

**Effect of interpregnancy interval on adverse perinatal outcomes in Southern China:  
a retrospective cohort study, 2000-2015**

Lifang Zhang,<sup>1,2\*</sup> Songying Shen,<sup>1\*</sup> Jianrong He,<sup>1,2</sup> Fanfan Chan,<sup>1,2</sup> Jinhua Lu,<sup>1,2</sup> Weidong Li,<sup>1,2</sup>  
Ping Wang,<sup>1,2</sup> Kin Bong Hubert Lam,<sup>3</sup> Ben Willem J. Mol,<sup>4,5</sup> Shiu Lun Au Yeung,<sup>6</sup>  
Huimin Xia,<sup>1,7†</sup> C Mary Schooling,<sup>6</sup> Xiu Qiu<sup>1,2†</sup>

\* contributed equally

† contributed equally

**Author affiliations**

1. Division of Birth Cohort Study, Guangzhou Women and Children's Medical Center, Guangzhou Medical University, Guangzhou, China
2. Department of Woman and Child Health Care, Guangzhou Women and Children's Medical Center, Guangzhou Medical University, Guangzhou, China
3. Nuffield Department of Population Health, University of Oxford, Oxford, UK
4. The Robinson Research Institute, School of Pediatrics and Reproductive Health, University of Adelaide, Adelaide, SA, Australia
5. Institute of Applied Health Research, University of Birmingham, Birmingham, UK
6. School of Public Health, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong SAR, China
7. Department of Neonatal Surgery, Guangzhou Women and Children's Medical Center, Guangzhou Medical University, Guangzhou, China

Corresponding authors

Xiu Qiu

Division of Birth Cohort Study and Department of Woman and Child Health Care, Guangzhou Women and Children's Medical Center, Guangzhou Medical University, Guangzhou, China,

Email: [xiu.qiu@bigcs.org](mailto:xiu.qiu@bigcs.org)

or

Huimin Xia

Division of Birth Cohort Study and Department of Neonatal Surgery, Guangzhou Women and Children's Medical Center, Guangzhou Medical University, Guangzhou, China,

Email: [huimin.xia@bigcs.org](mailto:huimin.xia@bigcs.org)

## Abstract

**Background:** In January 2016, a universal two-child policy was introduced in China. The association of interpregnancy interval (IPI) with perinatal outcomes has not previously been assessed among Chinese population. We investigated the effect of IPI after live birth on the risks of preterm delivery, and small, and large for gestational age births in China.

**Methods:** We conducted a cohort study among 227 352 Chinese women with their first and second delivery during 2000 to 2015. IPI was calculated as months from first live delivery to conception of the second pregnancy. Poisson regression models with robust variance were fit to evaluate associations of IPI with risk of adverse perinatal outcomes, adjusted for potential confounders.

**Results:** Compared to IPI of 24-29 months, IPI <18 months was associated with higher risks of preterm birth (PTB) and small for gestational age (SGA). For IPI <6 months, the adjusted relative risk (RR) for PTB and SGA were 2.04 (95% confidence interval [CI] 1.83, 2.27) and 1.43 (95% CI 1.31, 1.57), respectively. Women with IPI ≥60 months had higher risks of PTB and large for gestational age (LGA). For IPI ≥120 months, the adjusted RRs for PTB and LGA were 1.67 (95% CI 1.43, 1.94) and 1.10 (95% CI 0.97, 1.26).

**Conclusions:** Women with IPI <18 months after live birth had higher risk of PTB and SGA, and IPI ≥60 months was associated with higher risk of PTB and LGA. These findings may provide information to Chinese couples about the appropriate interpregnancy interval for a second pregnancy.

Key words: interpregnancy interval; preterm birth; small for gestational age; large for

gestational age;

## Introduction

Interpregnancy interval (IPI) has been viewed as a potential risk factor for adverse perinatal outcomes.<sup>1-5</sup> The associations between IPI and adverse perinatal outcomes have been studied in both developed and developing countries.<sup>3, 6</sup> However, there is a lack of information from large-scale prospective studies exploring the effect of IPI among Chinese women due to the one-child policy which was introduced in 1979. The one-child policy was strictly enforced for urban residents and public-sector workers. From 1984 onwards rural couples in most provinces were allowed to have a second child if their first child was a girl. The implication of the one-child policy for modern China was a substantial reduction in the total fertility rate.<sup>7</sup>

In October 2015, the Chinese government announced that the one-child policy was to be replaced by a universal two-child policy, which came into effect in January 2016.<sup>7, 8</sup> It allowed approximately 90 million primiparous women of child-bearing age to have the option of a second pregnancy.<sup>9</sup> The Chinese National Health and Family Planning Commission estimated that 60% of these 90 million women will be aged over 35 years, which increases the risk of maternal complications during pregnancy. In addition, most mothers taking advantage of the two-child policy will have a long interval between the two pregnancies. Both short and long IPIs have been associated with increased risk of adverse perinatal outcomes, including preterm birth (PTB),<sup>1, 10, 11</sup> low birthweight (LBW),<sup>5, 12, 13</sup> small for gestational age (SGA),<sup>14, 15</sup> large for gestational age (LGA)<sup>14</sup> and perinatal mortality.<sup>16</sup> Thus, clinical recommendations encourage adequate spacing between pregnancies. The

American College of Obstetricians & Gynecologists recommends a minimum spacing of 18 months after a live birth and the World Health Organization recommends 24 months; but no upper limit has been suggested.<sup>17, 18</sup> However, evidence from relevant, large-scale population based studies in China is lacking, although many Chinese women may have become pregnant again after the two-child policy was introduced. As such, it is of clinical importance to develop guidance for interconception care to encourage adequate IPI based on scientific evidence from large-scale cohort studies in China.

Guangzhou is the third largest city in China, with a population of 14.0 million in 2016 and an increasing proportion of second or higher order births, up from 19.1% in 2000 to 49.5% in 2015.<sup>19, 20</sup> In this setting, we took advantage of comprehensive, routinely collected birth surveillance data to test the hypothesis that short and long IPIs after live birth are associated with increased risk of adverse perinatal outcomes, including PTB, SGA and LGA in a Chinese population.

## **Methods**

### ***Study design and participants***

The study is based on information obtained from the Guangzhou Perinatal Health Care and Delivery Surveillance System (GPHCDSS), which was established in 2000 to collect information on all live births in the city,<sup>19, 20</sup> and recorded 2.4 million births from 2000 to 2015. The following information was extracted: maternal birthdate, maternal educational, maternal ethnicity, delivery hospital, gravidity and parity, newborn's birthdate, newborn sex,

gestational age and birthweight. Using the unique Resident Identity Card number, we identified women with first (parity=1) and second live births (parity=2) between 26 to 43 completed weeks of gestation from January 1 2000 to December 31 2015. Local average disposable income in Guangzhou from 2010 to 2015 was extracted from the census. To assess whether associations from 2000-2015 were similar to those after the implementation of the two-child policy, we similarly identified women who had a second child in 2016 (n=70 248) to use for validation. Women of non-Chinese nationality were excluded.

This study was conducted in compliance with local and national regulations and was approved by the Institutional Ethical Committee board of Guangzhou Women and Children's Medical Center.

### ***Definition of interpregnancy interval***

IPI was calculated as the time (in months) elapsed between the date of delivery of the first live birth and the date of conception for the second pregnancy, which in turn was calculated as the delivery date minus gestational age (in days). Long-standing implementation of the one-child policy means that many women have a long IPI, so IPIs were categorized as: <6, 6-<12, 12-<18, 18-<24, 24-<30, 30-<36, 36-<60, 60-<120, and  $\geq 120$  months.

### ***Perinatal outcomes***

Outcomes included in this study were PTB (gestational age <37 weeks), moderate to late preterm (32 to 36 weeks), extremely to very preterm (<32 weeks), SGA and LGA among the

second births. Gestational age was based on routine ultrasound examinations in the first or second trimester. When the ultrasound examination was not available (estimated as <10% of all births), the last menstrual period (LMP) would be used.<sup>20</sup> SGA and LGA were defined as birthweight <10th and >90th percentile, respectively, of sex- and gestational age specific birthweight based on the INTERGROWTH-21st standards.<sup>21</sup> Birthweight z-score relative to these standards was also calculated.

### ***Covariates***

Potential confounders that were considered included maternal ethnicity (Han and non-Han ethnic minority), maternal age at conception of the second pregnancy (<25, 25-29, 30-34 and ≥35 years), maternal education ≤9 years [middle school or below], 10-12 years [high school], 13-15 years [vocational/technical college], and ≥16 years [undergraduate or above]], and calendar year of birth at second pregnancy.

### ***Statistical analysis***

The relationship between IPI and the outcomes was tested using generalized additive models (GAM). We selected the number of degrees of freedom (df), from 3 to 10, based on model fit assessed from the Akaike Information Criterion (AIC). Prevalence of PTB, SGA, and LGA for the second child by IPI category was plotted using cubic B-spline functions with 4 df. Poisson regression models with robust variance were used to estimate unadjusted and adjusted relative risk (RR) and 95 % confidence interval (CI) for the association between IPI groups and the risk of adverse birth outcomes, with women who had an IPI of 24-30



months as the reference group. The multivariable models were adjusted for maternal ethnicity, maternal age at second conception, maternal education, and the year of delivery.

Preliminary analysis of the characteristics of first and second children born during 2000 to 2015 (Table S1) showed that first children were more likely to be girls. Therefore, we stratified the analysis by sex of the first child. Women who had a second pregnancy because of the loss of the previous child (selective fertility) are likely to have poor fetal outcomes and we also stratified by pregnancy loss between the two deliveries.<sup>22</sup> We undertook several other sensitivity analyses by restricting the study to women with the same partner, stratifying by maternal age at conception of the second pregnancy (<30 years versus ≥30 years), and limiting the analysis to infants born during 2010 to 2015. Furthermore, we additionally adjusted for local average disposable income. Since the main findings relate to a period before the implementation of the universal two-child policy, we compared the characteristics of mothers having a second child in 2000-2015 with those having a second child in 2016, and assessed their associations of IPI with birth outcomes. Furthermore, we undertook a sensitivity analysis, based on E-values, to evaluate the extent to which unmeasured confounding may have played a role in shaping the observed associations.<sup>23</sup> For an observed risk ratio of RR:  $E\text{-value} = RR + \sqrt{RR \times (RR - 1)}$ . The formula was applied to a RR greater than 1; for a RR less than 1, we first took the inverse of the observed RR and then applied the formula.

## Results

There were 2 419 184 births recorded in GPHCDSS between the start of 2000 and the end of 2015. We excluded women with multiple births (n=69 979), non-Chinese women (n=4805) and duplicate records (n=15 011). Among the remaining women, 229 311 births were matched to a previous birth by the same Resident Identity Card number, indicating a first and second child with the same mother. After excluding women without a delivery date (n=1 854) or without gestational age (n=105), a total of 227 352 mother-infant trios were included in the main analyses (Figure 1).

Among mothers with a live first birth during the study period (2000-2015), 15% had a second child during the same period, with the majority (84.0%) born between 2010 and 2015. Table S1 gives the characteristics of the whole study population. Mean (standard deviation [SD]) maternal age at first birth was 24.0 (3.5) years and overall, 0.5% (n=1128) of mothers were aged  $\geq 35$  years. There was an upward trend in maternal age at second birth, of 0.24 years per calendar year, giving a mean of 27.9 (SD 4.3) years with a relatively high proportion (7.1%; n=16 028) of them aged  $\geq 35$  years compared to maternal age at first birth. The remarriage rate in the study was 3.6%. The median IPI in this sample was 30 months (interquartile range [IQR] 15-51 months). The distribution of IPI by month is shown in Figure S1. Longer IPIs were observed among women who gave birth to their first child at 25-29 years (median 33 months) than for either the younger (<20 years; 21 months) or older mothers ( $\geq 35$  years; 22 months). Mothers with a higher educational level tended to have a longer IPI: those with undergraduate education or above had a median IPI of 42 months. Non-Han (ethnic minorities in China) women had shorter IPIs than the Han-Chinese (30 vs 33

months).

Table S2 shows the distribution of birthweight and gestational age for the first and second child of the same woman by different IPI categories. Overall, the second child had higher birthweight z-score (0.05 vs -0.22), but shorter gestational age than the first child (39.1 vs 39.2 weeks). The birthweight z-score in second children was higher among longer IPI groups. Small proportions of the second pregnancies had IPI <6 months (4.1%) or  $\geq 120$  months (1.1%).

Table 1 shows maternal characteristics and birth outcomes for the second children by IPI category. For women aged  $\geq 35$  years at the second pregnancy, 11% had IPI  $\geq 120$  months. In addition, 60% of those with an IPI <6 months were aged <25 years. As shown in Figure 2, a J-shaped relationship between IPI and the prevalence of PTB was observed, with PTB prevalence being lowest when the IPI was 24-<30 months. The prevalence of SGA was inversely related to IPI, while there was a positive relationship between LGA and IPI.

Relative risks of birth outcomes according to IPI are presented in Table S3 and Figure 3.

Compared to women with IPI of 24-<30 months, women with shorter IPIs (<6, 6-<12, and 12-<18 months) had higher risk of PTB and SGA. After adjustment for maternal characteristics, the associations remained. Women with long IPI ( $\geq 120$  months) had higher risks of PTB and LGA. Long IPI of 60-<120 months were also associated with a higher risk of PTB and LGA. The E-values for observed RR varied from 1.11 to 3.50 for three adverse birth outcomes, which

indicated considerable unmeasured confounding would be needed to explain away these associations.

The findings regarding the association between IPI and sub-categories of PTB are shown in Table 2. Women with IPI other than 24-<30 months had higher risk of moderate to late PTB. Women with short IPI (<12 months) had higher risk of extreme to very PTB.

Subgroup analysis and sensitivity analysis indicated that the previous findings were unlikely due to confounding by the sex of the first child (Table S4 and S5), selective fertility (Table S6 and S7), maternal age (Table S8 and S9), different partner (i.e. re-marriage) (Table S10) or time period (birth during 2010 to 2015) (Table S11), although some of the associations were no longer significant because of smaller samples sizes and potentially chance differences on stratification. Women who had second child in 2016 were older with higher IPI than women who had a second child before the implementation of the two-child policy (Table S12); IPI <18 and  $\geq 60$  months were still associated with higher risk of PTB, but not with SGA and LGA after adjustment in 2016 (Table S13).

## **Comment**

### **Principal findings**

In large-scale study of contemporary Chinese women, we found a J-shape association between IPI and risk of PTB, with higher risks for both short and long intervals between the first and second pregnancy (IPIs <6, 6-<12, 12-<18, 60-<120 and  $\geq 120$  months). Higher risk of

SGA was associated with short IPI (<18 months), whereas LGA was associated with longer IPI (60-<120 and  $\geq 120$  months). These associations were independent of maternal age, socioeconomic status, ethnicity, selective fertility, sex of the first child, different family structure (i.e. re-marriage) and birth year.

### **Interpretation**

The mechanism(s) underlying the effect of short and long IPI on adverse birth outcomes is still unclear. Several hypotheses have been proposed.<sup>24</sup> The 'maternal depletion' hypothesis,<sup>4, 25</sup> proposes that women with a short time period between successive pregnancies do not have adequate time to recover from the physiological stresses of intra-uterine development and as a consequence, a depletion of maternal nutrient stores, especially folate deficiency, leads to an increase in the risk of adverse perinatal outcomes. Birth defects may contribute to the occurrence of preterm birth,<sup>26</sup> and mediate the association between short IPI and PTB. Folate deficiency could lead to a birth defect (e.g., spina bifida), and also contribute to preterm delivery. Infant birth defects are not available in the present study, but previous studies showed that IPIs shorter than 6 months are associated with preterm birth, and major congenital malformations.<sup>14</sup> Others have argued that the observed association with short IPIs is confounded by lower socioeconomic status and health behaviors including unstable lifestyle and lower utilization rate of health services.<sup>3, 13, 14, 27</sup> In the present study, an association remained after adjusting for socioeconomic status, but residual and/or unmeasured confounding could not be completely ruled out, although the E-values indicated considerable unmeasured

confounding would be needed to eliminate these associations.

A hypothesis for the effect of long IPI on birth outcomes is 'the physiological regression hypothesis',<sup>13</sup> which arose in the light of evidence that pregnancy outcomes in women with long IPI were similar to those of primigravida mothers. The hypothesis states that after years of recovery, the benefits from a preceding pregnancy for physiological reproductive adaption are attenuated, returning to a condition similar to primigravida.<sup>13</sup> However, in our study birthweight was higher and gestational age shorter in second births born to women with a long IPI compared to first births. Moreover, we did not find a higher risk of SGA in women with long IPI, which is inconsistent with previous studies.<sup>3, 13-15</sup> As such, the 'physiological regression hypothesis' does not explain the outcomes observed our population. Another possible explanation is that factors associated with underlying subfertility or repeated miscarriage may increase both time to the next pregnancy and adverse birth outcomes thereby overestimating the effect of long IPI.<sup>28</sup> We have no data about subfertility or repeated miscarriage to test this possibility, sensitivity analyses restricted to women without previous pregnancy loss gave similar results (Table S6).

Conversely, we observed a higher risk of LGA in women with long IPI. Most of the previous studies that investigated the effect of IPI on birth outcomes focused on PTB and SGA.<sup>3, 5, 12, 13</sup> Among the few studies that assessed LGA, an increased risk of LGA in women with short or long IPI was reported,<sup>14</sup> but in our study, an increased risk of LGA was only found among women with long IPI. One possible explanation is that in our study the second births in

women with long IPI tended to take place in recent years. As Guangzhou has experienced dramatic socio-economic development in the past decades, income as well as nutritional status of women has improved,<sup>29</sup> potentially contributing to a rise in LGA, independent of IPI. Another potential explanation is that women with longer IPI were older, had higher pre-pregnancy body mass index (BMI), greater gestational weight gain and more gestational diabetes than women with shorter IPI. However, we do not have information on BMI, gestational weight gain or gestational diabetes.

The high sex ratio of the second child suggests selective abortion<sup>30</sup>, which is illegal in China, making it difficult to obtain reliable data. Abortion is associated with higher risk of PTB.<sup>31, 32</sup> History of abortion was considered as a confounder because it could also increase IPI. Excluding women with previous pregnancy loss little changed the estimates (Table S6).

### **Strengths of the study**

As far as we know, this is the first large-scale cohort study to investigate the association between IPI and birth outcomes in China. We also obtained information from a comprehensive birth registration system comprising 99% of deliveries in Guangzhou over a long time period (16 years). Given the announcement that China's one-child policy was to be replaced by a universal two-child policy effective January 1st, 2016., the number of women with second live births in the present study (227 352) was very large. This paper provides timely evidence to inform future Chinese public health guidance on family planning and birth spacing, which is urgently required given the recent change to a two-child policy in

China.

### **Limitations of the data**

Some limitations should be taken into consideration. First, although we were able to adjust for some potential confounders, residual and unmeasured confounding could not be completely ruled out, such as maternal obesity, prior gestational diabetes or other pregnancy complications. Sensitive analysis using E-values (Table S3) indicated that relatively influential unmeasured confounders would be needed to negate the observed associations, for example an unmeasured confounder associated with IPI and PTB by a RR of 3.06-fold above and beyond the measured confounders to move an observed RR of 2.04 to the null. Second, only live births were considered in the present study, pregnancy losses and stillbirths were not included. Hence, effects of IPI after pregnancy loss on pregnancy outcomes, as well as effects of IPI on miscarriage or pregnancy loss should be clarified in further studies. Third, the effects of IPI may differ depending on whether the previous pregnancy resulted in a loss (i.e., miscarriage) versus a live birth, which means selective fertility may play a role.<sup>22</sup> However, associations were similar when births following pregnancy loss were excluded (Table S6). Shachar and colleagues<sup>33</sup> found that IPIs of <6 months or 6–11 months after live birth was associated with higher odds of PTB, while short IPI after pregnancy termination showed a lower OR of 0.87 (95% CI 0.81–0.94). A large study conducted in Latin American women (n=258 108) found that IPI after pregnancy termination (both miscarriage and induced) of less than 6 months was associated with higher risk of PTB in the next pregnancy.<sup>34</sup> Fourth, information on months of pregnancy attempt was



unavailable in the present study making it difficult to identify the role of subfertility versus long IPI in adverse birth outcomes.

Finally, selection bias is possible, because attributes of women who had a second child before the implementation of two-child policy, may have generated this pattern of associations. The one-child policy was strictly enforced for urban residents and public sector workers.<sup>7</sup> Women working in the private sector or from rural areas would be more likely to have a second child and could be more prone to poor birth outcomes. Similarly, women in this study may differ from those who will have a second birth in future. However, similar findings concerning higher risk of PTB were found for second births in 2016, shortly after the implementation of the two-child policy in China, although women who were able to have a second child shortly after the implementation of the new policy may also be atypical and perhaps healthier. Selection bias could also have arisen from the choice of study period.

However, similar results were obtained for births in 2010 to 2015 (Table S11).

Generalizability of our findings in China post-2015 should be interpreted with caution. The study population only represents a small proportion of all childbearing women in China, so, the findings here should be confirmed by studies in other places.

## **Conclusions**

In this large sample from China, we found IPI <18 months after live birth was associated with increased risk of PTB and SGA, whereas IPI ≥60 months was associated with higher risk of PTB and LGA. With the universal introduction of the two-child policy in China, an increasing

proportion of women will have a second child. Development of clinical guidance is urgently required to inform Chinese women of the recommended interval between pregnancies. The guidance should be developed based on further high-quality studies conducted in the Chinese population.

## **Acknowledgments**

This study is supported by the Guangzhou Science and Technology Bureau, Guangzhou, China (2011Y2-00025 and 201508030037). The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. We thank all the staff work for the GPHCDSS for their contribution to this study. We thank Dr Suzanne Bartington, University of Birmingham for English language review that greatly improved the manuscript.

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## Figure legends

### Figure 1. Selection process of study population.

GPHCDSS, Guangzhou Perinatal Health Care and Delivery Surveillance System.

### Figure 2. The prevalence of second delivery outcomes by interpregnancy interval.

PTB, preterm birth, defined as birth < 37 completed weeks of gestation. SGA, small for gestational age, defined as birthweight <10th percentile for gestational age based on the INTERGROWTH-21ST standards by gestational age and infant sex. LGA, large for gestational age, defined as birthweight >90th percentile for gestational age on the basis of INTERGROWTH-21ST standards by gestational age and infant sex. The dots are the prevalence of second delivery outcomes by interpregnancy intervals in months. The shaded areas indicated the 95% confidence intervals for prevalence (solid line). Prevalence of second delivery outcomes across different IPIs was plotted using generalized additive models using cubic B-spline functions.

### Figure 3. Adjusted relative risks for delivery outcomes of the second child during 2000 to 2015 in Guangzhou.

RR, relative risk. PTB, preterm birth, defined as birth < 37 completed weeks of gestation.

SGA, small for gestational age, defined as birthweight<10th percentile for gestational age based on the INTERGROWTH-21ST standards by gestational age and infant sex. LGA, large for gestational age, defined as birthweight >90th percentile for gestational age on the basis of INTERGROWTH-21ST standards by gestational age and infant sex. The crude and adjusted RRs

were estimated from Poisson regression models with robust variance. The adjusted RRs were adjusted for maternal ethnicity, maternal age at second conception, maternal educational years, and year of delivery.

## Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

**Figure S1.** The distributions of interpregnancy interval by months of the whole population during 2000 to 2015.

**Table S1.** The characteristic of the whole population during 2000 to 2015.

**Table S2.** The distributions of birthweight and gestational age of the first and second child in different interpregnancy intervals during 2000 to 2015.

**Table S3.** Crude and adjusted relative risks for delivery outcomes of the second child during 2000 to 2015 in Guangzhou.

**Table S4.** Crude and adjusted relative risk for delivery outcomes of the second child among women whose the first child was a boy during 2000 to 2015 in Guangzhou.

**Table S5.** Crude and adjusted relative risk for delivery outcomes of the second child among women whose the first child was a girl during 2000 to 2015 in Guangzhou.

**Table S6.** Crude and adjusted relative risk for delivery outcomes of the second child among women without pregnancy loss between two deliveries during 2000 to 2015 in Guangzhou.

**Table S7.** Crude and adjusted relative risk for delivery outcomes of the second child among women with pregnancy loss between two deliveries during 2000 to 2015 in Guangzhou.

**Table S8.** Crude and adjusted relative risk for delivery outcomes of the second child among women with maternal age at conception for the second pregnancy <30 years during 2000 to 2015 in Guangzhou.

**Table S9.** Crude and adjusted relative risk for delivery outcomes of the second child among

women with maternal age at conception for the second pregnancy  $\geq 30$  years during 2000 to 2015 in Guangzhou.

**Table S10.** Crude and adjusted relative risk for delivery outcomes of the second child among women with the same partner during 2000 to 2015 in Guangzhou.

**Table S11.** Crude and adjusted relative risk for delivery outcomes of the second child during 2010 to 2015 in Guangzhou.

**Table S12.** Comparison of characteristics among women who had second child during 2000-2015 and 2016 in Guangzhou.

**Table S13.** Crude and adjusted relative risk for delivery outcomes of the second child in 2016 in Guangzhou (N=70248).