UNIVERSITY OF LAUSANNE

MASTER'S DEGREE IN MEDICINE

PLEASE DIE DURING OFFICE HOURS: PERIODICITY OF CARDIOVASCULAR EVENTS IN SWITZERLAND BETWEEN 1969 AND 2007

MICHELLE REAVEY, 2010-2011

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Tutor: Pedro Marques-Vidal Expert: Professor Hugo Saner, Bern

UNIL | Université de Lausanne

Centre hospitalier universitaire vaudois

IUMSP
Institut universitaire de médecine sociale et préventive, Lausanne
www.iumsp.ch

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M. Reavey, P. Marques-Vidal. *Please die within working hours: periodicity of cardiovascular deaths in Switzerland* (poster P433)

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ABSTRACT

Purpose: to evaluate and compare the periodical patterns of death from cardiovascular disease (*CVD*), including acute myocardial infarction (*AMI*) and stroke in the Swiss population between the years 1969 and 2007.

Methods: Swiss mortality database for the period of 1969- 2007 (2'362'430 deaths overall). The number of deaths due to CVD, AMI and stroke according to the time of day, day of the week and month were assessed, overall and after dividing the events according to gender and age (< 65 or ≥65 years old).

Results: In general and for all four subgroups according to age and sex, there is a daily variation in the number of deaths with a first peak in the morning (8h00 -12h00) and a smaller second peak in the late afternoon (14h – 18h). Both males and females have similar hourly patterns, although the magnitude of the difference diminishes in older patients particularly for people who die from stroke. For the weekly variation, there seems to be a significant trend only in the younger population with the lowest mortality rates on Sunday and the highest on Mondays for all diseases. When it comes to seasonal variation according to month, the trend is more significant in the elder patients with the highest death rates during the winter months (+31%) and the lowest in the summer (July/August).

Conclusion: There is a timely pattern for CVD, AMI and stroke deaths in Switzerland. This pattern changes according to the age and sex of the patients. Knowing this trend, its triggering factors and consequences, perhaps there could be measures put in place to prevent, diagnose and treat the population which is the most vulnerable at certain times.

Keywords: Trends; pattern; seasonality; CVD; AMI; stroke; hourly variation; daily; death rate; Switzerland

INTRODUCTION

Seasonality of mortality from cardiovascular diseases (CVD) such as acute myocardial infarction (*AMI*) and stroke is a phenomenon that has been observed and analysed worldwide. Several hypotheses have been put forward to explain this seasonal, monthly, weekly and hourly variation such as alterations in blood pressure due to temperature change (1), stress-levels (2), thrombotic activity (3), fibrogen concentration (4) or cholesterol level due to change in diet (5;6) but no concrete causality has been scientifically proven as yet.

In regards to seasonal or monthly variation, it has been shown that winter months lead to more deaths by AMI and stroke (3;7;8) particularly in areas subject to heterogeneous weather throughout the year. In areas with minimal seasonal climatic changes such as Taiwan, there appears to be no such seasonal variation in the incidence of stroke (9). Many studies have also observed that older patients (≥65 years of age) are more influenced by seasonal changes than the younger patients (<65 years of age).(10), possibly because the temperature extremes affect their thrombotic activity more seriously (3). Conversely, the summer months usually present the lowest mortality rates from CVD (11;12).

In regards to the variation according to the day of the week, interesting observations have been found. For instance young men present a stronger weekly variation than their older counterparts, both regarding stroke (13) and AMI (14) mortality. In the younger subgroup, the peak incidence occurred on Mondays for strokes (13) and on Mondays and Saturdays for AMI (14). This pattern may be explained by work-related stress inducing a release of catecholamines (Blue Monday) or the “weekend warrior phenomenon” by which normally sedative office workers participate in more strenuous physical activities resulting in an increase incidence of sudden death on Saturdays.

Finally, a circadian rhythm has also been noted for all CVD. According to several studies, strokes and AMI are more likely to occur in the morning (6am-noon) with a second and smaller peak in the afternoon (~3pm) (8;15;16), while a nadir has been observed during night hours. Taking into account the array of cardiovascular risk factors, some of the studies have put forward a few prevention strategies to protect those people who are at higher risk (17).

Switzerland is characterized by a low mortality from CVD and also by a consistent season pattern, with large temperature amplitude. Still, to our knowledge, no study has ever focused on the periodicity of CVD mortality. Hence, we used the data from the Swiss mortality database to assess the seasonal, daily and hourly death rates due to CVD such as acute myocardial infarction and strokes.

METHODOLOGY

Databases

Mortality data was provided by the federal office of statistics (www.bfs.ch). The database records all deaths occurring in Switzerland since 1969. The data collected include gender, age at death, main and surrogate causes of death, date and hour of death. Regarding the hour of death, the information was only available for the period of 1979 and 2007. Two international classifications of diseases (ICD) of the world health organization were employed: ICD-8 (before 1995) and ICD-10 (after 1994). Only adults (≥18 years of age) were included in this analysis.

Causes of death

For this analysis, only the main cause of death was considered. Acute myocardial infarction (AMI) was defined as an ICD-8 code 41 or an ICD-10 code I21X, where X=any number. Stroke was defined as an ICD-8 code 43 or an ICD-10 code I6X, where X=any number. Sudden death was defined as an ICD-8 code 795 or an ICD-10 code starting with R96, R97 or R98. Other CVD was defined as an ICD-8 code 42 or an ICD-10 code I3X, I4X (X=any number), I50, I51 and I52. CVD was defined as any one of the previous conditions (AMI, stroke, sudden death and other CVD).

Statistical analysis

Statistical analysis was conducted using SAS version 9.2 (SAS Inc, Cary, NC, USA). Results are expressed as mean standard deviation, as number of deaths and their corresponding percentages relative to the day, week or year. Statistical analyses were performed using chi-square under the null hypothesis of an identical distribution of deaths during the day, week or year. Statistical significance was retained for $p<0.05$.

RESULTS

Characteristics of the subjects

The population included in this study consists of all subjects, male or female, who died of CVD (including AMI and stroke) in Switzerland within the years of 1969 to 2007. Overall, there were 869,863 deaths from CVD, of which 454,565 (52.3%) were women and 776,134 (89.2%) were aged 65 or older. The mean age at death was 78.8 (SD: 11.4, range: 18-110) years.

Deaths from cardiovascular disease

The number of deaths according to month stratified by age and gender are summarized in **figure 1**.

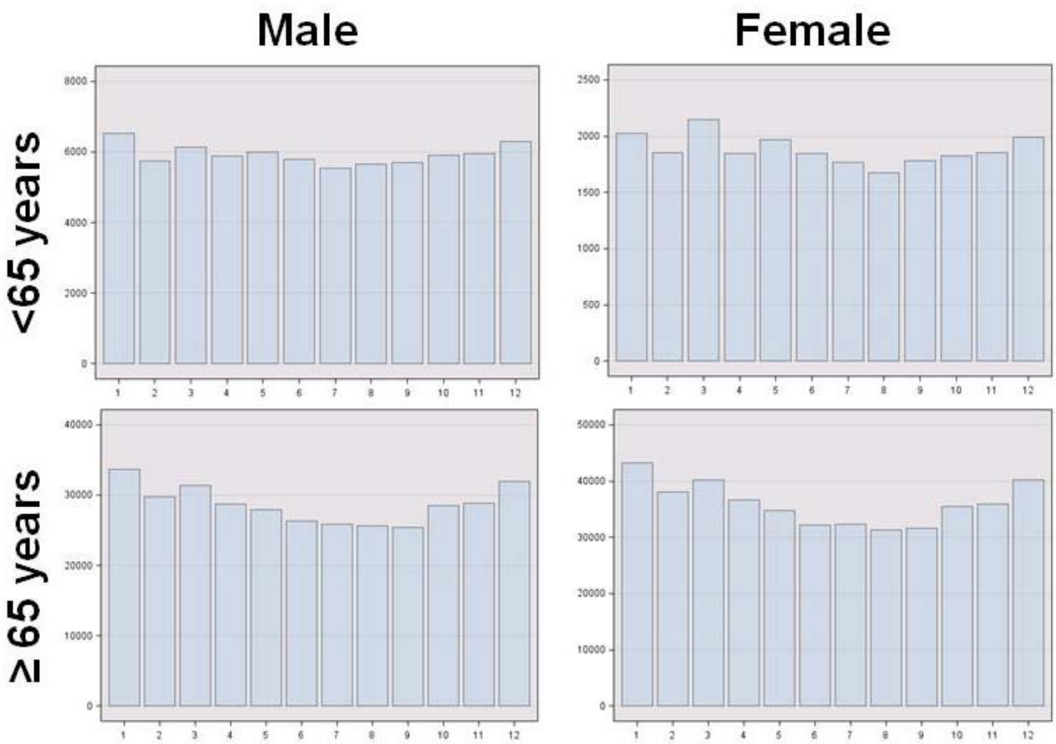

Figure 1*: deaths from CVD per month, according to age and gender***.**

In all subgroups, the number of deaths was higher in winter and lower in summer, although the magnitude of the variation was somewhat lower among the young subjects. For instance, among young men, the peak month (January) represented 10% more than the average, while in older men it represented 18%; the corresponding values for young and old women were 8% and 20%, respectively. Similarly, among young men, the nadir month (July) represented 6% less than the average, while in older men it represented 11%; the corresponding values for young and old women were 6% and 10%, respectively.

The number of deaths according to day of week by age and gender is presented in **figure 2**. We observe a daily variation mostly in the younger population and also that the pattern tends to flatten as the patients get older. In young men, the number of deaths due to CVD increases on Mondays (5% more than the weekly average) and Saturdays (6% more than the weekly average). In young women, the number of deaths increases on Mondays (5% more than the weekly average). According to our statistics, the older female and male groups do not have any statically significant variation in the number of deaths during the week.

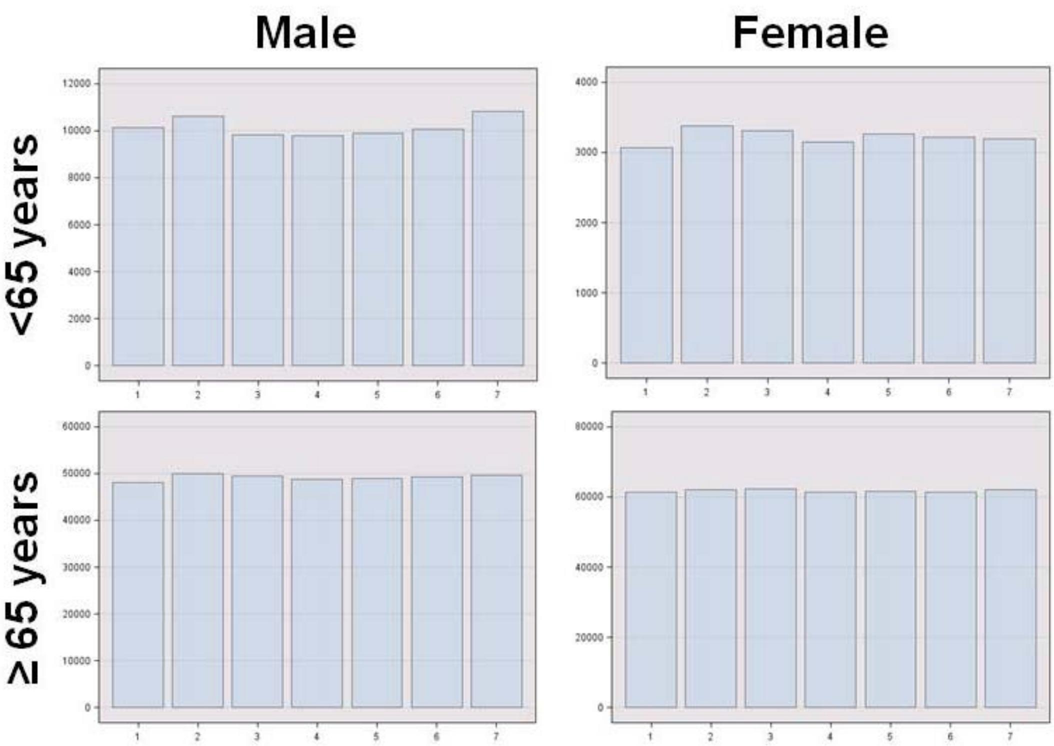

Figure 2: *deaths from CVD per day of week, according to age and gender.*

The number of deaths from CVD according to the hour of the day between 1979 and 2007 are shown in **figure 3.** We can observe an hourly variation in the number of

CVD deaths according to the hour of the day. There are two peaks, the first during the morning hours of 6am-12am and the second, smaller peak during the afternoon between 2pm and 7pm. For all subjects, the nadir occurs during the night between 7pm and 5am.

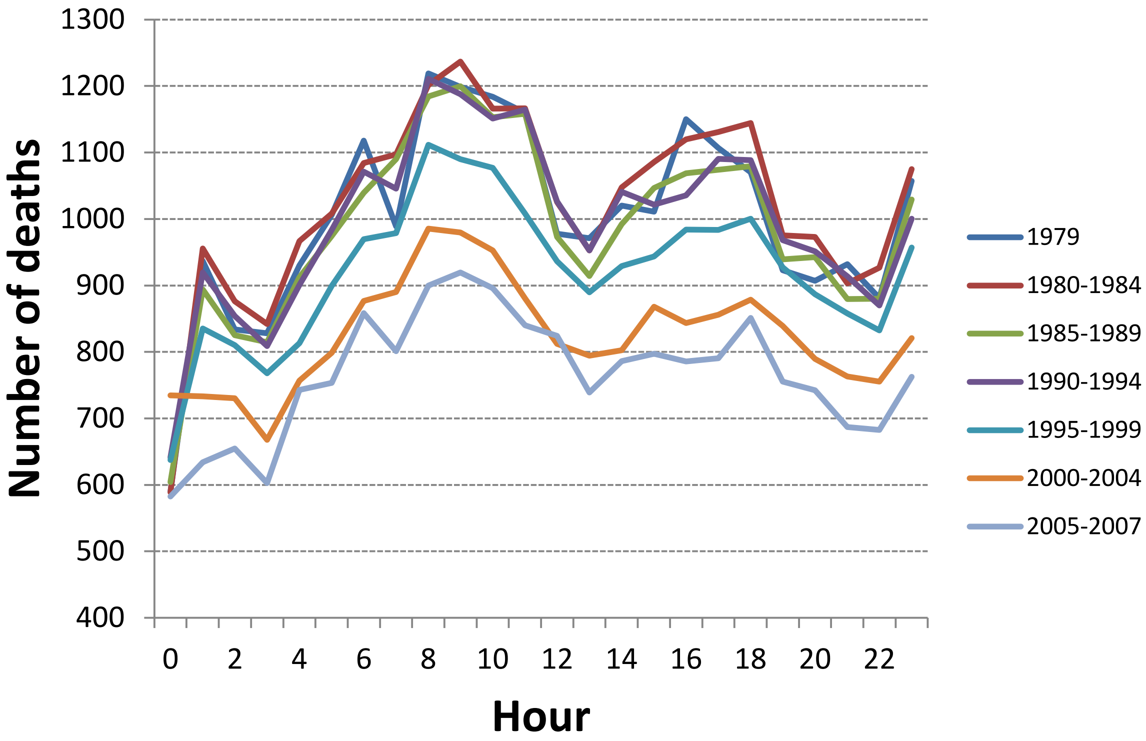

Figure 3: *deaths from CVD per hour of day, according to study period.*

The number of deaths per hour of day was further divided into four subgroups based on sex (male or female) and age (<65 and ≥65 years of age). This gives us a better appreciation of the risk of the various types of population and the results are summarized in **figure 4**. All four groups presented the same pattern of two daily spikes as noted previously. The hour with the lowest number of deaths for all subgroups is midnight which represents only 2.8% of the average number of deaths, and the number of deaths remains low till 5am where a gradual increase is noted.

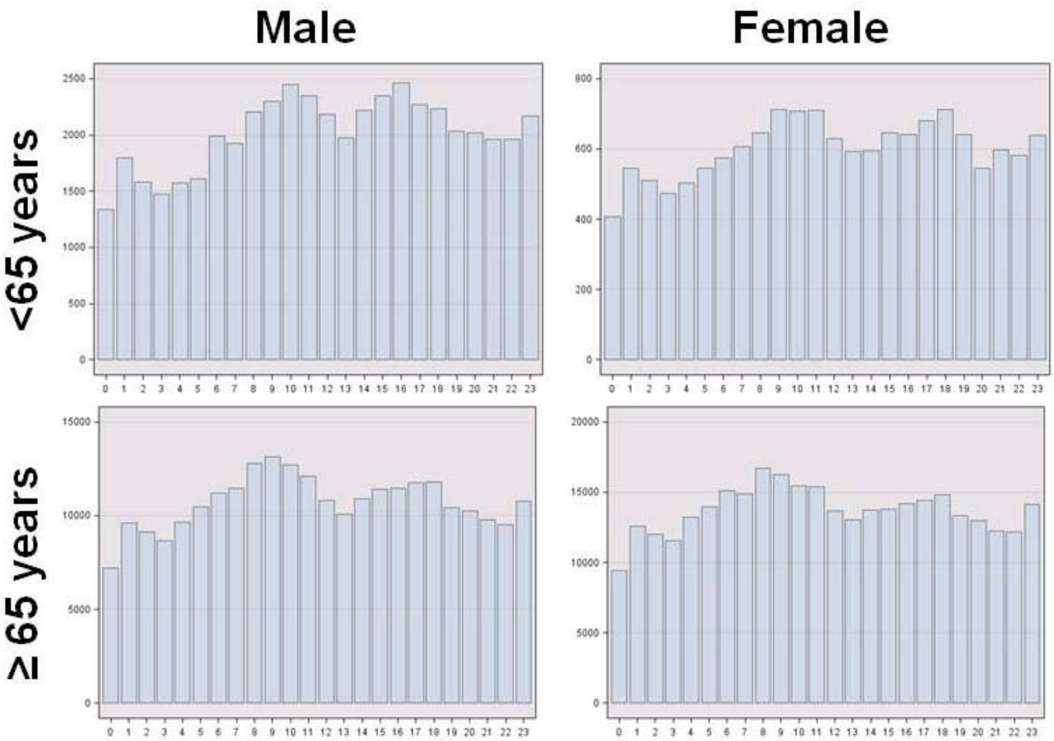

Figure 4: *deaths from CVD per hour of day, according to age and gender.*

Deaths from acute myocardial infarction

The number of deaths from AMI per month is shown in **Figure 5.** The seasonal variation of the number of deaths is more prominent in the older female and male groups. Men > 65 years of age are 13.5% more likely to die of an AMI during the months of December and January than during the warmer months. The older females are likewise 15% more likely to die during that same period. The variation between the highest and lowest number of deaths from AMI is 22.5% in the younger subgroups compared to 28.5% in the old subgroups. The maximum number of deaths in young women is March (15% increase risk) and the minimum number of deaths in all subgroups is during the months of July and August.

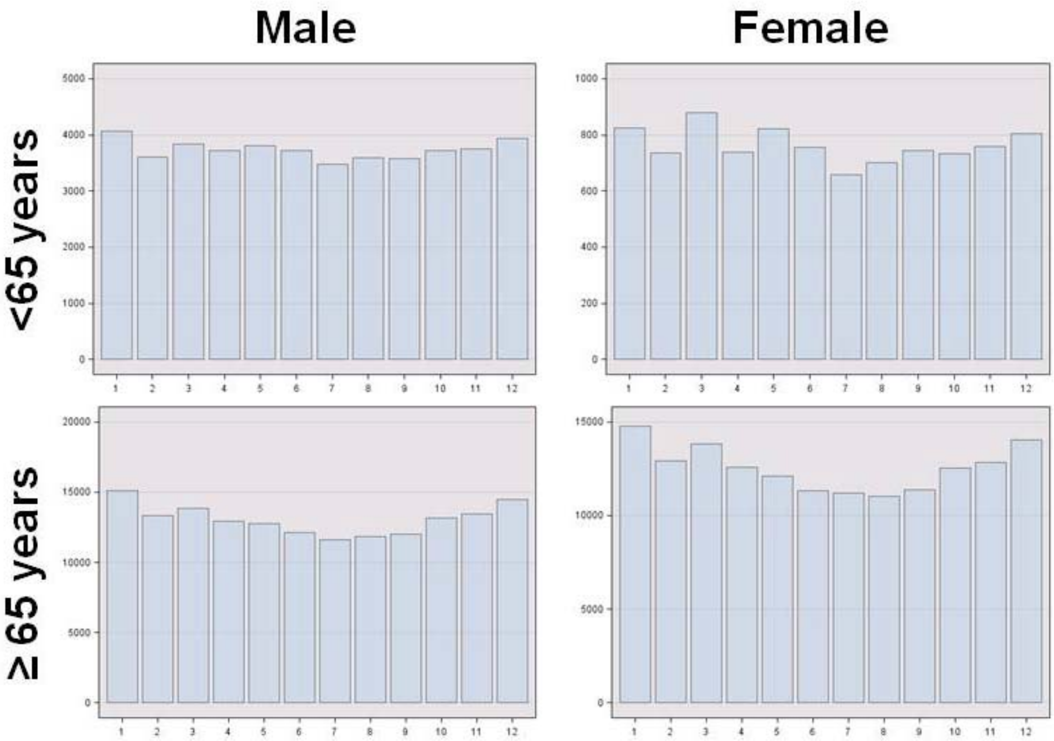

Figure 5: *deaths from AMI per month, according to age and gender.*

Figure 6 represents the number of deaths by AMI according to the day of the week per age and gender.

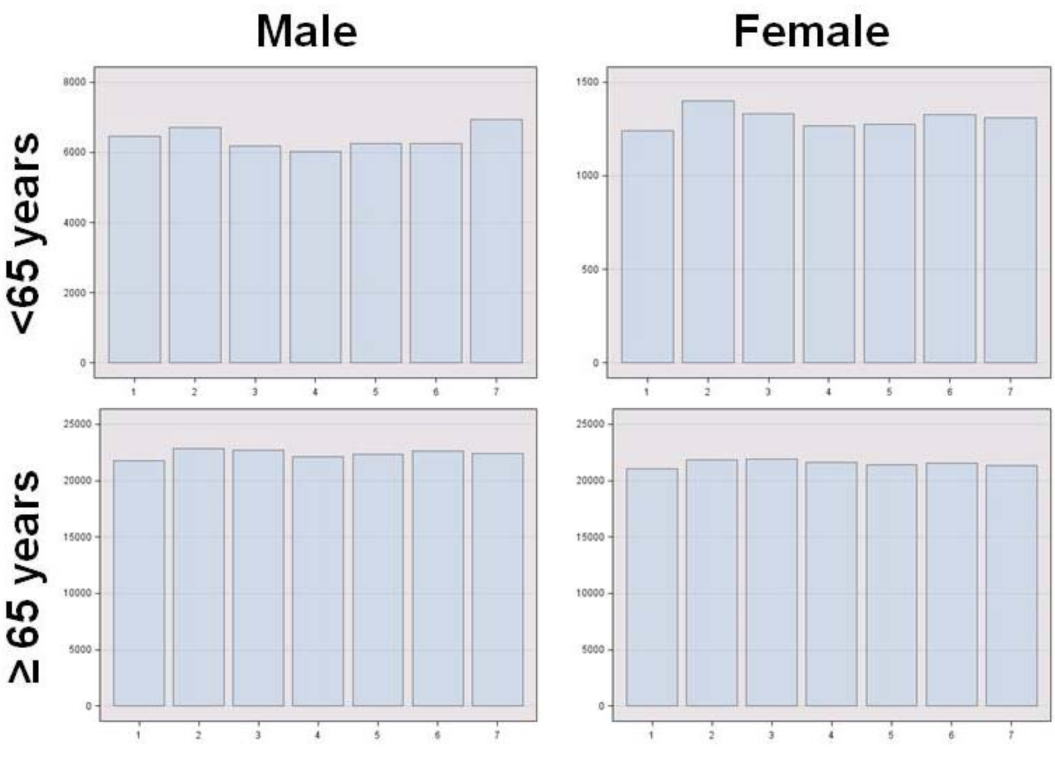

Figure 6: *deaths from AMI per day of week, according to age and gender.*

The younger population, particularly young men, have a more significant weekly variation than the older males and females. In the younger males, Monday and Saturday are statistically the highest rating days of death from AMI with an increase of 5% and 8% respectively. In the females <65 years old, Monday is also the peak of the week with an increase in risk of 7%. In the older subgroups, the maximum weekly variation from the average for the males is 3% and respectively only 2% for the females. We can thus conclude that the weekly variation is only significant in the younger subgroups, and that the older population are less influenced by the day of the week with regards to dying from an AMI. Concerning the number of deaths by AMI per hour of the day, all ages and sexes included, the circadian variation is significant throughout the population (**Figure 7)** There is an 12.3% increase in the number of deaths between 6am and 12am and 7% increase in the afternoon from 2pm to 6pm. The nadir occurred at midnight, with a minimum number of deaths between 12pm and 5am.

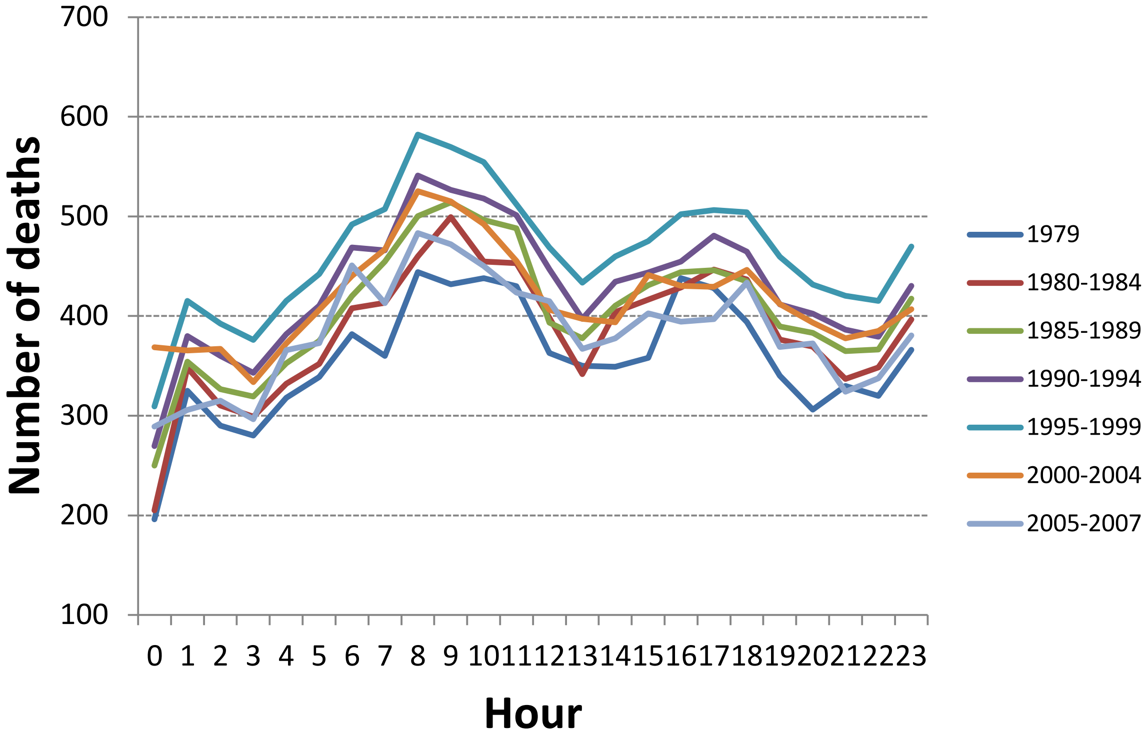

Figure 7: *deaths from AMI per hour of day, according to study period.*

The number of deaths according to the hour of day by age and gender is represented in **Figure 8.** There is a double-peak variation present in all four subgroups during a 24-hour period. In the young males the number of deaths due to AMI increases by up to 21% in the morning hours (6am to 12am) and also by 21% in the afternoon (2pm to 6pm) compared to the nightly hours of 12pm to 5am. In the young females, there is an increase of 21% at 8am compared to the lowest prevalence of the day. In the older subgroups, the males show an increased number of deaths by 29% at their morning peak of 9am, while the females peak at 8am with an increase of 26%. Both older subgroups have a second peak in the late afternoon (5-6pm) with an increase of 12% in the older males and 9% in the females. Again, the daily low for older males and females is midnight with a decrease of 34% and 32% respectively.

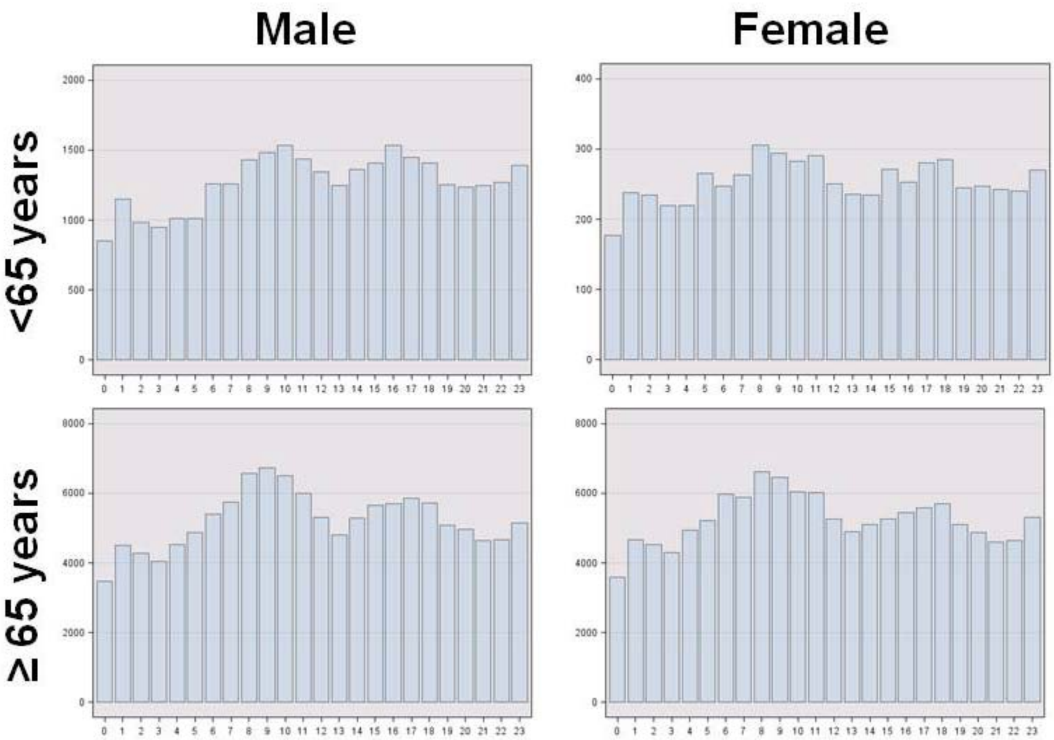

Figure 8: *deaths from AMI per hour of day, according to age and gender.*

Deaths from stroke

The seasonal variation in the number of deaths from stroke is shown in **figure 9**. In the older subgroups, there is a seasonal variation in the number of deaths from stroke with an increase of 11.5% of deaths in older men and 11.8% in women during the colder winter months of December to March. During those same winter months, the increase in the number of among the younger subgroups is somewhat smaller: 5.8% for young men and 5.5% for young women. The warmer months of August and September present the lowest number of deaths, while the highest numbers occur during the colder winter months of December and January all ages and gender combined.

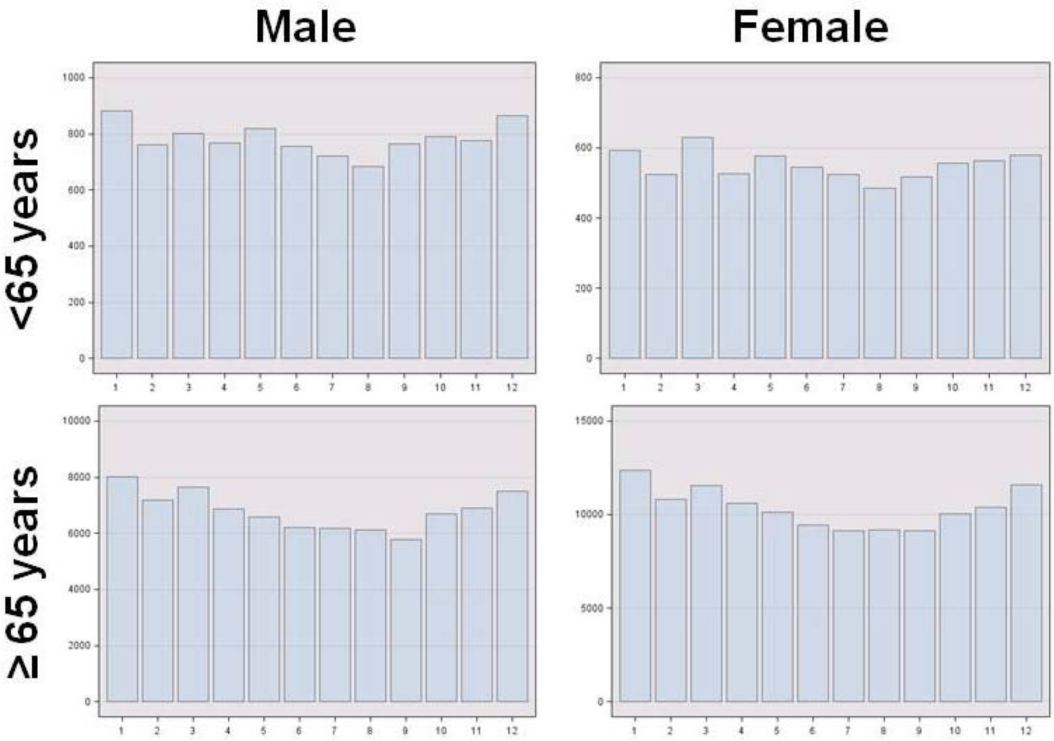

Figure 9: *deaths from stroke per month, according to age and gender.*

There was little variation in the daily number of deaths by stroke (**Figure 10**). Overall, Mondays present the higher number of deaths (14.5%) and Saturdays and Sundays the lowest (13.9%). However, this death rate is relatively stable throughout the week for all subgroups studied. For instance, the excess number of deaths on Mondays is 1% for men <65 and 1% for older men.

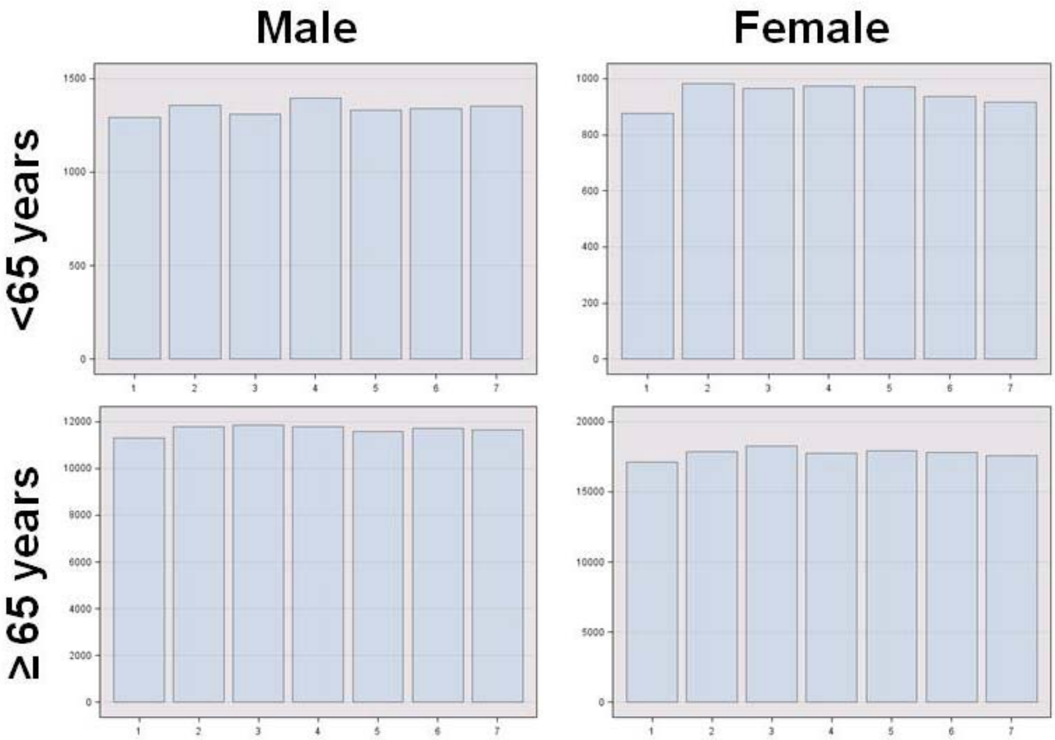

Figure 10: *deaths from stroke per day of week, according to age and gender.*

The hourly number of deaths by stroke is summarized in **Figure 11**.

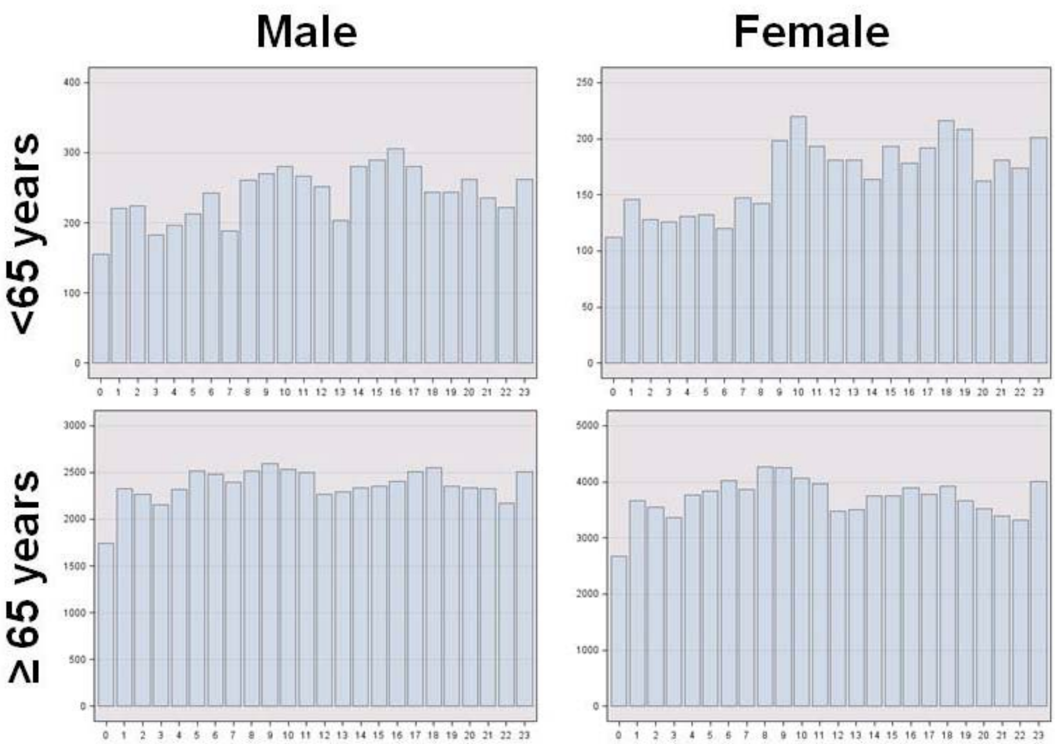

Figure 11: *deaths from stroke per hour of day, according to age and gender.*

Overall, there was a two-peak pattern, one in the early morning between 8am and 11am and a second in the late afternoon between 4pm to 6 pm. In the older subgroups the hourly variation was less evident.

DISCUSSION

To our knowledge, this is the first study to assess the periodicity of death from CVD in Switzerland. Our results confirm the findings of previous studies conducted in other countries and provide interesting data for a better seasonal and daily planning of the emergency management of CVD.

A seasonal pattern of increased CVD mortality in winter and lower mortality in summer was found for all subgroups and causes of death analyzed; this pattern was more pronounced among subjects aged over 65. These findings are in agreement with a previous study by Green et al. (1), which showed an increase of the death rate in the winter months of 50% for men and 44% for women. The study also showed that the risk of death by ischemic heart disease and stroke during the winter months further increased if those months were colder than the average, and that this increase was independent of other diseases such as Influenza and Pneumonia infections. The most probable trigger might be an increase in cardiac output and blood pressure as a response to decreased ambient temperature, as observed by Izzo et al (18). Conversely, a study conducted in Germany by Wolf et al. (19) showed that it wasn't only the absolute temperature that can influence CVD and AMI rates, but also the variation in temperature from one day to the next or even during the same day, meaning that sudden colder weather, even in the summer raises the risk of CVD. The authors observed increases in the relative risk of 7% if the temperature dropped by 10°c in a 24-hour time frame. Although the temperature is a factor, other possible triggers such as increased fat consumption or decreased physical activity during winter months cannot be ruled out. Indeed, Stout & Crawford (4) showed a monthly variation of fibrinogen levels, which increased by 23% in the colder, winter months. We can also hypothesise that the December Christmas holidays lead to a change in diet and emotional state. People are more likely to consume heavy, fatty, alcohol-accompanied meals and then walk out into the cold which are conditions conducive to increased risk of CVD and AMI. For some people, the holiday season may also be associated with emotional stress and depression which creates a strain on the heart and metabolism. Kloner refers to this phenomenon and the "Christmas Coronary" (20).

Switzerland is a country with mild summers and cold winters. It has been observed in several studies that warmer areas such as California (21) are more susceptible to an increase in AMI if they have unusually cold winters. Conversely, cold areas like Minnesota (22) show less seasonality because the population are more diligent in protecting themselves from the cold, harsh winters. A study conducted in Switzerland (23) showed that being born at high altitude had a beneficial effect on coronary heart disease mortality independent of the classic CVD risk factors, and that this benefit could be due to climacteric parameters.

Deaths from CVD and AMI were higher on Mondays and lower on Sundays, and this weekly variation diminished as the patients got older. These findings are in agreement with most studies (2;14;15) but not with a French study (24) that found higher incidence and mortality rates for AMI on weekends among young subjects, while a trend towards higher mortality on Mondays was found for older subjects. Possible explanations for this observed pattern include work-related stress when commencing the weekly work activity ("Monday Blues") or higher blood pressure and strenuous physical activity on weekends ("Weekend Warrior"), particularly for young men who are otherwise sedentary during the week but who engage in sports and labour over the weekend. Indeed, the number of deaths from AMI evened out over the days of the week among subjects aged over 65. This is in agreement with the "Monday blues" hypothesis, which would affect the working young subjects but not the older, retired subjects. Finally, the much lower daily variation in deaths from stroke would speak against an effect of increased blood pressure

A daily pattern of two peaks was found for CVD and AMI, and to a lesser degree also for stroke. The first peak occurred in the morning between 8am and 12am, and the in the afternoon between 2pm and 6pm. Our findings are in agreement with other studies (20), namely one study conducted in Massachusetts in 1983 (25) which showed two peaks in sudden cardiac deaths, the first between 7am and 11am and the second between 5pm and 6pm. Several hypotheses have been put forward to explain this pattern, such as an increase in blood pressure and heart rate, the influence of wakeup time, postprandial influences on lipids, stress and emotional upset. Some studies have submitted their patients to EKG tests over a 24-hour period to find a relation between wakeup time and possible cardiac abnormalities. For instance, Millar-Craig (26) showed that waking up in the morning induced an increase in blood pressure and heart rate, thus possibly provoking a higher risk of ischemic ST-segment depression in the hours shortly following waking up. Similarly, Kriszbacjer et al. (16) hypothesized that the circadian rhythm of the body influences certain parameters such as blood pressure, body temperature and platelet aggregation. Thus, the effect of the body awakening can trigger an MI by influencing these parameters. In this study, we observed that older males present a stronger morning peak than their younger counterparts. It may be that their bodies are more sensitive to the natural awakening phenomenon, inducing a larger variation in blood pressure and/or other biological triggers. Alternatively, this stronger peak might simply indicate that elderly subjects have a lesser capability of adaptation to varying circadian metabolic rhythms.

This study has some limitations worth acknowledging. First, we were unable to obtain temperature data for the whole study period and for all the regions/cantons of Switzerland. Hence, it was not possible to analyze the associations between changes in temperature and mortality. A smaller, local study is currently under way in Lausanne to better assess this point. Second, it is possible that mortality numbers might be artificially decreased in summer due to the holidays, people going abroad and dying outside Switzerland. However, the number of deaths occurring outside Switzerland represented less than 1% of CVD deaths, so the possible influence of vacationing patients seems insignificant.

In summary, our results indicate that in Switzerland there are seasonal, weekly and circadian patterns for the number of deaths from CVD, AMI and stroke. These patterns appear to be influenced by different factors and their importance varies according to gender and age. This information could be applied to optimize preventive and emergency health resources.

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