Supplementary information

Variants in the fetal genome near pro-inflammatory cytokine genes on 2q13 associate with gestational duration

Liu et al.
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Discovery stage
European ancestry infants from 20 studies
   Gestational duration: N=84,689
   Early preterm birth: N=1,139
   Preterm birth: N=4,775
   Postterm birth: N=7,888
   Term controls: N=60,148

GWAS scan
HRC 1.1 or 1000 G phase3 imputation
   and additive genetic model

Study level QC
MAF≥1%, info (from SNPTTEST and QTool) ≥0.4 or info (from r2_Hat) ≥0.3

Fixed-effects inverse variance
meta-analysis within study
Meta-analysis of sub-samples within
   SSI-GE and IPSYCH, to get SSI-GE\textsubscript{joined}
   and IPSYCH\textsubscript{joined}
   (variants appear in > 50% sub-samples)

Fixed-effects inverse variance
meta-analysis of studies
Meta-analysis for gestational duration,
   early preterm, preterm and postterm birth
   (variants appear in > 50% studies)
   7,646,297 SNPs in gestational duration
   7,588,467 SNPs in early preterm birth
   7,545,601 SNPs in preterm birth
   7,583,965 SNPs in postterm birth

Replication of 1 SNP for gestational
duration and postterm birth,
   2 SNPs for early preterm birth
   Gestational duration: N=9,291
   Early preterm birth cases: N=107
   Postterm birth cases: N=670

Combined discovery and replication for gestational duration,
   early preterm and postterm birth
   Gestational duration: N=93,980
   Early preterm birth cases: N=1,246
   Postterm birth cases: N=8,558
Supplementary Figure 2. Manhattan plots of $-\log_{10} P$ values across the chromosomes (left panel) and corresponding quantile-quantile plot of observed versus expected $-\log_{10} P$ values (right panel). (A) gestational duration, (B) postterm birth, (C) early preterm birth and (D) preterm birth.
Supplementary Figure 3. Regional association plots of the 2q13 locus, conditioning on rs7594852, for (A) gestational duration and (B) postterm birth. SNP position is shown on the x-axis and -log10 P value on the left y-axis. The conditional analyses were based on 51,357 samples from the iPSYCH study. The SNPs are colored to reflect their linkage disequilibrium with the lead SNP rs7594852 (based on pairwise $r^2$ values from the DNBC). Estimated recombination rates are from HapMap (right y-axis).
Supplementary Figure 4. Regional association plots of the 2q13 locus for (A) early preterm birth, and (B) preterm birth. SNP position is shown on the x-axis and -log10 P value on the left y-axis. The SNPs are colored to reflect their linkage disequilibrium with the lead SNP for gestational duration, rs7594852 (based on pairwise r² values from the DNBC). Estimated recombination rates are from HapMap (right y-axis).
**Supplementary Figure 5.** Frequency of allele rs7594852-C in 51,357 samples from the iPSYCH study grouped into bins by gestational age. The samples were divided into 5 groups by gestational duration, each red diamond represents a group, the location along the x-axis is the mean gestational age of the group, while the y-axis is the frequency of allele rs7594852-C in the group. Each circle represents the corresponding bootstrap mean allele frequency and the error-bars are given as the bootstrap standard deviation. The dashed line shows the overall mean allele frequency. Source data are provided as a Source Data file.
**Supplementary Figure 6.** Regional association plots of the 3q28 and 1p33 loci for early preterm birth. The lead SNPs, rs112912841 (A) and rs1877720 (B) are both represented by a purple diamond, and the other SNPs are colored to reflect their LD with the lead SNP (based on pairwise $r^2$ values from the DNBC cohort). Estimated recombination rates are from HapMap (right y-axis).

**Supplementary Figure 7.** Regional association plots of the 3q28 and 1p33 loci for early preterm birth, conditioning on the lead SNP at each locus, rs112912841 (A), and rs1877720 (B). Conditional analyses were conducted based on 452 iPSYCH early preterm cases and 38,238 controls. The SNPs are colored to reflect their linkage disequilibrium (LD) with the lead SNP (based on pairwise $r^2$ values from the DNBC cohort).
Supplementary Figure 8. Forest plots showing associations between rs112912841 (A), rs1877720 (B) and early preterm birth in contributing cohorts. The plots show odd ratio estimates with 95% confidence intervals. Source data are provided as a Source Data file.

Supplementary Figure 9. Quantile-quantile plot of gestational duration associations for 39 SNPs, which were known to be associated with cytokines. To be considered already known, the association had to be reported in the GWAS catalog with \( P < 5 \times 10^{-8} \). Observed versus expected –log10 \( P \) values are plotted for all SNPs and the orange line represents expected –log10 \( P \) values under the null distribution. The gray area defines the 95% concentration bands, which are an approximation to the 95% confidence intervals around the expected line. Source data are provided as a Source Data file.
Supplementary Figure 10. Statistical power to detect associated variants in the discovery stage for (A) gestational duration and (B) postterm birth, preterm birth, and early preterm birth. The power is calculated assuming a significance level of $5 \times 10^{-8}$, and population incidences of 1% for early preterm birth and 5% for preterm and postterm birth, respectively. Source data are provided as a Source Data file.
Supplementary Figure 11. Reference-based bimodal gestational duration quantile transformation. Source data are provided as a Source Data file.
**Supplementary Tables**

**Supplementary Table 1.** Power calculations for replication stage analyses.

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Chromosome Position (bp) SNP (effect/alternate allele)</th>
<th>Population effect allele frequency</th>
<th>Number</th>
<th>Beta/OR</th>
<th>Power</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases</td>
<td>Controls</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gestational duration</td>
<td>2</td>
<td>113521754 rs7594852 (C/T)</td>
<td>0.53</td>
<td>9291</td>
<td>0.034</td>
</tr>
<tr>
<td>Postterm birth</td>
<td>2</td>
<td>113521754 rs7594852 (C/T)</td>
<td>0.53</td>
<td>670</td>
<td>1.1</td>
</tr>
<tr>
<td>Early preterm birth</td>
<td>3</td>
<td>187987683 rs112912841 (G/A)</td>
<td>0.061</td>
<td>107</td>
<td>1.64</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>48824407 rs1877720 (T/C)</td>
<td>0.076</td>
<td>107</td>
<td>1.64</td>
</tr>
</tbody>
</table>

For the quantitative trait of quantile transformed gestational duration the sample size is given in the "Controls" column, while the effect size Beta is in units of standard deviation. For the dichotomous traits postterm and early preterm birth, odds ratio (OR) estimates are given. The power is calculated assuming a significance level of 0.05, and population incidences of 1% and 5% for early preterm birth and postterm birth, respectively.
Supplementary Table 2. Discovery, replication and combined results for the two lead SNPs in the early preterm birth analysis. Effect size is given as odds ratio (OR) estimates assuming an additive genetic effect; CI, confidence interval; $I^2$, heterogeneity estimate; $P_{\text{het}}$, $P$ value from the Cochran Q test of heterogeneity.

<table>
<thead>
<tr>
<th>Chromosome Position (bp)</th>
<th>SNP (effect/alternate allele)</th>
<th>Sample sets</th>
<th>Effect allele frequency</th>
<th>Number</th>
<th>OR (95% CI)</th>
<th>$P$</th>
<th>$I^2$ (95% CI)</th>
<th>$P_{\text{het}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Combined discovery</td>
<td>0.074</td>
<td>0.046</td>
<td>1139</td>
<td>60148</td>
<td>1.64 (1.37−1.96)</td>
<td>4.33 × 10$^{-8}$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>FIN</td>
<td>0.065</td>
<td>0.076</td>
<td>107</td>
<td>865</td>
<td>0.85 (0.48−1.51)</td>
<td>0.59</td>
</tr>
<tr>
<td></td>
<td></td>
<td>All combined</td>
<td>1246</td>
<td>61013</td>
<td>1.55 (1.31−1.84)</td>
<td>4.03 × 10$^{-7}$</td>
<td>78.2 (0.0−99.9)</td>
<td>0.032</td>
</tr>
<tr>
<td>1 48824407</td>
<td>rs1877720 (T/C)</td>
<td>Combined discovery</td>
<td>0.093</td>
<td>0.061</td>
<td>1139</td>
<td>60148</td>
<td>1.64 (1.38−1.94)</td>
<td>9.85 × 10$^{-9}$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>FIN</td>
<td>0.042</td>
<td>0.061</td>
<td>107</td>
<td>865</td>
<td>0.67 (0.33−1.35)</td>
<td>0.26</td>
</tr>
<tr>
<td></td>
<td></td>
<td>All combined</td>
<td>1246</td>
<td>61013</td>
<td>1.56 (1.32−1.84)</td>
<td>1.11 × 10$^{-7}$</td>
<td>83.2 (15.7−99.9)</td>
<td>0.015</td>
</tr>
</tbody>
</table>
**Supplementary Table 3.** Replication results based on mother-father-child trios from Iowa for the two lead SNPs in the early preterm birth discovery analysis. Effect size is given as odds ratio from the transmission disequilibrium test (TDT).

<table>
<thead>
<tr>
<th>Chromosome Position (bp) SNP (effect/alternate allele)</th>
<th>Effect allele frequency</th>
<th>Number of informative families</th>
<th>Transmitted minor allele count</th>
<th>Untransmitted allele count</th>
<th>TDT odds ratio</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 48824407 rs1877720 (T/C)</td>
<td>0.041</td>
<td>41</td>
<td>18</td>
<td>24</td>
<td>0.75</td>
<td>0.35</td>
</tr>
<tr>
<td>3 187987177 rs2306375 (A/C)*</td>
<td>0.075</td>
<td>54</td>
<td>28</td>
<td>27</td>
<td>1.04</td>
<td>0.89</td>
</tr>
</tbody>
</table>

*rs2306375 was used as a proxy for rs112912841. These SNP are in perfect LD ($r^2=1.0$, $D'=1.0$) in the European populations of the 1000 Genomes Project.
**Supplementary Table 4.** Association between rs7594852 (effect/non-effect allele: C/T) and gene expression in placenta. All cis genes (among 118 genes within 500kb from the SNP) where the eQTL association $P$ value was below 0.05 are listed.

<table>
<thead>
<tr>
<th>Transcript ID</th>
<th>Gene</th>
<th>$R^2$</th>
<th>BETA</th>
<th>SE</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>ENSG00000144136</td>
<td>SLC20A1</td>
<td>0.13</td>
<td>-0.50</td>
<td>0.13</td>
<td>0.00027</td>
</tr>
<tr>
<td>ENSG00000136688</td>
<td>IL36G</td>
<td>0.095</td>
<td>-0.44</td>
<td>0.14</td>
<td>0.0017</td>
</tr>
<tr>
<td>ENSG00000115008</td>
<td>IL1A</td>
<td>0.072</td>
<td>-0.38</td>
<td>0.14</td>
<td>0.0065</td>
</tr>
<tr>
<td>ENSG00000180152</td>
<td>AC079753.4</td>
<td>0.044</td>
<td>-0.28</td>
<td>0.13</td>
<td>0.033</td>
</tr>
<tr>
<td>ENSG00000136695</td>
<td>IL36RN</td>
<td>0.040</td>
<td>0.29</td>
<td>0.14</td>
<td>0.043</td>
</tr>
</tbody>
</table>

**Supplementary Table 5.** Association between rs7594852 (effect/non-effect allele: C/T) and levels of 10 biomarkers measured in peripheral blood taken a few days after birth from 8,138 participants of the iPSYCH study.

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>BETA</th>
<th>SE</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>BDNF</td>
<td>0.0004</td>
<td>0.0082</td>
<td>0.9566</td>
</tr>
<tr>
<td>CRP</td>
<td>0.0267</td>
<td>0.0183</td>
<td>0.1445</td>
</tr>
<tr>
<td>EPO</td>
<td>0.0108</td>
<td>0.0106</td>
<td>0.3124</td>
</tr>
<tr>
<td>IgA</td>
<td>0.0069</td>
<td>0.0095</td>
<td>0.4712</td>
</tr>
<tr>
<td>IL-18</td>
<td>0.0011</td>
<td>0.0075</td>
<td>0.8876</td>
</tr>
<tr>
<td>IL8</td>
<td>-0.0136</td>
<td>0.0087</td>
<td>0.1175</td>
</tr>
<tr>
<td>MCP1</td>
<td>0.0047</td>
<td>0.0052</td>
<td>0.3644</td>
</tr>
<tr>
<td>S100B</td>
<td>-0.0110</td>
<td>0.0148</td>
<td>0.4571</td>
</tr>
<tr>
<td>TARC</td>
<td>-0.0087</td>
<td>0.0109</td>
<td>0.423</td>
</tr>
<tr>
<td>VEGFA</td>
<td>-0.0021</td>
<td>0.0067</td>
<td>0.7559</td>
</tr>
</tbody>
</table>
**Supplementary Table 6.** Genomic inflation factors for each phenotype in each study.

<table>
<thead>
<tr>
<th>Study</th>
<th>Early preterm birth</th>
<th>Preterm birth</th>
<th>Postterm birth</th>
<th>Gestational duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALSPAC</td>
<td>NA</td>
<td>1.003</td>
<td>1.014</td>
<td>1.006</td>
</tr>
<tr>
<td>CHOP</td>
<td>1.012</td>
<td>1.009</td>
<td>NA</td>
<td>1.017</td>
</tr>
<tr>
<td>COPSAC2000</td>
<td>NA</td>
<td>NA</td>
<td>1.012</td>
<td>1.052</td>
</tr>
<tr>
<td>COPSAC2010</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>1.010</td>
</tr>
<tr>
<td>COPSAC_REGISTRY</td>
<td>NA</td>
<td>NA</td>
<td>1.004</td>
<td>0.998</td>
</tr>
<tr>
<td>DNBC</td>
<td>1.014</td>
<td>0.998</td>
<td>NA</td>
<td>1.010</td>
</tr>
<tr>
<td>EFSOCH</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>1.003</td>
</tr>
<tr>
<td>GenR</td>
<td>NA</td>
<td>NA</td>
<td>1.007</td>
<td>0.998</td>
</tr>
<tr>
<td>HAPO</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>0.994</td>
</tr>
<tr>
<td>INMA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>1.000</td>
</tr>
<tr>
<td>MoBa_2008</td>
<td>0.969</td>
<td>0.981</td>
<td>NA</td>
<td>0.992</td>
</tr>
<tr>
<td>NFBC1966</td>
<td>NA</td>
<td>1.007</td>
<td>1.005</td>
<td>1.009</td>
</tr>
<tr>
<td>NFBC1986</td>
<td>NA</td>
<td>1.011</td>
<td>NA</td>
<td>1.007</td>
</tr>
<tr>
<td>Raine Study</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>0.994</td>
</tr>
<tr>
<td>SSI-GE</td>
<td>NA</td>
<td>NA</td>
<td>0.975</td>
<td>1.007</td>
</tr>
<tr>
<td>STRIP</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>1.011</td>
</tr>
<tr>
<td>1958BC (DIL-T1DGC)</td>
<td>NA</td>
<td>0.986</td>
<td>0.996</td>
<td>0.991</td>
</tr>
<tr>
<td>1958BC (WTCCC)</td>
<td>NA</td>
<td>0.981</td>
<td>1.014</td>
<td>1.002</td>
</tr>
<tr>
<td>iPSYCH</td>
<td>1.007</td>
<td>1.007</td>
<td>1.026</td>
<td>1.044</td>
</tr>
<tr>
<td>GPN</td>
<td>0.989</td>
<td>0.988</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>
Supplementary Methods

Semi-parametric bootstrap of binned allele frequencies to test for non-linearity.

As described in the main text, no association was seen at the 2q13 locus in case-control analyses of early preterm birth or preterm birth. This may suggest that other mechanisms could be playing a greater role in causing early parturition before the mechanisms mediating the effect of the locus get their chance to influence the phenotype. To further investigate this question, we binned the 51,357 births from the largest contributing study (iPSYCH) in five groups by gestational duration. We then estimated the frequency of the rs7594852-C allele in each group and in the whole sample.

In the overall meta-analysis, each additional fetal rs7594852-C allele was associated with increased gestational duration (Table 1). The frequency of the rs7594852-C allele in the group with the shortest gestational duration was only slightly lower than the frequency in the whole sample (Supplementary Figure 5). The lowest allele frequency (0.518) was seen in the second group, representing a mean gestational duration of 276.5 days. The allele frequency then gradually increased in the next groups with the highest frequency (0.555) observed for the group representing the longest gestational duration (mean of 298.3 days) (Supplementary Figure 5).

To investigate if this pattern in allele frequencies represents a statistically significant deviation from what is expected under the hypothesis that the strength of the association is independent of gestational duration, we carried out semi-parametric bootstrapping under the assumption $H_0$: "the variant contributes equally to higher gestational duration no matter when the child is born". We chose a semi-parametric bootstrap approach to avoid assuming normal-distributed residuals in the untransformed distribution of gestational duration.

Our test statistic is based on bootstrapping allele frequencies in the five bins under $H_0$. If the variant influences gestational duration less in the early part of the distribution, then the observed allele frequency $f_1$ in the first bin will be closer to the overall frequency than expected under $H_0$, while the allele frequency in the second bin ($f_2$) will be lower than expected under $H_0$ and in the fifth bin ($f_5$) the allele frequency will be higher than expected under $H_0$.

Semi-parametric bootstrap was performed based on imputed genotype dosages and gestational duration in days from the 51,357 iPSYCH samples.

First, observed allele frequencies ($f_1, \ldots, f_5$) in the gestational duration intervals (0,273), [273,280), [280,287), [287,294) and [294,315) were calculated, as stated above and in the main text.

Next, expected gestational duration conditional on genotype was estimated using least squares regression assuming a linear relationship in the whole range of gestational duration:

$$E[y | g] = a + b * g$$

(1)

Empirical residuals were then extracted based on the expected gestational duration given the genotype:

$$r = y - \hat{a} - \hat{b} * g$$

(2)

Given the genotype $g$, gestational duration was now bootstrapped under the null hypothesis with resampling of the empirical residuals:

$$y_{boot} = \hat{a} + \hat{b} * g + r_{boot}$$

(3)
Based on the bootstrapped gestational duration, bootstrapped allele frequencies \( f_1^{\text{boot}}, ..., f_5^{\text{boot}} \) in the intervals \((0,273), [273,280), [280,287), [287,294) \) and \([294,315) \) were estimated. The bootstrap procedure was repeated 10,000 times.

The non-linearity \( P \) value was calculated as:

\[
P = \frac{1}{10000} \sum_{\text{boot}=1}^{10000} 1(f_1^{\text{boot}} > f_1) \times 1(f_2^{\text{boot}} < f_2) \times 1(f_5^{\text{boot}} > f_5)
\]

(4)

The expected allele frequency under \( H_0 \) in interval \( i \) was estimated as the mean of the bootstrapped allele-frequencies \( f_i^{\text{boot}} \), and the standard deviations of the respective bootstrapped distributions were likewise calculated.

Based on 10,000 joint bootstrap distributions of gestational age and genotype, we estimate that the probability under \( H_0 \) of observing more deviating allele frequencies is \( P = 0.0013 \). The expected binned allele frequencies under \( H_0 \) obtained from the bootstrap procedure are illustrated in Supplementary Figure 5.

Reference-based bimodal gestational duration quantile transformation

The DNBC and MoBa_2008 cohorts represent case-control studies of preterm birth, which means that the distribution of gestational duration is bimodal for these studies. In these two cohorts, we transformed gestational duration to be on the same scale as the population-based cohorts. For that purpose, we used gestational duration and sex of a representative (random) population based sample from Denmark and Norway, respectively, as reference data.

In the population based reference sample, we first regressed gestational duration on infant sex. We stored the coefficients (intercept \( a_{\text{ref}} \) and effect of sex \( b_{\text{ref}} \)) and calculated the residuals \( x_{\text{ref}} \) in the population based reference sample \( (x_{\text{ref}} = \text{gestational duration} - (a_{\text{ref}} + b_{\text{ref}} \times \text{sex})) \). We mapped the reference residuals, \( x_{\text{ref}} \), to quantile transformed residuals, \( q_{\text{ref}} \), using a rank-based inverse normal transformation and we stored the pairs \( (x_{\text{ref}}, q_{\text{ref}}) \) of residual and transformed reference residual. Having established a transformation from gestational duration to quantile transformed residuals in the population based reference sample, we calculated the equivalent transformation of the gestational duration in the corresponding case-control studies (DNBC and MoBa_2008, respectively). To do so, we first calculated pseudo residuals, \( x_{\text{cc}} \), from gestational duration in the case-control study based on the stored coefficients from the reference sample \( (x_{\text{cc}} = \text{gestational duration} - (a_{\text{ref}} + b_{\text{ref}} \times \text{sex})) \). Based on the pseudo residual, \( x_{\text{cc}} \), in the case-control study, a transformed pseudo residual, \( q_{\text{cc}} \), was obtained by linear interpolation from the pairs \( (x_{\text{ref}}, q_{\text{ref}}) \) of residuals and transformed residuals from the reference population sample. Finally, the transformed pseudo residuals were used for association testing in the DNBC and MoBa_2008 cohorts. The reference-based quantile transformation is illustrated in Supplementary Figure 11.
Supplementary Notes

Supplementary Note 1. EGG Membership

Full list of EGG Consortium members (as of July 2019), listed in alphabetical order.


1. Department of Nutrition, University of North Carolina, Chapel Hill, NC 27599, USA.
2. Department of Clinical Sciences, Diabetes and Endocrinology, Lund University Diabetes Centre, Malmö, SE-205 02, Sweden.
3. COPSAC, Copenhagen Prospective Studies on Asthma in Childhood, Herlev and Gentofte Hospital, University of Copenhagen, Copenhagen, 2900 Hellerup, Denmark.
4. Novo Nordisk Foundation Center for Basic Metabolic Research, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, DK-2200, Denmark.
5. Steno Diabetes Center Copenhagen, Gentofte, 2820, Denmark.
6. Division of Obstetrics and Gynaecology, The University of Western Australia, Crawley, WA, 6009, Australia.
7. Institute of Biomedicine, School of Medicine, University of Eastern Finland, Kuopio, 70211, Finland.
9. University of Lausanne, Lausanne, CH-1015, Switzerland.
10. Department of Epidemiology and Biostatistics, MRC-PHE Centre for Environment & Health, School of Public Health, Imperial College London, London, W2 1PG, UK.
11. Department of Biological Psychology, Vrije Universiteit Amsterdam, Amsterdam, 1081 BT, The Netherlands.
14. Netherlands Twin Register, Department of Biological Psychology, VU University, Amsterdam, 1081 HV, The Netherlands.
16. Department of Nutrition and Dietetics, University of San Carlos, Cebu City, 6000, Philippines.
18. Quantinuum Research LLC, San Diego, CA, 92101, USA.
20. Universitat Pompeu Fabra (UPF), Barcelona, 08003, Spain.
21. CIBER de Epidemiología y Salud Pública (CIBERESP), Madrid, 28029, Spain.
22. Department of Tropical Hygiene, Faculty of Tropical Medicine, Mahidol University, Bangkok, 10400, Thailand.
23. Institute for Molecular Bioscience, University of Queensland, QLD, Australia.
24. Medical Research Council Lifecourse Epidemiology Unit, University of Southampton, Southampton, SO17 1BJ, UK.
25. Division of Human Genetics, The Children’s Hospital of Philadelphia, Philadelphia, PA 19104, USA.
26. Department of Genetics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, 19104, USA.
27. Division of Infection Immunity and Respiratory Medicine, School of Biological Sciences, The University of Manchester, Manchester Academic Health Science Centre, and Manchester University NHS Foundation Trust, Manchester, M13 9NT, UK.
28. Department of Paediatrics, Imperial College London, London, SW7 2AZ, UK.
29. Medical Research Council Unit for Lifelong Health and Ageing at UCL, Institute of Cardiovascular sciences, UCL, London, WC1B 5JU, UK.
30. MRC Epidemiology Unit, University of Cambridge School of Clinical Medicine, Cambridge, CB2 0QQ, UK.
31. Department of Nutrition and Dietetics, School of Health Science and Education, Harokopio University, Athens, 17671, Greece.
33. Department of General Practice and Primary Health Care, University of Helsinki and Helsinki University Hospital, Helsinki, 00014, Finland.
34. Folkhälsan Research Center, Helsinki, 00250, Finland.
35. Medical Research Council Integrative Epidemiology Unit at the University of Bristol, Bristol, BS8 2BN, UK.
36. Population Health Sciences, Bristol Medical School, University of Bristol, Bristol, BS8 2BN, UK.
37. University of Queensland Diamantina Institute, Translational Research Institute, Brisbane, QLD, 4072, Australia.
38. Department of Epidemiology Research, Statens Serum Institute, Copenhagen, DK-2300, Denmark.
39. The Generation R Study Group, Erasmus MC, University Medical Center Rotterdam, Rotterdam, 3015 CE, The Netherlands.
40. Department of Epidemiology, Erasmus MC, University Medical Center Rotterdam, Rotterdam, 3015 CE, The Netherlands.
41. Department of Pediatrics, Erasmus MC, University Medical Center Rotterdam, Rotterdam, 3015 CE, The Netherlands.
42. Department of Radiology, Children's Hospital Los Angeles, Los Angeles, CA 90027, USA.
43. Department of Pediatrics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA 19104, USA.
44. Institute for Molecular Medicine Finland FIMM, University of Helsinki, Helsinki, Finland.
45. Department of Pediatrics, University of California San Francisco School of Medicine, San Francisco, CA 94143, USA.
46. NIHR Exeter Clinical Research Facility, University of Exeter College of Medicine and Health and Royal Devon and Exeter NHS Foundation Trust, Exeter, EX2 5DW, UK.
47. Department of Medicine, Division of Endocrinology, Metabolism, and Molecular Medicine, Feinberg School of Medicine, Northwestern University, Chicago, IL 60611, USA.
48. Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy, University Hospital Essen, University of Duisburg-Essen, Essen, 45141, Germany.
49. Institute of Epidemiology, Helmholtz Zentrum München - German Research Center for Environmental Health, Neuherberg, Germany.
50. Institute and Outpatient Clinic for Occupational, Social and Environmental Medicine, University Hospital of Ludwig Maximilians University, Munich, Germany.
51. KG Jebsen Center for Diabetes Research, Department of Clinical Science, University of Bergen, Bergen, N-5020, Norway.
52. Department of Pediatrics, Haukeland University Hospital, Bergen, 5021, Norway.
53. Department of Genetics and Bioinformatics, Domain of Health Data and Digitalisation, Norwegian Institute of Public Health, Oslo, N-0473, Norway.
54. Department of Paediatrics and Adolescent Medicine, Aarhus University Hospital, Aarhus N, DK-8200, Denmark.
55. Programs in Metabolism and Medical & Population Genetics, Broad Institute of Harvard and MIT, Cambridge, MA 02142, USA.
56. Department of Genetics, Harvard Medical School, Boston, MA 02115, USA.
57. Division of Endocrinology and Center for Basic and Translational Obesity Research, Boston Children’s Hospital, Boston, MA, 02115, USA.
58. Department of Population Medicine, Harvard Pilgrim Health Care Institute, Harvard Medical School, Boston, MA 02215, USA.
59. Diabetes Center, Massachusetts General Hospital, Boston, MA 02114, USA.
60. Department of Medicine, Universite de Sherbrooke, Sherbrooke, QC J1K 2R1, Canada.
61. Fifth Department of Medicine, University Medical Centre Mannheim, University of Heidelberg, Heidelberg, Germany.
62. Reproductive and Genetic Hospital of CITIC-Xiangya, Changsha, China.
63. Human Development & Health, Faculty of Medicine, University of Southampton, Southampton, SO16 6YD, UK.
64. Wellcome Centre for Human Genetics, University of Oxford, Oxford, OX3 7BN, UK.
66. RIKEN, Centre for Integrative Medical Sciences, Laboratory for Endocrinology, Metabolism and Kidney diseases, Yokohama, Kanagawa, 230-0045, Japan.
67. Australian Centre for Precision Health, University of South Australia Cancer Research Institute, Adelaide, SA, 5001, Australia.
68. South Australian Health and Medical Research Institute, Adelaide, SA, 5001, Australia.
69. Population, Policy and Practice, UCL Great Ormond Street Institute of Child Health, University College London, London, WC1N 1EH, UK.
70. Department of Obstetrics and Gynecology, Sahlgrenska Academy, University of Gothenburg, Diagnosvägen 15, SE-416 85 Gothenburg, Sweden.
71. Biocenter Oulu, University of Oulu, Oulu, 90220, Finland.
72. Unit of Primary Care, Oulu University Hospital, Oulu, 90220, Finland.
73. Center for Life Course Health Research, Faculty of Medicine, University of Oulu, Oulu, FI-90014, Finland.
74. Department of Life Sciences, College of Health and Life Sciences, Brunel University London, Middlesex, UB8 3PH, UK.
75. Department of Medical Genetics, Haukeland University Hospital, Bergen, Norway.
76. Division of Gastroenterology, Hepatology and Nutrition, Cincinnati Children's Hospital Medical Center, Cincinnati, OH 45229, USA.
77. Pediatric Research Center, Department of Women’s & Child Health, University of Leipzig, Leipzig, 04109, Germany.
78. IFB Adiposity Diseases, University of Leipzig, Leipzig, 04109, Germany.
79. Department of Child Health, School of Medicine, Cardiff University, Cardiff, CF10 3AT, UK.
80. Danish Pediatric Asthma Center, Copenhagen University Hospital, Gentofte, DK-2100, Denmark.
81. Institute of Social and Preventive Medicine, Lausanne University Hospital (CHUV), Lausanne, 1011, Switzerland.
82. Swiss Institute of Bioinformatics, Lausanne, 1015, Switzerland.
83. Department of Clinical Physiology and Nuclear Medicine, Kuopio University Hospital, Kuopio, 70210, Finland.
84. Kuopio Research Institute of Exercise Medicine, Kuopio, 70100, Finland.
85. Division of Endocrinology, Department of Medicine, Creighton University, Omaha, NE 68178, USA.
86. Bristol NIHR Biomedical Research Centre, Bristol, UK.
87. Department of Clinical Chemistry, Fimlab Laboratories, Tampere University Hospital, Tampere, Finland.
88. Department of Clinical Chemistry, Finnish Cardiovascular Research Center - Tampere, Faculty of Medicine and Health Technology, Tampere University, Tampere, 33520, Finland.
89. Li Ka Shing Centre for Health Information and Discovery, The Big Data Institute, University of Oxford, Oxford, OX3 7LF, UK.
90. The Broad Institute of Harvard and MIT, Cambridge, USA.
91. Center for Clinical Research and Prevention, Bispebjerg and Frederiksberg Hospital, The Capital Region, Frederiksberg, 2000, Denmark.
92. Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark.
93. Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Hong Kong, China.
94. Li Ka Shing Institute of Health Sciences, The Chinese University of Hong Kong, Hong Kong, China.
95. Hong Kong Institute of Diabetes and Obesity, The Chinese University of Hong Kong, Hong Kong, China.
96. Estonian Genome Center, University of Tartu, Tartu, 50090, Estonia.
97. Centre for Fertility and Health, Norwegian Institute of Public Health, Oslo, N-0403, Norway.
98. Oxford NIHR Biomedical Research Centre, Oxford University Hospitals NHS Foundation Trust, John Radcliffe Hospital, Oxford, OX3 9DU, UK.
99. Centre for Genetic Origins of Health and Disease (GOHaD), The University of Western Australia, Crawley, WA, 6000, Australia.
100. Department of Medicine, Stanford School of Medicine, Stanford, CA 94305, USA.
101. Department of Genetics, University of North Carolina, Chapel Hill, NC 27599, USA.
102. Department of Clinical Epidemiology, Leiden University Medical Center, Leiden, 2333 ZA, The Netherlands.
103. Department of Public Health and Primary Care, Leiden University Medical Center, Leiden, 2333 ZA, The Netherlands.
104. Department of Public Health, Section of Epidemiology, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Copenhagen, DK-1014, Denmark.
105. Department of Biostatistics, University of Liverpool, Liverpool, L69 3GL, UK.
106. Human Genetics Division, Cincinnati Children’s Hospital Medical Center, Cincinnati, OH 45229, USA.
107. Center for Prevention of Preterm Birth, Perinatal Institute, Cincinnati Children’s Hospital Medical Center, Department of Pediatrics, University of Cincinnati College of Medicine, Cincinnati, OH 45229, USA.
108. March of Dimes Prematurity Research Center Ohio Collaborative, Cincinnati, OH 45229, USA.
109. Department of Pediatrics, University of Iowa, Iowa City, IA 52242, USA.
110. Department of Genetics and Bioinformatics, Norwegian Institute of Public Health, Oslo, N-0403, Norway.
111. Research Unit for Gynaecology and Obstetrics, Institute of Clinical Research, University of Southern Denmark, Odense, DK-5000, Denmark.
112. William Harvey Research Institute, Barts and the London School of Medicine and Dentistry, Queen Mary University of London, London, EC1M 6BQ, UK.
113. Medical Research Council (MRC), Social, Genetic and Developmental Psychiatry Centre, Institute of Psychiatry, Psychology & Neuroscience, King’s College London, London, SE5 8AF, UK.
114. Division of Pediatric Endocrinology, Diabetes, and Metabolism, Department of Pediatrics, Columbia University Medical Center, New York, NY 10032, USA.
115. Obesity Prevention Program, Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, MA 02215, USA.
116. Department of Paediatrics, University of Cambridge, Cambridge, CB2 0QQ, UK.
117. Wellcome Sanger Institute, Hinxton, Cambridgeshire, CB10 1HH, UK.
118. School of Medicine and Public Health, Faculty of Medicine and Health, The University of Newcastle, Callaghan, NSW, 2308, Australia.
119. Research Centre of Applied and Preventive Cardiovascular Medicine, University of Turku, Turku, 20014, Finland.
120. Max Planck Institute for Psycholinguistics, Nijmegen, 6525 XD, The Netherlands.
121. Section of Genomics of Common Disease, Department of Medicine, Imperial College London, London, SW7 2AZ, UK.
122. Department of Clinical Physiology and Nuclear Medicine, Turku University Hospital, Turku, 20520, Finland.
123. BHF Centre for Cardiovascular Science, University of Edinburgh, Queen’s Medical Research Institute, Edinburgh, EH16 4TJ, UK.
124. Department of Psychology, Mid Sweden University, Östersund, SE-831 25, Sweden.
125. Department of Medicine, Division of Endocrinology, Boston Children’s Hospital, Boston, MA 02115, USA.
126. Program in Medical and Population Genetics, Broad Institute of Harvard and MIT, Cambridge, MA 02142, USA.
127. Center for Basic and Translational Obesity Research, Boston Children’s Hospital, Boston, MA 02115, USA.
128. Saw Swee Hock School of Public Health, National University of Singapore, National University Health System, Singapore, 119077, Singapore.
129. Singapore Eye Research Institute, Singapore, 168751, Singapore.
130. Department of Genomics of Complex Diseases, Imperial College, London, UK.
131. Department of Epidemiology, Cancer Center, University of Hawaii (Manoa), Honolulu, Hawaii, 96813, USA.
132. Department of Obstetrics and Gynecology, Erasmus MC, University Medical Center Rotterdam, Rotterdam, 3015 CE, The Netherlands.
133. Population Health Research Institute, St George’s University of London, London, SW17 0RE, UK.
134. IMIM (Hospital del Mar Medical Research Institute), Barcelona, 08003, Spain.
136. Life Sciences Institute, National University of Singapore, Singapore, 117456, Singapore.
137. Division of Metabolic and Nutritional Medicine, Dr. von Hauner Children's Hospital, University of Munich Medical Center, Munich, 80337, Germany.
138. European Centre for Environment and Human Health, University of Exeter, Truro, TR1 3HD, UK.
139. Department of Internal Medicine, Erasmus MC, University Medical Center Rotterdam, Rotterdam, 3015 CE, The Netherlands.
140. Department of Public Health, Amsterdam Public Health Research Institute, Amsterdam UMC, location Academic Medical Center, University of Amsterdam, Amsterdam, 1105 AZ, The Netherlands.
141. Institute of Medical Statistics and Epidemiology, Technical University Munich, Munich, D-80333, Germany.
142. Institute of Medical Informatics, Biometry and Epidemiology, Ludwig Maximilians University, Munich, 81377, Germany.
143. Usher Institute for Population Health Sciences and Informatics, University of Edinburgh, Edinburgh, EH8 9AG, UK.
144. MRC Human Genetics Unit, Institute of Genetics and Molecular Medicine, University of Edinburgh, Edinburgh, EH4 2XU, UK.
145. Department of Clinical Epidemiology, Biostatistics and Bioinformatics, Amsterdam Public Health Research Institute, Amsterdam UMC, location Academic Medical Center, University of Amsterdam, Amsterdam, 1105 AZ, The Netherlands.
146. Institute of Translational Genomics, Helmholtz Zentrum München – German Research Center for Environmental Health, Neuherberg, Germany.
Supplementary Note 2. iPSYCH-BROAD Working Group

Collaborators in the iPSYCH-BROAD Working Group listed in alphabetical order.

Esben Agerbo\textsuperscript{1,2,3}, Jonas Bybjerg-Grauholm\textsuperscript{1,4}, Marie Bækved-Hansen\textsuperscript{1,4}, Mark J. Daly\textsuperscript{5,6,7}, Benjamin M. Neale\textsuperscript{5,6,7}, Carsten Bøcker Pedersen\textsuperscript{1,2,3}, Marianne Giørtz Pedersen\textsuperscript{1,2,3}.

1. iPSYCH, The Lundbeck Foundation Initiative for Integrative Psychiatric Research, Aarhus, Denmark.
2. National Centre for Register-Based Research, Aarhus University, Aarhus, Denmark.
3. Centre for Integrated Register-based Research, Aarhus University, Aarhus, Denmark.
4. Statens Serum Institut, Center for Neonatal Screening, Department for Congenital Disorders, Copenhagen, Denmark.
5. Analytic and Translational Genetics Unit, Department of Medicine, Massachusetts General Hospital and Harvard Medical School, Boston, USA.
6. Stanley Center for Psychiatric Research, Broad Institute of Harvard and MIT, Cambridge, Massachusetts, USA.
7. Program in Medical and Population Genetics, Broad Institute of Harvard and MIT, Cambridge, Massachusetts, USA.
Supplementary Note 3. Additional acknowledgements by study

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INMA: INMA researchers would like to thank all the participants for their generous collaboration. A full roster of the INMA Project Investigators can be found at http://www.proyectoinma.org/presentacioninma/listado-investigadores/en_listado-investigadores.html.

MoBa_2008 and MoBa_HARVEST: The Norwegian Mother and Child Cohort Study (MoBa) is a prospective population-based pregnancy cohort study conducted by the Norwegian Institute of Public Health. Participants were recruited from all over Norway from 1999-2008. The women consented to participation in 41% of the pregnancies. The cohort now includes 114,500 children, 95,200 mothers and 75,200 fathers. Blood samples were obtained from both parents during pregnancy and from mothers and children (umbilical cord) at birth. We are grateful to all the participating families in Norway who take part in this ongoing cohort study.

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