**ORIGINAL ARTICLE** 





# Maternal pregnancy smoking in three Brazilian cities: trends and differences according to education, income, and age

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## Abstract

**Objectives** To estimate and assess pregnancy smoking trends since 1978, according to sociodemographic characteristics, in three Brazilian sites.

**Methods** We used cross-sectional data from the perinatal studies of nine birth cohorts, located in the southeast (Ribeirão Preto—1978/1979, 1994, and 2010), south (Pelotas—1982, 1993, 2004, and 2015), and northeast (São Luís—1997/1998 and 2010) regions of Brazil. We estimated the prevalence of pregnancy smoking at each time point according to age, education, and family income, in each cohort, and evaluated smoking trends.

**Results** We analyzed data of 17,275 women in Ribeirão Preto, 19,819 in Pelotas, and 7753 in São Luís. Smoking decreased by 59% in Ribeirão Preto (p < 0.001), 54% in Pelotas (p < 0.001), and 32% in São Luís (p < 0.001). However, among those with 0–4 years of education, smoking did not change in Ribeirão Preto (p-trend = 0.501) nor São Luís (p = 0.556) and increased in Pelotas (p-trend = 0.003).

**Conclusions** Pregnancy smoking has been declining during the last decades. However, among less-educated women, pregnancy smoking did not change in two sites and increased in one of them.

Keywords Smoke · Pregnancy · Trend · Population-based · Schooling · Income

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# Introduction

There is overwhelming evidence on the short- and longterm negative impact of maternal pregnancy smoking, including intrauterine growth restriction, stillbirth, spontaneous abortion, placenta previa, premature delivery, premature rupture of membranes, sudden infant death, neurodevelopmental and behavioral problems, obesity, hypertension, type 2 diabetes, impaired growth, asthma and wheezing, among others (Horta et al. 1997; George et al. 2006; Bruin et al. 2010; Matijasevich et al. 2011; Zhang et al. 2011; Werhmeister et al. 2015; Banderali et al. 2015).

According to the World Health Organization (WHO), smoking prevalence has been dropping worldwide and Brazil has shown one of the fastest declines. From 1990 to 2015, Brazil had a 55% overall reduction and for that same year (2015) it had one of the lowest rates of smoking (WHO 2015; Reitsma et al. 2017; World Health Organization 2017). National population-based studies have also reported that the prevalence of smoking among Brazilian women has decreased from 27% in 1989 to 11% in 2013, and that the highest drop was in those between 18 and 44 years old (childbearing age) (Instituto Nacional de Câncer (Brasil) 2010; Levy et al. 2013).

Sociodemographic characteristics have shown to be important variables when characterizing smoking trends worldwide. It seems that those less educated or living below the poverty line smoke more and have had a less pronounced decline during the last decades (Jamal et al. 2015), something that has also been observed for pregnancy smoking (Ekblad et al. 2014; Kuntz and Lampert 2016).

On the other hand, evidence from low- and middle-income countries regarding pregnancy smoking trends is scarce. Population-based studies in Pelotas (southern Brazil) have reported a decrease in the prevalence of maternal smoking. It dropped from 35.6% in 1982 to 27.6% in 2004 and 21% in 2015. However, those in the lowest socioeconomic position were lagging (Silveira et al. 2016). Other studies in similar Brazilian settings have reported similar trends and patterns, but they have studied shorter periods, which make any comparison difficult (Dias-Damé and Cesar 2015).

In spite of the decrease in tobacco pregnancy smoking, the proportion of smoking mothers should be considered high, if we take into account the negative consequences of smoking on maternal and offspring health (Horta et al. 1997; George et al. 2006; Bruin et al. 2010; Matijasevich et al. 2011; Zhang et al. 2011; Werhmeister et al. 2015; Banderali et al. 2015). Therefore, from a public health point of view, it is important to evaluate trends of pregnancy smoking, identify those groups that are lagging, and develop more efficient and targeted policies against tobacco use and prevention in pregnancy.

Given the wealth of information on pregnancy and birth from nine birth cohorts from three cities in Brazil, starting back in 1978, the RPS consortium (Ribeirão Preto, Pelotas, and São Luís consortium of birth cohorts) is a privileged source of data for studying what happened to pregnancy smoking in Brazil, in the past 40 years. Therefore, we set up this study to assess the trends of pregnancy smoking in three Brazilian cities, from 1978 to 2015, according to the sociodemographic characteristics of the mothers.

We analyzed trends of maternal pregnancy smoking, in

three Brazilian cities, using cross-sectional data from the

# Methods

## Study design

perinatal studies of nine birth cohorts. Three were from Ribeirão Preto (1978/1979, 1994, and 2010), four from Pelotas (1982, 1993, 2004, and 2015), and two from São Luís (1997/1998 and 2010).

## Participants and procedures

Ribeirão Preto is a southeastern Brazilian city located at 320 km of the city of Sao Paulo, a rich and industrialized region, with a Human-Municipal Development index (measure of well-being that takes into account income, health and education) of 0.626 in 1991 and 0.800 in 2000. From June 1, 1978, to May 31, 1979, 98% of all liveborn singletons delivered at the eight public and private maternity hospitals of the city (n = 6827) were recruited and their mothers interviewed. In 1994 (April 25 to August 25), 1/3 of all births in the year were identified, newborns were and mothers interviewed after delivery recruited. (n = 2846) (Cardoso et al. 2007). During the whole year of 2010, liveborn singletons delivered at the public and private maternity hospitals of the city and their mothers were once again recruited (n = 7702). In all cohorts from Ribeirão Preto, mothers were interviewed on sociodemographic and behavioral characteristics, including maternal age at birth, education (total amount of years the mother attended to school), and family income. Interviews were conducted in the hospitals by trained fieldworkers, as early as possible, normally within the first 36 h after delivery (da Silva et al. 1992; Bettiol et al. 1998; Cardoso et al. 2007).

Pelotas is a southern Brazilian city located near to the Uruguayan border with a Human-Municipal Development index of 0.558 in 1991 and of 0.739 in 2000. In 1982, 1993, 2004, and 2015, all maternity hospitals were visited daily, and the deliveries identified. Those mothers who lived in the urban area of the city were interviewed on demographic, socioeconomic, reproductive, behavioral, careseeking, and morbidity variables. Interviews were conducted by a trained fieldworker, within the first 48 h after delivery, while mothers were still in the hospitals (Victora et al. 2006; Barros et al. 2006; Hallal et al. 2017).

In São Luís, a northeastern Brazilian city, with a Human-Municipal Development index of 0.562 in 1991 and of 0.768 in 2000, two birth cohorts have been carried out. From March 1997 to February 1998 and from January to December 2010, all liveborn singletons born in any maternity hospital in the city which performed more than 100 births per year (10 hospitals) were identified, corresponding to 96.3% of all births in the city, and 2443 liveborn were randomly selected and recruited (1/7 of all births). In 2010, 98.0% of all births were identified and a total of 5166 liveborn were recruited (1/3 of all births). Losses due to refusal or mother's early discharge from hospital accounted for 5.8% of cases in the first and 4.6%

in the second cohort. Perinatal interviews in both cohorts were conducted by trained undergraduate or graduate students, in the first 12–36 h after delivery in the hospitals. Further details on the studies methodologies have been published elsewhere (da Silva et al. 2001, 2015; Cardoso et al. 2007).

#### Measures

In Ribeirão Preto, for the 1978/1979 and 1994 cohorts, information on family income was collected in minimum wages; for the 2010 birth cohort, we asked for the total amount of money earned by all family members during the last month. Regarding smoking, for the 1978/1979 cohort, the mother was asked whether she had smoked during pregnancy and how often; in the 1994 and 2010 cohorts, she was asked whether she smoked during pregnancy (yes/ no) and the number of cigarettes smoked (da Silva et al. 1992; Bettiol et al. 1998; Cardoso et al. 2007).

For Pelotas, we included maternal age at birth, education (completed years of formal education in a school), and family income during the last month. For the 1982 cohort, information on family income was only collected as minimum wages; for all other cohorts, we asked for the total amount of money earned by all family members during the last month. The 2015 cohort started following mothers during pregnancy; however, for this study we only used information from the perinatal study to maintain comparability between cohorts.

In the 1982 Pelotas cohort, mothers were asked about the number of cigarettes they smoked per day (none/1–14/ 15 or more); those who reported smoking at least one cigarette per day were considered as smokers. The other Pelotas cohorts asked directly to the mother whether she smoked during pregnancy (yes/no). Further information on the methodology of these studies has been published elsewhere (Victora et al. 2006; Barros et al. 2006, 2008; Hallal et al. 2017).

In the 1997/1998 São Luís cohort, those mothers who reported smoking at least one cigarette per day during pregnancy were considered as smokers. In 2010, mothers were asked whether they smoked during pregnancy (yes/ no) and the number of cigarettes. Additionally, in both cohorts, we collected information on maternal age at birth (numeric variable), education (total amount of years the mother attended to school), and family income (amount earned during the last month) (Silva et al. 2001, 2015; Cardoso et al. 2007).

To compare all cohorts and sites, we only considered information collected during the perinatal period. Because smoking, our outcome, was assessed using different questions across cohorts and sites, we considered smokers all who reported smoking tobacco during pregnancy (yes/no), regardless of the number of cigarettes and duration. This type of smoking did not include any kind of passive or secondhand smoking.

The categorization of all sociodemographic variables was the same for all sites and cohorts. Income was categorized in tertiles: those who earned the less were in the 1st tertile, and those who earned the most in the 3rd. Education was categorized in 0–4 years of formal education, 5–8, 9–11, 12, or more. Maternal age was categorized in less than 20, 20–29, and 30 or more years of age.

#### **Statistical analysis**

We calculated maternal pregnancy smoking proportions in all cohorts and 95% confidence intervals (CI). We then compared them, within sites, to evaluate how pregnancy smoking changed over time in each city. We also assessed whether these changes were similar or not according to the categories of each of the sociodemographic variables assessed.

In the case of Ribeirão Preto and Pelotas, to assess changes through time, we used the Wilcoxon-type test for trend analyzes. We preferred to use this nonparametric test because in most cases the proportion of change between time points in each site was not constant, and for Ribeirão Preto periods of assessment were not similar; therefore, linearity could not be assumed. Since São Luís only had two perinatal studies (two time points), a trend was not calculated. We used the Chi-squared test for heterogeneity to evaluate whether there was a change in pregnancy smoking from one time point to another and observed whether the proportion of one time point was not included in the CI of the other time point proportion.

We used STATA version 12.1 for the analysis.

## Results

We analyzed 17,275 women in Ribeirão Preto (1978/1979, 1994 and 2010), 19,819 in Pelotas (1982, 1993, 2004 and 2015), and 7753 in São Luís (1997/1998 and 2004). These were the women who had information in each site for at least the smoking variable.

Figure 1 shows that the overall prevalence of pregnancy smoking decreased in all three sites, by 59% (95% CI 56–62%) in Ribeirão Preto from 1978/1979 to 2010 (p < 0.001), by 54% (95% CI 50–57%) in Pelotas from 1982 to 2015 (p < 0.001), and by 32% (95% CI 17–45%) in São Luís from 1997/1998 to 2010 (p < 0.001). However, Pelotas had the highest prevalence and São Luís the lowest, across the studied years, and the difference was higher across sites than within.

**Fig. 1** Total prevalence of pregnancy smoking in the Brazilian cohorts of Ribeirão Preto (1978, 1994, 2010), Pelotas (1982, 1993, 2004, 2015), and São Luís (1997, 2010). *p* Value for trends in Ribeirão Preto (p < 0.001) and Pelotas (p < 0.001) and Chi-squared test of heterogeneity in São Luís (p < 0.001)



In general, maternal age and education increased through the years. The proportion of mothers with 4 or fewer years of education decreased in every site (3.7–12.8 times), while the proportion of mothers with 30 or more years of age increased (Table 1).

Figure 2 shows that the prevalence of pregnancy smoking decreased along time for nearly all groups of maternal education, especially among those with the highest education (12 years or more), 83% (95% CI 78–86%) in Ribeirão Preto (*p* trend < 0.001), 78% (95% CI 73–84%) in Pelotas (*p*-trend < 0.001), and 91% (95% CI 61–98%) in São Luís over the same period. However, among those with 0–4 years of education smoking prevalence did not change in Ribeirão Preto (*p*-trend = 0.501) or São Luís (*p*-trend = 0.556) and increased in Pelotas from 1982 to 2015 (*p*-trend = 0.003), 13% (95% CI 2–23%). In São Luís among mothers with 5–8 years of education, smoking increased from 5.9% in 1997 to 8.7% in 2010 (*p* = 0.014).

With regard to family income, all categories showed a decrease in smoking prevalence; however, in Ribeirão Preto and Pelotas, the top tertile of income showed a reduction of 76% (95% CI 71–80%) and 77% (95% CI 72–81%), respectively, and the lowest tertile, 41% (95% CI 35–47%) and 35% (95% CI 28–41%). For São Luís we observed a similar pattern, however, trend's p values from the highest and lower tertiles were 0.06 and 0.24, respectively (Fig. 2).

Figure 2 shows that in Ribeirão Preto (1978) and Pelotas (1982) the prevalence of smoking was higher among younger mothers (less than 20 years old). However,

through the years, smoking prevalence decreased for all age groups, and in 2010 (Ribeirão Preto) and 2015 (Pelotas), we found no difference in smoking by age (p = 0.093). For São Luís, in 1997, the prevalence of smoking was higher among older mothers (p < 0.001), but in 2010 the highest prevalence was found among the youngest.

# Discussion

In general, the prevalence of pregnancy smoking decreased, and the patterns of reduction were similar for all sites. Despite this, pregnancy smoking remained higher in Pelotas and Ribeirão Preto. The reduction and heterogeneity in the prevalence of maternal pregnancy smoking have also been observed in the general Brazilian population, where the highest prevalence is still observed in southern Brazil (Barros et al. 2011).

Smoking reduction seemed higher among groups of higher income and education. In Ribeirão Preto and Pelotas, the relative smoking reduction in the highest tertile of income was two times the reduction of the lowest tertile. Similarly, in those with 0–4 years of formal education, smoking increased in Pelotas and did not change in the other sites. It is important to mention that our data showed that in all sites education increased, suggesting that those who remain in the lowest categories of education could represent an extremely vulnerable population.

Concerning maternal age, in Ribeirão Preto and Pelotas, in the earlier cohorts (1978/1979 and 1982), women with

Table 1	Sociodemographic characteristics along time in the perinatal studies of the cohorts of Ribeirão Preto (1978, 199	4, 2010), J	Pelotas (198	32
1993, 2	004, 2015), and São Luís (1997, 2010)			

	Ribeirão Preto			Pelotas				São Luís		
	1978/1979 N (%)	1994 N (%)	2010 N (%)	1982 N (%)	1993 N (%)	2004 N (%)	2015 N (%)	1997/1998 N (%)	2010 N (%)	
Maternal education (years)	<i>p</i> < 0.001			<i>p</i> < 0.001			<i>p</i> < 0.001			
0–4	3409 (51.0)	651 (25.0)	301 (4.0)	2002 (33.4)	1466 (28.0)	663 (15.6)	390 (9.1)	437 (17.3)	213 (4.2)	
5–8	1691 (25.3)	1012 (38.8)	1676 (22.0)	2493 (41.6)	2424 (46.3)	1758 (41.5)	1094 (25.6)	1077 (42.6)	1167 (22.8)	
9–11	907 (13.6)	597 (22.9)	3851 (50.5)	657 (11.0)	923 (17.6)	1395 (32.9)	1457 (34.1)	895 (35.4)	2952 (57.7)	
12 or more	681 (10.2)	346 (13.3)	1792 (23.5)	846 (14.1)	427 (8.1)	422 (10.0)	1330 (31.1)	122 (4.8)	785 (15.3)	
Family income (tertiles)	p < 0.001			p < 0.001			p < 0.001			
1	2434 (43.8)	568 (29.6)	2136 (33.7)	1961 (33.2)	2020 (38.5)	1445 (34.1)	1516 (35.5)	1299 (54.9)	1412 (33.6)	
2	1725 (31.0)	602 (31.4)	2086 (32.9)	1978 (33.5)	2257 (43.1)	1400 (33.0)	1338 (31.3)	607 (25.7)	1384 (33.0)	
3	1404 (25.2)	750 (39.1)	2120 (33.4)	1963 (33.3)	963 (18.4)	1393 (32.9)	1416 (33.2)	458 (19.4)	1404 (33.4)	
Maternal age (years)	p < 0.001			p < 0.001			p < 0.001			
< 20	929 (13.9)	466 (17.9)	972 (12.8)	921 (15.4)	915 (17.5)	811 (19.1)	622 (14.6)	742 (29.3)	943 (18.4)	
20–29	4141 (61.9)	1439 (55.2)	3952 (51.9)	3481 (58.0)	2797 (53.4)	2116 (49.9)	2015 (47.2)	1472 (58.2)	2977 (58.2)	
30 or more	1618 (24.2)	701 (26.9)	2696 (35.4)	1596 (26.6)	1528 (29.2)	1311 (30.9)	1634 (38.3)	317 (12.5)	1197 (23.4)	
Total	6688	2606	7620	5998	5240	4238	4271	2531	5117	

p values for heterogeneity in each site through the studied years

less than 20 years of age smoked between 60 and 90% more than those older than 30 years. Worldwide, a great percentage of countries, including Brazil, achieved greater rates of decline in smoking prevalence from 1990 to 2005, probably due to the implementation of strong anti-tobacco policies (Levy et al. 2012; Reitsma et al. 2017; World Health Organization 2017). However, rates have been declining since before, and a study using data from 185 countries showed that from 1980 to 2012, those with less than 20 years have shown the biggest reduction per year (Ng et al. 2014). Our data show that smoking during the late 1970s and early 1980s was more common among mothers under the age of 20. During the 1990s, that same generation of mothers would be in the category of less than 30 years old but might have continued with the same smoking behavior, suggesting that the fall in pregnancy smoking was driven by new generations of mothers. In addition, data from São Luís show that in 1997 mothers with more than 30 years of age smoked more and that in 2010 there were no more age differences.

It is important to mention that we have not presented confidence intervals for each specific time point in Fig. 2 since we considered that they might have made it too polluted and hard to read. However, we did calculate them and used them for specific comparisons between only two time points. This was especially important for São Luís since, as explained before, it only had two time points to compare and trends were not possible to calculate. Visual inspection of proportions and CI in this site did not change the interpretation of the results of the Chi-squared test. Therefore, we preferred to show the *p* values of the latter test rather than the CI for each proportion in each time point by each sociodemographic characteristic. The CI would only have been important for São Luís to evaluated change over time, since in a trend analysis, like Pelotas and Ribeirão Preto, even when in two time points one of the proportions is included in the CI of other proportion, the total trend could still be real and not due to chance.

Worldwide, the prevalence of smoking has decreased both among males and females, and in general, this decline has been higher among those with a higher socioeconomic



**◄ Fig. 2** Prevalence of pregnancy smoking according to maternal sociodemographic characteristics at birth, in the Brazilian cohorts of Ribeirão Preto (1978, 1994, 2010), Pelotas (1982, 1993, 2004, 2015), and São Luís (1997, 2010). a According to maternal education (number of years of education). p values for trends in Ribeirão Preto (0-4 years p = 0.501, 5-8 years p < 0.001, 9-11 years p < 0.001, $\geq$  12 years p < 0.001) and Pelotas (0-4 years p = 0.003, 5-8 years p < 0.001, 9–11 years p < 0.001,  $\geq 12$  years p < 0.001); and Chisquared test of heterogeneity in São Luís (0–4 years p = 0.553, 5-8 years p = 0.014, 9-11 years p = 0.343,  $\geq 12$  years p < 0.001). **b** According to the tertile of family income at birth. *p* values for trends in Ribeirão Preto (1st tertile p < 0.001, 2nd tertile p < 0.001, 3rd tertile p < 0.001) and Pelotas (1st tertile p < 0.001, 2nd tertile p < 0.001, 3rd tertile p < 0.001) and Chi-squared test of heterogeneity in São Luís (1st tertile p = 0.059, 2nd tertile p = 0.005, 3rd tertile p = 0.224). **c** According to maternal age. p values for trends in Ribeirão Preto. (< 20 years p < 0.001, 20–29 years p < 0.001,  $\ge 30$ years p < 0.001) and Pelotas (< 20 years p < 0.001, 20–29 years  $p < 0.001, \ge 30$  years p < 0.001) and Chi-squared test of heterogeneity in São Luís (< 20 years p = 0.775, 20–29 years p = 0.058,  $\geq$  30 years p < 0.001)

status. Therefore, the burden of smoking remains higher among the poorest (Instituto Nacional de Câncer (Brasil) 2010; WHO 2015; World Health Organization 2017). The reduction in the proportion of mothers who smoke during pregnancy could be a consequence of a drop in general tobacco use since it apparently follows the same patterns.

Most literature regarding trends of pregnancy smoking is from high-income countries, and in periods of less than 20 years, which are even shorter in studies published in Brazil. However, it is consistent across studies that the reduction is driven by women with higher socioeconomic status (Mohsin et al. 2011; Ekblad et al. 2014; Dias-Damé and Cesar 2015; Kuntz and Lampert 2016).

A study from southern Brazil showed that pregnancy smoking decreased from 22% in 2007 to 18% in 2013, and, similarly to what we found, this reduction was mainly driven by women from high socioeconomic status (Dias-Damé and Cesar 2015). Studies from other countries have found similar patterns. For example, in Australia (1994–2007), the prevalence of pregnancy smoking in New South Wales declined from 22.1 to 13.5% but the largest decrease was among the highest socioeconomic group (67.9% decline) (Mohsin et al. 2011).

Inequalities in health are of great concern worldwide, and here we might be in front of what has been called the inverse equity hypothesis. It proposes that it is the wealthier segments of a population who would initially adopt newly introduced health interventions, increasing absolute inequalities in health, leaving those with a higher vulnerability lagging. Recent research has shown this hypothesis to be true for inequalities in population coverage for institutional deliveries (Victora et al. 2018), and this might also be the case for smoking policies. Brazil provides an outstanding public health success story in reducing deaths due to smoking and serves as a model for other low- and middle-income nations. However, most of the data and estimations on how anti-tobacco policies have reduced or prevented deaths do not include maternal pregnancy smoking (Levy et al. 2012). Surprisingly, no specific big public health intervention has been done in Brazil for pregnancy smoking prevention and its reduction has been practically taken for granted, a consequence of the smoking reduction in the general population. It has indeed decreased; however, for some groups it is still stable or has even increased.

This is something of real concern in terms of public health since, as mentioned before, those who are in these groups might be an extremely vulnerable population which newborns are at even a higher risk of developing many different health problems due to the harmful consequences of tobacco use during pregnancy and will have even more difficulties in treating them or preventing long-term effects and consequences.

Regarding the study limitations, we should point out that information on number of cigarettes smoked was available for most of these cohorts. However, how the information was collected across sites and cohorts was not similar. Therefore, comparisons, even within sites, would have been difficult or probably misleading. The smoking intensity would have given us a better understanding of the magnitude of the problem and how it has changed over time. Sadly, this was not possible with the information we had.

Some studies have shown that there is a considerable amount of women (around 40%) who quit smoking specifically during pregnancy and that these quitting percentages have been rising (Halal et al. 1993; Colman and Joyce 2003). In our study, we were not able to evaluate this since we did not have information on smoking during the whole pregnancy or evaluated "quitting pregnancy smoking" for some of the cohorts. We did not have information on secondhand or passive smoking either.

On the other hand, questions regarding ever smoking during pregnancy were similar across cohorts, which made our comparison strong. All cohorts were population-based, and losses were less than 5%, therefore selection bias is unlikely. Most of the studies on trends of pregnancy smoking are from high-income settings and use periods of less than 20 years, which are even shorter in low-middleincome settings. Our study is based on unique data from three different sites, with different contexts and scenarios, especially in terms of socioeconomic development, and has evaluated periods of more than 30 years in two of the three sites. We used simple and comparable data across the years, including income.

# Conclusions and public health implications

Finally, in this study, we have analyzed data from more than 44,000 individuals across different sites in Brazil and shown that pregnancy smoking has been declining for the last three to four decades. However, while this reduction seems to be higher in the wealthiest, among less-educated populations pregnancy smoking has not changed, and in the southern region might be increasing.

Pregnancy smoking trends seem to be following general population patterns. However, it is still increasing or at least not decreasing in some vulnerable groups. Future research should focus on the predictors of pregnancy smoking in these populations and most importantly in the development of effective and efficient interventions to reduce tobacco use and prevent pregnancy smoking in the most vulnerable populations. They are most likely not benefiting from current anti-tobacco public health policies. Therefore, we might need to reinvent some of the current anti-tobacco strategies being used in the general public to access those with the highest risk of smoking during pregnancy.

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## **Compliance with ethical standards**

**Conflict of interest** The authors declare that they have no conflict of interests.

Ethics approval and consent to participate The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. For all cohorts, written informed consent was required to participate. In Pelotas, perinatal studies were approved by the ethics committee of the Federal University of Pelotas, in Ribeirão Preto by the ethics committee from the "Hospital Das Clínicas" of the Medical School of Ribeirão Preto, and in São Luíz by the Research Ethics Committee of the University Hospital of the Federal University of Maranhão.

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