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Cardiovascular Events Following Smoke-Free Legislations: An Updated Systematic Review and Meta-Analysis

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Abstract
Background Legislations banning smoking in indoor public places and workplaces are being implemented worldwide to protect the population from secondhand smoke exposure. Several studies have reported reductions in hospitalizations for acute coronary events following the enactment of smoke-free laws.
Objective We set out to conduct a systematic review and meta-analysis of epidemiologic studies examining how legislations that ban smoking in indoor public places impact the risk of acute coronary events.
Methods We searched MEDLINE, EMBASE, and relevant bibliographies including previous systematic reviews for studies that evaluated changes in acute coronary events, following implementation of smoke-free legislations. Studies were identified through December 2013. We pooled relative risk (RR) estimates for acute coronary events comparing post- vs. pre-legislation using inverse-variance weighted random-effects models.
Results Thirty-one studies providing estimates for 47 locations were included. The legislations were implemented between 1991 and 2010. Following the enactment of smoke-free legislations, there was a 12 % reduction in hospitalizations for acute coronary events (pooled RR: 0.88, 95 % CI: 0.85- 0.90). Reductions were 14 % in locations that implemented comprehensive legislations compared to an 8 % reduction in locations that only had partial restrictions. In locations with reductions in smoking prevalence post-legislation above the mean (2.1 % reduction) there was a 14 % reduction in events compared to 10 % in locations below the mean. The RRs for acute coronary events associated with enacting smoke-free legislation were 0.87 vs. 0.89 in locations with smoking prevalence pre-legislation above and below the mean (23.1 %), and 0.87 vs. 0.89 in studies from the Americas vs. other regions.
Conclusion The implementation of smoke-free legislations was related to reductions in acute coronary event hospitalizations in most populations evaluated. Benefits are greater in locations with comprehensive legislations and with greater reduction in smoking prevalence post-legislation. These cardiovascular benefits reinforce the urgent need to enact and enforce smoke-free legislations that protect all citizens around the world from exposure to tobacco smoke in public places.

Keywords Tobacco smoke pollution · Smoke-free policy · Cardiovascular diseases · Legislations

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Introduction

Epidemiological and experimental studies have shown that short-term and long-term exposure to secondhand smoke can have substantial adverse impacts on the cardiovascular system [1]. Governments worldwide, in compliance with Article 8 of the World Health Organization Framework Convention on Tobacco Control (FCTC), are implementing legislation banning smoking in indoor public places and worksites to protect citizens from exposure to secondhand smoke (SHS) [2]. The tobacco industry has also acknowledged the effectiveness of smoke-free legislations in reducing tobacco use [3–7]. Smoke-free legislations range from partial bans where smoking is allowed in some public places (e.g., bars and/or restaurants) to comprehensive smoking bans whereby smoking is banned in all public places and workplaces. To date, only 16 % of the world's population is protected from exposure to secondhand smoke by comprehensive, national smoke-free laws [8••].

Several systematic reviews have reported significant reductions in acute coronary events hospitalizations following the enactment of smoke-free legislations, with reductions ranging from 5 to 70 % across studies (Supplementary Table 1) [9–11, 12•, 13–16]. Reductions in events following legislation were generally greater in studies with longer follow-up post-legislation [11, 13, 14]. The greater reductions in events observed in studies with longer follow-up may reflect larger reductions in secondhand smoke exposure after vs. before legislation. Secondhand smoke exposure before and after legislation implementation varies among studies for a variety of reasons including smoking prevalence pre-legislation, type of ban (comprehensive vs. partial), and the change in the smoking prevalence following legislation implementation. These factors are likely to influence effect size and explain heterogeneity across studies. Previous systematic reviews, however, have not examined the role of these factors as they relate to the changes in acute coronary events. Our objective was to systematically review the evidence on the impact of smoke-free legislation on subsequent hospitalizations for acute coronary events. We also aimed to investigate the potential impact of factors such as smoking ban coverage, pre-legislation smoking prevalence, and changes in smoking prevalence following the legislation on the magnitude of the change in acute coronary events.

Methods

Search Strategy and Study Selection

We searched MEDLINE (PubMed) and EMBASE databases for studies assessing the association between smoke-free legislation and cardiovascular disease by using the following as free text, synonyms, explosion, and Medical Subject Headings (MeSH): tobacco smoke pollution, secondhand smoke, environmental tobacco smoke, smoke-free legislation, and cardiovascular disease. The search was conducted without language restrictions on all articles from the beginning of indexing in each database through December 2013. In addition, we manually reviewed the reference lists from relevant research and review articles, including previous systematic reviews summarized in Table 1. Our exclusion criteria were: (1) study not conducted in humans; (2) publications containing no original data, including reviews, editorials, and commentaries; (3) no data comparing pre- and post-smoking legislation; (4) no acute coronary syndrome outcomes (e.g., hospitalizations or mortality); and (5) case reports. Articles that did not have available full-text (e.g., abstracts from meetings) and non-peer reviewed literature were excluded. For studies that were not in English, the article was translated by a native speaker if the information in the abstract was insufficient to include/exclude the article. We also excluded two studies that used simulations to estimate the impact of smoke-free legislations [17, 18]. When several papers had been published on the same population [19–30], we selected the publication with the longest follow-up period or the most recent publication (if follow-up periods were equivalent) [19, 26–29]. Several studies reported the impact of city smoking legislation [21, 23, 31–36] and were later followed by publications reporting state-wide (for US studies) or national legislation [22, 37, 38]. Due to the potential for overlap in study populations, we excluded studies that reported the impact of city legislations and reported data from state/country-wide studies.

Data Abstraction

Two investigators (M.R.J. and L.L.) independently abstracted study data from articles that met the inclusion criteria. Data included the study design, population, smoke-free legislation type (partial vs. comprehensive), follow-up time periods, outcome (acute coronary syndrome vs. acute myocardial infarction), measure of association (e.g., relative risk, rate ratio, percent reduction) and potential confounders accounted for in the statistical analysis. For studies with multiple levels of adjustment, we abstracted the measure of association obtained from the model adjusted for the most covariates. Discrepancies were resolved by consensus.

Characteristics of Location and Study Population

Characteristics of the city or country enacting legislation were extracted from data reported in the publication and included region (the Americas, Europe, and Other), type of ban (comprehensive vs. partial) and pre-legislation smoking prevalence. A comprehensive smoking ban includes banning smoking in public places including restaurants and bars. Partial restrictions exclude bars and/or restaurants. Pre-legislation smoking prevalence was defined based on data reported in the

Table 1 Characteristics of included studies

First author, year	Population	Date of legislation enactment	Extent of legislation	Study follow-up period	Smoking prevalence	
					Pre-legislation	Post-legislation
Americas						
Gaudreau, 2013	Prince Edward Island, Canada	June 2003	Comprehensive	Apr 1995- Dec 2008	24.5	17.1
Johnson, 2013	Grand Forks, North Dakota, USA	Aug 2010	Comprehensive	Apr 2010- Dec 2010	18.6	18.1
Sebrie, 2013	Uruguay	Mar 2006	Comprehensive	Mar 2004- Feb 2008	29.8	24.8
Barr, 2012	Illinois, Ohio, Minnesota, New York, Washington, New Jersey, Arizona, Massachusetts and Delaware, USA	Jan 2000- Dec 2007	Comprehensive	Jan 1999- Dec 2008	22.3	17.3
Ferrante, 2012	Santa Fe, Argentina	Aug 2006	Comprehensive	Aug 2005- July 2007	27.3	26.6
	Buenos Aires city, Argentina	Oct 2006	Comprehensive	Oct 2005- Sept 2007	27.4	26.1
Hurt, 2012	Olmsted County, Minnesota, USA	Oct 2007	Comprehensive	Apr 2006- Apr 2009	19.8	14.9
Lippert, 2012	District of Columbia, USA	Jan 2007	Comprehensive	2006- 2009	17.9	15.2
	Hawaii, USA	Nov 2006	Comprehensive	2005- 2009	17	15.3
	Illinois, USA	Jan 2008	Comprehensive	2007- 2009	20.1	18.5
	Iowa, USA	July 2008	Comprehensive	2007- 2009	19.8	17.1
	Louisiana, USA	Jan 2007	Partial	2006- 2009	23.4	22
	Maryland, USA	Feb 2008	Comprehensive	2007- 2009	17.1	15.1
	Nevada, USA	Dec 2006	Partial	2005- 2009	23.1	22
	New Hampshire, USA	Sept 2007	Comprehensive	2006- 2009	18.7	15.7
	New Jersey, USA	Apr 2006	Comprehensive	2005- 2009	18	15.8
	New Mexico, USA	June 2007	Comprehensive	2006- 2009	20.1	17.9
	Pennsylvania, USA	Sept 2008	Partial	2007- 2009	21	20.2
	Puerto Rico, USA	Mar 2007	Comprehensive	2006- 2009	12.5	10.5
	Utah, USA	May 2006	Partial	2006- 2009	9.8	9.8
Loomis, 2012	Florida, USA	July 2003	Partial	1990- 2006	23.6	21
	New York, USA	Mar 2003	Comprehensive	Jan 1995- Dec 2006	21.5	18.2
Rodu, 2012	California, USA	Jan 1995	Partial	1991- 1995	20.1	15.5
	South Dakota, USA	July 2002	Partial	1999- 2003	22.5	22.7
	Delaware, USA	Nov 2002	Comprehensive	1999- 2003	25.4	21.9
Vander Weg, 2012	579 US counties, USA	1991- 2008	Comprehensive	1991- 2008	–	–
Bruintjes, 2011	Greeley, Colorado, USA	Dec 2003	Comprehensive	July 2002- June 2006	20.4	17.9
Gupta, 2011	Kanawha County, West Virginia, USA	Jan 2004	Comprehensive	Jan 2000- Sept 2008	32	24
Hahn, 2011	Lexington, Kentucky, USA	Apr 2004	Comprehensive	Jan 2001- Dec 2006	30.9	28.5
Herman, 2011	Arizona, USA	May 2007	Comprehensive	Jan 2004- May 2008	18.5	15.9
Dove, 2010	Massachusetts, USA	July 2004	Comprehensive	Jan 1999- Dec 2006	19.4	17.8
Naiman, 2010	Toronto, Ontario, Canada	June 2004	Comprehensive	Jan1996- Apr 2006	22	20
Alsever, 2009	Pueblo, Colorado, USA	July 2003	Comprehensive	Jan 2002- June 2006	25.9	20.6

Table 1 (continued)

First author, year	Population	Date of legislation enactment	Extent of legislation	Study follow-up period	Smoking prevalence	
					Pre-legislation	Post-legislation
Lemstra, 2008	Saskatoon, Saskatchewan, Canada	July 2004	Comprehensive	July 2000- June 2005	24.1	18.2
Khuder, 2007	Bowling Green, Ohio, USA	Mar 2002	Partial	Jan 1999- June 2005	27.6	22.3
Seo, 2007	Monroe County, Indiana, USA	Jan 2005	Comprehensive	Aug 2001- May 2005	27.5	27.3
Sargent, 2004	Helena, Montana, USA	June 2002	Comprehensive	Dec 1997- Nov 2003	20.5	20
Europe						
Aguero, 2013	Girona, Spain	Jan 2006	Partial	2002- 2008	31.7	33.9
Séguret, 2013	France	Jan 2008	Comprehensive	Jan 2003- Dec 2009	25	31.5
Stallings-Smith, 2013	Ireland	Mar 2004	Comprehensive	Jan 2000- Dec 2007	27	29
Sargent, 2012	Germany	Aug 2007- July 2008	Partial	Jan 2004- Dec 2008	27.4	29
Barone-Adesi, 2011	Italy	Jan 2005	Comprehensive	Jan 2002- Nov 2006	26.6	24.3
Bonetti, 2011	Graubunden, Switzerland	Mar 2008	Comprehensive	Mar 2006- Feb 2010	29	27
Sims, 2010	England	July 2007	Comprehensive	July 2002- Sept 2008	26	21
Villalbi, 2009	Barcelona, Spain	Jan 2006	Partial	2004- 2006	28.1	29.5
Pell, 2008	Scotland	Mar 2006	Comprehensive	June 2005- Mar 2007	26.7	25.7
Other						
Barnett, 2009	Christchurch, New Zealand	Dec 2004	Comprehensive	Jan 2003- Dec 2006	23.4	18.7

Study follow-up period is the beginning and end of the study follow-up for pre-legislation and post-legislation periods

Smoking prevalence information is the adult smoking prevalence during the pre-legislation period and post-legislation study periods

publication [19, 27, 39–43]. When pre-legislation smoking prevalence was not reported, it was estimated using data from the country for non-US studies [44–56] and the state/province or city for studies in the US or Canada [57–60]. One study [61] combined data from nine US states; for this study, the smoking prevalence was defined as the mean prevalence across the states. Vander Weg et al [62]. estimated the impact of 938 smoking legislations implemented in 731 cities, 175 counties, and 32 states in the US, however, this study did not provide information regarding the study locations to estimate pre- or post-smoking prevalence and therefore was excluded from the smoking prevalence analyses. Studies were defined as having a high or low pre-legislation prevalence of smoking and high or low reductions in prevalence of smoking following legislation using the mean pre-legislation prevalence (23.1 %) and mean prevalence reduction (2.1 %) as cutpoints.

Statistical Analysis

Relative risks (RR) for acute coronary events post- vs. pre-legislation and their standard errors or 95 % confidence intervals (CI) were abstracted or derived using the data reported in each publication. The studies were then pooled using inverse-variance weighted random-effects models. For those that reported stratified data only [38, 63–65], an overall estimate was calculated by pooling the stratified estimates using inverse-variance weighted random-effects models.

To evaluate the consistency of findings by location characteristics, pooled RRs were estimated separately for studies stratified by region, type of ban, pre-legislation smoking prevalence, and the change in prevalence post-legislation. Random-effects meta-regression was conducted to assess the association between the change in events after legislation with region (Americas vs. Other), pre-legislation smoking prevalence (above and below the mean), and change in smoking prevalence pre- vs. post-legislation (above and below the mean). Statistical heterogeneity was evaluated with the I [2] statistic to quantify the proportion of variability in effect estimates due to heterogeneity between studies versus sampling error within studies. The relative influence of each study on pooled estimates was estimated by omitting one study at a time. Finally, we assessed publication bias using funnel plots. All statistical analyses were performed using Stata version 13.1 (StataCorp, College Station, Texas).

Results

Study Selection

Of 1,672 studies identified, 31 studies [22, 26–29, 37–43, 61–77] met the inclusion criteria and were included in this review (Supplementary Figure 1). The article from McAlister et al [78]. included in the most recently published systematic review[12] was excluded, as it did not meet our eligibility criteria (this study estimated the effects of tobacco control activities, especially smoking cessation programs, but did not include a smoking ban in public places). We also excluded meeting abstracts and articles from non-peer reviewed literature that were included in the systematic review from Tan et al [15]. Four US studies included estimates from multiple states [26–28, 62]. For the three studies [26–28] that provided estimates stratified by state, we considered the state-specific estimates as independent observations. The 31 included studies provided estimates from 47 locations.

Study Characteristics

Thirty-seven study locations were in the Americas (three in Canada, three in South America, and 31 in the US), nine in Europe, and one in New Zealand (Table 1). Legislations were implemented between 1991 and 2010, and study follow-up ranged from three months to 5.5 years post-legislation. Of the 47 total study locations, 35 were comprehensive smoking bans and 12 were partial smoking bans. The mean pre- and post-legislation smoking prevalences were 23.1 and 21.0 %, respectively, for locations included in this review.

Smoking Legislations and Acute Coronary Events

Changes in hospitalizations for acute coronary events ranged from a 52 % reduction in Monroe County, Indiana [77] to a 9 % increase in South Dakota [26]. Overall, the enactment of smoking legislations was associated with a 12 % reduction in acute coronary events (pooled RR: 0.88, 95 % CI: 0.85-0.90). Comprehensive smoke-free legislations were associated with a 14 % reduction in hospitalizations (pooled RR: 0.86, 95 % CI: 0.83-0.89) (Fig. 1, Table 2) compared to an 8 % reduction for partial smoking restrictions (Pooled RR: 0.92, 95 % CI: 0.85, 0.98) (Fig. 2, Table 2). Reductions were largely similar in studies conducted in the Americas (Pooled RR: 0.87, 95 % CI: 0.83, 0.91) compared to elsewhere (Pooled RR: 0.89, 95 % CI: 0.84, 0.94).

Median (Interquartile range [IQR]) pre- and post-legislation smoking prevalence were 23.3 (19.8- 27.0) % and 20.1 (17.1- 25.7) %, respectively. The reduction in acute coronary events following smoking legislation was greater among populations with higher smoking prevalences pre-legislation compared to populations with lower smoking prevalences (Pooled RR [95 % CI]: 0.87 [0.83, 0.91] for pre-legislation smoking prevalence above the mean vs. 0.89 [0.85, 0.93] for pre-

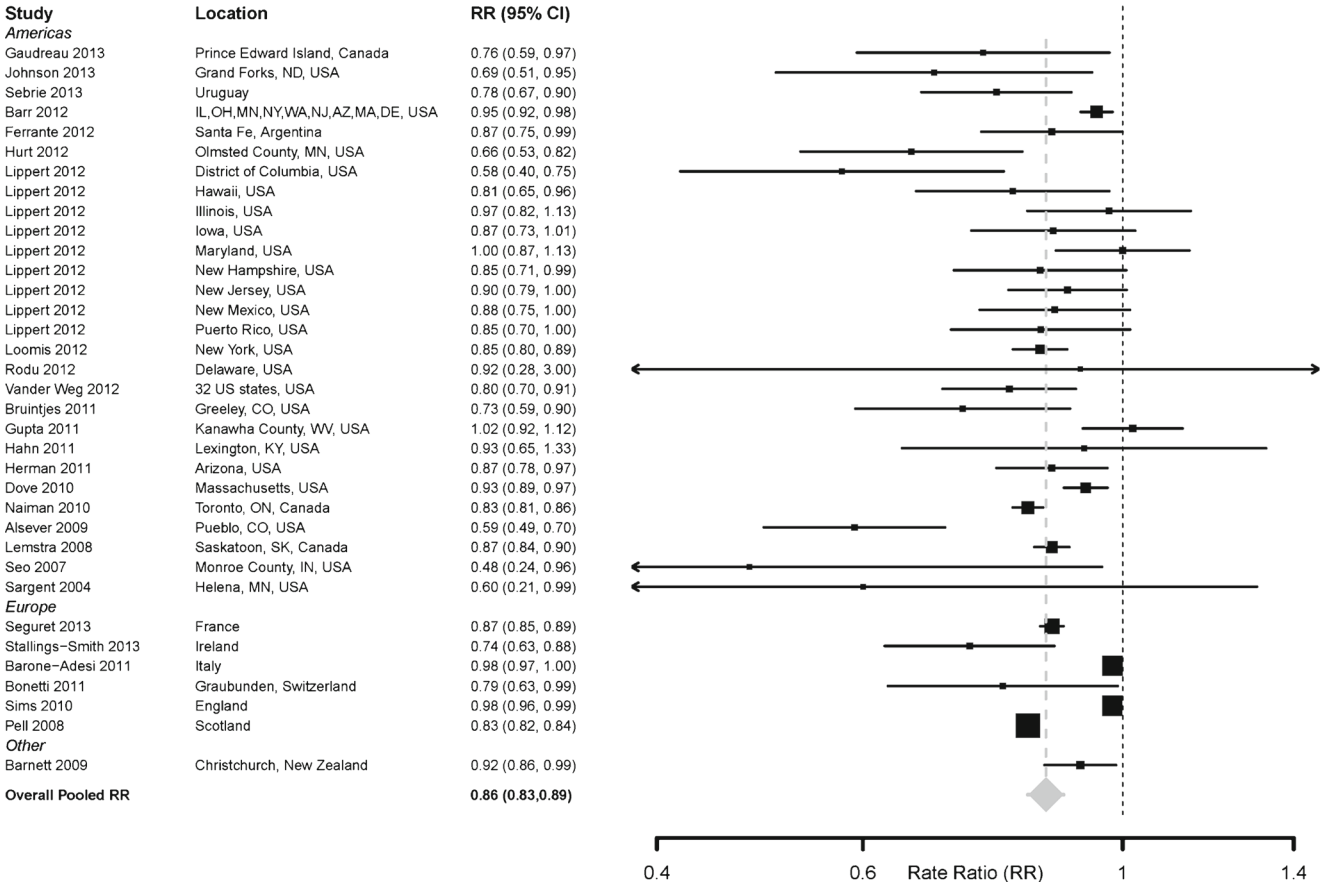

Fig. 1 Forest plot of random-effects meta-analysis of studies examining the effect of comprehensive smoke-free legislation on acute coronary events

legislation smoking prevalence below the mean) (Table 2). Following enactment of smoke-free legislation, the prevalence of smoking decreased on average by 2.1 %, with seven locations observing no change or an increase in smoking prevalence in the post-legislation period [26, 27, 37, 65, 73, 76, 79]. The reduction in events following legislation was also larger in locations with reductions in smoking prevalence above versus below the mean (Pooled RR: 0.86 [95 % CI: 0.83, 0.89] vs 0.90 [95 % CI: 0.88, 0.93]) (Table 2).

Discussion

Following the enactment of smoke-free legislations, there was a 12 % reduction in hospitalizations for acute coronary events

Table 2 Pooled estimates of the effect of smoking legislation on acute coronary events by type of legislation and smoking prevalence data

	No of estimates	Pooled RR (95 % CI)
Overall	47	0.88 (0.85, 0.90)
Type of legislation		
Comprehensive (smoke-free)	35	0.86 (0.83, 0.89)
Partial smoking restriction	12	0.92 (0.85, 0.98)
Pre-legislation smoking prevalence		
Below the mean (≤23.1 %)	22	0.89 (0.85, 0.93)
Above the mean (>23.1 %)	24	0.87 (0.83, 0.91)
Reduction in smoking prevalence post vs. pre-legislation		
Below the mean (≤2.1 % reduction)	23	0.90 (0.88, 0.93)
Above the mean (>2.1 % reduction)	23	0.86 (0.83, 0.89)

Pooled estimates from random-effects meta-analyses

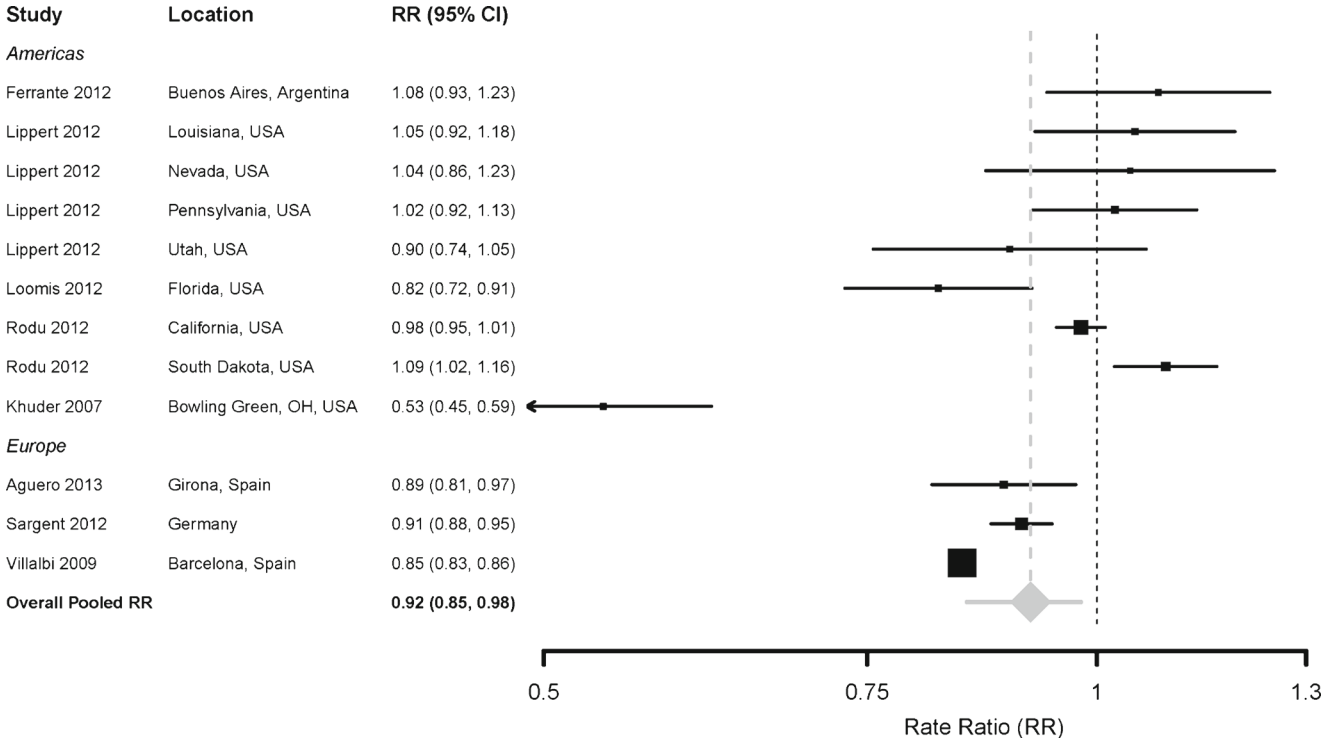

Fig. 2 Forest plot of random-effects meta-analysis of studies examining the effect of partial smoke-free legislation on acute coronary events

with greater reductions with comprehensive, as opposed to partial, smoke-free legislation. Comprehensive smoke-free laws have been shown to be more effective than partial laws in reducing exposure to secondhand tobacco smoke [80, 81]. Indeed, while a reduction in fine particulate matter ($PM_{2.5}$) concentrations had been observed in France, Greece, Ireland, Italy, Portugal, Scotland, and Turkey following enactment of smoke-free legislations, the countries that enacted comprehensive smoke-free legislation (France, Ireland, Italy, Scotland, and Turkey) experienced greater reductions in $PM_{2.5}$ concentrations [82]. In studies in Malaysia and Chile, which have partial smoking legislations, exposure to secondhand smoke, measured by air nicotine and $PM_{2.5}$ concentrations, remained high in hospitality venues following enactment of legislation [83, 84]. In Spain, which also enacted partial smoking restrictions, there was no change in concentrations of salivary cotinine among nonsmoking hospitality workers [85] and an increase in concentrations of airborne nicotine in hospitality venues [86] following legislation enactment. These findings demonstrate that partial smoking ban legislations do not provide protection from secondhand smoke to employees working in those venues. In contrast, among nonsmoking adults in Scotland, which enacted comprehensive smoking legislation, there was a 39 % decrease in salivary cotinine concentrations following enactment [87].

With increasing time, larger reductions in cardiovascular hospitalizations [11, 13, 14] and increasing support for smoking bans [88–90] have been found. Consistent with previous systematic reviews [11, 13, 14], we found greater reductions in events following legislation in locations with follow-up above versus below the mean (25.8 months) (Pooled RR: 0.83 [95 % CI: 0.78, 0.88] vs 0.91 [95 % CI: 0.87, 0.94]). The larger reductions in hospitalizations over time may reflect greater reductions in secondhand smoke exposure in the population as well as decreases in the magnitude of active smoking (due to potential decreases in cigarette consumption and increases in smoking cessation) [30, 64]. Additionally, comprehensive smoke-free legislations have been associated with greater quit attempts and quit successes following legislation enactment compared to the enactment partial smoke-free legislations [91, 92]. In our study we observed greater reductions in coronary events in populations that enacted comprehensive smoke-free legislations and in populations that had greater reductions in smoking prevalence post-legislation.

Two recent papers published in January 2014 and February 2014 found no association between the enactment of the legislation and a reduction in cardiovascular events [93, 94]. The studies were conducted in Colorado and Panama. In Panama, the smoking prevalence prior to the legislation was very low (9 %) [94]. In the study conducted in Colorado [93], the statewide comprehensive legislation had been preceded by several city-wide smoking ordinances, including two cities included in this review [19, 67], which found significant decreases in acute myocardial infarction hospitalization after implementation of these local smoking ordinances. Following the enactment of these legislations, the prevalence of smoking

was reduced by 2.4 % and 2.6 % in Colorado and Panama, respectively [57, 94]. Adding those studies to the overall pooled estimates resulted in similar findings: RR: 0.88 (95 % CI: 0.86, 0.91).

Possible Mechanisms

Mechanisms by which secondhand smoke may increase the risk for an acute coronary event include platelet activation, induction of endothelial dysfunction, increase in arterial stiffness, enhanced oxidative stress, reduced antioxidant defense, induction of inflammation, decreased parasympathetic output, and an increase in insulin resistance [1, 95–97]. These consequences have been observed at low exposure doses and within minutes or hours following exposure. This might explain why the beneficial effects of reducing secondhand smoke exposure seem to occur rapidly with declines in hospitalizations within a few months following legislation. Indeed, reductions were seen in studies with post-legislation periods as soon as a few months following the enactment of the legislation showing that the enactment of smoke-free legislation can result in immediate reductions in hospital admissions and these reductions increase over time following legislation enactment.

Strengths and Limitations

This study has several strengths. Our results are consistent with those of prior systematic reviews and meta-analyses [9–11, 12•, 13–15], which also reported a significant reduction in hospitalizations for acute coronary events following the implementation of smoke-free legislations, and include additional recent studies and several larger population studies (Supplementary Table 1). Moreover, we evaluated differences in the association between legislation and acute coronary events by several characteristics, including type of legislation, pre-legislation smoking prevalence, and changes in smoking prevalence. Our findings add to the current literature regarding the benefits of smoke-free legislation.

Some limitations should be noted. In this review, we examined differences in hospitalizations with changes in prevalence of smoking, however, as many of the studies do not have information on changes in secondhand smoke exposure pre- vs. post legislation, it is difficult to determine what portion of the observed decreases in hospital admissions could be attributed to reduced exposure to secondhand tobacco smoke in nonsmokers as opposed to reduced consumption or quitting among smokers. Also, there were small sample sizes in some studies, and most of the studies were ecological in design. The studies also differed by population demographics included in the study, for example, the age limits for inclusion, which may impact differences in the effects of the smoke-free legislations observed. Lastly, we were unable to evaluate the influence of enforcement or compliance with the legislation, remaining secondhand smoke exposure in areas not covered by the legislation (e.g., private vehicles and homes), or baseline rates of acute coronary events. These factors could also influence the magnitudes of the reductions following the implementation of smoke-free legislation. Additionally, countries and cities can implement other type of FCTC articles that can also impact smoking prevalence and coronary events, for example, tobacco tax increases and reductions in tobacco advertising and promotion [94]. We were unable to evaluate the influence of other such measures that may have occurred concurrently with the smoking bans in public places. This analysis examines changes in cardiovascular events following the implementation of smoke-free legislations compared to the time period prior to the legislations as reported in the studies. For comprehensive legislations, especially those conducted in the US, the pre-legislation period may include partial smoke-free legislations. Therefore, we were limited to examining the gradual changes in cardiovascular events that occur as smoke-free legislations are implemented (i.e., when there are no restrictions followed by the implementation of a partial smoke-free legislation and then comprehensive legislation).

Conclusion

The implementation of smoke-free legislations was related to a reduction in hospitalizations for acute coronary events. These cardiovascular benefits were greater in studies conducted in populations with comprehensive smoking bans, and in populations with greater reductions in smoking prevalence. These data support the urgent need to enact and enforce smoke-free legislations that protect all people from exposure to secondhand tobacco smoke.

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Compliance with Ethics Guidelines

Conflict of Interest Miranda R. Jones, Joaquin Barnoya, Saverio Stranges, Lia Losonczy, and Ana Navas-Acien declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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