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Mediating Factors between Parental Socioeconomic Status and Small for Gestational Age in Infants: Results from the Hokkaido Study on Environment and Children's Health

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Abstract

Objectives: Previous studies indicated a significant association between small for gestational age (SGA) in infants and their parents' socioeconomic status (SES). Thus, this study aimed to examine if parental factors, such as maternal smoking, and the pre-pregnancy body mass index (BMI) could mediate the associations between parental SES and SGA.

Methods: The participants of this study were pregnant women who enrolled in an ongoing birth cohort study, the Hokkaido study, during the first trimester of their pregnancies. A total of 14,593 live singleton births were included in the statistical analysis, of which 1,011 (6.9%) were SGA. Two structural equation models were employed to evaluate the associations between parental SES, parental characteristics, and SGA.

Results: The effect of low SES on SGA was directly mediated by maternal pre-pregnancy BMI, smoking during the third trimester, and alcohol consumption during the first trimester in the first model, which was based the assumption of independent associations between mediating factors. In the second model, which additionally considered the mediating factors from the first model, smoking during pregnancy mediated decline in parental SES, consequently increased SGA.” Moreover, an

increase in pregnancy smoking status increased the prevalence of lower maternal pre-pregnancy BMI and its effect on SGA.

Conclusions for Practice: In this study, we observed the independent mediating effect of maternal pre-pregnancy BMI, smoking, and alcohol consumption during pregnancy on low SES and, consequently, SGA, with the additional mediating pathway of SES to smoking to low BMI on SGA.

Significance

What is already known on this subject?

Studies on the risk factors for small for gestational age (SGA) suggested that parental socioeconomic status (SES) is indirectly associated with SGA. However, the mediators and the gravity of their effect are unclear.

What this study adds

By using structural equation models, we observed that the maternal pre-pregnancy BMI, smoking during the third trimester, and alcohol consumption during the first trimester were significant mediators of the effect of parental SES on SGA. Parental SES may affect SGA through the pathway of maternal smoking to that result in low BMI.

Keywords: Birth cohort study, Parental tobacco smoking, Small for gestational age, Socioeconomic status, Structure equation modeling

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Introduction

Small for gestational age (SGA) is defined as being smaller than the fetal reference size at a particular gestational age (Itabashi et al. 2014). SGA is associated with an increased risk of childhood death beyond the neonatal period (Ludvigsson et al. 2018). SGA has severe health impacts, including neurological, metabolic, and cardiovascular morbidities, not only during the neonatal period and infancy but also throughout life (Barker 1995; Bonamy et al. 2008). Hence, the need to examine the risk factors of SGA based on the Developmental Origins of Health and Disease (Gluckman and Hanson 2004). Despite being an advanced developed country, the low birth weight rate of Japan increased from 5.2% in 1980 to 9.5% in 2014 and has remained at this level since then (Mother's & Children's Health Welfare Association 2016).

Parental socioeconomic status (SES), such as parental educational level and household income, was reported as a risk factor for SGA (Fujiwara, et al. 2013; Mortensen 2013; Shah and Knowledge Synthesis Group on Determinants of LBW/PT births 2010; Tsukamoto et al. 2007). In a previous study, we examined parental characteristics as risk factors for preterm births, very low birth weight (VLBW), and term-SGA. Parental age and using reproductive medicine were associated with preterm births and VLBW. Maternal alcohol consumption during the first trimester of pregnancy and parental educational levels have been identified as risk factors for term-SGA (Tamura et al. 2018). Moreover, Tamura et al. (2018) reported that among mothers with a low educational level, a low BMI was a risk factor of term-SGA. Therefore, in contrast to Preterm births and VLBW, term-SGA would have been more affected by parental SES and behaviors.

Although the association between parental socioeconomic characteristics and SGA in infants has been elucidated (Blumenshine et al. 2010), SES is likely to affect SGA through mediating factors. Sheehan (1998) reported psychosocial stressors in a full structural equation model to show their influence on addictive behavior and low birth weight. Therefore, we assumed that explanatory variables treated as independent in this previous analysis might have mutually linked associations.

This study aimed to examine if parental risk factors such as parental age, maternal pre-pregnancy BMI, smoking, and alcohol consumption mediate the association between parental socioeconomic characteristics and SGA.

Methods

Participants

The Hokkaido Study on Environment and Children's Health is an ongoing birth cohort that was initiated in 2002. Details of the study have been described previously

(Kishi et al. 2011, 2013, 2017). Briefly, between February 2003 and March 2012, the Hokkaido cohort enrolled women during the first trimester of pregnancy (13 weeks of gestational age) who visited one of the delivery units of the 37 participating hospitals and clinics covering the entire Hokkaido prefecture for prenatal health.

The original cohort included 20,926 pregnant women; however, 1,347 were lost to follow-up before giving birth (Figure 1). Participants with no information to determine SGA (birth weight, gestational age, infant sex, maternal parity), parental education, or annual household income were excluded (n = 4,084). We further excluded women who experienced miscarriages, stillbirths, or multiple births and those with pregnancy-induced hypertension or gestational diabetes (n = 902). Thus, we eliminated the pathological causes of SGA, which could have masked and underestimated the risk factors of parental characteristics. A total of 14,593 participants were included in the final analysis.

[Insert Figure 1 here]

Baseline Questionnaire and Biochemical Analysis

Upon entry into the study, the participants completed a self-administered questionnaire including questions on the following parental characteristics: maternal age at study entry (<35, ≥35 years) (Heffner. 2004), paternal age at study entry (<40, ≥40 years) (Isabelle Bray, et al. 2006). In addition,, maternal BMI before pregnancy (<18.5, ≥18.5 kg/m^2) (WHO Expert Consultation. 2004); parental medical history; maternal regular use of any medications; maternal regular use of any supplement(s); paternal smoking during the first trimester; parental alcohol consumption during the first trimester; and use of any assisted reproductive technologies (ART).

Paternal and maternal educational levels (≤9, 10-12, 13-15, >16 years) and annual household income (<3.0, 3.0-4.9, 5.0-7.9, ≥8.0 million yen) were also obtained from the questionnaire as socioeconomic indicators, it was shown that both are important in young adulthood (Galobardes et al. 2006). In Japan, compulsory education ranges from Grade 1 to 9, then, most children go on to high school for 3 years, and after that to universities and graduate school. Therefore, we classified the cutoffs for parental educational level as ≤9, 10-12, 13-15, >16 years, with ≤9 years defined as the highest-risk group. There was no official definition of a low annual household income in Japan. In this study, we defined a couple with one child and an annual household income of <3.0 million yen as a low annual household income (Kobayashi and Nishikawa 2010). Annual household income was classified as <3.0, 3.0-4.9, 5.0-7.9, ≥8.0 million yen, with the <3.0 million yen group defined as the highest-risk group.

Maternal smoking status was classified into 3 categories based on plasma cotinine levels measured in maternal blood samples that were collected during the third trimester, as follows: never smoked (≤0.21 ng/mL), passive smoking (0.22–11.47 ng/mL), and active smoking (≥11.48 ng/mL) (Sasaki et al. 2011).

Definition of Small for Gestational Age

SGA was defined as a birth weight below the 10th percentile of the reference birth weight according to gestational age, sex, and parity in live birth infants. We used the database for birth weight published by the Japan Pediatric Society as a reference (Itabashi et al. 2014).

Ethics Statement

All participating women provided written informed consent before participation in the Hokkaido study. The ethics review board for epidemiological studies of the Hokkaido University Graduate School of Medicine (March 31, 2003) and the Hokkaido University Center for Environmental and Health Sciences (reference no.14, March 22, 2012) approved the study protocol. The study was conducted following the principles of the Declaration of Helsinki.

Data Analysis

Parental socioeconomic characteristics are presented as frequencies and percentages. The relative risks (RRs) of SGA by parental characteristics were estimated using multiple generalized linear models (GLM: distribution; binominal, link function, logarithm).

To identify the relative contribution of potential mediators, the total effect of the parental SES on infant SGA was classified into the natural direct effect (effect unexplained by mediators). Whereas, the indirect effects via maternal and paternal age at study entry, maternal BMI before pregnancy, parental medical history, regular use of any medications and supplement(s), maternal smoking status based on plasma cotinine levels at third trimester, paternal smoking during the first trimester, parental alcohol consumption during the first trimester, and use of any ART.

The SES assumed a non-observed variable based on parental educational levels and annual household income. To investigate the factors mediating the effect of SES on SGA, we used structure equation modeling (SEM) (Oshio 2011; Toyoda 1998, 2007). We included the parental characteristics that showed an association with SGA ($p < 0.10$) as mediating factors in the GLM analysis. In the SEM analysis, we employed two models. Model 1 was based on the assumption of independent associations between mediating factors, whereas Model 2 assumed dependent associations between mediating factors ($p < 0.05$). In Model 1, the indirect effect of SES on SGA is multiplied by the mediating factors of the low SES, and the factor of the arrow extending from the mediating factor to SGA was calculated. In Model 2, arrows were added when associations between intermediary factors of the Directed Acyclic Graph were assumed (Tamura et al. 2018). The observed variables were computed with the residual term but were omitted from the Figures. The model fitness was evaluated with the Chi-square test value, goodness of fit index (GFI), adjusted goodness of fit index (AGFI), comparative fit index (CFI), and root mean square error of approximation (RMSEA). We then analyzed the fitness indices of Model 1 and 2. Generally, the predicted and measured Chi-square test values have a $p > 0.05$; the p-value is closer to 1 when the GFI, AGFI, and CFI are ≥ 0.90; the smaller the RMSEA value, the better the model conforms.

We used the JMP Clinical 5 statistical software (SAS Institute Inc., NC, USA) and Amos 22 (IBM. SPSS, NC, USA) for the statistical analyses.

Results

Table 1 shows maternal, paternal, and parental socioeconomic characteristics, while Table 2 depicts the infants' birth outcomes. The mean gestational age of the neonates was 274.2 days (standard deviation [SD]: 10.5 days), and their mean birth weight was 3,039.9 g (SD: 413.1 g). Male infants comprised 50.3% of the total sample (n = 7,340). The proportion of infants who were SGA was 6.9% (n = 1,011). The mean birth weight and gestational age observed in this study were comparable to SGA data obtained from recent vital statistics in Japan (Mother's & Children's Health Welfare Association 2016).

[Insert Table 1 here]

[Insert Table 2 here]

When we analyzed the association between SGA and parental characteristics, we found that the maternal pre-pregnancy BMI, smoking status during the third trimester, alcohol consumption during the first trimester, supplement intake during the first trimester, and regular medication intake during the first trimester were significantly associated with increasing RRs of SGA ($p < 0.10$; Table 3). The result of analysis for the association between SGA and parental socioeconomic status shows that the RR of being born SGA was significantly lower in infants whose mothers had >16 years (vs. ≤9 years) of education (RR = 0.69; 95% CI: 0.50–0.96).

[Insert Table 3 here]

The results of the SEM analysis (Model 1) are shown in Figure 2. The numbers on the arrows show the standardized regression weights, the β values. Solid line arrows indicate a $p < 0.05$, whereas dotted line arrows indicate a $p \geq 0.05$. The analysis of SEM of independent mediators identified the maternal pre-pregnancy BMI, maternal smoking status during the third trimester, alcohol consumption during the first trimester, and supplement intake during the first trimester as mediating factors. In the analysis of covariance using Model 1, we found a significant association on these arrows for both the SES and mediating factor and the effect on SGA from the mediating factor. The maximum factor showing a direct effect on SGA in this model was the maternal pre-pregnancy BMI, with a normalized β of 0.071. The indirect effects of the mediators in Model 1 were maternal smoking status during the third trimester, pre-pregnancy BMI, alcohol consumption during the first trimester, and supplement intake during pregnancy.

Among these, maternal smoking status during the third trimester suggested the largest indirect effect on SGA, with a standardized β of 0.018 (0.428*0.042); the second largest indirect effect was maternal pre-pregnancy BMI, with a standardized β of 0.002 (0.028*0.071). For Model 1, the goodness of fit testing revealed a Chi-square test value of 158.509 (<0.01), GFI: 0.997, AGFI: 0.994, CFI: 0.976, and RMSEA: 0.024. Except for the Chi-squared test value, all values were within the applicable ranges.

[Insert Figure 2 here]

We then added arrows of associations between the mediating factors to Model 1; the results of the analysis of Model 2 are shown in Figure 3. Referring to the DAG model in Tamura et al. (2018), the arrows between the mediating factors were derived from the pregnancy cotinine values to the maternal pre-pregnancy BMI and from alcohol consumption during the first trimester of pregnancy to maternal pre-pregnancy BMI; these three additional arrows were added in Model 2 from Model 1. For a decline in the socioeconomic status, no significant association of the maternal pre-pregnancy BMI was seen. However, a decline in parental socioeconomic status increased never to passive smoking during pregnancy; moreover, an increase in pregnancy smoking status increased prevalence of lower maternal pre-pregnancy BMI; and the effect of a decrease of maternal pre-pregnancy BMI on the increase in SGA. The mediating effects of maternal alcohol consumption from SES to SGA were independent of the path to maternal BMI. The goodness of fit indices for Model 2 included a Chi-square test value of 116.181 (<0.01), GFI: 0.998, AGFI: 0.994, CFI: 0.983 and RMSEA: 0.022; except for the Chi-square test value that showed good fitness.

[Insert Figure 3 here]

The fitness indices of the two models were evaluated using the Chi-square test value, GFI, AGFI, CFI, and RMSEA (Amorim et al. 2010). Among these values, only the Chi-square test values were outside the applicable range. The low Chi-square test value was related to the explanatory power of the model. We speculated that the SES was out of the range of conformity due to the high Chi-square test value of determining SGA. The sample size of this study was too large for performing a covariance structure analysis (Wolf et al. 2013). In such an analysis, the fitness of the model must be comprehensively evaluated based on several indicators (Oshio 2011).

Discussion

In this study, we described the mediating factors between parental SES and SGA. We observed that the maternal pre-pregnancy BMI, smoking during the third trimester, and alcohol consumption during the first trimester were mediators of the effect of low SES on SGA in SEM analysis, which assumed independent associations between the mediating factors (Model 1). In SEM analysis, which assumed dependent associations between the mediating factors (Model 2), considering the associations between mediating factors from Model 1, a decline in parental SES increased the effect of smoking during pregnancy on increase in SGA. In addition, an increase in pregnancy smoking status increased the effect of the decrease in the maternal pre-pregnancy BMI on the increase in SGA

We identified the association between SES and SGA was mediated by the maternal pre-pregnancy BMI and smoking status during the third trimester in SEM analysis, which assumed independent associations between the mediating factors. Van Den Berg and colleagues reported the factors, breastfeeding duration, maternal smoking during pregnancy, and pre-pregnancy BMI mediated the association between maternal education and weight gain during the first year of an infant’s life (Van Den Berg et al. 2013); the same associations were seen in this study. The outcomes used by Van Den

Berg et al. (2013) were different from SGA, however, their results agreed with our study.

When SEM analysis was assumed, dependent associations between mediating factors (Figure 3), a low SES increased the effect of smoking during pregnancy on increase in SGA. A previous review paper similarly reported that the prevalence of smoking was higher among pregnant women with a low household income, education below the university level, and those who have not recently had a job in Australia, Iceland, USA, Scotland, and Finland (Boucher and Konkle 2016). An earlier study using data from the same Hokkaido study cohort pointed out that smoking during pregnancy may reduce the gestational age and birth weight of the fetus, which is consistent with the results of this present study (Kobayashi et al. 2019). The maternal smoking status during the third trimester of pregnancy could mediate the effect of the parental SES on SGA, with a large indirect effect of the SES on SGA. In addition to the direct path of smoking from low SES to SGA, we found an additional path of low SES (which is to increase smoking during pregnancy and low maternal pre-pregnancy BMI) on the increase in SGA. Travier et al. (2009) reported in a meta-analysis of European cohorts that current female smokers had a significantly lower BMI than never smokers (Travier et al., 2009). Thus, finding of this additional path is reasonable.

On the other hand, the significant effect of the SES on the maternal pre-pregnancy BMI, as seen in Model 1, which assumed independent associations between mediating factors, disappeared in Model 2 that assumed dependent associations between mediating factors. A low BMI could have been widespread among young Japanese women, irrespective of their SES. A previous paper reported that Japanese women are obsessed with a slender figure, which may harm unborn children and create long-term health problems in the Japanese population (Itoh et al. 2018, Normile 2018). A survey of 1,681 pregnant women showed that 54% reported that their ideal gestational weight gain was below the recommendations 12.0kg (Ogawa et al. 2018). Further studies are needed to uncover the associations between SES, maternal BMI, and SGA among infants in Japan.

In Japan, the relative child poverty rate defined as the proportion of household with child(ren) with a net income below a defined threshold was 16.3% in 2012, and 13.9% in 2015 (Ministry of Health, Labor and Welfare 2016). Although there has been a reduction in the child poverty rate in Japan, it remains lower than the Organization for Economic Co-operation and Development average (Thévenon et al. 2018). The Japanese government started implementing a free education system in public senior high schools from 2010. However, the participants of this study were not supported by the free education system in public senior high schools, because they were recruited from 2003 to 2012. Therefore, some high school students cannot continue school because of high tuition fees. In this study, it has been shown that parental SES may indirectly affect children's health. Tamura et al. (2018) reported the RR of being born term-SGA was significantly lower in infants whose mothers and fathers had >16 years vs. 10–12 years of education (RR = 0.76; 95% CI, 0.61–0.94) and (RR = 0.86; 95% CI, 0.75–1.00) respectively. Further policy interventions are needed to open up access to higher education so that children can receive equal education to reduce gaps. Furthermore, interventions such as school education for health and disease, and improving food intake for younger generations would be required.

We excluded women who had pregnancy-induced hypertension and gestational diabetes; thus, target participants of this study are those in pregnancies uncomplicated by these conditions. Pregnancy-induced hypertension and gestational diabetes have already been reported to have a decreased or increased effect on gestational age and birth weight (Tairaku et al. 2012, Heude et al. 2012). These pathological factors could mask and underestimate the effect of parental socioeconomic status associated with SGA. By excluding mothers with hypertension and gestational diabetes, we could determine the impact of parental characteristics as a risk factor for SGA without pathological basis. On the other hand, there was a report about association of socioeconomic status and maternal hypertension with the gestational age (Brink et al. 2020). We think more studies focusing on the effect of parental socioeconomic status to SGA through pregnancy-induced hypertension and gestational diabetes are needed.

Strength and Limitations

The main strength of this research is that we conducted a prospective birth cohort analysis of the general population of Japanese women participating in a Hokkaido prefectural-wide prospective cohort study (Hanaoka et al. 2017). In this birth cohort study, only 6.4% of participants were lost to follow-up. Therefore, the effect of bias due to dropout was likely reduced.

This study has three main limitations. First, we excluded women with missing data on parental educational levels and annual household income, both of which were used to assess the participants' SES. Tamura et al. (2018) reported that in their study, 4.4% of data on maternal education level, 5.8% of data on paternal education level, and 17.9% of data on annual household income were missing. Moreover, because the questionnaire was self-administered, the participants might have avoided some specific answers due to privacy concerns (Hulley et al. 2014; Streiner et al. 2016). The group analyzed could potentially be based on biased sampling as participants with a low SES were excluded from the population. The effect of a low SES on SGA may have been underestimated, and our results must be interpreted accordingly. Second, the arrow from maternal smoking status during the third trimester to the pre-pregnancy BMI in Model 2 did not make chronological sense. However, we assumed that pregnant women who never smoked would not start smoking after pregnancy. Therefore, we assumed that maternal smoking status during the third trimester indicates maternal passive or active smoking before pregnancy, making it possible to test if the maternal smoking status during the third trimester affected the maternal pre-pregnancy BMI. Finally, we may not have analyzed all potential confounders. In this study, the parental characteristics that were analyzed were limited to the information collected in the questionnaire. Therefore, the effects of other mediators that were not included in the questionnaire cannot be excluded.

Conclusions

In this study, we observed that the maternal pre-pregnancy BMI, maternal smoking during the third trimester, and maternal alcohol consumption during the first trimester were significant mediators of the effect of a low SES on SGA. We also identified significant pathways showing that 1) a low parental SES increased the effect of smoking during pregnancy; 2) an increase in the smoking status during pregnancy increased the effect of a low maternal pre-pregnancy BMI, and 3) the effect of a decrease in the maternal BMI on the increase in SGA. Further studies are needed to uncover the associations between SES, maternal BMI, and SGA in infants in Japan. This study showed to require that school education for the health effects of tobacco smoking and improving food intake from lower grades.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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Tables

Table 1. Parental characteristics selected from the Hokkaido Study on Environment and Children's Health (n = 14,593)

	N (%) or Mean ± SD		N (%) or Mean ± SD
Maternal characteristics		**Paternal characteristics**	
Age at study entry, years		Age at entry (years old)	
<25	1,512 (10.4)	<25	970 (6.6)
25-34	9,998 (68.5)	25-39	12083 (82.8)
≥35	3,081 (21.1)	≥40	1406 (9.6)
Missing	2 (0.0)	missing	134 (0.9)
Body mass index (kg/m^2) before pregnancy		Smoking	
<18.5	2,467 (16.9)	No	4,303 (29.5)

18.5-25.0	10,390	(	71.2	)	Yes	8,544	(	58.5	)
25.0-29.9	1,162	(	8.0	)	Missing	1,746	(	12.0	)
≥30.0	325	(	2.2	)	Alcohol consumption during first trimester				
Missing	249	(	1.7	)	No	3,983	(	27.3	)
Cotinine level during third trimester					Yes	10,497	(	71.9	)
Never (<0.22 ng/mL)	5,028	(	34.5	)	Missing	113	(	0.8	)
Passive smoking (0.22–11.49 ng/mL)	5,546	(	38.0	)	Medical history				
Active smoking(>11.49 ng/mL)	1,821	(	12.5	)	No	9,610	(	65.9	)
Missing	2,198	(	15.1	)	Yes	4,963	(	34.0	)
Alcohol consumption during first trimester					Missing	20	(	0.1	)
No	12,789	(	87.6	)	**Socioeconomic characteristics**				

Yes	1,730	(11.9)	Maternal education level, years		
Missing	74	(0.5)	≤9	713	(4.9)
Medical history			10-12	6,236	(42.7)
No	8,182	(56.1)	13-15	6,014	(41.2)
Yes	6,351	(43.5)	≥16	1,630	(11.2)
Missing	60	(0.4)	Paternal educational level, years		
Regular use of any medication			≤9	1,108	(7.6)
No	12,952	(88.8)	10-12	6,064	(41.6)
Yes	1,566	(10.7)	13-15	3,446	(23.6)
Missing	75	(0.5)	≥16	3,975	(27.2)
Regular use of any supplement			Annual household income, million yen		
No	9,805	(67.2)	≤3.0	3,312	(22.7)

Yes	4,731 (32.4)		3.0-4.9	6,509 (44.6)
Missing	57 (0.4)		5.0-7.9	3,698 (25.3)
Use of ART			≥8.0	1,074 (7.4)
No	13,918 (95.4)			
Yes	633 (4.3)			
Missing	42 (0.3)			

ART: Assisted Reproductive Technology; SD: standard deviation

Table 2. Characteristics of the infants born into the participate parents

	N (%) or Mean ± SD
Birth weight, g	3,039.9 ± 413.1
Gestational age, days	274.2 ± 10.5
Sex	
Male	7,340 (50.3)
Female	7,253 (49.7)
Number of siblings	
0	5,417 (37.1)
≥1	7,961 (54.6)
Missing	1,215 (8.3)
Small for gestational age	
No	13,582 (93.1)
Yes	1,011 (6.9)

SD: Standard deviation

Table 3. The relative risk of infants being small for gestational age by parental characteristics (n = 14,593)

	SGA		Crude			
	N	%	RR	95% CI		p-value
Maternal characteristics						
Age at study entry, years						
<35	796	6.9		ref		
≥35	215	7.0	1.01	0.87	1.16	0.92
Pre-pregnancy Body mass index (kg/m^2)						
<18.5	269	10.9	**1.79**	**1.57**	**2.05**	**<0.01**
≥18.5	724	6.1		**ref**		
Cotinine level in third trimester						
Never (<0.22 ng/mL)	297	5.9		**ref**		
Passive smoking (0.22–11.49 ng/mL)	358	6.5	1.09	0.94	1.27	0.24
Active smoking(>11.49 ng/mL)	184	10.1	**1.71**	**1.43**	**2.04**	**<0.01**
Alcohol consumption during first trimester						
No	832	6.5		**ref**		
Yes	170	9.8	**1.51**	**1.29**	**1.77**	**<0.01**

Medical history						
No	567	6.9		ref		
Yes	440	6.9	1.00	0.89	1.13	1.00
Regular use of any medication						
No	873	6.7		**ref**		
Yes	132	8.4	**1.25**	**1.05**	**1.49**	**0.02**
Regular use of any supplement						
No	653	6.7		**ref**		
Yes	354	7.5	**1.12**	**0.99**	**1.27**	**0.07**
Use of ART						
No	966	6.9		ref		
Yes	44	7.0	1.00	0.75	1.34	0.99
Paternal characteristics						
Age at study entry, years						
<40	900	6.9		ref		
≥40	100	7.1	1.03	0.85	1.26	0.75
Active smoking during first trimester						
No	288	6.7		ref		
Yes	615	7.2	1.08	0.94	1.23	0.28
Alcohol consumption						

Never	288	7.2		ref		
Current drinker	713	6.8	0.94	0.82	1.07	0.36
Medical history						
No	661	6.9		ref		
Yes	349	7.0	1.02	0.90	1.16	0.73
Socioeconomic characteristics						
Maternal education level, years						
≤9	55	7.7		ref		
10-12	429	6.9	0.89	0.68	1.17	0.41
13-15	429	7.1	0.92	0.71	1.21	0.57
≤16	87	5.3	**0.69**	**0.50**	**0.96**	**0.03**
Paternal education level, years						
≤9	76	6.9		ref		
10-12	426	7.0	1.02	0.81	1.30	0.84
13-15	258	7.5	1.09	0.85	1.40	0.48
≤16	240	6.0	0.88	0.69	1.13	0.32
Household Income, million yen						
<3.0	240	7.2		ref		
3.0-4.9	431	6.6	0.91	0.78	1.06	0.25
5.0-7.9	257	6.9	0.96	0.81	1.14	0.63

≥8.0	72	6.7	0.93	0.72	1.19	0.55

ART: Assisted Reproductive Technology; CI: confidence interval; ref: reference; RR: relative risk; SGA: small for gestational agea

RRs were calculated using generalized linear models.

Figures

Figure 1 top

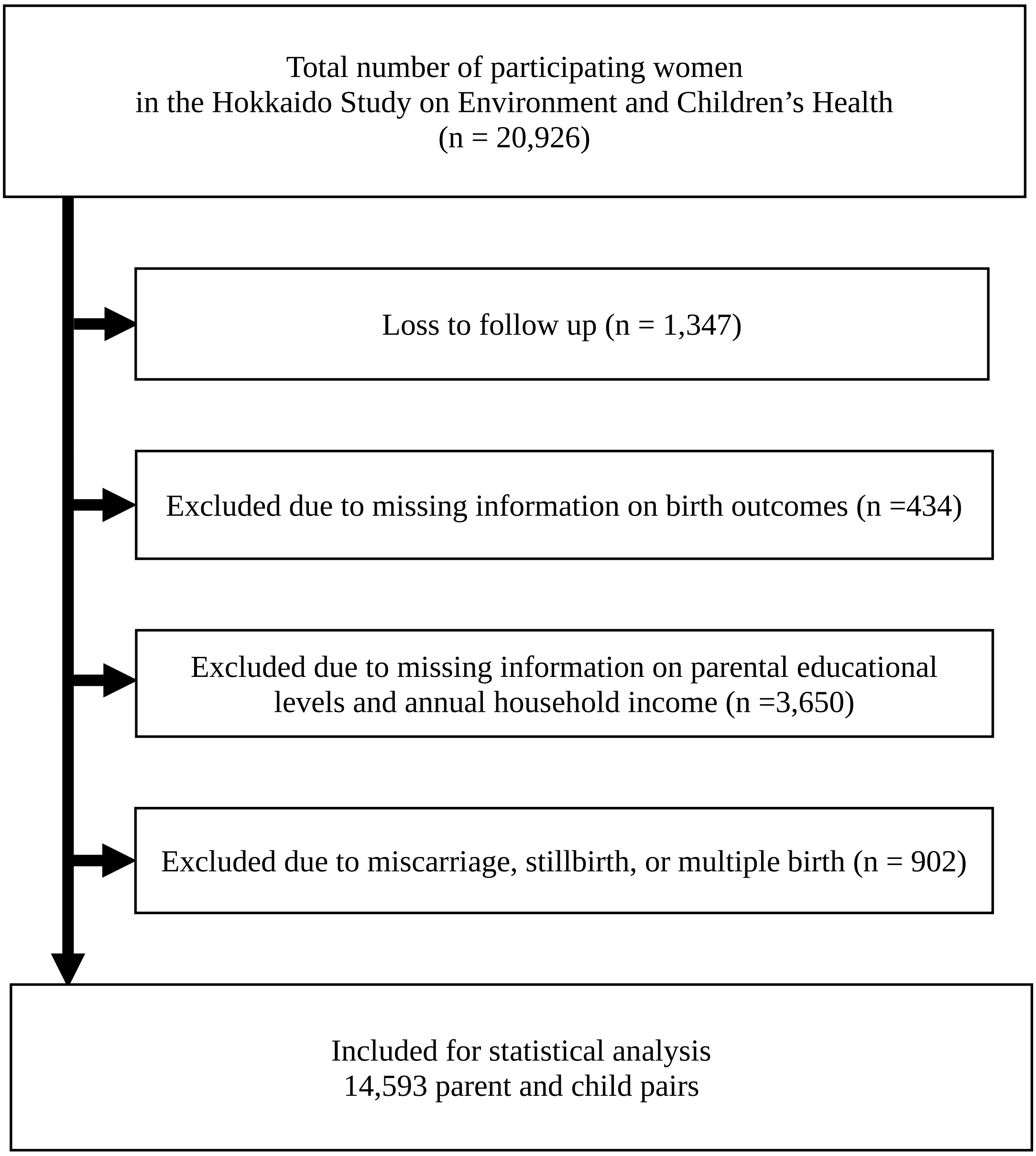
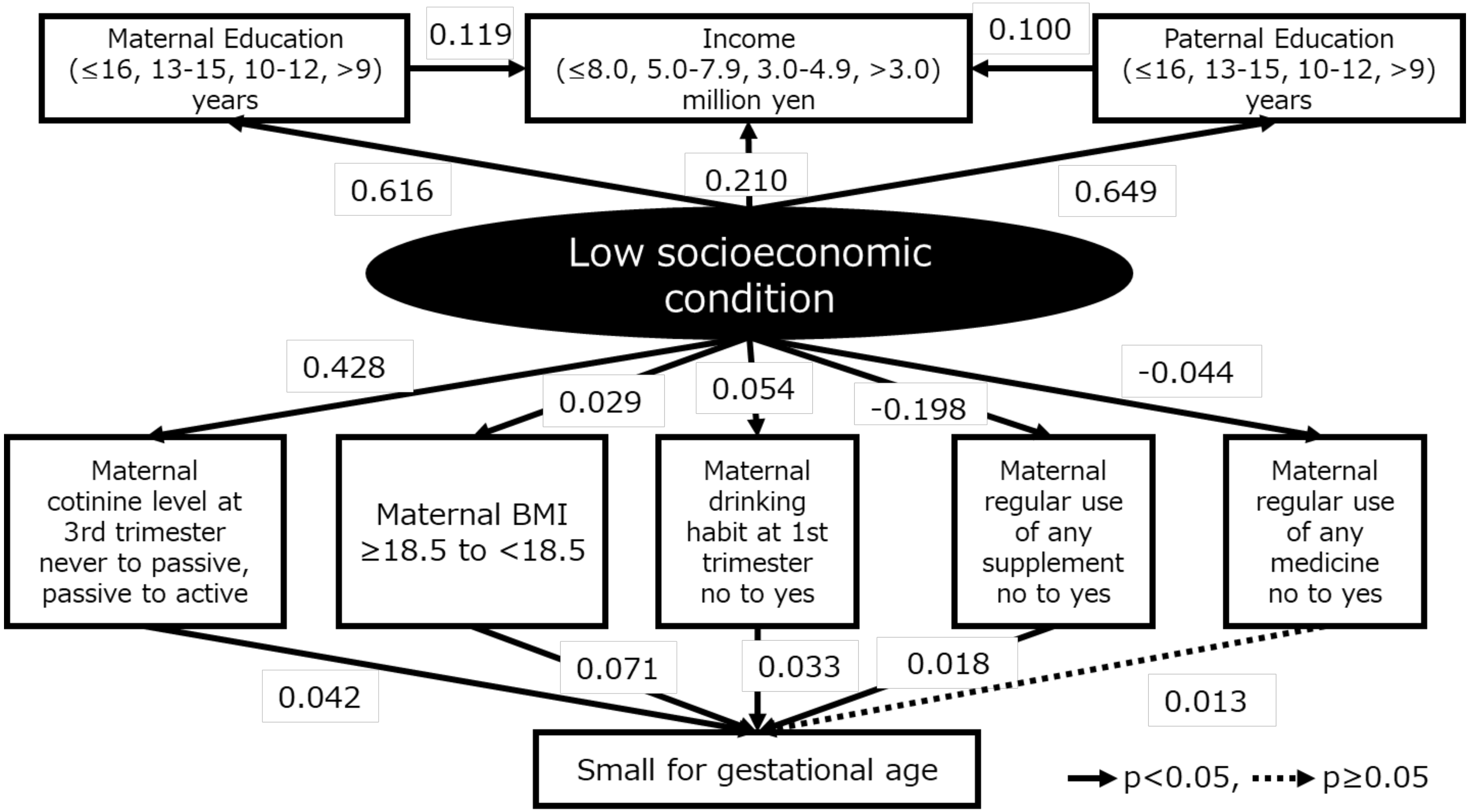


Figure 2 top



Maternal Education
(≤16, 13-15, 10-12, >9)
years
0.119
Income
(≤8.0, 5.0-7.9, 3.0-4.9, >3.0)
million yen
0.100
Paternal Education
(≤16, 13-15, 10-12, >9)
years
0.616
0.210
0.649
Low socioeconomic condition
0.428
0.029
0.054
-0.198
-0.044
Maternal cotinine level at 3rd trimester never to passive, passive to active
Maternal BMI ≥18.5 to <18.5
Maternal drinking habit at 1st trimester no to yes
Maternal regular use of any supplement no to yes
Maternal regular use of any medicine no to yes
0.042
0.071
0.033
0.018
0.013
Small for gestational age
p<0.05, p≥0.05

Figure 3 top

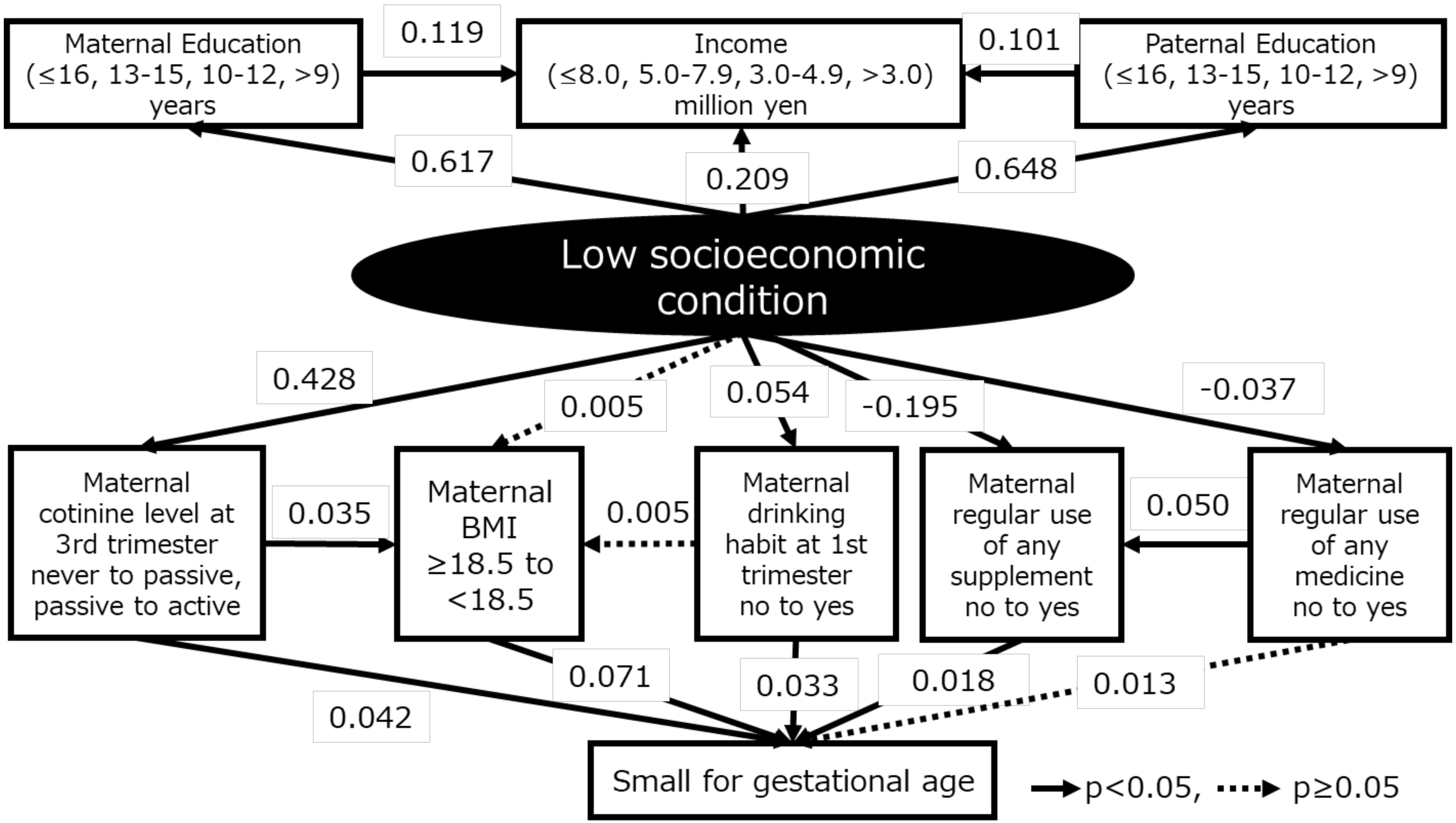

Maternal Education
(≤16, 13-15, 10-12, >9)
years
0.119
Income
(≤8.0, 5.0-7.9, 3.0-4.9, >3.0)
million yen
0.101
Paternal Education
(≤16, 13-15, 10-12, >9)
years
0.617
0.209
0.648
Low socioeconomic condition
0.428
0.005
0.054
-0.195
-0.037
Maternal cotinine level at 3rd trimester never to passive, passive to active
0.035
Maternal BMI ≥18.5 to <18.5
0.005
Maternal drinking habit at 1st trimester no to yes
Maternal regular use of any supplement no to yes
0.050
Maternal regular use of any medicine no to yes
0.071
0.033
0.018
0.013
0.042
Small for gestational age
p<0.05, p≥0.05

Figure Captions

Figure 1. Flow chart of the participants included in the statistical analysis selected from the Hokkaido Study on Environment and Children's Health

Figure 2. Model 1: Structure Equation Modeling between parental socioeconomic characteristics and small for gestational age, independent covariation factors (n = 12,131）

The numbers on the arrows show the standardized regression weights, the β value. Solid line arrows indicate $p < 0.05$, whereas dotted line arrows indicate $p \geq 0.05$

Figure 3. Model 2: Structure Equation Modeling between parental socioeconomic characteristics and small for gestational age, dependent covariation factors (n = 12,131）

The numbers on the arrows show the standardized regression weights, the β value. Solid line arrows indicate $p < 0.05$, whereas dotted line arrows indicate $p \geq 0.05$