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CARDIOVASCULAR DISEASE

On the relationship between smoking bans and incidence of acute myocardial infarction

Antonio Gasparrini · Giuseppe Gorini · Alessandro Barchielli

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Abstract During the last few years several studies have reported a substantial reduction of acute myocardial infarction (AMI) in the general population few months after the enforcement of comprehensive smoking bans. We reviewed the consistency and plausibility of this association, investigating the effect of the Italian law, entered into force on January 10, 2005. We compared the AMI incidence on the first year after the ban with the period before (2000–2004) in the Tuscany population aged 30–64 years. The analysis was performed with a Poisson model of the monthly time-series, adjusting for seasonality and comparing different models with linear and non-linear long-term trends. While the model with linear time trend estimated a decrease of 5.4% (RR 0.95; 95% CI: 0.89–1.00), this effect completely disappeared once the linearity assumption was relaxed (RR 1.01; 95% CI: 0.93–1.10). The model with non-linear terms showed a significantly improved fit (*P*-value = 0.01). The estimate of the effect of the ban seems to be highly sensitive to the model specification and to the effects of unaccounted factors which could modify the trend of AMI incidence, such as changes in the prevalence of other risk factors or the modification of diagnostic criteria. Several arguments which are put forward to inspect the causal relation between smoking bans and AMI indicate that the plausible effects could be lower than the estimates reported so far.

Keywords Smoking ban · Smoke free-law · Myocardial infarction

Abbreviations

AMI	Acute myocardial infarction
SHS	Second-hand smoke
ICD-9	International classification of diseases, 9th version
AIC	Akaike information criterion

A. Gasparrini (✉)
Public and Environmental Health Research Unit, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, UK
e-mail: antonio.gasparrini@lshtm.ac.uk

A. Gasparrini · G. Gorini
Environmental and Occupational Epidemiology Unit, ISPO Cancer Prevention and Research Institute, Florence, Italy

A. Barchielli
Epidemiology Unit, Local Health Unit, Florence, Italy

Introduction

During the previous years, many states or local communities in several countries around the world have promoted smoking bans in indoor public places, mainly in public venues and workplaces [1]. The main reason to implement these laws was the increasing evidence of the relationship between chronic exposure to second-hand smoke (SHS) and various health effects, especially cardiovascular and respiratory diseases and lung cancer [2–4]. In particular, the association with cardiovascular diseases has been proved by a large number of epidemiological studies, and the pooled estimate of the increase in risk, as published in different meta-analyses, is about 30% [4–6]. A large number of clinical and sub-clinical symptoms have been proposed to characterize the patho-physiological mechanisms, and it is widely accepted that SHS exposure increases the risk through both chronic and acute pathways [5, 7, 8]. The former includes atherosclerosis, decrease in high-density lipoproteins level and arterial stiffness, while the acute pathway acts through endothelial dysfunctions, oxidative stress and inflammation and increased platelet aggregation.

Several studies extensively assessed the effects of smoking bans, and they consistently described a large reduction of SHS concentrations in public venues immediately after the enforcement, ranging from 70 to 97% [9–12]. In addition, other studies reported a significant decrease of both SHS exposure and respiratory symptoms in hospitality workers [11, 13, 14].

More recently, several investigators have investigated the association between the implementation of smoking bans and hospital admissions for cardiovascular diseases, especially acute myocardial infarction (AMI), in USA [15–19], Canada [20], Italy [21–23], and Scotland [24]. The results are astonishing: in the first months after the ban, the estimated reduction ranged from 11% to 70%, without any noticeable lag between the enforcement and the claimed effect. All these studies are characterized by similar aspects: the ecological design, the comparison of admission rates before and after the enforcement of the law, and often the use of a nearby area where the ban was not applied as a control, in order to account for changes in the distributions of other risk factors.

Nonetheless, these studies are also affected by some important limitations. First of all, they rarely reported the actual decrease in SHS exposure experienced by the study populations, and the results were explained only through the concurrent reduction of SHS concentrations in the settings covered by the ban. In addition, the size of the effect is surprising, with a substantial fraction of the overall AMI incidence attributed exclusively to short-term SHS exposure in public places. Finally, these studies rarely took into account the potential effect of the long-term trend of AMI, and even when considered, it was imposed with a linear constraint, without checking this strong assumption.

The aim of this study is to assess the short-term effect of the Italian smoke-free law on the incidence rates for AMI in Tuscany population, with particular attention on the consequences of an incorrect specification of the time trend effect. Then, we broadly discuss the strengths and weaknesses of the association, considering plausibility and consistency of the published results.

Methods

Study population

The Tuscany region is located in Central Italy, with a population of about 3,550,000 individuals. Consistently with previous studies, we focused the analysis to the active population (aged 30–64 years), exposed to changes in SHS exposure both in public venues and in workplaces. The Italian smoking ban entered into force on January 10, 2005, and the study period included the years 2000–2004 as pre-intervention and 2005 as post–intervention.

We computed the number of incident cases due to mortality or hospitalization for AMI among Tuscany population occurred during the study period. The data were collected from the Acute Myocardial Infarction Registry of Tuscany (Tosc-AMI) [25]. This population-based registry links current hospital admissions (principal discharge diagnosis: ICD9 code 410) and mortality (principal death diagnosis: ICD9 codes 410–414), identifying the total number of events due to hospitalised AMI cases and out-of-hospital coronary deaths. Multiple events in the same patients were discarded if the interval between two events was less than 28 days. Validation of diagnostic codes and standardised criteria ensures the reliability of the information. The data consisted of the monthly number of AMI episodes, stratified by sex and 5-year age groups. We obtained the age and sex distribution of the population in the study period from the Tuscany Regional Mortality Registry.

Statistical analysis

We computed directly age-standardized rates of annual AMI episodes, using the European population as reference. The effect of the smoking ban was assessed by a Poisson regression analysis of the time series, aggregating the AMI cases for each month and including the person-years (population) as an offset, in order to model the rates of AMI directly [26, 27]. The model compared the rates of AMI before and after the ban, adjusting for seasonality and long-term trend. In order to correct for changes in the age distribution of the population during the study period, we computed monthly age and sex-standardized incidence rates, using the population distribution in the first month of the series as reference. Then, we calculated the adjusted person-years and entered them as the offset variable in the model. This method allows adjusting for changes in the population distribution, keeping in the model, as the response variable, the actual number of incident cases observed each month.

Let the monthly time series of the number of cases of AMI be defined by the random variable $\{Y_t\}_{t=1}^{n}$, following a Poisson distribution with mean μ_t, according to the equation:

$$\log \mu_t = \log n_t + \beta_0 + \beta_{\text{ban}} \cdot Z_t + f(t|\varphi_1, \ldots, \varphi_{k+1}, k) + s(m_t|\gamma_{11}, \ldots, \gamma_{1p}, \gamma_{21}, \ldots, \gamma_{2p}, p)$$

being t the sequence of times of observations and m the variable indicating the month (1 as January, 2 as February and so on until 12 as December). The indicator variable Z takes values 1 if the ban is present, 0 otherwise. The coefficients β_0 and β_{ban} estimate the intercept and the effect of the ban, respectively, while n is the person-years, included as an offset in the model.

The function $f(t)$ was used to account for the long-term trend, with a different parameterization to describe linear or non-linear dependencies. The former was specified including in the model the t variable itself, while a restricted cubic spline transformation of the same variable was used to allow for a non linear relationship. The spline was defined by $k+1$ parameters φ for the basis variables created by k inner knots and 2 boundary knots, forcing the curve to be continuous at the formers and linear beyond the boundary knots [28]. The number of knots k was used to control the degree of non-linearity. The inner knots were set at equally spaced quantiles of the monthly series, while the boundary knots were placed at the beginning of the series and at the end of the pre-ban period.

The function $s(m_t)$ describes the seasonal effect and was specified by harmonic terms [29]. It was defined by orthogonal waveform components with different frequencies, represented by a Fourier series of sine and cosine terms:

$$s(m_t) = \sum_{j=1}^{p} \gamma_{1j} \sin(j\omega m_t) + \gamma_{2j} \cos(j\omega m_t)$$

where $\omega = 2\pi/12$, γ_{1j} and γ_{2j} are respectively, the coefficients of the sine and cosine terms at the harmonic number$j$, to be estimated by the regression model. The total number of harmonic terms p was used to specify the degree of approximation of the seasonal effect.

The goodness of fit of the model was assessed using the Pearson test based on the ratio between residual deviance and degrees of freedom, and examining the distribution and autocorrelation of the residuals. The likelihood ratio (LR) test and akaike information criterion (AIC) were used to compare models with different specifications of the long trend and seasonal components. Finally, we performed a sensitivity analysis, repeating the analysis with sex-specific rates and checking the robustness of the results against different specifications of temporal trend and seasonal effect. All the analyses were performed with the statistical packages R 2.7.1 (Team R Development Core) and STATA/SE 10 (StataCorp, College Station, TX).

Results

During the study period 13,456 new cases of AMI occurred in the Tuscany population aged 30–64 years, with 2,190 cases in the post-ban period. The annual age-standardized rates for AMI are reported in Table 1, together with the risk ratios for each year compared to the earliest in analysis. The incidence of AMI shows an initial raise until 2002, followed by a gradual reduction.

Table 1 Age-standardized rates (standard: European population) and rate ratios between different years (2000 as reference) for Tuscany population aged 30–64

Year	n	Rate (×1,000)	RR	95% CI
2000	2,180	1.20	1.00	–
2001	2,244	1.25	1.04	0.98–1.10
2002	2,319	1.29	1.07	1.01–1.13
2003	2,269	1.25	1.04	0.98–1.10
2004	2,254	1.23	1.03	0.97–1.09
2005	2190	1.20	1.00	0.94–1.06

Table 2 Estimated effects (relative risk, RR) of the ban from models with linear and non-linear trend

	Model with linear trend		Model with non-linear trend	
	RR	95% CI	RR	95% CI
Males	0.95	0.89–1.01	1.01	0.92–1.10
Females	0.94	0.82–1.09	1.05	0.87–1.27
Total	0.95	0.89–1.00	1.01	0.93–1.10

The results for the effect of the ban are summarized in Table 2, reporting the relative risk (RR) comparing the periods after and before the ban. The model with linear time trend shows a decrease of 5.4% in AMI rates during 2005, compared with the pre-ban period (2000–2004), very close to the statistical significance (RR 0.95; 95% CI: 0.89–1.00, P-value = 0.07). On the contrary, when the linearity assumption is relaxed, this protective effect completely disappears (RR 1.01; 95% CI: 0.93–1.10, P-value = 0.76). Furthermore, the latter model, specified by a natural spline with just 1 knot, seems to perform better than the model with a linear constraint, with a significant LR test (P-value = 0.01) and a smaller value of AIC (583.9 vs. 588.2), suggesting a significant deviation from linearity, confirmed by the analysis of residuals. The different fits of the two models, and the impact of different specifications of the time trend on the estimated effect of the ban, are also clearly displayed in (Fig. 1).

Sex-specific analyses are highly consistent, showing similar effects (Table 2): for males, the inclusion of a non-linear term for time trend changes the estimate of the risk ratio from 0.95 to 1.01, while for females the adjustment is from 0.94 to 1.05. Finally, sensitivity analysis shows that the results are fairly insensitive to the choice of the number and location of the knots for the spline transformation or the number of harmonic terms for seasonality.

Discussion

Differently from the results published to date, this study did not find a comparable effect of the smoke-free law on the

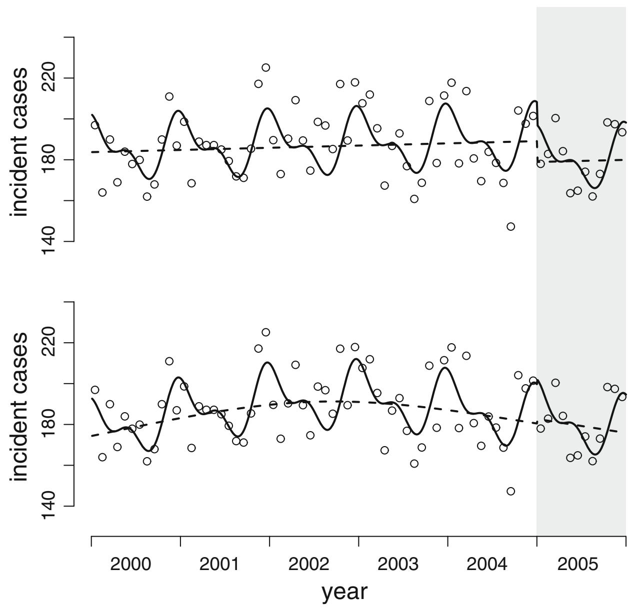

Fig. 1 Observed (*circles*) and predicted (*dashed lines*) AMI cases in Tuscany population aged 30–64, by the regression models with linear (*above*) and non-linear (*below*) time trend. The *dashed line* represents the temporal trend, and the step at the beginning of the *grey* area (post-ban period) is the estimated effect of the ban

incidence of AMI during the first year after the implementation of the ban. Our estimate and the related uncertainty suggest that the expected reduction is likely to be lower. As well, the results published so far show a large variation: earlier studies from Italy reported a decrease of about 11–13%, while the study from Scotland found a reduction of 17%, and results from USA estimated reductions ranging from 20 to 70%. The discrepancy between studies carried out in Italy can be hardly attributable to different prevalence of active and passive smoke before the ban, showing similar patterns among the three regions [30]. In addition, the impact of the ban in terms of decrease of nicotine and particulate levels in public places shows no difference between regions [9, 11, 31], with percentages similar to the other countries where similar bans have been implemented [10, 12, 32].

Several other reasons could be brought forward to explain the difference in the estimates of the effects of the bans. In this paper, we focused on the specification of the time trend, a key problem in studies with a before-after design. Among the 10 investigations published so far, only five studies considered the effect of the temporal trend [17, 21–24], and only three of them [17, 22, 23] directly in the statistical model. None of them dealt with the issue of non-linearity. As showed, wrong assumptions about the shape of the trend could lead to important biases on the estimate of the effect of the ban. Therefore, the linearity of the AMI rates should be tested in order to provide non-biased effect estimates. A non-linearity of the time effect can be explained by the concomitant effect of other time-varying factors, like changes in the distribution of known risk factors, health care improvements and development of diagnostic criteria. For example, a highly specific test based on troponin level, likely to produce an apparent increase of AMI incidence [33, 34], was introduced by the new guidelines for AMI in 2000 [35], and gradually implemented thereafter. The effect of such factors on the trend of AMI rates should be assessed by future investigations.

As a matter of fact, the very strong and immediate decrease found in some of the studies above is hard to be explained only by the effect of a smoking ban, as suggested by a number of reasonable arguments. Firstly, several investigators have already shown that the changes in active smoking habits in the range of those measured in the post-ban periods, even postulating a causal relation with the law, might explain not more than 2% of the short-term decrease in AMI [21, 22, 36]. In relation to SHS, the assessment of the potential effect should rely on the actual exposure experienced by the study population before and after the ban. From this point of view, we should point out that an important proportion of the population is composed by smokers or non-smokers who were never exposed to SHS and are therefore less sensitive to any decrease in SHS exposure. In addition, the smoking bans do not cover all the settings where an exposure could occur, such as in private settings. As noted above, the actual reduction of SHS exposure in the general population has seldom been reported: a survey in Scotland showed that salivary cotinine, a specific marker of SHS exposure, fell by 39% (from 0.43 to 0.26 ng/ml) in a representative sample of non-smokers after the ban entered into force [37], indicating that the settings covered by the ban were responsible only for a part of the SHS exposure in the general population. Moreover, also the estimate of 30% of increase in risk extensively cited to explain the short-term effect of the smoking bans was borrowed from studies assessing the effects of SHS on a longer temporal scale, summing the contributions of acute and chronic pathways. As already reported, exposure to SHS is related to several acute effects on cardiovascular system, but the relative importance of the associated risk through this short-term pathway is unknown, and the overall estimate of the risk ratio of 1.3 is likely to overestimate the true short-term effects.

Notably, some estimates of the expected decrease in AMI incidence following the enforcement of a smoking ban have recently been published [38], considering several scenarios for the prevalence of exposure to active and passive smoking before the ban, their decrease after the implementation and the associated acute risks on AMI. The estimated potential reduction is 8.6%, with a plausible range of 5–15%, lower than many other estimates already published and coherent with the range of uncertainty we have reported here in this study. In addition, these figures are consistent with other investigations assessing the overall mortality burden for ischemic heart diseases attributable to SHS, performed before the implementation of the bans. A study computed the population attributable fraction for the UK population aged 20–64 in 2003, reporting that 9.9% of the mortality was due to SHS exposure at home and only 2.2% to workplace exposure [39]. Other investigators performed the same calculation for Italy in 2002, estimating the fraction of attributable deaths as 2.8 and 5.9% for partner smoking at home and 5.5 and 3.7% for workplace exposure in males and females, respectively [40].

The implementation of smoking bans in public places represents a milestone in the history of public health. The relationship with a decrease of both active and passive smoke is unquestionable, with conclusive evidences on the reductions of a number of health outcomes after the enforcement. In particular, a decrease of cardiovascular events in the long run is expected, given the conclusive association with chronic SHS exposure. On the other hand, the estimate of the short-term effect of smoking bans on cardiovascular diseases is still uncertain, and the range of reduction showed by some of the studies published to date is likely to be an overestimate, not consistent with previous knowledge about the burden of cardiovascular diseases attributable to SHS. Moreover, several other factors, like changes in diagnostic criteria, have a strong influence on the trend of cardiovascular diseases, and it seems very problematic to properly control for their effects with this study design. Nonetheless, as this study has shown, the resulting bias could be substantial.

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