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Impact of Isolation measures on pregnancy outcome during the COVID-19 pandemic

Yu Tao a, Yang Xiao a, Fangyi Wang a, Yuxiu Liang a, Jin Zhang a, Xiaokang Ji b, Yongchao Wang b, Zhiping Wang a,b,*

a School of Public Health, Cheeloo College of Medicine, Shandong University, Jinan, Shandong, China
b Institute for Medical Dataology, Shandong University, Jinan, China

ARTICLE INFO

Keywords:
COVID-19
Lockdown
Isolation period
Birth weight

ABSTRACT

This study aims to explore the impact of isolation measures implemented during the COVID-19 pandemic on childbirth outcomes in pregnant women. The design was a retrospective cohort study. The pregnant women during the outbreak lockdown and isolation from February 1 to April 30, 2020, were defined as the exposed population, and the pregnant women in the same time frame in 2019 as the non-exposed population. All data for the study were obtained from the National Health Care Data Platform of Shandong University. Generalized linear regression models were used to analyze the differences in pregnancy outcomes between the two study groups. A total of 34,698 pregnant women from Shandong Province, China in the data platform met the criteria and were included in the study. The proportions were 11.53% and 8.93% for macrosomia in the exposed and the non-exposed groups and were 3.47% and 4.37% for low birth weight infants, respectively, which were significantly different. They were 22.55% and 25.94% attributed to average exposed effect for macrosomia and low birth weight infants. Meanwhile, the mean weight and standard deviation of full-term infants in the exposure group were 3414.80 ± 507.43 g, which were significantly higher than in the non-exposed group (3347.22 ± 502.57 g, P < 0.001). The effect of exposure was significant in the third trimester. In conclusion, the isolation during the COVID-19 pandemic increases the birth weight of infants and the probability of macrosomia, regardless of which trimester a pregnant woman was, while the third trimester is the sensitive window of exposure. Our findings provide a basis for health care and policy development during pregnancy in COVID-19, due to COVID-19 still showing a pandemic trend around the world in 2022.

1. Introduction

In December 2019, a group of patients with pneumonia of unknown cause were found in Wuhan, China. After investigation, they were determined to be caused by the new coronavirus, and the virus was named 2019-nCoV (Zhu et al., 2020). With the further development of the epidemic and its rapid spread in many regions, on January 20, 2020, the National Health Commission of China formally notified that coronavirus pneumonia (COVID-19) should be included in the category B infectious disease and be managed by the category A infectious disease (Anon, 2020). The first-level response to major public health emergencies has been launched nationwide, and the strictest scientific prevention and control measures have been implemented by the management methods for Class A infectious diseases. Starting from the end of January 2020, the Shandong provincial government, like other regions, implemented home isolation measures across the province. During the isolation period, all schools, restaurants, and factories were closed; everyone was required to work from home; gatherings of many people were not allowed, and work would not resume until the end of April (government, 2020; Lin et al., 2021).

As of June 2022, the novel coronavirus pneumonia (COVID-19), as a global public health event, has caused more than 613 million infections and more than 6.52 million deaths worldwide (Tang and Abbasi, 2021; WHO. Coronavirus disease, 2019a). It is known that COVID-19 mainly causes respiratory system infection (WHO. Coronavirus disease, 2019b) and heart damage (Li et al., 2020) in the general population. COVID-19 patients will also be combined with cardiovascular and cerebrovascular diseases such as hypertension, coronary heart disease, and endocrine system diseases such as diabetes, increasing the risk of disease (Zhou et al., 2021). Furthermore, the large-scale epidemic of COVID-19 will
also cause people mental health problems such as anxiety, tension, and depression, and produce a series of psychosocial dysfunction (Bridgland et al., 2021).

Pregnant women are a special group. The special psychological and physiological changes during pregnancy make this group more susceptible, which will cause harm to the intrauterine growth and development of the fetus, and should be paid attention to. Most of the previous studies on the impact of COVID-19 on pregnant women have focused on case reports, such as passive immunity in COVID-19 patients during pregnancy (Toner et al., 2020); COVID-19 patients with multiple systems inflammatory syndrome during pregnancy (Gulersen et al., 2021), and vertical transmission of COVID-19 patients during pregnancy (Sukhikh et al., 2021), acute infection and other reports (Giavoli et al., 2020). Studies have also pointed out the analysis of the status of new coronary pneumonia in pregnant women (Fox and Melka, 2020), the clinical manifestations of COVID-19 patients during pregnancy (Sabharwal et al., 2021), and the study of adverse childbirth outcomes (Sun et al., 2021). In addition, some scholars have also paid attention to the impact of the epidemic lockdown and isolation on premature birth, stillbirth (Khalil et al., 2020; Handley et al., 2021), and low birth weight of newborns (Llorca et al., 2021; Cuesta et al., 2021). Previous studies have found a decrease in preterm births (McDonnell et al., 2020) and an increase in stillbirths (Khalil et al., 2020) as a result of isolation, demonstrating that the isolation of pregnant women in COVID-19 affects pregnancy outcomes. Isolation has also been found to reduce the incidence of low and very low birth weight infants as well (Alshaikh et al., 2022). However, this type of study covered all neonates. Since the birth weight of a newborn is closely related to the mother's gestational age, preterm birth significantly reduces the birth weight of the fetus. While most of the reasons affecting the occurrence of preterm birth are pathological factors, this pathological mechanism is crucial for the influence of birth weight, and it is difficult for us to exclude the influence of pathological factors on birth weight. In addition, the effect of isolation on full-term newborns is not fully understood. The effect of isolation on birth weight in full-term neonates exposed to an epidemic simply because birth indicators appear normal is often overlooked, so this paper focuses on studies in full-term neonates. We hypothesized that COVID-19 lockdowns would affect infant birth outcomes through maternal isolation measures. This provides recommendations for the maternal care of pregnant women after home isolation in similar outbreaks in the future.

This article used a retrospective cohort study design, and the results of the study can truly verify the etiological hypothesis that the order of causal inference of exposure before outcome after outcome meets the requirements of etiological inference. Firstly, we defined the exposure group for the pregnant women whose pregnancy was from February 1 to April 30, 2020, which received the epidemic lockdown and isolation, and the non-exposed for the pregnant women whose pregnancy was at the same time in 2019. The data of information for the study population and the outcomes was obtained from the National Health and Medical Big Data Research Center of Shandong University. Secondly, differences in pregnancy outcomes between the two cohorts were compared and effects from exposure were identified. This was followed by exploring which trimester of exposure had a more pronounced effect on pregnancy outcomes. Finally, stratified analysis was carried out according to region and age, and the differences in the increase in birth weight of offspring in different regions and ages in different pregnancy periods were analyzed.

2. Method
2.1. Study design

In this study, a retrospective cohort study was carried out based on the whole population and life cycle health care data cohort in the provincial platform database of the National Health and Medical Big Data Research Institute of Shandong University. Relevant research data and research outcomes were collected retrospectively. The study defined February 1 to April 30, 2020, as the home isolation exposure period for the COVID-19 epidemic, and February 1 to April 30, 2019, as the non-exposure period. Delivery outcomes were obtained for all populations in the cohort. That is, both exposure factors (isolation measures) and outcomes were established before the start of this study.

2.2. Study population

From the maternal medical data in the database of the platform, the pregnant women with complete examination records of pregnant women in the pregnancy files from February 1, 2019, to April 30, 2020, were compiled as a retrospective cohort of the source population component. We inferred whether a pregnant woman was in an exposed (non-exposed) period for the three gestational stages (first, second and third trimester) based on the date of her last menstrual period and the date of delivery.

We used the period as a screening criterion, February to April of 2020, which was the exposure period studied for home isolation due to the outbreak. We included pregnant women in the exposure group of the study if they spent more than 80% of the exposure period in the first, second, and third-trimester stages. Similarly, February to April of 2019 was the non-exposed period for our study. We included pregnant women in the non-exposure group of the study if they spent more than 80% of the non-exposure period in any of the first, second, and third-trimester stages. Pregnancy periods involving pregnant women exposed to the COVID-19 isolation lockdown period in the article were defined as Exposure to the first trimester: pregnant women were in the first trimester (1–12 weeks of gestation) during the COVID-19 isolation period; Exposure to the second trimester: pregnant women were in the second trimester (13–27 gestational weeks) during the COVID-19 isolation period; Exposure to the third trimester: pregnant women were in the third trimester (28–42 gestational weeks) during the COVID-19 isolation period; Exposure to any of the three trimesters: pregnant women who were in the first, second, and third trimesters during the COVID-19 isolation period were included.

The specific inclusion criteria of the study population were as follows:①Pregnant women over 18 years old; ②The date of the last menstruation of the pregnant women was recorded; ③Full-term delivery (gestational age greater than or equal to 37 weeks, less than 42 weeks); ④Data on hospital deliveries and delivery outcomes were available; ⑤The medical data of pregnant women could provide basic information of pregnant women, such as age, nation, marital status, region, height, pre-pregnancy weight, and gravidity; ⑥The place of residence of the pregnant woman was in the province. Additional inclusion criteria for study subjects in the exposure group were that the study subjects were in isolation (2020–2.1–2020–04–30) for three months or more than 80% of the time at any stage of the trimester (the first, second, or third trimesters). Additional inclusion criteria for the non-exposed group were that the subject was non-exposed for three months or more than 80% of the time (2019–2.1–2019–04–30) at any stage of the trimester (the first, second, or third trimesters).

The exclusion criteria for study subjects were as follows:① Pregnant women with missing last menstrual period and date of delivery, and missing basic information data; ②Pregnant women with preterm and post-term delivery outcomes and twins or multiple birth outcomes; ③Data Outliers Pregnant Women/Outliers refer to pregnant women whose height is greater than 200 cm, weight is less than 30 kg or more than 100 kg; ④ Study subjects were exposed (non-exposed) for less than three months or no more than 80% of the time in each trimester.

2.3. Data sources and information collection

The whole population and whole life cycle health and medical data cohort in the database was a large-scale sample of 5 million people.
drawn by stratified cluster random sampling based on the Shandong province’s entire population information database and combined with residents’ health information (Xue, 2019). In the platform database, basic information such as age, nation, marital status, region, height, pre-pregnancy weight, gravidity, and last menstrual date was selected from the maternal outpatient medical data. Using the maternal hospital delivery database to collect information on childbirth outcomes, including date of delivery, gestational age, neonatal birth weight, singleton, or multiple births.

2.4. Sensitivity analysis

To ensure the comparability between the exposed group and the non-exposed group and balance the differences between the two groups, the database was reconstructed by the matching method of the propensity score for analysis. The propensity score would use the matching package in R software to select the new non-exposed population from the non-exposed group according to the same matching factors as the exposed group. The software was used to set the matching criteria to 0.1 and the matching ratio to one-to-one matching. The matching factors included age, region, gravidity, and pre-pregnancy BMI. In the reconstructed database, there were 5905 subjects in both the exposure group and the non-exposed group.

2.5. Statistical analysis

The rank-sum test was performed on the single ordinal categorical variable data, and the chi-square test was performed on the disordered categorical variable data to compare the basic demographic characteristics of the study subjects in the exposure group and the non-exposed group. The chi-square test was used to compare the birth weight categories of the offspring of the exposed group and the non-exposed group. Two independent samples mean t-tests were used to compare the differences of full-term birth weight babies delivered after the exposure group and the non-exposed group in different pregnancy periods. The birth weight was expressed by mean ± standard deviation (SD). Pregnancy outcomes were analyzed using chi-square tests and percent imputed risk (AR%). AR% indicates the effect of isolation measures on the proportion of giant babies and low birth weight babies alone. AR% = (incidence rate in the exposed group - incidence rate in the non-exposed group)/incidence rate in the exposed group. The generalized linear model was an extension of the standard linear model that establishes the relationship between the mathematical expectation of the response variable and the linear combination of predictor variables through a linkage function (Liu et al., 2020). We used a generalized linear multivariate regression model to explore the influence of the isolation period on the birth weight of full-term infants.

The generalized linear regression model was used to analyze the risk factors, and the influence of basic demographic characteristics and maternal factors was studied based on exploring the influence of the isolation period on the birth weight of full-term infants. Such as pregnant women’s age, marital status, nation, region, pre-pregnancy BMI, and gravidity. The multi-factor model was divided into three layers, we used different models to screen which of the covariates was the most dominant variable affecting birth weight. The first model was the basic demographic characteristics; the second model added the mother’s pregnancy characteristics; the third model also added the regional factors at the economic level. Stratified analysis was conducted according to regions and ages to further explore the differences in the increase of offspring birth weight during the isolation period in different regions and ages.

The data processing performed by the research institute used Microsoft Office Excel 2019, and the statistical analysis was performed using R 4.0.5. The matching process of propensity score was implemented by the Matching package in R software. Both studies adopted a two-sided test, and the test level was $\alpha = 0.05$. (Fig. 1).

2.6. Definition and hierarchy of variables

The marital status of pregnant women was divided into married and other (unmarried, divorced, widowed, etc.). Nationalities were divided into Han nationality and other nationalities. The region was divided into three categories according to the economic status of Shandong Province (Fig. 2) (Anon, 2021): the first category was high-developed cities: Qingdao, and Jinan, and the second category was medium-developed cities: Yantai, Weifang, Jining, Linyi, and the third category was low-developed Cities: Zibo, Heze, Tai’an, Binzhou, Liaocheng, Rizhao. The pre-pregnancy BMI of the subjects was calculated from the height and pre-pregnancy weight of the pregnant women. Underweight = BMI < 18.5, normal weight = 18.5–23.9, overweight = 24–27.9, obese = BMI ≥ 28 (Li et al., 2015).

In addition, the delivery outcome variables were defined as follows. Macrosomia was defined as a fetus with a birth weight greater than or equal to 4000 g, a low birth weight infant was defined as a fetus with a birth weight less than 2500 g, and a full-term normal weight infant was defined as a fetus with a birth weight greater than or equal to 2500 g and less than 4000 g.

![Fig. 1. The summary graph on article abstracts.](image-url)
3. Result

3.1. Demographic characteristics of study subjects

A total of 34,698 pregnant women met the inclusion criteria of the study subjects and were included in the study. The screening process of the study subjects is shown in Fig. 3. Among them, 5905 pregnant women were in the COVID-19 exposure period and 28,793 were in the non-exposed period. The age range of the study subjects was between 18 and 50 years. The average age of the study subjects in the exposure period was 30.53 ± 4.36 years old, and in the non-exposed period, it was 29.60 ± 4.77 years old. There were differences in age statistics between the two groups, $P < 0.001$. And most of the research subjects were of Han nationality, and their marital status was married. Except for nation and pre-pregnancy BMI, there were no differences between the exposure and non-exposed groups, other variables were different, and $P < 0.001$. See Table 1.
Birth weight categories of the offspring of the exposed and non-exposed subjects in the epidemic isolation and lockdown.

Table 2
Birth weight categories of the offspring of the exposed and non-exposed subjects in the epidemic isolation and lockdown.

| Exposure time          | Neonatal category | Exposure group | Non-exposed group | χ² | P     |
|------------------------|-------------------|----------------|-------------------|----|-------|
|                        |                   | N   | %     | N   | %     |        |        |
| Exposure during any of the three trimesters | Full-term infant | 5905 | 100.00 | 28793 | 100.00 | 46.333 | < 0.001 |
|                        | Macrotermia       | 5019 | 85.00 | 24963 | 86.70 |        |        |
|                        | Low birth weight infant | 205 | 3.47  | 1258  | 4.37  |        |        |
| Exposure to the first trimester | Full-term infant | 1091 | 100.00 | 3252 | 100.00 |        |        |
|                        | Normal weight infant | 928 | 85.06 | 2856 | 87.82 | 7.102 | 0.029  |
|                        | Macrotermia       | 119  | 10.91 | 269  | 8.27  |        |        |
|                        | Low birth weight infant | 44  | 4.03  | 127  | 3.91  |        |        |
| Exposure to the second trimester | Full-term infant | 2577 | 100.00 | 11146 | 100.00 | 16.485 | < 0.001 |
|                        | Normal weight infant | 2196 | 85.22 | 9659 | 86.65 |        |        |
|                        | Macrotermia       | 291  | 11.29 | 999  | 8.96  |        |        |
|                        | Low birth weight infant | 90  | 3.49  | 488  | 4.39  |        |        |
| Exposure to the third trimester | Full-term infant | 2237 | 100.00 | 14395 | 100.00 | 27.328 | < 0.001 |
|                        | Normal weight infant | 1895 | 84.72 | 12448 | 86.47 |        |        |
|                        | Macrotermia       | 271  | 12.11 | 1304 | 9.06  |        |        |
|                        | Low birth weight infant | 71  | 3.17  | 643  | 4.47  |        |        |

When the third trimester was in isolation, the proportion of macrosomia was 12.11% and its AR% = 25.19%. The low birth weight infants delivered by the exposed group in the isolation period and the non-exposed group of any trimester were 3.47% and 4.37%, respectively, and the attributable risk percentage AR% = 41.01%. See Table 2.

3.3. Neonatal Birth Weight Study Results

When studying the effect of isolation measures on the birth weight of full-term newborns of the study subjects, we obtained the following results (Table 3). For the subjects exposed to the isolation period in any trimester, the average birth weight of full-term infants was 3414.80 g, which was greater than the average birth weight of 3347.22 g in the non-exposed group, with a difference of 67.58 g, and the difference was statistically significant (P < 0.001). The mean birth weights of the full-term infants who were exposed to the isolation period in the first, second, and third trimesters of pregnancy were all greater than those in the non-exposed group, with differences of 54.03 g, 52.92 g, and 88.46 g, respectively. Similarly, the birth weight results of normal-weight infants delivered in both groups were similar to those of full-term infants, with differences of 33.67 g, 23.05 g, and 50.27 g after three trimesters of exposure, respectively.

In addition, among the subjects exposed to the isolation period in any trimester, the mean birth weight of the macrosomia was 4237.22 g greater than that in the non-exposed group, 4219.36 g, a difference of 17.86, but the difference was not statistically significant (P = 0.087). The results of isolation in the second and third trimesters were similar to those of exposure during any trimester. In the study of subjects exposed to the isolation period in any trimester and first trimester, the average birth weight of the low birth weight infants was greater than the average birth weight in the non-exposed group, the difference was 2.03 g and 57.68 g, respectively, but the difference was not statistically significant (P = 0.942, P = 0.362). On the contrary, the average birth weight of low birth weight infants in the isolation period exposed in the second and third trimesters was lower than that in the non-exposed group, the difference was 4.12 g and 27.79 g, respectively, but the difference was also not statistically significant (P = 0.925, P = 0.541).

When applying the generalized linear regression model to study the influence of the single factor of isolation period on the birth weight of full-term infants and full-term normal-weight infants, we found that the birth weight difference between full-term infants and full-term normal-weight infants delivered by pregnant women in any trimester periods during the exposure group and the non-exposed group was statistically

Table 1
Demographic characteristics of study subjects in exposure and non-exposed groups.

| Variable                          | Exposure group (5905) | Non-exposed group (28793) | χ² | P     |
|-----------------------------------|-----------------------|---------------------------|----|-------|
| Age (years)                       | 18-24                 | 509                        | 8.62 | 4112  | 14.28 |
|                                   | 25-34                 | 4457                      | 75.48 | 20540 | 71.34 |
|                                   | ≥ 35                  | 939                       | 15.90 | 4141  | 14.38 |
| Marital status                    | married               | 5800                      | 98.22 | 27889 | 96.86 |
|                                   | other                 | 105                       | 1.78  | 904   | 3.14  |
| Nation                            |                        |                           |      |       |
|                                   | region 1              | 396                       | 6.71  | 8470  | 29.42 |
|                                   | region 2              | 3810                      | 64.52 | 4504  | 15.64 |
|                                   | region 3              | 1699                      | 28.77 | 15819 | 54.94 |
| Pre-pregnancy BMI (kg/m²)         |                       |                           | -1.489 | 0.136 |
| < 18.5                            | 499                   | 8.45                      | 2439  | 8.47  |
| 18.5-23.9                         | 3604                  | 61.03                     | 17888 | 62.13 |
| 24-27.9                           | 1313                  | 22.24                     | 6198  | 21.53 |
| ≥ 28                              | 489                   | 8.28                      | 2268  | 7.88  |
| Gravidity                         |                       |                           | -13.493 | < 0.001 |
| 1                                 | 3062                  | 51.85                     | 12168 | 42.26 |
| 2                                 | 1810                  | 30.65                     | 10134 | 35.20 |
| ≥ 3                               | 1033                  | 17.49                     | 6491  | 22.54 |

Indicates a single ordered data, the result after the rank-sum test is used.
and gravidity based on Model 1; Model 3 adds regional variables based on Model 2. In the second trimester, third trimester, and third trimester, the average birth weight of the non-exposed group of 3325.90 g, a difference of 133.90 g. Statistical significance remained after model adjustment, but the difference remained statistically significant in either trimester or third trimester, with \( P < 0.001 \). Outcomes in term normal-weight infants were similar to those in term-born infants.

### 3.4. Results of stratified analysis by region and age

After further comparison of regional differences in weight gain of full-term infants of the offspring of study subjects exposed to isolation during different pregnancies (Table 5). We found that there was a significant difference between the exposure group and the non-exposed group in the second category region, the difference was 58.7 g, and it was still statistically significant after model adjustment, \( P < 0.001 \). Among the exposures in the three trimesters, only the exposure in the third trimester had the same result, the difference was as large as 125.26 g, and it was statistically significant. The same result also appeared in the birth weight of full-term normal-weight infants (see appendix).

The results in Table 6 show that the average birth weight of the offspring of the full-term offspring of the subjects who were 35 years old and older exposed to the isolation period was 3459.80 g greater than the average birth weight of the non-exposed group of 3325.90 g, a difference of 133.90 g. Statistical significance remained after model adjustment, \( P < 0.001 \). Likewise, exposures were consistent in the first, second, and third trimesters. Birth outcomes of pregnant women aged 25

### Table 4

A generalized linear model of the effect of isolation measures on the weight (\( g \)) of full-term infants and term-normal-weight infants.

| Model | Exposure period | Full-term infant (34698) |  | Term normal weight infant (29982) |  |
|-------|-----------------|-------------------------|---|----------------------------------|---|
|       |                 | Partial regression coefficient | Partial regression coefficient | 95% CI |  |
|       |                 | \( \beta \) | \( 95\% CI \) |  | \( \beta \) | \( 95\% CI \) |  |
| **Univariate analysis (isolation)** | Any pregnancy period | 67.583 | 53.489-81.678 | \(< 0.001\) | 36.214 | 25.878-46.550 | \(< 0.001\) |
|       | First trimester | 54.035 | 20.075-87.995 | \(< 0.001\) | 33.666 | 8.134-59.217 | 0.010 |
|       | Second trimester | 52.920 | 31.329-74.512 | \(< 0.001\) | 23.055 | 7.413-38.697 | 0.004 |
|       | Third trimester | 88.468 | 65.974-110.961 | \(< 0.001\) | 33.710 | 8.171-59.243 | 0.010 |
| **Model 1** | Any pregnancy period | 66.515 | 52.408-80.621 | \(< 0.001\) | 35.424 | 25.080-45.768 | \(< 0.001\) |
|       | First trimester | 53.300 | 19.309-78.289 | \(< 0.001\) | 32.280 | 8.124-56.457 | 0.010 |
|       | Second trimester | 51.960 | 30.355-73.565 | \(< 0.001\) | 22.257 | 6.607-37.907 | 0.005 |
|       | Third trimester | 87.864 | 65.346-110.383 | \(< 0.001\) | 49.782 | 33.204-66.359 | \(< 0.001\) |
| **Model 2** | Any pregnancy period | 67.262 | 53.206-81.323 | \(< 0.001\) | 35.957 | 25.637-46.276 | \(< 0.001\) |
|       | First trimester | 55.767 | 22.035-89.498 | \(< 0.001\) | 34.313 | 8.913-59.713 | 0.008 |
|       | Second trimester | 52.733 | 31.158-74.307 | \(< 0.001\) | 22.365 | 6.721-38.010 | 0.005 |
|       | Third trimester | 87.955 | 65.528-110.383 | \(< 0.001\) | 50.870 | 34.347-67.393 | \(< 0.001\) |
| **Model 3** | Any pregnancy period | 43.513 | 27.909-59.116 | \(< 0.001\) | 27.945 | 16.501-39.390 | \(< 0.001\) |
|       | First trimester | 23.006 | -15.760-61.777 | 0.245 | 17.897 | -11.340-47.125 | 0.230 |
|       | Second trimester | 22.761 | -1.913-46.535 | 0.061 | 15.035 | -2.210-32.280 | 0.088 |
|       | Third trimester | 79.036 | 54.279-103.794 | \(< 0.001\) | 45.675 | 27.467-63.883 | \(< 0.001\) |

Model adjustment variables: Model 1 adjusts maternal age, marital status, nation, and other demographic characteristics variables; Model 2 adds pre-pregnancy BMI and gravidity based on Model 1; Model 3 adds regional variables based on Model 2.
Table 5
Comparison of regional differences in weight gain of full-term infants of the offspring of study subjects exposed to isolation during different pregnancies.

| Regional stratification | Sample size | Birth weight (g, ̄x ± s) | Single-factor analysis | Model * | Partial regression coefficient β | Partial regression coefficient β 95%CI | t     | P      | Partial regression coefficient β | Partial regression coefficient β 95%CI | t     | P      |
|-------------------------|-------------|--------------------------|------------------------|---------|----------------------------------|----------------------------------------|-------|--------|----------------------------------|----------------------------------------|-------|--------|
|                         |             | Exposure group           | Non-exposed group      | Difference value | Partial regression coefficient β | Partial regression coefficient β 95%CI |       |        | Partial regression coefficient β | Partial regression coefficient β 95%CI |       |        |
| Exposure during any of the three trimesters |             |                          |                        |          |                                  |                                        |       |        |                                  |                                        |       |        |
| region 1                | 8866        | 3367.80 ± 546.80         | 3326.91 ± 520.56      | 40.89    | 40.890                           | -11.693-93.472                         | 1.524 | 0.128  | 36.729                           | -15.910-89.368                         | 1.368 | 0.171  |
| region 2                | 8314        | 3441.98 ± 502.07         | 3383.28 ± 500.12      | 58.7     | 58.702                           | 37.085-80.319                          | 5.322 | < 0.001 | 55.490                           | 33.958-77.022                         | 5.051 | < 0.001 |
| region 3                | 17518       | 3364.81 ± 505.10         | 3347.82 ± 492.76      | 16.99    | 16.986                           | -7.733-41.705                          | 1.347 | 0.178  | 28.170                           | 3.485-52.855                          | 2.237 | 0.025  |
| Exposure to the first trimester |             |                          |                        |          |                                  |                                        |       |        |                                  |                                        |       |        |
| region 1                | 817         | 3480.00 ± 71.18          | 3337.21 ± 497.07      | 142.79   | 142.789                          | -420-402-705.980                       | 0.497 | 0.619  | 270.521                           | -296.980-838.023                       | 0.934 | 0.350  |
| region 2                | 1461        | 3422.70 ± 520.69         | 3423.45 ± 487.42      | -0.75    | -0.744                           | -52.838-51.349                         | -0.028 | 0.978  | 4.616                            | -46.934-56.167                        | 0.176 | 0.861  |
| region 3                | 2065        | 3371.71 ± 474.20         | 3337.42 ± 486.53      | 34.29    | 34.291                           | -25.492-94.074                         | 1.124 | 0.261  | 53.443                           | -6.911-113.798                        | 1.736 | 0.083  |
| Exposure to the second trimester |             |                          |                        |          |                                  |                                        |       |        |                                  |                                        |       |        |
| region 1                | 3772        | 3314.44 ± 433.80         | 3334.32 ± 512.71      | -19.88   | -19.876                          | -132.433-92.682                        | -0.346 | 0.729  | -28.573                           | -141.135-83.989                       | -0.498 | 0.619  |
| region 2                | 3612        | 3428.62 ± 499.24         | 3407.00 ± 495.78      | 21.62    | 21.617                           | -10.985-54.220                         | 1.3   | 0.194  | 19.790                           | -12.724-52.304                        | 1.193 | 0.233  |
| region 3                | 6339        | 3359.03 ± 527.98         | 3337.33 ± 497.28      | 21.7    | 21.699                           | -14.260-57.657                         | 1.183 | 0.237  | 33.453                           | -2.666-69.573                         | 1.815 | 0.070  |
| Exposure to the third trimester |             |                          |                        |          |                                  |                                        |       |        |                                  |                                        |       |        |
| region 1                | 4277        | 3380.58 ± 574.07         | 3317.90 ± 532.25      | 62.68    | 62.673                           | 0.955-124.390                          | 1.99  | 0.047  | 57.730                           | -4.187-119.647                        | 1.827 | 0.068  |
| region 2                | 3241        | 3468.71 ± 493.53         | 3343.45 ± 506.45      | 125.26   | 125.259                          | 90.397-160.122                         | 7.042 | < 0.001 | 116.667                          | 81.575-151.765                        | 6.516 | < 0.001 |
| region 3                | 9114        | 3370.33 ± 483.30         | 3356.67 ± 490.97      | 13.66    | 13.6626                          | -29.071-56.396                         | 0.627 | 0.531  | 23.352                           | -19.144-65.847                        | 1.077 | 0.282  |

Note: * Indicates that the model adjusted for other covariates, such as maternal age, marital status, nation, pre-pregnancy BMI, and gravidity.
Table 6
Comparison of age differences in weight gain of full-term infants of the offspring of study subjects exposed to isolation during different pregnancies.

| Regional stratification | Sample size | Birth weight (g, X ± s) | Single-factor analysis | Model* * |
|-------------------------|-------------|-------------------------|------------------------|----------|
|                         |             | Exposure group          | Non-exposed group      | Difference value | Partial regression coefficient β | Partial regression coefficient β 95%CI | t       | P       | Partial regression coefficient β | Partial regression coefficient β 95%CI | t       | P       |
| Exposure during any of the three trimesters |             |                         |                        |                  |                          |                          |        |         |                          |                          |        |         |
| 18~ 4621                | 3323.86 ± 493.88 | 3303.78 ± 479.15 | 20.08 | 20.076 | -24.211-64.364 | 0.888 | 0.374 | 17.219 | -29.256-63.693 | 0.726 | 0.468   |
| 25~ 24997               | 3415.71 ± 497.37 | 3360.21 ± 491.74 | 55.50 | 55.496 | 39.537-71.455 | 6.815 | < 0.001 | 30.530 | 12.771-48.288 | 3.370 | < 0.001 |
| 35~ 5080                | 3459.80 ± 553.21 | 3325.90 ± 570.59 | 133.90 | 133.899 | 93.694-174.104 | 6.527 | < 0.001 | 108.011 | 62.579-153.443 | 4.660 | < 0.001 |
| Exposure to the first trimester |             |                         |                        |                  |                          |                          |        |         |                          |                          |        |         |
| 18~ 477                 | 3342.14 ± 447.08 | 3274.53 ± 518.39 | 67.61 | 67.609 | -48.103-183.321 | 1.145 | 0.253 | 34.284 | -108.926-177.494 | 0.469 | 0.639   |
| 25~ 3209                | 3400.79 ± 501.51 | 3370.31 ± 470.32 | 30.28 | 30.284 | -7.444-68.013 | 1.573 | 0.116 | -0.740 | -43.460-41.980 | -0.034 | 0.973   |
| 35~ 657                 | 3488.96 ± 563.27 | 3343.66 ± 553.23 | 145.30 | 145.295 | 46.757-243.834 | 2.89 | 0.004 | 115.190 | 2.532-227.848 | 2.004 | 0.046   |
| Exposure to the second trimester |             |                         |                        |                  |                          |                          |        |         |                          |                          |        |         |
| 18~ 1742                | 3299.71 ± 511.84 | 3305.95 ± 478.12 | -6.24 | -6.234 | -69.961-57.494 | -0.192 | 0.848 | -36.852 | -104.180-30.477 | -1.073 | 0.284   |
| 25~ 10005               | 3405.69 ± 489.78 | 3360.41 ± 493.02 | 45.28 | 45.288 | 20.790-69.787 | 3.623 | < 0.001 | 17.696 | -9.346-44.738 | 1.283 | 0.200   |
| 35~ 1976                | 3484.91 ± 581.15 | 3329.07 ± 568.60 | 119.84 | 119.845 | 56.904-182.785 | 3.732 | < 0.001 | 84.190 | 12.716-155.663 | 2.309 | 0.021   |
| Exposure to the third trimester |             |                         |                        |                  |                          |                          |        |         |                          |                          |        |         |
| 18~ 2402                | 3353.07 ± 487.38 | 3307.39 ± 472.59 | 45.68 | 45.681 | -30.749-122.111 | 1.171 | 0.242 | 61.366 | -15.682-138.413 | 1.561 | 0.119   |
| 25~ 11783               | 3434.37 ± 503.23 | 3357.63 ± 495.60 | 76.74 | 76.742 | 51.209-102.275 | 5.891 | < 0.001 | 61.357 | 32.907-89.806 | 4.227 | < 0.001 |
| 35~ 2447                | 3458.64 ± 571.41 | 3319.24 ± 576.05 | 139.40 | 139.404 | 77.314-201.495 | 4.4 | < 0.001 | 133.889 | 63.808-203.970 | 3.744 | < 0.001 |

Note: * * Indicates that the model adjusted for other covariates, such as marital status, nation, region, pre-pregnancy BMI, and gravidity.
years or older than 35 years also differed when comparing the exposure group with the non-exposed group, by 30.53 g. However, only the exposure differed by 61.36 g in the third trimester, which was statistically significant, \( P < 0.001 \). The results in term normal-weight infants were the same as above (see appendix).

### 3.5. Sensitivity Analysis Results

Sensitivity analysis results showed that when the exposed group was matched 1:1 with the non-exposed group, the results were roughly the same as before. Compared with the non-exposed group, the birth rate of macrosomia was increased in the exposed group, and the birth rate of low birth weight infants was decreased in the exposed group, and the effects attributable to exposure measures were 15.09% and 13.03%, respectively. The mean weight and standard deviation of full-term infants and full-term normal-weight infants in the exposure group were 3414.80 ± 507.43 g and 3358.56 ± 343.96 g, respectively, which were significantly higher than the average birth weight of the non-exposed group (3370.16 ± 498.23 g and 3330.75 ± 334.51 g, respectively, \( P < 0.001 \)). The results of the model after adjusting for covariates were consistent with those of univariate analysis. However, there was no significant difference in mean birth weight between macromacia and low birth weight infants compared with the non-exposed group. The results of the analysis of different stages of pregnancy showed that the birth weights of full-term infants and full-term normal-weight infants in the study subjects in the third trimester during the isolation period were significantly higher than those in the non-exposed group (\( P < 0.001 \)). The results of the stratified analysis showed that the birth weight of the offspring in the third trimester was 30.53 g higher than that of the non-exposed group (\( P < 0.001 \)) (see appendix).

### 4. Discussion

In the study, we found that the lockdown during the COVID-19 pandemic will increase the birth weight of full-term infants and full-term normal-weight infants delivered by pregnant women. Among the average effects of exposure, there was a significant change in the proportion of macrosomia and low birth weight infants. The isolation period in the third trimester is a sensitive exposure window. The weight of macrosomia and low birth weight infants did not change significantly. After multivariate analysis, the results remained the same, showing that isolation exposure measures were independent factors for weight gain in term infants. Pregnant women who were in other trimesters (first and second trimester) during the COVID-19 pandemic lockdown period also had increased birth weights for their full-term and full-term normal-weight infants. But after multiple model adjustments, the results became insignificant. By reviewing the literature, we found that no studies have been found on the relationship between the COVID-19 pandemic lockdown and full-term birth weight.

A foreign scholar studied the changes in birth weight of newborns from 2013 to 2018 (Marete et al., 2020), and domestic scholars also studied the trend of birth weight changes of newborns from 2010 to 2019 (Chen et al., 2021a). They all came to similar conclusions: The birth weight of newborns in recent years has not varied significantly from year to year (Dong et al., 2019). We mentioned in the article that the birth weight of full-term infants in 2019 was similar to the birth weight of newborns mentioned in an article in China. These studies all support the results of this paper, which can not only show that the data collected by our big data platform in 2019 is true and reliable but also show that the lockdown and isolation measures implemented by the COVID-19 epidemic have increased the birth weight of full-term babies born to pregnant women.

Changes in the weight impact of isolation measures on low birth weight infants were reported in Spain (Llorca et al., 2021) and Argentina (Cuestas et al., 2021). In their study, lockdowns during the COVID-19 pandemic reduced the proportion of low-birth-weight births. Our study also yielded the same result. Interestingly, we also found a significant increase in the birth rate of macrosomia in the exposed group. These results all prove the isolation measures to promote the increase in the birth weight of newborns delivered by pregnant women. This weight gain is a double-edged sword, reducing the risk of low birth weight infants and increasing the risk of macrosomia.

Separating different trimesters to analyze the effect of isolation measures, after model adjustment, we found that only the third trimester was a sensitive period. Pregnant women exposed to isolation in the third trimester increased birth weight in full-term infants and term normal-weight infants. Because our study selected non-exposed subjects of the same period to avoid the influence of factors such as seasons on embryonic development, the results of the study on the effect of isolation measures on neonatal weight are credible. Our study focused on full-term infants and therefore avoided the effect of gestational age on birth weight. In addition, during the lockdown period during the COVID-19 pandemic, most people (especially pregnant women) were working and staying indoors. At this time, the amount of exercise was greatly reduced, which would indirectly affect the delivery outcome of pregnant women, that is, the birth weight of the newborn. A study shows that poor psychological conditions can reduce fertility in pregnant women (Nillni et al., 2016). Studies have also shown that stress can cause the ovaries to produce reactive oxygen species (ROS). ROS accumulates in large quantities to generate oxidative stress, which affects the quality of oocytes, reduces reproductive outcomes, and produces adverse pregnancy outcomes (Prasad et al., 2016). The COVID-19 epidemic, an infectious disease in the world pandemic, will also affect the psychological conditions of pregnant women, resulting in adverse pregnancy outcomes (Chen et al., 2021b; Romero-Gonzalez et al., 2021). And staying indoors for a long time during the pandemic will result in more nutrient intake than before, which will also affect the outcomes of pregnant women in childbirth (Salavati et al., 2020a, 2020b; Lechtig et al., 1975). The third trimester of pregnancy itself is the period with the fastest fetal growth and development (Ermamp et al., 2020), and the impact of lockdown and isolation during this period will be greater than that in the first and second trimesters. Therefore, multiple factors contribute to the increased birth weight of full-term infants and term normal-weight infants delivered by pregnant women exposed to isolation in the third trimester of pregnancy.

We also found that maternal age may influence differences in birth weights of term births delivered by pregnant women exposed to isolation versus control. The greater the age, the greater the difference in birth weights of term births between pregnant women exposed to the isolation group and the non-exposed group. In previous studies on the relationship between age and birth weight, various studies have demonstrated that maternal gestational age is related to neonatal birth weight, but the results are inconsistent. One study showed that older pregnant women were associated with lower birth weight and more low-birth-weight infants (Aeefa and Ayele, 2020). Another study found that infants born to older mothers had higher birth weights than those born to women of normal childbearing age (Zhang et al., 2021). Both findings are consistent with our findings. However, after adjusting for age, our study still found that the older the study subjects, the greater the difference in birth weight between the offspring born after the exposure group and the non-exposed group. The possible reason is that pregnant women of advanced age are more prone to anxiety during pregnancy (Wang et al., 2021), and whether this is caused by the isolation period of the new crown epidemic is worthy of further discussion.

We used different models to screen which of the covariates was the most dominant variable influencing birth weight. Finally, we found that regional factors were the main variables affecting birth weight. When the region variable was entered into the model, the difference in weight from exposure in the first and second trimesters was no longer significant. Only the third-trimester exposure significantly increased birth weight. Regional factors among demographic variables influence the...
birth weight of full-term infants and term normal-weight infants delivered to pregnant women exposed to isolation in the third trimester. Different regions caused different effects of Covid-19 (Armillei et al., 2021). In particular, in the second category of the regional classification, in cities with moderate economic development, the difference in birth weight of full-term infants born during the exposure group and the non-exposed group was greater. The reasons may be as follows: regional factors are not the determinants of birth weight growth during the isolation period; birth weight growth during the isolation period does not depend on the degree of economic development among regions. We therefore speculate: The first level of regional classification, that is, areas with good economic development, such as Qingdao and Jinan, pregnant women have a high level of education and a large proportion of sports resources (Wang, 2015). During the COVID-19 pandemic, pregnant women have some control over their diet and exercise during the lockdown period. Therefore, there was no significant difference in birth weight changes between the exposure group and the non-exposed group. In the third tier of the regional classification, that is, areas with the average economy, such as Zibo, Heze, etc., the pregnant women received average education, and their living standards did not change much during the exposure group and the non-exposed groups, so the results were similar to the first tier of the regional classification. The second level of regional classification is areas with economic development between the first two, such as Yantai, Weifang, Jining, Linyi, and other places. Pregnant women are more sensitive to coronavirus isolation measures. During the COVID-19 pandemic, the diet and exercise of pregnant women during the lockdown period were controlled to some extent but may not be controlled enough, so the birth weights during the exposure group and the non-exposed group varied greatly.

The main advantage of our study is that it innovatively explores the relationship between the COVID-19 lockdown and isolation period on the delivery outcomes of pregnant women exposed to it at different stages of pregnancy, which fills the gap in previous research. Furthermore, our study uses the large sample database of the National Health and Medical Big Data Research Center of Shandong University, covering the entire Shandong Province of China, to monitor the medical and health-related information of the whole province in real time, making the research results more authentic and credible. During the study design stage, the researchers fully considered the representative of the sample data. The data in the big data platform adopts a strict random sampling method. Based on the full population information database of Shandong Province and the information of residents’ health records, a large-scale sample (5 million) that can reflect the real world and has good representation, and covers the whole life course of the whole population is selected as the representative population. The sampling process took into account regional distribution, urban-rural ratio, age group, gender ratio, etc. The data for our study comes from a large sample of 5 million in the data platform and is therefore also representative. Finally, we have conducted a large-scale cleaning of the research data, and our research subjects have also undergone strict inclusion and exclusion criteria, making them more reliable and persuasive. In addition, our study also has certain limitations. Our research data comes from the Shandong Health Information Cloud Platform in China. The data lacks individual variables of the research subjects, so a more comprehensive multivariate analysis cannot be carried out. And the database relies on the uploaded data from hospitals in various regions. In our reuse of the data, we found a certain amount of missing information in the database. We did not have the means to apply this part of the data, resulting in insufficient information on some of our study subjects.

Birth weight is the most important measure of neonatal development and is a powerful predictor of neonatal outcomes (Garmendia et al., 2021). Overall, our study is the first to find that COVID – 19 lockdowns increase birth weight in full-term infants and term normal-weight infants delivered to pregnant women. However, we are thinking only in terms of newborns, and we do not have access to the rest of the population. Since the onset of the COVID-19 outbreak, isolation, and lockdown have been in place to varying degrees due to the variability and rampant nature of the virus. Are others gaining weight during isolation? Does it also affect the development of chronic diseases including hypertension and diabetes due to obesity? Our study provides a new idea for subsequent studies. In addition, residents during the outbreak simply complied with government regulations for home isolation. However, the government only notified the precautions of isolation and did not make corresponding guiding measures and suggestions. Therefore, this study can provide us with good suggestions regarding the health care of pregnant women during the lockdown and isolation period. In this case, we advise pregnant women, regardless of the time of pregnancy, to take care of their pregnancy and to take certain measures to cope with the effects on their pregnancy of the restricted movement caused by isolation measures. Moreover, our research has helped the government to implement policies related to isolation measures. For example, during the implementation of the quarantine policy, the government can promote science through the news media on home exercise and proper diet for residents. It can also suggest additional exercise facilities in the community and community-wide safety awareness education.

CRediT authorship contribution statement

All authors contributed to the research. The research design was proposed by Zhiping Wang and Yu Tao. Data collection and analysis were performed by Yu Tao. The first draft of the article was written by Yu Tao, and all authors revised the manuscript. Xiao Kang, Li and Yongchao Wang contributed to obtaining the research data. Yang Xiao, Fangyi Wang, Yuxiu Liang and Jin Zhang contributed to data cleaning. All authors approved the final manuscript.

Conflict of Interest

None.

Data Availability

The authors do not have permission to share data.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ehb.2022.101196.

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