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Incidence, trends and risk factors for obstetric massive blood transfusion in China from 2012-2019: a facility-based study

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Title page

Title: Incidence, trends and risk factors for obstetric massive blood transfusion in China from 2012-2019: a facility-based study

Short Title: obstetric massive blood transfusion in China

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Abstract

Objectives: To ascertain the incidence and trends of obstetric massive blood transfusion (MBT) from 2012-2019 in China and determine its risk factors and clinical outcomes.

Design: Retrospective hospital-based cohort study.

Settings: 326 districts or counties throughout 30 provinces of China.

Participants: 11,667,406 women who had given birth or ended their pregnancy during 2012-2019

Results: Obstetric MBT occurred in 27,626 cases, corresponding to an incidence of 23.68 per 10,000 maternities, which exhibited an increasing trend in China during 2012-2019 (14.03 to 29.59 per 10,000 maternities, \( p \) for trend < 0.001). Obstetric MBT was mainly associated with amniotic fluid embolism, uterine atony, abnormal placenta, severe anemia, ectopic pregnancy, abortion, caesarean section, advanced maternal age, and multiparous from biological effect. While from sociological effects, uterine atony, severe anemia, and placenta previa are the top three complications which more likely to undergo obstetric MBT in the Chinese population.

Conclusion: To minimize the incidence of obstetric MBT, more attention should be paid to females who are multiparous and have an advanced age, amniotic fluid embolism, uterine atony, severe anemia, and placenta previa.

Key words: obstetric, massive blood transfusion, secular trends, amniotic fluid embolism, severe anemia, ectopic pregnancy, uterine atony, placenta abnormal, multiparous, population etiologic fraction.
**Strengths and limitations of this study**

- The study covers the most geographically extensive pregnancy population in mainland China, the data are from 326 districts or counties throughout 30 provinces.

- The study provides describes the incidence, trends, risk factors, and main reasons of obstetric MBT in China from 2012 to 2019.

- Obstetric massive blood transfusion is a binary variable, and the lack of a specific blood transfusion volume limits our ability to conduct additional analyses.
Background

Obstetric hemorrhage remains a common obstetric emergency and is the leading cause of maternal deaths worldwide\(^1\), similarly in China\(^2\). In addition to strengthening the patient's uterus contractions, drug hemostasis, surgery, etc., massive blood transfusion (MBT) also plays a key role in the treatment of obstetric hemorrhage\(^3\)-\(^6\). MBT occurs when large volumes of blood products are administered over a short period of time, as a ‘maternal near miss event’, it signifies major obstetric hemorrhage and requires extensive coordination of the obstetric, anesthesia, and blood bank teams.\(^7\)\(^8\).

The incidence of MBT in relation to delivery or postpartum hemorrhage (PPH) has been reported to be 2.3-10.0 per 10,000 maternities in high-resource countries\(^9\)-\(^13\), and an increasing trend in the rate of MBT postpartum has been reported in Sweden\(^10\). However, only two small studies focused on obstetric MBT in China\(^14\)-\(^15\). One study concluded that the incidence of MBT in relation to PPH was stable (25-27 per 10,000 maternities) during 2006-2015\(^15\). Another reported that the MBT rate attributed to PPH was 0.31% in women undergoing cesarean delivery\(^14\). China’s universal two-child policy was announced in October 2015\(^16\). Due to the new policy, the characteristics of mothers in China have changed greatly; for example, the monthly percentage of multiparous mothers increased by 9.1% from a baseline mean level of 46.4%, and the monthly mean percentage of older women grew from 8.5% to 13.5%\(^17\). However, there is no research on obstetrics MBT after the policy was implemented in China. In addition, current studies on MBT are generally limited to PPH, cesarean section, or maternal delivery after a certain gestational age\(^10\)\(^11\)\(^13\)\(^14\)\(^18\). There are
many other obstetric diseases, such as abortion and ectopic pregnancy, that require MBT, and MBT is not performed only after a specific gestational age\(^{19, 20}\). Emergency MBT is often needed to save these women. Therefore, exploring the current status, characteristics and potential risk factors for obstetric MBT can be extremely helpful for formulating an emergency plan that involves multidisciplinary cooperation for preventing adverse outcomes. The specific aims of our present study were 1) to determine the incidence and trends of obstetric MBT during 2012-2019; 2) to determine the risk factors and main reasons for obstetric MBT; and 3) to determine the outcomes after obstetric MBT.

Materials and methods

Data sources

Individual-level data were collected from China’s National Maternal Near Miss Surveillance System (NMNMSS) from 1 January 2012 to 31 December 2019. The NMNMSS system was first established in 2010 and covers 441 health facilities that treated more than 1000 deliveries annually. The included hospitals are located in 326 districts or counties throughout 30 provinces in mainland China, excluding Tibet. The detailed sample methods have been described elsewhere\(^ {21-23}\). Within each hospital, sociodemographic and obstetric information were collected from all the pregnant or postpartum women admitted to the obstetric department. The doctors responsible for patient care collected the data, which included the date of delivery, the number of antenatal visits, the maternal education and marital statuses, the maternal age, the gestational age at delivery, the mode of delivery, the number of fetuses, and the maternal complications (at any time during hospitalization).
Institutional data were collected from each hospital through the NMNMSS in 2012, 2015, and 2018, including information on the hospital (hospital level, type), human resources (number, titles and degrees of the obstetricians) and service capability (whether there is safe blood storage in the hospital, etc.).

**Definitions**

The usual definitions of maternal age, marital status, number of antenatal care visits, educational level, delivery method, history of cesarean section, and parity were used, as detailed elsewhere. Based on the hospital’s location, we classified regions as eastern, central or western, and the hospital level (level 1–3) was defined based on the size of hospital (number of beds, number of doctors and number of equipment) and the medical service capacity. Level 1 represents the smallest hospitals and level 3 the largest.

MBT was defined as the transfusion of ≥5 units of red blood cells or ≥1000 ml of whole blood. The definition used in our study is consistent with that used in the World Health Organization (WHO) multi-country survey on maternal and newborn health. Definition of pregnancy complications reference to Obstetrics and Gynecology textbooks (8 edition) used in China. Major complications associated with obstetric MBT were identified based on previously published studies, including obstetric hemorrhage-related conditions and complications that may cause obstetric hemorrhage. The obstetric hemorrhage-related conditions were abortion, ectopic pregnancy, placenta previa, placenta accreta, placenta abruptio, placenta retained, uterine atony, uterine rupture, and soft birth canal lacerations. Complications that may cause obstetric hemorrhage include hypertensive disorders in pregnancy, HELLP syndrome, puerperal infection, amniotic fluid embolism (AFE), and...
severe anemia\(^3\). Severe anemia was defined as hemoglobin concentration of \(< 70 \text{ g/L}\) and its definition excluded postpartum hemorrhage.

In addition, the percentage of safe blood storage was defined as the amount of stored blood that can be guaranteed for general emergency blood use within the time period when the blood sent to the bank or delivered by the blood bank, is generally not less than that needed for 3 days of use\(^2\).

**Statistical methods**

In the study, multiple pregnancies were treated as one case. All statistical calculations were performed using Stata software, version 16.0 (Stata Corp LP., College Station, United States of America). A 2-sided \(p\) value of less than 0.05 was considered statistically significant.

The discrete data were summarized as frequencies and percentages. The \(p\) for trends were determined by logistic regression. Then, we used the \(\chi^2\)-test to examine the differences in distribution between the nulliparous and multiparous women.

Multivariable logistic regression was used to examine the associations between the maternal characteristics, relevant clinical factors and proportion of cases needing obstetric MBT. The findings from two models were reported. Model 1 presented the crude odds ratios (ORs) and 95% confidence intervals (CIs), considering the clustering of births within hospitals. Model 2 further provided the adjusted ORs and 95% CIs after the model was adjusted for (i) the clustering of births within hospitals; (ii) the hospital region, birth location (urban/rural), and hospital level; (iii) the mother’s education level, marital status, age, parity, antenatal care, gestational week, multiple gestations, the presence of uterine scarring, and the delivery method; and (iv) other major morbidities associated with obstetric MBT.
To identify the main causes of the obstetric MBT incidence at the population level, we calculated the population etiologic fraction (PEF):

\[
\text{Population etiologic fraction} = \frac{P(aOR - 1)}{[P(aOR - 1) + 1]} \times 100\%
\]

where \( P \) is the proportion of cases that are exposed to pregnancy complications and \( aOR \) is the adjusted OR for the effect on obstetric MBT incidence.

**Ethics approval and consent to participate**

Ethical approval for the NMNMSS was provided by the Ethics Committee of West China Second University Hospital, Sichuan University, China. Informed consent from the patient was waived from the Ethics Committee, as the data used in this study were obtained from a national routine surveillance system established by the government. Data use was authorized by the National Health Commission, and data provided to us were de-identified.

**Patient and public involvement**

Patients and members of the public were not involved in the design of this study.

**Results**

1. *Overall incidence and trends of obstetric MBT*

From 2012 to 2019, 11,667,406 women who had given birth or ended their pregnancy were included in the present study. Obstetric MBT occurred in 27,626 cases, corresponding to an incidence of 23.68 per 10,000 maternities. As shown in *Figure 1*, the incidence of obstetric MBT increased from 14.03 per 10,000 maternities in 2012 to 29.59 per 10,000 maternities in 2019 (\( p \) for trend < 0.001). Similar trends were observed in the east, central, and west of
China. In addition, 350 health facilities had reported the institutional data for 2012, 2015 and 2018. The overall percentage of safe blood storage increased from 2012 to 2018 (77.71% to 82.57%), and this increase remained after the data were stratified by hospital level (level 1: 30.61% to 38.8%; level 2: 78.95% to 84.74%; level 3: 96.40% to 98.20%) (Figure 2).

2. Subgroup incidence and risk factors

Table 1 displays the incidence and risk of needing obstetric MBT according to different maternal characteristics. As shown, being elderly, a lower level of education, a history of fewer antenatal treatments, uterine scarring, multiparity, having a small gestational age delivery, cesarean section and multiple gestations were associated with a higher risk of needing obstetric MBT. Furthermore, the association between abortion and MBT was strong, with an aOR of 1.77 (95% CI: 1.42–2.21).

As Table 2 shows, AFE (411.42 per 1,000 maternities), placenta accrete (157.53 per 1,000 maternities) and HELLP syndrome (92.36 per 1,000 maternities) had the 3 highest incidence values for obstetric MBT. The main risk factor for obstetric MBT was amniotic fluid embolism, which led to a 127-fold increased risk, with an aOR of 126.85 (95% CI: 96.88–166.10). Women who had severe anemia or uterine atony were nearly 36 times (severe anemia: aOR: 36.00, 95% CI: 32.09–40.41; uterine atony: aOR: 36.45, 95% CI: 30.88–43.04) more likely to undergo obstetric MBT. We also found abnormal placenta to represent a major risk factor, with an aORs of 6.93 (95% CI: 6.05–7.94) for placenta previa, 11.65 (95% CI: 9.48–14.31) for placenta accrete, 6.53 (95% CI: 5.73–7.45) for placenta abruptio and 3.01 (95% CI: 2.48–3.65) for placenta retained. In addition, compared with non-HELLP syndrome, maternal HELLP syndrome led to a higher risk of needing obstetric MBT, with an
aOR of 13.02 (95% CI: 10.58–16.02). Furthermore, the association between ectopic pregnancy and uterine rupture and obstetric MBT was strong, with aORs of 9.70 (95% CI: 7.57–12.42) and 5.05 (95% CI: 3.67–6.95), respectively. Moreover, preeclampsia or eclampsia, soft birth canal lacerations and puerperal infection were also associated with the incidence of obstetric MBT.

3. Characteristics of multiparous women

We further compared the differences in obstetric MBT-related risk factors in addition to hysterectomy and MMR during hospitalization between the nulliparous and multiparous women. An advanced maternal age, a lower education level, less antenatal care, abortion, ectopic pregnancy, placental abnormalities, severe anemia, uterine rupture, amniotic fluid embolism, hysterectomy and mortality during hospitalization were more likely to occur in women who were multiparous (Table 3).

4. Population etiologic fraction for complications

We calculated the PEF for the different complications to identify the main reasons for obstetric MBT at the population perspective. As Table 4 presents, the three highest PEFs were 42.28% for uterine atony, 12.33% for severe anemia and 6.08% for placenta previa.

5. Clinical outcomes and trends in the MBT population

Of the 27,626 women, 4,010 underwent hysterectomy, and 376 died during hospitalization. The secular trends of hysterectomy incidence (25.07% to 9.92%) and MMR during hospitalization (21.41‰ to 7.48‰) from 2012-2019 among women who underwent MBT showed decreasing trends ($p$ for trend < 0.001) (Figure 3).


Discussion

The incidence of obstetric MBT during 2012-2019 was 23.66 per 10,000 maternities, and there was an increasing trend in China. An advanced maternal age, uterine scarring, a multiparous status, and multiple gestations were associated with a higher risk of needing obstetric MBT. AFE, uterine atony, and severe anemia were major complications associated with obstetric MBT. The top three PEFs were 42.28% for uterine atony, 12.33% for severe anemia and 6.08% for placenta previa.

Obstetric MBT has been internationally reported in recent years. However, due to differences in the definition of MBT, the incidence of MBT varies greatly across countries; for example, the incidence is 5.3 per 10,000 maternities in Sweden, 10.0 per 10,000 maternities in New York, 6.5 per 10,000 births in the Netherlands, and 2.3 per 10,000 maternities in the UK. The definition of MBT is generally limited to 24 hours after giving birth. However, different amounts of blood, typically 5-10 units of red blood cells, have been used. MBT involves ≥10 units of red blood cells in Sweden and New York, ≥8 units of red blood cells in the UK and Netherlands. In our study, obstetric MBT was defined as the transfusion of ≥5 units of red blood cells or ≥1000 ml of whole blood. Despite these differences in the incidence of MBT, the increasing trend is consistent across countries, except in the Netherlands. The incidence of obstetric MBT also showed an increasing trend from 2012 to 2019 in China (14.03 per 10,000 maternities to 29.59 per 10,000 maternities). Regarding excessive maternal bleeding, if there are no adequate blood resources, it is difficult to save the mother’s life. Our results showed that the percentage of safe blood storage at level 3 hospitals in 2012 was 96.4%, while that at level 1 hospitals was...
30.6%. In recent years, primary medical institutions have been increasingly constructed in China. In addition, the rate of blood supply in China showed a steadily increasing trend (from 1.23 to 1.74 units per 1,000 population) from 2012-2014. As a result, the percentage of safe blood storage increased the most in level 1 hospitals increasing from 30.6% to 38.8% during 2012-2018.

The increased incidence of MBT plays a key role in reducing adverse outcomes in pregnancies. On the one hand, it is possible to prevent the occurrence of maternal deaths. From 2012 to 2019, the MMR due to obstetric hemorrhage with MBT in nationwide hospitals showed a decreasing trend (decreased by 68.8%), and the magnitude of decrease was larger than that in the population-based obstetric hemorrhage MMR reported by National Maternal Death Monitoring during the same period (54.6%). On the other hand, the uterus can be saved by timely MBT. When severe obstetric hemorrhage fails to respond to other treatments, hysterectomy is usually performed. Although an increased hysterectomy rate was found among the MBT women in Sweden, we found a decreasing trend in Chinese women. Retaining the uterus can not only realize their dream of becoming a mother but also preserve their quality of life.

Every woman who needs obstetric MBT might have a fatal obstetric hemorrhage, and the slightest error in treatment can kill them before they undergo blood transfusion. Therefore, recognizing the possible risk factors for MBT and preventing their occurrence are effective strategies to ensure the safety of women. We found that higher parity is associated with an increased risk of needing obstetric MBT. In our study, advanced maternal age, lower education level, less antenatal care, and obstetric hemorrhage-related conditions were more
likely to occur in women who were multiparous. Of course, these factors are also positively associated with obstetric MBT. Due to the new fertility policy, the characteristics of Chinese maternal population have changed greatly. In our study, 44.99% of women were multiparous, among whom 36.35% had uterine scars, which may be related to the high cesarean section rate during the one-child policy (46.2%)\textsuperscript{32}. Uterine scarring is associated with an increase in the risk of abnormal placenta, infection, and uterine rupture\textsuperscript{33, 34}. Women with these complications may experience extremely large volumes of blood loss during or soon after delivery, ranging from 2000 to 6000 m\textsuperscript{3}\textsuperscript{35, 36}.

In agreement with previous studies, we found that uterine atony, abnormal placenta, uterine rupture, and preeclampsia were strongly associated with obstetric MBT\textsuperscript{9, 10}. However, we also found that AFE was the main risk factor for obstetric MBT (aOR: 126.85, 95% CI: 96.88–166.10). AFE, although rare, remains one of the leading direct causes of maternal mortality in high-income countries, and its management principles include the active correction of coagulation disorders, the aggressive treatment of uterine atony and the use of high-dose glucocorticoids as early as possible\textsuperscript{37, 38}. The total incidence of AFE was 13.4 per 100,000 maternities in our study, which was higher than that previously reported (1.7–7.7 per 100,000 maternities)\textsuperscript{37, 39}. This finding may explain why AFE is considered the primary risk factor for obstetric MBT in our study.

Our study also showed that women with severe anemia, abortion, or ectopic pregnancy were at a higher risk of needing obstetric MBT. Severe anemia has been associated with an increased prevalence of postpartum hemorrhage\textsuperscript{40, 41}. Similarly, our study showed that severe anemia increases the risk of needing obstetric MBT by 36-fold (OR: 36.00, 95% CI:}
32.09–40.41). No studies have focused on ectopic pregnancy, abortion. We found that the association between ectopic pregnancy and MBT was strong, with an aOR of 9.70 (95% CI: 7.57–12.42), and maternal abortion showed a relatively weaker association with the risk of needing obstetric MBT (aOR: 1.77, 95% CI: 1.42–2.21). Both of them often occur at young gestational ages and may put the woman at risk of intraperitoneal bleeding or related complications in the short term and can even lead to death.42

However, the OR reflects only the biological effect of a certain disease, while PEF integrates information about the effect estimate’s magnitude with information about the prevalence of the disease and can reflect sociological effects. Our data were retrieved from a facility-based surveillance system, which covered almost all of China, excluding Tibet. Routinely calculating complication-specific PEFs will allow us to identify the populations most affected for targeted interventions. The top three complications according to the PEFs were uterine atony, severe anemia, and placenta previa in the Chinese population. Women with such complications should be highly concerned because these complications have a high prevalence in Chinese mothers, and they also lead to a high risk of needing obstetric MBT. Although AFE leads to the highest risk of obstetric MBT, its PEF was low due to its relatively low maternal incidence. Our findings indicated that it is necessary to focus on the tertiary prevention of uterine atony, severe anemia, and placenta previa to reduce the risk of needing obstetric MBT in China and minimize the occurrence of adverse maternal outcomes.

The main strength is that we included all women who had given birth or ended their pregnancy during 2012-2019 from the nationwide data in China. One major limitation of our retrospective study was that the MBT variable we assessed is a binary variable, and the lack
of a specific blood transfusion volume limits our ability to conduct additional analyses. In addition, although we recorded the types of blood transfusions performed, we could not use the data for analysis due to the lack of quantitative information.

**Conclusion**

The incidence of obstetric MBT is increasing in China, but the hysterectomy rate and MMR are decreasing among women undergoing MBT. To minimize the incidence of obstetric MBT, more attention should be paid to multiparous women with an advanced age, AFE, uterine atony, severe anemia, and placenta previa. Appropriate blood transfusion preparations and the antenatal identification for high-risk women might improve the outcomes and reduce the adverse outcomes.

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**Contributorship statement**

All authors have contributed to the conduction of this study. YX., XW, JL and JZ developed the study design with contributions from all authors. YX., and XW performed the statistical analysis and drafted the manuscript with support from JZ and JL, YM, ML, YW., LD, XL., ML., QL, ZL and PC. participated in reviewing, editing, and revising the manuscript.

**Competing interests**

The authors declare no conflicts of interest.

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Data sharing statement

The datasets generated and/or analysed during the current study are not publicly available due
to the terms of our contract with the Chinese National Health Commission but are available
from the corresponding author on reasonable request.

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Table 1. The incidence and risk of massive blood transfusion (MBT) among different maternal characteristics (N=11,667,406).

| Characteristics          | Case / Total deliveries | Incidence of MBT (1/10,000) | Crude OR* (95% CI) | Adjusted OR** (95% CI) |
|--------------------------|-------------------------|------------------------------|--------------------|-----------------------|
| Age(years)               |                         |                              |                    |                       |
| <20                      | 473/287790              | 16.44                        | 1.15(1.03–1.28)    | 1.09(0.97–1.21)       |
| 20-24                    | 3030/2114730            | 14.33                        | reference          | reference             |
| 25-29                    | 8024/4642235            | 17.28                        | 1.21(1.12–1.30)    | 0.99(0.94–1.06)       |
| 30-34                    | 8116/2900510            | 27.98                        | 1.96(1.77–2.16)    | 1.05(0.97–1.13)       |
| 35-39                    | 5151/1125337            | 45.77                        | 3.20(2.89–3.55)    | 1.13(1.03–1.24)       |
| >=40                     | 1860/278675             | 66.74                        | 4.68(4.23–5.19)    | 1.24(1.10–1.40)       |
| Missing                  | 972/318129              | 30.55                        | 2.14(1.62–2.81)    | 1.30(1.07–1.56)       |
| Education                |                         |                              |                    |                       |
| College or higher        | 7977/4315935            | 18.48                        | reference          | reference             |
| High school              | 7264/3118196            | 23.30                        | 1.26(1.08–1.48)    | 1.25(1.11–1.40)       |
| Middle school            | 9186/3581050            | 25.65                        | 1.39(1.07–1.80)    | 1.59(1.33–1.91)       |
| Primary school           | 1552/344874             | 45.00                        | 2.44(1.97–3.02)    | 1.59(1.38–1.84)       |
| Illiteracy               | 412/60294               | 68.33                        | 3.72(2.76–5.01)    | 1.94(1.56–2.40)       |
| Missing                  | 1235/247057             | 49.99                        | 2.71(1.24–5.95)    | 1.27(0.76–2.12)       |
| Marital status           |                         |                              |                    |                       |
| Unmarried                | 639/196743              | 32.48                        | 1.38(1.17–1.63)    | 1.15(0.95–1.39)       |
| Married                  | 26979/11468023          | 23.53                        | reference          | reference             |
| Missing                  | 8/2640                  | 30.30                        | 1.29(0.58–2.86)    | 1.07(0.50–2.30)       |
| Parity                   |                         |                              |                    |                       |
| Nulliparous              | 9788/6400896            | 15.29                        | reference          | reference             |
| 1                        | 12628/4438595           | 28.45                        | 1.86(1.72–2.02)    | 1.19(1.12–1.26)       |
| 2                        | 5142/810139             | 63.47                        | 4.17(3.64–4.78)    | 1.83(1.65–2.03)       |
| Missing                  | 68/17776                | 38.25                        | 2.51(0.53–11.91)   | 0.66(0.13–3.48)       |
| Antenatal care           |                         |                              |                    |                       |
| None                     | 1802/253698             | 71.03                        | 4.45(3.00–6.61)    | 1.99(1.40–2.82)       |
| 1–3                      | 3512/947952             | 37.05                        | 2.32(1.75–3.06)    | 1.49(1.18–1.88)       |
| 4–6                      | 7217/3193661            | 22.60                        | 1.41(1.14–1.74)    | 1.44(1.23–1.69)       |
| 7–9                      | 7038/3390343            | 20.76                        | 1.30(1.06–1.58)    | 1.31(1.11–1.54)       |
| Birth location | N  | OR  | 95% CI  | Reference |
|----------------|----|-----|---------|-----------|
| City           | 20316/6985253 | 29.08 | 1.87(1.43~2.43) | 1.36(1.04~1.78) |
| Rural          | 7310/4682153  | 15.61 | 2.45(0.75~8.00) | 1.30(0.74~2.27) |

| Previous scar | N  | OR  | 95% CI  | Reference |
|---------------|----|-----|---------|-----------|
| No            | 17804/9736123 | 18.29 | 1.23(0.85~1.79) | 1.75(1.29~2.37) |
| Yes           | 9719/1908222 | 50.93 | 2.79(2.54~3.08) | 1.35(1.24~1.46) |

| Region        | N  | OR  | 95% CI  | Reference |
|---------------|----|-----|---------|-----------|
| East          | 8762/3366371 | 26.03 | 1.23(0.85~1.79) | 1.75(1.29~2.37) |
| Central       | 11075/4621694 | 23.96 | 1.13(0.84~1.53) | 1.75(1.31~2.33) |

| Hospital level | N  | OR  | 95% CI  | Reference |
|----------------|----|-----|---------|-----------|
| Level 1        | 1225/1297341 | 9.44  | 1.23(0.85~1.79) | 1.75(1.29~2.37) |
| Level 2        | 8940/5298378 | 16.87 | 1.79(1.31~2.44) | 1.22(0.85~1.73) |

| Multiple gestations | N  | OR  | 95% CI  | Reference |
|---------------------|----|-----|---------|-----------|
| No                  | 24973/11422786 | 21.86 | 4.83(4.31~5.43) | 1.54(1.35~1.75) |

| Gestational week | N  | OR  | 95% CI  | Reference |
|------------------|----|-----|---------|-----------|
| <28              | 3048/490420  | 62.15 | 4.25(3.57~5.06) | 2.06(1.59~2.66) |
| 28-32            | 2313/167840  | 137.81 | 9.49(8.44~10.67) | 2.21(1.94~2.51) |

Mode of delivery:

| N  | OR  | 95% CI  | Reference |
|----|-----|---------|-----------|
| Vaginal | 5676/6167464 | 9.20 | 4.04(3.93~4.17) | 2.08(1.89~2.28) |
| CS | 18551/4998004 | 37.12 | 7.35(7.04~7.67) | 1.77(1.42~2.21) |

| Missing | N  | OR  | 95% CI  | Reference |
|---------|----|-----|---------|-----------|
| 50/3795 | 131.75 | 14.49(10.95~19.18) | 0.73(0.34~1.57) |

CI, confidence interval; CS, caesarean section; OR, odds ratio.

* Adjusted for the clustering of births within hospitals.

** Adjusted for: the clustering of births within hospitals; region; hospital level; antenatal care; birth location; multiple gestations; gestational week; mother’s education, marital status, age and parity; the delivery method and other factors thought to be associated with massive blood transfusion, such as a placenta previa; placenta accrete; placenta abruptio; placenta retained; all hypertensive disorders in pregnancy; HELLP syndrome; severe anemia; uterine atony; ruptured uterus; soft birth canal lacerations; puerperal infection and amniotic fluid embolism.
Table 2. The incidence and risk of mass transfusion (MBT) among different complications (N=11,667,406).

| Characteristics               | Cases | Incidence of MBT (1/1000) | Crude OR* (95% CI) | Adjusted OR** (95% CI) |
|-------------------------------|-------|---------------------------|--------------------|------------------------|
| Ectopic pregnancy†           | 45648 | 33.52                     | 15.41(12.02~19.76) | 9.70(7.57~12.42)       |
| Placenta abnormal             |       |                           |                    |                        |
| Placenta praevia†             | 126105| 61.56                     | 38.054(33.79~42.85)| 6.93(6.05~7.94)        |
| Placenta accreta†             | 21545 | 157.53                    | 89.68(70.31~114.39)| 11.65(9.48~14.31)      |
| Placenta abruptio†            | 54460 | 47.26                     | 22.95(19.45~27.07) | 6.53(5.73~7.45)        |
| Placenta retained‡            | 141113| 24.83                     | 12.14(9.93~14.85)  | 3.01(2.48~3.65)        |
| Hypertensive disorders        |       |                           |                    |                        |
| Chronic hypertension†         | 37732 | 4.51                      | 1.91(1.59~2.29)    | 1.27(1.04~1.55)        |
| Gestational hypertension†     | 158526| 4.88                      | 2.10(1.89~2.32)    | 1.62(1.46~1.79)        |
| Superimposed preeclampsia†    | 11951 | 8.53                      | 3.64(2.90~4.56)    | 1.32(0.99~1.74)        |
| Preeclampsia or eclampsia†    | 257096| 10.53                     | 4.86(4.43~5.33)    | 2.23(2.05~2.43)        |
| HELLP syndrome†               | 6702  | 92.36                     | 43.83(36.12~53.19) | 13.02(10.58~16.02)     |
| Severe anemia‡                | 46898 | 76.17                     | 39.75(35.30~44.75) | 36.00(32.09~40.41)     |
| Uterine atony‡                | 240063| 49.65                     | 37.95(31.97~45.05) | 36.45(30.88~43.04)     |
| Uterine rupture‡              | 22748 | 36.09                     | 16.23(11.76~22.39) | 5.05(3.67~6.95)        |
| Soft birth canal lacerations‡ | 127320| 7.61                      | 3.31(2.36~4.65)    | 4.28(3.31~5.54)        |
| Puerperal infection‡          | 13468 | 33.71                     | 14.93(12.25~18.20) | 3.47(2.78~4.34)        |
| Amniotic fluid embolism‡      | 1558  | 411.42                    | 301.49(245.43~370.37)| 126.85(96.88~166.10)  |

CI, confidence interval; OR, odds ratio.

* Adjusted for the clustering of births within hospitals.

** Adjusted for: the clustering of births within hospitals; region; hospital level; antenatal care; birth location; multiple gestations; gestational week; mother’s education, marital status, age and parity; the delivery method and other factors thought to be associated with massive blood transfusion, such as a placenta previa; placenta accrete; placenta abruptio; placenta retained; all hypertensive disorders in pregnancy; HELLP syndrome; severe anemia; uterine atony; ruptured uterus; soft birth canal lacerations; puerperal infection and amniotic fluid embolism.
embolism.
### Table 3. Distribution of population characteristics among nulliparous and multiparous.

| Age(years) | Nulliparous (n=6400896) | Multiparous (n=5248734) | p value |
|------------|-------------------------|--------------------------|---------|
| <20        | 251758                  | 35758                    | 0.68    |
| 20-24      | 1579681                 | 533099                   | 10.16   |
| 25-29      | 2974516                 | 1662322                  | 31.67   |
| 30-34      | 1163423                 | 1731286                  | <0.001  |
| 35-39      | 225639                  | 896562                   | 17.08   |
| >=40       | 37056                   | 240833                   | 4.59    |
| Missing    | 168823                  | 148874                   | 2.4     |

| Education  | Nulliparous (n=6400896) | Multiparous (n=5248734) | p value |
|------------|-------------------------|--------------------------|---------|
| College or higher | 2958476                | 1356322                  | 25.84   |
| High school | 1678091                 | 1439229                  | 27.42   |
| Middle school | 1493516                | 2086280                  | 39.75   |
| Primary school | 92973                  | 251616                   | 4.79    |
| Illiteracy  | 18019                   | 42232                    | 0.80    |
| Missing     | 159821                  | 73055                    | 1.39    |

| Marital status | Nulliparous (n=6400896) | Multiparous (n=5248734) | p value |
|----------------|-------------------------|--------------------------|---------|
| Unmarried      | 144904                  | 51496                    | 0.98    |
| Married        | 6254591                 | 5196325                  | 99.00   |
| Missing        | 1401                    | 913                      | 0.02    |

| Antenatal care | Nulliparous (n=6400896) | Multiparous (n=5248734) | p value |
|----------------|-------------------------|--------------------------|---------|
| None           | 105550                  | 147720                   | 2.81    |
| 1~3            | 384122                  | 563520                   | 10.74   |
| 4~6            | 1545500                 | 1647691                  | 31.39   |
| 7~9            | 1902485                 | 1487130                  | 28.33   |
| >=10           | 2263094                 | 1241147                  | 23.65   |
| Missing        | 200145                  | 161526                   | 3.08    |

| Gestational week | Nulliparous (n=6400896) | Multiparous (n=5248734) | p value |
|------------------|-------------------------|--------------------------|---------|
| <28              | 193739                  | 294731                   | 5.62    |
| 28-32            | 85754                   | 80828                    | 1.54    |
| 33-36            | 349958                  | 303554                   | 5.78    |
| 37-41            | 5711544                 | 4507546                  | 85.88   |
| >=41             | 40410                   | 34812                    | 0.66    |
| Missing          | 19491                   | 27263                    | 0.52    |

| Previous CS      | Nulliparous (n=6400896) | Multiparous (n=5248734) | p value |
|------------------|-------------------------|--------------------------|---------|
| 0                | 1907972                 | 36.35                    | <0.001  |
| Abortion         | 196141                  | 299465                   | 5.71    |
| Ectopic pregnancy| 12529                   | 33000                    | 0.63    |

| Placenta abnormal | Nulliparous (n=6400896) | Multiparous (n=5248734) | p value |
|-------------------|-------------------------|--------------------------|---------|
| Placenta praevia  | 50169                   | 75112                    | 1.43    |
| Placenta accreta  | 7229                    | 14267                    | 0.27    |
| Placenta abruptio | 27828                   | 26568                    | 0.51    |
| Placenta retained | 70442                   | 70483                    | 1.34    |
| Hypertensive disorders                  | Event 1 | Event 2 | Event 3 | p-value |
|----------------------------------------|---------|---------|---------|---------|
| Chronic hypertension                   | 18671   | 0.29    | 18894   | <0.001  |
| Gestational hypertension               | 88443   | 1.38    | 69688   | <0.001  |
| Superimposed preeclampsia              | 4946    | 0.08    | 6996    | <0.001  |
| Preeclampsia or eclampsia              | 150558  | 2.35    | 105218  | <0.001  |
| HELLP syndrome                         | 3159    | 0.05    | 3435    | <0.001  |
| Severe anemia                          | 20511   | 0.32    | 26363   | <0.001  |
| Uterine atony                          | 138065  | 2.16    | 101834  | <0.001  |
| Uterine rupture                        | 1777    | 0.03    | 20844   | <0.001  |
| Soft birth canal lacerations           | 72098   | 1.13    | 55186   | <0.001  |
| Puerperal infection                    | 8476    | 0.13    | 4941    | <0.001  |
| Amniotic fluid embolism                | 637     | 0.01    | 918     | <0.001  |
| Hysterectomy                           | 1278    | 0.02    | 4735    | <0.001  |
| Died during hospitalization            | 431     | 0.01    | 505     | <0.001  |
**Table 4.** Population etiologic fraction (PEF) for complications.

| Condition                  | Num.     | P (1/10,000) | PEF (95%CI)          |
|----------------------------|----------|--------------|----------------------|
| Abortion                   | 498143   | 426.95       | 3.18% (1.76~4.91%)   |
| Ectopic pregnancy          | 45648    | 39.12        | 3.29% (2.51~4.28%)   |
| Placenta praevia           | 126105   | 108.08       | 6.08% (5.18~6.98%)   |
| Placenta accreta           | 21545    | 18.47        | 1.93% (1.54~2.41%)   |
| Placenta abruptio          | 54460    | 46.68        | 2.52% (2.16~2.92%)   |
| Placenta retained          | 141113   | 120.95       | 2.37% (1.76~3.09%)   |
| Chronic hypertension       | 37732    | 32.34        | 0.09% (0.01~0.18%)   |
| Gestational hypertension   | 158526   | 135.87       | 0.84% (0.62~1.06%)   |
| Superimposed preeclampsia  | 11951    | 10.24        | 0.03% (0%~0.08%)     |
| Preeclampsia or eclampsia  | 257096   | 220.35       | 2.64% (2.26~3.05%)   |
| HELLP syndrome             | 6702     | 5.74         | 0.69% (0.55~0.86%)   |
| Severe anaemia             | 46898    | 40.20        | 12.33% (11.11~13.67%)|
| Uterine atony              | 240063   | 205.76       | 42.28% (38.07~46.38%)|
| Uterine rupture            | 22748    | 19.50        | 0.78% (0.52~1.15%)   |
| Soft birth canal lacerations| 127320  | 109.12       | 3.46% (2.46~4.72%)   |
| Puerperal infection        | 13468    | 11.54        | 0.28% (0.21~0.38%)   |
| Amniotic fluid embolism    | 1558     | 1.34         | 1.65% (1.26~2.16%)   |
Figure legends:

**Figure 1** The secular trends and incidence of massive blood transfusion (1/10,000) during 2012-2019.

**Figure 2** Changes in the proportion of safe blood storage (%) in different health facilities (level 1, level 2 and level 3).

**Figure 3** The secular trends and incidence of hysterectomy (%) (a) and maternal mortality ratio during hospitalization (‰) (b) among MBT population during 2012-2019.
Figure 1 The secular trends and incidence of massive blood transfusion (1/10,000) during 2012-2019.
Figure 2 Changes in the proportion of safe blood storage (%) in different health facilities (level 1, level 2 and level 3).

166x94mm (150 x 150 DPI)
Figure 3 The secular trends and incidence of hysterectomy (%) (a) and maternal mortality ratio during hospitalization (‰) (b) among MBT population during 2012-2019.

158x53mm (220 x 220 DPI)
Incidence, trends and risk factors for obstetric massive blood transfusion in China from 2012-2019: an observational study

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Title page

Title: Incidence, trends and risk factors for obstetric massive blood transfusion in China from 2012-2019: an observational study

Short Title: obstetric massive blood transfusion in China

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Abstract

Objectives: This study aims to use the high-quality national monitoring data from the China’s National Maternal Near Miss Surveillance System (NMNMSS) to ascertain the incidence, trends, and risk factors of obstetric massive blood transfusion (MBT) from 2012-2019 in China and determine its clinical outcomes.

Settings: Observational study of hospitalized pregnancies who had given birth or ended their pregnancy among member hospitals of NMNMSS.

Participants: 11,667,406 women were included in the present study.

Primary and secondary outcome measures: We screened for the incidence, trends, risk factors, and main reasons for obstetric MBT, and the outcomes after obstetric MBT. MBT was defined as the transfusion of ≥5 units of red blood cells or ≥1000 ml of whole blood. The incidence of MBT was defined as the MBT cases per 10,000 pregnancies.

Results: Obstetric MBT occurred in 27,626 cases, corresponding to an incidence of 23.68 per 10,000 maternities, which exhibited an increasing trend in China during 2012-2019 (14.03 to 29.59 per 10,000 maternities, \( p \) for trend < 0.001). Obstetric MBT was mainly associated with amniotic fluid embolism, uterine atony, abnormal placenta, severe anemia, ectopic pregnancy, abortion, caesarean section, advanced maternal age, and multiparous from biological effect. While from sociological effects, uterine atony, severe anemia, and placenta previa are the top three complications which more likely to undergo obstetric MBT in the Chinese population. Overall, the secular trends of hysterectomy incidence (25.07% to 9.92%) and MMR during hospitalization (21.41 ‰ to 7.48 ‰) among women who underwent MBT showed decreasing trends (\( p \) for trend < 0.001).
Conclusion: To minimize the incidence of obstetric MBT, more attention should be paid to education on the importance of the antenatal visit, evidence-based transfusion practice, and females who are multiparous and have an advanced age, amniotic fluid embolism, uterine atony, severe anemia, and placenta previa.

Key words: obstetric, massive blood transfusion, risk factors, hysterectomy, maternal mortality rate
Strengths and limitations of this study

- Study was based on a national surveillance data covering 441 hospitals across 30 provinces.

- This study firstly evaluated the incidence, trends, risk factors, and main reasons of obstetric massive blood transfusion (MBT) at national level in China.

- Limitation include the obstetric MBT is a binary variable, which does not allow us for additional analyses.

- Our analysis was also limited to information presented in the National Maternal Near Miss Surveillance System (NMNMSS) record.
Obstetric hemorrhage remains a common obstetric emergency and is the leading cause of maternal deaths worldwide\(^1\), similarly in China\(^2\). In addition to strengthening the patient's uterus contractions, drug hemostasis, surgery, etc., massive blood transfusion (MBT) also plays a key role in the treatment of obstetric hemorrhage\(^3-6\). MBT occurs when large volumes of blood products are administered over a short period of time, as a ‘maternal near miss event’, it signifies major obstetric hemorrhage and requires extensive coordination of the obstetric, anesthesia, and blood bank teams\(^7 8\).

The incidence of MBT in relation to delivery or postpartum hemorrhage (PPH) has been reported to be 2.3-10.0 per 10,000 maternities in high-resource countries\(^9-13\), and an increasing trend in the rate of MBT postpartum has been reported in Sweden\(^10\). However, only two small studies focused on obstetric MBT in China\(^14 15\). One study concluded that the incidence of MBT in relation to PPH was stable (25-27 per 10,000 maternities) during 2006-2015\(^15\). Another reported that the MBT rate attributed to PPH was 0.31% in women undergoing cesarean delivery\(^14\). China’s universal two-child policy was announced in October 2015\(^16\). Due to the new policy, the characteristics of mothers in China have changed greatly; for example, the monthly percentage of multiparous mothers increased by 9.1% from a baseline mean level of 46.4%, and the monthly mean percentage of older women grew from 8.5% to 13.5%\(^17\). However, there is no research on obstetrics MBT after the policy was implemented in China. In addition, current studies on MBT are generally limited to PPH, cesarean section, or maternal delivery after a certain gestational age\(^10 11 13 14 18\). There are many other obstetric diseases, such as abortion and ectopic pregnancy, that require MBT, and MBT is not performed only after a specific gestational age\(^19 20\). Emergency MBT is often
needed to save these women. Therefore, it would be extremely helpful for establishing an emergency plan aims to prevent adverse outcomes by exploring the current status, characteristics, and potential risk factors of obstetric MBT.

We aim to use the high-quality national monitoring data from the China’s National Maternal Near Miss Surveillance System (NMNMSS) during 2012-2019 to determine the incidence and trends of obstetric MBT, the risk factors and main reasons for obstetric MBT, and the adverse outcomes after obstetric MBT.

Materials and methods

Data sources

Individual-level data were collected from NMNMSS from 1 January 2012 to 31 December 2019. The NMNMSS system was first established in 2010 and covers 441 health facilities that treated more than 1000 deliveries annually. The included hospitals are located in 326 districts or counties throughout 30 provinces in mainland China, excluding Tibet. The detailed sample methods have been described elsewhere. Within each hospital, sociodemographic and obstetric information were collected from all the pregnant or postpartum women admitted to the obstetric department. The doctors responsible for patient care collected the data, which included the date of delivery, the number of antenatal visits, the maternal education and marital statuses, the maternal age, the gestational age at delivery, the mode of delivery, the number of fetuses, and the maternal complications (at any time during hospitalization), and maternal near miss, including whether obstetric MBT have occurred. The inclusion criteria included the hospitalized pregnancies who had given birth or ended
their pregnancy among member hospital of NMNMSS.

Institutional data were collected from each hospital through the NMNMSS in 2012, 2015, and 2018, including information on the hospital (hospital level, type), human resources (number, titles and degrees of the obstetricians) and service capability (whether there is safe blood storage in the hospital, etc.).

**Definitions**

The usual definitions of maternal age, marital status, number of antenatal care visits, educational level, delivery method, history of cesarean section, and parity were used, as detailed elsewhere. Based on the hospital’s location, we classified regions as eastern, central or western, and the hospital level was defined based on the size of hospital (number of beds, number of doctors and number of equipment), medical service capacity (clinical service and clinical expert available, etc.), and the management level of the hospital. Level 1 represents the smallest hospitals and level 3 the largest.

We defined MBT as the transfusion of \( \geq 5 \) units of red blood cells or \( \geq 1000 \) ml of whole blood, which is consistent with that used in the World Health Organization (WHO) multi-country survey on maternal and newborn health, listed in the appendix. Multiple blood component transfusions require transfusion volume conversion, the conversion standard is 200 ml of plasma / whole blood = 1 units of red blood cells, while the other blood components were not included in the calculation of total blood transfusion.

Definition of pregnancy complications reference to Obstetrics and Gynecology textbooks (8 edition) used in China. Major complications associated with obstetric MBT were identified based on previously published studies, including obstetric hemorrhage-related conditions and
complications that may cause obstetric hemorrhage\textsuperscript{9-11 15}. Abortion, ectopic pregnancy, placenta previa, placenta accreta, placenta abruptio, placenta retained, uterine atony, uterine rupture, and soft birth canal lacerations were included in the obstetric hemorrhage-related conditions, while hypertensive disorders in pregnancy, HELLP syndrome, puerperal infection, amniotic fluid embolism (AFE), and severe anemia\textsuperscript{3} were included in the complications. Severe anemia was defined as hemoglobin concentration of < 70 g/L and its definition excluded postpartum hemorrhage.

In addition, the percentage of safe blood storage was defined as the amount of stored blood that can be guaranteed for general emergency blood use within the time period when the blood sent to the bank or delivered by the blood bank, is generally not less than that needed for 3 days of use\textsuperscript{27}.

**Statistical methods**

In the study, multiple pregnancies were treated as one case. All statistical calculations were performed using Stata software, version 16.0 (Stata Corp LP., College Station, United States of America). A 2-sided \( p \) value of less than 0.05 was considered statistically significant.

The discrete data were summarized as frequencies and percentages. The \( p \) for trends were determined by logistic regression. Then, we used the \( \chi^2 \)-test to examine the differences in distribution between the nulliparous and multiparous women.

Multivariable logistic regression was used to examine the associations between the maternal characteristics, relevant clinical factors and proportion of cases needing obstetric MBT. The findings from two models were reported. Model 1 presented the crude odds ratios (ORs) and 95% confidence intervals (CIs), considering the clustering of births within hospitals. Model 2
further provided the adjusted ORs and 95% CIs after the model was adjusted for (i) the clustering of births within hospitals; (ii) the hospital region, birth location (urban/rural), and hospital level; (iii) the mother’s education level, marital status, age, parity, antenatal care, gestational week, multiple gestations, the presence of uterine scarring, and the delivery method; and (iv) other major morbidities associated with obstetric MBT.

To identify the main causes of the obstetric MBT at the sociological level, we calculated the population etiologic fraction (PEF).

\[
\text{Population etiologic fraction (PEF)} = \frac{P(aOR - 1)}{P(aOR - 1) + 1} * 100\%
\]

where \( P \) is the proportion of cases that are exposed to pregnancy complications and aOR is the adjusted OR for the effect on obstetric MBT incidence.

**Patient and public involvement**

Patients and members of the public were not involved in the design of this study.

**Results**

1. **Overall incidence and trends of obstetric MBT**

From 2012 to 2019, 11,667,406 women who had given birth or ended their pregnancy were included in the present study. Obstetric MBT occurred in 27,626 cases, corresponding to an incidence of 23.68 per 10,000 maternities. As shown in Figure 1, the incidence of obstetric MBT increased from 14.03 per 10,000 maternities in 2012 to 29.59 per 10,000 maternities in 2019 (\( p \) for trend < 0.001). Similar trends were observed in the east, central, and west of China. In addition, 350 health facilities had reported the institutional data for 2012, 2015 and...
2018. The overall percentage of safe blood storage increased from 2012 to 2018 (77.71% to 82.57%), and this increase remained after the data were stratified by hospital level (level 1: 30.61% to 38.8%; level 2: 78.95% to 84.74%; level 3: 96.40% to 98.20%) (Figure 2).

2. Subgroup incidence and risk factors of obstetric MBT

Table 1 displays the incidence and risk of obstetric MBT according to maternal characteristics. Being elderly, a lower level of education, a history of fewer antenatal treatments, uterine scarring, multiparity, having a small gestational age delivery, cesarean section and multiple gestations were associated with a higher risk of needing obstetric MBT. Furthermore, the association between abortion and MBT was strong, with an aOR of 1.77 (95% CI: 1.42~2.21).

As Table 2 shows, AFE, placenta accrete and HELLP syndrome had the 3 highest incidence values for obstetric MBT. The main risk factor for obstetric MBT was amniotic fluid embolism, which led to a 127-fold increased risk, with an aOR of 126.85 (95% CI: 96.88~166.10). Women who had severe anemia or uterine atony were nearly 36 times more likely to undergo obstetric MBT. We also found abnormal placenta to represent a major risk factor, with an aORs of 6.93 (95% CI: 6.05~7.94) for placenta previa, 11.65 (95% CI: 9.48~14.31) for placenta accrete, 6.53 (95% CI: 5.73~7.45) for placenta abruptio and 3.01 (95% CI: 2.48~3.65) for placenta retained. In addition, compared with non-HELLP syndrome, maternal HELLP syndrome led to a higher risk of needing obstetric MBT. Furthermore, the association between ectopic pregnancy and uterine rupture and obstetric MBT was strong. Moreover, preeclampsia or eclampsia, soft birth canal lacerations and puerperal infection were also associated with the incidence of obstetric MBT.
3. Characteristics of multiparous women

We further compared the differences in obstetric MBT-related risk factors in addition to hysterectomy and MMR during hospitalization between the nulliparous and multiparous women. An advanced maternal age, a lower education level, less antenatal care, abortion, ectopic pregnancy, placental abnormalities, severe anemia, uterine rupture, amniotic fluid embolism, hysterectomy and mortality during hospitalization were more likely to occur in women who were multiparous (Appendix Table).

4. Population etiologic fraction for complications

We calculated the PEF for the different complications to identify the main reasons for obstetric MBT at the population perspective. As Table 3 presents, the three highest PEFs were 42.28% for uterine atony, 12.33% for severe anemia and 6.08% for placenta previa.

5. Clinical outcomes and trends in the MBT population

Of the 27,626 women, 4,010 underwent hysterectomy, and 376 died during hospitalization. As Figure 3 shows, the trends of hysterectomy (25.07% to 9.92%) and MMR during hospitalization (21.41‰ to 7.48‰) from 2012-2019 among women who underwent MBT was decrease (p for trend < 0.001). A decrease trend in hysterectomy and the MMR during hospitalization in level 1 and level 2 hospitals as well as in level 3 hospitals were also observed. As appendix Figure shows, a greater decline in level hospital and level 2 hospitals for hysterectomy, and a greater decline in level 2 hospitals for maternal mortality rate was observed.

Discussion
The incidence of obstetric MBT during 2012-2019 was 23.66 per 10,000 maternities, and there was an increasing trend in China. An advanced maternal age, uterine scarring, a multiparous status, and multiple gestations were associated with a higher risk of needing obstetric MBT. AFE, uterine atony, and severe anemia were major complications associated with obstetric MBT. The top three PEFs were 42.28% for uterine atony, 12.33% for severe anemia and 6.08% for placenta previa.

Obstetric MBT has been internationally reported in recent years\textsuperscript{9-13}. However, due to differences in the definition of MBT, the incidence of MBT varies greatly across countries; for example, the incidence is 5.3 per 10,000 maternities in Sweden\textsuperscript{10}, 10.0 per 10,000 maternities in New York\textsuperscript{9}, 6.5 per 10,000 births in the Netherlands\textsuperscript{13}, and 2.3 per 10,000 maternities in the UK\textsuperscript{11}. The definition of MBT is generally limited to 24 hours after giving birth. However, different amounts of blood, typically 5-10 units of red blood cells, have been used. MBT involves $\geq$10 units of red blood cells in Sweden and New York\textsuperscript{9,10} and $\geq$8 units of red blood cells in the UK and Netherlands\textsuperscript{11,13}. In our study, obstetric MBT was defined as the transfusion of $\geq$5 units of red blood cells or $\geq$1000 ml of whole blood.\textsuperscript{28} Despite these differences in the incidence of MBT, the increasing trend is consistent across countries, except in the Netherlands\textsuperscript{10,13}. The incidence of obstetric MBT also showed an increasing trend from 2012 to 2019 in China (14.03 per 10,000 maternities to 29.59 per 10,000 maternities). Regarding excessive maternal bleeding, if there are no adequate blood resources, it is difficult to save the mother’s life.\textsuperscript{29} Our results showed that the percentage of safe blood storage at level 3 hospitals in 2012 was 96.4%, while that at level 1 hospitals was 30.6%. In recent years, primary medical institutions have been increasingly constructed in
China. In addition, the rate of blood supply in China showed a steadily increasing trend (from 1.23 to 1.74 units per 1,000 population) from 2012-2014. As a result, the percentage of safe blood storage increased the most in level 1 hospitals increasing from 30.6% to 38.8% during 2012-2018. In addition, educational awareness to patients and clinicians on optimal blood utilization practices, and relatively better access to blood products or implementation of a protocol for the management of massive obstetric hemorrhage both contributed to the rising trend of MBT.

The increased incidence of MBT plays a key role in reducing adverse outcomes in pregnancies. On the one hand, it is possible to prevent the occurrence of maternal deaths. From 2012 to 2019, the MMR due to obstetric hemorrhage with MBT in nationwide hospitals showed a decreasing trend (decreased by 68.8%), and the magnitude of decrease was larger than that in the population-based obstetric hemorrhage MMR reported by National Maternal Death Monitoring during the same period (54.6%). On the other hand, the uterus can be saved by timely MBT. When severe obstetric hemorrhage fails to respond to other treatments, hysterectomy is usually performed. Although an increased hysterectomy rate was found among the MBT women in Sweden, we found a decreasing trend in Chinese women. Retaining the uterus can not only realize their dream of becoming a mother but also preserve their quality of life. This trend was observed at all three levels (level1-level3).

Every woman who needs obstetric MBT might have a fatal obstetric hemorrhage, and the slightest error in treatment can kill them before they undergo blood transfusion. Therefore, recognizing the possible risk factors for MBT and preventing their occurrence are effective strategies to ensure the safety of women. We found that higher parity is associated with an
increased risk of needing obstetric MBT. In our study, advanced maternal age, lower education level, less antenatal care, and obstetric hemorrhage-related conditions were more likely to occur in women who were multiparous. Of course, these factors are also positively associated with obstetric MBT. Due to the new fertility policy, the characteristics of Chinese maternal population have changed greatly. In our study, 44.99% of women were multiparous, among whom 36.35% had uterine scars, which may be related to the high cesarean section rate during the one-child policy (46.2%). Uterine scarring is associated with an increase in the risk of abnormal placenta, infection, and uterine rupture. Women with these complications may experience extremely large volumes of blood loss during or soon after delivery, ranging from 2000 to 6000 ml.

In agreement with previous studies, we found that uterine atony, abnormal placenta, uterine rupture, and preeclampsia were strongly associated with obstetric MBT. However, we also found that AFE was the main risk factor for obstetric MBT (aOR: 126.85, 95% CI: 96.88–166.10). AFE, although rare, remains one of the leading direct causes of maternal mortality in high-income countries, and its management principles include the active correction of coagulation disorders, the aggressive treatment of uterine atony and the use of high-dose glucocorticoids as early as possible. The total incidence of AFE was 13.4 per 100,000 maternities in our study, which was higher than that previously reported (1.7-7.7 per 100,000 maternities). This finding may explain why AFE is considered the primary risk factor for obstetric MBT in our study.

Our study also showed that women with severe anemia, abortion, or ectopic pregnancy were at a higher risk of needing obstetric MBT. Severe anemia has been associated with an
increased prevalence of postpartum hemorrhage. Similarly, our study showed that severe anemia increases the risk of needing obstetric MBT by 36-fold (OR: 36.00, 95% CI: 32.09–40.41). No studies have focused on ectopic pregnancy, abortion. We found that the association between ectopic pregnancy and MBT was strong, with an aOR of 9.70 (95% CI: 7.57–12.42), and maternal abortion showed a relatively weaker association with the risk of needing obstetric MBT (aOR: 1.77, 95% CI: 1.42–2.21). Both of them often occur at young gestational ages and may put the woman at risk of intraperitoneal bleeding or related complications in the short term and can even lead to death.

However, the OR reflects only the biological effect of a certain disease, while PEF integrates information about the effect estimate’s magnitude with information about the prevalence of the disease and can reflect sociological effects. Our data were retrieved from a facility-based surveillance system, which covered almost all of China, excluding Tibet. Routinely calculating complication-specific PEFs will allow us to identify the populations most affected for targeted interventions. The top three complications according to the PEFs were uterine atony, severe anemia, and placenta previa in the Chinese population. Women with such complications should be highly concerned because these complications have a high prevalence in Chinese mothers, and they also lead to a high risk of needing obstetric MBT. Although AFE leads to the highest risk of obstetric MBT, its PEF was low due to its relatively low maternal incidence. Our findings indicated that it is necessary to focus on the tertiary prevention of uterine atony, severe anemia, and placenta previa to reduce the risk of needing obstetric MBT in China and minimize the occurrence of adverse maternal outcomes.

The main strength is that we included all women who had given birth or ended their
pregnancy during 2012-2019 from a large nationwide data in China. However, the retrospective nature of the study by itself is a limiting factor as access to all clinical and transfusion variables are not possible. The major limitation is the lack of availability of data on many confounding variables that may influence the MBT or adverse outcomes, and the lack of a specific blood transfusion volume limits our ability to conduct additional analyses. In addition, although we recorded the types of blood transfusions performed, we could not use the data for analysis due to the lack of quantitative information.

**Conclusion**

The incidence of obstetric MBT is increasing in China, but the hysterectomy rate and MMR are decreasing among women undergoing MBT. To minimize the incidence of obstetric MBT, more attention should be paid to education on the importance of the antenatal visit, evidence-based transfusion practice, multiparous women with an advanced age, AFE, uterine atony, severe anemia, and placenta previa. Appropriate blood transfusion preparations and the antenatal early identification for high-risk women might improve the outcomes and reduce the adverse outcomes.

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**Contributors**

All authors have contributed to the conduction of this study. YX., XW, JL and JZ developed the study design with contributions from all authors. YX. performed the statistical analysis
and drafted the manuscript with support from JZ XW., and JL, YM, ML, YW., LD, XL., ML., QL, ZL and PC. participated in reviewing, editing, and revising the manuscript.

Competing interests

The authors declare no conflicts of interest.

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Data sharing statement

The datasets generated and/or analysed during the current study are not publicly available due to the terms of our contract with the Chinese National Health Commission but are available from the corresponding author on reasonable request.

Ethics statements

Ethical approval for the NMNMSS was provided by the Ethics Committee of West China Second University Hospital, Sichuan University, China. Informed consent from the patient was waived from the Ethics Committee, as the data used in this study were obtained from a national routine surveillance system established by the government. Data use was authorized by the National Health Commission, and data provided to us were de-identified.
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Table 1. The incidence and risk of massive blood transfusion (MBT) among different maternal characteristics (N=11,667,406).

| Characteristics | Case / Total deliveries | Incidence of MBT (1/10,000) | Crude OR* (95% CI) | Adjusted OR** (95% CI) |
|-----------------|-------------------------|------------------------------|--------------------|------------------------|
| Age(years)      |                         |                              |                    |                        |
| <20             | 473/287790              | 16.44                        | 1.15(1.03~1.28)    | 1.09(0.97~1.21)        |
| 20-24           | 3030/2114730            | 14.33                        | Reference          | Reference              |
| 25-29           | 8024/4642235            | 17.28                        | 1.21(1.12~1.30)    | 0.99(0.94~1.06)        |
| 30-34           | 8116/2900510            | 27.98                        | 1.96(1.77~2.16)    | 1.05(0.97~1.13)        |
| 35-39           | 5151/1125337            | 45.77                        | 3.20(2.89~3.55)    | 1.13(1.03~1.24)        |
| >=40            | 1860/278675             | 66.74                        | 4.68(4.23~5.19)    | 1.24(1.10~1.40)        |
| Missing         | 972/318129              | 30.55                        | 2.14(1.62~2.81)    | 1.30(1.07~1.56)        |
| Marital status       | Unmarried                  | Married                      | Missing                  |
|----------------------|----------------------------|------------------------------|--------------------------|
|                      | 639/196743                 | 26979/11468023               | 8/2640                   |
|                      | 32.48                      | 23.53                        | 30.30                    |
|                      | 1.38(1.17~1.63)            | reference                    | reference                |
|                      | 1.25(1.11~1.39)            | reference                    | reference                |
| Parity               | Nulliparous 9788/6400896   | reference                    | reference                |
|                      | 15.29                      | reference                    | reference                |
|                      | 4.45(3.00~6.61)            | 1.99(1.40~2.82)              |                          |
|                      | 28.45                      | 1.86(1.72~2.02)              | 1.19(1.12~1.26)          |
|                      | 63.47                      | 4.17(3.64~4.78)              | 1.83(1.65~2.03)          |
|                      | 38.25                      | 2.51(0.53~11.91)             | 0.66(0.13~3.48)          |
|                      | 2436/376782                | 64.65                        |                          |
|                      | 1.87(1.43~2.43)            | 1.36(1.04~1.78)              |                          |
|                      | 17804/9736123              | 18.29                        |                          |
|                      | 2261/1908222               | 50.93                        |                          |
|                      | 68/17776                   | 16.04                        |                          |
|                      | 24973/11422786             | 21.86                        |                          |
|                      | 2261/215694                | 104.82                       |                          |
|                      | 392/28926                  | 135.52                       |                          |
|                      | 20316/6985253              | 29.08                        |                          |
|                      | 7310/4682153               | 15.61                        |                          |
|                      | 17804/9736123              | 18.29                        |                          |
|                      | 24973/11422786             | 21.86                        |                          |
|                      | 2261/215694                | 104.82                       |                          |
|                      | 392/28926                  | 135.52                       |                          |
|                      | 20316/6985253              | 29.08                        |                          |
|                      | 7310/4682153               | 15.61                        |                          |
|                      | 17804/9736123              | 18.29                        |                          |
|                      | 24973/11422786             | 21.86                        |                          |
|                      | 2261/215694                | 104.82                       |                          |
|                      | 392/28926                  | 135.52                       |                          |
|                      | 20316/6985253              | 29.08                        |                          |
|                      | 7310/4682153               | 15.61                        |                          |
|                      | 17804/9736123              | 18.29                        |                          |
|                      | 24973/11422786             | 21.86                        |                          |
|                      | 2261/215694                | 104.82                       |                          |
|                      | 392/28926                  | 135.52                       |                          |
|                      | 20316/6985253              | 29.08                        |                          |
|                      | 7310/4682153               | 15.61                        |                          |
|                      | 17804/9736123              | 18.29                        |                          |
|                      | 24973/11422786             | 21.86                        |                          |
|                      | 2261/215694                | 104.82                       |                          |
|                      | 392/28926                  | 135.52                       |                          |
|                      | 20316/6985253              | 29.08                        |                          |
|                      | 7310/4682153               | 15.61                        |                          |
|                      | 17804/9736123              | 18.29                        |                          |
|                      | 24973/11422786             | 21.86                        |                          |
| Mode of delivery          | Cases        | Incidence of MBT (1/1000) | Crude OR* (95% CI) | Adjusted OR** (95% CI) |
|---------------------------|--------------|---------------------------|--------------------|------------------------|
| Vaginal                   | 5676/6167464 | 9.20                      | reference          | reference              |
| CS                        | 18551/4998004 | 37.12                     | 4.04 (3.93~4.17)   | 2.08 (1.89~2.28)       |
| Abortion                  | 3349/498143  | 67.23                     | 7.35 (7.04~7.67)   | 1.77 (1.42~2.21)       |
| Missing                   | 50/3795      | 131.75                    | 14.49 (10.95~19.18) | 0.73 (0.34~1.57)       |

CI, confidence interval; CS, caesarean section; OR, odds ratio.

* Adjusted for the clustering of births within hospitals.

** Adjusted for: the clustering of births within hospitals; region; hospital level; antenatal care; birth location; multiple gestations; gestational week; mother’s education, marital status, age and parity; the delivery method and other factors thought to be associated with massive blood transfusion, such as a placenta previa; placenta accrete; placenta abruptio; placenta retained; all hypertensive disorders in pregnancy; HELLP syndrome; severe anemia; uterine atony; ruptured uterus; soft birth canal lacerations; puerperal infection and amniotic fluid embolism.

**Table 2.** The incidence and risk of mass transfusion (MBT) among different complications (N=11,667,406).
| Condition                          | N      | CI     | OR    | 95% CI      | 95% CI      |
|----------------------------------|--------|--------|-------|-------------|-------------|
| Gestational hypertension†        | 158526 | 4.88   | 2.10  | 1.89–2.32   | 1.62–1.79   |
| Superimposed preeclampsia†        | 11951  | 8.53   | 3.64  | 2.90–4.56   | 1.32–0.99   |
| Preeclampsia or eclampsia†        | 257096 | 10.53  | 4.86  | 4.43–5.33   | 2.23–2.43   |
| HELLP syndrome†                   | 6702   | 92.36  | 43.83 | 36.12–53.19 | 13.02–16.02 |
| Severe anemia†                    | 46898  | 76.17  | 39.75 | 35.30–44.75 | 36.00–40.41 |
| Uterine atony‡                    | 240063 | 49.65  | 37.95 | 31.97–45.05 | 36.45–43.04 |
| Uterine rupture‡                  | 22748  | 36.09  | 16.23 | 11.76–22.39 | 5.05–3.67   |
| Soft birth canal lacerations‡      | 127320 | 7.61   | 3.31  | 2.36–4.65   | 4.28–3.31   |
| Puerperal infection‡              | 13468  | 33.71  | 14.93 | 12.25–18.20 | 3.47–2.78   |
| Amniotic fluid embolism‡          | 1558   | 411.42 | 301.49| 245.43–370.37 | 126.85–166.10 |

CI, confidence interval; OR, odds ratio.

* Adjusted for the clustering of births within hospitals.

** Adjusted for: the clustering of births within hospitals; region; hospital level; antenatal care; birth location; multiple gestations; gestational week; mother’s education, marital status, age and parity; the delivery method and other factors thought to be associated with massive blood transfusion, such as a placenta previa; placenta accrete; placenta abruptio; placenta retained; all hypertensive disorders in pregnancy; HELLP syndrome; severe anemia; uterine atony; ruptured uterus; soft birth canal lacerations; puerperal infection and amniotic fluid embolism.
| Complication                        | Num.    | P (1/10,000) | PEF (95%CI)             |
|------------------------------------|---------|--------------|-------------------------|
| Abortion                           | 498143  | 426.95       | 3.18% (1.76~4.91%)      |
| Ectopic pregnancy                  | 45648   | 39.12        | 3.29% (2.51~4.28%)      |
| Placenta praevia                   | 126105  | 108.08       | 6.08% (5.18~6.98%)      |
| Placenta accreta                   | 21545   | 18.47        | 1.93% (1.54~2.41%)      |
| Placenta abruptio                  | 54460   | 46.68        | 2.52% (2.16~2.92%)      |
| Placenta retained                  | 141113  | 120.95       | 2.37% (1.76~3.09%)      |
| Chronic hypertension               | 37732   | 32.34        | 0.09% (0.01~0.18%)      |
| Gestational hypertension           | 158526  | 135.87       | 0.84% (0.62~1.06%)      |
| Superimposed preeclampsia          | 11951   | 10.24        | 0.03% (0%~0.08%)        |
| Preeclampsia or eclampsia          | 257096  | 220.35       | 2.64% (2.26~3.05%)      |
| HELLP syndrome                     | 6702    | 5.74         | 0.69% (0.55~0.86%)      |
| Severe anaemia                     | 46898   | 40.20        | 12.33% (11.11~13.67%)   |
| Uterine atony                      | 240063  | 205.76       | 42.28% (38.07~46.38%)   |
| Uterine rupture                    | 22748   | 19.50        | 0.78% (0.52~1.15%)      |
| Soft birth canal lacerations       | 127320  | 109.12       | 3.46% (2.46~4.72%)      |
| Puerperal infection                | 13468   | 11.54        | 0.28% (0.21~0.38%)      |
| Amniotic fluid embolism            | 1558    | 1.34         | 1.65% (1.26~2.16%)      |
Figure legends:

Figure 1 The secular trends and incidence of massive blood transfusion (1/10,000) during 2012-2019.

Figure 2 Changes in the proportion of safe blood storage (%) in different health facilities (level 1, level 2 and level 3).

Figure 3 The secular trends and incidence of hysterectomy (%) (a) and maternal mortality ratio during hospitalization (‰) (b) among MBT population during 2012-2019.

Appendix Figure The secular trends and incidence of hysterectomy (%) (a) and maternal mortality ratio during hospitalization (‰) (b) among MBT population in different levels of hospitals during 2012-2019.
Figure 1 The secular trends and incidence of massive blood transfusion (1/10,000) during 2012-2019.

155x97mm (150 x 150 DPI)
Figure 2 Changes in the proportion of safe blood storage (%) in different health facilities (level 1, level 2 and level 3).
Figure 3 The secular trends and incidence of hysterectomy (%) (a) and maternal mortality ratio during hospitalization (‰) (b) among MBT population during 2012-2019.

158x53mm (220 x 220 DPI)
The secular trends and incidence of hysterectomy (%) (a) and maternal mortality ratio during hospitalization (‰) (b) among MBT population in different levels of hospitals during 2012-2019.
**Appendix Table.** Distribution of population characteristics among nulliparous and multiparous.

|                      | Nulliparous(n=6400896) | Multiparous(n=5248734) | p value |
|----------------------|-------------------------|-------------------------|---------|
| **Age(years)**       |                         |                         |         |
| <20                  | 251758                  | 35758                   | 0.68    |
| 20-24                | 1579681                 | 533099                  | 10.16   |
| 25-29                | 2974516                 | 1662322                 | 31.67   |
| 30-34                | 1163423                 | 1731286                 | 32.98   |
| 35-39                | 225639                  | 896562                  | 17.08   |
| >=40                 | 37056                   | 240833                  | 4.59    |
| Missing              | 168823                  | 148874                  | 2.84    |
| **Education**        |                         |                         |         |
| College or higher    | 2958476                 | 1356322                 | 25.84   |
| High school          | 1678091                 | 1439229                 | 27.42   |
| Middle school        | 1493516                 | 2086280                 | 39.75   |
| Primary school       | 92973                   | 251616                  | 4.79    |
| Illiteracy           | 18019                   | 42232                   | 0.80    |
| Missing              | 159821                  | 73055                   | 1.39    |
| **Marital status**   |                         |                         |         |
| Unmarried            | 144904                  | 51496                   | 0.98    |
| Married              | 6254591                 | 5196325                 | 99.00   |
| Missing              | 1401                    | 913                     | 0.02    |
| **Antenatal care**   |                         |                         |         |
| None                 | 105550                  | 147720                  | 2.81    |
| 1-3                  | 384122                  | 563520                  | 10.74   |
| 4-6                  | 1545500                 | 1647691                 | 31.39   |
| 7-9                  | 1902485                 | 1487130                 | 28.33   |
| >=10                 | 2263094                 | 1241147                 | 23.65   |
| Missing              | 200145                  | 161526                  | 3.08    |
| **Gestational week** |                         |                         |         |
| <28                  | 193739                  | 294731                  | 5.62    |
| 28-32                | 85754                   | 80828                   | 1.54    |
| 33-36                | 349958                  | 303554                  | 5.78    |
| 37-41                | 5711544                 | 4507546                 | 85.88   |
| >=41                 | 40410                   | 34812                   | 0.66    |
| Missing              | 19491                   | 27263                   | 0.52    |
| **Previous CS**      | 0                       | 1907972                 | 36.35   |
| **Abortion**         | 196141                  | 299465                  | 5.71    |
| **Ectopic pregnancy**| 12529                   | 33000                   | 0.63    |
| **Placenta abnormal**|                         |                         | <0.001  |
| Placenta praevia     | 50169                   | 75112                   | 1.43    |
| Placenta accreta     | 7229                    | 14267                   | 0.27    |
| Placenta abruptio    | 27828                   | 26568                   | 0.51    |
| Placenta retained    | 70442                   | 70483                   | 1.34    |
| Hypertensive disorders                  |   |   |   |
|----------------------------------------|---|---|---|
| Chronic hypertension                   | 18671 | 0.29 | 18894 | 0.36 | <0.001 |
| Gestational hypertension               | 88443 | 1.38 | 69688 | 1.33 | <0.001 |
| Superimposed preeclampsia              | 4946 | 0.08 | 6996 | 0.13 | <0.001 |
| Preeclampsia or eclampsia              | 150558 | 2.35 | 105218 | 2.00 | <0.001 |
| HELLP syndrome                         | 3159 | 0.05 | 3435 | 0.07 | <0.001 |
| Severe anemia                          | 20511 | 0.32 | 26363 | 0.50 | <0.001 |
| Uterine atony                          | 138065 | 2.16 | 101834 | 1.94 | <0.001 |
| Uterine rupture                        | 1777 | 0.03 | 20844 | 0.40 | <0.001 |
| Soft birth canal lacerations           | 72098 | 1.13 | 55186 | 1.05 | <0.001 |
| Puerperal infection                    | 8476 | 0.13 | 4941 | 0.09 | <0.001 |
| Amniotic fluid embolism                | 637 | 0.01 | 918 | 0.02 | <0.001 |
| Hysterectomy                           | 1278 | 0.02 | 4735 | 0.09 | <0.001 |
| Died during hospitalization            | 431 | 0.01 | 505 | 0.01 | <0.001 |
### STROBE Statement—checklist of items that should be included in reports of observational studies

| Item No | Recommendation | Page No |
|---------|----------------|---------|
| **Title and abstract** | | |
| 1 | (a) Indicate the study’s design with a commonly used term in the title or the abstract | 1 |
| 2 | (b) Provide in the abstract an informative and balanced summary of what was done and what was found | 3 |
| **Introduction** | | |
| 2 | Explain the scientific background and rationale for the investigation being reported | 6 |
| **Objectives** | | |
| 3 | State specific objectives, including any prespecified hypotheses | 7 |
| **Methods** | | |
| 4 | Present key elements of study design early in the paper | 7 |
| 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | 7 |
| 6 | (a) **Cohort study**—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up **Case-control study**—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls **Cross-sectional study**—Give the eligibility criteria, and the sources and methods of selection of participants | 8 |
| 7 | (b) **Cohort study**—For matched studies, give matching criteria and number of exposed and unexposed **Case-control study**—For matched studies, give matching criteria and the number of controls per case | None |
| 8 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | 8-9 |
| 8* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group | 8-9 |
| 9 | Describe any efforts to address potential sources of bias | 9 |
| 10 | Explain how the study size was arrived at | 9-10 |
| 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | 9-10 |
| 12 | (a) Describe all statistical methods, including those used to control for confounding | 9-10 |
| 12 | (b) Describe any methods used to examine subgroups and interactions | 9-10 |
| 12 | (c) Explain how missing data were addressed | 9-10 |
| 12 | (d) **Cohort study**—If applicable, explain how loss to follow-up was addressed **Case-control study**—If applicable, explain how matching of cases and controls was addressed **Cross-sectional study**—If applicable, describe analytical methods taking account of sampling strategy | None |
| 12 | (e) Describe any sensitivity analyses | None |

Continued on next page
## Results

**Participants** 13*  
(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed 11  
(b) Give reasons for non-participation at each stage 11  
(c) Consider use of a flow diagram 11

**Descriptive data** 14*  
(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders 11  
(b) Indicate number of participants with missing data for each variable of interest 11  
(c) Cohort study—Summarise follow-up time (eg, average and total amount) 11

**Outcome data** 15*  
*Cohort study*—Report numbers of outcome events or summary measures over time 11  
*Case-control study*—Report numbers in each exposure category, or summary measures of exposure 11  
*Cross-sectional study*—Report numbers of outcome events or summary measures 11

**Main results** 16  
(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included 11-12  
(b) Report category boundaries when continuous variables were categorized None  
(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period none

**Other analyses** 17  
Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses 12-13

## Discussion

**Key results** 18  
Summarise key results with reference to study objectives 13

**Limitations** 19  
Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias 17

**Interpretation** 20  
Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence 13-17

**Generalisability** 21  
Discuss the generalisability (external validity) of the study results 17

## Other information

**Funding** 22  
Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based 18

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.