



Title	Mediating Factors Between Parental Socioeconomic Status and Small for Gestational Age in Infants : Results from the Hokkaido Study on Environment and Children ' s Health
Author(s)	Tamura, Naomi; Hanaoka, Tomoyuki; Ito, Kumiko; Araki, Atsuko; Miyashita, Chihiro; Ito, Sachiko; Kobayashi, Sumitaka; Ito, Yoichi; Minakami, Hisanori; Cho, Kazutoshi; Endo, Toshiaki; Baba, Tsuyoshi; Sengoku, Kazuo; Miyamoto, Toshinobu; Ogasawara, Katsuhiko; Kishi, Reiko
Citation	Maternal and Child Health Journal, 25(4), 645-655 <a href="https://doi.org/10.1007/s10995-020-03035-w">https://doi.org/10.1007/s10995-020-03035-w</a>
Issue Date	2021-04
Doc URL	<a href="http://hdl.handle.net/2115/84688">http://hdl.handle.net/2115/84688</a>
Rights	This is a post-peer-review, pre-copyedit version of an article published in Maternal and Child Health Journal. The final authenticated version is available online at: <a href="http://dx.doi.org/10.1007/s10995-020-03035-w">http://dx.doi.org/10.1007/s10995-020-03035-w</a>
Type	article (author version)
File Information	mediating_factor_R2_all.pdf



[Instructions for use](#)

1 **Running head:** Mediators between Socioeconomic Status and Small for Gestational

2 Age

3

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

7

8 **Authors' names and affiliations**

9 Naomi Tamura<sup>1,2,3</sup>, Tomoyuki Hanaoka<sup>1</sup>, Kumiko Ito<sup>1,4</sup>, Atsuko Araki<sup>1,2</sup>, Chihiro

10 Miyashita<sup>1</sup>, Sachiko Ito<sup>1</sup>, Sumitaka Kobayashi<sup>1</sup>, Yoichi M. Ito<sup>3</sup>, Hisanori Minakami<sup>5</sup>,

11 Kazutoshi Cho<sup>5</sup>, Toshiaki Endo<sup>6</sup>, Tsuyoshi Baba<sup>6</sup>, Kazuo Sengoku<sup>7</sup>, Toshinobu

12 Miyamoto<sup>7</sup>, Katsuhiko Ogasawara<sup>8</sup>, Reiko Kishi<sup>1</sup>.

13 <sup>1</sup> Hokkaido University Center for Environmental and Health Sciences, Sapporo, Japan

14 <sup>2</sup> Graduate School of Health Science, Hokkaido University, Sapporo, Japan

15 <sup>3</sup> Research Center for Medical and Health Data Science, The Institute of Statistical

16 Mathematics, Tokyo, Japan

17 <sup>4</sup> Graduate School of Medicine, Hokkaido University, Sapporo, Japan

- 18 <sup>5</sup> Departments of Obstetrics and Gynecology, Graduate School of Medicine, Hokkaido  
19 University, Sapporo, Japan
- 20 <sup>6</sup> Departments of Obstetrics and Gynecology, School of Medicine, Sapporo Medical  
21 University, Sapporo, Japan
- 22 <sup>7</sup> Departments of Obstetrics and Gynecology, Asahikawa Medical University,  
23 Asahikawa, Japan
- 24 <sup>8</sup> Faculties of Health Science, Hokkaido University, Sapporo, Japan

25 Abstract

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

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

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

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

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

49

50 **Significance**

51 *What is already known on this subject?*

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

55 *What this study adds*

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

61

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

64

65 **Corresponding author:**

66 Reiko Kishi

67 Postal address: Hokkaido University Center for Environmental and Health Sciences,

68 Kita 12, Nishi 7, Kita-ku, Sapporo, Hokkaido 060-0812, Japan

69 Email: rkishi@med.hokudai.ac.jp

70 Telephone number: +81-11-706-4746

## Introduction

71

72 Small for gestational age (SGA) is defined as being smaller than the fetal  
73 reference size at a particular gestational age (Itabashi et al. 2014). SGA is associated  
74 with an increased risk of childhood death beyond the neonatal period (Ludvigsson et al.  
75 2018). SGA has severe health impacts, including neurological, metabolic, and  
76 cardiovascular morbidities, not only during the neonatal period and infancy but also  
77 throughout life (Barker 1995; Bonamy et al. 2008). Hence, the need to examine the risk  
78 factors of SGA based on the Developmental Origins of Health and Disease (Gluckman  
79 and Hanson 2004). Despite being an advanced developed country, the low birth weight  
80 rate of Japan increased from 5.2% in 1980 to 9.5% in 2014 and has remained at this  
81 level since then (Mother's & Children's Health Welfare Association 2016).

82 Parental socioeconomic status (SES), such as parental educational level and  
83 household income, was reported as a risk factor for SGA (Fujiwara, et al. 2013;  
84 Mortensen 2013; Shah and Knowledge Synthesis Group on Determinants of LBW/PT  
85 births 2010; Tsukamoto et al. 2007). In a previous study, we examined parental  
86 characteristics as risk factors for preterm births, very low birth weight (VLBW), and  
87 term-SGA. Parental age and using reproductive medicine were associated with preterm  
88 births and VLBW. Maternal alcohol consumption during the first trimester of pregnancy

89 and parental educational levels have been identified as risk factors for term-SGA  
90 (Tamura et al. 2018). Moreover, Tamura et al. (2018) reported that among mothers with  
91 a low educational level, a low BMI was a risk factor of term-SGA. Therefore, in  
92 contrast to Preterm births and VLBW, term-SGA would have been more affected by  
93 parental SES and behaviors.

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

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

## 103 Methods

### 104 *Participants*

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



107 (Kishi et al. 2011, 2013, 2017). Briefly, between February 2003 and March 2012, the  
108 Hokkaido cohort enrolled women during the first trimester of pregnancy (13 weeks of  
109 gestational age) who visited one of the delivery units of the 37 participating hospitals  
110 and clinics covering the entire Hokkaido prefecture for prenatal health.  
111 The original cohort included 20,926 pregnant women; however, 1,347 were lost to  
112 follow-up before giving birth (Figure 1). Participants with no information to determine  
113 SGA (birth weight, gestational age, infant sex, maternal parity), parental education, or  
114 annual household income were excluded (n = 4,084). We further excluded women who  
115 experienced miscarriages, stillbirths, or multiple births and those with pregnancy-  
116 induced hypertension or gestational diabetes (n = 902). Thus, we eliminated the  
117 pathological causes of SGA, which could have masked and underestimated the risk  
118 factors of parental characteristics. A total of 14,593 participants were included in the  
119 final analysis.

120

121 [Insert Figure 1 here]

### 122 *Baseline Questionnaire and Biochemical Analysis*

123 Upon entry into the study, the participants completed a self-administered  
124 questionnaire including questions on the following parental characteristics: maternal age

125 at study entry (<35, ≥35 years) (Heffner. 2004), paternal age at study entry (<40, ≥40  
126 years) (Isabelle Bray, et al. 2006). In addition,, maternal BMI before pregnancy (<18.5,  
127 ≥18.5 kg/m<sup>2</sup>) (WHO Expert Consultation. 2004); parental medical history; maternal  
128 regular use of any medications; maternal regular use of any supplement(s); paternal  
129 smoking during the first trimester; parental alcohol consumption during the first  
130 trimester; and use of any assisted reproductive technologies (ART).

131 Paternal and maternal educational levels (≤9, 10-12, 13-15, >16 years) and annual  
132 household income (<3.0, 3.0-4.9, 5.0-7.9, ≥8.0 million yen) were also obtained from the  
133 questionnaire as socioeconomic indicators, it was shown that both are important in  
134 young adulthood (Galobardes et al. 2006). In Japan, compulsory education ranges from  
135 Grade 1 to 9, then, most children go on to high school for 3 years, and after that to  
136 universities and graduate school. Therefore, we classified the cutoffs for parental  
137 educational level as ≤9, 10-12, 13-15, >16 years, with ≤9 years defined as the highest-  
138 risk group. There was no official definition of a low annual household income in Japan.  
139 In this study, we defined a couple with one child and an annual household income of  
140 <3.0 million yen as a low annual household income (Kobayashi and Nishikawa 2010).  
141 Annual household income was classified as <3.0, 3.0-4.9, 5.0-7.9, ≥8.0 million yen,  
142 with the <3.0 million yen group defined as the highest-risk group.

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

147

#### 148 *Definition of Small for Gestational Age*

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

153

#### 154 *Ethics Statement*

155 All participating women provided written informed consent before participation in  
156 the Hokkaido study. The ethics review board for epidemiological studies of the  
157 Hokkaido University Graduate School of Medicine (March 31, 2003) and the Hokkaido  
158 University Center for Environmental and Health Sciences (reference no.14, March 22,  
159 2012) approved the study protocol. The study was conducted following the principles of  
160 the Declaration of Helsinki.

161

162

### *Data Analysis*

163

Parental socioeconomic characteristics are presented as frequencies and

164

percentages. The relative risks (RRs) of SGA by parental characteristics were estimated

165

using multiple generalized linear models (GLM: distribution; binominal, link function,

166

logarithm).

167

To identify the relative contribution of potential mediators, the total effect of the

168

parental SES on infant SGA was classified into the natural direct effect (effect

169

unexplained by mediators). Whereas, the indirect effects via maternal and paternal age

170

at study entry, maternal BMI before pregnancy, parental medical history, regular use of

171

any medications and supplement(s), maternal smoking status based on plasma cotinine

172

levels at third trimester, paternal smoking during the first trimester, parental alcohol

173

consumption during the first trimester, and use of any ART.

174

The SES assumed a non-observed variable based on parental educational levels

175

and annual household income. To investigate the factors mediating the effect of SES on

176

SGA, we used structure equation modeling (SEM) (Oshio 2011; Toyoda 1998, 2007).

177

We included the parental characteristics that showed an association with SGA ( $p < 0.10$ )

178

as mediating factors in the GLM analysis. In the SEM analysis, we employed two

179 models. Model 1 was based on the assumption of independent associations between  
180 mediating factors, whereas Model 2 assumed dependent associations between mediating  
181 factors ( $p < 0.05$ ). In Model 1, the indirect effect of SES on SGA is multiplied by the  
182 mediating factors of the low SES, and the factor of the arrow extending from the  
183 mediating factor to SGA was calculated. In Model 2, arrows were added when  
184 associations between intermediary factors of the Directed Acyclic Graph were assumed  
185 (Tamura et al. 2018). The observed variables were computed with the residual term but  
186 were omitted from the Figures. The model fitness was evaluated with the Chi-square  
187 test value, goodness of fit index (GFI), adjusted goodness of fit index (AGFI),  
188 comparative fit index (CFI), and root mean square error of approximation (RMSEA).  
189 We then analyzed the fitness indices of Model 1 and 2. Generally, the predicted and  
190 measured Chi-square test values have a  $p > 0.05$ ; the p-value is closer to 1 when the GFI,  
191 AGFI, and CFI are  $\geq 0.90$ ; the smaller the RMSEA value, the better the model conforms.

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

194

195

## Results

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

204

205 [Insert Table 1 here]

206

207 [Insert Table 2 here]

208

209 When we analyzed the association between SGA and parental characteristics, we  
210 found that the maternal pre-pregnancy BMI, smoking status during the third trimester,  
211 alcohol consumption during the first trimester, supplement intake during the first  
212 trimester, and regular medication intake during the first trimester were significantly  
213 associated with increasing RRs of SGA ( $p < 0.10$ ; Table 3). The result of analysis for the

214 association between SGA and parental socioeconomic status shows that the RR of being  
215 born SGA was significantly lower in infants whose mothers had >16 years (vs. ≤9  
216 years) of education (RR = 0.69; 95% CI: 0.50–0.96).

217

218 [Insert Table 3 here]

219

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

232 Among these, maternal smoking status during the third trimester suggested the largest  
233 indirect effect on SGA, with a standardized  $\beta$  of 0.018 (0.428\*0.042); the second largest  
234 indirect effect was maternal pre-pregnancy BMI, with a standardized  $\beta$  of 0.002  
235 (0.028\*0.071). For Model 1, the goodness of fit testing revealed a Chi-square test value  
236 of 158.509 (<0.01), GFI: 0.997, AGFI: 0.994, CFI: 0.976, and RMSEA: 0.024. Except  
237 for the Chi-squared test value, all values were within the applicable ranges.

238

239 [Insert Figure 2 here]

240

241 We then added arrows of associations between the mediating factors to Model 1;  
242 the results of the analysis of Model 2 are shown in Figure 3. Referring to the DAG  
243 model in Tamura et al. (2018), the arrows between the mediating factors were derived  
244 from the pregnancy cotinine values to the maternal pre-pregnancy BMI and from  
245 alcohol consumption during the first trimester of pregnancy to maternal pre-pregnancy  
246 BMI; these three additional arrows were added in Model 2 from Model 1. For a decline  
247 in the socioeconomic status, no significant association of the maternal pre-pregnancy  
248 BMI was seen. However, a decline in parental socioeconomic status increased never to  
249 passive smoking during pregnancy; moreover, an increase in pregnancy smoking status



250 increased prevalence of lower maternal pre-pregnancy BMI; and the effect of a decrease  
251 of maternal pre-pregnancy BMI on the increase in SGA. The mediating effects of  
252 maternal alcohol consumption from SES to SGA were independent of the path to  
253 maternal BMI. The goodness of fit indices for Model 2 included a Chi-square test value  
254 of 116.181 (<0.01), GFI: 0.998, AGFI: 0.994, CFI: 0.983 and RMSEA: 0.022; except  
255 for the Chi-square test value that showed good fitness.

256

257 [Insert Figure 3 here]

258

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

267

## Discussion

268

269         In this study, we described the mediating factors between parental SES and SGA.

270     We observed that the maternal pre-pregnancy BMI, smoking during the third trimester,

271     and alcohol consumption during the first trimester were mediators of the effect of low

272     SES on SGA in SEM analysis, which assumed independent associations between the

273     mediating factors (Model 1). In SEM analysis, which assumed dependent associations

274     between the mediating factors (Model 2), considering the associations between

275     mediating factors from Model 1, a decline in parental SES increased the effect of

276     smoking during pregnancy on increase in SGA. In addition, an increase in pregnancy

277     smoking status increased the effect of the decrease in the maternal pre-pregnancy BMI

278     on the increase in SGA

279         We identified the association between SES and SGA was mediated by the

280     maternal pre-pregnancy BMI and smoking status during the third trimester in SEM

281     analysis, which assumed independent associations between the mediating factors. Van

282     Den Berg and colleagues reported the factors, breastfeeding duration, maternal smoking

283     during pregnancy, and pre-pregnancy BMI mediated the association between maternal

284     education and weight gain during the first year of an infant's life (Van Den Berg et al.

285     2013); the same associations were seen in this study. The outcomes used by Van Den

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

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

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

314 In Japan, the relative child poverty rate defined as the proportion of household  
315 with child(ren) with a net income below a defined threshold was 16.3% in 2012, and  
316 13.9% in 2015 (Ministry of Health, Labor and Welfare 2016). Although there has been a  
317 reduction in the child poverty rate in Japan, it remains lower than the Organization for  
318 Economic Co-operation and Development average (Thévenon et al. 2018). The  
319 Japanese government started implementing a free education system in public senior  
320 high schools from 2010. However, the participants of this study were not supported by  
321 the free education system in public senior high schools, because they were recruited

322 from 2003 to 2012. Therefore, some high school students cannot continue school  
323 because of high tuition fees. In this study, it has been shown that parental SES may  
324 indirectly affect children's health. Tamura et al. (2018) reported the RR of being born  
325 term-SGA was significantly lower in infants whose mothers and fathers had >16 years  
326 vs. 10–12 years of education (RR = 0.76; 95% CI, 0.61–0.94) and (RR = 0.86; 95% CI,  
327 0.75–1.00) respectively. Further policy interventions are needed to open up access to  
328 higher education so that children can receive equal education to reduce gaps.  
329 Furthermore, interventions such as school education for health and disease, and  
330 improving food intake for younger generations would be required.

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

340 socioeconomic status and maternal hypertension with the gestational age (Brink et al.  
341 2020). We think more studies focusing on the effect of parental socioeconomic status to  
342 SGA through pregnancy-induced hypertension and gestational diabetes are needed.

343 *Strength and Limitations*

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

349 This study has three main limitations. First, we excluded women with missing  
350 data on parental educational levels and annual household income, both of which were  
351 used to assess the participants' SES. Tamura et al. (2018) reported that in their study,  
352 4.4% of data on maternal education level, 5.8% of data on paternal education level, and  
353 17.9% of data on annual household income were missing. Moreover, because the  
354 questionnaire was self-administered, the participants might have avoided some specific  
355 answers due to privacy concerns (Hulley et al. 2014; Streiner et al. 2016). The group  
356 analyzed could potentially be based on biased sampling as participants with a low SES  
357 were excluded from the population. The effect of a low SES on SGA may have been

358 underestimated, and our results must be interpreted accordingly. Second, the arrow from  
359 maternal smoking status during the third trimester to the pre-pregnancy BMI in Model 2  
360 did not make chronological sense. However, we assumed that pregnant women who  
361 never smoked would not start smoking after pregnancy. Therefore, we assumed that  
362 maternal smoking status during the third trimester indicates maternal passive or active  
363 smoking before pregnancy, making it possible to test if the maternal smoking status  
364 during the third trimester affected the maternal pre-pregnancy BMI. Finally, we may not  
365 have analyzed all potential confounders. In this study, the parental characteristics that  
366 were analyzed were limited to the information collected in the questionnaire. Therefore,  
367 the effects of other mediators that were not included in the questionnaire cannot be  
368 excluded.

369

370

### *Conclusions*

371

372

373

374

375

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

376 increased the effect of a low maternal pre-pregnancy BMI, and 3) the effect of a  
377 decrease in the maternal BMI on the increase in SGA. Further studies are needed to  
378 uncover the associations between SES, maternal BMI, and SGA in infants in Japan. This  
379 study showed to require that school education for the health effects of tobacco smoking  
380 and improving food intake from lower grades.

381

382 **Funding:** This study was funded by a Grant-in-Aid for Scientific Research from the  
383 Japanese Ministry of Health, Labour, and Welfare (H26-Kagaku Ippan-002); the  
384 Ministry of Education, Culture, Sports, Science, and Technology; and the Japan Society  
385 for the Promotion of Science (Kiban-A No.16H02645).

386

387 **Conflict of Interest**

388 The authors declare that they have no conflict of interest.



389 **References**

390

391 Amorim, L. D., Fiaccone, R. L., Santos, C. A., Santos, T. N., Moraes, L. T., Oliveira, N.,  
392 et al. (2010). Structural equation modeling in epidemiology. *Cadernos de saúde*  
393 *pública*, 26(12), 2251-2262.

394 Barker, D. J. P. (1995). Fetal origins of coronary heart disease. *BMJ*, 311(6998), 171-  
395 174.

396 Blumenshine, P., Egerter, S., Barclay, C. J., Cubbin, C., & Braveman, P. A. (2010).  
397 Socioeconomic disparities in adverse birth outcomes: a systematic review.  
398 *American Journal of Preventive Medicine*, 39(3), 263-272.

399 Bonamy, A.-K. E., Norman, M., & Kaijser, M. (2008). Being Born Too Small, Too  
400 Early, or Both: Does it Matter for Risk of Hypertension in the Elderly? *American*  
401 *Journal of Hypertension*, 21(10), 1107-1110.

402 Boucher, J., & Konkle, A. T. (2016). Understanding Inequalities of Maternal Smoking--  
403 Bridging the Gap with Adapted Intervention Strategies. *International Journal of*  
404 *Environmental Research and Public Health*, 13(3), 282.

405 Brink, L. T., Nel, D. G., Hall, D. R., Odendaal, H. J. (2020). Association of  
406 socioeconomic status and clinical and demographic conditions with the  
407 prevalence of preterm birth. *International Journal of Gynecology & Obstetrics*,  
408 149, 359–369.

409 Fujiwara, T., Ito, J., & Kawachi, I. (2013). Income inequality, parental socioeconomic  
410 status, and birth outcomes in Japan. *American Journal of Epidemiology*, 177(10),  
411 1042-1052.

412 Galobardes, B., Shaw, M., Lawlor, D. A., Lynch, J. W., & Davey Smith, G. (2006a).  
413 Indicators of socioeconomic position (part 1). *Journal of Epidemiology and*  
414 *Community Health*, 60(1), 7-12.

415 Gluckman, P. D., & Hanson, M. A. (2004). Developmental origins of disease paradigm:  
416 a mechanistic and evolutionary perspective. *Pediatric Research*, 56(3), 311-317.

417 Hanaoka, T., Tamura, N., Ito, K., Sasaki, S., Araki, A., Ikeno, T., et al. (2018).  
418 Prevalence and Risk of Birth Defects Observed in a Prospective Cohort Study;  
419 the Hokkaido Study on Environment and Children's Health. *Journal of*  
420 *Epidemiology*, 28(3), 125-132.

421 Heffner LJ. (2004). Advanced maternal age—how old is too old? *New England Journal*  
422 *of Medicine*. 351:1927–1929.

423 Heude, B., Thièbaugeorges, O., Goua, V., Forhan, A., Kaminski, M., et al. (2012). Pre-  
424 Pregnancy Body Mass Index and Weight Gain During Pregnancy: Relations with  
425 Gestational Diabetes and Hypertension, and Birth Outcomes. *Maternal and*  
426 *Child Health Journal*, 16:355–363.

427 Hulley, S. B., Cummings, S. R., Browner, W. S., Grady, D. G., & Newman, T. B.  
428 (2014). *Designing Clinical Research*, 4th Edition [Japanese] (M. Kihara & M.  
429 Kihara, Trans.). Tokyo: Medical Sciences International, Ltd.

430 Isabelle Bray, David Gunnell, George Davey Smith. Advanced paternal age: How old is  
431 too old? (2006). *Journal of Epidemiol Community Health*. 60. 851–853.

432 Itabashi, K., Miura, F., Uehara, R., & Nakamura, Y. (2014). New Japanese neonatal  
433 anthropometric charts for gestational age at birth. *Pediatric International*, 56(5),  
434 702-708.

435 Itoh, H., Kohmura-Kobayashi, Y., Kawai, K., & Kanayama, N. (2018). Multiple  
436 causative factors underlie low birthweight [eLetters]. *Sciences*. Retrieved from  
437 <http://science.sciencemag.org/content/361/6401/440/tab-e-letters>

438 Kishi, R., Araki, A., Minatoya, M., Hanaoka, T., Miyashita, C., Itoh, S., et al. (2017).  
439 The Hokkaido Birth Cohort Study on Environment and Children's Health:  
440 cohort profile—updated 2017. *Environmental Health and Preventive Medicine*,  
441 22(1), 46.

442 Kishi, R., Kobayashi, S., Ikeno, T., Araki, A., Miyashita, C., Itoh, S., et al. (2013). Ten  
443 years of progress in the Hokkaido birth cohort study on environment and  
444 children's health: cohort profile—updated 2013. *Environmental Health and*  
445 *Preventive Medicine*, 18(6), 429-450.

446 Kishi, R., Sasaki, S., Yoshioka, E., Yuasa, M., Sata, F., Saijo, Y., et al. (2011). Cohort  
447 profile: the Hokkaido study on environment and children's health in Japan.  
448 *International Journal of Epidemiology*, 40(3), 611-618.

449 Kobayashi, S., & Nishikawa, Y. (2010). The Definition of People with Low Income in  
450 Japan: -Validity of the Criteria of “Persons Exempt from Municipal Taxes”-  
451 [Japanese]. *Journal of Nagoya Bunri University*, 10, 23-33.

452 Kobayashi, S., Sata, F., Hanaoka, T., Braimoh, T., Ito, K., Tamura, N. et al. (2019).  
453 Association between maternal passive smoking and increased risk of delivering  
454 small-for-gestational-age infants at full-term using plasma cotinine levels from  
455 The Hokkaido Study: a prospective birth cohort. *BMJ Open*, 9(2), e023200.

456 Ludvigsson, J. F., Lu, D., Hammarström, L., Cnattingius, S., & Fang, F. (2018). Small  
457 for gestational age and risk of childhood mortality: A Swedish population study.  
458 *PLOS Medicine*, 15(12), e1002717.

459 Ministry of Health, Labour, and Welfare (2016). Summary Report of Comprehensive  
460 Survey of Living Conditions 2016. Tokyo: Ministry of Health, Labour, and  
461 Welfare. <https://www.mhlw.go.jp/english/database/db-hss/cslc-report2016.html>  
462 Accessed 13 March, 2019.

463 Mortensen, L. H. (2013). Socioeconomic inequality in birth weight and gestational age  
464 in Denmark 1996-2007: using a family-based approach to explore alternative  
465 explanations. *Social Science & Medicine*, 76(1), 1-7.

466 Mother's & Children's Health Welfare Association. (2016). Maternal and Child Health  
467 Statistics of Japan. Tokyo, Japan: Katsuya Kamiya.

468 Normile, D. (2018). Staying slim during pregnancy carries a price. *Science*, 361(6401),  
469 440.

470 Ogawa, K., Morisaki, N., Sago, H., Fujiwara, T., & Horikawa, R. (2018). Association  
471 between women's perceived ideal gestational weight gain during pregnancy and  
472 pregnancy outcomes. *Scientific Reports*, 8, 11574.

473 Oshio, A. (2011). *Psychological Research Data Analysis by SPSS and Amos*. [Japanese]  
474 (2nd ed.). Tokyo: TokyoTosho.

475 Sasaki, S., Braimoh, T. S., Yila, T. A., Yoshioka, E., & Kishi, R. (2011). Self-reported  
476 tobacco smoke exposure and plasma cotinine levels during pregnancy--a  
477 validation study in Northern Japan. *The Science of the Total Environment*, 412-  
478 413, 114-118.

479 Shah, P. S., & Knowledge Synthesis Group on Determinants of LBW/PT births. (2010).  
480 Parity and low birth weight and preterm birth: a systematic review and meta-  
481 analyses. *Acta obstetrica et gynecologica Scandinavica*, 89(7), 862-875.

482 Streiner, D. L., Norman, G. R., & Cairney, J. (2016). Health Measurement Scales: A  
483 practical guide to their development and use, 5th Edition [Japanese] (M. Kihara,  
484 M. Kaji, & M. Kihara, Trans.). Tokyo: Medical Sciences International, Ltd.

485 Tairaku, S., Yamasaki, M., Makihara, N., Tanimura, K., Hazama, R., et al. (2012). A  
486 study of maternal progress during pregnancy complicated by chronic  
487 hypertension resulting in poor perinatal outcome. *ADVANCES IN*  
488 *OBSTETRICS AND GYNECOLOGY*, 64, 17–22.

489 Tamura, N., Hanaoka, T., Ito, K., Araki, A., Miyashita, C., Ito, S., et al. (2018). Different  
490 Risk Factors for Very Low Birth Weight, Term-Small-for-Gestational-Age, or  
491 Preterm Birth in Japan. *International Journal of Environmental Research &*  
492 *Public Health*, 15(2), 369.

493 Thévenon, O., Manfredi, T., Govind, Y., & Klauzner, I. (2018). Child poverty in the  
494 OECD. OECD Social, Employment, and Migration Working Papers. No. 218.  
495 Paris; Organisation for Economic Co-operation and Development. Retrieved  
496 from <https://www.oecd-ilibrary.org/content/paper/c69de229-en>.

497 Toyoda, H. (1998). *Covariance Structure Analysis :Structure Equation Modeling*.  
498 Tokyo: AsakuraShoten.

499 Toyoda, H. (2007). *Covariance Structure Analysis :Structure Equation Modeling* (Amos  
500 version). Tokyo: TokyoTosho.

501 Travier, N., Agudo A., May, A. M., Gonzalez, C., Luan, J., Besson, H. et al. (2009).  
502 Smoking and body fatness measurements: a cross-sectional analysis in the  
503 EPIC-PANACEA study. *Preventive Medicine*, 49(5), 365-373.

504 Tsukamoto, H., Fukuoka, H., Koyasu, M., Nagai, Y., & Takimoto, H. (2007). Risk  
505 factors for small for gestational age. *Pediatric International*, 49(6), 985-990.

506 Van Den Berg, G., Van Eijsden, M., Galindo-Garre, F., Vrijkotte, T., & Gemke, R.  
507 (2013). Low maternal education is associated with increased growth velocity in  
508 the first year of life and in early childhood: the ABCD study. *European Journal*  
509 *of Pediatrics*, 172(11), 1451-1457.

510 WHO Expert Consultation. (2004). Appropriate body-mass index for Asian populations  
511 and its implications for policy and intervention strategies. *Lancet*. 363(9403),  
512 157-163.

513 Wolf, E. J., Harrington, K. M., Clark, S. L., & Miller, M. W. (2013). Sample Size  
514 Requirements for Structural Equation Models: An Evaluation of Power, Bias,  
515 and Solution Propriety. *Educational and Psychological Measurement*, 76(6),  
516 913-934.

## Tables

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

	N (%) or Mean $\pm$ SD		N (%) or Mean $\pm$ SD
<b>Maternal characteristics</b>		<b>Paternal characteristics</b>	
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 )
$\geq$ 35	3,081 ( 21.1 )	$\geq$ 40	1406 ( 9.6 )
Missing	2 ( 0.0 )	missing	134 ( 0.9 )
Body mass index (kg/m <sup>2</sup> ) 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 )	<b>Socioeconomic characteristics</b>	



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**

	<b>N (%) or Mean <math>\pm</math> SD</b>
Birth weight, g	3,039.9 $\pm$ 413.1
Gestational age, days	274.2 $\pm$ 10.5
Sex	
Male	7,340 ( 50.3 )
Female	7,253 ( 49.7 )
Number of siblings	
0	5,417 ( 37.1 )
$\geq 1$	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			p-value
	N	%	RR	95% CI		
<b>Maternal characteristics</b>						
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 <sup>2</sup> )						
<18.5	269	10.9	<b>1.79</b>	<b>1.57</b>	<b>2.05</b>	<b>&lt;0.01</b>
≥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	<b>1.71</b>	<b>1.43</b>	<b>2.04</b>	<b>&lt;0.01</b>
Alcohol consumption during first trimester						
No	832	6.5		ref		
Yes	170	9.8	<b>1.51</b>	<b>1.29</b>	<b>1.77</b>	<b>&lt;0.01</b>

### 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			<b>ref</b>		
Yes	132	8.4	<b>1.25</b>	<b>1.05</b>	<b>1.49</b>	<b>0.02</b>	

### Regular use of any supplement

No	653	6.7			<b>ref</b>		
Yes	354	7.5	<b>1.12</b>	<b>0.99</b>	<b>1.27</b>	<b>0.07</b>	

### 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	
<b>Medical history</b>							
No	661	6.9			ref		
Yes	349	7.0	1.02	0.90	1.16	0.73	
<b>Socioeconomic characteristics</b>							
<b>Maternal education level, years</b>							
≤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	<b>0.69</b>	<b>0.50</b>	<b>0.96</b>	<b>0.03</b>	
<b>Paternal education level, years</b>							
≤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	
<b>Household Income, million yen</b>							
<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 age

RRs were calculated using generalized linear models.

## Figures

Figure 1 top

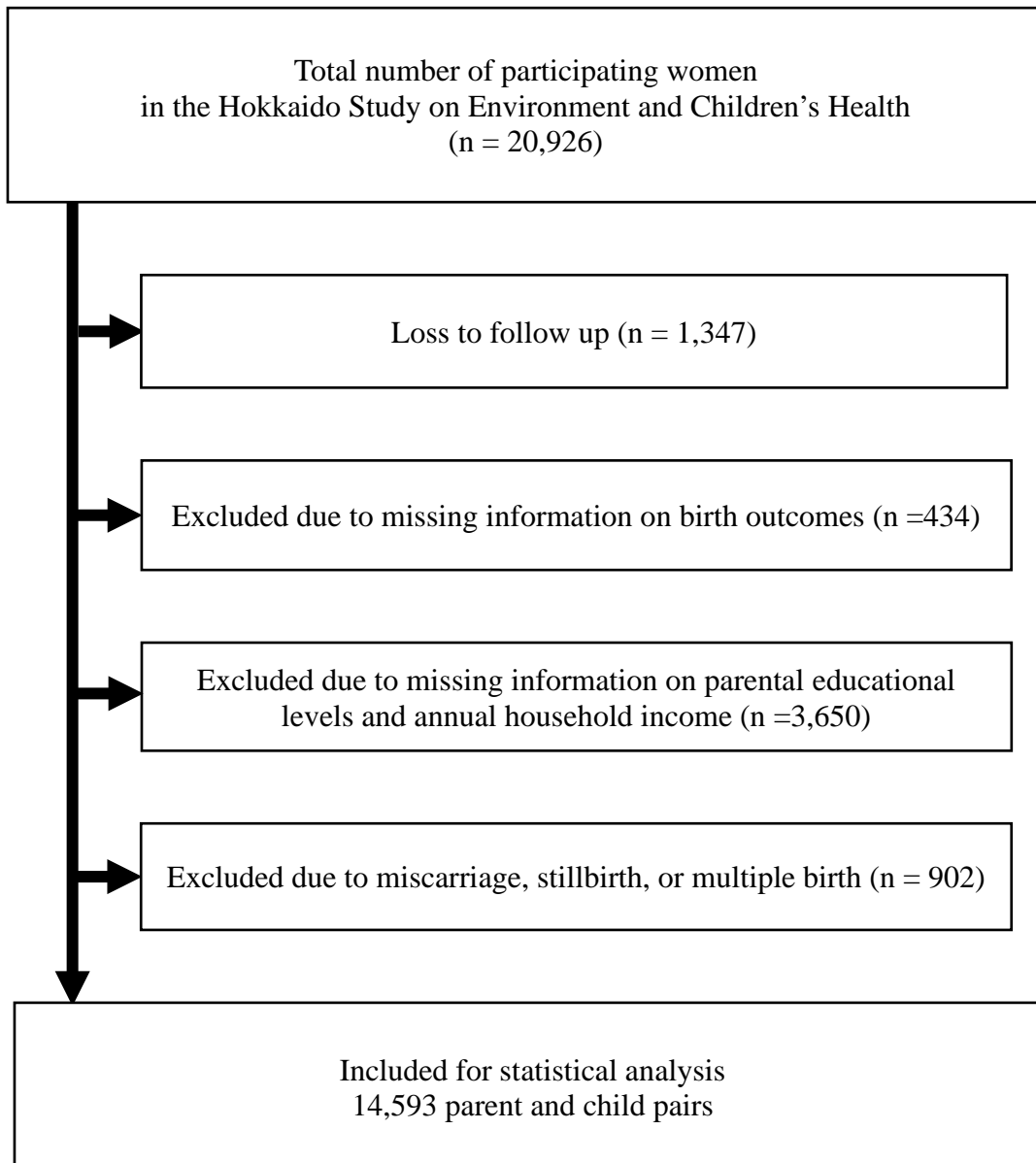




Figure 2 top

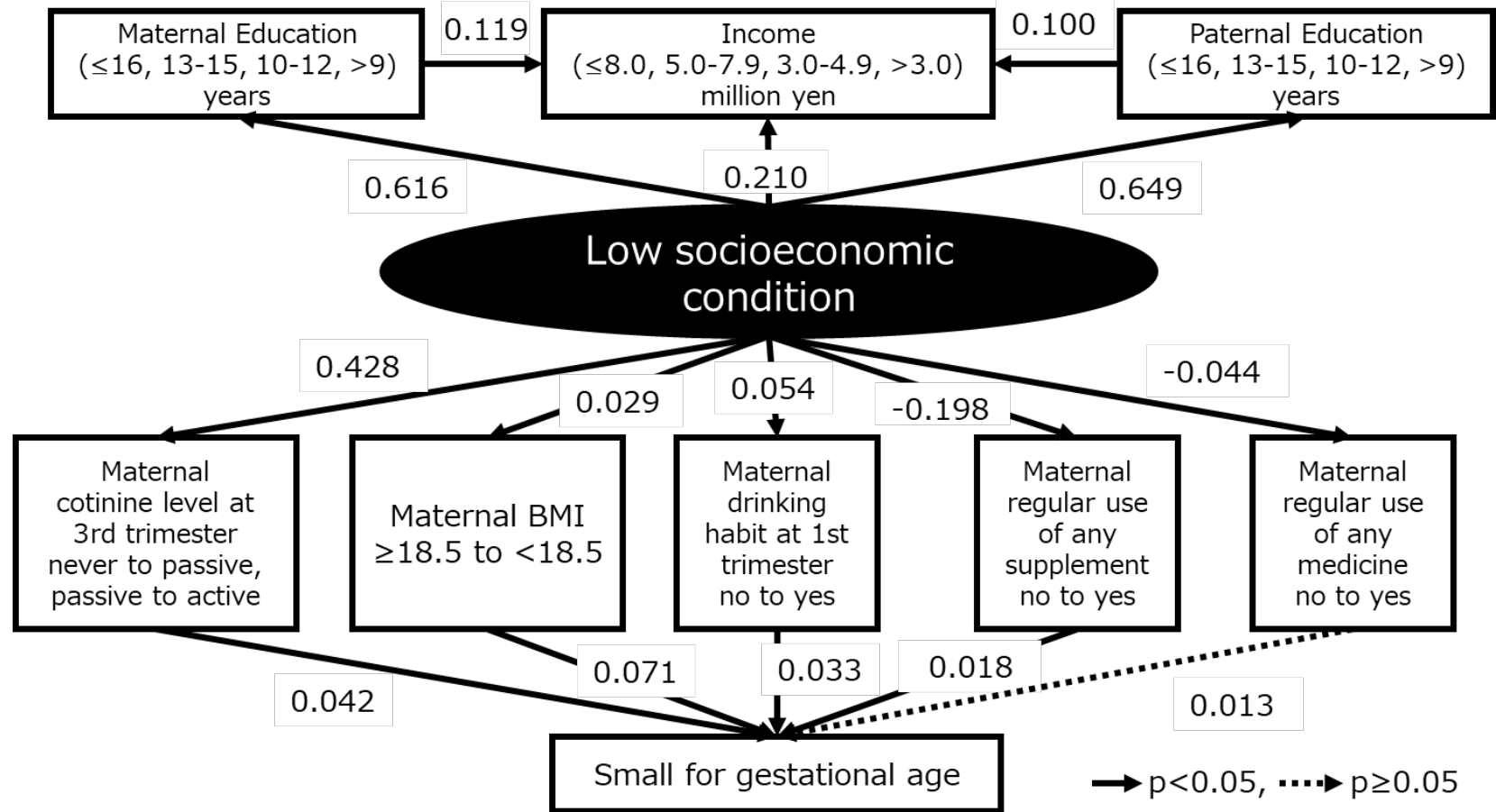
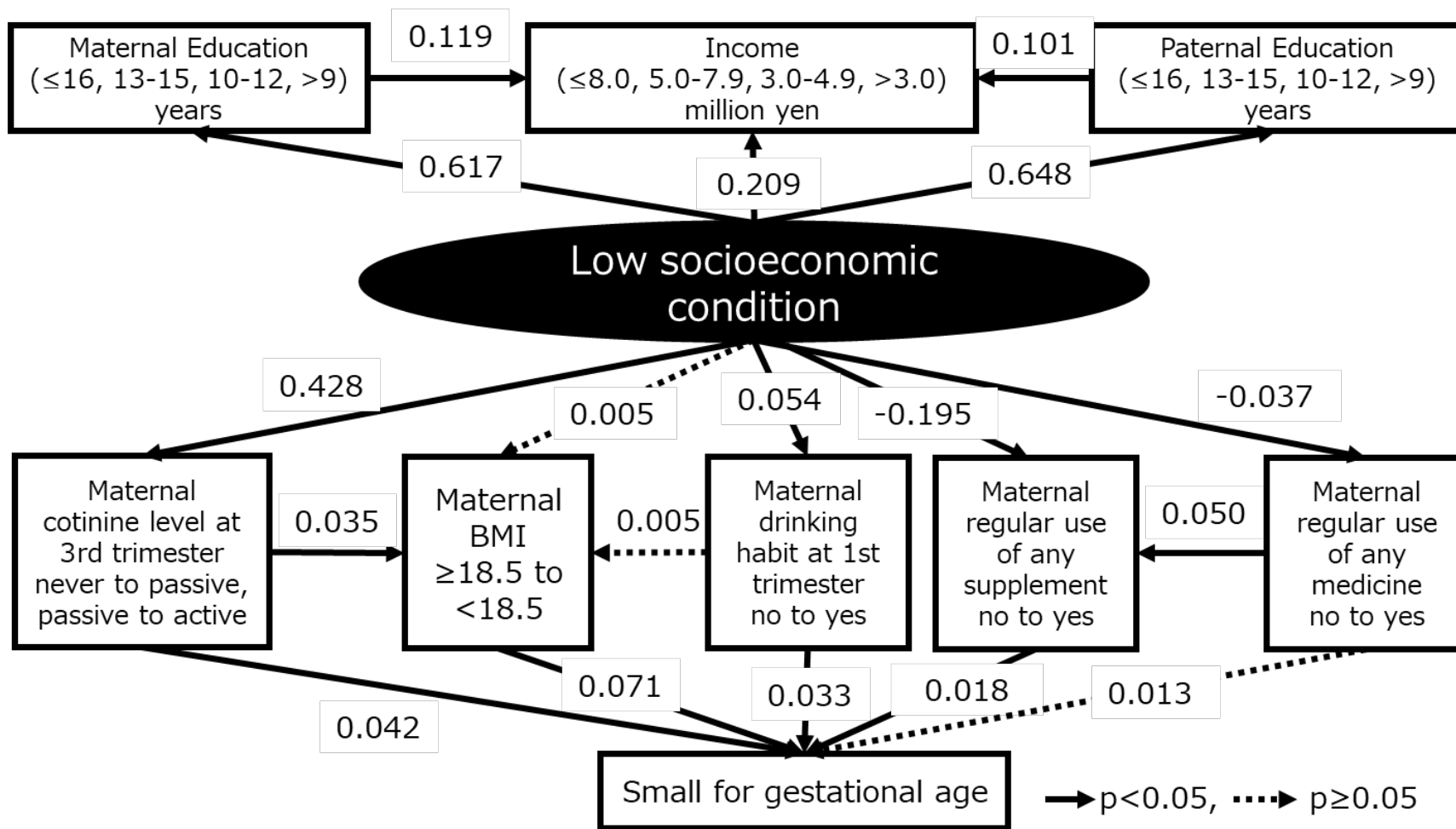


Figure 3 top



## 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  $\beta$  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  $\beta$  value. Solid line arrows indicate  $p < 0.05$ , whereas dotted line arrows indicate  $p \geq 0.05$