Association of maternal pre-pregnancy body mass index with adverse pregnancy outcomes according to maternal age: a population-based cohort study

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Abstract

Objective To clarify the association of pre-pregnancy body mass index (BMI) with adverse pregnancy outcomes according to maternal age in a large and diverse population in China. Design Retrospective cohort study. Setting Guangdong Province, China. Population 669101 women participated in the National Free Preconception Health Examination Project in Guangdong Province, China, from 2013 to 2017. Methods BMI were calculated and classified into four categories according to Chinese criteria: underweight (BMI <18.5kg/m2), normal weight (18.5-23.9kg/m2), overweight (24.0-27.9kg/m2), and obesity ([?]28.0kg/m2). Main outcome measures Outcomes were preterm birth (PTB), large for gestational age (LGA), small for gestational age (SGA), primary caesarean delivery, shoulder dystocia or birth injury, and stillbirth. Log-binomial models were employed to estimate the adjusted risk ratios (RRs) and 95% confidential intervals (95%CIs) for underweight, overweight and obesity. Results The incidence ratios PTB, LGA, SGA, primary caesarean delivery, shoulder dystocia or birth injury and stillbirth were 5.0%, 11.2%, 9.7%, 14.5%, 1.1% and 1.2respectively. Overall, compared with normal BMI, underweight was associated with increased risk of PTB (adjusted RR 1.06, 95%CI 1.04-1.09) and SGA (1.23, 1.22-1.26); overweight was associated with the increased risk of LGA (1.17, 1.14-1.19), primary caesarean delivery (1.18, 1.16-1.20) and stillbirths (1.44, 1.03-2.06); and obesity was associated with increased risk of PTB (1.12, 1.05-1.20), LGA (1.32, 1.27-1.37), primary caesarean delivery (1.45, 1.40-1.50). These associations were different according to maternal age. Conclusion Maternal pre-pregnancy abnormal BMI were associated with the risks of adverse pregnancy outcomes among Chinese population, but the risks differed according to maternal age.

Introduction

It has been suggested maternal abnormal body mass index (BMI) before pregnancy is associated with several adverse pregnancy outcomes including preterm birth (PTB), abnormal birthweight and neonatal mortality.[1-4] However, large cohort studies investigating the association between maternal BMI and adverse pregnancy outcomes have almost always been done in developed countries with high prevalence of overweight and obesity but low prevalence of underweight.[5] Little reliable evidence exists from China or other developing countries where the prevalence of overweight and obesity is increasing but the prevalence of underweight is still high.[6]

Although the cause of adverse pregnancy outcomes is usually unknown, maternal age is the strongest known risk factor. The risk of several adverse pregnancy outcomes (such as PTB and miscarriage) is slightly elevated in the youngest mothers and then rises sharply in older mothers.[1, 7-9] However, very little study has been done to investigate the association of pre-pregnancy BMI with adverse pregnancy outcomes according to the maternal age, which is vital for risk stratification and interventions tailored to subgroup population.

We aimed to clarify the association of maternal pre-pregnancy BMI with risk of several adverse pregnancy outcomes in a large population-based cohort study in China, and to quantify such risk by maternal age in order to provide accurate data for risk assessment and counselling in pre-pregnancies.

Methods

Study design and Participants

We undertook a retrospective cohort study of women with reproductive age who participated in the National Free Preconception Health Examination Project (NFPHEP) from 1st January 2013 to 31st December 2017, successfully became pregnant and then had pregnancy outcome in Guangdong Province, China. The NFPHEP has covered all rural counties/districts since 2013, with aim to decline adverse pregnancy outcomes through providing free health examination before conception, counselling services for reproductive couples. The study design, organization and implementation have been described previously[7-10].

In the current analysis, we excluded women who did not measure weight and height before pregnancy; women with chronic disease (including anaemia, hypertension, heart disease, hepatitis B, epilepsy, thyroid disease, chronic nephritis, cancer and diabetes) as they were prone to receive medical interventions before and during pregnancy. Women with multiple births or without information on gestational week, birth weight, delivery method, shoulder dystocia or injury birth or stillbirth were also excluded.

The NFPHEP was approved by the Institutional Review Board of the Chinese Association of Maternal and Child Health Studies. Written informed consent was obtained from the participants before recruitment. The present study was executed jointly by Guangzhou Medical University and Guangdong Institute of Family Planning Science and Technology, in which the review boards determined that this study was exempt for ethical approval owing to the use of de-identified data.

Procedure

Baseline

The NFPHEP was based on the primary health and family planning network. All the reproductive couples who had planned to conceive were recruited. Baseline information was collected by trained local community health workers, which included demographic characteristics (age, educational level, occupation, ethnicity, migration and address of residence), history of chronic disease (hypertension, diabetes, heart disease, chronic nephritis, anaemia, cancer and psychiatric diseases), history of pregnancy (gravidity and parity) and history of adverse pregnancy outcomes (preterm birth, miscarriage, induced abortion, birth defect and stillbirth), lifestyle (maternal active smoking, passive smoking, alcohol consumption and husband smoking). Clinical professionals from the local authorized medical institutions then did physical examinations. Body weight and height were measured by calibrated instruments with standard measurement procedures.[11]

Follow up

All the participated women were followed up by trained local community health worker by telephone every two months to determine whether they had conceived successfully. Local health worker interviewed the women face to face or by telephone within three months after conception, documenting their last menstrual period, active smoking, alcohol consumption, and husband smoking during the early stage of the pregnancy. Women were also interviewed face to face or by telephone within six weeks of delivery to collect information on the hospital where delivery took place. Local community health workers then collected data from the medical records at the reference hospital regarding pregnancy outcomes, including gestational age (weeks), birth weight (grams), obstetrical outcomes (caesarean delivery, shoulder dystocia or birth injury), neonatal information (singleton or multiple births and sex) and stillbirth (only collected from 46 counties in 13 cities).

All of these baseline data and fellow up data were transferred to Guangdong Institute of Family Planning Science and Technology where they were cleaned, complied and de-identified. The endpoint of this study was to observe the pregnancy outcomes of the participated mothers and the study was terminated on 31st December 2017.

Categories of Pre-pregnancy BMI

Pre-pregnancy BMI was calculated by dividing the weight in kilogram (kg) by the square of the height in meters (m), and was classified into four categories based on Chinese criteria[12]: underweight (BMI <18.5kg/m^2), normal weight (18.5-23.9kg/m^2), overweight (24.0-27.9kg/m^2), and obesity ([?]28.0kg/m^2).

Outcomes

Because the NFPHEP collected data of pregnancy outcomes from medical records, all the pregnancy outcomes documented were over gestational age of 28 weeks and 0 days. The outcomes in present study were PTB (livebirth between 28 weeks and 0 days, and 36 weeks and 6 days of gestational age), large for gestational age (LGA, birth weight above the 90th percentile for gestational age by infants' sex), small for gestational age (SGA, birth weight below the 10th percentile for gestational age by infants' sex), primary caesarean delivery, shoulder dystocia or birth injury, and stillbirth (occurs between 28 or more completed pregnancy weeks).

Statistical analysis

Mean and standard deviation were reported for continuous variables, and frequencies and percentage were reported for categorical variables. Chi-square tests were employed to compare the distribution of BMI categories according to different baseline characteristics. Log-binomial models based on Generalized Estimating Equations (GEE) were employed to estimate the adjusted risk ratios (RRs) and 95% CIs of the six outcomes for underweight, overweight and obesity. In each outcome, three models were fitted.

In Model 1, we adjusted for participants' sociodemographic characteristics, including age at baseline (19-24 years, 25-29 years, 30-34 years, 35-39 years, or 40-50 years), ethnicity (Han or others), educational level (primary school or below, junior high school, senior high school or college or above), occupation (farmer, worker, servicer or others), region (pearl river delta, non-pearl river delta), migrant population (yes or no). In model 2, we additionally adjusted for history of pregnancy and adverse pregnancy outcomes except for primary caesarean delivery,[13] including first pregnancy (yes or no), primipara (yes or no); history of PTB (yes or no), miscarriage (yes or no), induced abortion (yes or no), birth defects (yes or no), or stillbirth (yes or no). In model 3, we additionally adjusted for the lifestyles of the women and the husband, including smoking status of husband before pregnancy and during the early stage of pregnancy (yes or no), smoking and alcohol consumption of women before pregnancy and during the early stage of pregnancy (yes or no), and passive smoking of women before pregnancy (yes or no). Because infant's sex is associated with the six outcomes, we adjusted for this variable in all analysis in addition to others listed.

Sensitivity and subgroup analysis

To examine the robustness of the association of pre-pregnancy BMI with adverse pregnancy outcomes, we preformed other two sensitivity analysis with additional adjustment for the length of time from pre-pregnancy examination to the last menstrual period (continuous data) or inclusion of women with self-reported perceived economic pressure (yes or no).

In the subgroup analysis, we divided women into different subgroups on the basis of maternal age. Among these age subgroups, we examined the associations of pre-pregnancy BMI with adverse pregnancy outcomes except for stillbirth. Among all the sensitivity and subgroup analysis, we adjusted for the all covariates listed in model 4.

Data were missing in first pregnancy (2910, 0.4%), primipara (2910, 0.4%), active smoke before pregnancy (4960, 0.7%), passive smoke (4939, 0.7%), husband smoke before pregnancy (23837, 3.6%), alcohol before pregnancy (6777, 1.07%), active smoke during early-stage pregnancy (22225, 3.3%), husband smoke during early-stage pregnancy (22742, 3.4%), alcohol during early-stage pregnancy (22775, 3.4%). We imputed these missing covariates by using the multiple imputation methodology based on other socio-demographic covariates. The significance level was set at 0.05 and all tests were two-sided. Statistical analyses were conducted by using Stata (Version 14.0) and Statistic software R (version 3.5.2).

Patient and public involvement

There was no patient involvement in the study design, in the development of outcome measures, or in the conduct of the study. No Core outcome set has been used. There is no plan on disseminating results directly to laypeople, but the results will be communicated to gynaecologists in the local departments and annual meetings.

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Results

Participant characteristics

By 31st December 2017, 727999 women had pregnancy outcomes. We excluded 14096 women who did not measure pre-pregnancy BMI; 41943 women with chronic diseases; 1995 women with multiple births and 864 women without any data on gestational week, birthweight or delivery methods. The remaining 669101 participants from 121 counties in 21 cities were included in the final analysis to examine the association of pre-pregnancy BMI with PTB, LGA birth and SGA birth. After additional exclusion of 145 women without data on delivery method, 668956 participants were included in the analysis to examine the association of pre-pregnancy BMI with primary caesarean delivery, should dystocia or birth or birth injury. A subgroup of 256882 abstracted from 46 counties 13 cities, who had data on stillbirth was included in the analysis to investigate the association of pre-pregnancy BMI with stillbirth. Figure S1 shows the selection of participants for the present study. The sample size and the proportion of the migrant population in each city are shown in Table S1-S3.

Characteristics of the women who had information on gestational age and infants' birthweight are summarized in Table S4. Among the 669101 women included, 136287 (20.3%) were underweight, 69819 (10.4%) overweight and 14556 (2.2%) obesity. The distribution of BMI categories with respect to different baseline characteristics were all significant different (P <0.05). Characteristics of 668956 women who had information on delivery methods and 256882 women who had information on stillbirth are shown in Supplemental S5-S6.

Association of pre-pregnancy BMI with pregnancy outcomes

The characteristics of new-borns and frequencies of outcomes according to pre-pregnancy BMI are shown in Table 1. Overall, the incidence ratios of PTB, LGA, SGA, primary caesarean delivery, should dystocia or birth injury, and stillbirths were 5.0%, 11.5%, 9.7%, 14.5%, 1.1% and 1.2

The adjusted RRs and 95% CIs of the six outcomes for pre-pregnancy BMI are shown in Table 2. In the fully adjusted model (model 3), compared with normal weight, underweight was inversely associated with risk of LGA birth (adjusted RR 0.83, 95%CI 0.82-0.85), primary caesarean delivery (0.88, 0.87-0.90) and stillbirth (0.73, 0.53-0.99), but positively associated with risk of PTB (1.06, 1.04-1.09) and SGA (1.23, 1.22-1.26). Overweight was inversely associated with risk of SGA birth (0.92, 0.90-0.95) and shoulder dystocia or birth injury (0.86, 0.79-0.93), but positively associated with risk of LGA (1.17, 1.14-1.19), primary caesarean delivery (1.18, 1.16-1.20) and stillbirth (1.44, 1.03-2.06). Pre-pregnancy obesity was inversely associated with risk of SGA birth (0.92, 0.87-0.97) but was positively associated with risk of PTB (1.12, 1.05-1.20), LGA birth (1.32, 1.27-1.37), and primary caesarean delivery (1.45, 1.40-1.50). In all the three models of the six outcomes, the adjusted RRs did not substantially change.

Sensitivity and subgroup analyses

In the sensitivity analyses, the association of pre-pregnancy BMI with the six outcomes did not substantially change with additional adjustment for the length of time from pre-pregnancy examination to last menstrual period or inclusion of women self-reported with perceived economic pressure (Table S7).

The association of pre-pregnancy BMI with risk of the five outcomes by maternal age are shown in Figure 1 and 2. Underweight was inversely associated with risk of LGA birth among those younger than 40 years (0.88, 0.85-0.91; 0.82, 0.80-0.84; 0.77,0.73-0.81; and 0.65, 0.58-0.74 among those aged 19- 24 years, 25-29 years, 30-34 years, 35- 39 years, respectively), and primary caesarean delivery among those younger than 35 years (0.89, 0.87-0.92; 0.86, 0.84-0.88; and 0.92, 0.88-0.97 among those aged 19-24 years, 25-29 years and 30-34 years, respectively), but positively associated with risk of SGA among those younger than 35 years (1.2, 1.17-1.23; 1.24, 1.21-1.27; and 1.32, 1.26-1.39 among those aged 19-24 years, 25-29 years and 30-34 years, respectively).

Overweight was inversely associated with risk of SGA birth among those aged 25-29 years (0.92, 0.88-0.96) and 30-34 year (0.88, 0.82-0.92), but positively associated with risk of PTB among those aged 35-39 years (1.22, 1.10-1.36), LGA among all the age groups (19-24 years: 1.11, 1.06-1.16; 1.17, 25-29 years: 1.17, 1.13-1.21; 30-34 years: 1.21, 1.16-1.26; 35-39 years: 1.20, 1.14-1.27 and 40-50 year:1.17, 1.02-1.34), and primary caesarean delivery among those younger than 35 years (19-24 years: 1.21, 1.17-1.25; 25-29 years: 1.21, 1.17-1.24; 30-34 years: 1.10, 1.10-1.15), .

Obesity was inversely associated with risk of SGA among those aged 19-24 years (0.89, 0.80-0.99), but positively associated with risk of PTB among those aged younger than 40 years (25-29 years: 1.15, 1.03-1.29; 30-34 years: 1.16, 1.01-1.34; and 35-39 years: 1.25, 1.03-1.52), LGA among all age groups (19-24 years: 1.22, 1.13-1.33; 25-29 years: 1.34, 1.26-1.43; 30-34 years: 1.34, 1.25-1.45; 35-39 years: 1.36, 1.23-1.51 and 40-50 year:1.44, 1.14-1.83), and primary caesarean delivery among those younger than 40 years (19-24 years: 1.52, 1.43-1.62; 25-29 years: 1.42, 1.35-1.50; 1.42, 30-34 years: 1.31-1.54, and 35-39 years: 1.31, 1.12-1.53).

Discussion

The association of pre-pregnancy BMI with adverse pregnancy outcomes is not fully understand, especially in low-income and middle-income countries, where levels of maternal overweight/obesity is increasing and underweight is still high.[14] In this large cohort study conducted in China, we found that compared with women with normal weight, pre-pregnancy underweight was positively associated with risk of PTB and SGA but inversely associated with risk of LGA, primary caesarean delivery and stillbirth; overweight was positively associated with risk of LGA, primary caesarean delivery and stillbirth but inversely associated with risk of SGA and shoulder dystocia or birth injury; and obesity was positively associated with risk of PTB, LGA and primary caesarean delivery but inversely associated with risk of SGA. However, these associations differ according to maternal age.

In relation to other studies

Investigators leading several large, retrospective cohort studies, which were mostly done in developed countries, assessed the association of maternal BMI with several adverse pregnancy outcomes.[3, 15] Sohinee and colleagues [3] used data from the Aberdeen Maternity and Neonatal Databank (AMND) in UK, encompassing 24241 discharges from 1976 to 2015, and found a linear relationship between increasing BMI and the risk of developing macrosomia, caesarean delivery, while underweight women had better pregnancy outcomes than women with normal BMI. Judith and colleagues [15]analysed singleton pregnancies of 436414 women in California and found that increasing BMI was associated with increasing odds of adverse outcomes. Obese women (BMI=30-39.9) were nearly twice as likely to undergo caesarean (adjusted OR 1.82, 95%CI: 1.78-1.87) and twice more likely to give macrosomia (>4000g), compared with abnormal BMI (18.5-24.9). However, the association of pre-pregnancy BMI with PTB (<37 weeks) was only found among underweight women (1.22, 1.16-1.28). Ram and colleagues [16] analysed data from the Better Outcomes Registry & Network Ontario, Canada, encompassing 48780 singleton and 7860 twin births between 2012 and 2016, and found that the risk of caesarean delivery increased with high maternal BMI in both singleton and twin gestations, however, the risk of PTB (<32 weeks) is only associated with underweight (adjusted RR: 2.10, 95%CI: 1.44-3.08). Some studies conducted in China use self-reported and recalled pre-pregnancy BMI, or did not adjust for some important confounders including history of pregnancy and pregnancy and adverse pregnancy outcomes, both of which weakened the validity of the association between maternal BMI and pregnancy outcomes[17, 18].

The associations of maternal pre-pregnancy BMI with LGA, SGA and caesarean delivery have been consistent among previous study[3, 15, 16, 17, 18, 19], but not the association of maternal pre-pregnancy BMI with PTB, shoulder dystocia or birth injury and stillbirth. For example, some studies suggested that only underweight was associated with PTB [15, 16], while others suggested only obesity were associated with PTB[18, 19]. The findings of our large cohort study were, however, inconsistent with previous study, which found that both of underweight and obesity were associated with PTB. Evidence from a recent meta-analysis suggested that maternal pre-pregnancy obesity associated with an increased risk of shoulder dystocia (RR: 1.63, 95%CI 1.33-1.99)[20], which was also inconsistent with our findings. Another meta-analysis suggested that both obesity and overweight were associated with stillbirth (OR, 1.27, 95%CI 1.18-1.36 and 1.81, 95% CI 1.69-1.93, respectively) [21], however, in our finding we only find significant association of overweight with stillbirth. The discrepancies of the association of pre-pregnancy BMI with adverse pregnancy outcomes might be related to sample size, methods of research, regions, and the various characteristics within the study population, such as different prevalence of abnormal BMI, types and definition of adverse pregnancy outcomes.

To our best of knowledge, our study is the first to investigate the pre-pregnancy BMI with adverse pregnancy outcomes according to maternal age, and the findings suggested that the associations differed according to maternal age. A recent study used nationwide birth certificate data from the US National Vital Statistics System to investigate the association of pre-pregnancy obesity with PTB, also found that the association of obesity with PTB differed according to maternal age[1]. Both of these findings suggested that risk assessment and counselling about pre-pregnancy BMI on adverse pregnancy outcomes should be stratified by maternal age.

Interpretation

The causes of adverse pregnancy outcomes are complex and multifactorial. However, the associations of pre-pregnancy BMI with pregnancy outcomes could be explained by the uterine environment of the different weight phenotype. Compared with normal weight, underweight women have lower plasma volume and rennin-aldosterone response during pregnancy[22], which may be associated with uteropla-central insufficiency and the increased prevalence of SGA. Previous studies speculated that inflammatory or intrauterine infection may be on the causal pathway between pre-pregnancy underweight or obesity and PTB[23, 24], although increased prevalence of postpartum infective complications was not observed in several studies[4, 23].

The associations of pre-pregnancy obesity or overweight with adverse pregnancy outcomes might be related to abnormal metabolism of fat. Obese women have higher levels of cord blood tumour necrosis factor α (TNF- α) and RANTES during pregnancy, which are known contributors to gestational diabetes mellitus and associated with an increased risk of LGA[25], whilst LGA was associated with the increased risk of caesarean delivery, shoulder dystocia[26], and stillbirth[27]. Overweight and obese women have increased insulin resistance in early pregnancy that becomes manifest clinically in late gestation as glucose intolerance and fetal overgrowth, which also are known risk factors for adverse pregnancy outcomes, such as caesarean delivery, shoulder dystocia and stillbirth[28, 29]. Furthermore, overweight and obesity is likely to gain more weight during pregnancy, which is known risk factors of several pregnancy complications[30] (such as gestational diabetes mellitus, gestational hypertension) and associated with adverse pregnancy outcomes[31]. Overall, further studies are needed to uncover the potential mechanisms of adverse pregnancy outcomes related to pre-pregnancy BMI.

Strengths and Limitation

One of the major strengths of this study is the sample size. For this cohort, we recruited 669101 participants and followed up pregnancy outcomes with strict quality controls. The number of each category of pre-pregnancy BMI and pregnancy outcomes were enough that multivariable regression models were not over-fitted[10]. In fact, this is the first study from China using Chinese BMI classification to look at each separate category of pre-pregnancy BMI, therefore enabling the observation of a much clearer association of pre-pregnancy BMI with risk for several outcomes. Additionally, it is first time to examine the association of pre-pregnancy BMI with several outcomes according to maternal age group, making the results more practical for risk assessment and counselling before pregnancy.

The study has some limitations. First, although all of outcomes are abstracted from the medical records that is high credibility and accuracy, the outcomes are limited to an gestational age of 28 weeks and over, which may exist selection bias and underestimate the prevalence of several outcomes (PTB, caesarean delivery, shoulder dystocia or birth injury and stillbirth), thus may underestimate the association of pre-pregnancy BMI with the outcomes listed.[32] Second, some important information on pregnancy complications and obstetrics were missing too much or not collected in the NFPHEP. For example, data on gestational hypertension and diabetes were missing in 99.1% of participants due to low rate of screening, and data on gestational weight gain and causes of PTB (spontaneous versus indicated) were not collected, all of which make the interpretation of our results difficult. Thus, further studies are warranted to fully understand the association of pre-pregnancy BMI with adverse pregnancy outcomes. Furthermore, we were not able to examine the mediated effects of family income on the association of pre-pregnancy BMI with adverse pregnancy outcomes as such data also was missing for the vast majority of the participants. However, the adjusted RRs did not change substantially after additionally adjusting for economic pressure, which is correlated with family income.[33] Third, we may have underestimated the associations of BMI with adverse pregnancy outcomes because some policy interventions implemented in China, such as maternal system health care policy that has covered more than 95% pregnant and monitored several risk factors for adverse outcomes during the pregnancy.[32] Additionally, although we examined the associations of pre-pregnancy BMI with several adverse outcomes according to maternal age, the number of participants who had adverse pregnancy outcomes in 40-50 years group was not enough to calculate the precise adjusted RRs with precise confidence interval. Finally, the socio-demographic characteristics, economic, culture, nutritional models and medical service level might not be representative of other countries and regions, suggesting that results from the present study should be validated in different population.

Implications

Our findings have important clinical and public health implications. Abnormal pre-pregnancy BMI is common among reproductive age women around the world. Evidence of management of women with different weight in pregnancy were mainly from west countries where have high prevalence of overweight and obesity (including severe obesity) and have different BMI classification from China,[6] and which may not adopt to other developing countries like China. Our findings from more than 660000 women confirmed that compared with women with normal weight, a statistically significant increase in risk estimate by 6% of PTB, 23% of SGA in underweight women; 17% of LGA, 18% of primary caesarean delivery, and 44% of stillbirth in overweight women; and 12% of PTB, 32% of LGA, and 45% of primary caesarean delivery in obese women. This suggested that clinical evidence-based recommendation and counselling for management of BMI before and during pregnancy among reproductive age women might be necessary for reducing the risk of adverse pregnancy outcomes in China. The finding also suggested the recommendation and counselling should tailor to maternal age, as the association of pre-pregnancy BMI with adverse pregnancy differed according to maternal age.

Conclusion

In conclusion, for the first time, in this large retrospective cohort study, pre-pregnancy abnormal BMI was significantly associated with the risk of several adverse pregnancy outcomes, but the risk differs according to maternal age. Further investigation is warranted to determine whether and how counselling and interventions for women with abnormal BMI before pregnancy can reduce the risk of adverse pregnancy outcomes, and to understand the underlying mechanisms.

Disclosure of Interests

The authors of this paper do not have any competing interests.

Contribution to authorship

JT and QZ contributed to the project design and manage the data resource. XZ, ML, DH cleaned the data and JT performed the statistical analysis. JT and WB drafted the manuscript and interpreted the data. TH and RC interpreted the data and provided reviews, QZ administrated this study. JT, XZ, DH, ML, WB, RC, TH and QZ have approved the version for publication.

Details of ethics approval

Not required.

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