[Original article]

Environmental triggers of acute myocardial infarction: results of a nationwide multiple-factorial population study

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Objective The objective of this study was to study the independent environmental triggers of ST-elevation myocardial infarction (STEMI) in a multifactorial environmental population model.

Methods and results Daily counts of all STEMI patients who underwent urgent percutaneous coronary intervention over the period 2006-2009 in Belgium were associated with average daily meteorological data and influenza-like illness incidence data. The following meteorological measures were investigated: particulate matter less than 10 μM (PM_{10}) and less than 2.5 μM ($PM_{2.5}$), ozone, black smoke, temperature and relative humidity.

During the study period a total of 15,964 STEMI patients (mean age 63, 75% male) were admitted with a daily average admission rate of 11 ± 4 patients. A multivariate Poisson regression analysis showed that only the temperature was significantly correlated with STEMI, with an 8% increase in the risk of STEMI for each 10°C decrease in temperature (adjusted incidence risk ratio (IRR) 0.92, 95% CI 0.89-0.96). The effects of temperature were consistent among several subpopulations but the strongest effect was seen in diabetic patients (IRR 0.85, 95% CI 0.78 -0.95). There was a trend for an incremental risk of STEMI for each 10 $\mu g/m^3$ $PM_{2.5}$ increase and during influenza epidemics with IRR of 1.02 (95% CI 1.00-1.04) and 1.07 (95% CI 0.98-1.16), respectively.

Conclusion In a global environmental model, low temperature is the most important environmental trigger for STEMI, whereas air pollution and influenza epidemics only seem to have a modest effect.

Keyword *Myocardial infarction – epidemiology – risk factor – population.*

INTRODUCTION

Acute myocardial infarctions (AMIs) are a leading cause of cardiovascular mortality and are usually precipitated by acute thrombosis induced by a ruptured or eroded atherosclerotic coronary plaque, causing a sudden and critical reduction in blood flow[1,2].

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Although the exact trigger is not always evident, previous epidemiologic studies have identified several factors associated with the onset of AMI, including heavy exercise or physical exertion, diet, coffee and alcohol consumption, sexual activity, cocaine or marijuana abuse, emotional stress, and environmental conditions[3-6]. Among the environmental conditions, air pollution, influenza epidemics, and temperature changes are the most frequently reported environmental triggers for AMI[7-9]. Although the reported risk of environmental triggers was limited (adjusted risk ratio of 1.03-1.05), the public health relevance is considerable, as environmental triggers expose the entire population, elevating the general population's MI risk to comparable levels as would strenuous exercise or emotional stress[3,10].

Previous epidemiologic studies focused primarily on one or a limited set of environmental conditions, whereas due to their nature, most of these environmental triggers are to some extent related to each other and may attenuate or reinforce the triggering effect of a single environmental factor. In addition, although exposure to environmental triggers covers a total population, the effects might be different for different subpopulations. In general, low levels of acute environmental exposure can have minor effects on healthy people but may trigger more serious events in vulnerable subpopulations. Improved knowledge of these factors will help medical care providers and policy makers optimize prevention strategies for the target risk population.

Therefore, the present study evaluates the independent environmental triggers of acute myocardial infarction in a multifactorial nationwide environmental population model and seeks to identify subpopulations that are more vulnerable to the potentially harmful effects of their environmental exposures.

METHODS

Study population

Data on the incidence of ST-elevation myocardial infarction (STEMI) were extracted from the national percutaneous coronary intervention (PCI) database collecting data on all PCI procedures that took place in 32 PCI centres in Belgium. For the present study, all STEMI patients who received a PCI within 24 h after onset of the symptoms between 2006 and 2009 were included. Belgium has a population of ten million people as of the end of 2009 located on an area of 30,528 km^2, with a high population density and a high density of urban regions. At that time, approximately 60% of the STEMI patients received early invasive evaluations and treatments[11]. Figure 1 shows the regional distribution of PCI hospitals superimposed on a chart of the population density of the country.

A number of baseline characteristics for each patient were included: age, gender, history of hypertension, diabetes or hypercholesterolaemia, smoking habits, and extent of coronary artery disease (single versus multivessel disease).

Environmental exposures

Meteorological data were obtained from the Flemish Environment Institute and from the Environment centre at the Scientific Institute for Public Health. Air temperature, relative humidity, black smoke, ozone and particulate matter both less than 10 μM (PM_{10}) and less than 2.5 μM ($PM_{2.5}$) were measured daily at 73 background air monitoring sites equally distributed across Belgium (see figure 1). Particulate matter was measured by the beta absorption method or laser diffraction method after having tested the equivalence with the

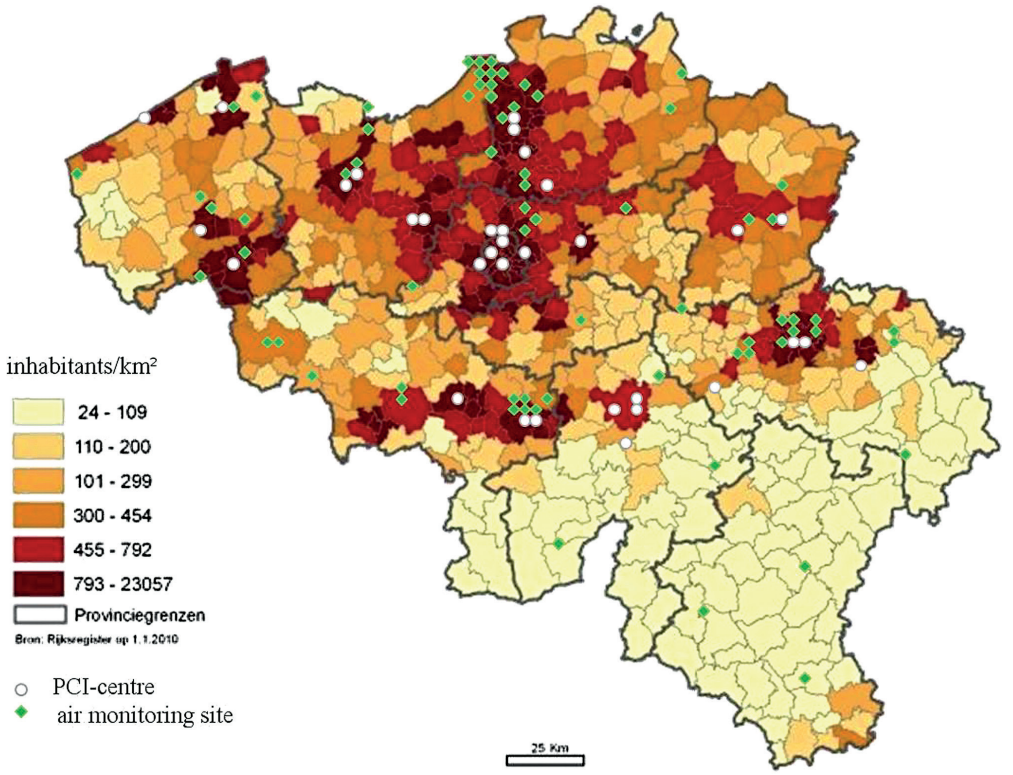


Fig. 1 Population density chart of Belgium with the regional distribution of PCI-capable centres and air monitoring sites.

European reference gravimetric method. For this study, the following meteorological parameters were selected for further analysis: temperature (°C), relative humidity (%), black smoke ($\mu g/m^3$), ozone ($\mu g/m^3$) and PM_{10} and $PM_{2.5}$ ($\mu g/m^3$). For all of these parameters, we calculated a single daily average based upon the average across all of the monitoring sites. We also calculated average exposure over 1-5 days before admission as previous studies have shown that equal or even larger RR can be achieved with a multi-day average instead of one-day values[12,13]. Summer was defined as the period between week 18 and week 43; winter was defined as the period between week 44 and week 17 of the next year.

As a measure of the seasonality of circulating airborne respiratory tract infections, we obtained daily counts of influenza-like illnesses (ILI) for each of the 9 Belgian provinces from the Communicable Diseases Surveillance Centre at the Scientific Institute for Public Health. Information on ILI outpatient cases was collected from a sentinel network of approximately 200 general physicians (GPs) coordinated by the Scientific Institute for Public Health. Estimated incidence rates of ILI were expressed per 10,000 inhabitants. The annual influenza vaccination status in Belgium, on average, is 20% for inhabitants aged < 65 years and 60% for those > 65 years [14].

The study was approved by the ethical committee of the Antwerp University hospital.

Statistical analysis

Continuous variables are presented as mean values with corresponding standard deviations (SD).

For all environmental parameters, a single daily average was calculated based upon the average across all of the monitoring sites. Regional variability was calculated from the standard deviation of all monitoring sites. The ratio of regional variability/range was calculated to assess the impact of regional variability on the temporal changes of the environmental levels. Spearman correlations were performed to assess the correlations between different environmental factors.

Independent triggers of AMI were determined by multiple Poisson regression analyses and reported as incidence risk ratios (IRRs) and 95% confidence intervals (CIs), both for the entire population and for subgroups. The issue of multicollinearity was assessed by calculating the variance inflation factor (VIF) for each covariate with a VIF of > 10, indicating the presence of collinearity between the model covariates. Different models were generated for different periods of exposure (lag 0 up to lag 7 days) and a lag 5 day model was selected as the best fitted model based on the Akaike Information Criterion (AIC). Comparison of the population attributable fraction (PAF) is a useful method for presenting the public health relevance of epidemiological findings[10,15]. It depends on the strength of the association between exposure to a risk factor and the prevalence of this risk factor within the population. The population attributable fraction (PAF) was calculated using (IRR-1)/IRR, taking into account 100% exposure to environmental triggers. A P-value of < 0.05 was considered significant. All statistical analyses were performed using SAS version 9.1 (SAS Institute, Cary, North Carolina).

RESULTS

Study population

During the study period, a total of 15,964 STEMI patients were admitted with a daily average admission rate of 11 ± 4. Patient characteristics are depicted in table 1. The study population, with an average age of 63 years, represents a typical STEMI population, which was predominantly male (75%) with a high prevalence of cardiac risk factors, such as hypertension (49%), hypercholesterolaemia (54%), smoking (45%) and diabetes mellitus (16%). Almost half of the patients had single-vessel disease.

Measurements of environmental factors

Daily data regarding climate factors (temperature and relative humidity) and air pollutants (PM_{10}, $PM_{2.5}$, black smoke and ozone) are shown in table 2. The regional variability was for most of the environmental factors less than 10% of the range observed over the 4-year study period.

Table 3 shows the ILI incidence rate across the five influenza seasons from 2006-2009 with the concomitant matching profile of vaccinations. The highest burdens were recorded in the winters of 2007 and 2009.

The majority of the measured factors are significantly correlated with each other, and each environmental factor is correlated with at least three other environmental

Table 1 Baseline characteristics of the study STEMI population

Characteristic	Proportion (numbers) or the mean ± SD
Age, years	63 ± 22
Male gender	75% (11,995/15,963)
Hypertension	49% (6,517/13,213)
Hypercholesterolaemia	54% (6,534/12,061)
Diabetes mellitus	16% (2,400/15,411)
Current smoking	45% (5,848/12,987)
Single-vessel disease	49% (7,674/15,780)

Table 2 Measurements of environmental factors averaged on a daily basis

Factor, units	Mean	Range	SD	Regional variability	Variability/range
Temperature, °C	11.3	34 (-6.8 , +27.6)	6.3	1.3	3.8%
Relative humidity, %	77.2	55 (40.2 , 95.2)	9.6	6.7	12%
PM_{10}, $\mu g/m^3$	30.3	107 (6.8 , 114)	15.5	9.3	8.7%
$PM_{2.5}$, $\mu g/m^3$	20.1	109 (2.5 , 112)	14.5	3.7	3.4%
Black smoke, $\mu g/m^3$	11.6	74.5 (5.1 , 79.7)	7.5	5.3	7.1%
Ozone, $\mu g/m^3$	42.7	128 (3.0 , 131)	20	10	7.8%

PM: particulate matter.

Table 3 Influenza epidemics

Average ILI/day Per 10,000 inhabitants	Average (peak)	Vaccination match
Winter 2006	2.4 (4.6)	Poor
Winter 2007	4.46 (11.1)	Good
Winter 2008	2.2 (5.2)	Relative
Winter 2009	3.2 (11.6)	Good
Autumn 2009	2.4 (7.6)	Good

ILI: influenza-like illness.

factors (table 4). The highest correlation found was between black smoke and particulate matter (correlation coefficient of 0.75) and between PM_{10} and $PM_{2.5}$ (correlation coefficient of 0.93).

Environmental triggers of STEMI

A univariate analysis revealed a significant inverse correlation between the incidence of STEMI and temperature and a positive correlation between the incidence of STEMI and humidity and influenza-like illness (table 5). The VIF for each covariate was less than 5, except for PM_{10} and $PM_{2.5}$. Therefore PM_{10} was excluded in the estimation of adjusted risk for STEMI. Multivariate Poisson regression analysis showed that temperature was significantly correlated with STEMI, with an 8% increase in the risk of STEMI for each 10°C decrease in the temperature (adjusted incidence risk ratio (IRR) 0.92, 95% CI 0.89-0.96). The PAF for temperature was 7.4%.

There was a trend for an incremental risk of STEMI for each 10 $\mu g/m^3$ $PM_{2.5}$ increase and during influenza

Table 4 Spearman correlation coefficients between exposure variables (*P*-value)

	Temp	Rel. hum.	PM_{10}	$PM_{2.5}$	Black smoke	Ozone	ILI
Temperature	1.00						
Rel. hum.	–0.43 (< 0.0001)	1.00					
PM_{10}	–0.12 (< 0.0001)	–0.10 (0.0001)	1.00				
$PM_{2.5}$	–0.22 (< 0.0001)	0.05 (0.07)	0.93 (< 0.0001)	1.00			
Black smoke	–0.31 (< 0.0001)	0.10 (0.0002)	0.75 (< 0.0001)	0.76 (< 0.0001)	1.00		
Ozone	0.51 (< 0.0001)	–0.59 (< 0.0001)	–0.24 (< 0.0001)	–0.35 (< 0.0001)	–0.55 (< 0.0001)	1.00	
ILI	–0.58 (< 0.0001)	0.28 (< 0.0001)	0.05 (0.06)	0.09 (0.0004)	0.24 (< 0.0001)	–0.35 (< 0.0001)	1.00

PM: particulate matter, ILI: influenza-like illness, rel. hum.: relative humidity.

Table 5 Unadjusted and adjusted estimates of the risk of STEMI for changes in environmental factors

	Unadjusted				Adjusted		
	IRR	95% CI	*P*-value	VIF	IRR	95% CI	*P*-value
Temp (unit 10°C)	0.93	(0.91-0.96)	< 0.0001	1.8	0.92	(0.89-0.96)	0.0001
Humidity (unit 10%)	1.03	(1.01-1.05)	0.0035	2.1	1.01	(0.98-1.05)	0.52
$PM_{2.5}$ (unit 10 $\mu g/m^3$)	1.01	(0.99-1.02)	0.28	12.8	1.02	(1.00-1.04)	0.07
PM_{10} (unit 10 $\mu g/m^3$)	1.00	(0.99-1.02)	0.61	14.1			
Black smoke (unit 10 $\mu g/m^3$)	1.00	(0.98-1.03)	0.7	3.5	0.94	(0.89-0.99)	0.02
Ozone (unit 10 $\mu g/m^3$)	0.99	(0.98-1.00)	0.05	2.7	1.01	(0.99-1.02)	0.41
ILI (unit 10/10,000)	1.14	(1.07-1.23)	0.0002	1.2	1.07	(0.98-1.16)	0.12

IRR: incidence risk ratio, PM: particulate matter, ILI: influenza-like illness.

epidemics with IRR of 1.02 (95% CI 1.00-1.04) and 1.07 (95% CI 0.98-1.16), respectively.

The effects of temperature were consistent among several subpopulations but the strongest effect was seen in diabetic patients (IRR 0.85, 95% CI 0.78-0.95) (see table 6).

For the other environmental triggers, a subgroup analysis revealed no significance effect, except for $PM_{2.5}$, which was associated with a more prominent STEMI risk in male patients (IRR 1.03, 95% CI 1.01-1.06) and in non-diabetic patients (IRR 1.03, 95% CI 1.0-1.06).

An additional analysis showed a significant interaction between the period of the year (summer versus winter) and the temperature-related risk of STEMI with the highest effect seen in summertime (adjusted IRR 0.82, 95% CI 0.76-0.90). As is shown in figure 2, the incidence of STEMI is the lowest during days with average temperature > 20° and is the highest during days with average temperature below 0°. Below a temperature of 15°C (corresponding with wintertime), there is no additional effect of temperature decrease on the occurrence of STEMIs which explains the absence of a significant IRR during winter (IRR 1.00, 95% CI 0.94-1.07).

DISCUSSION

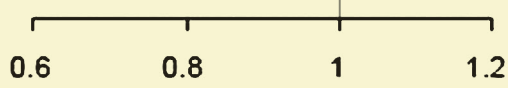
Strenuous physical activity or emotional upset are considered the most important triggers for acute coronary syndromes in textbooks on cardiology[4,6]. Environmental triggers have been under-recognized for many years but gained greater interest in the last decade, particularly after the first observations in the 1990s linking air pollution to cardiovascular mortality[16].

The present registry-based time-series study showed that air temperature was the most important environmental trigger for STEMI, whereas air pollution and influenza epidemics seems to have a modest effect.

Although temperature changes have been hypothesized to be an acute risk factor for cardiovascular disease, particularly MI, the relationship between temperature and incident MIs has been scarcely reported. The majority of the available studies could demonstrate an inverse correlation between temperature and incident MI including fatal MI[8,12,13,17,18]. In all of these studies, except for a German study, the temperature effect was not controlled for other environmental factors, such as air pollution or influenza epidemics, and therefore risk is likely to be overestimated. The German study by Wolf et al. observed an overall increase in the adjusted RR for incident MI of 10% per 10°C decrease in the 5-day average temperature (RR 1.10 99%CI 1.04-1.15) [12]. Our results, with an estimated RR of 1.08, concur with the German results. Interestingly, as was also observed in the German study, our study showed more pronounced effects of temperature decreases in summer as opposed to winter and provided a possible explanation for this "apparent paradox". Indeed, although the highest incidence of STEMI was reported in winter, the incremental effect of temperature decrease vanished when the average temperature was below 15°C (see figure 2). The fact that air temperature still plays a role outside of winter indicates that changes in temperature, particularly outdoor versus indoor, are more important than

Table 6 Adjusted estimates of the risk of STEMI per 10°C increase for several subgroups

Temperature (per 10°C increase)	IRR (95% CI)	p-value*
All patients	0.92 (0.89–0.96)	
Age		
≤ 65	0.92 (0.88–0.98)	0.94
> 65	0.92 (0.87–0.98)	
Gender		
Male	0.92 (0.89–0.97)	0.79
Female	0.91 (0.84–0.99)	
Arterial hypertension		
Yes	0.91 (0.86–0.97)	0.93
No	0.91 (0.86–0.97)	
Diabetes mellitus		
Yes	0.85 (0.78–0.95)	0.12
No	0.93 (0.89–0.98)	
Hypercholesterolaemia		
Yes	0.92 (0.86–0.98)	0.47
No	0.89 (0.83–0.95)	
Current smoking		
Yes	0.89 (0.84–0.96)	0.93
No	0.89 (0.85–0.95)	
Extent CAD		
Single VD	0.93 (0.88–0.98)	0.81
Multi VD	0.92 (0.87–0.97)	
Time period		
Winter	1.00 (0.94–1.07)	0.0007
Summer	0.82 (0.76–0.90)	



*P-value for interaction.
CAD, coronary artery disease; IRR, incidence risk ratio; VD, vessel disease.

the absolute air temperature. This explanation is further supported by the study of Barnett et al. that showed that populations in the coldest regions (Northern Sweden, North Karelia, and Kuopio) showed little temperature-induced change in coronary events, likely because people living in cold climates took more precautionary measures to protect against cold[19].

Potential mechanisms to explain the increased risk for incident coronary events in association with decreasing temperature include the stimulation of cold receptors in the skin and therefore the sympathetic nervous system, leading to a rise in the catecholamine level[20-22]. This causes vasoconstriction and an increased heart rate and blood pressure which may precipitate myocardial

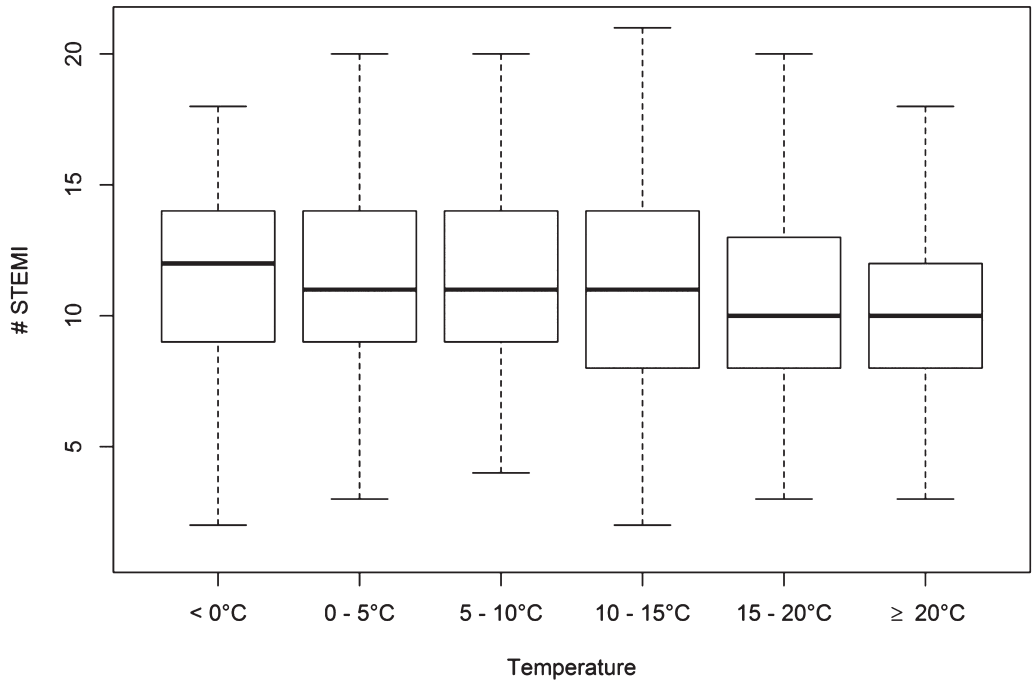


Fig. 2 Box plot showing the number of STEMI's (ST-elevation myocardial infarction) per day for different temperature levels.

ischaemia and coronary plaque instability. Moreover, a drop in temperature may be related to an increase in fibrinogen and C-reactive protein[23]. In cold conditions, the plasma concentrations of certain clotting factors, platelet count, and their in vitro aggregation are all increased and promote clotting[24,25]. Furthermore, reduced plasma volume and increased blood viscosity during cold exposure also tend to promote thrombosis.

Although the reported risk of temperature decrease was relatively low (adjusted risk ratio of 1.05-1.10), the public health relevance is considerable as exposure to environmental triggers covers a total population, and this places the population at an attributable risk of temperature decrease (PAF 7.4) at a higher level than strenuous exercise (PAF 6.1) or emotional stress (PAF 3.9) [3].

The effects of temperature were consistent among several subpopulations but with the strongest effect seen in diabetic patients. The increased vulnerability to temperature stress in these patients might be related to the pro-atherogenic and pro-thrombotic abnormalities found in endothelial function, platelet function and in plasma coagulation factors in diabetic patients[26].

Hence, adequate protection against temperature changes and/or avoidance of temperature stress may lead to reductions in the annual peaks in coronary events, particularly in high risk patients.

Since the 1990s, many epidemiological studies have demonstrated associations between air pollution levels and human health in terms of hospital admissions and cardiovascular mortality, with the largest effects observed after years or decades of chronic exposure[27-29]. However, the association between air pollution and near-term risk of myocardial infarction remains controversial. Some studies have shown an association, while other studies have found either no association or an association only for selected pollutants[3,9,30]. In a recent meta-analysis the most important pollutant was $PM_{2.5}$ with an RR of 1.02 (95% CI, 1.01-1.02) for every 10 $\mu g/m^3$ increase, which is in line with our findings[9]. Nevertheless, a more prominent effect of high local peaks (e.g., nearby traffic) cannot be excluded in our study, as this effect was not captured by our global analysis[31].

The relationship between influenza and acute coronary syndromes is still not clear despite various epidemiological observations showing positive correlations[7,32]. Many of these observational studies are hampered by a lack of a well-controlled patient population and/or by a lack of appropriate control for temperature and other environmental factors. In the present study, there was a strong correlation between temperature and influenza epidemics, and this is most likely the reason why the association between influenza and incident STEMI became non-significant after adjusting for temperature and other environmental factors. Beyond that, vaccination status, which occurred in up to 60% in patients > 65 y old, may have attenuated the relationship between influenza and incident STEMI, as was suggested by some recent influenza vaccination trials[33,34].

The results of this study should be considered in light of the following limitations.

We used only hospital admission data, which would have excluded myocardial infarctions resulting in death

before hospital admission; if some environmental triggers were associated with particularly severe and rapidly fatal myocardial infarctions, such effects might have been missed. Estimates of exposure that are based on measurements at urban monitoring stations may not be representative of exposures experienced indoors, while travelling, or while exercising. As this study was carried out in a region with a moderate climate, the effect of extreme cold or heat on incident AMI could not be assessed.

In conclusion, low temperature is the most important environmental trigger for STEMI, with an estimated attributable risk at population level that is even higher than strenuous exercise or emotional stress. This information should therefore get more emphasis in the communication and education of our students and our patients at risk for an acute myocardial infarction.

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CONFLICT OF INTEREST: none declared.

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