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Title:

Association between perinatal factors, genetic susceptibility to obesity and age at adiposity rebound in children of the EDEN mother-child cohort

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Abstract

Background: Early adiposity rebound (AR) has been associated with increased risk of overweight or obesity in adulthood. However, little is known about early predictors of age at AR. We aimed to study the role of perinatal factors and genetic susceptibility to obesity in the kinetics of AR.

Methods: Body mass index (BMI) curves were modelled by using mixed-effects cubic models, and age at AR was estimated for 1,415 children of the EDEN mother-child cohort study. A combined obesity risk-allele score was calculated from genotypes for 27 variants identified by genome-wide association studies of adult BMI. Perinatal factors of interest were maternal age at delivery, parental education, parental BMI, gestational weight gain, maternal smoking during pregnancy, and newborn characteristics (sex, prematurity, birth weight). We used a hierarchical level approach with multivariable linear regression model to investigate the association between these factors, obesity risk-allele score, and age at AR.

Results: A higher genetic susceptibility to obesity score was associated with an earlier age at AR. At the most distal level of the hierarchical model, maternal and paternal educational levels were positively associated with age at AR. Children born to parents with higher BMI were more likely to exhibit earlier age at AR. In addition, higher gestational weight gain was related to earlier age at AR. For children born small for gestational age, the average age at AR was 88 [\pm 39] days lower than for children born appropriate for gestational age and 91 [\pm 56] days lower than for children born large for gestational age.

Conclusion: The timing of AR seems to be an early childhood manifestation of the genetic susceptibility to adult obesity. We further identified low birth weight and gestational weight gain as novel predictors of early AR, highlighting the role of the intrauterine environment in the kinetics of adiposity.

1 **1. Introduction**

2 After birth, body mass index (BMI) increases to a peak during the first year of life and
3 declines between age 4 and 6 years, then increases again. This BMI increase following the
4 minimum is called adiposity rebound (AR).¹⁻³ This period has been characterized by cessation
5 in the decline of fat mass index (defined as fat mass divided by height square).⁴ The timing of
6 AR, independent of BMI itself, is considered a predictor of obesity in later childhood and
7 adulthood.⁵⁻⁷ More specifically, early AR is associated with increased risk of overweight or
8 obesity and cardiometabolic diseases in adulthood.⁸⁻¹⁰

9 To provide a track to prevent the development of obesity, one must follow children's
10 BMI growth curve and better understand the determinants of age at AR. Furthermore, the
11 DoHAD theory¹¹ suggests that the intrauterine and early postnatal environment are crucial to
12 the child's and adult's healthy development,¹² along with the existence of a nutritional and/or
13 metabolic programming of the development of obesity.¹³ As an example, excessive and
14 insufficient gestational weight gain was associated with increased risks of adverse childhood
15 outcomes for the offspring such as low and high birth weight¹⁴ and obesity in later life.^{15,16}
16 Similarly, several studies have shown being small or large for gestational age associated with
17 increased risk of overweight and obesity.^{17,18} Although the link between intrauterine and early
18 postnatal environment factors and age at AR has not been thoroughly investigated in the
19 literature, a set of early prenatal and postnatal determinants of age at AR have been identified.
20 A longitudinal study interested in pre-, perinatal, and parental determinants of the kinetics of
21 the BMI curve among 1,681 children showed that girls had earlier age at AR than boys.¹⁹
22 Parental educational level, especially low maternal level of education (< 7 years), is an
23 additional important risk factor for early AR.² In their retrospective study, Péneau *et al.*
24 examined the determinants of age at AR and reported that a larger maternal silhouette was
25 associated with early age at AR in both boys and girls, while the paternal silhouette was
26 related with early age at AR in girls only.²⁰ However, further evidence is needed to confirm
27 these findings with measured parental weight data instead of reported silhouettes.

28 Genome-wide associations studies have highlighted single nucleotide polymorphisms
29 implicated in increased risk of obesity^{21,22} and the use of genetic susceptibility scores has been
30 established. In a meta-analysis of four European cohorts,²³ Elks *et al.* showed that association
31 with this genetic susceptibility score emerges progressively associated in childhood with a

32 child's weight, height and BMI. However, to our knowledge, only one study has investigated
33 the role of this genetic susceptibility to obesity in the kinetics of BMI at the time of AR.²⁴

34 In this context, the purpose of this study was to investigate the role of parental education,
35 perinatal factors and genetic susceptibility to obesity in the kinetics of AR within the French
36 EDEN mother-child cohort. We hypothesize that the association between age at AR and
37 perinatal factors is independent of genetic susceptibility to obesity and that age at AR could
38 be programmed by a set of factors involved as early as in pregnancy.

39 2. Material and methods

40 2.1. Study population

41 The EDEN mother-child study is a prospective French cohort that aims to assess prenatal and
42 postnatal determinants of child growth, health and development. This cohort included 2,002
43 pregnant women (before 24 weeks of amenorrhea) recruited from 2003 to 2006 in two
44 university hospitals in Nancy and Poitiers. Exclusion criteria were less than 18 years of age,
45 multiple pregnancies, known diabetes before pregnancy, illiteracy, and intention to give birth
46 elsewhere than these two French hospitals or to move outside the region within the next 3
47 years. Details of the study protocol have been published elsewhere.²⁵

48 The study was approved by the relevant ethical research Committee of
49 Kremlin- Bicêtre Hospital and by the Data Protection Authority. Both parents gave their
50 written consent.

51 2.2. Data collection and variables generation

52 2.2.1. Data collection

53 Data were collected from medical and obstetrical records or by interviews, face-to-face or
54 self-administered questionnaires and clinical examinations. Biological samples,
55 anthropometric and clinical parameters measurements were collected during clinical
56 examinations at birth, 1, 3 and 5 years. In all children, weight and height from birth to early
57 adolescence were obtained during these visits or from health records. Children had a mean of
58 10 weight and height measurements (interquartile range 6- 14 and 5-13, respectively) from
59 birth to 13 years. Maternal smoking status during pregnancy (yes/no); parental characteristics
60 such as maternal age (years), maternal and paternal educational level and parental
61 anthropometric measurements were collected during pregnancy. Newborn characteristics as
62 well as sex, gestational age, and birth weight were taken at birth.²⁶ Preterm birth (yes/no) was
63 defined as babies born before 37 weeks of gestation. Birth weight customized z-scores were
64 calculated according to Gardosi references taking into account physiological fetal (sex and
65 gestational age) and maternal factors (weight, height, parity, origin).²⁷ Newborns were
66 classified, according to this customized approach, into 3 classes: small for gestational age
67 (SGA, $\leq 10^{\text{th}}$ percentile), appropriate for gestational age (AGA, $>10^{\text{th}}$ percentile to $\leq 90^{\text{th}}$
68 percentile), and large for gestational age (LGA, $>90^{\text{th}}$ percentile).

69

70 Maternal and paternal education level was considered as the number of years of study.
71 Parental weight and height were collected by interview at inclusion. Parental anthropometric
72 measurements were collected at inclusion were used to calculate parental BMI by dividing the
73 weight (kilograms) by the square of height (meters). Gestational weight gain (kilograms) was
74 collected from obstetric records.

75

2.2.2. Genotyping and BMI obesity risk-allele score

76 DNA samples were extracted from cord-blood at birth. Genotyping for 27 single-nucleotide
77 polymorphisms (SNPs) was performed by the Epidemiology Unit of the Medical Research
78 Council of Cambridge (iPLEX platform; Sequenom).²⁸ Genotyping quality-control criteria
79 (call rate, >95%; Hardy Weinberg balance, $P > 0.01$) were satisfactory for all variants. In the
80 present study, we considered 27 of 32 SNPs associated with BMI in adults,²¹ of which also
81 the 16 associated with childhood BMI in a meta-analysis of Elks *et al.*²³

82 For each child, combined obesity risk- allele scores across the 27 SNP loci were
83 calculated as the sum of risk alleles (0, 1, or 2 at each locus) associated with increased BMI.
84 The score indicating genetic predisposition to obesity ranged from 11 to 32. Combined
85 obesity risk- allele scores were available for 1,322 children of the EDEN cohort and their
86 mothers (N=1,678) and fathers (N=1,241).²⁹

87 A weighted obesity risk-allele score was also computed by multiplying each risk allele
88 by the effect estimate on adult BMI as assessed in the genome-wide association study²¹, for
89 sensitivity analyses.

90

2.2.3. Estimation of AR

91 Age at AR is defined as the last minimum (nadir) BMI before the continuous increase in BMI
92 over time.¹

93 We calculated BMI from weight and height measurements. We excluded children with
94 fewer than three BMI measurements from age 18 months to 13 years. Included children had
95 10 BMI values on average (interquartile range 6-14) from age 18 months to 13 years.
96 Individual growth curves were obtained by using mixed-effects cubic models separately for
97 girls and boys. The methods for growth modelling of age at AR were inspired by the model of
98 Sovio *et al.*³⁰ To this previously described model, we added random effects for the quadratic
99 and cubic terms for age with unstructured covariance matrix, which provided the best fit of

100 individual predicted curves. The model was then fitted for log-transformed BMI, separately
101 for boys and girls, as follows:

$$102 \quad \log(\text{BMI}) = \beta_0 + \mu_0 + (\beta_1 + \mu_1) \text{Age} + (\beta_2 + \mu_2) \text{Age}^2 + (\beta_3 + \mu_3) \text{Age}^3 + \varepsilon$$

103 where BMI is expressed in kilograms per square meter and age in days; β_0 , β_1 , β_2 , β_3 , and β_4 ,
104 are the fixed-effects terms; μ_0 , μ_1 , μ_2 and μ_3 are the individual-level random effects; and ε is
105 the residual.

106 For each participant, we estimated age at AR by the first and second derivatives of
107 individual BMI functions. Results of this modelling process are illustrated for a random
108 sample of 10 participants in [Supplementary figure S1](#).

109 **2.3. Sample selection**

110 Among the 1,907 newborns included in the EDEN cohort, we excluded 326 children without
111 BMI measurements after 18 months and a further 126 who had fewer than three BMI
112 measurements between age 18 months and 13 years. We also excluded 10 children for whom
113 AR could not be assessed because their BMI curve did not display any AR (see
114 [Supplementary figure S2](#)). Therefore, the final sample included 1,415 children; 69.8% (988)
115 had available obesity risk-allele scores ([Figure 1](#)).

116 **2.4. Statistical analysis**

117 Main characteristics of study population were described with mean \pm SD or percentage (N)
118 before any imputation. We tested differences between included and excluded populations with
119 chi-square tests for categorical variables and Student *t* for continuous variables. We also
120 described and compared covariates according to each quintile of age at AR by chi-square tests
121 and ANOVA. The associations between perinatal factors, obesity risk-allele score and age at
122 AR were investigated by linear multiple regression models.

123 By using the predictors identified in the literature, we developed a hierarchical level
124 approach to answer our research question ([Supplementary figure S3](#)), which assumes that
125 proximal variables have more direct effect than distal variables: the relevance of a factor is
126 determined in the model in which the variable was first entered, without considering its
127 performance in other models. This approach allows us to prevent that intermediate variables
128 affect the association between distal variables and the dependent variable.

129 Therefore, we tested four successive nested models. Model A included the most distal-
130 level variables corresponding to demographic and socio-economic factors (maternal age at
131 delivery, maternal and paternal educational level), along with recruitment center; model B
132 further included factors related to obesity risk such as child's obesity risk-allele score and
133 maternal and paternal BMI; model C included also variables corresponding to the intrauterine
134 and prenatal environment (gestational weight gain and maternal smoking during pregnancy);
135 model D corresponded to the most proximal level, with the inclusion of newborn
136 characteristics (sex, prematurity, and birth weight z-score). Birth weight z-score was
137 introduced with a squared term to test for a potential quadratic shape of the association.

138 To assign a value to missing data for covariates (Supplementary table S1), we first
139 performed multiple imputation analyses, assuming that data were missing at random. Using
140 the fully conditional specification method, we generated 40 independent datasets. Then, we
141 computed pooled effect estimates. Parental obesity risk-allele scores were used to impute
142 children's scores when these were missing. With multiple imputation, the main analysis
143 involved a sample of 1,415 children.

144 We conducted a first sensitivity analysis running our multivariable models with data for
145 the 866 children with complete cases. Most of the decline in sample size was due to the lack
146 of obesity risk-allele score for many children. As a second sensitivity analysis, we tested the
147 associations between weighted obesity risk-allele score, perinatal determinants and age at AR
148 in the fully adjusted model with multiple imputation. Finally, we conducted a sensitivity
149 analysis excluding children born prematurely.

150 As complementary analyses, we first performed association analyses between perinatal
151 factors, obesity risk-allele score, and risk of early AR, using logistic multiple regression
152 models, estimating odds ratios and 95% confidence intervals (OR [95% CI]). We defined
153 early AR as a rebound occurring before the first quintile of the distribution of age at AR.
154 Then, we investigated each polymorphism used to establish the obesity risk-allele score and
155 tested its individual association with age at AR. For this analysis, we assumed that the alleles
156 of a given SNP have co-dominant effects, as is the case for the score computation. Therefore,
157 we considered the SNPs (categorized as 0, 1 and 2) as continuous variables. The analysis of
158 each SNP involved linear regression analysis of complete cases with β corresponding to the
159 change in days for one additional mutated allele carried.

160 We considered nominal $p < 0.05$ as statistically significant. We used R v3.5.1 for
161 modelling BMI trajectories and estimating age at AR and SAS v9.4 (SAS, Cary, NC, on an
162 AIX 7.1 platform) for all other analyses.

163 3. Results

164 3.1. Population characteristics

165 Compared to mothers of excluded children, those of included children (n=1415) had on
166 average a higher number of years of study and were older at delivery ($p = 3.0 \times 10^{-10}$) (Table 1).
167 Included infants were born at higher gestational age ($p = 0.03$) and had higher birth weight (p
168 $= 0.03$) than excluded children but were similar in sex ($p = 0.79$) and maternal pre-gestational
169 BMI ($p = 0.08$).

170 Among the 1415 children included, the mean (\pm SD) age of AR was estimated at 5.5
171 (± 1.3) and 5.4 (± 1.4) years for boys and girls, respectively ($p = 0.08$). The first quintile of the
172 distribution of age at AR was estimated at 4.4 years.

173 The description of predictors according to the quintiles of age at AR is provided in
174 Supplementary table S2. Except for prematurity, gestational weight gain, maternal age at
175 delivery and obesity risk-allele score, all considered factors were significantly differed by
176 quintile of age at AR.

177 3.2. Determinants associated with the timing of AR

178 Multivariable associations with age at AR are displayed in Table 2. Model A showed that
179 high maternal and paternal educational level were associated with later AR (β [\pm SE] = 15.7
180 [\pm 6.2] and 14.4 [\pm 6.0] days per year of study, $p = 0.01$ and 0.02, respectively), with no
181 association with the other socio-demographic factors considered in this model. Furthermore,
182 all variables related to parental obesity (Model B) and prenatal and intrauterine factors (Model
183 C) were significantly associated with age at AR: age at AR decreased with mean obesity risk-
184 allele score (-9.2 [\pm 4.6] days per allele, $p = 0.05$), maternal and paternal BMI (-15.8 [\pm 3.1]
185 days per kg/m^2 , $p = 1.9 \times 10^{-7}$, and -15.6 [\pm 3.9] days per kg/m^2 , $p = 5.6 \times 10^{-5}$), gestational weight
186 gain (-7.5 [\pm 2.9] days per kg, $p = 0.001$) and smoking during pregnancy (-72.1 [\pm 32.6] days,
187 $p = 0.03$). Finally, birth weight z-score was the only child characteristic at birth associated with
188 age at AR with a significant quadratic effect ($p = 0.05$).

189 To illustrate this last result, the mean age of AR and their confidence interval by
190 category of birth weight z-score are presented in Figure 2. On average, children born SGA

191 had an age at AR 88 [\pm 39] days lower than children born AGA, and 91 [\pm 56] days earlier
192 than children born LGA.

193 **3.3. Sensitivity and complementary analyses**

194 In the sensitivity analysis, results were on the whole consistent with analyses limited to
195 children with no missing data (complete-case analysis) (Supplementary table S3). However,
196 the associations observed between maternal educational level (Model A), smoking during
197 pregnancy (Model C) and age at AR were no longer significant. We also observed that the
198 strength of association was higher with obesity risk-allele score and birth weight z-score, but
199 lower with parental BMI. Results with the weighted obesity risk-allele score were consistent
200 with, albeit slightly weaker, than those with the unweighted obesity risk-allele score
201 (Supplementary table S4). When preterm children were removed from the analyses, the
202 association between birth weight z-score and age at AR became stronger and the risk of early
203 AR for SGA was greater (2.23 [1.52–3.28]) (Supplementary table S5).

204 The results of logistic regression analyses testing the association between obesity risk-
205 allele score, perinatal factors, and odds of early AR, are summarized in Supplementary figure
206 4. Higher maternal educational level was associated with reduced odds of early AR. Odds of
207 early AR were increased with each additional obesity risk-allele, higher maternal and paternal
208 BMI, and higher gestational weight gain. Risk of early AR was higher for children born SGA
209 than AGA children. We found no association between LGA children and risk of early AR.
210 Risk of early AR was higher for girls than boys.

211 In analyses considering each polymorphism separately (Supplementary figure S5), we
212 found no significant association. The associations between rs10913469 at the locus harboring
213 SEC16B, rs713586 at the locus harboring RBJ/POMC and age at AR were at the limit of
214 significance.

215

216 **4. Discussion**

217 We found that genetic susceptibility to obesity was negatively associated with age at AR in
218 the EDEN mother-child study. Additionally, we confirmed that some previously described
219 perinatal factors, such as parental BMI, were associated with age at AR^{2,20} but also further
220 identified novel predictors such as birth weight and mother's gestational weight gain.
221 Probability of early AR was increased with high gestational weight gain and low birth weight.

222 This is the first study to simultaneously analyze the association between perinatal factors,
223 genetic predisposition to obesity and age at AR, taking the assumed hierarchical structure
224 between the potential predictors into account. At the most distal level, maternal and paternal
225 education were negatively associated with risk of early AR, in accordance with previous
226 studies.² This association was attenuated with the inclusion of the more proximal groups of
227 variables. A longitudinal study of 889 representative children in the United Kingdom showed
228 no association between parental educational level or socioeconomic factors and time of AR.³¹
229 This result was obtained after adjustment for parental BMI, which make our two studies
230 concordant. Future studies could use proper mediation analyses to quantify the mediating
231 contribution of each of these factors and help prioritize effective interventions to reduce social
232 inequalities in obesity.

233 The genetic susceptibility to obesity was associated with an increased probability of early
234 AR. The role of genetic factors in AR timing was investigated recently in a genome-wide
235 association study including up to 7,215 children in five European cohorts. In this study, Couto
236 Alves et al. identified an association between two single nucleotide polymorphisms (SNPs)
237 and age at AR. Although the rs1421085 (at the locus harboring *FTO*) was not associated with
238 age at AR, we noted a statistically significant association for rs10913469 (at the locus
239 harboring *SEC16B*) and an association at the limit of significance for rs713586 (at the locus
240 harboring *RBJ/POMC*) but with reduced statistical power. In accordance with our results, the
241 authors reported a negative association between an obesity risk-allele score, based on 97
242 SNPs, and child age at AR, but did not model the effects of other life factors.²⁴ Altogether,
243 these results illustrate that the observed association between a score of genetic susceptibility
244 to obesity and timing of AR is the result of a cumulative effect of individual SNPs. The
245 authors also highlighted the relevance of using cumulative scores to address the genetic
246 predisposition to early AR.

247 Consistent with previous research, we found that high parental BMI predicted early AR
248 in children. A longitudinal study of 248 families enrolled in North Carolina concluded high

249 maternal BMI as the robust predictor of early AR.² Another longitudinal study of a New
250 Zealand cohort found that mothers and fathers of children with early BMI rebound had
251 significantly heavier as compared with late rebounders.³² Two other investigations also
252 demonstrated that children with early AR had at least one parent with obesity.^{31,33} All these
253 analyses recognized maternal BMI as a proxy variable reflecting the child's susceptibility to
254 obesity. However, we found the association between parental BMI and age at AR was
255 independent of the obesity risk-allele score, which suggests that parental BMI might have an
256 effect independent of genetic predisposition to obesity. Indeed, parental BMI also reflects an
257 obesogenic environment (familial environment, food choices, eating patterns, and physical
258 activity) that may affect the kinetics of adiposity during childhood.^{34,35} Moreover, we
259 observed that the association of mother's pre-pregnancy BMI seemed to be slightly higher,
260 even if not significantly (results not shown), than that of paternal BMI, which also suggests a
261 role for nutritional environment during prenatal life.

262 Our results regarding gestational weight gain support this latter hypothesis. To our
263 knowledge, only one study has considered gestational weight gain as a potential predictor of
264 age at AR, but no significant association was shown.³⁶ However, previous reports focused on
265 the link between gestational weight gain and childhood overweight at various ages. In the
266 current EDEN cohort, a positive association was found between gestational weight gain and
267 child's BMI at age 5 to 6 years.³⁷ Likewise, a meta-analysis of 37 cohort studies from Europe,
268 North America, and Australia showed that high gestational weight gain was related with
269 increased risk of overweight/obesity in childhood, with stronger associations effects observed
270 at later ages.¹⁵ Our results suggest that the age of AR could in part mediate the association
271 between gestational weight gain and overweight/obesity in late childhood and adolescence
272 described in this meta-analysis, but further research would be necessary to confirm this
273 assumption.

274 We found a negative association between maternal smoking status during pregnancy and
275 the timing of AR but not risk of early AR. A longitudinal analysis, based on mothers from the
276 longitudinal Growth and Obesity Chilean Cohort Study, also showed no link between
277 smoking status during pregnancy and risk of early AR.³⁸ In previous analyses of the EDEN
278 cohort, Carles et al. applied a joint Bayesian model to explore the association between
279 maternal smoking status during pregnancy and growth:³⁹ children from mothers who smoked
280 throughout pregnancy were born smaller but had higher BMI in their first months of life until
281 age 5 as compared with children born to non-smokers. In the Generation R study, maternal
282 smoking during pregnancy was associated with increased BMI at age 4 years for children with

283 normal birth weight and SGA at birth.⁴⁰ Conversely, in the ALSPAC cohort, smoking during
284 pregnancy was not associated to child weight status at age 5 years.⁴¹ Thus, the association
285 between maternal smoking during pregnancy and rapid postnatal growth might be due to its
286 impact on fetal development but also to confounding by socioeconomic factors. Further
287 studies are needed to confirm or not any effect of smoking during pregnancy on age at AR.
288 For the first time, we identified birth weight for gestational age as a predictor of age at AR.
289 Some previous studies did include birthweight in their multiple models but did not find any
290 significant association with age at AR. For the “Children in Focus” group from the ALSPAC
291 cohort, no difference in birth weight was observed between the groups of very early, early and
292 later AR.⁴² In contrast, our results indicate that children born SGA were at increased risk of
293 early AR, whereas children born LGA were not. A cross-sectional study in Lausanne showed
294 an association between low birth weight and anthropometric obesity markers in adulthood.⁴³
295 Similarly, the review article of Hong and Chung highlighted the association between SGA
296 children and greater adiposity and obesity in later life.¹⁷ However, Kapral and colleagues
297 found this association only in preterm children.¹⁸ These findings highlight that SGA
298 newborns tend to rapidly “catch up”, and that this “catch-up” is characterized by an increase
299 in fat mass greater than lean mass.⁴⁴ Furthermore, several systematic reviews have shown a
300 strong association between rapid infancy weight gain and greater risk of obesity, overweight
301 or increased adiposity in later life.^{45,46} The catch-up phenomenon would be due to different
302 mechanisms of adaptation of a newborn exposed to undernutrition in utero, which could have
303 remote impact on age at AR.⁴⁷ The respective role of intra-uterine growth restriction versus
304 postnatal growth acceleration in this association still needs to be disentangled.

305 Even if some of our results need confirmation and replication, they highlight a number of
306 prenatal factors, including smoking during pregnancy, maternal pre-pregnancy BMI,
307 gestational weight gain and birth weight for gestational age, possibly involved in the timing of
308 AR. These findings strongly suggest that some intra-uterine programming may also be at
309 work in the etiology of this specific adiposity phenotype. Among the possible mechanisms,
310 altered fetal nutrition could lead to persistent changes in the structure and function of adipose
311 tissue, regulation of appetite and energy metabolism, which could affect the kinetics of
312 adiposity and its rebound.¹⁵ Epigenetic mechanisms could also be involved, but further studies
313 are needed to better understand these.⁴⁸

314 The main strength of this study is that anthropometric data were assessed repetitively and
315 prospectively from birth to age 13, which allowed us to estimate age at AR for a large number
316 of children. As is often the case in cohort studies, the presence of selection bias at inclusion

317 and missing data of covariates but also attrition bias limits the generalization of the results.
318 However, multiple imputations and growth modelling of individual growth curves helped
319 reduce the risk of these biases. Another limitation is that we could not consider ethnicity in
320 our analyses, because the information was not collected in the EDEN cohort. Nonetheless, for
321 85% of children in the EDEN cohort, both parents were born in France and came from French
322 regions where most of the population has a Caucasian origin. Moreover, the construction of
323 the genetic score relies on the assumption of a co-dominant effect of each allele of a given
324 SNP, which is not always true and could induce measurement errors. Our results, relying on
325 observational data, need to be replicated in other studies with larger samples and with distinct
326 designs to provide additional arguments for a causal interpretation of the observed
327 associations. Further studies are needed to examine postnatal factors involved in the kinetics
328 of BMI growth curve, to better characterize children at risk of early rebound. Indeed, the
329 detection of early age at AR might be a useful tool for tailored and personalized child's
330 growth monitoring aiming at preventing overweight/obesity and chronic disease in later life.

331 **5. Conclusion**

332 We confirmed that genetic susceptibility to adult obesity plays a predictive role in the timing
333 of age at AR. Timing of AR in early childhood may contribute to the path from genetic
334 susceptibility to obesity onset. Independent of this genetic background, we identified several
335 prenatal predictors, including two novel factors, gestational weight gain and birth weight.
336 These results strongly support that intra-uterine programming may also be at work in the
337 etiology of this specific adiposity phenotype.

338

339

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Author contributions

None of the authors have any financial relationships or conflict of interest to disclose.

AC and BH designed the research, wrote the manuscript and analyzed the data.

BH, KKO, MAC, AF and BLG were responsible for data collection and genotyping in EDEN.

All authors reviewed drafts, provided critical feedback, approved the final manuscript and were responsible for the final content of the paper. BH had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Conflict of interest

The authors declare that they have no conflict of interest.

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Table 1: Characteristics of the included and excluded EDEN cohort in the study of adiposity rebound.

	Mean (SD) or % (N)		P > t or χ^2
	Included N=1415	Excluded N= 492	
Sex (boys)	52.7 (746)	52.1 (254)	0.79
Preterm birth	5.5 (78)	6.5 (32)	0.41
Birth weight (kg)	3.29 (0.5)	3.23 (0.5)	0.03
Birth weight zscore			0.04
SGA	13.3 (184)	13.2 (62)	
AGA	77.4 (1070)	81.3 (383)	
LGA	9.3 (128)	5.5 (26)	
Gestational weight gain (kg)	13.3 (4.7)	13.8 (5.2)	0.03
Maternal BMI (kg/m²)	23.1 (4.4)	23.6 (5.1)	0.08
Paternal BMI (kg/m²)	25.1 (3.6)	24.7 (3.7)	0.03
Never smoking during pregnancy	78.6 (1088)	59.4 (275)	4.0×10^{-16}
Maternal age at delivery (years)	29.9 (4.7)	28.2 (5.2)	3.0×10^{-10}
Maternal educational level (years)	14.0 (2.6)	12.5 (2.5)	4.5×10^{-30}
Paternal educational level (years)	13.3 (2.6)	12.2 (2.4)	3.7×10^{-18}
Obesity risk- allele score	21.6 (3.2)	21.3 (3.4)	0.15
Age at adiposity rebound (years)			0.08 ^a
Boys	5.5 (1.3)	-	-
Girls	5.4 (1.4)	-	-

^a p value of mean age at adiposity rebound comparing boys and girls.

BMI, body mass index

Table 2: Multivariable linear regression of factors associated with age at adiposity rebound (N=1415^a)

Characteristics	Model A		Model B		Model C		Model D	
	β (SE)	p value	β (SE)	p value	β (SE)	p value	β (SE)	p value
Center (ref=Poitiers)	-0.8 (26.6)	0.98	-14.1 (26.2)	0.59	-22.3 (26.2)	0.40	-14.9 (26.3)	0.57
Level 1^b								
Maternal age at delivery (years)	2.8 (2.9)	0.33	5.1 (2.8)	0.070	3.7 (2.9)	0.19	3.9 (2.8)	0.17
Maternal educational level (years)	15.7 (6.2)	0.011	13.4 (6.1)	0.027	11.3 (6.1)	0.064	10.0 (6.1)	0.10
Paternal educational level (years)	14.4 (6.0)	0.017	8.5 (6.0)	0.16	7.4 (6.0)	0.22	7.0 (6.0)	0.24
Level 2								
Obesity risk-allele score			-9.2 (4.6)	0.045	-9.1 (4.6)	0.045	-9.0 (4.5)	0.047
Maternal BMI (kg/m ²)			-15.9 (3.1)	1.9×10 ⁻⁷	-18.2 (3.1)	6.3×10 ⁻⁹	-18.0 (3.1)	8.9×10 ⁻⁹
Paternal BMI (kg/m ²)			-15.6 (3.9)	5.6×10 ⁻⁵	-15.3 (3.9)	6.9×10 ⁻⁵	-15.3 (3.8)	6.7×10 ⁻⁵
Level 3								
Gestational weight gain (kg)					-7.5 (2.9)	0.009	-8.6 (3.0)	0.004
Smoking during pregnancy (ref=no)					-72.1 (32.6)	0.027	-62.3 (32.7)	0.057
Level 4								
Preterm birth (yes vs no)							39.4 (57.7)	0.50
Birth weight z-score							24.1 (12.4)	0.053
Birth weight z-score ²							-14.4 (7.3)	0.047
Sex (girls vs boys)							-47.2 (25.8)	0.067

^a Missing data for covariates were imputed with the fully conditional specification method.

^b Relevance of a variable during the hierarchical regression analyses was determined with the corresponding model in which the variable of interest is first entered, regardless of its performance in the subsequent model(s).

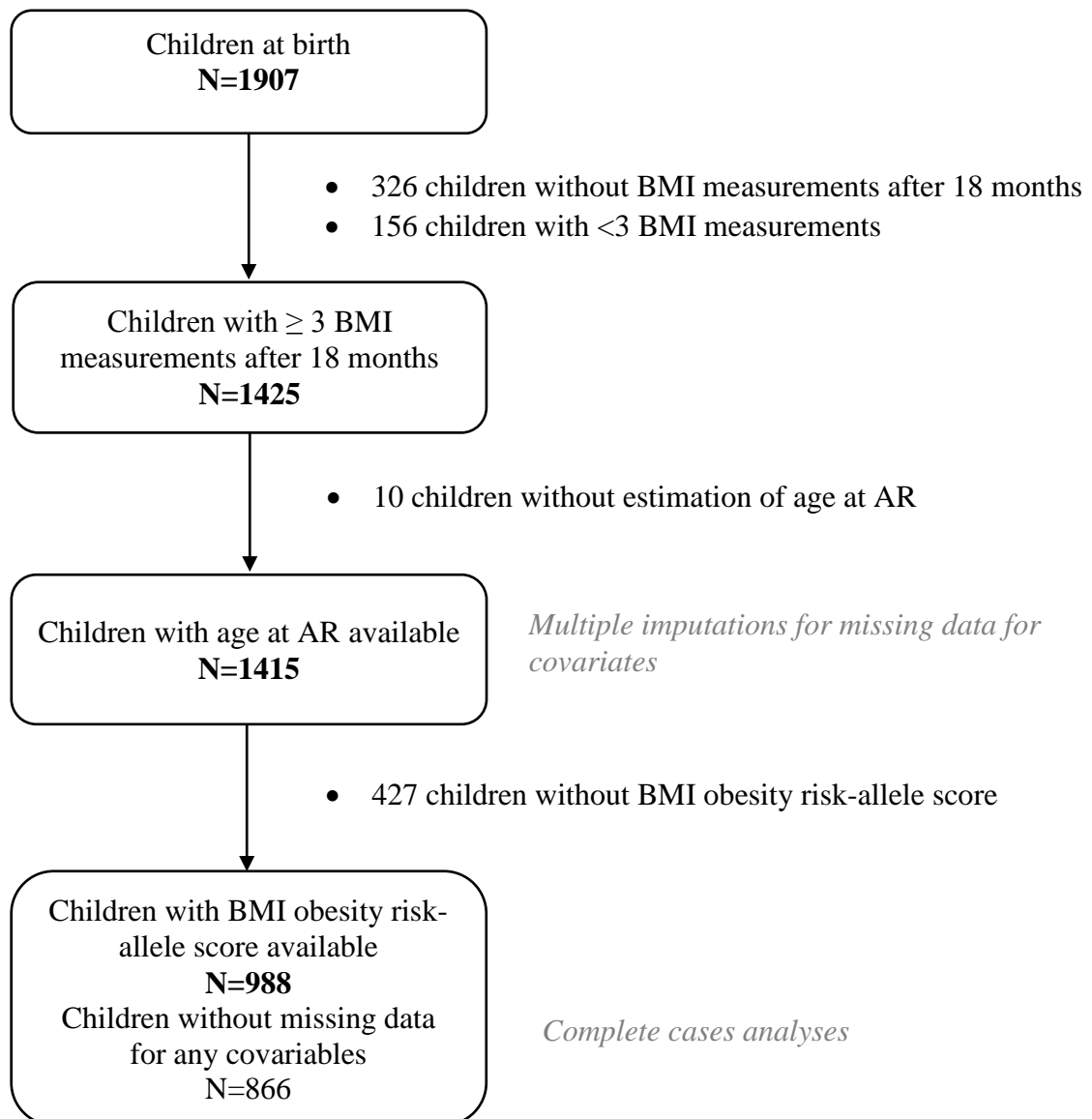


Figure 1: Flow chart of the population included in the study.

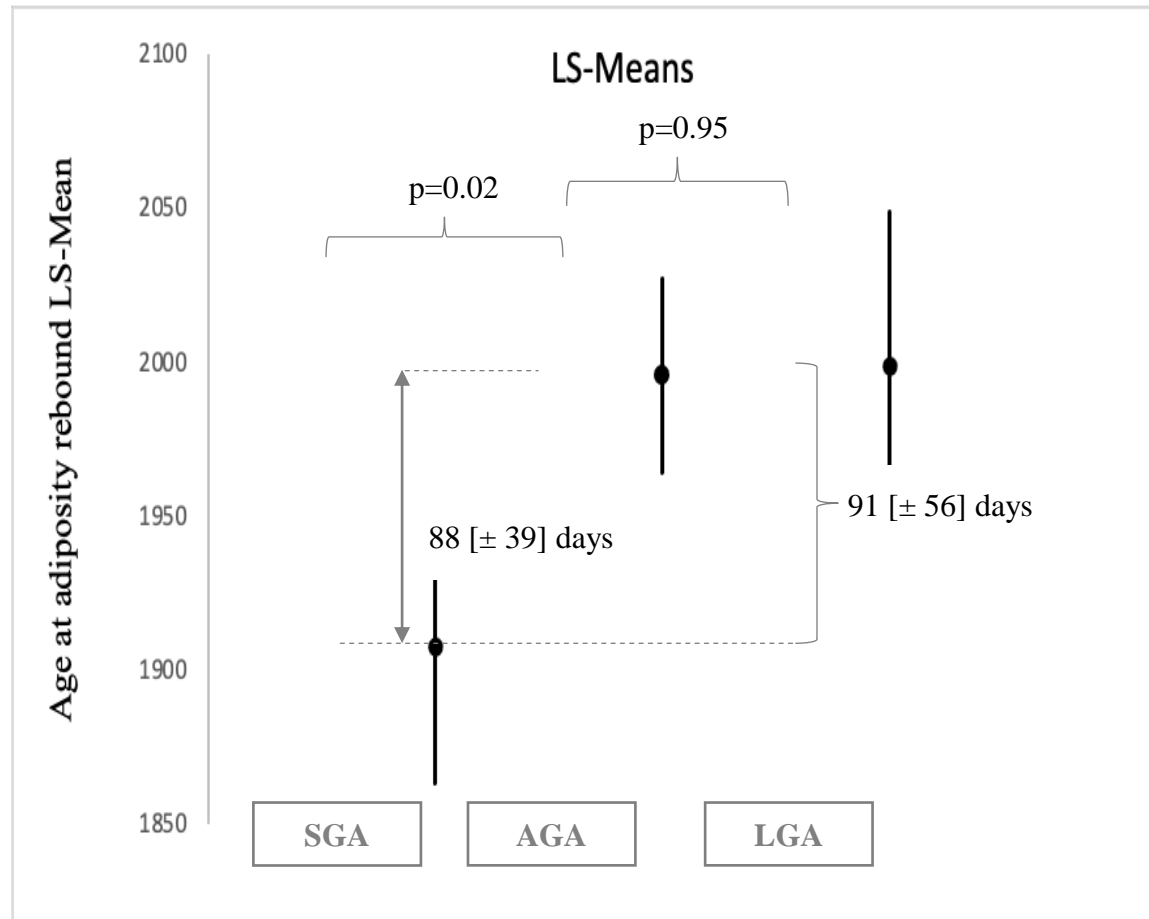


Figure 2: Adjusted means [SE] of age at adiposity rebound according to birth weight z-score categories (N=1415^a, model D^b).

^a Missing data for covariates were imputed with the fully conditional specification method.

^b Adjusted for center, maternal age at delivery, maternal and paternal educational level, maternal and paternal BMI, gestational weight gain, smoking during pregnancy, prematurity, birth weight s-score and sex.

Supplementary table S1: Details of the method used for multiple imputation

Variables	Type of variable	Model used to predict missing data ^a	Missing value (%)
Age at adiposity rebound	Continuous		0
Early adiposity rebound	Binary	Logistic regression	
Center	Binary	Logistic regression	0
Sex	Binary	Logistic regression	0
Birth weight	Continuous	Linear regression	0
Personalized birth weight z-score	Continuous	Linear regression	2.3
Gestational age	Continuous	Linear regression	0
Preterm birth	Binary	Logistic regression	0
Weight predicted at 5 years by Jenss-Bayley modelling ^b	Continuous	Linear regression	0
Height predicted at 5 years by Jenss-Bayley modelling ^b	Continuous	Linear regression	0
Child's obesity risk-allele score	Continuous	Linear regression	30.4
Maternal age at delivery	Continuous	Linear regression	0
Gestational weight gain	Continuous	Linear regression	1.9
Smoking during pregnancy	Binary	Logistic regression	2.2
Maternal education	Continuous	Linear regression	0
Maternal income	Ordinal (3 categories)	Multinomial regression	0.6
Maternal BMI	Continuous	Linear regression	1.8
Maternal obesity risk-allele score	Continuous	Linear regression	11.7
Paternal education	Continuous	Linear regression	0
Paternal BMI	Continuous	Linear regression	6.7
Paternal obesity risk-allele score	Continuous	Linear regression	31.5

BMI, body mass index

^a Fully conditional specification method.

^b Predicted weight and height were calculated by using previously modelled trajectories from the Jenss–Bayley model (1,2).

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Supplementary table S2: Characteristics by quintile of age at AR of the study population.

	1st quintile N=284	2nd quintile N=282	3rd quintile N=283	4th quintile N=283	5th quintile N=283	Comparison between quintiles
	Means (SD)	Means (SD)	Means (SD)	Means (SD)	Means (SD)	p^a
	or % (N)	or % (N)	or % (N)	or % (N)	or % (N)	
Sex (boys)	52.8 (150)	49.0 (138)	42.1 (119)	43.1 (122)	49.5 (140)	0.05
Preterm birth	4.58 (13)	3.9 (11)	6.4 (18)	6.7 (19)	6.0 (17)	0.53
Birth weight z-score	-0.26 (1.20)	-0.12 (1.05)	-0.07 (1.01)	-0.05 (1.07)	-0.14 (1.02)	0.18
SGA	19.6 (54)	12.7 (35)	10.2 (28)	10.4 (29)	13.7 (38)	0.04
AGA	70.2 (193)	78.2 (215)	81.0 (222)	79.3 (222)	78.4 (218)	.
LGA	10.2 (28)	9.1 (25)	8.8 (24)	10.4 (29)	7.9 (22)	.
Gestational weight gain (kg)	13.7 (5.4)	13.3 (5.0)	13.2 (4.5)	13.2 (4.6)	13.0 (3.8)	0.52
Maternal BMI (kg/m ²)	24.5 (5.0)	23.3 (4.7)	23.0 (4.0)	22.4 (3.9)	22.4 (4.1)	8.4×10 ⁻⁹
Paternal BMI (kg/m ²)	26.1 (3.8)	25.0 (3.7)	25.2 (3.5)	24.5 (3.3)	24.7 (3.4)	1.2×10 ⁻⁶
Never smoking during pregnancy	76.3 (212)	73.7 (204)	78.1 (218)	82.0 (227)	83.2 (227)	0.04
Maternal age at delivery (years)	30.0 (5.0)	29.6 (4.8)	29.5 (4.6)	30.1 (4.6)	30.4 (4.6)	0.09
Maternal educational level (years)	13.3 (2.4)	14.0 (2.6)	14.0 (2.7)	14.3 (2.6)	14.3 (2.7)	4.8×10 ⁻⁵
Paternal educational level (years)	12.8 (2.5)	13.3 (2.6)	13.2 (2.7)	13.5 (2.6)	13.8 (2.7)	0.0004
Obesity risk- allele score	22.2 (3.4)	21.7 (3.0)	21.4 (2.9)	21.5 (3.2)	21.3 (3.3)	0.08

^a p value of ANOVA for quantitative variable and χ^2 for qualitative variable

Supplementary table S3: Multivariable linear regression analyses of complete cases: factors associated with age at adiposity rebound (days). The EDEN study (N=866)

Characteristics	Model A		Model B		Model C		Model D	
	β (SE)	P value	β (SE)	P value	β (SE)	P value	β (SE)	P value
Center (ref=Poitiers)	-11.4 (34.6)	0.74	-22.3 (34.1)	0.51	-30.5 (34.2)	0.37	-25,2 (34,2)	0,46
Maternal age at delivery (years)	2.1 (3.7)	0.58	3.2 (3.7)	0.39	1.1 (3.8)	0.77	1,1 (3,8)	0,78
Maternal educational level (years)	11.4 (7.8)	0.15	8.9 (7.7)	0.25	7.0 (7.7)	0.37	5,3 (7,7)	0,49
Paternal educational level (years)	16.4 (7.6)	0.031	11.3 (7.5)	0.13	11.5 (7.5)	0.12	10,8 (7,5)	0,15
Obesity risk-allele score			-12.6 (5.3)	0.019	-12.7 (5.3)	0.017	-12.5 (5.3)	0.0181
Maternal BMI (kg/m ²)			-15.4 (4.1)	0.0002	-17.4 (4.2)	3.3×10 ⁻⁵	-16,9 (4,1)	5.0×10 ⁻⁵
Paternal BMI (kg/m ²)			-13.1 (4.9)	0.008	-12.6 (4.9)	0.011	-12,7 (4,9)	0,010
Gestational weight gain (kg)					-10.7 (3.8)	0.005	-12,6 (3,8)	0,001
Smoking during pregnancy (ref=no)					-31.2 (42.7)	0.47	-16,0 (42,7)	0,71
Preterm birth (yes vs no)							-7,4 (85,4)	0,93
Birth weight z-score							46,1 (16,3)	0,005
Birth weight z-score ²							-20,6 (9,7)	0,034
Sex (boys vs girls)							-45,2 (33,4)	0,18

^a Relevance of a variable during the hierarchical regression analyses was determined with the corresponding model in which the variable of interest is first entered, regardless of its performance in the subsequent model(s).

Supplementary table S4: Linear and logistic regression analyses with a weighted versus unweighted BMI obesity risk-allele score, with multiple imputation or with complete cases^a

Characteristics	N	Linear regression		Logistic regression
		β (SE)	p value	OR [95% CI]
Weighted obesity risk-allele score (multiple imputation)	1415	-9.3 (3.9)	0.017	1.05 [1.00–1.09]
Weighted obesity risk-allele score (complete cases)	866	-11.1 (4.7)	0.018	1.06 [1.01–1.11]
Unweighted obesity risk-allele score (multiple imputation)	1415	-9.0 (4.5)	0.047	1.06 [1.01–1.11]
Unweighted obesity risk-allele score (complete cases)	866	-12.5 (5.3)	0.0181	1.06 [1.01–1.11]

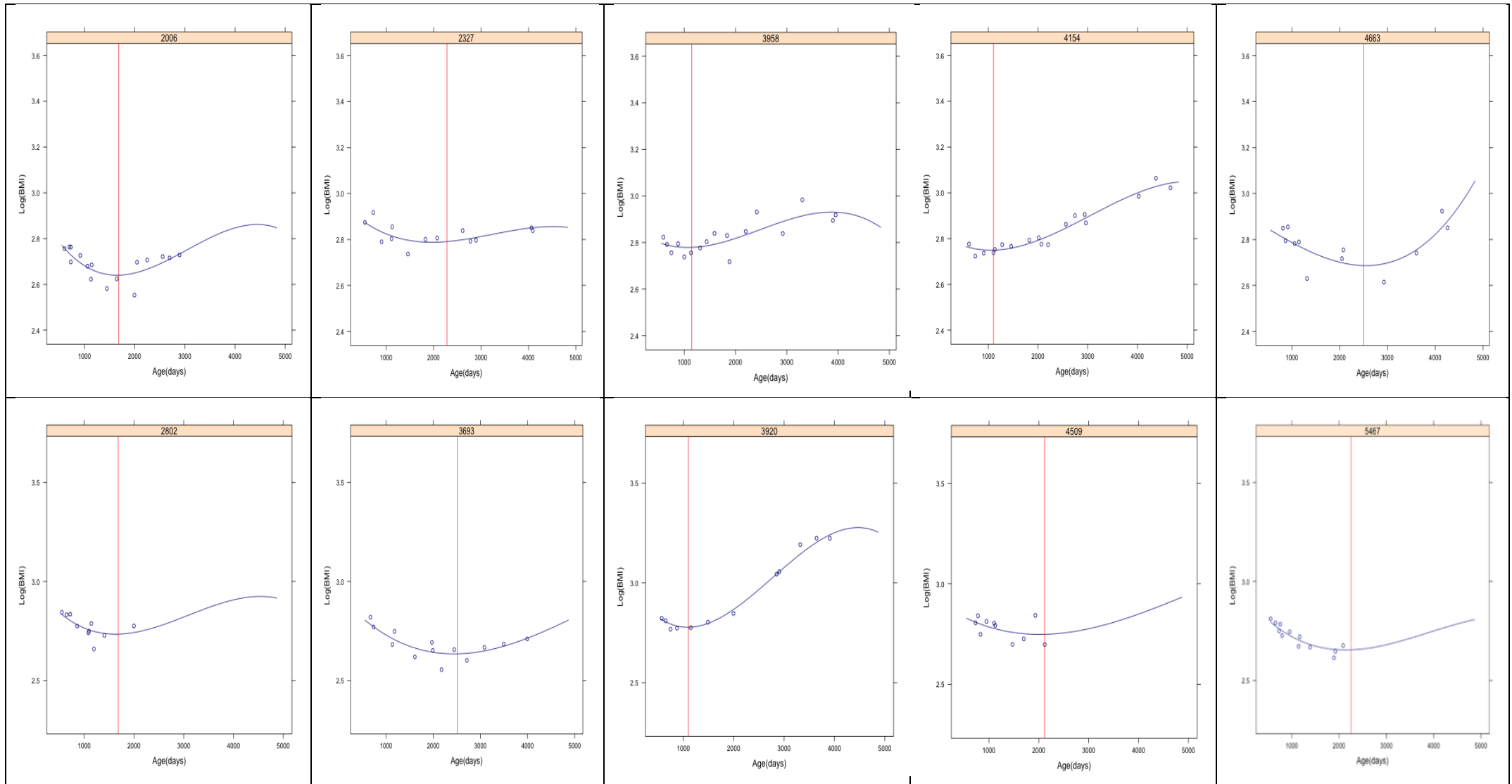
^a Adjusted for center, maternal age at delivery, maternal and paternal educational level, maternal and paternal BMI, gestational weight gain, smoking during pregnancy, preterm birth, birth weight z-score and sex (Model D)

OR, odds ratio; 95% CI, 95% confidence interval

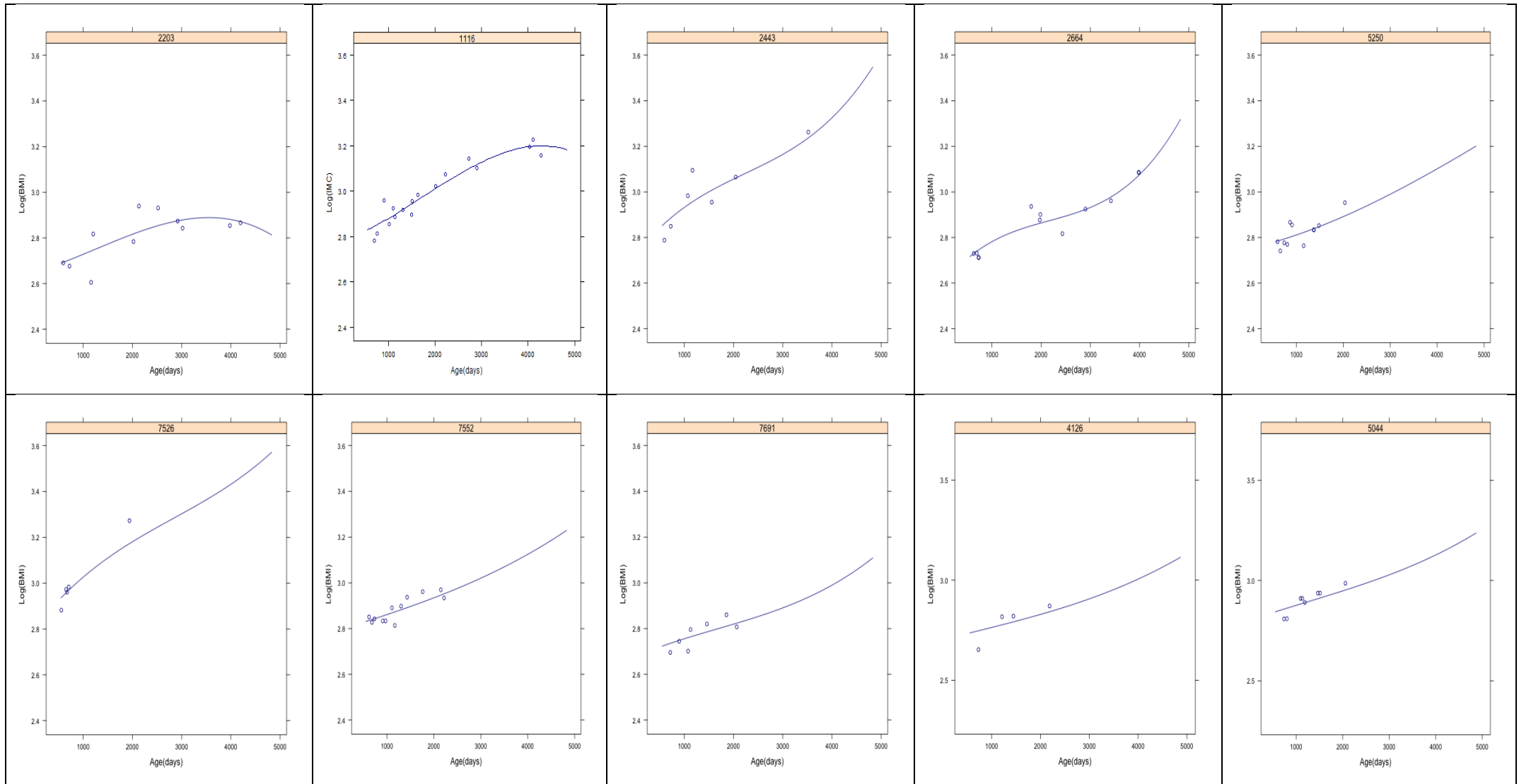
Supplementary table S5: Multivariable linear and logistic regression analyses with age at adiposity rebound in children born at term (N=1337^a)

Characteristics	Linear regression		Logistic regression
	β (SE)	P value	OR [95% CI]
Center (ref=Poitiers)	-16.3 (26.9)	0.54	0.97 [0.73–1.29]
Maternal age at delivery (years)	4.3 (2.9)	0.14	1.01 [0.98–1.04]
Maternal educational level (years)	9.8 (6.3)	0.12	0.92 [0.86–0.98]
Paternal educational level (years)	6.8 (6.1)	0.27	1.00 [0.93–1.06]
Obesity risk-allele score	-9.9 (4.6)	0.03	1.06 [1.01–1.11]
Maternal BMI (kg/m ²)	-17.3 (3.2)	9.3×10 ⁻⁸	1.07 [1.04–1.10]
Paternal BMI (kg/m ²)	-15.9 (3.9)	4.2×10 ⁻⁵	1.07 [1.03–1.11]
Gestational weight gain (kg)	-8.0 (3.1)	0.01	1.05 [1.01–1.08]
Smoking during pregnancy (ref=no)	-69.7 (33.2)	0.04	1.04 [0.74–1.47]
Birth weight z-score (ref=AGA)	-	-	-
SGA	-104.9 (40.6)	0.01	2.23 [1.52–3.28]
LGA	-11.8 (46.3)	0.80	1.23 [0.77–1.96]
Sex (ref=boys)	-35.1 (26.5)	0.19	1.32 [1.00–1.75]

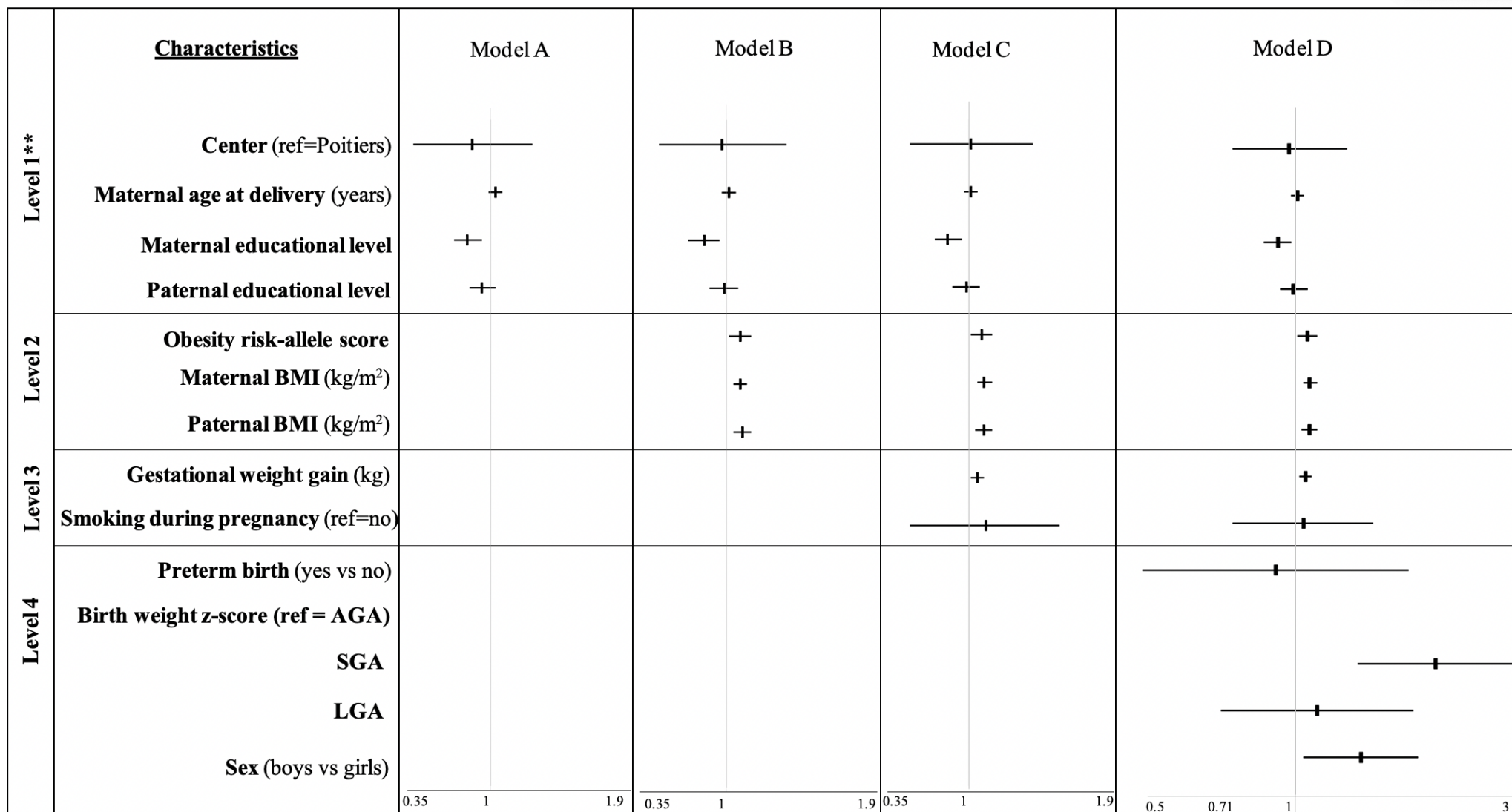
^a Missing data for covariates were imputed with the fully conditional specification method.
OR, odds ratio; 95% CI, 95% confidence interval



Supplementary figure S1: Modelling results approaches with a random sample of 10 participants. Points represent the log (BMI) values according to age, blue lines represent individual BMI curves from 18 months to 13 years and red lines the estimated age at adiposity rebound.



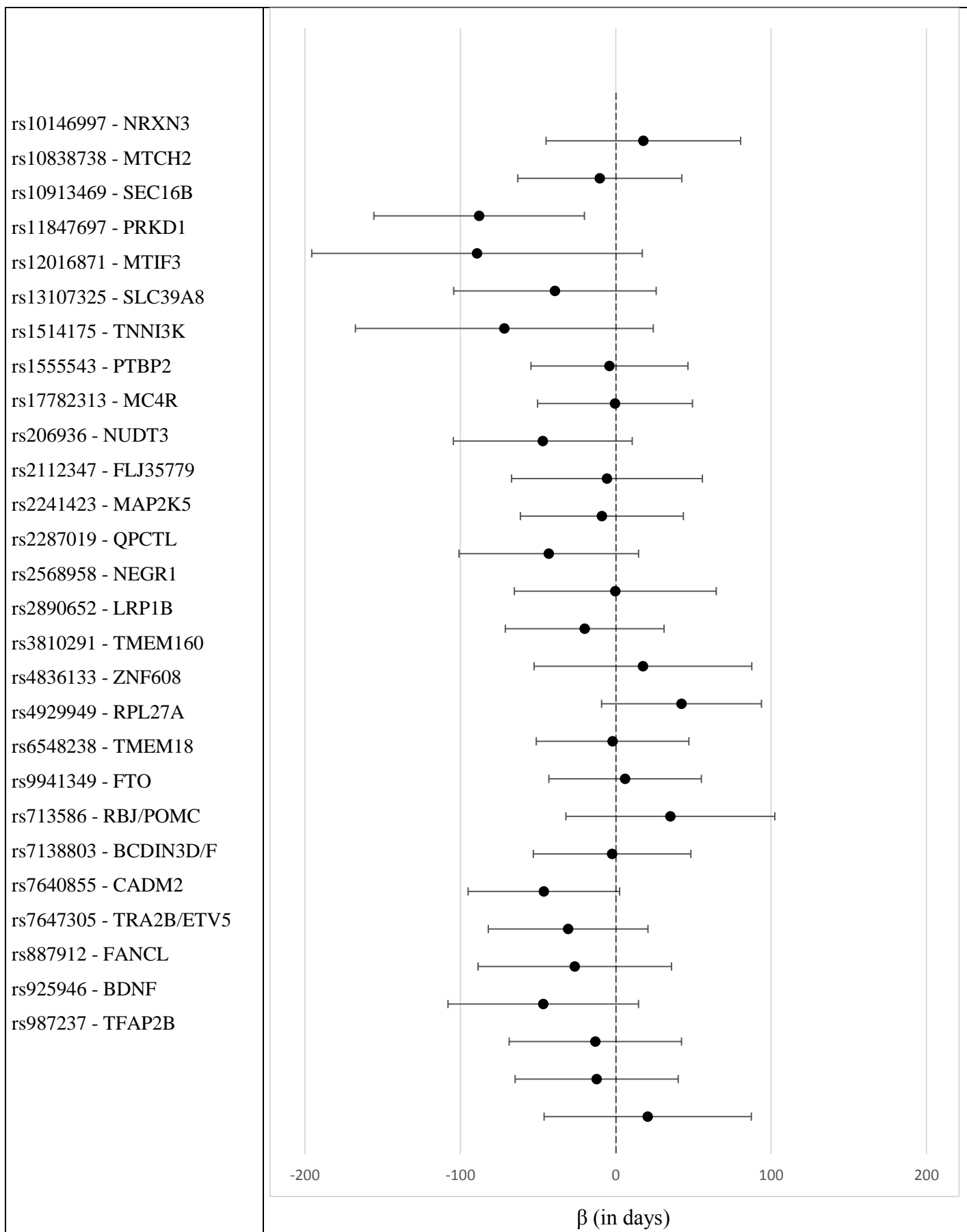
Supplementary figure S2: Modelling results for 10 participants without estimation of adiposity rebound. Points represent observations of BMI according to age.



Supplementary figure S4: Multivariable logistic regression analyses of factors associated with risk of early adiposity rebound defined as being in the lowest quintile of age at adiposity rebound. (N=1415*)

* Missing data for covariates were imputed with the fully conditional specification method.

** Relevance of a variable during the hierarchical regression analyses was determined with the corresponding model in which the variable of interest is first entered, regardless of its performance in the subsequent model(s).



Supplementary figure S5: Multiple logistic regression analyses for the risk of early age at AR (OR^a [95% CI]) on all individual polymorphisms (complete cases analysis, N=799)

^aAdjusted for center, maternal age at delivery, maternal and paternal educational level, maternal and paternal BMI, gestational weight gain, smoking during pregnancy, preterm birth, birth weight z-score and sex (Model D).