Supplement material for

**Preconception hemoglobin concentration with risk of spontaneous abortion: a population-based cohort study in over 3.9 million women across rural China.**

**Number of Table: 5**

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# Table S1. Altitude adjustments to measured hemoglobin concentrations and the distribution of participants according to the altitude

|  |  |  |  |
| --- | --- | --- | --- |
| **Altitude (m)** | **Measured Hb adjustment (g/L) \*** | **No. of participants** | **SA, n (%)** |
|
| <1000 | 0 | 3548580 | 84502 (2.38) |
| 1000-1500 | -2 | 173678 | 7316 (4.21) |
| 1500-2000 | -5 | 142763 | 4919 (3.45) |
| 2000-2500 | -8 | 66818 | 2592 (3.88) |
| 2500-3000 | -13 | 21299 | 1263 (5.93) |
| 3000-3500 | -19 | 11403 | 844 (7.40) |
| 3500-4000 | -27 | 5697 | 232 (4.07) |
| 4000-4500 | -35 | 716 | 21 (2.93) |
| >=4500 | -45 | 474 | 11 (2.32) |

Hb, hemoglobin. Altitude, meters above the sea level.

\* The measured Hb adjustment values at varying altitudes were developed by the US Centers for Disease Control and Prevention’s (CDC) Pediatric Nutrition Surveillance System using data from a study of children living in mountainous states. These adjustment values were also recommended by WHO to define anemia for residents living in elevations above 1000 meters. Therefore, Hb concentrations of women who lived in areas with altitude ≥ 1000 meters were adjusted by subtracting the adjustment values from the original Hb concentrations in the current study

# Table S2. The effect sizes of covariates in model C of Table2

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Variables** | **β** | **OR** | **95% CI** | | ***P* value** |
| **Low** | **high** |
| **Maternal Age at LMP, years** |  |  |  |  |  |
| 20-24 | ref |  |  |  |  |
| 25-29 | -0.03 | 0.97 | 0.96 | 0.99 | 0.002 |
| 30-34 | 0.02 | 1.02 | 0.99 | 1.04 | 0.205 |
| 35-39 | 0.31 | 1.36 | 1.31 | 1.41 | <0.001 |
| ≥40 | 0.85 | 2.34 | 2.21 | 2.48 | <0.001 |
| **Paternal age at LMP, years** |  |  |  |  |  |
| 20-24 | ref |  |  |  |  |
| 25-29 | 0.05 | 1.05 | 1.03 | 1.07 | <0.001 |
| 30-34 | 0.13 | 1.14 | 1.11 | 1.17 | <0.001 |
| 35-39 | 0.29 | 1.34 | 1.30 | 1.39 | <0.001 |
| ≥40 | 0.46 | 1.58 | 1.51 | 1.65 | <0.001 |
| **Han ethnicity** | -0.47 | 0.62 | 0.61 | 0.64 | <0.001 |
| **Higher education** | -0.05 | 0.95 | 0.94 | 0.97 | <0.001 |
| **Farmers** | -0.15 | 0.86 | 0.85 | 0.88 | <0.001 |
| **BMI, kg/m2** |  |  |  |  |  |
| <18.5 | 0.10 | 1.11 | 1.09 | 1.13 | <0.001 |
| 18.5-23.9 | ref |  |  |  |  |
| 24.0-27.9 | 0.05 | 1.05 | 1.03 | 1.07 | <0.001 |
| ≥28.0 | 0.12 | 1.13 | 1.09 | 1.17 | <0.001 |
| **Diabetes** | 0.11 | 1.11 | 1.05 | 1.18 | <0.001 |
| **Hypertension** | 0.17 | 1.19 | 1.14 | 1.25 | <0.001 |
| **Thyroid dysfunction** | 0.10 | 1.11 | 1.08 | 1.13 | <0.001 |
| **History of abortion** | 0.22 | 1.25 | 1.23 | 1.27 | <0.001 |
| **Parity (nulliparous)** | -0.29 | 0.75 | 0.74 | 0.76 | <0.001 |
| **Smoking before or during early pregnancy** | -0.03 | 0.97 | 0.96 | 0.99 | 0.001 |
| **Drinking before or during early pregnancy** | 0.12 | 1.13 | 1.08 | 1.17 | <0.001 |
| **Toxicants exposure****before or during early pregnancy** | 0.23 | 1.26 | 1.18 | 1.34 | <0.001 |
| **Abstain from animal products or vegetables before or during early pregnancy** | 0.12 | 1.13 | 1.10 | 1.15 | <0.001 |
| **Paternal smoking before or during early pregnancy** | 0.12 | 1.13 | 1.12 | 1.14 | <0.001 |
| **Paternal toxicants exposure****before pregnancy** | 0.13 | 1.14 | 1.08 | 1.20 | <0.001 |

# Table S3. Associations between maternal original preconception hemoglobin concentrations and risk of spontaneous abortion

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Hb, g/L** | **No. of participants** | **SA, n (%)** | **Model A** | |  | **Model B** | |  | **Model C** | |  | **Model D** | |
| **OR (95% CI)** | ***P* value** | **OR (95% CI)** | ***P* value** | **OR (95% CI)** | ***P* value** | **OR (95% CI)** | ***P* value** |
| **Class I** |  |  |  |  |  |  |  |  |  |  |  |  |  |
| <100 | 272047 | 5789 (2.13) | 0.83 (0.81-0.85) | <0.001 |  | 0.82 (0.80-0.84) | <0.001 |  | 0.82 (0.79-0.84) | <0.001 |  | 0.82 (0.80-0.85) | <0.001 |
| 110-149 | 3479116 | 89149 (2.56) | 1 | - |  | 1 | - |  | 1 | - |  | 1 | - |
| ≥150 | 220265 | 6762 (3.07) | 1.2 (1.17-1.24) | <0.001 |  | 1.17 (1.14-1.20) | <0.001 |  | 1.18 (1.15-1.21) | <0.001 |  | 1.1 (1.07-1.13) | <0.001 |
| **Class II** |  |  |  |  |  |  |  |  |  |  |  |  |  |
| <70 | 1697 | 68 (4.01) | 1.59 (1.25-2.02) | <0.001 |  | 1.42 (1.11-1.81) | 0.005 |  | 1.42 (1.11-1.81) | 0.005 |  | 1.41 (1.10-1.79) | 0.006 |
| 70-99 | 84728 | 2011 (2.37) | 0.92 (0.88-0.97) | 0.001 |  | 0.89 (0.85-0.93) | <0.001 |  | 0.88 (0.84-0.92) | <0.001 |  | 0.89 (0.85-0.93) | <0.001 |
| 100-109 | 185622 | 3710 (2.00) | 0.78 (0.75-0.80) | <0.001 |  | 0.78 (0.75-0.80) | <0.001 |  | 0.78 (0.75-0.80) | <0.001 |  | 0.79 (0.76-0.81) | <0.001 |
| 110-149 | 3479116 | 89149 (2.56) | 1 | - |  | 1 | - |  | 1 | - |  | 1 | - |
| 150-159 | 164345 | 5048 (3.07) | 1.21 (1.17-1.24) | <0.001 |  | 1.18 (1.14-1.21) | <0.001 |  | 1.18 (1.14-1.21) | <0.001 |  | 1.11 (1.08-1.14) | <0.001 |
| 160-169 | 36222 | 1137 (3.14) | 1.23 (1.16-1.31) | <0.001 |  | 1.19 (1.12-1.26) | <0.001 |  | 1.20 (1.13-1.27) | <0.001 |  | 1.09 (1.02-1.15) | 0.008 |
| ≥170 | 19698 | 577 (2.93) | 1.15 (1.06-1.25) | 0.001 |  | 1.10 (1.01-1.19) | 0.027 |  | 1.11 (1.02-1.21) | 0.013 |  | 1.01 (0.93-1.10) | 0.810 |

Hb, hemoglobin; SA, spontaneous abortion; OR, odd ratio; CI, confidence interval.

Model A: ORs were estimated from crude models. Model B: ORs were adjusted for sociodemographic characteristics of women (age at last menstrual period, education, ethnicity, occupation). Model C: ORs were additionally adjusted for maternal information (BMI, smoking, alcohol drinking, hypertension, diabetes, thyroid dysfunction, history of SA, toxicants exposure, abstain from animal products or vegetables) and paternal information (age at last menstrual period, smoking, toxicants exposure). Model D: in addition to those factors included in model C, ORs were also adjusted for altitude.

# Table S4. Associations between maternal preconception adjusted hemoglobin concentrations and risk of spontaneous abortion after excluding participants in areas with high prevalence of thalassemia \*

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Hb, g/L** | **No. of participants** | **SA, n (%)** | **Model A** | |  | **Model B** | |  | **Model C** | |
| **OR (95% CI)** | **P value** | **OR (95% CI)** | **P value** | **OR (95% CI)** | **P value** |
| **Class I** |  |  |  |  |  |  |  |  |  |  |
| <100 | 230051 | 5284 (2.30) | 0.90 (0.88-0.93) | <0.001 |  | 0.87 (0.85-0.90) | <0.001 |  | 0.86 (0.84-0.89) | <0.001 |
| 110-149 | 2773771 | 70271 (2.53) | 1 | - |  | 1 | - |  | 1 | - |
| ≥150 | 157095 | 4242 (2.70) | 1.07 (1.04-1.10) | <0.001 |  | 1.06 (1.02-1.09) | 0.001 |  | 1.07 (1.04-1.10) | <0.001 |
| **Class II** |  |  |  |  |  | 0 (0-0) |  |  |  |  |
| <70 | 1940 | 97 (5.00) | 2.03 (1.65-2.48) | <0.001 |  | 1.63 (1.33-2.01) | <0.001 |  | 1.61 (1.31-1.98) | <0.001 |
| 70-99 | 74435 | 1947 (2.62) | 1.03 (0.99-1.08) | 0.159 |  | 0.96 (0.92-1.01) | 0.078 |  | 0.94 (0.88-1.01) | 0.051 |
| 100-109 | 153676 | 3240 (2.11) | 0.83 (0.80-0.86) | <0.001 |  | 0.82 (0.79-0.85) | <0.001 |  | 0.81 (0.78-0.84) | <0.001 |
| 110-149 | 2773771 | 70271 (2.53) | 1 | - |  | 1 | - |  | 1 | - |
| 150-159 | 118919 | 3251 (2.73) | 1.08 (1.04-1.12) | <0.001 |  | 1.07 (1.03-1.11) | <0.001 |  | 1.08 (1.05-1.12) | <0.001 |
| 160-169 | 24254 | 641 (2.64) | 1.04 (0.97-1.13) | 0.280 |  | 1.03 (0.95-1.11) | 0.474 |  | 1.05 (0.97-1.14) | 0.243 |
| ≥170 | 13922 | 350 (2.51) | 0.99 (0.89-1.10) | 0.884 |  | 0.97 (0.87-1.08) | 0.546 |  | 0.99 (0.89-1.10) | 0.856 |

Hb, hemoglobin; SA, spontaneous abortion; OR, odd ratio; CI, confidence interval.

\* Areas including province of Guangdong, Guangxi, Hainan, Fujian, Yunnan, Guizhou, Sichuan. Model A: ORs were estimated from crude models. Model B: ORs were adjusted for sociodemographic characteristics of women (age at last menstrual period, education, ethnicity, occupation). Model C: ORs were additionally adjusted for maternal information (BMI, smoking, alcohol drinking, hypertension, diabetes, thyroid dysfunction, history of SA, toxicants exposure, abstain from animal products or vegetables) and paternal information (age at last menstrual period, smoking, toxicants exposure).

# Table S5. Odds ratios (95% confidence intervals) of spontaneous abortion with preconception Hb concentrations by stratified analysis

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Variables** | Hb groups, g/L | | | P for interaction \* |
| <110 | 110-149 | ≥150 |
| **Maternal Age at LMP, years** |  |  |  | <0.001 |
| <35 | 0.84 (0.81-0.86) | 1 | 1.11 (1.08-1.14) |  |
| ≥35 | 0.95 (0.88-1.03) | 1 | 1.04 (0.95-1.15) |  |
| **Paternal age at LMP, years** |  |  |  | <0.001 |
| <35 | 0.83 (0.81-0.85) | 1 | 1.11 (1.08-1.14) |  |
| ≥35 | 0.94 (0.88-1.00) | 1 | 1.08 (1.00-1.16) |  |
| **Ethnicity** |  |  |  | <0.001 |
| Han | 0.81 (0.79-0.84) | 1 | 1.12 (1.08-1.15) |  |
| Others | 1.06 (1.00-1.13) | 1 | 1.02 (0.95-1.11) |  |
| **Education** |  |  |  | 0.970 |
| Higher | 0.81 (0.77-0.85) | 1 | 1.14 (1.08-1.20) |  |
| Lower | 0.87 (0.85-0.90) | 1 | 1.09 (1.06-1.13) |  |
| **Occupation** |  |  |  | 0.005 |
| Farmers | 0.87 (0.85-0.90) | 1 | 1.09 (1.06-1.12) |  |
| Others | 0.78 (0.73-0.83) | 1 | 1.18 (1.10-1.26) |  |
| **BMI, kg/m2** |  |  |  | 0.311 |
| <24.0 | 0.84 (0.82-0.86) | 1 | 1.10 (1.06-1.13) |  |
| ≥24.0 | 0.88 (0.83-0.94) | 1 | 1.12 (1.05-1.19) |  |
| **Diabetes** |  |  |  | <0.001 |
| Yes | 0.69 (0.55-0.87) | 1 | 1.21 (0.98-1.50) |  |
| No | 0.85 (0.83-0.87) | 1 | 1.10 (1.07-1.13) |  |
| **Hypertension** |  |  |  | 0.052 |
| Yes | 0.84 (0.82-0.87) | 1 | 1.10 (1.07-1.13) |  |
| No | 1.06 (0.88-1.28) | 1 | 1.12 (0.95-1.31) |  |
| **Thyroid dysfunction** |  |  |  | 0.600 |
| Yes | 0.83 (0.78-0.89) | 1 | 1.13 (1.05-1.22) |  |
| No | 0.85 (0.83-0.87) | 1 | 1.10 (1.07-1.13) |  |
| **History of abortion** |  |  |  | 0.374 |
| Yes | 0.83 (0.79-0.88) | 1 | 1.13 (1.06-1.21) |  |
| No | 0.85 (0.82-0.87) | 1 | 1.10 (1.06-1.13) |  |
| **Parity** |  |  |  | <0.001 |
| Nulliparous | 0.73 (0.71-0.76) | 1 | 1.11 (1.07-1.16) |  |
| Parous | 0.95 (0.92-0.98) | 1 | 1.09 (1.05-1.14) |  |
| **Smoking before or during early pregnancy** |  |  |  | 0.473 |
| Yes | 0.86 (0.66-1.10) | 1 | 0.83 (0.62-1.11) |  |
| No | 0.85 (0.82-0.87) | 1 | 1.11 (1.08-1.14) |  |
| **Drinking before or during early pregnancy** |  |  |  | 0.236 |
| Yes | 0.93 (0.78-1.11) | 1 | 1.24 (1.05-1.46) |  |
| No | 0.84 (0.82-0.87) | 1 | 1.10 (1.07-1.13) |  |
| **Toxicants exposure****before or during early pregnancy** |  |  |  | 0.016 |
| Yes | 0.90 (0.71-1.13) | 1 | 0.97 (0.73-1.28) |  |
| No | 0.85 (0.82-0.87) | 1 | 1.10 (1.07-1.14) |  |
| **Abstain from animal products or vegetables before or during early pregnancy** |  |  |  | 0.006 |
| Yes | 0.87 (0.81-0.95) | 1 | 1.12 (1.03-1.22) |  |
| No | 0.84 (0.82-0.87) | 1 | 1.10 (1.07-1.14) |  |
| **Paternal smoking before or during early pregnancy** |  |  |  | <0.001 |
| Yes | 0.83 (0.80-0.87) | 1 | 1.16 (1.11-1.21) |  |
| No | 0.85 (0.82-0.88) | 1 | 1.07 (1.03-1.11) |  |
| **Paternal toxicants exposure****before pregnancy** |  |  |  | 0.581 |
| Yes | 0.95 (0.78-1.15) | 1 | 1.14 (0.91-1.42) |  |
| No | 0.84 (0.82-0.86) | 1 | 1.10 (1.07-1.13) |  |
| **Altitude, meter** |  |  |  | <0.001 |
| <1000 | 0.79 (0.77-0.82) | 1 | 1.12 (1.09-1.16) |  |
| ≥1000 | 0.99 (0.94-1.05) | 1 | 0.94 (0.88-1.00) |  |

Hb, hemoglobin; LMP, last menstrual period; BMI, body mass index.

Odds ratios were estimated using logistic regression models after adjusting for maternal information (age at last menstrual period, education, ethnicity, occupation, BMI, smoking, alcohol drinking, hypertension, diabetes, thyroid dysfunction, history of abortion, parity, toxicants exposure, abstain from animal products or vegetables) and paternal information (age at last menstrual period, smoking, toxicants exposure), except for stratifying factors.

\* P for interaction was tested by adding an interaction term (each binary variable × continuous Hb) to the regression models using restricted cubic spline.