less males died (42.50%) due to cerebrovascular diseases compared to females (57.50%). A majority of deaths in males and females were above 65 years age group in both IHD (Males: 96.26%, Females: 99.38%) and cerebrovascular deaths (Males: 89.13%, Females: 94.64%). Deaths due to unspecified cause was not included in the subgroup analysis.

Visually, the daily number of deaths were higher for ischemic heart disease compared to cerebrovascular disease (Suppl Fig. 1) and showed a relatively consistent seasonal pattern. Overall, the recorded deaths were higher in the coldest months (January-February) compared to the hottest months (June-August).

3.1. Overall effect of ambient temperature

Fig. 1 shows the cumulative exposure–response association between circulatory deaths and daily mean temperature observed over 0–27 lag days for the study period. The reference temperature (MMT) for comparing the overall temperature effects for circulatory mortality, IHD mortality and cerebrovascular mortality were 20.7°C, 18.8°C and 26.3°C respectively. Cold temperatures (5.3°C–12.6°C) were consistently related to circulatory mortality. The cold effect was strongly associated at 8.9°C(RR, 2.30, 95% CI, 1.64–3.22). However, the effects of hot temperatures (26.7°C–35°C) was inconsistent for total circulatory mortality (30.1°C: RR, 1.4, 95% CI, 0.98–2.00). When stratified by the cause of death, the risk for mortality due to ischaemic heart disease (8.9°C: RR, 1.85, 95% CI, 1.24–2.77), and cerebrovascular disease (8.9°C: RR, 3.80, 95% CI, 1.57–9.17) were strongly associated between 5.3°C–10.9°C and 5.3°C–11.9°C respectively. Similar to total circulatory mortality, the effects of hot temperatures were not related for IHD (30.1°C: RR 1.35, 95% CI, 0.75–2.2) and cerebrovascular deaths (30.1°C: RR, 1.4, 95% CI, 0.80–2.3).

3.2. Lag effect of cold and hot temperatures

The delayed effects temperatures were examined over 0–27 days to adjust for harvesting effects. Cooler temperatures (8.9–12.1°C) were consistently related to circulatory mortality over 4–18 days (1st percentile: RR 1.06, 95% CI, 1.04–1.09) and over 4–15 days (5th percentile: RR 1.05 95% CI, 1.03–1.06; 10th percentile: RR 1.04, 95% CI, 1.02–1.06) (Fig. 2). The cold effects on IHD mortality were
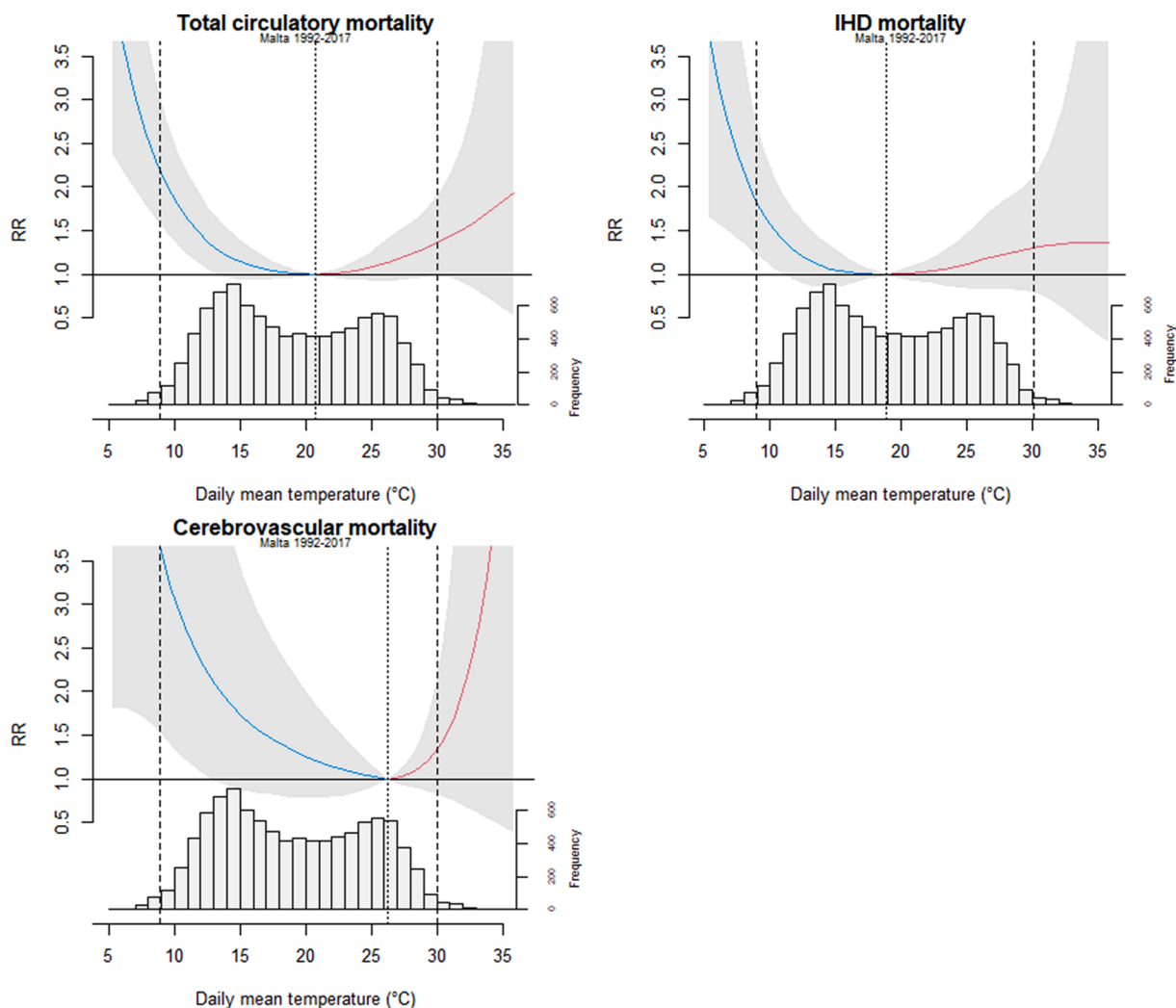
Fig. 1. The estimated overall cumulative exposure–response association (RR) using minimum mortality temperature as a reference temperature and frequency distribution of daily mean temperature. Note: dotted line is the percentile of the minimum mortality temperature; dashed lines at 1st and 99th percentiles of the temperature distribution; The blue lines (on the left) and red lines (on the right) below and above the MMT refer to the cold and hot effects. Shaded areas represent 95% confidence intervals (CI). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

also observed at 8.9–12.1°C over 4–15 days (8.9°C: RR 1.06, 95% CI, 1.03–1.09; 10.99°C: RR 1.05, 95% CI, 1.03–1.08;12.1°C: RR 1.04, 95% CI 1.02–1.07). Further, cold temperatures (8.9–12.1) were also associated with cerebrovascular deaths over 4–27 days (1st percentiles: RR, 1.10, 95% CI, 1.04–1.16; 5th percentile: RR, 1.07, 95% CI, 1.02–1.10) and over 7–24 days (10th percentile: RR, 1.06, 95% CI, 1.01–1.14).

In contrast to cold temperatures, the effects of hot temperatures were immediate and observed at shorter lag days (0–5 days). Hotter temperatures (90th–99th percentiles) were related to circulatory mortality only over 0–5 lag days (26.7°C: RR, 1.05, 95% CI, 1.01–1.09; 27.9°C: RR, 1.08, 95% CI, 1.03–1.12; 30.1°C: RR, 1.16, 95% CI, 1.11–1.20) (Fig. 3). Similarly, the risk of cerebrovascular-related deaths was higher at 27.9 (95th percentiles) and 30.1 °C (99th percentiles) over 0–5 days (27.9°C: RR, 1.04, 95% CI, 1.02–1.08; 30.1°C: RR, 1.15, 95% CI, 1.03–1.19). However, a moderate effect of hotter temperatures on IHD mortality was observed at 30.1°C (RR: 1.15, 95% CI, 1.10–2.12) over shorter lag days (lag 2–3 days).

3.3. Effect of cold and hot temperatures among gender and age groups

Table 1 shows the effect of cold and hot temperatures on total circulatory, IHD and cerebrovascular mortality for different age groups and gender over 0–27 days. Cold effects (8.9°C) on total circulatory mortality were strongly observed among males (RR, 1.77, 95% CI, 1.22–2.57), females (RR, 2.34, 95% CI, 1.33–4.11), males over 65 years (RR, 1.71, 95% CI, 1.14–2.58) and females over 65 years (RR 2.29, 95% CI, 1.25–4.21).

While colder temperatures (8.9°C) had a similar effect on IHD mortality among males (RR, 1.94, 95% CI, 1.05–3.59) and females (RR, 1.95, 95% CI, 1.2–3.59), the effect of colder temperatures (8.9–12.6°C) on cerebrovascular deaths was observed in females only (8.9°C: RR, 8.32, 95% CI, 2.58–26.80; 10.99°C: RR, 5.61, 95% CI, 1.91–16.53; 12.06°C: RR, 4.67, 95% CI, 1.62–13.42). Additionally, colder temperatures was related to the higher mortality in elderly females (females > 65 years) due to IHD (8.92 °C: RR, 1.94, 95% CI, 1.19–3.18; 10.99°C: RR, 1.33, 95% CI, 1.03–1.72) and cerebrovascular diseases (8.92°C: RR, 8.84, 95% CI, 2.64–29.61; 10.99°C: RR, 5.75, 95% CI, 1.88–17.58; 12.06°C: RR, 4.71, 95% CI, 1.58–14.06). Due to small sample sizes, the adverse effect of cold and hot temperatures could not be measured for younger age groups (males and females < 65 years old). While heat effects were immediate and moderate (over 0 to 7 days) for total circulatory, IHD and cerebrovascular mortality among different age and gender subgroups, there was less evidence for long-term lag effects (0–27) (Suppl Figs. 2-4).
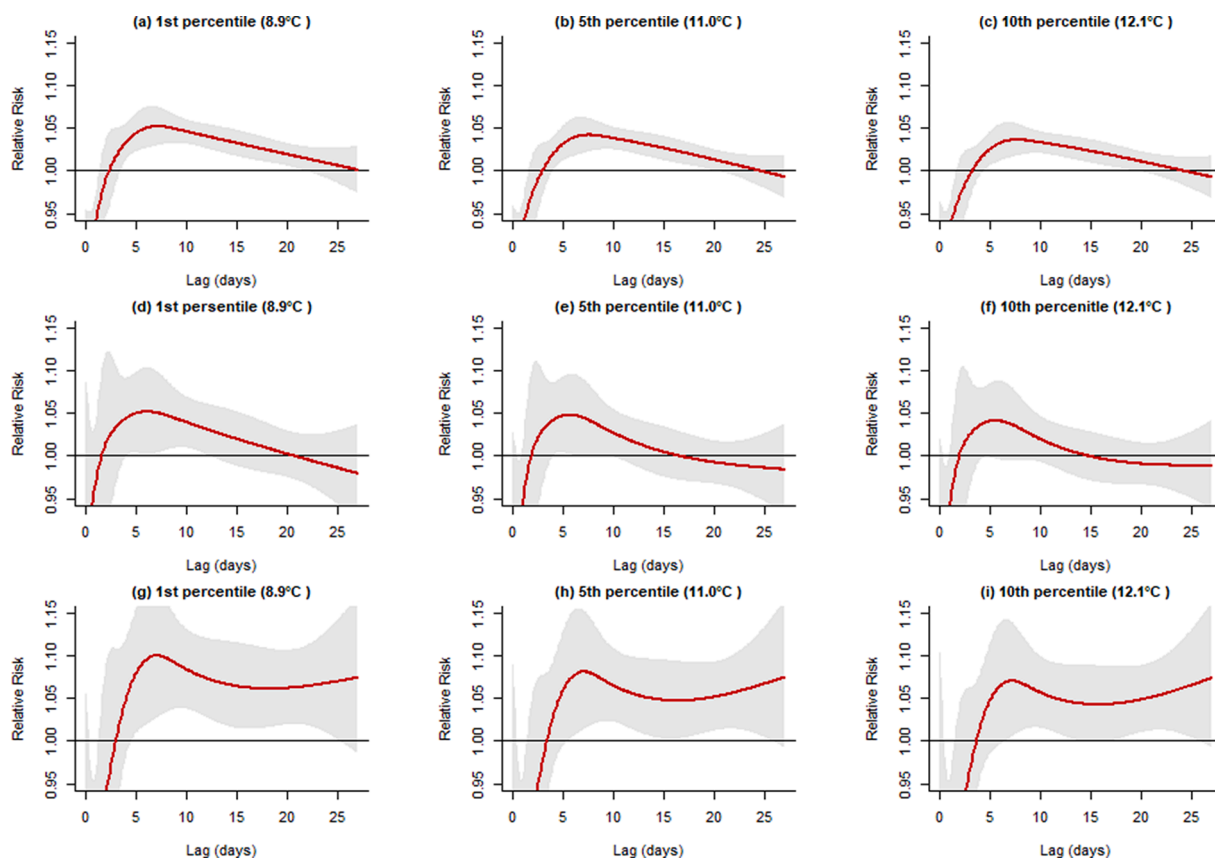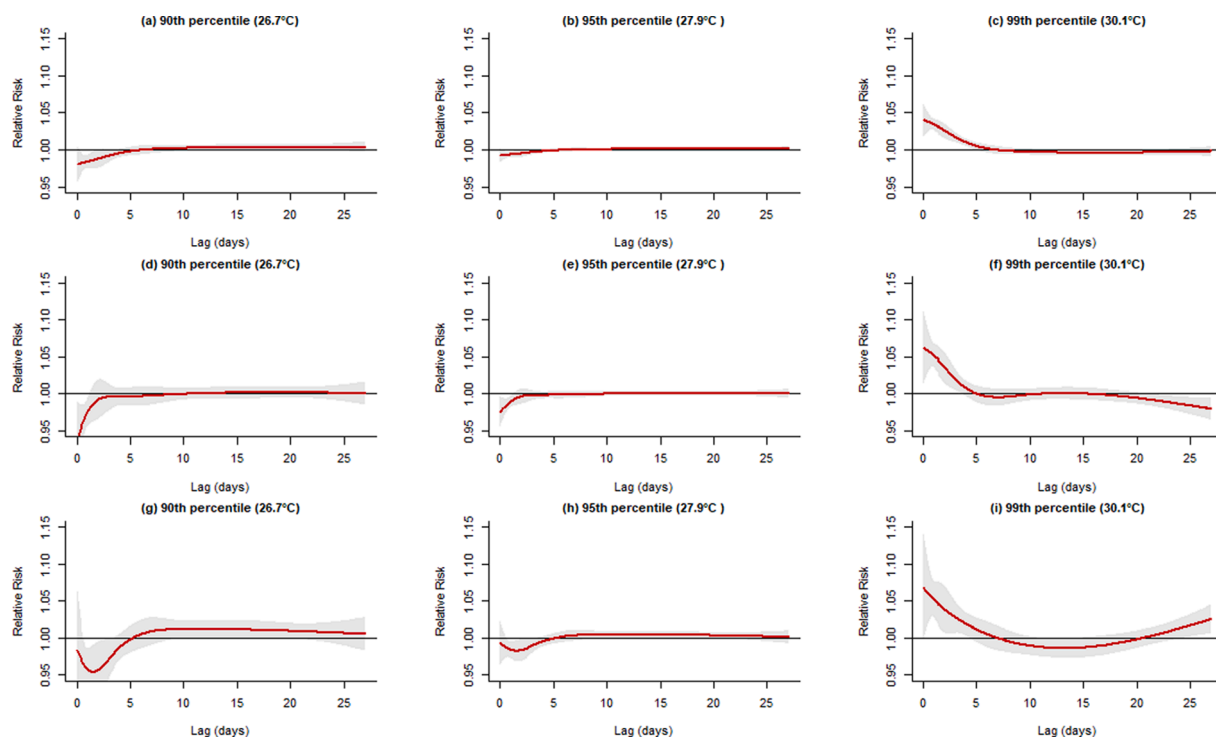

Fig. 2. The estimated relative risk (RR) of total circulatory (a, b, c), IHD (d, e, f) and cerebrovascular mortality (g, h, i) by different cold temperatures from 0 to 27 lag days.

Fig. 3. The estimated relative risk (RR) of total circulatory mortality (a, b, c), IHD (d, e, f) and cerebrovascular mortality (g, h, i) by different hot temperatures from 0 to 27 lag days.

Table 1
Estimated cumulative Relative Risk (RR) for total circulatory, IHD and cerebrovascular mortality by different temperatures in different groups over 0–27 lag days.

Temp (percentiles)	Males RR (95% CI)	Females RR (95% CI)	Males > 65 RR (95% CI)	Females > 65 RR (95% CI)
Circulatory deaths				
8.92 (1st)	**1.77 (1.22–2.57)**	**2.34 (1.33–4.11)**	**1.71 (1.14–2.58)**	**2.29 (1.25–4.21)**
10.99 (5th)	1.35 (0.99–1.84)	1.74 (1.03–2.93)	1.32 (0.96–1.84)	1.67 (0.95–2.94)
12.06 (10th)	1.22 (0.91–0.63)	1.55 (0.93–2.59)	1.2 (0.88–1.63)	1.48 (0.85–2.58)
26.70 (90th)	1.1 (0.81–1.5)	1.05 (0.91–1.21)	1.17 (0.79–1.71)	1.04 (0.89–1.21)
27.86 (95th)	1.12 (0.79–1.57)	1.03 (0.94–1.12)	1.19 (0.78–1.81)	1.02 (0.93–1.11)
30.05 (99th)	1.14 (0.76–1.71)	0.97 (0.85–1.11)	1.18 (0.72–1.94)	0.98 (0.85–1.14)
IHD deaths				
8.92 (1st)	**1.94 (1.05–3.59)**	**1.95 (1.20–3.18)**	1.82 (0.97–3.40)	**1.94 (1.19–3.18)**
10.99 (5th)	1.61 (0.94–2.76)	**1.33 (1.03–1.70)**	1.54 (0.89–2.62)	**1.33 (1.03–1.72)**
12.06 (10th)	1.48 (0.88–2.48)	1.16 (0.98–1.38)	1.42 (0.84–2.40)	1.16 (0.97–1.39)
26.70 (90th)	1.16 (0.77–1.74)	1.36 (0.68–2.72)	1.14 (0.75–1.73)	1.34 (0.67–2.68)
27.86 (95th)	1.18 (0.74–1.89)	1.42 (0.68–2.97)	1.16 (0.72–1.87)	1.40 (0.67–2.92)
30.05 (99th)	1.16 (0.63–2.13)	1.62 (0.71–3.68)	1.13 (0.61–2.10)	1.59 (0.70–3.61)
Cerebrovascular deaths				
8.92 (1st)	1.42 (0.64–3.14)	**8.32 (2.58–26.80)**	1.80 (0.77–4.18)	**8.84 (2.64–29.61)**
10.99 (5th)	1.18 (0.75–1.83)	**5.61 (1.91–16.53)**	1.30 (0.82–2.08)	**5.75 (1.88–17.58)**
12.06 (10th)	1.10 (0.78–1.54)	**4.67 (1.62–13.42)**	1.16 (0.82–1.64)	**4.71 (1.58–14.06)**
26.70 (90th)	1.17 (0.42–3.31)	1.00 (0.99–1.01)	1.42 (0.47–4.27)	1.00 (0.98–1.02)
27.86 (95th)	1.25 (0.42–3.77)	1.03 (0.90–1.18)	1.62 (0.50–5.21)	1.03 (0.90–1.16)
30.05 (99th)	1.53 (0.42–5.53)	1.35 (0.74–2.46)	2.41 (0.62–9.41)	1.29 (0.70–2.36)

Note: Bold figures indicate statistical significance.

3.4. Effect by different time periods

While both hot and cold effects were less observed for total circulatory mortality, cold temperatures (at 8.9°C) were strongly related to both IHD and cerebrovascular mortality across different time periods (Table 2). Colder temperatures (at 8.9°C) were highly associated with IHD mortality for later periods (2001–2009: RR, 2.45, 95% CI, 1.19–5.04; 2010–2017: RR, 1.97, 95% CI, 1.03, 3.75) compared to the earlier period (1992–2000). In contrast, during the earlier period (1992–2000), the risk for cerebrovascular deaths (RR, 6.11, 95% CI, 1.19–31.44) was higher at 8.9°C, however, the cold effect was less observed for later periods (2001–2017).

In comparison to cold effects, the heat effects were less consistent across different time periods after adjusting for lag effects (0–27 days). The higher mortality risk due to IHD was visible at 30.1°C during the year 2010–2017 (RR, 3.33, 95% CI, 1.3–8.54). However,

Table 2
The estimated cumulative relative risk (RR) of total circulatory deaths, IHD and cerebrovascular mortality for different daily mean temperatures across different time periods over 0–27 lag days.

Daily mean temperature (percentiles)	1992–2000 RR (95 %CI)	2001–2009 RR (95 %CI)	2010–2017 RR (95 %CI)
Circulatory deaths			
8.9 (1st)	0.94 (0.19,4.72)	5.54 (0.77,39.65)	1.49 (0.55, 4.01)
10.99(5th)	1.42 (0.35, 5.83)	7.08 (0.94, 44.05)	1.17 (0.72, 1.89)
12.06 (10th)	1.57 (0.41, 6.06)	7.27 (1.21, 43.6)	1.07 (0.78, 1.47)
26.7 (90th)	1.43 (0.56, 3.65)	1.16 (0.61, 2.2)	1.16 (0.22, 6.09)
27.86 (95th)	1.73 (0.58, 5.14)	1.07 (0.74, 1.57)	1.26 (0.22, 7.11)
30.05 (99th)	2.77 (0.62, 12.4)	0.94 (0.59, 1.49)	1.85 (0.31, 11.07)
IHD deaths			
8.9 (1st)	1.8 (0.63, 5.16)	**2.45 (1.19, 5.04)**	**1.97 (1.03, 3.75)**
10.99(5th)	1.63 (0.58, 4.57)	1.61 (0.86, 2.99)	1.42 (0.84, 2.37)
12.06 (10th)	1.56 (0.57, 4.32)	1.37 (0.76, 2.47)	1.25 (0.77, 2.02)
26.7 (90th)	1.00 (1.00, 1.00)	1.1 (0.64, 1.88)	1.79 (0.88, 3.64)
27.86 (95th)	1.03 (0.93,1.13)	1.14 (0.62, 2.08)	2.16 (0.99, 4.69)
30.05 (99th)	1.25 (0.86, 1.82)	1.22 (0.52, 2.88)	**3.33 (1.3, 8.54)**
Cerebrovascular deaths			
8.9 (1st)	**6.11 (1.19, 31.44)**	2.87 (0.89, 9.2)	4.57 (0.76, 27.53)
10.99 (5th)	3.9 (0.79, 19.26)	2.66 (0.94, 7.54)	2.6 (0.5, 13.59)
12.06 (10th)	3.26 (0.68, 15.74)	2.48 (0.91, 6.75)	2.14 (0.42, 10.79)
26.7 (90th)	1 (0.98, 1.02)	1.27 (0.71, 2.28)	1.26 (0.8, 1.98)
27.86 (95th)	1.05 (0.92, 1.2)	1.45 (0.72, 2.92)	1.13 (0.89, 1.42)
30.05 (99th)	1.68 (0.95, 2.97)	1.99 (0.64, 6.23)	0.84 (0.59, 1.19)

*Note: **Bold** figures indicate statistical significance.*
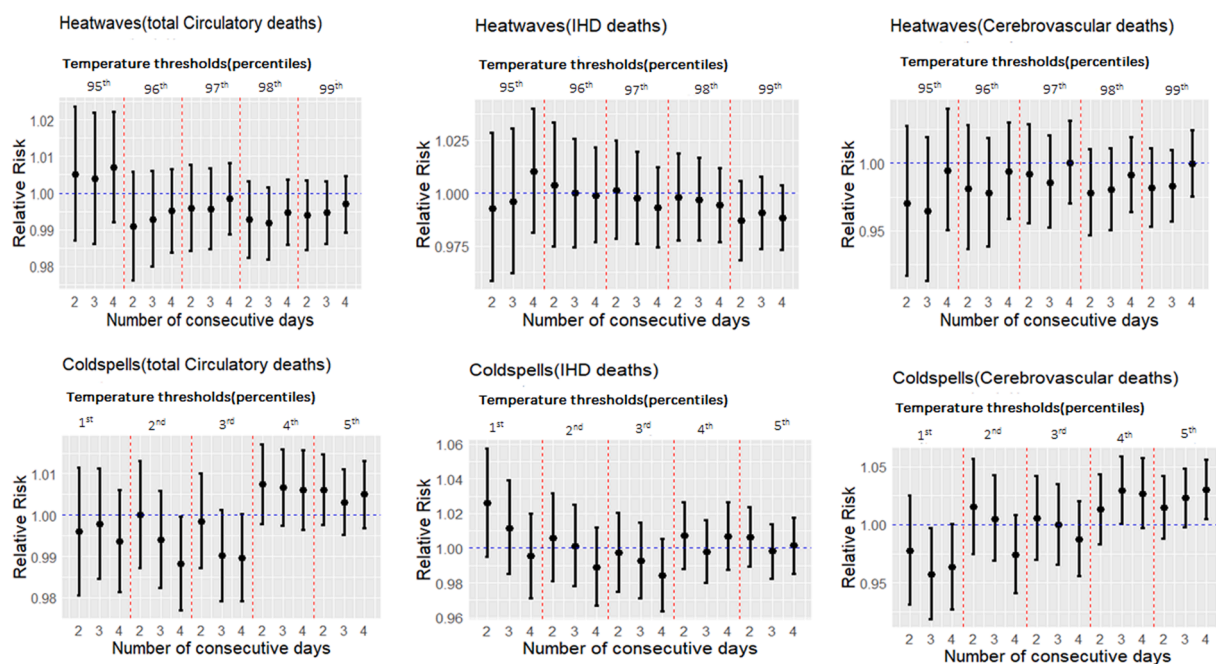
Fig. 4. RR estimates for added effect of heatwaves and cold spells for total circulatory, IHD and cerebrovascular mortality in Malta, 1992–2017.

heat effects on cerebrovascular deaths were less observed across the different time periods examined.

3.5. Effects of heatwaves and cold spells on circulatory mortality

Although the evidence for an effect of heatwaves (Fig. 4) was not clear for mortality due to total circulatory, IHD and cerebrovascular disease, there was some effect of cold spells on cerebrovascular deaths at 0.6°C (99th percentiles) temperature thresholds (RR, 1.03, 95% CI, 1.01–1.06). However, the effect was inconsistent for 2–4 consecutive days.

3.6. Sensitivity analysis

The estimated relative risks for total mortality, IHD and cerebrovascular mortality by case-crossover analysis (i.e., 30 days strata) were similar to the results obtained from the DLNM model (Suppl Fig. 5). A double threshold model was also employed to analyse cold and hot temperatures at the same time, however, we found similar results to those already presented (Suppl Fig. 6). The varied degree of freedom for temperature (3–5/df), yearly trends (6–8/df) also didn't show any significant changes in the relationships between temperature and circulatory mortality. Models adjusted for shorter lag periods (0–14 days) showed an immediate effect of hotter temperatures on circulatory mortality over 0–3 days similar to those already presented for long term lags (0–27 days) (Suppl Fig. 7).

4. Discussion

This study examined 26 years of mortality data to extensively explore the adverse effect of cold and hot temperatures and extreme events (heatwaves and cold spells) on circulatory mortality. The study conducted a stratified analysis to assess the risk for mortality due to specific causes, ischemic heart disease and cerebrovascular disease. The risk was also assessed for different age groups, gender and across different time periods. Similar to previous studies from Europe, this study found U shaped association between temperature and circulatory mortality with greater effects for cold temperatures (Iñiguez et al., 2021; Rocklöv et al., 2009; Kendrovski, 2006). While the heat effects (at the 90-99th percentile of temperature) were immediate and less observed over longer lag days (0–27 days), cold effects (at 1st to 10th percentile of temperature) were consistent across different lag days. A strong risk for circulatory mortality was observed at 8.9°C (RR, 2.30, 95% CI, 1.64–3.22).

The stratified analysis by cause of deaths found higher cold effects (5.3°C-12.6°C) on IHD and cerebrovascular mortality compared to heat effects. At 8.9°C, the risk for mortality was strongly observed due to ischaemic heart disease (RR, 1.85, 95% CI, 1.24–2.77) and cerebrovascular disease (RR, 3.80, 95% CI, 1.57–9.17). In contrast to previous studies, this study observed a high degree of uncertainty in the results related to heat effects with wide 95% CI estimates. This could be due to a lower number of daily cause-specific death counts during the study period. Moreover, the number of deaths was higher during the winter months compared to the summer months. In countries with a milder winter, there could also be a possibility that as people have progressively adapted to heat, they have gradually de-adapted to colder weather (Healy, 2003; England, 2010; Linares et al.,2020) and are more reactive to cold temperatures. Also, the local population might be more adapted to hotter climates due to different levels of public health intervention (England et al., 2010).

Previously, many studies have discussed that the variation in cold and hot effects depends on temperature variability (Analitis et al, 2008; D'Ippoliti et al., 2010; Guo et al., 2016). A greater heat effect has been observed in countries with both hotter or colder climates due to higher average temperatures and frequent and intense extreme weather events or higher temperature variability respectively (Guo et al., 2016). In contrast, a cold effect was observed in countries with warmer winters due to greater inter-annual variability in winter temperatures compared to countries with consistent year to year winter temperatures (Fowler et al., 2015; Healy, 2003). D'Ippoliti et al. (2010) examined the impact of heatwave on mortality in European cities and observed a greater risk for mortality in Mediterranean cities compared to North-continental cities.

The study observed some short-term lag effects of specific hot temperatures (90th and 99th percentiles) on circulatory mortality over 0–5 lag days, cerebrovascular deaths (95th percentiles: 2%-8%; 99th percentiles: 3%-19%) over 0–5 days and IHD deaths (99th percentiles: 10%-112 %) at 2–3 lag days. However, these effects were inconsistent over other lag days. As an increase in the mortality risk was observed in the initial lag days followed by a decrease these effects could be attributed towards a harvesting effect (Guo et al., 2011). In contrast, the effect of cold temperatures (8.9–12.1°C) was persistent across different lag days and strongly observed for both cerebrovascular deaths and IHD deaths over 4–27 days. At 8.9°C (1st percentiles), the mortality risk due to ischemic heart disease and cerebrovascular disease increased by 3%-9% and 4%-16% over 4–15 days respectively. A cold effect (5th and 10th percentiles) on cerebrovascular mortality was also visible over 20–27 lag days (5th percentiles: 2%-10%; 10th percentiles: 1%-14%).

Similar to these findings, most European studies examined lag effects of ambient temperatures on cardiovascular mortality and reported an increase in mortality risk with an increase in temperature on hot days (lag 0) or following hot days (lag 1–6) that declined sharply displaying evidence of a harvesting effect (Rocklöv et al., 2009; Kouis et al., 2019), whereas cold effects lasted for longer periods (0–23 days) (Analitis et al., 2008; Pascal et al., 2018).

In this study, we also found a higher risk for circulatory mortality among females and the elderly (above 65 years). Previous research has identified different vulnerable groups varying across study locations and study populations. Most of these studies observed similar results (D'Ippoliti et al., 2010; Tong et al., 2014; Yang et al., 2012; Zhou et al., 2017), however, a few other studies reported higher mortality risk among males (Cheng et al., 2014; Zhai et al., 2020; Yang et al.,2015) and younger age groups (below 65 years) (Achebak et al. 2019; Atsumi et al. 2013; Davídkovová et al. 2014; O'Neill et al., 2003; Kysely et al., 2009). These findings are plausible due to differences in the physiological structure, hormonal and thermoregulatory capacity across different age groups, and

between males and females (Schwartz, 2005; Hajat et al., 2007; Petkova et al., 2021). Women are likely to have a lower sweating capacity compared to men to generate an equivalent amount of metabolic heat and might respond higher to heat stress (Gagnon and Kenny, 2011 & 2012; Gagnon et al. 2013). In contrast, limited evidence is available explaining cold stress-related mortality in females. Women usually experience lower core temperatures and metabolic heat production and less shivering heat generation in response to cold stress (Petkova et al., 2021). In addition to diminished thermoregulatory function, elderly people might be socially isolated, living alone, have limited coping resources (i.e., availability of air conditioning/heating, protective clothing), have pre-existing chronic conditions, and limited access to health care services that could affect their ability to responds to heat or cold stress (Bunker et al. 2016; Hajat & Kosatky, 2010; Lane et al. 2018).

In the current study, cold and hot temperatures were strongly associated with IHD mortality observed during the year 2010–2017 (8.9°C: RR, 1.97, 95% CI, 1.03–3.75; 30.05°C: RR, 3.33, 95% CI, 1.3–8.54), compared to the earlier period. Although heat effects were less observed, the effect of colder temperatures (1st percentile) was highly observed for cerebrovascular mortality during the earliest time period (1992–2000: RR, 6.11, 95% CI, 1.19–31.44). During the last two decades of the study period, there has also been a significant increase in the use of air conditioning in Malta which could help to mitigate heat stress explaining a less observed heat effect on IHD and cerebrovascular mortality (Trend Economy, 2020). Despite global warming and increase of temperatures in Europe, the estimated relative risks over time seem to decrease due to changes in adaptive and mitigation strategies (Swart et al., 2009). In spite of a substantial increase in the use of air conditioning in Malta during last two decades, we have observed some effect of hot temperatures (30°C) on IHD mortality during the last seven years (2010–2017) plausibly due to population aging and socio-demographic vulnerability, higher prevalence of chronic illnesses and greater temperature variability (Linares et al., 2020). Moreover, climate change over time might cause further inter–annual variability in winter temperatures declining the mortality risk in later years.

In this study, we explored the added effect of both heatwaves (over 0–10 lag days) and cold spells (over 0–27 lag days) on circulatory mortality; however, there was no consistent effect of these events on mortality due to total circulatory, Ischaemic heart disease and cerebrovascular disease. Although there was some borderline effect of cold spells on cerebrovascular mortality (RR, 1.03, 95% CI, 1.01–1.06), the effect was inconsistent on 2–4 consecutive days. In contrast to other studies examining heat waves, fewer studies have examined the effect of cold waves and reported an increase in circulatory mortality during cold days (Carmona et al., 2016; Montero et al., 2010; Linares et al., 2015; Kysely et al., 2009; Davídkovová et al., 2014. A limited number of studies examined the effect of both heatwaves and cold spells on circulatory mortality, and some of them reported a greater mortality risk due to heatwaves (Linares et al., 2015) and others reported a greater mortality risk due to cold spells (Huynen et al., 2001; Carmona et al., 2016).

Several factors could be explaining these results. A central heating system is very rare to find in Malta with the use of portable gas/electric heaters more widespread. Additionally, old housing in Malta is more adapted to hotter temperatures with high ceilings as opposed to more modern housing. During the last decade in Europe, significant emphasis has been made to increase public awareness, improve adaptation strategies (i.e., air conditioning and heater use), modify building designs (i.e., insulated roofs, facades and exposed walls in housing infrastructure) and improve health services to mitigate the effects of the climate particularly in the hotter months (Vicedo-Cabrera et al., 2018; Díaz et al., 2018 a, b). Countries in the Mediterranean basin mostly observe higher temperatures and heatwaves. Regardless of the predicted temperature rises and increase in the frequency of heatwave under climate change scenarios, the effect of cold temperatures and cold spells will persist over time. Thus, health care providers and policy makers may need to consider cold spells as an equal threat to health and upgrade their climatic impacts adaptation and mitigation strategies.

The study has some important strengths. First, to the best of our knowledge, this is the first study from Malta to extensively explore the effect of ambient temperature and extreme events on cause specific circulatory deaths (ischemic heart disease and cerebrovascular disease). The findings provide good evidence to confirm the adverse effect of cold and hot temperatures on circulatory mortality across different time periods, cause of deaths, age groups and gender. Second, this study utilized high quality and accurate mortality data from the National death registry of Malta consisting of a relatively large sample size and linked to a long-time series of meteorological data from Malta. This provides a relatively high degree of statistical power and confidence to explore and establish every plausible association. Third, the study employed a range of sophisticated and complex statistical models in order to provide robust and accurate results for a better understanding of the exposure–response associations and delayed effects after allowing for possible harvesting effects (0–27 lag days) of daily mean temperature on circulatory mortality.

Some limitations should be mentioned. First, the meteorological data were collected from the only official climatological station in Malta, so it was difficult to estimate the degree of site-specific exposure. However, Malta is a densely populated small country, so the chances of estimation bias is minimal. Secondly, while this study provided some statistical evidence on the relationship between ambient temperature and circulatory deaths, there could be other factors such as, seasonal influenza, pre-existing health condition, level of exposure (i.e., housing type, indoor temperature, coping measures, air quality) and physical comorbidities which could be considered in the analysis for a better understanding of the relationship. Thirdly, the sample size for cerebrovascular deaths was comparatively low which may compromise the strength of any association. Additionally, the number of deaths under 65 years of age was considerably low, so the relative risk for younger people could not be reliably estimated.

5. Conclusion

The study results indicate that cold temperatures have considerably greater effects on circulatory mortality in Malta compared to heat effects. Although there was some added effect of cold spells on cerebrovascular mortality, the effect of heatwaves was less observed. The risk for circulatory mortality could be increased during extreme cold days especially in elderly groups with a dysfunctional thermoregulatory system. However, the cold effect on circulatory mortality could be greatly influenced by other

potentially interacting, individual and environmental factors, which need to be further explored. Increasing public awareness, implementing active early warnings system, adapting preventive measures based on the weather forecast and implementing timely interventions targeting vulnerable groups might help to mitigate the effects of cold stress and temperature variability on circulatory mortality.

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Ethical approval

Ethical approval was taken from the Human Research Ethics Committee of Queensland University of Technology (Reference Number: 2021000259).

Declaration of Competing Interest

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.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.crm.2022.100463.

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