Public health importance of triggers of myocardial infarction: a comparative risk assessment

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Summary

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Background Acute myocardial infarction is triggered by various factors, such as physical exertion, stressful events, heavy meals, or increases in air pollution. However, the importance and relevance of each trigger are uncertain. We compared triggers of myocardial infarction at an individual and population level.

Methods We searched PubMed and the Web of Science citation databases to identify studies of triggers of non-fatal myocardial infarction to calculate population attributable fractions (PAF). When feasible, we did a meta-regression analysis for studies of the same trigger.

Findings Of the epidemiologic studies reviewed, 36 provided sufficient details to be considered. In the studied populations, the exposure prevalence for triggers in the relevant control time window ranged from 0·04% for cocaine use to 100% for air pollution. The reported odds ratios (OR) ranged from 1·05 to 23·7. Ranking triggers from the highest to the lowest OR resulted in the following order: use of cocaine, heavy meal, smoking of marijuana, negative emotions, physical exertion, positive emotions, anger, sexual activity, traffic exposure, respiratory infections, coffee consumption, air pollution (based on a difference of 30 μg/m³ in particulate matter with a diameter <10 μm [PM_{10}]). Taking into account the OR and the prevalences of exposure, the highest PAF was estimated for traffic exposure (7·4%), followed by physical exertion (6·2%), alcohol (5·0%), coffee (5·0%), a difference of 30 μg/m³ in PM_{10} (4·8%), negative emotions (3·9%), anger (3·1%), heavy meal (2·7%), positive emotions (2·4%), sexual activity (2·2%), cocaine use (0·9%), marijuana smoking (0·8%) and respiratory infections (0·6%).

Interpretation In view of both the magnitude of the risk and the prevalence in the population, air pollution is an important trigger of myocardial infarction, it is of similar magnitude (PAF 5–7%) as other well accepted triggers such as physical exertion, alcohol, and coffee. Our work shows that ever-present small risks might have considerable public health relevance.

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Introduction

Although the primary prevention of myocardial infarction has to be based on the development of atherosclerosis, the factors that precipitate the occurrence of myocardial infarction and that are amenable to intervention should also be addressed for public health and to help decision makers. To do so, however, one needs to know the relevance of these triggers to efficiently allocate the scarce resources to protect and enhance the health of the public. The role of triggers such as alcohol,[1] anger,[2,3] physical exertion,[3,4] and use of marijuana[5] in the onset of myocardial infarction is well recognised. Evidence of associations between the onset of acute cardiovascular outcomes, such as myocardial infarction, and air pollution is also substantial.[6–8] Measures such as the population attributable fraction (PAF) are useful methods to present the public health relevance of epidemiological findings.[9–11] The population attributable risk depends on the strength of the association between exposure to a risk factor and the prevalence of this risk factor within the population. Therefore, it is probably the most useful epidemiological

variable for public health administrators. In this study, we used the PAF approach to compare triggers of myocardial infarction in populations.

Methods

Search strategy and selection criteria

We searched PubMed and the Web of Science citation databases from January, 1960, to January, 2010, to identify studies of triggers for myocardial infarction published in English that would enable a computation of PAFs. We compiled all studies of trigger events defined as stimuli or activities occurring within a relevant period (1 h to 10 days) before the onset of acute myocardial infarction. We initially used "myocardial infarction" and "trigger" as key terms. We also searched for studies including both terms "myocardial infarction" and "case-crossover" because the design of case-crossover studies is typical for assessment of triggers. We did additional searches in which we replaced trigger by "onset" or "preceding". We also considered references found in our literature search and review articles.

We excluded studies done exclusively at an ecological level but we included all population-based or hospital-based case-control and case-crossover studies with sufficient information about number of patients and exposure. We selected only studies that used particulate matter with aerodynamic diameter of 10 μm or less (PM$_{10}$) or 2·5 μm or less (PM$_{2.5}$) as indicators of air pollution.

Statistical analysis

For triggers studied in more than one study, a meta-analytical pooled effect estimate was derived from the point estimate of each separate study weighted by the inverse of the variance (1/SE²). We used random effect estimates. The association between outdoor air pollution and health outcome is usually described by an exposure-response function that expresses the relative increase in adverse health for a specific increment in air pollution. So, we calculated the pooled relative risk (with upper and lower 95% CI) for two scenarios of change in PM$_{10}$—namely, increases by 30 μg/m³ and 10 μg/m³. When data for only PM$_{2.5}$ were available,[12–15] we converted the odds ratios (ORs) with the assumption that PM$_{10}$ consists of 70% of PM$_{2.5}$.[16] However, other conversion factors were also considered as part of sensitivity analyses.

Sensitivity of the findings was examined by recalculation of the pooled association sizes after exclusion of studies one by one. If the variables of a non-significant air pollution effect were not reported, the investigators of the paper were contacted to avoid bias resulting from the exclusion of non-significant studies, which is an important problem in any meta-analysis.[17,18] If no additional information was made available, the non-significant ORs were assumed to be 1 and the non-significant p values to be 0·50.[17,19]

The prevalence of exposure to air pollution in the population was estimated as 100%, which is in line with the assumptions made by the epidemiological studies providing the effect estimates. For consistency with other triggers, and in the absence of detailed population surveys, the prevalence of exposure in the general population was estimated from the control group (for case-control studies) or the control period (for case-crossover studies) from the identified studies. When several studies existed for a same trigger, the average prevalence of the risk factor was calculated by weighting by the sample size of each study.

As opposed to most triggers for which the excess risk is expressed for a binary exposure (yes or no), the effects of air pollution need to be expressed on a continuous scale. We, therefore, presented three scenarios to estimate the effect of PM$_{10}$ on the incidence of myocardial infarction in the population: the effect of lowering PM$_{10}$ by 30 μg/m³, 10 μg/m³, and 1 μg/m³.

Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. T Nawrot and L Perez had full access to all the data in the study. The corresponding author had final responsibility for the decision to submit for publication (all authors gave permission).

Results

We identified 36 studies[2–5,12–15,20–47] that investigated, at an individual level, 13 types of triggers of acute myocardial infarction (figure 1); 28 case-crossover studies, seven time-series, and one case-control study. The prevalence of the reported triggers ranged from 0·2% to 100%. The mean age of the people studied ranged from 44 years, for studies of cocaine or marijuana use, to 72 years, for studies of respiratory infections (table 1). Most studies had a time window before the onset of myocardial infarction ranging from less than 2 h to 1 day, apart from respiratory infections, which ranged from 1 to 10 days (table 1). Across all studies, the reported ORs ranged from 1·5 to 23·7 (table 1). The attributable fraction in exposed people ranged from 33% for drinking coffee to 96% for cocaine use.

We identified more than one study for six triggers: 14 studies of air pollution (n=593 480),[12–15,20,21,40–47] four studies[2,3,24,25] on anger (n=422), three studies[25,28,29] of negative emotions (n=1885), six[3,4,31–34] of physical exertion (n=5208), four[33,35–37] of respiratory infection (n=76 770), and three[33,38,39] of sexual activity (n=2802), for which combined estimates were developed (table 2). One
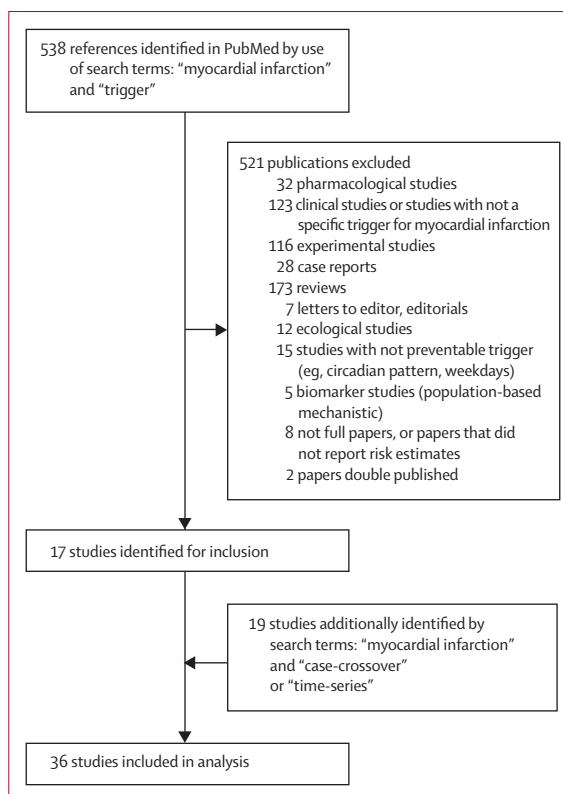

Figure 1: **Flow chart of included studies**

study assigned the effect of participation in traffic (as driver or passenger in a vehicle or as a cyclist) as a trigger of myocardial infarction.[22] Although the findings of that study could be interpreted as an effect of exposure to traffic-related air pollution, the study did not provide quantitative data for air pollution nor control for other traffic-related stressors (eg, noise, stress due to driving, or congestion). Consequently, all that can be derived from that analysis is that participation in traffic might trigger myocardial infarction. Therefore,

	n	Mean age (years)	Hazard period before MI episode	Exposure metric	Exposure frequency in controls or control period*	Odds ratio (95% CI)	Attributable fraction of exposed people (95% CI)
Alcohol							
Gerlich[23]	250	60	12 h	Drinking any alcohol	3·2%	3·1 (1·4–6·9)	67·7% (28·6–85·5)
Anger							
Mittleman[2]	1623	61	2 h	Anger scale >5 (very angry, furious, or enraged)	1·0%	2·3 (1·7–3·2)	56·5% (41·2–68·8)
Möller[24]	660	60	2 h	Anger scale >5 (very angry, furious, or enraged)	0·3%	5·7 (3·0–10·6)	52·3% (66·7–90·6)
Strike[3]	295	60	2 h	Anger scale >5 (very angry, furious, or enraged)	6·7%	2·06 (1·12–3·92)	51·5% (10·7–74·5)
Lipovetzky[25]	209	52	1 h	Anger scale >4 (moderately angry, hassled in voice) at workplace	0·6%	9·0 (1·1–71·0)	88·9% (9·1–98·5)
Cocaine use							
Mittleman[26]	38	44	1 h	Person-time exposed to cocaine (average yearly exposure×1 h)	0·04%	23·7 (8·1–66·3)	95·8% (87·7–98·5)
Coffee							
Baylin[27]	503	57	1 h	Drinking coffee	10·6%	1·5 (1·2–1·9)	33·3% (16·7–47·4)
Emotions (positive)							
Lipovetsky[25]	209	52	1 h	Standardised mood scale, PANAS questionnaire; emotions at workplace	1·0%	3·5 (0·7–16·8)	71·4% (0·0–94·0)
Emotions (negative)							
Lipovetsky[25]	209	52	1 h	Standardised mood scale, PANAS questionnaire; emotions at workplace	0·6%	14 (1·8–106·5)	92·8% (44·4–99·1)
Steptoe[28]	295	60	2 h	Depressed mood was assessed on a 5-point scale	6·1%	2·5 (1·05–6·5)	60·0% (4·8–84·6)
Möller[29]	1381	59	24 h	Work related stress: deadline	0·2%	6·0 (1·8–20·4)	83·3% (44·4–95·1)
Heavy meal							
Lipovetzky[30]	209	52	1 h	Did you eat a meal much larger than usual?	0·4%	7·0 (0·8–66)	85·7% (0·0–98·5)
Marijuana							
Mittleman[5]	124	44	1 h	Smoking marijuana	0·2%	4·8 (2·9–9·5)	79·1% (65·5–89·5)
Physical exertion							
Mittleman[4]	1228	62	1 h	≥6 metabolic equivalents	0·7%	5·9 (4·6–7·7)	83·1% (78·3–87·0)
Willich[31]	1194	61	1 h	≥6 metabolic equivalents	3·9%	2·1 (1·1–3·6)	74·3% (9·1–72·2)
Hallqvist[32]	660	NR	1 h	≥6 metabolic equivalents	1·9%	3·3 (2·4–4·5)	69·7% (58·3–77·8)
Baylin[33]	530	57	1 h	≥6 metabolic equivalents	2·3%	4·94 (3·73–6·54)	79·6% (73·0–84·6)
Strike[3]	295	60	1 h	≥6 metabolic equivalents	2·8%	3·5 (1·4–10·6)	71·4% (28·6–90·6)
Von Klot[34]	1301	61†	2 h	≥6 metabolic equivalents	~3%	5·7 (3·6–9·0)	82·4% (72·2–89·0)
Respiratory infection							
Meier[35]	1922	~60	1–10 days	Acute bronchitis, pneumonia, and productive cough	1·04%	2·7 (1·6–4·7)	62·9% (37·5–78·7)
Smeeth[36]	20 921	72†	1–3 days	Acute bronchitis, pneumonia, chest infections, influenza	0·3%	4·95 (4·43–5·53)	79·8% (76·7–81·8)
Baylin[33]	499	57	1–6 days	NR	1·3%	1·48 (0·92–2·38)	32·4% (0·0–58·3)
Clayton[37]	11 155	71	1–7 days	Acute bronchitis, pneumonia, and productive cough	0·3%	2·55 (1·71–3·80)	60·7% (41·2–73·7)
Sexual activity							
Muller[38]	1633	61	2 h	Frequency of sexual activity	1·2%	2·5 (1·7–3·7)	60·0% (41·2–73·0)
Baylin[33]	470	57	2 h	Frequency of sexual activity	0·3%	5·47 (2·71–11·0)	81·7% (63·0–90·9)
Möller[39]	699	NR	1 h	Frequency of sexual activity	1·3%	2·1 (0·7–6·5)	52·4% (0·0–84·6)
Traffic exposure							
Peters[22]	625	60	1 h	Time spent in cars, on public transportation, and on motorcycles and bicycles	4·1%	2·92 (2·22–3·83)	65·8% (54·5–73·7)

MI=myocardial infarction. PANAS=positive and negative affect schedule. NR=not reported. *In the absence of detailed population surveys, the prevalence of exposure in the general population was estimated from the control group (for case-control studies) or the control period (for case-crossover studies). †Median.

Table 1: **Triggers for non-fatal myocardial infarction**

we analysed participation in traffic separately from air pollution.

Of the four studies of respiratory infections, one study[37] was based on the case-control design. The OR reported in this study (2·55, 95% CI 1·71–3·80) and did not differ significantly from the overall combined estimate of three case-crossover studies[33,35,36] (2·77, 1·25–6·12). The combined estimate for anger was driven mainly by the observations of Lipovetzky and colleagues;[25] after exclusion of this study, the combined estimate dropped to 2·91 (1·66–5·09). The combined estimate for negative emotions was driven by Steptoe and colleagues' study,[28] after exclusion of this study the combined estimate increased from 4·46 (1·85–10·8) to 7·49 (2·64–21·3). The combined estimates for physical exertion, respiratory infection, and sexual activity did not show heterogeneity of effects across studies (data not shown).

We identified 14 studies[12–15,20,21,40–47] relating particulate matter air pollution with non-fatal myocardial infarction. Seven studies[14,20,21,40–42,46] were time-series analyses and seven studies[12,13,15,43–45,47] were case-crossover studies (table 3). For the 14 studies, the combined risk estimate included 593 480 individuals and was 1·02 (95% CI 1·01–1·02; p≤0·0001) for an increase of 10 µg/m³ in PM$_{10}$. The corresponding pooled OR for an increase of 30 µg/m³ was 1·05 (1·03–1·07). Estimates were not affected by exclusion of two studies[19,40,46] for which the association size was reported as non-significant, but details of the statistical variables were not available. Exclusion of Barnett et al[12] led to a drop in the pooled OR to 1·013 (1·007–1·0019; p≤0·0001), whereas the pooled estimate increased to 1·019 (1·010–1·027; p≤0·0001) after exclusion of the study of Zanobetti and colleagues.[47] The combined estimate expressed for a 10 µg/m³ increase in PM$_{10}$ was 1·01 (1·00–1·02) for time-series studies and 1·03 (1·01–1·03) for case-crossover studies.

For all the triggers studied, the ORs were inversely associated with their exposure prevalence (table 2; r=–0·81; p<0·0001), indicating that high risks are infrequent, whereas low risks are frequent. Triggers ordered from the highest to the lowest OR were: use of cocaine, heavy meal, smoking of marijuana, negative emotions, physical exertion, positive emotions, alcohol, anger, sexual activity, traffic exposure, respiratory infections, coffee consumption, and air pollution (table 2). When the estimated prevalence of exposure within the population was taken into account, the highest attributable fractions were calculated for participation in traffic, followed by a 30 µg/m³ change in PM$_{10}$, physical exertion, and coffee consumption (figure 2). The PAF for participation in traffic alone was 7·36% (95% CI 4·81–10·49) (table 2). A change of 30 µg/m³ in the daily mean PM$_{10}$ would be associated with a 4·8% (2·6–7·1) change in incidence of myocardial infarction, and a change in PM$_{10}$ by only 10 µg/m³ would be expected to change incidence by 1·6% (0·9–2·4). A change of 1 µg/m³ in PM$_{10}$ would result in a change in myocardial

	Prevalence of exposure*	OR† (95% CI)	PAF (95% CI)
Air pollution, 10 µg/m³ reduction (n=11)†	100%	1·02 (1·01–1·02)	1·57% (0·89 to 2·15)
Air pollution, 30 µg/m³ reduction (n=11)†	100%	1·05 (1·03–1·07)	4·76% (2·63 to 6·28)
Alcohol	3·2%	3·1 (1·4–6·9)	5·03% (2·91 to 7·06)
Anger (n=4)†	1·5%	3·11 (1·8–5·4)	3·07% (1·19 to 6·16)
Cocaine use	0·04%	23·7 (8·1–66·3)	0·90% (0·28 to 2·55)
Coffee	10·6%	1·5 (1·2–1·9)	5·03% (2·08 to 8·71)
Emotions positive	1·0%	3·5 (0·7–16·8)	2·44% (–0·30 to 13·64)
Emotions negative (n=3)†	1·2%	4·46 (1·85–10·77)	3·92% (0·99 to 10·34)
Heavy meal	0·5%	7·00 (0·8–66)	2·69% (–0·09 to 23·00)
Marijuana	0·2%	4·8 (2·9–9·5)	0·75% (0·38 to 1·67)
Physical exertion (n=6)†	2·4%	4·25 (3·17–5·68)	6·16% (4·20 to 8·64)
Respiratory infection (n=4)†	0·4%	2·73 (1·51–4·95)	0·57% (0·17 to 1·29)
Sexual activity (n=2)†	1·1%	3·11 (1·79–5·43)	2·21% (0·84 to 4·53)
Traffic exposure	4·1%	2·92 (2·22–3·83)	7·36% (4·81 to 10·49)

OR=odds ratio. PAF=population attributable fraction. *Prevalence was based on control time window. It was estimated from the control group (for case-control studies) or the control period (for case-crossover studies). When several studies existed for a same trigger, the average prevalence of the risk factor was calculated by weighting by the sample size of each study. For triggers studied in more than one study, the prevalence was based on the weighted average. †OR based on pooled OR and prevalence based on weighted means. Individual estimates are given in tables 1 and 3.

Table 2: Prevalence of exposure within the population, pooled OR, and PAF for the studied triggers of myocardial infarction

	Design	n	Hazard period before MI episode	OR (95% CI) for 10 µg/m³ increase
Linn[41]	Time series	~51 465	24 h	1·01 (1·00–1·01)
Peters[43]	Case-crossover	772	24 h	1·18 (1·04–1·36)
Ye[46]	Time series	~7380	24 h	NS
Mann[42]	Time series	19 690	24 h	1·00 (0·99–1·01)
Koken[40]	Time series	~4073	24 h	NS
Sullivan[45]*	Case-crossover	5793	24 h	1·01 (0·99–1·05)
Zanobetti[47]	Case-crossover	302 453	24 h	1·01 (1·00–1·01)
Peters[15]	Case-crossover	851	24 h	1·02 (0·97–1·06)
Pope[44]	Case-crossover	4818	24 h	1·02 (1·01–1·05)
Zanobetti[13]*	Case-crossover	15 578	24 h	1·10 (1·01–1·20)
Cendon[21]	Time series	724	24 h (ICU)	1·03 (1·02–1·09)
		717	24 h (infirmary)	1·05 (1·00–1·10)
Lanki[20]	Time series	26 854	24 h	1·00 (0·99–1·01)
Barnett[12]*	Case-crossover	~30 660	24 h (age ≥65 years)	1·05 (1·02–1·08)
Zanobetti[14]*	Time series	121 652	48 h	1·02 (1·01–1·02)
Combined estimate		593 480	..	1·02 (1·01–1·02)

MI=myocardial infarction. OR=odds ratio. NS=not significant but no details were reported. ICU=intensive care unit. PM$_{2.5}$=particulate matter with aerodynamic diameter of 2·5 µm or less. PM$_{10}$=particulate matter with aerodynamic diameter of 10 µm or less. *Based on PM$_{2.5}$ and converted into PM$_{10}$, with the assumption that 70% of PM$_{10}$ consists of PM$_{2.5}$.

Table 3: Characteristics of the studies on particulate air pollution and non-fatal myocardial infarction

infarction incidence by 0·16% (0·09–0·24). Ranking of the other triggers showed PAFs from highest to lowest for physical exertion, alcohol, coffee, negative emotions, anger, heavy meal, positive emotions, sexual activity, cocaine use, marijuana smoking, and respiratory
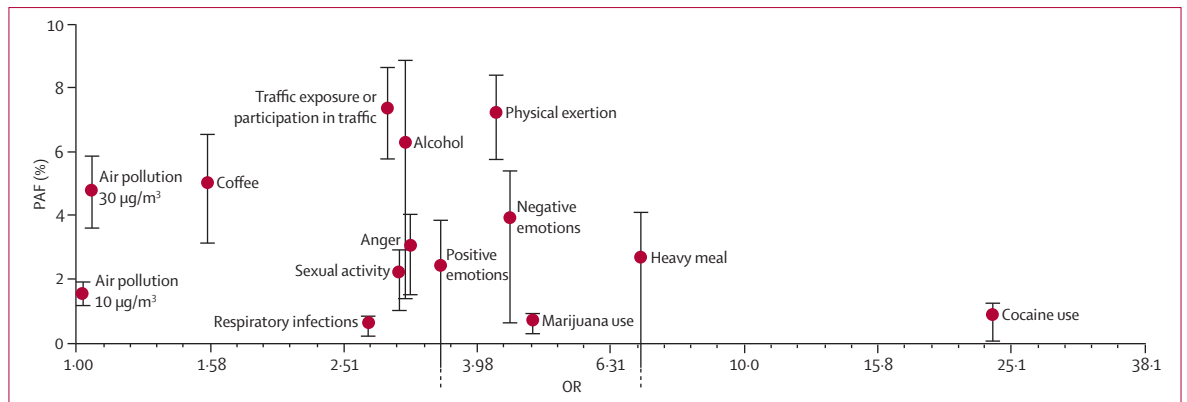
Figure 2: **Relation between OR and the PAF for each studies trigger**
PAFs were calculated and reported with their 95% CI (error bars). Not significant triggers show 95% CIs that are lower than 0%. X-axis is log scale, and ORs are given as anti-logs. OR=odds ratio. PAF=population attributable fraction.

infections (table 2). PAFs differed only marginally when we assumed that PM_{10} consisted of 50% of $PM_{2.5}$ instead of 70% (PAF for a 10 μg/m³ changed from 1·6% when we used a factor of 0·7 to 1·2% when with a factor of 0·5). We assumed that the respective changes in air pollution affect 100% of the population.

Discussion
Of the triggers for myocardial infarction studied, cocaine is the most likely to trigger an event in an individual, but traffic has the greatest population effect as more people are exposed to the trigger. Clinical, epidemiological, and experimental studies increase our knowledge of triggers, but they do not indicate their relevance in terms of public health. This knowledge can be obtained by calculation of PAFs, which give a measure of how much disease would be avoided if the risk was no longer present.[11]

No agreement exists about how long before the onset of symptoms an activity can take place to be regarded as an acute trigger rather than a more general causal factor. Trigger studies typically assess activities in the period ranging from a few minutes to 24 h before the onset of myocardial infarction or, in the case of infections, a few days before onset. Of the relevant studies identified, three-quarters used the case-crossover design. The case-crossover design represents a powerful approach to study acute health effects.[48–50] The major advantage of the approach is the ability to control for confounding. In the case-crossover design, all the individuals studied had the event. The hazard period is defined as the average time that is relevant for the acute effect of the event, and this period is compared with control times. Identification of the timing of events is crucial to identify the roles of short-term potential triggers, such as anger, and data from hospital interviews are needed to establish the time of onset of the myocardial infarction. Our study shows that the highest PAFs for myocardial infarction were related to participation in traffic, and to a 30 μg/m³ change in PM_{10}. However, the effect of a decrease in PM_{10}

of only 10 μg/m³ was still within the range of the public health relevance of the other known triggers.

Results for both participation in traffic and air pollution expressed as PM_{10} need to be interpreted with caution. The study that assessed participation in traffic as a trigger of myocardial infarction did not have measurements of air pollution.[22] Hence, to what extent air pollutants, stress, noise, or other factors related to commuting could explain the associations is unclear. Our impact assessment for air pollution is based on two scenarios, a decrease by 30 μg/m³ or 10 μg/m³ in the daily mean PM_{10}. Other scenarios will obviously change the results, and a locally relevant scenario for PM_{10} should be used to compare its relevance with the other public health issues. Obviously, the high PAF for outdoor air pollution is essentially driven by our assumption that the prevalence of exposure to this risk is 100%. This assumption is reasonable since people cannot avoid exposure to air pollution and because the epidemiological studies generally assign the outdoor average level to everyone. Moreover, we quantified the risk in terms of a change in air pollution, and given that the shape of the relation between daily mortality and changes in daily PM_{10} is linear without a threshold,[6] our model is applicable to many populations. Although air pollution is a mixture of several pollutants, epidemiological evidence suggests that PM per se might have an important role in the causation of adverse effects. The effects detected with other indicators of pollution such as nitric oxide might indicate exposure to PM as well, but they are narrowed to a specific source. By selecting PM_{10} as a common indicator, we aimed to capture all effects of different sources and components of PM that might trigger myocardial infarction.

Our assessment of PM_{10} is based solely on the acute effects of pollution. Animal studies[51] and some cross-sectional observations[52] show that particulate pollution could also be an underlying cause of the development of atherosclerosis,[53] and one study[54] reported an association of PM and traffic proximity with 2–3 years of progression

of intimamedia thickness, an accepted marker of atherogenesis. Thus, the real PAFs for air pollution are substantially higher when its chronic effects are taken into account in addition to the acute effects.[55]

Our estimated PAF should be interpreted within the context of its limitations. The prevalence of triggers within the studied populations might differ from that in the general population; consequently, the ranking of the factors might also differ. In our selection of studies we did not take quality into account. Clearly, some triggers are defined less accurately than others, thus providing potentially less robust risk estimates. This is particularly true for qualitative triggers such as emotions, and for triggers such as cocaine use. However, we decided not to attribute quality scores to the published studies or to exclude methodologically poor articles and we took heterogeneity of the results into account when applicable.

Some well documented triggers of myocardial infarction, such as earthquakes,[56,57] Football World Cup,[57] exposure to environmental tobacco smoke,[58,59] outdoor temperature[60–63] and participation in wars[64,65] were not amenable for inclusion in our analysis because they have only been studied at the aggregate (or ecological) level, and not by means of case-crossover, time series, or case-control studies in which the relation between risk factor and outcome can be assessed within individuals.

The time between the exposure to the trigger and the onset of a cardiac event can vary substantially. Extension of the hazard period to longer durations can lead to an increase in the prevalence of trigger-mediated myocardial infarction. Anger, for example, was reported to precede 2% and 8% of acute myocardial infarctions in the 2 h and 24 h before the onset of symptoms, respectively.[4] Different triggering factors, such as stress, physical activity, and air pollution could interact. Interaction between triggers has not been addressed directly but two studies[22,34] provide indirect evidence of such interactions. In Peters and colleagues' study,[22] participation in traffic was used as a marker of exposure to traffic-related air pollution; the risk was higher in cyclists (3·94, 95% CI 2·14–7·24) than in those who used cars (2·60, 1·89–3·57), suggesting an interaction between physical activity and exposure to traffic-related air pollution. In another study,[34] the odds ratio for acute myocardial infarction onset was significantly higher when physical exertion was done outdoors (10, 4·3–24) than indoors (2·3, 1·2–4·4). A possible explanation for this finding is an interaction between physical exertion and environmental stressors such as air pollution or outdoor temperature.

The age distribution between some risk factors and the age of onset of myocardial infarction might differ. Studies of cocaine use,[26] marijuana,[5] positive emotions,[25] and heavy meal[30] had a lower mean age (<52 years) than did most of the other studies (about 60 years). Sixth, air pollution is a continuous exposure[66,67] whereas other risk triggers are usually reported as dichotomous. The

scenario of 30 μg/m³ reduction does not apply for all cities (eg, Scandinavian cities where PM_{10} <20 μg/m³). Assumption of only a 5 μg/m³ decrease in daily PM_{10} in countries with lower average concentrations of particulate matter might prevent 1% (95% CI 0·5–1·2) of all myocardial infarctions. As most of the studied triggers are based on questionnaires, only non-fatal events can be studied. Therefore, we included only studies of non-fatal events of myocardial infarction. However, results from two large studies[68,69] in which air pollution was a trigger of fatal myocardial infarction showed similar estimates as did our meta-analysis based on non-fatal endpoints.

Some triggers, such as physical activity or air pollution, have been studied many times whereas for others such as cocaine use, we have only one report. Finally, some triggers should be interpreted within the context of their role in prevention of myocardial infarction. Thus, that regular physical activity protects against coronary heart disease is well established. Studies show that physical exertion acts as a strong trigger of myocardial infarction, mainly in those who do not regularly exercise. For Europe 62·4% of European adults are estimated to be inactive, ranging from 43·3% (Sweden) to 87·7% (Portugal).[70] Similarly, regular moderate alcohol consumption without heavy drinking has a protective effect for myocardial infarction. However, the effect of alcohol consumption before the event has received little attention, and we retrieved only one study.[23]

Both during heat waves and cold spells, morbidity and mortality from cardiovascular disorders rise,[61–63] but the temperature with the lowest population mortality is country specific.[71,72] Assuming that 2·7% of days of a year are hot days (30°C or more), as observed in Belgium, Netherlands, Germany, and Northern France,[61,63] and assuming a relative risk (RR) of 1·25,[60] our approach would assign 0·7% of the myocardial infarctions to heat waves. The observed heat-related effects in some studies might partly be explained by exposure to ozone, as the incidence of myocardial infarction rose by 5·0% per 5 μg/m³ increase in daily ozone concentrations.[73] A recent analysis of UK data[74] showed an effect of cold weather rather than heat. On days below the average temperature, the risk of myocardial infarction was about 4% higher (lag 0–1). Assuming 50% of days of a year are below the used reference (in this study average temperature of 11°C) and assuming a RR of 1·04 below this temperature (lag 0–1 or average across lag 2–7), our approach would assign 2% of myocardial infarctions to the colder period of the year.

We were not able to quantify the role of passive smoking as a trigger of myocardial infarction in our analysis, because this type of trigger has not been studied in individuals. However, as with polluted ambient air, environmental tobacco smoke is largely composed of an aerosol of particles derived from combustion, therefore, our conclusions for outdoor air pollution and those for

passive smoking mutually support each other, even in terms of the relative magnitudes of the effect.[75] Pooled aggregated data showed that after the implementation of legal smoking bans in public places, the rate of admittance to hospital for acute myocardial infarction during the following 12 months decreased by 17% (95% CI 20–13) on average.[59]

With the assumption of a causal relation between present levels of air pollution and morbidity or mortality, our analysis shows that the magnitude of the effect of realistic changes in PM_{10} is comparable with the effect of prevention of other well appreciated triggers. Participation in traffic was the most important trigger at the population level. In view of the uncertainty of its meaning (air pollution, stress, or a combination) further research is needed into this trigger.

Our estimates are conservative and realistic for many countries. Most urban areas worldwide have PM_{10} concentrations greater than the WHO target of 20 µg/m³, with a change in the population mean PM_{10} of 10 µg/m³ being achievable, and in most large cities a decrease of at least 30 µg/m³ will be needed to match the WHO guidelines set to protect public health. A more accurate, but much more complex computation of benefits would need knowledge of the spatial and temporal distribution of air pollution. However, the simplified model using the average reduction for all 365 days will result in the same means in PAF if the risk function is linear. In conclusion, we identified that acute effects of both participation in traffic and exposure to particulate matter air pollution are substantial contributors to the triggering of myocardial infarction in the population. Improvement of the air we breath is a very relevant target to reduce the incidence of this disease in the general population.

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