The American Journal of Human Genetics, Volume *99*

Supplemental Data

Platelet-Related Variants Identified by Exomechip

Meta-analysis in 157,293 Individuals

John D. Eicher, Nathalie Chami, Tim Kacprowski, Akihiro Nomura, Ming-Huei Chen, Lisa R. Yanek, Salman M. Tajuddin, Ursula M. Schick, Andrew J. Slater, Nathan Pankratz, Linda Polfus, Claudia Schurmann, Ayush Giri, Jennifer A. Brody, Leslie A. Lange, Ani Manichaikul, W. David Hill, Raha Pazoki, Paul Elliot, Evangelos Evangelou, Ioanna Tzoulaki, He Gao, Anne-Claire Vergnaud, Rasika A. Mathias, Diane M. Becker, Lewis C. Becker, Amber Burt, David R. Crosslin, Leo-Pekka Lyytikäinen, Kjell Nikus, Jussi Hernesniemi, Mika Kähönen, Emma Raitoharju, Nina Mononen, Olli T. Raitakari, Terho Lehtimäki, Mary Cushman, Neil A. Zakai, Deborah A. Nickerson, Laura M. Raffield, Rakale Quarells, Cristen J. Willer, Gina M. Peloso, Goncalo R. Abecasis, Dajiang J. Liu, Global Lipids Genetics Consortium, Panos Deloukas, Nilesh J. Samani, Heribert Schunkert, Jeanette Erdmann, CARDIoGRAM Exome Consortium, Myocardial Infarction Genetics Consortium, Myriam Fornage, Melissa Richard, Jean-Claude Tardif, John D. Rioux, Marie-Pierre Dube, Simon de Denus, Yingchang Lu, Erwin P. Bottinger, Ruth J.F. Loos, Albert Vernon Smith, Tamara B. Harris, Lenore J. Launer, Vilmundur Gudnason, Digna R. Velez Edwards, Eric S. Torstenson, Yongmei Liu, Russell P. Tracy, Jerome I. Rotter, Stephen S. Rich, Heather M. Highland, Eric Boerwinkle, Jin Li, Ethan Lange, James G. Wilson, Evelin Mihailov, Reedik Mägi, Joel Hirschhorn, Andres Metspalu, Tõnu Esko, Caterina Vacchi-Suzzi, Mike A. Nalls, Alan B. Zonderman, Michele K. Evans, Gunnar Engström, Marju Orho-Melander, Olle Melander, Michelle L. O'Donoghue, Dawn M. Waterworth, Lars Wallentin, Harvey D. White, James S. Floyd, Traci M. Bartz, Kenneth M. Rice, Bruce M. Psaty, J.M. Starr, David C.M. Liewald, Caroline Hayward, Ian J. Deary, Andreas Greinacher, Uwe Völker, Thomas Thiele, Henry Völzke, Frank J.A. van Rooij, André G. Uitterlinden, Oscar H. Franco, Abbas Dehghan, Todd L. Edwards, Santhi K. Ganesh, Sekar Kathiresan, Nauder Faraday, Paul L. Auer, Alex P. Reiner, Guillaume Lettre, and Andrew D. Johnson

Supplemental Note

1. Datasets examined in expression quantitative trait loci (eQTL) analyses

We queried PLT and MPV loci in over 100 separate expression quantitative trait loci (eQTL) datasets in a wide range of tissues. Datasets were collected through publications, publically available sources, or private collaboration. A general overview of a subset of >50 eQTL studies has been published (PMID: 24973796), with specific citations for >100 datasets included in the current query following here. As our investigation focused primarily on a blood cell and secondarily and overlap of genetic associations with lipids, we only present eQTLs in blood and adipose related tissues.

Blood cell related eQTL studies included fresh lymphocytes (17873875), fresh leukocytes (19966804), leukocyte samples in individuals with Celiac disease (19128478), whole blood samples (18344981, 21829388, 22692066, 23818875, 23359819, 23880221, 24013639, 23157493, 23715323, 24092820, 24314549, 24956270, 24592274, 24728292, 24740359, 25609184, 22563384, 25474530, 25816334, 25578447), lymphoblastoid cell lines (LCL) derived from asthmatic children (17873877, 23345460), HapMap LCL from 3 populations (17873874), a separate study on HapMap CEU LCL (18193047), additional LCL population samples (19644074, 22286170, 22941192, 23755361, 23995691, 25010687, 25951796), neutrophils (26151758, 26259071), CD19+ B cells (22446964), primary PHA-stimulated T cells (19644074, 23755361), CD4+ T cells (20833654), peripheral blood monocytes (19222302, 20502693, 22446964, 23300628, 25951796, 26019233), long non-coding RNAs in monocytes (25025429) and CD14+ monocytes before and after stimulation with LPS or interferon-gamma (24604202). Micro-RNA QTLs (21691150, 26020509), DNase-I QTLs (22307276), histone acetylation QTLs

(25799442), and ribosomal occupancy QTLs (25657249) were also queried for LCL. Splicing QTLs (25685889) and micro-RNA QTLs (25791433) were queried in whole blood.

Non-blood cell tissue eQTLs searched included omental and subcutaneous adipose (18344981, 21602305, 22941192, 23715323, 25578447), visceral fat (25578447) stomach (21602305), arterial wall (25578447) and heart tissue from left ventricles (23715323, 24846176) and left and right atria (24177373). Micro-RNA QTLs were also queried for gluteal and abdominal adipose (22102887).

Additional eQTL data was integrated from online sources including the Broad Institute GTEx Portal, and the Pritchard Lab (eqtl.uchicago.edu). Results for GTEx Analysis V4 for 13 tissues were downloaded from the GTEx Portal and then additionally filtered as described below [www.gtexportal.org: aortic artery, tibial artery, skeletal muscle, heart (left ventricle), stomach, whole blood, and subcutaneous adipose (23715323)]. Splicing QTL (sQTL) results generated with sQTLseeker with false discovery rate $P \leq 0.05$ were retained. For all gene-level eQTLs, if at least 1 SNP passed the tissue-specific empirical threshold in GTEx, the best SNP for that eQTL was always retained. All gene-level eQTL SNPs with $P<1.67E-11$ were also retained, reflecting a global threshold correction of P=0.05/(30,000 genes X 1,000,000 tests).

Figure S1: Q-Q plots for discovery meta-analysis of PLT in African (AA), European (EA), and combined all (All) ancestry groups and inflation metrics as measured by lambda.

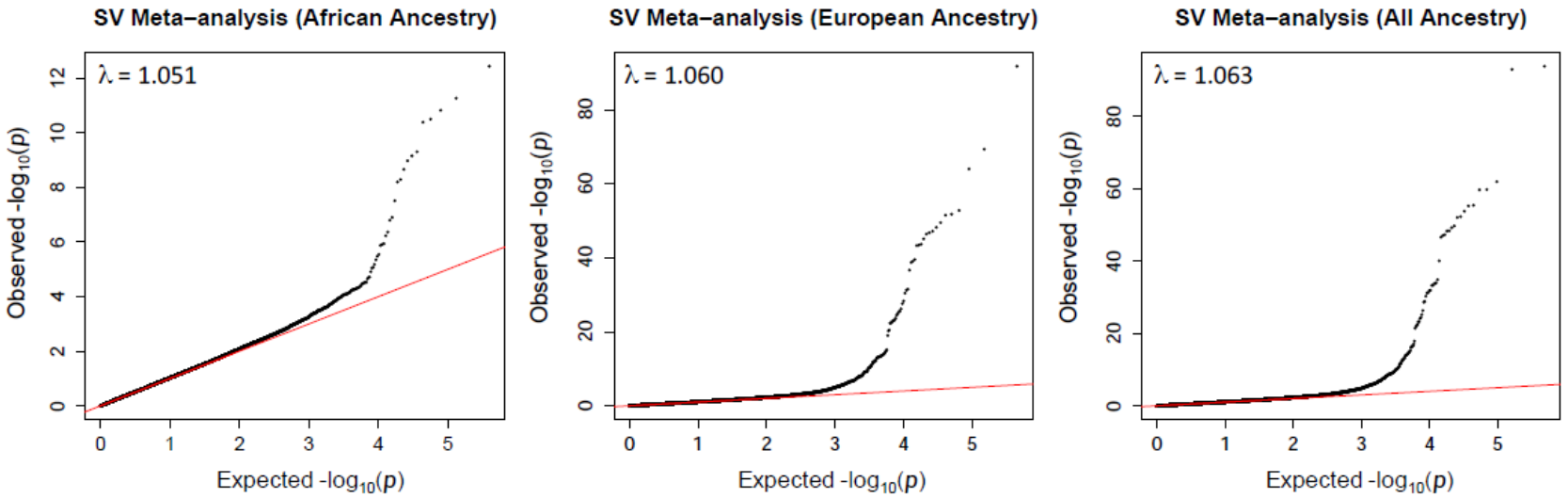


Figure S2: Q-Q plots for discovery meta-analysis of MPV in African (AA), European (EA), and combined all (All) ancestry groups and inflation metrics as measured by lambda.

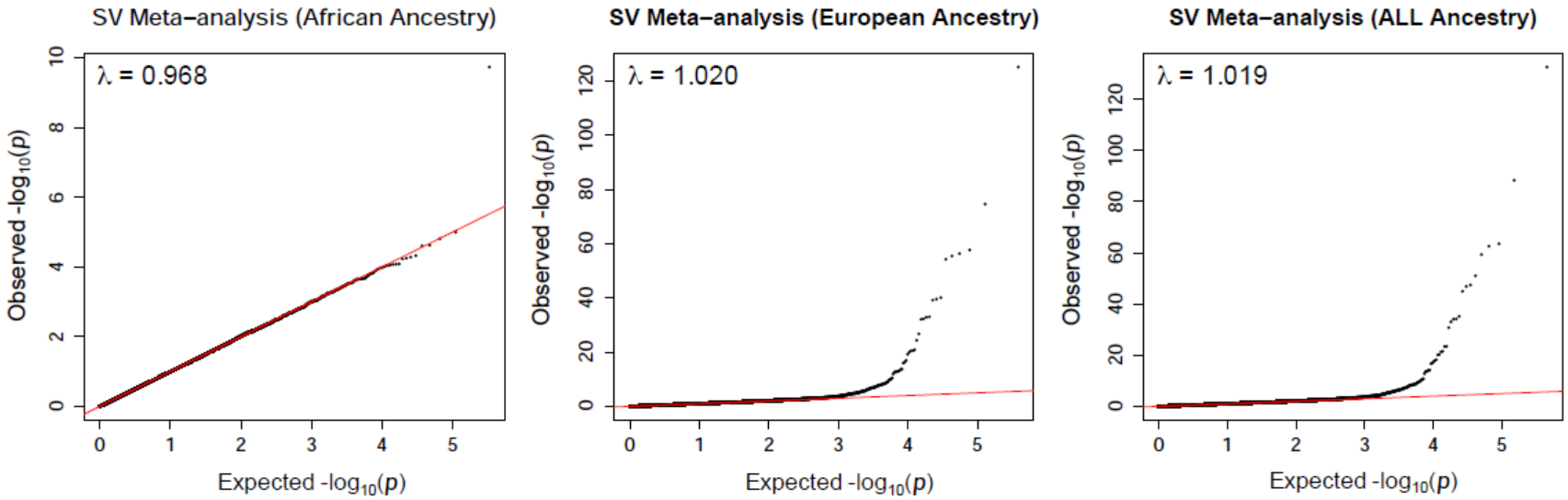


Figure S3: LocusZoom plot of *IQGAP2* locus for PLT in European ancestry (EA). Only rs34592828 showed significant independent association with PLT.

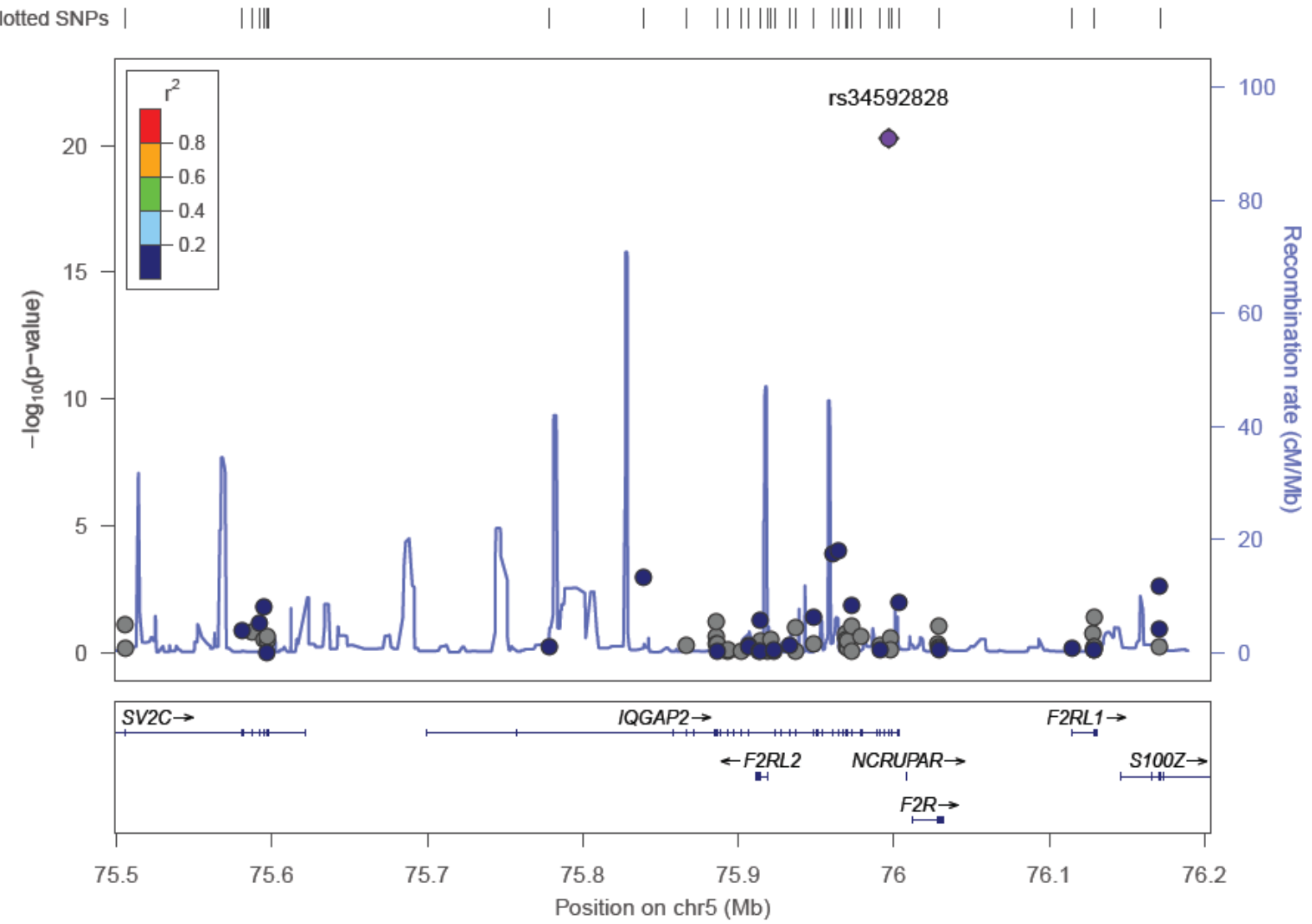


Figure S4: LocusZoom plot of *IQGAP2* locus for MPV in European ancestry (EA). rs34592828, rs34968964, and rs34950321 all showed significant independent association with MPV.

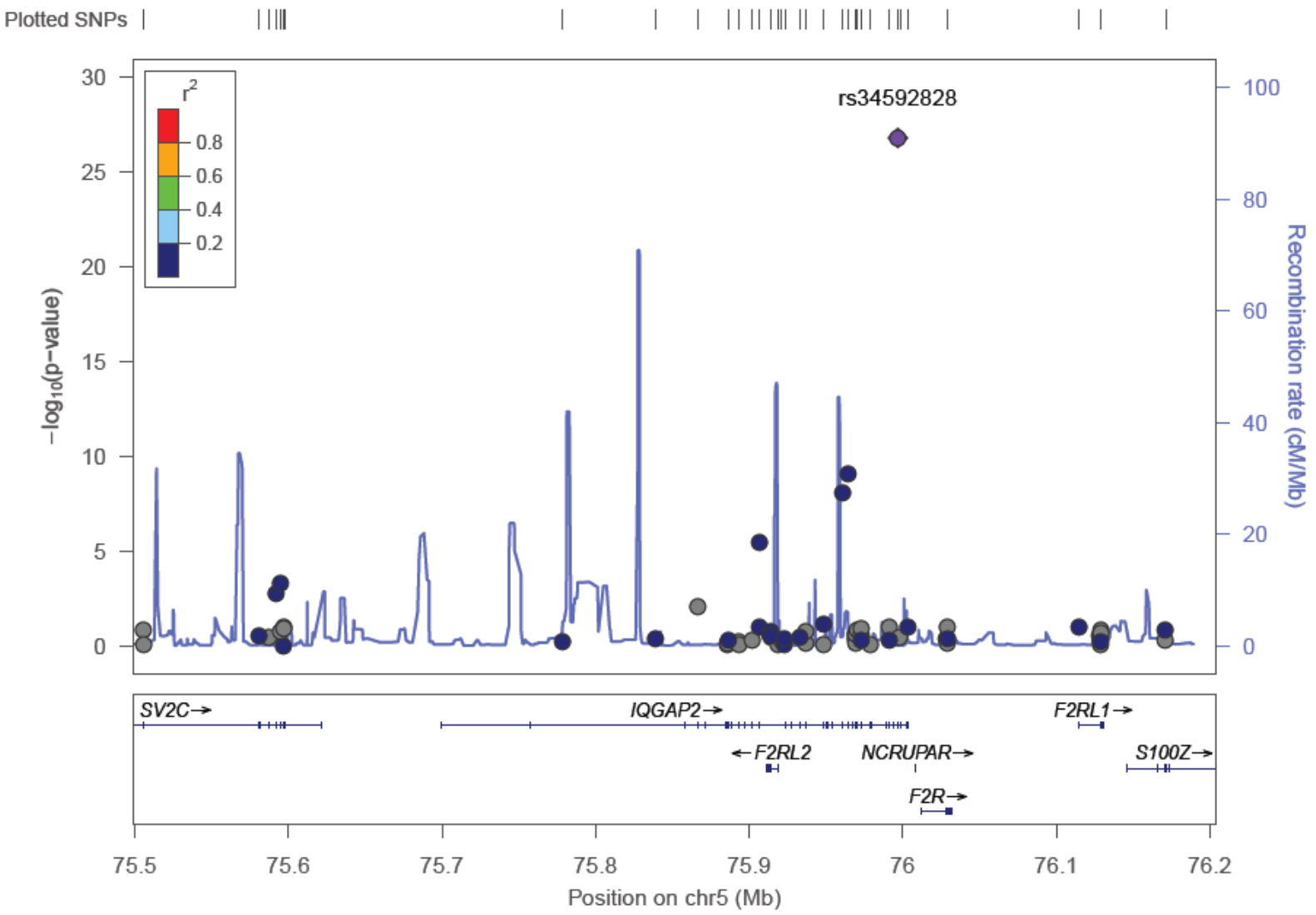


Figure S5: LocusZoom plot of *ARFGAP3*/*PACSIN2* locus for PLT in European ancestry (EA). rs1018448 showed association with PLT. However, rs1018448 is a reported eQTL for both ARFGAP3 and PACSIN2 gene expression.

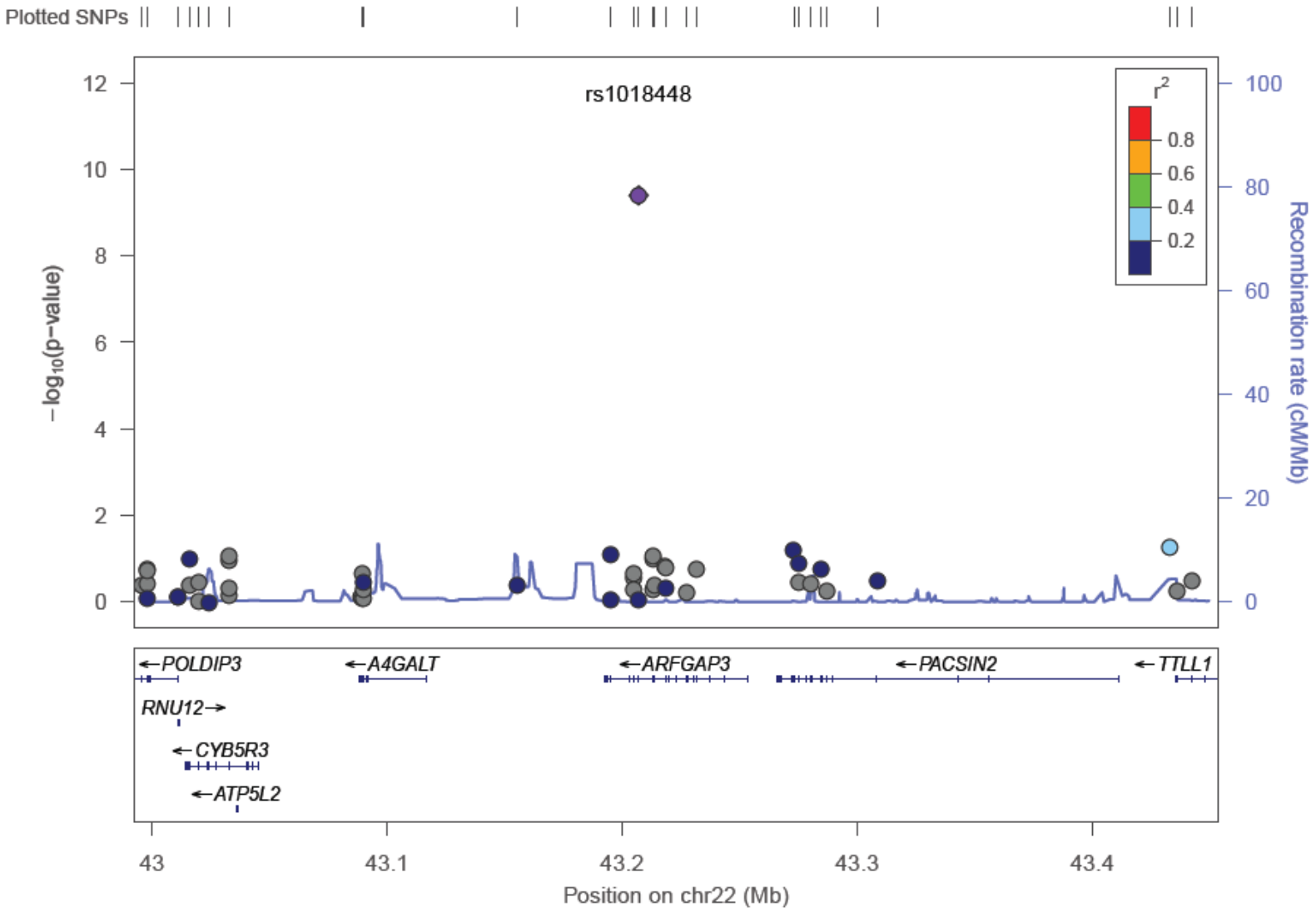
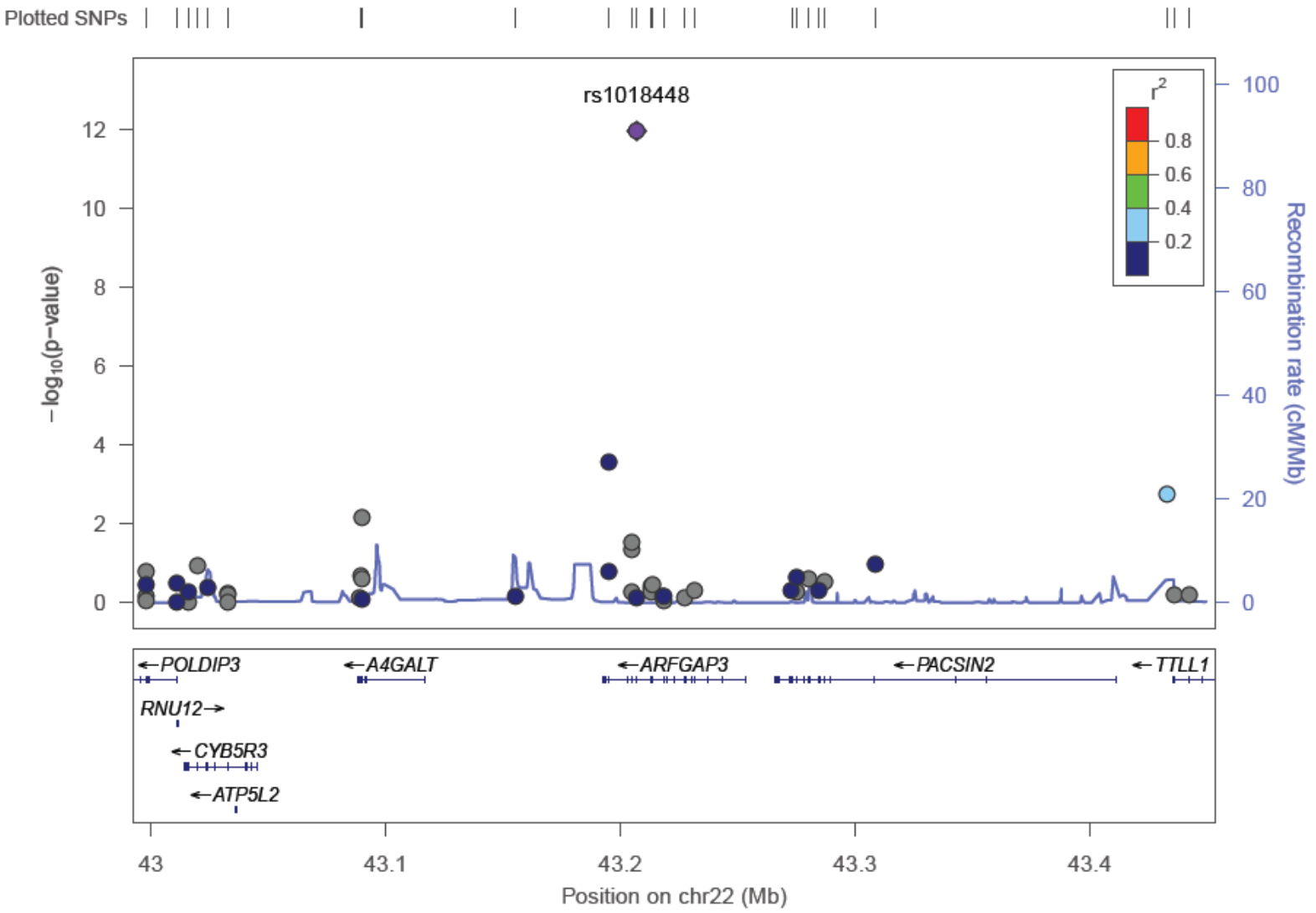


Figure S6: LocusZoom plot of *ARFGAP3*/*PACSIN2* locus for PLT in European ancestry (EA). rs1018448 showed association with MPV. However, rs1018448 is a reported eQTL for both ARFGAP3 and PACSIN2 gene expression.



Additional Funding Information

AGES

ARIC
The authors thank the staff of the ARIC study for their important contributions. The Atherosclerosis Risk in Communities (ARIC) Study is carried out as a collaborative study supported by National Heart, Lung, and Blood Institute contracts (HHSN268201100005C, HHSN268201100006C, HHSN268201100007C, HHSN268201100008C, HHSN268201100009C, HHSN268201100010C, HHSN268201100011C, and HHSN268201100012C), R01HL087641, R01HL59367 and R01HL086694; National Human Genome Research Institute contract U01HG004402; and National Institutes of Health contract HHSN268200625226C. Infrastructure was partly supported by Grant Number UL1RR025005, a component of the National Institutes of Health and NIH Roadmap for Medical Research. The meta-analysis and meta-regression analyses were funded by grant R01 HL086694 from the National Heart, Lung, and Blood Institute.

BioMe
The Mount Sinai IPM Biobank Program is supported by The Andrea and Charles Bronfman Philanthropies.

BIOVU
The dataset used in the analyses described were obtained from Vanderbilt University Medical Center's BioVU which is supported by institutional funding and by the Vanderbilt CTSA grant UL1 TR000445 from NCATS/NIH. Genome-wide genotyping was funded by NIH grants RC2GM092618 from NIGMS/OD and U01HG004603 from NHGRI/NIGMS. Funding for TLE and DRVE was provided by 1R21HL12142902 from NHLBI/NIH. Funding for the BioVU replication cohort was provided by 5R01HD074711 from NICHD/NIH.

CARDIA
The CARDIA Study is conducted and supported by the National Heart, Lung, and Blood Institute in collaboration with the University of Alabama at Birmingham (HHSN268201300025C & HHSN268201300026C), Northwestern University (HHSN268201300027C), University of Minnesota (HHSN268201300028C), Kaiser Foundation Research Institute (HHSN268201300029C), and Johns Hopkins University School of Medicine (HHSN268200900041C). CARDIA is also partially supported by the Intramural Research Program of the National Institute on Aging. Exome Chip genotyping was supported from grants R01-HL093029 and U01- HG004729 to MF. This manuscript has been reviewed and approved by CARDIA for scientific content.

CHS
A full list of CHS investigators and institutions can be found at www.chs-nhlbi.org. This CHS research was supported by NHLBI contracts HHSN268201200036C, HHSN268200800007C, N01HC55222, N01HC85079, N01HC85080, N01HC85081, N01HC85082, N01HC85083, N01HC85086; and NHLBI grants HL080295, HL087652, HL103612, HL105756, HL120393, and R01HL068986 with additional contribution from the National Institute of Neurological Disorders and Stroke (NINDS). Additional support was provided through AG023629 from the

National Institute on Aging (NIA). The provision of genotyping data was supported in part by the National Center for Advancing Translational Sciences, CTSI grant UL1TR000124, and the National Institute of Diabetes and Digestive and Kidney Disease Diabetes Research Center (DRC) grant DK063491 to the Southern California Diabetes Endocrinology Research Center.

ECGUT
EGCUT would like to thank co-workers at Estonian Biobank. This study was supported by EU H2020 grants 692145, 676550, 654248, Estonian Research Council Grant IUT20-60, NIASC, EIT – Health and NIH-BMI grant 2R01DK075787-06A1.

Framingham Heart Study (FHS)
Genotyping, quality control, and calling of the Illumina HumanExome BeadChip in the Framingham Heart Study were supported by funding from the National Heart, Lung and Blood Institute Division of Intramural Research (Daniel Levy and Christopher J. O'Donnell, Principle Investigators). Support for the centralized genotype calling was provided by Building on GWAS for NHLBI-diseases: the U.S. CHARGE consortium through the National Institutes of Health (NIH) American Recovery and Reinvestment Act of 2009 (5RC2HL102419). The NHLBI's Framingham Heart Study is a joint project of the National Institutes of Health and Boston University School of Medicine and was supported by contract N01-HC-25195.

HANDLS
The Healthy Aging in Neighborhoods of Diversity across the Life Span Study (HANDLS) research was supported by the Intramural Research Program of the NIH, National Institute on Aging and the National Center on Minority Health and Health Disparities (project # Z01-AG000513 and human subjects protocol # 2009-149). Data analyses for the HANDLS study utilized the computational resources of the NIH HPC Biowulf cluster at the National Institutes of Health, Bethesda, MD (http://hpc.nih.gov).

JHS
The JHS is supported by contracts HHSN268201300046C, HHSN268201300047C, HHSN268201300048C, HHSN268201300049C, HHSN268201300050C from the National Heart, Lung, and Blood Institute and the National Institute on Minority Health and Health Disparities.

LBC1921 and LBC1936
The Lothian Birth Cohorts thank the team members who contributed to these studies. Phenotype collection in the Lothian Birth Cohort 1921 was supported by the UK's Biotechnology and Biological Sciences Research Council (BBSRC), The Royal Society, and The Chief Scientist Office of the Scottish Government. Phenotype collection in the Lothian Birth Cohort 1936 was supported by Age UK (The Disconnected Mind project). Genotyping was supported by Centre for Cognitive Ageing and Cognitive Epidemiology (Pilot Fund award), Age UK, and the Royal Society of Edinburgh. The work was undertaken by The University of Edinburgh Centre for Cognitive Ageing and Cognitive Epidemiology, part of the cross council Lifelong Health and Wellbeing Initiative (MR/K026992/1). Funding from the BBSRC and Medical Research Council (MRC) is gratefully acknowledged. WDH is supported by a grant from Age UK (Disconnected Mind Project).

MDCS-CC
The Malmö Diet and Cancer cohort acknowledges the contributions of all the study investigators and field staff of Malmo Diet and Cancer Study. The Malmö Diet and Cancer cohort studies were supported by grants from the Swedish Research Council, the Swedish Heart and Lung Foundation, the Påhlsson Foundation, the Novo Nordic Foundation and European Research Council starting grant StG-282255. AN was supported by the Yoshida Scholarship Foundation. SK was supported by a Research Scholar award from the Massachusetts General Hospital (MGH), the Howard Goodman Fellowship from MGH, the Donovan Family Foundation, R01HL107816, and a grant from Fondation Leducq.

MESA
MESA thanks its Coordinating Center, MESA investigators, and study staff for their valuable contributions. A full list of participating MESA investigators and institutions can be found at www.mesa-nhlbi.org. MESA and the MESA SHARe project are conducted and supported by the National Heart, Lung, and Blood Institute (NHLBI) in collaboration with MESA investigators. Support for MESA is provided by contracts HHSN268201500003I, N01-HC-95159, N01-HC-95160, N01-HC-95161, N01-HC-95162, N01-HC-95163, N01-HC-95164, N01-HC-95165, N01-HC-95166, N01-HC-95167, N01-HC-95168, N01-HC-95169, UL1-TR-001079, UL1-TR-000040, and DK063491. MESA Family is conducted and supported by the National Heart, Lung, and Blood Institute (NHLBI) in collaboration with MESA investigators. Support is provided by grants and contracts R01HL071051, R01HL071205, R01HL071250, R01HL071251, R01HL071258, R01HL071259, by the National Center for Research Resources, Grant UL1RR033176, and the National Center for Advancing Translational Sciences, Grant UL1TR000124. Funding support for the inflammation dataset was provided by grant HL077449. The MESA Epigenomics & Transcriptomics Study was funded by NIA grant 1R01HL101250-01 to Wake Forest University Health Sciences.

MHIBB
This work was supported by the Fonds de Recherche du Québec–Santé (FRQS, scholarship to NC), the Canadian Institute of Health Research (Banting-CIHR, scholarship to SL and operating grant MOP#123382 to GL), the Canada Research Chair program (to GL, JDR, and JCT), and the MHI Foundation. PLA was supported by NHLBI R21 HL121422-02. JCT holds the Canada Research Chair in translational and personalized medicine and the Université de Montréal endowed research chair in atherosclerosis.

RS
The generation and management of the Illumina exome chip v1.0 array data for the Rotterdam Study (RS-I) was executed by the Human Genotyping Facility of the Genetic Laboratory of the Department of Internal Medicine, Erasmus MC, Rotterdam, The Netherlands. The Exome chip array data set was funded by the Genetic Laboratory of the Department of Internal Medicine, Erasmus MC, from the Netherlands Genomics Initiative (NGI)/Netherlands Organisation for Scientific Research (NWO)-sponsored Netherlands Consortium for Healthy Aging (NCHA; project nr. 050-060-810); the Netherlands Organization for Scientific Research (NWO; project number 184021007) and by the Rainbow Project (RP10; Netherlands Exome Chip Project) of the Biobanking and Biomolecular Research Infrastructure Netherlands (BBMRI-NL; www.bbmri.nl). We thank Ms. Mila Jhamai, Ms. Sarah Higgins, and Mr. Marijn Verkerk for their help in creating the exome chip database, and Carolina Medina-Gomez, MSc, Lennard Karsten, MSc, and Linda

Broer PhD for QC and variant calling. Variants were called using the best practice protocol developed by Grove et al. as part of the CHARGE consortium exome chip central calling effort. The Rotterdam Study is funded by Erasmus Medical Center and Erasmus University, Rotterdam, Netherlands Organization for the Health Research and Development (ZonMw), the Research Institute for Diseases in the Elderly (RIDE), the Ministry of Education, Culture and Science, the Ministry for Health, Welfare and Sports, the European Commission (DG XII), and the Municipality of Rotterdam. The authors are grateful to the study participants, the staff from the Rotterdam Study and the participating general practitioners and pharmacists.

SHIP and SHIP-TREND
SHIP is part of the Community Medicine Research net of the University of Greifswald, Germany (www.community-medicine.de), which is funded by the Federal Ministry of Education and Research (grants no. 01ZZ9603, 01ZZ0103, and 01ZZ0403), the Siemens AG, the Ministry of Cultural Affairs as well as the Social Ministry of the Federal State of Mecklenburg-West Pomerania, and the network 'Greifswald Approach to Individualized Medicine (GANI_MED)' funded by the Federal Ministry of Education and Research (grant 03IS2061A). ExomeChip data have been supported by the Federal Ministry of Education and Research (grant no. 03Z1CN22) and the Federal State of Mecklenburg-West Pomerania.

STABILITY and SOLID TIMI-52
The STABILITY and SOLID TIMI-52 studies were funded by GlaxoSmithKline.

WHI
WHI thanks investigators and staff for their dedication in making the program possible. The WHI program is funded by the National Heart, Lung, and Blood Institute, the US National Institutes of Health and the US Department of Health and Human Services (HHSN268201100046C, HHSN268201100001C, HHSN268201100002C, HHSN268201100003C, HHSN268201100004C and HHSN271201100004C). The authors thank the WHI investigators and staff for their dedication, and the study participants for making the program possible. A full listing of WHI investigators can be found at:
http://www.whi.org/researchers/Documents%20%20Write%20a%20Paper/WHI%20Investigator%20Short%20List.pdf. Exome chip data and analysis were supported through the Exome Sequencing Project (NHLBI RC2 HL-102924, RC2 HL-102925 and RC2 HL-102926), the Genetics and Epidemiology of Colorectal Cancer Consortium (NCI CA137088), and the Genomics and Randomized Trials Network (NHGRI U01-HG005152). PLA was supported by NHLBI R21 HL121422-02.

Airwave
The Airwave Study is funded by the Home Office (grant number 780-TETRA) with additional support from the National Institute for Health Research (NIHR) Imperial College Healthcare NHS Trust (ICHNT) and Imperial College Biomedical Research Centre (BRC) (Grant number BRC-P38084). Paul Elliott is an NIHR Senior Investigator and is supported by the ICHNT and Imperial College BRC, the MRC-PHE Centre for Environment and Health and the NIHR Health Protection Research Unit on Health Impact of Environmental Hazards.

FINCAVAS
This work was supported by the Competitive Research Funding of the Tampere University Hospital (Grant 9M048 and 9N035), the Finnish Cultural Foundation, the Finnish Foundation for Cardiovascular Research, the Emil Aaltonen Foundation, Finland, and the Tampere Tuberculosis Foundation.

GeneSTAR
GeneSTAR was supported by the National Institutes of Health/National Heart, Lung, and Blood Institute (U01 HL72518, HL087698, and HL112064) and by a grant from the National Institutes of Health/National Center for Research Resources (M01-RR000052) to the Johns Hopkins General Clinical Research Center. Genotyping services were provided through the RS&G Service by the Northwest Genomics Center at the University of Washington, Department of Genome Sciences, under U.S. Federal Government contract number HHSN268201100037C from the National Heart, Lung, and Blood Institute.

NWIGM
This phase of the eMERGE Network was initiated and funded by the NHGRI through the following grants: U01HG8657 (Group Health Cooperative/University of Washington); U01HG8685 (Brigham and Women's Hospital); U01HG8672 (Vanderbilt University Medical Center); U01HG8666 (Cincinnati Children's Hospital Medical Center); U01HG6379 (Mayo Clinic); U01HG8679 (Geisinger Clinic); U01HG8680 (Columbia University Health Sciences); U01HG8684 (Children's Hospital of Philadelphia); U01HG8673 (Northwestern University); U01HG8701 (Vanderbilt University Medical Center serving as the Coordinating Center); U01HG8676 (Partners Healthcare/Broad Institute); and U01HG8664 (Baylor College of Medicine). NWIGM dataset please also add "Additional support was provided by the University of Washington's Northwest Institute of Genetic Medicine from Washington State Life Sciences Discovery funds (Grant 265508).

REGARDS
We thank the investigators, staff and participants of the REGARDS study for their valuable contributions. A full list of participating REGARDS investigators and institutions can be found at http://www.regardsstudy.org.The genotyping for this project was provided by NIH/NCRR center grant 5U54RR026137-03. This research project is supported by a cooperative agreement U01 NS041588 from the National Institute of Neurological Disorders and Stroke, National Institutes of Health, Department of Health and Human Service. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute of Neurological Disorders and Stroke or the National Institutes of Health.

YFS
The Young Finns Study has been financially supported by the Academy of Finland: grants 285902, 286284, 134309 (Eye), 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 X51001); Juho Vainio Foundation; Paavo Nurmi Foundation; Finnish Foundation of Cardiovascular Research ; Finnish Cultural Foundation; Tampere Tuberculosis Foundation ; Emil Aaltonen Foundation; and Yrjö Jahnsson Foundation.