Common maternal and fetal genetic variants show expected polygenic effects on the probability of being born small- or large-for-gestational-age (SGA or LGA), except in the smallest 3% of babies

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Abstract

Babies born clinically Small- or Large-for-Gestational-Age (SGA or LGA; sex- and gestational age-adjusted birth weight (BW) <10th or >90th percentile, respectively), are at higher risks of complications. SGA and LGA include babies who have experienced growth-restriction or overgrowth, respectively, and babies who are naturally small or large. However, the relative proportions within each group are unclear. We aimed to assess the extent to which the genetics of normal variation in birth weight influence the probability of SGA/LGA. We calculated independent fetal and maternal genetic scores (GS) for BW in 12,125 babies and 5,187 mothers. These scores capture the direct fetal and indirect maternal (via intrauterine environment) genetic contributions to BW, respectively. We also calculated maternal fasting glucose (FG) and systolic blood pressure (SBP) GS. We tested associations between each GS and probability of SGA or LGA. For the BW GS, we used simulations to assess evidence of deviation from an expected polygenic model.

Higher BW GS were strongly associated with lower odds of SGA and higher odds of LGA (OR_{fetal}=0.65 (0.60,0.71) and 1.47 (1.36,1.59); $OR_{maternal}$=0.80 (0.76,0.87) and 1.23 (1.15,1.31), respectively per 1 decile higher GS). Associations were in accordance with a polygenic model except in the smallest 3% of babies (P_{fetal}=0.0034, $P_{maternal}$=0.023). Higher maternal GS for FG and SBP were associated with higher odds of LGA and SGA respectively (both P<0.01). While lower maternal FG and SBP are generally considered healthy in pregnancy, we found some evidence of association with higher odds of SGA (P=0.015) and LGA (P=0.14) respectively.

We conclude that common genetic variants contribute to risk of SGA and LGA, but that additional factors become more important for risk of SGA in the smallest 3% of babies. Naturally low maternal glucose and blood pressure levels may additionally contribute to risk of SGA and LGA, respectively.

Author Summary

Babies in the lowest or highest 10% of the population distribution of birth weight (BW) for a given gestational age are referred to as Small- or Large-for-Gestational-Age (SGA or LGA) respectively. These babies have higher risks of complications compared to babies with BW closer to the mean. SGA and LGA babies may have experienced growth restriction or overgrowth, respectively, but may alternatively just be at the tail ends of the normal growth distribution. The relative proportions of normal vs. sub-optimal growth within these groups is unclear. To examine the role of common genetic variation in SGA and LGA, we tested their associations with a fetal genetic score (GS) for BW in 12,125 European-ancestry individuals. We also tested associations with maternal GS (5,187 mothers) for offspring BW, fasting glucose and systolic blood pressure, each of which influences fetal growth via the *in utero* environment. We found all fetal and maternal GS were associated with SGA and LGA, supporting strong maternal and fetal genetic contributions to birth weight in both tails of the distribution. However, within the smallest 3% of babies, the maternal and fetal GS for BW were higher than expected, suggesting factors additional to common genetic variation are more important in determining birth weight in these very small babies.

Introduction

Size at birth is an important factor in new-born and infant survival. Term-born babies are most frequently admitted to the neonatal unit when born at the extremes of the birth weight distribution [1]. Small for Gestational Age (SGA; defined as birth weight adjusted for sex and gestational age that is below the 10th percentile of the population or customized standard) is often used as a proxy indicator of fetal or intrauterine growth restriction (FGR or IUGR [2]). A fetus is described as growth-restricted when it has failed to reach its growth potential due to impaired placental function [3] or due to fetal or maternal reasons, and SGA fetuses are at higher risk of adverse outcomes such as stillbirth [4]. It is likely that SGA infants who are genetically small are at a lower risk of future morbidity than FGR infants. Risks of adverse outcomes are increased in preterm babies, and the mechanisms associated with SGA in preterm babies are likely to be different to those born at term. SGA and FGR are often used interchangeably since fetal growth can be difficult to measure. [2,3] However, they are not synonymous: not all growth-restricted fetuses are small enough to be considered SGA [5], and the SGA group itself is heterogeneous with an estimated 50-70% being constitutionally small babies with normal placental function and outcomes [6], in addition to babies expected to be small due to chromosomal anomalies [7].

At the upper end of the birth weight distribution, large for gestational age (LGA, defined as sex- and gestational age-adjusted birth weight >90th percentile) is associated with a higher risk of obstructed labour, which can lead to complications for both mother and baby, including injury, neonatal hypoglycaemia and even fetal death [8]. LGA may indicate excessive growth of the fetus, for example due to elevated maternal glycemia, which is a major determinant of fetal growth [9]. However, maternal fasting hyperglycemia only explains 2-13% of variation in birth weight [10,11], and most LGA babies are not born to

99 diabetic mothers [12]. This indicates that other factors are also important, for example, many
100 LGA babies may be constitutionally large.
101
102 The contribution of common genetic variation to either SGA or LGA is not known, though
103 associations between LGA and fetal genetic scores for birth weight have been demonstrated
104 [13,14]. It is possible that a mismatch between a genetic score for birth weight and the actual,
105 measured birth weight could help to identify babies who have either fallen short of, or
106 exceeded, their growth potential. In clinical practice, this could be helpful if it improved the
107 identification of FGR babies among those classified as SGA. Genetic studies of adult height
108 previously investigated a similar question and showed that a genetic score composed of
109 common variants was associated with adult height at the extremes of the population
110 distribution [15]. However, the genetic score was not as extreme as expected in people with
111 very short stature, suggesting that additional factors (e.g. rare mutations) were more
112 important than common genetic variation in determining height in that group.
113
114 In the current study, we investigated the genetic contribution to SGA and LGA in mothers
115 and babies of European ancestry, using common genetic variants identified in the most recent
116 genome wide association study (GWAS) of birth weight [16]. The genetic variants at the 190
117 most strongly-associated loci have individually small effects, but collectively explain 7% of
118 the variation in birth weight. These genetic variants have either a direct fetal effect on birth
119 weight (i.e. those inherited by the fetus and acting via fetal pathways), or an indirect maternal
120 effect (i.e. through a primary effect on the intrauterine environment), or some combination of
121 the two (Fig. 1). The correlation between maternal and fetal genotypes means that
122 associations between maternal genotype and birth weight can be confounded by fetal
123 genotype effects, and vice-versa. To overcome this limitation, Warrington et al [16] estimated

124 the independent maternal and fetal effect sizes at each of these loci. We used these
125 independent effect sizes to calculate maternal and fetal genetic scores (GS) for birth weight.
126 These GSs are designed to capture the independent maternal and fetal genetic contributions to
127 birth weight. We tested for associations of these GSs with SGA and LGA. We then used
128 simulations to test whether the GS in the SGA and LGA groups was consistent with the
129 polygenic model. To investigate further the maternal genetic contribution to intrauterine
130 factors known to be important across the birth weight distribution [16,17], we calculated
131 genetic scores for fasting glucose (FG) and systolic blood pressure (SBP) and additionally
132 tested their associations with SGA and LGA.

133 **Results**

134 Prevalence of SGA and LGA is strongly associated with maternal and fetal genetic scores for
135 birth weight

136 The prevalence of SGA and LGA by percentile of fetal or maternal GS in ALSPAC
137 (N=6,621) is shown in Figures S1 and S2, and the mean BW in ALSPAC by percentile of
138 fetal and maternal GS is shown in Figure S3. Both the fetal and maternal genetic scores for
139 birth weight showed strong associations with LGA and SGA (Figure 2, Table S4a) in the
140 expected directions. A 1 decile increase in the fetal GS for birth weight was associated with a
141 greater odds of LGA (OR=1.49 [95%CI: 1.40,1.58]; $P=1.8x10^{-42}$) and a lower odds of SGA
142 (OR=0.68 [0.64,0.72]; $P=2.7x10^{-36}$). Similarly, the maternal GS showed strong associations
143 with LGA (1.25 [1.17,1.33]; $P=6.2x10^{-12}$) and SGA (0.80 [0.75,0.86]; $P=4.6x10^{-11}$). These
144 results were very similar to those of a sensitivity analysis of fetal GS conditional on maternal
145 GS (and vice versa) in mother-child pairs (Table S4b), indicating that the use of the adjusted
146 fetal and maternal weights [15] resulted in fetal and maternal GSs that were already
147 independent of one another (Table S4).

148

149 Evidence that the GS in the lowest 3% of the population was higher than expected

150 Using simulation analyses in ALSPAC and EFSOCH (N=5,187) we identified evidence of
151 deviation from the expected additive polygenic model in the lowest 10% bin of the phenotype
152 distribution, which we then narrowed down to the lowest 3% bin for both the fetal and
153 maternal GS for birth weight ($P_{fetal}=0.0034$, $P_{maternal}=0.023$; Figure 3; Table S5). The birth
154 weight GS for both maternal and fetal genotype were higher than expected within this group
155 indicating that there is a proportion of the SGA group whose birth weight is lower than would
156 be expected given their GS.

157

158 There was no evidence of deviation from the expected additive polygenic model for the fetal
159 GS in the top 10% of the phenotype distribution (P_{fetal}= 0.1082). We saw some evidence of a
160 lower maternal GS than expected in the top 10% group ($P_{maternal}$=0.012) but in the top 3% of
161 the phenotype distribution there was no evidence of deviation ($P_{maternal}$=0.15; Table S5).
162
163 Prevalence of SGA and LGA are associated with maternal genetic scores for fasting glucose
164 and SBP
165 The maternal GS for fasting glucose was associated with higher odds of LGA (1.49
166 [1.19,1.87]; P=5.7x10^{-4}), and the maternal SBP GS was associated with higher odds of SGA
167 (1.31 [1.07,1.60]; P=9.5x10^{-3}). These effects, observed across the genetic score distribution,
168 are consistent with the known effects, respectively, of maternal gestational diabetes and
169 hypertension on birth weight. Warrington et al [16] previously demonstrated continuous
170 associations of both FG and SBP with BW in the healthy range. As a consequence of these
171 continuous associations, we found some evidence of associations between lower genetic
172 susceptibility to high FG and SBP and risk of SGA or LGA. Maternal fasting glucose GS was
173 associated with lower odds of SGA (0.74 [0.58,0.94]; P=1.5x10^{-2}). There was little evidence
174 of an association between maternal SBP GS and LGA (0.87 [0.72,1.05]; P=1.4x10^{-1}),
175 although confidence intervals were wide and it would be informative to look at this
176 association in studies with larger sample size (Figure 4, Table S6).

177 **Discussion**

178 We have shown that common birth weight-associated genetic variation in both the mother
179 and the fetus contribute to the probability that term infants will be born small or large for
180 gestational age. While these results indicate that a large proportion of those infants classified
181 as SGA/LGA represent the tail ends of the normal distribution of birth weight, we also found
182 some evidence of an excess of individuals with a higher GS for birth weight than expected
183 under the polygenic model in the bottom 3% of the birth weight distribution.

184

185 The terms IUGR and SGA are often used interchangeably [23], which can imply that the
186 majority of SGA babies have experienced restriction to their uterine growth, although it has
187 been estimated [6] that 50-70% of babies classified as SGA are constitutionally small. The
188 strong association in our study between SGA and the fetal GS for birth weight, together with
189 the deviation from the polygenic model in only the lowest 3% of babies, is consistent with
190 any subset of growth-restricted babies being much smaller than those who are
191 constitutionally small. Our results are also consistent with the observation that the risk of
192 adverse outcomes increases with decreasing birth weight within the SGA group, and the
193 highest rates of adverse outcomes are in those with birth weight below the 3rd centile [24].
194 The higher than expected GS in the bottom 3% observed in the present study indicates that
195 this group may be enriched for growth-restricted babies, although this finding would benefit
196 from replication in larger studies.

197

198 We found no evidence that the fetal GS for birth weight deviated from the polygenic model
199 in the top 10% of the birth weight distribution, but there was some evidence of deviation for
200 the maternal GS in this group. When we looked in smaller percentile groups, however, there
201 was no evidence of association in the top 3% of the distribution. Overall our results do not

202 suggest strong deviation from the polygenic model in babies with high birth weights, but we
203 cannot rule out that smaller deviations would be detectable in a larger sample.
204
205 Although we have used a population based definition of SGA, customised birth weight
206 standards including maternal height, weight and ethnic group, for defining SGA have been
207 shown to increase association between SGA classification and neonatal morbidity and
208 perinatal death compared to using population based definitions [2], although it has been
209 suggested that this could be an artefact due to inclusion of more preterm births classified as
210 SGA under this definition [25]. Babies born preterm have increased risk of neonatal
211 morbidity and mortality compared to term babies, and it is likely that different mechanisms
212 affect growth in preterm babies compared to IUGR babies born at term. Additionally,
213 individuals classified as SGA by population-based growth standards but not by customised
214 standards are not at increased risk of perinatal mortality and morbidity compared to those of
215 appropriate weight [26–28]. Including genetics in the definitions of SGA has the potential to
216 further refine the identification of babies who have failed to properly reach their growth
217 potential, as shown by the association between SGA and birth weight GS demonstrated here.
218
219 Fetal genetic effects on birth weight represent the constitutional growth potential of the fetus,
220 while maternal genetics influence birth weight indirectly by modifying the intrauterine
221 environment. The strong effects of the maternal GS for birth weight observed in our study
222 indicate that maternal genetic variation acting via the in utero environment contributes to
223 variation in SGA and LGA risk independently of the fetal genotype. Previous studies have
224 shown that maternal FG and SBP have causal effects on birth weight in the normal range
225 [15,16]. In women at highest genetic risk for raised FG and SBP, these could potentially
226 contribute to LGA and SGA, respectively. We therefore investigated the associations

227 between maternal genetic scores for FG or SBP and the risk of SGA or LGA. In line with
228 known consequences of maternal gestational diabetes or hypertension, respectively, a higher
229 maternal FG GS is associated with higher odds of LGA, while a higher maternal SBP GS
230 increased odds of SGA. A lower GS for maternal FG was also associated with higher odds of
231 SGA. This is consistent with naturally low maternal glucose levels contributing to SGA risk.
232 A lower GS for maternal SBP showed weak evidence of association with LGA. Replication
233 in larger studies will be necessary to determine the potential contribution of lower maternal
234 blood pressure to LGA risk.
235
236 The current study has a number of strengths and limitations. Strengths include the fact that
237 we have been able to construct independent maternal and fetal GS for birth weight.
238 Separating maternal and fetal genetic contributions to birth weight is important because
239 maternal and fetal genotype are correlated. This means that to avoid confounding, it is
240 necessary to account for this correlation and obtain independent estimates of maternal and
241 fetal genetic effects. Both a limitation and strength of our study is that all of the cohorts used
242 were of European ancestry. There is a need for genetic studies in populations of ancestries
243 other than Europeans, however, the GS were discovered in European ancestry individuals and
244 are not necessarily applicable to other ancestry populations. A further limitation is that the
245 cohorts analysed in this study contributed to the GWAS meta-analysis that identified SNPs
246 contributing to the GS. However, these studies only constitute 3.8% of the fetal and 4.2% of
247 the maternal samples included in the GWASs so any impact of winner's curse on the
248 associations in the current study is likely to be small. The use of only singleton, term babies
249 in our analysis means that our results do not necessarily translate to pre-term babies or
250 multiple births. While we had sufficient sample size to estimate the association of birth
251 weight GS with SGA/LGA, the limited number of mother-child pairs which were available to

252 examine the associations of FG and SBP GS with SGA/LGA meant that these estimates had
253 large confidence intervals. Larger numbers of mother-child pairs would allow for more
254 precise estimates, for example of the association of low SBP on LGA which has potentially
255 clinically relevant implications. Although SGA and FGR are often used synonymously, there
256 are differences between the terms. In our study do not have information required to
257 distinguish FGR babies from SGA ones, meaning that we were not able to examine the
258 association between BW GS and FGR specifically.
259
260 Our analysis has shown that common birth weight-associated genetic variation contributes to
261 the risk of babies being born small or large for gestational age, and that the genetics
262 underlying maternal fasting glucose and systolic blood pressure in the normal range also
263 contribute to this risk. We found evidence of deviation from the polygenic model in the
264 smallest 3% of babies, consistent with enrichment for fetal growth restriction in this group.
265

266 **Methods**

267 Cohort descriptions

268 Our analysis included a total of 6,938 individuals with birth weight and fetal genotype data,
269 from 2 studies, plus 5,187 mother-offspring pairs with maternal and fetal genotype data and
270 birth weight from 2 further studies. Studies are described below, and summary data is shown
271 in Table 1.

272

273 *ALSPAC*

274 The ALSPAC (Avon Longitudinal Study of Parents and Children) is a longitudinal cohort
275 study covering the area of the former county of Avon, UK [18,19]. Women who were
276 pregnant, living in the study area and had an expected delivery date between 1 April 1991
277 and 31 December 1992 were eligible for inclusion in the study. Birth weight and related data
278 were abstracted from medical records. Children were genotyped on the Illumina
279 HumanHap550 chip and mothers were genotyped using the Illumina human660W quad chip.
280 QC was undertaken as described previously [16] and imputation was to the HRC reference
281 panel yielding data available for 8884 mothers and 8860 children with genotype data
282 available. Of these, 4570 mother-child pairs with phenotype data were available for analysis.

283

284 *EFSOCH*

285 The Exeter Family Study of Childhood Health (EFSOCH) is a prospective study of children
286 born between 2000 and 2004 in the Exeter region, UK, and their parents [20]. Birth weight
287 measurements were performed as soon as possible after delivery. Individuals were genotyped
288 using the Illumina Infinium HumanCoreExome-24 array. Genotype QC and imputation have
289 been described previously [13]. After genotype QC, 938 mothers and 712 children with

290 genotype data remained. Of these, 617 mother-child pairs with phenotype data were available
291 for analysis.
292
293 *NFBC66*
294 The Northern Finland Birth Cohort 1966 (NFBC66) consists of mothers expected to give
295 birth in the provinces of Oulu and Lapland in 1966 [21]. Birth weight and related
296 characteristics were measured by examinations occurring directly after birth. Samples were
297 genotyped on the Infinium 370cnvDuo. QC and imputation to the 1000 genomes reference
298 panel were done centrally, resulting in 5402 children with genotype data. A total of 3690
299 children with phenotype data were available for analysis.
300
301 *NFBC86*
302 The Northern Finland Birth Cohort 1986 (NFBC86) consists of individuals born in the
303 northern-most provinces of Finland between 1st July 1985 and 30th June 1986. Birth weight
304 data was collected from hospital records after delivery. Following genotype QC, 3742
305 children with genotype data were available, with 3248 of these having phenotype data [22].
306
307 Phenotype definitions
308 Since different mechanisms may lead to SGA and LGA in term and preterm infants, and in
309 multiple births, we focused on term, singleton infants. Within each cohort, birth weight was
310 regressed against sex and gestational age in term births (gestational age >= 37 weeks), and
311 residuals from the regression model were calculated. Individuals with the lowest and highest
312 10% of this adjusted birth weight within each cohort respectively were defined as SGA and
313 LGA. Controls for comparison with SGA were taken as birth weight >=10%, and for
314 comparison with LGA as birth weight <=90%.

315

316 Genetic scores (GS) for birth weight, fasting glucose (FG) and systolic blood pressure (SBP)
317 were calculated for all included individuals in each cohort. GS were calculated using
318 equation (1) where N_{SNP} is the total number of SNPs, w_i is the weight for SNP i and g_i is the
319 genotype at SNP i. The same SNPs were included in the maternal and fetal GS. The SNP
320 weightings, w_i, were taken from the structural equation model-adjusted effect estimates in
321 [16]. These adjusted effect estimates are designed to capture the independent maternal and
322 fetal contribution at each SNP, which would otherwise be confounded by the correlation
323 between maternal and fetal genotype. For the weights in the FG and SBP scores, we used
324 effect estimates reported in large GWAS of FG and SBP, respectively, and the same weights
325 were used for both maternal and fetal GS. SNPs and weights used in each score are given in
326 Tables S1-3.

327

328 $$GS = \frac{N_{SNP}}{\sum_i w_i} \sum_i w_i g_i \quad (1)$$

329

330 Association analysis

331

332 *Associations between SGA/LGA and maternal or fetal genetic scores for birth weight*
333 Fetal genotypes (total n=12,125) were available in ALSPAC (N=4,570), EFSOCH (N=617),
334 NFBC66 (N=3,690) and NFBC86 (N=3,248). Associations were tested between the fetal GS
335 for birth weight and outcomes (SGA/LGA) using logistic regression, including sex and
336 gestational age as covariates to control for residual confounding. Maternal genotypes were
337 also available in ALSPAC (N=4,570) and EFSOCH (N=617). In these cohorts, associations
338 between SGA/LGA and maternal GSs for birth weight were also tested in analogous
339 regression models. Additional analyses including both maternal and fetal GS in the same

340 regression model were performed to control for any residual correlation between maternal
341 and fetal genotype. Results were meta-analysed using inverse variance weighted meta-
342 analysis.
343
344 *Investigating Deviations from the expected Polygenic Model in SGA/LGA*
345 We performed simulations to assess whether there was any evidence of deviation from the
346 expected polygenic model. Briefly, within ALSPAC and EFSOCH we calculated the
347 associations of each fetal and maternal SNP with birth weight within each cohort, adjusted
348 for maternal and fetal genotype, respectively. We simulated genotypes under the allele
349 frequencies observed within each cohort. GSs were calculated for each simulated individual
350 using simulated genotypes weighted by the within-cohort effect sizes. Phenotypes were then
351 simulated as
352 $$p_s = x_s + GS_s$$
353 where p_s is the simulated phenotype for individual s, GS_s is the simulated genetic score for
354 sample s and x_s is sampled from a normal distribution
355 $$x_s \sim N(0,1 - \sum_i \sigma^2{}_{SNP_i})$$
356 where $\sigma^2{}_{SNP_i}$ is the variance explained by SNP i. The mean GS within each bin of simulated
357 phenotype was calculated. Simulations were performed 10,000 times to generate a simulated
358 expected distribution of GS under an additive polygenic model. The observed mean GS was
359 then compared to the expected distribution and an empirical p value was calculated. These p
360 values were then meta-analysed.
361
362 *Associations between SGA/LGA and maternal genetic scores for fasting glucose or systolic*
363 *blood pressure*

364 In ALSPAC and EFSOCH, where maternal genotypes were available, we tested the
365 associations between the maternal GSs for FG and SBP, with outcomes (SGA/LGA) using
366 linear regression, including sex and gestational age as covariates to control for residual
367 confounding. Additional analyses including both maternal and fetal GS in the same
368 regression model were performed to control for the correlation between maternal and fetal
369 genotype. Results were meta-analysed using inverse variance weighted meta-analysis.

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380 Please note that the study website contains details of all the data that is available through a
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420

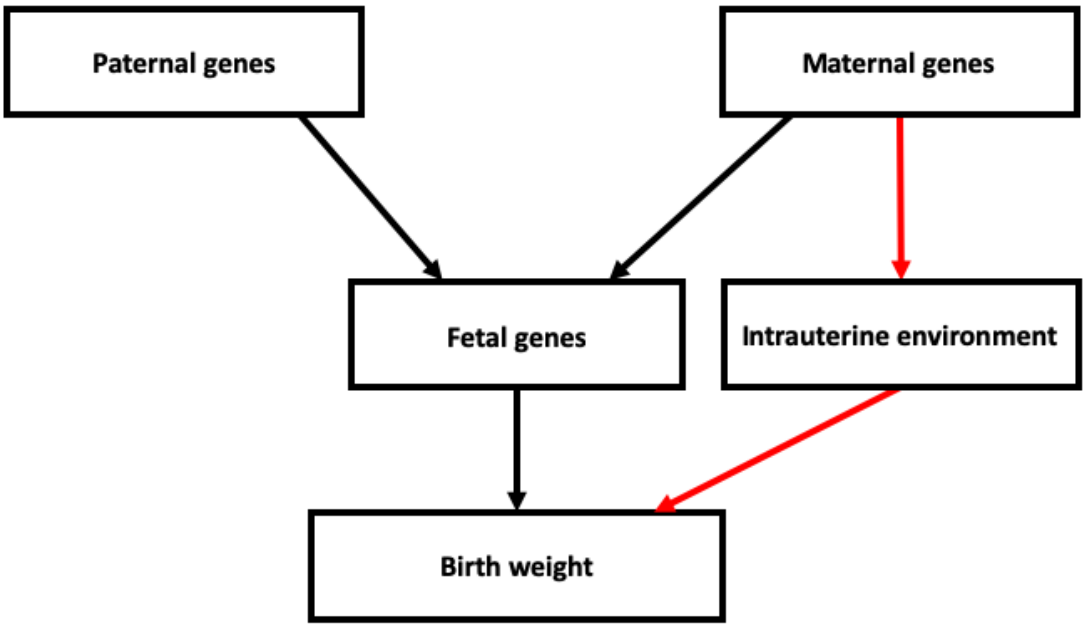
421 **References**

422 1. Hilby SE, Apps R, Chazara O, Farrell LE, Magnus P, Trogstad L, et al. Maternal KIR in
423 combination with paternal HLA-C2 regulate human birth weight. J Immunol. 2014;509:385–
424 8.
425 2. Clausson B, Gardosi J, Francis A, Cnattingius S. Perinatal outcome in SGA births defined
426 by customised versus population-based birthweight standards. Br. J. Obstet. Gynaecol.
427 2001;108:830–4.
428 3. Gordijn SJ, Beune IM, Wynia K. Consensus definition of fetal growth restriction : a Delphi
429 procedure. Ultrasound Obs. Gynecol. 2016;48:333–9.
430 4. Gardosi J, Madurasinghe V, Williams M, Malik A. Maternal and fetal risk factors for
431 stillbirth : population based study. BMJ. 2013;108:1–14.
432 5. McCowan LM, Figueras F, Anderson NH. Evidence-based national guidelines for the
433 management of suspected fetal growth restriction : comparison , consensus , and controversy.
434 Am. J. Obstet. Gynecol.; 2018;218:S855–68.
435 6. Alberry M, Soothill P. Management of fetal growth restriction. Arch Dis Child Fetal
436 Neonatal Ed. 2007;92:62–7.
437 7. Snijders R.J.M., Sherrod C., Gosden C.M. NKH. Fetal growth retardation: associated
438 malormations and chromosomal abnormalities. Am. J. Obstet. Gynecol. 1993;168:547–55.
439 8. Moffett A, Hiby SE, Sharkey AM. The role of the maternal immune system in the
440 regulation of human birthweight. Philos Trans R Soc L. B Biol Sci. 2015;370:20140071.
441 9. Metzger, B.E., Lowe, L.P., Dyer, A.R., Trimble, E.R., Chaovarindr, U., Coustan DR,
442 Hadden, D.R., McCance, D.R., Hod M e. al. Hyperglycemia and Adverse Pregnancy
443 Outcomes. N. Engl. J. Med. 2008;358:1991–2002.
444 10. Sacks DA, Liu AI, Wolde-tsadik G, Amini SB, Huston-presley L, Catalano PM. What
445 proportion of birth weight is attributable to maternal glucose among infants of diabetic

446 women ? Am. J. Obstet. Gynecol. 2006;194:501–7.
447 11. Breschi, M.C., Seghieri, G., Bartolomei, G., Gironi, A., Baldi, S. and Ferrannini E.
448 Relation of birthweight to maternal plasma glucose and insulin concentrations during normal
449 pregnancy. Diabetologia. 1993;36:1315–21.
450 12. Surkan PJ, Hsieh C, Johansson AL V, Dickman PW, Cnattingius S. Reasons for
451 Increasing Trends in Large for Gestational Age Births. Obs. Gynecol. 2004;104:720–6.
452 13. Hughes AE, Nodzenski M, Beaumont RN, Talbot O, Shields BM, Scholtens DM, et al.
453 Fetal Genotype and Maternal Glucose Have Independent and Additive Effects on Birth
454 Weight. Diabetes. 2018;67:1024–9.
455 14. Chawla R, Badon SE, Rangarajan J, Reisetter AC, Armstrong LL, Lowe LP, et al.
456 Genetic Risk Score for Prediction of Newborn Adiposity and Large-for-Gestational-Age
457 Birth. J Clin Endocrinol Metab. 2014;99:2377–86.
458 15. Chan Y, Holmen OL, Dauber A, Vatten L, Havulinna AS, Kvaløy K, et al. Common
459 Variants Show Predicted Polygenic Effects on Height in the Tails of the Distribution , Except
460 in Extremely Short Individuals. PLOS Genet. 2011;7.
461 16. Warrington, N.M., Beaumont, R.N., Horikoshi M et al. Maternal and fetal genetic effects
462 on birth weight and their relevance to cardio-metabolic risk factors. Nat. Genet.
463 2019;51:804–14.
464 17. Tyrrell J, Richmond RC, Palmer TM, Feenstra B, Rangarajan J, Metrustry S, et al.
465 Genetic Evidence for Causal Relationships Between Maternal Obesity-Related Traits and
466 Birth Weight. JAMA. 2016;315:1129–40.
467 18. Fraser A, Macdonald-wallis C, Tilling K, Boyd A, Golding J, Smith GD, et al. Cohort
468 Profile : The Avon Longitudinal Study of Parents and Children : ALSPAC mothers cohort.
469 Int. J. Epidemiol. 2013;42:97–110.
470 19. Boyd A, Golding J, Macleod J, Lawlor DA, Fraser A, Henderson J, et al. Cohort Profile :

471 The ‘ Children of the 90s ’— the index offspring of the Avon Longitudinal Study of Parents
472 and Children. Int. J. Epidemiol. 2013;42:111–27.
473 20. Knight B, Shields BM, Hattersley AT. The Exeter Family Study of Childhood Health
474 (EFSOCH): study protocol and methodology. Paediatr Perinat Epidemiol. 2006;20:172–9.
475 21. Sabatti C, Service SK, Hartikainen A, Pouta A, Ripatti S, Brodsky J, et al. Genome-wide
476 association analysis of metabolic traits in a birth cohort from a founder population. Nat
477 Genet. 2009;41:35–46.
478 22. Sebert S, Lowry E, Aumu N, Bjerregaard LG, Rooij SR De, Silva M De, et al. Cohort
479 Profile : The DynaHEALTH consortium – a European consortium for a life-course bio-
480 psychosocial model of healthy ageing of glucose homeostasis. 2019;
481 23. Murki S, Sharma D. Intrauterine Growth Retardation - A Review Article. J. Neonatal
482 Biol. 2014;3.
483 24. McIntyre DD, Bloom SL, Casey BM, Leveno KJ. Birth Weight In Relation To Morbidity
484 And Mortality Among Newborn Infants. N. Engl. J. Med. 1999;340:1234–8.
485 25. Zhang X, Platt RW, Cnattingius S, Joseph KS. The use of customised versus population-
486 based birthweight standards in predicting perinatal mortality. BJOG. 2007;114:474–7.
487 26. Odibo AO, Francis A, Cahill AG, Macones GA, Crane P, Gardosi J, et al. Association
488 between pregnancy complications and small-for – gestational-age birth weight defined by
489 customized fetal growth standard versus a population-based standard. J. Matern. Neonatal
490 Med. 2011;24:411–7.
491 27. Sovio U, Smith GCS. The effect of customization and use of a fetal growth standard on
492 the association between birthweight percentile and adverse perinatal outcome. Am. J. Obstet.
493 Gynecol.; 2018;218:S738–44
494 28. Iliodromiti S, Mackay DF, Smith GCS, Pell JP, Sattar N, Lawlor DA, et al. Customised
495 and Noncustomised Birth Weight Centiles and Prediction of Stillbirth and Infant Mortality

496 and Morbidity : A Cohort Study of 979 , 912 Term Singleton Pregnancies in Scotland. PLoS
497 Med. 2017;14:1–16.



498

499 **Figure 1:** Diagram showing the possible pathways through which parental genotypes can

500 influence birth weight. The black path represents direct fetal genetic effects on birth weight,

501 and the red path represents maternal genetic factors which have an indirect effect on birth

502 weight by modifying the intrauterine environment.

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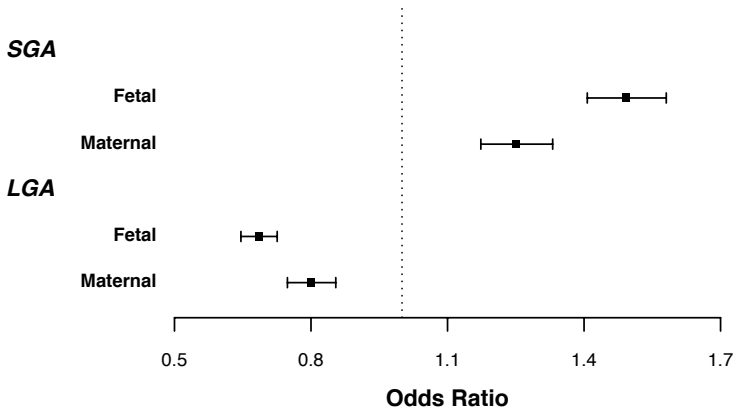

504

505 **Figure 2:** Odds of SGA or LGA per 1 decile higher fetal (N=12,125; ALSPAC, EFSOCH,

506 NFBC66, NFBC86) or maternal (N=5,187; ALSPAC, EFSOCH) GS for birth weight. Error

507 bars represent 95% confidence intervals, and weights used for fetal and maternal GS are

508 independent of maternal and fetal effect respectively.

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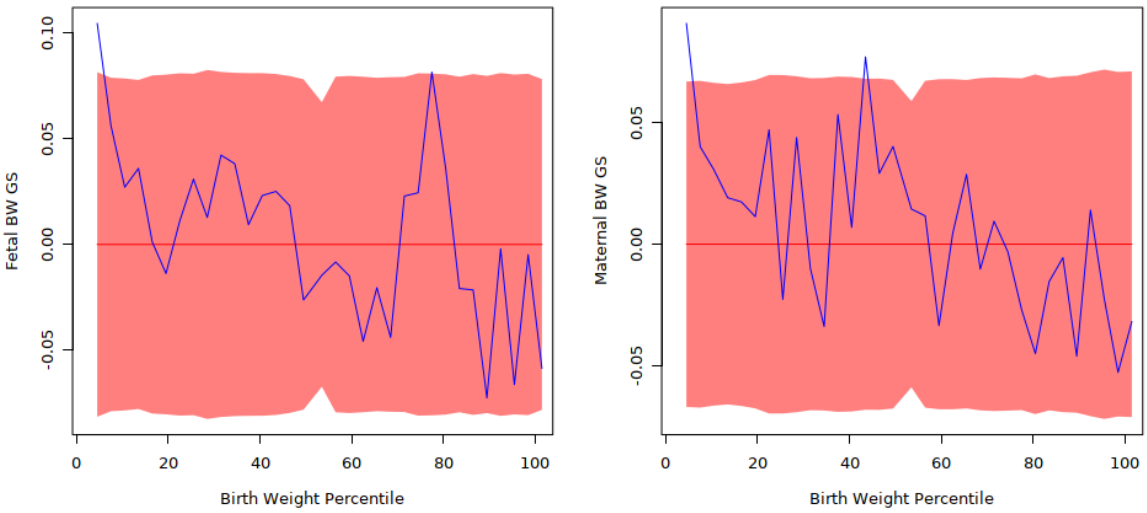

510

511 **Figure 3:** Difference between observed mean GS (blue line) and simulated mean of birth

512 weight GS (under a fully polygenic model; red line) by 3% phenotype bins for fetal GS (left)

513 and maternal GS (right) in ALSPAC. The shaded red area represents the 95% CI of the

514 simulated mean.

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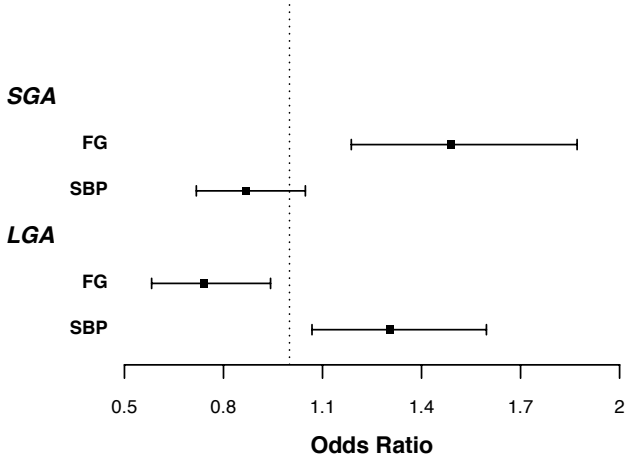

Figure 4: Odds of LGA/SGA 1 per decile higher maternal fasting glucose or SBP GS, corrected for fetal GS in ALSPAC and EFSOCH (N=5,187). Error bars represent 95% confidence intervals.

Study	Country of origin	Year(s) of birth	Sample size (Male/Female (offspring sex))	Data collection	Mean (SD) birth weight (grams)			Mean Maternal age (SD)	Mean Maternal BMI (SD)	Median (IQR) GA (weeks) at delivery
					Males	Females	Combined			
ALSPAC	UK	~1992	4570 (2262/3207)	Identified from obstetric data, records from the ALSPAC measurements, and birth notification	3553 (491)	3423 (450)	3490 (476)	28.0 (4.96)	22.9 (3.83)	40 (40-41)
EFSOCH	UK	2000-2004	617 (322/294)	Measured within 12 hours of birth	3585 (463)	3447 (475)	3519 (474)	30.4 (5.28)	28.0 (4.44)	40 (39-41)
NFBC66	Finland	1966	3690 (1838/1851)	Measured in hospitals	3607 (506)	3480 (466)	3541 (489)			40 (39-41)
NFBC86	Finland	1986	3077 (1487/1589)	Measured in hospitals	3626 (543)	3519 (521)	3572 (535)			40 (39-40)

Table 1: Descriptive statistics of studies contributing to analysis. EFSOCH and ALSPAC sample size is the number of mother-child pairs in the analysis. NFBC66 and NFBC86 sample size is the number of offspring in the analysis.

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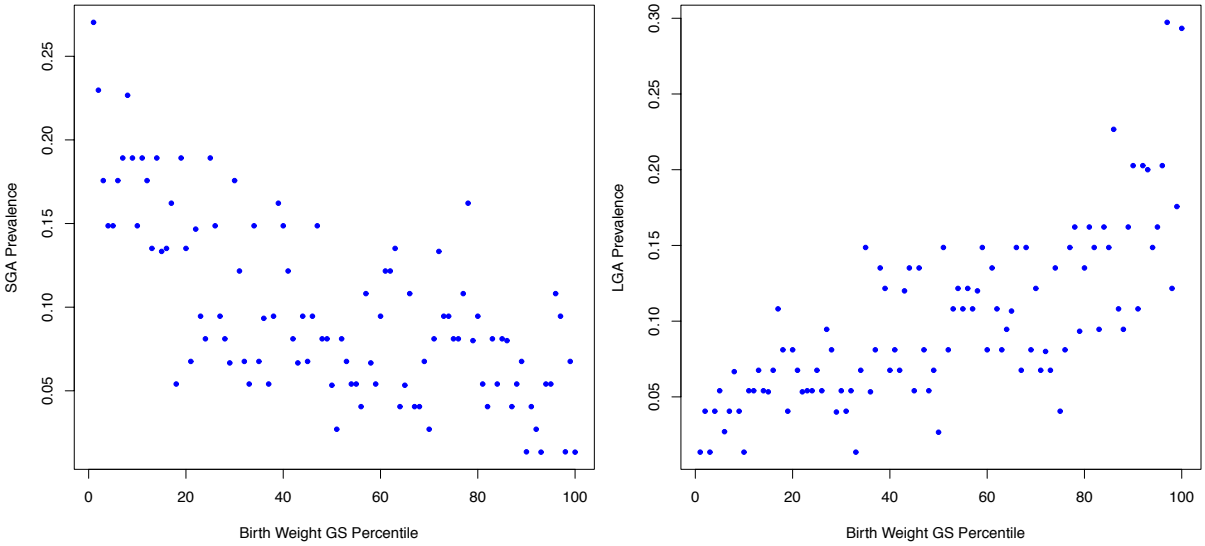

523

524 **Figure S1:** Fraction of babies born SGA (left) or LGA (right) by percentile bins of fetal birth

525 weight GS in ALSPAC (N=6,621)

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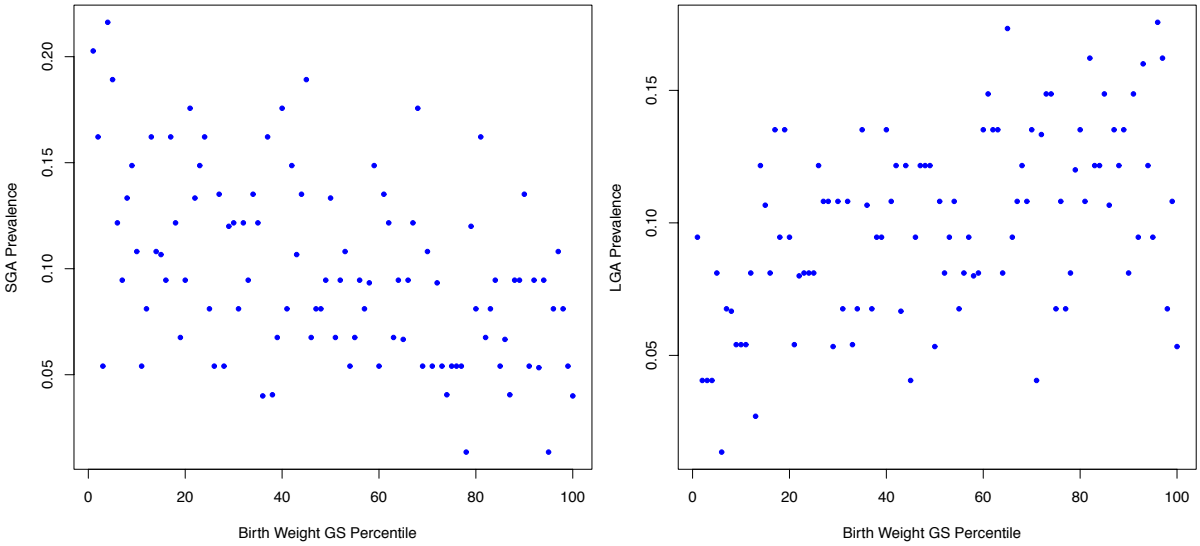

527

528 **Figure S2:** Fraction of babies born SGA (left) or LGA (right) by percentile bins of maternal

529 birth weight GS in ALSPAC (N=6,621)

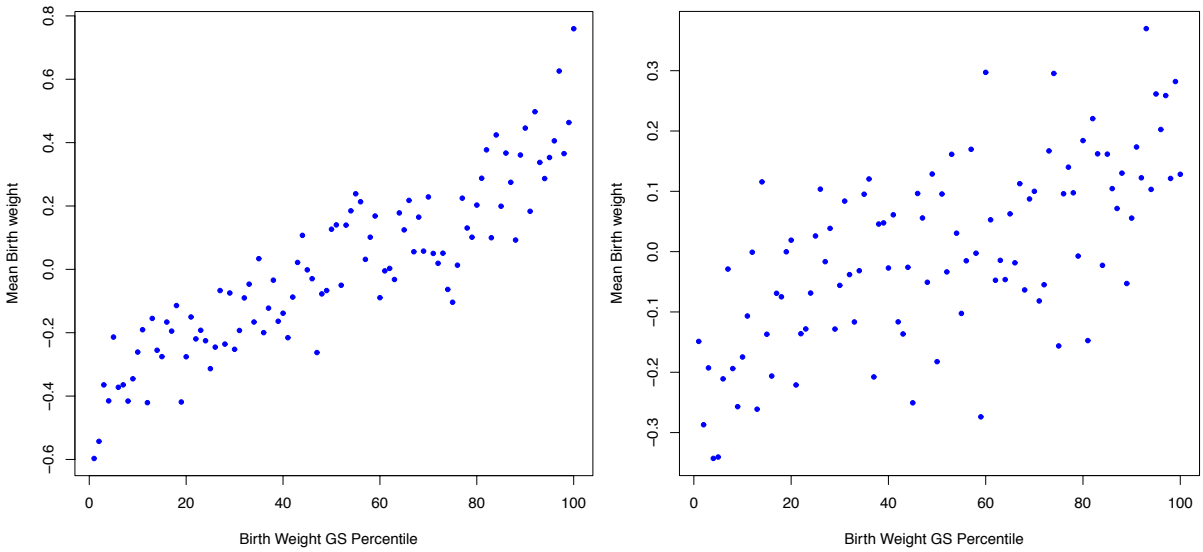

Figure S3: Mean birth weight in ALSPAC by percentile bins of fetal (left) and maternal (right) birth weight GS (N=6,621)