Pregnancy outcomes in Italy during COVID-19 pandemic: a population-based cohort study.

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Abstract

Objective. To compare the estimates of preterm birth (PTB; 22-36 weeks gestational age, GA) and stillbirth rates during COVID-19 pandemic in Italy with those recorded in the three previous years. Design. A population-based cohort study of liveborn and stillborn infants was conducted using data from Regional Health Systems and comparing the pandemic period (March 1st, 2020-March 31st, 2021, N= 362,129) to an historical period (January 2017- February 2020, N=1,117,172). The cohort covered 84.3% of the births in Italy. Methods. Logistic regressions were run in each Region and meta-analyses were performed centrally. We used an interrupted time series regression analysis to study the trend of preterm births from 2017 to 2021. Main Outcome Measures. The primary outcomes were PTB and stillbirths. Secondary outcomes were late PTB (32-36 weeks' GA), very PTB (<32 weeks' GA), and extreme PTB (<28 weeks' GA), overall and stratified into singleton and multiples. Results. The pandemic period compared with the historical one was associated with a reduced risk for PTB (Odds Ratio: 0.90;

95% Confidence Interval, CI: 0.87, 0.93), late PTB (0.91; 0.87, 0.94), very PTB (0.87; 0.84, 0.91), and extreme PTB (0.88; 0.82, 0.94). In multiples, point estimates were not very different, but had wider CIs. No association was found for stillbirths (1.01; 0.90, 1.13). A linear decreasing trend in PTB rate was present in the historical period, with a further reduction after the lockdown. Conclusions We demonstrated a decrease in PTB rate after the introduction of COVID-19 restriction measures, without an increase in stillbirths.

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Running title: COVID- 19 pandemic and pregnancy outcomes in Italy

Abstract

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Methods . Logistic regressions were run in each Region and meta-analyses were performed centrally. We used an interrupted time series regression analysis to study the trend of preterm births from 2017 to 2021.

Main Outcome Measures. The primary outcomes were PTB and stillbirths. Secondary outcomes were late PTB (32-36 weeks' GA), very PTB (<32 weeks' GA), and extreme PTB (<28 weeks' GA), overall and stratified into singleton and multiples.

Results. The pandemic period compared with the historical one was associated with a reduced risk for PTB (Odds Ratio: 0.90; 95% Confidence Interval, CI: 0.87, 0.93), late PTB (0.91; 0.87, 0.94), very PTB (0.87; 0.84, 0.91), and extreme PTB (0.88; 0.82, 0.94). In multiples, point estimates were not very different, but had wider CIs. No association was found for stillbirths (1.01; 0.90, 1.13). A linear decreasing trend in PTB rate was present in the historical period, with a further reduction after the lockdown.

Conclusions

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Tweetable abstract

We show a decrease in preterm birth rates during COVID-19 pandemics in Italy and no increase in stillbirths.

Introduction

Soon after the onset of the COVID-19 pandemic, several reports showed an increased risk of severe illness in pregnant women with SARS-CoV-2 compared with those non-pregnant, and adverse pregnancy outcomes including preterm birth.[1] On the other hand, a more recent Italian study showed that most infected pregnant women and newborns had good outcomes.[2] Recently, the Euro-Peristat Research Network[3] raised concern about the fact that one major gap in assessing the real effects of the pandemic on maternal and child health was the limited availability of comprehensive population-based routine data.

Research has also accumulated on the effects of the pandemic on the general population of pregnant women and their infants, possibly due to mitigation strategies and changes in women everyday life. During the early months of the pandemic, a reduced preterm birth (PTB) rate, in comparison with that in the previous years, was recorded in Denmark,[4] in one hospital in Ireland,[5] and in one Italian Region,[6] where also an increase in stillbirths was observed. Another study, performed in a single hospital in London, reported only an increase in stillbirths but not in PTB rates.[7] These reports were based on relatively small samples, and limited, especially for stillbirths, also by a possible change in referral patterns of pregnant women.

A first systematic review and meta-analysis of 31 studies published until January 8th 2021 addressing the indirect effects of the pandemic on perinatal outcomes confirmed a slight reduction in PTB (< 37 weeks gestational age, GA) in high-income but not in low-income countries and, vice versa, an increase in stillbirths in low-income countries only.[8]

A more recent systematic review and meta-analysis of 44 studies[9] found that the odds of PTB during the pandemic period were significantly reduced in single-centre/single-health-authority studies, while there was no difference in larger studies based on regional/national data. No difference was documented in the rate of stillbirths in the pandemic period compared to the non-pandemic one, though these conclusions might be hampered, according to the authors, by more limited data. The review once again concludes that there is still a need of studies in bigger countries largely affected by COVID-19 pandemic like India, Brazil, UK and Italy and based on national registries, to investigate the impact of the pandemic on perinatal health at a population level.

The aim of the present study was to provide national population-based estimates of the PTB and stillbirth rates during the pandemic period compared to a historical period. In order to account for the natural variation in PTB over time, and the abrupt implementation of public health measures and disruption of routines of care, we also analysed the temporal trend in monthly incidence of PTB before and after the implementation of mitigation measures.

Methods

We analysed data from the birth certificate (CeDAP), which is filled in at birth for each delivery.

Ten Italian Regions and one Autonomous Province (Piedmont, Lombardy, Veneto, Emilia-Romagna, Friuli-Venezia Giulia, and the Province of Trento in Northern Italy; Tuscany and Lazio in Central Italy; Apulia, Campania, and Sicily in Southern Italy) agreed to participate. These Regions cover 84.3% of all the births in Italy.[10]

We defined March 1st, 2020 - March 31st, 2021 as the pandemic period: this time covered the first two waves of COVID-19 in Italy, corresponding to several restrictions measures. The historical period included the three previous years, from January 2017 to February 2020. For the Campania Region the comparison period started from January 2018 because 2017 data were not available.

The primary outcomes were PTB (live births between 22 and 36 weeks' GA) and stillbirths, both in singleton and multiple pregnancies. Secondary outcomes were late PTB (32-36 weeks' GA), very PTB (<32 weeks' GA), and extremely PTB (<28 weeks' GA). GA at birth was calculated in completed weeks.

We used univariable and multivariable logistic regression models to examine the association between birth period (pandemic vs historical) and percentage of preterm births estimating odds ratios (ORs) of each outcome. Adjusted analysis included the following variables: maternal country of birth (foreigner vs Italian), maternal age at index birth (continuous), parity (yes/no), maternal education (none or elementary school or primary school diploma; secondary school diploma; University degree), maternal employment (yes/no), pregnancy conceived with assisted reproductive technology (ART, yes/no), sex of the child (female/male). Most of these variables could be in fact considered as mediators or effect modifiers rather than true confounders:[11] i.e. mitigation strategies due to COVID-19 could have influenced maternal lifestyle in pregnancy in a different way according to mother's origin, age, education, employment, and parity. Pregnancy conceived with ART, on the other hand, is an intermediate variable. We therefore chose as the main analysis the unadjusted one. In the adjusted analysis the Lazio Region was not considered because the information on ART was not available for the whole study period.

We further analysed separately singletons and multiples, which could be differently affected by the pandemic restrictions.

Due to privacy regulations, individual data were not shared, and logistic regression analyses were run in each Region. A meta-analysis was performed centrally at the Regional Health Agency of Tuscany.

To estimate the heterogeneity of effects in different Regions, the I^2 index was calculated.[12] When there was no evidence of heterogeneity, the pooled estimate of the effect (OR) was calculated using the inverse variance method (fixed effect model); otherwise, the DerSimonian–Laird weights (random effects model) were used.[13] Forest plots were provided to graphically illustrate the effect size estimates for each study as well as the pooled estimate.

We also studied the monthly trend of PTB rates from 2017 to the end of March 2021 using an interrupted time series regression analysis,[14] with March 1st 2020 as the date of interruption. In this quasi-experimental technique, one looks for a sharp change in outcomes following public health interventions (the interruption corresponding to the implementation date of COVID-19 mitigation measures). After a visual check of data points, we carried out a log-linear regression analysis of the (log of the) monthly prevalence of PTB over calendar months and introduced a term estimating the level of discontinuity (gap) on March 1st 2020 [at month 38/39], i.e. at the "interruption". As the prevalence of PTB showed a seasonal trend, we modelled it using Fourier terms (2 pairs of sine and cosine functions).[14] In addition, we used the robust Newey-West standard errors for effect estimates to account for residual autocorrelation in the data ("newey" command in Stata).

In all models, we also tested whether the slope had been altered by mitigation measures by running a model including a statistical interaction between slope and period (historical vs pandemic period). As there was no evidence of interaction and the models without interaction had better fit to the data (lower residual MSE), we always used models without interaction.

As a further check of the overall effect of mitigation measures, we carried out a regression of the log of the monthly frequency of PTB over calendar months until February 2020 (just before the pandemic), correcting for seasonal trend and autocorrelation as above. We then computed the expected frequencies for the months following the lockdown (i.e., under the counterfactual scenario of no intervention), and compared them to actual frequencies.

All the analyses were performed using STATA version 15.1 (StataCorp LP, College Station, TX, USA).

Results

A total of 362,129 live births (351,139 singletons and 10,990 multiples) occurred during the pandemic period, and 1,117,172 live births (1,079,259 singletons and 37,913 multiples) during the historical period. The number and percentage of PTB in different categories of GA and of stillbirths in the two periods are presented in Table 1, together with unadjusted and adjusted overall OR of adverse perinatal outcomes based on meta-analysis. The pandemic period compared with the historical period was associated with a reduced risk for PTB (< 37 weeks' GA), late PTB (32-36 weeks' GA), very PTB (< 32 weeks' GA), and extremely PTB (< 28 weeks' GA), with very similar estimates in unadjusted and adjusted analyses. No association was instead found for stillbirths. Forest plots for unadjusted estimates are reported in Figures 1a-1d (for liveborn PTB) and S Figure 1 (for stillbirths), while those for adjusted estimates are reported in S Figures 2-6.

Singletons contributed 72.9% of all PTB, and in these the associations remained very similar to those in the whole population of neonates; for PTB the unadjusted OR was 0.92 [95% CI: 0.89; 0.95], for late PTB: 0.92 [95% CI: 0.89; 0.96], for very PTB: 0.88 [95% CI 0.84; 0.92], and for extreme PTB: 0.92 [95% CI: 0.85;1.00]. (S Figures 7-14)

Multiples represented 3.3% of all births and contributed 27.1% of all PTB; in all classes of PTB point estimates were not very different from those of singletons, but with wider CIs which encompassed the null value: PTB unadjusted OR: 0.93 [95% CI: 0.84;1.03]; late PTB: 0.94 [95% CI: 0.84; 1.04], very PTB: 0.90 [95% CI: 0.78; 1.4], and extreme PTB: 0.77 [95% CI: 0.58; 1.01]. (S Figures 15-22).

The interrupted time series regression analyzed 38 months before lockdown and 13 months after it, showing a decreasing trend in the overall percentage of PTB in the three years before the pandemic superimposed to a biannual seasonal oscillation. The de-seasonalized trend (estimated relative change of PTB percentage) was -0.17% per month, 95% CI: -0.26%; -0.09%. A further reduction of PTB prevalence (estimated relative

change -4.2% compared with the previous period, 95%CI: -8.4%; 0.0%) after lockdown and other mitigation strategies was demonstrated (Figure 2), in addition to the continuing decreasing trend.

The comparison between the counterfactual scenario and actual trend after lockdown confirmed the drop in PTB prevalence (estimated mean decrease = -3.8%, 95%CI: -7.5%, -0.1%), which was particularly marked in the last months of 2020. (Figure S 23)

Similar results were found for the subclass of late PTB (trend in frequency before the pandemic: -0.14% per month, 95% CI: -0.22%; -0.06%; further change after lockdown: -4.3%, 95%CI: -8.4%; -2.9%), but not for very or extremely PTB, which had much lower frequencies and more scattered data (S Figures 24-26).

Interrupted time series analysis in singletons mirrored the results of the whole population (Figures S27-S30); no interruption was detected for multiple births (data not shown).

Discussion

Main findings

In this study covering 84.3 % of the live births in Italy, we found that being born during COVID-19 pandemics was associated with a reduction of the risk of PTB, as a whole and in all subgroups, compared with the years before. On the contrary, stillbirth rate was not affected. Even though in Italy a decreasing trend in the overall prevalence of PTB was already present in the historical period (from 2017 onwards), we were able to show a further reduction once the lockdown and mitigation strategies were enforced. The reduction was particularly evident for all the Regions and all GA classes in the last months of 2020.

Strengths and limitations

Our population-based study, together with the recent one of Gurol-Urganci et al.[15] in UK, is the largest ever done as regards both the number of PTB and stillbirths during the COVID-19 pandemic. This is due not only to the fact that both Italy and UK have a larger number of births in comparison to those in northern European countries which previously published nationwide results like Denmark,[4]The Netherlands,[16] and Sweden,[17] but also to the wider time span considered as pandemic period.

The longer pandemic period considered, besides increasing the sample size, made it possible to study women who were exposed to mitigation strategies during their whole pregnancy.

The large sample size allowed us to study the different categories of PTB and to analyze separately singletons and multiples, though the relative low number of multiple pregnancies precludes definitive answers in this subgroup.

As a further limitation, the dataset used does not contain information on lifestyle and social behaviors of pregnant women, which precludes an analysis of possible important and widespread causes for the observed decrease of PTB among the general population.

In estimating the total effect of COVID-19 pandemic on pregnancy outcomes we did not consider the effect of the SARS-CoV2 infection on pregnant women – for which the data were not available. The COVID-19 infection is however known to increase PTB[1,2] so that excluding COVID-19-positive women would probably yield further reduced PTB rates.

Finally, our study was a retrospective one using routinely collected data, which are prone to registration errors, although data are filled in by midwifes and doctors soon after birth and are annually checked for the CeDAP report from the Ministry of Health.

Interpretation

Our data on a reduction in PTB concomitant with the COVID-19 pandemic period are concordant with those of two recent national-based studies published after the systematic review and meta-analysis of Yang and coll.,[9] which concluded that a reduction in the odds of PTB was observed only in single-center studies. The

first of these studies was conducted in Israel,[18] on birth data from the Israel national newborn screening program and showed a 10% decline in all preterm deliveries during the COVID-19 pandemic national lockdown period. The second one, in UK,[15] used administrative hospital records and found a slightly lower frequency of preterm birth rates (from 6.1% to 6.0%) during the entire pandemic period compared to pre-lockdown.

In our study, we considered events (PTB and stillbirths) up to the end of March 2021, when most mitigation strategies stopped in Italy. Most of the previous nationwide studies in Europe[4,16,17] and large regional studies in other countries,[19-21] were instead restricted to 2020- mostly to the first months of the year. The larger time span considered allowed us to also study women who experienced changes in care and social activities for most of or all the pregnancy. This is not trivial, as multiple factors at different times during pregnancy might have had an impact on the rate of preterm deliveries. Though there are not, so far, studies available on this interesting topic, we can speculate in accordance with others[15,18] that lifestyle and behavior (more rest, working from home, reduced exposure to other respiratory pathogens), might have contributed to PTB reduction. Other possible pandemic-related changes, which are known to impact on PTB, might have been the adoption of a different and healthier diet,[22] and diminished exposure to air pollution.[23]

Finally, the large reduction in activity of Medical Assisted Reproduction services at the beginning of the pandemic period (end of February-April 2020)[24] could be responsible of the marked drop in PTB prevalence we observed in the last months of 2020.

In univariable and multivariable logistic analyses we found an inverse association between being born in the pandemic period and being late PTB, but also very PTB and extremely PTB. With the interrupted time series regression analysis we were able to demonstrate a reduction in the frequency of PTB after the lockdown only for the subgroup of late PTB, and not for the other subgroups which had much lower frequencies and thus more scattered data. Similar results were reported with this type of analysis by Been et al.[16] in the Netherlands and by Bian et al.[25] in China, while in Canada Shah et al.[20] did not find any significant change either in the rates of all PTB or in the subgroups.

We also analyzed separately singletons and multiples; as expected for singletons, who constituted 72.9% of all PTB, we found results very similar to those of the total population, while for multiples we probably had a lower power to reach conclusive results. In detail, for multiples, all point estimates were very similar to those of singletons and below 1, indicating a reduction in PTB during the pandemic, but the CIs in the logistic analyses were wide, and encompassing the null value, especially for very preterm and extremely preterm infants. No data are available in the literature on the pattern of preterm multiples during the COVID-19 pandemic in comparison to previous years. These data would have been interesting, considering that PTB is largely represented in multiple pregnancies (in our data 61.7% of all multiples are born before 37 weeks' GA) which are in turn associated with assisted conception which possibly decreased during the COVID-19 period. A sub analysis on multiples pregnancies would probably require an international collaboration to have larger sample sizes.

Finally, though we elected as the main analysis the unadjusted one, because we wanted to abstain to correct for variables which could not be considered "true" confounder, our results were unchanged after adjustment for many covariates considered in previous studies like maternal ethnicity /country of birth, socioeconomic background/income/ education, maternal age, parity, and pregnancy conceived with ART.[15,17,19,]

Conclusions

We demonstrated a decrease in the rate of PTB after implementation of measures for COVID-19 mitigation in Italy, without an increase in stillbirths. Our results are in line with those obtained in other developed countries and, above all, in many European countries, where both COVID 19 restrictions and women lifestyle are more similar to those in Italy.

Finally, a lesson to be learned from the decrease in PTB rate seen in many countries during the pandemic is the possible importance of lifestyle and environmental aspects related to the occurrence of pregnancies ending preterm. The pandemic period and its restriction measures could therefore represent a large "natural

experiment" to explore the prevention of preterm birth, one of the most important goals encouraged by WHO.[26]

Disclosure of interests

None declared.

Contribution to authorship

FR conceived the study, provided overall guidance, drafted the article and reviewed the final version. MP and MP conducted the centralized statistical analysis, assisted with data collection, collaborated in drafting the article and reviewed the final version. SB, LG

and AN collaborated to statistical analysis, collaborated in drafting the article and reviewed the final version. FZ supervised, collaborated in drafting the article and reviewed the final version. PB, SC, SF, MG, EP, EP, RP, EET, LVDP: supervised, conducted Regional statistical analyses, collaborated in drafting the article and reviewed the final version. EC, DF, OL, MM, AP, RR, AS: supervised, assisted with Regional statistical analysis, collaborated in drafting the article and reviewed the final version All authors have read and agreed to the published version of the article.

Ethics approval

This study used routinely collected administrative hospital data collected in the Certificato di assistenza al parto (CeDAP). CeDAP is mandatory by law and is run by the Regional Health Systems which can use personal data without individual consent to evaluate service provision and performance. (Italian Ministry of Health. Decree July 16, 2001. [https://www.gazzettaufficiale.it/eli/id/2001/09/19/001G0405/sg]

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Table 1. Prevalence of preterm live births and stillbirths in the pandemic period and in the historical period and the overall relative odds of adverse perinatal outcomes during the pandemic vs the historical period, based on meta-analysis

	Births, N (%)	**Births, N (%)**	**OR (95% CI)**	**OR (95% CI)**
Outcome	**Pandemic period**	**Historical period**	**Unadjusted**	**Adjusted[a]**
PTB	25,550 (7.06)	85,947 (7.69)	0.90 (0.87;0.93)	0.91 (0.88;0.95)
Late PTB	22,463 (6.2)	75,047 (6.72)	0.91 (0.87;0.94)	0.92 (0.89;0.95)
Very PTB	3,087 (0.85)	10,900 (0.98)	0.87 (0.84;0.91)	0.87 (0.83;0.91)
Extreme PTB	999 (0.28)	3,504 (0.31)	0.88 (0.82;0.94)	0.88 (0.82;0.95)
Stillbirths	960 (0.26)	3,004 (0.27)	1.01 (0.90;1.13)	0.96 (0.89;1.04)

PTB= preterm birth (< 37 weeks' gestational age, GA); Late PTB (32-36 weeks' GA); Very PTB (<32 weeks' GA); extreme PTB (<28 weeks' GA); [a] = adjusted analysis included the following variables: maternal country of birth, maternal age at index birth, parity, maternal educational degree, maternal employment, pregnancy conceived with assisted reproductive technology, sex of the child. Observation with missing variables were excluded from the model. The Lazio Region is not included in adjusted analyses.

Figure legends

Figure 1: Forest plot for odds of liveborn preterm birth in pandemic vs historical period in the studied Regions. Unadjusted analysis.

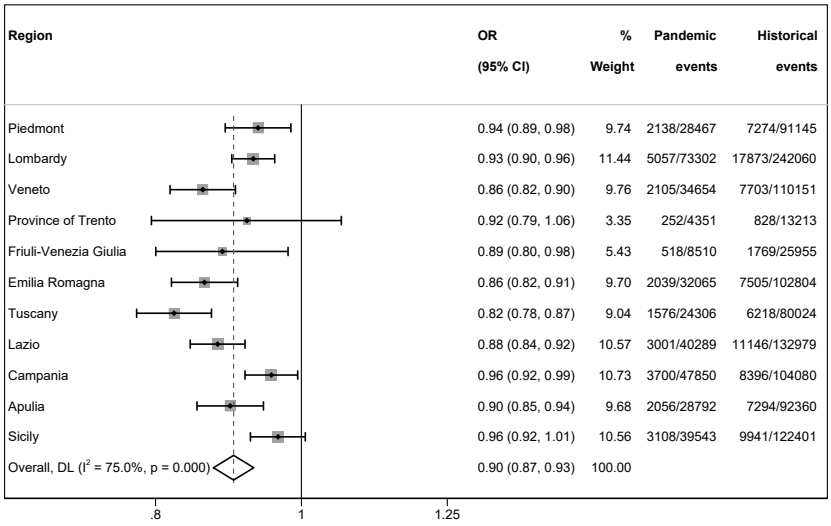
Panel a: preterm birth - PTB (< 37 weeks' GA); panel b: late PTB (32-36 weeks' GA); panel c: very PTB (< 32 weeks' GA); panel d: extremely PTB (< 28 weeks' GA)

Cohort-specific and overall OR and 95% CI are shown; I-squared: percentage of between-studies heterogeneity and relative P value; % Weight: set of weights attributed to each cohort; pandemic and historical events: number of preterm births over total live births in the 2 periods

Figure 2. Interrupted time series regression. Each dot represents the average monthly frequency of liveborn preterm births (< 37 weeks' GA) over total births. Time starts at January 1st 2017. Solid line: predicted

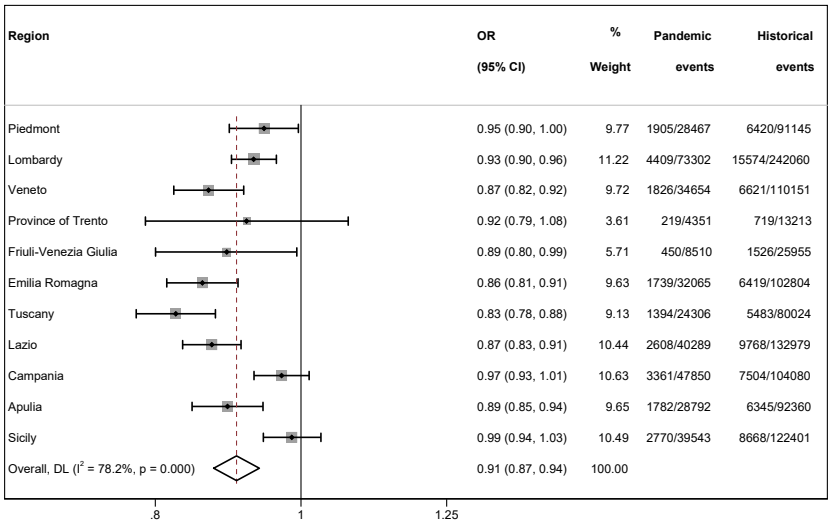
trend based on the seasonally adjusted regression model. Dashed line: de-seasonalized trend. The date of implementation of mitigation measures (March 1st 2020) is shown as a vertical line.

a



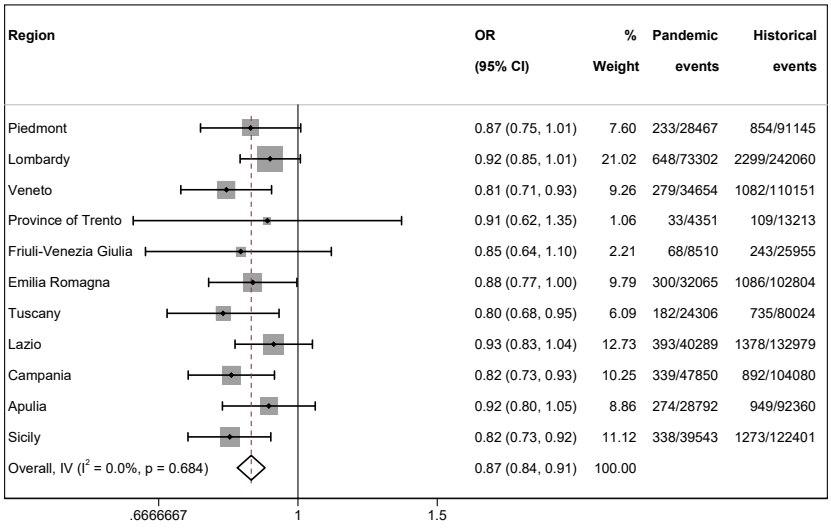
NOTE: Weights are from random-effects model

b



NOTE: Weights are from random-effects model

c



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