Analyzing the influence of COVID-19 on influenza activity in Fujian Province (2020-2023): A regression discontinuity study

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Author contributions
Hongjin Li conceptualized the study, supervised all research phases, administered project resources, developed the methodology, curated and validated surveillance data, performed formal statistical analyses, wrote the original draft, reviewed and edited subsequent versions, and secured funding. Yanhua Zhang processed and managed research datasets. Yuwei Weng participated in manuscript writing and editing.

Competing interests
The authors declare no conflicts of interest.

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Abbreviations
ILI, influenza-like illness; SARS-CoV-2, syndrome coronavirus; RD, regression discontinuity; IVR, Immunization Vaccine Response; CI,confidence interval.

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Abstract

Background: The COVID-1's impact on influenza activity is of interest to inform future flu prevention and control strategies. Our study aim to examine COVID-19's effects on influenza in Fujian Province, China, using a regression discontinuity design. **Methods:** We utilized influenza-like illness (ILI) percentage as an indicator of influenza activity, with data from all sentinel hospitals between Week 4, 2020, and Week 51, 2023. The data is divided into two groups: the COVID-19 epidemic period and the post-epidemic period. Statistical analysis was performed with R software using robust RD design methods to account for potential confounders including seasonality, temperature, and influenza vaccination rates. **Results:** There was a discernible increase in the ILI percentage during the post-epidemic period. The robustness of the findings was confirmed with various RD design bandwidth selection methods and placebo tests, with certwo bandwidth providing the largest estimated effect size: a 14.6-percentage-point increase in the ILI percentage ($\beta = 0.146$; 95% CI: 0.096–0.196). Sensitivity analyses and adjustments for confounders consistently pointed to an increased ILI percentage during the post-epidemic period compared to the epidemic period. **Conclusion:** The 14.6 percentage-point increase in the ILI percentage in Fujian Province, China, after the end of the COVID-19 pandemic suggests that there may be a need to re-evaluate and possibly enhance public health measures to control influenza transmission. Further research is needed to fully understand the factors contributing to this rise and to assess the ongoing impacts of post-pandemic behavioral changes.

Keywords: COVID-19; influenza-like illness; regression discontinuity design; influenza

Introduction

The COVID-19 pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), emerged in December 2019 and rapidly spread globally [1]. To curb the spread of COVID-19, Fujian Province, located on the east coast of China with a population of over 41.8 million people, initiated a level I provincial public health emergency response on January 24, 2020. The province implemented measures to control COVID-19 according to the national guidelines that classified it as a Class B infectious disease managed under Class A measures [2]. Subsequently, the province implemented COVID-19 prevention and control measures in accordance with national requirements.

Research from China, South Korea, and Thailand has shown that during the implementation of public interventions and control measures to combat COVID-19, there was a significant reduction in seasonal influenza activity [3–5]. These studies indicate that the control measures implemented may not only effectively controlled the transmission of COVID-19 but also potentially provided additional protection against the transmission of seasonal influenza. Assessing the impact of COVID-19 prevention and control policies on influenza is of significant public health importance, as influenza is a globally significant public health issue, imposing a heavy disease burden on countries [6]. It is estimated that there are 291, 243–645, 832 deaths worldwide each year related to seasonal influenza [7].

The percentage of influenza-like cases is an important public health indicator for measuring the level of influenza prevalence and the overall disease burden [8–10]. Previous studies have indicated a potential association between COVID-19 control policies and a decrease in the percentage of influenza-like cases [3, 11]. In different stages or fluctuations of the COVID-19 pandemic, authorities in charge of prevention and control adjust the policies to respond to the situation [12]. China took proactive measures to optimize COVID-19 prevention and control measures on December 7, 2022. Following up on December 26, 2022, China transitioned its response to the COVID-19 outbreak from a Class B infectious disease under Class A controls to a standard Class B management protocol. This shift may suggest a possible change in the COVID-19 event. However, to the best of our knowledge, there is few research examining the impact of the COVID-19 event fluctuations on influenza activity. The regression discontinuity (RD) design is a quasi-experimental methodology specifically designed to mitigate confounding bias when evaluating events, treatments, and interventions that rely on a cutoff rule or threshold [13]. Therefore, we have designed a regression discontinuity study to explore the impact of the COVID-19 event fluctuations on the percentage of influenza-like cases in Fujian Province from February 2020 to December 2023.

Materials and methods

Research design

To investigate the impact of the COVID-19 event variations on the influenza activity, a RD design approach was employed. Previous studies have indicated that the percentage of influenza-like cases is a critical public health indicator for assessing the level of influenza activity [8–10]. In our study, we have chosen influenza-like illness (ILI) percentage as a proxy measure to reflect influenza activity. Our research timeframe spans from Week 4 of 2020 to Week 51 of 2023, with the 4th week of 2020 defined as Week 1 and the 51st week of 2023 defined as Week 205. On December 26, 2022, China has decided to downgrade the management of COVID-19 (novel coronavirus infection) from Class B with Class A control measures ("B level with A management") to the standard Class B management measures ("B level with B management"). This change may indicate a shift in the COVID-19 event. The 153rd week serves as the cutoff point for our RD design approach, delineating the COVID-19 epidemic period from the post-epidemic period. Data from weeks leading up to the 153rd week are categorized as belonging to the COVID-19 epidemic period group, while data from the 153rd week onwards fall under the post-epidemic period group.

Data collection

The study collected pathogen surveillance data from all influenza surveillance sentinel hospitals in Fujian Province, which were exported from the "China Influenza Surveillance Information System". Initially, data were gathered from 18 designated sentinel hospitals from Week 1, 2020, to Week 17, 2023. Throughout the period from Week 18 to Week 51 of 2023, the number of sentinel hospitals experienced fluctuations. These changes are depicted in Supplementary Figure S1, which illustrates the temporal adjustments to the sentinel hospitals network. Additionally, Supplementary Figure S2 provides a detailed visual representation of the geographical distribution of the sentinel hospitals in Fujian Province throughout the duration of our study. Please find the supplementary material attached. The data covered the period from the 4th week of 2020 to the 51st week of 2023. Weekly reports of ILI cases were provided by the staff of the sentinel hospitals and laboratories.

Case definition and ILI identification

ILI cases were identified based on a standard case definition, which included individuals with a body temperature ≥ 38°C accompanied by cough or sore throat, and without any other definitive diagnosis [14]. The ILI percentage was calculated as the proportion of total outpatient visits attributable to ILI [15]. Formula: ILI Percentage (decimal values) = (Number of outpatient visits due to ILI/Total number of outpatient visits).

Control variables

In addition to the ILI data, potential confounding factors such as seasonality, temperature, and influenza vaccine coverage data were collected [14]. The seasons were categorized based on the seasonal classification provided in the Fujian Provincial Climate Bulletin, issued by the Fujian Meteorological Bureau. The seasons were classified as winter (December to February), spring (March to April), rainy season (May to June), summer (July to September), and autumn (October to November). The temperature data used in the study were quarterly averages from the Fujian Provincial Climate Bulletin published by the Fujian Meteorological Bureau. The estimation of influenza vaccine coverage data was obtained from previous studies [16, 17].

Statistical analysis

In our study, we conducted a detailed statistical analysis on the ILI data collected from sentinel hospitals across Fujian province from 2020 to 2023 using the R software version 4.3.1. The "Robust" package was employed for RD design analyses to evaluate the causal impact of fluctuations in COVID-19 events on the percentage of ILI cases. Prior to performing RD design analysis, we utilized the McCrary test to examine any potential manipulation or sorting around the cutoff point. Models then were developed to account for various potential confounding factors, including seasonality, temperature, and influenza vaccination rates. Furthermore, extensive sensitivity analyses were deployed to ascertain the robustness of our findings, adopting different bandwidth selection methods—namely, "certwo," "cersum," "mserd," "cercomb1," and "cercomb2" options from the Rdrobust package for constructing RD design models. Placebo tests were also completed during sensitivity analysis to further validate our results.

Acknowledging discrepancies in the reporting frequency by sentinel hospitals over the duration of our study, as depicted in Supplementary Figures S1, we expanded our sensitivity analyses to include a consistent subset of 18 sentinel hospitals that reported data continuously between 2020 and 2023. An identical analytical approach, incorporating the aforementioned bandwidth selections, placebo tests, and consistent breakpoints, was applied to the data from

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these 18 selected hospitals to corroborate the accuracy of our study's outcomes. Supplementary Figure S2 provides a graphical depiction of the regression discontinuity design applied to evaluate the impact of the change in the COVID-19 event on the percentage of ILI. The absolute change in ILI percentage (measured in percentage points) is obtained by scaling the RD coefficient β by 100: Δ (ILI %) = $\beta \times 100$. All tests performed adhered to a two-sided statistical approach, with a significance level set at $P < 0.05$ to determine statistical significance.

Ethical considerations

Our study is based on anonymized information data and does not involve individual sensitive information. According to China's newly revised "Measures for Ethical Review of Life Sciences and Medical Research Involving Humans," released on February 18, 2023, the requirement for ethical review is exempted [18]. This document specifies the scope of biomedical research projects requiring ethical review, and our study meets the conditions for this exemption. More details can be found in the official notice (https://www.gov.cn/zhengce/zhengceku/2023-02/28/content_5743658.htm).

Results

Descriptive statistics

During the study period, the analysis of influenza surveillance metrics in Table 1 shows that the mean ILI percentage was 4.65%, with variability ranging from 1.66% to 19.12%. The mean Immunization Vaccine Response (IVR) percentage was 2.53%, indicating relative consistency with a range between 1.10% and 3.84%. Ambient temperature averaged 20.80°C, ranging from 11.50°C to 28.50°C. The average number of ILI cases was 9,690, ranging from 2,020 to 54,950, while ILI visits averaged 177,926, with a range from 57,115 to 474,887, showing notable variability in visits.

RD results. As shown in Figure 1, both sides of the predetermined cutoff exhibited a significant upward trend in the ILI percentage over time, with an increase noted at week 153, the chosen threshold. Our analytical approach noted a discontinuity at this point by evaluating two separate linear models for observations pre- and post-cutoff. Before and after the cutoff at week 153, a significant positive trend in ILI percentage over time was detected (prior to the cutoff: $P = 0.02$; after the cutoff: $P < 0.001$), even after accounting for variables such as seasonal effects, vaccination rates, and temperature. This increasing trend accelerated after the cutoff. Furthermore, the validity of our cutoff point was further supported by the McCrary Density Test, which yielded an estimated discontinuity value of 0.14 at week 153, with a non-significant p-value of 0.81. This indicates no significant discontinuity in the density of observations around the cutoff, thereby alleviating concerns over manipulation of the assignment variable.

Table 1 Descriptive statistics summary of influenza indicators

Influenza data and Temp	Min	Mean	SD	P25	Midian	P75	Max
ILI percentage (%)	1.66	4.65	2.92	2.83	3.38	5.63	19.12
IVR (%)	1.10	2.53	0.86	1.95	2.47	2.47	3.84
Temp (°C)	11.50	20.80	0.59	16.30	20.30	26.20	28.50
ILI cases	2,020	9,690	106	3,999	5,137	9,200	54,950
ILI visits	57,115	177,926	10,668	140,139	158,486	173,521	474,887

Temp, temperature; Min, minimum; Max, maximum; SD, standard deviation; P25, 25th percentile; P75, 75th percentile; IVR, influenza vaccination rate; ILI, influenza-like illness.

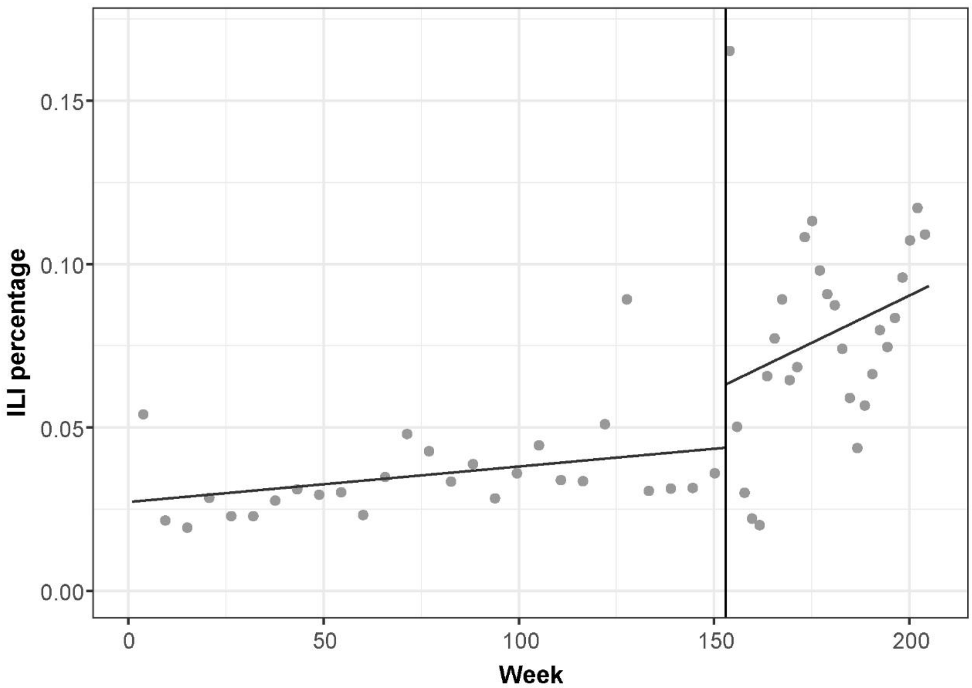

Figure 1 Evaluating the impact of the oscillation in the COVID-19 event on the ILI percentage in Fujian Province during 2020-2023. ILI, influenza-like illness. Note: The values of "ILI percentage" in this figure are presented as decimal values.

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Bandwidth selection. In Figure 2, we examine the robustness of our estimations using diverse bandwidth selection methods in combination with bias-corrected techniques, conventional estimations, and robust standard errors. Positive effects are consistently observed across these methodologies, indicating the reliability of our findings. Specifically, using the bias-corrected method ('certwo'), the largest estimated effect was observed: a 14.6-percentage-point increase in ILI percentage (β = 0.146; 95% confidence interval (CI): 0.096 to 0.196 in coefficient units, equivalent to 9.6 to 19.6 percentage points). Traditional estimation methods yielded slightly attenuated effects, for instance, 'certwo' having an estimated effect of 0.125 (95% CI: 0.075 to 0.175). We observed a noticeable increase in ILI percentages post-epidemic period compared to the during the COVID-19 epidemic period, and this trend holds true across the various bandwidth selection strategies employed in this study, indicating its robustness.

Placebo cutoff. As shown in Figure 3, the results indicated no significant effects at the placebo breakpoints for weeks 151, 152, 154, and 155. Notably, during week 153, we observed a pronounced effect. For these weeks, the estimated effect sizes and confidence intervals derived from the Bias-Corrected, Robust, and Conventional methods were similar, indicating the robustness of our study findings.

Potential confounding variables. As presented in Figure 4, after adjusting for confounders such as seasonality, vaccination coverage, and temperature-humidity factors within the model individually and collectively, the analysis consistently showed an upward trend in the percentage of ILI during the post epidemic periods. The bias-corrected estimations showed that, after controlling for seasonality, the effect estimate was 0.149 with a 95% CI ranging from 0.018 to 0.280. When adjusting for vaccination coverage and temperature-humidity factors, the effect estimates were similar: 0.139 (95% CI: 0.070 to 0.209) and 0.137 (95% CI: 0.007 to 0.267), respectively. Accounting for all three confounders simultaneously, the estimate was 0.146 with a narrower CI from 0.096 to 0.196, suggesting the effect's robustness. Other estimations using conventional and robust methods yielded similar effect sizes, although slightly lower when controlling for all factors at once, with the effect estimate being significant across all models.

Our extensive sensitivity analysis, drawing upon data from all sentinel hospitals as well as a consistent subset of 18 hospitals reporting throughout the 2020–2023 period in Fujian Province, has shown the significant impact of fluctuations in COVID-19 events on the percentage of ILI cases. The robust effect estimates, presented in Supplementary Table S1 via an array of RD design bandwidth selection methods consistently aligns across all hospitals and the subset. The estimates, remarkably coherent in conventional, bias-corrected, and robust analyses, persistently indicate a substantial increase in ILI percentage post-epidemic. For instance, using the 'certwo' method, the conventional estimate for all hospitals is calculated at 0.125 (0.075, 0.175) and is similar at 0.125 (0.074, 0.176) for the subset. Moreover, our analysis assesses the robustness of the results by analyzing effects across multiple thresholds from 151 to 155 (Supplementary Table S2). The consistent nature of these findings across different cutoffs, methods, and hospital subsets corroborates the reliability of our estimates.

Supplementary Table S3 advances this analysis by integrating additional models that incorporate pivotal control variables including seasonality, vaccination rates, and temperature. Reinforcing the robustness of our primary conclusions, the consistent results, even after factoring in these variables, solidifies the evidence of a sizeable increase in ILI percentages across both the complete dataset and the 18-hospital subset post-epidemic. In summary, our robust research results indicate a significant association between the fluctuation in COVID-19 events and changes in the ILI percentage. The ILI percentage shows a significant increase during the post-epidemic period compared to the epidemic period.

Discussion

Our study has examined the association between the fluctuation in the COVID-19 event and the subsequent changes in the influenza activity. By leveraging a robust RD design analysis, we have unearthed a 14.6-percentage-point augmentation in ILI occurrences during the post-epidemic period compared to the COVID-19 epidemic period in Fujian Province, suggesting that the fluctuations in COVID-19 events may have an impact on the dissemination of influenza. Our study provides valuable insights for strengthening influenza monitoring and control measures in the post-COVID-19 period. Additionally, it provides directions for investigating the activity changes in other respiratory diseases beyond influenza after the easing of COVID-19 public health measures. This research presents meaningful insights into achieving a balance between public health interventions and the normalization of social life, ultimately aiding in the maximization of prevention and control efforts for influenza and other respiratory infectious diseases.

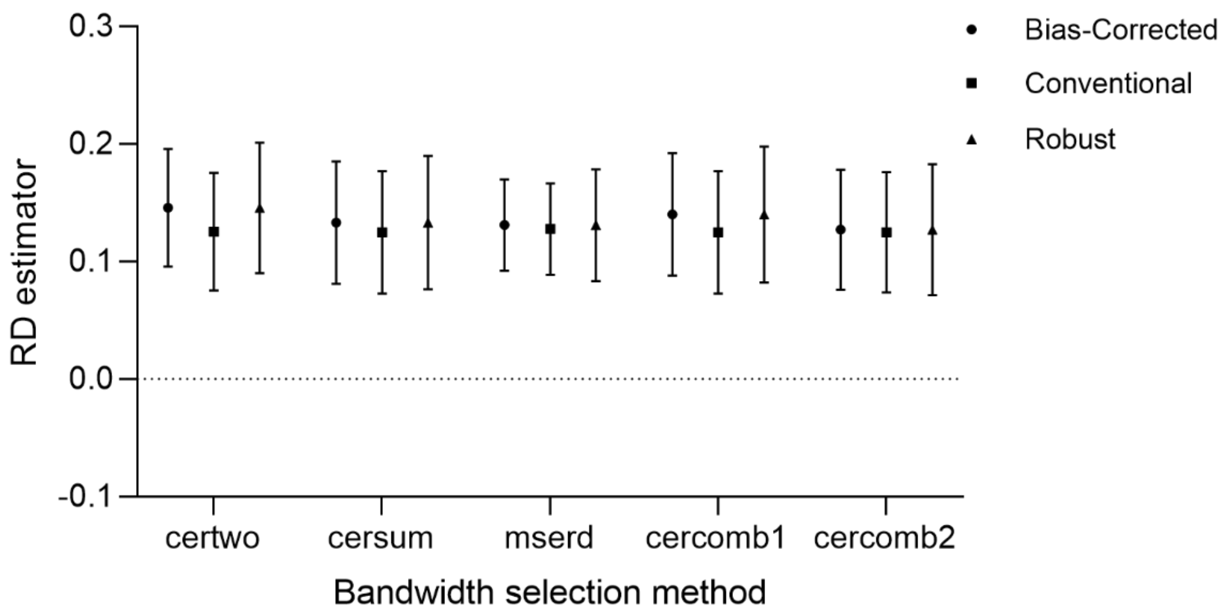

Figure 2 Impact of the fluctuation in the COVID-19 event on ILI percentage in Fujian Province (2020–2023): estimation using different bandwidths selection methods. ILI, influenza-like illness.

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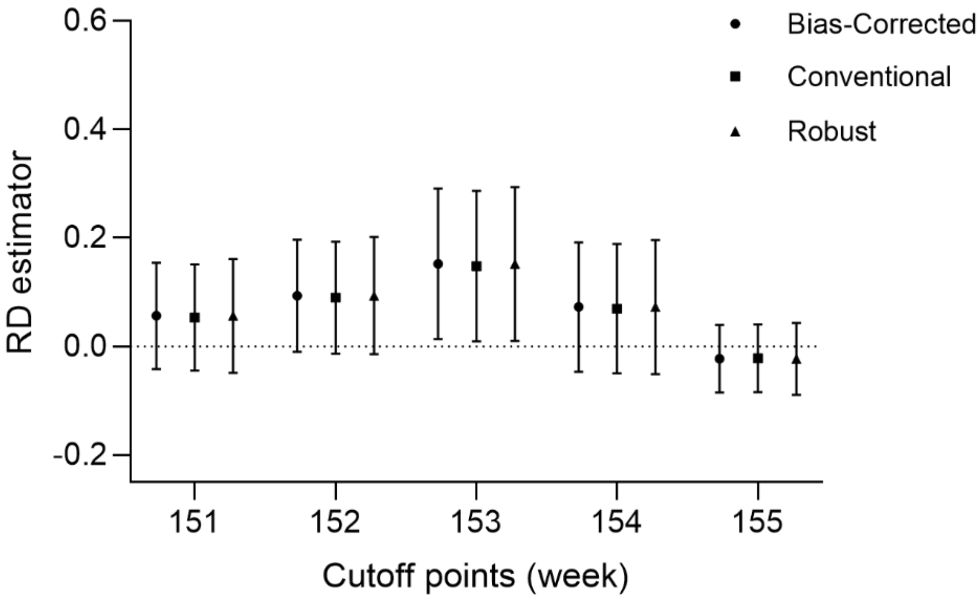

Figure 3 Impact of the variation in the COVID-19 event on ILI percentage in Fujian Province during 2020–2023: estimates with placebo and actual cutoffs. ILI, influenza-like illness.

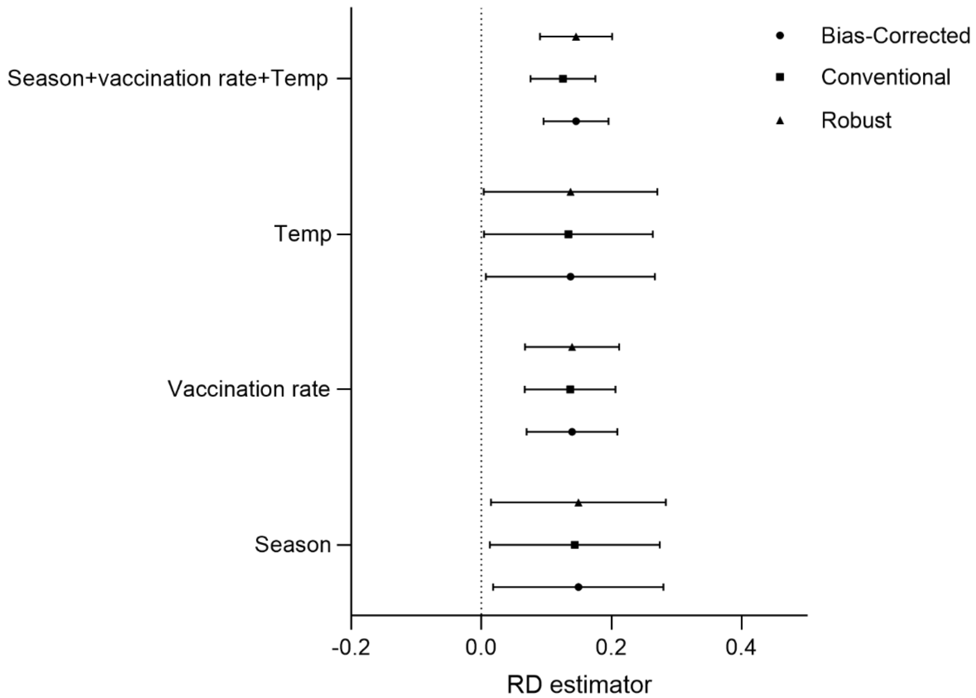

Figure 4 Impact of the change in the COVID-19 on ILI percentage in Fujian Province during 2020–2023: estimates with additional control variables. ILI, influenza-like illness. Temp, temperature.

Studies conducted in Hong Kong, Taiwan and Zhejiang and Hong Kong, China, have demonstrated a decline in influenza activity amid the enactment of preventative measures for COVID-19, which may suggest that influenza transmission was disrupted by policies aimed at controlling the SARS-CoV-2 [3, 19, 20]. Similar outcomes have emerged from studies in Korea, Singapore and Thailand, reinforcing the interpretation that control efforts for COVID-19 have had an ancillary impact on influenza virus spread [4, 5, 21]. Likewise, research from the United States, Australia, Chile, and South Africa indicates a decrease in influenza activity indicators post the recognition of extensive community spread of the SARS-CoV-2 around mid-to-late February 2020 [22].

Further evidence from Japan suggests a correlation between compliance with non-pharmaceutical interventions during the COVID-19 pandemic and a decrease in seasonal influenza activity, reinforcing the significance of public health interventions to mitigate the health consequences of influenza outbreaks [23]. Similarly, an abrupt cessation of the 2019/20 influenza season was observed in Denmark, Norway, and Sweden following the implementation of COVID-19 precautions [24]. In the Americas, Mexico experienced a decline in influenza cases after public health measures were put in place, while an observational study based on the Canadian national influenza surveillance system highlighted changes in the incidence of seasonal flu in response to social distancing measures for COVID-19 [25, 26]. The restrictions imposed due to COVID-19 may have also precipitated an earlier end to the 2019–2020 influenza season in

Finland and contributed to a decrease in infant respiratory syncytial virus, demonstrating the broader effect of these measures on respiratory viral infections [27].

These declines of influenza activity during the COVID-19 pandemic could plausibly be linked to broad implementation of interventions designed to mitigate the transmission of SARS-CoV-2, with these observations having biological plausibility. Both influenza and SARS-CoV-2 are predominantly transmitted via droplets; however, the seasonal influenza virus (R0 = 1.28) is less transmissible compared to SARS-CoV-2 (R0 = 2–3.5) [28]. As COVID-19 countermeasures are altered, we may observe an uptick in the transmission of respiratory viruses once more [29]. Our study, utilizing empirical research methods, provides collateral support to these findings despite variations in geographic locations and timelines among previous research. To our knowledge, precedent studies have not engaged empirical methods to explore the impact of the fluctuations in the COVID-19 event on influenza activity. Our work emphasizes the increase in influenza activity during the later stages of the COVID-19 epidemic, highlighting the need to consider the dynamics of influenza transmission in the post-COVID-19 period.

Our study has several strengths. One of the principal strengths of our study lies in its methodological rigor. The RD design approach serves as a quasi-experimental design, approximating the random assignment in controlled trials and thus enhancing the causality of the findings [30, 31]. By employing various bandwidth selection methods, bias-correction techniques and implementing stringent sensitivity checks, including placebo tests, our analysis strives to minimize false findings and bolsters the credibility of the detected effect estimates. Moreover, our data set's comprehensiveness – encompassing all sentinel hospitals across Fujian Province and spanning nearly four years – empowers the study with a solid representative character and temporal scope. The granularity of the surveillance data, paired with the meticulous consideration of confounders such as seasonality, temperature, humidity, and vaccination rates, provides a robust scaffold for analysis. Corroborating the robustness of our primary analysis, the consistency of results across both the complete data set and the subset of 18 sentinel hospitals post-epidemic underscores considerable implications. Even after incorporating the multifaceted variables into our analysis, the persistence of a sizeable increase in ILI percentages robustly underscores the public health significance of our findings.

Nevertheless, there are certain limitations to be acknowledged. The surveillance data, while comprehensive, was limited to Fujian Province and may not be generalizable to other regions with differing meteorological factors [32]. Additionally, reliance on ILI percentages as a proxy for influenza activity may be inherently imperfect, given that not all ILI cases can be attributable to influenza viruses [33]. Importantly, despite the well-established sentinel surveillance network in Fujian, the impact of the COVID-19 pandemic may have disrupted ILI reporting in sentinel hospitals (e.g., through altered healthcare access or resource reallocation), potentially influencing the representativeness of our data. Future studies should explicitly assess this disruption. To address these limitations, future research should incorporate laboratory testing results to identify confirmed cases of influenza virus infections and categorize them based on different viral subtypes for further investigation. This will help to gain a more accurate understanding of the relationship between confirmed cases of influenza and influenza activity.

Moreover, our results might be impacted by some potential unmeasured confounding variables in the study, such as the concurrent prevalence of other respiratory viruses and changes in healthcare-seeking behavior during the post epidemic period [34]. The potential policy adjustments resulting from the fluctuations in COVID-19 events could introduce variables that were not adequately considered in this study, which could potentially have an impact on the research outcomes [34]. Therefore, future research needs to explore in depth the potential effects of these policy changes, in order to better understand and predict how they may influence social, economic, and other relevant domains. By employing more systematic analysis and model building, researchers can better measure and control these variables, thereby enhancing the reliability of conclusions and the effectiveness of policy recommendations.

Additionally, potential changes in social behavior and hygiene practices, such as mask-wearing and maintaining social distancing, due to the end of the COVID-19 pandemic, may not have been quantified in this study, possibly affecting influenza transmission [35]. There might also be issues related to the quality or accuracy of existing data, such as precise data entry, which could influence the study findings. Addressing these factors in future research will be crucial for obtaining a more comprehensive understanding of influenza dynamics in the post-pandemic context.

Conclusion

The 14.6-percentage-point increase in the ILI percentage in Fujian Province, China, during the post-COVID-19 period suggests a potential need to re-evaluate and possibly strengthen public health measures for better control of influenza transmission. Further research is required to explore the underlying factors behind this rise, particularly sustained behavioral modifications (e.g., care-seeking patterns)—to enable precision policy-making in the aftermath of the pandemic.

Data availability

Researchers can request access to our data by sending an email to (hongjinli_93@126.com) to our research team. When making the request, please include a brief research proposal and a data use plan. Our team will respond preliminarily within 7 working days after receiving the request, and may ask for more details about the purpose of the researcher's study. Eligible requests will be reviewed by our data sharing committee. Once approved, a data sharing agreement will be signed to ensure that the data is used only for approved research purposes.

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