Summary of the Ph.D. Thesis

Effects of variability of weather and temperature extremes on cardiovascular diseases

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1 Summary

Elevated mortality represents one of the main impacts of temperature extremes on human society. Increases in cardiovascular mortality during heat waves have been reported in many European countries; much less is known about which particular cardiovascular disorders are most affected during heat waves, and whether similar patterns are found for morbidity (hospital admissions). Relatively less understood is also cold-related mortality and morbidity in winter, when the relationships between weather and human health are more complex, less direct, and confounded by other factors such as epidemics of influenza/acute respiratory infections.

This thesis comprises a collection of four papers, three of which address the impacts of extreme temperatures on cardiovascular disease (CVD) in the population of the Czech Republic with a focus on ischaemic heart disease (IHD) and cerebrovascular disease (CD). The three papers are complemented by a study analysing trends in cardiovascular mortality and hospitalizations in the Czech Republic. The first paper focuses on comparing the effects of hot and cold spells on mortality from CVD in the population of the Czech Republic during 1986–2006 and examines differences between population groups. The second paper analyses effects of hot and cold spells on IHD mortality in the Czech population between 1994 and 2009 with an emphasis on differences in effects on acute myocardial infarction (AMI) and chronic IHD. The third study compares impacts of hot spells on CVD mortality and morbidity (hospital admissions) in the Czech population between 1994 and 2009 with an emphasis on possible differences between CD and IHD. The last paper examines trends in hospital admissions and in-hospital case-fatality of selected cardiovascular diagnoses, compares them with national CVD mortality during 1994–2009, and estimates the potential contribution of improved in-hospital case-fatality rates to declining mortality from AMI and stroke.
2 Introduction

Climatic conditions and weather patterns have affected human physiology and health for centuries. However, the patterns of present and future health risks are expected to change in the context of changing climate (McMichael and Lindgren 2011). Rising mean summer temperatures are very likely to lead to an increase in the frequency, duration, and severity of heat waves in future (Ballester et al. 2010), and, even in a warming climate, the intensity and duration of extreme cold events may persist into the late 21st century (Kodra et al. 2011).

In the mid-latitudes, heat waves are the extreme weather events having the most adverse impacts on human health (Kovats and Hajat 2008). The exceptional heat waves of summer 2003 in Western Europe are examples of episodes which had a devastating impact on the population in terms of mortality (García-Herrera et al. 2010). Greater vulnerability to heat-induced stress has been associated predominantly with women, the elderly, and people with pre-existing diseases (D'Ippoliti et al. 2010; deCastro et al. 2011; Gabriel and Endlicher 2011). In contrast, the effects of low temperature extremes on human health are less understood. Extreme cold episodes are associated with excess mortality, but the effects of low temperatures on health are more complex and less direct than are those of heat waves and are confounded by epidemics of influenza and acute respiratory infections (Kyselý et al. 2009). The question also remains whether similar patterns occur for hospitalizations.

3 Aims of the thesis

- To analyse impacts of hot and cold spells on cardiovascular disease (CVD) in the population of the Czech Republic, with focus on ischaemic heart disease (IHD) and cerebrovascular disease (CD).
- To compare the effects of hot and cold spells on mortality for CVD and examine differences between population groups.
- To analyse the effects of hot and cold spells on IHD mortality, with emphasis upon differences in the effects on acute myocardial infarction (AMI) and chronic IHD.
- To compare the effects of hot spells on CVD mortality and morbidity (hospital admissions), with emphasis on possible differences between CD and IHD.
4 Data and methods

4.1 Data on mortality and hospital admissions

Data for the analyses carried out in all of the papers presented in this thesis were obtained from the national mortality and hospitalization registers covering the entire population of the Czech Republic. The databases were provided by the Institute of Health Information and Statistics of the Czech Republic (IHIS).

Mortality datasets cover all deaths with CVD coded as a primary cause of death during 1986–2009 in the Czech Republic using the International Classification of Diseases (with 9th revision (ICD-9) codes 390–459 for 1986–1993 and 10th revision (ICD-10) codes I00–I99 for 1994–2009). The following ICD-10 codes were processed: IHD: I20–I25, AMI: I21–I22, chronic IHD: I25, heart failure: I50, CD: I60–I69, and stroke: I60–I64. The national dataset covering 1986–2006 contains daily death counts stratified by gender and divided into five age groups (0–24, 25–59, 60–69, 70–79, and 85+ years). Since 1994, the national mortality database has been based on individual records (including each individual’s date of death, age at death, gender, district, and primary cause of death). Two age groups (0–64 and 65+ years) were considered in the analysis of hot and cold spell effects on CVD, IHD, and CD. For investigations of trends in CVD mortality, data were divided into several age groups (20–49, 50–64, 65–74, and 75+ years).

The hospitalization database, obtained from the National Registry of Hospitalized Patients (administered by IHIS), includes all admissions of residents to any hospital in the Czech Republic between 1994 and 2009 having CVD as the condition most responsible for the patient’s hospitalization. Each record includes the patient’s demographic information (age, gender, occupation, and district), date of admission, and primary diagnosis according to ICD-10. The same diagnoses as for mortality were analysed with the addition of hypertension (I10–I15) and angina pectoris (I20), for which numbers of deaths were small. The age groups studied were the same as for mortality, but not those related to aggregated CVD mortality data.

4.2 Standardization of mortality and morbidity data

To analyse temperature–mortality/morbidity relationships, an indirect standardization method was applied: excess daily mortality/morbidity was determined in each examined population group as deviations between observed and expected (baseline) numbers of deaths (cf. Gosling et al. 2009). The following equations were used to calculate the expected number of deaths/hospital admissions $M_0(y,d)$ for year $y$ [(i) $y = 1986, \ldots 2006$; (ii) $y = 1994, \ldots 2009$] and day $d$ ($d = 1, \ldots 365$):

(i) $M_0(y,d) = M_0(d)Y(y)$

(ii) $M_0(y,d) = M_0(d)W(y,d)Y(y)$
The first equation was used to estimate baseline mortality in a less detailed dataset covering the 21-year period. To enable comparison of mortality and morbidity, the equation was supplemented with an additional correction factor for the strong weekly cycle observed in morbidity data. $M_d(d)$ denotes the mean daily number of deaths/hospital admissions on day $d$ in a year (computed from the mean annual cycle, with epidemics excluded from the data from which the mean annual cycle was determined); $W(y,d)$ is a correction factor for the observed weekly cycle of mortality/morbidity, calculated separately for individual days of the week and defined as the ratio of the mean mortality/morbidity on a given day to the overall mean mortality/morbidity; and $Y(y)$ is a correction factor for the observed year-to-year changes in mortality/morbidity, defined as the ratio of the number of deaths/hospital admissions in year $y$ to the mean annual number of deaths/hospital admissions during the analysed period. The correction factors for year-to-year changes $Y(y)$ and weekly cycle $W(y,d)$ were calculated over April–November, a period when the effects of influenza and acute respiratory infections are negligible (Kynčl et al. 2005; Kyselý et al. 2009). Prior to calculating the correction factor for the weekly cycle $W(y,d)$, all public holidays were excluded.

To analyse trends in cardiovascular mortality and hospitalization, a direct standardization method was used. Annual counts of CVD hospitalizations and deaths, separately for each diagnosis, were stratified by gender and divided into 5-year age groups (from 0 to 85+ years). Age-adjusted rates of admissions, mortality, and in-hospital case-fatality per 100,000 persons were calculated using the mid-year population of the Czech Republic and the WHO European standard population as the standard.

### 4.3 Meteorological data

Daily air temperature data were provided by the Czech Hydrometeorological Institute. A mean air temperature series was calculated by averaging data from 46 high-quality weather stations covering the Czech Republic. Stations were selected so as to be representative for the area and population under study.

### 4.4 Hot and cold spells

Definitions of hot and cold spells are based on anomalies of mean daily temperature from the mean annual cycle. Hot (cold) spells were defined as periods of at least two consecutive days with anomalies of mean daily temperature above the 95% quantile (below the 5% quantile) or above the 90% quantile (below the 10% quantile). Quantiles were set from the empirical distribution of anomalies over running 61-day periods centred on a given day of the year.

Hot spells were analysed in summer (June–August) and cold spells in winter (December–February). The definitions led to reasonably large samples of hot and cold spells over the examined periods: 29 hot spells and 27 cold spells were identified during
1986–2006 using the definition based on the 95%/5% quantile, and the average length of individual hot (cold) spells was 2.9 (3.3) days. Between 1994 and 2009, a total of 35 hot spells and 37 cold spells were identified using the definition based on the 90%/10% quantile, and the average length of individual hot (cold) spells was 3.1 (3.8) days. Finally, 18 hot spells were identified in summer between 1994 and 2009 using the 95% quantile, with an average length of about 2.7 days.

4.5 Methods

Relative deviations of mortality from the baseline were averaged over all hot/cold spells, in sequences spanning from 3 days prior to \((D−3)\) until 16 days after \((D+16)\) the onset of a hot/cold spell. In the study of hot spell effects on mortality and hospitalization for CVD, IHD, and CD, the sequence of days after the onset of a hot/cold spell was extended by 4 days (up to day \(D+20\)) due to estimation of the mortality displacement effect’s magnitude.

Statistical significance was evaluated by comparison with the 90% and 95% confidence bounds around the zero line, estimated from the 2.5%, 5%, 95% and 97.5% quantiles of a distribution calculated using the Monte Carlo method. Periods in which mortality data were affected by epidemics of influenza/acute respiratory infections were excluded from all calculations.

Trends in age-standardized rates were assessed by linear regression and expressed as the mean annual relative change. Statistical significance was evaluated using a \(t\)-test.

5 Results and discussion

5.1 Hot and cold spell effects on CVD mortality

Both hot and cold spells were associated with significant excess cardiovascular mortality, but with differences in the timing and magnitude of the effects. Hot spell effects were more direct and concentrated within the few days of a hot spell, while cold spells were associated with indirect mortality impacts persisting after the end of a cold spell. The effects of cold spells on mortality in the Czech population were of at least similar importance for cardiovascular health as were those of hot spells. Due to lagged effects, the magnitude of the overall impacts on CVD mortality was larger for cold spells than it was for hot spells in spite of a much smaller peak of excess deaths. These findings highlight the importance of mitigation measures to decrease the burden of cold-related cardiovascular mortality.

The most vulnerable population groups differed between hot and cold spells. The adverse health effects of hot spells were much more pronounced in women than they were in men, and the magnitude of the effects increased with age. For cold spells, by contrast, relative excess CVD mortality was largest in the middle-aged population (25–
59 years), and pronounced mortality effects in this age group were found in males only. In older age groups, the mortality effects of cold spells were more lagged and differences between mortality in males and females were relatively minor. This suggests that older age and social structure of the population as well as physiological mechanisms including pre-existing chronic diseases, which commonly manifest in elderly women, play a role in women’s reduced tolerance for heat. In addition, the physiological mechanisms playing dominant roles in cold-related mortality differed between the middle-aged population and older age groups.

5.2 Hot and cold spell effects on IHD mortality

Overall, the magnitude and duration of IHD mortality effects of hot and cold spells were similar to those found for CVD mortality, showing that the effects of hot spells on IHD mortality were direct and concentrated within days with elevated ambient temperatures, while IHD mortality impacts of cold spells were indirect and persisted after a cold spell end.

During cold spells, relative excess IHD mortality was most pronounced in the younger age group (0–64 years), while excess IHD mortality in this age group was much lower during hot spells. In the elderly, the effects of cold exposure were more lagged, with an observed IHD mortality peak several days after the end of a typical cold spell. This finding is consistent with results for aggregated CVD mortality showing that low temperature extremes affect cardiovascular health more markedly in the middle-aged population than they do in older age groups.

The investigation of hot and cold spells effects on mortality separately by IHD subtypes revealed excess AMI and chronic IHD mortality at both temperature extremes but with different patterns, suggesting that different physiological mechanisms played dominant roles in extreme heat/cold exposures. Significant excess AMI mortality was associated predominantly with low temperatures and persisted up to almost 2 weeks after the onset of a cold spell. The peak in excess deaths from AMI was much higher in the younger population than it was in the elderly. On the other hand, the effects of hot spells on AMI mortality were much weaker and significant on only a single day. These findings suggest that cold exposure was a triggering factor for acute cardiac events, with younger people being more vulnerable.

For hot spells, chronic IHD was responsible for most excess deaths due to IHD for both males and females, with much more pronounced impacts in the elderly. For cold spells, on the other hand, considerably elevated cold-related mortality due to chronic IHD was observed predominantly in the younger age group (0–64 years). In other words, the presence of chronic IHD increases mortality risk associated with extreme heat more than that with extreme cold, and, by contrast, exposure to cold may lead to death from acute events rather than from chronic IHD in the elderly.
The analysis of the average effects of hot and cold spells on acute and chronic IHD mortality shows that IHD mortality effects of a cold spell were on average considerably larger than were those associated with a hot spell. This is consistent with the results for CVD mortality. For hot spells, much larger cumulative excess mortality was observed for chronic IHD compared to AMI in all examined population groups. For cold spells, in contrast, cumulative excess AMI mortality substantially exceeded chronic IHD mortality in all population groups except for the younger age group, where the difference was small.

5.3 Comparison of mortality effects of hot spells on IHD and CD

The results provide evidence of an association between hot spells and significant excess mortality from CD in all examined population groups except for the younger age group. Overall, for the population as a whole the pattern of heat-related excess mortality for CD was comparable to that found for heat-related CVD and IHD mortality. Nevertheless, the analysis of average effects of hot spells revealed differences between individual CVDs: CD displayed a much larger cumulative excess mortality magnitude than did IHD in the elderly, in males, and in the population as a whole. It is also interesting to note that average effects of hot spells on IHD mortality were comparable in the younger population and the elderly, while for CD a large significant increase was found only in the elderly.

In general, gender-related differences were similar to those found for CVD mortality, with women showing greater vulnerability to heat than men. However, the difference was much more pronounced for IHD (significant excess deaths due to IHD in women compared to smaller excesses in men), while for CD the differences between females and males were relatively small.

The results also show that the effects of heat on deaths from IHD were more immediate (excess IHD mortality already on day D+0), while increases in deaths from CD were more lagged (excess CD mortality starting on day D+1, with a peak on day D+2 in males and D+3 in females). This suggests that temperature changes and above-average temperatures occurring at the onset of a hot spell have an immediate impact on the cardiovascular health of vulnerable people, with consequences leading to acute cardiac complications. High temperatures lasting for several days, on the other hand, cause a gradual worsening of health conditions due to accumulation of physiological changes caused by heat stress that is more likely to result in cerebrovascular accidents.

5.4 Hospital admissions and hot spells

Heat-related excess cardiovascular mortality was not accompanied by increases in hospital admissions, and below-expected levels of admissions following the onset of a hot spell prevailed, particularly for IHD in the elderly. In addition, the average effects of hot spells on CVD, IHD, and CD admissions were mostly negligible. These findings are
in agreement with current research comparing CVD mortality and morbidity during hot spells (e.g. Bustinza et al. 2013; Monteiro et al. 2013) which shows that observed increases in mortality are not associated with comparable increases in hospitalization. This supports the hypothesis that during hot spells people die rapidly from cardiovascular causes before reaching hospital or receiving medical attention. The results of this thesis suggest that out-of-hospital deaths represent a major part of excess CVD mortality during heat and that for in-hospital excess deaths CVD is a masked comorbid condition rather than the primary diagnosis responsible for hospitalization. This corresponds well with several studies which have included also secondary diagnoses into analyses and showed the importance of CVDs as an underlying condition in heat-related morbidity (e.g. Williams et al. 2012).

5.5 Harvesting effect

The results show declines in IHD mortality after hot spells, while a similar effect was not observed for cold spells. The reduction in deaths during subsequent weeks after hot spells to some extent offsets the previous increase; this short-term displacement points to the presence of people with short life expectancy for whom the heat precipitates death. The short-term mortality displacement accounted for slightly more than half of the excess deaths due to CVD in the Czech population. This harvesting effect was manifested differently for individual diseases, as seen in the large difference between CD and IHD mortality where a much larger displacement effect was found for mortality due to CD than due to IHD. This difference may be associated with the comorbid diseases and generally worsened health conditions typically associated with CD, while for IHD a larger percentage of victims are among the “healthy” (and younger) population.

5.6 Trends in cardiovascular mortality, hospital admissions, and in-hospital case-fatality

Overall, mortality from all CVDs declined significantly between 1994 and 2009. Rapid declines were observed for deaths from AMI and stroke but not for deaths from chronic IHD and heart failure. The positive change in IHD mortality seems to be driven mainly by declining mortality from AMI across age groups and genders. In contrast to AMI, mortality from chronic IHD has increased since 2000, predominantly among people aged 75 years and older. These contradictory trends may be explained by the fact that improved treatment, leading to higher survival of patients with acute coronary events, and better secondary prevention might increase the number of people with chronic IHD. In combination with population ageing, this is likely to underlie the rising mortality rates from chronic IHD in the older population. Males were more likely to die from CVD than were females, and the difference was more pronounced in middle-aged individuals. In the oldest age group (75+ years), the most common cause of death was chronic IHD. The greatest improvement in CVD mortality was achieved among young
men (20–49 years) where mortality fell by 60% mainly due to declines in AMI, chronic IHD, and stroke. The corresponding mortality rates for women 20–49 years of age declined less sharply but from a lower baseline.

Age-standardized CVD hospitalization rates remained high and relatively stable during the study period, but in-hospital case-fatality rate (CFR) declined considerably. Both angina pectoris and chronic IHD admission rates decreased steadily, while AMI admission rates experienced a more modest decline. In contrast, hospitalizations due to heart failure increased dramatically in all age groups, and by 2009 heart failure had become the most common cause of CVD hospitalizations in the elderly. It is likely that heart failure morbidity will continue rising in future because of population ageing and improved survival attributable to improved secondary prevention and treatment. A favourable change in hypertension morbidity was found only in the youngest age group (20–49 years) in men and women. Among those aged 75+ years, hospitalization rates increased continually during the study period and the rate of admission for hypertension in women was almost double that of men.

In-hospital CFR declined significantly in both males and females for all diseases examined. The main cause of in-hospital deaths was stroke, despite a large annual reduction in CFR, and the largest improvement in CFR was attributed to AMI. The Czech Republic has one of the highest levels of AMI treatment in Europe, with reperfusion therapy widely available (Widimský et al. 2010). Improvements in treatment, including percutaneous coronary angioplasty and thrombolytic therapy, have led to better survival of patients with acute coronary syndrome and significantly reduced in-hospital CFR. The estimates suggest that approximately 24% and 41% of the national decline in mortality from IHD and AMI, respectively, could have been due to reduced in-hospital CFR. The magnitude of the contribution of treatment is consistent with the approximately 40% estimated in different countries by the IMPACT model (e.g. Bennett et al. 2006; Bandosz et al. 2012). According to the calculations, a rapid decline observed in in-hospital CFR for stroke may have had a major impact on national mortality from stroke. The fact that mortality and in-hospital CFR declined for both ischaemic and haemorrhagic strokes supports the view that improved survival is probably related to improved inpatient care.

### 6 Conclusions

The analysis based on national data provides evidence that both hot and cold spells were associated with excess cardiovascular mortality in the Czech population, but the most vulnerable population groups differed and increases in mortality were related to different prevailing cardiovascular health outcomes for heat and cold.

The mortality effects of cold spells were of at least similar importance as were those of hot spells in the Czech population. Due to lagged effects, the magnitude of the overall impacts on CVD mortality was larger for cold spells than it was for hot spells in spite of
a much smaller peak of excess deaths. The adverse health effects of hot spells were much more pronounced in women than they were in men and the magnitude of the effects increased with age. For cold spells, by contrast, relative excess CVD mortality was largest in the middle-aged population (25–59 years) and pronounced mortality effects in this age group were related to males only. Different patterns in the effects of hot and cold spells on AMI and chronic IHD mortality suggest that excess deaths from IHD during hot spells occurred particularly among people with histories of chronic diseases whose health had already been compromised, while cardiovascular changes induced by cold stress may have resulted in deaths from acute coronary events rather than chronic IHD. A comparison of mortality and morbidity impacts of hot spells revealed that excess mortality for IHD and CD during hot spells was not accompanied by increases in hospital admissions and below-expected levels of morbidity prevailed, particularly for IHD in the elderly. This suggests that out-of-hospital deaths represented a major part of excess CVD mortality during heat and that for in-hospital excess deaths CVD was a masked comorbid condition rather than the primary diagnosis responsible for hospitalization. Finally, the study showed that overall CVD hospitalization rates remained high but the in-hospital case-fatality rate declined considerably. Improved case-fatality seems to have made a substantial contribution to the decline in national CVD mortality, particularly for AMI and stroke.

The analyses yield new insights into links between temperature extremes and cause-specific cardiovascular mortality and morbidity which could help to better identify populations most at risk of temperature-related disorders. Better understanding of heat- and cold-related effects on cardiovascular health is an essential step towards developing and implementing efficient preventive measures which may mitigate the negative human health consequences of both types of extremes in future. Public health warning systems and biometeorological forecast alerts should take into account that the most vulnerable population groups as well as the most affected cardiovascular diseases differ between hot and cold spells. As the elderly constitute that segment of the population most vulnerable to temperature extremes, special consideration should be given to providing them with adequate social services.

7 References


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8 Curriculum Vitae

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List of publications

Publications related to the Dissertation


Publications unrelated to the Dissertation


International conference presentations


Urban A, Davidkovová H, Kyselý J (2013) Heat- and cold-stress effects on cardiovascular mortality and morbidity among urban and rural populations in the Czech Republic. EGU General Assembly, Vienna, Austria. 7 – 12 April 2013


Davidkovová H, Kyselý J, Kříž B (2011) Effects of hot and cold spells on cardiovascular mortality in individual population groups. 11th EMS Annual Meeting, Berlin, Germany. 12 – 16 September 2011


**Participation in research projects**


Effects of short-term and long-term variability of weather on mortality (GA ČR, 205/07/1254, 2010)