Heat-related cardiovascular morbidity and mortality in Switzerland: a clinical perspective

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Summary
AIMS: Previous studies found increased cardiovascular mortality during hot days, while emergency hospital admissions were decreasing. We explored potential underlying reasons by analysing clinically similar cardiovascular disease groups taking into account primary, underlying and immediate causes of death.

METHODS AND RESULTS: We assessed associations of daytime maximum temperature in relation to cardiovascular deaths and emergency hospital admissions between 1998 and 2016 in Switzerland. We applied conditional quasi-Poisson models with non-linear distributed lag functions to estimate relative risks (RRs) of daily cardiovascular mortality and morbidity for temperature increases from the median (22 °C) to the 98th percentile (32 °C) of the warm season temperature distribution with 10 days of lag. Cardiovascular mortality (n = 163,856) increased for total cardiovascular disease (RR 1.13, 95% confidence interval [CI] 1.08–1.19) and the disease groups hypertension (1.18, 1.02–1.38), arrhythmia (1.29, 1.08–1.55), heart failure (1.22, 1.05–1.43) and stroke of unknown origin (1.20, 1.02–1.4). In contrast, emergency hospital admissions (n = 447,577) decreased for total cardiovascular disease (0.91, 0.88–0.94), hypertension (0.72, 0.64–0.81), heart failure (0.83, 0.76–0.9) and myocardial infarction (0.88, 0.82–0.95). Opposing heat effects were most pronounced for disease groups associated with diuretic and antihypertensive drug use, with the age group ≥75 years at highest risk.

CONCLUSIONS: Volume depletion and vasodilation from heat stress plausibly explain the risk reduction of heat-related emergency hospital admissions for hypertension and heart failure. Since primary cause of death mostly refers to the underlying chronic disease, the seeming paradoxical heat-related mortality increase can plausibly be explained by an exacerbation of heat effects by antihypertensive and diuretic drugs. Clinical guidelines should consider recommending strict therapy monitoring of such medication during heatwaves, particularly in the elderly.

Introduction
Climate change has been described as the biggest global health threat of the 21st century, partly due to more frequent and intense heatwaves [1]. Previous studies have described increasing mortality rates at high ambient temperature compared with the country- or city-specific optimal temperature range [2–9]. There is evidence that cardiovascular diseases, which are the leading cause of death globally [10], are among the main causes of heat-related deaths [11].

Heat effects on cardiovascular morbidity are less clear [12]. Previous studies reported a slight heat-related morbidity increase for cardiovascular diseases, or no effect with a tendency for a decrease [2, 13, 14]. In Switzerland, decreasing daily emergency hospital admissions for cardiovascular disease were observed during the hot summer of 2015 [15].

The reasons for different heat effects on mortality and morbidity are unclear. Some authors suggested that people die before being admitted to the hospital [14]. A deeper look into heat effects on different cardiovascular disease groups has rarely been done [2]. Existing literature reports varying effects, such as an increase in emergency hospital admissions for ischaemic heart disease or stroke, but a decrease for hypertension [16]. Furthermore, to our knowledge, previous studies took into account only the primary cause of death.

The aim of this study was to explore the reasons for different heat effects on cardiovascular mortality and morbidity to better inform clinical decisions and public health interventions during hot spells. We therefore carried out a detailed comparative analysis of heat-related mortality and emergency hospital admissions. We used clinically relevant cardiovascular disease groups and took into account primary, underlying and immediate causes of death.

Materials and methods
Health and temperature data
The Swiss Federal Statistical Office (FSO) provided us with daily mortality and emergency hospital admission data between 1998 and 2016 from the official cause of death
statistics and the medical statistics of Swiss hospitals. Data included cardiovascular primary causes of death and emergency hospital admissions of Swiss residents according to the International Classification of Diseases codes, 10th Revision (ICD-10, I00-I99). The primary cause of death is defined by the FSO based on a standardised procedure evaluating information from the death certificates on underlying, immediate and contributing causes of death. The primary cause of death is for most disease groups identical to the underlying cause of death and decisive for all publications [17]. Health data were aggregated into daily deaths and daily number of emergency hospital admissions by age (<75, ≥75 years), sex, disease group and seven geographic areas across Switzerland (so-called Swiss great regions, supplementary fig. S1 in the appendix). Before starting the data analyses, we created a diagnostic framework comprising nine cardiovascular disease groups (supplementary table S1): hypertension (I10–15), myocardial infarction (I21–22), pulmonary embolism (I26), arrhythmia (I44–49), heart failure (I50), haemorrhagic stroke (I60–62), ischaemic stroke (I63), stroke of unknown origin (I64) and deep vein thrombosis (I80). Disease groups were defined based on common clinical diagnoses that have a plausible cause-effect relationship with heat. We assumed that the following heat effects may have an influence on the diseases: volume depletion and peripheral vasodilation with subsequent reduction of cardiac preload and afterload on hypertension and heart failure [18–20], sweating with subsequent electrolyte imbalances on cardiac arrhythmias [21, 22], and pro- and anticoagulation effects on thrombotic, infarction and bleeding events [22–24]. To support these heat sensitivity pathways and to evaluate potential other contributing effects of heat-related mortality, we also compared the primary cause of death with underlying (to describe chronic conditions) and immediate causes of death by disease group.

Daily temperature data were collected from the IDAWEB database, a service provided by MeteoSwiss, the Swiss Federal Office of Meteorology and Climatology. We restricted the analysis to the warm season (May to September). Numbers of daily deaths and emergency hospital admissions of each great region were linked to daily daytime (6:00–18:00) maximum temperature measurements (Tmax) from a close-by representative monitoring station. A map showing the locations of the measurement stations is provided in the appendix (fig. S1).

Statistical analysis
We analysed the short-term temperature-mortality and temperature-morbidity relationships for cardiovascular disease using conditional quasi-Poisson regression models. We applied distributed lag non-linear models (DLNM) to allow for non-linear and delayed effects of temperature [25]. All regions were pooled into one dataset. To control for potential differences by year, month, weekday and region, a stratum variable was included in the model that matched the same days of the week in the same month of the same year and the same geographic region.

The model specifications were optimised for both mortality (using primary cause of death) and morbidity models using the total number of cardiovascular deaths and emergency hospital admissions, and model coefficients were then estimated for the individual disease groups. For the temperature dimension of the so-called cross-basis function of the DLNM, we chose a model with a natural spline function with three internal knots at the 10th, 75th and 90th percentiles. For the lag dimension of the cross-basis, we used a natural spline function with two equally spaced internal knots on the log scale. We chose a 10-day lag period to capture delayed effects and potential harvesting. We selected the model specifications based on similar studies on the effect of heat on health [6, 26]. To validate the model, we tested different numbers and positions of knots in a sensitivity analysis, which showed similar results (figs S2 and S3).

Associations between Tmax and health outcomes were expressed as cumulative relative risks (RRs) over the whole lag period. We used the median warm season Tmax over all geographic areas and years as the reference. Cumulative and lag-specific RRs were estimated for the 98th percentile of Tmax, defined as a “hot day” (similar to previous research [4–6, 9]). To identify vulnerable population subgroups, we also assessed the effects by age (<75, ≥75 years). All analyses were conducted using the statistical software environment R (version 3.4.4) with the package dlmn [25].

Access to data and computing code
The health data used for this study are available under license from the Federal Statistical Office, Switzerland. The computing code is available on request by e-mail from the authors. All analysis was done on aggregated data, for which no ethical approval is required in Switzerland.

Results
In total, our dataset contained 163,856 cardiovascular deaths and 447,577 cardiovascular emergency hospital admissions. The age distribution was balanced for the hospital admissions (49% <75 years, 51% ≥75 years). Most deaths (80%) occurred in the population aged ≥75 years. Fifty-six percent of deaths and 70% of emergency hospital admissions were analysed in detail as part of our diagnostic framework.

For the individual disease groups, the proportion of patients ≥75 years ranged between 37% (myocardial infarction) and 74% (heart failure) for emergency hospital admissions, and between 62% (haemorrhagic stroke) and 92% (heart failure) for mortality. The detailed demographic structure of the data is shown in supplementary figures S6 (deaths) and S7 (admissions) and supplementary table S2.

Primary and underlying causes of death were the same for most disease groups from the framework (69%). The highest agreement was found for heart failure (94%) and hypertension (92%). For myocardial infarction, agreement with immediate cause of death was higher (72%, for details see table S4).

Recorded Tmax during the warm season of the years 1998–2016 in the seven geographic regions in Switzerland ranged between 3 °C and 40 °C. The median and 98th percentile of Tmax varied across monitoring stations between
19–25 °C and 29–34 °C, respectively; resulting in an overall median of 22 °C and 98th percentile of 32 °C.

For all cardiovascular diseases combined, an increase of Tmax from 22 °C (median) to 32 °C (98th percentile) was significantly associated with a 13% increase in deaths (95% CI 8–19%) and a 9% decrease in emergency hospital admissions (95% CI 6–12%). A similar pattern was observed for hypertension and heart failure (fig. 1, table 1). For arrhythmia and stroke of unknown origin, mortality increased with temperature, whereas morbidity did not. For myocardial infarction, emergency hospital admissions decreased, accompanied by a tendency for a mortality increase at very high temperatures. The remaining disease groups were smaller (<10,000 cases) and did not show significant associations between temperature and mortality or emergency hospital admissions, except a significant reduction in hospital admissions for deep vein thrombosis (fig. S6).

Stratified results by age showed exposure-response associations similar to those of the total population (figs S7 and S8, table S3). The mortality increase was greater in the age group ≥75 years, whereas the reduction in emergency hospital admissions was more prevalent in the age group <75 years. In the age group <75 years, we found a significant heat-related mortality increase for ischaemic stroke (RR 2.24), albeit with a large confidence interval (95% CI 1.07–4.73).

The time lag between high temperature and health outcomes differed between disease groups but was mostly around 0–4 days (figs. S9 and S10). For myocardial infarction and heart failure, we observed a mostly insignificant mortality reduction after an initial mortality increase.

Discussion

With increasing temperature, cardiovascular emergency hospital admissions decreased whereas mortality increased. Specifically, mortality due to hypertension, arrhythmia, heart failure and stroke of unknown origin as primary causes of death increased with temperature. Daily emergency hospital admissions decreased for hypertension, heart failure and myocardial infarction and remained unchanged for stroke of unknown origin and arrhythmia. Except for myocardial infarction, the primary cause of death mainly refers to the underlying disease and not the acute cause of death.

Both the overall effect and the results for the specific cardiovascular disease groups were in good agreement with previous work [15]. Increased heat-related mortality due to heart failure, stroke and arrhythmia, and reductions in rates of emergency hospital admissions for hypertension and heart failure have been observed previously [16, 29]. A tendency for a heat-related increase of myocardial infarction mortality was seen only at very high temperatures (>33 °C) and was thus less pronounced than in other studies. For myocardial infarction, we found a decrease in hospital admissions instead of an increase [33].

Direct heat effects can plausibly explain decreasing emergency hospital admissions due to hypertension and heart failure. Volume depletion through sweating and peripheral vasoconstriction reduces cardiac preload [21], cardiac afterload [23] and blood pressure [18, 35]. In volume-overloaded heart failure patients, this moves the operating point on the Frank-Starling-curve (which represents the relationship between distension of the heart and the force generated by contraction) to a more optimal location [36], similar to a targeted pharmacotherapy [28, 37]. Reduced emergency hospital admissions due to these diseases are the result.

Against this background, the heat-related mortality increases for hypertension and heart failure seem counterintuitive. However, the primary causes of death “hypertension” and “heart failure” derive mostly from the underlying, not the acute cause of death. The corresponding immediate cause of death was mostly unspecified (table

![Figure 1: Relative risks (RRs) for emergency hospital admissions (EHA) and mortality for cardiovascular (CVD) disease groups with more than 10,000 cases by daytime maximum temperature. RRs are cumulative over the lag period of 10 days. Median daytime maximum temperature over the study period is used as reference.](image)
S4). Therefore, the excess mortality refers to patients dying with, not of, chronic hypertension or heart failure. Consequently, these patients did not necessarily suffer from acute hypertension or acute congestive heart failure at the time of death. They were likely taking antihypertensive or diuretic medications though, which are the standard treatment for chronic hypertension and heart failure [27, 28, 37, 38]. Antihypertensive medication can exacerbate heat effects [39–42], which has led to recommendations for a dose reduction during hot spells in some countries [43, 44]. During routine post-mortem examination, heat effects are difficult to identify [45]. Thus, if a patient dies from antihypertensive drug effects exacerbated by heat stroke, an unspecific immediate cause of death would likely be recorded. Meanwhile, in the absence of a better reason, it is likely that the patients’ known chronic disease would be recorded as the underlying, and ultimately primary, cause of death. This can show as a heart-related mortality increase for chronic diseases associated with antihypertensive drugs, as observed in our analysis (fig. 2).

Increased heat vulnerability due to pathophysiological changes offers an alternative explanation for the mortality increase in heart failure [42], but cannot explain the corresponding decrease in emergency hospital admissions or the results for hypertension.

An exacerbation of heat effects by antihypertensive drugs can also partly explain the heat-related mortality increase in cardiac arrhythmia and stroke of unknown origin, if comorbidities are considered. For atrial fibrillation, hypertension is reported as a comorbidity in about 77% of cases [34]. For stroke, a Swiss study detected hypertension in 63.5% of the patients, and the CARes study from Texas even in 86.5% of the cases. CARes also explicitly looked for antihypertensive drug use and found it in 83% of stroke patients [31, 32]. Thus, patients with atrial fibrillation or stroke of unknown origin as primary cause of death were likely also treated with antihypertensive drugs. The largest part of the mortality increase for arrhythmia corresponds to unexplained deaths: “cardiac arrest”, which is unspecific, was the most frequent primary cause of death in the arrhythmia group (data not shown). Although the available data do not allow conclusions to be drawn about the causes for heat-related excess mortality for this subgroup, a contribution of direct heat effects or antihypertensive drugs can also not be ruled out.

A contribution of heat-induced electrolyte imbalances to the mortality increase for cardiac arrhythmia is also possible, but does not explain the absence of an increase in rates of emergency hospital admission.

Our results did not show a consistent picture regarding previously hypothesised impairment of the coagulation system by heat [22–24]. For myocardial infarction, the observed slight decrease in emergency hospital admissions may be explained by cardioprotective effects from warm weather, such as reduction of cardiac pre- and afterload or reduced oxidative stress [46]. Patients were also younger on average in this group, suggesting that their thermoregulatory control was better maintained than in older individuals [47].

### Table 1:
Summary of results for heat-related emergency hospital admissions (EHA) and mortality, comparison with the literature and possible explanations for observed heat effects for cardiovascular disease groups >10,000 cases.

| Disease group | Class | Number of cases | RR (95% CI) | Effect | Results from previous literature | Diagnosis invol\-ves antihypertensive drug use | Plausible explanations for effect in our study |
|---------------|-------|----------------|-------------|--------|----------------------------------|-----------------------------------------------|-----------------------------------------------|
| Hypertension (I10–15) | EHA | 29,533 | 0.72 (0.64–0.81) | ↓ | 10.0% (95% CI 13.1–6.7%) risk reduction of ER visits per 10°F. NB: 12.7% (95% CI 8.3–17.4%) excess risk for ER visits due to hypotension [16] | Yes [27] | EHA reduction: Direct heat effect, Mortality increase: Heat-induced amplification of anti-hypertensive drug effects |
| Deaths | 17,142 | 1.18 (1.02–1.38) | ↑ | No data found |
| Heart failure (I50) | EHA | 57,440 | 0.83 (0.76–0.90) | ↓ | Insignificant decrease [16] | Yes [28] | EHA reduction: Direct heat effect, Mortality increase: Heat-induced amplification of anti-hypertensive drug effects, Disease physiology may contribute |
| Deaths | 14,753 | 1.22 (1.05–1.43) | ↑ | 3.6% (95% CI 2.4–4.8) mortality increase per 1 °C temperature increase above region-specific heat threshold [20] |
| Stroke of unknown origin (I64) | EHA | 11,280 | 1.04 (0.86–1.26) | ↔ | No significant heat effect for combined stroke events [30] | Yes [31, 32]a | Mortality increase: Heat-induced amplification of anti-hypertensive drug effects possible due to comorbidities |
| Deaths | 15,296 | 1.2 (1.02–1.4) | ↑ | RR 1.53 (95% CI 0.9–2.15) on hot days for ischemic and hemorrhagic stroke combinedb |
| Arrhythmia (I44–49) | EHA | 49,835 | 0.97 (0.89–1.05) | ↔ | 2.8% (95% CI 0.9–4.9) increase of emergency room visits per 10 °F [16] | Some diagnoses (e.g., atrial fibrillation)c | Mortality increase: Heat-induced amplification of anti-hypertensive drug effects may contribute |
| Deaths | 11,323 | 1.29 (1.08–1.55) | ↑ | 5% (95% CI 3.2–6.9) mortality increase per 1 °C temperature increase above region-specific heat threshold [20] |
| Myocardial infarction (I21-22) | EHA | 68,861 | 0.88 (0.82–0.95) | ↓ | RR 1.016 (95% CI 1.004–1.028) for 1 °C increase [33] | Yesd | EHA reduction: cardioprotective heat effects possible |
| Deaths | 20,081 | 1.01 (0.88–1.16) | ↔ | RR 1.039 (95% CI 1.087–2.470) for a heatwave [26] |

CI: confidence interval; ER: emergency room; RR: relative risk

a For deaths: based on primary cause of death representing the underlying (not the immediate) cause of death, except for myocardial infarction (details in Table S4)
b Comparison of the 98th percentile of the daytime maximum temperature with the median
c Data available only for aggregated stroke events
d Via comorbidities, e.g., hypertension [31, 32, 34]
pertension and diuretic treatment during hot days may thus be less relevant for these specific patients.

For myocardial infarction and heart failure, there was a tendency for a slight but mostly insignificant reduction in emergency hospital admissions after an initial mortality increase. Thus, an initial mortality increase may have contributed to reduced admissions and mortality rates in the subsequent days for these specific disease groups.

Strengths and limitations
To the best of our knowledge, the present study is the first comparative study on heat-related mortality and morbidity that takes into account data on primary, underlying and immediate causes of death. We analysed all cardiovascular deaths and emergency hospital admissions that occurred in the warm season between 1998 and 2016 in Switzerland without any selection bias, resulting in a large dataset of ~160,000 cardiovascular deaths and ~250,000 emergency admissions. We included only frequent, clinically relevant diagnoses with established cause-effect relationships with heat using a non-standardised framework. By doing so, we could include the majority of cases (55% of all cardiovascular emergency admissions and 70% of all cardiovascular deaths) while maintaining some coherence with the ICD-10 coding framework. However, the use of aggregated data is a limitation of this paper, and statistical power was low for some disease groups. Similar analyses in other countries are warranted to validate the results.

We used only one temperature measurement per great region and could therefore not account for within-region or altitude variability. However, relative day-to-day temperature variations are most relevant for this type of time-series analysis and are well captured by a representative meteorological station within the study area. To check, we also conducted additional analyses with data restricted to a small area around each meteorological station, which produced similar results, although with larger confidence intervals.

We focused on Tmax only and did not consider other temperature indices such as daily minimum or mean temperature. Previous work on temperature-health associations in Switzerland showed very similar results across temperature indices [5]. Other potential environmental (e.g., air pollution) and weather (e.g., humidity) risk factors were not included. The role of these variables as confounders of heat-related health effects is still debatable [48, 49]. Our framework can be used to examine such potential environmental risk factors and cumulative days of extreme temperature that may enhance the heat effect [12, 50].

Inherently, considerable uncertainty remains regarding the habits of doctors during the process of cause of death coding. Although including data on underlying and immediate causes of death offered some insights, this limitation should be addressed by future qualitative research on the death coding process in practice. Finally, a study directly examining antihypertensive treatment as a possible risk factor during periods of heat is warranted.

Figure 2: Heat-related “gap” between emergency hospital admissions and mortality for two key cardiovascular diseases. The reduction in emergency hospital admissions and the increase in deaths can be explained by a combined effect of heat and antihypertensive drugs. RR: relative risk

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Emergency hospitalization – mortality – gap in heat

More deaths

Direct heat effects + anti-hypertensive drugs

Less emergency hospital admissions

Direct heat effects:

Vasodilatation + volume depletion

Daytime maximum temperature (°C)
Conclusions
A significant mortality increase for hypertension, heart failure, stroke of unknown origin and arrhythmia was accompanied by a significant decrease in emergency hospital admissions for hypertension, heart failure and myocardial infarction in high ambient temperatures. The opposite heat effect was most prevalent for diseases routinely treated with antihypertensive drugs. Pathophysiological considerations, comorbidity patterns and the coding of chronic diseases as primary cause of death indicate that an amplification of antihypertensive drug effects by heat plausibly explains the seemingly paradoxical mortality increase. Given the projected increase of heatwaves in the future, public health programmes and clinicians should increase vigilance for signs of heat-related illness in patients on antihypertensive drugs during periods of heat.

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Potential competing interests
Florian Schulte holds a position at the German Climate Change and Health Alliance (KLUG). KLUG had no role in the design or analysis of this study, which was completed before the start of the position. Martina Ragettli and Martin Röösli declare no conflict of interest.

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Appendix: Supplementary material

Figure S1. Map of Switzerland showing the seven study regions and corresponding measurement station of temperature of the Swiss Monitoring Network.
Figure S2: Sensitivity analysis: All models use natural splines for the temperature- and the lag dimension. The model descriptions refer to the position of knots in the temperature dimension, followed by the lag period (e.g. 10-75-90_lag10: Knots at the 10th, 75th and 90th percentile of the Tmax distribution, maximum lag period 10 days). For the lag dimension, two equally spaced knots on the log scale were used. Results from the model used in the main analysis is colored in black. Disease groups >10,000 cases.
**Figure S3:** Sensitivity analysis: All models use natural splines for the temperature- and the lag dimension. The model descriptions refer to the position of knots in the temperature dimension, followed by the lag period (e.g. 10-75-90_lag10: Knots at the 10th, 75th and 90th percentile of the Tmax distribution, maximum lag period 10 days). For the lag dimension, two equally spaced knots on the log scale were used. Model used in the main analysis is colored in black. Disease groups <10,000 cases.
Figure S4: Deaths by disease groups, sex and age. Area size is proportional to the numbers of cases.
**Figure S5:** Emergency hospital admissions by disease groups, sex and age. Area size is proportional to the numbers of cases.
**Figure S6:** Relative risks (RR) for emergency hospital admissions (EHA) and mortality, for cardiovascular disease groups <10,000 cases, by daytime maximum temperature, all age groups. RR are cumulative over the lag period of 10 days. Median daytime maximum temperature over the study period used as reference.
**Figure S7:** Relative risks (RR) for emergency hospital admissions (EHA) and mortality, for cardiovascular disease groups >10,000 cases, by age group and daytime maximum temperature. RR are cumulative over the lag period of 10 days. Median daytime maximum temperature over the study period used as reference.
**Figure S8:** Relative risks (RR) for emergency hospital admissions (EHA) and mortality, for cardiovascular disease groups <10,000 cases, by daytime maximum temperature and age group. RR are cumulative over the lag period of 10 days. Median daytime maximum temperature over the study period used as reference.
Figure S9: Lag – specific risk ratio at the 98th percentile of the temperature distribution by disease group. Disease groups ≥ 10,000 cases
Figure S10: Lag – specific risk ratio at the 98th percentile of the temperature distribution by disease group. Disease groups <10,000 cases
| Disease group       | ICD-Codes | Exact ICD name                                      | Assumed heat sensitivity pathway                                                                 |
|---------------------|-----------|-----------------------------------------------------|--------------------------------------------------------------------------------------------------|
| Hypertension        | I10-15    | Hypertension                                        | Heat > sweating, volume depletion, peripheral vasodilation > reduced preload, reduced afterload > reduced blood pressure 18,32 |
| Heart failure       | I50       | Heart failure                                        | Heat > sweating, volume depletion, peripheral vasodilation > reduced preload, reduced afterload 19,20 |
| Arrhythmia          | I44       | Atrioventricular and left bundle branch block        | Heat > Sweating > electrolyte imbalances > arrhythmia 14,15                                      |
|                     | I45       | Other conduction disorders                          |                                                                                                 |
|                     | I46       | Cardiac arrest                                       |                                                                                                 |
|                     | I47       | Paroxysmal tachycardia                               |                                                                                                 |
|                     | I48       | Atrial fibrillation and flutter                      |                                                                                                 |
|                     | I49       | Other cardiac arrhythmia                             |                                                                                                 |
| Myocardial infarction (MI) | I21 | Acute myocardial infarction                         | Heat > Sweating > Blood volume reduction > effects on coagulation, like hypercoagulability or faster clot lysis 21,22 |
|                     | I22       | Subsequent myocardial infarction                     |                                                                                                 |
| Pulmonary embolism  | I26       | Pulmonary Embolism                                   | Heat > Sweating > Blood volume reduction > effects on coagulation, like hypercoagulability or faster clot lysis |
| Category                          | Code | Description                              | Details                                                                 |
|----------------------------------|------|------------------------------------------|-------------------------------------------------------------------------|
| **Haemorrhagic stroke**          | I60  | Subarachnoid haemorrhage                | Heat > Sweating > Blood volume reduction > effects on coagulation,     |
|                                  | I61  | Intra-cerebral haemorrhage              |                                                                         |
|                                  | I62  | Other non-traumatic intracranial haemorrhage |                                                                         |
| **Ischaemic stroke**             | I63  | Cerebral infarction                     | Heat > Sweating > Blood volume reduction > effects on coagulation,     |
| **Stroke of unknown origin**     | I64  | Stroke, not specified as haemorrhage or infarction | Heat > Sweating > Blood volume reduction > effects on coagulation,     |
| **Deep vein thrombosis**         | I80  | Phlebitis and Thrombophlebitis          | Heat > Sweating > Blood volume reduction > effects on coagulation,     |
Table S2: Daily deaths and emergency hospital admissions (EHA) per cardiovascular disease group, sex and age group (<75, ≥75 years) from May to September between 1998-2016 in Switzerland

| Disease group                          | Deaths (% of total CVD) | EHA (% of total CVD) |
|----------------------------------------|-------------------------|----------------------|
| **All cardiovascular diseases (I00–I99*)** | total: 163.856 (100%)  | 447.577 (100%)       |
|                                        | male: 74.039            | 250.228              |
|                                        | female: 89.817          | 197.349              |
|                                        | <75: 31.316             | 228.849              |
|                                        | ≥75: 132.540            | 218.728              |
| **Arrhythmia (I44-49)**                | total: 11.323 (6.9%)    | 49.835 (11.1%)       |
|                                        | male: 5.170             | 26.269               |
|                                        | female: 6.153           | 23.566               |
|                                        | <75: 2.740              | 24.878               |
|                                        | ≥75: 8.583              | 24.957               |
| **Deep vein thrombosis (I80)**         | total: 508 (0.3%)       | 7.922 (1.8%)         |
|                                        | male: 196               | 3.705                |
|                                        | female: 312             | 4.217                |
|                                        | <75: 153                | 4.760                |
|                                        | ≥75: 355                | 3.162                |
| Condition                  | Status | Count   | Percentage |
|----------------------------|--------|---------|------------|
| Heart failure (I50)        | total  | 14.753  | 9.0%       |
|                            | male   | 5.423   | 29.384     |
|                            | female | 9.330   | 28.056     |
|                            | <75    | 1.168   | 14.889     |
|                            | ≥75    | 13.585  | 42.551     |
| Haemorrhagic stroke (I60-62)| total  | 5.745   | 3.5%       |
|                            | male   | 2.513   | 9.758      |
|                            | female | 3.232   | 8.736      |
|                            | <75    | 2.163   | 10.364     |
|                            | ≥75    | 3.582   | 8.130      |
| Hypertension (I10-15)      | total  | 17.142  | 10.5%      |
|                            | male   | 5.762   | 10.809     |
|                            | female | 11.380  | 18.724     |
|                            | <75    | 2.070   | 12.393     |
|                            | ≥75    | 15.072  | 17.140     |
| Condition                        | Total       | Percentage | Total       | Percentage |
|---------------------------------|-------------|------------|-------------|------------|
| **Ischaemic stroke (I63)**      | 3,594 (2.2%)| 44,873 (10%)|             |            |
| male                            | 1,662       | 24,494     |             |            |
| female                          | 1,932       | 20,379     |             |            |
| <75                             | 717         | 21,041     |             |            |
| ≥75                             | 2,877       | 23,832     |             |            |
| **Myocardial infarction (I21-22)** | 20,081 (12.3%) | 68,861 (15.4%) |             |            |
| male                            | 11,641      | 47,777     |             |            |
| female                          | 8,440       | 21,084     |             |            |
| <75                             | 6,794       | 43,708     |             |            |
| ≥75                             | 13,287      | 25,153     |             |            |
| **Pulmonary embolism (I26)**    | 2,426 (1.5%)| 24,543 (5.5%)|             |            |
| male                            | 884         | 11,821     |             |            |
| female                          | 1,542       | 12,722     |             |            |
| <75                             | 690         | 14,259     |             |            |
| ≥75                             | 1,736       | 10,284     |             |            |
| Stroke of unknown origin (I64) | total | 15.296 (9.3%) | 11.280 (2.5%) |
|-------------------------------|-------|---------------|---------------|
|                               | male  | 5.551         | 5.576         |
|                               | female| 9.745         | 5.704         |
| <75                           |       | 1.404         | 4.070         |
| ≥75                           |       | 13.892        | 7.210         |

*ICD-10: International classification of diseases codes, 10th revision
Table S3: Cumulative relative risks (RR) estimates for cardiovascular disease (CVD) mortality and emergency hospital admissions (EHA) associated with daytime maximum temperature (Tmax) in the total population and by age group*.

| Disease group | Age group | EHA | 95% CI | Mortality | 95% CI |
|---------------|-----------|-----|--------|-----------|--------|
| All CVD (I00-I99) | all | 0.91 | 0.88-0.94 | 1.13 | 1.08-1.19 |
|                | ≥75 | 0.91 | 0.88-0.95 | 1.16 | 1.1-1.22 |
|                | <75 | 0.91 | 0.87-0.95 | 1.04 | 0.93-1.16 |
| Arrhythmia (I44-I49) | all | 0.97 | 0.89-1.05 | 1.29 | 1.08-1.55 |
|                | ≥75 | 1.01 | 0.9-1.14 | 1.32 | 1.07-1.63 |
|                | <75 | 0.92 | 0.81-1.04 | 1.2 | 0.83-1.73 |
| Deep vein thrombosis (I80) | all | 0.78 | 0.63-0.97 | 0.67 | 0.28-1.6 |
|                | ≥75 | 0.99 | 0.7-1.38 | 0.83 | 0.29-2.39 |
|                | <75 | 0.66 | 0.5-0.88 | 0.39 | 0.08-2.03 |
| Heart failure (I50) | all | 0.83 | 0.76-0.9 | 1.22 | 1.05-1.43 |
|                | ≥75 | 0.86 | 0.78-0.95 | 1.24 | 1.06-1.46 |
|                | <75 | 0.74 | 0.63-0.87 | 1.03 | 0.61-1.74 |
| Condition                      | All   | 0.88-1.19 | 0.97   | 0.75-1.26 |
|-------------------------------|-------|-----------|--------|-----------|
| Haemorrhagic stroke (I60-I62) | 1.02  | 0.76-1.19 | 1.05   | 0.76-1.45 |
| ≥75                           | 0.95  | 0.76-1.19 | 1.05   | 0.76-1.45 |
| <75                           | 1.07  | 0.88-1.31 | 0.86   | 0.56-1.31 |

| Condition                      | All   | 0.64-0.81 | 1.18   | 1.02-1.38 |
|-------------------------------|-------|-----------|--------|-----------|
| Hypertension (I10-I15)        | 0.72  | 0.66-0.9  | 1.21   | 1.03-1.42 |
| ≥75                           | 0.77  | 0.66-0.9  | 1.21   | 1.03-1.42 |
| <75                           | 0.64  | 0.53-0.77 | 1.03   | 0.67-1.6  |

| Condition                      | All   | 0.84-1.01 | 1.03   | 0.75-1.41 |
|-------------------------------|-------|-----------|--------|-----------|
| Ischaemic stroke (I63)        | 0.92  | 0.86-1.11 | 0.85   | 0.6-1.21  |
| ≥75                           | 0.98  | 0.86-1.11 | 0.85   | 0.6-1.21  |
| <75                           | 0.87  | 0.76-1.1  | 2.24   | 1.07-4.73 |

| Condition                      | All   | 0.82-0.95 | 1.01   | 0.88-1.16 |
|-------------------------------|-------|-----------|--------|-----------|
| Myocardial infarction (I21-I22)| 0.88  | 0.71-0.92 | 1      | 0.85-1.19 |
| ≥75                           | 0.81  | 0.71-0.92 | 1      | 0.85-1.19 |
| <75                           | 0.93  | 0.84-1.02 | 1.03   | 0.81-1.3  |

| Condition                      | All   | 0.83-1.06 | 0.92   | 0.63-1.34 |
|-------------------------------|-------|-----------|--------|-----------|
| Pulmonary embolism (I26)      | 0.94  | 0.81-1.17 | 0.84   | 0.54-1.3  |
| ≥75                           | 0.97  | 0.81-1.17 | 0.84   | 0.54-1.3  |
| <75                           | 0.92  | 0.78-1.08 | 1.11   | 0.53-2.33 |
| Stroke of unknown origin (I64) | all     | 1.04 | 0.86-1.26 | 1.2    | 1.02-1.4 |
|--------------------------------|---------|------|-----------|--------|----------|
|                               | ≥75     | 0.91 | 0.72-1.16 | 1.18   | 1-1.39   |
|                               | <75     | 1.32 | 0.97-1.8  | 1.39   | 0.84-2.29 |

* Cumulative effect over the total lag period (0-10 days), comparing the 98th percentile (22°C) with the median of the daytime maximum temperature distribution over the study period (32°C)
Table S4: Agreement of primary cause of death with underlying and immediate cause of death by disease group

| Disease Group according to primary cause of death | ICD-Codes | primary cause of death (n) | “Primary” and “underlying” cause of death in the same disease group (n) | %  | “Primary” and “immediate” cause of death in the same disease group (n) | %  | Top 3 associated “immediate” causes of death |
|--------------------------------------------------|-----------|----------------------------|---------------------------------------------------------------------|-----|---------------------------------------------------------------------|-----|--------------------------------------------|
| Arrhythmia                                       | 144-49    | 11.323                     | 7.147                                                               | 63% | 5.030                                                               | 44% | Not specified Cardiac arrest (I46.9) Sudden cardiac death (I46.1) |
| Deep vein thrombosis                            | 180       | 508                        | 453                                                                 | 89% | 8                                                                   | 2%  | Pulmonary embolism (I26.9) Cardiac arrest (I46.9) Not specified     |
| Heart failure                                    | 150       | 14.753                     | 13.875                                                              | 94% | 891                                                                | 6%  | Cardiac arrest (I46.9) Not specified Pneumonia                     |
| Haemorrhagic stroke                              | 160-62    | 5.745                      | 4.261                                                               | 74% | 1.501                                                               | 26% | Not specified Intracerebral bleeding (I61.9) Cardiac arrest (I46.9) |
| Hypertension                                     | 110-15    | 17.142                     | 15.760                                                              | 92% | 99                                                                  | 1%  | Cardiac arrest (I46.9) Not specified Heart failure (I50.9)         |
| Diagnosis                  | ICD Code | Cases | Controls | Incidence | Cases | Controls | Participation Rate | Cases | Controls | Participation Rate |
|---------------------------|----------|-------|----------|------------|-------|----------|-------------------|-------|----------|-------------------|
| Ischaemic stroke          | I63      | 3.594 | 2.934    | 82%        | 494   | 310      | Not specified     | 1.094 | 395      | 14%               |
|                           |          |       |          |            |       |          | Pneumonia (J69.0) |       |           |                   |
|                           |          |       |          |            |       |          | Ischaemic stroke  |       |           |                   |
|                           |          |       |          |            |       |          | (I63.9)           |       |           |                   |
| Myocardial infarction     | I21-22   | 20.081| 5.421    | 27%        | 14.123| 310      | Acute myocardial  | 12.648| 2.318    | 70%               |
|                           |          |       |          |            |       |          | infarction        |       |           |                   |
|                           |          |       |          |            |       |          | Not specified     |       |           |                   |
|                           |          |       |          |            |       |          | Cardiac arrest    |       |           |                   |
| Pulmonary embolism        | I26      | 2.426 | 1.989    | 82%        | 351   | 351      | Not specified     | 769   | 422      | 14%               |
|                           |          |       |          |            |       |          | Cardiac arrest    |       |           |                   |
|                           |          |       |          |            |       |          | (I46.9)           |       |           |                   |
|                           |          |       |          |            |       |          | Pulmonary embolism|       |           |                   |
|                           |          |       |          |            |       |          | (I26.9)           |       |           |                   |
| Stroke of unknown origin  | I64      | 15.296| 10.707   | 70%        | 4.437 | 351      | Stroke of unknown | 4.437 | 3.651    | 29%               |
|                           |          |       |          |            |       |          | origin (I64)      |       |           |                   |
|                           |          |       |          |            |       |          | Not specified     |       |           |                   |
|                           |          |       |          |            |       |          | Cardiac arrest    |       |           |                   |
|                           |          |       |          |            |       |          | (I46.9)           |       |           |                   |