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Incidence of myocardial infarction and associated mortality varies by latitude and season: findings from a Swedish Registry Study

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ABSTRACT

Background We investigated whether the incidence of death following myocardial infarction (MI) varied by season and latitude in the Swedish population.

Methods We studied deaths following MI from January 1987 to December 2009, using the Swedish National Cause of Death Register. County of residence was used to determine latitude and population density. An extension of Poisson regression was used to study the relationship between risk of death following MI with age, latitude, time (from 1987), population density and calendar days.

Results Over the study period, there was a secular decrease in the incidence of MI-related death. In men, MI-related death incidence increased by 1.3% [95% confidence interval (CI) = 1.1–1.5] per degree of latitude (northwards). In women, MI-related death incidence increased by 0.6% (95% CI = 0.4–0.9) per degree of latitude. There was seasonal variation in the risk of MI-related death with peak values in the late winter and a nadir in the summer months in both the north and the south of Sweden. Findings were similar with incident MI as the outcome.

Conclusions The incidence of MI-related death varied markedly by season and latitude in Sweden, with summer months and more southerly latitude associated with lower rates than winter months and more northerly latitude.

Keywords death, latitude, myocardial infarction, season, vitamin D

Introduction

Myocardial infarction (MI) is a leading cause of death in the western world. It is well documented that such events are most common during winter months in the northern hemisphere although the reason for this is not clear.[1–5] Variation in health behaviours, diet and physical activity across the year may all play a role, together with effects of temperature and air pollution. There has been much interest in recent years in the potential role of vitamin D in cardiovascular disease, with evidence from observational studies suggesting links between low circulating 25(OH)-vitamin D [25(OH)D] concentrations and greater risk of MI, heart failure and cardiovascular death.[6–8] Whilst these findings, together with the known seasonal variation in 25(OH)D, which largely corresponds to the seasonal variation in the incidence of MI, might implicate 25(OH)D in these associations, evidence from intervention studies has been rather less convincing.[6–8] Furthermore, recent work has suggested an alternative solar-dependent influence in nitric oxide-related species, which are

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released in the skin as a result of sunshine exposure and have been linked to blood pressure through effects on endothelial function.[9] Exposure to solar radiation at the ecological level is related to season and latitude, with lower levels from south to north and in winter/spring versus summer/autumn (in the northern hemisphere).[10]

Sweden is an excellent country in which to examine such associations since it covers a wide range of latitude, and there is marked variation in solar radiation over the year. We have previously used population registries in Sweden to demonstrate substantial variation in age- and sex-specific hip fracture rates by season and latitude.[11] Demonstration of similar relationships for MI would inform potential mechanistic understanding and also approaches to public health policy. Since an individual has the ability to decide when to seek medical care when experiencing symptoms of MI, which could then lead to, for example, a reduced care seeking in summer (vacation) months, we focused on the incidence of MI-related death as our primary outcome. However, since there may be uncertainty regarding cause of death, particularly for those events occurring out of hospital, we included a further analysis using incident MI as the outcome. Thus, our aim was to use registries covering the entire Swedish population to investigate variation in the risk of MI-related death (or incident MI itself) by season and latitude, also considering calendar time and population density.

Methods

We examined the incidence of MI-related death in Sweden as a function of latitude and season. Importantly, Sweden is a long country south–north, covering a wide variation in latitude (55–69°N) and marked differences in levels of ambient solar radiation by season.

In the primary analysis, we studied MI-related deaths between January 1987 and December 2009, ascertaining outcomes from the Swedish National Cause of Death Register. In a secondary analysis, we used incidence of MI as the outcome. A unique personal identifier permitted the tracking of individuals. This register comprises records of all deaths in Sweden and is more than 99% complete. MI mortality was assessed from relevant International Classification of Diseases (ICD) code (ICD 9: 410x or ICD 10: I210-I214 or I219 before and after 1996, respectively).[12] The cases were documented by age, sex and county of residence within Sweden. The latter was used to determine latitude and population density. The population demography was determined from the same source. The county of residence was given for each hospital episode from 1987 to MI death, death from other causes or 2009.

Statistical analysis

An extension of Poisson regression model[13] was used to study the relationship between the risk of incident MI-related death (or incident MI) with age (1 year age intervals), latitude, time (from 1987), population density and calendar days.[11] In contrast to logistic regression, the Poisson regression utilizes the length of each individual's follow-up period, and the hazard function is assumed to be $\exp(\beta_0 + \beta_1 \cdot \text{minimum}(\text{age}, 75) + \beta_2 \cdot \text{maximum}(\text{age-75}, 0) + \beta_3 \cdot \text{latitude} + \beta_4 \cdot \text{minimum}(T, 10) + \beta_5 \cdot \text{maximum}(\text{minimum}(T\text{-}10, 14\text{-}10), 0) + \beta_6 \cdot \text{maximum}(T\text{-}14, 0) + \beta_7 \cdot \text{population density } 0/1 + \beta_8 \cdot \text{spline } 1 + \beta_9 \cdot \text{spline } 2 + \beta_{10} \cdot \text{spline } 3 + \beta_{11} \cdot \text{spline } 4 + \beta_{12} \cdot \text{spline } 5)$. The observation period of each participant was divided in intervals of 1 month. Population density, an index of urban/rural status, was acquired as a continuous variable[14] and then transformed to a zero-one variable and given the value 1 if the number of inhabitants of the home community per km^2 of land area exceeded $\exp(7)$ i.e. 1097 per km^2. This population density is comparable with the larger cities of Sweden (Stockholm, Malmo and Gothenburg). Latitude was considered as a continuous variable and was determined for each county of Sweden. The extremes in Sweden are latitude 69° and 55°N. Unless otherwise stated, the terms north and south refer to the most northerly and southerly conurbations of Sweden (northern latitude of 66° corresponding to Luleå and southern latitude of 56° corresponding to Lund).

For all MI-related deaths, the exact date of death was included in the calculations. The determination of the beta coefficients was performed separately for each sex. The seasonal variation was determined by a series of spline functions incorporated into the model as detailed in the appendix. The variables included in the main analyses are also shown in the appendix (Online Supplementary Tables A1 and A2) where T is time in years since 1987. Splines 1–5 are all functions of the number of days since the first of January of the current year. The resulting smooth curve of days since the beginning of the year was constructed, so it started and ended at the same level. The maximum and minimum functions of age and time (T) allow the correlations to differ for different intervals in age and time. The breakpoint in age is 75 years, and breakpoints in time are 10 and 14 years from 1987. A second analysis substituted incident MI for MI-related death as the outcome (findings presented in the Online Supplementary Material).

Further analyses were performed in order to determine whether the variation throughout the year differed depending on latitude and whether there was an interaction between latitude and calendar time. The beta coefficients labelled Splines 1–5 in Online Supplementary Tables A1 and A2 describe the variation during the year (VY). We used the beta coefficients

to define a function reflecting the VY. The argument of the function was the number of days since the start of the year to derive the variable VY. VY and the product, latitude × VY, were used as new variables in a Poisson regression analysis. The model also included the product age × VY. Covariates comprised age, latitude and calendar year. For the purposes of illustration, we computed the amplitude of the seasonal variation as the difference in the hazard of MI death between the apogee and nadir. In order to present the findings most clearly in particular tables and figures, we predicated exemplar models for seasonal variation on the year 2001 and for latitude and population density on the last day of June 2001. In separate analyses, as described above, we investigated any interaction with calendar time.

Results

Over the period of 23 years, there were 167,440 MI deaths in 47,665,497 person-years (py) amongst men and 120,782 MI deaths in 52,231,984 py amongst women. The model output is summarized in Tables A1 and A2 of the appendix for men and women, respectively. Age, latitude, time since baseline (1987), population density, season (the number of days since the first of January of each year) and the spline functions were significant covariates in both men and women. Throughout, the patterns and relationships observed with the outcome of MI-related death were very similar to those with incident MI, and so these results are presented in the Online Supplementary Material, with a table and figure corresponding to each of those in the main article.

Overall secular patterns of MI-related death

Between 1987 and 2009, there were statistically significant secular decreases in annual incidence. Amongst women, rates of MI death decreased by 4–7% per year [hazard ratio (HR) for the period rates in 2009 versus 2001 = 0.95; 95% confidence interval (CI): 0.95–0.96; $P < 0.001$]. In men, rates of MI death decreased by 3–5% per year [HR for rates in 2009 versus 2001 = 0.96; 95% CI: 0.96–0.97; $P < 0.001$]. These findings are summarized in Fig. 1.

Latitude

As expected, the greatest predictor of MI-related death was age. Independently of age, risk of MI-related death rose with increasing latitude (Fig. 2, Table 1). Over the calendar period as a whole, in men, there was an increase in the incidence of MI-related death of 1.3% (95% CI: 1.1–1.5; $P < 0.0001$) per degree of latitude (northwards). In women, rate of MI-related death increased by 0.6% (95% CI, 0.4–0.9) per degree of latitude. Thus, in the very northern part of Sweden, men had a 20% higher risk than men in the very south of Sweden (latitude 69° versus 55°N). The corresponding relative difference in risk for women was 9.5%. There was evidence of an interaction between latitude and calendar time on the incidence of MI-related death ($P < 0.001$), with the positive association between latitude and incidence reducing in magnitude over the period 1987–2007 (Table 2), such that the association was close to null in 2007 for both men and women (Table 2).

Seasonal variation

There was a marked seasonal variation in the risk of MI-related death by calendar day with peak values in the late winter and a nadir in the summer months in both the north and the south of Sweden (Fig. 3). Amongst men, MI-related death rates in the winter in the south were similar to summer rates in the north. Overall, the highest risk during the year was 28% higher than the lowest risk for men aged 80 years in south; the corresponding figure for women was 27%. There was no evidence of any interaction between season and calendar year.

Interaction between latitude and seasonal variation

Although there were no significant interactions of amplitude of variation in the incidence of MI-related deaths by season with latitude for men ($P > 0.30$), such an interaction was observed amongst women ($P = 0.023$), so that the seasonal variation during the year was more pronounced in the south of Sweden than in the north. For example, in women at the age of 50 years from the north of Sweden, the risk of MI-related death was 2% higher in winter than in summer, whereas the corresponding difference was 15% in the south (Fig. 4). For men, the corresponding figures were 9 and 13%. For men and women, we found significant interaction with age ($P < 0.001$), in that the seasonal variation in MI-related mortality risk during the year was more pronounced at higher ages (Fig. 4).

Population density

Population density was significantly and independently associated with incidence of MI-related death. The incidence was lower in the big cities (HR 0.90; 95% CI: 0.89–0.91; $P < 0.0001$ for men and HR 0.86; 95% CI: 0.85–0.87; $P < 0.0001$ for women). Since population density is higher in the south of Sweden, the exclusion of this variable would be expected to strengthen the effect of latitude. These associations did not materially change by calendar year.

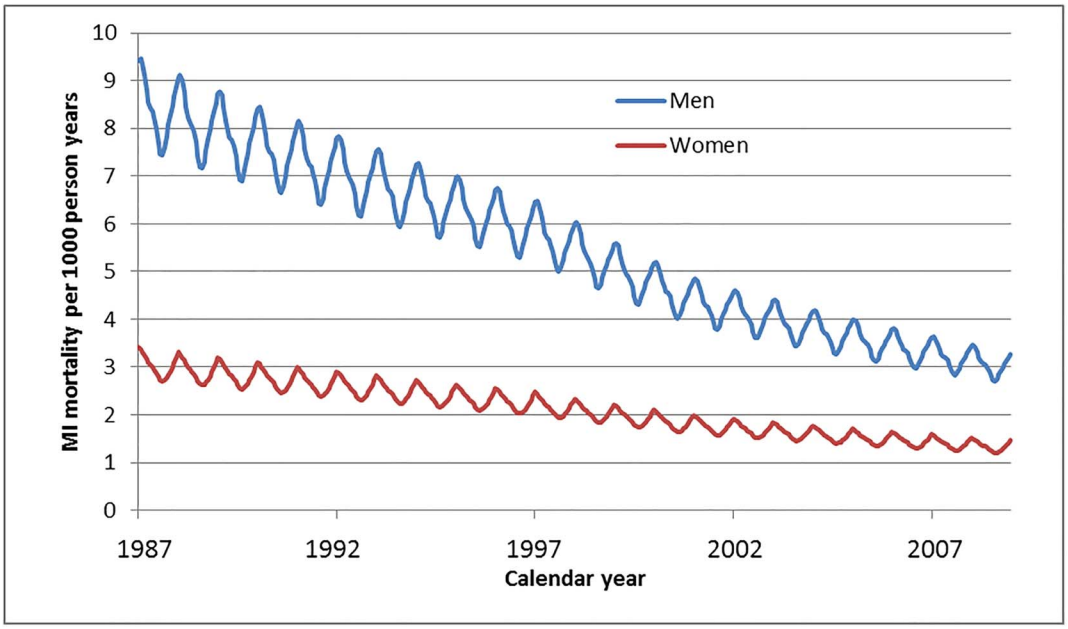

Fig. 1 MI mortality in men and women from Sweden 1987 and 2009. Age was set at 70 years, latitude to 60°N and population density to 0 (<1097 inhabitants per km^2).

Discussion

Main findings of the study

In this study of the entire Swedish population, we have demonstrated, on a background of declining age- and sex-adjusted incidence, that risk of MI-related death varies by season and latitude. Thus, incidence was higher in winter than in summer and rose from south to north although the relationship with latitude became less apparent in the later years of the follow-up period. Furthermore, incidence was lower in big cities than in rural areas.

What is already known on this topic

Our observation of a declining age- and sex-adjusted incidence of MI and related death is consistent with findings

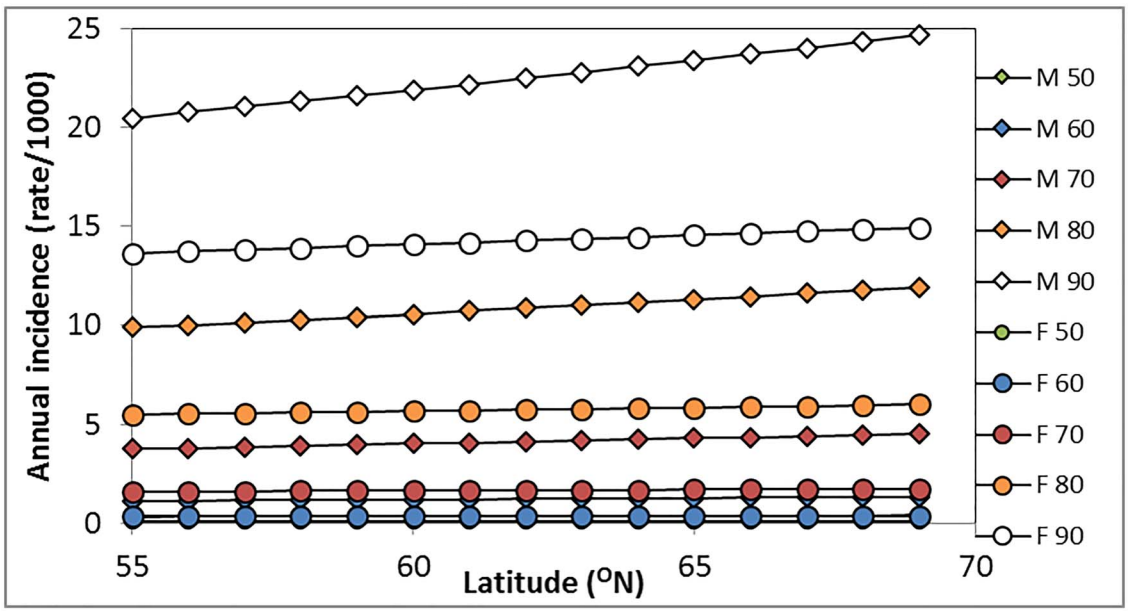

Fig. 2 Annual incidence of MI deaths (rate/1000) in men and women by latitude, stratified by age band. Data calculated using the estimated hazard functions. Calendar date was set at the last day of June 2001. Population density was set to 0 (<1097 inhabitants per km^2).

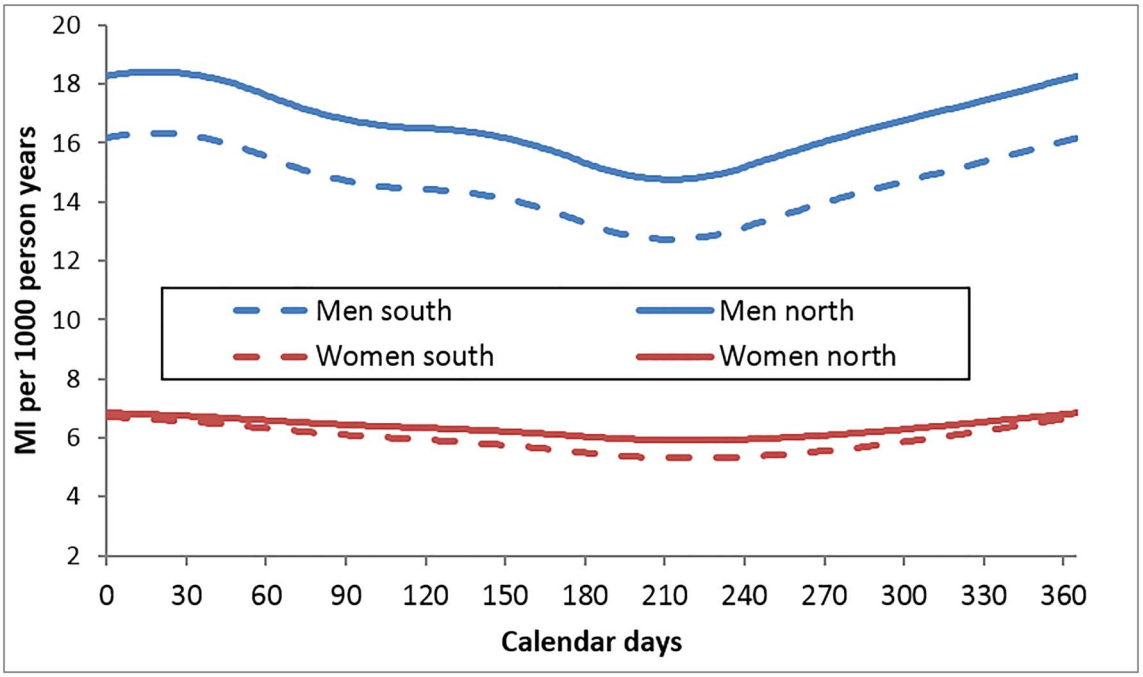

Fig. 3 MI mortality hazard in men and women aged 80 years from the north (latitude 66°N) and south of Sweden (56°N) by calendar day where the year was set to 2001. Population density set to 0 (<1097 inhabitants per km^2). The curves were obtained by use of the model including both interaction between seasonal variation and latitude and the interaction between seasonal variation and age.

Table 1. Incidence of death following MI (per 1000 person years) in men and women according to age and latitude. Calendar date set at the last day of June, 2001. Population density set to 0 (less than 1097 inhabitants per km^2)

	Men			*Women*		
Age group	*55°N*	*60°N*	*65°N*	*55°N*	*60°N*	*65°N*
60	1.1	1.2	1.3	0.3	0.4	0.4
70	3.8	4.1	4.4	1.6	1.7	1.8
80	9.8	10.5	11.3	5.4	5.7	6.0
90	19.9	21.4	23.0	13.4	14.0	14.7

from other studies of secular changes in the incidence of MI.[15,16] A similar decline was noted in Gothenburg[16] and in the incidence of recurrent MI in a further Swedish registry study.[15] The reasons underlying such changes are unclear, but it is notable that similar declines in age- and sex-adjusted incidence of hip fracture have been documented, with evidence of effects from birth cohort, and period, with only a modest impact of advances in treatment.[17] Whilst such changes are welcome, the predicted increase in the ageing population is likely to lead to a greater burden of overall disease in coming decades.[18,19] Interestingly, the south to north increase in the incidence of MI-related deaths became less marked with calendar year. This change has most likely been driven by improvements in primary care prevention programmes and clinical care post-MI, in the north of Sweden, and is consistent with those changes documented in previous studies.[20,21]

Seasonal variations in the rate of admission for MI have been noted in a number of countries globally. Thus, a greater risk of MI has been noted during winter months in northern Norway,[1] New Zealand,[2] Bangladesh,[3] and the United States.[4,5] Rather fewer studies have examined variation in rates of deaths associated with MI, with a large Chinese population-based study demonstrating the greatest seasonal attributable fraction for death from MI in winter compared with other months,[22] and the case fatality rate in Korean patients being lowest in summer, in the context of the

Table 2 HR (95% CI) MI-related death per 1 degree of latitude (northwards) by calendar year

	HR (95% CI)	
	Men	*Women*
Overall	1.013 (1.011, 1.015)	1.006 (1.004, 1.009)
By calendar year		
1987	1.028 (1.025, 1.032)	1.026 (1.021, 1.030)
1992	1.021 (1.018, 1.023)	1.016 (1.013, 1.019)
1997	1.013 (1.011, 1.015)	1.007 (1.004, 1.009)
2002	1.005 (1.003, 1.008)	0.998 (0.995, 1.001)
2007	0.998 (0.994, 1.002)	0.989 (0.984, 0.993)

greatest admission rate with MI during winter months.[23] Other studies have investigated the relationship between ambient temperature and rates of MI, suggesting that cold temperatures, and extreme high temperatures, or marked changes in temperature are all associated with greater risk of these ischaemic cardiac events.[24–28] Whilst there are a few previous studies which have explored geographic variation in rates of MI occurrence, these have not permitted a systematic evaluation of relationship with latitude over a wide range north–south.[29–34]

What this study adds

We studied the entire population of Sweden, using accurately ascertained, consistent outcomes and detailed information relating to season, latitude and population density. Our findings of a secular decrease in incidence of MI-related death, and indeed of myocardial function itself, are consistent with previous observations in Sweden. The value of our current analysis lies in the combination of observation across season and latitude, demonstrating findings consistent with the notion that the incidence of MI and related deaths might be inversely associated with levels of ambient UVB radiation. There are several potential factors which might contribute to mechanisms underlying our findings; two candidates with known biological dependency on ambient solar radiation are vitamin D and nitric oxide. Thus in temperate climes, seasonal variation in circulating 25(OH)-vitamin D [25(OH)D] is well documented, with, for example in the UK, a peak in late summer/early autumn and a nadir in early spring, and levels tend to be lower with more northern elevation.[10,35] Evidence linking 25(OH)D status with cardiovascular health is inconsistent, with observational studies often demonstrating lower risk of events such as MI with high 25(OH)D concentrations.[6–8] Such studies are limited by considerations such as cross-sectional design, low numbers and variable case definition and, given their observational nature, are likely to be influenced by reverse-causality and confounding. Large trials of vitamin D supplementation are ongoing, but trial evidence to date has not confirmed benefits of such approaches for the prevention of cardiovascular disease.[6–8] An alternative approach to causal analysis employs a genetic instrument as the exposure (Mendelian Randomisation), and this methodology has been used to indicate that greater 25(OH)D might be protective from hypertension but is unlikely to reduce

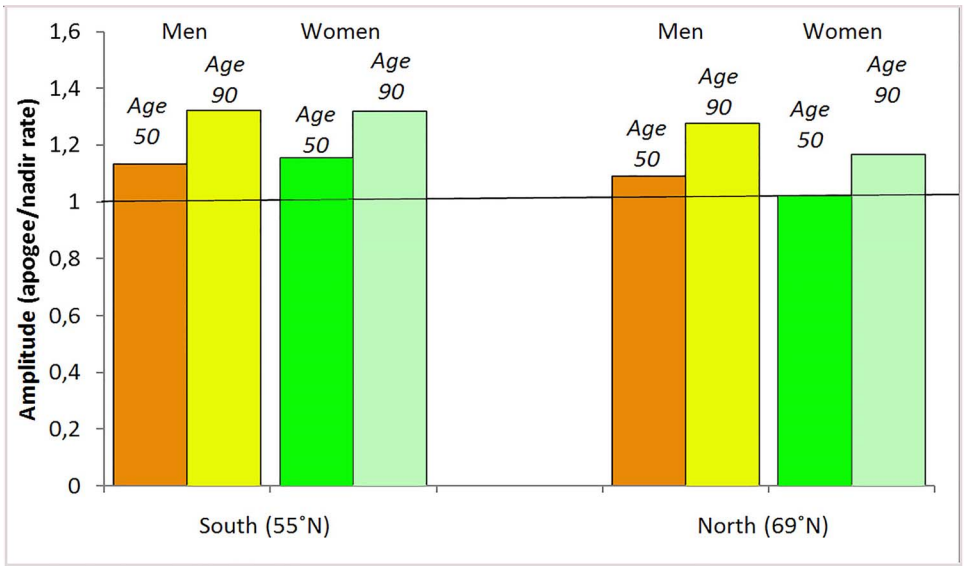

Fig. 4 Amplitude of the seasonal variation (apogee/nadir rate) in risk of MI-related death in men and women at specific ages and latitudes where the calendar year was set to 2001. Population density set to 0 (<1097 inhabitants per km^2). Apogee is here 1st of January and nadir is 8th of August.

cardiovascular mortality.[36] A further study demonstrated no association between genetically determined 25(OH)D and mortality.[37] This literature carries its own limitations, not least the myriad of assumptions necessary and that the genetic instruments themselves usually only account for a few percent of the variation in the exposure. Given the widespread expression of the vitamin D receptor and enzyme necessary to convert 25(OH)-vitamin D to $1,25(OH)_2$-vitamin D, including in the vascular endothelium and myocardium, a role for vitamin D seems biologically plausible, but further investigation of this underlying biology, and the clinical approach, will be required.[38–43] Recent work has implicated nitric oxide-related species in modulation of blood pressure partly affected by solar radiation.[9, 44] Thus, such species are abundant in the skin, and exposure to sunlight leads to a rapid reduction in blood pressure. Evidence in accumulating that nitric oxide-related species may thus represent a further potential mechanism linking cardiovascular pathology with predictors linked to sunshine exposure such as season and latitude.[9]

Limitations of this study

There are several limitations that should be considered in the interpretation of our findings. Whereas individuals may be less prone to seek medical attention during the summer holiday months, this is very unlikely to affect ascertainment of deaths from MI, the outcome used in the present analysis. However, there may be uncertainty regarding cause of death, particularly where death occurs in the community; indeed, our findings were very similar using either MI-related death or MI itself, supporting the validity of our results. Second, although we used standard ICD classification of outcomes reported via the national registries, we were not able to examine the clinical circumstances of each event. However, if anything, this is likely to have a conservative effect on our findings. Third, we did not consider actual measures of UV exposure relevant to vitamin D metabolism or nitric oxide-related species, so we cannot judge the expected apogee and nadir for either. Fourth, we did not have, at this population level, specific measures such as body mass index, smoking status, ethnicity and socioeconomic class or other specific cardiovascular risk factors such as blood pressure, lipid status or family history of cardiovascular events. It is unlikely that many of these factors would contribute substantially the seasonal relationships, but they could at least partly explain the differences in mortality by latitude in particular. Indeed, we were also unable to include any measure of physical activity or dietary patterns, which clearly might vary by both season and latitude, and so might also potentially contribute to the relationships seen. Finally, we were unable to examine how healthcare provision-related factors such as access to healthcare, local and national health programmes and public health interventions might vary by latitude and season although as described above there is evidence for a potential effect of cardiovascular-focused health interventions in the north of Sweden.

In conclusion, we have demonstrated marked variation in rates of MI-related death (and MI itself) by season and latitude in Sweden, with summer months and more southerly latitude associated with lower rates than winter months and more northerly latitude. The amelioration of the south to north increase in risk of MI-related death over the calendar period as a result of public health and clinical interventions confirms the possibility of overcoming such health disparities. Whilst these findings inform approaches to public health policy in Sweden, the underlying biology, possibly related to vitamin D or nitric oxide-related species, remains to be elucidated.

Supplementary data

Supplementary data are available at the *Journal of Public Health* online.

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Author contributions

NCH contributed to conception and design, contributed to analysis and interpretation, drafted article and gave final approval. ML contributed to conception and design, contributed to acquisition and analysis, critically revised article and gave final approval. JAK contributed to conception and design, contributed to acquisition, analysis and interpretation, critically revised article and gave final approval. EVM contributed to conception and design, contributed to acquisition, analysis and interpretation, critically revised article and gave final approval. HJ contributed to conception and design,

contributed to acquisition analysis and interpretation, drafted article, critically revised article and gave final approval.

Conflict of interest

The authors that they have no conflicts of interest with regard to this manuscript.

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