Abstract

Objective

Studies have related air pollution to myocardial infarction (MI) events over days or weeks, with few data on very short-term risks. We studied risk of ST-segment elevation MI (STEMI) within hours of exposure to air pollution while adjusting for weather.

Methods

We performed a case-crossover study of STEMI cases in Stockholm, Sweden (Jan 2000 – June 2014) based on SWEDEHEART. Exposures during hazard periods up to 24 hours prior to admission were compared to bidirectionally sampled control periods. Risks attributable to sulphur dioxide (SO_2), nitrogen dioxide (NO_2), ozone and particulate pollutants ($PM_{2.5}$, PM_{10}) were studied in conditional logistic regression models for 1-unit interquartile range increments.

Results

Risk of STEMI (n=14,601) was associated with NO_2 (strongest at 15-hour lag) and with $PM_{2.5}$ (strongest at 20-hour lag), in single-pollutant models adjusting for air temperature and humidity (NO_2: odds ratio (OR; 95% confidence interval) 1.065 (1.031 – 1.101); $PM_{2.5}$: 1.026 (1.001 – 1.054)). A significant risk was seen for atmospheric pressure at lags of 14 – 24 hours, and an inverse relationship to wind velocity at 22 – 24 hours. After adjusting models for pressure, NO_2 remained significant (1.057 (1.022 – 1.094)) but not $PM_{2.5}$ (1.024 (0.997 – 1.052)). No associations were seen for SO_2, ozone or PM_{10}. Air temperature exhibited a non-linear effect: risk function was flat at low to intermediate temperatures, but a steep increase was seen over 15.2°C.

Conclusion

Risk of STEMI rises within hours of exposure to air pollutants, with strongest impact of NO_2. These data suggest stable and warm weather contributes to risk.

1. Introduction

Air pollution is believed to be a key risk factor for cardiovascular disease [1] and the risk of myocardial infarction (MI) is likely to start rising within hours of exposure.[2] Previous reports have differed considerably in terms of temporal resolution, with most studies using long exposure times ranging from 24 hours up to several weeks.[3–5] This is due to limitations inherent to many data sources: administrative or registry data are commonly available at daily resolution, and an apparent paucity of data on short-term risk has been recognised.[6] In one of the few analyses of data at very fine temporal resolution (MINAP registry in U.K.), a role was suggested for both nitrogen dioxide (NO_2) and particulate air pollution (PM_{10}), although, as exposure-to-event lags were analysed as 6-hour terms, the actual hour-by-hour risk pattern remains uncertain.[7] Similarly, an earlier investigation of very short-term lags prior to MI events suggested a role of fine particles ($PM_{2.5}$), but confidence intervals were wide due to small sample size (n = 772), and analyses were limited to lags up to 6 hours.[2] Lastly, air pollution acts in concert with weather to create an environment predisposing to MI,[8] which must be taken into account when estimating risk attributable to air pollution.[9]

On this background, we investigated the relationship between air pollution and MI events, after adjusting for weather, in the prospective clinical registry SWEDEHEART (Swedish Web System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies),[10] a nationwide database of MI cases in Sweden, admission times for which are documented to the nearest minute i.e. at very high temporal resolution. To leverage maximally on this strength, we chose *pre-hoc* to focus on ST-segment elevation MI (STEMI) cases as the distinct symptom onset that characterizes this group should minimize the inherent uncertainty produced by delays between actual onset and admission.[2,11] Our aim was to study the role of air pollutants in the hours leading up to STEMI admission after adjusting for weather.

2. Material and Methods

The study was performed as a case-crossover analysis[12] with methodology as follows.[13]

2.1 Study population

We considered for inclusion all MI patients entered in SWEDEHEART at 1 of 10 acute hospitals in the greater Stockholm area (defined below) for whom date and time of admission were known. Patients with a final diagnosis other than STEMI were excluded (e.g. chest pain or angina pectoris, non-ST elevation MI (NSTEMI), Tako-Tsubo cardiomyopathy, type II myocardial infarction events etc).

The rationale and organisation of SWEDEHEART has been described in detail elsewhere.[10] In brief, patients are included prospectively on admission to a dedicated cardiac unit for chest pain or MI at one of 65 hospitals in Sweden. The registry contains variables describing infarct type, co-morbidities, treatment on admission as well as in-hospital, and any complications. Data accuracy is approximately 96% as ascertained through a process of continuous monitoring.[14]

Greater Stockholm is the largest conurbation in northern Europe, encompassing municipalities on lake Mälaren and the Baltic Sea coast of eastern Sweden (Supplementary figure 1).

The study was approved by the regional ethics committee in Stockholm, Sweden (Dnr 2012/60-13/2) and adheres to the Declaration of Helsinki. As this project was a national registry study, requirement for written informed consent was waived.

2.2 Data on air pollution and weather

Air pollution data were obtained from Swedish Environmental Research Institute (www.ivl.se) at hourly resolution for gaseous air pollutants: NO_2, generic nitrogen oxide levels (NO_X, comprising nitric oxide (NO) and NO_2), sulphur dioxide (SO_2) and tropospheric ozone, as well as suspended particulate matter subdivided based on diameter: 2.5 μm or less ($PM_{2.5}$) vs. < 10 μm (PM_{10}). Monitoring stations with hourly data were used as shown in Supplementary figure 1. In brief, all air pollution data were obtained from two inner city monitoring stations located within a radius of 100 metres: particulate pollutants ($PM_{2.5}$ and PM_{10}) were obtained at *Hornsgatan*, which is considered a street – roof-top station, located at a height of 3 metres (i.e. not 'kerb-side') along a street where an estimated 23,000 cars pass each day. Gaseous pollutants (SO_2, NO_2, NO_X, ozone) were obtained at *Torkel Knutssonsgatan*, a roof-top station located 20 metres above the street. Meteorological

data were obtained as follows. Atmospheric pressure was available from the monitoring station at *Bromma Flygplats* which is located 14 metres above sea level, close to Bromma Airport, 12 km North-West of the city centre of Stockholm. All other meteorological variables were obtained from the monitoring station at *Tullinge Flygfält*, located 45 metres above sea level, 23 km south of the city centre of Stockholm (Supplementary figure 1).

2.3 Myocardial infarction data

Acute admissions in the catchment area described above occurred through emergency departments at public hospitals in operation during the study period. Of note, all hospitals offering emergency services for acute chest pain or MI in Stockholm are public. Admissions recorded in SWEDEHEART may therefore be considered an unselected population, and coverage satisfactory.

2.4 Statistics

The relationship between air pollutants and incident MI was analysed after adjusting for weather in a case-crossover design as originally described by Maclure.[12] In brief, this method studies the effects of an intermittent exposure on an acute outcome in a time-stratified fashion such that hazard periods are compared to control periods. Exposure was defined during each period as averages over 3-hour windows with bidirectional sampling of control periods exactly 2 weeks before and after the hazard window (i.e. ± 336 hours; 2 controls per case). While case-crossover studies eliminate within-subject confounders by design, any impact of temporal trends are minimised as control periods are sampled both before and after the case period. Lags of up to 24 hours prior to admission were analysed in conditional logistic regression with nesting on each set of case and control periods. Regression was performed after standardisation of covariates through transformation to the interquartile range scale, achieved by dividing each by its own interquartile range. Precipitation was extremely skewed: 80.1% of all hours exhibited zero precipitation, and a dichotomous variable was therefore created based on any precipitation vs. none. A non-linear association with temperature[5,15] was explored using restricted cubic splines[16] with 3 degrees of freedom as this minimised Akaike information criteria. Spline coefficients were interpreted numerically using conventional significance testing but also by visual assessment of plots including 95% confidence intervals (CI_{95}). Univariate analyses were performed by regressing STEMI risk on

predictors at each individual lag. Multivariable single-pollutant models were built by also entering non-linear effects of potential confounders to univariate models: non-linearly analysed temperature and relative humidity were chosen for consideration *pre-hoc*. [17] Missing data for pollution and weather variables were interpolated linearly. All analyses were done in R version 3.4.

2.5 Supplementary analyses

Supplementary analyses performed include a differently specified model which used Bayesian hierarchical analysis to exclude that a type I error induced by multiplicity of null-hypothesis significance testing was responsible for key findings of main analyses, while taking into account clustering of observations within strata (case-control nesting, as well as across the 24 lags considered). Sensitivity analyses were performed to demonstrate robustness of results: (1) Seasonal infections were entered as potential confounders (influenza and respiratory syncytial virus). (2) Distance to weather and pollution stations were considered by excluding hospitals located outside of the Stockholm City area.

3. Results

Study period and accordingly also population size were determined in the following manner: (i) SWEDEHEART had incomplete coverage prior to 2000, and $PM_{2.5}$ was available in Stockholm only after 1 Jan 2000 which was accordingly considered the earliest date possible for analysing hourly data. To accommodate bidirectional sampling, the final study period therefore began on 15 Jan 2000. (ii) Data were available for this project from SWEDEHEART until 1 June 2014 which was accordingly considered the end of the study period. (iii) SO_2 was available only until 31 Oct 2005 and analyses of this pollutant was therefore restricted to that period, i.e. ended on 15 Oct 2005. Main analyses therefore spanned a total of 117,240 hours or 13.4 years, and SO_2 analyses spanned 50,400 hours or 5.75 years. The population in the catchment area averaged 2,159,616 (Supplementary Table 1). There were 14,601 admissions for STEMI that met inclusion criteria for the main analysis (5,611 for analysis of SO_2), corresponding to 1,091 admissions annually or 51 admissions per 100,000 inhabitants per year (50.0 admissions for SO_2) (Supplementary Table 2).

Patient characteristics are shown in Supplementary Table 3.

3.1 Air pollution and weather variables

Aggregate data on air pollution and weather variables are shown in Table 1. Counts for missing data are shown in Supplementary Table 4.

3.2 STEMI risk in relation to air pollution and weather

Associations for lags up to 24 hours are shown in Fig 1 with statistical significance for estimates indicated as 95% confidence intervals. Two air pollutants exhibited a statistically significant association with STEMI risk: (i) NO_2 at a 15-hour lag (odds ratio (95% confidence interval): 1.042 (1.011 – 1.073) (P = 0.007) and (ii) $PM_{2.5}$ at a 20-hour lag: 1.027 (1.001 – 1.054) (P = 0.042). Interquartile range intervals were 12.9 μg/m^3 for NO_2 and 9.4 μg/m^3 for $PM_{2.5}$.

Atmospheric pressure was positively related to STEMI risk at lags ≥ 15 hours and highest at 19 hours: 1.028 (1.002 – 1.055) (P = 0.034). A non-linear relationship was found between temperature and STEMI risk which was strongest at a lag of 10 hours and indicated a flat risk function at low and intermediate temperatures but a relatively steep increase at higher temperatures which reached statistical significance over 15.2°C (Figure 2). An inverse association was also seen with wind velocity which was statistically significant above lags of 21 hours (Figure 1). Raw data on levels of NO_2 and $PM_{2.5}$ at 15 hours and 20 hours, respectively, are tabulated in Supplementary Table 5.

3.3 Multivariable analysis

As shown in Table 2, multivariable analyses of NO_2 and $PM_{2.5}$ in single-pollutant models that adjusted for non-linear effects of temperature and relative humidity showed an independent association with STEMI risk of both NO_2 (1.065 (1.031 – 1.101); $p < 0.001$) and $PM_{2.5}$ (1.026 (1.001 – 1.054); P = 0.046). Temperature also remained independently associated with STEMI risk in the model containing relative humidity and NO_2 ($p < 0.01$ for high-temperature spline). When additional adjustment was performed for atmospheric pressure, NO_2 retained a similar effect size with a high degree of statistical significance (1.057 (1.022 – 1.094); P = 0.001) but the estimate of $PM_{2.5}$ straddled the null (1.024 (0.997 – 1.052); P = 0.083).

3.4 Supplementary analyses

Supplementary analyses including sensitivity testing showed robust and directionally similar effect estimates to the main analyses (Supplementary Table 6).

4. Discussion

We related STEMI events to air pollutants after adjusting for weather in the greater Stockholm area and focused on very short-term risk. Key findings of this project were that, firstly, very short-term risk was most strongly related to exposure to the gaseous pollutant NO_2, with a weaker effect of fine particulate air pollution ($PM_{2.5}$). Secondly, several weather variables exhibited relationships with risk: high temperature and atmospheric pressure were both positively associated with STEMI events, and an inverse relationship with wind velocity was also seen, suggesting risk in the short-term is higher in stable and warm weather. After taking this into account, $PM_{2.5}$ was rendered non-significant but NO_2 remained independently correlated to STEMI risk.

4.1 Impact of air pollution on STEMI risk

The existence of very short-term effects of air pollutants on MI risk is supported by mechanistic studies which have demonstrated that inhalation of diesel exhaust is pro-ischaemic and pro-thrombotic in subjects with ischaemic heart disease within an hour of exposure.[18] Nonetheless, a majority of previous reports in this field have been based on administrative or clinical registry data with low temporal resolution, and studies have typically linked daily means for environmental variables with daily counts of MI events,[4] studying lag times of several days or even weeks.[5,19] Accordingly, few published reports have achieved as high a temporal resolution as the present study.

The present report noted elevated STEMI risk within hours of exposure to the gaseous pollutant NO_2, as well as the particulate pollutant $PM_{2.5}$. Bhaskaran et al. investigated events in the nationwide MINAP registry in UK and found a relationship with NO_2 levels at a lag of 1 – 6 hours: a 2% increase in risk was seen for each 10 $\mu g/m^3$ increment, i.e. a similar effect to that seen in the present study: we found a 4.2% increase in the odds of STEMI for a 12.9 $\mu g/m^3$ increment in

NO_2.[7] Short-term effects of particulate pollution on MI risk was studied by Peters et al:[2] $PM_{2.5}$ was associated with an increased MI risk within an hour of exposure. As the analysis was truncated at 6 hours, the longer lags where the present analysis found an association with $PM_{2.5}$ (highest at 20 hours) were not included.

Interestingly, we noted a positive relationship between STEMI risk and atmospheric pressure which was sustained over the lags were statistically significant associations were seen with NO_2 and $PM_{2.5}$. While earlier reports have reported conflicting data regarding the association between MI risk and atmospheric pressure,[20] a U-shaped association has been proposed[21] as has an increased risk the day after a decrease in pressure which was suggested to be due to an increase in risk once pressure begins to rise again.[22] When atmospheric pressure was taken into account, we found that NO_2 was still independently associated with STEMI but not $PM_{2.5}$.

One possibility is that elevated levels of atmospheric pressure and $PM_{2.5}$ may both occur during times of stable and relatively less windy weather due to limited atmospheric mixing—an interpretation supported by the inverse relationship between STEMI risk and wind velocity seen for lags above 21 hours. So-called inversion layers may form when cool air is trapped under a layer of warmer air which act as a 'lid' which does not allow the dense, lower layer to escape, leading to trapping of pollutants.[23] As inversion layers can form under different seasons and weather conditions, analyses of surface recordings of data such as those in the present study offer limited understanding of spatial distribution of pollutants. While most research in this area have studied the impact of inversion layers on respiratory health, an association with cardiovascular risk will requires future study based on other data sources.[24,25]

The present report also suggested that different pollutants appear to exert maximal effects at different lags: the effect of NO_2 was highest at a lag of 15 hours whereas the relatively weaker effect seen for $PM_{2.5}$ was noted at a longer lag of 20 hours. This is noteworthy as it suggests that pollutants may, firstly, not have synchronised effects on risk post-exposure. While most atmospheric emissions are typically of NO, atmospheric conversion to NO_2 occurs in the presence of ozone and ultraviolet light. NO_2 together with nitrate aerosols and hydrocarbons form an important fraction of $PM_{2.5}$.[26] The fact that the 2 air pollutants noted to associate to short-term

STEMI risk in this report (NO_2 and $PM_{2.5}$) are thus closely related raises the possibility that the seemingly more rapid impact of NO_2 may reflect differences in 'incubation time'. While both are known to cause airway inflammation, NO_2 is poorly water soluble which enables it to reach the distal airways rapidly, where it undergoes conversion to nitric and nitrous acids. It is conceivable that this facilitates a faster effect of NO_2 on endothelial function or oxidative microvascular stress than the more heterogeneous pollutant $PM_{2.5}$ which is more mixed in terms of physical properties and chemical composition.[27,28] An interesting corollary of this finding is that models may not be specified well that make an assumption of simultaneous effects. [29]

4.2 Impact of temperature on STEMI risk

Temperature was noted to relate non-linearly to STEMI risk in the present report. This confirms earlier studies showing non-linearity of the association between temperature and various health outcomes.[15] We noted that STEMI risk was significantly elevated at temperatures above approximately 15.2°C, which is an almost identical relationship to that demonstrated between temperature and all-cause death in Stockholm during the years 1990 – 2000 in an earlier publication.[15] Similarly, a study of out-of-hospital cardiac arrests in Stockholm between the years 2000 – 2010 showed an approximately U-shaped association with temperature with an inflexion point at 12 degrees.[30] Data from a national registry in Japan found an increased risk of STEMI with increased temperature.[5] A large Korean registry study on patients admitted with MI showed a similar flat risk function at low to intermediate temperatures but a steep rise at high temperatures.[31]

4.3 Limitations

Several limitations apply to this study. Firstly, data in time series at hourly intervals will inevitably have an inherent temporal dependency structure: this report therefore aims to convey the important message that short-term effects of air pollution do exist, but relatively less emphasis should probably be placed on the exact lags identified. Secondly, central monitoring sites were used as a surrogate for population exposure which introduces questions of within-city heterogeneity and representativeness of measurements; wearable sensors may provide a means to obtaining a more direct estimate of exposure in future studies.[32] Thirdly, studies of routinely

acquired data on pollutant levels and weather variables need to take into account measurement error which can be a source of analytical noise. Fourthly, case-crossover analyses rely on appropriate choice of control periods. While the present study was designed to avoid sampling of control periods too close to the case period—based on temperature reportedly having impact on MI risk which is sustained up to 2 weeks prior to events—it is possible that differently sampled controls may have given rise to different results.[19]

5. Conclusion

We found associations between STEMI risk and the gaseous pollutant NO_2 within hours of exposure which were independent of effects of temperature, relative humidity and atmospheric pressure. Inverse relationships with wind velocity and positive relationships with high temperatures and atmospheric pressure suggest that stable, warm weather may predispose to short-term toxicity. The particulate pollutant $PM_{2.5}$ was also related to STEMI risk in univariable analysis but non-significant in multi-variable models that adjusted for weather. These data are complementary to earlier reports in this field, by showing the importance of very short-term fluctuations in air pollution for STEMI risk, which has not been widely acknowledged previously.

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Conflicts of interest

The authors report no relationships that could be construed as a conflict of interest.

Data availability

Datasets on air pollution and weather can be downloaded as described. Access to SWEDEHEART is available to collaborators with appropriate approvals including that of the registry steering committee and after ethics committee review.

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Tables

Variable	*Value*
Weather	
Atmospheric pressure, mmHg	1,012.0 (11.6)
Precipitation, cm	0.06 (0.27)
Relative humidity, %	80.9 (16.0)
Temperature, °C	5.8 (8.5)
Wind velocity, m/s	2.9 (1.8)
Pollution	
Gaseous pollutants	
NO_2, µg/m^3	15.0 (10.9)
NO_X, µg/m^3	19.5 (19.8)
Ozone, µg/m^3	51.1 (21.9)
SO_2,* µg/m^3	2.4 (2.8)
Particles	
$PM_{2.5}$, µg/m^3	13.5 (9.4)
PM_{10}, µg/m^3	38.4 (43.8)

Table 1 Air pollution and weather in Greater Stockholm from 1 Jan 2000 – 1 June 2014, except *SO_2 which is shown from 1 Jan 2000 – 31 Oct 2005. All data are mean (SD).

Model	*Lag*	*Odds Ratio*	*P*
Univariate analyses			
NO_2	15	1.042 (1.011 – 1.073)	0.007
$PM_{2.5}$	20	1.027 (1.001 – 1.054)	0.042
Multivariable, single-pollutant model 1			
NO_2	15	1.065 (1.031 – 1.101)	<0.001
$PM_{2.5}$	20	1.026 (1.001 – 1.054)	0.046
Multivariable, single-pollutant model 2			
NO_2	15	1.057 (1.022 – 1.094)	0.001
$PM_{2.5}$	20	1.024 (0.997 – 1.052)	0.083

Table 2 STEMI risk associated with air pollutants in univariate, as well as multivariable single-pollutant models. Estimates in model 1 were adjusted for non-linear effects of temperature and relative humidity, and in model 2 also for atmospheric pressure. Odds ratios are estimated based on 1-unit increments in predictors on the interquartile range scale.

Figure legends

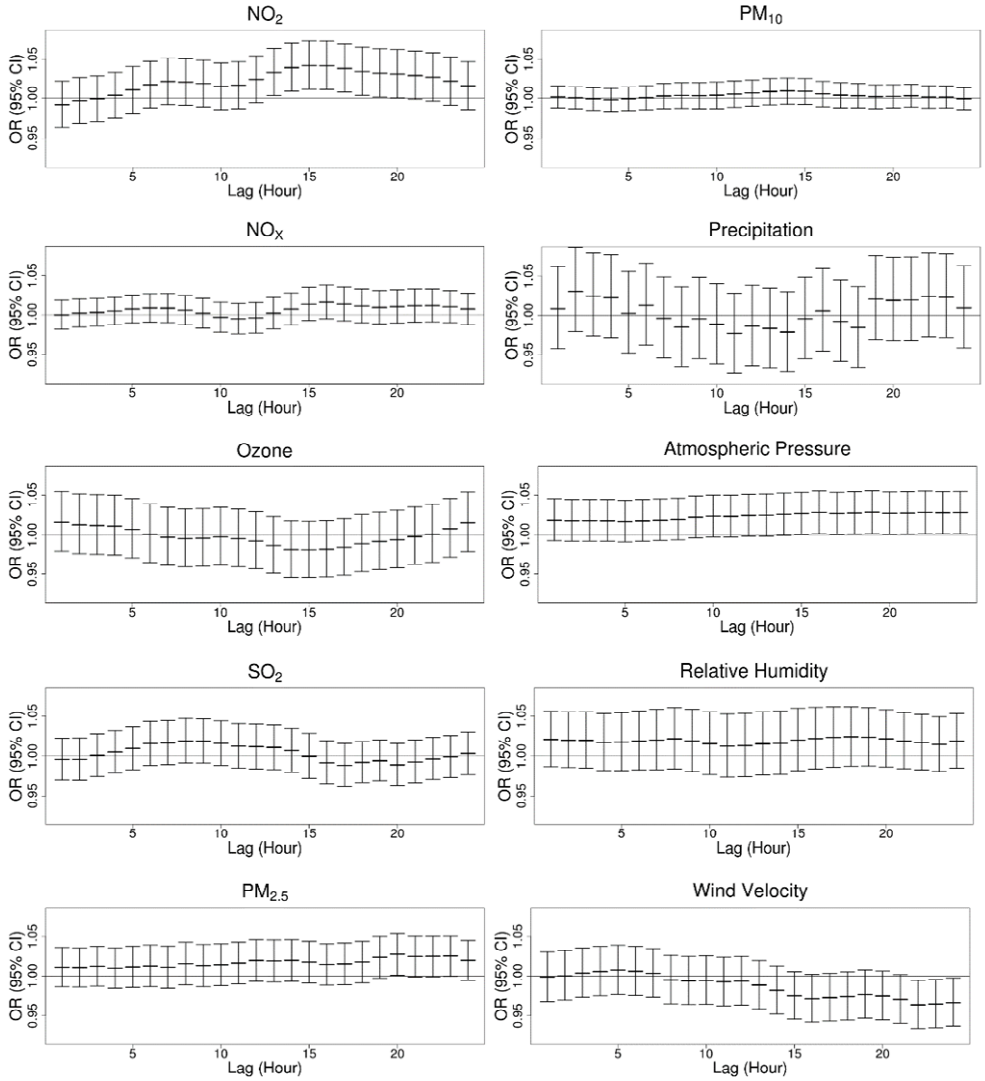

Fig 1 Lag-response diagrams showing risk of STEMI as odds ratios with 95% confidence intervals for interquartile range increments in predictor variables except precipitation which is modelled after dichotomising into any vs. none.

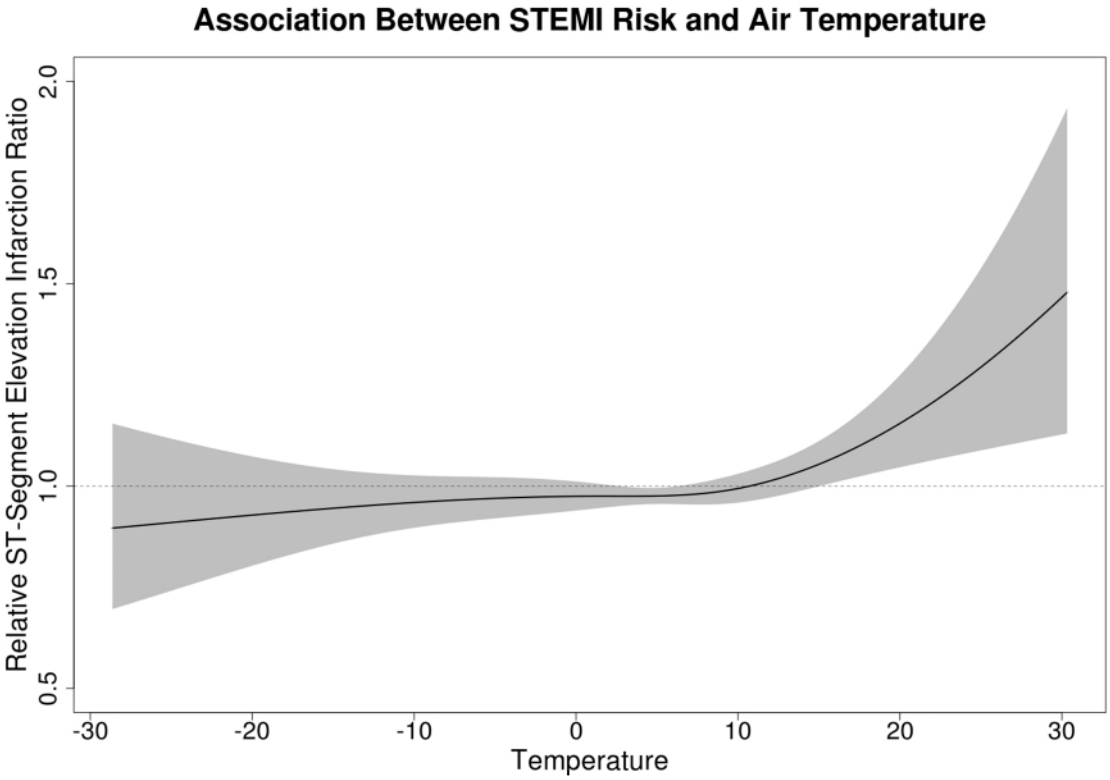

Fig 2 Non-linear relationships modelled between air temperature and relative risk of ST-segment elevation myocardial infarction (STEMI) at a 10-hour lag. Shaded area represents 95% confidence interval: for temperatures exceeding 15.2°C, estimates no longer straddle the line of null.