

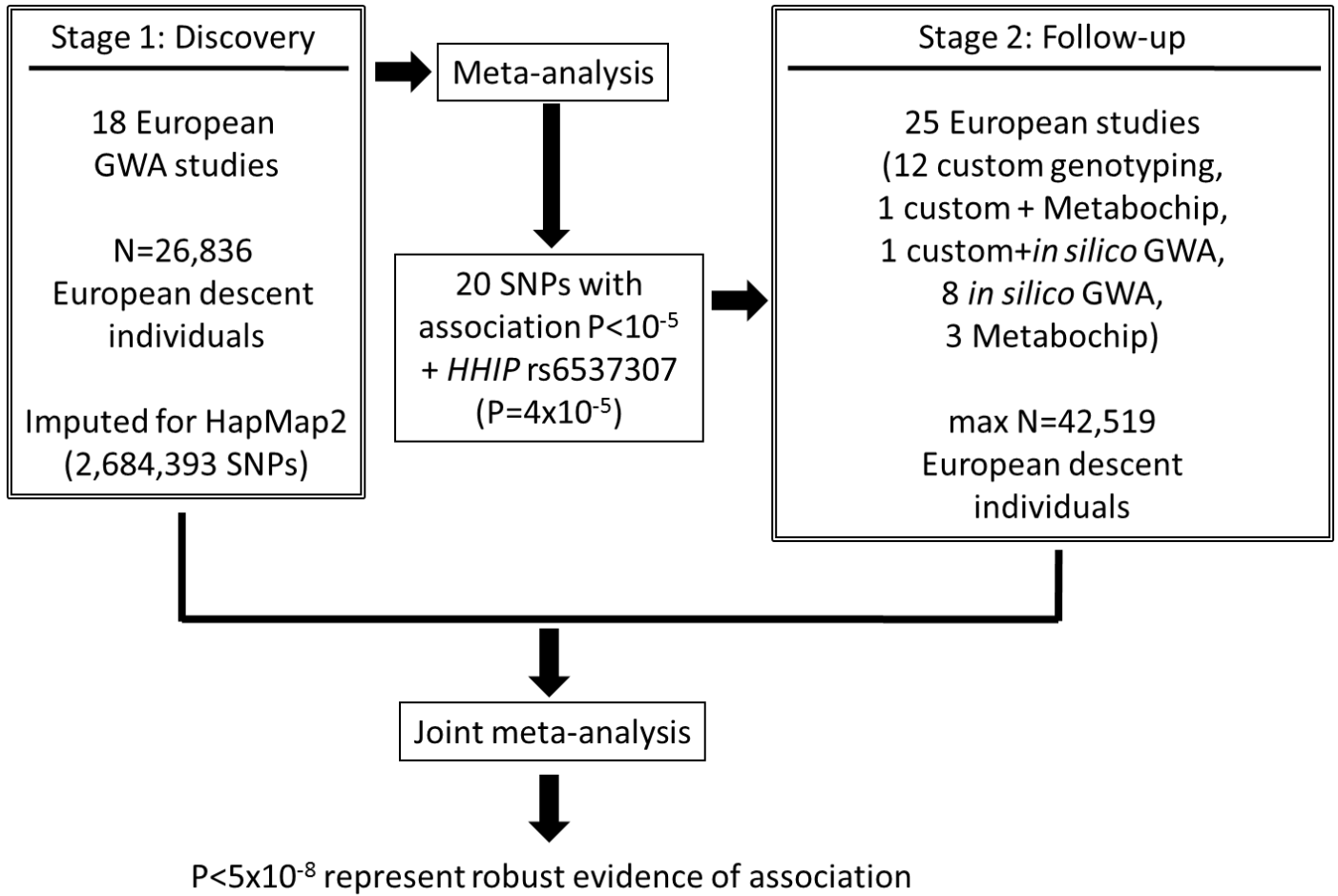
## SUPPLEMENTARY ONLINE MATERIAL

### **New loci associated with birth weight identify genetic links between intrauterine growth and adult height and metabolism**

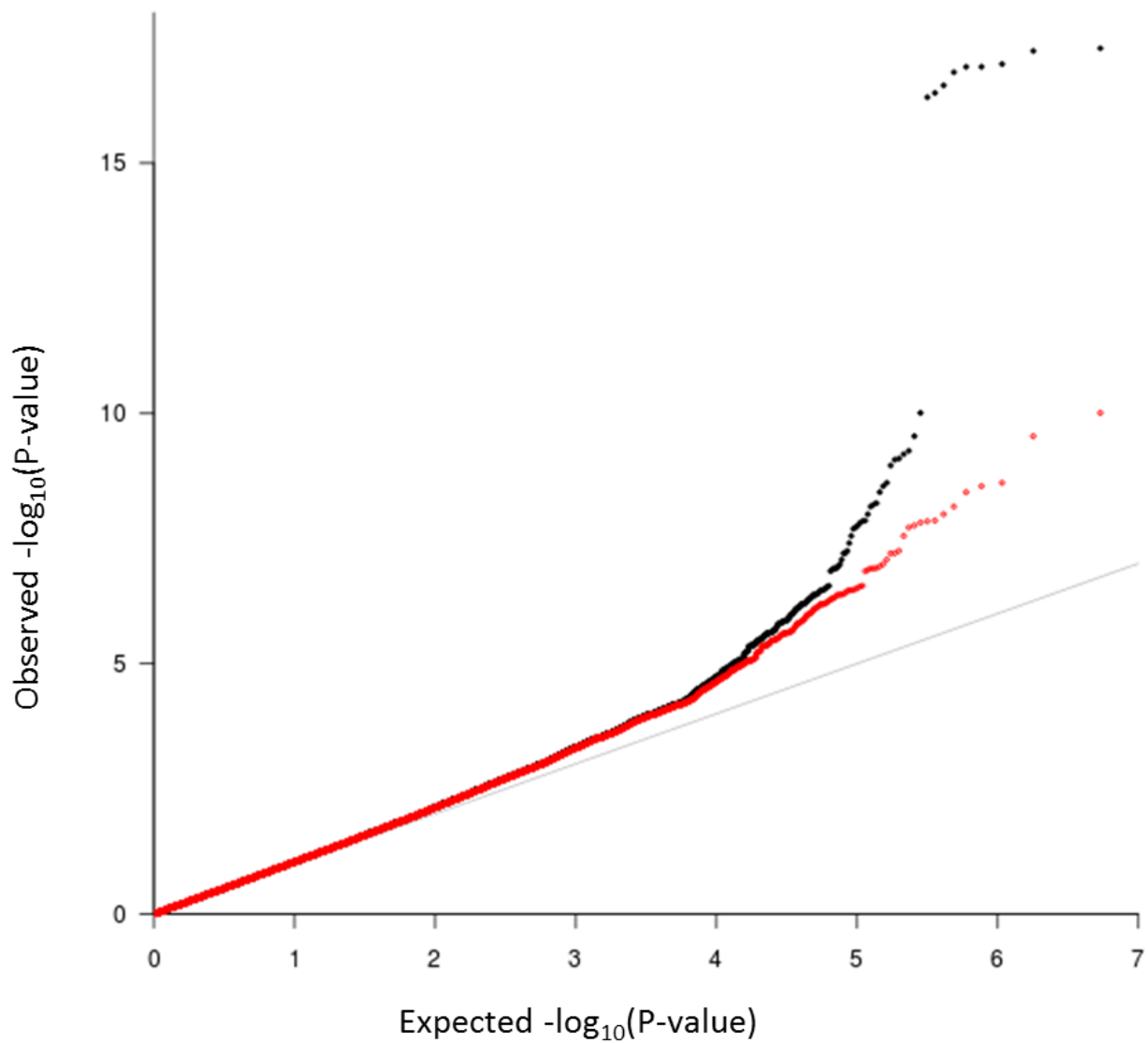
Momoko Horikoshi, Hanieh Yaghootkar, Dennis O. Mook-Kanamori, Ulla Sovio, H. Rob Taal, Branwen J. Hennig, Jonathan P. Bradfield, Beate St. Pourcain, David M. Evans, Pimphen Charoen, Marika Kaakinen, Diana L. Cousminer, Terho Lehtimäki, Eskil Kreiner-Møller, Nicole M. Warrington, Mariona Bustamante, Bjarke Feenstra, Diane J. Berry, Elisabeth Thiering, Thiemo Pfab, Sheila J. Barton, Beverley M. Shields, Marjan Kerkhof, Elisabeth M. van Leeuwen, Anthony J. Fulford, Zoltán Kutalik, Jing Hua Zhao, Marcel den Hoed, Anubha Mahajan, Virpi Lindi, Liang-Kee Goh, Jouke-Jan Hottenga, Ying Wu, Olli T. Raitakari, Marie N. Harder, Aline Meirhaeghe, Ioanna Ntalla, Rany M. Salem, Karen A. Jameson, Kaixin Zhou, Dorota M. Monies, Vasiliki Lagou, Mirna Kirin, Jani Heikkinen, Linda S. Adair, Fowzan S. Alkuraya, Ali Al-Odaib, Philippe Amouyel, Ehm Astrid Andersson, Amanda J. Bennett, Alexandra I.F. Blakemore, Jessica L. Buxton, Jean Dallongeville, Shikta Das, Eco J. C. de Geus, Xavier Estivill, Claudia Flexeder, Philippe Froguel, Frank Geller, Keith M. Godfrey, Frédéric Gottrand, Christopher J. Groves, Torben Hansen, Joel N. Hirschhorn, Albert Hofman, Mads V. Hollegaard, David M. Hougaard, Elina Hyppönen, Hazel M. Inskip, Aaron Isaacs, Torben Jørgensen, Christina Kanaka-Gantenbein, John P. Kemp, Wieland Kiess, Tuomas O. Kilpeläinen, Norman Klopp, Bridget A. Knight, Christopher W. Kuzawa, George McMahon, John P. Newnham, Harri Niinikoski, Ben A. Oostra, Louise Pedersen, Dirkje S. Postma, Susan M. Ring, Fernando Rivadeneira, Neil R. Robertson, Sylvain Sebert, Olli Simell, Torsten Slowinski, Carla M.T. Tiesler, Anke Tönjes, Allan Vaag, Jorma S. Viikari, Jacqueline M. Vink, Nadja Hawwa Vissing, Nicholas J. Wareham, Gonke Willemsen, Daniel R. Witte, Haitao Zhang, Jianhua Zhao, The Meta-Analyses of Glucose- and Insulin-related traits Consortium (MAGIC), James F. Wilson, Michael Stumvoll, Andrew M. Prentice, Brian F. Meyer, Ewan R. Pearson, Colin A.G. Boreham, Cyrus Cooper, Matthew W. Gillman, George V. Dedoussis, Luis A Moreno, Oluf Pedersen, Maiju Saarinen, Karen L. Mohlke, Dorret I. Boomsma, Seang-Mei Saw, Timo A. Lakka, Antje Körner, Ruth J.F. Loos, Ken K. Ong, Peter Vollenweider, Cornelia M. van Duijn, Gerard H. Koppelman, Andrew T. Hattersley, John W. Holloway, Berthold Hofer, Joachim Heinrich, Chris Power, Mads Melbye, Mònica Guxens, Craig E. Pennell, Klaus Bønnelykke, Hans Bisgaard, Johan G. Eriksson, Elisabeth Widén, Hakon Hakonarson, André G. Uitterlinden, Anneli Pouta, Debbie A. Lawlor, George Davey Smith, Timothy M. Frayling, Mark I. McCarthy, Struan F.A. Grant, Vincent W.V. Jaddoe, Marjo-Riitta Jarvelin, Nicholas J. Timpson, Inga Prokopenko, and Rachel M. Freathy for the Early Growth Genetics (EGG) Consortium.

**Contents**

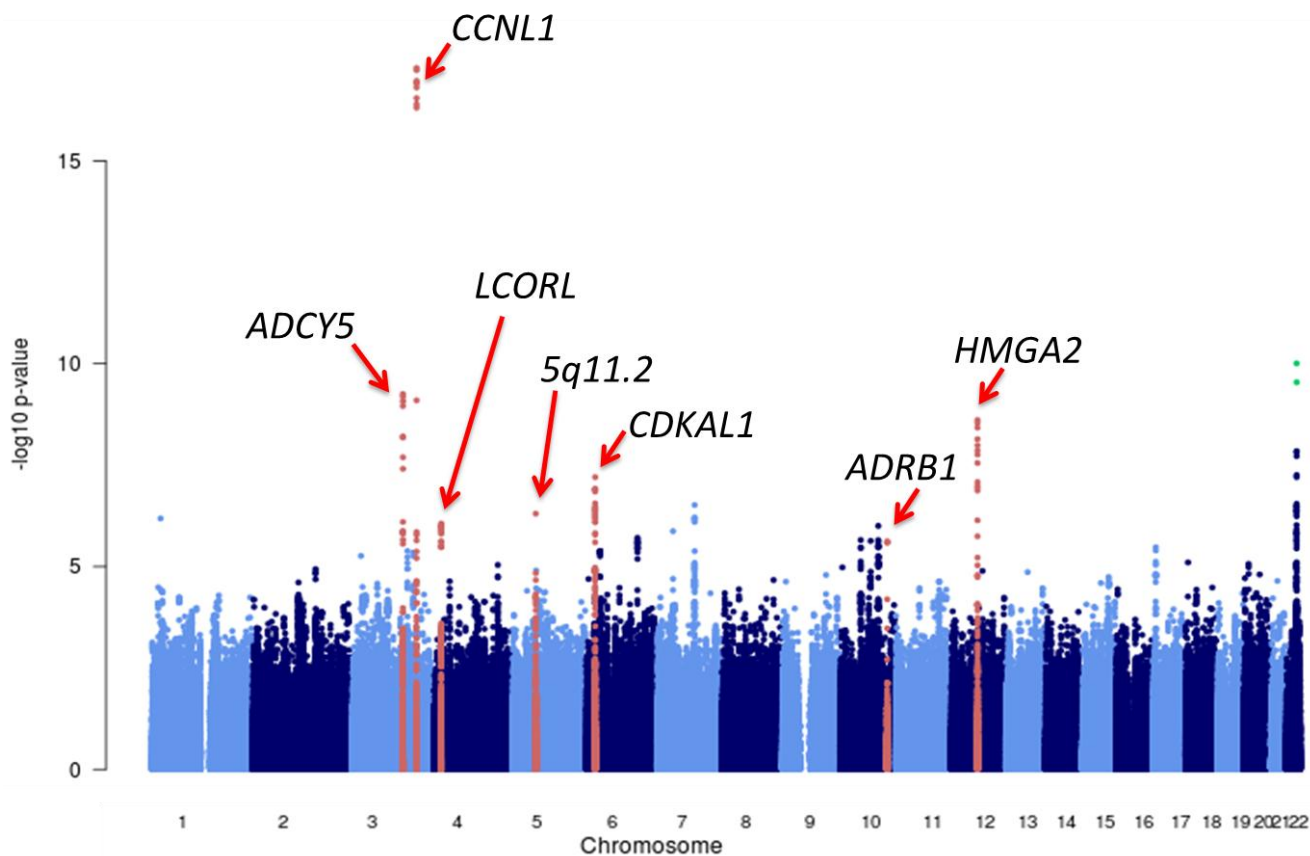
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**Supplementary Figure 1.** Summary of study design.

**Supplementary Figure 2.** Quantile-quantile plot of 2,684,393 single nucleotide polymorphisms (SNPs) from the meta-analysis of up to N=26,836 discovery samples. The black dots represent observed  $P$  values and the black line represents the expected  $P$  values under the null distribution. The red dots represent observed  $P$  values after excluding the previously identified *ADCY5* and *CCNL1* signals.

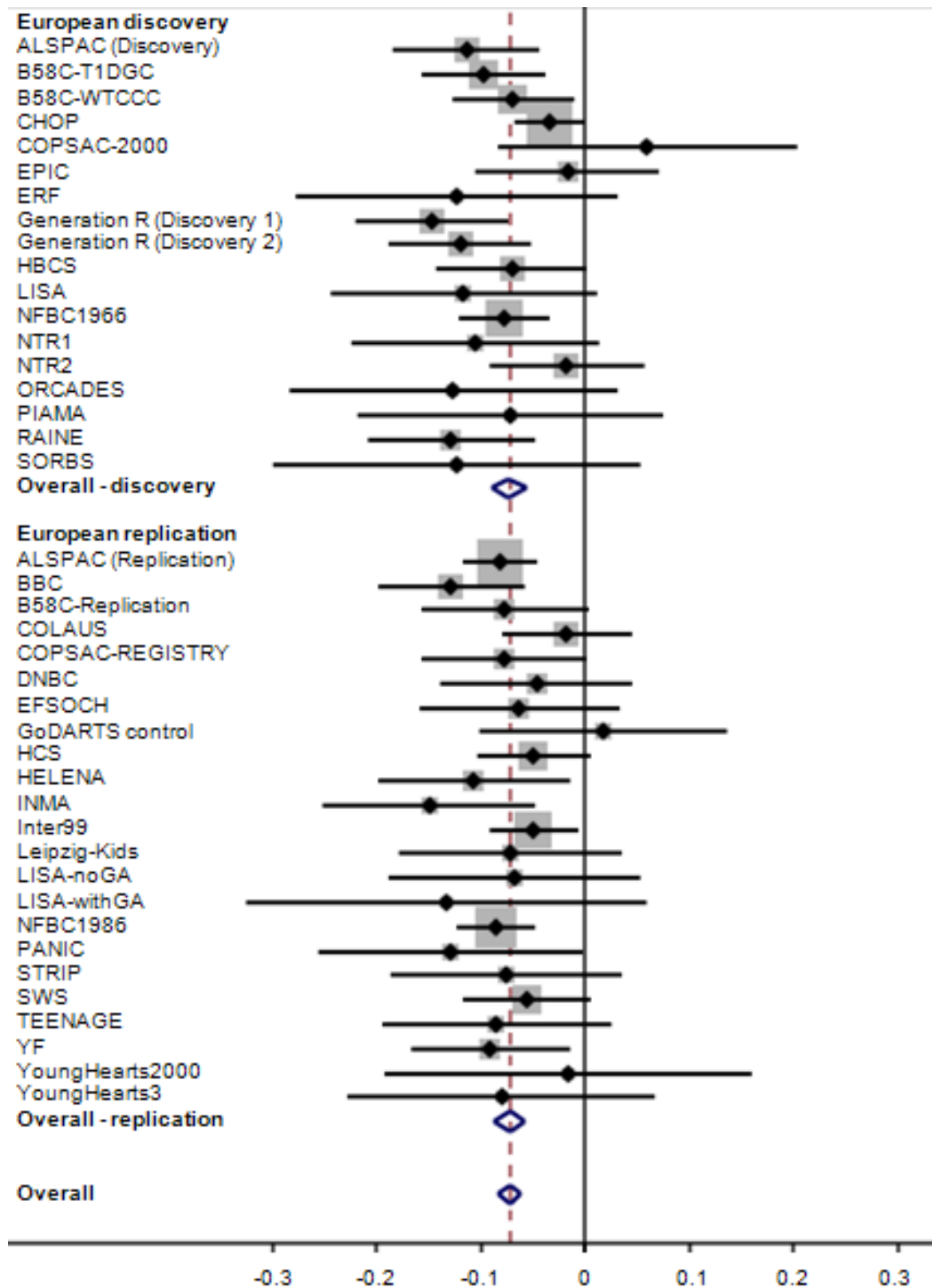


**Supplementary Figure 3.** Manhattan plot of the association  $P$  values for birth weight from the **discovery** meta-analysis ( $n =$  up to 26,836). The  $-\log_{10}$  of the  $P$  value for each of 2,684,393 SNPs (y-axis) is plotted against the genomic position (NCBI Build 36; x-axis). Association signals that reached genome-wide significance ( $P < 5 \times 10^{-8}$ ) in the global meta-analysis of discovery and follow-up studies are shown in red.

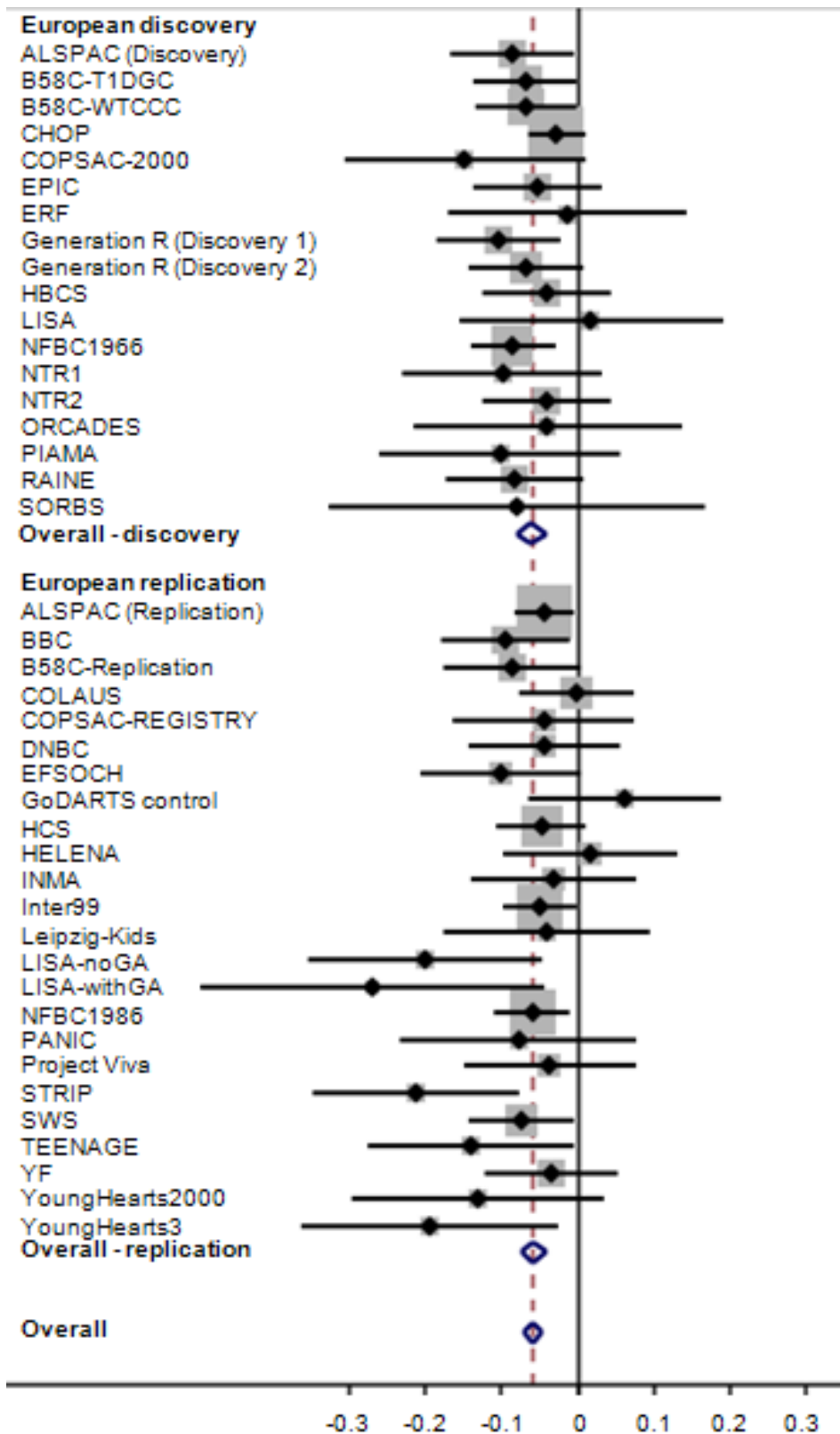


**Supplementary Figure 4.** Forest plots of the associations between birth weight and (a) *CCNL1*, (b) *ADCY5*, (c) *HMGGA2*, (d) *CDKAL1*, (e) *5q11.2*, (f) *LCORL* and (g) *ADRB1* in Europeans. In each plot, the dashed red line indicates the effect size from the overall meta-analysis of discovery and follow-up samples.

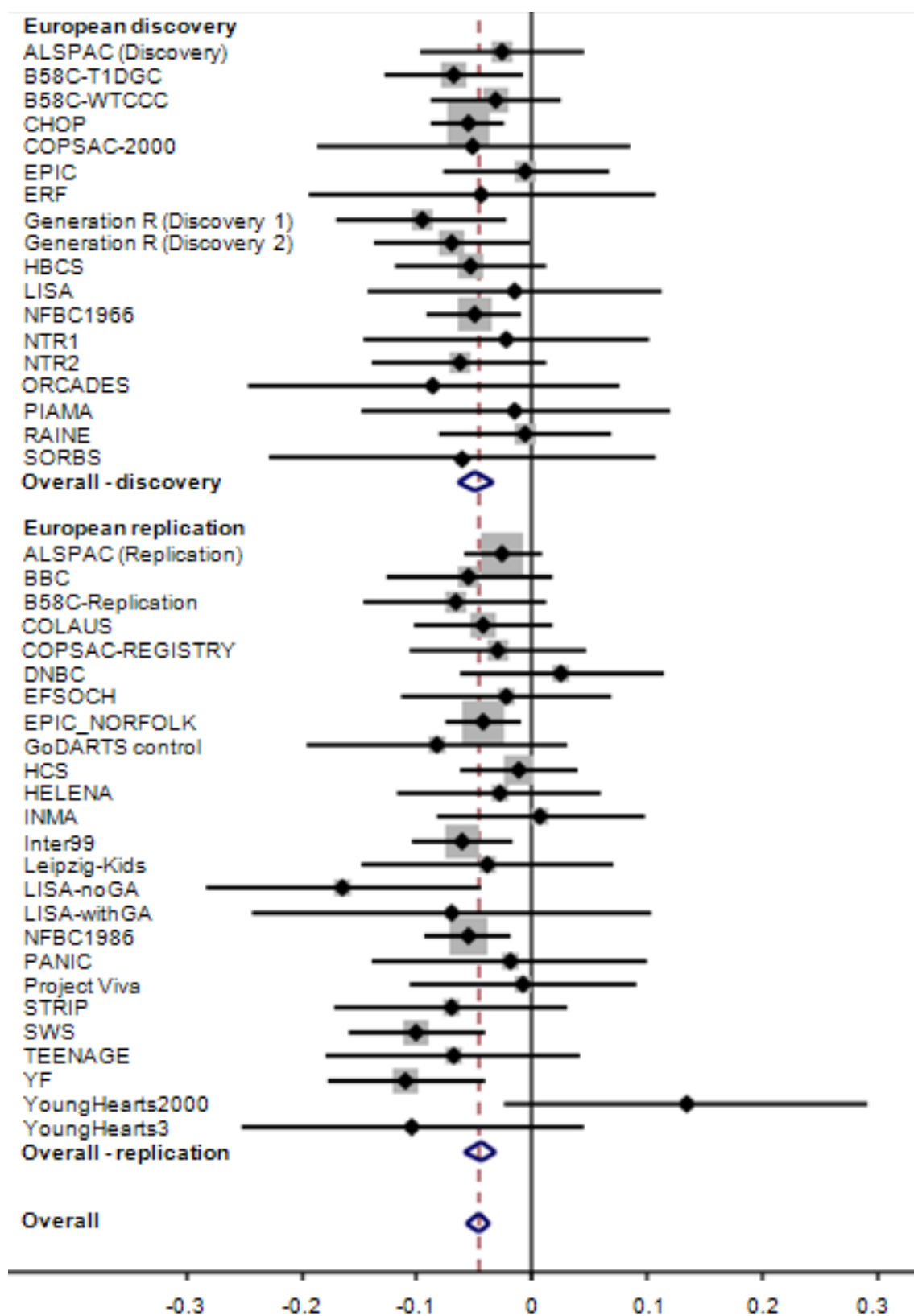
(a) *CCNL1* (overall  $n = 61,142$ ;  $P = 3.6 \times 10^{-38}$ ; heterogeneity  $P = 0.49$ )



(b) *ADCY5* (overall  $n = 61,509$ ;  $P = 5.5 \times 10^{-20}$ ; heterogeneity  $P = 0.69$ )

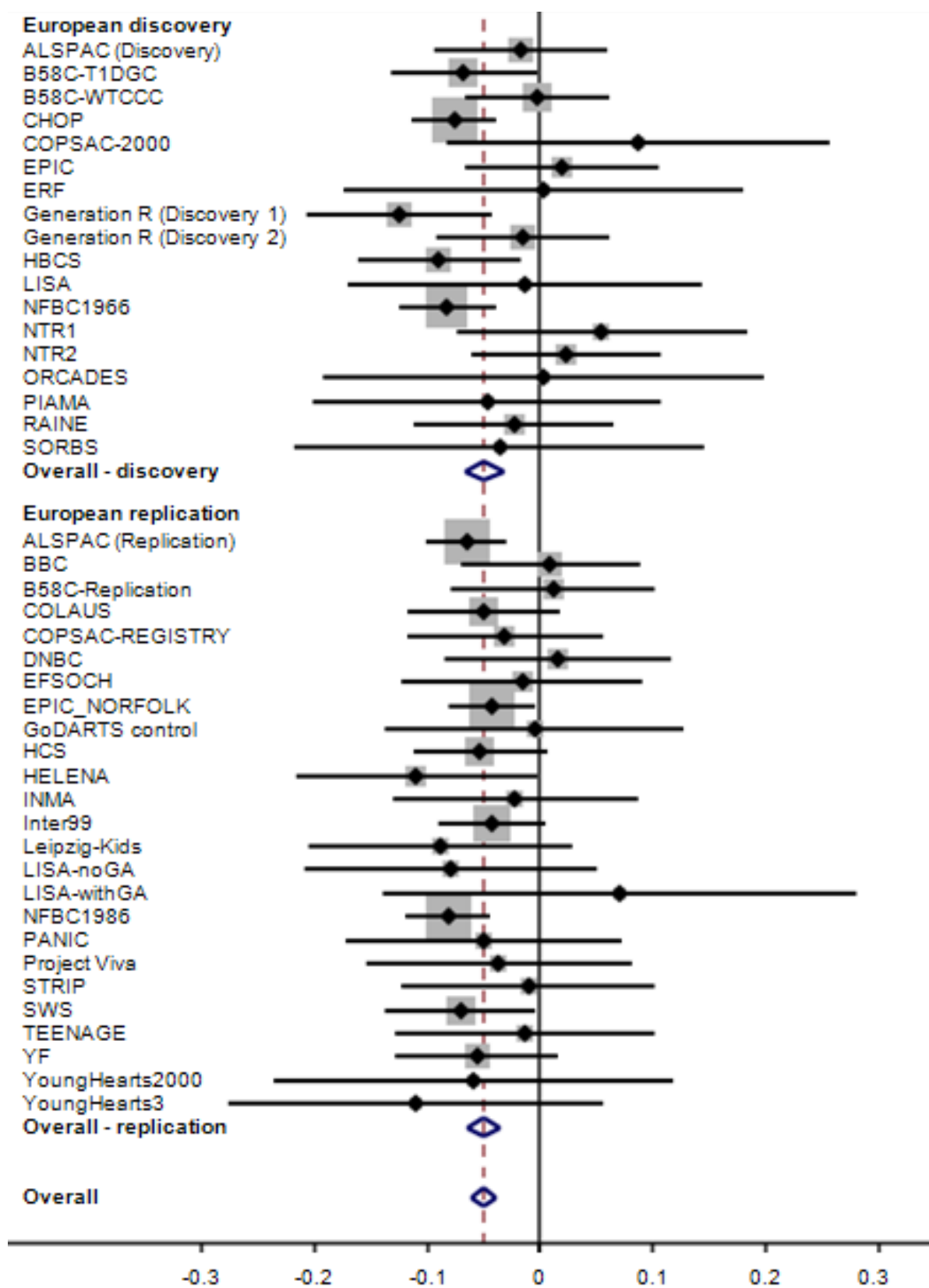


(c) *HMGA2* (overall  $n = 68,655$ ;  $P = 1.4 \times 10^{-19}$ ; heterogeneity  $P = 0.82$ )

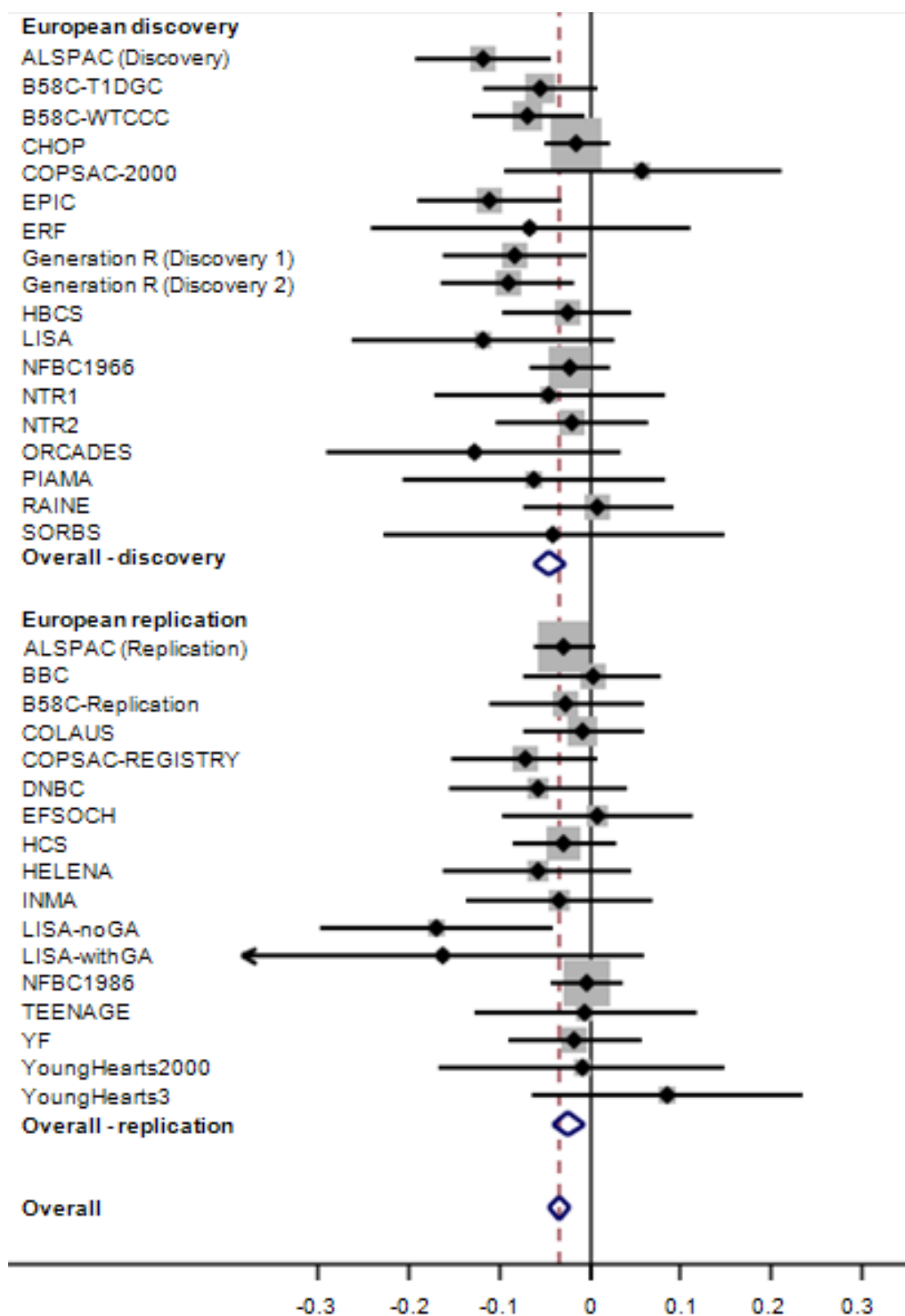




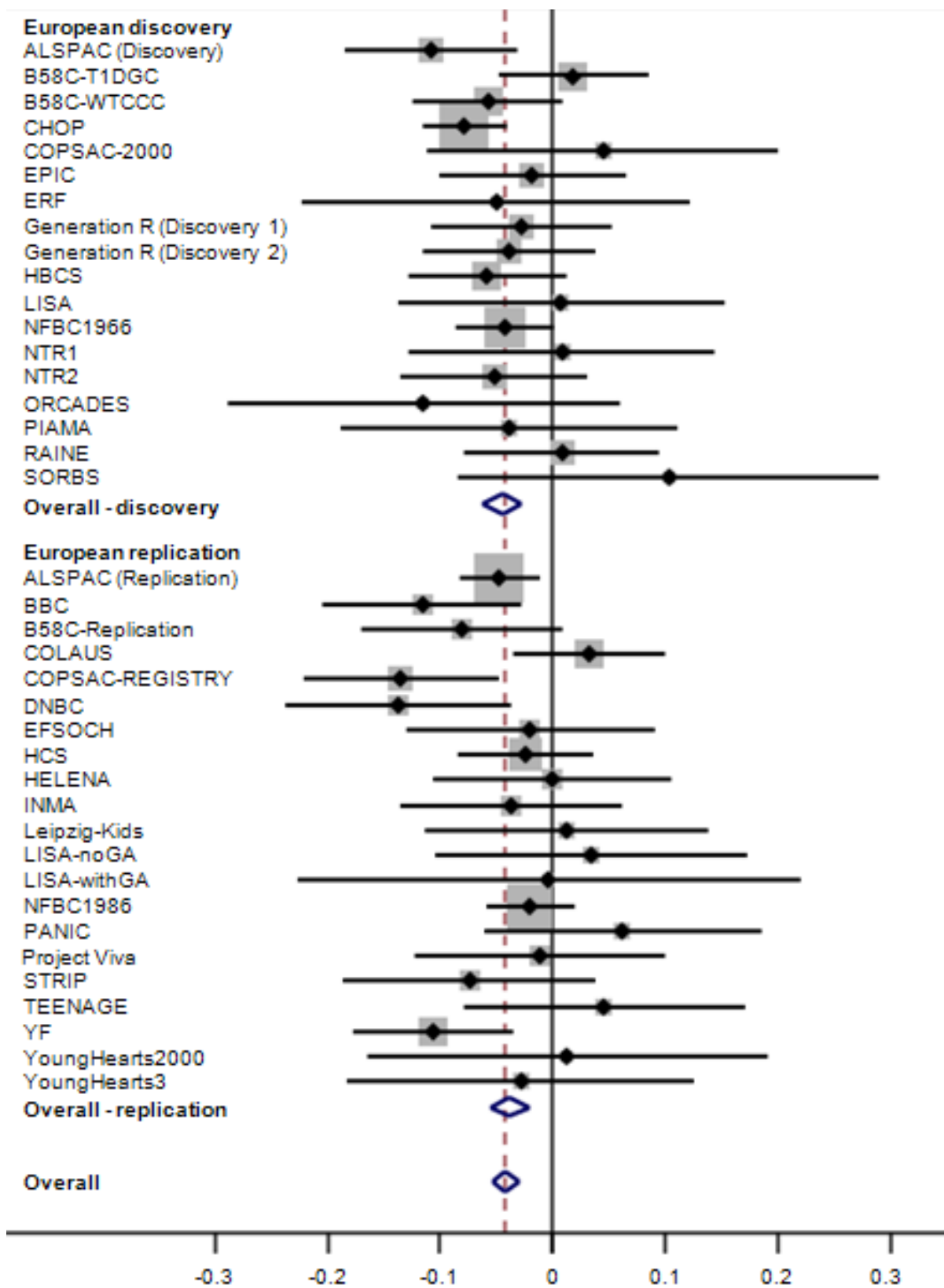
(d) *CDKAL1* (overall  $n = 68,822$ ;  $P = 1.5 \times 10^{-18}$ ; heterogeneity  $P = 0.57$ )



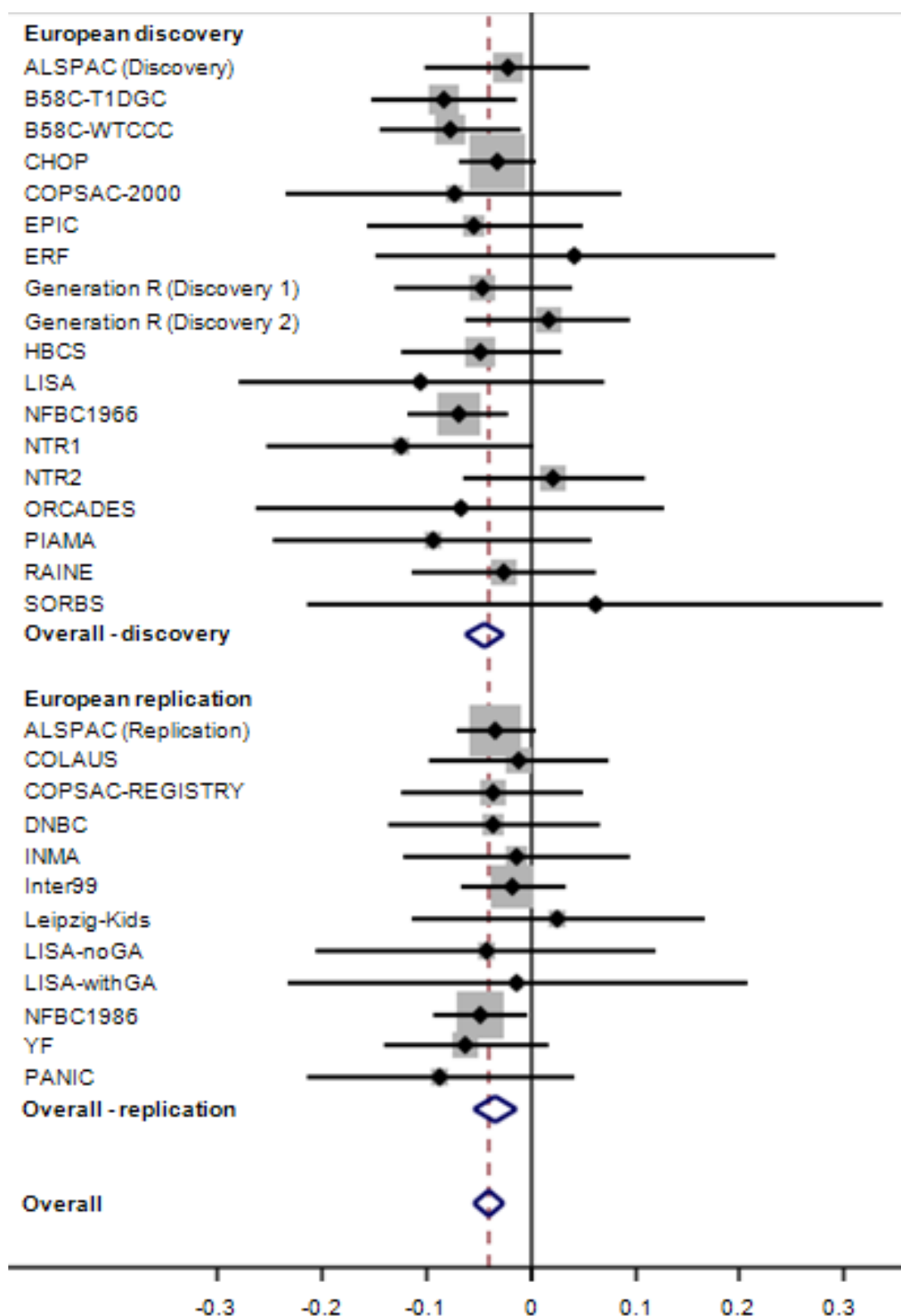
(e) 5q11.2 (overall  $n = 53,619$ ;  $P = 4.6 \times 10^{-8}$ ; heterogeneity  $P = 0.40$ )



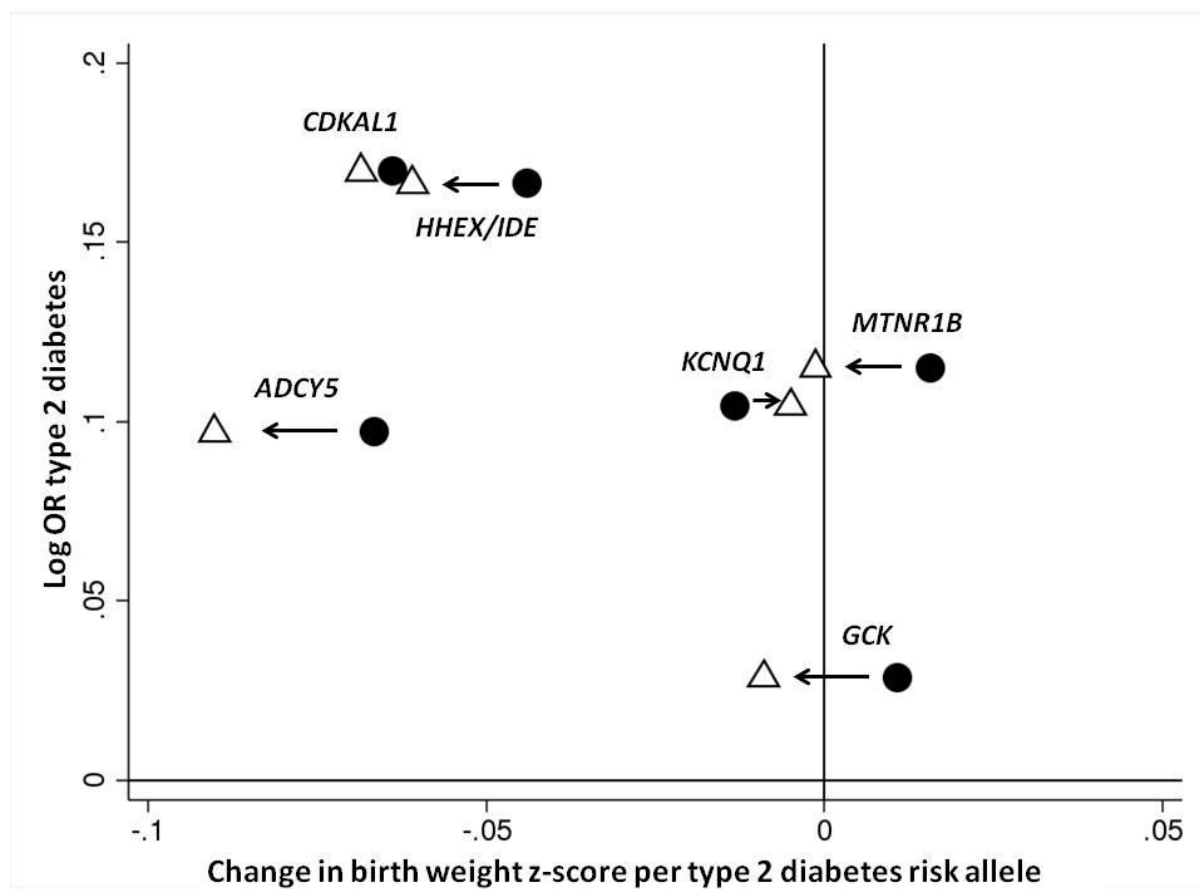
(f) *LCORL* (overall  $n = 55,877$ ;  $P = 4.6 \times 10^{-11}$ ; heterogeneity  $P = 0.16$ )



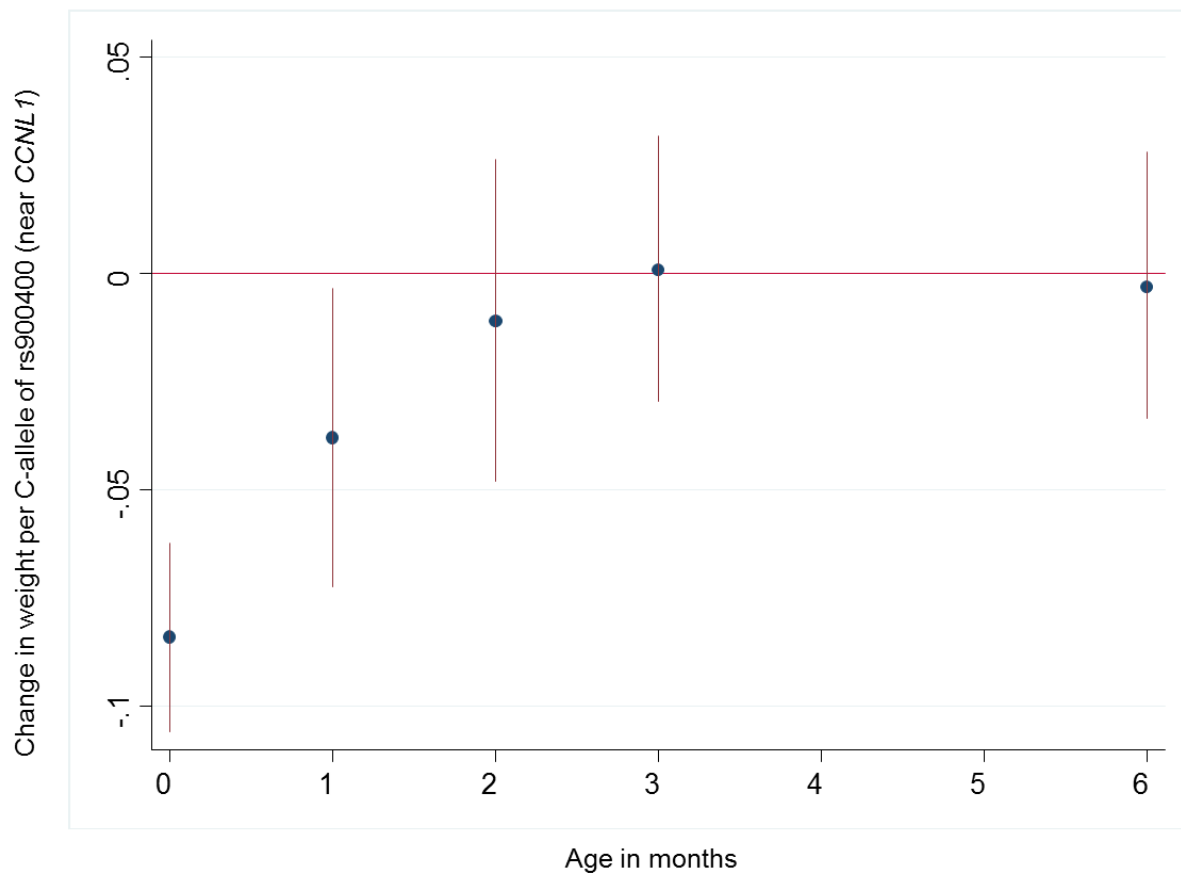
(g) *ADRB1* (overall  $n = 49,660$ ;  $P = 3.6 \times 10^{-9}$ ; heterogeneity  $P = 0.97$ )



**Supplementary Figure 5.** Plot of type 2 diabetes effect size against birth weight effect size (n=5,327 ALSPAC mother-child pairs) for loci achieving  $P < 0.01$  in the discovery meta-analysis. Circles are unadjusted for maternal genotype; triangles are adjusted for maternal genotype.

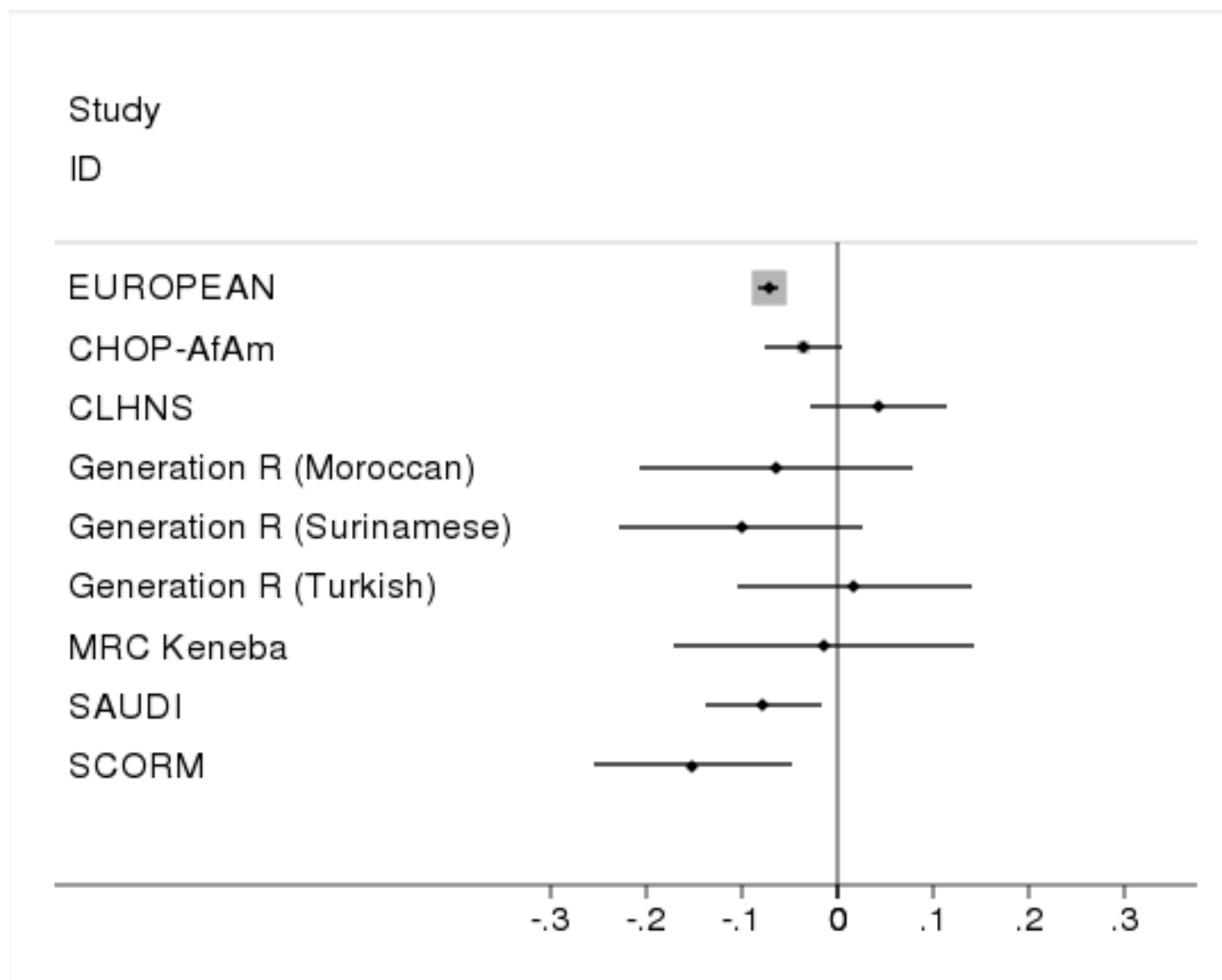


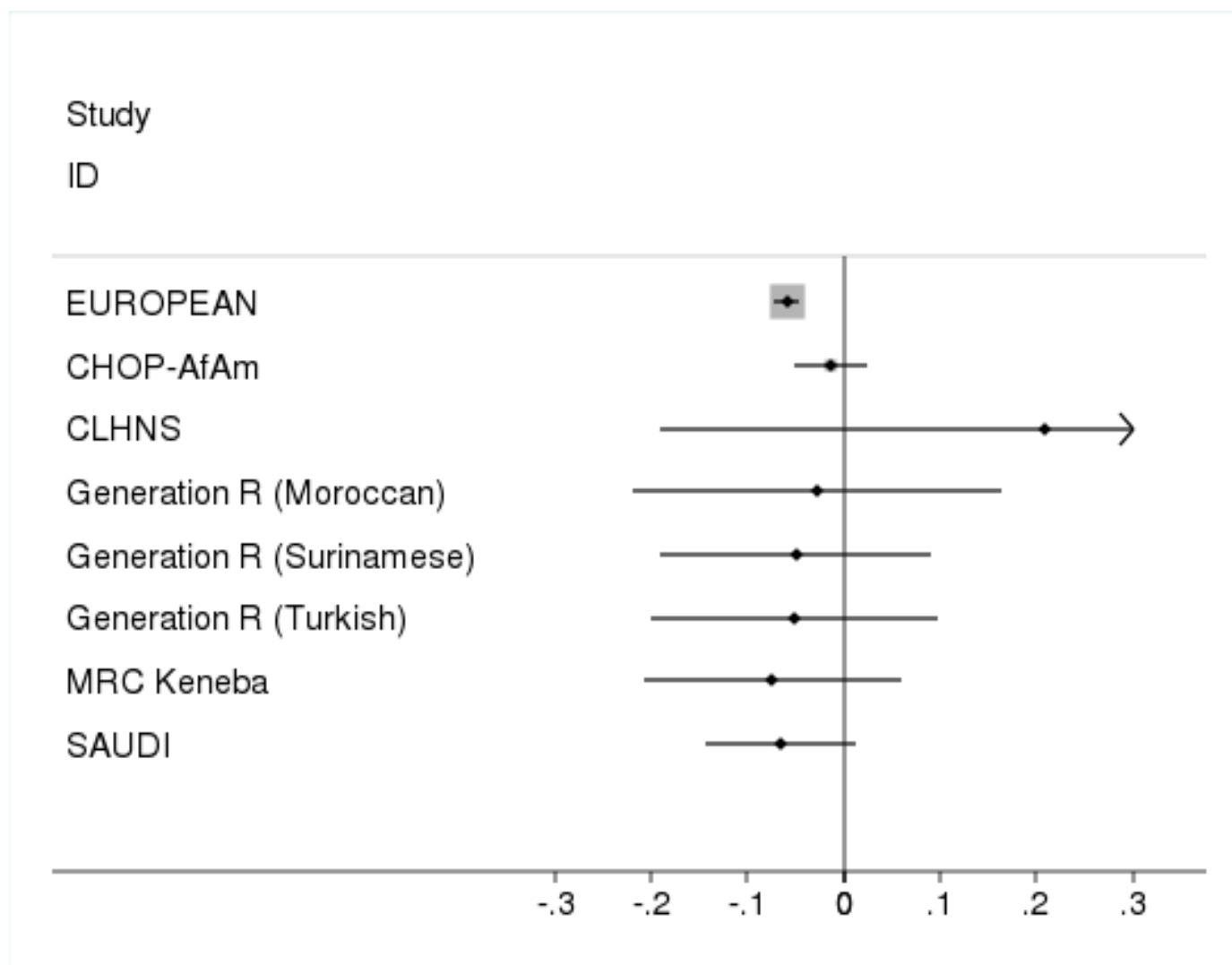
**Supplementary Figure 6.** Associations between SNP rs900400 near *CCNL1* and weight from birth to 6 months in seven studies with available postnatal data. The vertical lines show 95% confidence intervals around the effect size estimates. Total sample sizes:  $n = 15,090$  (0 months);  $n = 6,952$  (1 month);  $n = 5,720$  (2 months);  $n = 7,857$  (3 months);  $n = 7,535$  (6 months).



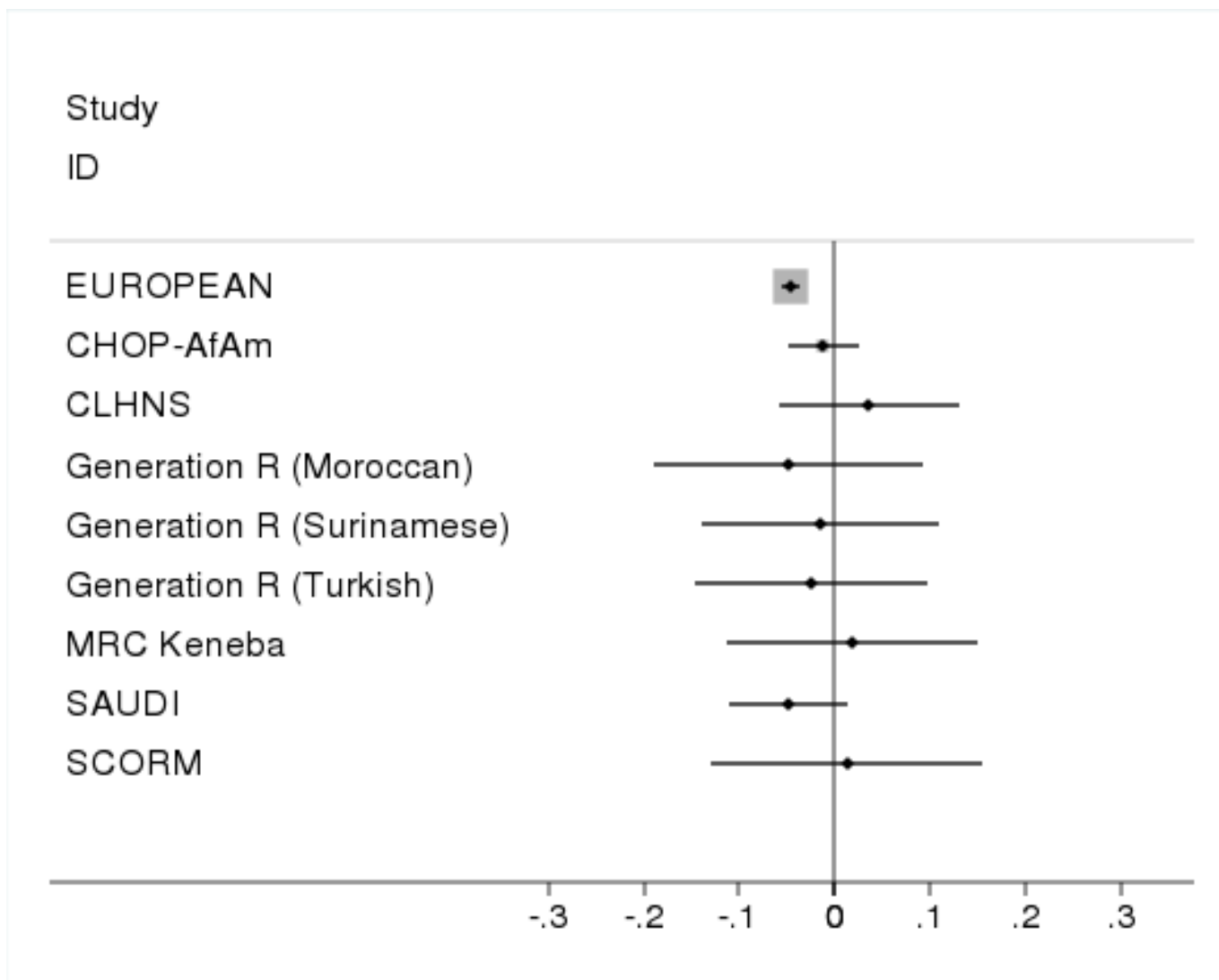
**Supplementary Figure 7.** Forest plots of the associations between birth weight and (a) *CCNL1*, (b) *ADCY5*, (c) *HMGA2*, (d) *CDKAL1*, (e) *5q11.2*, (f) *LCORL* and (g) *ADRB1* in non-Europeans. The overall European result is shown for comparison. The non-European studies are from East/Southeast Asia (Chinese [SCORM] and Filipino [CLHNS]), Africa (African-American [CHOP-AfAm], Mandinka [MRC Keneba] and Moroccan [Generation R]), Middle East (Arab [SAUDI], Turkish [Generation R]), and South America (Surinamese [Generation R]).

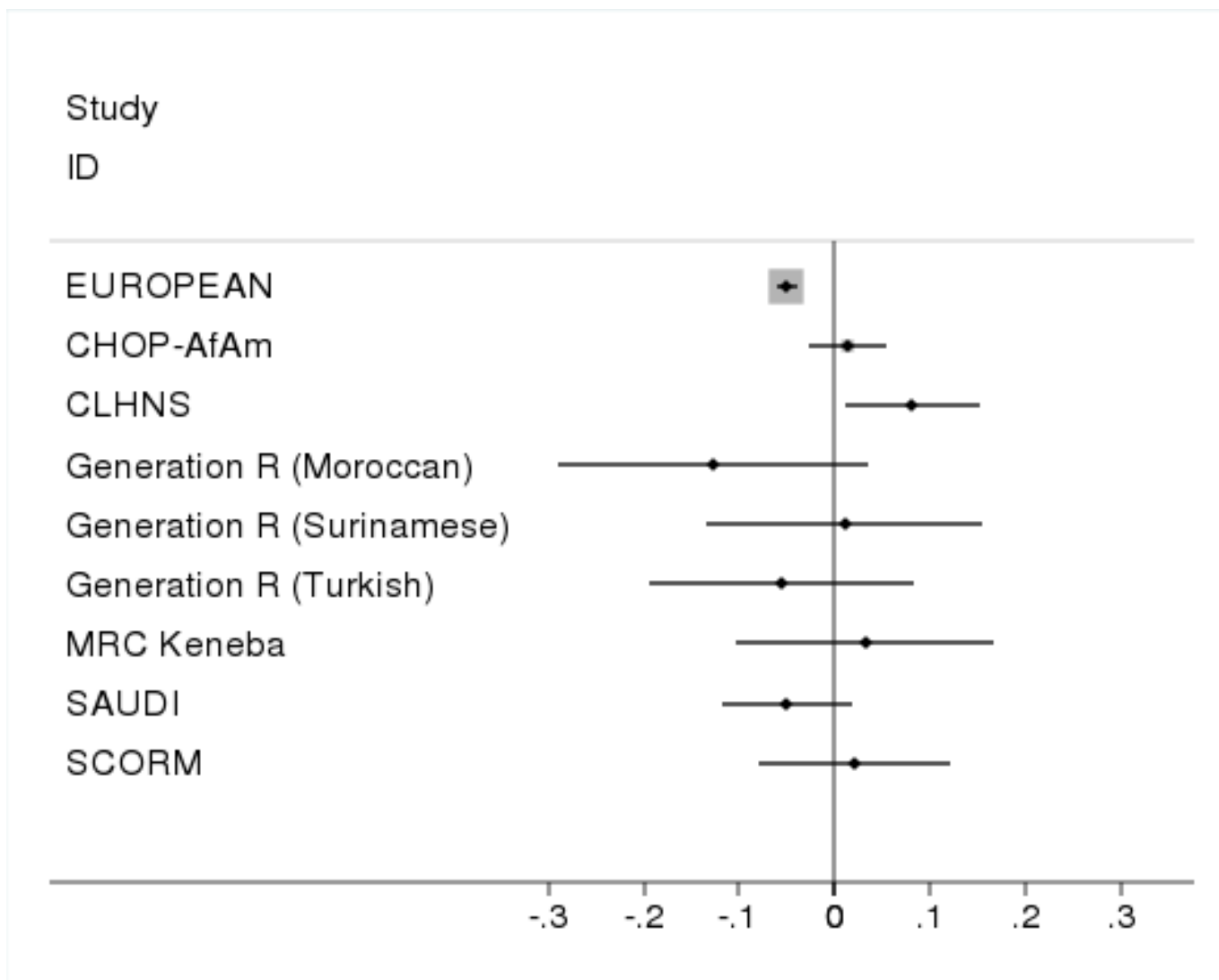
(a) *CCNL1*



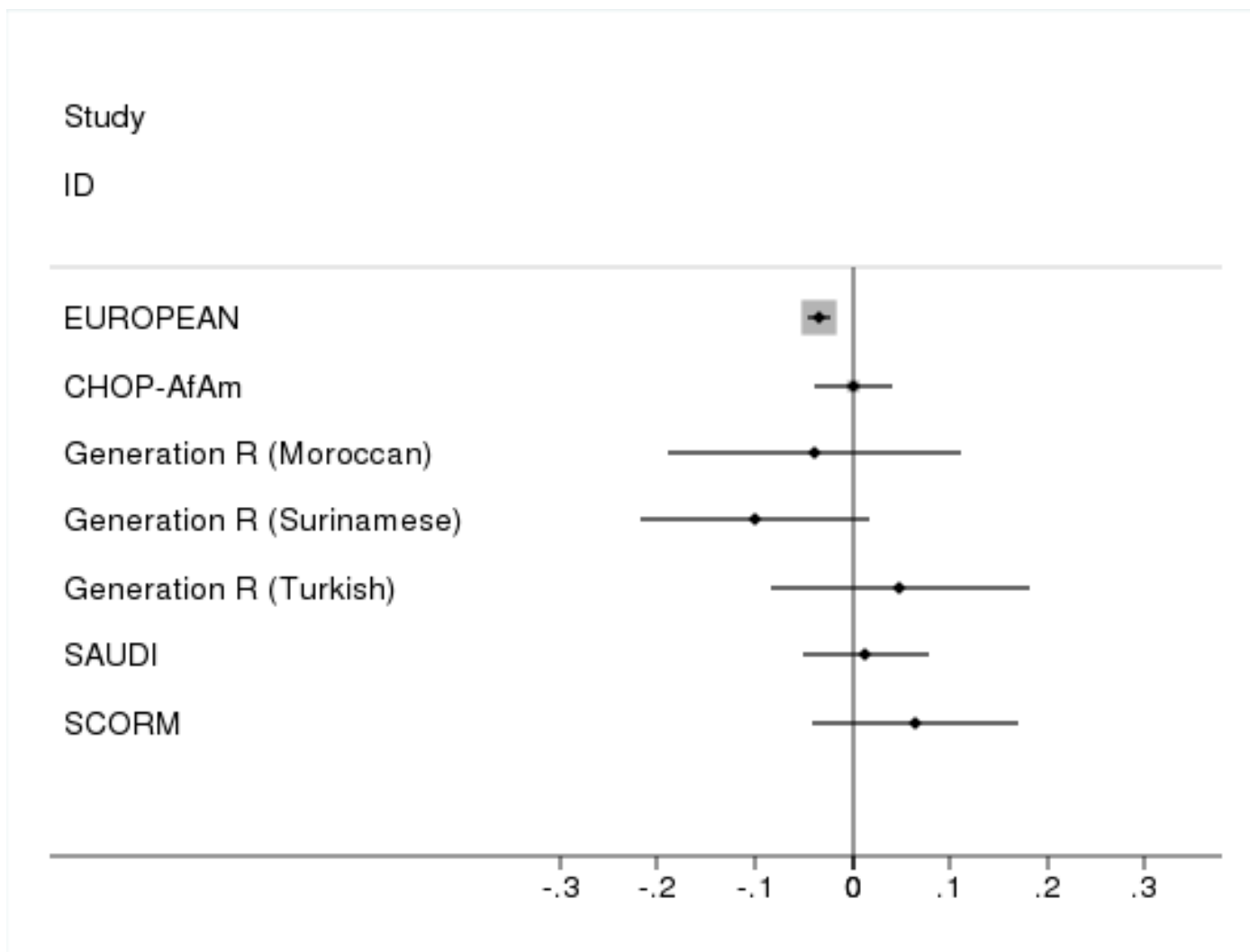
(b) *ADCY5*

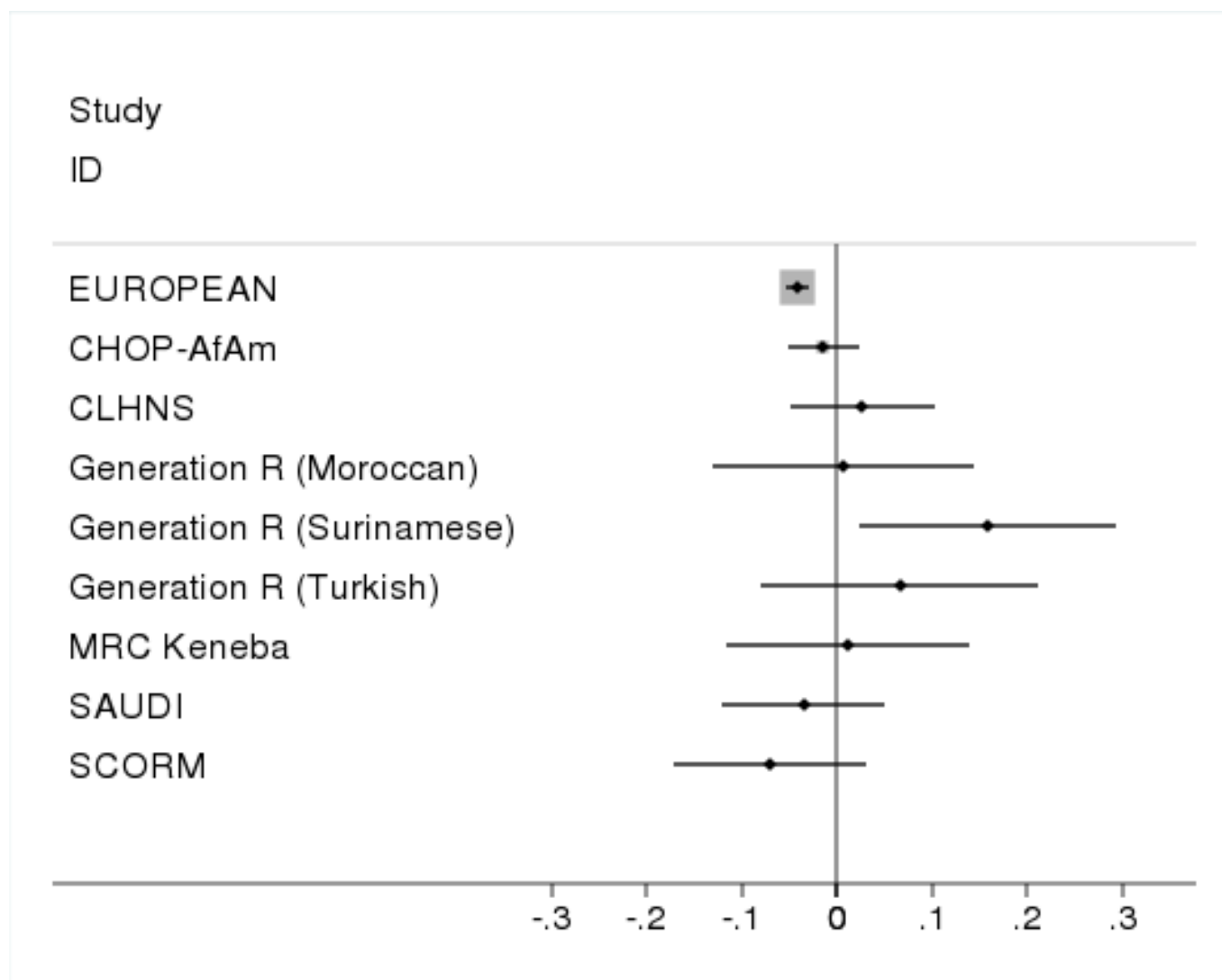


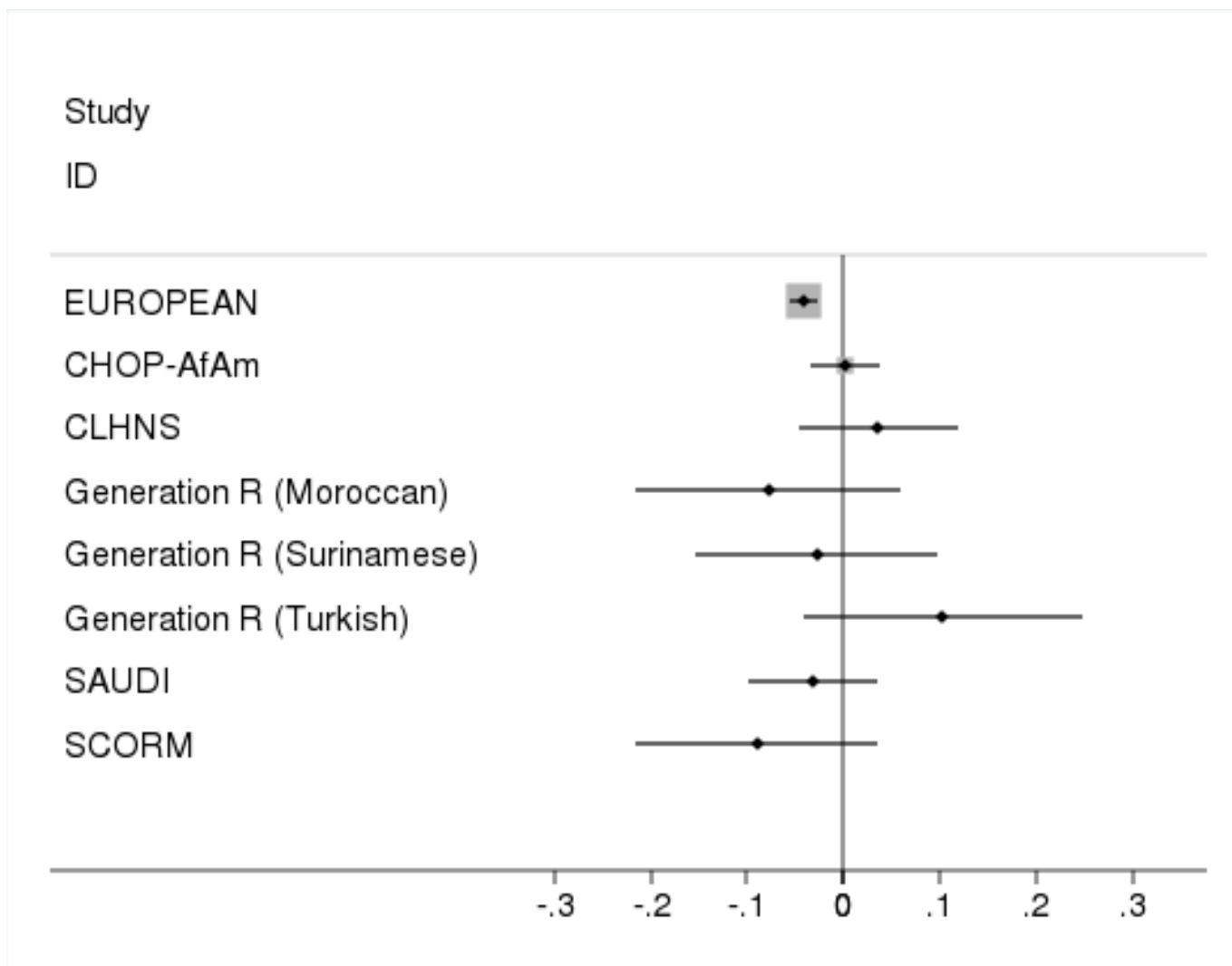
(c) *HMGA2*

(d) *CDKAL1*

(e) 5q11.2



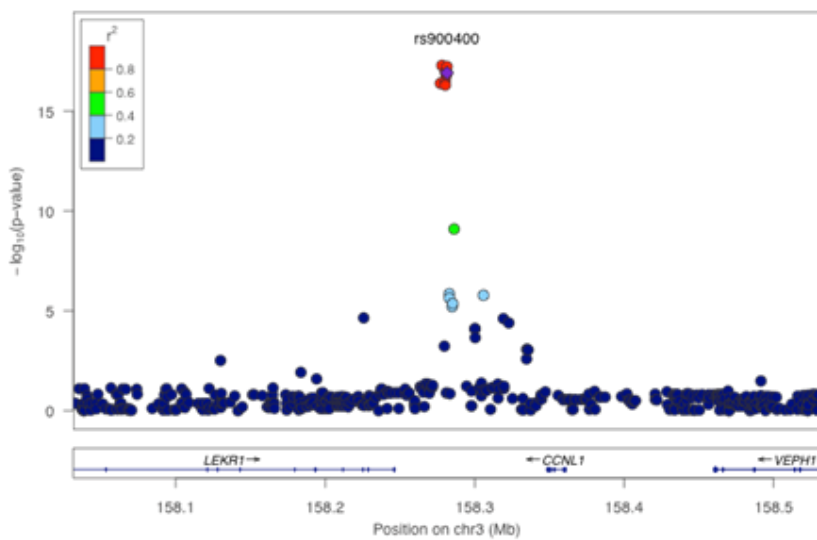
(f) *LCORL*

(g) *ADRB1*

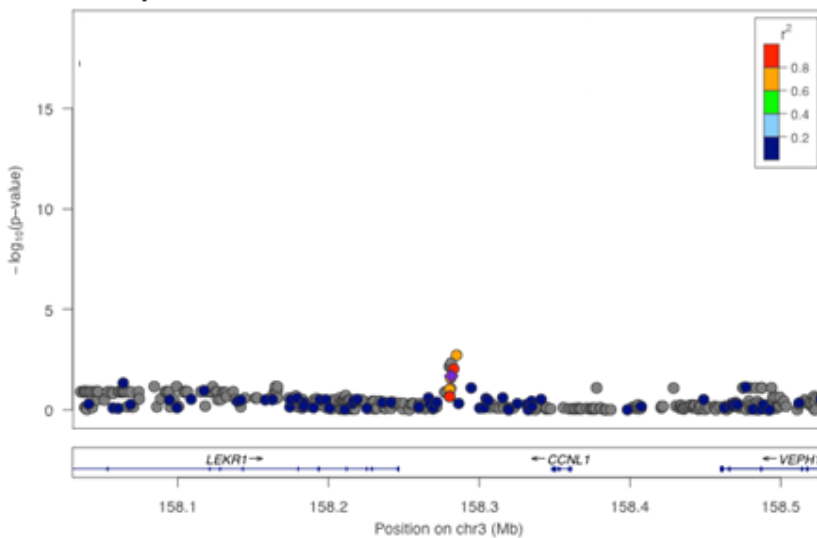
**Supplementary Figure 8.** Ethnicity-specific regional plots for (a) *CCNL1* and (b) *ADCY5* in European (n=26,813), East/Southeast Asian (n=2,135) and African American (n=6,315). Directly genotyped or imputed SNPs are plotted as a function of genomic position (NCBI Build 36). In each panel, the European discovery stage SNP taken forward for follow-up, i.e. rs900400 in *CCNL1* and rs9883204 in *ADCY5*, is represented by a purple diamond. Estimated recombination rates are plotted to reflect the local LD structure around these SNPs (according to a blue to red scale from  $r^2 = 0$  to 1, based on pairwise  $r^2$  values from HapMap CEU, JPT+CHB, and YRI, respectively).

(a) *CCNL1*

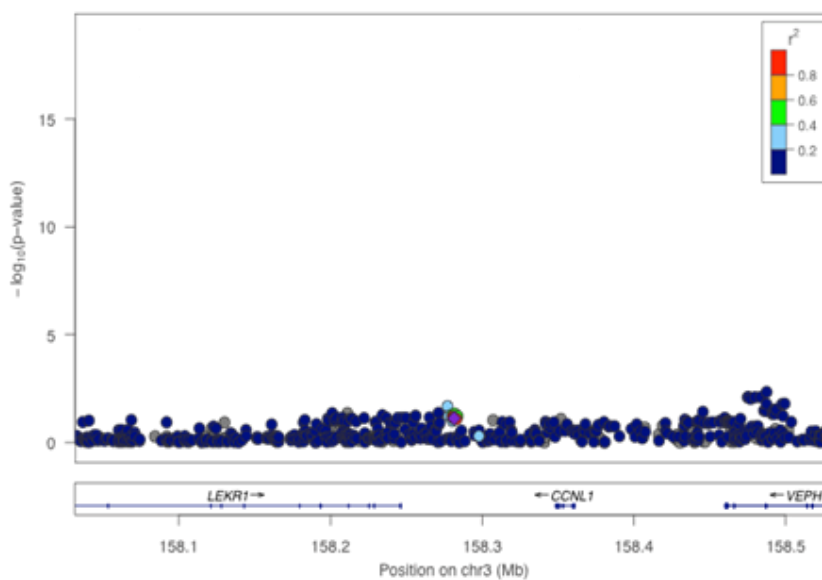
European



East/Southeast Asian

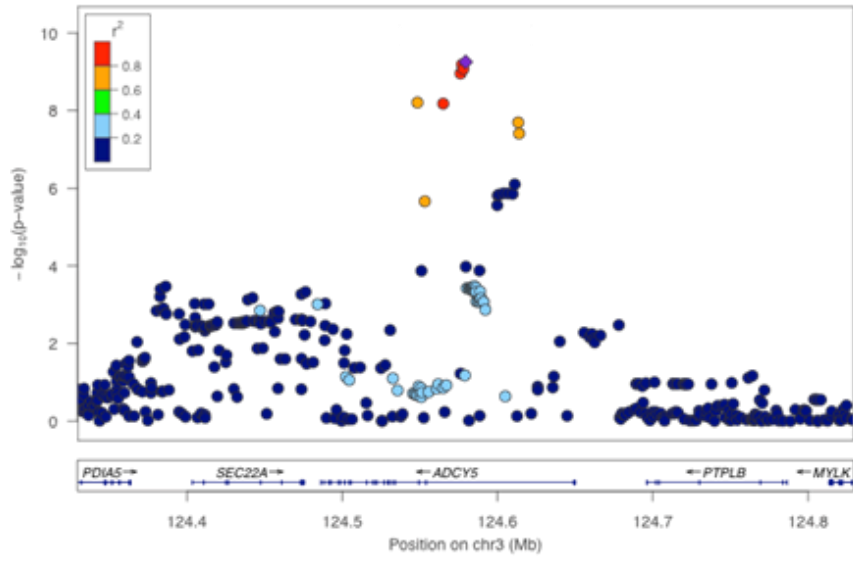


African American

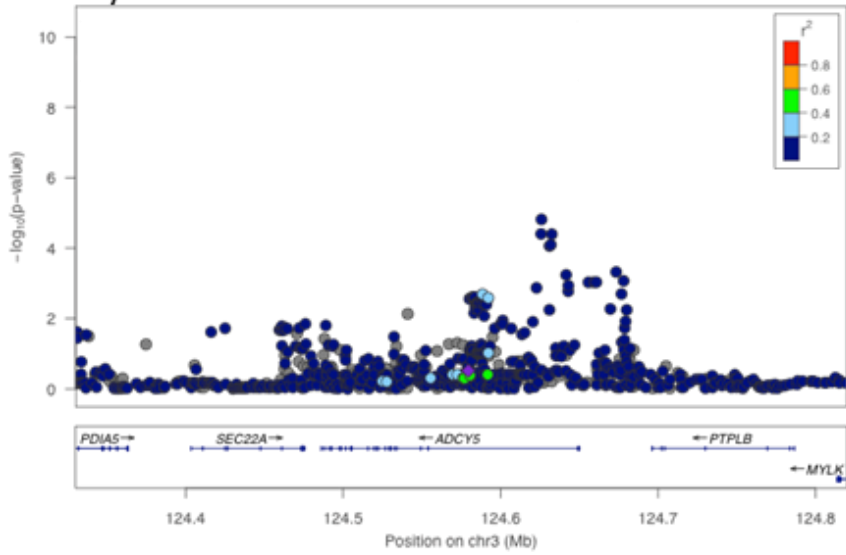


### (b) *ADCY5*

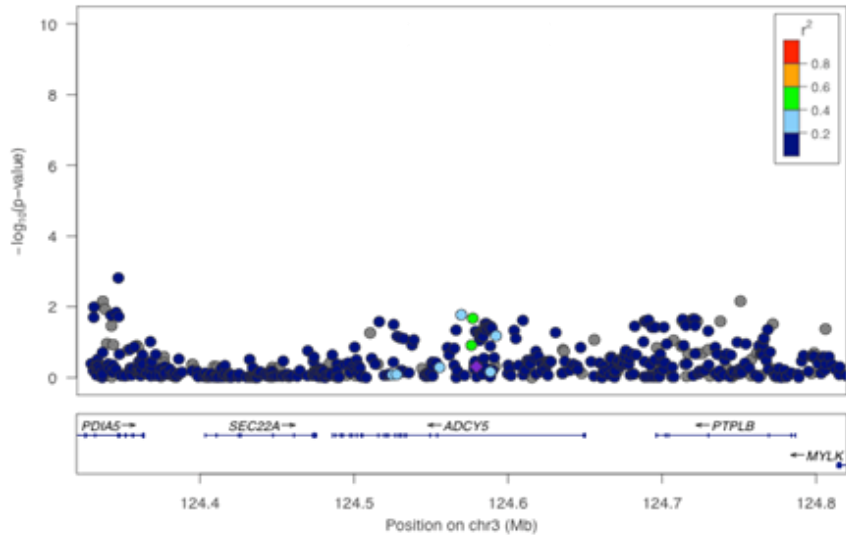
European



East/Southeast Asian

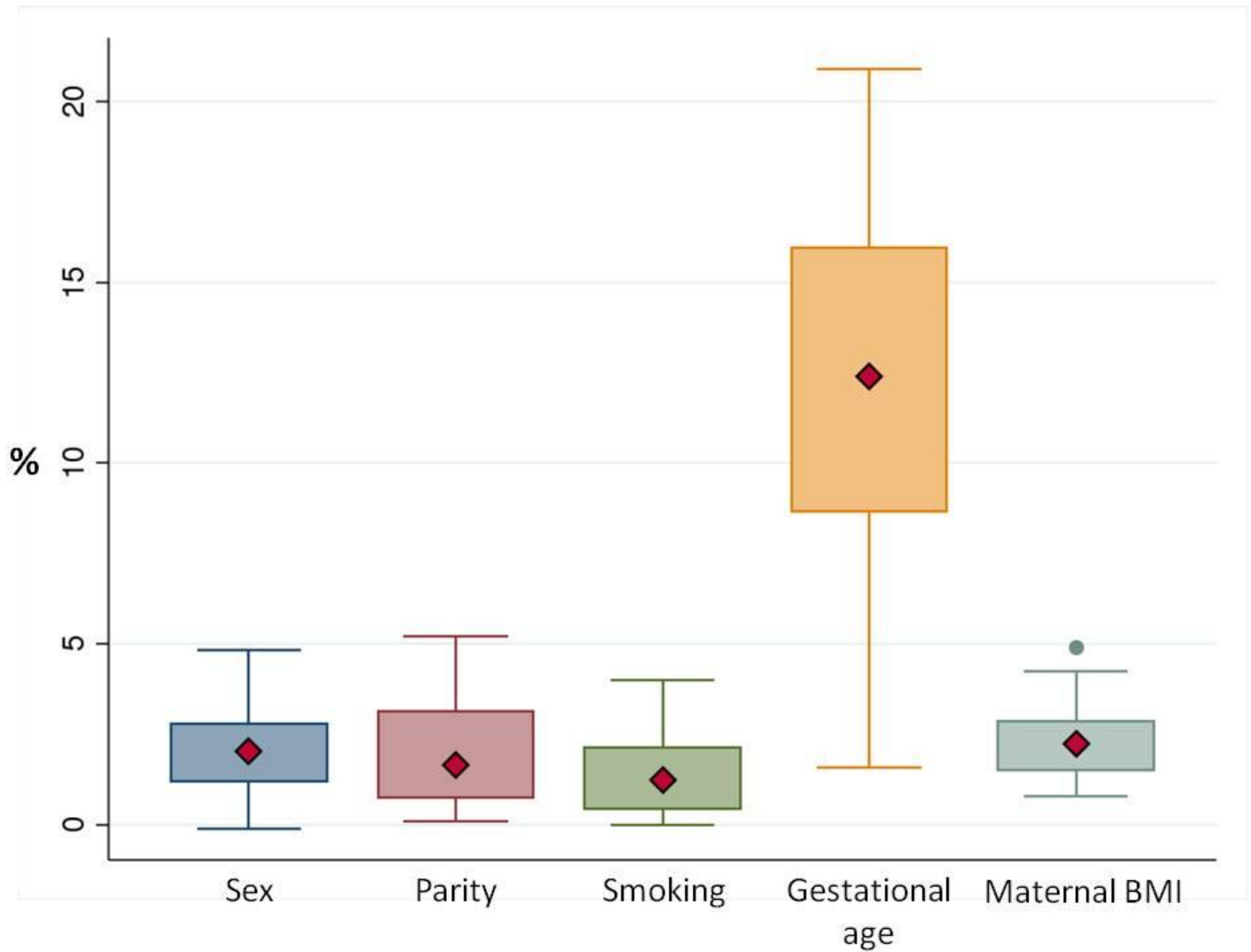


African American





**Supplementary Figure 9.** Box plot showing the percentage variance in birth weight explained by five related characteristics (x-axis) in all 43 European studies. Diamond = median; box = interquartile range; whiskers = median  $\pm$  2\*interquartile range; circle = outlier.



## SUPPLEMENTARY NOTE

### ACKNOWLEDGMENTS

The data annotation, exchange and storage were facilitated by the SIMBioMS platform (simbioms.org). PMID: 19633095.

**Personal funding for the research in this paper:** J.L.B. is supported by a Wellcome Trust fellowship grant (WT088431MA); S.D. by Medical Research Council, UK (G0600705, G0600331); R.M.F. by a Sir Henry Wellcome Postdoctoral Fellowship (Wellcome Trust grant: 085541/Z/08/Z); K.M.G. by the National Institute for Health Research; A.T.H., B.A.K. and B.M.S. are employed as core members of the Peninsula NIHR Clinical Research Facility; M.H. by Manpei Suzuki Diabetes Foundation Grant-in-Aid for the young scientists working abroad; E.H. by Career Scientist Award, Department of Health, UK; V.W.V.J. received an additional grant from the Netherlands Organization for Health Research and Development (ZonMw 90700303, 916.10159); J.P.K. is funded by a Wellcome Trust 4-year PhD studentship in molecular, genetic, and life course epidemiology (WT083431MA); V.L. and I.P. are funded in part through the European Community's Seventh Framework Programme (FP7/2007-2013), ENGAGE project, grant agreement HEALTH-F4-2007- 201413; I.N. has been awarded a PhD grant "HERAKLEITOS II" by the Greek Ministry of Education, Lifelong Learning, and Religious Affairs; U.S. by Medical Research Council studentship grant G0500539; H.R.T. additional support was provided by a grant from the Dutch Kidney Foundation (C08.2251); and K.Z. is a Sir Henry Wellcome Postdoctoral Fellow.

### Acknowledgments by study:

**The British 1958 Birth Cohort (B58C):** Analyses were funded by the UK Medical Research Council Grant (grant G0601653). 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. Replication genotyping was supported in part by MRC G0601261, Wellcome Trust 085301, 090532, 083270, Diabetes UK grant RD08/0003704. Ethical approval for the biomedical survey was given by the South-East Multi-Centre Research Ethics Committee (ref. 01/1/44) and the Joint UCL/UCLH Committees on the Ethics of Human Research (Committee A) (ref:08/H0714/40). Written informed consent for the use of information in medical studies was obtained from the participants.

**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. The UK Medical Research Council (Grant ref: 74882) the Wellcome Trust (Grant ref: 076467, WT088806) and the University of Bristol provide core support for ALSPAC. This publication is the work of the authors and Nicholas J. Timpson and Rachel M. Freathy will serve as guarantors for the contents of this paper. The GWAS genotyping of the ALSPAC children samples was supported by 23andMe. The replication genotyping of the ALSPAC children samples was supported by Diabetes UK grant RD08/0003692. Ethical approval for the study was obtained from the ALSPAC Law and Ethics Committee and the Local Research Ethics Committees.

**Berlin Birth Cohort (BBC):** The Berlin Birth Cohort study was funded by the Deutsche Forschungsgemeinschaft (DFG), Else Kröner-Fresenius Foundation, Jackstädt-Foundation and a research grant of the University of Potsdam, Germany. Details of the study are provided in: *Pharmacogenet Genomics*. 2009;19(9):710-8.; *Circulation*. 2006 Oct 17;114(16):1687-92 and *Lancet*. 2000 Apr 8;355(9211):1241-2. We deeply acknowledge the contribution of the participating families. Replication genotyping was supported in part by MRC G0601261, Wellcome Trust 085301, 090532, 083270, Diabetes UK grant RD08/0003704.

**Children's Hospital Of Philadelphia (CHOP):** The authors thank the network of primary care clinicians and the patients and families for their contribution to this project and to clinical research facilitated by the Pediatric Research Consortium (PeRC) at The Children's Hospital of Philadelphia. R. Chiavacci, E. Dabaghyan, A. (Hope) Thomas, K. Harden, A. Hill, C. Johnson-Honesty, C. Drummond, S. Harrison, F. Salley, C. Gibbons, K. Lilliston, C. Kim, E. Frackelton, F. Mentch, G. Otieno, K. Thomas, C. Hou, K. Thomas and M.L. Garris provided expert assistance with genotyping and/or data collection and management. The authors would also like to thank S. Kristinsson, L.A. Hermannsson and A. Krisbjörnsson of Raförninn ehf for extensive software design and contributions. 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.

**Cebu Longitudinal Health and Nutrition Survey (CLHNS):** We thank the Office of Population Studies Foundation research and data collection teams and the study participants who generously provided their time for this study. This work was supported by National Institutes of Health grants DK078150, TW05596, HL085144, HD054501, RR20649, ES10126, and DK56350. Informed consent was obtained from all CLHNS subjects, and the University of North Carolina Institutional Review Board for the Protection of Human Subjects approved the study protocol.

**CoLaus (Cohorte Lausannoise) study:** The CoLaus study received financial contributions from GlaxoSmithKline, the Faculty of Biology and Medicine of Lausanne, and the Swiss National Science Foundation (33CSCO-122661). The authors thank Gerard Waeber, Vincent Mooser and Dawn Waterworth, Co-PIs of the CoLaus study. Special thanks to Murielle Bochud, Yolande Barreau, Mathieu Firmann, Vladimir Mayor, Anne-Lise Bastian, Binasa Ramic, Martine Moranville, Martine Baumer, Marcy Sargette, Jeanne Ecoffey and Sylvie Mermoud for data collection. The Study was approved by the Institutional Ethic's Committee of the University of Lausanne

**The Copenhagen Prospective 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 listed on [www.copsac.com](http://www.copsac.com). The Lundbeck Foundation; The Danish Strategic Research Council; the Pharmacy Foundation of 1991; Augustinus Foundation; the Danish Medical Research Council and The Danish Pediatric Asthma Centre provided the core support for COPSAC research center. No pharmaceutical company was involved in the study. The funding agencies did not have any role in design and conduct of the study; collection, management, and interpretation of the data; or preparation, review, or approval of the manuscript. The COPSAC cohorts were approved by the Ethics Committee for Copenhagen (KF 01-289/96 and H-B-2008-103) and The Danish Data Protection Agency (2008-41-1754 and 2008-41-2622).

**Danish National Birth Cohort (DNBC):** The Danish National Birth Cohort is a result of major grants from the Danish National Research Foundation, the Danish Pharmacists' Fund, the Egmont Foundation, the March of Dimes Birth Defects Foundation, the Augustinus Foundation, and the Health Fund of the Danish Health Insurance Societies. The generation of GWAS genotype data for the Danish National Birth Cohort samples was carried out within the Gene Environment Association Studies (GENEVA) consortium with funding provided through the National Institutes of Health's Genes, Environment, and Health Initiative (U01HG004423; U01HG004446; U01HG004438). The study protocol was approved by the Danish Scientific Ethical Committee and the Danish Data Protection Agency.

**Exeter Family Study Of Childhood Health (EFSOCH):** The EFSOCH study was supported by South West NHS Research and Development, Exeter NHS Research and Development, the Darlington Trust, and the Peninsula NIHR Clinical Research Facility at the University of Exeter. We are extremely grateful to the EFSOCH study participants and the EFSOCH study team. The opinions given in this paper do not necessarily represent those of NIHR, the NHS or the Department of

Health. Genotyping of EFSOCH DNA samples was supported by Diabetes UK grant RD08/0003692. The local research ethics committees approved the study, and all adult participants gave informed written consent.

**The European Prospective Investigation of Cancer (EPIC/EPIC-Norfolk):** The EPIC Norfolk Study is funded by Cancer Research United Kingdom and the Medical Research Council. All participants signed an informed written consent. We thank all staff from the MRC Epidemiology Unit Functional Group Team. Ethical approval for the study was granted by the Norwich Local Research Ethics Committee. All subjects gave written informed consent.

**The Erasmus Rucphen Family (ERF):** The study was supported by grants from The Netherlands Organisation for Scientific Research (including NWO middel #40-00506-98-11025), Erasmus MC, the Centre for Medical Systems Biology (CMSB) and EUROSPAN (European Special Populations Research Network) FP6 STRP grant number 018947 (LSHG-CT-2006-018947). We are grateful to all general practitioners for their contributions, to Petra Veraart for her help in genealogy, Jeannette Vergeer for the supervision of the laboratory work and Peter Snijders for his help in data collection. All participants of the ERF cohort gave informed consent and the study was approved by the Medical Ethics Committee of Erasmus Medical Center in Rotterdam.

**The Generation R Study:** 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. We also acknowledge the contribution of Cornelia van Duijn for her intellectual input in this project. 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. The study has been approved by the Medical Ethics Committee of the Erasmus Medical Center, Rotterdam. Written informed consent was obtained from all participants or their parent(s).

**Genetics of Diabetes Audit and Research Tayside Study (GoDARTS):** We are grateful to all the participants who took part in this study, to the general practitioners, to the Scottish School of

Primary Care for their help in recruiting the participants, and to the whole team, which includes interviewers, computer and laboratory technicians, clerical workers, research scientists, volunteers, managers, receptionists, and nurses. The Wellcome Trust provides support for Wellcome Trust United Kingdom Type 2 Diabetes Case Control Collection (GoDARTS) and informatics support is provided by the Chief Scientist Office. The study was approved by the Tayside Regional Ethics Committee and informed consent was obtained from all subjects.

**Helsinki Birth Cohort Study (HBCS/HBCS 1934-44):** 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 Public Health Institute, Helsinki, Finland. The study design was approved by the local ethics committee.

**The Hertfordshire Cohort Study (HCS):** This study was supported by the Medical Research Council UK and the University of Southampton UK. The study has ethical approval from the Hertfordshire and Bedfordshire Local Research Ethics Committee and all participants have given written informed consent

**Healthy Lifestyle in Europe by Nutrition in Adolescence (HELENA):** The HELENA received funding from the European Union's Sixth RTD Framework Programme (Contract FOOD-CT-2005-007034). The protocol was approved by the appropriate investigational review board for each investigating centre. Written informed consent was obtained from each adolescent and both of his or her parents or legal representatives. Participation in the study was voluntary.

**The INMA - Infancia y Medio Ambiente (Environment and Childhood) Project:** This study was funded by grants from 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, Conselleria de Sanitat Generalitat Valenciana, and Fundación Roger Torné. The authors are grateful to Silvia Fochs, Anna Sánchez, Maribel López, Nuria Pey, Muriel Ferrer, Amparo Quiles, Sandra Pérez, Gemma León, Elena Romero, 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](http://www.proyectoinma.org/presentacion-inma/listado-investigadores/en_listado-investigadores.html). Informed consent was obtained from all participants and the study was approved by the Hospital Ethics Committees in each participating region.

**Inter99:** The study was supported by grants from the Lundbeck Foundation Centre of Applied Medical Genomics for Personalized Disease Prediction, Prevention and Care (LuCAMP), the

Danish Strategic Research Council, Hagedorn Research Institute, the Novo Nordisk Foundation Center for Basic Metabolic Research, the PhD School of Molecular Metabolism University of Southern Denmark and the Copenhagen Graduate School of Health Sciences. The Inter99 was initiated by T. Jørgensen (principal investigator), K. Borch-Johnsen (co-principal investigator), H. Ibsen and T. F. Thomsen. The Steering Committee comprises the former two and C. Pisinger. All Inter99 participants gave written informed consent and the protocol was in accordance with the Helsinki Declaration, approved by Copenhagen County ethic committee and registered with ClinicalTrials.gov (NCT00289237).

**Leipzig-Childhood-IFB:** This work was supported by grants from Integrated Research and Treatment Centre (IFB) Adiposity Diseases, from the German Research Foundation for the Clinical Research Group “Atherobesity” KFO 152 (KO3512/1 to AK), and by the European Commission (Beta-JUDO) and by EFRE (LIFE Child Obesity). We are grateful to all the patients and families for contributing to the study. We highly appreciate the support of the Obesity Team and Auxo Team of the Leipzig University Children’s Hospital for management of the patients and to the Pediatric Research Center Lab Team for support with DNA banking.

**Lifestyle – Immune System – Allergy plus environment and genetics study (LISApplus) Munich & German infant study on the influence of nutrition intervention (GINIplus) Munich:** We wish to acknowledge the LISApplus & GINIplus Study Groups: Helmholtz Zentrum München, German Research Center for Environmental Health, Institute of Epidemiology, Munich (Heinrich J, Wichmann HE, Sausenthaler S, Chen CM, 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). Department of Pediatrics, Municipal Hospital “St. Georg”, Leipzig (Borte M, Diez U), Pediatric Practice, Bad Honnef (Schaaf B); Helmholtz Centre for Environmental Research – UFZ, Department of Environmental Immunology/Core Facility Studies, Leipzig (Lehmann I, Bauer M, Röder S); University of Leipzig, Institute of Hygiene and Environmental Medicine, Leipzig (Herbarth O, Dick C, Magnus J); Technical University Munich, Department of Pediatrics, Munich (Bauer CP, Hoffmann U); ZAUM – Center for Allergy and Environment, Technical University, Munich (Behrendt H).

Both studies were partly funded by the Munich Center of Health Sciences (MC Health) as part of the Ludwig-Maximilians University Munich (LMU) innovative. The regional ethics committees approved both studies and parents gave written informed consent.

**MRC Keneba core-villages cohort:** We thank the study participants, lab and field workers at MRC Keneba, and Dr Pura Rayco-Solon for sample collection and phenotyping. The Medical Research Council supported this work as part of funding to the MRC International Nutrition

Group (MC-A760-5QX00). Ethics approval was granted by the joint Gambia Government/MRC Ethics Committee and all subjects and/or legal guardians provided written, informed consent.

**Northern Finland Birth Cohort 1966/1986 (NFBC1966/NFBC1986):** NFBC1966 and 1986 received financial support from the Academy of Finland (project grants 104781, 120315, 129269, 1114194, 139900/24300796, 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, G0600331, PrevMetSyn/SALVE, PS0476) and the Wellcome Trust (project grant GR069224, WT089549), UK.

Replication genotyping was supported in part by MRC grant G0601261, Wellcome Trust grants 085301, 090532 and 083270, and Diabetes UK grants RD08/0003704 and BDA 08/0003775.

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 (emerita) 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 Academician of Science Leena Peltonen.

**Netherland Twins Register studies (NTR1 & NTR2):** Funding was obtained from the Netherlands Organization for Scientific Research (NWO: MagW/ZonMW grants 904-61-090, 985-10-002, 904-61-193, 480-04-004, 400-05-717, Addiction-31160008 Middelgroot-911-09-032, Spinozapremie 56-464-14192), Center for Medical Systems Biology (CMSB, NWO Genomics), NBIC/BioAssist/RK(2008.024), Biobanking and Biomolecular Resources Research Infrastructure (BBMRI –NL), the VU University's Institute for Health and Care Research (EMGO+ ) and Neuroscience Campus Amsterdam (NCA), the European Science Foundation (ESF, EU/QLRT-2001-01254), the European Community's Seventh Framework Program (FP7/2007-2013), ENGAGE (HEALTH-F4-2007-201413); the European Research Council (ERC Advanced, 230374), Rutgers University Cell and DNA Repository (NIMH U24 MH068457-06), and the National Institutes of Health (NIH, R01D0042157-01A). Part of the genotyping and analyses were funded by the Genetic Association Information Network (GAIN) of the Foundation for the US National Institutes of Health, and by grants from GAIN and the NIMH (MH081802).

**The Orkney Complex Disease Study (ORCADES):** ORCADES was supported by the Chief Scientist Office of the Scottish Government, the Royal Society, the MRC Human Genetics Unit, Arthritis Research UK and the European Union framework program 6 EUROSPAN project (contract no. LSHG-CT-2006-018947). DNA extractions were performed at the Wellcome Trust Clinical Research Facility in Edinburgh. We would like to acknowledge the invaluable contributions of



Lorraine Anderson and the research nurses in Orkney, the administrative team in Edinburgh and the people of Orkney.

**The Physical Activity and Nutrition in Children (PANIC) Study:** The PANIC Study has been financially supported by grants from the Ministry of Social Affairs and Health of Finland, the Ministry of Education and Culture of Finland, the Finnish Innovation Fund Sitra, the Social Insurance Institution of Finland, the Finnish Cultural Foundation, the Juho Vainio Foundation, the Foundation for Paediatric Research, the Paavo Nurmi Foundation and the Kuopio University Hospital (EVO-funding number 5031343). The PANIC Study protocol was approved by the Research Ethics Committee of the Hospital District of Northern Savo in 2006. Both children and their parents gave their written informed consent.

**Prevention and Incidence of Asthma and Mite Allergy (PIAMA) Study:** The PIAMA study is supported by the Dutch Asthma Foundation (grant 3.4.01.26, 3.2.06.022, 3.4.09.081 and 3.2.10.085CO), the ZonMw (a Dutch organization for health research and development; grant 912-03-031), and the ministry of the environment. Genome-wide genotyping was funded by the European Commission as part of GABRIEL (A multidisciplinary study to identify the genetic and environmental causes of asthma in the European Community); contract number 018996 under the Integrated Program LSH-2004-1.2.5-1 Post genomic approaches to understand the molecular basis of asthma aiming at a preventive or therapeutic control. The Medical Ethical Committees of the participating institutes approved the study and written parental consent was obtained from all individuals.

**Project Viva:** The authors thank the study participants and their families. Project Viva is funded by the National Institutes of Health (NIH), the March of Dimes Foundation, and the U.S. Centers for Disease Control and Prevention. Genotyping was supported by NIH Grant (R01DK075787) and March of Dimes (6-FY09-507) awarded to J.N.H. The Project Viva study was conducted with approval from the local institutional review board, and informed consent was obtained from parents/guardians of all study participants.

**The Raine 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). The study was conducted with appropriate institutional ethics approval, and

written informed consent was obtained from mothers at all follow-ups and participants at the year 17 follow-up.

**Saudi Newborn Cohort:** King Faisal Specialist Hospital & Research Centre, Riyadh, KSA; National Laboratory for Newborn Screening, Riyadh KSA. Consent was waived by KFSHRC IRB based on use of existing bloodspots from Newborn screening and anonymity.

**The Singapore Cohort Study Of the Risk Factors for Myopia (SCORM) study:** Funded by the Biomedical Research Council, Singapore BMRC 06/1/21/19/466. The study was approved by the National University of Singapore and Singapore Eye Research Institute Institutional Review Boards.

**The Sorbs Study (SORBS):** This work was supported by grants from the Interdisciplinary Centre for Clinical Research at the University of Leipzig (B27 to AT, MS) from the German Diabetes Association (to AT), a Travel Grant from BIF (to AT) and by the DHFD, Diabetes Hilfs- und Forschungsfonds Deutschland (MS). We thank all those who participated in the study. Sincere thanks are given to Peter Kovacs who was significantly involved in the design and performing of the Sorbs study. We also thank Knut Krohn (Microarray Core Facility of the Interdisciplinary Centre for Clinical Research, University of Leipzig) for the genotyping support.

**Special Turku Coronary Risk Factor Intervention Project (STRIP):** This work was supported by the Finnish Ministry of Education and Culture; Finnish Cultural Foundation; Juho Vainio Foundation; Finnish Cardiac Research Foundation; Academy of Finland (grants 206374 and 251360); Sigrid Juselius Foundation; Special Governmental Grants for Health Sciences Research, Turku University Hospital; Yrjö Jahnsson Foundation; C.G. Sundell Foundation; Foundation for Pediatric Research; and Turku University Foundation. The Joint Commission on Ethics of the Turku University and the Turku University Central Hospital approved the STRIP study. Informed consent was obtained from the parents of the children at the beginning of the trial.

**Southampton Women's Survey (SWS):** Funding for the components of the Southampton Women's Survey contributing to this research came from the Medical Research Council, the University of Southampton, and the Dunhill Medical Trust. KMG is supported by the National Institute for Health Research through the NIHR Southampton Biomedical Research Centre. We thank the general practitioners and midwives in Southampton for their support. We are grateful to the research nurses and other staff of the Southampton Women's Survey for all their work in recruiting and interviewing the participants, and processing the data and samples. We also thank the women of Southampton and their children who gave their time to take part in the study.

**TEENs of Attica: Genes and Environment (TEENAGE) study:** The authors are grateful to all TEENAGE study participants and their families; and to the research staff who have contributed to the recruitment and data collection. This research has been co-financed by the European Union (European Social Fund – ESF) and Greek national funds through the Operational Program

"Education and Lifelong Learning" of the National Strategic Reference Framework (NSRF) - Research Funding Program: Heracleitus II. Investing in knowledge society through the European Social Fund. Replication genotyping was supported in part by MRC G0601261, Wellcome Trust 085301, 090532, 083270, Diabetes UK grant RD08/0003704. TEENAGE research study design was approved by the Institutional Review Board of Harokopio University and the Greek Ministry of Education.

**Young Finns (YF) Study:** 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 and 9N035 for TeLeht), Juho Vainio Foundation, Paavo Nurmi Foundation, Finnish Foundation of Cardiovascular Research and Finnish Cultural Foundation, Tampere Tuberculosis Foundation and Emil Aaltonen Foundation (T.L). The expert technical assistance in the statistical analyses by Irina Lisinen is gratefully acknowledged. The study design was approved by the local ethics committee.

**The Northern Ireland Young Hearts Project (YH3, YH2000):** 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. Ethical approval was obtained from the Research Ethics Committee of the Queen's University of Belfast, and written informed consent for participation was obtained from all participants, and from each participant's parent or guardian.

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## SUPPLEMENTARY NOTE

### Early Growth Genetics Consortium (EGG) Membership and Affiliations

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