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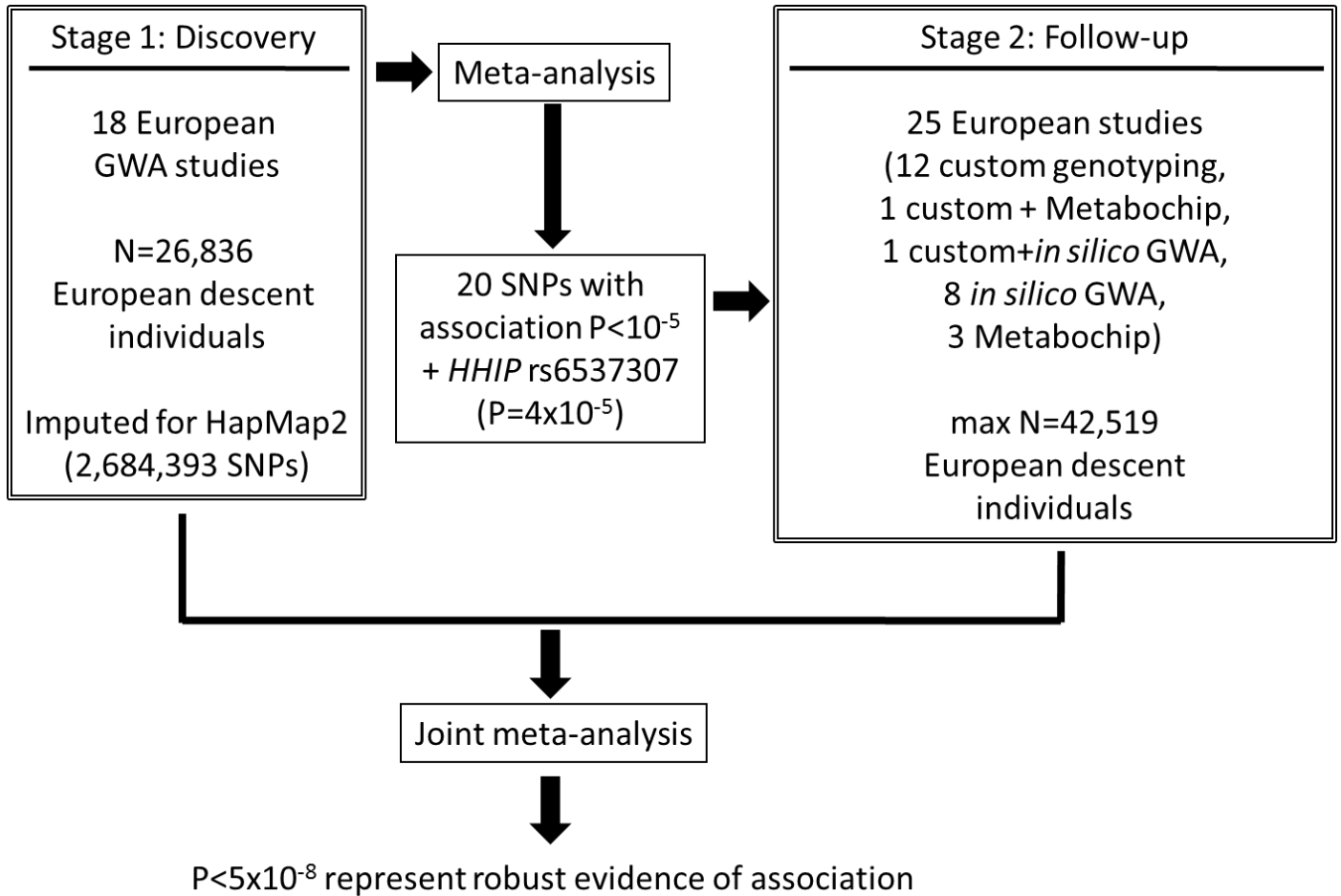
SUPPLEMENTARY ONLINE MATERIAL

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

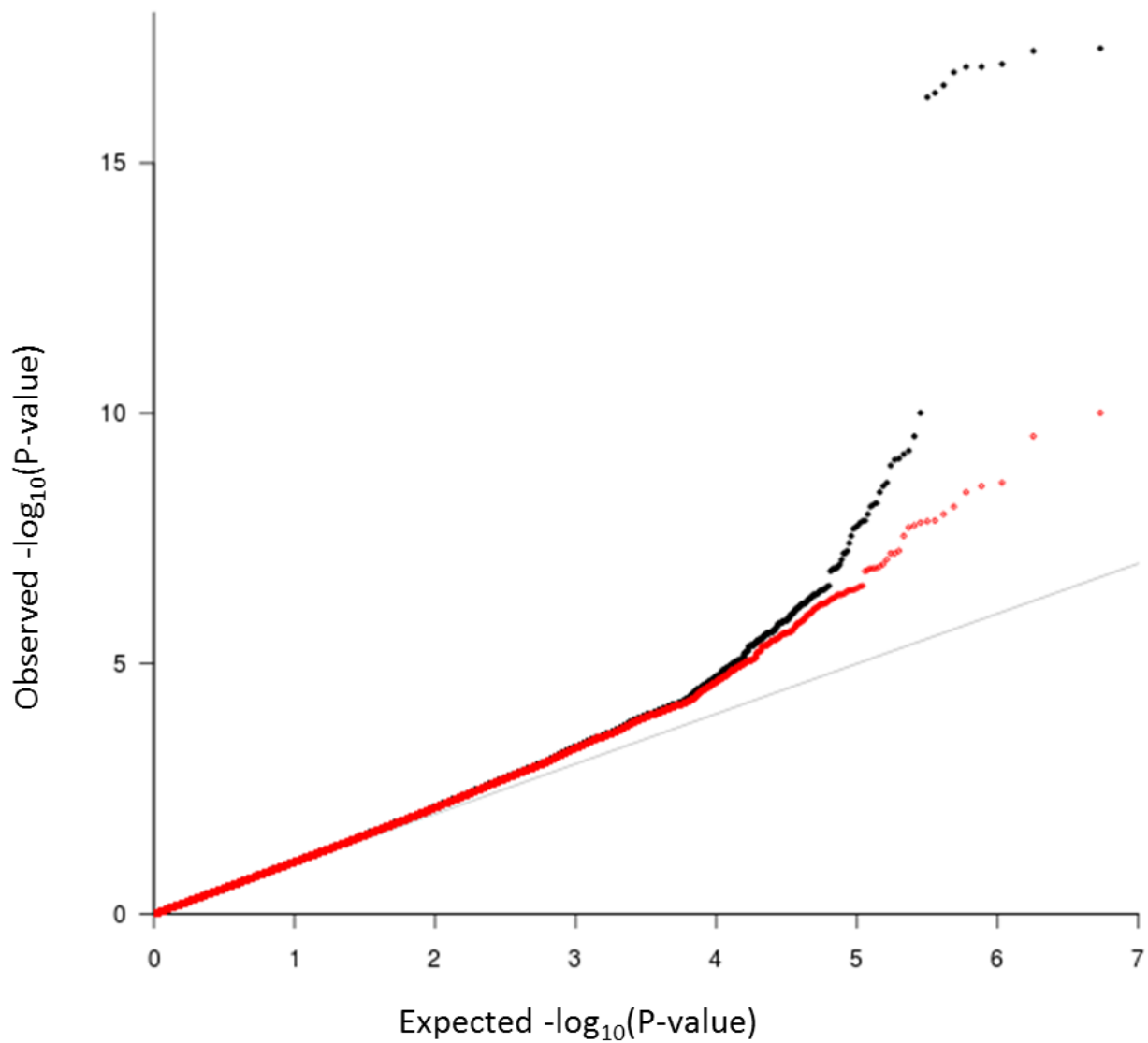
Momoko Horikoshi, Hanieh Yaghootkar, Dennis O. Mook-Kanamori, Ulla Sovio, H. Rob Taal, Branwen J. Hennig, Jonathan P. Bradfield, Beate St. Pourcain, David M. Evans, Pimphen Charoen, Marika Kaakinen, Diana L. Cousminer, Terho Lehtimäki, Eskil Kreiner-Møller, Nicole M. Warrington, Mariona Bustamante, Bjarke 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.

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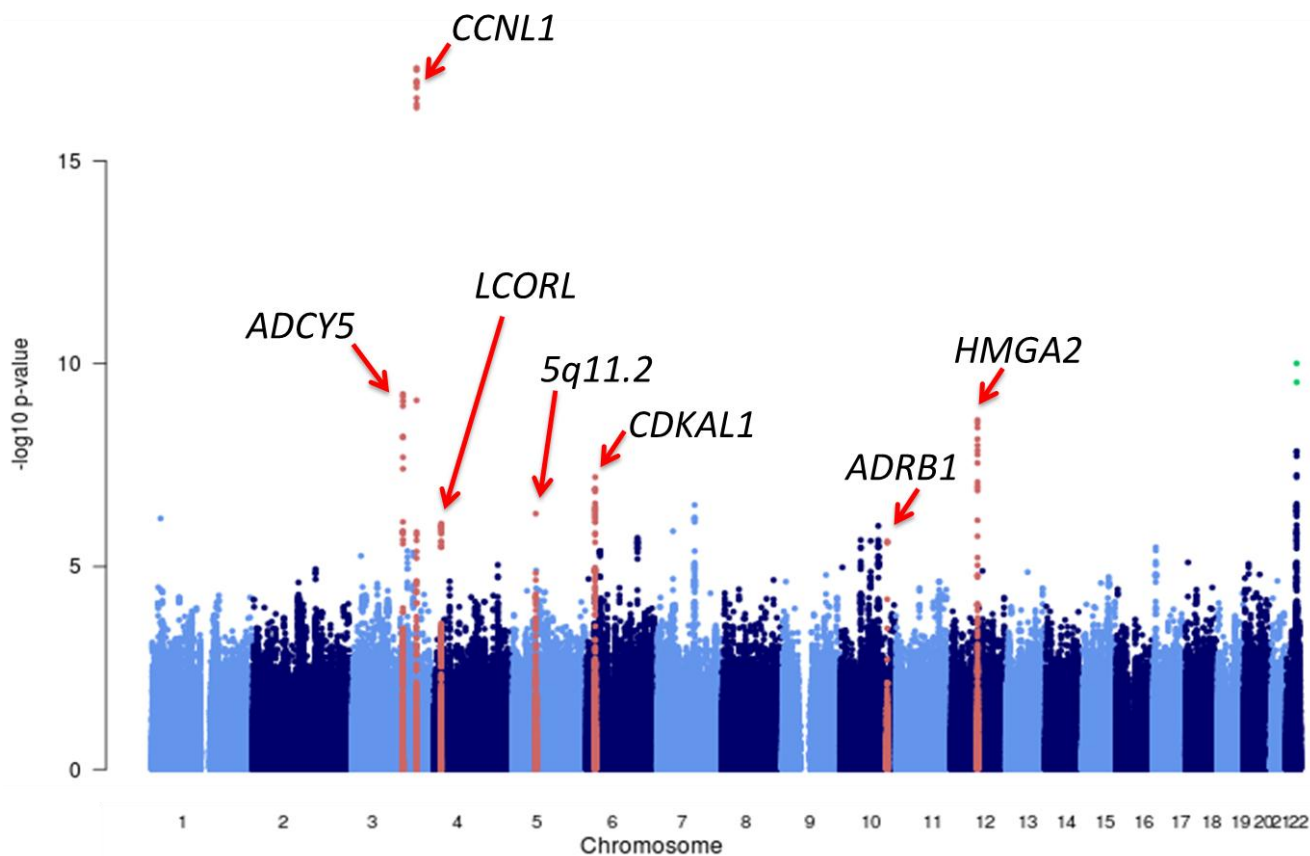
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Supplementary Figure 1. Summary of study design.

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.

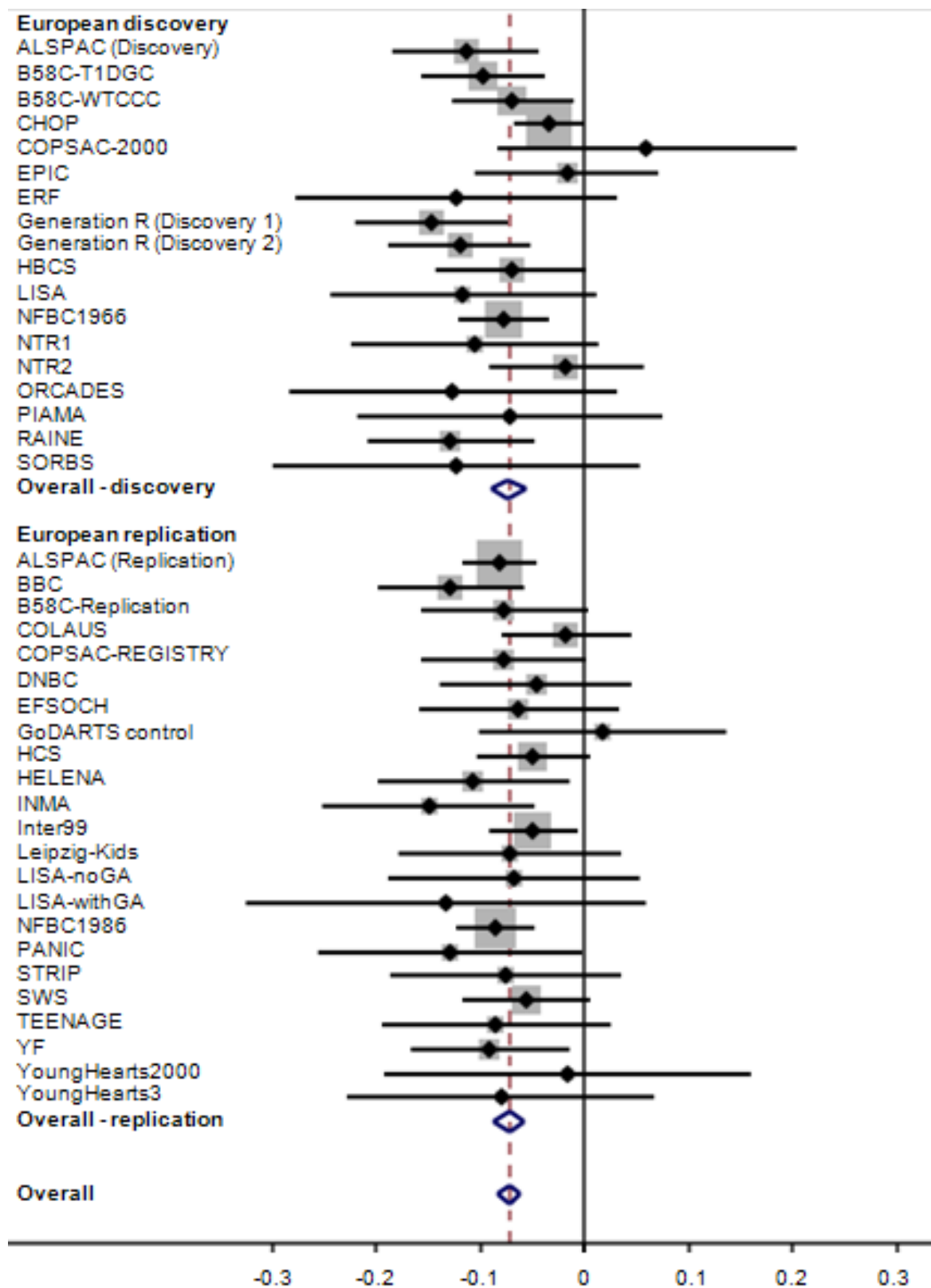


Supplementary Figure 3. Manhattan plot of the association P values for birth weight from the **discovery** meta-analysis ($n =$ up to 26,836). The $-\log_{10}$ of the P value for each of 2,684,393 SNPs (y-axis) is plotted against the genomic position (NCBI Build 36; x-axis). Association signals that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

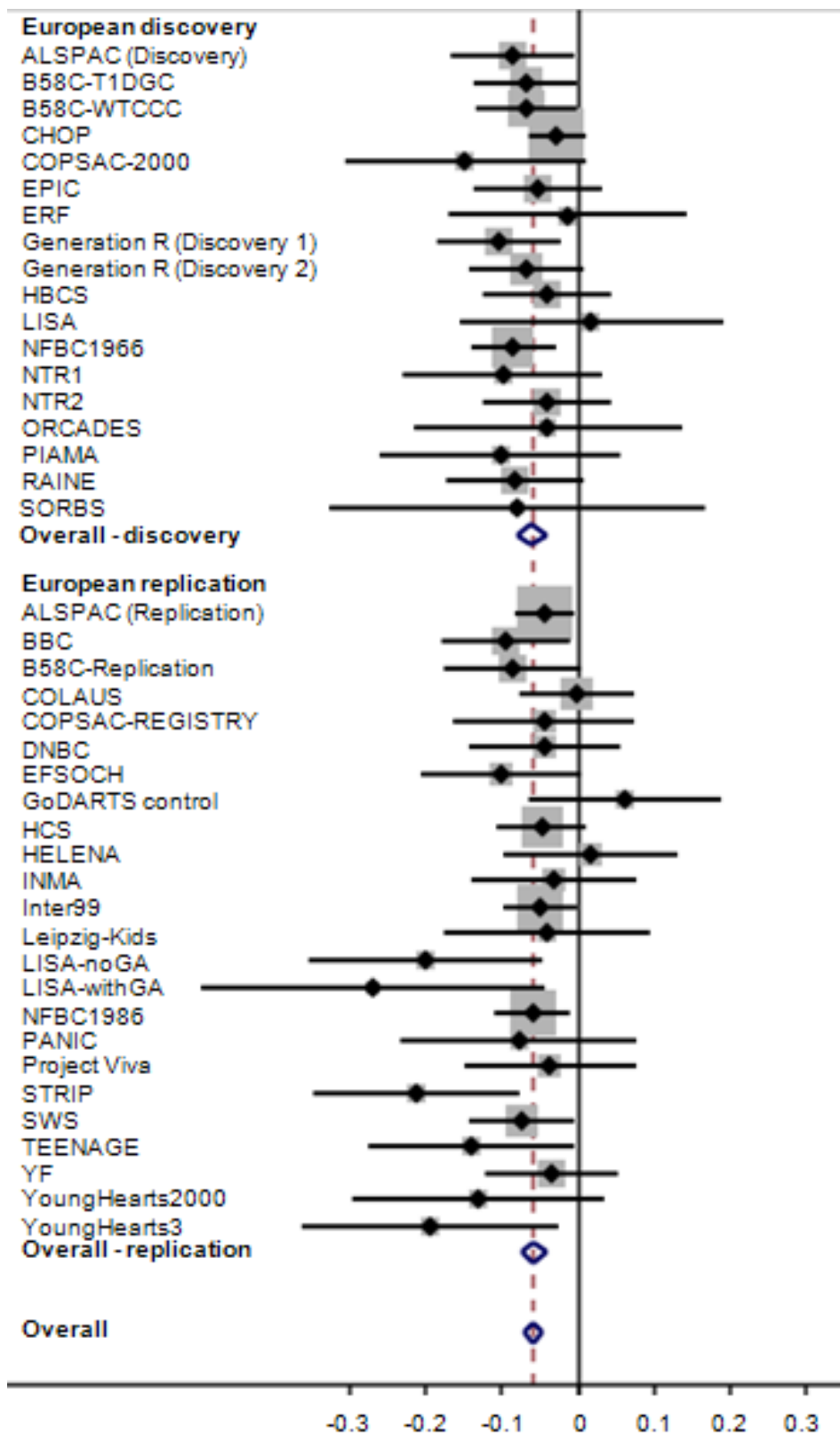


Supplementary Figure 4. Forest plots of the associations between birth weight and (a) *CCNL1*, (b) *ADCY5*, (c) *HMGA2*, (d) *CDKAL1*, (e) *5q11.2*, (f) *LCORL* and (g) *ADRB1* in Europeans. In each plot, the dashed red line indicates the effect size from the overall meta-analysis of discovery and follow-up samples.

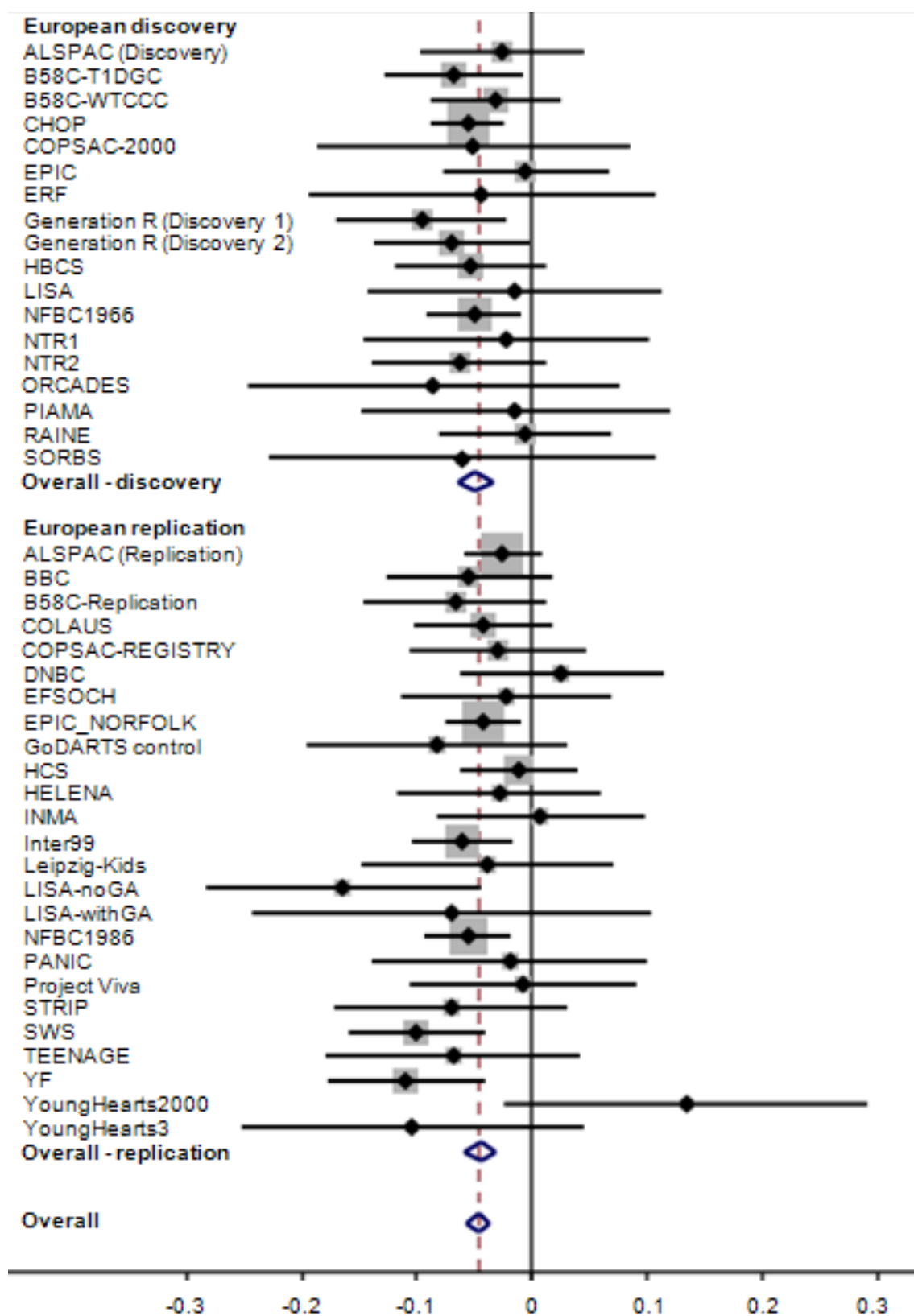
(a) *CCNL1* (overall $n = 61,142$; $P = 3.6 \times 10^{-38}$; heterogeneity $P = 0.49$)



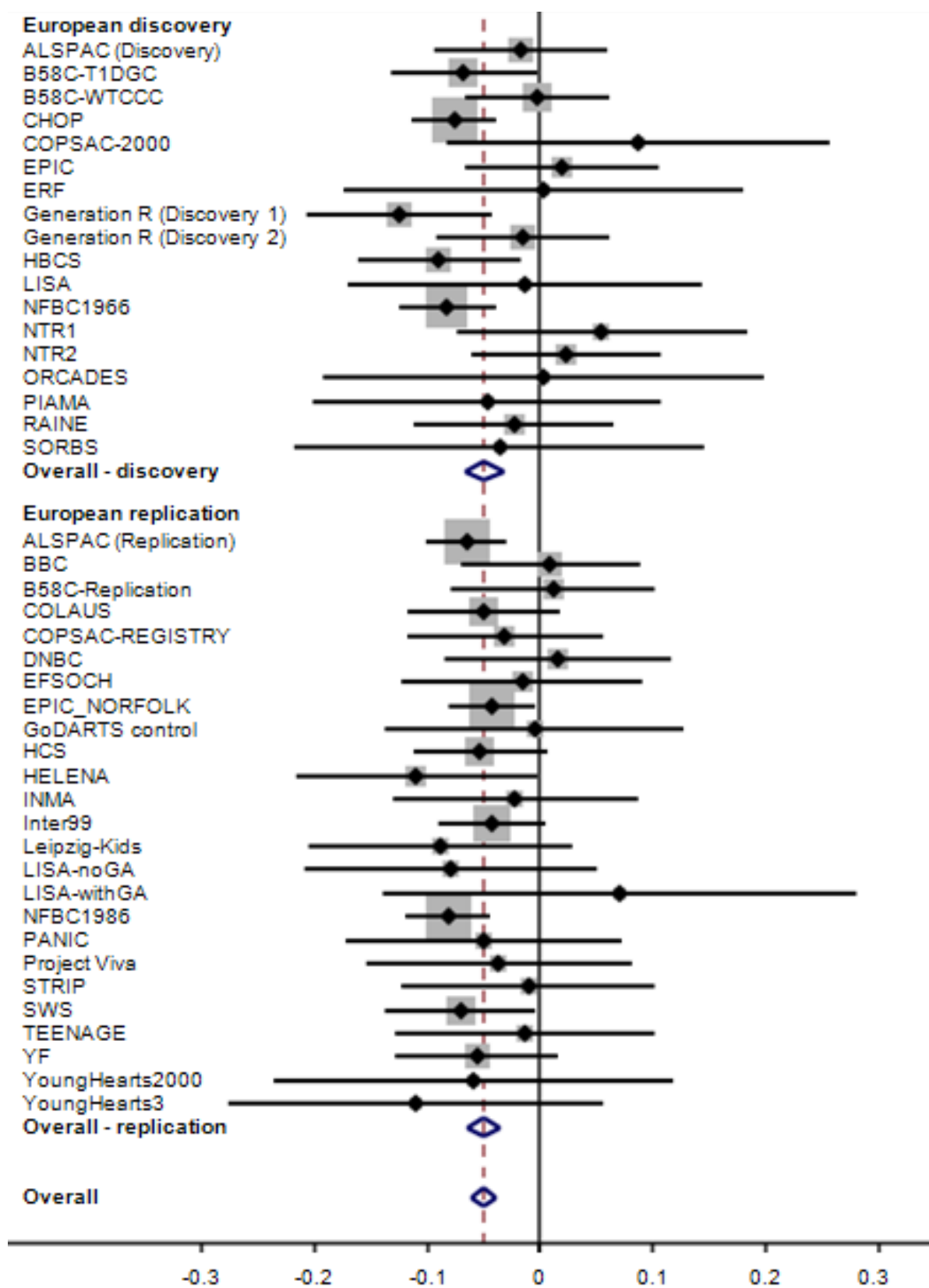
(b) *ADCY5* (overall $n = 61,509$; $P = 5.5 \times 10^{-20}$; heterogeneity $P = 0.69$)



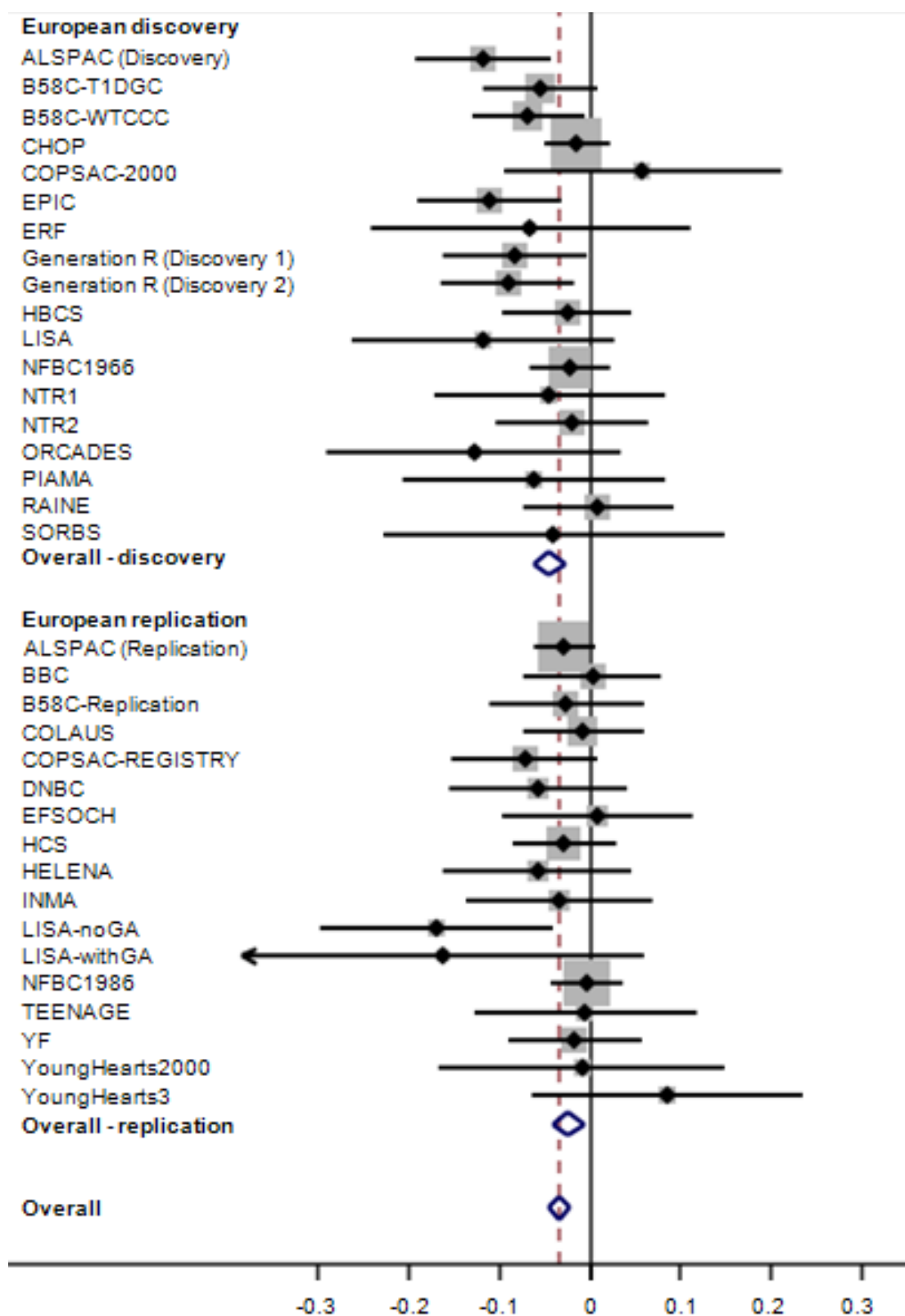
(c) *HMGA2* (overall $n = 68,655$; $P = 1.4 \times 10^{-19}$; heterogeneity $P = 0.82$)



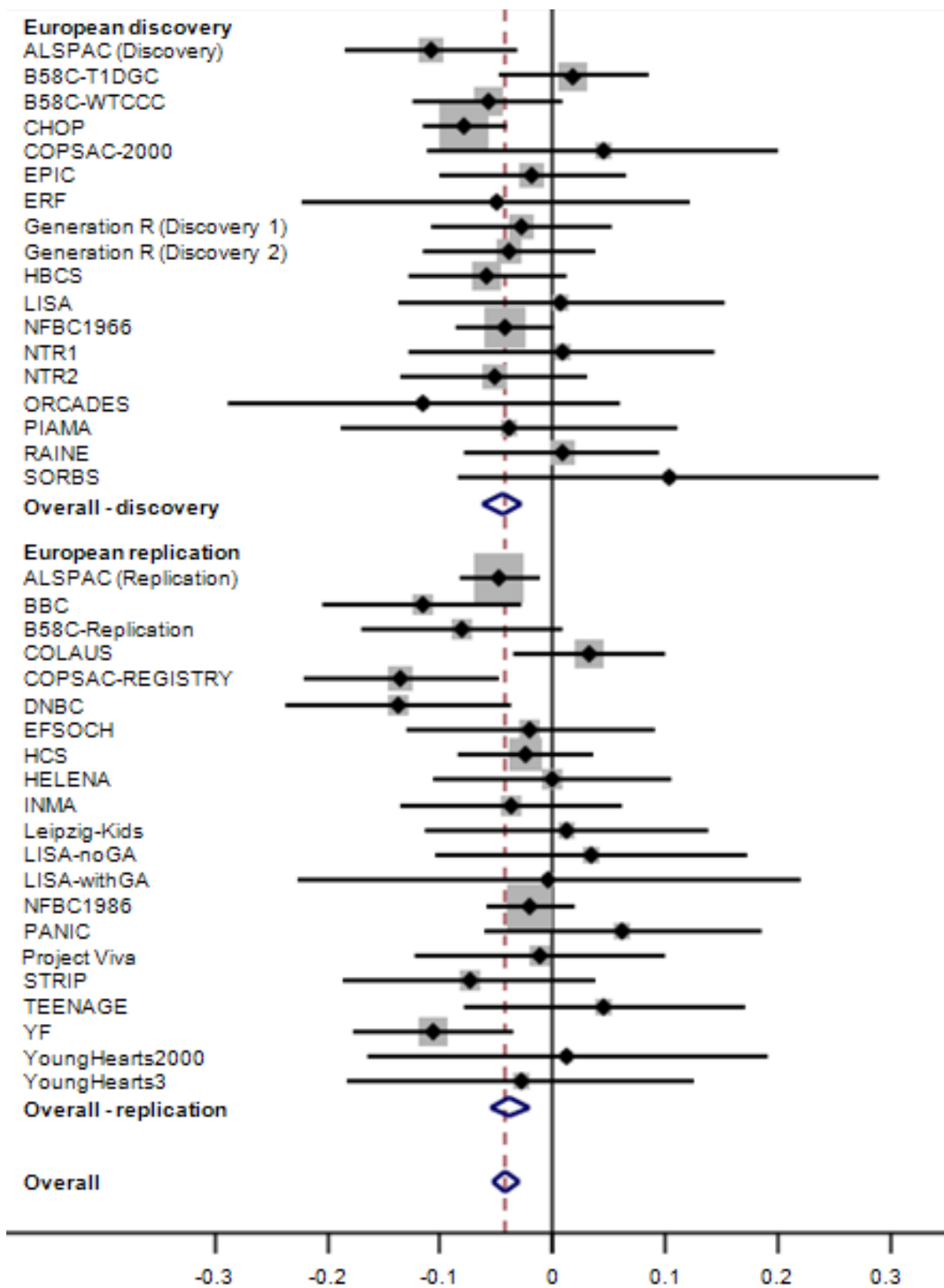
(d) *CDKAL1* (overall $n = 68,822$; $P = 1.5 \times 10^{-18}$; heterogeneity $P = 0.57$)



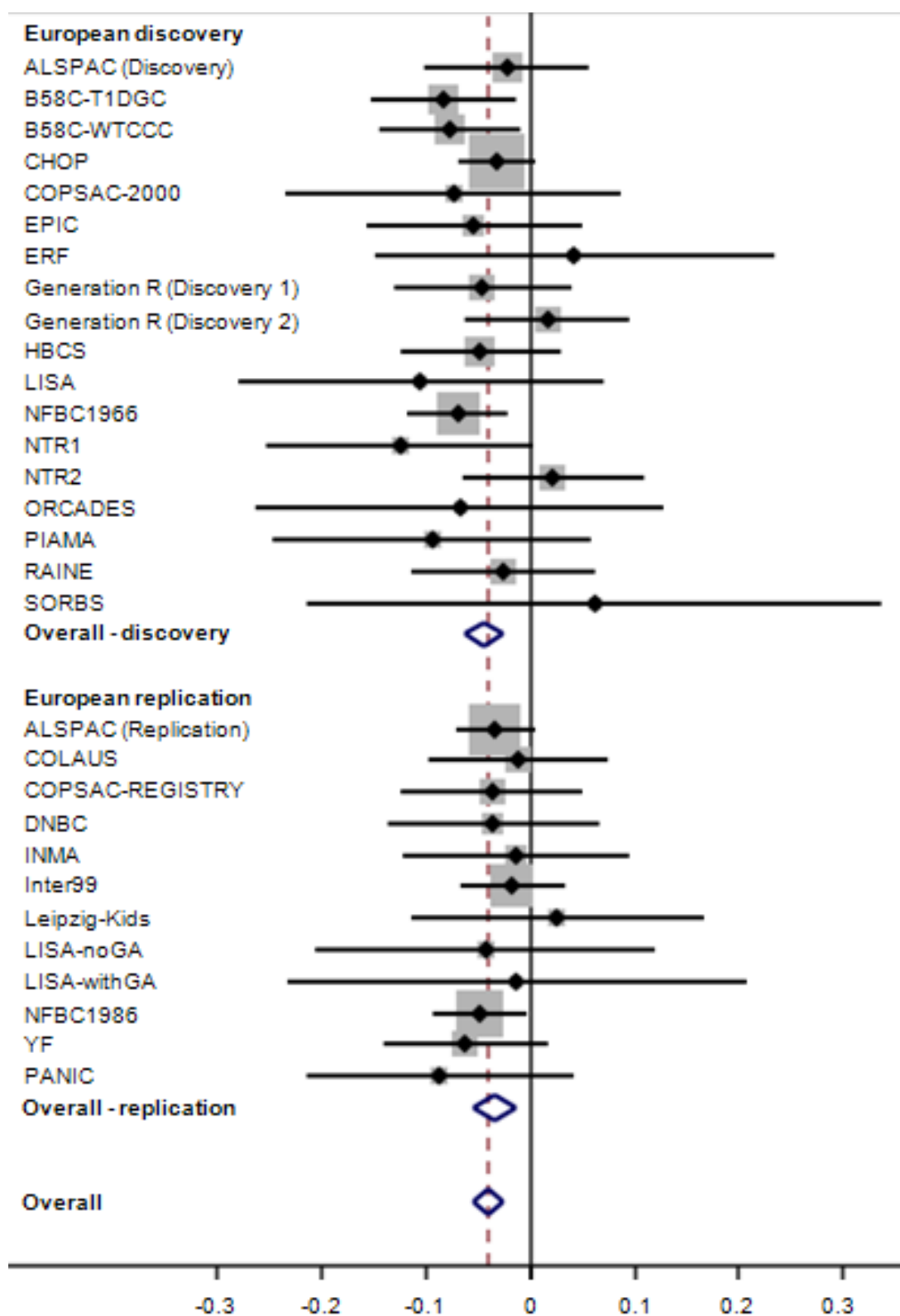
(e) 5q11.2 (overall $n = 53,619$; $P = 4.6 \times 10^{-8}$; heterogeneity $P = 0.40$)



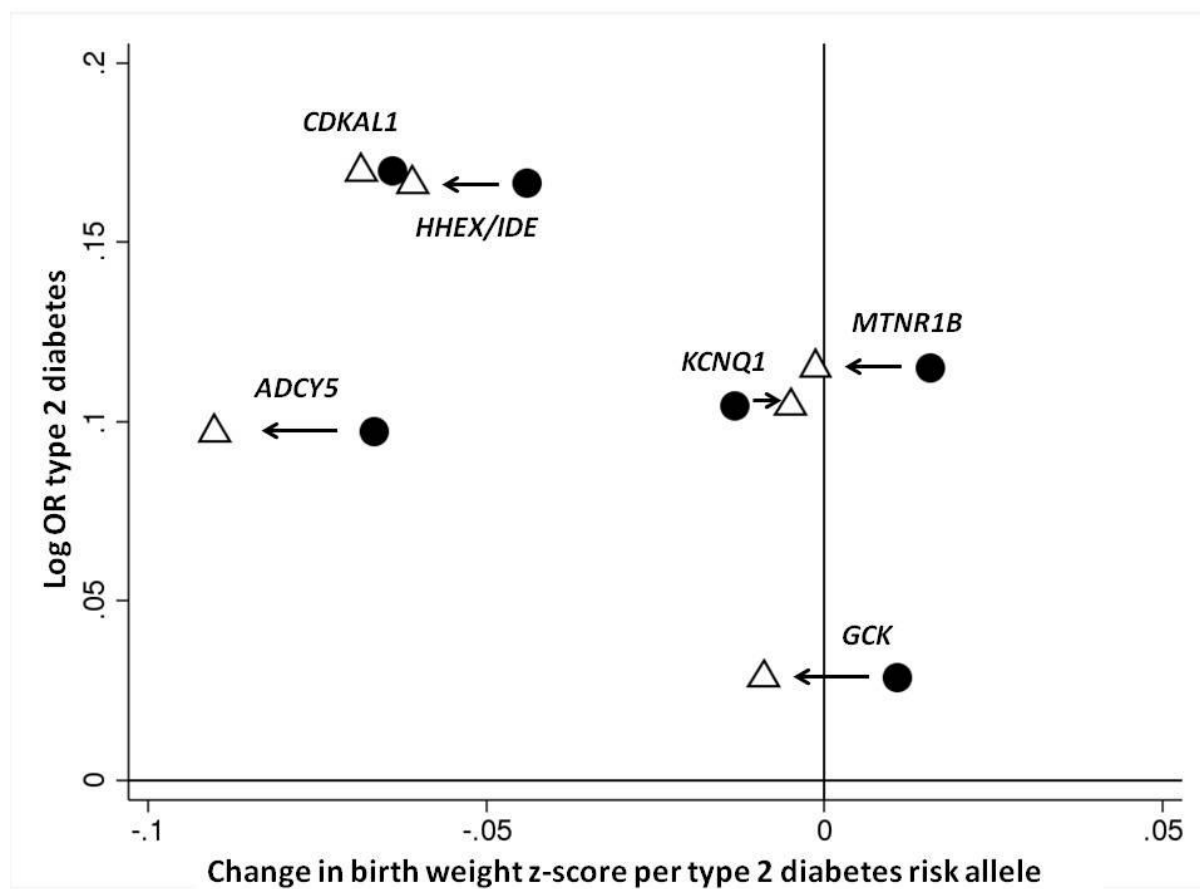
(f) *LCORL* (overall $n = 55,877$; $P = 4.6 \times 10^{-11}$; heterogeneity $P = 0.16$)



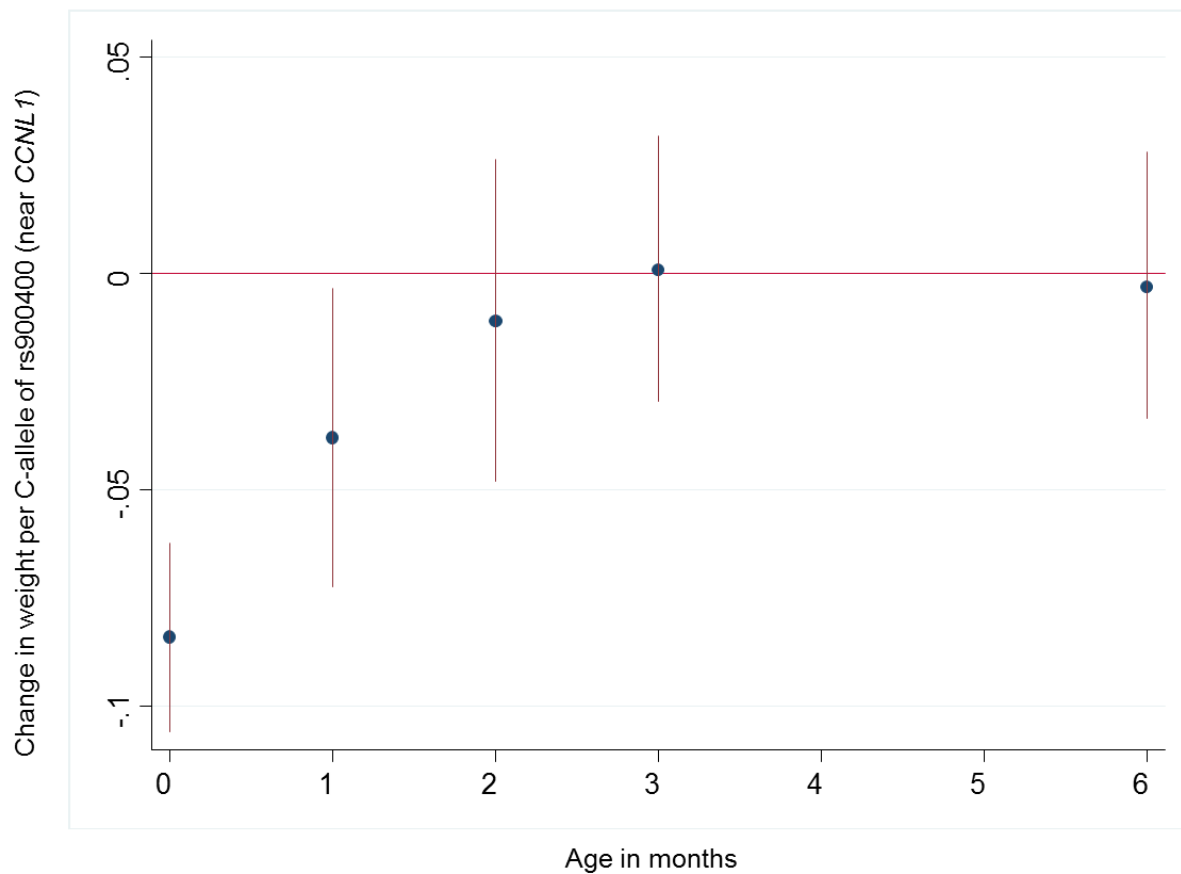
(g) *ADRB1* (overall $n = 49,660$; $P = 3.6 \times 10^{-9}$; heterogeneity $P = 0.97$)



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.

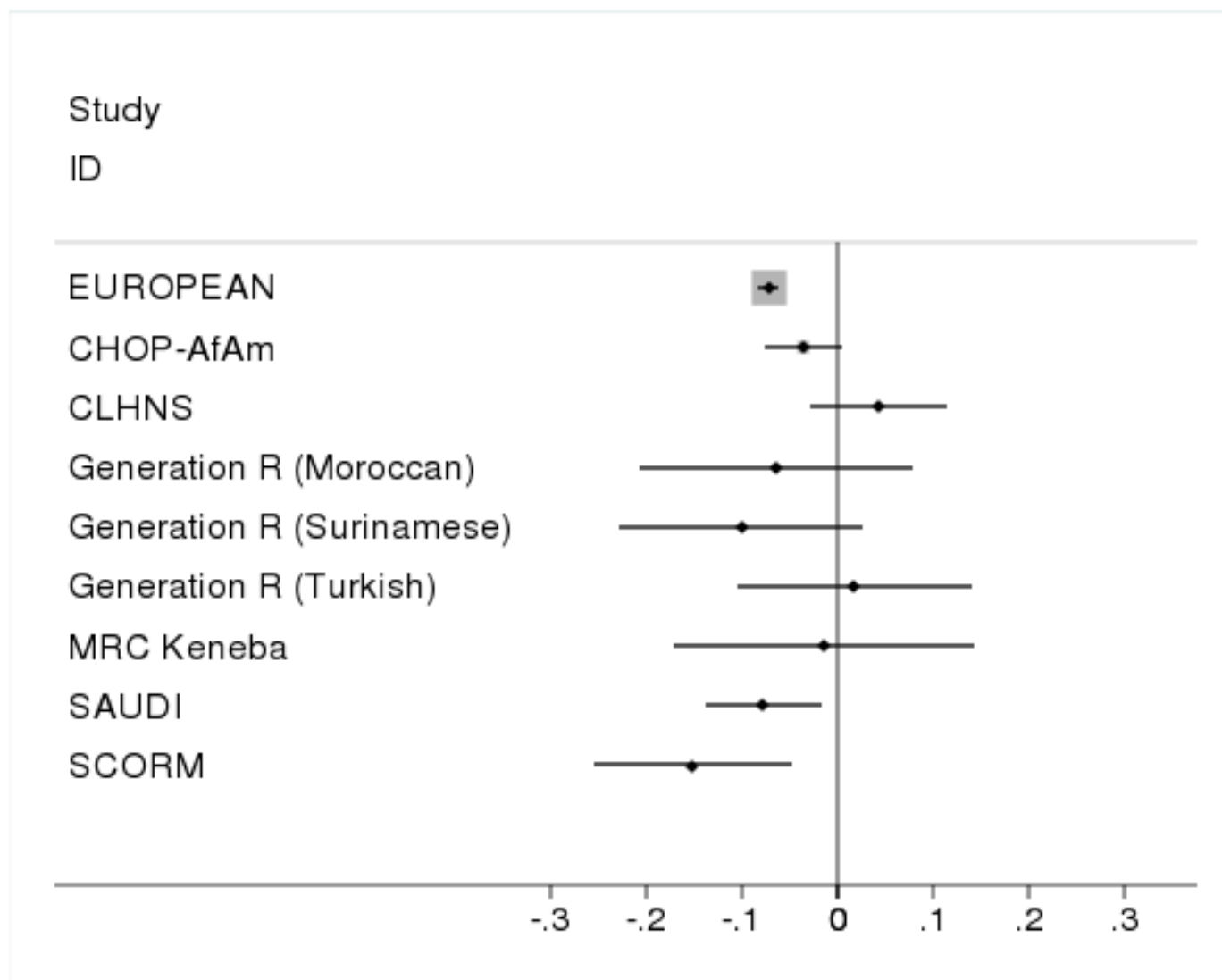


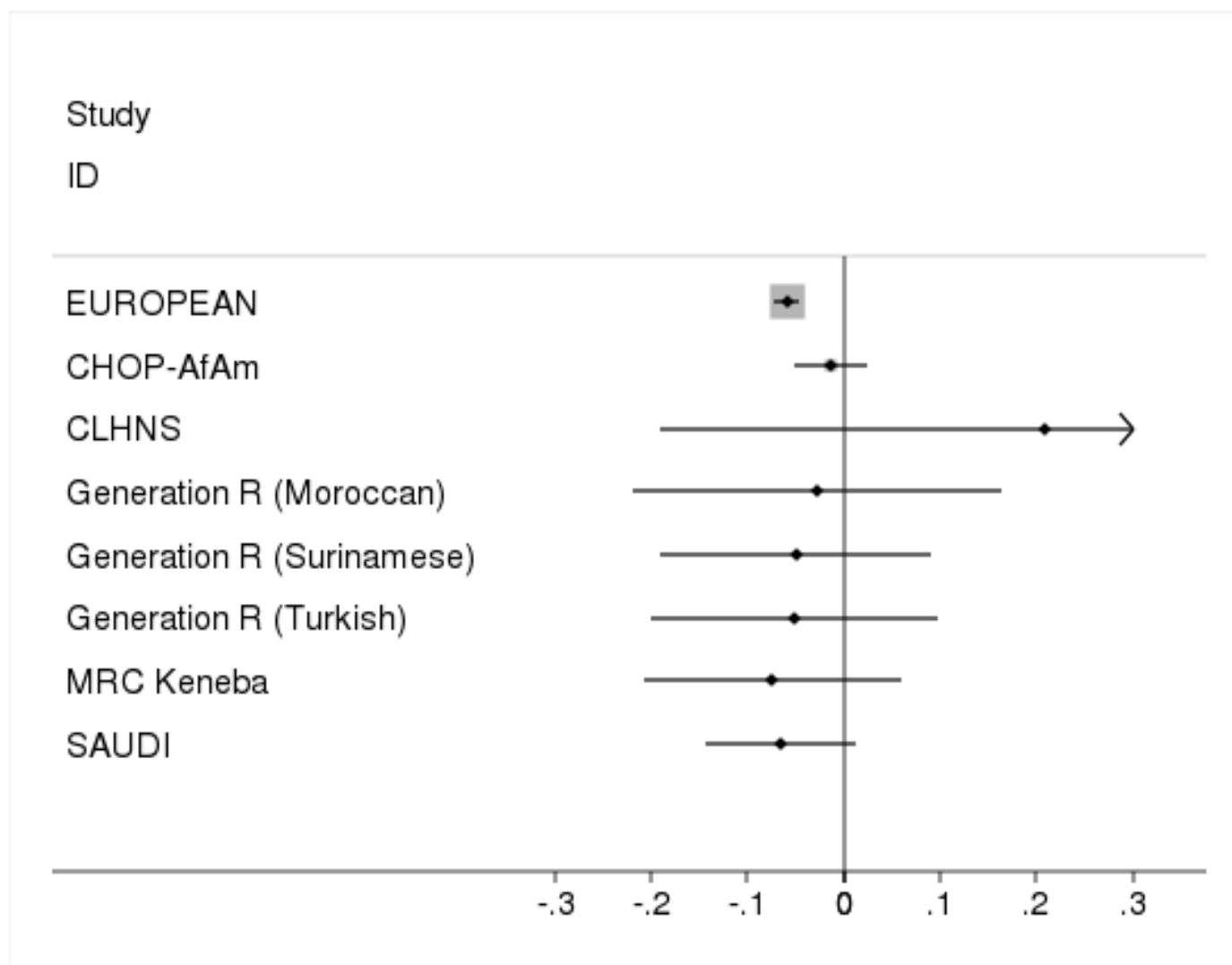
Supplementary Figure 6. Associations between SNP rs900400 near *CCNL1* and weight from birth to 6 months in seven studies with available postnatal data. The vertical lines show 95% confidence intervals around the effect size estimates. Total sample sizes: $n = 15,090$ (0 months); $n = 6,952$ (1 month);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



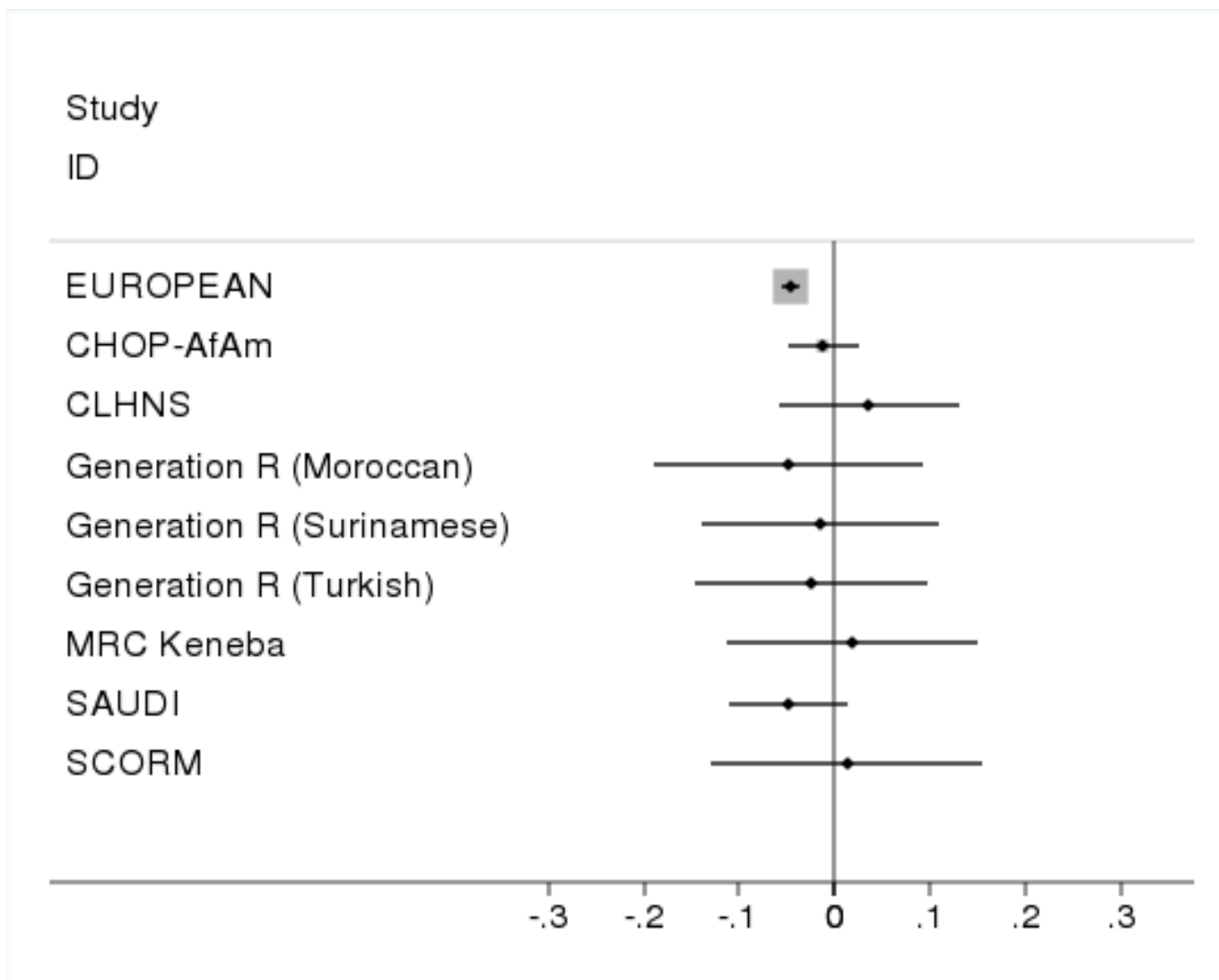
Supplementary Figure 7. Forest plots of the associations between birth weight and (a) *CCNL1*, (b) *ADCY5*, (c) *HMGA2*, (d) *CDKAL1*, (e) *5q11.2*, (f) *LCORL* and (g) *ADRB1* in non-Europeans. The overall European result is shown for comparison. The non-European studies are from East/Southeast Asia (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]).

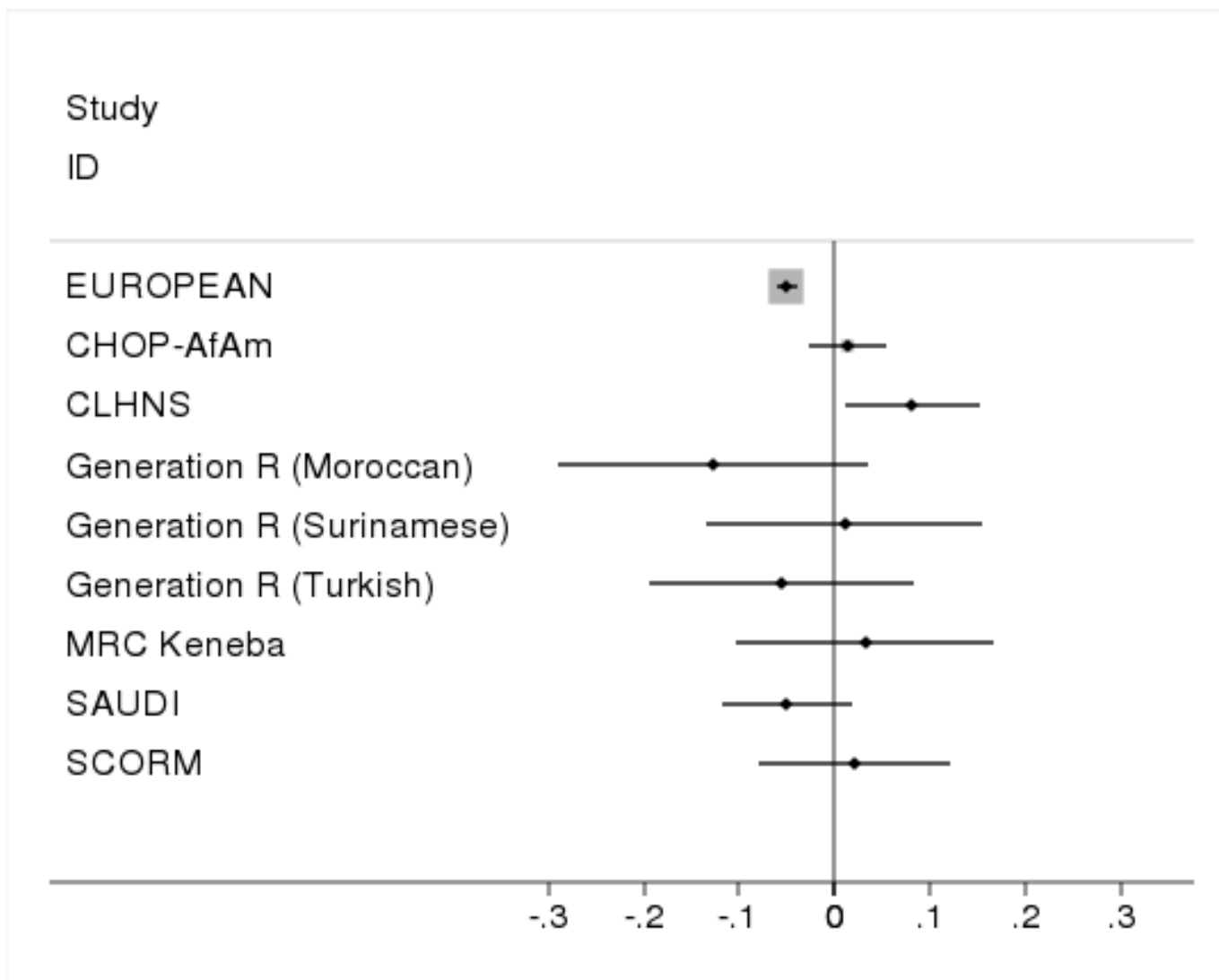
(a) *CCNL1*



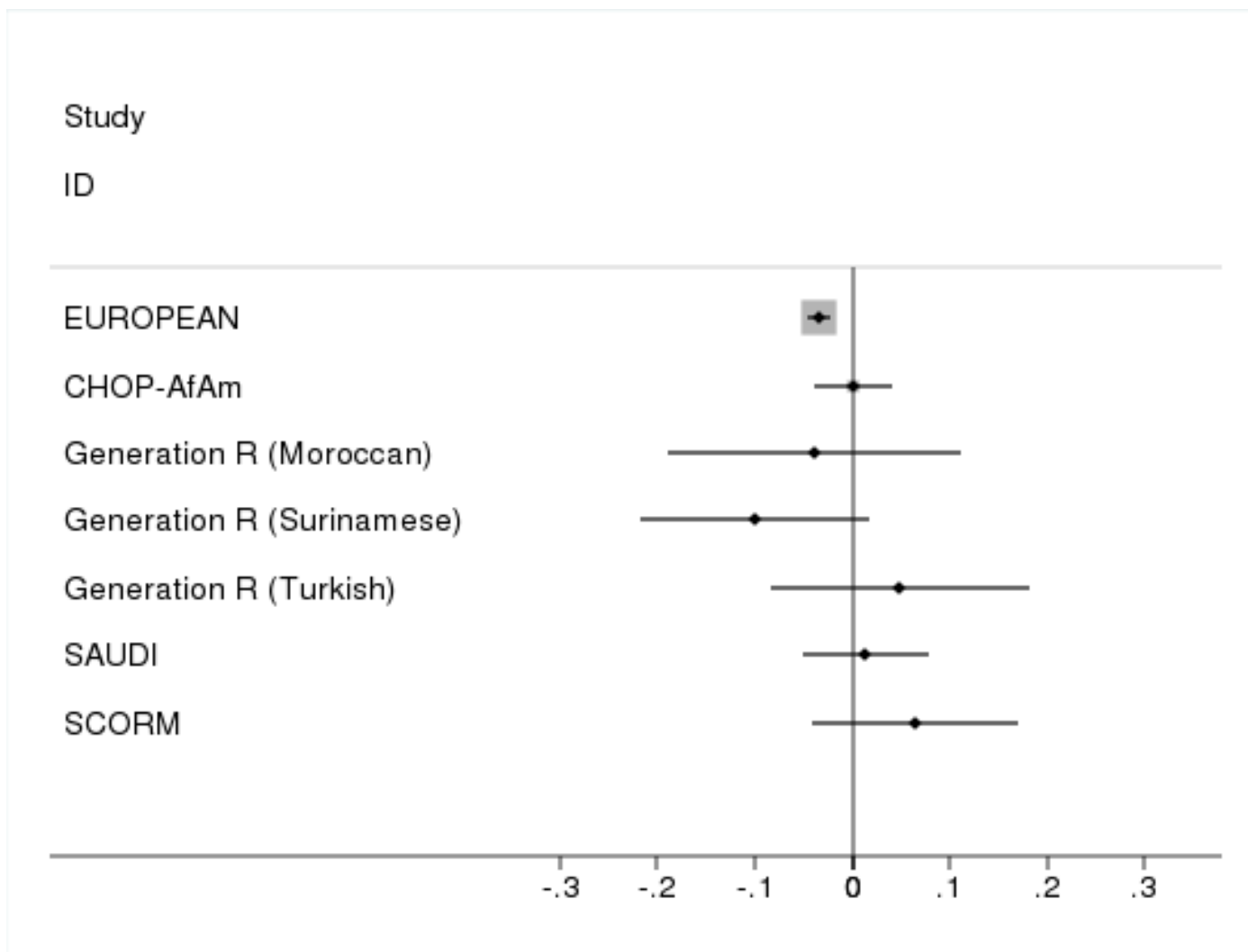
(b) *ADCY5*

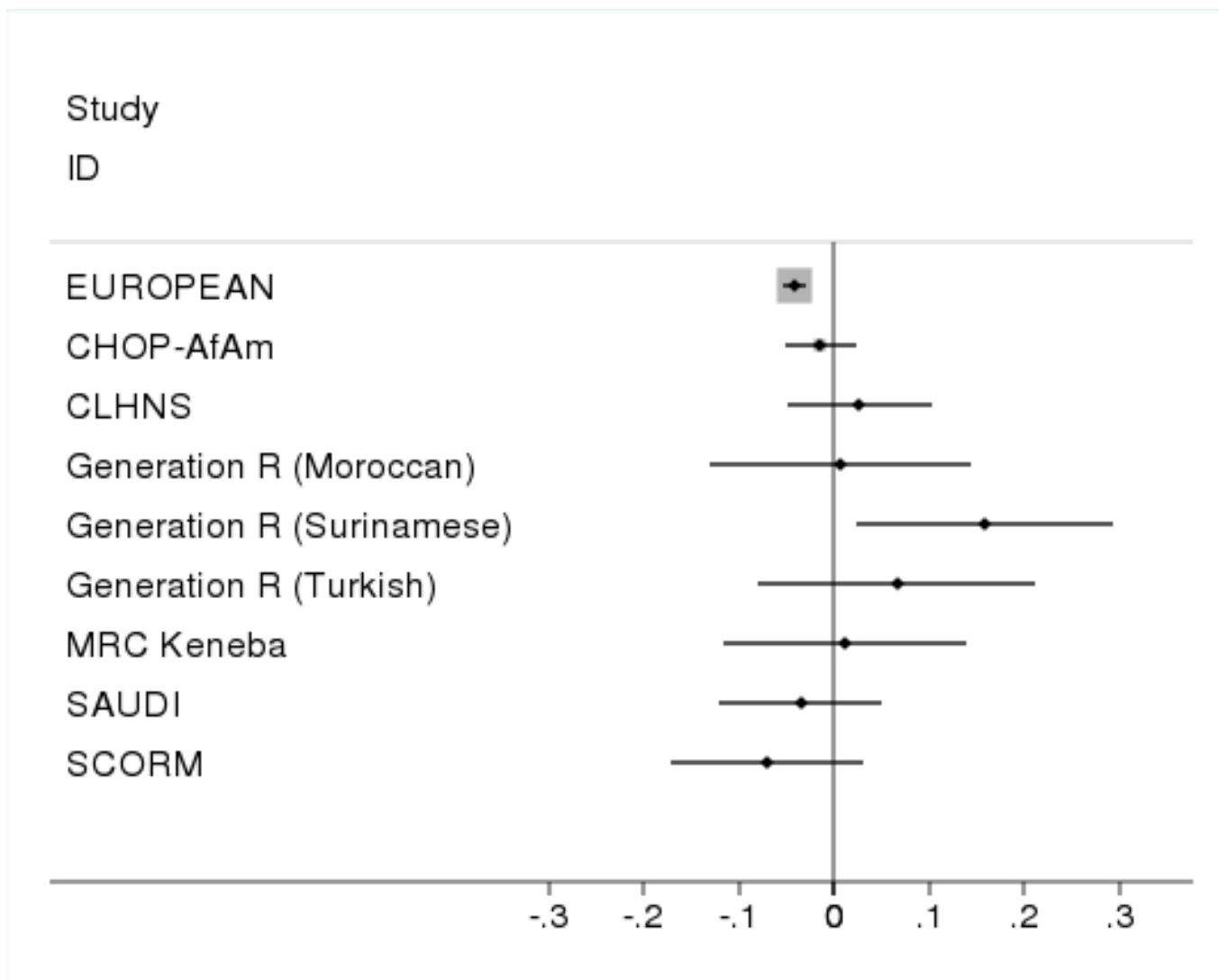
(c) *HMGA2*

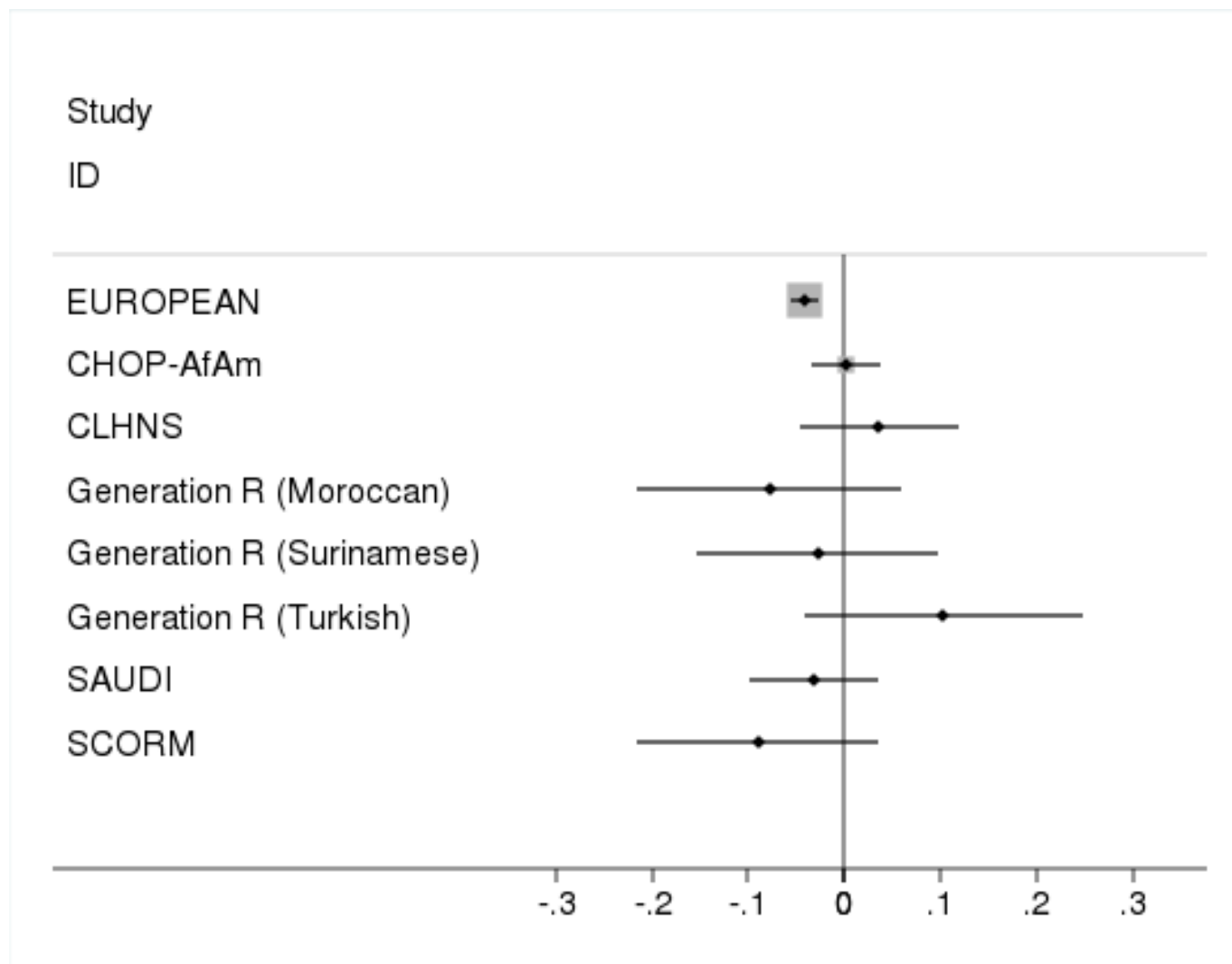


(d) *CDKAL1*

(e) 5q11.2



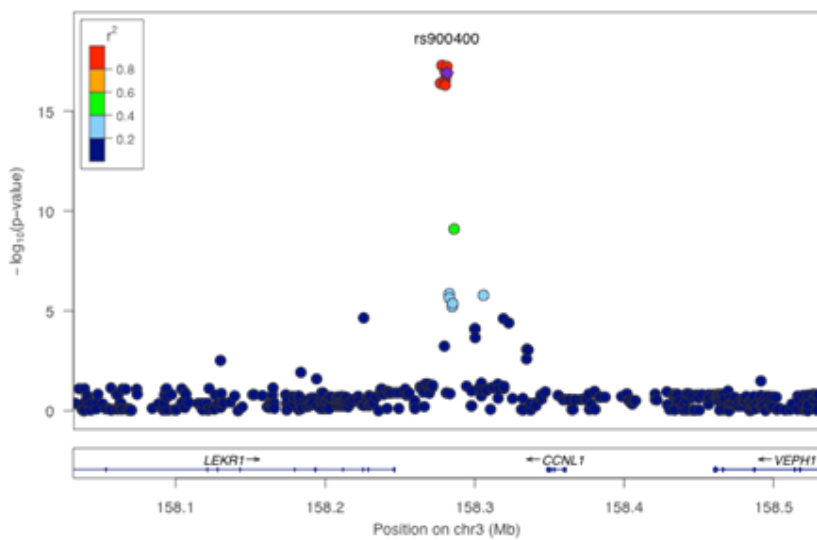
(f) *LCORL*

(g) *ADRB1*

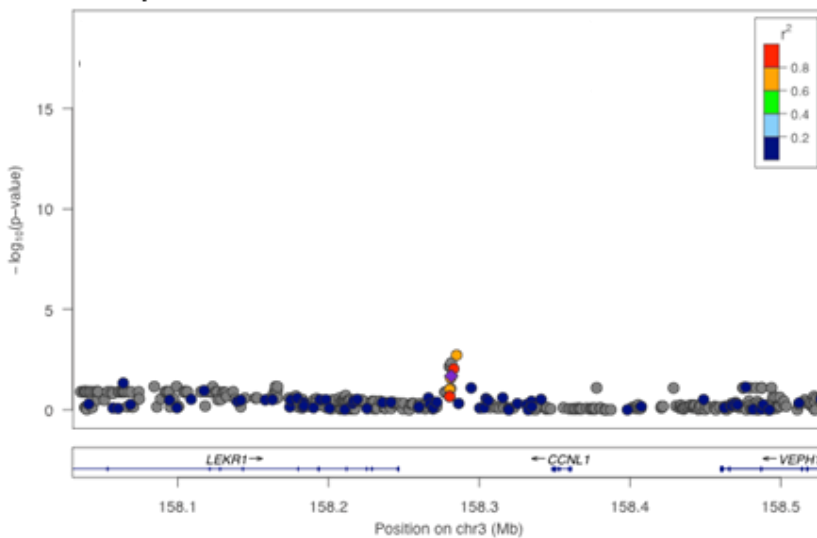
Supplementary Figure 8. Ethnicity-specific regional plots for (a) *CCNL1* and (b) *ADCY5* in European (n=26,813), East/Southeast Asian (n=2,135) and African American (n=6,315). Directly genotyped or imputed SNPs are plotted as a function of genomic position (NCBI Build 36). In each panel, the European 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*

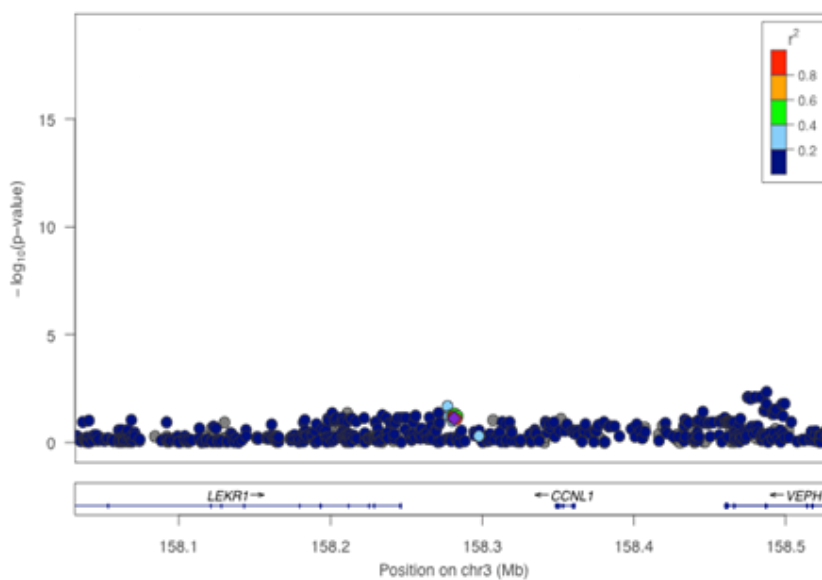
European



East/Southeast Asian

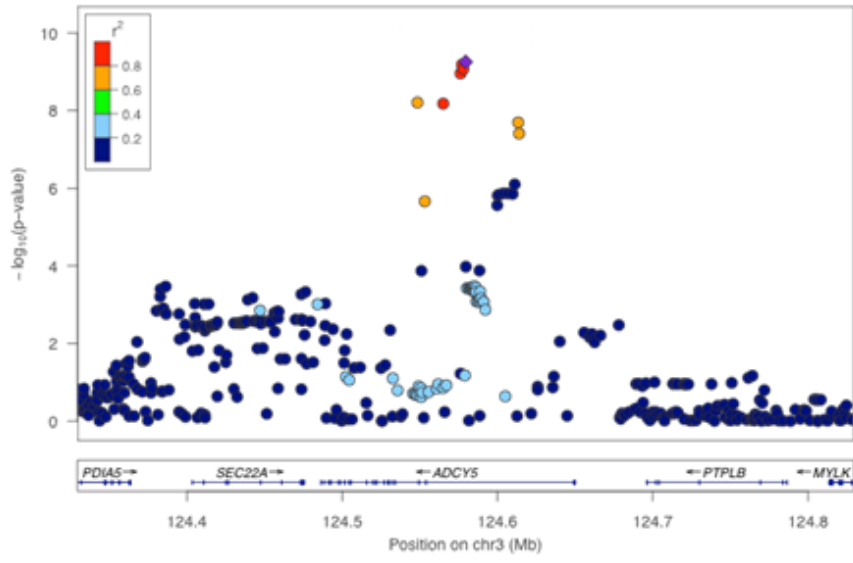


African American

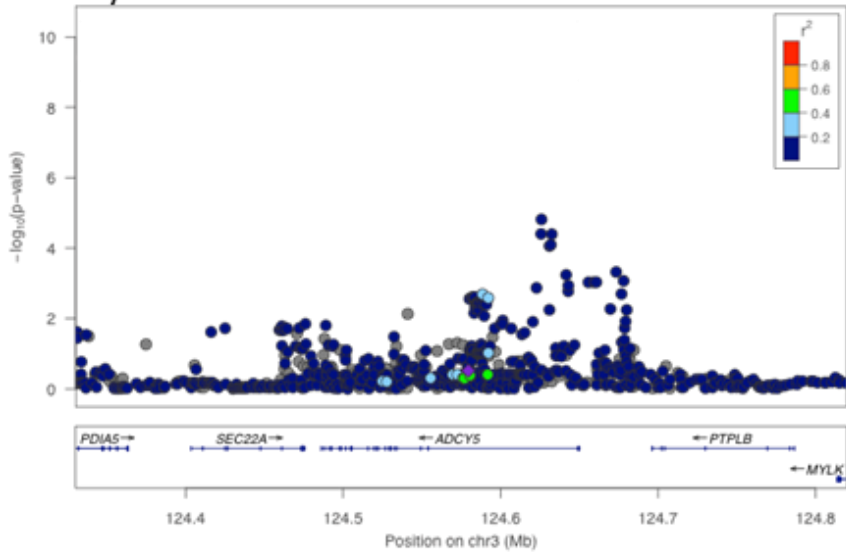


(b) *ADCY5*

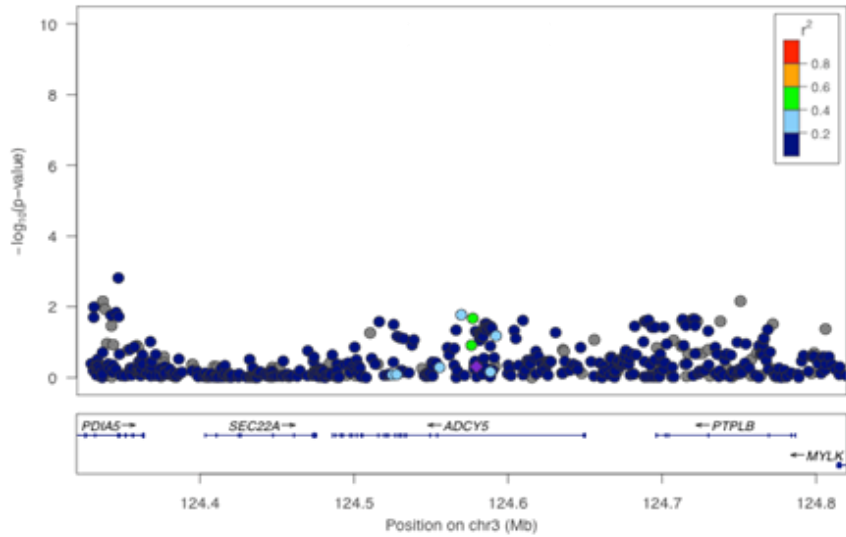
European



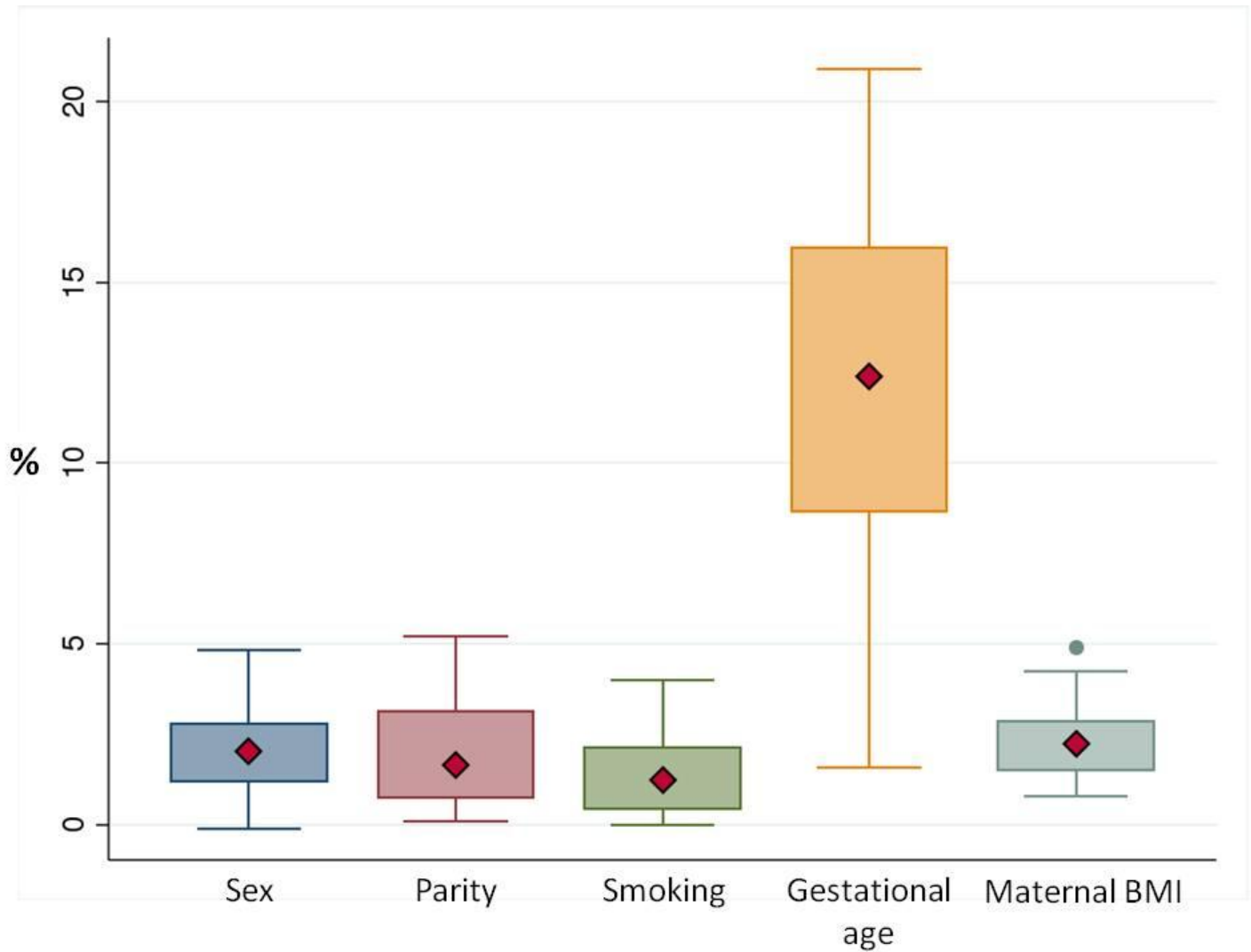
East/Southeast Asian



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 +/- 2*interquartile range; circle = outlier.



SUPPLEMENTARY NOTE

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SUPPLEMENTARY NOTE

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