**GWAS on longitudinal growth traits reveals different genetic factors influencing infant, child and adult BMI**

Alexessander Couto Alves1\*, N. Maneka G. De Silva1**\***, Ville Karhunen1, Ulla Sovio4, Shikta Das1**,** H. Rob Taal5,6, Nicole M. Warrington7,8,72, Alexandra M. Lewin1,9, Marika Kaakinen1,10,11, Diana Cousminer12, Elisabeth Thiering13,14, Nicholas J. Timpson15,16, Tom Bond1, Estelle Lowry2, Christopher D. Brown17, Xavier Estivill18-22,, Virpi Lindi23, Jonathan P. Bradfield24, Frank Geller25, Doug Speed77, Lachlan J.M. Coin1,26, Marie Loh1,2,27, Sheila J. Barton28, Lawrence J. Beilin29, Hans Bisgaard30, Klaus Bønnelykke30,31, Rohia Alili32, Ida J. Hatoum32,,34, Katharina Schramm35,36, Rufus Cartwright1,37, Marie-Aline Charles38, Vincenzo Salerno1, Karine Clément32,38, Annique A.J. Claringbould39, BIOS consortium, Cornelia M. van Duijn40, Elena Moltchanova41, Johan G. Eriksson42-44, Cathy Elks45, Bjarke Feenstra25, Claudia Flexeder13, Stephen Franks37, Timothy M. Frayling46, Rachel M. Freathy46, Paul Elliott1, Elisabeth Widén47, Hakon Hakonarson12,24,48,49, Andrew T. Hattersley46, Alina Rodriguez1,50, Marco Banterle9, Joachim Heinrich13, Barbara Heude38, John W. Holloway51, Albert Hofman6,40, Elina Hyppönen52,53, Hazel Inskip28, Lee M. Kaplan33,34, Asa K. Hedman54,55, Esa Läärä56, Holger Prokisch35,36, Harald Grallert57,58, Timo A. Lakka23,59,60, Debbie A. Lawlor15,16, Mads Melbye25, Tarunveer S. Ahluwalia30 , Marcella Marinelli20,21,61, Iona Y. Millwood62,63, Lyle J. Palmer64, Craig E. Pennell7, John R. Perry45, Susan M.Ring15,16,65, Markku Savolainen66, Kari Stefansson67,68, Gudmar Thorleifsson67, Fernando Rivadeneira40,69, Marie Standl13, Jordi Sunyer19-21,61, Carla M.T. Tiesler 13,14, Andre G. Uitterlinden40,69, William Schierding70, Justin M. O’Sullivan70,71, Inga Prokopenko10,54,72,Karl-Heinz Herzig3,73-75, George Davey Smith15,16, Paul O'Reilly1,76 , Janine F. Felix5,6,40, Jessica L. Buxton77, Alexandra I.F. Blakemore78,79, Ken K. Ong45, Vincent W.V. Jaddoe5,6,40,**$**, Struan F.A. Grant12,24,48,49,**$**, Sylvain Sebert1-3**$**, Mark I. McCarthy54,72,80,**$**, Marjo-Riitta Järvelin1-3,74,78,81**$** for the Early Growth Genetics (EGG) Consortium.

1. Department of Epidemiology and Biostatistics, MRC-PHE Centre for Environment and Health, School of Public Health, Imperial College London, London, UK.
2. Center for Life Course Health Research, Faculty of Medicine, University of Oulu, Oulu, Finland.
3. Biocenter Oulu, University of Oulu, Oulu, Finland.
4. Department of Obstetrics and Gynaecology, University of Cambridge, Cambridge, UK.
5. Department of Paediatrics, Erasmus MC, Sophia Children’s Hospital, Rotterdam, the Netherlands.
6. The Generation R Study Group, Erasmus MC, University Medical Center Rotterdam, the Netherlands.
7. School of Women’s and Infants’ Health, The University of Western Australia, Adelaide, Australia.
8. The University of Queensland Diamantina Institute, The University of Queensland, Translational Research Institute, Brisbane, Queensland, Australia.
9. Department of Medical Statistics, London School of Hygiene and Tropical Medicine, London, UK.
10. Department of Genomics of Common Disease, School of Public Health, Imperial College London, Hammersmith Hospital, London, UK.
11. Centre for Pharmacology and Therapeutics, Division of Experimental Medicine, Department of Medicine, Imperial College London, Hammersmith Hospital, London, UK
12. Division of Human Genetics, The Children’s Hospital of Philadelphia, Philadelphia, Pennsylvania, USA.
13. Institute of Epidemiology I, Helmholtz Zentrum München -, German Research Center for Environmental Health, Munich Neuherberg, Germany.
14. Ludwig-Maximilians-University of Munich, Dr. von Hauner Children's Hospital, Division of Metabolic Diseases and Nutritional Medicine, Dr von Hauner Children’s Hospital, Ludwig-Maximilians University Munich, Munich, Germany.
15. MRC Integrative Epidemiology Unit at the University of Bristol, Bristol, UK.
16. School of Social and Community Medicine, University of Bristol, Bristol, UK.
17. Department of Genetics and Institute for Biomedical Informatics , Perelman School of Medicine, University of Pennsylvania
18. Genomics and Disease Group, Bioinformatics and Genomics Programme, Centre for Genomic Regulation (CRG), Barcelona, Catalonia, Spain.
19. Pompeu Fabra University (UPF), Barcelona, Catalonia, Spain.
20. Hospital del Mar Medical Research Institute (IMIM), Barcelona, Catalonia, Spain.
21. Spanish consortium for Research on Epidemiology and Public Health (CIBERESP), Spain.
22. Sidra Medical and Research Center, Doha, Qatar.
23. Institute of Biomedicine, Department of Physiology, University of Eastern Finland, Kuopio, Finland.
24. Center for Applied Genomics, Abramson Research Center, The Children’s Hospital of Philadelphia, Philadelphia, Pennsylvania, USA.
25. Department of Epidemiology Research, Statens Serum Institut, Copenhagen, Denmark.
26. Institute for Molecular Bioscience, The University of Queensland, Brisbane, Australia.
27. Translational Laboratory in Genetic Medicine (TLGM), Agency for Science, Technology and Research (A\*STAR), Singapore.
28. MRC Lifecourse Epidemiology Unit, University of Southampton, Southampton General Hospital, Southampton, UK.
29. School of Medicine and Pharmacology, Royal Perth Hospital, The University of Western Australia, Perth, Australia.
30. COPSAC, The Copenhagen Prospective Studies on Asthma in Childhood, Faculty of Health Sciences, University of Copenhagen, Copenhagen, Denmark.
31. The Danish Pediatric Asthma Center, Copenhagen University Hospital, Gentofte, Denmark.
32. CRNH Ile de France, Hôpital Pitié-Salpêtrière, Paris, France.
33. Obesity, Metabolism, and Nutrition Institute and Gastrointestinal Unit, Massachusetts General Hospital, Boston, MA, USA.
34. Department of Medicine, Harvard Medical School, Boston, MA, USA.
35. Institute of Human Genetics, Helmholtz Center Munich, German Research Center for Environmental Health, Neuherberg, Germany.
36. Institute of Human Genetics, Technische Universität München, München, Germany.
37. Institute for Reproductive and Developmental Biology, Imperial College London, London, UK.
38. Inserm, UMR 1153 (CRESS), Villejuif; Paris Descartes University, France
39. University Medical Centre Groningen, Department of Genetics, Antonius Deusinglaan 1, 9713 AV, Groningen, The Netherlands
40. Department of Epidemiology, Erasmus MC, University Medical Center Rotterdam, the Netherlands.
41. University of Canterbury, Department of Mathematics and Statistics, Christchurch, New Zealand.
42. Department of General Practice and Primary Health Care, University of Helsinki, and Helsinki University Hospital, Helsinki, Finland.
43. Department of Chronic Disease Prevention, National Institute for Health and Welfare, Helsinki, Finland.
44. Folkhalsan Research Center, Helsinki, Finland.
45. MRC Epidemiology Unit, University of Cambridge School of Clinical Medicine, Institute of Metabolic Science, Cambridge Biomedical Campus, Cambridge, UK.
46. Institute of Biomedical and Clinical Science, University of Exeter Medical School, University of Exeter, Royal Devon and Exeter Hospital, Exeter, UK.
47. Institute for Molecular Medicine Finland, University of Helsinki, Helsinki, Finland.
48. Department of Paediatrics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA.
49. Institute of Diabetes, Obesity and Metabolism, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA.
50. School of Psychology, College of Social Science, University of Lincoln Brayford Pool Lincoln, Lincolnshire, UK.
51. Human Genetics and Medical Genomics, Faculty of Medicine, University of Southampton, UK.
52. School of Population Health, University of South Australia, Adelaide, Australia.
53. Centre for Paediatric Epidemiology and Biostatistics, University College London, Institute of Child Health, London, UK.
54. Wellcome Trust Centre for Human Genetics, University of Oxford, Oxford, UK.
55. Cardiovascular Medicine unit, Department of Medicine, Karolinska Institute, Stockholm, Sweden.
56. Research Unit of Mathematical Sciences, University of Oulu, Finland.
57. Research Unit of Molecular Epidemiology, Helmholtz Zentrum München, German Research Center for Environmental Health, Neuherberg, Germany.
58. German Center for Diabetes Research (DZD), Neuherberg, Germany.
59. Kuopio Research Institute of Exercise Medicine, Kuopio, Finland.
60. Department of Clinical Physiology and Nuclear Medicine, Kuopio University Hospital, Kuopio, Finland.
61. ISGlobal, Centre for Research in Environmental Epidemiology (CREAL), Barcelona, Spain Center for Research in Environmental Epidemiology (CREAL), Barcelona, Catalonia, Spain.
62. Clinical Trial Service Unit and Epidemiological Studies Unit (CTSU), University of Oxford, Old Road Campus, Oxford, UK.
63. Medical Research Council Population Health Research Unit (MRC PHRU) at the University of Oxford, Oxford, UK.
64. School of Public Health and Robinson Research Institute, University of Adelaide, Australia.
65. Avon Longitudinal Study of Parents and Children, School of Social and Community Medicine, University of Bristol, Bristol, UK.
66. Division of Internal Medicine, and Biocenter of Oulu, Faculty of Medicine, Oulu University, Finland.
67. deCODE genetics, Reykjavik, Iceland.
68. University of Iceland, Faculty of Medicine, Reykjavik, Iceland.
69. Department of Internal Medicine, Erasmus MC, University Medical Center Rotterdam, the Netherlands.
70. Liggins Institute, The University of Auckland, Auckland, New Zealand
71. A Better Start - National Science, Challenge, The University of Auckland, Auckland, New Zealand
72. Oxford Centre for Diabetes, Endocrinology and Metabolism, University of Oxford, Churchill Hospital, Oxford, UK.
73. Research Unit of Biomedicine, University Oulu, Oulu, Finland.
74. Medical Research Center and Oulu University Hospital, University of Oulu, Oulu, Finland.
75. Department of Gastroenterology and Metabolism, Poznan University of Medical Sciences, Poznan, Poland.
76. MRC Social, Genetic and Developmental Psychiatry Centre, Institute of Psychiatry, King’s College London, De Crespigny Park, London, UK.
77. UCL Genetics Institute, Department of Genetics, Evolution and Environment, University College London, London, UK.
78. Department of Life Sciences, College of Health and Life Sciences, Brunel University London, London, UK.
79. Section of Investigative Medicine, Division of Diabetes, Endocrinology & Metabolism, Imperial College London, UK.
80. Oxford NIHR Biomedical Research Centre, Churchill Hospital, Old Road, Headington, Oxford, UK.
81. Unit of Primary Care, Oulu University Hospital, Finland.

**\***These authors equally contributed to the work.

$These authors jointly directed this work.

Correspondence should be addressed to M-R.J. (m.jarvelin@imperial.ac.uk), M.I.M.

(mark.mccarthy@drl.ox.ac.uk), S.F.A.G. (grants@chop.edu), S. S. (sylvain.sebert@oulu.fi)

**Abstract (300 max) currently 299 words**

Early childhood growth patterns are associated with adult health, yet the genetic factors and the developmental stages involved are not fully understood. We performed meta-analyses of genome-wide association studies (GWAS) in up to 22,769 children of European ancestry covering six early growth traits, modelled using longitudinal data for height and weight collected from birth to 13 years. We considered the well-established traits: peak height and weight velocity, age and body mass index (BMI) at adiposity peak (Age-AP, BMI-AP) and at adiposity rebound (Age-AR, BMI-AR). GWAS results were followed up for functional, pathway, genetic correlation and genetic risk score analyses to determine how developmental timings, molecular pathways and genetic determinants of these traits overlap with those of adult health.

We identified three variants significantly associated (P<5x10-8) with AR traits (rs1421085 (*FTO*), rs2817419 (*TFAP2B*) and rs10938397 (*GNPDA2*)), all of which had previously been associated with adult BMI, obesity and waist circumference. Both Age-AR and BMI-AR had robust genetic correlations with adult BMI, waist circumference, body fat percentage and multiple cardio-metabolic traits. However, AP traits were distinct: neither Age-AP and BMI-AP are associated with adult BMI traits, and adult BMI-associated variants (and the corresponding genetic risk score) showed no association with Age-AP and BMI-AP. We identified an entirely novel association between variants (led by rs9436303) near the leptin receptor gene and BMI-AP, and showed that this variant colocalized with eQTLs for both *LEPR* and *LEPROT,* and also influences circulating soluble leptin receptor levels in adults*.* Loci associated with AP and AR traits colocalized with variants regulating gene expression in different adult tissues.

The present study supports the accrual of shared genetic determinants between later childhood (>4y) and adult BMI, but not with infant BMI, indicating that genetic influences on BMI are partly different at these two developmental stages. In light of the epidemic of obesity in children, these findings are important to inform the timing and the targets of prevention strategies.

**Main text: 3630 (Abstract, introduction, results and discussion)**

**Methods: 3740**

**Introduction**

Childhood obesity and its relation to later adult health, social inequality and psycho-social well-being remains one of the most important unsolved health concerns of the 21st Century[[1](#_ENREF_1)]. Epidemiological studies have revealed unambiguous associations between alterations of childhood BMI trajectory and risk of adult obesity and multi-morbidities, including type 2 diabetes[[2](#_ENREF_2)] and other cardio-metabolic diseases[[3](#_ENREF_3)]. From a life-course perspective, genetic and environmental factors driving child growth may have a lasting influence on maintaining health[[4](#_ENREF_4)]. Within this framework, identification of the genetic determinants of the critical periods in child development is important for understanding the mechanisms underpinning adult health and preventing disease development.

To date, we have gained considerable insights into the shared genetic makeup of childhood and adult BMI[[5](#_ENREF_5), [6](#_ENREF_6)]. These previous studies were designed to identify genetic variants associated with BMI and obesity acting through the ages of 2 to 18 years. However, BMI does not remain constant, or follow a linear pattern throughout life, particularly not from birth until the age of adiposity rebound [[7](#_ENREF_7), [8](#_ENREF_8)]. On the contrary, the BMI trajectory in healthy individuals (**Supplementary Figure 1**) encompasses three periods characterized by i) a rapid increase in BMI up to the age of 9 months (adiposity peak, AP); ii) a rapid decline in BMI up to the age of 5-6 years (adiposity rebound point, AR); followed by iii) a steady increase until early adulthood, when BMI growth rate decelerates. We have yet to determine whether changes in timing, velocity or amplitude of this trajectory, during infancy and childhood are influenced by specific genetic factors, acting at different developmental stages. The identification of genetic determinants of early growth traits is a fundamental step towards understanding the etiology of obesity, and could be important in informing future strategies to prevent and treat it.

The present study set out to model sex-specific individual postnatal growth velocity and BMI curves in children using high-density longitudinal data collected from primary health care or clinical research visits. We first conducted a genome-wide association study (GWAS) on six harmonized early growth traits: peak height and weight velocity, age and BMI at adiposity peak, age and BMI at adiposity rebound. We then analyzed the GWAS summary statistics for these six early growth traits to gain insights into the genes and molecular pathways involved, and to assess the overlap between the genetic etiology of early growth traits and adult phenotypes. In particular, we tracked the changes in the genetic determinants of BMI occurring throughout infancy, later childhood and adulthood.

**Results**

We conducted two-stage meta-analyses of genome-wide association studies on six early growth traits: peak height velocity (PHV; cm/month), peak weight velocity (PWV; kg/month), age at adiposity peak (Age-AP; year), BMI at adiposity peak (BMI-AP, kg/m2), age at adiposity rebound (Age-AR; year), and BMI at adiposity rebound (BMI-AR, kg/m2). **Supplementary Figure 2** summarizes the study design, while participant characteristics, genotyping arrays, imputation and quality control for the discovery and follow-up studies are presented in **Supplementary Tables 1 and 2, and Supplementary Figure 3**. In the discovery stage (stage 1), we meta-analyzed GWAS from four population-based studies comprising between 6,051 to 7,215 term-born children of European ancestry that had both genetic and early growth trait data (stage 1; **Online Methods**, **Supplementary Table 1,** **Supplementary Figure 4**). From the stage 1 inverse variance meta-analyses, we selected a total of 8 loci with either *P* < 1 x 10-7 or with *P* < 1 x 10-5 in/near genes known to be associated with obesity and metabolic traits in published GWAS or candidate gene studies (**Supplementary Table 3**). In stage 2 of the meta-analysis, we followed-up these results in up to 16,550 term-born children from up to 11 additional studies (stage 2; **Online Methods, Supplementary Table 2**). In the combined stage 1+2 meta-analysis of the discovery and follow-up studies (including up to 22,769 children), we identified a common variant in each of four independent loci, associated at *P* < 5 x 10-8 with one or more of the early growth traits (**Table 1, Figure 3, Supplementary Figure 5)**.

**Adiposity rebound SNPs associate with adult BMI**

Three of the four SNPs were associated with age and BMI at adiposity rebound. These 3 GWAS variants were previously associated (P<5x10-8) with adult BMI and adult weight in the literature (**Supplementary Table 4**) and in the UK Biobank PheWAS[[9](#_ENREF_9)] (**Supplementary Table 5**), as well as with several adiposity-related phenotypes in PhenoScanner[[10](#_ENREF_10)] (**Online methods**). The lead SNPs at each of these three loci were: rs1421085 at the locus harboring *FTO* (encoding a 2-oxoglutarate-dependent demethylase) and rs2817419 at the locus harboring *TFAP2B (*encoding transcription factor AP-2 beta) loci associated with Age-AR, and rs10938397 near *GNPDA2* (encoding adiposity regulating glucosamine-6-phosphate deaminase) locus associated with BMI-AR (**Table 1, Supplementary Figure 5**). Each lead SNP (rs1421085, rs2817419 and rs10938397) associated with Age-AR and BMI-AR explains approximately 0.2 % variance in the relevant early growth trait (**Online Methods**).

**A new variant in LEPR/LEPROT associated with BMI at adiposity peak**

The BMI-AP-associated SNP rs9436303 at the locus harboring *LEPR/LEPROT* (encoding the Leptin Receptor and the Leptin Receptor Overlapping Transcript) is novel. The risk allele (G) of this variant increases both BMI-AP and adult plasma soluble leptin receptor levels (P=1.19x10-9)[[11](#_ENREF_11)] (**Supplementary Table 5**). The *LEPR/LEPROT* locus is in a chromosomal region, 1p31.3, that harbors another independent signal (rs11208659, MAF=0.06, distance=82.6Kbp, R2=0.01) associated with early onset obesity[[12](#_ENREF_12)] but our SNP rs9436303 is associated with BMI-AP independently of this variant (see conditional analysis in **Supplementary Table 6**). There was some effect heterogeneity between studies for this variant (**Supplementary Figure 6a & 6d**), but excluding the two studies with inflated estimates eliminated heterogeneity (*I*2=0) in the stage 1+2 meta-analysis (**Supplementary Figure 6c, 6f**) without a substantial impact on effect sizes or significance levels. This SNP explains 0.3 % variance in BMI-AP (**Online Methods**).

The SNP rs9436303 overlaps a regulatory region in a *LEPR* intron, and is downstream from a processed transcript of *LEPROT* gene (**Supplementary Table 7**). *LEPROT* and the *LEPR* overlap and share the same promoter, but encode distinct transcripts with specific biological functions[[13](#_ENREF_13)]. The known biological function and molecular mechanism of the proteins encoded by the nearest genes in the four loci discovered are given in **Supplementary Table 8**. However, as with most GWAS-identified loci, the expression of these genes may not necessarily be influenced by the underlying causal variant/s tagged by the GWAS SNP[[14](#_ENREF_14), [15](#_ENREF_15)], so we sought further evidence that the BMI-AP associated variants influences expression in the following section.

**Cis colocalization of GWAS and eQTL signals**

To identify GWAS and eQTLs signals that share the same causal variants, we performed Bayesian colocalization analyses [[16](#_ENREF_16)] using our stage 1 GWAS meta-analysis summary statistics and eQTL data from 44 *post-mortem* tissues generated by the Genotype-Tissue Expression (GTEx) consortium [[15](#_ENREF_15)](**Methods**). The lead GWAS variants with high (>95%) posterior probability (PP) of co-localization were followed-up in 5 separate studies (**online methods**) using cis-eQTL data from five *ex-vivo* tissues and combined with genomic annotation data (**Supplementary Table 9,10**). In these analyses, we found high posterior probabilities of colocalization with local causal variants (>95%) driving the expression of *LEPR and LEPROT* (**Table 2, Supplementary Figure 7**). The colocalization results for each gene are markedly tissue-specific (**Figure 2, Supplementary Figure 8**). In *ex-vivo* samples, the *LEPR/LEPROT* variant was in high LD with the top eQTLs of *LEPR* and *LEPROT* genes in omental fat, subcutaneous fat and whole blood (**Supplementary Table 9)**. Direct lookup of *LEPR/LEPROT* variant in eQTL data indicated that the G allele of this variant that raised BMI-AP in our GWAS, up-regulated the NM017526 transcript of *LEPROT* and down regulated the AK023598 transcript from the same gene in adult tissues (**Supplementary Table 10)**. This observation was consistent across two different eQTL studies and four tissues, suggesting the involvement of alternative splicing of a cassette exon. The *LEPR/LEPROT* variant overlapped DNA binding motifs of transcription factors, and regulatory regions, as well as enhancer and promoter histone marks in multiple tissues **(Supplementary Figure 9)**. In ALSPAC, the same *LEPR/LEPROT* variant was associated with higher DNA methylation levels of a *LEPR* intron measured in blood samples taken from mother and offspring. In particular, an association was found during mother’s pregnancy, in offspring’s adolescence, but not at offspring’s birth, during childhood or in mother’s middle age[[17](#_ENREF_17)] (**Supplementary Table 11**). This observation might be consistent with the regulation of a constitutively expressed transcript, which is also supported by evidence that lower *LEPR* intron DNA methylation levels were associated with higher serum leptin concentrations[[18](#_ENREF_18)]. Taken together, these results suggest that shared causal variants in these loci regulate BMI trajectory at adiposity peak, orchestrate changes in gene expression in different tissues and modulate methylation of the nearest genes during mother’s pregnancy and at specific developmental stages of the offspring.

**Genetic determinants of adult BMI overlap with those determining adiposity rebound but not adiposity peak**

In our study, Age-AR and BMI-AR have moderate to very strong genetic correlations with adult BMI and other adult adiposity-related phenotypes, but BMI-AP does not (**Figure 3**, **Supplementary Table 15, Online Methods**). Age and BMI at adiposity rebound had genetic correlations with multiple (>4) adult complex phenotypes, including adult waist circumference (Age-AR rg=−0.62, BMI-AR rg=0.48), and adult body fat percentage (Age-AR rg=−0.49, BMI-AR rg=0.44). Adult BMI and adult obesity had strong genetic correlations with BMI-AR (rg=0.64, rg=0.66) and Age-AR (rg=−0.72, rg=−0.75), but weak correlation with BMI-AP (rg=0.29, rg=0.33). The traits with genetic and phenotypic correlations that were directionally consistent (**Supplementary Note 1)** are reported in **Supplementary Table 16**. Genetic correlations of Age-AP with other traits could not be quantified, due to low mean chi-square of the GWAS summary statistics. In summary, genetic correlation analyses suggest that the genetics factors influencing adult BMI, body fat percentage, waist circumference, and obesity are also associated with BMI-AR and Age-AR, but their overlap with BMI-AP is either absent or weak.

**Genetic risk score for adult BMI is associated with age and BMI at adiposity rebound, but not at adiposity peak**

To gain further insight into the observed genetic correlations with adult BMI, and to understand the developmental timing of the adult BMI-associated variants, we constructed an adult BMI genetic risk score based on the 97 adult BMI SNPs identified by the GIANT consortium [[19](#_ENREF_19)] (**Figure 4 and** **Supplementary Table 17**) and applied it to the six early growth traits (**Online Methods**). The adult BMI variants and the genetic risk score (GRS) were consistently and robustly associated with Age-AR (*h*2grs=0.035, P=2.6x10-48) and BMI-AR (*h*2grs=0.030, P=1.7x10-41), but not with other early growth traits (**Figure 4, Supplementary Table 18**). In the remaining four early growth traits, the GRS explained a negligible proportion of variance (*h*2grs<0.001) and the adult BMI variants had inconsistent genetic effects (**Supplementary Figure 10, Supplementary Table 18)**. In particular, the adult BMI variants effects on BMI-AP and PWV were highly heterogeneous (Phet<2x10-4), with evidence of horizontal pleiotropy (MR-PRESSO P<2x10-4). This suggests that, in contrast with their effects on Age-AR and BMI-AR, the top loci associated with adult BMI do not have robust associations with the remaining four early growth traits. Thus, the underlying genetic determinants of adult BMI might differ from those influencing BMI-AP. Taken together, these data indicate that many GWAS variants associated with adult BMI have effects that begin in later childhood (4-6 years), as early as the age at adiposity rebound, but not as early as adiposity peak (around 9 months).

**Gene set analyses suggests little overlap between pathways and networks controlling adiposity peak and adiposity rebound**

To combine information on the effects of common variants’ in biological pathways and networks underlying early growth, we applied a gene set enrichment analysis (MAGENTA)[[20](#_ENREF_20)] to the discovery stage GWAS results (**Online Methods**). We identified enrichment of gene sets (**Supplementary Tables 12 and 13),** but did not find evidence for overlap of enriched pathways and networks among early growth traits. Age-AR associated regions are involved in the IGF-1 signaling pathway (false discovery rate (*FDR)* < 0.05). The IGF-1 signaling pathway has a well-established role in neonatal and pubertal growth [[21](#_ENREF_21), [22](#_ENREF_22)] and in the regulation of energy metabolism, through the activation of PI3K/AKT pathway via either the insulin- or the IGF-1 receptors [[23](#_ENREF_23)].

**SNP-heritability of Age-AR and BMI-AR is larger than BMI-AP**

We estimated the chip SNP heritability (the proportion of variance explained by common SNPs) for the six early growth traits using LD-Score (see methods). The heritability estimates for BMI-AR (h2=0.38) and Age-AR (h2=0.36), PWV (h2=0.32) and BMI-AP (h2=0.29) were significant (P<0.05, **Table 3**). LD-score and SumHer[[24](#_ENREF_24)] SNP-heritability estimates (**Supplementary Table 14**) ranked these phenotypic heritabilities in a similar way. The BMI-AP and BMI-AR estimates compared well with LD-Score estimates for adult BMI (h2=0.27) in a much larger sample of the UK Biobank (N=152,736). Twin and family studies heritability estimates for BMI at adiposity peak (h2=0.75-0.78)[[25](#_ENREF_25), [26](#_ENREF_26)] and at adiposity rebound (h2=0.4-0.6)[[27](#_ENREF_27), [28](#_ENREF_28)] were higher than the SNP-heritability estimated here . However, the ratio of the SNP-heritability obtained from LD-score regression and the total heritability obtained from family and twin studies suggests that a considerable (39-95%, see methods) proportion of BMI heritability can be attributed to common variants. As the LD-score heritability estimates of BMI-AP, BMI-AR and adult BMI are comparable, the differences in the genetic etiology observed in our study cannot be trivially attributed to large disparities in the variance explained by genetic factors. Hence, taken together, these data suggest that distinct, heritable developmental processes control the BMI trajectory at adiposity peak and adiposity rebound.

**Discussion**

There are few reports of studies investigating the genetic bases of these well-established growth and BMI trajectories [[29](#_ENREF_29), [30](#_ENREF_30)], and to our knowledge no genome-wide meta-analyses have been carried out to date. In the present study, we identified 4 variants at 4 independent loci associated with 3 early growth traits, determined by modeling growth trajectories using high-density longitudinal data for height and weight. Our study provides insights into the developmental timings at which the genetic makeup of early and later measures of BMI overlap or differ, and seeks to elucidate mechanisms and molecular pathways of early growth patterns.

The three common variants at *FTO*, *TFAP2B*, and *GNPDA2,* associated with timing of and/or BMI at adiposity rebound, are robustly associated with adult BMI and other adiposity traits. In contrast, the newly discovered variant at the *LEPR/LEPROT* locus associated with BMI-AP did not associate with later growth traits reported here, in previous studies on childhood/adult BMI and obesity, or in the UK Biobank PheWAS. This may indicate that genetic variants involved in adult BMI only start influencing BMI around the period of adiposity rebound, but not as early as adiposity peak. This is further corroborated by two additional lines of evidence provided by our study: i) we observed strong genetic correlations of adult BMI, body fat percentage, and waist circumference with age and BMI at adiposity rebound, but not with age and BMI at adiposity peak; and ii) the genetic risk score constructed using adult BMI variants was robustly associated with age and BMI at adiposity rebound, but not with age and BMI at adiposity peak.

The difference in the genetic determinants of BMI at adiposity peak and BMI at adiposity rebound and onwards may be attributed to three factors: i) BMI explains a relatively small proportion of body fat percentage (R2<0.3) in infancy (0<age≤7month)[[31](#_ENREF_31)], but increasingly larger proportions (0.36<R2≤0.8) in childhood (2≤age<18y)[[32-37](#_ENREF_32)] and adulthood (R2≈0.8, age >18y) [[38](#_ENREF_38)]; ii) The genes involved in the regulation of BMI during infancy seem to differ from those acting in later childhood onwards, which suggests two distinct biological processes acting throughout these developmental stages; and iii) sustained changes in the infant environment after weaning and onwards, may progressively unmask the effects of adult BMI variants. Consistent with this view, there is some evidence on how infants’ and children’s environment modifies the effect of genetic factors. Breastfeeding, an intervention that seems to protects against childhood and adult obesity[[39](#_ENREF_39), [40](#_ENREF_40)], modifies the strength of association of the *FTO* variant with BMI [[41](#_ENREF_41), [42](#_ENREF_42)] and with BMI growth trajectories[[30](#_ENREF_30)]. Interestingly, *FTO* and *MC4R* are not associated with infant BMI [[29](#_ENREF_29)], but *FTO’s* strength of association with BMI progressively increases in later childhood (4-11y)[[27](#_ENREF_27)]. Likewise, BMI heritability increases throughout childhood up to young adulthood (4-19y)[[25](#_ENREF_25), [27](#_ENREF_27), [28](#_ENREF_28), [43](#_ENREF_43), [44](#_ENREF_44)], as offspring BMI starts resembling adult BMI as an anthropometric marker of adiposity, and as the shared environment between adults and offspring progressively increases. Consistently, BMI heritability increased between adiposity peak and adiposity rebound and a considerable proportion of heritability was explained by common variants in our study. The increase in BMI heritability indicates a progressive decrease in the variance explained by the environment. The increase in heritability with age might be explained by genotype-environment correlations, in which small genetic differences are magnified as children progressively select, modify and create environments correlated with their genetic propensities, which in turn unmasks the effects of other genetic variants, in a feedforward loop. Thus, gradually increasing the phenotype variance explained by genetic factors and thereby increasing, throughout development, BMI heritability. All in all, our study supports the accrual of shared genetic determinants between later childhood and adult BMI[[5](#_ENREF_5), [6](#_ENREF_6)], but not with infant BMI.

In our study, the IGF-1 pathway that links diet with growth was enriched for variants associated with Age-AR, but not Age-AP in the MAGENTA analysis. Higher IGF-1 levels, via genetic and/or nutritional factors, can reduce GH levels via a negative feedback[[46](#_ENREF_46), [47](#_ENREF_47)]. Subsequent lower circulating levels of GH can suppress lipolysis and contribute to fat accumulation[[48](#_ENREF_48), [49](#_ENREF_49)], changing BMI trajectories and Age-AR, and, thereby, increasing risk of obesity and metabolic disorders. The regulation of the GH/IGF-1 axis is modulated by leptin and adiponectin levels[[50](#_ENREF_50)], two hormones regulated by *LEPR, LEPROT* and *TFAP2B* genes respectively.

The variant at *LEPR/LEPROT* colocalized with causal variants regulating the expression of *LEPR* and *LEPROT* in different tissues. *LEPROT* and the *LEPR* genes share the same promoter, but encode distinct transcripts[[13](#_ENREF_13)]. *LEPROT* is co-transcribed with the *LEPR* and both are expressed in multiple tissues with different functionality. LEPR is widely distributed in peripheral tissues, shows signaling capability, and is thought to transport leptin across the blood-brain barrier (25). Some LEPR isoforms may function in leptin clearance or buffering (soluble LEPR). In our eQTL data, the G allele which raises BMI at AP up-regulates the NM017526 transcript of *LEPROT,* but down-regulates AK023598 transcript from the same gene in adult tissues. This observation was consistent across the different eQTL studies and tissues, suggesting this variant may regulate the alternative splicing of a cassette exon in adult blood, and subcutaneous and omental adipose tissue. In addition, the *LEPR/LEPROT* variant was associated with methylation levels in the *LEPR* intron during mother’s pregnancy and at specific developmental stages of the offspring. Taken together, this functional analysis suggests that distinct molecular mechanisms in different tissues are involved in the expression regulation of these genes at different developmental stages.

*LEPROT* and the *LEPR* downstream mechanisms involved on the regulation of BMI are likely to be developmental stage-dependent. In humans, loss-of-function mutations in the *LEPR* markedly increase weight of infants after birth that persists through adulthood [[52](#_ENREF_52), [53](#_ENREF_53)]. However, the regulatory elements of *LEPROT* and the *LEPR* tagged by our GWAS SNP are not associated with BMI or any measure of adiposity in adults or in later childhood, despite being associated with BMI in infancy. On the other hand, this regulatory variant is involved in the control of the circulating levels of the soluble LEPR in adults. Hence, the regulatory variant identified is involved in regulation of adult LEPR through a mechanism that does not alter BMI after later childhood (age>4y). More work is necessary to identify the impact of *LEPROT* mutations in weight gain and growth, as well as in the identification of the tissues and regulatory elements of the different LEPR isoforms.

Our study has limitations that should be taken into consideration when interpreting the data. **First**, dense longitudinal growth and GWAS data are only available in a few population studies worldwide, so we had limited power to detect genetic variants with smaller effects and/or low allele frequencies. Nevertheless, a post-hoc power analysis showed that we are well powered to detect the reported effect sizes (β=0.065 SD units, power=80% and significance level *P*<5 x10-8, see methods). **Second**, it is noteworthy that these derived growth traits are likely to be influenced by a degree of measurement error and some heterogeneity as some studies have fewer repeated measures around the time points being estimated. Despite this, we were still able to discover genetic variants showing robust associations with these derived growth traits. **Finally**, we did not identify any variants associated with PHV, PWV and Age-AP at genome-wide levels of significance, and this may be due to a combination of smaller genetic effects on growth at this stage of development, reduced statistical power due to smaller sample size or because environmental factors confound the genetic influences at this age. The interplay between genetic variants, infant feeding and other environmental factors also warrants additional research[[30](#_ENREF_30)].

In conclusion, this longitudinal GWAS study, based on derived traits from growth modelling, has uncovered a completely new BMI variant in *LEPR/LEPROT* locus that specifically associates with the peak of adiposity in infancy. The present study identified two BMI developmental stages in infancy and later childhood with distinct genetic makeup. Our results supports the notion that genetic determinants of adult BMI progressively start acting in later childhood, but not necessarily before the adiposity peak in infancy [[5](#_ENREF_5), [6](#_ENREF_6)]. This finding may corroborate a model of BMI development consisting of the superimposition of two biological processes with distinct genetic drivers (**Figure 5**), which, in turn, suggests that interventions in childhood aiming to modify BMI and achieve long lasting reductions in the risk of adult obesity need to take into account the developmental stage. We believe that the identification of genetic factors underpinning the BMI trajectory is a fundamental step towards understanding the etiology of obesity, and may inform strategies to prevent and treat it.

**Methods**

**Longitudinal growth modeling and derivation of early growth traits**

Early growth traits were derived from sex-specific individual growth curves using mixed effects models of height, weight and BMI measurements from birth to 13 years (**Figure 1**). All height and weight data were collected prospectively via either self-reported data or clinical measurements (**Supplementary Table 1 and 2**). These traits were derived separately in each cohort (**Supplementary Note 2)**.

***Derivation of peak height velocity (PHV) and peak weight velocity (PWV)* -** The methods for growth modeling and derivation of growth parameters from the fitted curves is described in detail in a previous publication[[59](#_ENREF_59)] Parametric Reed1 growth model was fitted in sex stratified non-linear random-effect model as described previously[[60](#_ENREF_60)]. Term-born singletons (defined as ≥ 37 completed weeks of gestation) with at least three height or weight measurements from birth to 24 months of age were included in the Reed1 model fitting. Maximum-likelihood method for best fitting curves for each individual was used to estimate the growth parameter, PHV (cm/months) and PWV (kg/months).

***Derivation of age and BMI at adiposity peak (AP) and adiposity rebound (AR)* -** The methods used for growth modeling of age and BMI has been previously described in detail by Sovio et al, 2011[[29](#_ENREF_29)]. Due to the specificity of longitudinal changes in BMI *i.e.* succession of peak and nadir as described in figure 1, the data was divided into two age windows for modeling i) growth in infancy using height and weight data from 2 weeks to 18 months of age and ii) growth in childhood using growth and weight data from 18 months to 13 years of age. Each cohort contributed most data available within any of these two age windows. In studies where the data available consisted of both height and weight data within a given window, then the data point nearest to the mid time points of that window were used as a proxy for the BMI measurement. Prior to model fitting, age was centered using the median age of the relevant age window. For example, in the infant growth model at 0-1.5 years, the median age was 0.75 years (which was close to the average age at AP), and in the childhood growth model at >1.5-13 years, the median age was 7.25 years (on average shortly after AR). Linear Mixed Effects (LME) models were then fitted for log-transformed BMI. We used sex and its interaction with age as covariates, with random effects for intercepts *i.e.* baseline BMI, and linear slope *i.e.* linear change in BMI over time. In addition to linear age effect, quadratic and cubic terms for age were included in the fixed effects to account for nonlinearity of BMI change over time.

***Growth in Infancy*** - The following model was used to calculate the age and BMI at adiposity peak (AP), and the analysis was restricted to singletons with BMI measures from two weeks to 18 months of age. The model is as follows:

*log(BMI) = β0 + β1 Age + β2 Age2 + β3 Age3 + β4 Sex + u0 + u1 (Age) + ε*

where BMI is expressed in kg/m2 and age in year. β0, β1, β2, β3, β4 are the fixed effects terms, u0 and u1 are the individual level random effects and ε is the residual error. The age at AP was calculated from the model as the age at maximum BMI between 0.25 and 1.25 year according to preliminary research [[59](#_ENREF_59), [61](#_ENREF_61)].

**Growth in Childhood.** The model used to measure the age and BMI at adiposity rebound (AR) in childhood is as follows:

*log(BMI) = β0 + β1 Age + β2 Age2 + β3 Age3 + β4 Sex + β5 Age \* Sex + β6 Age2 \* Sex + u0 + u1 (Age) + ε*

Where BMI is expressed in kg/m2 and age in year. β0, β1, β2, β3, β4, β5 and β6 are the fixed effects, u0 and u1 are the individual level random effects and ε is the residual error. Age at AR was calculated as the age at minimum BMI between 2.5 and 8.5 year according to preliminary research [[59](#_ENREF_59), [61](#_ENREF_61)].

**Stage 1 genome-wide association studies, genotyping and imputation**

Stage 1 genome-wide association analyses included up to 7215 children of European descent from five studies (four studies for each early growth trait) that had growth data and genome-wide data. These included the Helsinki Birth Cohort Study (HBCS, Finland), Northern Finland Birth Cohort 1966 (NFBC1966, Finland), Lifestyle-Immune System-Allergy Study (LISA, Germany), The Western Australian Pregnancy Cohort Study (Raine, Australia) and Generation R (Netherlands) (**Figure 2**). Informed consent was obtained from all study participants (or parental consent, as appropriate) and the local ethics committees as appropriate approved all study protocols. Study characteristics, genotyping platform, imputation and association test software used, as well as sample and genotyping and imputation quality control steps in each stage 1 study are given in **Supplementary Table 1**. The Stage 1 consisted of a GWAS based on ~2.5 million directly genotyped or imputed SNPs. Imputation of non-genotyped SNPs was undertaken either with MACH or with IMPUTE and were imputed to HapMap Phase 2 CEU reference panel after excluding genotyped SNPs with a minor allele frequency (MAF) < 1%, call rate of at least >95%, and a Hardy-Weinberg Equilibrium (HWE) *P*-value cut off as given in **Supplementary Table 1**.

**Stage 1 genome-wide association analyses and meta-analyses**

According to the availability of dense enough data for growth modeling, a total of up to 7215, 6222, 6219 and 6051 children were used to analyze PHV/PWV, Age-AP, BMI-AP and Age-AR /BMI-AR respectively (**Figure 2**). We only included children who were born between 37 and 41 completed weeks of gestation (i.e.: term born) from singleton pregnancies and children who had more than three growth measurements available within the age range in question. Gestational age was either defined from the date of the last menstrual period or ultrasound scans depending on the study. All six early growth traits except for Age-AP and Age-AR were natural log transformed to reduce skewness, and all traits were converted to z-scores prior to association testing to facilitate the comparison of results across the studies. We tested the directly genotyped and imputed variants for association with each of the six early growth traits in a linear regression model assuming an additive genetic effect. The regression models were adjusted for sex and principal components (PC) derived from the genome-wide data to control for potential population substructure (the necessary number of principal components included varied by study). The regression models were also adjusted for gestational age, except for Age-AR and BMI-AR. The genome-wide association analyses (i.e. stage 1) were performed using either SNPTEST or MACH2QTL in each cohort, and data exchange facilities were provided by the AIMS server [[62](#_ENREF_62)]. All stage 1 study beta estimates and their standard errors were meta-analyzed using the inverse-variance fixed effects method in the METAL software[[63](#_ENREF_63)]. SNPs with poor imputation quality (*e.g.* r2< 0.3 for MACH and ‘proper\_info’ score < 0.4 for IMPUTE) and/or a HWE *P* <1 x 10-4 were excluded prior to the meta-analyses. Double genomic control[[64](#_ENREF_64)] was applied: firstly, to adjust the statistics generated within each cohort and secondly, to adjust the overall meta-analysis statistics. Results are reported as a change in standard deviation (SD) units per risk allele as reported in **Table 1**.

**Selection of SNPs for stage 2 follow up.**

All loci reaching *P* < 1 x 10-7 from stage 1 GWAS of each early growth trait were selected for follow-up in stage 2. These included the two SNPs associated with Age-AR in the *FTO locus* (rs1421085) and in the intergenic region between *RANBP3L* and *SLC1A3* (rs2956578), and the SNP associated with BMI-AP in *LEPR/LEPROT* (rs9436303). Four further SNPs (one SNP associated with BMI-AP *near PCSK1* (rs10515235)*,* one SNP associated with Age-AR in *TFAP2B* (rs2817419), and two SNPs associated with BMI-AR near *GNPDA2* (rs10938397) and in *DLG2* (rs2055816) were selected for follow-up on the basis of showing an association with an early growth trait at *P* < 1 x 10-5 and being in/near genes with established links to adiposity and metabolic phenotypes except for *DLG2*, a possible candidate gene involved in glucose metabolism[[65](#_ENREF_65)]. In addition, one locus with a plausible association (*P* = 5.91 x 10-5) with PWV, near *TMEM18* (rs2860323)*,* was also selected for follow-up based on previous reports showing an association with severe early onset obesity[[12](#_ENREF_12)] and its association with BMI in adulthood[[66](#_ENREF_66)] and childhood[[6](#_ENREF_6)] (**Supplementary Table 3**). No loci for PHV or AGE-AP passed the p-value threshold or other selection criteria used for follow up. **Supplementary Table 3** showsthe SNP selection criteria and proxies used in more detail**.**

**Stage 2 follow up of lead SNPs**

For follow up of lead signals selected from stage 1 we used data from up to 16,550 children of European descent from 12 additional population based studies (up to 11 studies for each early growth trait), namely the Avon Longitudinal Study of Parents and Children (ALSPAC, United Kingdom), Cambridge Baby Growth Study (CBGS, United Kingdom), Children’s Hospital of Philadelphia (CHOP, United States of America), Copenhagen Prospective Study on Children (COPSAC, Denmark), Danish National Birth Cohort (DNBC, Denmark), Étude des Déterminants pré- et postnatals du développement et de la santé de l’ENfant (EDEN, France), The Exeter Family Study of Childhood Health (EFSOCH, United Kingdom), INfancia y Medio Ambiente Project (INMA, Spain), Lifestyle-Immune System–Allergy Study (LISA (R), Germany), Northern Finland Birth Cohort Study 1986 (NFBC1986, Finland), The Physical Activity and Nutrition in Children (PANIC, Finland) and Southampton Women's Survey (SWS, United Kingdom). We used de novo SNP genotyped or imputed data for the eight SNPs (or proxies of r2 >0.8) selected from stage 1 and tested their association in a total of 5367, 16550, 12256, 12192 children of European ancestry with PWV, BMI-AP, Age-AR, BMI-AR respectively (**Figure 2**). Direct genotyping was performed in some follow-up studies by KBiosciences Ltd. (Hoddesdon, UK) using their own novel system of fluorescence-based competitive allele-specific PCR (KASPar). The call rates for all genotyped SNPs were >95%. Study characteristics, genotyping platform, imputation and association test software used, as well as sample and genotyping and imputation quality control steps in each stage 1 study are given in **Supplementary Table 2**. We used the same methods as in stage 1 for sample selection, genotyping quality control, association testing and meta-analysis.

**Combined analysis of stage 1 and stage 2 samples.**

All stage 1 and 2 results were meta-analyzed using the inverse-variance fixed effects method in either METAL[[63](#_ENREF_63)] or R (version 3.2.0; http://www.r-project.org/). In these combined analyses, loci reaching *P* < 5 x 10‑8 were considered as genome-wide significant and loci reaching *P* < 5 x 10-6 were considered as a suggestive association. Heterogeneity between studies was tested by Cochran's Q tests and the proportion of variance due to heterogeneity was assessed using *I2*index for each individual SNP at each stage.

**Estimation of genetic variance explained**

The variance explained (h2snp) by each SNP was calculated using the risk allele frequency (*f*) and beta (β) from the meta-analyses using the formula h2snp = β2 (1 − *f*)2*f*.

**Analysis of the phenotypic effects of the lead GWAS SNPs in published genetic studies**

The phenotypic implication of the lead GWAS SNP on 778 phenotypes was obtained from the Gene ATLAS[[9](#_ENREF_9)] phenome-wide association study (PheWAS) conducted on 452,264 white British individuals from UK Biobank. In addition, we looked up the lead GWAS SNP or a proxy on published large-scale GWAS data sets using PhenoScanner[[10](#_ENREF_10)] available at http://www.phenoscanner.medschl.cam.ac.uk/phenoscanner. Only proxy SNPs from the 1000G panel in high LD (R2>0.8) with the lead GWAS SNP were considered. We then searched for all SNPs with phenotypic associations in the same chromosomal region of our lead GWAS signals using the GWAS catalogue[[67](#_ENREF_67)] available at https://www.ebi.ac.uk/gwas/. We reported associations obtained from these analyses with significance cut-off *P* <5 x 10-8. Finally, we searched for non-GWAS genetic studies, i.e. family, pedigree, and clinical studies with PubMed queries available at https://www.ncbi.nlm.nih.gov/pubmed/.

**Conditional analyses**

We conducted conditional analysis of the lead and proxy SNP expected dosages using a linear regression model adjusted for sex and gestational age in 3459 children from the NFBC1966 study. We considered two models to judge the effect of both SNPs. First, the early growth trait is regressed on the lead SNP adjusting for the study covariates sex and gestational age. Second, the proxy SNP is added to the previous model. The lead and proxy SNP effects are considered independent if the effect size estimate of the lead SNP in model 2 did not vary more than 20% of the effect estimate of model 1, and the corresponding P value reached a nominal significance (α=0.05).

**Variance effect prediction analysis**

We obtained information about the putative effect of the lead GWAS SNPs using VEP (https://www.ensembl.org/Homo\_sapiens/Tools/VEP) [[68](#_ENREF_68)]. The analysis included pathogenicity, splicing and conservation predictions as well as regulatory annotations.

**Overlap of the genetic makeup of early growth traits with adult and childhood phenotypes**

To gain insights into the potential overlap in the genetic makeup of early growth traits with adult and childhood phenotypes, we searched databases and the literature for the phenotypic implications of our four GWAS SNPs. First, we retrieved from the Gene Atlas[[9](#_ENREF_9)] phenome-wide association study (PheWAS) in the UK Biobank data all phenotypic associations (P<5x10-8) with our four GWAS SNPs (**Supplementary Table 4**). Second, we retrieved from the PhenoScanner[[10](#_ENREF_10)] database all SNPs with phenotypic associations (P<5x10-8) and in high LD (R2>0.8) with our four GWAS lead variants (**Supplementary Table 5**). Third, we systematically searched in the GWAS catalog[[67](#_ENREF_67)] database all SNPs with phenotypic associations (P<5x10-8) in the chromosomal regions of our four GWAS lead variants.

**Bayesian colocalization**

Colocalisation analyses were performed using our stage 1 GWAS results with multi tissue eQTL results from GTEx data (https://www.gtexportal.org/home/datasets)[[15](#_ENREF_15)]. For each GTEx tissue (n=48 tissues) we first identified all genes with significant cis-eQTLs at <5% FDR. For each such gene, we retrieved the GWAS summary statistics for each of the three traits (BMI-AP, BMI-AR and Age-AR), for all SNPs in common between the GWAS and the eQTL data (typically everything within 1MB of the gene TSS). If the GWAS locus contained one or more eQTL variant at p< 5 x 10-6 we implemented the computational procedure outlined in the coloc package in R (https://github.com/chr1swallace/coloc/blob/master/R/coloc-package.R)[[69](#_ENREF_69)] with default parameters and using the minor allele frequencies of European ancestry individuals from 1000G study.

**Expression quantitative trait locus (eQTL).**

We searched for cis-eQTLs in liver, skin, whole blood, subcutaneous fat and omental fat *ex-vivo* tissues made available by the MuTHER[[70](#_ENREF_70)], KORA[[71](#_ENREF_71)], DeCode[[72](#_ENREF_72)], Lee Kaplan[[73](#_ENREF_73)] and BIOS[[74](#_ENREF_74)] studies. The association analyses were performed with the GWAS lead SNP following the procedure described previously [[75](#_ENREF_75)]. The analysis of eQTLs was limited to genes in cis within a +/- 1Mb window of the lead SNP. For each GWAS lead SNP, we separately report the top eQTL in the locus and the coincident cis-eQTLs with significance cut-offs of *P*<1 x10-3 and FDR<5% respectively. For studies where gene expression was measured using a microarray technology the microarray probes were annotated with information accessed on ProbeDB (available at http://www.ncbi.nlm.nih.gov/probe/). If the probe ids were not available in the ProbeDB, we aligned the probe sequence to HG38 with blast algorithm available at https://blast.ncbi.nlm.nih.gov/Blast.cgi, and then annotated the transcripts overlapping the genomic coordinates using consensual information in GenBank, RefSeq, ENCODE, and UCSC databases.

**Methylation quantitative trait locus.**

We searched for cis-methylation QTL in blood at five different life stages using mQTLdb (http://www.mqtldb.org/). Methylation QTL data was generated as previously described[[17](#_ENREF_17)] using ALSPAC study data. Only GWAS SNPs that colocalized with eQTL data were looked up.

**Genetic correlations using linkage-disequilibrium (LD) score regression analyses**

We used the LD hub [[76](#_ENREF_76)] available at http://ldsc.broadinstitute.org to quantify the genetic correlation between each of the six early growth traits and a selection of 49 disease/traits of interest from 33 GWAS studies in the following pre-compiled categories: education, anthropometric traits, lipids, glycaemic traits, bone mineral density, neurological / psychiatric diseases and other traits (including adiponectin, CAD, T2D, menarche). For systolic and diastolic blood pressure (SBP and DBP), we used the UK Biobank GWAS summary statistics (125,334 subjects)[[77](#_ENREF_77)] (**Supplementary Note 3**) because LD hub did not have blood pressure traits. We carried out the LD score regression analyses for blood pressure traits using the Python scripts provided on the developer’s website at https://github.com/bulik/ldsc. Prior to running the LD score regression analyses, each summary statistics file was reformatted using the munge\_sumstats.py Python script which filtered the SNPs to HAPMAP 3 SNPs as recommended on the developer’s website to minimise any bias from poor imputation quality. SNPs were also excluded if MAF<0.01, ambiguous strand, duplicate rsID and reported sample size is less than 60% of the total available. If the sample size for each SNP was available we used the –N-col to specify the relevant sample size column in the GWAS summary statistics file, and when no sample size column was available we used the maximum sample size reported in the GWAS meta-analysis. After the GWAS summary statistics files were reformatted we then used the ldsc.py Python script to run the LD score regression analyses between each of the six early growth traits and SBP and DBP. The pre-complied European LD scores calculated from 1000G data available on the developer’s website was used for LD score regression.

**Adult BMI genetic risk score**

We calculated a weighted genetic risk scores of adult BMI with the 97 SNPs associated with BMI at genome-wide levels of significance in the GIANT consortium [[19](#_ENREF_19)] using the R package gtx and following the procedure described in [[78](#_ENREF_78)]. Briefly, a risk score estimating the pleiotropic effect of adult BMI variants on each early growth trait was inferred from summary statistics obtained from the stage 1 GWAS meta-analyses. Risk score models with evidence of heterogeneity (Phet<0.05, only BMI-AP) were refitted using a downwards elimination of SNPs with largest effect size until the model is not heterogeneous (Phet>0.05). In addition, we estimated the evidence of horizontal pleiotropy between adult BMI and each early growth trait with the package MR-PRESSO[[79](#_ENREF_79)].

**Pathway enrichment analysis**

To explore the pathways associated with early growth traits, we applied a Meta-Analysis Gene-set Enrichment of variaNT Associations (MAGENTA, version 2) [[20](#_ENREF_20)] to the stage 1 GWAS results. Briefly, each gene in the genome is mapped to a single SNP with the lowest *P*-value within a 110 Kb upstream or 40kb downstream window of the gene. The corresponding *P*-value, representing each gene, is corrected for confounding factors such as gene size, LD patterns, SNP density and other genetic factors. The adjusted *P*-values are ranked and the observed number of genes in a given pathway above a specified *P*-value threshold (75th and 95th percentiles used) is calculated. This number is compared with that from repeating the process based on 10000 randomly permuted pathways of identical size. In doing so, an empirical gene set enrichment association (GSEA) *P*-value for each pathway is computed. In our study, individual pathways with a FDR < 0.05 and nominal GSEA *P* < 0.05 were deemed significant, and, unless otherwise stated, results for the 95th percentile cut-off analysis are reported.

**SNP-heritability**

We estimated the SNP-heritability, the proportion of variance explained by common SNPs (MAF>1%), with LD-Score as implemented in LD-hub and using our six stage 1 GWAS meta-analyses on early growth traits. (Please see next paragraph for detailed information on post-processing of GWAS data for LD-Score analysis). LD-score regression estimates were obtained using a regression model with intercept, which aims at correcting for systematic confounders in GWAS summary statistics such as population stratification. In addition, we provide SumHer[[24](#_ENREF_24)] SNP-heritability estimates due to the current debate on the (mainly downward) bias of LD-Score regression estimates. SumHer estimates were obtained using a regression model including an intercept. The estimates of heritability using family and twin studies were obtained from the literature using PubMed searches complemented with google scholar. The proportion of heritability explained by common SNPs is the ratio of the SNP-heritability obtained from LD-score regression and the overall heritability obtained from family and twin studies.

**Post-hoc power analysis**

We conducted a post-hoc power analysis to determine the effect size in standard deviations units we are powered to detect (power=80%). The following experimental setup is considered to parameterize the null hypothesis: stage 1 meta-analysis sample size (*n*=6222), the smallest minimum allele frequency observed among the four lead GWAS SNPs (MAF=0.22, most conservative), imputation quality R2=0.8, significance level *P* <5 x 10-8, and genotypes assumed to be in Hardy-Weinberg equilibrium. Analysis was conducted as previously described[[80](#_ENREF_80)]. Briefly, the non-centrality parameter (NCP) gives the expected value of the test statistic under the null hypothesis parameterized above. The power to detect an effect size *b* > NCP is the probability of obtaining an effect larger or equal to NCP under the alternative hypothesis parameterized by the normal distribution with mean *b*, and standard deviation set equal to the standard error of NCP.

**ACKNOWLEDGEMENTS**

This publication is the work of the authors, and Marjo-Riitta Jarvelin, Mark McCarthy, Struan Grant, Ken Ong, Vincent Jaddoe, Justin M. O’Sullivan and Paul O’Reilly will serve as guarantors for the contents. All the authors acknowledge the following sponsors for their support. The UK Medical Research Council and Wellcome (Grant ref: 102215/2/13/2), NIH grant R01 HD056465, Danish National Research Foundation, the NIH Genes, Environment and Health Initiative [GEI, U01HG004423], NIH GEI [U01HG004438], Lundbeck Foundation [R19-A2059] and the Danish Medical Research Council [09-065592]. French Ministry of Research, Institut National de la Santé et de la Recherche Médicale [INSERM], South West NHS Research and Development, Exeter NHS Research and Development, The Netherlands Organization for Health Research and Development (VIDI 016. 136. 361), the European Union’s Horizon 2020 research and innovation programme under grant agreement No 633595 (DynaHEALTH) and No 733206 (LIFECYCLE); European Research Council (ERC Consolidator Grant, ERC-2014-CoG-648916); Academy of Finland [project grants 209072, 129255 grant] and British Heart Foundation and the Academy of Finland [grants 134839 and 129287], the National Public Health Institute, Helsinki, Finland; Instituto de Salud Carlos III [CB06/02/0041, FIS PI041436, PI081151, PI041705, and PS09/00432, FIS-FEDER 03/1615, 04/1509, 04/1112, 04/1931, 05/1079, 05/1052, 06/1213, 07/0314, and 09/02647], Spanish Ministry of Science and Innovation [SAF2008-00357], European Commission [ENGAGE project and grant agreement HEALTH-F4-2007-201413], Fundació La Marató de TV3, Generalitat de Catalunya-CIRIT 1999SGR 00241. Federal Ministry for Environment [IUF Düsseldorf, FKZ 20462296], Federal Ministry for Environment [IUF Düsseldorf, FKZ 20462296]. National Health and Medical Research Council of Australia [Grant ID 403981 and ID 003209] and the Canadian Institutes of Health Research [Grant ID MOP-82893], Royal Society of New Zealand Marsden Fund [Grant 16-UOO-072], Academy of Finland [project grants 104781, 120315, 129269, 1114194, Center of Excellence in Complex Disease Genetics and SALVE], University Hospital Oulu, Biocenter, University of Oulu, Finland [75617], the European Commission [EURO-BLCS, Framework 5 award QLG1-CT-2000-01643], NHLBI grant 5R01HL087679-02 through the STAMPEED program [1RL1MH083268-01], NIH/NIMH [5R01MH63706:02], the Medical Research Council, UK [G0500539, G0600705, PrevMetSyn/SALVE] and the Wellcome Trust [project grant GR069224], EU Framework Programme 7 EurHEALTHAgeing 277849. This research has been conducted using the UK Biobank Resource. We thank SpiroMeta consortium for providing the GWAS summary statistics data of lung function measures. Cohort specific acknowledgements are given in the **Supplementary Note 4**.

**AUTHOR CONTRIBUTIONS**

All authors contributed in reviewing the paper. **Supplementary Table 19** presents the contribution of each individual author. The names of individuals who contributed to specific statistical analysis and drafting the paper are given below.

***Writing and discussion group on analyses specific to the project****:* A.C.A., N.M.G.D.S., S.S., S.D., U.S., M.K., I.J.M., J.B., R.C., H. R.T., A.M.L., A.R., A.B., V.W.V.J., J.F., P.O., K.O., S.G., M.I.M and M.-R.J.

***GWAS meta-analysis working group****:* S.D., H.R.T., U.S. and V.K.

***Conditional analysis****:* S.D.

***Variant Effect Prediction; PheWAS, GWAS catalog, meQTL and eQTL look ups; pathway analyses; SNP-heritability with LD-score; genetic risk core; post-hoc power analysis****:* A.C.A

***Bayesian colocalization analyses****:* C.B

***PhenoScanner lookup, Genetic correlations using LD score regression****:* N.M.G.D.S

***BMI SNP look-ups****: A.C.A., N.M.G.D.S*

***GWAS of blood pressure in the UKBiobank***: J.R.P.

**SNP-heritability with SumHer**: D.S.

**COMPETEING FINANCIAL INTERESTS**: The authors declare no competing interest

**References**

1. Franks PW, Hanson RL, Knowler WC, Sievers ML, Bennett PH, Looker HC. Childhood Obesity, Other Cardiovascular Risk Factors, and Premature Death. New Engl J Med. 2010;362(6):485-93. doi: DOI 10.1056/NEJMoa0904130. PubMed PMID: WOS:000274397200005.

2. Bjerregaard LG, Jensen BW, Angquist L, Osler M, Sorensen TIA, Baker JL. Change in Overweight from Childhood to Early Adulthood and Risk of Type 2 Diabetes. New Engl J Med. 2018;378(14):1302-12. doi: 10.1056/NEJMoa1713231. PubMed PMID: WOS:000429105700006.

3. Sovio U, Kaakinen M, Tzoulaki I, Das S, Ruokonen A, Pouta A, et al. How do changes in body mass index in infancy and childhood associate with cardiometabolic profile in adulthood? Findings from the Northern Finland Birth Cohort 1966 Study. International journal of obesity. 2014;38(1):53-9. doi: 10.1038/ijo.2013.165. PubMed PMID: 24080793.

4. Ben-Shlomo Y, Kuh D. A life course approach to chronic disease epidemiology: conceptual models, empirical challenges and interdisciplinary perspectives. Int J Epidemiol. 2002;31(2):285-93. PubMed PMID: 11980781.

5. Bradfield JP, Taal HR, Timpson NJ, Scherag A, Lecoeur C, Warrington NM, et al. A genome-wide association meta-analysis identifies new childhood obesity loci. Nature genetics. 2012;44(5):526-+. doi: 10.1038/ng.2247. PubMed PMID: WOS:000303416300012.

6. Felix JF, Bradfield JP, Monnereau C, van der Valk RJ, Stergiakouli E, Chesi A, et al. Genome-wide association analysis identifies three new susceptibility loci for childhood body mass index. Human molecular genetics. 2016;25(2):389-403. doi: 10.1093/hmg/ddv472. PubMed PMID: 26604143; PubMed Central PMCID: PMC4854022.

7. Rolland-Cachera MF, Deheeger M, Bellisle F, Sempe M, Guilloud-Bataille M, Patois E. Adiposity rebound in children: a simple indicator for predicting obesity. The American journal of clinical nutrition. 1984;39(1):129-35. PubMed PMID: 6691287.

8. Peneau S, Gonzalez-Carrascosa R, Gusto G, Goxe D, Lantieri O, Fezeu L, et al. Age at adiposity rebound: determinants and association with nutritional status and the metabolic syndrome at adulthood. International journal of obesity. 2016;40(7):1150-6. doi: 10.1038/ijo.2016.39. PubMed PMID: WOS:000379498200016.

9. Canela-Xandri O, Rawlik K, Tenesa A. An atlas of genetic associations in UK Biobank. bioRxiv. 2017. doi: 10.1101/176834.

10. Staley JR, Blackshaw J, Kamat MA, Ellis S, Surendran P, Sun BB, et al. PhenoScanner: a database of human genotype-phenotype associations. Bioinformatics. 2016;32(20):3207-9. doi: 10.1093/bioinformatics/btw373. PubMed PMID: 27318201; PubMed Central PMCID: PMC5048068.

11. Sun Q, Cornelis MC, Kraft P, Qi L, van Dam RM, Girman CJ, et al. Genome-wide association study identifies polymorphisms in LEPR as determinants of plasma soluble leptin receptor levels. Human molecular genetics. 2010;19(9):1846-55. doi: 10.1093/hmg/ddq056. PubMed PMID: 20167575; PubMed Central PMCID: PMC2850621.

12. Wheeler E, Huang N, Bochukova EG, Keogh JM, Lindsay S, Garg S, et al. Genome-wide SNP and CNV analysis identifies common and low-frequency variants associated with severe early-onset obesity. Nature genetics. 2013;45(5):513-U76. doi: 10.1038/ng.2607. PubMed PMID: WOS:000318158200012.

13. Bailleul B, Akerblom I, Strosberg AD. The leptin receptor promoter controls expression of a second distinct protein. Nucleic acids research. 1997;25(14):2752-8. PubMed PMID: 9207021; PubMed Central PMCID: PMC146799.

14. Consortium GT, Laboratory DA, Coordinating Center -Analysis Working G, Statistical Methods groups-Analysis Working G, Enhancing Gg, Fund NIHC, et al. Genetic effects on gene expression across human tissues. Nature. 2017;550(7675):204-13. doi: 10.1038/nature24277. PubMed PMID: 29022597; PubMed Central PMCID: PMC5776756.

15. Consortium G. Genetic effects on gene expression across human tissues. Nature. 2017;550(7675):204-13. doi: 10.1038/nature24277. PubMed PMID: 29022597; PubMed Central PMCID: PMCPMC5776756.

16. Giambartolomei C, Vukcevic D, Schadt EE, Franke L, Hingorani AD, Wallace C, et al. Bayesian test for colocalisation between pairs of genetic association studies using summary statistics. Plos Genet. 2014;10(5):e1004383. doi: 10.1371/journal.pgen.1004383. PubMed PMID: 24830394; PubMed Central PMCID: PMC4022491.

17. Gaunt TR, Shihab HA, Hemani G, Min JL, Woodward G, Lyttleton O, et al. Systematic identification of genetic influences on methylation across the human life course. Genome Biol. 2016;17:61. doi: 10.1186/s13059-016-0926-z. PubMed PMID: 27036880; PubMed Central PMCID: PMCPMC4818469.

18. Yousefi M, Karmaus W, Zhang H, Ewart S, Arshad H, Holloway JW. The methylation of the LEPR/LEPROT genotype at the promoter and body regions influence concentrations of leptin in girls and BMI at age 18 years if their mother smoked during pregnancy. Int J Mol Epidemiol Genet. 2013;4(2):86-100. PubMed PMID: 23875062; PubMed Central PMCID: PMCPMC3709113.

19. Locke AE, Kahali B, Berndt SI, Justice AE, Pers TH, Day FR, et al. Genetic studies of body mass index yield new insights for obesity biology. Nature. 2015;518(7538):197-206. doi: 10.1038/nature14177. PubMed PMID: 25673413; PubMed Central PMCID: PMC4382211.

20. Segre AV, Consortium D, investigators M, Groop L, Mootha VK, Daly MJ, et al. Common inherited variation in mitochondrial genes is not enriched for associations with type 2 diabetes or related glycemic traits. Plos Genet. 2010;6(8). doi: 10.1371/journal.pgen.1001058. PubMed PMID: 20714348; PubMed Central PMCID: PMC2920848.

21. LeRoith D, Roberts CT, Jr. The insulin-like growth factor system and cancer. Cancer letters. 2003;195(2):127-37. PubMed PMID: 12767520.

22. Vincent AM, Feldman EL. Control of cell survival by IGF signaling pathways. Growth hormone & IGF research : official journal of the Growth Hormone Research Society and the International IGF Research Society. 2002;12(4):193-7. PubMed PMID: 12175651.

23. Siddle K. Signalling by insulin and IGF receptors: supporting acts and new players. Journal of molecular endocrinology. 2011;47(1):R1-10. doi: 10.1530/JME-11-0022. PubMed PMID: 21498522.

24. Speed D, Balding D. Better estimation of SNP heritability from summary statistics provides a new understanding of the genetic architecture of complex traits. bioRxiv. 2018. doi: 10.1101/284976.

25. Choh AC, Curran JE, Odegaard AO, Nahhas RW, Czerwinski SA, Blangero J, et al. Differences in the heritability of growth and growth velocity during infancy and associations with FTO variants. Obesity. 2011;19(9):1847-54. doi: 10.1038/oby.2011.175. PubMed PMID: 21720422; PubMed Central PMCID: PMCPMC4013792.

26. Johnson W, Choh AC, Lee M, Towne B, Czerwinski SA, Demerath EW. Characterization of the infant BMI peak: sex differences, birth year cohort effects, association with concurrent adiposity, and heritability. Am J Hum Biol. 2013;25(3):378-88. doi: 10.1002/ajhb.22385. PubMed PMID: 23606227; PubMed Central PMCID: PMCPMC3988701.

27. Haworth CM, Carnell S, Meaburn EL, Davis OS, Plomin R, Wardle J. Increasing heritability of BMI and stronger associations with the FTO gene over childhood. Obesity. 2008;16(12):2663-8. doi: 10.1038/oby.2008.434. PubMed PMID: 18846049.

28. Dubois L, Ohm Kyvik K, Girard M, Tatone-Tokuda F, Perusse D, Hjelmborg J, et al. Genetic and environmental contributions to weight, height, and BMI from birth to 19 years of age: an international study of over 12,000 twin pairs. Plos One. 2012;7(2):e30153. doi: 10.1371/journal.pone.0030153. PubMed PMID: 22347368; PubMed Central PMCID: PMCPMC3275599.

29. Sovio U, Mook-Kanamori DO, Warrington NM, Lawrence R, Briollais L, Palmer CNA, et al. Association between Common Variation at the FTO Locus and Changes in Body Mass Index from Infancy to Late Childhood: The Complex Nature of Genetic Association through Growth and Development. Plos Genet. 2011;7(2). doi: ARTN e1001307

10.1371/journal.pgen.1001307. PubMed PMID: WOS:000287697300022.

30. Wu VY, Lye S, Briollais L. The role of early life growth development, the FTO gene and exclusive breastfeeding on child BMI trajectories. Int J Epidemiol. 2017;46(5):1512-22. doi: 10.1093/ije/dyx081. PubMed PMID: WOS:000414561600034.

31. Bell KA, Wagner CL, Perng W, Feldman HA, Shypailo RJ, Belfort MB. Validity of Body Mass Index as a Measure of Adiposity in Infancy. J Pediatr-Us. 2018;196:168-+. doi: 10.1016/j.jpeds.2018.01.028. PubMed PMID: WOS:000432452300032.

32. Kerruish KP, O'Connor J, Humphries IRJ, Kohn MR, Clarke SD, Briody JN, et al. Body composition in adolescents with anorexia nervosa. American Journal of Clinical Nutrition. 2002;75(1):31-7. PubMed PMID: WOS:000172884400008.

33. Mei ZG, Grummer-Strawn LM, Pietrobelli A, Goulding A, Goran MI, Dietz WH. Validity of body mass index compared with other body-corn position screening indexes for the assessment of body fatness in children and adolescents. American Journal of Clinical Nutrition. 2002;75(6):978-85. PubMed PMID: WOS:000175783200004.

34. Taylor RW, Jones IE, Williams SM, Goulding A. Body fat percentages measured by dual-energy X-ray absorptiometry corresponding to recently recommended body mass index cutoffs for overweight and obesity in children and adolescents aged 3-18 y. American Journal of Clinical Nutrition. 2002;76(6):1416-21. PubMed PMID: WOS:000179414600031.

35. Freedman DS, Wang J, Maynard LM, Thornton JC, Mei Z, Pierson RN, et al. Relation of BMI to fat and fat-free mass among children and adolescents. International journal of obesity. 2005;29(1):1-8. doi: 10.1038/sj.ijo.0802735. PubMed PMID: WOS:000225710800001.

36. Sachdev HS, Fall CH, Osmond C, Lakshmy R, Biswas SKD, Leary SD, et al. Anthropometric indicators of body composition in young adults: relation to size at birth and serial measurements of body mass index in childhood in the New Delhi birth cohort. American Journal of Clinical Nutrition. 2005;82(2):456-66. PubMed PMID: WOS:000231293100027.

37. Ejtahed HS, Asghari G, Mirmiran P, Hosseinpour-Niazi S, Sherafat-KazemZadeh R, Azizi F. Body Mass Index as a Measure of Percentage Body Fat Prediction and Excess Adiposity Diagnosis among Iranian Adolescents. Arch Iran Med. 2014;17(6):400-5. PubMed PMID: WOS:000339782800003.

38. Deurenberg P, Weststrate JA, Seidell JC. Body-Mass Index as a Measure of Body Fatness - Age-Specific and Sex-Specific Prediction Formulas. Brit J Nutr. 1991;65(2):105-14. doi: Doi 10.1079/Bjn19910073. PubMed PMID: WOS:A1991FN98000003.

39. Arenz S, Ruckerl R, Koletzko B, von Kries R. Breast-feeding and childhood obesity--a systematic review. International journal of obesity and related metabolic disorders : journal of the International Association for the Study of Obesity. 2004;28(10):1247-56. doi: 10.1038/sj.ijo.0802758. PubMed PMID: 15314625.

40. Owen CG, Martin RM, Whincup PH, Smith GD, Cook DG. Effect of infant feeding on the risk of obesity across the life course: a quantitative review of published evidence. Pediatrics. 2005;115(5):1367-77. doi: 10.1542/peds.2004-1176. PubMed PMID: 15867049.

41. Horta BL, Victora CG, Franca GVA, Hartwig FP, Ong KK, Rolfe EL, et al. Breastfeeding moderates FTO related adiposity: a birth cohort study with 30 years of follow-up. Sci Rep. 2018;8(1):2530. doi: 10.1038/s41598-018-20939-4. PubMed PMID: 29416098; PubMed Central PMCID: PMCPMC5803210.

42. Abarin T, Yan Wu Y, Warrington N, Lye S, Pennell C, Briollais L. The impact of breastfeeding on FTO-related BMI growth trajectories: an application to the Raine pregnancy cohort study. Int J Epidemiol. 2012;41(6):1650-60. doi: 10.1093/ije/dys171. PubMed PMID: 23154192.

43. Lajunen HR, Kaprio J, Keski-Rahkonen A, Rose RJ, Pulkkinen L, Rissanen A, et al. Genetic and environmental effects on body mass index during adolescence: a prospective study among Finnish twins. International journal of obesity. 2009;33(5):559-67. doi: 10.1038/ijo.2009.51. PubMed PMID: 19337205; PubMed Central PMCID: PMCPMC2704063.

44. Nan C, Guo B, Warner C, Fowler T, Barrett T, Boomsma D, et al. Heritability of body mass index in pre-adolescence, young adulthood and late adulthood. Eur J Epidemiol. 2012;27(4):247-53. doi: 10.1007/s10654-012-9678-6. PubMed PMID: 22426805.

45. Plomin R, DeFries JC. Origins of individual differences in infancy : the Colorado Adoption Project. Orlando: Academic Press; 1985. xv, 406 p. p.

46. Berryman DE, Glad CAM, List EO, Johannsson G. The GH/IGF-1 axis in obesity: pathophysiology and therapeutic considerations. Nat Rev Endocrinol. 2013;9(6):346-56. doi: 10.1038/nrendo.2013.64. PubMed PMID: WOS:000319335900008.

47. Loche S, Cappa M, Borrelli P, Faedda A, Crino A, Cella SG, et al. Reduced Growth-Hormone Response to Growth Hormone-Releasing Hormone in Children with Simple Obesity - Evidence for Somatomedin-C Mediated Inhibition. Clin Endocrinol. 1987;27(2):145-53. doi: DOI 10.1111/j.1365-2265.1987.tb01139.x. PubMed PMID: WOS:A1987J305200001.

48. Juul A, Bang P, Hertel NT, Main K, Dalgaard P, Jorgensen K, et al. Serum Insulin-Like Growth Factor-I in 1030 Healthy-Children, Adolescents, and Adults - Relation to Age, Sex, Stage of Puberty, Testicular Size, and Body-Mass Index. J Clin Endocr Metab. 1994;78(3):744-52. doi: Doi 10.1210/Jc.78.3.744. PubMed PMID: WOS:A1994MZ30700040.

49. Juul A, Pedersen SA, Sorensen S, Winkler K, Jorgensen JOL, Christiansen JS, et al. Growth-Hormone (Gh) Treatment Increases Serum Insulin-Like Growth-Factor Binding Protein-3, Bone Isoenzyme Alkaline-Phosphatase and Forearm Bone-Mineral Content in Young-Adults with Gh Deficiency of Childhood-Onset. Eur J Endocrinol. 1994;131(1):41-9. PubMed PMID: WOS:A1994NY88600007.

50. Cui H, Lopez M, Rahmouni K. The cellular and molecular bases of leptin and ghrelin resistance in obesity. Nat Rev Endocrinol. 2017;13(6):338-51. doi: 10.1038/nrendo.2016.222. PubMed PMID: 28232667.

51. Balland E, Dam J, Langlet F, Caron E, Steculorum S, Messina A, et al. Hypothalamic Tanycytes Are an ERK-Gated Conduit for Leptin into the Brain. Cell Metab. 2014;19(2):293-301. doi: 10.1016/j.cmet.2013.12.015. PubMed PMID: WOS:000330722600014.

52. Clement K, Vaisse C, Lahlou N, Cabrol S, Pelloux V, Cassuto D, et al. A mutation in the human leptin receptor gene causes obesity and pituitary dysfunction. Nature. 1998;392(6674):398-401. doi: 10.1038/32911. PubMed PMID: 9537324.

53. Farooqi IS, Wangensteen T, Collins S, Kimber W, Matarese G, Keogh JM, et al. Clinical and molecular genetic spectrum of congenital deficiency of the leptin receptor. The New England journal of medicine. 2007;356(3):237-47. doi: 10.1056/NEJMoa063988. PubMed PMID: 17229951; PubMed Central PMCID: PMC2670197.

54. Gat-Yablonski G, Ben-Ari T, Shtaif B, Potievsky O, Moran O, Eshet R, et al. Leptin reverses the inhibitory effect of caloric restriction on longitudinal growth. Endocrinology. 2004;145(1):343-50. doi: 10.1210/en.2003-0910. PubMed PMID: 14525912.

55. Touvier T, Conte-Auriol F, Briand O, Cudejko C, Paumelle R, Caron S, et al. LEPROT and LEPROTL1 cooperatively decrease hepatic growth hormone action in mice. J Clin Invest. 2009;119(12):3830-8. doi: 10.1172/JCI34997. PubMed PMID: 19907080; PubMed Central PMCID: PMCPMC2786784.

56. Couturier C, Sarkis C, Seron K, Belouzard S, Chen P, Lenain A, et al. Silencing of OB-RGRP in mouse hypothalamic arcuate nucleus increases leptin receptor signaling and prevents diet-induced obesity. P Natl Acad Sci USA. 2007;104(49):19476-81. doi: 10.1073/pnas.0706671104. PubMed PMID: WOS:000251525800056.

57. Touvier T, Conte-Auriol F, Briand O, Cudejko C, Paumelle R, Caron S, et al. LEPROT and LEPROTL1 cooperatively decrease hepatic growth hormone action in mice. J Clin Invest. 2009;119(12):3830-8. doi: 10.1172/JCI34997. PubMed PMID: WOS:000272386400030.

58. Gat-Yablonski G, Phillip M. Nutritionally-induced catch-up growth. Nutrients. 2015;7(1):517-51. doi: 10.3390/nu7010517. PubMed PMID: 25594438; PubMed Central PMCID: PMCPMC4303852.

59. Sovio U, Bennett AJ, Millwood IY, Molitor J, O'Reilly PF, Timpson NJ, et al. Genetic Determinants of Height Growth Assessed Longitudinally from Infancy to Adulthood in the Northern Finland Birth Cohort 1966. Plos Genet. 2009;5(3). doi: ARTN e1000409

10.1371/journal.pgen.1000409. PubMed PMID: WOS:000266320100015.

60. Berkey CS, Reed RB. A model for describing normal and abnormal growth in early childhood. Human biology. 1987;59(6):973-87. PubMed PMID: 3443447.

61. Tzoulaki I, Sovio U, Pillas D, Hartikainen AL, Pouta A, Laitinen J, et al. Relation of immediate postnatal growth with obesity and related metabolic risk factors in adulthood: the northern Finland birth cohort 1966 study. American journal of epidemiology. 2010;171(9):989-98. doi: 10.1093/aje/kwq027. PubMed PMID: 20360243.

62. Krestyaninova M, Zarins A, Viksna J, Kurbatova N, Rucevskis P, Neogi SG, et al. A System for Information Management in BioMedical Studies--SIMBioMS. Bioinformatics. 2009;25(20):2768-9. doi: 10.1093/bioinformatics/btp420. PubMed PMID: 19633095; PubMed Central PMCID: PMC2759553.

63. Willer CJ, Li Y, Abecasis GR. METAL: fast and efficient meta-analysis of genomewide association scans. Bioinformatics. 2010;26(17):2190-1. doi: 10.1093/bioinformatics/btq340. PubMed PMID: WOS:000281738900017.

64. Devlin B, Roeder K. Genomic control for association studies. Biometrics. 1999;55(4):997-1004. doi: DOI 10.1111/j.0006-341X.1999.00997.x. PubMed PMID: WOS:000084218000001.

65. Palmer ND, Mychaleckyj JC, Langefeld CD, Ziegler JT, Williams AH, Bryer-Ash M, et al. Evaluation of DLG2 as a positional candidate for disposition index in African-Americans from the IRAS family study. Diabetes Res Clin Pr. 2010;87(1):69-76. doi: 10.1016/j.diabres.2009.10.015. PubMed PMID: WOS:000275101200012.

66. Lindgren CM, Heid IM, Randall JC, Lamina C, Steinthorsdottir V, Qi L, et al. Genome-Wide Association Scan Meta-Analysis Identifies Three Loci Influencing Adiposity and Fat Distribution. Plos Genet. 2009;5(6). doi: ARTN e1000508

10.1371/journal.pgen.1000508. PubMed PMID: WOS:000268444600004.

67. MacArthur J, Bowler E, Cerezo M, Gil L, Hall P, Hastings E, et al. The new NHGRI-EBI Catalog of published genome-wide association studies (GWAS Catalog). Nucleic acids research. 2017;45(D1):D896-D901. doi: 10.1093/nar/gkw1133. PubMed PMID: WOS:000396575500124.

68. McLaren W, Gil L, Hunt SE, Riat HS, Ritchie GR, Thormann A, et al. The Ensembl Variant Effect Predictor. Genome Biol. 2016;17(1):122. doi: 10.1186/s13059-016-0974-4. PubMed PMID: 27268795; PubMed Central PMCID: PMCPMC4893825.

69. Wallace C, Rotival M, Cooper JD, Rice CM, Yang JH, McNeill M, et al. Statistical colocalization of monocyte gene expression and genetic risk variants for type 1 diabetes. Human molecular genetics. 2012;21(12):2815-24. doi: 10.1093/hmg/dds098. PubMed PMID: 22403184; PubMed Central PMCID: PMC3363338.

70. Grundberg E, Small KS, Hedman AK, Nica AC, Buil A, Keildson S, et al. Mapping cis- and trans-regulatory effects across multiple tissues in twins. Nature genetics. 2012;44(10):1084-+. doi: 10.1038/ng.2394. PubMed PMID: WOS:000309550200006.

71. Holle R, Happich M, Lowel H, Wichmann HE, Grp MKS. KORA - A research platform for population based health research. Gesundheitswesen. 2005;67:S19-S25. doi: 10.1055/s-2005-858235. PubMed PMID: WOS:000231365200008.

72. Emilsson V, Thorleifsson G, Zhang B, Leonardson AS, Zink F, Zhu J, et al. Genetics of gene expression and its effect on disease. Nature. 2008;452(7186):423-U2. doi: 10.1038/nature06758. PubMed PMID: WOS:000254341300022.

73. Greenawalt DM, Dobrin R, Chudin E, Hatoum IJ, Suver C, Beaulaurier J, et al. A survey of the genetics of stomach, liver, and adipose gene expression from a morbidly obese cohort. Genome Res. 2011;21(7):1008-16. doi: 10.1101/gr.112821.110. PubMed PMID: WOS:000292298000002.

74. Zhernakova DV, Deelen P, Vermaat M, van Iterson M, van Galen M, Arindrarto W, et al. Identification of context-dependent expression quantitative trait loci in whole blood. Nature genetics. 2017;49(1):139-45. doi: 10.1038/ng.3737. PubMed PMID: 27918533.

75. Bonnelykke K, Matheson MC, Pers TH, Granell R, Strachan DP, Alves AC, et al. Meta-analysis of genome-wide association studies identifies ten loci influencing allergic sensitization. Nature genetics. 2013;45(8):902-6. doi: 10.1038/ng.2694. PubMed PMID: 23817571; PubMed Central PMCID: PMC4922420.

76. Zheng J, Erzurumluoglu AM, Elsworth BL, Kemp JP, Howe L, Haycock PC, et al. LD Hub: a centralized database and web interface to perform LD score regression that maximizes the potential of summary level GWAS data for SNP heritability and genetic correlation analysis. Bioinformatics. 2016. doi: 10.1093/bioinformatics/btw613. PubMed PMID: 27663502.

77. Sudlow C, Gallacher J, Allen N, Beral V, Burton P, Danesh J, et al. UK biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. PLoS medicine. 2015;12(3):e1001779. doi: 10.1371/journal.pmed.1001779. PubMed PMID: 25826379; PubMed Central PMCID: PMC4380465.

78. Ehret GB, Munroe PB, Rice KM, Bochud M, Johnson AD, Chasman DI, et al. Genetic variants in novel pathways influence blood pressure and cardiovascular disease risk. Nature. 2011;478(7367):103-9. doi: 10.1038/nature10405. PubMed PMID: WOS:000295575400043.

79. Verbanck M, Chen CY, Neale B, Do R. Detection of widespread horizontal pleiotropy in causal relationships inferred from Mendelian randomization between complex traits and diseases. Nature genetics. 2018;50(5):693-+. doi: 10.1038/s41588-018-0099-7. PubMed PMID: WOS:000431394900012.

80. Visscher PM, Wray NR, Zhang Q, Sklar P, McCarthy MI, Brown MA, et al. 10 Years of GWAS Discovery: Biology, Function, and Translation. Am J Hum Genet. 2017;101(1):5-22. doi: 10.1016/j.ajhg.2017.06.005. PubMed PMID: 28686856; PubMed Central PMCID: PMCPMC5501872.