Effect of comprehensive smoke-free legislation on neonatal mortality and infant mortality across 106 middle-income countries

Effect of comprehensive smoke-free legislation on neonatal mortality and infant mortality across 106 middle-income countries: a synthetic control study

Márta K Radó, Frank J van Lenthe, Anthony A Laverty, Filippos T Filippidis, Christopher Millett, Aziz Sheikh, Jasper V Been

Summary

Background There are few quantitative studies into the effect of comprehensive smoke-free legislation on neonatal and infant mortality in middle-income countries. We aimed to estimate the effects of implementing comprehensive smoke-free legislation on neonatal mortality and infant mortality across all middle-income countries.

Methods We applied the synthetic control method using 1990–2018 country-level panel data for 106 middle-income countries from the WHO, World Bank, and Penn World datasets. Outcome variables were neonatal (age 0–28 days) mortality and infant (age 0–12 months) mortality rates per 1000 livebirths per year. For each middle-income country with comprehensive smoke-free legislation, a synthetic control country was constructed from middle-income countries without comprehensive smoke-free legislation, but with similar prelegislation trends in the outcome and predictor variables. Overall legislation effect was the mean average of country-specific effects weighted by the number of livebirths. We compared the distribution of the legislation effects with that of the placebo effects to assess the likelihood that the observed effect was related to the implementation of smoke-free legislation and not merely influenced by other processes.

Findings 31 (29%) of 106 middle-income countries introduced comprehensive smoke-free legislation and had outcome data for at least 3 years after the intervention. We were able to construct a synthetic control country for 18 countries for neonatal mortality and for 15 countries for infant mortality. Comprehensive smoke-free legislation was followed by a mean yearly decrease of 1·63% in neonatal mortality and a mean yearly decrease of 1·33% in infant mortality. An estimated 12 392 neonatal deaths in 18 countries and 8932 infant deaths in 15 countries were avoided over 3 years following the implementation of comprehensive smoke-free legislation. We estimated that an additional 104 063 infant deaths (including 95 850 neonatal deaths) could have been avoided over 3 years if the 72 control middle-income countries had introduced this legislation in 2015. 220 (43%) of 514 placebo effects for neonatal mortality and 112 (39%) of 289 for infant mortality were larger than the estimated aggregated legislation effect, indicating a degree of uncertainty around our estimates. Sensitivity analyses showed results that were consistent with the main analysis and suggested a dose–response association related to comprehensiveness of the legislation.

Interpretation Implementing comprehensive smoke-free legislation in middle-income countries could substantially reduce preventable deaths in neonates and infants.

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Division of Neonatology, Department of Paediatrics, Erasmus MC Sophia Children's Hospital (M K Radó PhD, J V Been PhD) **and Department of Public Health, Erasmus MC** (M K Radó, Prof F J van Lenthe PhD, J V Been), **University Medical Centre Rotterdam, Rotterdam, Netherlands; Institute for Analytical Sociology, Department of Management and Engineering, Linköping University, Norrköping, Sweden** (M K Radó); **Public Health Policy Evaluation Unit, School of Public Health, Imperial College London, London, UK** (A A Laverty PhD, F T Filippidis PhD, Prof C Millett PhD); **NOVA National School of Public Health, Public Health Research Centre, NOVA University of Lisbon, Lisbon, Portugal** (Prof C Millett); **Comprehensive Health Research Center, Lisbon, Portugal** (Prof C Millett); **Centre for Medical Informatics, Usher Institute, University of Edinburgh, Edinburgh, UK** (Prof A Sheikh MD, J V Been)

Correspondence to:
Dr Jasper V Been, Division of Neonatology, Department of Paediatrics, Erasmus MC Sophia Children's Hospital, University Medical Centre Rotterdam, Rotterdam 3000 CB, Netherlands
j.been@erasmusmc.nl

Introduction

An estimated 56 000 children younger than 10 years die due to tobacco smoke exposure (TSE) worldwide each year. Active smoking or passive TSE during pregnancy increases the risk of adverse perinatal outcomes, including stillbirth, preterm birth, and neonatal and infant death.[1–5] Both antenatal and postnatal TSE further increase the risk of infant mortality and asthma exacerbations and severe respiratory infections during childhood.[6,7] Fetuses and children are especially vulnerable to TSE and have low ability or no ability to avoid exposure.[8] There is a need to reduce TSE during pregnancy and childhood to achieve the goals of reducing neonatal and under-5 mortality rates, as described in the UN Sustainable Development Goals 3.2.1 and 3.2.2.[9,10]

Smoke-free legislation, especially comprehensive smoke-free legislation that covers all enclosed public places and workplaces, has been identified as a key intervention to protect fetuses and children from the adverse effects of TSE.[11] Our systematic review and meta-analysis in 2017 found that smoke-free legislation covering enclosed public places in high-income countries (HICs) was followed by an immediate 3·8% decrease in preterm birth rates, a 9·8% decrease in rates of hospital attendance for asthma exacerbations, and an

Research in context

Evidence before this study

Tobacco smoke exposure and maternal smoking during or after pregnancy are linked to several adverse early-life health outcomes, including neonatal and infant mortality. Comprehensive smoke-free legislation has the potential to reduce this burden. Our systematic review and meta-analysis, published in 2017, found that comprehensive smoke-free legislation (ie, prohibiting smoking in enclosed public places and workplaces) in high-income countries (HICs) was associated with decreases in preterm birth, hospital attendance for asthma, and hospital attendance for lower respiratory tract infections. Additionally, smoke-free legislation in England was associated with a 7·6% (95% CI 3·4–11·7) reduction in neonatal mortality and a 6·3% (2·9–9·6) reduction in infant mortality. To identify any subsequent studies on this topic in middle-income countries (MICs), we searched PubMed for studies published between Jan 1, 2017, and Feb 23, 2022, using the terms ("smoke-free" OR "smokefree" OR "tobacco*") AND ("infant*" OR "neonat*"), with no language restrictions. We identified three single-country assessments in MICs of associations between smoke-free legislation and child health, assessing neonatal mortality, infant mortality, and low birthweight. Although these case studies supported the positive effects of smoke-free legislation in MICs, they were derived from a small number of countries (Brazil, Peru, and Thailand) of wealthier MICs where tobacco control is stronger than in most other MICs. Thus, whether these findings are generalisable to other MICs with less favourable economic, cultural, and environmental conditions remains unclear.

Added value of this study

Although the health benefits of comprehensive smoke-free legislation in HICs are well established, this study is, to our knowledge, the first to assess the effects on neonatal mortality and infant mortality across all MICs that introduced this legislation and had outcome data for at least 3 years after the intervention. We used the synthetic control method, which provides a robust estimation of what would have happened without comprehensive smoke-free legislation, based on similar control countries that had not implemented such legislation. Using this method provided a methodological advantage, given that almost all previous studies in HICs and MICs did not include a control unit. We found evidence of a substantial reduction in two key child health outcomes, neonatal mortality and infant mortality, after the introduction of comprehensive smoke-free legislation in MICs. Results were consistent across sensitivity analyses, but the placebo test indicated some degree of uncertainty around our estimates. Additionally, sensitivity analyses indicated higher child survival benefits with better compliance and comprehensiveness of the smoke-free legislation.

Implications of all the available evidence

Taken together, the previous evidence and additional evidence from this study show that comprehensive smoke-free legislation substantially improves neonatal and infant survival both in HICs and MICs. Given the large numbers of people living in MICs, the higher rates of early-life mortality, and the relative scarcity of implementation of smoke-free policies compared with HICs, the potential health gains are substantial. This analysis supports the introduction of comprehensive smoke-free legislation in MICs to achieve Sustainable Development Goal 3.2 of reducing preventable child deaths.

18·5% decrease in rates of hospital attendance for lower respiratory tract infections.[12] Evidence also suggests that implementing comprehensive smoke-free legislation is associated with reduced neonatal mortality and infant mortality.[12–15]

Previous evidence is, however, predominantly derived from studies in HICs and cannot be directly generalised to low-income and middle-income countries (LMICs), because of their different economic, social, and environmental backgrounds, higher rates of neonatal and infant deaths, and often weaker implementation of smoke-free legislation.[12,16] The influence of the tobacco industry and the awareness of the TSE-related harms is considerably less favourable in LMICs than in HICs, which might hinder the success of tobacco-control policies.[11,17–21] Although smoking prevalence among women in their reproductive years (including in pregnant women) is much lower in LMICs than in HICs, the proportion of men who smoke is much higher in many LMICs, thus potentially leading to greater passive TSE among pregnant women.[17,22–24] Additionally, the tobacco industry is shifting its focus to the lower-income parts of the world, where tobacco control measures commonly remain in their infancy.[22,25] Three studies have evaluated the effects of smoke-free legislation on child health outcomes in middle-income countries (MICs), in Brazil, Peru, and Thailand.[14,15,26] Although these studies also showed the positive effects of smoke-free legislation, they were conducted in countries known to be tobacco-control leaders and with a higher gross domestic product (GDP) per capita than many other MICs.[11] Thus, it is unclear whether the child health benefits of comprehensive smoke-free legislation identified in these studies are generalisable to all 106 World Bank MICs. As implementation progress has stalled in many MICs and more than 75% of the world's population is not protected by comprehensive smoke-free legislation, contextually relevant evidence is needed to reinvigorate this effort.[27] We aimed to estimate the effects of implementing comprehensive smoke-free legislation on neonatal mortality and infant mortality across all MICs.

Methods

Study design

We used an extension of the synthetic control method[28–33] and analysed yearly country-level data to estimate the effects of comprehensive smoke-free legislation on neonatal mortality and infant mortality in 106 MICs (appendix p 3). To estimate legislation effects, we compared the neonatal mortality and infant mortality trends in countries that had comprehensive smoke-free legislation in place for at least 3 years by Dec 31, 2018 (intervention countries) with their synthetic counterparts (ie, the combination of multiple control MICs that did not have comprehensive smoke-free legislation).[29,31] We calculated the average legislation effect for the years following the implementation of the legislation across multiple intervention countries by weighting to their number of livebirths. This study did not require ethical approval, as only aggregated and publicly available data were used.

Procedures

We focused on countries that had been defined as MICs (ie, upper-MICs or lower-MICs) in 2018 by the World Bank.[34] Intervention countries were countries that had implemented comprehensive smoke-free legislation in 2015 or earlier (31 countries; appendix p 3). We excluded Cambodia, Guyana, and Laos from the calculation of the overall legislation effect because they had not had legislation in place for at least 3 years by the end of the observation period (ie, by Dec 31, 2018). The remaining 72 MICs that had not implemented such legislation by 2018 were considered as control countries. We obtained information about smoke-free legislation in MICs from the WHO Report on the Global Tobacco Epidemic 2019.[11] Following WHO recommendations, smoke-free legislation was considered to be comprehensive when it entirely banned smoking without allowing designated smoking rooms in indoor workplaces, health-care facilities, educational facilities, government facilities, public transport, bars, and restaurants.[35] For each country, the prelegislation observation period was 10 years and the postlegislation observation period ended on Dec 31, 2018 (thus the length of the postlegislation observation period differed between countries).

The outcomes of interest were the national-level neonatal (age 0–28 days) mortality and infant (age 0–12 months) mortality rates per 1000 livebirths per year, based on World Bank data. Variables predicting these rates in synthetic control countries included indicators of demographics, social and economic status, quality of and access to health-care facilities, air pollution, and prelegislation values of the outcome variables (definitions and data sources are shown in table 1), given that these variables had previously been shown to affect the outcome variables.[15,33,36] Openness to trade was extracted from the Penn World dataset, whereas all other variables were obtained from the World Bank database.[37,38] If an intervention country had no prelegislation data for one of the predictors, we excluded the predictor from the model, whereas if a control country had no prelegislation data for one of the predictors, we excluded the country from the analysis (appendix pp 4–5).

	Definition
Neonatal mortality*	The number of babies who die within 28 days after birth per 1000 livebirths
Infant mortality*	The number of children younger than 1 year who die per 1000 livebirths
GDP	Gross domestic product (purchasing power parity)
Rural population	The proportion of the population living in rural areas, as defined by national statistical offices
Female primary education completion rate	The ratio of the number of new female entrants in the last grade of primary education (regardless of age) and the number of female entrants at the entrance age for the last grade of primary education
Fertility rate	The mean number of children born to a woman (given women survive the childbearing age and fertility is in line with age-specific fertility rates of the specified year)
Openness to trade	The share of exports plus imports compared with nominal GDP
Health expenditure	Current health expenditure per capita expressed in international dollars (purchasing power parity)
Hospital beds	The number of hospital beds available per 1000 people
Drinking water	The proportion of the population with access to basic drinking water (ie, collection time <30 min)
Clean cooking	The proportion of the population with access to clean fuels and technologies for cooking
CO_2	Carbon dioxide emissions in megatons

*The prelegislation trend in these variables were predictors in the model. These variables were also the primary outcomes in the postlegislation follow-up period.

Table 1: **Definitions of variables**

Statistical analysis

We separately estimated the legislation effects for each intervention country using the synthetic control method.[28–30] First, for each intervention country, we constructed a synthetic control country. A synthetic control country was modelled as the optimal combination of all available control countries (ie, MICs that had not implemented comprehensive smoke-free legislation by 2015), and such that the difference (ie, the root mean squared prediction error [RMSPE], as described in appendix p 6) between the intervention country and its final synthetic control country in a set of prelegislation predictors and prelegislation outcome variables was minimised, based on Broyden, Fletcher, Goldfarb, and Shanno's and quasi-Newton algorithms.[39] Second, for each intervention country and per year following intervention, we calculated the absolute risk reduction as the difference in the incidence of the outcome variable between the intervention country and its synthetic control country (appendix p 6). We also calculated the relative risk reduction associated with the legislation as the ratio between the legislation effect in the given intervention

See Online for appendix

	Full sample		Intervention countries with comprehensive smoke-free legislation		Control countries without comprehensive smoke-free legislation	
	1999–2008	2009–18	1999–2008	2009–18	1999–2008	2009–18
Number of countries	106	106	34	34	72	72
Annual mean neonatal mortality, deaths per 1000 livebirths	20·09 (11·16)	15·82 (9·67)	17·46 (9·73)	13·17 (9·88)	21·37 (11·59)	17·10 (9·88)
Annual mean infant mortality, deaths per 1000 livebirths	35·82 (23·29)	25·92 (17·57)	29·52 (17·69)	20·63 (18·78)	38·87 (25·01)	28·49 (18·78)
GDP, purchasing power parity per billion US$	247·04 (758·39)	506·37 (1830·86)	253·78 (468·61)	442·57 (829·22)	243·74 (865·79)	536·80 (2150·10)
Rural population, proportion of the population	49·38% (19·54)	45·54% (20·03)	40·98% (20·8)	37·27% (20·40)	53·40% (17·52)	49·50% (18·61)
Female primary education completion rate, proportion of the population	87·26% (19·35)	92·57% (14·57)	87·84% (15·75)	93·92% (11·51)	86·97% (20·90)	91·92% (15·81)
Fertility rate, mean number of children per woman	3·17 (1·31)	2·85 (1·15)	2·80 (1·05)	2·48 (0·80)	3·34 (1·38)	3·01 (1·19)
Openness to trade, exports plus imports or nominal GDP	85·64 (36·86)	87·21 (35·35)	81·87 (34·18)	82·22 (33·63)	87·36 (37·91)	89·98 (35·97)
Health expenditure per capita, purchasing power parity, US$	358·20 (265·93)	568·49 (419·05)	488·62 (291·65)	82·22 (33·63)	296·21 (228·21)	488·75 (387·82)
Hospital beds, per 1000 people	3·54 (2·71)	3·01 (2·34)	3·69 (2·77)	2·94 (2·29)	3·45 (2·68)	3·06 (2·39)
Drinking water access, proportion of the population	82·54% (15·52)	86·91% (13·03)	85·85% (14·65)	90·07% (12·00)	80·94% (15·68)	85·40% (13·24)
Clean cooking, proportion of the population	51·70% (31·85)	59·48% (31·66)	59·51% (30·58)	68·11% (29·01)	48·35% (31·82)	55·78% (32·04)
CO_2, megaton	126·35 (553·12)	189·25 (966·79)	110·12 (281·52)	132·13 (433·58)	134·40 (646·95)	216·60 (1155·32)

Data are n or mean (SD). GDP=gross domestic product.

Table 2: **Unweighted mean values of the outcome and predictor variables in the intervention and control countries during the observation period (1999–2008 and 2009–18)**

country and the incidence of the outcome variable in its synthetic control country (appendix p 6). We considered legislation effects only for those countries for which a synthetic control country could be constructed that adequately reproduced the prelegislation outcomes in the given intervention country (defined as an RMSPE of <0·3, in keeping with previous work).[15] We used the Synth package to construct a synthetic control that ran in the R (version 4.0.0) environment.

To determine the overall legislation effects across multiple intervention countries, we aggregated the country-specific effects using an extension of the synthetic control method.[31–33] The overall legislation effect was calculated as the mean of the separate country-specific effect estimates, weighted by their yearly number of livebirths (appendix p 6). Weighting was used to ensure that countries with a higher number of livebirths contributed proportionally more to the overall legislation effects on neonatal and infant mortality rates. We estimated the numbers of deaths that were averted by the comprehensive smoke-free legislation in the first 3 years of implementation in all intervention countries for which an adequate synthetic control could be constructed (ie, RMSPE of <0·3) by multiplying year-specific mean legislation effects with the number of livebirths in the given country and then summing these across the 3 years (appendix p 7). Using a similar method, we also estimated the additional numbers of deaths that could have been averted in 3 years (starting in 2015) by the comprehensive smoke-free legislation in the control countries that did not introduce such a measure.

For each intervention country, we applied a placebo test to assess the likelihood that the observed effect was related to the implementation of smoke-free legislation and not merely influenced by other processes.[29,30] The placebo effect refers to the estimate that we would get if we fictitiously assumed that a control country had introduced legislation at the same time as the intervention country. The placebo effect was calculated by constructing a synthetic control country for the control country of interest using the same predictors and year of implementation as for constructing a synthetic control country for its intervention country, and then calculating the postlegislation difference between the outcome of the control country and that of its synthetic control country. These effects were obtained for the control country of each intervention country (appendix p 7). We only included placebo effects where the prelegislation differences in the predictors between the control country and its synthetic control country were acceptable (RMSPE

of <0·3). We assessed uncertainty around the estimated aggregated legislation effect by assessing the proportion of placebo effects that was larger than the legislation effect, and by comparing the distribution of country-specific legislation effects to the distribution of placebo effects.

We explored the robustness of our findings by conducting eight sensitivity analyses. First, we tested the sensitivity of our results to methodological choices by investigating the association between comprehensive smoke-free legislation and neonatal and infant mortality between 1990 and 2018 using fixed-effect panel regressions. As outcome variables were not normally distributed across countries and over time, their values were log-transformed. We controlled for the same predictor variables that were used in the synthetic control analysis (table 1). Missing values in these predictor variables were imputed through linear interpolation and extrapolation using available data from other years in the given country. Second, we excluded countries with the top 10% highest increase in their GDP between 2013 and 2018, because a large increase could lead to decreases in the outcomes that were likely to be unrelated to the smoke-free legislation (eg, due to better health care). Third, we aggregated effect estimates for intervention countries with less well-fitting synthetic control countries (RMSPE of <0·5) than in the main analysis (RMSPE of <0·3), which allowed us to evaluate more countries. Fourth, we controlled for prelegislation yearly cigarette consumption for MICs obtained from the International Cigarette Consumption Database.[40] This measure was available for only 46 MICs (36 control countries and ten intervention countries), but it approximates smoking prevalence rates for which otherwise yearly data were not available despite being a potentially important predictor. Fifth, in a post-hoc sensitivity analysis, we controlled for exposure to fine particulate matter (particulate matter with a diameter of <2·5 μm; $PM_{2·5}$) air pollution obtained from the World Bank dataset.[37] $PM_{2·5}$ has been shown to be associated with adverse early-life outcomes,[41] but concentrations of $PM_{2·5}$ are highly variable within countries,[37] so we did not include it in our main analysis. Sixth, we assessed the sensitivity of our results to missing data. We used the Amelia R (version 4.0.0) package (one imputation) to impute missing values for time series data. Seventh, we excluded control countries that had partial smoke-free legislation, to provide a cleaner comparison. In the final sensitivity analysis, we excluded intervention countries that had low compliance scores (ie, <4 points on a 10-point scale system according to WHO, 3–5 years after implementation).[42]

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

	Neonatal mortality			Infant mortality		
	RMSPE	Relative risk reduction	Placebo test (proportion of placebo effects that were greater than the country-specific legislation effect)	RMSPE	Relative risk reduction	Placebo test (proportion of placebo effects that were greater than the country-specific legislation effect)
Upper-MICs						
Albania	0·72*	..	..	0·27	6·56%	5/15
Argentina	0·18	1·34%	18/29	0·19	5·05%	6/17
Brazil	0·16	1·05%	22/29	0·89*	..	..
Bulgaria	0·05	17·70%	9/31	0·12	8·20%	6/21
Colombia	0·06	5·70%	9/27	0·10	7·09%	7/22
Costa Rica	0·06	3·98%	16/28	0·13	11·10%	6/22
Ecuador	0·12	2·42%	21/31	0·19	4·28%	3/19
Guatemala	0·05	1·93%	16/27	0·04	1·20%	13/21
Iran	0·10	9·19%	5/25	0·09	4·56%	8/19
Jamaica	0·08	–0·01%	23/36	0·41*	..	..
Lebanon	0·28	7·86%	12/25	0·74*	..	..
North Macedonia	0·29	10·76%	7/25	0·35*	..	..
Peru	0·22	6·77%	11/28	1·04*	..	..
Romania	0·37*	..	..	0·19	9·82%	3/22
Russia	0·19	14·92%	7/30	0·19	1·71%	12/21
Suriname	0·23	3·44%	12/34	0·05	1·35%	12/18
Thailand	0·23	14·83%	2/23	0·24	9·17%	5/19
Lower-MICs						
El Salvador	0·72*	..	..	0·23	0·68%	10/20
Honduras	0·23	11·61%	6/28	0·69*	..	..
Papua New Guinea	0·08	0·13%	22/31	0·06	–0·38%	15/21
West Bank and Gaza Strip	0·05	–3·65%	25/27	0·18	–3·88%	10/12

In countries with an RMSPE of less than 0·3, a well-fitting synthetic control could be created and thus intervention effect was estimated. Countries for which no well-fitting synthetic control could be created are omitted from this table (see their RMSPE values in appendix p 17). Relative risk reductions at 5 years and 7 years after implementation of comprehensive smoke-free legislation are shown in the appendix (p 17). MICs=middle-income countries. RMSPE=root mean squared prediction error. *RMSPE value of 0·3 or greater, thus intervention effect not estimated.

Table 3: **Effect estimates of comprehensive smoke-free legislation on neonatal mortality and infant mortality in intervention countries compared with their synthetic control countries, 3 years after implementation of the legislation (relative risk reduction in outcomes and RMSPE in prelegislation period)**

Results

The unweighted mean neonatal mortality rate decreased from 20·09 per 1000 livebirths per year in 1999–2008 to 15·82 per 1000 livebirths per year in 2009–18 and the unweighted mean infant mortality rate decreased from 35·82 per 1000 livebirths per year in 1999–2008 to 25·92 per 1000 livebirths per year in 2009–18 across all 106 MICs. The differences in the outcome and predictor variables between the intervention countries that introduced comprehensive smoke-free legislation and the unweighted mean of control countries without smoke-free legislation are shown in table 2 (outcomes by intervention countries are shown in appendix pp 8–9). In total, 31 (29%) of 106 countries introduced comprehensive smoke-free legislation by 2015 and had

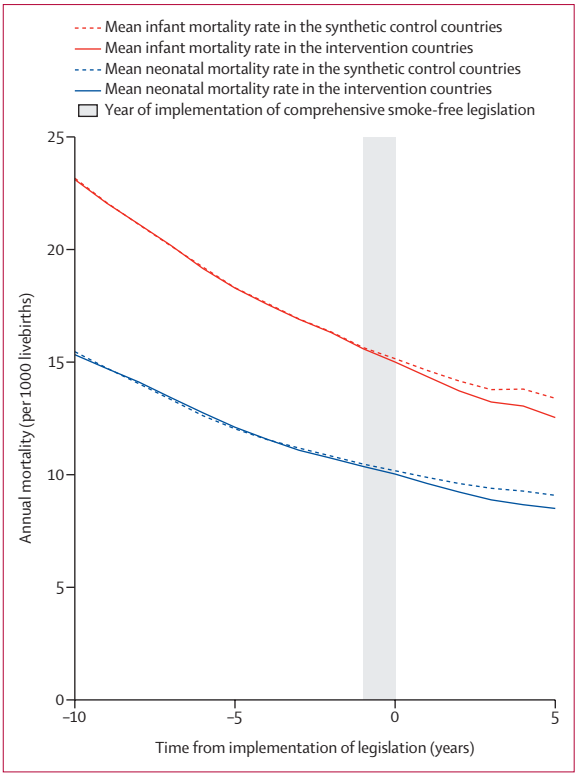

Figure 1: **Trends in annual neonatal mortality and infant mortality in all intervention countries versus their synthetic control countries, weighted by the relative number of livebirths**

We calculated overall legislation effect for intervention countries that had comprehensive smoke-free legislation in place for at least 3 years at the end of the observation period (2018), thus the 4-year and 5-year effects in this figure do not contain countries that had the legislation in place for less than 4 years or 5 years, respectively.

outcome data for at least 3 years after the intervention. We were able to construct a well-fitting synthetic control country (ie, RMSPE of <0·3) for 18 intervention countries for neonatal mortality and 15 intervention countries for infant mortality (table 3). The synthetic control countries adequately reproduced the mean prelegislation temporal trends in the outcomes of the intervention countries (appendix pp 10–16).

3 years after the implementation of smoke-free legislation, neonatal mortality rates had decreased in 16 (89%) of 18 intervention countries compared with their synthetic control country, and infant mortality rates had decreased in 13 (87%) of 15 intervention countries compared with their synthetic control country (figure 1, table 3; appendix p 17). In only one country (West Bank and Gaza Strip), the temporal trends in neonatal and infant mortality rates consistently increased compared with its synthetic control country during the observation period (appendix pp 10–17). The weighted mean relative risk reduction in neonatal mortality was 5·47% over 3 years (ie, 1·63% decrease per year) and in infant mortality was 3·99% over 3 years (ie, 1·33% decrease per year; weights are shown in appendix pp 18–19). These risk reductions translated to an estimated 12 392 averted neonatal deaths in 18 countries with comprehensive smoke-free legislation and 8932 averted infant deaths in 15 countries with comprehensive smoke-free legislation over 3 years, assuming that the mean treatment effect occurred in all countries. We estimated that an additional 104 063 infant deaths (including 95 850 neonatal deaths) could have been averted over 3 years if the remaining 72 MICs without comprehensive smoke-free legislation had introduced this legislation in 2015 and had the same average treatment effect as we estimated for the intervention countries.

In total, 220 (43%) of 514 placebo effects for neonatal mortality and 112 (39%) 289 for infant mortality were larger than the estimated aggregated legislation effect (table 3; appendix pp 20–27). The median yearly placebo absolute risk reduction for neonatal mortality was 0·35 deaths (IQR –0·21 to 0·91) per 1000 livebirths and for infant mortality was 0·25 deaths (–0·28 to 0·78) per 1000 livebirths. By comparison, for the legislation effect, the median yearly absolute risk reduction for neonatal mortality was 0·43 deaths (IQR 0·12 to 0·74) per 1000 livebirths and for infant mortality was 0·60 deaths (0·26 to 0·94) per 1000 livebirths. Although the distributions of the estimated legislation and placebo effects were overlapping, the median legislation effect was larger than that of the placebo effects for each outcome (figure 2).

Our sensitivity analysis using traditional quasi-experimental panel regressions indicated that the implementation of comprehensive smoke-free legislation was associated with an immediate 4·25% (95% CI 0·89–7·49) decrease in neonatal mortality and a 4·58% (1·66–7·41) decrease in infant mortality (appendix p 28). The findings of the synthetic control method were robust when we included countries with less well-fitting synthetic control (RMSPE of <0·5; appendix p 29), excluded countries with the highest (top 10%) increase in their GDP between 2013 and 2018 (appendix p 29), controlled for prelegislation estimated yearly cigarette consumption (appendix p 30), and controlled for $PM_{2·5}$ (appendix p 30), and when we used missing value imputation (appendix p 31). Additionally, the legislation effect was larger (a 3·77% decrease per year in neonatal mortality and a 1·46% decrease per year in infant mortality) than in the main analysis after removing 54 control countries that implemented partial smoke-free legislation by 2018 (appendix p 31). Finally, the legislation effect was also larger than in the main analysis after we excluded countries with low compliance with the legislation (a 1·71% decrease per year in neonatal mortality and a 1·60% decrease per year in infant mortality; appendix p 32).

Discussion

In this analysis of data from 106 MICs, we found that the implementation of comprehensive smoke-free legislation

was associated with a 1·63% decrease per year in neonatal mortality and a 1·33% decrease per year in infant mortality. In absolute terms, we estimated that a total of 12 392 neonatal deaths in 18 countries and 8932 infant deaths in 15 countries were averted over 3 years by the introduction of comprehensive smoke-free legislation. We estimated that an additional 104 063 infant deaths (including 95 850 neonatal deaths) could have been averted over 3 years if all other World Bank MICs had also introduced comprehensive smoke-free legislation in 2015. Several placebo tests had larger effect sizes than the intervention effect, indicating a degree of uncertainty around our estimates.

To our knowledge, this study is the first to have assessed the effect of smoke-free legislation on early-life mortality across all MICs that introduced this legislation by 2018. Previous studies on this topic have involved only single-country assessments for three countries (Brazil, Peru, and Thailand).[12,16–22] Our analyses confirm the positive impact of comprehensive smoke-free legislation in these countries. Linking comparable country-level data from various sources, we were able to extend the evidence to most MICs that implemented comprehensive smoke-free legislation. The estimated overall legislation effects of comprehensive smoke-free legislation were clinically relevant (neonatal mortality decreased by 1·63% per year and infant mortality decreased by 1·33% per year following smoke-free legislation) and similar to the benefits of other reforms or rapid economic developments. Namely, a previous systematic review found that a 10% increase in GDP per capita purchasing power parity in low-income countries is followed by a 10% decrease in infant mortality[43] and each quartile increase in population safe drinking water access is followed by a 1·17% decrease in deaths in children younger than 5 years.[44] Furthermore, the estimated legislation effects were significantly larger than the yearly variance in neonatal mortality (mean 0·029 [SD 0·008]) and infant mortality (mean 0·032 [SD 0·008]) in MICs between 1990 and 2018. Smoke-free legislation can protect pregnant women and their fetuses, as well as neonates and infants directly, from the harm of tobacco smoke by reducing TSE in places that are covered by the policy and by denormalising smoking, which, in turn, reduces active smoking among pregnant women and parents and reduces TSE in places not covered by the policy, most importantly at home.[45,46] These pathways have a potentially important role in LMICs. Although TSE at home is the main source of exposure for pregnant women, TSE outside of the home (eg, in workplaces) remains very high in LMICs.[24,46,47]

Another advantage of our study is that we used the synthetic control method, which substantially improved the internal validity of the study.[28–33] This method provides a robust, transparent, and data-driven estimation of what would have happened without policy implementation when appropriate control time series are not available.

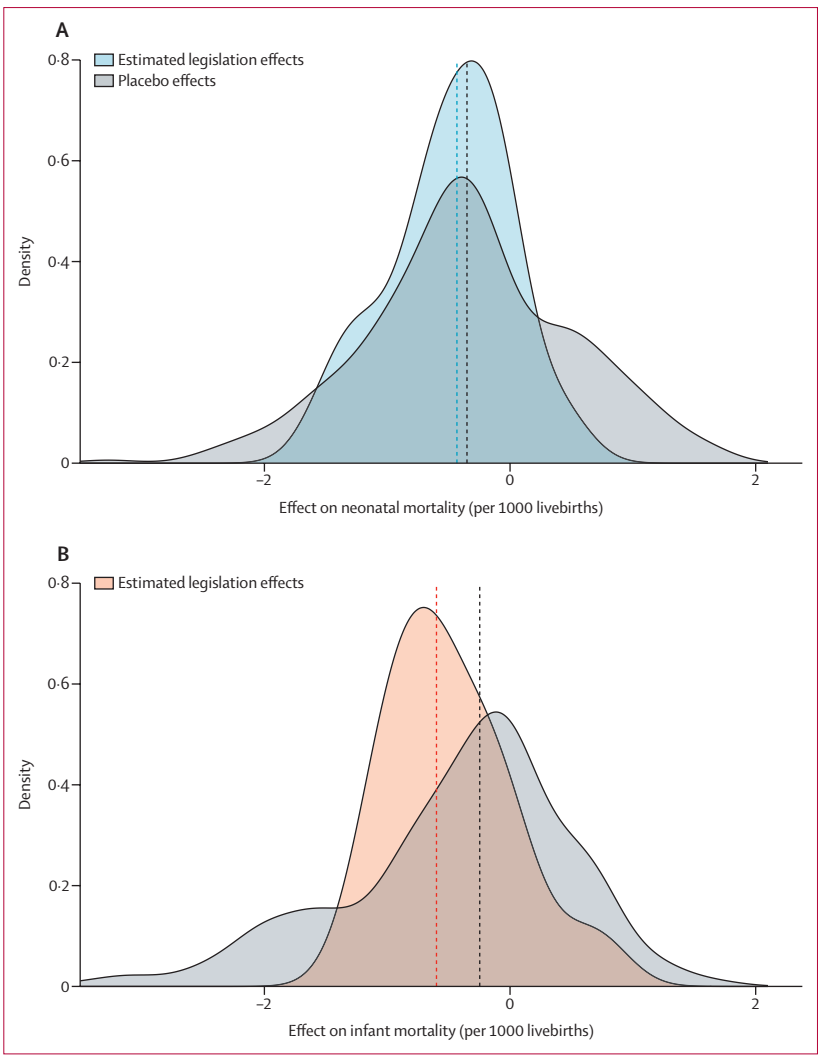

Figure 2: **Distributions of placebo effects and intervention effects on neonatal mortality and infant mortality 3 years after implementation of comprehensive smoke-free legislation (density and median)**
(A) Neonatal mortality. (B) Infant mortality. Dashed vertical lines are median values.

This estimate is obtained by constructing a synthetic control country that optimally mirrors the intervention country (ie, country that introduced comprehensive smoke-free legislation) before the legislation was implemented, using a weighted combination of data from multiple control countries without comprehensive smoke-free legislation. This method provides methodological advantages compared with almost all previous studies, which have not had an actual control unit (ie, interrupted time series analysis).

Our findings of the negative association between comprehensive smoke-free legislation and neonatal mortality and infant mortality were consistent across almost all intervention countries and in sensitivity analyses. This consistency strengthened our confidence that this association was indeed likely to be attributable to the introduction of comprehensive smoke-free

legislation. We found a benefit in all countries, except for West Bank and Gaza Strip, Papua New Guinea, and Jamaica. The absence of a benefit could be explained by low compliance with the smoke-free legislation in the case of West Bank and Gaza Strip (compliance was only 2 on a 10-point scale based on a WHO evaluation 5 years after the legislation was implemented) and Papua New Guinea (compliance was only 3 on the 10-point scale 3 years after the legislation was implemented), whereas Jamaica has been reported to have high tobacco industry interference and low tobacco taxes.[11,35,48,49] Although the benefits of smoke-free legislation were absent mainly in lower-MICs, this should be interpreted with caution, given that we could only estimate legislation effects for four lower-MICs. Our findings were robust in the various model specifications. Also, the sensitivity analyses that removed control countries with partial smoke-free legislation and removed intervention countries with low compliance resulted in larger effect estimates than the main analysis, which supports a dose–response association. However, the sensitivity analyses need to be interpreted with caution, because they estimated effects based on a low number of observed countries or allowed less statistically rigorous evaluations (ie, RMSPE of <0·5), permitting less robust estimations than the main analysis did.

A common limitation of research evaluating national policy interventions, such as smoke-free legislation, is that such interventions are not implemented in a randomised way, which inherently limits the ability to rule out the influence of residual confounders and co-exposures. This limitation is especially challenging in MICs, where health outcomes might be more volatile due to prominent external shocks and interventions other than smoke-free regulations. We could not control for some of these factors, such as local conflicts or health-care reforms, because longitudinal country-level data for these variables were not available. We aimed to overcome these challenges by applying the state-of-the-art synthetic control method for multiple intervention units, which reduces the risk that our effect estimates capture merely the effect of a single co-intervention. Nevertheless, we must exercise caution in overinterpreting the findings applied to individual countries. To further assess the confidence of our results, we compared the distribution of legislation effects with that of placebo effects obtained for each control country of each intervention country by fictitiously assuming that smoke-free legislation was implemented there at the same time as in its intervention country. Although the distributions of the legislation and placebo effects overlapped, legislation effects were on average larger than placebo effects. Note that the placebo test does not provide a confidence interval in the traditional sense, it only answers the question of whether or not the estimated effect is large relative to the distribution of placebo effects.[30] To scrutinise our findings, we also ran panel regressions as a sensitivity analysis and found significant effects. Although this sensitivity analysis was useful in strengthening our confidence in the results, this exercise might be subject to the aforementioned limitations of traditional modelling approaches. Another limitation is that we needed to drop predictors for intervention countries when there was no prelegislation data for the predictors. Nevertheless, prelegislation neonatal mortality and infant mortality was always the strongest predictor, and these data were not missing for any intervention country. Finally, we acknowledge that there are limitations in the data sources. When mortality statistics are absent, World Bank estimation is derived from surveys or applying indirect estimations to censuses or survey data, which might affect the comparability of the results across countries. Nevertheless, these data are still the most reliable source on child mortality from LMICs, where otherwise only poor health statistics are available, and the applied World Bank data are often used for international impact evaluation.[33,50]

This research builds on previous studies that were conducted mostly in higher-income settings, which showed significant reductions in perinatal and child TSE and improvements in child health and survival following implementation of comprehensive smoke-free legislation.[12–15,26] The magnitude of our overall legislation effects estimates across all intervention MICs is lower than that of the previous work from selected MICs.[14,15] Nevertheless, our results suggest that a similarly large relative reduction in neonatal and infant deaths can be achieved by comprehensive smoke-free legislation in MICs as in high-income settings, despite the less favourable socioeconomic and environmental backgrounds in MICs.[13] Additionally, the existing findings are consistent with ours in terms of the additional child health benefits of moving from partial to comprehensive smoke-free legislation.[14] Given that 74% of neonatal deaths and 72% of infant deaths in 2018 occurred in MICs, in absolute terms, smoke-free legislation can bring much higher child survival benefits in MICs than in HICs.

An in-depth assessment of local barriers and facilitators is required to explore variation in effectiveness across countries and identify the potential factors that facilitate successful smoke-free legislation in MICs. As the number of countries implementing comprehensive smoke-free legislation increases, further studies should also extend the scope of research to low-income countries (and strengthen the evidence for lower-MICs). Furthermore, other types of tobacco control policies should also be evaluated. For these analyses, alternative types of predictor variables or model specifications might be needed (eg, analysis of the effects of tobacco taxes needs to consider variations in tax structures).[51]

In conclusion, this analysis of 106 MICs, using the synthetic control method, showed evidence for clinically

relevant neonatal and infant survival benefits of comprehensive smoke-free legislation. Although the majority of countries worldwide have implemented partial smoke-free legislation in selected enclosed public places, more than 75% of the global population are still not protected by comprehensive measures as recommended by WHO.[27] The findings of this study provide support for implementing comprehensive smoke-free legislation in MICs, where otherwise Sustainable Development Goal 3.2 might not be achieved.[52,53] Babies should be urgently protected from the harm of TSE before and after birth by entirely eliminating smoking in enclosed public areas and workplaces.

Contributors

JVB obtained the funding for the study. MKR, FJvL, and JVB were involved in designing the study. MKR did the data cleaning and analysis, supervised by FJvL and JVB. All authors interpreted the data. MKR wrote the first draft of the manuscript, which was revised by FJvL, AAL, FTF, CM, AS, and JVB. MKR and JVB had access to and verified the underlying data. All authors read and approved the final manuscript. JVB had final responsibility for the decision to submit for publication.

Declaration of interests

We declare no competing interests.

Data sharing

This study used publicly available data that can be found online at https://data.worldbank.org/.

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