Variants in *ADCY5* and near *CCNL1* are associated with fetal growth and birth weight

Rachel M Freathy*, Dennis O Mook-Kanamori*, Ulla Sovio*, Inga Prokopenko*, Nicholas John Timpson*, Diane J Berry*, Nicole M Warrington*, Elisabeth Widen, Jouke Jan Hottenga, Marika Kaakinen, Leslie A Lange, Jonathan P Bradfield, Marjan Kerkhof, Julie A Marsh, Reedik Mägi, Chih-Mei Chen, Helen N Lyon, Mirna Kirin, Linda S Adair, Yurii S Aulchenko, Amanda J Bennett, Judith B Borja, Nabila Bouatia-Naji, Pimphen Charoen, Lachlan J M Coin, Diana L Cousminer, Eco J. C. de Geus, Panos Deloukas, Paul Elliott, David M Evans, Philippe Froguel, The Genetic Investigation of ANthropometric Traits (GIANT) Consortium, Beate Glaser, Christopher J Groves, Anna-Liisa Hartikainen, Neelam Hassanali, Joel N Hirschhorn, Albert Hofman, Jeff M P Holly, Elina Hyppönen, Stavroula Kanoni, Bridget A Knight, Jaana Laitinen, Cecilia M Lindgren, The Meta-Analyses of Glucose and Insulin-related traits Consortium (MAGIC), Wendy L McArdle, Paul F O'Reilly, Craig E Pennell, Dirkje S Postma, Anneli Pouta, Adaikalavan Ramasamy, Nigel W Rayner, Susan M Ring, Fernando Rivadeneira, Beverley M Shields, David P Strachan, Ida Surakka, Anja Taanila, Carla Tiesler, Andre G Uitterlinden, Cornelia M van Duijn, The Wellcome Trust Case Control Consortium (WTCCC), Alet H Wijga, Gonneke Willemsen, Haitao Zhang, Jianhua Zhao, James F Wilson, Eric A P Steegers, Andrew T Hattersley, Johan G Eriksson, Leena Peltonen, Karen L Mohlke, Struan F A Grant, Hakon Hakonarson, Gerard H Koppelman, George V Dedoussis, Joachim Heinrich, Matthew W Gillman, Lyle J Palmer, Timothy M Frayling, Dorret I Boomsma†, George Davey Smith†, Chris Power†, Vincent W V Jaddoe†, Marjo-Riitta Jarvelin† and Mark I McCarthy† for the Early Growth Genetics (EGG) Consortium.

SUPPLEMENTARY INFORMATION

Supplementary Table 1. Basic characteristics, exclusions, genotyping, quality control and imputation in discovery studies [see accompanying Excel file].

Supplementary Table 2. Basic characteristics, exclusions, genotyping, quality control and imputation in European replication studies and non-European/admixed studies [see accompanying Excel file].

Supplementary Table 3. Mean birth weight (SD) by genotype and individual association results in the non-European or admixed samples

Study type	Study	Year(s) of birth	Total N[a]	% male	Locus 3q25: index SNP rs900400[b], nearest genes: *CCNL1*, *LEKR1*				Locus 3q21: index SNP rs9883204[b], nearest gene: *ADCY5*			
					TT	CT	CC		TT	CT	CC	
					Mean BW in g (SD)	Mean BW in g (SD)	Mean BW in g (SD)	*P* value[c]	Mean BW in g (SD)	Mean BW in g (SD)	Mean BW in g (SD)	*P* value[c]
Non-European / admixed	CLHNS	1983-4	1415	52.2	3057 (394)	3047 (394)	3002 (393)	0.07	NA	2957 (394)	3042 (394)	0.28
	Generation R (B)	2002-6	448	47.3	3353 (420)	3286 (423)	3271 (421)	0.09	3310 (431)	3366 (429)	3345 (432)	0.97
	Generation R (M)	2002-6	298	51.7	3573 (376)	3481 (372)	3472 (373)	0.05	3504 (386)	3511 (385)	3525 (390)	0.79
	Generation R (T)	2002-6	333	50.2	3633 (229)	3461 (377)	3435 (381)	0.81	3567 (375)	3419 (380)	3468 (381)	0.95

BW, birth weight; NA, not available due to low minor allele frequency (1%). All birth weight values are adjusted for sex and gestational age. [a]Study N in the birth weight association analysis for rs900400 genotype. [b]If the index SNP was unavailable, this was substituted with a closely-correlated (HapMap r^2>0.9) proxy (rs1482853 or rs900399 for rs900400; rs2877716 or rs6798189 for rs9883204). [c]*P* value is from linear regression of birth weight Z score against SNP (additive model), with sex and gestational age as covariates.
Key to study names: CLHNS, Cebu Longitudinal Health and Nutrition Survey; Generation R (B), (M), (T), African descended, Moroccan and Turkish subsets, respectively.

Supplementary Table 4. Association between offspring genotype and birth weight before and after adjustment for maternal genotype (using European samples with genotype available for both mother and child)

Index SNP (if unavailable, a HapMap proxy [r^2>0.9] was used)	[1] Association between offspring genotype and birth weight, adjusted for sex and gestational age			[2] Association between offspring genotype and birth weight, adjusted for sex, gestational age and maternal genotype		
	N in meta-analysis	Per-C allele effect size in Z-scores (95% CI)	*P* value	N in meta-analysis	Per-C allele effect size in Z-scores (95% CI)	*P* value
rs900400	7659	-0.102 (-0.131, -0.072)	$9x10^{-12}$	7659	-0.113 (-0.147, -0.079)	$5x10^{-11}$
rs9883204	7910	-0.065 (-0.097, -0.033)	$8x10^{-5}$	7910	-0.087 (-0.124, -0.049)	$5x10^{-6}$

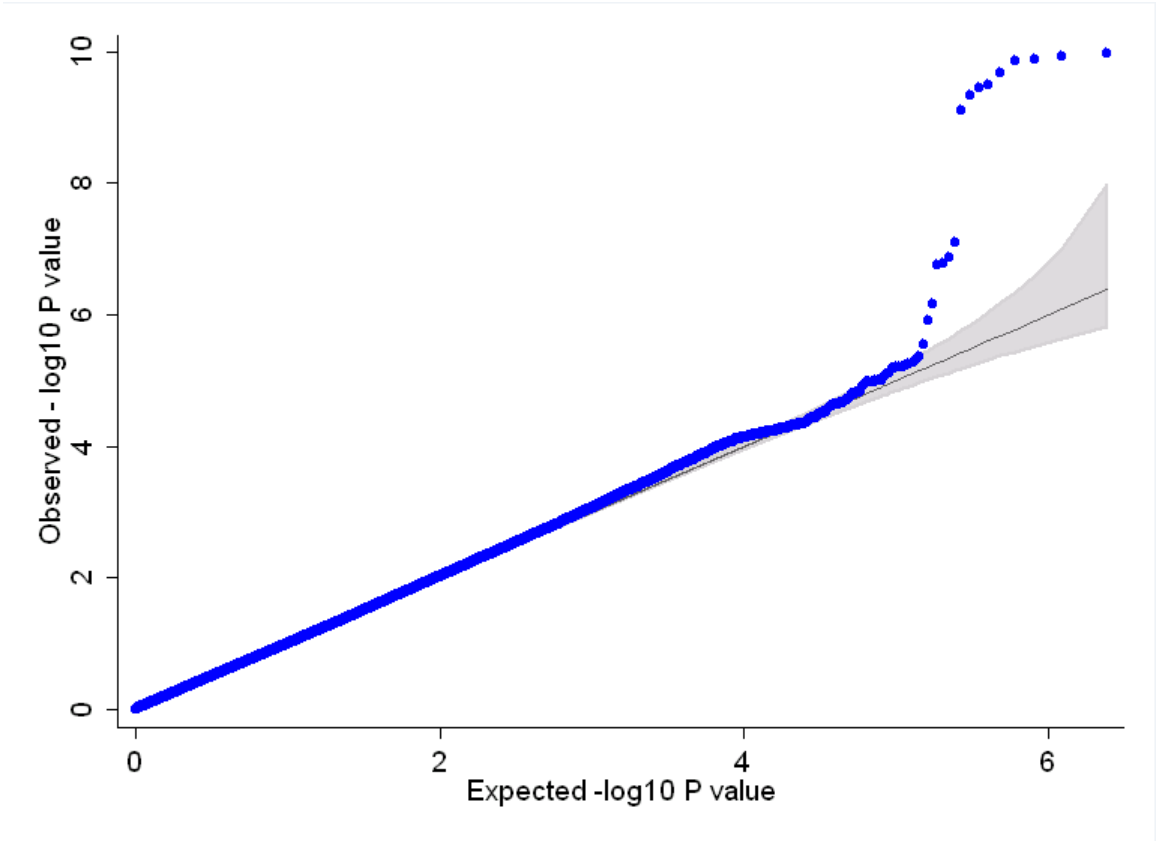
Contributing studies were (Ns for rs900400 signal and rs9883204 signal, respectively): ALSPAC (N=4419, N=4653); EFSOCH (N=644, N=646); Generation R Discovery (N=1012, N=1020); Generation R Replication (N=1584, N=1591). There was no evidence of between-study heterogeneity of effect sizes (all *P*>0.39; I^2=0%).

These analyses were also run in the CLHNS (Filipino) study (rs900400 N=1221; rs2877716 N=1217). Again, the results did not materially change on adjustment for maternal genotype (data not shown).

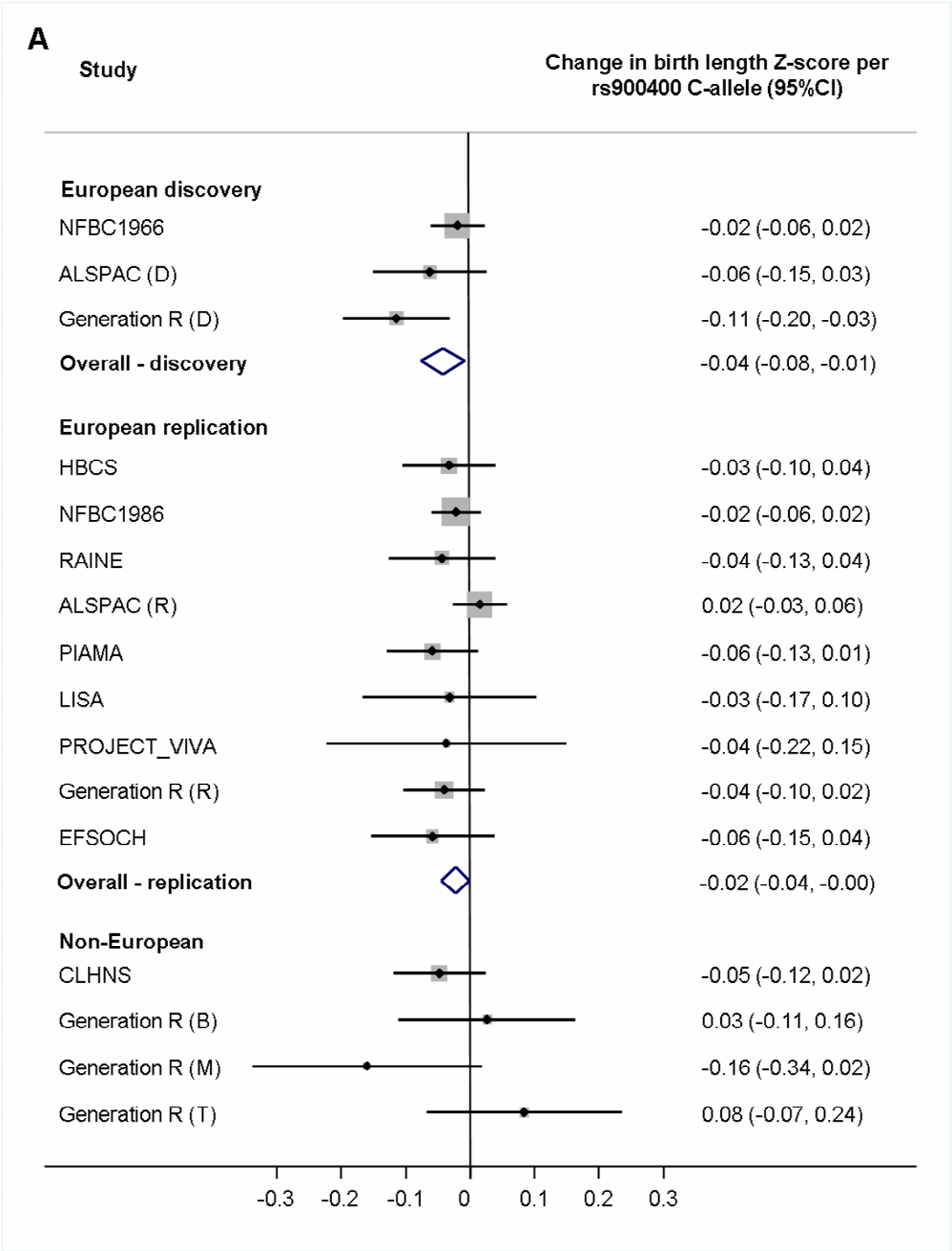
Supplementary Table 5. Associations between known risk loci for type 2 diabetes (T2D) or raised fasting glucose (FPG) and birth weight

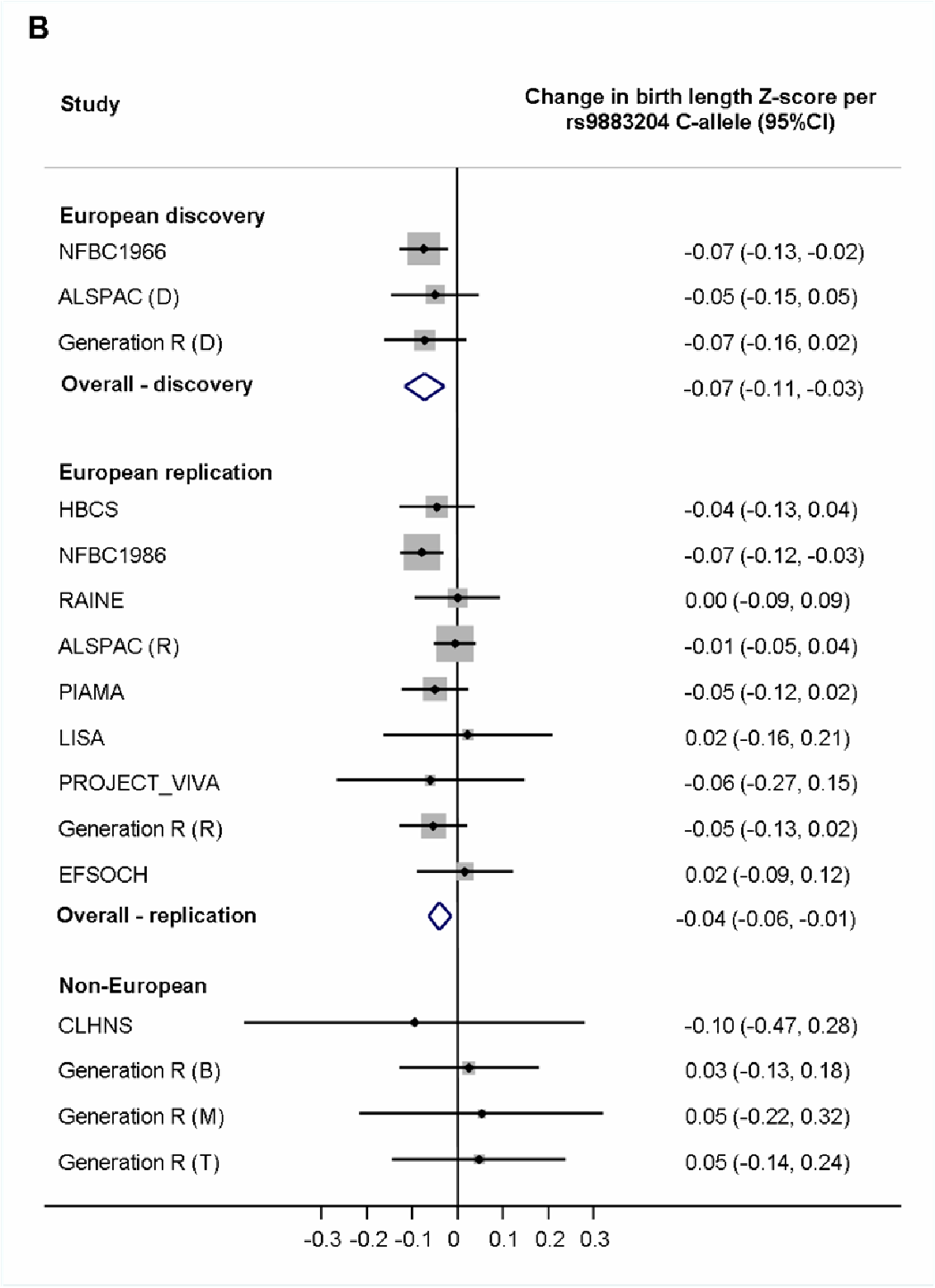
SNP	Gene(s) marking association signal	Trait	Risk allele	Other allele	Per-risk allele association with BW Z-score (adjusted for sex and gestational age) in discovery meta-analysis (N=10623)	SE	*P* value
rs10923931	*NOTCH2*	T2D	g	t	0.0047	0.0207	0.82
rs7578597	*THADA*	T2D	c	t	0.0034	0.0232	0.88
rs1801282	*PPARG*	T2D	g	c	0.0061	0.0186	0.74
rs4607103	*ADAMTS9*	T2D	c	t	0.0137	0.0158	0.39
rs4402960	*IGF2BP2*	T2D	g	t	0.0039	0.0143	0.79
rs10010131	*WFS1*	T2D	g	a	-0.0116	0.0135	0.39
rs10946398	*CDKAL1*	T2D	c	a	-0.0519	0.0138	0.0002
rs864745	*JAZF1*	T2D	c	t	0.0015	0.0132	0.91
rs10811661	*CDKN2A,CDKN2B*	T2D	c	t	-0.0197	0.0182	0.28
rs12779790	*CDC123,CAMK1D*	T2D	g	a	0.0227	0.0173	0.19
rs1111875	*IDE,KIF11,HHEX*	T2D	c	t	-0.0095	0.0133	0.48
rs2237892	*KCNQ1*	T2D	c	t	-0.0257	0.0286	0.37
rs5215	*KCNJ11*	T2D	c	t	-0.0118	0.0134	0.38
rs7961581	*TSPAN8*	T2D	c	t	-0.0121	0.0158	0.45
rs8050136	*FTO*	T2D	c	a	-0.0106	0.0135	0.43
rs4430796	*TCF2*	T2D	g	a	0.009	0.015	0.55
rs7901695	*TCF7L2*	T2D, FPG	c	t	0.0204	0.015	0.17
rs13266634	*SLC30A8*	T2D, FPG	c	t	0.0251	0.0145	0.08
rs10830963	*MTNR1B*	T2D, FPG	g	c	0.0331	0.0158	0.04
rs2877716	*ADCY5*	T2D, FPG	c	t	-0.0835	0.0158	0.0000001
rs2191349	*DGKB*	T2D, FPG	g	t	-0.0022	0.0132	0.87
rs780094	*GCKR*	T2D, FPG	c	t	-0.0169	0.0136	0.21
rs4607517	*GCK*	T2D, FPG	g	a	-0.0442	0.0181	0.01
rs340874	*PROX1*	T2D, FPG	c	t	-0.0113	0.0133	0.40
rs7034200	*GLIS3*	FPG	c	a	0.0146	0.0132	0.27
rs11605924	*CRY2*	FPG	c	a	-0.0014	0.0133	0.92
rs7944584	*MADD*	FPG	t	a	0.0134	0.0156	0.39
rs11071657	*FAM148B*	FPG	g	a	0.0062	0.0139	0.66
rs174550	*FADS1*	FPG	c	t	0.0191	0.0137	0.16
rs10885122	*ADRA2A*	FPG	g	t	-0.011	0.0207	0.60
rs560887	*G6PC2*	FPG	c	t	-0.0225	0.0143	0.12
rs11920090	*SLC2A2*	FPG	t	a	-0.0131	0.0192	0.50

Supplementary Figure 1. Quantile-quantile plot of 2,427,548 SNPs from the meta-analysis of N=10,623 discovery samples. The blue dots represent observed *P* values and the black line represents expected *P* values under the null distribution. The grey area defines the 95% concentration bands, which are an approximation to the 95% confidence intervals around the expected line.

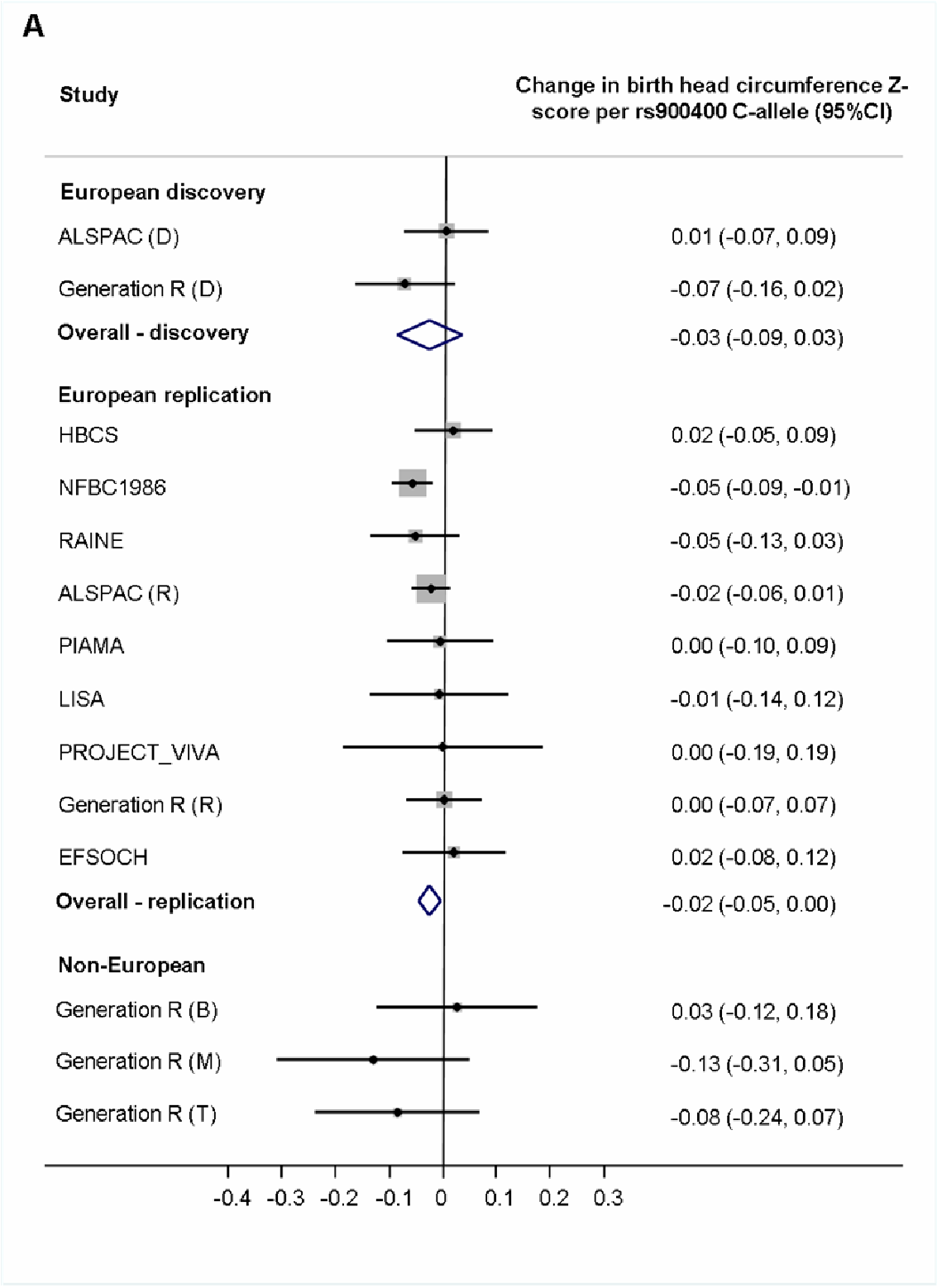


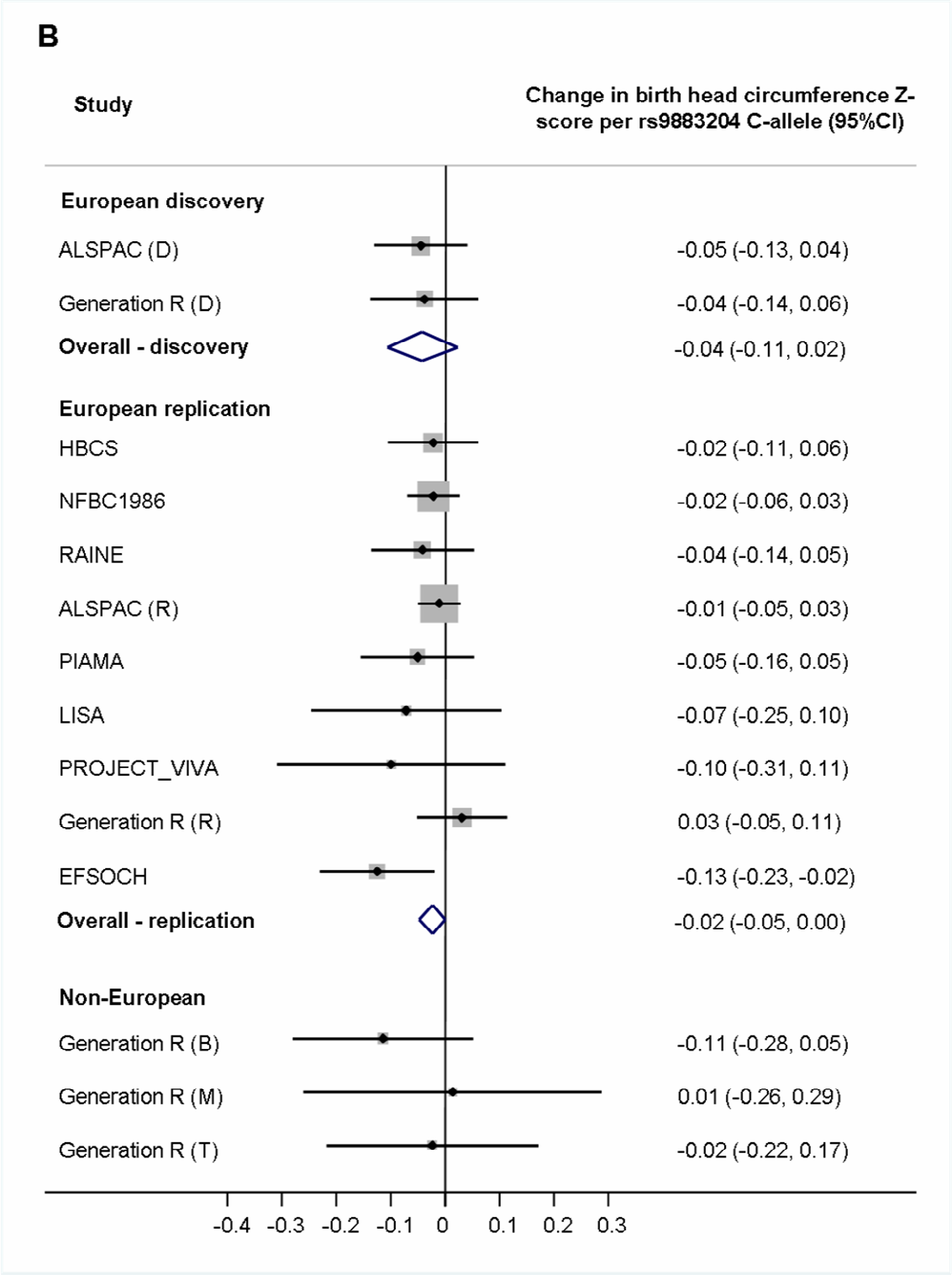
Supplementary Figure 2. Forest plots of the association between birth length and each additional C-allele of **[A]** rs900400 at 3q25 and **[B]** rs9883204 at 3q21 in all available studies. If the index SNP was unavailable, a closely-correlated proxy (HapMap r^2>0.9) was used.



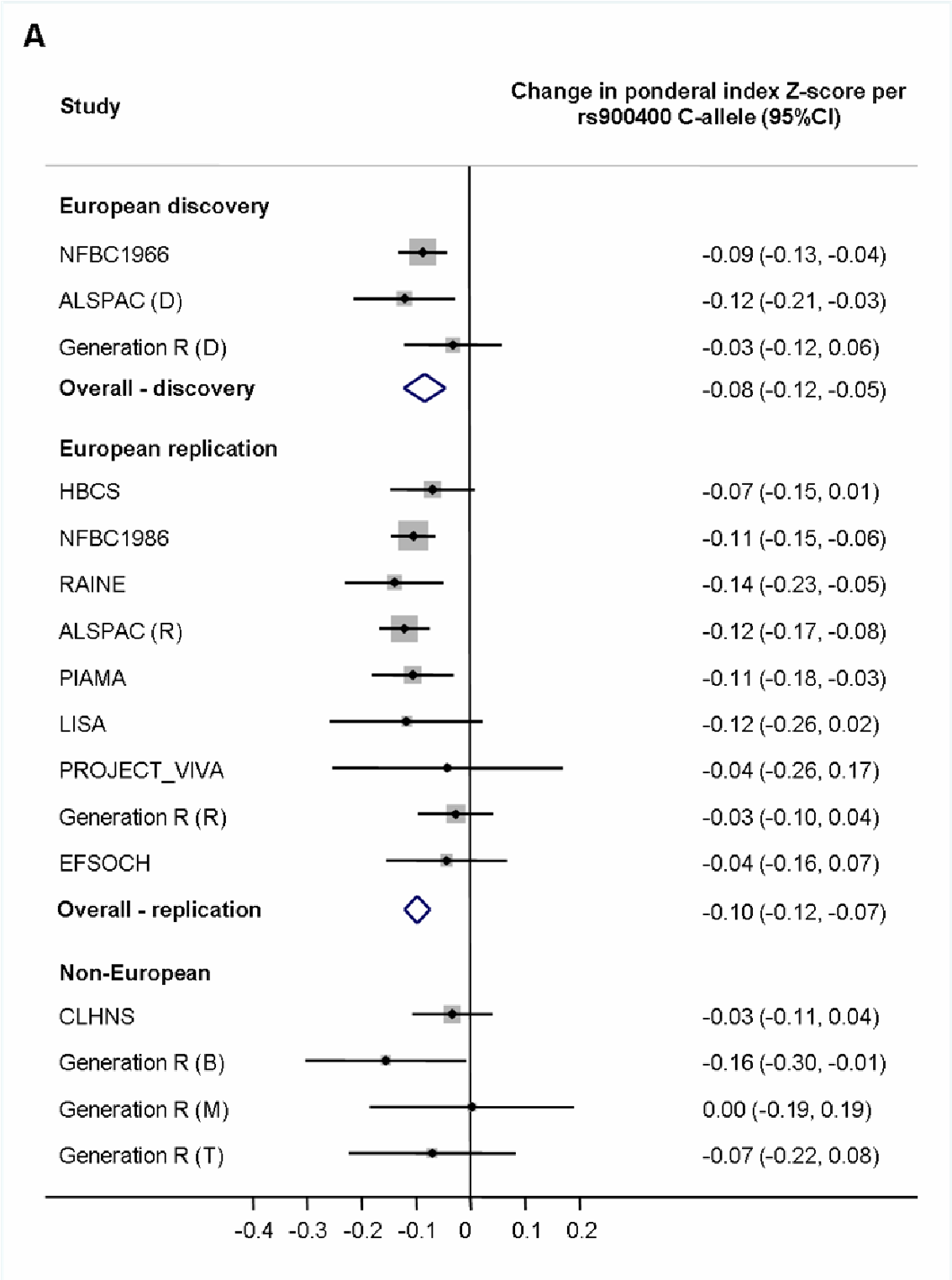

B
Study
Change in birth length Z-score per rs9883204 C-allele (95%CI)
European discovery
NFBC1966
-0.07 (-0.13, -0.02)
ALSPAC (D)
-0.05 (-0.15, 0.05)
Generation R (D)
-0.07 (-0.16, 0.02)
Overall - discovery
-0.07 (-0.11, -0.03)
European replication
HBCS
-0.04 (-0.13, 0.04)
NFBC1986
-0.07 (-0.12, -0.03)
RAINE
0.00 (-0.09, 0.09)
ALSPAC (R)
-0.01 (-0.05, 0.04)
PIAMA
-0.05 (-0.12, 0.02)
LISA
0.02 (-0.16, 0.21)
PROJECT_VIVA
-0.06 (-0.27, 0.15)
Generation R (R)
-0.05 (-0.13, 0.02)
EFSOCH
0.02 (-0.09, 0.12)
Overall - replication
-0.04 (-0.06, -0.01)
Non-European
CLHNS
-0.10 (-0.47, 0.28)
Generation R (B)
0.03 (-0.13, 0.18)
Generation R (M)
0.05 (-0.22, 0.32)
Generation R (T)
0.05 (-0.14, 0.24)
-0.3 -0.2 -0.1 0 0.1 0.2 0.3

Supplementary Figure 3. Forest plots of the association between birth head circumference and each additional C-allele of **[A]** rs900400 at 3q25 and **[B]** rs9883204 at 3q21 in all available studies. If the index SNP was unavailable, a closely-correlated proxy (HapMap r^2>0.9) was used.

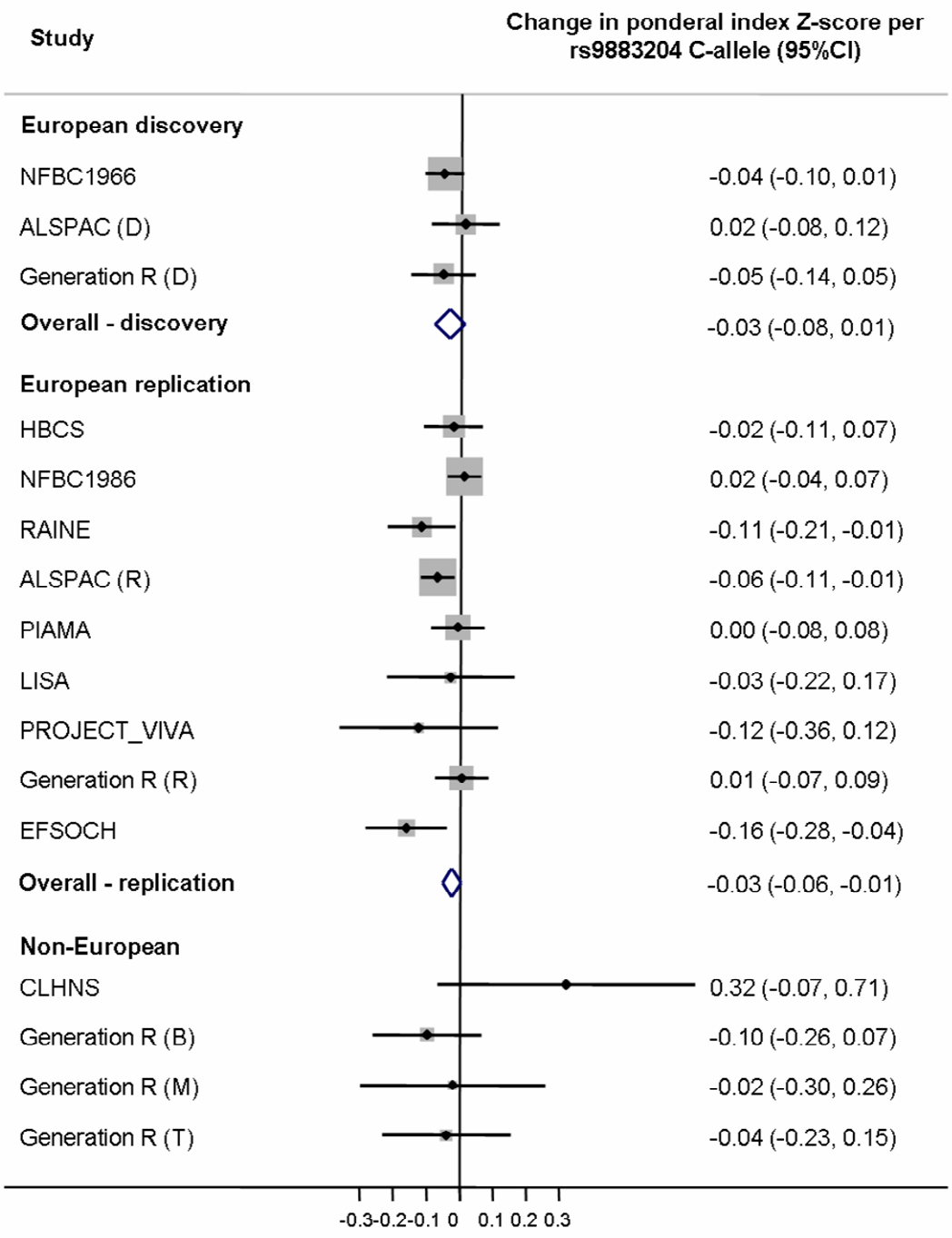



B
Study
Change in birth head circumference Z-score per rs9883204 C-allele (95%CI)
European discovery
ALSPAC (D)
-0.05 (-0.13, 0.04)
Generation R (D)
-0.04 (-0.14, 0.06)
Overall - discovery
-0.04 (-0.11, 0.02)
European replication
HBCS
-0.02 (-0.11, 0.06)
NFBC1986
-0.02 (-0.06, 0.03)
RAINE
-0.04 (-0.14, 0.05)
ALSPAC (R)
-0.01 (-0.05, 0.03)
PIAMA
-0.05 (-0.16, 0.05)
LISA
-0.07 (-0.25, 0.10)
PROJECT_VIVA
-0.10 (-0.31, 0.11)
Generation R (R)
0.03 (-0.05, 0.11)
EFSOCH
-0.13 (-0.23, -0.02)
Overall - replication
-0.02 (-0.05, 0.00)
Non-European
Generation R (B)
-0.11 (-0.28, 0.05)
Generation R (M)
0.01 (-0.26, 0.29)
Generation R (T)
-0.02 (-0.22, 0.17)
-0.4 -0.3 -0.2 -0.1 0 0.1 0.2 0.3

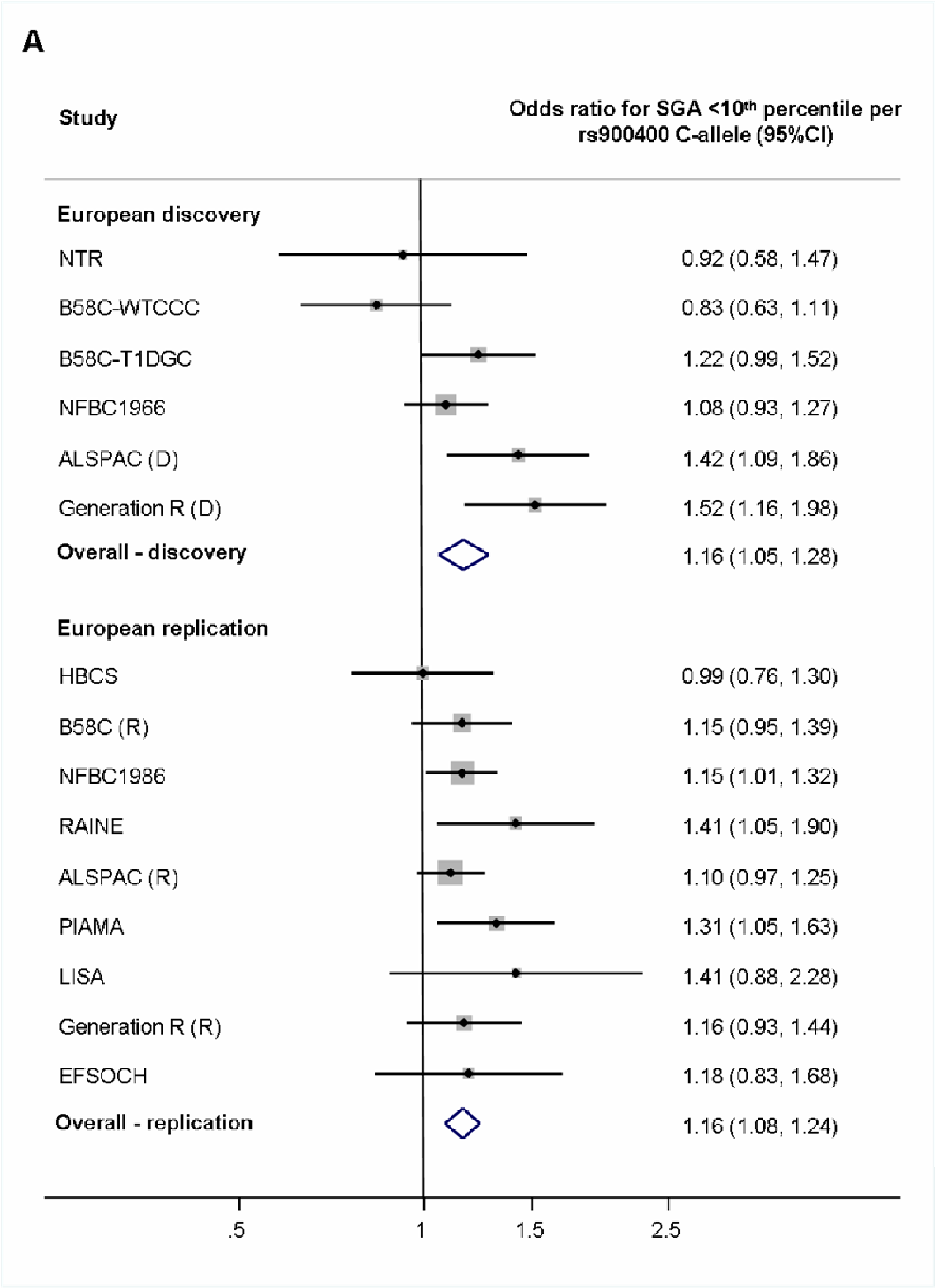
Supplementary Figure 4. Forest plots of the association between ponderal index at birth Z-score and each additional C-allele of **[A]** rs900400 at 3q25 and **[B]** rs9883204 at 3q21 in all available studies. If the index SNP was unavailable, a closely-correlated proxy (HapMap r^2>0.9) was used.



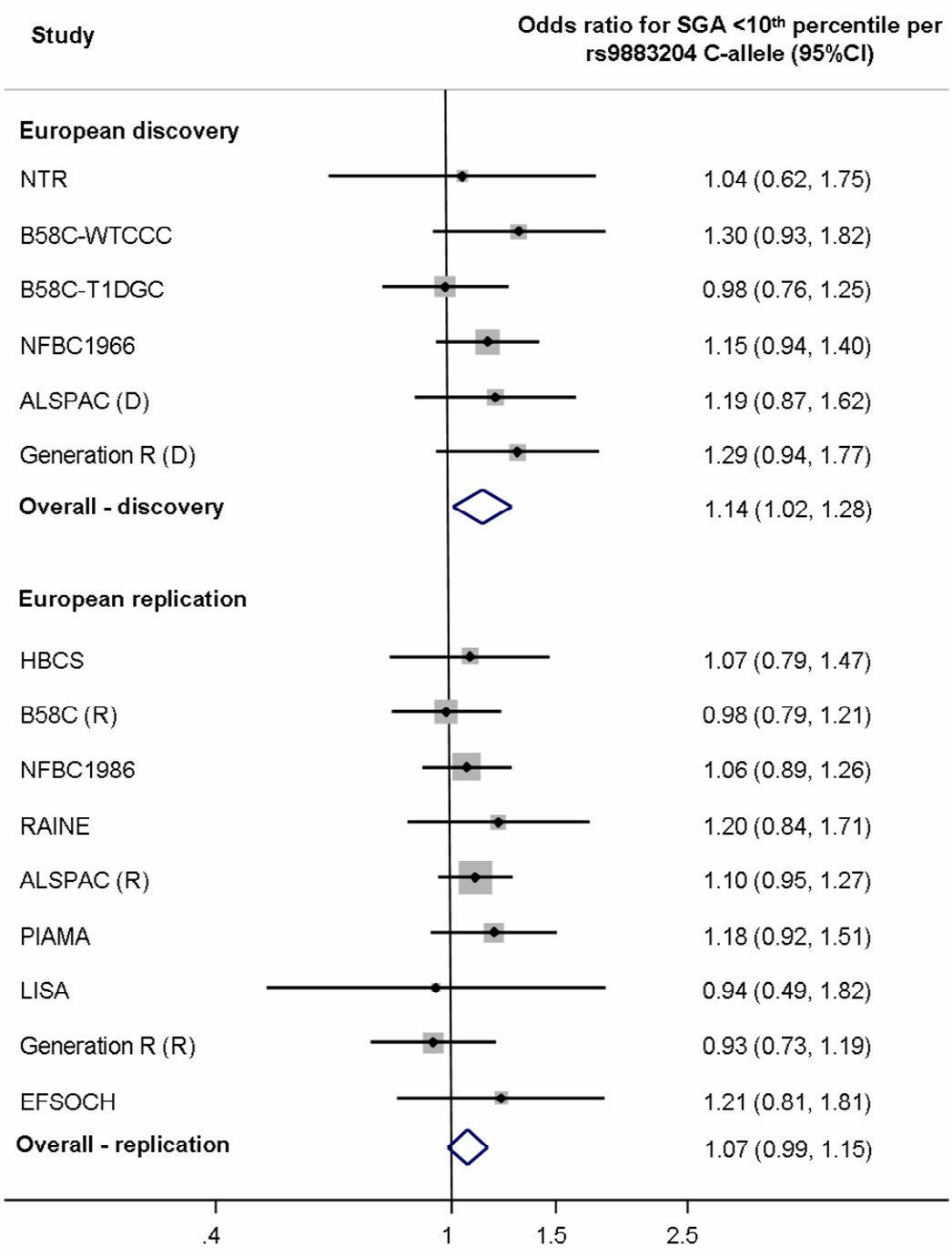
B


Study
Change in ponderal index Z-score per rs9883204 C-allele (95%CI)
European discovery
NFBC1966
-0.04 (-0.10, 0.01)
ALSPAC (D)
0.02 (-0.08, 0.12)
Generation R (D)
-0.05 (-0.14, 0.05)
Overall - discovery
-0.03 (-0.08, 0.01)
European replication
HBCS
-0.02 (-0.11, 0.07)
NFBC1986
0.02 (-0.04, 0.07)
RAINE
-0.11 (-0.21, -0.01)
ALSPAC (R)
-0.06 (-0.11, -0.01)
PIAMA
0.00 (-0.08, 0.08)
LISA
-0.03 (-0.22, 0.17)
PROJECT_VIVA
-0.12 (-0.36, 0.12)
Generation R (R)
0.01 (-0.07, 0.09)
EFSOCH
-0.16 (-0.28, -0.04)
Overall - replication
-0.03 (-0.06, -0.01)
Non-European
CLHNS
0.32 (-0.07, 0.71)
Generation R (B)
-0.10 (-0.26, 0.07)
Generation R (M)
-0.02 (-0.30, 0.26)
Generation R (T)
-0.04 (-0.23, 0.15)
-0.3 -0.2 -0.1 0 0.1 0.2 0.3

Supplementary Figure 5. Forest plots showing the odds of being born small for gestational age (SGA, <10th percentile) associated with each additional C-allele of **[A]** rs900400 at 3q25 and **[B]** rs9883204 at 3q21, in 15 available studies. If the index SNP was unavailable, a closely-correlated proxy (HapMap r^2>0.9) was used.



B


Study
Odds ratio for SGA <10th percentile per rs9883204 C-allele (95%CI)
European discovery
NTR
1.04 (0.62, 1.75)
B58C-WTCCC
1.30 (0.93, 1.82)
B58C-T1DGC
0.98 (0.76, 1.25)
NFBC1966
1.15 (0.94, 1.40)
ALSPAC (D)
1.19 (0.87, 1.62)
Generation R (D)
1.29 (0.94, 1.77)
Overall - discovery
1.14 (1.02, 1.28)
European replication
HBCS
1.07 (0.79, 1.47)
B58C (R)
0.98 (0.79, 1.21)
NFBC1986
1.06 (0.89, 1.26)
RAINE
1.20 (0.84, 1.71)
ALSPAC (R)
1.10 (0.95, 1.27)
PIAMA
1.18 (0.92, 1.51)
LISA
0.94 (0.49, 1.82)
Generation R (R)
0.93 (0.73, 1.19)
EFSOCH
1.21 (0.81, 1.81)
Overall - replication
1.07 (0.99, 1.15)
.4
1
1.5
2.5

SUPPLEMENTARY NOTE

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GENETIC INVESTIGATION OF ANTHROPOMETRIC TRAITS (GIANT) CONSORTIUM MEMBERSHIP AND AFFILIATIONS

Cristen J. Willer[1]*, Elizabeth K. Speliotes[2,3]*, Ruth J.F. Loos[4,5]*, Shengxu Li[4,5]*, Cecilia M. Lindgren[6], Iris M. Heid[7], Sonja I. Berndt[8], Amanda L. Elliott[9,10], Anne U. Jackson[1], Claudia Lamina[7], Guillaume Lettre[9,11], Noha Lim[12], Helen N. Lyon[3,11], Steven A. McCarroll[9,10], Konstantinos Papadakis[13], Lu Qi[14,15], Joshua C. Randall[6], Rosa Maria Roccasecca[16], Serena Sanna[17], Paul Scheet[18], Michael N. Weedon[19], Eleanor Wheeler[16], Jing Hua Zhao[4,5], Leonie C. Jacobs[20], Inga Prokopenko[6,21], Nicole Soranzo[16,22], Toshiko Tanaka[23], Nicholas J. Timpson[24], Peter Almgren[25], Amanda Bennett[26], Richard N. Bergman[27], Sheila A. Bingham[28,29], Lori L. Bonnycastle[30], Morris Brown[31], Noël P. Burtt[9], Peter Chines[30], Lachlan Coin[32], Francis S. Collins[30], John M. Connell[33], Cyrus Cooper[34], George Davey Smith[24], Elaine M. Dennison[34], Parimal Deodhar[30], Paul Elliott[32], Michael R. Erdos[30], Karol Estrada[20], David M. Evans[24], Lauren Gianniny[9], Christian Gieger[7], Christopher J. Gillson[4,5], Candace Guiducci[9], Rachel Hackett[9], David Hadley[13], Alistair S. Hall[35], Aki S. Havulinna[36], Johannes Hebebrand[37], Albert Hofman[38], Bo Isomaa[39], Kevin B. Jacobs[40], Toby Johnson[41,42,43], Pekka Jousilahti[36], Zorica Jovanovic[5,44], Kay-Tee Khaw[45], Peter Kraft[46], Mikko Kuokkanen[9,47], Johanna Kuusisto[48], Jaana Laitinen[49], Edward G. Lakatta[50], Jian'an Luan[4,5], Robert N. Luben[45], Massimo Mangino[51], Wendy L. McArdle[52], Thomas Meitinger[53,54], Antonella Mulas[17], Patricia B. Munroe[55], Narisu Narisu[30], Andrew R. Ness[56], Kate Northstone[52], Stephen O'Rahilly[5,44], Carolin Purmann[5,44], Matthew G. Rees[30], Martin Ridderstråle[57], Susan M. Ring[52], Fernando Rivadeneira[20,38], Aimo Ruokonen[58], Manjinder S. Sandhu[4,45], Jouko Saramies[59], Laura J. Scott[1], Angelo Scuteri[60], Kaisa Silander[47], Matthew A. Sims[4,5], Kijoung Song[12], Jonathan Stephens[61], Suzanne Stevens[51], Heather M. Stringham[1], Y.C. Loraine Tung[5,44], Timo T. Valle[62], Cornelia M. Van Duijn[38], Karani S. Vimaleswaran[4,5], Peter Vollenweider[63], Gerard Waeber[63], Chris Wallace[55], Richard M. Watanabe[64], Dawn M. Waterworth[12], Nicholas Watkins[61], The Wellcome Trust Case Control Consortium[65], Jacqueline C.M. Witteman[38], Eleftheria Zeggini[6], Guangju Zhai[22], M. Carola Zillikens[20], David Altshuler[9,10], Mark J. Caulfield[55], Stephen J. Chanock[8], I. Sadaf Farooqi[5,44], Luigi Ferrucci[23], Jack M. Guralnik[66], Andrew T. Hattersley[67], Frank B. Hu[14,15], Marjo-Riitta Jarvelin[32], Markku Laakso[48], Vincent Mooser[12], Ken K. Ong[4,5], Willem H. Ouwehand[16,61], Veikko Salomaa[36], Nilesh J. Samani[51], Timothy D. Spector[22], Tiinamaija Tuomi[68,69], Jaakko Tuomilehto[62], Manuela Uda[17], André G. Uitterlinden[20,38], Nicholas J. Wareham[4,5], Panagiotis Deloukas[16], Timothy M. Frayling[19], Leif C. Groop[25,70], Richard B. Hayes[8], David J. Hunter[9,14,15,46], Karen L. Mohlke[71], Leena Peltonen[9,16,72], David Schlessinger[73], David P. Strachan[13], H-Erich Wichmann[7,74], Mark I. McCarthy[6,21,75]***, Michael Boehnke[1]***, Inês Barroso[16]***, Gonçalo R. Abecasis[18]***, Joel N. Hirschhorn[3,11,76]***

1. Department of Biostatistics, School of Public Health, University of Michigan, Ann Arbor, MI 48109, USA
2. Division of Gastroenterology, Massachusetts General Hospital, Boston, MA 02114, USA
3. Metabolism Initiative and Program in Medical and Population Genetics, Broad Institute of Harvard and MIT, Boston, MA 02142, USA
4. MRC Epidemiology Unit, Addenbrooke's Hospital, Cambridge CB2 0QQ, UK
5. Institute of Metabolic Science, Addenbrooke's Hospital, Cambridge CB2 0QQ, UK
6. Wellcome Trust Centre for Human Genetics, University of Oxford, Oxford OX3 7BN, UK
7. Institute of Epidemiology, Helmholtz Zentrum München, Ingolstaedter Landstr. 1, 85764 Neuherberg, Germany
8. Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Department of Health and Human Services, Bethesda, MD 20892, USA
9. Program in Medical and Population Genetics, Broad Institute of MIT and Harvard, Cambridge, MA 02142, USA
10. Department of Molecular Biology, Massachusetts General Hospital, Cambridge, MA 02144, USA
11. Program in Genomics and Divisions of Endocrinology and Genetics, Children's Hospital, Boston, MA 02115, USA

12. Medical Genetics/Clinical Pharmacology and Discovery Medicine, PA 19406, USA
13. Division of Community Health Sciences, St George's, University of London, London SW17 0RE, UK
14. Department of Nutrition, Harvard School of Public Health, Boston, MA 02115, USA
15. Channing Laboratory, Department of Medicine, Brigham and Women's Hospital, Boston, MA 02115, USA
16. Wellcome Trust Sanger Institute, Hinxton, Cambridge CB10 1SA, UK
17. Istituto di Neurogenetica e Neurofarmacologia, Consiglio Nazionale delle Ricerche, Cagliari, Italy
18. Center for Statistical Genetics, Department of Biostatistics, University of Michigan, Ann Arbor, MI 48109, USA
19. Genetics of Complex Traits, Peninsula Medical School, Exeter EX1 2LU, UK
20. Department of Internal Medicine, Erasmus MC, PO Box 2400, NL-3000-CA Rotterdam, The Netherlands
21. Oxford Centre for Diabetes, Endocrinology and Metabolism, University of Oxford, Churchill Hospital, Oxford OX3 7LJ, UK
22. Department of Twin Research and Genetic Epidemiology, King's College London, London SE1 7EH, UK
23. National institute of Aging, Clinical research branch - Longitudinal Studies Section, Baltimore, MD 21225, USA
24. MRC Centre for Causal Analyses in Translational Epidemiology, Department of Social Medicine, University of Bristol, Bristol BS8 2PR, UK
25. Lund University Diabetes Centre, Department of Clinical Sciences, Lund University, 20502 Malmö, Sweden
26. DRL, OCDEM, Churchill Hospital, Headington, Oxford OX3 7LJ, UK
27. Physiology and Biophysics, University of Southern California School of Medicine, Los Angeles, CA 90033, USA
28. MRC Dunn Human Nutrition Unit, Wellcome Trust/MRC Building, Cambridge CB2 0XY, UK
29. MRC Centre for Nutritional Epidemiology in Cancer Prevention and Survival, Cambridge CB1 8RN, UK
30. National Human Genome Research Institute, Bethesda, MD 20892, USA
31. Clinical Pharmacology Unit, University of Cambridge, Addenbrooke's Hospital, Cambridge, UK
32. Department of Epidemiology and Public Health, Imperial College London, St Mary's Campus, Norfolk Place, W2 1PG London, UK
33. BHF Glasgow Cardiovascular Research Centre, Faculty of Medicine, University of Glasgow, Glasgow G12 8TA, UK
34. MRC Epidemiology Resource Centre, (University of Southampton), Southampton General Hospital, Southampton SO16 6YD, UK.
35. Yorkshire Heart Centre, Leeds General Infirmary, Leeds LS1 3EX, UK
36. KTL-National Public Health Institute, FI-00300 Helsinki, Finland
37. Department of Child and Adolescent Psychiatry, University of Duisburg-Essen, Virchowstr. 174, 45147 Essen, Germany
38. Department of Epidemiology, Erasmus MC, PO Box 2400, NL-3000-CA Rotterdam, The Netherlands
39. Folkhalsan Research Center, Malmska Municipal Health Center and Hospital, Jakobstad, Finland
40. Bioinformed Consulting Services, Gaithersburg, MD 20877, USA
41. Department of Medical Genetics, University of Lausanne, 1005 Lausanne, Switzerland
42. University Institute for Social and Preventative Medicine, Centre Hospitalier Universitaire Vaudois (CHUV), 1005 Lausanne, Switzerland
43. Swiss Institute of Bioinformatics, Switzerland
44. University of Cambridge Metabolic Research Laboratories, Addenbrooke's Hospital, Cambridge CB2 0QQ, UK
45. Department of Public Health and Primary Care, Institute of Public Health, University of Cambridge, Cambridge CB2 0SR, UK
46. Program in Molecular and Genetic Epidemiology, Harvard School of Public Health, Boston, MA 02115, USA
47. Department of Molecular Medicine, National Public Health Institute, FIN-00300 Helsinki, Finland
48. Department of Medicine, University of Kuopio, 70210 Kuopio, Finland
49. Finnish Institute of Occpational Health, Aapistie 1, Fin-90220 Oulu, Finland
50. Laboratory of Cardiovascular Science, Gerontology Research Center, National Institute on Aging,Baltimore, MD 21224, USA
51. Department of Cardiovascular Sciences, University of Leicester, Clinical Sciences, Glenfield General Hospital, Leicester LE3 9QP, UK
52. ALSPAC, Department of Social Medicine, University of Bristol, Bristol BS8 1TQ, UK
53. Institute of Human Genetics, Helmholtz Zentrum München, Ingolstaedter Landstr. 1, 85764 Neuherberg, Germany

54. Institute of Human Genetics, Technical University Munich, D-81765, Munich, Germany
55. Clinical Pharmacology, The William Harvey Research Institute, Bart's and The London, Queen Mary's School of Medicine and Dentistry, Charterhouse Square, London EC1M 6BQ, UK
56. Department of Oral & Dental Science, Bristol BS1 2LY, UK
57. Department of Clinical Sciences, Lund University, 20502 Malmö, Sweden
58. Department of Clinical Chemistry, University of Oulu, Fin-90220, Oulu, Finland
59. Savitaipale Health Center, Savitaipale, Finland
60. Unita' Operativa Geriatria - Istituto Nazionale Ricovero e Cura Anziani - Rome, Italy
61. Department of Haematology, University of Cambridge/NHS Blood & Transplant, Cambridge CB2 2PR, UK
62. National Public Health Institute, Department of Epidemiology and Health Promotion, Mannerheimintie 166, FIN-00300 Helsinki, FINLAND
63. Department of Internal Medicine, BH-10 Centre Hospitalier Universitaire Vaudois (CHUV), 1011 Lausanne, Switzerland
64. Department of Preventive Medicine, Division of Biostatistics, Keck School of Medicine, University of Southern California, CHP-220, Los Angeles, CA 90089, USA
65. The membership of this consortium is listed in the supplementary material.
66. Laboratory of Epidemiology, Demography, and Biometry; Gerontology Research Center, National Institute on Aging, Bethesda, MD 20892, USA
67. Peninsula Medical School, Exeter EX5 2DW, UK
68. 3 Department of Medicine, Helsinki University Central Hospital, Helsinki, Finland
69. Research Program of Molecular Medicine, University of Helsinki, Helsinki, Finland
70. Department of Medicine, Helsinki University, Helsinki, Finland
71. Department of Genetics, University of North Carolina, CB #7264, Chapel Hill, NC 27599, USA
72. Institute of Molecular Medicine, University of Helsinki, Finland
73. Laboratory of Genetics, NIH Biomedical Research Center, National Institute on Aging, Baltimore, MD 21224, USA
74. Institute of Medical Information Processing, Biometry, and Epidemiology, Ludwig-Maximilians-University München, Marchioninistr. 15, 81377 München, Germany
75. NIHR Oxford Biomedical Research Centre, University of Oxford, Old Road, Headington, Oxford OX3 7LJ, UK
76. Department of Genetics, Harvard Medical School, Boston, MA 02115, USA

META-ANALYSES OF GLUCOSE AND INSULIN-RELATED TRAITS CONSORTIUM (MAGIC) MEMBERSHIP AND AFFILIATIONS

Josée Dupuis[1,2], Claudia Langenberg[3], Inga Prokopenko[4,5], Richa Saxena[6,7], Nicole Soranzo[8,9], Anne U Jackson[10], Eleanor Wheeler[11], Nicole L Glazer[12], Nabila Bouatia-Naji[13], Anna L Gloyn[4], Cecilia M Lindgren[4,5], Reedik Mägi[4,5], Andrew P Morris[5], Joshua Randall[5], Toby Johnson[14–16], Paul Elliott[17,176], Denis Rybin[18], Gudmar Thorleifsson[19], Valgerdur Steinthorsdottir[19], Peter Henneman[20], Harald Grallert[21], Abbas Dehghan[22], Jouke Jan Hottenga[23], Christopher S Franklin[24], Pau Navarro[25], Kijoung Song[26], Anuj Goel[5,27], John R B Perry[28], Josephine M Egan[29], Taina Lajunen[30], Niels Grarup[31], Thomas Sparsø[31], Alex Doney[32], Benjamin F Voight[6,7], Heather M Stringham[10], Man Li[33], Stavroula Kanoni[34], Peter Shrader[35], Christine Cavalcanti-Proença[13], Meena Kumari[36], Lu Qi[37], Nicholas J Timpson[38], Christian Gieger[21], Carina Zabena[39], Ghislain Rocheleau[40,41], Erik Ingelsson[42,43], Ping An[44], Jeffrey O'Connell[45], Jian'an Luan[3], Amanda Elliott[6,7], Steven A McCarroll[6,7], Felicity Payne[11], Rosa Maria Roccasecca[11], François Pattou[46], Praveen Sethupathy[47], Kristin Ardlie[48], Yavuz Ariyurek[49], Beverley Balkau[50], Philip Barter[51], John P Beilby[52,53], Yoav Ben-Shlomo[54], Rafn Benediktsson[55,56], Amanda J Bennett[4], Sven Bergmann[14,16], Murielle Bochud[15], Eric Boerwinkle[57], Amélie Bonnefond[13], Lori LBonnycastle[47], Knut Borch-Johnsen[58,59], Yvonne Böttcher[60], Eric Brunner[36], Suzannah J Bumpstead[8], Guillaume Charpentier[61], Yii-Der Ida Chen[62], Peter Chines[47], Robert Clarke[63], Lachlan J MCoin[17], Matthew N Cooper[64], Marilyn Cornelis[37], Gabe Crawford[6], Laura Crisponi[65], Ian N M Day[38], Eco J C de Geus[23], Jerome Delplanque[13], Christian Dina[13], Michael R Erdos[47], Annette C Fedson[64,66], Antje Fischer-Rosinsky[67,68], Nita G Forouhi[3], Caroline S Fox[2,69], Rune Frants[70], Maria Grazia Franzosi[71], Pilar Galan[72], Mark O Goodarzi[62], Jürgen Graessler[73], Christopher J Groves[4], Scott Grundy[74], Rhian Gwilliam[8], Ulf Gyllensten[75], Samy Hadjadj[76], Göran Hallmans[77], Naomi Hammond[8], Xijing Han[10], Anna-Liisa Hartikainen[78], Neelam Hassanali[4], Caroline Hayward[25], Simon C Heath[79], Serge Hercberg[80], Christian Herder[81], Andrew A Hicks[82], David R Hillman[66,83], Aroon D Hingorani[36], Albert Hofman[22], Jennie Hui[52,84], Joe Hung[85,86], Bo Isomaa[87,88], Paul R V Johnson[4,89], Torben Jørgensen[90,91], Antti Jula[92], Marika Kaakinen[93], Jaakko Kaprio[94–96], Y Antero Kesaniemi[97], Mika Kivimaki[36], Beatrice Knight[98], Seppo Koskinen[99], Peter Kovacs[100], Kirsten Ohm Kyvik[101], G Mark Lathrop[79], Debbie A Lawlor[38], Olivier Le Bacquer[13], Cécile Lecoeur[13], Yun Li[10], Valeriya Lyssenko[102], Robert Mahley[103], Massimo Mangino[9], Alisa K Manning[1], María Teresa Martínez-Larrad[39], Jarred B McAteer[6,104,105], Laura J McCulloch[4], Ruth McPherson[106], Christa Meisinger[21], David Melzer[28], David Meyre[13], Braxton D Mitchell[45], Mario A Morken[47], Sutapa Mukherjee[66,83], Silvia Naitza[65], Narisu Narisu[47], Matthew J Neville[4,107], Ben A Oostra[108], Marco Orrù[65], Ruth Pakyz[45], Colin N A Palmer[109], Giuseppe Paolisso[110], Cristian Pattaro[82], Daniel Pearson[47], John F Peden[5,27], Nancy L Pedersen[42], Markus Perola[96,111,112], Andreas F H Pfeiffer[67,68], Irene Pichler[82], Ozren Polasek[113], Danielle Posthuma[23,114], Simon C Potter[8], Anneli Pouta[115], Michael A Province[44], Bruce M Psaty[116,117], Wolfgang Rathmann[118], Nigel W Rayner[4,5], Kenneth Rice[119], Samuli Ripatti[96,111], Fernando Rivadeneira[22,120], Michael Roden[81,121], Olov Rolandsson[122], Annelli Sandbaek[123], Manjinder Sandhu[3,124], Serena Sanna[65], Avan Aihie Sayer[125], Paul Scheet[126], Laura J Scott[10], Udo Seedorf[127], Stephen J Sharp[3], Beverley Shields[98], Gunnar Sigurðsson[55,56], Eric J G Sijbrands[22,120], Angela Silveira[128], Laila Simpson[64,66], Andrew Singleton[129], Nicholas L Smith[130,131], Ulla Sovio[17], Amy Swift[47], Holly Syddall[125], Ann-Christine Syvänen[132], Toshiko Tanaka[133,134], Barbara Thorand[21], Jean Tichet[135], Anke Tönjes[60,136], Tiinamaija Tuomi[87,137], André G Uitterlinden[22,120], Ko Willems van Dijk[70,138], Mandy van Hoek[120], Dhiraj Varma[8], Sophie Visvikis-Siest[139], Veronique Vitart[25], Nicole Vogelzangs[140], Gérard Waeber[141], Peter J Wagner[96,111], Andrew Walley[142], G Bragi Walters[19], Kim L Ward[64,66], Hugh Watkins[5,27], Michael N Weedon[28], Sarah H Wild[24], Gonneke Willemsen[23], Jaqueline C M Witteman[22], John W G Yarnell[143], Eleftheria Zeggini[5,8], Diana Zelenika[79], Björn Zethelius[43,144], Guangju Zhai[9], Jing Hua Zhao[3], M Carola Zillikens[120], DIAGRAM Consortium[145], GIANT Consortium[145], Global B P gen Consortium [145], Ingrid B Borecki[44], Ruth J F Loos[3], Pierre Meneton[80], Patrik K E Magnusson[42], David M Nathan[104,105], Gordon

H Williams[69,105], Andrew T Hattersley[98], Kaisa Silander[96,111], Veikko Salomaa[146], George Davey Smith[38], Stefan R Bornstein[73], Peter Schwarz[73], Joachim Spranger[67,68], Fredrik Karpe[4,107], Alan R Shuldiner[45], Cyrus Cooper[125], George V Dedoussis[34], Manuel Serrano-Ríos[39], Andrew D Morris[109], Lars Lind[132], Lyle J Palmer[64,66,84], Frank B Hu[147,148], Paul W Franks[149], Shah Ebrahim[150], Michael Marmot[36], WH Linda Kao[33,151,152], James S Pankow[153], Michael J Sampson[154], Johanna Kuusisto[155], Markku Laakso[155], Torben Hansen[31,156], Oluf Pedersen[31,59,157], Peter Paul Pramstaller[82,158,159], H Erich Wichmann[21,160,161], Thomas Illig[21], Igor Rudan[24,162,163], Alan F Wright[25], Michael Stumvoll[60], Harry Campbell[24], James F Wilson[24], Anders Hamsten on behalf of Procardis Consortium[128], Richard N Bergman[164], Thomas A Buchanan[164,165], Francis S Collins[47], Karen L Mohlke[166], Jaakko Tuomilehto[94,167], Timo T Valle[167], David Altshuler[6,7,104,105], Jerome I Rotter[62], David S Siscovick[168], Brenda WJ H Penninx[140], Dorret I Boomsma[23], Panos Deloukas[8], Timothy D Spector[8,9], Timothy M Frayling[28], Luigi Ferrucci[169], Augustine Kong[19], Unnur Thorsteinsdottir[19,170], Kari Stefansson[19,170], Cornelia M van Duijn[22], Yurii S Aulchenko[22], Antonio Cao[65], Angelo Scuteri[65,171], David Schlessinger[47], Manuela Uda[65], Aimo Ruokonen[172], Marjo-Riitta Jarvelin[17,93,173], Dawn M Waterworth[26], Peter Vollenweider[141], Leena Peltonen[8,48,96,111,112], Vincent Mooser[26], Goncalo R Abecasis[10], Nicholas J Wareham[3], Robert Sladek[40,41], Philippe Froguel[13,142], Richard M Watanabe[164,174], James B Meigs[35,105], Leif Groop[102], Michael Boehnke[10], Mark I McCarthy[4,5,107], Jose C Florez[6,7,104,105] & Inês Barroso[11] for the MAGIC investigators

[1]Department of Biostatistics, Boston University School of Public Health, Boston, Massachusetts, USA.
[2]National Heart, Lung, and Blood Institute's Framingham Heart Study, Framingham, Massachusetts, USA.
[3]Medical Research Council (MRC), Epidemiology Unit, Institute of Metabolic Science, Addenbrooke's Hospital, Cambridge, UK.
[4]Oxford Centre for Diabetes, Endocrinology and Metabolism, University of Oxford, Oxford, UK.
[5]Wellcome Trust Centre for Human Genetics, University of Oxford, Oxford, UK.
[6]Program in Medical and Population Genetics, Broad Institute, Cambridge, Massachusetts, USA.
[7]Center for Human Genetic Research, Massachusetts General Hospital, Boston, Massachusetts, USA.
[8]Wellcome Trust Sanger Institute, Hinxton, Cambridge, UK.
[9]Twin Research and Genetic Epidemiology Department, King's College London, St Thomas' Hospital Campus, London, UK.
[10]Center for Statistical Genetics, Department of Biostatistics, University of Michigan School of Public Health, Ann Arbor, Michigan, USA.
[11]Metabolic Disease Group, Wellcome Trust Sanger Institute, Hinxton, Cambridge, UK. [12]Cardiovascular Health Research Unit and Department of Medicine, University of Washington, Seattle, Washington, USA.
[13]Centre National de la Recherche Scientifique–Unité Mixte de Recherche 8090, Pasteur Institute, Lille 2–Droit et Santé University, Lille, France.
[14]Department of Medical Genetics, University of Lausanne, Lausanne, Switzerland. [15]University Institute of Social and Preventative Medicine, Centre Hospitalier Universitaire Vaudois (CHUV) and University of Lausanne, Lausanne, Switzerland.
[16]Swiss Institute of Bioinformatics, Lausanne, Switzerland.
[17]Department of Epidemiology and Public Health, Imperial College London, Faculty of Medicine, Norfolk Place, London, UK.
[18]Boston University Data Coordinating Center, Boston, Massachusetts, USA.
[19]deCODE Genetics, Reykjavik, Iceland.
[20]Department of Human Genetics, Leiden University Medical Centre, Leiden, The Netherlands.
[21]Institute of Epidemiology, Helmholtz Zentrum Muenchen, German Research Center for Environmental Health, Neuherberg, Germany.
[22]Department of Epidemiology, Erasmus Medical College, Rotterdam, The Netherlands. [23]Department of Biological Psychology, VU University Amsterdam, Amsterdam, The Netherlands.
[24]Centre for Population Health Sciences, University of Edinburgh, Edinburgh, UK.
[25]MRC Human Genetics Unit, Institute of Genetics and Molecular Medicine, Edinburgh, UK.
[26]Division of Genetics, Research and Development, GlaxoSmithKline, King of Prussia, Pennsylvania, USA.
[27]Department of Cardiovascular Medicine, University of Oxford, Oxford, UK.
[28]Genetics of Complex Traits, Institute of Biomedical and Clinical Sciences, Peninsula College of Medicine and Dentistry, University of Exeter, Exeter, UK.
[29]National Institute of Aging, Baltimore, Maryland, USA.

[30]Unit for Child and Adolescent Health and Welfare, National Institute for Health and Welfare, Biocenter Oulu, University of Oulu, Oulu, Finland.
[31]Hagedorn Research Institute, Gentofte, Denmark.
[32]Department of Medicine and Therapeutics, Level 7, Ninewells Hospital and Medical School, Dundee, UK.
[33]Department of Epidemiology, Bloomberg School of Public Health, Johns Hopkins University, Baltimore, Maryland, USA.
[34]Department of Nutrition–Dietetics, Harokopio University, Athens, Greece.
[35]General Medicine Division, Massachusetts General Hospital, Boston, Massachusetts, USA.
[36]Department of Epidemiology and Public Health, University College London, London, UK.
[37]Departments of Nutrition and Epidemiology, Harvard School of Public Health, Boston, Massachusetts, USA.
[38]MRC Centre for Causal Analyses in Translational Epidemiology, University of Bristol, Bristol, UK.
[39]Fundación para la Investigación Biomédica del Hospital Clínico San Carlos, Madrid, Spain.
[40]Departments of Medicine and Human Genetics, McGill University, Montreal, Canada. [41]Genome Quebec Innovation Centre, Montreal, Canada.
[42]Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden.
[43]Department of Public Health and Caring Sciences, Uppsala University, Uppsala, Sweden.
[44]Division of Statistical Genomics, Department of Genetics, Washington University School of Medicine, St. Louis, Missouri, USA.
[45]Division of Endocrinology, Diabetes and Nutrition, University of Maryland School of Medicine, Baltimore, Maryland, USA.
[46]INSERM U859, Universite de Lille-Nord de France, Lille, France.
[47]Genome Technology Branch, National Human Genome Research Institute, Bethesda, Maryland, USA.
[48]The Broad Institute, Cambridge, Massachusetts, USA.
[49]Leiden Genome Technology Center, Leiden University Medical Center, Leiden, The Netherlands.
[50]INSERM U780, Paris Sud University, Villejuif, France.
[51]The Heart Research Institute, Sydney, New South Wales, Australia.
[52]PathWest Laboratory of Western Australia, Department of Molecular Genetics, J Block, QEII Medical Centre, Nedlands West Australia, Australia.
[53]School of Surgery and Pathology, University of Western Australia, Nedlands West Australia, Australia.
[54]Department of Social Medicine, University of Bristol, Bristol, UK.
[55]Landspitali University Hospital, Reykjavik, Iceland.
[56]Icelandic Heart Association, Kopavogur, Iceland.
[57]The Human Genetics Center and Institute of Molecular Medicine, University of Texas Health Science Center, Houston, Texas, USA.
[58]Steno Diabetes Center, Gentofte, Denmark.
[59]Faculty of Health Science, University of Aarhus, Aarhus, Denmark.
[60]Department of Medicine, University of Leipzig, Leipzig, Germany.
[61]Endocrinology–Diabetology Unit, Corbeil-Essonnes Hospital, Essonnes, France. [62]Medical Genetics Institute, Cedars-Sinai Medical Center, Los Angeles, California, USA. [63]Clinical Trial Service Unit and Epidemiological Studies Unit, University of Oxford, Oxford, UK.
[64]Centre for Genetic Epidemiology and Biostatistics, University of Western Australia, Perth, Australia.
[65]Istituto di Neurogenetica e Neurofarmacologia (INN), Consiglio Nazionale delle Ricerche, c/o Cittadella Universitaria di Monserrato, Monserrato, Cagliari, Italy. [66]Western Australian Sleep Disorders Research Institute, Queen Elizabeth Medical Centre II, Perth, Australia.
[67]Department of Endocrinology, Diabetes and Nutrition, Charite-Universitaetsmedizin Berlin, Berlin, Germany.
[68]Department of Clinical Nutrition, German Institute of Human Nutrition Potsdam-Rehbruecke, Nuthetal, Germany.
[69]Division of Endocrinology, Diabetes, and Hypertension, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA.
[70]Department of Human Genetics, Leiden University Medical Centre, Leiden, The Netherlands.
[71]Department of Cardiovascular Research, Istituto di Ricerche Farmacologiche 'Mario Negri', Milan, Italy.
[72]Institut National de la Santé et de la Recherche Médicale, Institut National de la Recherche Agronomique, Université Paris 13, Bobigny Cedex, France.
[73]Department of Medicine III, Division Prevention and Care of Diabetes, University of Dresden, Dresden, Germany.
[74]Center for Human Nutrition, University of Texas Southwestern Medical Center, Dallas, Texas, USA.
[75]Department of Genetics and Pathology, Rudbeck Laboratory, Uppsala University, Uppsala, Sweden.
[76]Centre Hospitalier Universitaire, de Poitiers, Endocrinologie Diabetologie, CIC INSERM 0802, INSERM U927, Université de Poitiers, Unité de Formation et de Recherche, Médecine Pharmacie, Poitiers, France.
[77]Department of Public Health and Clinical Medicine, Section for Nutritional Research, Umeå University, Umeå, Sweden.
[78]Department of Clinical Sciences, Obstetrics and Gynecology, University of Oulu, University of Oulu, Finland.

[79]Centre National de Génotypage/Institut de génomique/Commissariat à l'énergie atomique, Evry Cedex, France.
[80]INSERM U872, Faculté de Médecine Paris Descartes, Paris Cedex, France.
[81]Institute for Clinical Diabetology, German Diabetes Center, Leibniz Center for Diabetes Research at Heinrich Heine University Düsseldorf, Düsseldorf, Germany.
[82]Institute of Genetic Medicine, European Academy Bozen/Bolzano (EURAC), Viale Druso, Bolzano, Italy, Affiliated Institute of the University Lübeck, Lübeck, Germany. [83]Department of Pulmonary Physiology, Sir Charles Gairdner Hospital, Perth, Australia. [84]Busselton Population Medical Research Foundation, Sir Charles Gairdner Hospital, Perth, Australia.
[85]Heart Institute of Western Australia, Sir Charles Gairdner Hospital, Nedlands West Australia, Australia.
[86]School of Medicine and Pharmacology, University of Western Australia, Nedlands West Australia, Australia.
[87]Folkhalsan Research Centre, Helsinki, Finland. 88Malmska Municipal Health Care Center and Hospital, Jakobstad, Finland.
[89]Nuffield Department of Surgery, University of Oxford, Oxford, UK.
[90]Research Centre for Prevention and Health, Glostrup University Hospital, Glostrup, Denmark.
[91]Faculty of Health Science, University of Copenhagen, Copenhagen, Denmark. [92]National Institute for Health and Welfare, Unit of Population Studies, Turku, Finland. [93]Institute of Health Sciences and Biocenter Oulu, University of Oulu, Oulu, Finland. [94]Department of Public Health, Faculty of Medicine, University of Helsinki, Helsinki, Finland.
[95]National Institute for Health and Welfare, Unit for Child and Adolescent Mental Health, Helsinki, Finland.
[96]Institute for Molecular Medicine Finland (FIMM), University of Helsinki, Helsinki, Finland.
[97]Department of Internal Medicine and Biocenter Oulu, Oulu, Finland.
[98]Diabetes Genetics, Institute of Biomedical and Clinical Science, Peninsula College of Medicine and Dentistry, University of Exeter, Exeter, UK.
[99]National Institute for Health and Welfare, Unit of Living Conditions, Health and Wellbeing, Helsinki, Finland.
[100]Interdisciplinary Centre for Clinical Research, University of Leipzig, Leipzig, Germany. [101]The Danish Twin Registry, Epidemiology, Institute of Public Health, University of Southern Denmark, Odense, Denmark.
[102]Department of Clinical Sciences, Diabetes and Endocrinology, Lund University, University Hospital Malmö, Malmö, Sweden.
[103]Gladstone Institute of Cardiovascular Disease, University of California, San Francisco, California, USA.
[104]Diabetes Research Center, Diabetes Unit, Massachusetts General Hospital, Boston, Massachusetts, USA.
[105]Department of Medicine, Harvard Medical School, Boston, Massachusetts, USA. [106]Division of Cardiology, University of Ottawa Heart Institute, Ottawa, Ontario, Canada. [107]Oxford National Institute for Health Research, Biomedical Research Centre, Churchill Hospital, Oxford, UK.
[108]Department of Clinical Genetics, Erasmus Medical College, Rotterdam, The Netherlands.
[109]Biomedical Research Institute, University of Dundee, Ninewells Hospital and Medical School, Dundee, UK.
[110]Department of Geriatric Medicine and Metabolic Disease, Second University of Naples, Naples, Italy.
[111]National Institute for Health and Welfare, Unit of Public Health Genomics, Helsinki, Finland.
[112]Department of Medical Genetics, University of Helsinki, Helsinki, Finland. [113]Department of Medical Statistics, Epidemiology and Medical Informatics, Andrija Stampar School of Public Health, Medical School, University of Zagreb, Rockefellerova, Zagreb, Croatia.
[114]Department of Clinical Genetics, VU University and Medical Center, Amsterdam, The Netherlands.
[115]Department of Obstetrics and Gynaecology, Oulu University Hospital, Oulu, Finland. [116]Departments of Medicine, Epidemiology and Health Services, University of Washington, Seattle, Washington, USA.
[117]Group Health Research Institute, Group Health Cooperative, Seattle, Washington, USA.
[118]Institute of Biometrics and Epidemiology, German Diabetes Centre, Leibniz Centre at Heinrich Heine University Düsseldorf, Düsseldorf, Germany.
[119]Department of Biostatistics, University of Washington, Seattle, Washington, USA. [120]Department of Internal Medicine, Erasmus Medical College, Rotterdam, The Netherlands.
[121]Department of Metabolic Diseases, Heinrich Heine University Düsseldorf, Düsseldorf, Germany.
[122]Department of Public Health and Clinical Medicine, Section for Family Medicine, Umeå University, Umeå, Sweden.
[123]School of Public Health, Department of General Practice, University of Aarhus, Aarhus, Denmark.
[124]Department of Public Health and Primary Care, Strangeways Research Laboratory, University of Cambridge, Cambridge, UK.
[125]MRC Epidemiology Resource Centre, University of Southampton, Southampton General Hospital, Southampton, UK.
[126]Department of Epidemiology, University of Texas, M.D. Anderson Cancer Center, Houston, Texas, USA.
[127]Leibniz-Institut für Arteriosklerosеforschung an der Universität Münster, Münster, Germany.
[128]Atherosclerosis Research Unit, Department of Medicine, Karolinska Institutet, Stockholm, Sweden.
[129]Laboratory of Neurogenetics, National Institute on Aging, Bethesda, Maryland, USA. [130]Department of Epidemiology, University of Washington, Seattle, Washington, USA. [131]Seattle Epidemiologic Research and Information Center, Department of Veterans Affairs Office of Research and Development, Seattle, Washington, USA.
[132]Department of Medical Sciences, Uppsala University, Uppsala, Sweden.

[133]Medstar Research Institute, Baltimore, Maryland, USA.
[134]Clinical Research Branch, National Institute on Aging, Baltimore, Maryland, USA. [135]Institut interrégional pour la santé (IRSA), La Riche, France.
[136]Coordination Centre for Clinical Trials, University of Leipzig, Leipzig, Germany. [137]Department of Medicine, Helsinki University Hospital, University of Helsinki, Helsinki, Finland.
[138]Department of Internal Medicine, Leiden University Medical Centre, Leiden, The Netherlands.
[139]Research Unit, Cardiovascular Genetics, Nancy University Henri Poincaré, Nancy, France.
[140]EMGO Institute for Health and Care Research, Department of Psychiatry, VU University Medical Center, Amsterdam, The Netherlands.
[141]Department of Internal Medicine, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland.
[142]Genomic Medicine, Imperial College London, Hammersmith Hospital, London, UK. [143]Epidemiology and Public Health, Queen's University Belfast, Belfast, UK.
[144]Medical Products Agency, Uppsala, Sweden. 145See Supplementary Note for a full list of authors.
[146]National Institute for Health and Welfare, Unit of Chronic Disease Epidemiology and Prevention, Helsinki, Finland.
[147]Departments of Nutrition and Epidemiology, Harvard School of Public Health, Boston, Massachusetts, USA.
[148]Channing Laboratory, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts, USA.
[149]Genetic Epidemiology and Clinical Research Group, Department of Public Health and Clinical Medicine, Section for Medicine, Umeå University Hospital, Umeå, Sweden. [150]London School of Hygiene and Tropical Medicine, London, UK.
[151]Department of Medicine, School of Medicine, Johns Hopkins University, Baltimore, Maryland, USA.
[152]The Welch Center for Prevention, Epidemiology, and Clinical Research, School of Medicine and Bloomberg School of Public Health, Johns Hopkins University, Baltimore, Maryland, USA.
[153]Division of Epidemiology and Community Health, School of Public Health, University of Minnesota, Minneapolis, Minnesota, USA.
[154]Department of Endocrinology and Diabetes, Norfolk and Norwich University Hospital National Health Service Trust, Norwich, UK.
[155]Department of Medicine, University of Kuopio and Kuopio University Hospital, Kuopio, Finland.
[156]Faculty of Health Science, University of Southern Denmark, Odense, Denmark. [157]Institute of Biomedical Science, Faculty of Health Science, University of Copenhagen, Copenhagen, Denmark.
[158]Department of Neurology, General Central Hospital, Bolzano, Italy.
[159]Department of Neurology, University of Lübeck, Lübeck, Germany.
[160]Institute of Medical Informatics, Biometry and Epidemiology, Ludwig-Maximilians-Universität, Munich, Germany.
[161]Klinikum Grosshadern, Munich, Germany.
[162]School of Medicine, University of Split, Split, Croatia.
[163]Gen-Info Ltd., Zagreb, Croatia.
[164]Department of Physiology and Biophysics, Keck School of Medicine, University of Southern California, Los Angeles, California, USA.
[165]Department of Medicine, Division of Endocrinology, Keck School of Medicine, University of Southern California, Los Angeles, California, USA.
[166]Department of Genetics, University of North Carolina, Chapel Hill, North Carolina, USA.
[167]National Institute for Health and Welfare, Unit of Diabetes Prevention, Helsinki, Finland.
[168]South Ostrobothnia Central Hospital, Seinajoki, Finland.
[169]Departments of Medicine and Epidemiology, University of Washington, Seattle, Washington, USA.
[170]Longitudinal Studies Section, Clinical Research Branch, National Institute on Aging, NIH, Baltimore, Maryland, USA.
[171]Faculty of Medicine, University of Iceland, Reykjavík, Iceland.
[172]Lab of Cardiovascular Sciences, National Institute on Aging, National Institutes of Health, Baltimore, Maryland, USA.
[173]Department of Clinical Sciences/Clinical Chemistry, University of Oulu, University of Oulu, Oulu, Finland.
[174]National Institute of Health and Welfare, Oulu, Finland.
[175]Department of Preventive Medicine, Keck School of Medicine, University of Southern California, Los Angeles, California, USA.
[176]MRC–Health Protection Agency Centre for Environment and Health, Imperial College London, London, UK.

WELLCOME TRUST CASE CONTROL CONSORTIUM (WTCCC) MEMBERSHIP AND AFFILIATIONS

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Rheumatoid Arthritis: Anne Barton[40], Ian N Bruce[40], Hannah Donovan[40], Steve Eyre[40], Paul D Gilbert[40], Samantha L Hider[40], Anne M Hinks[40], Sally L John[40], Catherine Potter[40], Alan J Silman[40], Deborah PM Symmons[40], Wendy Thomson[40], Jane Worthington[40]
Type 1 Diabetes: David G Clayton[2], David B Dunger[2,41], Sarah Nutland[2], Helen E Stevens[2], Neil M Walker[2], Barry Widmer[2,41], John A Todd[2]
Type 2 Diabetes (Exeter): Timothy M Frayling[42,43], Rachel M Freathy[42,43], Hana Lango[42,43], John R B Perry[42,43], Beverley M Shields[43], Michael N Weedon[42,43], Andrew T Hattersley[42,43]; **(London):** Graham A Hitman[44]; **(Newcastle):** Mark Walker[45]; **(Oxford):** Kate S Elliott[3,7], Christopher J Groves[7], Cecilia M Lindgren[3,7], Nigel W Rayner[3,7], Nicholas J Timpson[3,46], Eleftheria Zeggini[3,7], Mark I McCarthy[3,7]

Tuberculosis (Gambia): Melanie Newport[47], Giorgio Sirugo[47]; **(Oxford):** Emily Lyons[3], Fredrik Vannberg[3], Adrian VS Hill[3]
Ankylosing Spondylitis: Linda A Bradbury[48], Claire Farrar[49], Jennifer J Pointon[48], Paul Wordsworth[49], Matthew A Brown[48,49]
AutoImmune Thyroid Disease: Jayne A Franklyn[50], Joanne M Heward[50], Matthew J Simmonds[50], Stephen CL Gough[50]
Breast Cancer: Sheila Seal[51], Michael R Stratton[51,52], Nazneen Rahman[51]
Multiple Sclerosis: Maria Ban[53], An Goris[53], Stephen J Sawcer[53], Alastair Compston[53]
Gambian Controls (Gambia): David Conway[47], Muminatou Jallow[47], Melanie Newport[47], Giorgio Sirugo[47]; **(Oxford):** Kirk A Rockett[3], Dominic P Kwiatkowski[3,5]
DNA, Genotyping, Data QC and Informatics (Wellcome Trust Sanger Institute, Hinxton): Suzannah J Bumpstead[5], Amy Chaney[5], Kate Downes[2,5], Mohammed JR Ghori[5], Rhian Gwilliam[5], Sarah E Hunt[5], Michael Inouye[5], Andrew Keniry[5], Emma King[5], Ralph McGinnis[5], Simon Potter[5], Rathi Ravindrarajah[5], Pamela Whittaker[5], Claire Widden[5], David Withers[5], Panos Deloukas[5]; **(Cambridge):** Hin-Tak Leung[2], Sarah Nutland[2], Helen E Stevens[2], Neil M Walker[2], John A Todd[2]
Statistics (Cambridge): Doug Easton[12], David G Clayton[2]; **(Leicester):** Paul R Burton[1], Martin D Tobin[1]; **(Oxford):** Jeffrey C Barrett[3], David M Evans[3], Andrew P Morris[3], Lon R Cardon[3]; **(Oxford):** Niall J Cardin[11], Dan Davison[11], Teresa Ferreira[11], Joanne Pereira-Gale[11], Ingeleif B Hallgrimsdóttir[11], Bryan N Howie[11], Jonathan L Marchini[11], Chris CA Spencer[11], Zhan Su[11], Yik Ying Teo[3,11], Damjan Vukcevic[11], Peter Donnelly[11]
PIs: David Bentley[5,54], Matthew A Brown[48,49], Lon R Cardon[3], Mark Caulfield[38], David G Clayton[2], Alistair Compston[53], Nick Craddock[23], Panos Deloukas[5], Peter Donnelly[11], Martin Farrall[39], Stephen CL Gough[50], Alistair S Hall[26], Andrew T Hattersley[42,43], Adrian VS Hill[3], Dominic P Kwiatkowski[3,5], Christopher G Mathew[29], Mark I McCarthy[3,7], Willem H Ouwehand[8,9], Miles Parkes[27], Marcus Pembrey[18,20], Nazneen Rahman[51], Nilesh J Samani[10], Michael R Stratton[51,52], John A Todd[2], Jane Worthington[40]

[1] Genetic Epidemiology Group, Department of Health Sciences, University of Leicester, Adrian Building, University Road, Leicester, LE1 7RH, UK; [2] Juvenile Diabetes Research Foundation/Wellcome Trust Diabetes and Inflammation Laboratory, Department of Medical Genetics, Cambridge Institute for Medical Research, University of Cambridge, Wellcome Trust/MRC Building, Cambridge, CB2 0XY, UK; [3] Wellcome Trust Centre for Human Genetics, University of Oxford, Roosevelt Drive, Oxford OX3 7BN, UK; [4] Department of Psychological Medicine, Henry Wellcome Building, School of Medicine, Cardiff University, Heath Park, Cardiff CF14 4XN, UK; [5] The Wellcome Trust Sanger Institute, Wellcome Trust Genome Campus, Hinxton, Cambridge CB10 1SA, UK; [6] The Wellcome Trust, Gibbs Building, 215 Euston Road, London NW1 2BE, UK; [7] Oxford Centre for Diabetes, Endocrinology and Medicine, University of Oxford, Churchill Hospital, Oxford, OX3 7LJ, UK; [8] Department of Haematology, University of Cambridge, Long Road, Cambridge, CB2 2PT, UK; [9] National Health Service Blood and Transplant, Cambridge Centre, Long Road, Cambridge, CB2 2PT, UK; [10] Department of Cardiovascular Sciences, University of Leicester, Glenfield Hospital, Groby Road, Leicester, LE3 9QP, UK; [11] Department of Statistics, University of Oxford, 1 South Parks Road, Oxford OX1 3TG, UK; [12] Cancer Research UK Genetic Epidemiology Unit, Strangeways Research Laboratory, Worts Causeway, Cambridge CB1 8RN, UK; [13] National Health Service Blood and Transplant, Sheffield Centre, Longley Lane, Sheffield S5 7JN, UK; [14] National Health Service Blood and Transplant, Brentwood Centre, Crescent Drive, Brentwood, CM15 8DP, UK; [15] The Welsh Blood Service, Ely Valley Road, Talbot Green, Pontyclun, CF72 9WB, UK; [16] The Scottish National Blood Transfusion Service, Ellen's Glen Road, Edinburgh, EH17 7QT, UK; [17] National Health Service Blood and Transplant, Southampton Centre, Coxford Road, Southampton, SO16 5AF, UK; [18] Avon Longitudinal Study of Parents and Children, University of Bristol, 24 Tyndall Avenue, Bristol, BS8 1TQ, UK; [19] Division of Community Health Services, St George's University of London, Cranmer Terrace, London SW17 0RE, UK; [20] Institute of Child Health, University College London, 30 Guilford St, London WC1N 1EH, UK; [21] University of Aberdeen, Institute of Medical Sciences, Foresterhill, Aberdeen, AB25 2ZD, UK; [22] Department of Psychiatry, Division of Neuroscience, Birmingham University, Birmingham, B15 2QZ, UK; [23] Department of Psychological Medicine, Henry Wellcome Building, School of Medicine, Cardiff University, Heath Park, Cardiff CF14 4XN, UK; [24] SGDP, The Institute of Psychiatry, King's College London, De Crespigny Park Denmark Hill London SE5 8AF, UK; [25] School of Neurology, Neurobiology and Psychiatry, Royal Victoria Infirmary, Queen Victoria Road, Newcastle upon Tyne, NE1 4LP, UK; [26] LIGHT and LIMM Research Institutes, Faculty of Medicine and Health, University of Leeds, Leeds, LS1 3EX, UK; [27] IBD Research Group, Addenbrooke's Hospital, University of Cambridge, Cambridge, CB2 2QQ,

UK; [28] Gastrointestinal Unit, School of Molecular and Clinical Medicine, University of Edinburgh, Western General Hospital, Edinburgh EH4 2XU UK; [29] Department of Medical & Molecular Genetics, King's College London School of Medicine, 8th Floor Guy's Tower, Guy's Hospital, London, SE1 9RT, UK; [30] Institute for Digestive Diseases, University College London Hospitals Trust, London, NW1 2BU, UK; [31] Department of Gastroenterology, Guy's and St Thomas' NHS Foundation Trust, London, SE1 7EH, UK; [32] Department of Gastroenterology & Hepatology, University of Newcastle upon Tyne, Royal Victoria Infirmary, Newcastle upon Tyne, NE1 4LP, UK; [33] Gastroenterology Unit, Radcliffe Infirmary, University of Oxford, Oxford, OX2 6HE, UK; [34] Medicine and Therapeutics, Aberdeen Royal Infirmary, Foresterhill, Aberdeen, Grampian AB9 2ZB, UK; [35] Clinical Pharmacology Unit and the Diabetes and Inflammation Laboratory, University of Cambridge, Addenbrookes Hospital, Hills Road, Cambridge CB2 2QQ, UK; [36] Centre National de Genotypage, 2, Rue Gaston Cremieux, Evry, Paris 91057.; [37] BHF Glasgow Cardiovascular Research Centre, University of Glasgow, 126 University Place, Glasgow, G12 8TA, UK; [38] Clinical Pharmacology and Barts and The London Genome Centre, William Harvey Research Institute, Barts and The London, Queen Mary's School of Medicine, Charterhouse Square, London EC1M 6BQ, UK; [39] Cardiovascular Medicine, University of Oxford, Wellcome Trust Centre for Human Genetics, Roosevelt Drive, Oxford OX3 7BN, UK; [40]arc Epidemiology Research Unit, University of Manchester, Stopford Building, Oxford Rd, Manchester, M13 9PT, UK; [41] Department of Paediatrics, University of Cambridge, Addenbrooke's Hospital, Cambridge, CB2 2QQ, UK; [42] Genetics of Complex Traits, Institute of Biomedical and Clinical Science, Peninsula Medical School, Magdalen Road, Exeter EX1 2LU UK; [43] Diabetes Genetics, Institute of Biomedical and Clinical Science, Peninsula Medical School, Barrack Road, Exeter EX2 5DU UK; [44] Centre for Diabetes and Metabolic Medicine, Barts and The London, Royal London Hospital, Whitechapel, London, E1 1BB UK; [45] Diabetes Research Group, School of Clinical Medical Sciences, Newcastle University, Framlington Place, Newcastle upon Tyne NE2 4HH, UK; [46] The MRC Centre for Causal Analyses in Translational Epidemiology, Bristol University, Canynge Hall, Whiteladies Rd, Bristol BS2 8PR, UK; [47] MRC Laboratories, Fajara, The Gambia; [48] Diamantina Institute for Cancer, Immunology and Metabolic Medicine, Princess Alexandra Hospital, University of Queensland, Woolloongabba, Qld 4102, Australia; [49] Botnar Research Centre, University of Oxford, Headington, Oxford OX3 7BN, UK; [50] Department of Medicine, Division of Medical Sciences, Institute of Biomedical Research, University of Birmingham, Edgbaston, Birmingham B15 2TT, UK; [51] Section of Cancer Genetics, Institute of Cancer Research, 15 Cotswold Road, Sutton, SM2 5NG, UK; [52] Cancer Genome Project, The Wellcome Trust Sanger Institute, Wellcome Trust Genome Campus, Hinxton, Cambridge CB10 1SA, UK; [53] Department of Clinical Neurosciences, University of Cambridge, Addenbrooke's Hospital, Hills Road, Cambridge CB2 2QQ, UK; [54] PRESENT ADDRESS: Illumina Cambridge, Chesterford Research Park, Little Chesterford, Nr Saffron Walden, Essex, CB10 1XL, UK.