UC San Diego

UC San Diego Previously Published Works

Title

A genome-wide association meta-analysis identifies new childhood obesity loci

Permalink

https://escholarship.org/uc/item/9r69s4pk

Journal

Nature Genetics, 44(5)

ISSN

1061-4036

Authors

Bradfield, Jonathan P
Taal, H Rob
Timpson, Nicholas J
et al.

Publication Date

2012-05-01

DOI

10.1038/ng.2247

Peer reviewed

eScholarship.org Powered by the California Digital Library
University of California

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

HHS Public Access

Author manuscript

Nat Genet. Author manuscript; available in PMC 2012 July 01.

Published in final edited form as:

Nat Genet. 2012 May ; 44(5): 526–531. doi:10.1038/ng.2247.

A genome-wide association meta-analysis identifies new childhood obesity loci

A full list of authors and affiliations appears at the end of the article.

Abstract

Multiple genetic variants have been associated with adult obesity and a few with severe obesity in childhood; however, less progress has been made to establish genetic influences on common early-onset obesity. We performed a North American-Australian-European collaborative meta-analysis of fourteen studies consisting of 5,530 cases (≥95th percentile of body mass index (BMI)) and 8,318 controls (<50th percentile of BMI) of European ancestry. Taking forward the eight novel signals yielding association with $P < 5\times10^{-6}$ in to nine independent datasets (n = 2,818 cases and 4,083 controls) we observed two loci that yielded a genome wide significant combined *P*-value, namely near *OLFM4* on 13q14 (rs9568856; $P=1.82\times10^{-9}$; OR=1.22) and within *HOXB5* on 17q21 (rs9299; $P=3.54\times10^{-9}$; OR=1.14). Both loci continued to show association when including two extreme childhood obesity cohorts (n = 2,214 cases and 2,674 controls). Finally, these two loci yielded directionally consistent associations in the GIANT meta-analysis of adult BMI[1].

Obesity is the major, increasingly prevalent health problem affecting modern societies. The problem is particularly severe for children in developed countries, where the prevalence of obesity is on the increase. Obesity present in adolescence is associated with increased overall mortality in later life[2]. Whereas the change in prevalence of obesity is likely to be explained by environmental changes over the last 30 years, there is also strong evidence for a genetic component to the risk of obesity. This is reflected in familial occurrences of

[72]A full list of members is provided in the Supplementary Note.

Users may view, print, copy, download and text and data- mine the content in such documents, for the purposes of academic research, subject always to the full Conditions of use: http://www.nature.com/authors/editorial_policies/license.html#terms

Correspondence should be addressed to S.F.A.G. (grants@chop.edu).

[73]These authors contributed equally to this work.

AUTHOR CONTRIBUTIONS

Project design was carried out by J.P.B., H.R.T., N.J.T., A.S., N.M.W., E.H., C.H., R.M.S., F.R.S., D.L.C., J.Z., R.I.B., R.J.P.v.d.V., J.C.d.J., D.I.B., W.J.G., L.A.M., M.L., H.B., F.D.G., J.H., I.B., S.O., A.M., T.I.A.S., C.P., L.J.P., A.H., E. Widen, I.S.F., M.I.M., P.F., D.M., J. Hebebrand, M.-R.J., V.W.V.J., G.D.S., H.H. and S.F.A.G. Sample collection and phenotyping was performed by H.R.T., R.M.S., R.I.B., C.E.P., A. Hofman, F.R., A.G.U., C.M.v.D., J.C.d.J., D.S.P., W.J.G., R.M., C.A.G.B., C.E.N., L.A.M., A. Pouta, A.-L.H., O.R., T.L., J.G.E., A. Palotie, J.D., P.D., G.M., S.M.R., J.P.K., J.L.B., A.I.F.B., M.B., M.G., J.N.H., M.W.G., H.B., F.D.G., J.H., I.B., S.O., A.M., T.I.A.S., C.P., L.J.P., A.H., I.S.F., M.I.M., P.F., D.M., J. Hebebrand, M.-R.J., V.W.V.J., G.D.S., H.H. and S.F.A.G. Genotyping was performed by R.M.S., C.E.P., D.M.E., D.J.B., A. Hofman, F.R., A.G.U., C.M.v.D., R.J.P.v.d.V., J.C.d.J., D.S.P., W.J.G., R.M., A. Pouta, A.-L.H., O.R., T.L., J.G.E., A. Palotie, J.D., P.D., G.M., S.M.R., J.P.K., J.L.B., A.I.F.B., M.B., J.N.H., M.W.G., H.B., J.H., I.B., S.O., A.M., T.I.A.S., C.P., L.J.P., A.H., E. Widen, I.S.F., M.I.M., P.F., D.M., J. Hebebrand, M.-R.J., V.W.V.J., G.D.S., H.H. and S.F.A.G. Statistical analysis was performed by J.P.B., H.R.T., N.J.T., A.S., C.L., N.M.W., E.H., C.H., B.V., E.T., R.M.S., F.R.S., D.L.C., P.M.A.S., J.Z., K.S.V., I.J., D.M.E., B.S.P., D.J.B., D.O.M.-K., F.R., R.J.P.v.d.V., J.C.d.J., D.S.P., W.J.G., M.T.H., C.M.L., R.M., P.E., A. Pouta, M.L., O.R., T.L., J.G.E., S.D., A.I.F.B., M.B., E.K.-M., E.W., A.M., A.H., E. Widen., I.S.F., D.M., M.-R.J., V.W.V.J., H.H. and S.F.A.G. The manuscript was written by J.P.B., H.R.T., N.J.T., A.S., J.Z., T.I.A.S., A.H., M.I.M., D.M., M.-R.J., V.W.V.J., H.H. and S.F.A.G.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

childhood obesity, where concordance for fat mass among monozygotic twins is reported to be higher than in dizygotic twins.

In the past four years, many genetic loci have been implicated for body mass index (BMI) / obesity from the outcomes of genome-wide association studies (GWAS), primarily in adults. The first locus reliably found to harbor variation associated with adiposity, the fat mass- and obesity-associated gene (*FTO*)[3], has been shown subsequently to be associated with obesity in all sufficiently sized study groups. Subsequent larger studies have revealed additional BMI/obesity genes. The largest meta-analysis of adult BMI to date came from the GIANT consortium, which confirmed fourteen known obesity susceptibility loci and revealed eighteen new loci associated with BMI in a study involving a total of 249,796 individuals[1]. However, these loci only account for a small fraction of the heritability that is known to contribute to obesity. There has been some work on extreme obesity in childhood (>99.5th percentile of BMI) but little progress has been made on less marked definitions of obesity more relevant to public health.

We reasoned that distillation of the genetic component in this complex phenotype should be easier in children, where environmental exposure and impact has been for a relatively short period of their lifetime. The relationship between BMI and body fat in children varies widely with age and with pubertal maturation. The Center for Disease Control and Prevention defined overweight as at or above the 95th percentile of BMI for age[4]. By late adolescence, these percentiles approach those used for adult definitions; the 95th percentile is then approximately 30 kg/m^2 [5].

In an effort to systematically search for childhood obesity susceptibility loci, we performed a large scale meta-analysis of fourteen existing GWAS datasets for childhood obesity, totaling 5,530 cases (≥95th percentile of BMI achieved before the age of 18 years old, representing 5–30% of any given cohort) and 8,318 controls (relatively conservatively defined as <50th percentile of BMI consistent throughout all measures during childhood) of European ancestry (see Supplementary Table 1 and Supplementary Note).\

Following the meta-analysis of 2.7 million SNPs (directly genotyped or imputed), signals at seven discrete locations reached genome-wide significance at $P < 5.0\times10^{-8}$. All these loci have been previously reported within GWAS for adult BMI (*FTO, TMEM18, POMC, MC4R, FAIM2, TNNI3K and SEC16B*), and robustly reflect previous reports on individual pediatric cohorts[6,7]. *FTO* gave the strongest evidence for association while *TNNI3K* and *POMC*, which were only detected in adult studies when using hundreds of thousands of participants, were readily detected in our relatively small sample size (Figure 1 and Supplementary Tables 2 and 3). Excluding the French and German studies from the meta-analysis, we did not observe association with variants previously reported by these groups as novel, where they defined childhood obesity was at a higher threshold[8], at the loci harboring *TNKS-MSRA* (rs17150703; $P = 0.22$) and *SDCCAG8* (rs12145833; $P = 0.57$).

We took forward all eight novel signals yielding association with $P < 5.0\times10^{-6}$ (Table 1 and Supplementary Table 4, the latter of which includes a heterogeneity analysis showing that the different distributions in each study did not affect our results; in addition Supplementary

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Table 5 shows the results after applying a second genomic control correction to the overall discovery meta-analysis results) in order to test for replication in multiple independent existing datasets, the majority of which were *in silico* analyses. In our replication effort, we initially tested these eight SNPs in nine study groups that had a comparable set of affected subjects i.e. BMI distributed normally from the 95th percentile upwards (n = 2,818 cases and 4,083 controls). From this attempt we observed two loci that yielded consistent evidence of association when combined with the discovery cohort, namely near olfactomedin 4 (*OLFM4*) on 13q14 (rs9568856; $P_{combined} = 1.82\times10^{-9}$; OR = 1.22) and within the gene encoding homeobox B5 (*HOXB5*) on 17q21 (rs9299; $P_{combined} = 3.54\times10^{-9}$; OR = 1.14) (Table 1; see also the regional plots in Supplementary Figures 1 and 2 for the discovery meta-analysis data).

Previous GWAS reports for extreme obesity case-control samples have demonstrated both confirmation of signals seen in less extreme or population based samples, such as *FTO*, as well as novel signals that are distinct from those seen at the population level[8]. We reasoned therefore that further exploration in existing extreme datasets [two cohorts totaling 2,214 cases (exclusively individuals approximately >4 standard deviations above the mean, equating to BMI>99.5th percentile] and 2,674 controls) would offer further insight in to how these signals operate, acknowledging the phenotypic differences and limits of sample size. Indeed, both loci emerging from the main replication step continued to show association folding in this more extreme phenotype (*OLFM4*; rs4833407; $P_{overall} = 5.33\times10^{-9}$; OR = 1.18 and *HOXB5*; rs9299; $P_{overall} = 1.54\times10^{-8}$; OR = 1.13) (Supplementary Table 6).

As the ALSPAC cohort leveraged BMI measures made before the age of two years old as part of defining cases and controls, we ran sensitivity analyses limiting case and control definitions to children over two years of age (Supplementary Tables 7–9). In addition to no diminishment in the odds ratios for the *OLFM4* and *HOXB5* loci, we observed support for rs4864201 at *BC041448* and rs4833407 at *ALPK1* (Supplementary Tables 8 and 9).

Finally, we were interested to see whether our two main signals of interest, namely at *OLFM4* and *HOXB5*, were evident in the GIANT adult BMI meta-analysis results (n = 123,864). Indeed, both loci yielded evidence of association in this quantitative setting (*P*-values= 7.75×10^{-5} and 0.015, respectively) with the same alleles in the same direction. Overall, seven of the eight signals initially taken forward in to the replication stage yielded consistent directionality, albeit not all being statistically significant, with the exception being rs1290002 (Supplementary Table 10).

Overall, these data indicate that the genetic architecture of BMI and obesity overlap to a large extent in children as well as adults. In addition to the previously reported loci, we have uncovered at least two new loci associated with obesity in early life. The adult BMI data available from GIANT[1] reveals that the influence of these two loci is also detected in adulthood. Interestingly, in addition to *OLFM4* and *HOXB5*, GIANT also supports an association with three more of the eight loci initially taken forward in to the replication effort, namely rs4864201 at *BC041448*, rs4833407 at *ALPK1* and rs2300095 at *MTORANGPTL7* loci, despite these signals not formally replicating in the main defined

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

overall pediatric setting, suggesting that these loci should be followed up further to fully understand their role in the pathogenesis of obesity as a whole.

The gene encoding olfactomedin 4 (*OLFM4*) is the nearest gene to rs9568856 but is still approximately 500kb from the associated signal; the gene product has never been directly implicated in obesity but has been extensively studied in the context of various cancers. OLFM4 is a secreted glycoprotein that facilitates cell adhesion via lectins and cadherin on the cell surface. Although the function of OLFM4 is not well understood, there are several intriguing observations that link it to gut microflora and to a relationship between the gut microbiome and obesity risk. For example, the *OLFM4* gene product down regulates innate immunity against infection by the stomach bacterium, *Helicobacter pylori*[9], with obese subjects having a higher occurrence of *Helicobacter pylori* infection than lean counterparts[10,11]; indeed, weight-loss induced by obesity surgery eradicates *Helicobacter pylori*[12].

rs9299 is in the 3' untranslated region of the gene encoding homeobox B5 (*HOXB5*) within a homeobox B cluster. HOXB5 is spatially and temporarily regulated during gut development[13], but its role in obesity has been suggested by a study observing up-regulation of homeobox transcription factors after fat loss[14]. Taken together, it is possible that *OLFM4* and *HOXB5* may impact BMI via different aspects of gut function.

In summary, as a consequence of extensive North American-Australian-European collaborative genome-wide meta-analyses on children, we have uncovered two novel obesity loci which have their strongest evidence for association with elevated adiposity in the first eighteen years of life. Further functional characterization of these signals is required to elucidate the precise mechanism behind these observations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Authors

Jonathan P. Bradfield[1,73], H. Rob Taal[2,3,4,73], Nicholas J. Timpson[5], André Scherag[6], Cecile Lecoeur[7], Nicole M. Warrington[8], Elina Hypponen[9], Claus Holst[10], Beatriz Valcarcel[11], Elisabeth Thiering[12], Rany M. Salem[13,14,15,16,17,18], Fredrick R. Schumacher[19], Diana L. Cousminer[20], Patrick M.A. Sleiman[1,21,22], Jianhua Zhao[21], Robert I. Berkowitz[23,24], Karani S. Vimaleswaran[9], Ivonne Jarick[25], Craig E. Pennell[8], David M. Evans[5], Beate St. Pourcain[5], Diane J. Berry[9], Dennis O Mook-Kanamori[2,3,4,26], Albert Hofman[2,3], Fernando Rivadeinera[3,27], André G. Uitterlinden[3,27], Cornelia M. van Duijn[3], Ralf J.P. van der Valk[2,28,29], Johan C. de Jongste[2,29], Dirkje S. Postma[30], Dorret I. Boomsma[31], William J. Gauderman[19], Mohamed T. Hassanein[19], Cecilia M. Lindgren[32], Reedik Mägi[32,33], Colin A.G. Boreham[34], Charlotte E. Neville[35], Luis A. Moreno[36,37], Paul Elliott[11], Anneli Pouta[38], Anna-Liisa Hartikainen[39], Mingyao Li[40], Olli Raitakari[41], Terho Lehtimäki[42], Johan G. Eriksson[43,44,45,46], Aarno Palotie[18,20,47,48], Jean Dallongeville[49], Shikta Das[11], Panos Deloukas[47], George McMahon[50], Susan M.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Ring[50], John P. Kemp[5], Jessica L. Buxton[51], Alexandra I.F. Blakemore[51], Mariona Bustamante[52,53,54,55], Mònica Guxens[52,53,54], Joel N. Hirschhorn[13,14,15,16,17,18], Matthew W. Gillman[56], Eskil Kreiner-Møller[57], Hans Bisgaard[57], Frank D. Gilliland[19], Joachim Heinrich[12], Eleanor Wheeler[47], Inês Barroso[47,58,59], Stephen O'Rahilly[58,59], Aline Meirhaeghe[49], Thorkild I.A. Sørensen[10,60], Chris Power[9], Lyle J. Palmer[61,62], Anke Hinney[63], Elisabeth Widen[20], I. Sadaf Farooqi[58,59], Mark I. McCarthy[64,65,66], Philippe Froguel[7,67], David Meyre[7,68], Johannes Hebebrand[63], Marjo-Riitta Jarvelin[11,38,69,70], Vincent W.V. Jaddoe[2,3,4], George Davey Smith[5], Hakon Hakonarson[1,21,22,71], Struan F.A. Grant[1,21,22,71], and for the Early Growth Genetics (EGG) Consortium[72]

Affiliations

[1]Center for Applied Genomics, Abramson Research Center, The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, USA [2]The Generation R Study Group, Erasmus Medical Center, Rotterdam, The Netherlands [3]Department of Epidemiology, Erasmus Medical Center, Rotterdam, The Netherlands [4]Department of Pediatrics, Erasmus Medical Center, Rotterdam, The Netherlands [5]The Medical Research Council (MRC) Centre for Causal Analyses in Translational Epidemiology, School of Social and Community Medicine, University of Bristol, Bristol, UK [6]Institute for Medical Informatics, Biometry and Epidemiology, University of Duisburg-Essen, Essen, Germany [7]Centre National de la Recherche Scientifique (CNRS) 8199, Université Lille Nord de France, Pasteur Institute, Lille, France [8]School of Women's and Infants' Health, University of Western Australia, Perth, Western Australia, Australia [9]Centre for Paediatric Epidemiology and Biostatistics, MRC Centre of Epidemiology for Child Health, University College of London Institute of Child Health, London, UK [10]Institute of Preventive Medicine, Copenhagen University Hospital, Copenhagen, Denmark [11]Department of Epidemiology and Biostatistics, MRC–Health Protection Agency (HPA) Centre for Environment and Health, School of Public Health, Faculty of Medicine, Imperial College London, London, UK [12]Helmholtz Zentrum Muenchen, German Research Centre for Environmental Health, Institute of Epidemiology I, Neuherberg, Germany [13]Division of Genetics, Children's Hospital, Boston, Massachusetts, USA [14]Division of Endocrinology, Children's Hospital, Boston, Massachusetts, USA [15]Program in Genomics, Children's Hospital, Boston, Massachusetts, USA [16]Metabolism Program, Broad Institute, Cambridge, Massachusetts, USA [17]Program in Medical and Population Genetics, Broad Institute, Cambridge, Massachusetts, USA [18]Department of Genetics, Harvard Medical School, Boston, Massachusetts, USA [19]Department of Preventive Medicine, Keck School of Medicine, University of Southern California, Los Angeles, California, USA [20]Institute for Molecular Medicine Finland (FIMM), University of Helsinki, Helsinki, Finland [21]Division of Human Genetics, The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, USA [22]Department of Pediatrics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA [23]Department of Child and Adolescent Psychiatry and Behavioral Sciences, The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, USA [24]Center for Weight and Eating

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Disorders, Department of Psychiatry, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA [25]Institute of Medical Biometry and Epidemiology, Philipps-University of Marburg, Marburg, Germany [26]Department of Physiology and Biophysics, Weill Cornell Medical College - Qatar, Doha, Qatar [27]Department of Internal Medicine, Erasmus Medical Center, Rotterdam, The Netherlands [28]Department of Pediatric Pulmonology and Pediatric Allergology, Beatrix Children's Hospital, University Medical Center Groningen, Groningen Research Institute for Asthma and COPD (GRIAC) Research Institute, University of Groningen, Groningen, The Netherlands [29]Division of Respiratory Medicine, Department of Pediatrics, Erasmus University Medical Center - Sophia Children's Hospital, Rotterdam, The Netherlands [30]Department of Pulmonary Medicine and Tuberculosis, University Medical Center Groningen, GRIAC Research Institute, University of Groningen, Groningen, The Netherlands [31]Department of Biological Psychology, Vrije Universiteit Amsterdam, Amsterdam, The Netherlands [32]Genetic and Genomic Epidemiology Unit, The Wellcome Trust Centre for Human Genetics, University of Oxford, Oxford, UK [33]Estonian Genome Center, University of Tartu, Tartu, Estonia [34]Institute for Sport and Health, University College Dublin, Ireland [35]Centre for Public Health, Institute of Clinical Science B, Queen's University Belfast, Belfast, UK [36]Growth, Exercise, Nutrition and Development (GENUD) Research Group, Universidad de Zaragoza, Zaragoza, Spain [37]School of Health Sciences (EUCS), Universidad de Zaragoza, Zaragoza, Spain [38]Department of Lifecourse and Services, National Institute for Health and Welfare, Oulu, Finland [39]Institute of Clinical Medicine/Obstetrics and Gynecology, University of Oulu, Oulu, Finland [40]Department of Biostatistics and Epidemiology, University of Pennsylvania, Philadelphia, Pennsylvania, USA [41]Department of Clinical Physiology, Turku University Hospital and University of Turku, Turku, Finland [42]Department of Clinical Chemistry, Tampere University Hospital and University of Tampere, Tampere, Finland [43]National Institute for Health and Welfare, Helsinki, Finland [44]Department of General Practice and Primary Health Care, University of Helsinki, Helsinki, Finland [45]Unit of General Practice, Helsinki University Central Hospital, Helsinki, Finland [46]Folkhälsan Research Center, Helsinki, Finland [47]Wellcome Trust Sanger Institute, Wellcome Trust Genome Campus, Hinxton, Cambridge, UK [48]Department of Medical Genetics, University of Helsinki and University Central Hospital, Helsinki, Finland [49]Institut National de la Santé et la Recherche Médicale (INSERM), U744, Institut Pasteur de Lille, Université Lille Nord de France, Lille, France [50]School of Social and Community Medicine, University of Bristol, Bristol, UK [51]Section of Integrative Medicine, Imperial College London, London, UK [52]Center for Research in Environmental Epidemiology (CREAL), Barcelona, Spain [53]Hospital del Mar Research Institute (IMIM), Barcelona, Spain [54]Consorcio de Investigación Biomédica en Red (CIBER) Epidemiologia y Salud Pública (CIBERESP), Barcelona, Spain [55]Genes and Disease Program, Center for Genomic Regulation (CRG) and Pompeu Fabra University (UPF), Barcelona, Spain [56]Obesity Prevention Program, Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, Massachusetts, USA [57]Copenhagen

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Prospective Studies on Asthma in Childhood, Health Sciences, University of Copenhagen and Copenhagen University Hospital, Gentofte, Denmark [58]University of Cambridge Metabolic Research Laboratories, Institute of Metabolic Science, Addenbrooke's Hospital, Cambridge, UK [59]National Institute for Health Research (NIHR) Cambridge Biomedical Research Centre, Institute of Metabolic Science, Addenbrooke's Hospital, Cambridge, UK [60]Novo Nordisk Foundation Center for Basic Metabolic Research, Section on Metabolic Genetics, University of Copenhagen, Copenhagen, Denmark [61]Ontario Institute for Cancer Research, Toronto, Ontario, Canada [62]Samuel Lunenfeld Research Institute, Toronto, Ontario, Canada [63]Department of Child and Adolescent Psychiatry, University of Duisburg-Essen, Essen, Germany [64]Oxford Centre for Diabetes, Endocrinology and Metabolism, University of Oxford, Oxford, UK [65]Wellcome Trust Centre for Human Genetics, University of Oxford, Oxford, UK [66]Oxford NIHR Biomedical Research Centre, Churchill Hospital, Headington, Oxford, UK [67]Department of Genomics of Common Disease, Imperial College London, London, UK [68]Department of Clinical Epidemiology & Biostatistics, McMaster University, Hamilton, Ontario, Canada [69]Institute of Health Sciences, University of Oulu, Oulu, Finland [70]Biocenter Oulu, University of Oulu, Oulu, Finland [71]Institute of Diabetes, Obesity and Metabolism, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA

Acknowledgements

Avon Longitudinal Study of Parents and Children (ALSPAC)

We are extremely grateful to all the families who took part in this study, the midwives for their help in recruiting them, and the whole ALSPAC team, which includes interviewers, computer and laboratory technicians, clerical workers, research scientists, volunteers, managers, receptionists and nurses. We would also like to acknowledge 23andMe for our genotyping collaboration. The UK Medical Research Council (Grant ref: 74882) the Wellcome Trust (Grant ref: 076467) and the University of Bristol provide core support for ALSPAC. This publication is the work of the authors and JPB and SFAG will serve as guarantors for the contents of this paper.

Northern Finnish Birth Cohort Studies 1966 and 1986

BV was supported by the Economic Social Research Council (ESRC award no. ES/H016058/1). JB is supported by a Wellcome Trust fellowship grant, number WT088431MA. NFBC1966 and 1986 received financial support from the 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), ENGAGE project and grant agreement HEALTH-F4-2007-201413, the Medical Research Council, UK (G0500539, G0600705, PrevMetSyn/SALVE) and the Wellcome Trust (project grant GR069224), UK. The DNA extractions, sample quality controls, biobank up-keeping and aliquotting was performed in the National Public Health Institute, Biomedicum Helsinki, Finland and supported financially by the Academy of Finland and Biocentrum Helsinki. We thank Professor (emeriti) Paula Rantakallio (launch of NFBC1966 and 1986), and Ms Outi Tornwall and Ms Minttu Jussila (DNA biobanking). The authors would like to acknowledge the contribution of the late Academian of Science Leena Peltonen.

British 1958 Birth Cohort (B58C)

Dr Elina Hyppönen holds the Department of Health (UK) Public Health Career Scientist Award. Analyses were funded by the British Heart Foundation (PG/09/023) and as part of the Public Health Research Consortium (supported by the Department of Health Policy Research Programme). Cecilia M. Lindgren is a Wellcome Trust Research Career Development Fellow (086596/Z/08/Z). Reedik Mägi was funded by FP7 grants (201413, 245536),

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

grant from Estonian Government SF0180142s08, from the EU through the European Regional Development Fund, in the frame of Centre of Excellence in Genomics and Univ. of Tartu grant SP1GVARENG. The views expressed in the publication are those of the authors and not necessarily those of the Department of Health. Information about the wider programme of the PHRC is available from www.york.ac.uk/phrc. Collection of DNA in the 1958 Birth Cohort was funded by the Medical Research Council grant G0000934 and Wellcome Trust grant 068545/Z/02. Dr Sue Ring and Dr Wendy McArdle (University of Bristol), and Mr Jon Johnson (Centre for Longitudinal Studies, Institute of Education, London) are thanked for help with data linkage. This research used resources provided by the Type 1 Diabetes Genetics Consortium, a collaborative clinical study sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), National Institute of Allergy and Infectious Diseases, National Human Genome Research Institute, National Institute of Child Health and Human Development, and Juvenile Diabetes Research Foundation International (JDRF) and supported by U01 DK062418. This study makes use of data generated by the Wellcome Trust Case-Control Consortium II. A full list of investigators who contributed to generation of the data is available from the Wellcome Trust Case-Control Consortium website. Funding for the project was provided by the Wellcome Trust under award 083948.Work was undertaken at Great Ormond Street Hospital /University College London, Institute of Child Health which received a proportion of funding from the Department of Health's National Institute of Health Research ('Biomedical Research Centres' funding). The Medical Research Council provides funds for the MRC Centre of Epidemiology for Child Health.

French Young study (FRENCH YOUNG)

We thank the subjects and families who participated in this study. This work was supported by grants from the ‘‘Agence Nationale de la Recherche,’’ the ‘‘Conseil Régional Nord-Pas de Calais/Fonds européen de développement économique et regional,’’ Genome Quebec/Genome Canada and the Medical Research Council.

Lifestyle – Immune System – Allergy Study and German Infant Study on the influence of Nutrition Intervention (LISA+GINI)

The LISAplus study was funded by Helmholtz Zentrum München. The GINIplus study was funded by Helmholtz Zentrum München and grants of the Federal Ministry for Education, Science, Research and Technology 292 (Grant No. 01 EE 9401-4). In addition both studies were partly supported by the ‘Competence Network Obesity’ funded by the Federal Ministry of Education and Research (FKZ: 01GI0826) and the Munich Center of Health Sciences (MC Health) as part of the Ludwig-Maximilians University Munich (LMU) innovative.

Western Australian Pregnancy Cohort study (RAINE)

The authors are grateful to the Raine Study participants and their families, and to the Raine Study research staff for cohort coordination and data collection. The authors gratefully acknowledge the NH&MRC for their long term contribution to funding the study over the last 20 years and also the following Institutions for providing funding for Core Management of the Raine Study: The University of Western Australia (UWA), Raine Medical Research Foundation, UWA Faculty of Medicine, Dentistry and Health Sciences, The Telethon Institute for Child Health Research, Curtin University and Women and Infants Research Foundation. The authors gratefully acknowledge the assistance of the Western Australian DNA Bank (National Health and Medical Research Council of Australia National Enabling Facility). The authors also acknowledge the support of the 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).

Children’s Hospital of Philadelphia (CHOP)

We thank the network of primary care clinicians, their patients and families for their contribution to this project and clinical research facilitated through the Pediatric Research Consortium (PeRC) at The Children’s Hospital of Philadelphia. Rosetta Chiavacci, Elvira Dabaghyan, Hope Thomas, Kisha Harden, Andrew Hill, Kenya Fain, Crystal Johnson-Honesty, Cynthia Drummond, Shanell Harrison and Sarah Wildrick, Cecilia Kim, Edward Frackelton, George Otieno, Kelly Thomas, Cuiping Hou, Kelly Thomas and Maria L. Garris provided expert assistance with genotyping or data collection and management. We would also like to thank Smari Kristinsson, Larus Arni Hermannsson and Asbjörn Krisbjörnssonof Raförninn ehf for their extensive software design and contribution. This research was financially supported by an Institute Development Award from the Children’s Hospital of Philadelphia, a Research Development Award from the Cotswold Foundation and NIH grant R01 HD056465.

Essen Obesity Study (ESSEN)

We thank all the participants of this study. This work was supported by grants from the Federal Ministry of Education and Research (BMBF: 01KU0903, NGFN-Plus: 01GS0820 and 01GS0830) and the Deutsche Forschungsgemeinschaft (DFG; HE 1446/4-1).

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Helsinki Birth Cohort Study (HBCS)

The Helsinki Birth Cohort Study (HBCS/HBCS 1934–44) thanks Professor David Barker, Professor Clive Osmond, Associate Professors Eero Kajantie and Tom Forsen. Major financial support was received from the Academy of Finland (project grants 209072, 129255 grant) and British Heart Foundation. The DNA extraction, sample quality control, biobank up-keep and aliquotting was performed at the National Institute for Health and Welfare, Helsinki, Finland.

Cardiovascular Risk in Young Finns Study (YF)

The Young Finns Study has been financially supported by the Academy of Finland: grants 126925, 121584, 124282, 129378 (Salve), 117787 (Gendi), and 41071 (Skidi), the Social Insurance Institution of Finland, Kuopio, Tampere and Turku University Hospital Medical Funds (grant 9M048 for TeLeht), Juho Vainio Foundation, Paavo Nurmi Foundation, Finnish Foundation of Cardiovascular Research and Finnish Cultural Foundation, Tampere Tuberculosis Foundation and Emil Aaltonen Foundation. The expert technical assistance in the statistical analyses by Irina Lisinen is gratefully acknowledged.

Copenhagen Study on Asthma in Childhood (COPSAC)

We thank all the families participating in the COPSAC cohort for their effort and commitment. We thank the COPSAC study team. COPSAC is funded by private and public research funds all listed on www.copsac.com. The Lundbeck Foundation; the Pharmacy Foundation of 1991; Augustinus Foundation; the Danish Medical Research Council and The Danish Pediatric Asthma Centre provided core support for COPSAC. The funding agencies did not have any role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

CM-GOYA study (CM-GOYA)

This study was conducted as part of the activities of the Danish Obesity Research Centre (DanORC, www.danorc.dk) and the MRC centre for Causal Analyses in Translational Epidemiology (MRC CAiTE).

Generation R Study (GENERATIONR)

The Generation R Study is conducted by the Erasmus Medical Center in close collaboration with the School of Law and Faculty of Social Sciences of the Erasmus University Rotterdam, the Municipal Health Service Rotterdam area, Rotterdam, the Rotterdam Homecare Foundation, Rotterdam and the Stichting Trombosedienst & Artsenlaboratorium Rijnmond (STAR-MDC), Rotterdam. We gratefully acknowledge the contribution of children and parents, general practitioners, hospitals, midwives and pharmacies in Rotterdam. The generation and management of GWAS genotype data for the Generation R Study were done at the Genetic Laboratory of the Department of Internal Medicine, Erasmus MC, The Netherlands. We would like to thank Karol Estrada, Dr. Tobias A. Knoch, Anis Abuseiris, Luc V. de Zeeuw, and Rob de Graaf, for their help in creating GRIMP, BigGRID, MediGRID, and Services@MediGRID/D-Grid, (funded by the German Bundesministerium fuer Forschung und Technology; grants 01 AK 803 A-H, 01 IG 07015 G) for access to their grid computing resources. We thank Mila Jhamai, Manoushka Ganesh, Pascal Arp, Marijn Verkerk, Lizbeth Herrera and Marjolein Peters for their help in creating, managing and QC of the GWAS database. Also, we thank Karol Estrada and Carolina Medina-Gomez for their support in creation and analysis of imputed data. The Generation R Study is made possible by financial support from the Erasmus Medical Center, Rotterdam, the Erasmus University Rotterdam and the Netherlands Organization for Health Research and Development (ZonMw 21000074). Vincent Jaddoe received an additional grant from the Netherlands Organization for Health Research and Development (ZonMw 90700303, 916.10159). Additional support was provided by a grant from the Dutch Kidney Foundation (C08.2251).

Healthy Lifestyle in Europe by Nutrition in Adolescence (HELENA)

The HELENA Study received funding from the European Union's Sixth RTD Framework Program (Contract FOOD-CT-2005-007034). This work was also supported by the Conseil Régional du Nord-Pas de Calais, ERDF (European Regional Development Fund) in the frame of the CPER Cardio-diabète (convention 09220016).

Young Hearts studies

The Young Hearts Project has received support from the British Heart Foundation, the Wellcome Trust, and the Department of Health and Social Services in Northern Ireland.

German Infant Study on the influence of Nutrition Intervention (GINI)

German Infant Study on the influence of Nutrition Intervention (GINI) Munich : The study team wishes to acknowledge the following : Helmholtz Zentrum München, German Research Center for Environmental Health,

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Institute of Epidemiology, Munich (Heinrich J, Wichmann HE, Sausenthaler S, Chen C-M, Thiering E, Tiesler C, Standl M, Schnappinger M, Rzehak P); Department of Pediatrics, Marien-Hospital, Wesel (Berdel D, von Berg A, Beckmann C, Groß I); Department of Pediatrics, Ludwig Maximilians University, Munich (Koletzko S, Reinhard D, Krauss-Etschmann S); Department of Pediatrics, Technical University, Munich (Bauer CP, Brockow I, Grübl A, Hoffmann U); IUF - Institut für Umweltmedizinische Forschung at the Heinrich-Heine-University, Düsseldorf (Krämer U, Link E, Cramer C); Centre for Allergy and Environment, Technical University, Munich (Behrendt H)

Children's Health Study (CHS)

We are indebted to the school principals, teachers, students and parents in each of the 12 (13) study communities for their cooperation and especially to the members of the health testing field team for their efforts. This work was supported by the Southern California Environmental Health Sciences Center (5P30ES007048) funded by the National Institute of Environmental Health Sciences; the Children's Environmental Health Center (5P01ES009581, R826708-01 and RD831861-01) funded by the National Institute of Environmental Health Sciences and the Environmental Protection Agency; the National Institute of Environmental Health Sciences (5P01ES011627, 5R01ES014447, 5R01ES014708, 5R01ES016535, 5R03ES014046); the National Heart, Lung and Blood Institute (5R01HL061768, 5R01HL076647, 5R01HL087680, 1RC2HL101543, 1RC2HL101651); the Environmental Protection Agency (R831845); and the Hastings Foundation.

SCOOP-UK (Severe Childhood Onset Obesity Project United Kingdom)

We acknowledge support of the Wellcome Trust (grant 077016/Z/05/Z), UK Medical Research Council and NIHR Cambridge Biomedical Research Centre.

INfancia y Medio Ambiente [Environment and Childhood] Project (INMA)

This study was funded by grants from Instituto de Salud Carlos III (CB06/02/0041, G03/176, 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, Conselleria de Sanitat Generalitat Valenciana, and Fundación Roger Torné. The authors are grateful to Silvia Fochs, Anna Sànchez, Maribel López, Nuria Pey, Muriel Ferrer, Amparo Quiles, Sandra Pérez, Gemma León, Elena Romero, Maria Andreu, Nati Galiana, Maria Dolores Climent and Amparo Cases for their assistance in contacting the families and administering the questionnaires. The authors would particularly 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/presentacion-inma/listado-investigadores/en_listado-investigadores.html.

Project Viva (VIVA)

We thank the staff and participants of Project Viva and Sheryl Rifas-Shiman for expert statistical programming. This work was supported by NIH grant R01DK075787.

Prevention and incidence of asthma and mite allergy birth cohort study (PIAMA)

The PIAMA birth cohort study is a collaboration of the Institute for Risk Assessment Sciences, University Utrecht (Prof. B. Brunekreef), Centre for Prevention and Health Services Research, National Institute for Public Health and the Environment, Bilthoven (Dr. A.H. Wijga, Prof. H.A. Smit), Department of Pediatrics, Division of Respiratory Medicine, Erasmus MC – Sophia's Children Hospital, Rotterdam (Prof. J.C. de Jongste), the Departments of Epidemiology (Dr. M. Kerkhof), Pulmonology (Prof D.S. Postma), Pediatric Pulmonology and Pediatric Allergology (Prof. G.H. Koppelman) of the GRIAC research Institute, the University Medical Center Groningen and University of Groningen, the Department of Immunopathology, Sanquin Research, Amsterdam (Prof. R.C. Aalberse), The Netherlands. The study team gratefully acknowledges the participants in the PIAMA birth cohort study, and all coworkers who helped conducting the medical examinations, field work and data management. The PIAMA study was funded by grants from the Dutch Asthma Foundation (grant 3.4.01.26, 3.2.06.022, 3.4.09.081 and 3.2.10.085CO), the ZON-MW Netherlands Organization for Health Research and Development (grant 912-03-031), the Stichting Astmabestrijding, the Ministry of the Environment and ZON-MW BBMRI-NL.

REFERENCES

1. Speliotes EK. Association analyses of 249,796 individuals reveal 18 new loci associated with body mass index. Nat Genet. 2010; 42:937–948. [PubMed: 20935630]
2. Must A. Does overweight in childhood have an impact on adult health? Nutr Rev. 2003; 61:139–142. [PubMed: 12795448]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

3. Frayling TM. A common variant in the FTO gene is associated with body mass index and predisposes to childhood and adult obesity. Science. 2007; 316:889–894. [PubMed: 17434869]
4. Flegal KM, Wei R, Ogden C. Weight-for-stature compared with body mass index-for-age growth charts for the United States from the Centers for Disease Control and Prevention. Am J Clin Nutr. 2002; 75:761–766. [PubMed: 11916765]
5. Daniels SR, et al. Overweight in children and adolescents: pathophysiology, consequences, prevention, and treatment. Circulation. 2005; 111:1999–2012. [PubMed: 15837955]
6. Zhao J, et al. The Role of Obesity-associated Loci Identified in Genome-wide Association Studies in the Determination of Pediatric BMI. Obesity. 2009; 17:2254–2257. [PubMed: 19478790]
7. den Hoed M, et al. Genetic susceptibility to obesity and related traits in childhood and adolescence: influence of loci identified by genome-wide association studies. Diabetes. 2010; 59:2980–2988. [PubMed: 20724581]
8. Scherag A, et al. Two new Loci for body-weight regulation identified in a joint analysis of genome-wide association studies for early-onset extreme obesity in French and german study groups. PLoS Genet. 2010; 6:e1000916. [PubMed: 20421936]
9. Liu W, et al. Olfactomedin 4 down-regulates innate immunity against Helicobacter pylori infection. Proc Natl Acad Sci U S A. 2010; 107:11056–11061. [PubMed: 20534456]
10. Arslan E, Atilgan H, Yavasoglu I. The prevalence of Helicobacter pylori in obese subjects. Eur J Intern Med. 2009; 20:695–697. [PubMed: 19818289]
11. Abdullahi M, et al. The eradication of Helicobacter pylori is affected by body mass index (BMI). Obes Surg. 2008; 18:1450–1454. [PubMed: 18443890]
12. Keren D, et al. Sleeve gastrectomy leads to Helicobacter pylori eradication. Obes Surg. 2009; 19:751–756. [PubMed: 18830786]
13. Fu M, Lui VC, Sham MH, Cheung AN, Tam PK. HOXB5 expression is spatially and temporarily regulated in human embryonic gut during neural crest cell colonization and differentiation of enteric neuroblasts. Dev Dyn. 2003; 228:1–10. [PubMed: 12950074]
14. Dankel SN, et al. Switch from stress response to homeobox transcription factors in adipose tissue after profound fat loss. PLoS One. 2010; 5:e11033. [PubMed: 20543949]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

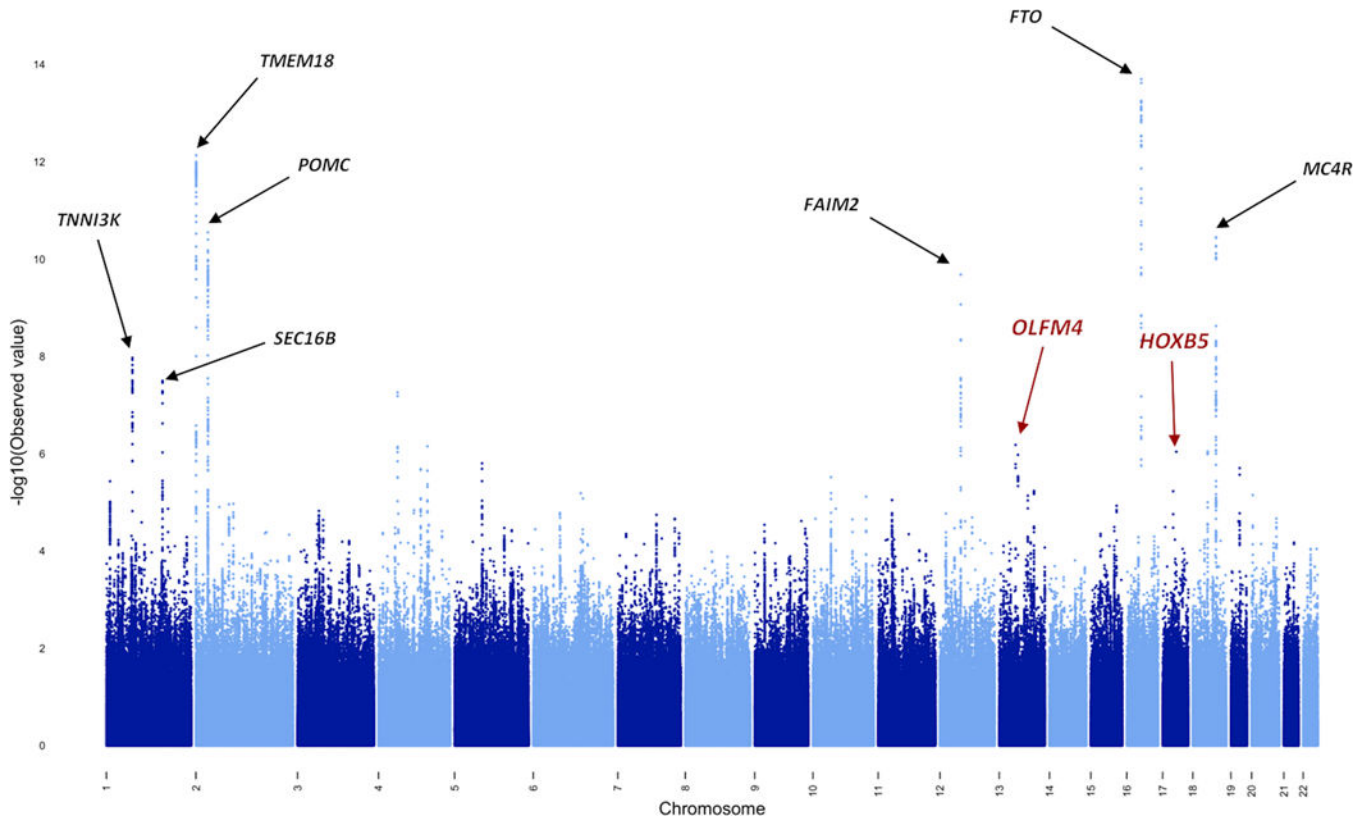

Figure 1.

Manhattan Plot of the meta-analysis of childhood obesity GWAS runs in the discovery stage (5,530 cases and 8,318 controls), with each locus achieving genome wide significance ($P < 5\times10^{-8}$) indicated in black text. In addition, the novel loci uncovered in this study are indicated in red text.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Nat Genet. Author manuscript; available in PMC 2012 July 01.

Table 1

The two key novel loci established to be associated with common early-onset obesity

They did not reach genome wide significance but yielded $P < 5x10^{-6}$ in the discovery stage (5,530 cases and 8,318 controls). The outcome of the replication effort of these loci taken forward in to nine comparable independent cohorts (n = 2,818 cases and 4,083 controls) is also indicated. Separate discovery and replication data plus combined data are shown, with the latter indicating genome wide significance in both instances.

	Locus	SNP	Allele1/2	Nearest Gene	Direction	OR [95% C.I.]	*P*-value
Discovery	13q14	rs9568856	A/G	*OLFM4*	++++++++++++-+	1.210 [1.123, 1.305]	6.58×10^{-7}
	17q21	rs9299	T/C	*HOXB5*	++-++-++++++++	1.144 [1.084, 1.207]	9.12×10^{-7}
Replication	13q14	rs9568856	A/G	*OLFM4*	+-++++-++	1.225 [1.089, 1.378]	7.13×10^{-4}
	17q21	rs9299	T/C	*HOXB5*	++-++++++	1.145 [1.056, 1.242]	0.00104
Combined	13q14	rs9568856	A/G	*OLFM4*		1.215 [1.140, 1.294]	1.82×10^{-9}
	17q21	rs9299	T/C	*HOXB5*		1.144 [1.094, 1.196]	3.54×10^{-9}

Discovery cohorts

1. Avon Longitudinal Study of Parents and Children (ALSPAC)
2. Northern Finland 1966 Birth Cohort (NFBC1966)
3. British 1958 Birth Cohort – Type 1 Diabetes Genetics Consortium subset (B58C-T1DGC)
4. British 1958 Birth Cohort – Wellcome Trust Case Control Consortium Subset (B58C-WTCCC)
5. French Young study (FRENCH YOUNG) PCA adjusted
6. Lifestyle Immune System Allergy Study (LISA)
7. Western Australian Pregnancy Cohort study (RAINE)
8. Children's Hospital of Philadelphia (CHOP) PCA adjusted
9. Essen Obesity Study (ESSEN) PCA adjusted
10. Helsinki Birth Cohort Study (HBCS)
11. Cardiovascular Risk in Young Finns Study (YF)
12. Copenhagen Study on Asthma in Childhood (COPSAC)
13. CM-GOYA study (CM-GOYA)
14. Generation R Study (GENERATIONR)

Comparable replication cohorts

1. Healthy Lifestyle in Europe by Nutrition in Adolescence study (HELENA)

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

2. Young Hearts studies
3. Lifestyle – Immune System – Allergy Study plus German Infant Study on the influence of Nutrition Intervention LISA+GINI)
4. Children's Health Study (CHS)
5. INfancia y Medio Ambiente [Environment and Childhood] Project (INMA) (2 proxies used - rs965013 and rs11099020 for rs4833407)
6. Project Viva (VIVA)
7. Prevention and incidence of asthma and mite allergy birth cohort study (PIAMA)
8. Northern Finland 1986 Birth Cohort (NFBC1986) (2 proxies used - rs10779751 for rs230095; rs4883723 for rs9568856)
9. Avon Longitudinal Study of Parents and Children ALSPAC)