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Effect of induction of labor on maternal and perinatal outcomes in low-risk singleton pregnancies: a retrospective case-control study

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Abstract. – OBJECTIVE: The aim of the study was to investigate the effect of induction of labor on maternal and fetal outcomes.

PATIENTS AND METHODS: This retrospective case-control study included 4386 pregnant women with low-risk singleton pregnancies who underwent regular prenatal examination and successful vaginal delivery at ≥41 weeks and 0 days of gestation in Fujian Maternal and Child Health Hospital between January 2014 and December 2018. Clinical data of women were retrospectively divided into the induction of labor group (2007 cases) and spontaneous onset of labor group (2361 cases) based on the mode of labor initiation. Two-sample independent *t*-test and χ^2 tests were used to analyze the differences in clinical characteristics, such as maternal age and parity between the two groups.

RESULTS: The induction of the labor group had a significantly longer total duration of labor (9.37±5.37 *vs.* 8.82±5.13 h; *p*<0.001), more postpartum blood loss (219.18±188.32 *vs.* 199.95±124.69 mL; *p*=0.01) and a significantly higher incidence of severe postpartum hemorrhage (PPH) comparing to the spontaneous onset of labor group [0.8% (16/2007) *vs.* 0.33% (8/2361); *p*=0.041]. However, no significant difference was found in the neonatal outcomes. After adjusting for age, induction of labor in nulliparous women was more likely to lead to PPH than the spontaneous onset of labor [2.74% (55/2007) *vs.* 1.65% (39/2361); odds ratio=1.557; 95% confidence interval: 1.039-2.332; *p*<0.05].

CONCLUSIONS: Induction of labor increases the duration of labor and postpartum blood loss, especially in primary parturient, leading to an increased risk of PPH. This increase may be related to the overall higher duration of labor, associated with IOL. Therefore, low-risk nulliparous women should try to avoid induction of labor without medical indications.

Key Words:
Later than term, Low-risk pregnancy, Induction of labor, Postpartum hemorrhage.

Abbreviations

IOL = induction of labor; PPH = postpartum hemorrhage; sPPH = severe postpartum hemorrhage; NICU=neonatal intensive care unit.

Introduction

Induction of labor (IOL) is a common intervention that initiates the labor process by human stimulation of uterine contraction before the spontaneous onset of labor. It is aimed to achieve the purpose of delivery when the risks of continuing pregnancy outweigh the benefits. IOL rate is approximately 4-12% in the developing states and is much more common in developed countries (26% in Australia and 23.3% in the United Kingdom). The proportion of IOL in Queensland in 2014 was reported to be 24.9%[1]. As the pregnancy progresses, the risk to mothers and fetus increases, especially in the third trimester. Pregnancy over 41 weeks of gestation is associated with an increased risk of adverse pregnancy outcomes, with worse outcomes after 42 weeks of gestation. It is recommended, therefore, that the gestational age of delivery does not exceed 42 weeks[2], and women with low-risk pregnancies are advised to terminate the pregnancy between 41 and 42 weeks of gestation. Therefore, IOL is often recommended for women at >41 weeks of gestation without spontaneous parturition[3].

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A large multicenter randomized controlled study conducted between 2014 and 2017 found that low risk primigravida that underwent IOL after 39 weeks of gestation could avoid one cesarean section for every 28 induced deliveries. IOL was associated with a lower risk of perinatal death and a lesser incidence rate of severe neonatal complications[4]. Based on that study, the Society of Maternal-Fetal Medicine recommends offering elective IOL after 39 weeks of gestation to low-risk nulliparous women who check the gestational age accurately[2].

Currently, the effect of IOL on pregnancy outcomes in low-risk pregnant women remains controversial. The goal of the present study is to retrospectively analyze the clinical data from low-risk, later-than-term pregnant women with successful vaginal delivery to assess the effect of IOL on pregnancy outcomes in women with low-risk pregnancies.

Patients and Methods

Ethics

The study was approved by the Ethics Committee of the Fujian Provincial Maternity and Children's Hospital and was conducted by the Chinese law and the Guidelines of the National Human Biomedical Research Policies (No. FJSFY2020KD). Written informed consent was not required because the data were anonymous and did not affect the patient's treatment.

Study Design and Data Source

This retrospective cohort study included a total of 4386 pregnant women with low-risk singleton pregnancies who underwent regular prenatal examination and successful vaginal delivery at ≥41 weeks gestation between January 2014 and December 2018 in Fujian Maternal and Child Health Hospital, which is affiliated with Fujian Medical University. According to the mode of labor initiation, the women were retrospectively divided into the IOL group (any method) and the spontaneous onset of the labor group.

Study Selection and Data Extraction

Women between the ages of 18 and 45 years that had a vaginal birth after 41 weeks of gestation, with reliable dating and no obstetric or medical complications were eligible, regardless of the availability of cervical examination. Women were excluded if they had a scarred uterus and underwent a cesarean section. Patients with the missing data on the gestational age and the volume of vaginal bleeding at the time of delivery were also excluded.

Potential Confounders and Other Variables of Interest

A pregnant woman was considered "full term" if she gave birth anytime from 37 to 42 weeks' gestation. The gestational age (in weeks' gestation) was further divided as follows: early term, 37-38; full term, 39-40; late-term, >41; and post-term, >42. The gestational age was determined by the crown-rump length measured by ultrasound during early pregnancy. If the estimated gestational week difference was >5 days when the gestational age was <9 weeks or >7 days between 9- and 14-weeks' gestation, the gestational week was determined based on the ultrasound results. A volume of vaginal bleeding of ≥500 mL and >1000 mL within 24 h after the vaginal birth was considered postpartum hemorrhage (PPH) and severe postpartum hemorrhage (sPPH), respectively. Parity and assisted conception pregnancies were self-reported.

Statistical Analysis

The normally distributed measurement data were analyzed using a two-sample independent *t*-test and expressed as x±s. The countable data were presented as percentages, and the χ^2 test was used to analyze the differences between the two groups. The outcomes were reported as mean differences for continuous outcomes or odds ratios (ORs) for binary outcomes, with their accompanying 95% confidence intervals (CIs). The difference was considered statistically significant at $p<0.05$.

Results

Medical records of 48,719 pregnant women that underwent pregnancy examination were evaluated. Women who did not meet our study criteria (n=44,020) or had obstetric or medical complications (n=331) were excluded. Finally, 4386 pregnant women with low-risk singleton pregnancies who had a successful vaginal delivery at ≥41 weeks of gestation were included in the analysis. They were retrospectively divided into the IOL group (n=2007) and the spontaneous onset of labor group (n=2361) (Figure 1).

Baseline Characteristics

The baseline characteristics of all study participants are summarized in Table I. Most wom-

Table I. Baseline characteristics.

Baseline characteristics	Spontaneous onset of labor (n=2,361) n (%)	Induction of labor (n=2,007) n (%)	*p*-value
Maternal age at delivery year, No. (%)	28.59 (28.59±3.87)	28.55 (28.55±3.80)	0.732
<18	5 (0.2%)	5 (0.2%)	NC
18-34	2188 (92.7%)	1853 (92.3%)	NC
35-39	147 (6.2%)	130 (6.5%)	NC
≥40	21 (0.9%)	19 (0.9%)	NC
Mean gestational age (days)	288.33±1.62	289.26±1.54	0
Nulliparous, No. (%)*	1573 (66.6%)	1425 (71.0%)	0.002

*p <0.05. Normally distributed measurement data were analyzed using two-sample independent t-test and expressed as x±s. The countable data were presented as percentages, and the χ^2 test was used to analyze the differences between the two groups. Abbreviations: NC: not calculate; NICU: neonatal intensive care unit

en in the study were between 18 and 34 years, with a median maternal age of 28.5 years. There was no significant difference in the average age and distribution of each age range between the two groups (p>0.05). The IOL group had a significantly greater number of nulliparous women (71.0% *vs.* 66.6%) and a longer gestational age (289.26±1.54 *vs.* 288.33±1.62 days) compared to the spontaneous onset of labor group (p<0.05).

IOL and Secondary Pregnancy Outcomes

As shown in Table II, the incidence of chorioamnionitis and rate of operative vaginal birth was significantly higher in the IOL group than in the spontaneous onset of labor group (4.33% *vs.* 2.33%; p<0.05 and 3.5% *vs.* 5.0%; p<0.05, respectively). However, there was no significant difference in the incidence of third-degree amniotic fluid contamination (15.5% *vs.* 14.7%; p>0.05) and placental

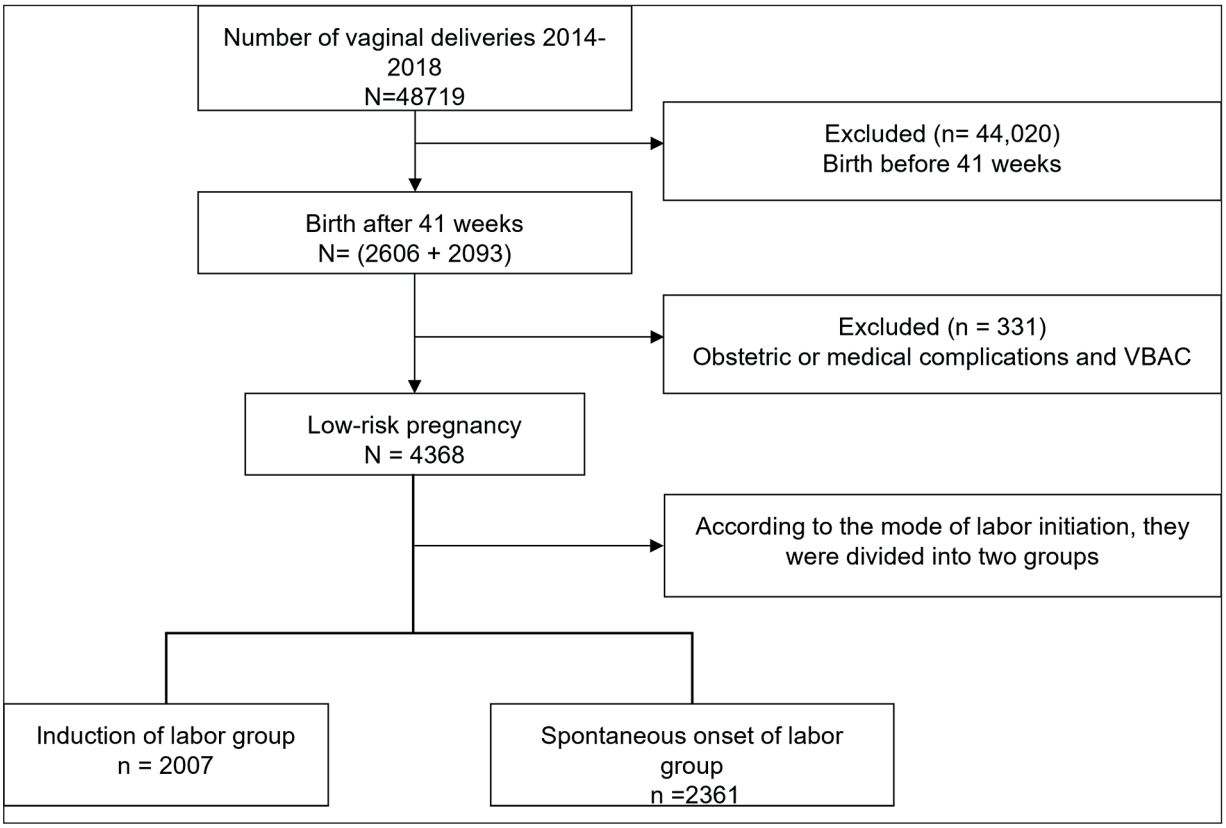

Figure 1. Flowchart of subject selection. VBAC=vaginal birth after cesarean section.

Table II. IOL and secondary pregnancy outcomes.

Baseline characteristics	Spontaneous onset of labor (n=2,361) n (%)	Induction of labor (n=2,007) n (%)	*p*-value
Maternal outcomes, No. (%)			
Operative vaginal birth, No. (%)*	82 (3.5%)	101 (5.0%)	0.01
Chorioamnionitis, No. (%)*	55 (2.33%)	87 (4.33%)	0.0002
Placental abruption, No. (%)	7 (2.96%)	9 (4.48%)	0.408
Amniotic fluid contamination, No. (%)	348 (14.7%)	291 (14.5%)	0.823
Postpartum blood loss (mL)*	199.95±124.69	219.18±188.32	0.01
Postpartum hemorrhage, no. (%)	66 (2.8%)	77 (3.8%)	0.054
Severe postpartum hemorrhage, no. (%)*	8 (0.33%)	16 (0.8%)	0.041
Neonatal outcomes, No. (%)			
Apgar score at 1 min (4-7)	3 (0.1%)	8 (0.4%)	0.074
Apgar score at 1 min (<4)	1 (0)	0 (0)	0.357
Hyperbilirubinemia	628 (26.6%)	583 (29.05%)	0.072
Perinatal death	0	0	NC
Neonatal sepsis	21 (0.89%)	16 (0.8%)	0.74
Neonatal pneumonia	22 (0.93%)	16	0.633
Neonatal brain injury	1 (0)	0 (0)	0.357
Neonatal intracranial hemorrhage	2 (0.09%)	1 (0.05%)	0.66
NICU admission*	51 (2.16%)	75 (3.74%)	0.002
Sex of the newborn, No. (%)			
Male	1098 (46.51%)	950 (47.33%)	0.584
Female	1263 (53.49%)	1057 (52.67%)	0.584
Birth weight (g), No. (%)			
≤2500	3 (0.1%)	3 (0.1%)	0.84
2501-3999	2169 (91.9%)	1864 (92.9%)	0.21
≥4000	189 (8.0%)	140 (7.0%)	0.20

*p <0.05. Normally distributed measurement data were analyzed using two-sample independent t-test and expressed as x±s. The countable data were presented as percentages, and the χ^2 test was used to analyze the differences between the two groups. Abbreviations: NC: not calculate; NICU: neonatal intensive care unit

abruption (4.48% *vs.* 2.96%; p>0.05) between the IOL and spontaneous onset of labor groups.

The neonatal intensive care unit (NICU) admission rate of newborns was significantly higher in the IOL group than in the spontaneous onset of labor group (3.74% *vs.* 2.16%; p<0.05). However, there was no significant difference between the two groups in terms of birth weight and its distribution, sex of the newborn, the incidence of neonatal brain injury, the incidence of neonatal intraventricular hemorrhage, perinatal death, neonatal hyperbilirubinemia, neonatal septicemia, neonatal pneumonia, and Apgar score ≤7 at birth (p>0.05).

Association of IOL with a Longer Duration of Labor

As summarized in Table III, the duration of the first (8.62±5.12 *vs.* 8.17±4.88 h) and the second (0.65±0.78 *vs.* 0.55±0.69 h) stages of labor and the total duration of labor (9.37±5.37 *vs.* 8.82±5.13 h) were significantly higher in the IOL group compared to the spontaneous onset of labor groups (p<0.05).

The total duration of labor in the nulliparous group was the longest, with an average length of 11.07±5.12 h. Duration of labor shortened with an increase in the number of parturitions, and the average total duration of labor in multipara women was 8 h (Table IV).

IOL Increases Postpartum Blood Loss

The IOL group was associated with higher postpartum blood loss (219.18±188.32 *vs.* 199.95±124.69 mL; p=0.01) and a significantly increased risk of sPPH (0.8% [16/2007] *vs.* 0.33% [8/2361]; p=0.041) compared with the spontaneous onset of the labor group. No significant difference was found in the incidence of PPH (3.8% [77/2007] *vs.* 2.8% [66/2361]; p=0.054).

As shown in Figure 2, the volume of vaginal bleeding rose with the increase in the total duration of labor. The most significant rise was observed when the total duration of labor exceeded

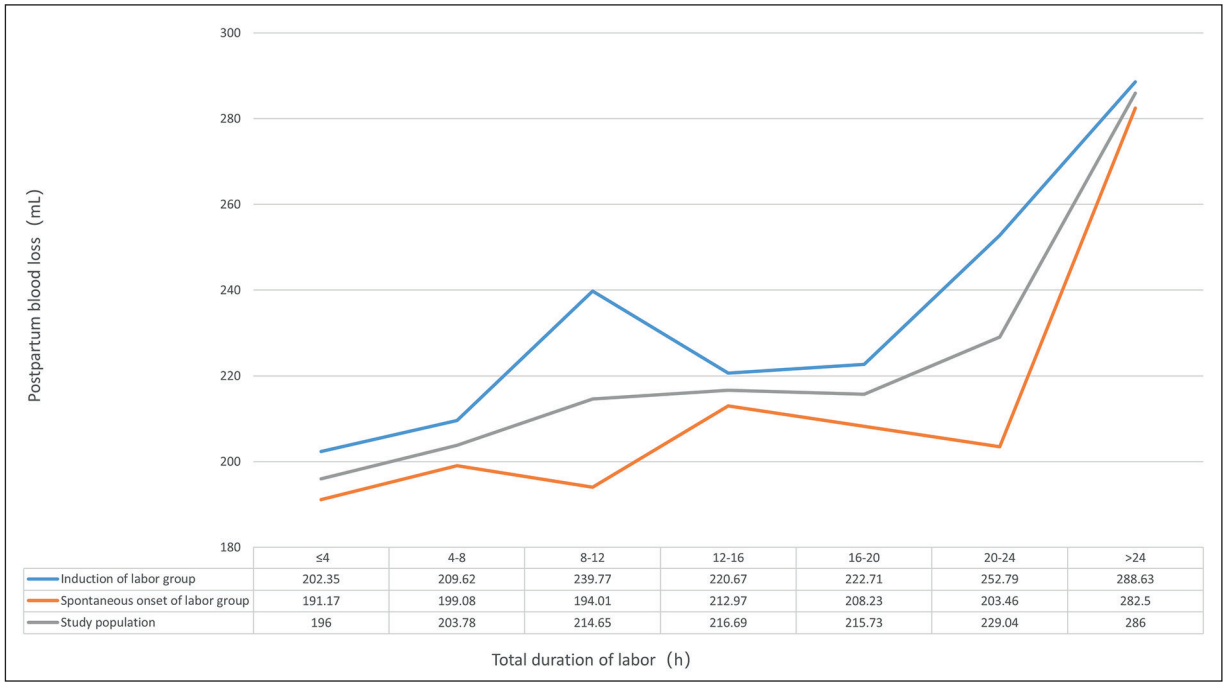

Figure 2. Relationship between the total duration of labor and postpartum blood loss. Postpartum blood loss increases with the prolongation of the total duration of labor. Moreover, the induction of labor group had higher postpartum blood loss than the spontaneous onset of labor group for the same total duration of labor.

Table III. Correlation between the duration of labor and induction of labor.

	Spontaneous onset of labor (n=2361) n (%)	Induction of labor (n=2007) n (%)	*p*-value
Duration of labor (h)			
First stage of labor*	8.17±4.88	8.62±5.12	0.003
Second stage of labor*	0.55±0.69	0.65±0.78	<0.001
Third stage of labor	0.11±0.11	0.12±0.12	0.314
Total stages of labor*	8.82±5.13	9.37±5.37	0.001

*$p<0.05$.

Table IV. Induction of labor in nulliparous women with a longer duration of labor.

	Parity			
	1	2	3	>3
Duration of labor (h)				
Total duration of labor (h)	11.07±5.12	5.29±3.32	4.29±2.82	4.18±0.77
p	<0.001			

Data presented as mean±SD.

Table V. Induction of labor and postpartum hemorrhage in nulliparous women.

		Parity			
Group	**Cases**	**1**	**2**	**3**	**>3**
Spontaneous onset of labor group	2361	39 (1.65%)	25 (1.06%)	2 (0.08%)	0
Induction of labor group	2007	55 (2.74%)	3 (0.15%)	1 (0.05%)	0
OR (95% CI)	-	1.557 (1.039-2.332)	1.103 (0.635-1.917)		
p	-	0.03	0.671	0.794	NC

OR: odds ratio; CI: confidence interval; NC: not calculate.

20 h (Figure 2). IOL increased the risk of PPH compared with spontaneous onset of labor (2.74% *vs.* 1.65%; OR: 1.557, 95% CI: 1.039-2.332; p=0.03) in nulliparous women, but there was no significant difference in multipara women (Table V).

Discussion

This retrospective case-control study selected women with low-risk delayed pregnancy and vaginal delivery and compared and analyzed the pregnancy outcomes between the IOL and spontaneous onset of labor groups. Our results showed that IOL was associated with higher incidences of chorioamnionitis in women, an increased rate of operative vaginal birth, and higher rate of neonatal NICU admissions. Moreover, IOL also correlated with the longer duration of labor and more significant postpartum blood loss. It increases postpartum blood loss, leading to an increased risk of PPH, which is possibly caused by prolonged labor. Therefore, we suggest that low-risk nulliparous women should avoid IOL without medical indications.

Since maternal and fetal risks increase in the third trimester of pregnancy, IOL is an important measure to terminate a pregnancy when the benefits of termination are greater than those of pregnancy continuation. Therefore, correctly identifying the timing of IOL can optimize pregnancy outcomes. Currently, the effect of IOL on pregnancy outcomes in low-risk pregnant women remains controversial.

Vahratian et al[5] showed that the labor process in pregnant women with IOL was significantly longer compared to women with the spontaneous onset of labor, which is consistent with our findings. We showed that the increase in the duration of labor in the IOL group was predominantly in the first stage of labor, extended by nearly 0.5 h. Further stratified analysis of parity showed that the total duration of labor in the IOL group was negatively correlated with an increase in parity, with the duration being the longest in nulliparous women with IOL (11.07±5.12 h). The average duration of labor was usually <8 h in multipara women. The proportion of multipara women in the spontaneous onset of labor group in our study was higher than that in the IOL group, which suggests that multipara women are more likely to start labor spontaneously and their duration of labor is shorter.

Cheng et al[6] found that the extension of the first stage of labor increases the duration of the second stage of labor and is associated with an increased risk of PPH[7,8]. We showed that IOL was associated with more postpartum blood loss compared to the spontaneous onset of labor (219.18±188.32 *vs.* 199.95±124.69 mL). The average postpartum blood loss increased with the prolongation of the total stages of labor, which led to an increase in the risk of PPH and even sPPH, especially when the total duration of labor exceeded 20 h. Compared with the spontaneous onset of labor group with the same total duration of labor, the IOL group had a higher volume of vaginal bleeding with more postpartum blood loss, suggesting that prolonged labor is not the only reason. We may speculate that IOL procedures can lead to an additional increase in postpartum blood loss. Since the significantly longer total duration of labor in nulliparous women is associated with a higher incidence of PPH, and IOL can lead to an increase in postpartum blood loss, attention should be paid to avoiding selective IOL in nulliparous women without medical indication as far as possible.

This study showed a higher incidence of operative vaginal birth and chorioamnionitis in the IOL group, which coincided with a higher risk of admission to the NICU. However, it did not lead to an increase in other adverse maternal and

perinatal outcomes, which is consistent with the results of the previous studies[9,10]. Additionally, as opposed to other studies[11,12], our research included only low-risk, later-than-term pregnant women with successful vaginal delivery, without obstetric or medical complications. This allowed eliminating the influence of confounding factors to better explain the impact of IOL on perinatal outcomes.

Our study has some limitations. There were no data on the use of oxytocin for labor induction during delivery. Additionally, we did not look at the specific methods of IOL and their association with a longer total duration of labor and greater frequency of adverse outcomes.

Conclusions

IOL prolongs the total duration of labor, increases postpartum blood loss, and is associated with a higher incidence of NICU admission in offspring. Our study design eliminated the influence of some confounding factors in the transition to a cesarean section and developed tools to assess postpartum blood loss rather than the success rate of the IOL.

Based on the results of this study, the clinical decision-making of IOL without medical indications for low-risk nulliparous women needs to be more prudent. Low-risk pregnant women should try to avoid IOL without medical indications.

Conflicts of Interest

The authors declare no conflicts of interest.

Ethics Approval and Consent to Participate

The study was approved by the Ethics Committee of the Fujian Provincial Maternity and Children's Hospital and was conducted by Chinese law and the Guidelines of the National Human Biomedical Research Policies. Informed consent was not required owing to the retrospective study design. Permission to access anonymized (non-identified) data was granted by the Fujian Provincial Maternity and Children's Hospital Database steering committee.

Consent for Publication

Not applicable.

Data Availability Statement

Data were anonymized and no patient identifying information was included to preserve patient confidentiality. All data to evaluate the conclusions in the paper are available for scientific purposes if needed.

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Author Contribution Statement

Zhang Qinjian and Chen Siwen designed the analyses, and Zhang Qinjian drafted the manuscript. Yan Jianying conceptualized the study; and Xu Xia and Zhang Huale contributed to data acquisition. All authors have revised the manuscript for important intellectual content.

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