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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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ABSTRACT

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

Design Retrospective cohort study.

Setting Wuhan, Hubei, China.

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

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

-0.026). The indirect effect of SES was strengthened by PIH (B=-0.029), a multi-vitamin supplement (B=-0.021), pre-pregnancy body mass index (BMI) ≥18.5 (B=-0.009) and pre-pregnancy BMI≥18.5 to gestational weight gain (GWG) not below Institute of Medicine (IOM) (B=-0.003).

Conclusions Our research suggested that high SES was a positive protector against SGA. Avoiding PIH, taking a multi-vitamin supplement during early pregnancy, keeping normal pre-pregnancy BMI and gaining reasonable gestation weight may represent important protectors for SGA infants among pregnant women from low SES.

Keywords socio-economic status (SES), SGA, primiparae, mediators, pathway analysis

Strengths and limitations of this study

Face-to-face interviews, medical records and medical measurements provided rich covariate data, which allowed us to adjust for potential confounders for SGA.

SES index was combined with parental education and occupation. This index was more robust when it was compared to education and occupation separately in China.

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

Some of our variables, such as a micronutrient supplement, physical activity and sleep quality during pregnancy relied on self-report, which are subjective.

Abbreviations

BMI	Body mass index
GWG	Gestational weight gain
IOM	Institute of Medicine
SES	Socio-economic status
SGA	Small-for-gestational age
AGA	Appropriate-for-gestational age
CI	Confidence interval
OR	Odds ratio
PIH	Pregnancy-induced hypertension syndrome

INTRODUCTION

Small-for-gestational age (SGA) infants is defined as birthweight below the tenth percentile of a standard optimal reference population for a given gestational age and sex.[1] SGA infants are at increased risk of perinatal morbidity and mortality[2] as well as long-term adverse health[3] and developmental outcomes.[4] In 2010, the overall prevalence of SGA infants was 27% of live births in 138 low- and middle-income countries.[5] Another pooled country analysis research identified that the relative risks for babies who were SGA were 1.83 for neonatal mortality and 1.90 for post-neonatal mortality among 20 cohorts (providing data for 2,015,019 livebirths) from Asia, Africa and Latin America.[6] Therefore, it is important to recognize the potential risk

factors for SGA infants during pregnancy so that preventive measures can be targeted at risk subgroups of pregnant women. A review from France found major risk factors identified were previous SGA birth, disease during pregnancy, body mass index (BMI<18.5 kg/m^2) and socio-economic disadvantage.[7] Socio-economic disparities in SGA infants have been relatively intractable over the past decades. However, the mechanisms by which socio-economic disadvantage leads to higher risk of SGA remain unclear.

Socio-economic status (SES) is a complex phenomenon predicted by a broad spectrum of variables. It is often conceptualized as a combination of financial, occupational and educational influences.[8] The level of SES can partly explain the risk at birth outcome,[9] children's anthropometric status,[10] and neurodevelopment.[11] The risk of SGA was higher in the lower SES groups compared to the highest SES group in Finland,[12] Australia,[13] Japan[9] and others. These estimates were based mainly on findings from developed countries, with little reliable evidence from China. Moreover, in the Hong Kong population, researchers demonstrated parental education, housing, income and occupation were not clearly linearly associated with SGA.[14] As the economy of Hong Kong is more developed than that of China mainland, it makes great sense to explore the association between SES and SGA infants in mainland China.

Wang found that among 10,372 people from 28 provinces of China, those from high SES promoted their health via health-related lifestyles.[15] Another study reviewed the evidence focusing on aetiological factors that could mediate the socio-economic

disparities in intrauterine growth restriction. Factors included maternal anthropometry, micronutrients, physical activity, cigarette smoking and psychosocial factors.[16] However, this review used a bibliographic method to find these evidence and it was hard to reveal mediators without the pathway analysis. Furthermore, the gap between the most and least deprived groups did not narrow for birthweight outcomes over the four decades.[17] In the current study, we examined the association between SES and SGA infants and aimed to uncover one of the potential mechanisms that could show how SES affects SGA infants among Chinese primiparae in the Health Baby Cohort (HBC).

METHODS

Study Population

All participants were selected from the prospective Health Baby Cohort (HBC) study in China, which has been described elsewhere.[18] It is an ongoing prospective cohort study, which aims to explore how environmental and genetic factors affect child health and development. Participants who had had a stillborn infant were excluded. Briefly, the cohort enrolled 11,311 pregnant women who gave birth to a live singleton infant in the Women and Children Medical and Health-care Centre of Wuhan between September 2012 and October 2014. In our study, we selected 9622 primiparae and then, we excluded another 885 participants because of missing values in at least one variable of interest, such as parental education and a nutritional supplement. Therefore,

a total of 8737 primiparae were finally included in our study. All participating women provided their written informed consent at the time of recruitment.

Diagnosis of SGA

Birthweight and infant's gender were obtained from delivery records. Gestational age was calculated from the date of the last menstrual period or the clinical estimate of gestational age based on the clinical case system. Labour and delivery outcomes were extracted from birth records. Nude birthweight was measured for each infant within one hour after birth by trained nurses using standardized procedures. We defined small-for-gestational age (SGA) as a birthweight lower than the 10th percentile of our population for a specific completed gestational age by gender.[6] On the other hand, we defined appropriate for gestational age (AGA) as a birthweight equal to or higher than the 10th centile for gestational age.

Assessment of Covariates

The trained nurses conducted standardized face-to-face interviews with the participants after delivery. Participants were asked to complete a questionnaire that collected information on maternal age, maternal and paternal education level (years of education), occupations (eight major categories of Chinese occupation), the use of a multi-vitamin supplement during the first trimester of pregnancy (yes or no), physical activity during the last trimester of pregnancy (almost none, 1–2 days, 3–4 days, 5–6 days, 7 days) per week, and sleep quality in the month before the birth (bad or good).

Information regarding pregnancy-induced hypertension syndrome (PIH) was extracted from medical records excluding chronic hypertension. PIH was defined as "yes" or "no". We calculated pre-pregnancy body mass index (BMI) from the self-reported pre-pregnancy weight in kg divided by height in m^2. BMI was categorized into four groups based on recommendations by the Working Group on Obesity in China of the Chinese Ministry of Health: underweight (<18.5 kg/m^2); normal weight (18.5–23.9 kg/m^2); overweight (24–27.9 kg/m^2); and obese (≥ 28 kg/m^2). Gestational weight gain (GWG) was calculated by subtracting the pre-pregnancy weight from the weight measured within 3 days of the delivery day. GWG was also categorized as below, within, or above the recommendations according to the Institute of Medicine (IOM).[19] Specifically, GWG within the IOM recommendations was defined as 12.5–18 kg, 11.5–16 kg, 7–11.5 kg and 5–9 kg for underweight, normal weight, overweight, and obese women, respectively. Finally, we changed pre-BMI and GWG by IOM as dichotomous variable (pre-BMI<18.50 or ≥18.5; GWG below IOM or not below).

Assessment of Socio-economic Status

SES index was measured by a combination of the education and occupation categories. The scores of education and occupation are listed in Supplementary Table 1 and Supplementary Table 2. SES index was measured based on the formula, SES= ((0.7 * maternal education) + (0.4 * maternal occupation) + (0.7 * paternal education) + (0.4* paternal occupation))/2. Finally, the SES index categorization demonstrates that below one third of the study population distribution had low SES and the remainder had high

SES.[20]

Statistical Analysis

Firstly, data were described as mean ± SD for continuous variables or as percentage for categorical variables. Differences between SGA and AGA were compared using the Student's t-test for continuous variables and chi-square test for categorical variables. Pearson's correlation was carried out between study variables. Logistic regression models were used to examine the associations between SES and SGA. Secondly, we used the pathway analysis to explore the hypothesized underlying relations between variables of interested. The model was evaluated using the following goodness-of-fit: the comparative-fit index (CFI)>0.95, the root-mean-square error of approximation (RMSEA)<0.05. Modification indices were used to detect misspecifications in the model. Estimation was carried out by a robust weighted least-squares estimator (WLSMV). Because most of our variables were categorical variables, WLSMV was one of the best methods for analysing our data set. Effect sizes of the predictors on the outcome variables were expressed as unstandardized estimates (B) and standardized estimates (ß). The total effects of the predictors on the outcomes were computed by adding the indirect and direct effects together.[21] Decoding of each response for further analysis was present in Table 1. All of the analyses were conducted with R 3.2.2. All *P* values reported were two-sided and 0.05 was used as significance level.

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.

RESULTS

Study Population

A total of 8737 primiparae met our criterion and they finally included in our study. The mean maternal age was 27.70 ± 3.24 years. In total, 927 (10.61%) infants were diagnosed with SGA. There were 4499 boys and 4238 girls with a boy-to-girl ratio of 1.06.

Characteristics of the Sample

The basic demographic characteristics among SGA are presented in Table 2. Mean maternal age was younger, mean pre-pregnancy BMI was lower and gestational

weight gain below IOM was more likely with women who had SGA infants. Compared with women with AGA infants, women with SGA infants were more likely to have PIH and came from low SES. Women with AGA infants tended to be more positive regarding taking a multi-vitamin supplement during the first trimester of pregnancy. Correlations of the variables are presented in Supplementary Table 3.

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

Variables	N(%) or Mean ±SD	SGA	AGA	*P*
		N(%) or Mean ±SD	N(%) or Mean ±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
≥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±3.24	27.32±3.50	27.75±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.

Associations between SES and SGA

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

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

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

SGA	SES	OR	95%CI	*P*
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.

Mediation Model for SGA

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

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

multi-vitamin supplement (B=-0.021, *P*=0.010), pre-pregnancy BMI≥18.5 (B=-0.009, *P*=0.010) and pre-pregnancy BMI≥18.5 to GWG not below IOM (B=-0.003, *P*=0.007).

In our model, the indirect effect came from the coefficient "a" multiplying by coefficient "b". For example, woman with high SES had more chance of taking a multi-vitamin supplement (B=0.317, *P*<0.001). Then, a multi-vitamin supplement taking decreased the SGA (B=-0.066, *P*<0.05). Thus, the indirect effect of SES to SGA was 0.317*-0.066=-0.021 through taking a multi-vitamin supplement.

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	ß
	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-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.

DISCUSSION

The findings of our study indicated that high SES was related to a reduced risk of SGA after adjustment for potential confounders. In the pathway analysis, the direct effect was not significant. These mediators completely mediated the relationship between SES and SGA. We observed that PIH, taking a multi-vitamin supplement during the first trimester of pregnancy, pre-pregnancy underweight and GWG below IOM were the mediators between SES and SGA.

One of the strengths of our study was the large sample size. In addition, face-to-face interviews, medical records and measurements provided rich covariate data, which allowed us to adjust for potential confounders for SGA. Thirdly, SES was combined parental education and occupation which was more robust compared with education and occupation separately in China. We acknowledge that there were also some limitations. Firstly, information on education and occupation was obtained using face-to-face questionnaires, which might have bias. Occupation can fluctuate over time, and it is more likely to lead to misclassification. Secondly, although we carefully adjusted for several potential confounders for SGA, we were unlikely to fully rule out the possibility of residual confounding by other unmeasured factors such as parents' history of SGA, maternal stress during pregnancy. Thirdly, some of our variables including a micronutrient supplement, physical activity and sleep quality during pregnancy relied on self-reporting, which were subjective.

Predictably, high SES was a protector of SGA in our study. A large

population-based study from Finland reported that SES determined by women's occupation was inversely associated with the risk of SGA.[12] A birth cohort study conducted in France reported that low SES determined by neighbourhood deprivation may affect foetal growth, especially in rural areas.[22] These two studies were consistent with our results. However, Clayborne et al. did not find a direct association between SES measured by neighborhood deprivation and the risk of SGA in Canada.[23] Because of the different measures of SES, these studies may not be easily compared. The underlying mechanisms responsible for increased risk of SGA among primiparae with low SES remain speculative. In our study, we found that some mediators could completely mediate SES and SGA.

In the pathway analysis, we observed that PIH was a mediator between SES and SGA. We demonstrated that SES was associated with PIH among primiparae. A meta-analysis including 51 studies found that low SES was associated with higher blood pressure. This association was particularly evident in the level of education.[24] Adherence to knowledge of hypertension and more social resources to maintain healthy behaviours could explain why SES likely affects PIH among pregnant women. The rate of SGA infants from the PIH group was significantly higher compared with the no PIH group in our study. PIH is associated with a reduction in placental perfusion, which influences the size of the placenta.[25] In SGA infants, the size of the placental disc was smaller and the birthweight was lighter.[26] Placenta is an important organ for foetus and supplies all the nutrients needed for foetal development. The pathology of placental was potentially causing or contributing to SGA and

hypertension was one of the factors in aetiology.[27] The growth and development of the placenta being influenced by PIH may be suggested an explanation for lower birthweight.[26]

Taking a multi-vitamin supplement during the first trimester of pregnancy was another mediator between SES and SGA. Women with low SES defined by family income had less chance to obtain optimal nutrient supplements in a meta-analysis including 12 randomized controlled trials.[28] A double-blind cluster randomized controlled trial in rural China reported birthweight was 42 g higher in the multiple micronutrients group compared with the folic acid group.[29] Another birth cohort from Denmark reported that regular periconceptional multi-vitamins use was associated with a reduced risk of SGA births.[30] A multi-vitamin supplement during early pregnancy might reduce the risk of alcohol use in relation to SGA.[31] This result evidenced that a multi-vitamin supplement during early pregnancy was a protector factor for SGA, which was similar to our study. Multi-vitamins are important for human physical function and they play vital roles in numerous metabolic processes and physiological functions in the human body. A multi-vitamin supplement during pregnancy reduced the risk of pregnancy complications, involving oxidative stress and pre-eclampsia. Pre-eclampsia could decrease blood to the placenta, which causes growth retardation.[32]

Pre-pregnancy underweight and pre-pregnancy underweight to GWG below IOM were the two pathways between SES and SGA. The chances of having a SGA infant was significantly higher among underweight women compared to normal

pre-pregnancy BMI in our study, which was consistent with a study in Lebanon. As Lebanon is a developing country in Asia, and its people are similar to Chinese people, we deemed these results could support our findings. Smoking, poor diet, and medical illness like anaemia which are risk factors for SGA among underweight women, occurred more often. Deficiency of maternal plasma volume among underweight women has been suggested as a cause of SGA.[33] In our study, underweight women were more likely to have insufficient weight gain during pregnancy and below normal weight gain significantly increased the odds of SGA. As expected, GWG below IOM in women with pre-pregnancy underweight was reportedly more likely to affect the birthweight of their neonates.[34] Poor nutrition or unhealthy psychological state among pregnant women with GWG below IOM may explain causes of SGA.

CONCLUSION

We demonstrated that SES was inversely associated with SGA after adjustment for potential confounders among primiparae. In this population, we also found that mediators could completely mediate SES and SGA. Monitoring of blood pressure, avoiding pre-pregnancy underweight, keeping normal GWG during pregnancy and taking a multi-vitamin supplement during the first trimester of pregnancy are practical and feasible measurements to reduce the risk of SGA. As we all know, SGA is a public health issue and SES disparities are difficult to change over a short time. It had great sense to maintain normal blood pressure and keep a healthy lifestyle to reduce cases of SGA infants among primiparae, especially for women of child-bearing age

who are have a low SES. A future research direction should focus on identifying interventions to successfully reduce socio-economic disparities in SGA.

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Disclosure of interests

The authors declare that there is no competing interest including relevant financial, personal, political, intellectual or religious interests.

Contribution to Authorship

X.L. contributed to acquisition of data, statistical analysis, interpretation of data and manuscript writing. F.L.L., H.T.G., F.H., X.Y.X., X.L., H.M., S.Q.X., interpretation of the data. J.J.Z., R.R.S. supervised the project and wrote the manuscript. All authors approved the final version to be published. R.R.S. is the guarantor of this work.

Details of Ethics Approval

The research protocol was approved by the ethics committees of the Tongji Medical College, Huazhong University of Science and Technology, and the Women and

Children Medical and Healthcare Centre of Wuhan. All participating women provided their written informed consent at the time of recruitment.

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Data sharing statement

No additional data is available.

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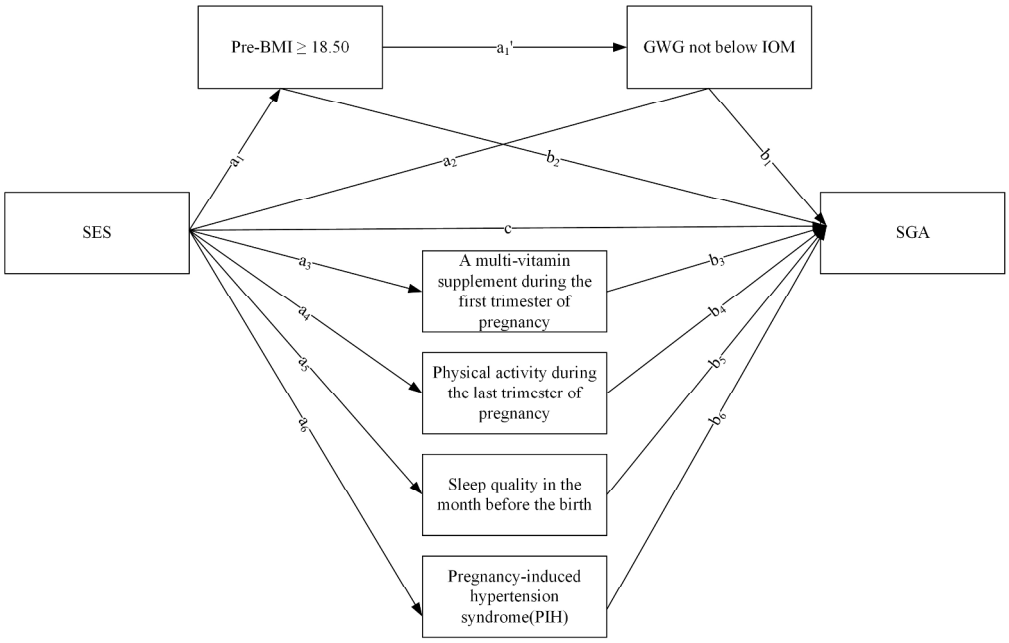

Figure 1. Pathway model of the associations between socio-economic status (SES) and small-for-gestational age (SGA). Unstandardized regression coefficients are a_1, a_1',a_2, a_3, a_4, a_5, a_6,b_1, b_2, b_3, b_4, b_5,b_6, c.

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 matric 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

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
Introduction			
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
Methods			
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*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	6
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
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*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	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) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—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
Discussion			
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
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	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.

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

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

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ABSTRACT

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

Design Retrospective cohort study.

Setting Wuhan, Hubei, China.

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

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

PIH (B=-0.029), a multi-vitamin supplement (B=-0.021), pre-pregnancy body mass index (BMI) ≥18.50 (B=-0.009) and pre-pregnancy BMI≥18.50 to gestational weight gain (GWG) not below Institute of Medicine (IOM) recommendations (B=-0.003).

Conclusions Women from high SES predicted lower risk of PIH, more chance to take a multi-vitamin supplement during early pregnancy, keeping pre-pregnancy BMI ≥18.50kg/cm^2 and gaining adequate gestational weight which was not below IOM recommendations. Furthermore, lower risk of PIH, more chance to take a multi-vitamin supplement, pre-pregnancy BMI ≥18.50kg/cm^2 and GWG not below IOM recommendations were associated with a lower risk of SGA infants.

Keywords socio-economic status (SES), SGA, primiparae, mediators, pathway analysis

Strengths and limitations of this study

It was a large population-based cohort study of pregnant women in Wuhan, China.

Face-to-face interviews, medical records and medical measurements provided rich covariate data, which allowed us to adjust for potential confounders for SGA.

SES index was combined with parental education and occupation. This index was more representative and reasonable to represent SES compared with using only education or occupation in China.

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

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

quality during pregnancy relied on self-report, which are subjective.

Abbreviations

BMI	Body mass index
GWG	Gestational weight gain
IOM	Institute of Medicine
SES	Socio-economic status
SGA	Small-for-gestational age
AGA	Appropriate-for-gestational age
CI	Confidence interval
OR	Odds ratio
PIH	Pregnancy-induced hypertension syndrome

INTRODUCTION

Small-for-gestational age (SGA) infants is defined as birthweight below the tenth percentile of a standard optimal reference population for a given gestational age and sex.[1] SGA infants are at increased risk of perinatal morbidity and mortality[2] as well as long-term adverse health[3] and developmental outcomes.[4] In 2010, the overall prevalence of SGA infants was 27% of live births in 138 low- and middle-income countries, using the Alexander reference population (US National Center for Health Statistics, 1991; n=3,134,879 livebirths).[5] Another pooled country analysis research identified that the relative risks for babies who were SGA were 1.83 for neonatal

mortality and 1.90 for post-neonatal mortality among 20 cohorts (providing data for 2,015,019 livebirths) from Asia, Africa and Latin America.[6] Therefore, it is important to recognize the potential risk factors for SGA infants during pregnancy so that preventive measures can be targeted at risk subgroups of pregnant women. A review from France found major risk factors identified were previous SGA birth, disease during pregnancy, maternal underweight and socio-economic disadvantage.[7] Socio-economic disparities in SGA infants have been relatively intractable over the past decades. However, the mechanisms by which socio-economic disadvantage leads to higher risk of SGA remain unclear.

Socio-economic status (SES) is a complex phenomenon predicted by a broad spectrum of variables. It is often conceptualized as a combination of financial, occupational and educational influences.[8] The level of SES can partly explain the risk at birth outcome,[9] children's anthropometric status,[10] and neurodevelopment.[11] The risk of SGA was higher in the lower SES groups compared to the highest SES group in Finland,[12] Australia,[13] Japan[9] and others. These estimates were based mainly on findings from developed countries, with little reliable evidence from China. Moreover, in the Hong Kong population, researchers demonstrated parental education, housing, income and occupation were not clearly linearly associated with SGA.[14] As the economy of Hong Kong is more developed than that of China mainland, it makes great sense to explore the association between SES and SGA infants in mainland China.

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

high SES promoted their health via health-related lifestyles.[15] Another study reviewed the evidence focusing on aetiological factors that could mediate the socio-economic disparities in intrauterine growth restriction. Factors included maternal anthropometry, micronutrients, physical activity, cigarette smoking and psychosocial factors.[16] However, this review used a bibliographic method to find these evidence and it was hard to reveal mediators without the pathway analysis. Furthermore, the gap between the most and least deprived groups did not narrow for birthweight outcomes over the four decades.[17] In the current study, we examined the association between SES and SGA infants and aimed to uncover one of the potential mechanisms that could show how SES affects SGA infants among Chinese primiparae in the Health Baby Cohort (HBC).

METHODS

Study Population

All participants were selected from the prospective Health Baby Cohort (HBC) study in China, which has been described elsewhere.[18] It is an ongoing prospective cohort study, which aims to explore how environmental and genetic factors affect child health and development. Participants who had had a stillborn infant were excluded. Briefly, the cohort enrolled 11,311 pregnant women who gave birth to a live singleton infant in the Women and Children Medical and Health-care Centre of Wuhan between September 2012 and October 2014. In our study, we selected 9623 primiparae and

then, we excluded another 886 participants because of missing values in at least one variable of interest, such as parental education and a multi-vitamin supplement. Therefore, a total of 8737 primiparae were finally included in our study. The present study was approved by the ethics committees of the Tongji Medical College, Huazhong University of Science and Technology, and the Women and Children Medical and Healthcare Centre of Wuhan. All participating women provided their written informed consent at the time of recruitment.

Diagnosis of SGA

Birthweight and infant's gender were obtained from delivery records. Most of the gestational age was calculated from the date of the last menstrual period (LMP) which was recorded on their clinical cases. We estimated gestational age by B-mode ultrasound if the date of LMP couldn't be obtained. We didn't exclude any specific gestational weeks from our studied population. Labour and delivery outcomes were extracted from birth records. Nude birthweight was measured for each infant within one hour after birth by trained nurses using standardized procedures. We defined small-for-gestational age (SGA) as a birthweight lower than the 10th percentile of our population for a given gestational age and sex.[6] On the other hand, we defined appropriate for gestational age (AGA) as a birthweight equal to or higher than the 10th centile for gestational age.

Assessment of Covariates

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

≥18.50; GWG below IOM recommendations or not below).

Assessment of Socio-economic Status

SES index was measured by a combination of the education and occupation categories. The scores of education and occupation are listed in Supplementary table 1 and Supplementary table 2.[21] SES index was measured based on the formula, SES= ((0.7 * maternal education) + (0.4 * maternal occupation) + (0.7 * paternal education) + (0.4* paternal occupation))/2.[22] Finally, the SES index categorization demonstrates that below one third of the study population distribution had low SES and the remainder had high SES.[23]

Statistical Analysis

Firstly, data were described as mean ± SD for continuous variables or as percentage for categorical variables. Differences between SGA and AGA were compared using the Student's t-test for continuous variables and chi-square test for categorical variables. Pearson's correlation was carried out between studied variables. Univariate logistic regression analysis was used to assess the risk of having a SGA newborn among primiparae from low SES. Multivariate logistic regressions were used to explore the risk after adjustment for potential confounders. We selected the list of potential confounders according to two reasons as following. Firstly, variables, such as maternal age, pre-pregnancy BMI, gestational weight gain (GWG) and a multi-vitamin supplement during the first trimester of pregnancy, were significant

different between two groups according to the results of single factor analysis. Secondly, other confounders (sleep quality in the month before the birth, physical activity during last trimester and passive smoking during pregnancy) were all the lifestyles of pregnancy women. As these lifestyles associated with infants' birth weight were repeatedly reported by literatures, we added them in model 2 although they were not significant. Basing on model 2, we brought in PIH as another confounder in model 3. PIH was an obvious risk factor according to the literature review where women with PIH had twice the risk of having a SGA, compared with women having no PIH.[7]

Secondly, we used the pathway analysis to explore the hypothesized underlying relations between variables of interested. The model was evaluated using the following goodness-of-fit: the comparative-fit index (CFI)>0.95, the root-mean-square error of approximation (RMSEA)<0.05. Modification indices were used to detect misspecifications in the model. Estimation was carried out by a robust weighted least-squares estimator (WLSMV). Because most of our variables were categorical variables, WLSMV was one of the best methods for analysing our data set. Effect sizes of the predictors on the outcome variables were expressed as unstandardized estimates (B) and standardized estimates (ß). Indirect effect was defined as the effect of the exposure that acted through a given set of mediators of interest. Direct effect was refer to the effect of the exposure unexplained by those same mediators.[24] The total effects of the predictors on the outcomes were computed by adding the indirect and direct effects together.[25] Decoding of each response for

further analysis was present in table 1. All of the analyses were conducted with R 3.2.2. All *P* values reported were two-sided and 0.05 was used as significance level.

Patient Involvement

No patients were involved in setting the research question or the outcome measures, nor were they involved in developing plans for recruitment, design, or implementation of the study. No patients were asked to advise on interpretation or writing up of results. There are no plans to disseminate the results of the research to study participants or the relevant patient community.

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.

RESULTS

Study Population

A total of 8737 primiparae met our criterion and they finally included in our study. The mean maternal age was 27.70 ± 3.24 years. The range of gestational age was 28-42 weeks. In total, 927 (10.61%) infants were diagnosed with SGA. There were 4499 boys and 4238 girls with a boy-to-girl ratio of 1.06.

Characteristics of the Sample

The basic demographic characteristics among SGA are presented in table 2. Mean maternal age was younger, mean pre-pregnancy BMI was lower and gestational weight gain below IOM recommendations was more likely with women who had SGA infants. Compared with women with AGA infants, women with SGA infants were more likely to have PIH and came from low SES. Women with AGA infants tended to be more positive regarding taking a multi-vitamin supplement during the first trimester of pregnancy. Correlations of the variables are presented in Supplementary table 3.

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

Variables	N(%) or Mean ±SD	SGA	AGA	*P*
		N(%) or Mean ±SD	N(%) or Mean ±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
≥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±3.24	27.32±3.50	27.75±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.

Associations between SES and SGA

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

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

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

SGA	SES	OR	95%CI	*P*
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.

Mediation Model for SGA

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

(B=-0.067, 95% CI=-0.108, -0.026) via PIH (B=-0.029, *P*=0.021), a multi-vitamin supplement (B=-0.021, *P*=0.010), pre-pregnancy BMI≥18.5 (B=-0.009, *P*=0.010) and pre-pregnancy BMI≥18.5 to GWG not below IOM recommendations (B=-0.003, *P*=0.007).

In our model, the indirect effect came from the coefficient "a" multiplying by coefficient "b". For example, woman with high SES had more chance of taking a multi-vitamin supplement (B=0.317, *P*<0.001). Then, a multi-vitamin supplement taking decreased the SGA (B=-0.066, *P*<0.05). Thus, the indirect effect of SES to SGA was 0.317*-0.066=-0.021 through taking a multi-vitamin supplement.

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	ß
	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.

DISCUSSION

The findings of our study indicated that high SES was related to a reduced risk of SGA after adjustment for potential confounders. In the pathway analysis, PIH, taking a multi-vitamin supplement during early pregnancy, keeping normal pre-pregnancy BMI and gaining reasonable gestational weight were all the significant mediators which completely mediated the relationship between SES and SGA. There were four pathways between SES and SGA as following. ① High SES of pregnancy women predicted lower risk of PIH. The risk of SGA was reduced by no-PIH. ② Women from high SES had more chance to take a multi-vitamin supplement during early pregnancy. A multi-vitamin supplement could lead to a lower risk of SGA infants. ③ Women from high SES were more likely to be pre-pregnancy BMI ≥18.50kg/cm2. Furthermore, pre-pregnancy BMI ≥18.50kg/cm2 decreased the risk of SGA infants afterwards. ④ Women from high SES predicted pre-pregnancy BMI ≥18.50kg/cm2. Pregnancy women with pre-pregnancy BMI ≥ 18.50kg/cm2 could gain adequate gestational weight which was not below IOM recommendations. And the GWG not below IOM recommendations decreased the risk of SGA infants.

One of the strengths of our study was the large sample size. In addition, face-to-face interviews, medical records and measurements provided rich covariate data, which allowed us to adjust for potential confounders for SGA. Thirdly, SES index was combined with parental education and occupation. This index was more representative and reasonable to represent SES compared with using only education or

occupation in China. We acknowledge that there were also some limitations. Firstly, information on education and occupation was obtained using face-to-face questionnaires, which might have bias. Occupation can fluctuate over time, and it is more likely to lead to misclassification. Secondly, although we carefully adjusted for several potential confounders for SGA, we were unlikely to fully rule out the possibility of residual confounding by other unmeasured factors such as parents' history of SGA, maternal stress during pregnancy. Thirdly, some of our variables including a micronutrient supplement, physical activity and sleep quality during pregnancy relied on self-reporting, which were subjective.

Predictably, high SES was a protector of SGA in our study. A large population-based study from Finland reported that SES determined by women's occupation was inversely associated with the risk of SGA.[12] A birth cohort study conducted in France reported that low SES determined by neighbourhood deprivation may affect foetal growth, especially in rural areas.[26] These two studies were consistent with our results. However, Clayborne et al. did not find a direct association between SES measured by neighborhood deprivation and the risk of SGA in Canada.[27] Because of the different measures of SES, these studies may not be easily compared. The underlying mechanisms responsible for increased risk of SGA among primiparae with low SES remain speculative. In our study, we found that some mediators could completely mediate SES and SGA.

In the pathway analysis, we observed that PIH was a mediator between SES and SGA. We demonstrated that SES was associated with PIH among primiparae. A

meta-analysis including 51 studies found that low SES was associated with higher blood pressure. This association was particularly evident in the level of education.[28] Adherence to knowledge of hypertension and more social resources to maintain healthy behaviours could explain why SES likely affects PIH among pregnant women. The rate of SGA infants from the PIH group was significantly higher compared with the no PIH group in our study. PIH is associated with a reduction in placental perfusion, which influences the size of the placenta.[29] In SGA infants, the size of the placental disc was smaller and the birthweight was lighter.[30] Placenta is an important organ for foetus and supplies all the nutrients needed for foetal development. The pathology of placental was potentially causing or contributing to SGA and hypertension was one of the factors in aetiology.[31] The growth and development of the placenta being influenced by PIH may be suggested an explanation for lower birthweight.[30]

Taking a multi-vitamin supplement during the first trimester of pregnancy was another mediator between SES and SGA. Women with low SES defined by family income had less chance to obtain optimal nutrient supplements in a meta-analysis including 12 randomized controlled trials.[32] A double-blind cluster randomized controlled trial in rural China reported birthweight was 42 g higher in the multiple micronutrients group compared with the folic acid group.[33] Another birth cohort from Denmark reported that regular periconceptional multi-vitamins use was associated with a reduced risk of SGA births.[34] A multi-vitamin supplement during early pregnancy might reduce the risk of alcohol use in relation to SGA.[35] This result

evidenced that a multi-vitamin supplement during early pregnancy was a protector factor for SGA, which was similar to our study. Multi-vitamins are important for human physical function and they play vital roles in numerous metabolic processes and physiological functions in the human body. A multi-vitamin supplement during pregnancy reduced the risk of pregnancy complications, involving oxidative stress and pre-eclampsia. Pre-eclampsia could decrease blood to the placenta, which causes growth retardation.[36] In China, most people believe that they should obtain vitamins from daily diet, i.e. fresh vegetables and fruits, which is a natural way instead of taking multi-vitamin supplements every day. Pregnant women are recommended to take multi-vitamin supplements, since they are unable to obtain an adequate nutrient status from their diet alone. Most pregnant women take folic acid, because the government provides folic acid free of charge. For the multi-vitamin supplements, pregnant women decide to take them or not depending on their own opinions. The different dietary habits and customs might explain part of why taking multi-vitamin supplements is significant. Our results showed that high SES was significantly related to a daily supplement of multi-vitamin. As our large-scale studied population came from the city of Wuhan, the results of our study could extend to pregnancy women in Hubei province, which included 12 cities. However, extrapolation of our findings to Chinese women should be cautious. Multicenter cohort studies from different cities of China will be needed in further studies.

Pre-pregnancy underweight and pre-pregnancy underweight to GWG below IOM recommendations were the two pathways between SES and SGA. The chances of

having a SGA infant was significantly higher among underweight women compared to normal pre-pregnancy BMI in our study, which was consistent with a study in Lebanon. As Lebanon is a developing country in Asia, and its people are similar to Chinese people, we deemed these results could support our findings. Smoking, poor diet, and medical illness like anaemia which are risk factors for SGA among underweight women, occurred more often. Deficiency of maternal plasma volume among underweight women has been suggested as a cause of SGA.[37] In our study, underweight women were more likely to have insufficient weight gain during pregnancy and below normal weight gain significantly increased the odds of SGA. As expected, GWG below IOM recommendations in women with pre-pregnancy underweight was reportedly more likely to affect the birthweight of their neonates.[38] Poor nutrition or unhealthy psychological state among pregnant women with GWG below IOM recommendations may explain causes of SGA.

CONCLUSION

We demonstrated that SES was inversely associated with SGA after adjustment for potential confounders among primiparae. In this population, we also found that mediators could completely mediate SES and SGA. Monitoring of blood pressure, avoiding pre-pregnancy underweight, keeping sufficient GWG during pregnancy and taking a multi-vitamin supplement during the first trimester of pregnancy are practical and feasible measurements to reduce the risk of SGA. As we all know, SGA is a public health issue and SES disparities are difficult to change over a short time. It had

great sense to maintain normal blood pressure and keep a healthy lifestyle to reduce cases of SGA infants among primiparae, especially for women of child-bearing age who have a low SES. A future research direction should focus on identifying interventions to successfully reduce socio-economic disparities in SGA.

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Competing interests None declared.

Patient consent Obtained.

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Data sharing statement No additional data is available.

Figure legends

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

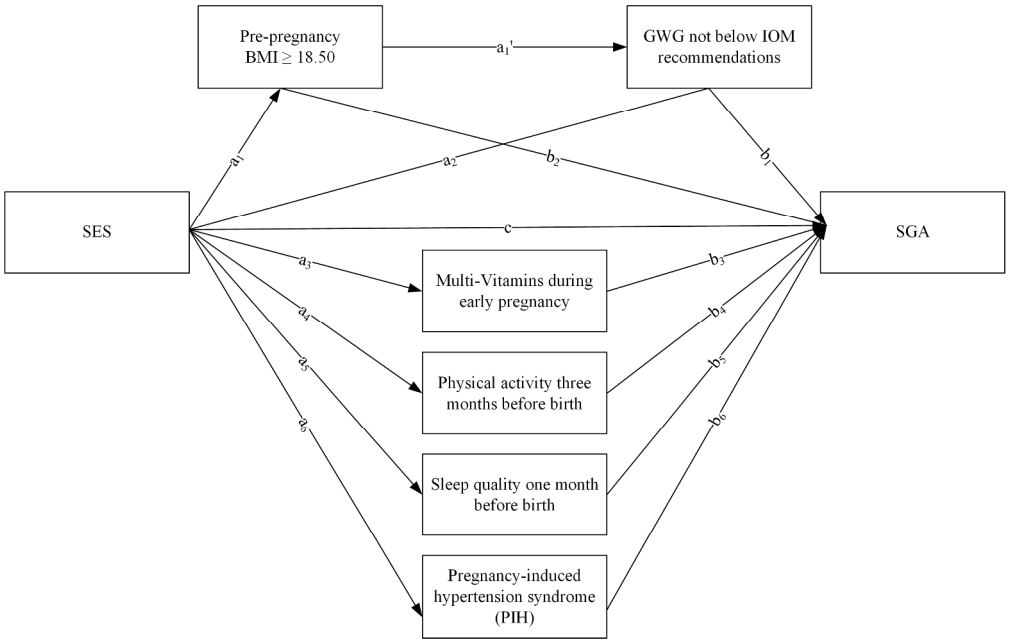

Figure 1. Serial mediation models of the indirect associations socioeconomic status (SES) and small-for-gestational age (SGA). Unstandardized regression coefficients are a1, a1', a2, a3, a4, a5, a6, b1, b2, b3, b4, b5, b6, c. Adjusted for maternal age and passive smoking during pregnancy.

245x155mm (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	Ⅳ	46
Agriculture and forestry	Ⅴ	34
Laborer	Ⅵ	42
Soldier	Ⅶ	53
Others	Ⅷ	49

Supplementary table 3.Correlation matric 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
Introduction			
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
Methods			
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*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	6
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
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*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	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) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	11
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	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
Discussion			
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
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	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.