

1 **Which modifiable prenatal factors mediate the relation between socioeconomic position**  
2 **and a child's weight and length at birth?**

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20 **Short running title:** Mediators of the social gradient in birth size

21 Words count for the abstract: 212

22 Words count for the main body: 3,173

23 Number of references: 37

24 Number of tables: 3 Number of figures: 2

## 25 **ACKNOWLEDGEMENTS**

26 We are extremely grateful to all the families who took part in this study, the midwives and  
27 psychologists who recruited and followed them, and the whole EDEN team, including  
28 research scientists, engineers, technicians and managers and especially Josiane Sahuquillo and  
29 Edith Lesieux for their commitment and their role in the success of the study. We also  
30 acknowledge the commitment of the members of the EDEN Mother-Child Cohort Study  
31 Group: I. Annesi-Maesano, J.Y. Bernard, J. Botton, M.A. Charles, P. Dargent-Molina, B. de  
32 Lauzon-Guillain, P. Ducimetière, M. de Agostini, B. Foliguet, A. Forhan, X. Fritel, A. Germa,  
33 V. Goua, R. Hankard, B. Heude, M. Kaminski, B. Larroque†, N. Lelong, J. Lepeule, G.  
34 Magnin, L. Marchand, C. Nabet, F Pierre, R. Slama, M.J. Saurel-Cubizolles, M. Schweitzer,  
35 O. Thiebaugeorges. We thank Jo Ann Cahn for her help in preparing the manuscript.

## 36 **CONTRIBUTORS**

37 MB, SL, BH and JB conceived and designed the work, with advice from MAC. MB analyzed  
38 the data with advice from BH, JB and SL. MB, BH and SL drafted and revised the  
39 manuscript. All authors interpreted the data and criticized the manuscript for important  
40 intellectual content. MAC and BH designed and led the EDEN mother-child cohort. AF is  
41 responsible for the EDEN data management. All authors have read and approved the final  
42 version of the manuscript. This article is the work of the authors. MB serves as guarantor for  
43 the contents of this article. All authors had full access to all of the data (including statistical  
44 reports and tables) in the study and take the responsibility for the integrity of the data and the  
45 accuracy of the data analysis. All researchers are independent of the funding bodies. All  
46 members in the EDEN mother-child cohort study group designed the study.

## 47 **SOURCE OF FUNDING**

48 - Fondation pour la Recherche Médicale

- 49 - French Ministry of Research
- 50 - Institut Fédératif de Recherche and Cohort Program
- 51 - INSERM Nutrition Research Program
- 52 - French Ministry of Health Perinatal Program
- 53 - French Agency for Environment Security (AFFSET)
- 54 - French National Institute for Population Health Surveillance (INVS)
- 55 - Paris-Sud University
- 56 - French National Institute for Health Education (INPES)
- 57 - Nestlé
- 58 - Mutuelle Générale de l'Éducation Nationale
- 59 - French Speaking Association for the Study of Diabetes and Metabolism (Alfediam)
- 60 - National Agency for Research (ANR nonthematic program)
- 61 - National Institute for Research in Public Health (IRESP TGIR Cohorte Santé 2008
- 62 Program)

63 The study sponsors were not involved in the study design, data collection, or data analyses.

#### 64 **CONFLICT OF INTEREST**

65 None of the authors had a conflict of interest.

66

67 **Abbreviations:** Body Mass Index (BMI)

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73 **Abstract**

74 Although several studies have shown a positive association between socioeconomic position  
75 and size at birth, not enough is known about the modifiable factors that may be involved. We  
76 aimed to investigate whether maternal prepregnancy body mass index (BMI), smoking, diet,  
77 and depression during pregnancy mediate the positive association between maternal education  
78 and birth size. Weight and length z-scores specific for gestational age and sex were calculated  
79 for 1,500 children from the EDEN mother-child cohort. A mediation analysis of the  
80 associations between maternal education and birth size was conducted with a counterfactual  
81 method, adjusted for recruitment center, parity, maternal height, and age. In the comparison of  
82 children of mothers with low vs. intermediate education levels, maternal smoking during  
83 pregnancy explained 52% of the total effect of education on birth weight. Similar findings  
84 were observed with birth length z-score (37%). The comparison of children of mothers with  
85 high vs. intermediate education levels yielded a non-significant total effect, which masked  
86 opposite mediating effects by maternal BMI and smoking during pregnancy on both birth  
87 weight and length. Prepregnancy BMI and maternal smoking during pregnancy mediate the  
88 positive association between maternal education and birth weight and length z-scores. These  
89 mediators, however, act in opposite directions, thereby masking the extent to which healthy  
90 prenatal growth is socially differentiated.

91 **Key words:** birth weight, birth length, maternal education, smoking, BMI, mediation analysis

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95 **INTRODUCTION**

96 The existence of social inequalities in growth and childhood overweight in high-income  
97 countries has been highlighted in recent years (Ballon et al., 2018; Barriuso et al., 2015;  
98 Howe et al., 2012; McCrory et al., 2017). These inequalities are observed as early as the first  
99 day of life, since positive associations have been described between socioeconomic position  
100 and both weight and length at birth (Ballon et al., 2018; Howe et al., 2012; Jansen et al., 2009;  
101 Mortensen, Helweg-Larsen, & Andersen, 2011). It is also well known that a lower birth  
102 weight, a marker of suboptimal fetal growth, is associated with a range of short- and long-  
103 term health issues, such as cardiovascular disease, diabetes, and obesity (D. J. Barker,  
104 Osmond, Forsen, Kajantie, & Eriksson, 2005; Jornayvaz et al., 2016; Shenkin, Starr, & Deary,  
105 2004; Zanetti et al., 2018). These findings suggest intergenerational transmission of health  
106 inequalities between the mother and her offspring (Aizer & Currie, 2014; D. Barker, Barker,  
107 Fleming, & Lampl, 2013). The development of interventions to prevent or reduce these social  
108 inequalities in health programming requires that the modifiable factors mediating the positive  
109 association between socioeconomic position and birth weight be identified.

110 Some studies have shown that prepregnancy body mass index (BMI) and smoking during  
111 pregnancy mediate the association between socioeconomic position and birth weight (Gissler,  
112 Merilainen, Vuori, & Hemminki, 2003; Jansen et al., 2009; van den Berg, van Eijsden,  
113 Vrijkotte, & Gemke, 2012), but only one study has investigated the joint effects of both  
114 factors on this birth outcome (Mortensen, Diderichsen, Smith, & Andersen, 2009). To our  
115 knowledge, only one study has examined factors involved in the association between  
116 socioeconomic position and length or height (Galobardes et al., 2012). This study described  
117 social inequalities for both prenatal and postnatal growth within a single longitudinal model.  
118 However they did not seek to identify mediators of the association between socioeconomic  
119 position and birth length specifically. Although weight and length at birth are strongly

120 correlated, their separate associations with socioeconomic position may differ by age and sex  
121 (Ballon et al., 2018) and thus involve different mediators. Moreover, other prenatal factors  
122 remain to be studied. Indeed, healthy dietary patterns during pregnancy have been shown to  
123 be positively associated with birth weight (Chia et al., 2019; Emmett, Jones, & Northstone,  
124 2015). Conversely, unhealthy dietary patterns and maternal depression during pregnancy  
125 have been shown to be associated with lower birth weight (Chia et al., 2019; Field, 2011).  
126 One study also reported a negative association between maternal depression and birth length  
127 (Field, 2011). Given that social inequalities have been described for these three factors  
128 (Emmett et al., 2015; Hein et al., 2014), the latter were considered as potential mediators of  
129 the relation between socioeconomic position and birth size (i.e. weight and length).

130 Recently, advanced methods for mediation analyses have been developed. In particular,  
131 counterfactual approaches allow for causal inference based on observational data by  
132 estimating direct and indirect effects with more power than allowed by traditional approaches  
133 (Lange, Rasmussen, & Thygesen, 2013; VanderWeele & Vansteelandt, 2014). Among the  
134 various existing approaches, the counterfactual method proposed by Lange et al. (Lange et al.,  
135 2013) enables the simultaneous assessment of the mediating effect of several factors as well  
136 as the consideration of an exposure variable in more than two categories.

137 The objective of this paper was to investigate whether any of maternal prepregnancy BMI,  
138 smoking, diet, and depression during pregnancy mediate the positive association between  
139 maternal education level and offspring birth size, i.e., weight and length.

#### 140 **KEY MESSAGES**

- 141 - A positive association exists between socioeconomic position and birth weight, but less  
142 research has been done on the prenatal factors involved

- 143 - Prepregnancy BMI and smoking during pregnancy were shown to be important mediators  
144 of the positive associations between maternal education and both birth weight and birth  
145 length.
- 146 - Other modifiable factors like dietary patterns and depressive symptoms were not shown  
147 to mediate these associations.
- 148 - These results suggest that promoting a healthy prepregnancy weight and preventing  
149 smoking during pregnancy are keys to addressing socioeconomic inequalities in healthy  
150 fetal growth.

151

## 152 **METHODS**

### 153 **Study design and participants**

154 The EDEN mother-child cohort was designed to assess the pre- and postnatal determinants of  
155 children's growth, health, and development. This cohort includes 2,002 pregnant women  
156 recruited in two French maternity hospitals (in Poitiers and Nancy) between 2003 and 2006.  
157 Exclusion criteria were multiple pregnancies, known diabetes, illiteracy, and intention to give  
158 birth elsewhere than these two university hospitals or to move outside the region within 3  
159 years. Due to the mode of recruitment and the selective acceptance of participation, urban and  
160 well-educated mothers are over-represented in the EDEN study compared to the national  
161 population (Heude et al., 2016). Details of the study protocol have been published elsewhere  
162 (Heude et al., 2016). Both parents provided written consent. The ethics committee of the  
163 Kremlin-Bicêtre Hospital approved this study, which was also submitted to the national  
164 commission for data protection and liberties (CNIL).

### 165 **Measurements**

166 Data come from obstetric and pediatric records at birth, as well as from self-reported  
167 questionnaires completed by the mothers and clinical examinations undertaken at different  
168 stages of follow-up.

### 169 *Socioeconomic position*

170 Maternal education level, commonly studied in relation to child birth size (Jansen et al., 2009;  
171 McCrory et al., 2017; Mortensen et al., 2009) and less likely to be affected by childbearing  
172 than income and occupation, was used as a proxy for socioeconomic position. Mothers were  
173 asked to self-report their highest educational attainment at study inclusion. Education level  
174 was categorized as low (did not complete high school), intermediate (high school diploma to  
175 2-year university degree, reference category) and high (3-year university degree or more).  
176 Intermediate category was chosen as the reference category in order to better disentangle the  
177 mediation process when comparing one category of level education to its adjacent one.

### 178 *Child weight and length*

179 At birth, weight and length were measured by midwives with an electronic scale (Seca Ltd)  
180 and a somatometer (Testut). As measurement errors are common for birth length, we used  
181 predicted length at birth, obtained from growth modeling of an average of 16 measurements  
182 of length/height between birth and 5 years (Botton et al., 2014; Carles et al., 2016). For  
183 children without predicted data available, measured length was used instead (7%). Birth  
184 weight and length z-scores specific for gestational age and sex were calculated according to  
185 Audipog references (Faculté de médecine RTH Laennec Lyon, 2008).

### 186 *Candidate mediators*

187 Women self-reported their prepregnancy weight at inclusion. Maternal height was measured  
188 by research midwives with a wall stadiometer (Seca 206) during clinical examinations  
189 conducted between 24 and 28 weeks of gestation. Prepregnancy BMI was calculated as  
190 weight (kg) divided by height (m) squared and categorized as underweight ( $<18.5 \text{ kg/m}^2$ ),



191 normal ( $\geq 18.5$  and  $< 25$  kg/m<sup>2</sup>), overweight ( $\geq 25$  and  $< 30$  kg/m<sup>2</sup>) or obese ( $\geq 30$  kg/m<sup>2</sup>)  
192 (WHO). During the first visit with research midwives (between 24 and 28 weeks of  
193 gestation), mothers reported their daily cigarette consumption and smoking habits at the  
194 beginning of pregnancy (smoking in the first trimester) and their smoking status at the time of  
195 the visit (smoking in the second trimester). After delivery, research midwives collected  
196 similar information for smoking at the end of the third trimester of pregnancy (third trimester  
197 smoking status). All this information was combined into one variable categorized as non-  
198 smokers, smokers only in the first trimester, and smokers throughout pregnancy. Depressive  
199 symptoms during pregnancy were assessed with the 20-item Center for Epidemiology Studies  
200 Depression Scale (CES-D) (Radloff, 1977). Each response was coded between 0 and 3 points,  
201 then summed into a depressive symptoms score (ranging from 0-60). Different cut-offs,  
202 ranging from 16 to 23 (Henry, Grant, & Cropsey, 2018; Radloff, 1977; Vilagut, Forero,  
203 Barbaglia, & Alonso, 2016), have been proposed to detect individuals with probable  
204 depression. We chose the threshold of 23 to define women with depressive symptoms, as  
205 suggested by a validation study for the French population (Fuhrer & Rouillon, 1989).  
206 Maternal diet in the last trimester of pregnancy was assessed during the maternity ward stay  
207 after delivery by a validated food frequency questionnaire (FFQ) (Deschamps et al., 2009).  
208 The 137 standardized items from the FFQ have previously been synthesized by principal  
209 component analysis into two dietary patterns (Yuan et al., 2017): the so-called Healthy dietary  
210 pattern, characterized by a high intake of fruit, vegetables, fish, and whole grains, whereas the  
211 Western dietary pattern was characterized by a high intake of processed and snacking foods.  
212 These variables were considered to be continuous scores reflecting adherence to each dietary  
213 pattern.

#### 214 *Other variables*

215 Gestational age, maternal age, and parity were collected at birth from medical records.  
216 Preterm birth (yes/no) was defined by a gestational age <37 weeks of gestation.

### 217 **Population studied**

218 Of the 1,907 children included in the EDEN cohort, 407 were excluded because of missing  
219 values for any of the variables of interest, (i.e., outcomes, exposure, mediators, and  
220 confounders). The final sample thus included 1,500 children.

### 221 **Statistical methods**

222 Participants included in the analysis were compared to those who were not included.  
223 Characteristics of the study population were described at birth according to maternal  
224 education level. The bivariate statistical analyses used chi-square tests, correlations, and  
225 ANOVA analyses as appropriate.

226 The counterfactual method developed by Lange et al. (Lange et al., 2013), based on marginal  
227 structural models, was used to conduct the mediation analysis. This allowed us to break down  
228 the total effect of maternal education level on birth size (i.e., weight and length z-scores) into  
229 natural direct and indirect effects through the candidate mediators. Based on this method, the  
230 total effect can be considered as the change in z-score that would be observed if, for example,  
231 maternal education level could change (e.g., from intermediate to high). The natural direct  
232 effect can be considered the difference in birth z-scores for a given change in education level  
233 (e.g., from intermediate to high), keeping mediators at the value they naturally take when  
234 maternal education is unchanged (e.g., at the intermediate level). The natural indirect effect is  
235 the difference in birth z-scores when maternal education remains unmodified, but the  
236 mediators change to the value they would naturally take if maternal education were to change  
237 (e.g., from intermediate to high). The validity of this statistical method depends on whether or  
238 not it satisfies specific hypotheses. First, for a given mediator, there should be no unmeasured  
239 confounders in associations between: 1) exposure and outcome, 2) mediator and outcome, 3)

240 exposure and mediator, 4) mediator and outcome conditional on the exposure. Second, no  
241 causal associations should exist between the mediators.

242 To select candidate mediators of the association between maternal education and birth  
243 outcomes, we first conducted separate mediation analyses for each of the following potential  
244 mediators, selected *a priori* as most likely to explain this relation: maternal prepregnancy  
245 BMI, smoking, depressive symptoms, and maternal dietary patterns during pregnancy. We  
246 checked that they were independent of each other, conditional on the exposure and the  
247 confounders in our sample, by running a multiple regression model of one mediator on the  
248 others, adjusting for maternal education and the confounders. When a statistically significant  
249 association was observed between candidate mediators, we used the residual method to obtain  
250 independent variables and verify the model's assumptions, by generating new variables as the  
251 residuals of the regression of one mediator on the others. Simple mediation analyses were  
252 then conducted with these new variables. All individually significant mediators were next  
253 included in two multivariable marginal structural models to assess how they jointly mediated  
254 the association between maternal education and each of the birth weight and length z-scores.  
255 To obtain robust 95% confidence intervals, we used a bootstrap approach with 5,000  
256 replications. Analyses were adjusted for center (i.e., Nancy or Poitiers), parity, maternal  
257 height, and age.

258 Because analyses were conducted on the database with no missing data for any of the five  
259 mediators (Population B, **Figure 1**), the first sensitivity analysis used the database with no  
260 missing data for the mediators selected for the final multivariable model (Population A,  
261 **Figure 1**). A second sensitivity analysis excluded 84 preterm infants from the sample  
262 (Population C, **Figure 1**). SAS v9.3 (SAS Institute, Cary, NC, US) was used for all but the  
263 mediation analyses, which were run under R v3.4.2 as proposed by Lange et al. (Lange et al.,

264 2013). Graphs were also plotted with R v3.4.2. Statistical significance was defined at  $P \leq$   
265 0.05.

## 266 **RESULTS**

### 267 **Population characteristics**

268 Mothers excluded from the analysis (n=407) had lower education levels and were more likely  
269 to have experienced depressive symptoms or to be underweight or obese than those who were  
270 included (low education level: 42.0% vs. 25.5%; depressive symptoms: 13.8% vs. 7.7%;  
271 underweight: 11.2% vs. 8.0%; obesity: 12.3% vs. 7.9%). No statistically significant  
272 differences were observed in birth weight and length z-scores between those included and  
273 excluded.

274 There was a positive gradient between maternal education level and both the mother's age and  
275 height and the z-scores for the child's birth weight and length (**Table 1**). All candidate  
276 mediators except depressive symptoms were strongly associated with both maternal education  
277 level and birth size z-scores (**Tables 1 & 2**).

### 278 **Simple mediation analysis**

279 Prepregnancy BMI and smoking during pregnancy were mediators of the association between  
280 maternal education and birth weight and length; the Western dietary pattern was a mediator of  
281 the association with birth length only (**Table 3**). Since this dietary pattern was strongly  
282 associated with prepregnancy BMI and smoking during pregnancy, we performed an  
283 additional simple mediation analysis by using the residuals of its regression on BMI, smoking  
284 during pregnancy, and confounders, as a new mediator. Because this new variable, which  
285 assessed variability in the Western dietary pattern independent of other variables, was not  
286 significant, the multiple mediation analyses used only prepregnancy BMI and smoking during  
287 pregnancy.

### 288 **Multiple mediation analyses of birth weight and length**

289 The multiple mediation analysis of birth weight showed that the total effect of maternal  
290 education level on birth weight in children of mothers with a low, compared with an  
291 intermediate, education level was negative, with a -0.14 difference in z-scores (**Figure 2**). The  
292 natural indirect effect through smoking was also negative, with a -0.07 difference. There was  
293 no significant natural direct or indirect effect through prepregnancy BMI. Smoking during  
294 pregnancy mediated 52% of this relation. Similar findings were observed with birth length,  
295 although the percentage of mediation was lower (37%, **Figure 2**).

296 The comparison of children from mothers with high and with intermediate education levels  
297 showed no total or direct effect of maternal education level on birth weight or length. There  
298 were, however, significant natural indirect effects through smoking and BMI and they worked  
299 in opposite directions for both birth weight and length (0.03 difference in z-score: positive  
300 and negative, respectively); this difference explains the absence of a total effect.

### 301 **Sensitivity analyses**

302 Results were on the whole consistent when analyses were performed for the complete  
303 database (Population B) for all mediators or repeated for the database with no missing items  
304 on smoking and BMI only (Population A, results not shown but available on request). Results  
305 remained consistent after the exclusion of children born preterm.

## 306 **DISCUSSION**

307 This study, using a validated method to assess multiple mediation, provides new and  
308 comprehensive insights into modifiable prenatal mediators of the social gradient in birth size.

### 309 **Mediators of birth weight and length**

310 Dietary patterns and depressive symptoms during pregnancy did not explain the association  
311 between maternal education level and birth size in this study. To our knowledge, no others  
312 have investigated these two candidate mediators, although this apparent lack of literature may  
313 reflect publication bias. Moreover, dietary patterns and depressive symptoms may be subject

314 to stronger measurement errors than prepregnancy BMI and smoking, which might have  
315 reduced statistical power for these two candidate mediators. Indeed, CES-D measure is a  
316 screening tool but not a diagnosis and dietary patterns were assessed through dietary intake  
317 during the last trimester of pregnancy, which could led to a recall bias. Further research is  
318 needed to confirm or infirm our findings. Perhaps stress during pregnancy, rather than  
319 depression, and energy intake, rather than diet during pregnancy, explain the association  
320 between maternal education and birth size.

321 Consistent with other studies (Jansen et al., 2009; Mortensen et al., 2009; van den Berg et al.,  
322 2012), smoking during pregnancy mediated about 52% of the association between maternal  
323 education and birth weight in the comparison of children of mothers with low, compared with  
324 intermediate, education levels. The pattern of mediation was different when we compared  
325 high vs. intermediate education levels: prepregnancy BMI and smoking during pregnancy  
326 mediated the association of interest, but their indirect effects were in opposite directions and  
327 thus cancelled each other out. Mortensen et al. also found that prepregnancy BMI and  
328 smoking during pregnancy mediated in opposite directions across the entire gradient (and did  
329 not differ whether low or high education levels were compared to the intermediate level)  
330 (Mortensen et al., 2009). Consistent findings for mediation observed with birth length are  
331 noteworthy in our study, which adds a novel and more comprehensive perspective into the  
332 social patterning of birth size.

333 The method proposed by Lange et al. (Lange et al., 2013) enabled us to investigate maternal  
334 education in three categories and observe differential effects in these three groups. However,  
335 the lack of any mediating effect by prepregnancy BMI between the groups with low and  
336 intermediate maternal education must be confirmed in cohorts with greater social variability.  
337 The women in these two subgroups of the Eden cohort were very similar in terms of  
338 prepregnancy BMI.

339 The fact that prepregnancy BMI and smoking during pregnancy cancelled each other out  
340 should not be taken lightly. It means that a baby born to an overweight mother who smokes  
341 has the same birth weight and length as another whose non-smoking mother has a normal  
342 weight. In the first case, birth size would be the result of growth restriction due to exposure to  
343 smoking, masked by excess growth due to maternal obesity (6% of the EDEN women  
344 combined these two characteristics) and misleadingly suggests that their children's growth is  
345 optimal, when it is not. For any given birth size, the distinct causes producing them are  
346 expected to affect later growth, development, and health differentially. Future studies,  
347 investigating metabolic biomarkers in cord blood, might provide evidence supporting (or  
348 contradicting) this hypothesis.

#### 349 **Potential explanation of mechanisms involved**

350 Smoking during pregnancy may affect birth size through different mechanisms. It could lead  
351 to vasoconstriction and to higher maternal and fetal bloods levels of carboxyhemoglobin  
352 (Wickstrom, 2007), which are responsible for fetal hypoxia. Exposure to smoking during  
353 pregnancy is also suspected of modifying regulation of fetal gene expression, by altering  
354 DNA methylation and microRNA expression (Knopik, Maccani, Francazio, & McGeary,  
355 2012). Maternal overweight or obesity is associated with higher birth size of her offspring  
356 (Gaudet, Ferraro, Wen, & Walker, 2014). Mothers with higher BMI have higher levels of  
357 circulating blood glucose (Harmon et al., 2011) and lipids, so that more of these nutrients are  
358 available for the fetus. Increased insulin secretion by the fetal pancreas in response to glucose  
359 in turn accelerates fetal growth (Group, 2009).

360 It is noteworthy that prepregnancy BMI and smoking during pregnancy are modifiable  
361 factors. As two reviews have shown, effective strategies already exist to reduce maternal BMI  
362 and smoking (Johnson et al., 2016; Lancaster, Stead, Silagy, & Sowden, 2000), and the  
363 consistency of our findings across birth weight and length suggests that promoting healthy

364 weight or preventing smoking during pregnancy in future mothers is likely to favorably and  
365 simultaneously affect the offspring's birth weight and length.

### 366 **Limitations and strengths**

367 Study limitations include our inability to consider all potential mediators, thus we did not  
368 fully explain the relation between maternal education and birth size. For example, we did not  
369 take health care utilization into account, although it is hypothesized to improve fetal  
370 monitoring and help prevent fetal growth anomalies. Mothers from the EDEN cohort were,  
371 however, very homogeneous in this respect given the mode of inclusion at the maternity ward  
372 before 24 weeks of gestation. Maternal stress during pregnancy and passive smoking (due to  
373 paternal smoking), unmeasured in the current study, are other relevant mediators to explore.  
374 Classification of prepregnancy BMI relies on self-reported weight. Although women are likely  
375 to under-estimate their prepregnancy weight, and more importantly when overweighted or  
376 obese (Bannon et al., 2017), previous studies have suggested that classification of  
377 prepregnancy BMI remains usually unchanged (Bannon et al., 2017; Holland, Moore Simas,  
378 Doyle Curiale, Liao, & Waring, 2013). Moreover, validity of prepregnancy weight was  
379 previously validated within the EDEN study using multiple pregnancy weights collected all  
380 over pregnancy (Diouf et al., 2014). The presence of selection bias at inclusion, as is often the  
381 case in cohort studies, has implications for the generalization of our findings. We can  
382 hypothesize that a better representation of disadvantaged families at baseline would have  
383 provided more variability and therefore more power to address the study objectives. Further  
384 research is needed to confirm our findings on more datasets with greater social variability.  
385 The method we used to conduct mediation analyses is validated and relevant. To our  
386 knowledge, no dedicated codes to conduct multiple imputation have however been developed  
387 to address missing data. Although there are about 20% missing data in the principal analysis,  
388 sensibility analysis on Population B, which includes only 6% missing data, led to the same



389 results. Furthermore, the Lange method relies on several assumptions. Residual confounding  
390 not taken into account cannot be ruled out; prepregnancy BMI and smoking during pregnancy  
391 might be proxies for other factors related to unhealthy lifestyles. Our data nonetheless met the  
392 principal assumption necessary for using this method: maternal smoking and prepregnancy  
393 BMI were conditionally independent of maternal education level. Examining the stability of  
394 estimates across the one-by-one mediation analysis, multiple mediation, and sensitivity  
395 analyses shows that the results appear robust. Moreover, a clear strength of our study is that  
396 data are from a prospective birth cohort and can thus identify mediators of the longitudinal  
397 association between maternal education level and birth parameters. To our knowledge, this  
398 study, as the first to investigate birth length, provides new insights into the existing literature.  
399 Finally, unlike most mediation analyses, we investigated maternal education level in three  
400 categories to examine the social gradient in birth size in more detail.

#### 401 **CONCLUSION**

402 Among the modifiable factors examined, dietary patterns and depressive symptoms did not  
403 mediate the positive association between maternal education and birth weight and length  
404 while prepregnancy BMI and maternal smoking during pregnancy did so. The latter two  
405 factors, however, act in opposite directions and thus mask the extent to which prenatal growth  
406 is socially differentiated. Although these original findings need to be replicated in more  
407 socially diverse samples, they suggest that promoting a healthy prepregnancy weight and  
408 preventing smoking during pregnancy are keys to addressing socioeconomic inequalities in  
409 healthy fetal growth and thereby attenuating the intergenerational transmission of  
410 socioeconomic health inequalities.

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540 **Figure legends**

541 **Figure 1:** Flow chart of the population included in the study. EDEN mother-child cohort

542 **Figure 2:** Total, direct, and mediated effects [ $\beta$  and 95%CI] for association between maternal  
543 education level and birth weight and length z-scores, mediated by smoking during pregnancy and  
544 prepregnancy BMI, adjusted for center, mother's height, parity, and mother's age at delivery

Table 1 Characteristics of the population at birth. The EDEN mother child cohort (N=1,500)

	Maternal education level <sup>1</sup>			P
	Low (n=383)	Intermediate (n=626)	High (n=491)	
	n (%) or mean ± sd			
<b>Center, Poitiers</b>	218 (56.9)	302 (48.2)	201 (40.9)	<b>&lt;0.0001</b>
<b>Birth weight z-score</b>	-0.15 ± 1.0	-0.03 ± 1.0	0.06 ± 0.9	<b>0.0076</b>
<b>Birth length z-score</b>	0.10 ± 1.0	0.30 ± 0.9	0.41 ± 0.9	<b>&lt;0.0001</b>
<b>Sex, girls</b>	171 (44.7)	298 (47.6)	232(47.3)	0.63
<b>Preterm birth, yes</b>	26 (6.8)	28 (4.5)	30 (6.1)	0.25
<b>Gestational age (weeks)</b>	39.0 ± 1.9	39.4 ± 1.5	39.3 ± 1.5	<b>0.0004</b>
<b>Mother's height, cm</b>	162.3 ± 5.8	163.4 ± 6.4	164.8 ± 5.8	<b>&lt;0.0001</b>
<b>Mother's age, years</b>	28.1 ± 5.7	29.4 ± 4.6	30.8 ± 4.0	<b>&lt;0.0001</b>
<b>Parity, yes</b>	151 (39.4)	301 (48.1)	216 (44.0)	<b>0.03</b>
<b>Depressive symptoms, yes</b>	41 (10.7)	49 (7.8)	25 (5.1)	<b>0.01</b>
<b>Smoking during pregnancy</b>				<b>&lt;0.0001</b>
No	218 (56.9)	471 (75.2)	416 (84.7)	
Only during the 1st trimester	30 (7.8)	56 (9.0)	33 (6.7)	
During pregnancy	135 (35.3)	99 (15.8)	42 (8.6)	
<b>Prepregnancy BMI<sup>2</sup></b>				<b>&lt;0.0001</b>
Underweight	37 (9.6)	47 (7.5)	36 (7.4)	
Normal	227 (59.3)	396 (63.2)	374 (76.2)	
Overweight	83 (21.7)	125 (20.0)	57 (11.6)	
Obesity	36 (9.4)	58 (9.3)	24 (4.8)	
<b>Healthy dietary pattern</b>	-0.2 ± 1.0	-0.1 ± 0.9	0.2 ± 1.0	<b>&lt;0.0001</b>
<b>Western dietary pattern</b>	0.4 ± 1.2	-0.0 ± 0.9	-0.3 ± 0.8	<b>&lt;0.0001</b>

<sup>1</sup>Low: less than high school; intermediate: high school diploma to 2-year university degree, reference category; high: 3-year university degree or more. <sup>2</sup> Underweight: <18.5kg/m<sup>2</sup>; Normal: ≥18.5 and <25kg/m<sup>2</sup>; Overweight: ≥25 and <30kg/m<sup>2</sup>; Obesity: ≥30kg/m<sup>2</sup>

Table 2 Unadjusted associations between birth size z-scores and candidate mediators. EDEN mother child cohort (N=1,500)

	Birth weight z-score		Birth length z-score	
	means $\pm$ sd	<i>P</i>	means $\pm$ sd	<i>P</i>
<b>Depressive symptoms</b>		0.860		0.244
No	-0.03 $\pm$ 0.95		0.30 $\pm$ 0.91	
Yes	-0.02 $\pm$ 1.08		0.19 $\pm$ 1.03	
<b>Smoking during pregnancy</b>		<b>&lt;0.0001</b>		<b>&lt;0.0001</b>
No	0.05 $\pm$ 0.93		0.39 $\pm$ 0.88	
Only during the 1st trimester	-0.06 $\pm$ 0.91		0.19 $\pm$ 0.87	
During pregnancy	-0.35 $\pm$ 1.01		-0.06 $\pm$ 0.97	
<b>Prepregnancy BMI</b>		<b>&lt;0.0001</b>		<b>&lt;0.0001</b>
Underweight	-0.41 $\pm$ 0.92		-0.01 $\pm$ 1.00	
Normal	-0.06 $\pm$ 0.93		0.28 $\pm$ 0.90	
Overweight	0.09 $\pm$ 1.01		0.45 $\pm$ 0.95	
Obesity	0.27 $\pm$ 0.96		0.41 $\pm$ 0.84	
	Corr <sup>1</sup>	<i>P</i>	Corr <sup>1</sup>	<i>P</i>
<b>Healthy dietary pattern</b>	0.06	<b>0.013</b>	0.05	<b>0.006</b>
<b>Western dietary pattern</b>	-0.07	0.056	-0.11	<b>&lt;0.0001</b>

<sup>1</sup>Pearson's correlation

552 Table 3 Natural indirect effect [ $\beta$  and 95%CI] of candidate mediators of the associations between maternal education and birth z-scores

	Birth weight z-score		Birth length z-scores	
	Maternal education level		Maternal education level	
	Low vs. Intermediate	High vs. Intermediate	Low vs. Intermediate	High vs. Intermediate
<b>Smoking during pregnancy</b>	-0.07 [-0.11; -0.04]	0.03 [0.01; 0.05]	-0.08 [-0.12; -0.05]	0.03 [0.02; 0.06]
<b>Prepregnancy BMI</b>	-0.00 [-0.03; 0.02]	-0.03 [-0.06; -0.01]	-0.00 [-0.02; 0.02]	-0.03 [-0.05; -0.01]
<b>Depressive symptoms</b>	0.00 [-0.01; 0.01]	-0.00 [-0.01; 0.01]	-0.00 [-0.01; 0.00]	0.00 [-0.00; 0.01]
<b>Healthy dietary pattern</b>	-0.00 [-0.01; 0.00]	0.01 [-0.01 ; 0.02]	0.00 [-0.00; 0.01]	0.00 [-0.01; 0.01]
<b>Western dietary pattern</b>	-0.02 [-0.04; 0.00]	0.01 [-0.00; 0.02]	-0.02 [-0.05; -0.01]	0.01 [0.00; 0.02]
<b>Western dietary pattern residuals<sup>1</sup></b>	-	-	-0.01 [-0.02; 0.00]	0.00 [-0.00; 0.01]

553 *Adjustment for center, mother's height, parity, and mother's age at delivery*

554 <sup>1</sup> *Residuals of the regression of the Western dietary pattern on BMI, smoking during pregnancy, and confounders*

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