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## Pathways Linking Socio-economic Status to Small-for-Gestational Age (SGA) Infants among Primiparae: A Birth Cohort Study

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Keywords:	Hypertension < CARDIOLOGY, EPIDEMIOLOGY, SOCIAL MEDICINE, SLEEP MEDICINE

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1 **Pathways Linking Socio-economic Status to Small-for-Gestational Age (SGA)**

2 **Infants among Primiparae: A Birth Cohort Study**

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18

19 **ABSTRACT**

20 **Objectives** Evidence about the relationship between socio-economic status (SES) and  
21 small-for-gestational age (SGA) infants was insufficient among Chinese primiparae.  
22 In addition, factors that may mediate this relationship are poorly understood. The  
23 purpose of this study was to investigate the risk of and mediators between SES and  
24 SGA.

25 **Design** Retrospective cohort study.

26 **Setting** Wuhan, Hubei, China.

27 **Method** Participants were recruited from patients who gave birth in the maternity care  
28 hospital of Wuhan between September 2012 and October 2014. Logistic regression  
29 models were used to estimate odds ratios (ORs) and 95% confidence intervals (CIs)  
30 for SGA in relation to SES. Pathway analysis was performed to examine the  
31 contribution of maternal lifestyles and pregnancy-induced hypertension syndrome  
32 (PIH) to the relationship between SES and SGA. Total effect, direct effect and indirect  
33 effect of SES on SGA were measured. Effect sizes were evaluated by unstandardized  
34 estimates (B) and standardized estimates ( $\beta$ ).

35 **Results** Among 8737 primiparae, 927 (10.61%) pregnant women had babies with  
36 SGA. High SES was inversely associated with risk of SGA (OR, 0.770; 95% CI,  
37 0.669, 0.886). After adjustment for potential confounders, the OR for SGA was 0.856  
38 (95% CI, 0.737, 0.995). Maternal obstetric characteristics, lifestyles and PIH  
39 completely mediated SES and SGA (indirect effect: B=-0.067, 95% CI=-0.108,

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4 40 -0.026). The indirect effect of SES was strengthened by PIH (B=-0.029), a  
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6 41 multi-vitamin supplement (B=-0.021), pre-pregnancy body mass index (BMI)  $\geq 18.5$   
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8 42 (B=-0.009) and pre-pregnancy BMI  $\geq 18.5$  to gestational weight gain (GWG) not  
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11 43 below Institute of Medicine (IOM) (B=-0.003).

12  
13 44 **Conclusions** Our research suggested that high SES was a positive protector against  
14  
15 45 SGA. Avoiding PIH, taking a multi-vitamin supplement during early pregnancy,  
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17 46 keeping normal pre-pregnancy BMI and gaining reasonable gestation weight may  
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19 47 represent important protectors for SGA infants among pregnant women from low  
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21 48 SES.

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25 49 **Keywords** socio-economic status (SES), SGA, primiparae, mediators, pathway  
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28 50 analysis

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31 51 **Strengths and limitations of this study**

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35 52 Face-to-face interviews, medical records and medical measurements provided rich  
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37 53 covariate data, which allowed us to adjust for potential confounders for SGA.  
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39 54 SES index was combined with parental education and occupation. This index was  
40  
41 55 more robust when it was compared to education and occupation separately in China.  
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43 56 This is the first study evaluating maternal lifestyles and PIH, which mediate  
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45 57 socio-economic status (SES) and SGA among primiparae in China.  
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47 58 Some of our variables, such as a micronutrient supplement, physical activity and sleep  
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49 59 quality during pregnancy relied on self-report, which are subjective.

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4 60 **Abbreviations**  
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8 61 **BMI** Body mass index  
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10 62 **GWG** Gestational weight gain  
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12 63 **IOM** Institute of Medicine  
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14 64 **SES** Socio-economic status  
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16 65 **SGA** Small-for-gestational age  
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18 66 **AGA** Appropriate-for-gestational age  
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20 67 **CI** Confidence interval  
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22 68 **OR** Odds ratio  
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24 69 **PIH** Pregnancy-induced hypertension syndrome  
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31 70 **INTRODUCTION**  
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35 71 Small-for-gestational age (SGA) infants is defined as birthweight below the tenth  
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37 72 percentile of a standard optimal reference population for a given gestational age and  
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39 73 sex.<sup>1</sup> SGA infants are at increased risk of perinatal morbidity and mortality<sup>2</sup> as well as  
40  
41 74 long-term adverse health<sup>3</sup> and developmental outcomes.<sup>4</sup> In 2010, the overall  
42  
43 75 prevalence of SGA infants was 27% of live births in 138 low- and middle-income  
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45 76 countries.<sup>5</sup> Another pooled country analysis research identified that the relative risks  
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47 77 for babies who were SGA were 1.83 for neonatal mortality and 1.90 for post-neonatal  
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49 78 mortality among 20 cohorts (providing data for 2,015,019 livebirths) from Asia,  
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51 79 Africa and Latin America.<sup>6</sup> Therefore, it is important to recognize the potential risk  
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4 80 factors for SGA infants during pregnancy so that preventive measures can be targeted  
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6 81 at risk subgroups of pregnant women. A review from France found major risk factors  
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8 82 identified were previous SGA birth, disease during pregnancy, body mass index  
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10 83 (BMI<18.5 kg/m<sup>2</sup>) and socio-economic disadvantage.<sup>7</sup> Socio-economic disparities in  
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12 84 SGA infants have been relatively intractable over the past decades. However, the  
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14 85 mechanisms by which socio-economic disadvantage leads to higher risk of SGA  
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16 86 remain unclear.

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20 87 Socio-economic status (SES) is a complex phenomenon predicted by a broad  
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22 88 spectrum of variables. It is often conceptualized as a combination of financial,  
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24 89 occupational and educational influences.<sup>8</sup> The level of SES can partly explain the risk  
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26 90 at birth outcome,<sup>9</sup> children's anthropometric status,<sup>10</sup> and neurodevelopment.<sup>11</sup> The  
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28 91 risk of SGA was higher in the lower SES groups compared to the highest SES group  
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30 92 in Finland,<sup>12</sup> Australia,<sup>13</sup> Japan<sup>9</sup> and others. These estimates were based mainly on  
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32 93 findings from developed countries, with little reliable evidence from China. Moreover,  
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34 94 in the Hong Kong population, researchers demonstrated parental education, housing,  
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36 95 income and occupation were not clearly linearly associated with SGA.<sup>14</sup> As the  
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38 96 economy of Hong Kong is more developed than that of China mainland, it makes  
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40 97 great sense to explore the association between SES and SGA infants in mainland  
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42 98 China.

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50 99 Wang found that among 10,372 people from 28 provinces of China, those from  
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52 100 high SES promoted their health via health-related lifestyles.<sup>15</sup> Another study reviewed  
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54 101 the evidence focusing on aetiological factors that could mediate the socio-economic  
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4 102 disparities in intrauterine growth restriction. Factors included maternal anthropometry,  
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6 103 micronutrients, physical activity, cigarette smoking and psychosocial factors.<sup>16</sup>  
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8 104 However, this review used a bibliographic method to find these evidence and it was  
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10 105 hard to reveal mediators without the pathway analysis. Furthermore, the gap between  
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12 106 the most and least deprived groups did not narrow for birthweight outcomes over the  
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14 107 four decades.<sup>17</sup> In the current study, we examined the association between SES and  
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16 108 SGA infants and aimed to uncover one of the potential mechanisms that could show  
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18 109 how SES affects SGA infants among Chinese primiparae in the Health Baby Cohort  
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20 110 (HBC).

## 21 22 23 24 25 26 27 111 **METHODS**

### 28 29 30 112 **Study Population**

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34 113 All participants were selected from the prospective Health Baby Cohort (HBC) study  
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36 114 in China, which has been described elsewhere.<sup>18</sup> It is an ongoing prospective cohort  
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38 115 study, which aims to explore how environmental and genetic factors affect child  
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40 116 health and development. Participants who had had a stillborn infant were excluded.  
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43 117 Briefly, the cohort enrolled 11,311 pregnant women who gave birth to a live singleton  
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45 118 infant in the Women and Children Medical and Health-care Centre of Wuhan between  
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47 119 September 2012 and October 2014. In our study, we selected 9622 primiparae and  
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49 120 then, we excluded another 885 participants because of missing values in at least one  
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51 121 variable of interest, such as parental education and a nutritional supplement. Therefore,  
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4 122 a total of 8737 primiparae were finally included in our study. All participating women  
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6 123 provided their written informed consent at the time of recruitment.  
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#### 9 124 **Diagnosis of SGA**

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12 125 Birthweight and infant's gender were obtained from delivery records. Gestational age  
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15 126 was calculated from the date of the last menstrual period or the clinical estimate of  
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17 127 gestational age based on the clinical case system. Labour and delivery outcomes were  
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20 128 extracted from birth records. Nude birthweight was measured for each infant within  
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22 129 one hour after birth by trained nurses using standardized procedures. We defined  
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24 130 small-for-gestational age (SGA) as a birthweight lower than the 10th percentile of our  
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26 131 population for a specific completed gestational age by gender.<sup>6</sup> On the other hand, we  
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28 132 defined appropriate for gestational age (AGA) as a birthweight equal to or higher than  
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30 133 the 10th centile for gestational age.  
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#### 34 134 **Assessment of Covariates**

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38 135 The trained nurses conducted standardized face-to-face interviews with the  
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40 136 participants after delivery. Participants were asked to complete a questionnaire that  
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42 137 collected information on maternal age, maternal and paternal education level (years of  
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44 138 education), occupations (eight major categories of Chinese occupation), the use of a  
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46 139 multi-vitamin supplement during the first trimester of pregnancy (yes or no), physical  
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48 140 activity during the last trimester of pregnancy (almost none, 1–2 days, 3–4 days, 5–6  
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50 141 days, 7 days) per week, and sleep quality in the month before the birth (bad or good).  
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4 142 Information regarding pregnancy-induced hypertension syndrome (PIH) was extracted  
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6 143 from medical records excluding chronic hypertension. PIH was defined as “yes” or  
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8 144 “no”. We calculated pre-pregnancy body mass index (BMI) from the self-reported  
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10 145 pre-pregnancy weight in kg divided by height in m<sup>2</sup>. BMI was categorized into four  
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12 146 groups based on recommendations by the Working Group on Obesity in China of the  
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14 147 Chinese Ministry of Health: underweight (<18.5 kg/m<sup>2</sup>); normal weight (18.5–23.9  
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16 148 kg/m<sup>2</sup>); overweight (24–27.9 kg/m<sup>2</sup>); and obese (≥ 28 kg/m<sup>2</sup>). Gestational weight gain  
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18 149 (GWG) was calculated by subtracting the pre-pregnancy weight from the weight  
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20 150 measured within 3 days of the delivery day. GWG was also categorized as below,  
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22 151 within, or above the recommendations according to the Institute of Medicine (IOM).<sup>19</sup>  
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24 152 Specifically, GWG within the IOM recommendations was defined as 12.5–18 kg,  
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26 153 11.5–16 kg, 7–11.5 kg and 5–9 kg for underweight, normal weight, overweight, and  
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28 154 obese women, respectively. Finally, we changed pre-BMI and GWG by IOM as  
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30 155 dichotomous variable (pre-BMI<18.50 or ≥18.5; GWG below IOM or not below).  
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### 39 156 **Assessment of Socio-economic Status**

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42 157 SES index was measured by a combination of the education and occupation categories.  
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44 158 The scores of education and occupation are listed in Supplementary Table 1 and  
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46 159 Supplementary Table 2. SES index was measured based on the formula,  $SES = ((0.7 * \text{maternal education}) + (0.4 * \text{maternal occupation}) + (0.7 * \text{paternal education}) + (0.4 * \text{paternal occupation}))/2$ . Finally, the SES index categorization demonstrates that below  
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53 162 one third of the study population distribution had low SES and the remainder had high

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3 163 SES.<sup>20</sup>  
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7 164 **Statistical Analysis**  
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10 165 Firstly, data were described as mean  $\pm$  SD for continuous variables or as percentage  
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12 166 for categorical variables. Differences between SGA and AGA were compared using  
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14 167 the Student's t-test for continuous variables and chi-square test for categorical  
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16 168 variables. Pearson's correlation was carried out between study variables. Logistic  
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18 169 regression models were used to examine the associations between SES and SGA.  
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20 170 Secondly, we used the pathway analysis to explore the hypothesized underlying  
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22 171 relations between variables of interested. The model was evaluated using the  
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24 172 following goodness-of-fit: the comparative-fit index (CFI) $>0.95$ , the  
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26 173 root-mean-square error of approximation (RMSEA) $<0.05$ . Modification indices were  
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28 174 used to detect misspecifications in the model. Estimation was carried out by a robust  
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30 175 weighted least-squares estimator (WLSMV). Because most of our variables were  
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32 176 categorical variables, WLSMV was one of the best methods for analysing our data set.  
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34 177 Effect sizes of the predictors on the outcome variables were expressed as  
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36 178 unstandardized estimates (B) and standardized estimates ( $\beta$ ). The total effects of the  
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38 179 predictors on the outcomes were computed by adding the indirect and direct effects  
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40 180 together.<sup>21</sup> Decoding of each response for further analysis was present in Table 1. All  
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42 181 of the analyses were conducted with R 3.2.2. All *P* values reported were two-sided  
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44 182 and 0.05 was used as significance level.  
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Table 1. Description of variables in pathway analysis.

Variables	Decoding of each response
SES	0="low", 1="high"
GWG by IOM	0="below", 1="within and above"
Pre-BMI	0="<18.5", 1="≥18.5"
Physical activity during the last trimester of pregnancy	0="almost none per week", 1="1-2 days per week", 2="3-4 days per week", 4="5-6 days per week", 5="7 days per week"
Sleep quality in the month before the birth	0="bad", 1="good"
A multi-vitamin supplement during the first trimester of pregnancy	0="no", 1="yes"
Infant's gender	0="girl", 1="boy"
Passive smoking during pregnancy	0="no", 1="yes"
PIH	0="no", 1="yes"
Maternal age	continuous variable
SGA	0="no", 1="yes"

SES, socio-economic status; BMI, body mass index; GWG, gestation weight gain; IOM, Institute of Medicine; SGA, small-for-gestational age; PIH, pregnancy-induced hypertension syndrome.

## 184 RESULTS

### 185 Study Population

186 A total of 8737 primiparae met our criterion and they finally included in our study.

187 The mean maternal age was  $27.70 \pm 3.24$  years. In total, 927 (10.61%) infants were

188 diagnosed with SGA. There were 4499 boys and 4238 girls with a boy-to-girl ratio of

189 1.06.

### 190 Characteristics of the Sample

191 The basic demographic characteristics among SGA are presented in Table 2. Mean

192 maternal age was younger, mean pre-pregnancy BMI was lower and gestational

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4 193 weight gain below IOM was more likely with women who had SGA infants.  
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6 194 Compared with women with AGA infants, women with SGA infants were more likely  
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8 195 to have PIH and came from low SES. Women with AGA infants tended to be more  
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11 196 positive regarding taking a multi-vitamin supplement during the first trimester of  
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13 197 pregnancy. Correlations of the variables are presented in Supplementary Table 3.  
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Table 2. Characteristics of participants with SGA and AGA among primiparae in Wuhan, China (N=8737)

Variables	N(%) or Mean $\pm$ SD	SGA	AGA	<i>P</i>
		N(%) or Mean $\pm$ SD	N(%) or Mean $\pm$ SD	
GWG by IOM				
Below	901(10.31)	208(22.44)	693(9.89)	<0.001
Within and above	7836(89.69)	719(77.56)	7117(90.11)	
Pre-BMI				
<18.5	2082(23.83)	309(33.33)	1773(21.74)	<0.001
$\geq$ 18.5	6655(76.17)	618(66.67)	6037(78.26)	
Physical activity during the last trimester of pregnancy				
almost none per week	834(9.55)	79(8.52)	755(8.65)	0.495
1-2 days per week	831(9.51)	86(9.28)	745(8.98)	
3-4 days per week	663(7.59)	61(6.58)	602(7.83)	
5-6 days per week	146(1.67)	17(1.83)	129(1.86)	
every days per week	6263(71.68)	684(73.79)	5579(72.81)	
Sleep quality in the month before the birth				
Bad	3063(35.06)	310(33.44)	2753(33.48)	0.275
Good	5674(64.94)	617(66.56)	5057(66.52)	
A multi-vitamin supplement during the first trimester of pregnancy				
No	3640(41.66)	434(46.82)	3206(36.51)	0.001
Yes	5097(58.34)	493(53.18)	4604(63.49)	
Infant's gender				
Boy	4499(51.49)	467(50.38)	4032(51.86)	0.517
Girl	4238(48.51)	460(49.62)	3778(48.14)	
Passive smoking during pregnancy				
No	7717(88.33)	813(87.7)	5206(89.7)	0.532
Yes	1020(11.67)	114(12.3)	598(10.3)	
Maternal age	27.70 $\pm$ 3.24	27.32 $\pm$ 3.50	27.75 $\pm$ 3.21	<0.001
PIH				
No	8468(96.92)	882(95.15)	7586(97.13)	0.001
Yes	269(3.08)	45(4.85)	224(2.87)	
SES				
Low	927(10.61)	361(38.94)	2572(9.82)	<0.001
High	7810(89.39)	566(61.06)	5238(75.45)	

SES, socio-economic status; BMI, body mass index; GWG, gestation weight gain; IOM, Institute of Medicine; SGA, small-for-gestational age; PIH, pregnancy-induced hypertension syndrome; AGA, appropriate-for-gestational age.

### 199 Associations between SES and SGA

200 To examine the association between SES and the risk of SGA, univariate and

201 multivariate logistic regression models were used in Table 3. Compared with women  
 202 with low SES, the OR of SGA was 0.770 (95% CI, 0.669, 0.886) for those with high  
 203 SES, in the unadjusted model. After adjustment for potential confounders, the ORs of  
 204 SGA were 0.846 (95% CI, 0.728, 0.983) and 0.856 (95% CI, 0.737, 0.995) in model 2  
 205 and model 3, respectively.

Table 3. Associations of SES with SGA among 8737 primiparae in Wuhan, China.

SGA	SES	OR	95%CI	<i>P</i>
Model 1	Low	Ref		
	High	0.770	0.669, 0.886	<0.001
Model 2	Low	Ref		
	High	0.846	0.728,0.983	0.029
Model 3	Low	Ref		
	High	0.856	0.737,0.995	0.043

ORs, odds ratios; SES, socio-economic status; SGA, small-for-gestational age; Model 1, unadjusted model; model 2 adjusted for maternal age, pre-BMI, gestational weight gain (GWG), a multi-vitamin supplement during the first trimester of pregnancy, sleep quality in the month before the birth, physical activity during last trimester and passive smoking during pregnancy; model 3 adjusted as model 2 plus PIH.

### 206 **Mediation Model for SGA**

207 We proposed a hypothetical model for SGA in Figure 1, including the mediators PIH,  
 208 a multi-vitamin supplement during first-trimester, pre-BMI, GWG by IOM, physical  
 209 activity during the last trimester of pregnancy and sleep quality in the month before  
 210 the birth. Covariates were maternal age and passive smoking during pregnancy.

211 Table 4 listed SGA with the best CFI and RMSEA, which were 0.012 and 0.967.  
 212 This model revealed that maternal obstetric characteristics, lifestyles and PIH  
 213 completely mediated SES and SGA. The indirect effect of SES was strengthened in  
 214 SGA (B=-0.067, 95% CI=-0.108, -0.026) via PIH (B=-0.029, *P*=0.021), a



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4 215 multi-vitamin supplement ( $B=-0.021$ ,  $P=0.010$ ), pre-pregnancy BMI $\geq$ 18.5 ( $B=-0.009$ ,  
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6 216  $P=0.010$ ) and pre-pregnancy BMI $\geq$ 18.5 to GWG not below IOM ( $B=-0.003$ ,  
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8 217  $P=0.007$ ).

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11 218 In our model, the indirect effect came from the coefficient “a” multiplying by  
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13 219 coefficient “b”. For example, woman with high SES had more chance of taking a  
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15 220 multi-vitamin supplement ( $B=0.317$ ,  $P<0.001$ ). Then, a multi-vitamin supplement  
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17 221 taking decreased the SGA ( $B=-0.066$ ,  $P<0.05$ ). Thus, the indirect effect of SES to  
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19 222 SGA was  $0.317 \times -0.066 = -0.021$  through taking a multi-vitamin supplement.  
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Table 4. Indirect and total effects of socio-economic status and maternal characteristics and lifestyles during pregnancy on SGA.

Pathway	SES→	Mediators→	B	SE	95%CI	P value	β
	Mediators	Birth outcomes					
	a	b	a*b				
<b>Small-for-gestational age (SGA)</b>							
Total effect			-0.067				-0.030
Direct effect (c)			-0.046	0.044	(-0.132, 0.040)	0.299	-0.034
Indirect effect			-0.067	0.021	(-0.108, -0.026)	0.001	-0.030
SES→ Pre-BMI≥18.50→GWG not below IOM	0.033*, -0.253**	0.321**	-0.003	0.001	(-0.005, -0.001)	0.007	-0.001
SES→ GWG not below IOM	-0.045	0.321**	-0.014	0.013	(-0.039, 0.011)	0.273	-0.006
SES→ Pre-BMI≥18.50	0.033*	-0.274**	-0.009	0.003	(-0.015, -0.003)	0.010	-0.004
SES→ a multi-vitamin supplement during the first trimester of pregnancy	0.317**	-0.066*	-0.021	0.008	(-0.037, -0.005)	0.010	-0.009
SES→ Physical activity during the last trimester of pregnancy	0.284**	0.017	0.005	0.003	(-0.001, 0.011)	0.063	0.002
SES→ Sleep quality in the month before the birth	0.150**	0.027	0.004	0.004	(-0.004, 0.012)	0.297	0.002
SES→ PIH	-0.176*	0.166**	-0.029	0.013	(-0.054, -0.004)	0.021	-0.013
Goodness-of-fit	RMSEA=0.012, CFI=0.967						

B, unstandardized coefficient; CI, confidence interval; B, standardized coefficient, \* $P < 0.05$ , \*\* $P < 0.001$ . RMSEA, the root mean square error of approximation; CFI, the comparative fit index; SES, socio-economic status; GWG, gestation weight gain; IOM, Institute of Medicine. Covariates of maternal age, passive smoking during pregnancy were adjusted for SGA.

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5 223 **DISCUSSION**  
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8 224 The findings of our study indicated that high SES was related to a reduced risk of  
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10 225 SGA after adjustment for potential confounders. In the pathway analysis, the direct  
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12 226 effect was not significant. These mediators completely mediated the relationship  
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14 227 between SES and SGA. We observed that PIH, taking a multi-vitamin supplement  
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16 228 during the first trimester of pregnancy, pre-pregnancy underweight and GWG below  
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18 229 IOM were the mediators between SES and SGA.  
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23 230 One of the strengths of our study was the large sample size. In addition, face-to-face  
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25 231 interviews, medical records and measurements provided rich covariate data, which  
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27 232 allowed us to adjust for potential confounders for SGA. Thirdly, SES was combined  
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29 233 parental education and occupation which was more robust compared with education  
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31 234 and occupation separately in China. We acknowledge that there were also some  
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33 235 limitations. Firstly, information on education and occupation was obtained using  
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35 236 face-to-face questionnaires, which might have bias. Occupation can fluctuate over  
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37 237 time, and it is more likely to lead to misclassification. Secondly, although we carefully  
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39 238 adjusted for several potential confounders for SGA, we were unlikely to fully rule out  
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41 239 the possibility of residual confounding by other unmeasured factors such as parents'  
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43 240 history of SGA, maternal stress during pregnancy. Thirdly, some of our variables  
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45 241 including a micronutrient supplement, physical activity and sleep quality during  
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47 242 pregnancy relied on self-reporting, which were subjective.  
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55 243 Predictably, high SES was a protector of SGA in our study. A large  
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4 244 population-based study from Finland reported that SES determined by women's  
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6 245 occupation was inversely associated with the risk of SGA.<sup>12</sup> A birth cohort study  
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8 246 conducted in France reported that low SES determined by neighbourhood deprivation  
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11 247 may affect foetal growth, especially in rural areas.<sup>22</sup> These two studies were consistent  
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13 248 with our results. However, Clayborne et al. did not find a direct association between  
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15 249 SES measured by neighborhood deprivation and the risk of SGA in Canada.<sup>23</sup> Because  
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18 250 of the different measures of SES, these studies may not be easily compared. The  
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21 251 underlying mechanisms responsible for increased risk of SGA among primiparae with  
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23 252 low SES remain speculative. In our study, we found that some mediators could  
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25 253 completely mediate SES and SGA.

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28 254 In the pathway analysis, we observed that PIH was a mediator between SES and  
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30 255 SGA. We demonstrated that SES was associated with PIH among primiparae. A  
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33 256 meta-analysis including 51 studies found that low SES was associated with higher  
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35 257 blood pressure. This association was particularly evident in the level of education.<sup>24</sup>  
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38 258 Adherence to knowledge of hypertension and more social resources to maintain  
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40 259 healthy behaviours could explain why SES likely affects PIH among pregnant women.  
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43 260 The rate of SGA infants from the PIH group was significantly higher compared with  
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45 261 the no PIH group in our study. PIH is associated with a reduction in placental  
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47 262 perfusion, which influences the size of the placenta.<sup>25</sup> In SGA infants, the size of the  
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50 263 placental disc was smaller and the birthweight was lighter.<sup>26</sup> Placenta is an important  
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53 264 organ for foetus and supplies all the nutrients needed for foetal development. The  
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55 265 pathology of placental was potentially causing or contributing to SGA and

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4 266 hypertension was one of the factors in aetiology.<sup>27</sup> The growth and development of the  
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6 267 placenta being influenced by PIH may be suggested an explanation for lower  
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8 268 birthweight.<sup>26</sup>  
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11 269 Taking a multi-vitamin supplement during the first trimester of pregnancy was  
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13 270 another mediator between SES and SGA. Women with low SES defined by family  
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15 271 income had less chance to obtain optimal nutrient supplements in a meta-analysis  
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17 272 including 12 randomized controlled trials.<sup>28</sup> A double-blind cluster randomized  
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19 273 controlled trial in rural China reported birthweight was 42 g higher in the multiple  
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21 274 micronutrients group compared with the folic acid group.<sup>29</sup> Another birth cohort from  
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23 275 Denmark reported that regular periconceptional multi-vitamins use was associated  
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25 276 with a reduced risk of SGA births.<sup>30</sup> A multi-vitamin supplement during early  
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27 277 pregnancy might reduce the risk of alcohol use in relation to SGA.<sup>31</sup> This result  
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29 278 evidenced that a multi-vitamin supplement during early pregnancy was a protector  
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31 279 factor for SGA, which was similar to our study. Multi-vitamins are important for  
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33 280 human physical function and they play vital roles in numerous metabolic processes  
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35 281 and physiological functions in the human body. A multi-vitamin supplement during  
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37 282 pregnancy reduced the risk of pregnancy complications, involving oxidative stress and  
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39 283 pre-eclampsia. Pre-eclampsia could decrease blood to the placenta, which causes  
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41 284 growth retardation.<sup>32</sup>  
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50 285 Pre-pregnancy underweight and pre-pregnancy underweight to GWG below IOM  
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52 286 were the two pathways between SES and SGA. The chances of having a SGA infant  
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54 287 was significantly higher among underweight women compared to normal  
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3 288 pre-pregnancy BMI in our study, which was consistent with a study in Lebanon. As  
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6 289 Lebanon is a developing country in Asia, and its people are similar to Chinese people,  
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8 290 we deemed these results could support our findings. Smoking, poor diet, and medical  
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10 291 illness like anaemia which are risk factors for SGA among underweight women,  
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13 292 occurred more often. Deficiency of maternal plasma volume among underweight  
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15 293 women has been suggested as a cause of SGA.<sup>33</sup> In our study, underweight women  
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17 294 were more likely to have insufficient weight gain during pregnancy and below normal  
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19 295 weight gain significantly increased the odds of SGA. As expected, GWG below IOM  
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21 296 in women with pre-pregnancy underweight was reportedly more likely to affect the  
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23 297 birthweight of their neonates.<sup>34</sup> Poor nutrition or unhealthy psychological state among  
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25 298 pregnant women with GWG below IOM may explain causes of SGA.  
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## 31 299 **CONCLUSION**

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35 300 We demonstrated that SES was inversely associated with SGA after adjustment for  
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37 301 potential confounders among primiparae. In this population, we also found that  
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39 302 mediators could completely mediate SES and SGA. Monitoring of blood pressure,  
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41 303 avoiding pre-pregnancy underweight, keeping normal GWG during pregnancy and  
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43 304 taking a multi-vitamin supplement during the first trimester of pregnancy are practical  
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45 305 and feasible measurements to reduce the risk of SGA. As we all know, SGA is a  
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47 306 public health issue and SES disparities are difficult to change over a short time. It had  
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49 307 great sense to maintain normal blood pressure and keep a healthy lifestyle to reduce  
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51 308 cases of SGA infants among primiparae, especially for women of child-bearing age  
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4 309 who are have a low SES. A future research direction should focus on identifying  
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6 310 interventions to successfully reduce socio-economic disparities in SGA.  
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20 315 Commission of Hubei Province (WJ2015MB019).  
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28 317 The authors declare that there is no competing interest including relevant financial,  
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30 318 personal, political, intellectual or religious interests.  
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34 319 **Contribution to Authorship**

35  
36  
37  
38 320 X.L. contributed to acquisition of data, statistical analysis, interpretation of data and  
39  
40 321 manuscript writing. F.L.L., H.T.G., F.H., X.Y.X., X.L., H.M., S.Q.X., interpretation of  
41  
42 322 the data. J.J.Z., R.R.S. supervised the project and wrote the manuscript. All authors  
43  
44 323 approved the final version to be published. R.R.S. is the guarantor of this work.  
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49 324 **Details of Ethics Approval**

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53 325 The research protocol was approved by the ethics committees of the Tongji Medical  
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55 326 College, Huazhong University of Science and Technology, and the Women and  
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3 327 Children Medical and Healthcare Centre of Wuhan. All participating women provided  
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6 328 their written informed consent at the time of recruitment.  
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17 332 Commission of Hubei Province (WJ2015MB019).  
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22 333 **Data sharing statement**  
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26 334 No additional data is available.  
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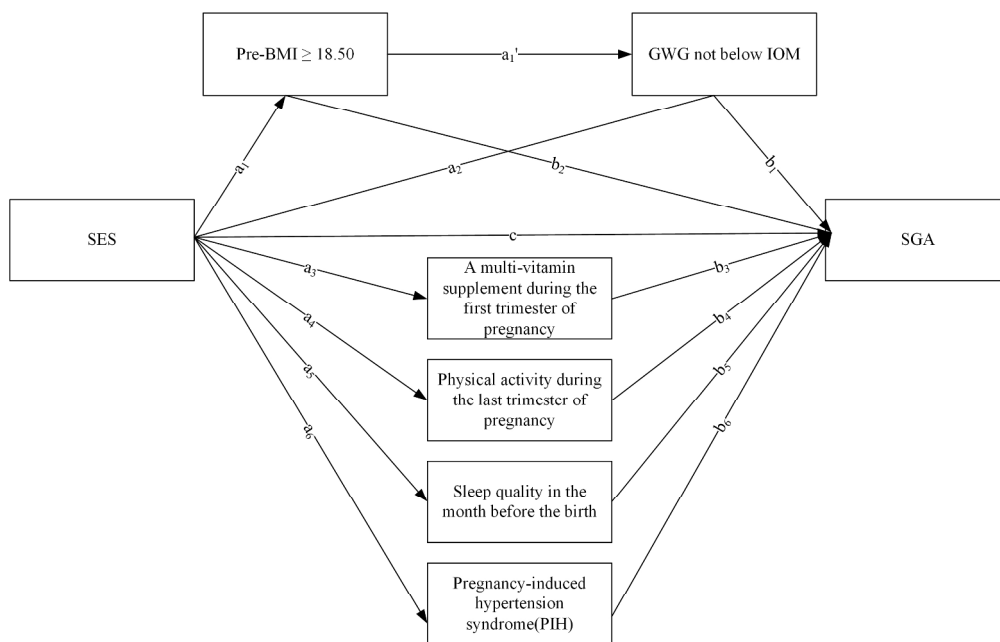


Figure 1. Pathway model of the associations between socio-economic status (SES) and small-for-gestational age (SGA). Unstandardized regression coefficients are  $a_1, a_1', a_2, a_3, a_4, a_5, a_6, b_1, b_2, b_3, b_4, b_5, b_6, c$ .

245x190mm (300 x 300 DPI)

Supplementary Table 1. Scores for coding education by number of years of school completed

Category	Total years	Scores	
		Males	Females
Doctor	22	69	73
Master	19	69	73
college	16	63	66
Junior school	15	61	63
high school	12	52	53
middle school	9	45	44
Elementary school	6	36	34
	3	33	32
	0	29	28

Supplementary Table 2. Average scores for categories of major occupational groups

Major occupational groups	Category	Scores
Managerial workers	I	59
professionals & technical	II	63
Office clerks	III	56
Service workers	I	46
Agriculture and forestry	IV	34
Laborer	V	42
Soldier	VI	53
Others	VII	49

Supplementary table 3. Correlation matrix of the study variables among primiparas in Wuhan, China (N=8737)

Variables	1	2	3	4	5	6	7	8	9	10	11
GWG by IOM	—										
Pre-BMI	-0.065**	—									
Physical activity during the last trimester of pregnancy	-0.001	0.002									
Sleep quality in the month before the birth	-0.001	0.017	-0.002	—							
A multi-vitamin supplement during the first trimester of pregnancy	-0.008	0.019	0.110**	-0.031**	—						
Infant's gender	-0.002	-0.012	-0.003	0.005	-0.008	—					
Passive smoking during pregnancy	-0.008	-0.031**	-0.009	0.017	0.046**	0.004	—				
Maternal age	-0.024*	0.133**	-0.021*	-0.017	0.156**	-0.015	-0.020	—			
PIH	-0.021*	0.058**	-0.001*	-0.016	-0.016	0.002	-0.007	0.037**	—		
SES	-0.020	0.069**	0.047**	0.047**	0.147**	-0.010	-0.060**	0.252**	-0.023*	—	
SGA	0.137**	-0.077**	0.016	0.012	-0.036**	0.008	0.007	-0.040**	0.035**	-0.039**	—

SES, socio-economic status; BMI, body mass index; GWG, gestation weight gain; IOM, Institute of Medicine; SGA, small-for-gestational age; AGA, appropriate-for-gestational age; PIH, pregnancy-induced hypertension syndrome. \* $P < 0.05$ , \*\* $P < 0.001$



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**STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology\***  
**Checklist for cohort, case-control, and cross-sectional studies (combined)**

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1-3
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
<b>Introduction</b>			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-6
Objectives	3	State specific objectives, including any pre-specified hypotheses	5-6
<b>Methods</b>			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-8
Participants	6	(a) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —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 <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	6
		(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-8
Data sources/ measurement	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	8-10
Bias	9	Describe any efforts to address potential sources of bias	
Study size	10	Explain how the study size was arrived at	10
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	8-9
		(b) Describe any methods used to examine subgroups and interactions	
		(c) Explain how missing data were addressed	
		(d) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed	

		<i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy	
		(e) Describe any sensitivity analyses	
<b>Results</b>			
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	10
		(b) Give reasons for non-participation at each stage	10
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10-12
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time	
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure	
		<i>Cross-sectional study</i> —Report numbers of outcome events or summary measures	12
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	12-13
		(b) Report category boundaries when continuous variables were categorized	
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	13-15
<b>Discussion</b>			
Key results	18	Summarise key results with reference to study objectives	16
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	16
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	16-19
Generalisability	21	Discuss the generalisability (external validity) of the study results	16-19
<b>Other information</b>			
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	21

\*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](http://www.strobe-statement.org).

# BMJ Open

## Pathways Linking Socio-economic Status to Small-for-Gestational Age (SGA) Infants among Primiparae: A Birth Cohort Study in China

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Manuscripts

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1 **Pathways Linking Socio-economic Status to Small-for-Gestational Age (SGA)**

2 **Infants among Primiparae: A Birth Cohort Study in China**

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17 Word count, 3318

18

19 **ABSTRACT**

20 **Objectives** Evidence about the relationship between socio-economic status (SES) and  
21 small-for-gestational age (SGA) infants was insufficient among Chinese primiparae.  
22 In addition, factors that may mediate this relationship are poorly understood. The  
23 purpose of this study was to investigate the risk of and mediators between SES and  
24 SGA.

25 **Design** Retrospective cohort study.

26 **Setting** Wuhan, Hubei, China.

27 **Method** Participants were recruited from patients who gave birth in the maternity care  
28 hospital of Wuhan between September 2012 and October 2014. Logistic regression  
29 models were used to estimate the association between SES and SGA. Pathway  
30 analysis was performed to examine the contribution of maternal lifestyles and  
31 pregnancy-induced hypertension syndrome (PIH) to the relationship between SES and  
32 SGA. Total effect, direct effect and indirect effect of SES on SGA were measured.  
33 Effect sizes were evaluated by unstandardized estimates ( $B$ ) and standardized  
34 estimates ( $\beta$ ).

35 **Results** Among 8737 primiparae, 927 (10.61%) pregnant women had babies with  
36 SGA. High SES was inversely associated with risk of SGA (OR, 0.856; 95% CI,  
37 0.737, 0.995) after adjustment for potential confounders. Maternal obstetric  
38 characteristics, lifestyles and PIH completely mediated SES and SGA (indirect effect:  
39  $B=-0.067$ , 95% CI= $-0.108$ ,  $-0.026$ ). The indirect effect of SES was strengthened by

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4 40 PIH (B=-0.029), a multi-vitamin supplement (B=-0.021), pre-pregnancy body mass  
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6 41 index (BMI)  $\geq 18.50$  (B=-0.009) and pre-pregnancy BMI  $\geq 18.50$  to gestational weight  
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8 42 gain (GWG) not below Institute of Medicine (IOM) recommendations (B=-0.003).

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10 43 **Conclusions** Women from high SES predicted lower risk of PIH, more chance to take  
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12 44 a multi-vitamin supplement during early pregnancy, keeping pre-pregnancy BMI  
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14 45  $\geq 18.50 \text{ kg/cm}^2$  and gaining adequate gestational weight which was not below IOM  
15  
16 46 recommendations. Furthermore, lower risk of PIH, more chance to take a  
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18 47 multi-vitamin supplement, pre-pregnancy BMI  $\geq 18.50 \text{ kg/cm}^2$  and GWG not below  
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20 48 IOM recommendations were associated with a lower risk of SGA infants.

21  
22 49 **Keywords** socio-economic status (SES), SGA, primiparae, mediators, pathway  
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24 50 analysis

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31 51 **Strengths and limitations of this study**

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35 52 It was a large population-based cohort study of pregnant women in Wuhan, China.  
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38 53 Face-to-face interviews, medical records and medical measurements provided rich  
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40 54 covariate data, which allowed us to adjust for potential confounders for SGA.  
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43 55 SES index was combined with parental education and occupation. This index was  
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45 56 more representative and reasonable to represent SES compared with using only  
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47 57 education or occupation in China.

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50 58 This is the first study evaluating maternal lifestyles and PIH, which mediate  
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52 59 socio-economic status (SES) and SGA among primiparae in China.

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55 60 Some of our variables, such as a micronutrient supplement, physical activity and sleep



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4 61 quality during pregnancy relied on self-report, which are subjective.  
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8 62 **Abbreviations**  
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11 63 **BMI** Body mass index  
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14 64 **GWG** Gestational weight gain  
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17 65 **IOM** Institute of Medicine  
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20 66 **SES** Socio-economic status  
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23 67 **SGA** Small-for-gestational age  
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26 68 **AGA** Appropriate-for-gestational age  
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29 69 **CI** Confidence interval  
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32 70 **OR** Odds ratio  
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35 71 **PIH** Pregnancy-induced hypertension syndrome  
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38 72 **INTRODUCTION**  
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41 73 Small-for-gestational age (SGA) infants is defined as birthweight below the tenth  
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44 74 percentile of a standard optimal reference population for a given gestational age and  
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47 75 sex.<sup>1</sup> SGA infants are at increased risk of perinatal morbidity and mortality<sup>2</sup> as well as  
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50 76 long-term adverse health<sup>3</sup> and developmental outcomes.<sup>4</sup> In 2010, the overall  
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53 77 prevalence of SGA infants was 27% of live births in 138 low- and middle-income  
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56 78 countries, using the Alexander reference population (US National Center for Health  
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59 79 Statistics, 1991; n=3,134,879 livebirths).<sup>5</sup> Another pooled country analysis research  
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80 identified that the relative risks for babies who were SGA were 1.83 for neonatal

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4 81 mortality and 1.90 for post-neonatal mortality among 20 cohorts (providing data for  
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6 82 2,015,019 livebirths) from Asia, Africa and Latin America.<sup>6</sup> Therefore, it is important  
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8 83 to recognize the potential risk factors for SGA infants during pregnancy so that  
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11 84 preventive measures can be targeted at risk subgroups of pregnant women. A review  
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13 85 from France found major risk factors identified were previous SGA birth, disease  
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15 86 during pregnancy, maternal underweight and socio-economic disadvantage.<sup>7</sup>  
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18 87 Socio-economic disparities in SGA infants have been relatively intractable over the  
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21 88 past decades. However, the mechanisms by which socio-economic disadvantage leads  
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23 89 to higher risk of SGA remain unclear.

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25 90 Socio-economic status (SES) is a complex phenomenon predicted by a broad  
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28 91 spectrum of variables. It is often conceptualized as a combination of financial,  
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31 92 occupational and educational influences.<sup>8</sup> The level of SES can partly explain the risk  
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33 93 at birth outcome,<sup>9</sup> children's anthropometric status,<sup>10</sup> and neurodevelopment.<sup>11</sup> The  
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35 94 risk of SGA was higher in the lower SES groups compared to the highest SES group  
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38 95 in Finland,<sup>12</sup> Australia,<sup>13</sup> Japan<sup>9</sup> and others. These estimates were based mainly on  
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41 96 findings from developed countries, with little reliable evidence from China. Moreover,  
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43 97 in the Hong Kong population, researchers demonstrated parental education, housing,  
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45 98 income and occupation were not clearly linearly associated with SGA.<sup>14</sup> As the  
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48 99 economy of Hong Kong is more developed than that of China mainland, it makes  
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51 100 great sense to explore the association between SES and SGA infants in mainland  
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53 101 China.

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55 102 Wang found that among 10,372 people from 28 provinces of China, those from

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4 103 high SES promoted their health via health-related lifestyles.<sup>15</sup> Another study reviewed  
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6 104 the evidence focusing on aetiological factors that could mediate the socio-economic  
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8 105 disparities in intrauterine growth restriction. Factors included maternal anthropometry,  
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10 106 micronutrients, physical activity, cigarette smoking and psychosocial factors.<sup>16</sup>  
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13 107 However, this review used a bibliographic method to find these evidence and it was  
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15 108 hard to reveal mediators without the pathway analysis. Furthermore, the gap between  
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18 109 the most and least deprived groups did not narrow for birthweight outcomes over the  
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20 110 four decades.<sup>17</sup> In the current study, we examined the association between SES and  
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23 111 SGA infants and aimed to uncover one of the potential mechanisms that could show  
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25 112 how SES affects SGA infants among Chinese primiparae in the Health Baby Cohort  
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28 113 (HBC).

## 31 114 **METHODS**

### 35 115 **Study Population**

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39 116 All participants were selected from the prospective Health Baby Cohort (HBC) study  
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41 117 in China, which has been described elsewhere.<sup>18</sup> It is an ongoing prospective cohort  
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44 118 study, which aims to explore how environmental and genetic factors affect child  
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46 119 health and development. Participants who had had a stillborn infant were excluded.  
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49 120 Briefly, the cohort enrolled 11,311 pregnant women who gave birth to a live singleton  
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51 121 infant in the Women and Children Medical and Health-care Centre of Wuhan between  
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53 122 September 2012 and October 2014. In our study, we selected 9623 primiparae and

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4 123 then, we excluded another 886 participants because of missing values in at least one  
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6 124 variable of interest, such as parental education and a multi-vitamin supplement.  
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8 125 Therefore, a total of 8737 primiparae were finally included in our study. The present  
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10 126 study was approved by the ethics committees of the Tongji Medical College,  
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12 127 Huazhong University of Science and Technology, and the Women and Children  
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14 128 Medical and Healthcare Centre of Wuhan. All participating women provided their  
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16 129 written informed consent at the time of recruitment.  
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### 21 130 **Diagnosis of SGA**

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24 131 Birthweight and infant's gender were obtained from delivery records. Most of the  
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26 132 gestational age was calculated from the date of the last menstrual period (LMP) which  
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28 133 was recorded on their clinical cases. We estimated gestational age by B-mode  
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30 134 ultrasound if the date of LMP couldn't be obtained. We didn't exclude any specific  
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32 135 gestational weeks from our studied population. Labour and delivery outcomes were  
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34 136 extracted from birth records. Nude birthweight was measured for each infant within  
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36 137 one hour after birth by trained nurses using standardized procedures. We defined  
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38 138 small-for-gestational age (SGA) as a birthweight lower than the 10th percentile of our  
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40 139 population for a given gestational age and sex.<sup>6</sup> On the other hand, we defined  
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42 140 appropriate for gestational age (AGA) as a birthweight equal to or higher than the  
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44 141 10th centile for gestational age.  
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## 142 **Assessment of Covariates**

143 The trained nurses conducted standardized face-to-face interviews with the  
144 participants after delivery. Participants were asked to complete a questionnaire that  
145 collected information on maternal age, maternal and paternal education level (years of  
146 education), occupations (eight major categories of Chinese occupation), the use of a  
147 multi-vitamin supplement during the first trimester of pregnancy (yes or no), physical  
148 activity during the last trimester of pregnancy (almost none, 1–2 days, 3–4 days, 5–6  
149 days, 7 days) per week, and sleep quality in the month before the birth (bad or good).  
150 Information regarding pregnancy-induced hypertension syndrome (PIH) was extracted  
151 from medical records excluding chronic hypertension. PIH was defined as “yes” or  
152 “no”. We calculated pre-pregnancy body mass index (BMI) from the self-reported  
153 pre-pregnancy weight in kg divided by height in m<sup>2</sup>. BMI was categorized into four  
154 groups based on recommendations by the Working Group on Obesity in China of the  
155 Chinese Ministry of Health: underweight (<18.5 kg/m<sup>2</sup>); normal weight (18.5–23.9  
156 kg/m<sup>2</sup>); overweight (24–27.9 kg/m<sup>2</sup>); and obese (≥ 28 kg/m<sup>2</sup>).<sup>19</sup> Gestational weight  
157 gain (GWG) was calculated by subtracting the pre-pregnancy weight from the weight  
158 measured within 3 days of the delivery day. GWG was also categorized as below,  
159 within, or above the recommendations according to the Institute of Medicine (IOM).  
160 Specifically, GWG within the IOM recommendations was defined as 12.5–18.0 kg,  
161 11.5–16.0 kg, 7.0–11.5 kg and 5.0–9.0 kg for underweight, normal weight, overweight,  
162 and obese women, respectively.<sup>20</sup> Finally, we changed pre-pregnancy BMI and GWG  
163 by IOM recommendations as dichotomous variable (pre-pregnancy BMI<18.50 or

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4 164  $\geq 18.50$ ; GWG below IOM recommendations or not below).  
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7 165 **Assessment of Socio-economic Status**  
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10 166 SES index was measured by a combination of the education and occupation categories.

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12 167 The scores of education and occupation are listed in Supplementary table 1 and

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15 168 Supplementary table 2.<sup>21</sup> SES index was measured based on the formula,  $SES = ((0.7 *$

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17 169 maternal education) + (0.4 \* maternal occupation) + (0.7 \* paternal education) + (0.4\*

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20 170 paternal occupation))/2.<sup>22</sup> Finally, the SES index categorization demonstrates that

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22 171 below one third of the study population distribution had low SES and the remainder

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25 172 had high SES.<sup>23</sup>  
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28 173 **Statistical Analysis**  
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31 174 Firstly, data were described as mean  $\pm$  SD for continuous variables or as percentage

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33 175 for categorical variables. Differences between SGA and AGA were compared using

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35 176 the Student's t-test for continuous variables and chi-square test for categorical

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37 177 variables. Pearson's correlation was carried out between studied variables. Univariate

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39 178 logistic regression analysis was used to assess the risk of having a SGA newborn

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41 179 among primiparae from low SES. Multivariate logistic regressions were used to

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43 180 explore the risk after adjustment for potential confounders. We selected the list of

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45 181 potential confounders according to two reasons as following. Firstly, variables, such

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47 182 as maternal age, pre-pregnancy BMI, gestational weight gain (GWG) and a

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49 183 multi-vitamin supplement during the first trimester of pregnancy, were significant  
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4 184 different between two groups according to the results of single factor analysis.  
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6 185 Secondly, other confounders (sleep quality in the month before the birth, physical  
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8 186 activity during last trimester and passive smoking during pregnancy) were all the  
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11 187 lifestyles of pregnancy women. As these lifestyles associated with infants' birth  
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13 188 weight were repeatedly reported by literatures, we added them in model 2 although  
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15 189 they were not significant. Basing on model 2, we brought in PIH as another  
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18 190 confounder in model 3. PIH was an obvious risk factor according to the literature  
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21 191 review where women with PIH had twice the risk of having a SGA, compared with  
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23 192 women having no PIH.<sup>7</sup>

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25 193 Secondly, we used the pathway analysis to explore the hypothesized underlying  
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28 194 relations between variables of interested. The model was evaluated using the  
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31 195 following goodness-of-fit: the comparative-fit index (CFI)>0.95, the  
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33 196 root-mean-square error of approximation (RMSEA)<0.05. Modification indices were  
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35 197 used to detect misspecifications in the model. Estimation was carried out by a robust  
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38 198 weighted least-squares estimator (WLSMV). Because most of our variables were  
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41 199 categorical variables, WLSMV was one of the best methods for analysing our data set.  
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43 200 Effect sizes of the predictors on the outcome variables were expressed as  
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45 201 unstandardized estimates (B) and standardized estimates ( $\beta$ ). Indirect effect was  
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47 202 defined as the effect of the exposure that acted through a given set of mediators of  
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50 203 interest. Direct effect was refer to the effect of the exposure unexplained by those  
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52 204 same mediators.<sup>24</sup> The total effects of the predictors on the outcomes were computed  
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55 205 by adding the indirect and direct effects together.<sup>25</sup> Decoding of each response for

206 further analysis was present in table 1. All of the analyses were conducted with R

207 3.2.2. All *P* values reported were two-sided and 0.05 was used as significance level.

## 208 Patient Involvement

209 No patients were involved in setting the research question or the outcome measures,

210 nor were they involved in developing plans for recruitment, design, or implementation

211 of the study. No patients were asked to advise on interpretation or writing up of results.

212 There are no plans to disseminate the results of the research to study participants or

213 the relevant patient community.

214

Table 1. Description of variables in analysis.

Variables	Decoding of each response
SES	0="low", 1="high"
GWG by IOM recommendations	0="below", 1="within and above"
Pre-pregnancy BMI	0="<18.5", 1="≥18.5"
Physical activity during the last trimester of pregnancy	0="almost none per week", 1="1-2 days per week", 2="3-4 days per week", 4="5-6 days per week", 5="7 days per week"
Sleep quality in the month before the birth	0="bad", 1="good"
A multi-vitamin supplement during the first trimester of pregnancy	0="no", 1="yes"
Infant's gender	0="girl", 1="boy"
Passive smoking during pregnancy	0="no", 1="yes"
PIH	0="no", 1="yes"
Maternal age	continuous variable
SGA	0="no", 1="yes"

SES, socio-economic status; BMI, body mass index; GWG, gestational weight gain; IOM, Institute of Medicine; SGA, small-for-gestational age; PIH, pregnancy-induced hypertension syndrome.



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4 215 **RESULTS**  
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7 216 **Study Population**  
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10 217 A total of 8737 primiparae met our criterion and they finally included in our study.

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13 218 The mean maternal age was  $27.70 \pm 3.24$  years. The range of gestational age was

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15 219 28-42 weeks. In total, 927 (10.61%) infants were diagnosed with SGA. There were

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18 220 4499 boys and 4238 girls with a boy-to-girl ratio of 1.06.  
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21 221 **Characteristics of the Sample**  
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25 222 The basic demographic characteristics among SGA are presented in table 2. Mean

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27 223 maternal age was younger, mean pre-pregnancy BMI was lower and gestational

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29 224 weight gain below IOM recommendations was more likely with women who had

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32 225 SGA infants. Compared with women with AGA infants, women with SGA infants

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34 226 were more likely to have PIH and came from low SES. Women with AGA infants

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37 227 tended to be more positive regarding taking a multi-vitamin supplement during the

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39 228 first trimester of pregnancy. Correlations of the variables are presented in

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42 229 Supplementary table 3.  
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Table 2. Characteristics of participants with SGA and AGA among primiparae in Wuhan, China (N=8737)

Variables	N(%) or Mean $\pm$ SD	SGA	AGA	<i>P</i>
		N(%) or Mean $\pm$ SD	N(%) or Mean $\pm$ SD	
GWG by IOM recommendations				
Below	901(10.31)	208(22.44)	693(9.89)	<0.001
Within and above	7836(89.69)	719(77.56)	7117(90.11)	
Pre-pregnancy BMI				
<18.5	2082(23.83)	309(33.33)	1773(21.74)	<0.001
$\geq$ 18.5	6655(76.17)	618(66.67)	6037(78.26)	
Physical activity during the last trimester of pregnancy				
almost none per week	834(9.55)	79(8.52)	755(8.65)	0.495
1-2 days per week	831(9.51)	86(9.28)	745(8.98)	
3-4 days per week	663(7.59)	61(6.58)	602(7.83)	
5-6 days per week	146(1.67)	17(1.83)	129(1.86)	
every days per week	6263(71.68)	684(73.79)	5579(72.81)	
Sleep quality in the month before the birth				
Bad	3063(35.06)	310(33.44)	2753(33.48)	0.275
Good	5674(64.94)	617(66.56)	5057(66.52)	
A multi-vitamin supplement during the first trimester of pregnancy				
No	3640(41.66)	434(46.82)	3206(36.51)	0.001
Yes	5097(58.34)	493(53.18)	4604(63.49)	
Infant's gender				
Boy	4499(51.49)	467(50.38)	4032(51.86)	0.517
Girl	4238(48.51)	460(49.62)	3778(48.14)	
Passive smoking during pregnancy				
No	7717(88.33)	813(87.7)	5206(89.7)	0.532
Yes	1020(11.67)	114(12.3)	598(10.3)	
Maternal age	27.70 $\pm$ 3.24	27.32 $\pm$ 3.50	27.75 $\pm$ 3.21	<0.001
PIH				
No	8468(96.92)	882(95.15)	7586(97.13)	0.001
Yes	269(3.08)	45(4.85)	224(2.87)	
SES				
Low	927(10.61)	361(38.94)	2572(9.82)	<0.001
High	7810(89.39)	566(61.06)	5238(75.45)	

SES, socio-economic status; BMI, body mass index; GWG, gestational weight gain; IOM, Institute of Medicine; SGA, small-for-gestational age; PIH, pregnancy-induced hypertension syndrome; AGA, appropriate-for-gestational age.

### 231 Associations between SES and SGA

232 To examine the association between SES and the risk of SGA, univariate and

233 multivariate logistic regression models were used in table 3. Compared with women  
 234 with low SES, the OR of SGA was 0.770 (95% CI, 0.669, 0.886) for those with high  
 235 SES, in the unadjusted model. After adjustment for potential confounders, the ORs of  
 236 SGA were 0.846 (95% CI, 0.728, 0.983) and 0.856 (95% CI, 0.737, 0.995) in model 2  
 237 and model 3, respectively.

Table 3. Associations of SES with SGA among 8737 primiparae in Wuhan, China.

SGA	SES	OR	95%CI	<i>P</i>
Model 1	Low	Ref		
	High	0.770	0.669, 0.886	<0.001
Model 2	Low	Ref		
	High	0.846	0.728,0.983	0.029
Model 3	Low	Ref		
	High	0.856	0.737,0.995	0.043

ORs, odds ratios; SES, socio-economic status; SGA, small-for-gestational age; Model 1, unadjusted model; model 2 adjusted for maternal age, pre-pregnancy BMI, gestational weight gain (GWG), a multi-vitamin supplement during the first trimester of pregnancy, sleep quality in the month before the birth, physical activity during last trimester and passive smoking during pregnancy; model 3 adjusted as model 2 plus PIH.

### 238 **Mediation Model for SGA**

239 We proposed a hypothetical model for SGA in Figure 1, including the mediators PIH,  
 240 a multi-vitamin supplement during first-trimester, pre-pregnancy BMI, GWG by IOM  
 241 recommendations, physical activity during the last trimester of pregnancy and sleep  
 242 quality in the month before the birth. Covariates (maternal age and passive smoking  
 243 during pregnancy) were added in pathway analysis to control potential relations. table  
 244 4 listed SGA with the best CFI and RMSEA, which were 0.012 and 0.967. This model  
 245 revealed that maternal obstetric characteristics, lifestyles and PIH completely  
 246 mediated SES and SGA. The indirect effect of SES was strengthened in SGA

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4 247 (B=-0.067, 95% CI=-0.108, -0.026) via PIH (B=-0.029,  $P=0.021$ ), a multi-vitamin  
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6 248 supplement (B=-0.021,  $P=0.010$ ), pre-pregnancy BMI $\geq$ 18.5 (B=-0.009,  $P=0.010$ ) and  
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8 249 pre-pregnancy BMI $\geq$ 18.5 to GWG not below IOM recommendations (B=-0.003,  
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11 250  $P=0.007$ ).

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13 251 In our model, the indirect effect came from the coefficient “a” multiplying by  
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15 252 coefficient “b”. For example, woman with high SES had more chance of taking a  
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18 253 multi-vitamin supplement (B=0.317,  $P<0.001$ ). Then, a multi-vitamin supplement  
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21 254 taking decreased the SGA (B=-0.066,  $P<0.05$ ). Thus, the indirect effect of SES to  
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23 255 SGA was  $0.317* -0.066 = -0.021$  through taking a multi-vitamin supplement.  
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Table 4. Indirect and total effects of socio-economic status and maternal characteristics and lifestyles during pregnancy on SGA.

Pathway	SES→ Mediators	Mediators→ Birth outcomes	B	SE	95%CI	P value	β
	a	b	a*b				
Small-for-gestational age (SGA)							
Total effect			-0.067				-0.030
Direct effect (c)			-0.046	0.044	(-0.132, 0.040)	0.299	-0.034
Indirect effect			-0.067	0.021	(-0.108, -0.026)	0.001	-0.030
SES→ Pre-pregnancy BMI≥18.50→GWG not below IOM recommendations	0.033*, -0.253**	0.321**	-0.003	0.001	(-0.005, -0.001)	0.007	-0.001
SES→ GWG not below IOM recommendations	-0.045	0.321**	-0.014	0.013	(-0.039, 0.011)	0.273	-0.006
SES→ Pre-pregnancy BMI≥18.50	0.033*	-0.274**	-0.009	0.003	(-0.015, -0.003)	0.010	-0.004
SES→ a multi-vitamin supplement during the first trimester of pregnancy	0.317**	-0.066*	-0.021	0.008	(-0.037, -0.005)	0.010	-0.009
SES→ Physical activity during the last trimester of pregnancy	0.284**	0.017	0.005	0.003	(-0.001, 0.011)	0.063	0.002
SES→ Sleep quality in the month before the birth	0.150**	0.027	0.004	0.004	(-0.004, 0.012)	0.297	0.002
SES→ PIH	-0.176*	0.166**	-0.029	0.013	(-0.054, -0.004)	0.021	-0.013
Goodness-of-fit	RMSEA=0.012, CFI=0.967						

B, unstandardized coefficient; CI, confidence interval; B, standardized coefficient, \* $P < 0.05$ , \*\* $P < 0.001$ . RMSEA, the root mean square error of approximation; CFI, the comparative fit index; SES, socio-economic status; GWG, gestational weight gain; IOM, Institute of Medicine. Covariates of maternal age, passive smoking during pregnancy were adjusted for SGA.

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5 256 **DISCUSSION**  
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8 257 The findings of our study indicated that high SES was related to a reduced risk of  
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10 258 SGA after adjustment for potential confounders. In the pathway analysis, PIH, taking  
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12 259 a multi-vitamin supplement during early pregnancy, keeping normal pre-pregnancy  
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14 260 BMI and gaining reasonable gestational weight were all the significant mediators  
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16 261 which completely mediated the relationship between SES and SGA. There were four  
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18 262 pathways between SES and SGA as following. ① High SES of pregnancy women  
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20 263 predicted lower risk of PIH. The risk of SGA was reduced by no-PIH. ② Women  
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22 264 from high SES had more chance to take a multi-vitamin supplement during early  
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24 265 pregnancy. A multi-vitamin supplement could lead to a lower risk of SGA infants. ③  
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26 266 Women from high SES were more likely to be pre-pregnancy BMI  $\geq 18.50\text{kg/cm}^2$ .  
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28 267 Furthermore, pre-pregnancy BMI  $\geq 18.50\text{kg/cm}^2$  decreased the risk of SGA infants  
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30 268 afterwards. ④ Women from high SES predicted pre-pregnancy BMI  $\geq 18.50\text{kg/cm}^2$ .  
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32 269 Pregnancy women with pre-pregnancy BMI  $\geq 18.50\text{kg/cm}^2$  could gain adequate  
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34 270 gestational weight which was not below IOM recommendations. And the GWG not  
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36 271 below IOM recommendations decreased the risk of SGA infants.  
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38 272 One of the strengths of our study was the large sample size. In addition,  
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40 273 face-to-face interviews, medical records and measurements provided rich covariate  
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42 274 data, which allowed us to adjust for potential confounders for SGA. Thirdly, SES  
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44 275 index was combined with parental education and occupation. This index was more  
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46 276 representative and reasonable to represent SES compared with using only education or  
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4 277 occupation in China. We acknowledge that there were also some limitations. Firstly,  
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6 278 information on education and occupation was obtained using face-to-face  
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8 279 questionnaires, which might have bias. Occupation can fluctuate over time, and it is  
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10 280 more likely to lead to misclassification. Secondly, although we carefully adjusted for  
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13 281 several potential confounders for SGA, we were unlikely to fully rule out the  
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15 282 possibility of residual confounding by other unmeasured factors such as parents'  
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17 283 history of SGA, maternal stress during pregnancy. Thirdly, some of our variables  
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19 284 including a micronutrient supplement, physical activity and sleep quality during  
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21 285 pregnancy relied on self-reporting, which were subjective.  
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25 286 Predictably, high SES was a protector of SGA in our study. A large  
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27 287 population-based study from Finland reported that SES determined by women's  
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29 288 occupation was inversely associated with the risk of SGA.<sup>12</sup> A birth cohort study  
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31 289 conducted in France reported that low SES determined by neighbourhood deprivation  
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33 290 may affect foetal growth, especially in rural areas.<sup>26</sup> These two studies were consistent  
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35 291 with our results. However, Clayborne et al. did not find a direct association between  
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37 292 SES measured by neighborhood deprivation and the risk of SGA in Canada.<sup>27</sup> Because  
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39 293 of the different measures of SES, these studies may not be easily compared. The  
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41 294 underlying mechanisms responsible for increased risk of SGA among primiparae with  
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43 295 low SES remain speculative. In our study, we found that some mediators could  
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45 296 completely mediate SES and SGA.  
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52 297 In the pathway analysis, we observed that PIH was a mediator between SES and  
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54 298 SGA. We demonstrated that SES was associated with PIH among primiparae. A  
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4 299 meta-analysis including 51 studies found that low SES was associated with higher  
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6 300 blood pressure. This association was particularly evident in the level of education.<sup>28</sup>  
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8 301 Adherence to knowledge of hypertension and more social resources to maintain  
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10 302 healthy behaviours could explain why SES likely affects PIH among pregnant women.  
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13 303 The rate of SGA infants from the PIH group was significantly higher compared with  
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15 304 the no PIH group in our study. PIH is associated with a reduction in placental  
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17 305 perfusion, which influences the size of the placenta.<sup>29</sup> In SGA infants, the size of the  
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19 306 placental disc was smaller and the birthweight was lighter.<sup>30</sup> Placenta is an important  
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21 307 organ for foetus and supplies all the nutrients needed for foetal development. The  
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23 308 pathology of placental was potentially causing or contributing to SGA and  
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25 309 hypertension was one of the factors in aetiology.<sup>31</sup> The growth and development of the  
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27 310 placenta being influenced by PIH may be suggested an explanation for lower  
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29 311 birthweight.<sup>30</sup>

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35 312 Taking a multi-vitamin supplement during the first trimester of pregnancy was  
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37 313 another mediator between SES and SGA. Women with low SES defined by family  
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39 314 income had less chance to obtain optimal nutrient supplements in a meta-analysis  
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41 315 including 12 randomized controlled trials.<sup>32</sup> A double-blind cluster randomized  
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43 316 controlled trial in rural China reported birthweight was 42 g higher in the multiple  
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45 317 micronutrients group compared with the folic acid group.<sup>33</sup> Another birth cohort from  
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47 318 Denmark reported that regular periconceptional multi-vitamins use was associated  
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49 319 with a reduced risk of SGA births.<sup>34</sup> A multi-vitamin supplement during early  
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51 320 pregnancy might reduce the risk of alcohol use in relation to SGA.<sup>35</sup> This result  
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3 321 evidenced that a multi-vitamin supplement during early pregnancy was a protector  
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6 322 factor for SGA, which was similar to our study. Multi-vitamins are important for  
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9 323 human physical function and they play vital roles in numerous metabolic processes  
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11 324 and physiological functions in the human body. A multi-vitamin supplement during  
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13 325 pregnancy reduced the risk of pregnancy complications, involving oxidative stress and  
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16 326 pre-eclampsia. Pre-eclampsia could decrease blood to the placenta, which causes  
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18 327 growth retardation.<sup>36</sup> In China, most people believe that they should obtain vitamins  
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20 328 from daily diet, i.e. fresh vegetables and fruits, which is a natural way instead of  
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23 329 taking multi-vitamin supplements every day. Pregnant women are recommended to  
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26 330 take multi-vitamin supplements, since they are unable to obtain an adequate nutrient  
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28 331 status from their diet alone. Most pregnant women take folic acid, because the  
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30 332 government provides folic acid free of charge. For the multi-vitamin supplements,  
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33 333 pregnant women decide to take them or not depending on their own opinions. The  
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35 334 different dietary habits and customs might explain part of why taking multi-vitamin  
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38 335 supplements is significant. Our results showed that high SES was significantly related  
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40 336 to a daily supplement of multi-vitamin. As our large-scale studied population came  
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43 337 from the city of Wuhan, the results of our study could extend to pregnancy women in  
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45 338 Hubei province, which included 12 cities. However, extrapolation of our findings to  
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48 339 Chinese women should be cautious. Multicenter cohort studies from different cities of  
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50 340 China will be needed in further studies.

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52 341 Pre-pregnancy underweight and pre-pregnancy underweight to GWG below IOM  
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55 342 recommendations were the two pathways between SES and SGA. The chances of  
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4 343 having a SGA infant was significantly higher among underweight women compared  
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6 344 to normal pre-pregnancy BMI in our study, which was consistent with a study in  
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8 345 Lebanon. As Lebanon is a developing country in Asia, and its people are similar to  
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10 346 Chinese people, we deemed these results could support our findings. Smoking, poor  
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12 347 diet, and medical illness like anaemia which are risk factors for SGA among  
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14 348 underweight women, occurred more often. Deficiency of maternal plasma volume  
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16 349 among underweight women has been suggested as a cause of SGA.<sup>37</sup> In our study,  
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18 350 underweight women were more likely to have insufficient weight gain during  
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20 351 pregnancy and below normal weight gain significantly increased the odds of SGA. As  
21  
22 352 expected, GWG below IOM recommendations in women with pre-pregnancy  
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24 353 underweight was reportedly more likely to affect the birthweight of their neonates.<sup>38</sup>  
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26 354 Poor nutrition or unhealthy psychological state among pregnant women with GWG  
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28 355 below IOM recommendations may explain causes of SGA.  
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## 36 **CONCLUSION**

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40 357 We demonstrated that SES was inversely associated with SGA after adjustment for  
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42 358 potential confounders among primiparae. In this population, we also found that  
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44 359 mediators could completely mediate SES and SGA. Monitoring of blood pressure,  
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46 360 avoiding pre-pregnancy underweight, keeping sufficient GWG during pregnancy and  
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48 361 taking a multi-vitamin supplement during the first trimester of pregnancy are practical  
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50 362 and feasible measurements to reduce the risk of SGA. As we all know, SGA is a  
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52 363 public health issue and SES disparities are difficult to change over a short time. It had  
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4 364 great sense to maintain normal blood pressure and keep a healthy lifestyle to reduce  
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6 365 cases of SGA infants among primiparae, especially for women of child-bearing age  
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8 366 who have a low SES. A future research direction should focus on identifying  
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11 367 interventions to successfully reduce socio-economic disparities in SGA.  
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45 489 **Contributors** X.L. contributed to acquisition of data, statistical analysis,  
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47 490 interpretation of data and manuscript writing. F.L.L., H.T.G., F.H., X.Y.X., X.L., H.M.,  
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49 491 S.Q.X., interpretation of the data. J.J.Z., R.R.S. supervised the project and wrote the  
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51 492 manuscript. All authors approved the final version to be published. R.R.S. is the  
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53 493 guarantor of this work.  
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7  
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15 499 **Data sharing statement** No additional data is available.

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20 500 **Figure legends**

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23 501 Figure 1. Serial mediation models of the indirect associations socioeconomic status  
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25 502 (SES) and small-for-gestational age (SGA). Unstandardized regression coefficients  
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27 503 are a1, a1', a2, a3, a4, a5, a6, b1, b2, b3, b4, b5, b6, c. Adjusted for maternal age and  
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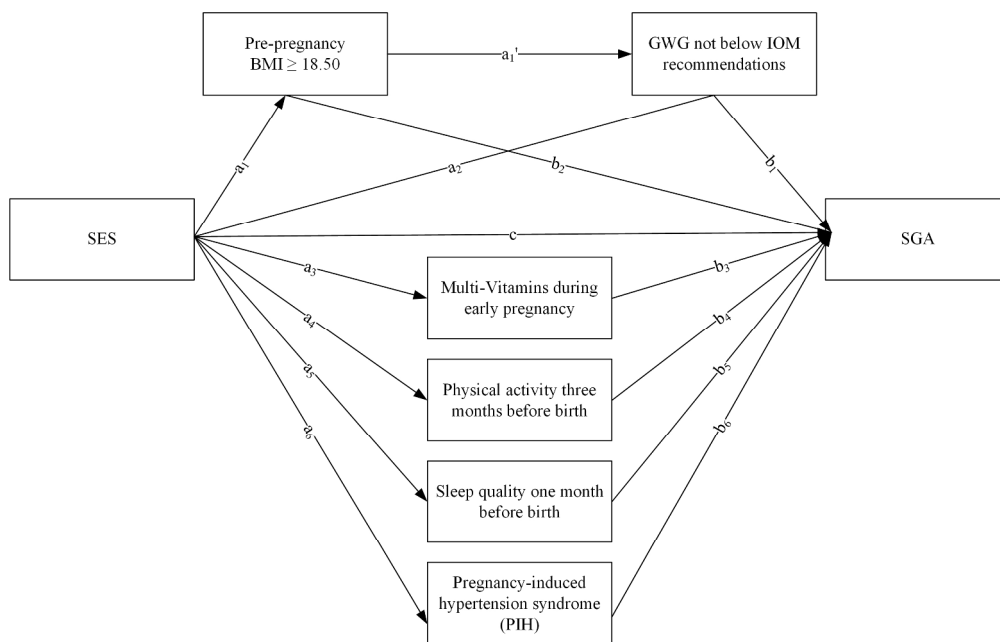


Figure 1. Serial mediation models of the indirect associations socioeconomic status (SES) and small-for-gestational age (SGA). Unstandardized regression coefficients are  $a_1$ ,  $a_1'$ ,  $a_2$ ,  $a_3$ ,  $a_4$ ,  $a_5$ ,  $a_6$ ,  $b_1$ ,  $b_2$ ,  $b_3$ ,  $b_4$ ,  $b_5$ ,  $b_6$ ,  $c$ . Adjusted for maternal age and passive smoking during pregnancy.

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Supplementary Table 1. Scores for coding education by number of years of school completed

Category	Total years	Scores	
		Males	Females
Doctor	22	69	73
Master	19	69	73
college	16	63	66
Junior school	15	61	63
high school	12	52	53
middle school	9	45	44
Elementary school	6	36	34
	3	33	32
	0	29	28

Supplementary Table 2. Average scores for categories of major occupational groups

Major occupational groups	Category	Scores
Managerial workers	I	59
professionals & technical	II	63
Office clerks	III	56
Service workers	IV	46
Agriculture and forestry	V	34
Laborer	VI	42
Soldier	VII	53
Others	VIII	49

Supplementary table 3. Correlation matrix of the study variables among primiparas in Wuhan, China (N=8737)

Variables	1	2	3	4	5	6	7	8	9	10	11
GWG by IOM recommendations	—										
Pre-pregnancy BMI	-0.065**	—									
Physical activity during the last trimester of pregnancy	-0.001	0.002									
Sleep quality in the month before the birth	-0.001	0.017	-0.002	—							
A multi-vitamin supplement during the first trimester of pregnancy	-0.008	0.019	0.110**	-0.031**	—						
Infant's gender	-0.002	-0.012	-0.003	0.005	-0.008	—					
Passive smoking during pregnancy	-0.008	-0.031**	-0.009	0.017	0.046**	0.004	—				
Maternal age	-0.024*	0.133**	-0.021*	-0.017	0.156**	-0.015	-0.020	—			
PIH	-0.021*	0.058**	-0.001*	-0.016	-0.016	0.002	-0.007	0.037**	—		
SES	-0.020	0.069**	0.047**	0.047**	0.147**	-0.010	-0.060**	0.252**	-0.023*	—	
SGA	0.137**	-0.077**	0.016	0.012	-0.036**	0.008	0.007	-0.040**	0.035**	-0.039**	—

SES, socio-economic status; BMI, body mass index; GWG, gestational weight gain; IOM, Institute of Medicine; SGA, small-for-gestational age; AGA, appropriate-for-gestational age; PIH, pregnancy-induced hypertension syndrome. \* $P < 0.05$ , \*\* $P < 0.001$

**STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology\***  
**Checklist for cohort, case-control, and cross-sectional studies (combined)**

Section/Topic	Item #	Recommendation	Reported on page #
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	1-2
<b>Introduction</b>			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-6
Objectives	3	State specific objectives, including any pre-specified hypotheses	5-6
<b>Methods</b>			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-8
Participants	6	(a) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —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 <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	6
		(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-9
Data sources/ measurement	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	11-13
Bias	9	Describe any efforts to address potential sources of bias	
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	9-10
		(b) Describe any methods used to examine subgroups and interactions	
		(c) Explain how missing data were addressed	
		(d) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed	

		<i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy	
		(e) Describe any sensitivity analyses	
<b>Results</b>			
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	6
		(b) Give reasons for non-participation at each stage	6
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	11-12
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time	
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure	
		<i>Cross-sectional study</i> —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	13-15
		(b) Report category boundaries when continuous variables were categorized	
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	14-16
<b>Discussion</b>			
Key results	18	Summarise key results with reference to study objectives	17
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	17-18
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	18-20
Generalisability	21	Discuss the generalisability (external validity) of the study results	20-21
<b>Other information</b>			
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	27

\*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](http://www.strobe-statement.org).