SUPPLEMENTAL MATERIAL

# Circulating metabolome and white matter hyperintensities in females and males

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## SUPPLEMENTAL METHODS



## SUPPLEMENTAL TABLES - 6 -



## SUPPLEMENTAL FIGURES - 13 -

*Tables S4-S22 are provided in a separate excel file:*

## Supplemental Methods

### Study populations

A short description of the participating cohort studies is given below. Technical details of the acquisition methods for WMH and metabolomic data in each study population are tabulated in Table S1, and population-specific characteristics are given in Table S2.

*Age, Gene/Environment Susceptibility-Reykjavik Study (AGES)*

The Age, Gene/Environment Susceptibility (AGES)-Reykjavik Study is a Reykjavik Study-based prospective cohort study initiated in 1967 by the Icelandic Heart Association. It is designed to study aging using multifaceted comprehensive approach that includes detailed measures of brain function and structure[16,79]. The cohort originally comprised of 30,795 men and women born 1907-1935 who lived in Reykjavik at the 1967 baseline examination. Re-examination of surviving participants (N=11,549) was initiated in 2002 as part of the AGES-Reykjavik Study; these examinations were concluded in February 2006, with a total sample size of 5,764[16]. As part of the examination, all participants answered a questionnaire, underwent a clinical examination, and had blood drawn. All consenting participants without contraindications were offered magnetic resonance imaging of the brain. AGES-Reykjavik was approved by the National Bioethics Committee in Iceland that acts as the institutional review board for the Icelandic Heart Association and by the National Institute on Aging Intramural Institutional Review Board[16]. A multistage consent is obtained for AGES-Reykjavik to cover participation, use of specimens and DNA, and access to administrative records. Icelandic Data Protection Authority reviews all requests to merge AGES-Reykjavik data with database information, and release of data for analysis is governed by rules by these bodies to protect the privacy of Icelandic participants[16].

*Framingham Heart Study (FHS)*

The Framingham Heart Study is a community-based, longitudinal cohort study that was started in 1948 when the National Heart Institute chose the town of Framingham, Massachusetts, USA, to conduct an epidemiological study[18]. The primary aim of the study was to identify determinants of cardiovascular disease to guide public health prevention[18]. The Original Cohort constitutes of 5,209 individuals most of whom were selected based on random sampling with an additional group of volunteers[80]. In 1971 and in 2002, respectively, the Offspring Cohort (FHS-GEN2) and the Third Generation (FHS-GEN3) were initiated: the participants of GEN2 (N=5,124) are children of the Original Cohort or spouses of these children, and the participants of GEN3 (N=4,095) have at least one parent in the GEN2 cohort[18]. In addition, two OMNI cohorts have begun (in years 1994 and 2003) to include individuals with diverse ethnic backgrounds[18]. Cohort follow-ups are conducted every 2-6 years for each FHS cohort: during the examination visits, broad range of health data, including blood sampling and imaging tests, are collected[18]. Written informed consent is obtained on every visit from all participants[18]. The institutional review board of Boston University Medical Center has approved the study protocol. In the present study, data from FHS-GEN2 and FHS-GEN3 were analyzed.

*Insight 46*

Insight 46 is a neuroscience sub-study of the Medical Research Council (MRC) National Survey of Health and Development (NSHD), one of the oldest British birth cohort studies that has followed 5,362 individuals since their birth in England, Scotland, and Wales during one week in March 1946[19]. The participants of Insight 46 are a randomly selected sample of 500 NSHD study members recruited from those who had attended a clinic-based assessment age 60-64, had previously intimated they were willing to attend a clinic visit in London, and for whom relevant life course data were available[19]. Data collection, which occurred during 2015-2019 (ages 69-73), covered clinical, neuropsychological, β-amyloid positron emission tomography and magnetic resonance imaging, as well as biomarker and genetic information. The aim of Insight 46 is to identify lifetime factors influencing brain health and cognitive ageing, with particular focus on Alzheimer's disease and cerebrovascular

disease[19]. All participants provided written informed consent, and the study was approved by the National Research Ethics Service (NRES) Committee London.

*Lothian Birth Cohort 1936 (LBC1936)*

The Lothian Birth Cohort 1936 (LBC1936) is a follow-up study of the Scottish Mental Survey 1947: it was initiated in 2004 with an aim to discover a wider range of people's differences in cognitive ageing[81]. During 2004-2007, altogether 3,686 individuals mostly from Edinburgh and the Lothians area of Scotland who might have taken part in the 1947 Survey were invited to participate in the LBC1936[81]. Of these, 2,318 responded, and a total of 1,091 interested and eligible individuals were assessed at Wave 1[81]. Follow-ups have taken place approximately triennially at Waves 2-5 (mean ages 73, 76, 79, and 82, respectively)[20]. The participants have taken part in a broad variety of investigations, including cognitive tests, lifestyle questionnaires, medical examinations, blood tests as well as brain magnetic resonance imaging scans. Ethics permission for the study protocol has been obtained from the Multi-Centre Research Ethics Committee for Scotland (MREC/01/0/56), the Lothian Research Ethics Committee (LREC/2003/2/29), and the Scotland A Research Ethics Committee (07/MRE00/58), and all participants have given their written, informed consent[20,82].

*Rotterdam Study (RS)*

The Rotterdam Study (RS) is a prospective cohort study initiated in 1990 in the city of Rotterdam, the Netherlands[22]. It was designed to study risk factors of diseases in the elderly, including cardiovascular, neurological, ophthalmological and endocrine diseases[22]. The initial cohort (RS-I) was among 7,983 persons aged 55-106 years living in the Ommoord district of Rotterdam[22]. The pilot phase of the study took place in 1989 and cohort recruitment in years 1990-1993 (RS-I-1): re-examinations of the original cohort members occurred in multiple cycles over the years (1993-1995, RS-I-2; 1997-1999, RS-I-3; 2002-2004, RS-I-4; 2009-2011, RS-I-5; 2014-2015, RS-I-6)[24]. Since year 2000, new cohorts have been initiated (RS-II, RS-III, RS-IV), and up to 2008, nearly 15,000 participants had been recruited[24]. Comprehensive data was collected at interviews and clinical examinations, with an emphasis on imaging of heart, blood vessels, eyes, skeleton, and later brain, and on collecting biospecimens for molecular and genetic analyses[24]. The study has been approved by the institutional board (Medical Ethics Committee) of the Erasmus Medical Center and by the review board of The Netherlands Ministry of Health, Welfare and Sports, and the approval has been renewed every 5 years and with the introduction of major new elements in the study[24]. In the present work, data from RS-I-3, RS-I-4, RS-II-3, and RS-III-2 were analyzed.

*Southall And Brent REvisited study (SABRE)*

Southall And Brent REvisisted (SABRE) is a population-based tri-ethnic follow-up study of the Southall and Brent baseline studies in London, UK, with an aim to improve understanding of the reasons underlying ethnic group differences in health, including cardiovascular and metabolic health as well as physical and brain function[28,83]. The target sample of the Southall study (1988-1991) included 3,000 men aged 40-69 years of Indian Asian, European, and African Caribbean descent, and the sample was supplemented with 600 women[83]. In the Brent study (1990-1991), the target sample was 300 participants in each sex and ethnic group (European and African Caribbean) aged 40-69 years[83]. Response rates ranged between 58% and 71%, resulting in 4,972 participants in the combined studies (2,346 of European descent; 1,711 of Indian Asian descent; 801 of African Caribbean descent; 114 'other')[83]. The SABRE study was initiated in 2008 as a 20-year follow-up of the two baseline studies: data collections of the follow-ups have been taking place during 2008-2011 and more recently during 2014-2019[28]. Participants have completed questionnaires and attended clinical examinations at Ealing Hospital and Wembley Stadium (1988-1991), and more recently at University College London, where magnetic resonance imaging scans of the brain took place. Ethics committee approval was obtained for the two baseline studies as well as for SABRE[83].

*Study of Health in Pomerania (SHIP)*

Study of Health in Pomerania (SHIP) is a population-based study with an overall objective to assess prevalence and incidence of common risk factors and diseases as well as to investigate the complex associations among risk factors and health outcomes[26,27]. Two independent cohorts, SHIP and SHIP-TREND, were selected in the same region of West Pomerania, a north-east region of Germany[27]. From the total of 213,057 inhabitants in the region in 1996, a two-stage stratified cluster sample of adults between 20-79 years of age were drawn, with a net sample of 6,265 eligible individuals[26,27]. These participants attended to the baseline examinations between 1997 and 2001 (SHIP-0), and follow-ups have taken place during 2002-2006 (SHIP-1) and 2008-2012 (SHIP-2). Examinations of a separate stratified random sample of 8,016 adults aged 20-79 took place between 2008 and 2012 (SHIP-TREND). During these examinations, comprehensive health data have been collected, including laboratory data such as serum lipids and metabolites (all samples) and whole-body magnetic resonance imaging (SHIP-2 and SHIP-TREND)[26,27]. All participants gave their written consent and the study was approved by a local ethics committee. We analyzed data from SHIP-2 and SHIP-TREND.

*Saguenay Youth Study (SYS)*

The Saguenay Youth Study (SYS) is a population-based study of adolescents and their middle-aged parents conducted in the Saguenay-Lac-Saint-Jean region of Quebec, Canada[25]. The primary aim of the study is at investigating the etiology and early stages of common cardiometabolic and brain diseases with an ultimate goal to identify effective means for increasing healthy life expectancy[25]. The cohort was recruited via adolescents attending high schools in the region; both maternal and paternal grandparents of the adolescents were required to be of French-Canadian ancestry and born in the region to ensure single ethnicity (European [French] ancestry) of the participants. The SYS includes 486 families with a total of 1,028 adolescents and 962 parents[25]. The data collection took place in two waves (2003-2012 and 2012-2015) during which the participants underwent an extensive phenotyping, including magnetic resonance imaging of the brain and abdomen as well as serum lipidomic and metabolomic profiling, among others. Written consent was obtained from all participants, and the study was approved by the research ethics committees of Chicoutimi Hospital (Chicoutimi, QC, Canada) and the Hospital for Sick Children (Toronto, ON, Canada). Data from SYS parent cohort were included in the present study.

## Supplemental Tables

**Table S1. A technical summary of the acquisition methods for WMH and metabolomic data in each study population.**

| Cohort | Scanner(s) | Software | WMH based on | WMH Acquisition Information | Biosample | Fasting | Metabolomic platform(s) |
|---|---|---|---|---|---|---|---|
| AGES | 1.5 T Signa Twinspeed EXCITE system | Image analysis pipeline derived from the AGES-RS/MNI pipeline | PD, T2 and FLAIR | See full details at [84]. | serum | overnight | Biocrates Absolute IDQ p180, $N_{metabolites}$=172 |
| FHS-GEN2 | 1 or 1.5 T Siemens Magnetom | QUANTA 6.2 | T2 | T2-weighted double spin-echo coronal imaging sequence were acquired in 4-mm contiguous slices (n=1379) and MRI scans with the FLAIR sequences were taken in 3-mm slices (n=113). | plasma | overnight | The Broad Institute (1995), $N_{metabolites}$=215 |
| FHS-GEN3 | 1 or 1.5 T Siemens Magnetom | QUANTA 6.2 | T2 | MRI scans with the FLAIR sequences were taken in 3-mm slices (n=621). All MR images were transferred to the centralized reading center at the University of California–Davis Medical Center and analyses were performed on QUANTA 6.2, a custom designed image analysis package operating on a Sun Microsystems Ultra 5 workstation. Images were analyzed and interpreted blind to subject data and in random order. Semi-automated analysis of pixel distributions, based on mathematical modeling of MRI pixel intensity histograms for cerebrospinal fluid (CSF) and brain matter (white matter and gray matter), were used to determine the optimal threshold of pixel intensity to best distinguish CSF from brain matter based on previously published methods. The intracranial vault above the tentorium was outlined manually to determine the total intracranial volume (TCV). | plasma | >8h | The Broad Institute (2005), $N_{metabolites}$=155 |
| Insight46 | Biograph mMR 3T<br>PET-MRI scanner (Siemens | Bayesian Model Selection (BaMoS) was used to segment white matter hyperintensities jointly from 3D T1 and FLAIR images, followed by visual quality control, generating a global white matter | 3D T1 and FLAIR | See full details at [19] (Table 4). | plasma | >12h | Metabolon (HD4), $N_{metabolites}$=983 |

| Cohort | Scanner(s) | Software | WMH based on | WMH Acquisition Information | Biosample | Fasting | Metabolomic platform(s) |
|---|---|---|---|---|---|---|---|
| | Healthcare, Erlangen) | hyperintensity volume (WMHV) including subcortical grey matter but excluding infratentorial regions[85]. | | | | | |
| LBC1936 | 1.5 T GE Signa Horizon HDx | MCMxxxVI (semiautomatic multispectral method) https://sourceforge.net/projects/bric1936/ | FLAIR and T2*-weighted | See full details at [21]. | plasma | non-fasting | National Phenome Centre (Biocrates Absolute IDQ p180, $N_{metabolites}$=177; modified Bruker B.I.-LISA, $N_{metabolites}$=105) |
| RS-I-3 | 1.5 T MRI unit, GE Healthcare | A fully automated brain tissue segmentation method segenting Cerebrospinalfluid (CSF), gray matter (GM) and white matter (WM) and white matter hyperintensities, as described by de Boer *et al*[86]. Cerebrospinalfluid (CSF), gray matter (GM) and white matter (WM) are segmented by an atlas-based k-nearest neighbor classifier on multi-modal magnetic resonance imaging data. This classifier is trained by registering brain atlases to the subject. The resulting GM segmentation is used to automatically find a white matter lesion (WML) threshold in a fluid-attenuated inversion recovery scan. | 3D T1, PD and FLAIR | T1-weighted 3D Fast RF Spoiled Gradient Recalled Acquisition in Steady State with an inversion recovery pre-pulse (FASTSPGR-IR) sequence (TR = 13.8 ms, TE = 2.8 ms, TI = 400 ms, FOV = 25 × 25 cm2, matrix = 416 × 256 (interpolated to 512 × 512 resulting in voxel sizes of 0.49 × 0.49 mm2), flip angle = 20°, NEX = 1, bandwidth (BW) = 12.50 kHz, 96 slices with slice thickness 1.6 mm zero-padded in the frequency domain to 0.8 mm), a proton density (PD) weighted sequence (TR = 12,300 ms, TE = 17.3 ms, FOV = 25 × 25 cm2, matrix = 416 × 256, NEX = 1, BW = 17.86 kHz, 90 slices with slice thickness 1.6 mm), and a FLAIR sequence (TR = 8000 ms, TE = 120 ms, TI = 2000 ms, FOV = 25 × 25 cm2, matrix = 320 × 224, NEX = 1, BW = 31.25 kHz, 64 slices with slice thickness 2.5 mm). | plasma | fasting | Metabolon ($N_{metabolites}$=698) |
| RS-I-4 | 1.5 T MRI unit, GE Healthcare | As above. | 3D T1, PD and FLAIR | As above. | plasma | fasting | Nightingale Health, $N_{metabolites}$=233 |
| RS-II-3 | 1.5 T MRI unit, GE Healthcare | As above. | 3D T1, PD and FLAIR | As above. | plasma | fasting | Nightingale Health, $N_{metabolites}$=225 |

| Cohort | Scanner(s) | Software | WMH based on | WMH Acquisition Information | Biosample | Fasting | Metabolomic platform(s) |
|---|---|---|---|---|---|---|---|
| RS-III-2 | 1.5 T MRI unit, GE Healthcare | As above. | 3D T1, PD and FLAIR | As above. | plasma | fasting | Nightingale Health, $N_{metabolites}$=225 |
| SABRE-EUR | 3T Philips Achieva scanner | Bayesian Model Selection (BaMoS) was used to segment white matter hyperintensities jointly from 3D T1 and FLAIR images, followed by visual quality control, generating a global white matter hyperintensity volume (WMHV) including subcortical grey matter but excluding infratentorial regions[85]. | 3D T1 and FLAIR | See full details at [87]. | serum | overnight | Nightingale Health (2013), $N_{metabolites}$=230 |
| SABRE-SA | 3T Philips Achieva scanner | As above. | 3D T1 and FLAIR | See full details at [87]. | serum | overnight | Nightingale Health (2013), $N_{metabolites}$=230 |
| SABRE-CARIB | 3T Philips Achieva scanner | As above. | 3D T1 and FLAIR | See full details at [87]. | serum | overnight | Nightingale Health (2013), $N_{metabolites}$=230 |
| SHIP-TREND | 1.5 T Siemens Magnetom Avanto | In-house[88] | T1 and T2-FLAIR | T1: orientation=axial plane, TR=1900ms, TE=3.37ms, flip angle=15°, slice thickness=1mm, and resolution 1mm x 1mm, FLAIR: orientation=axial plane, TR=5000ms, TE=325ms, flip angle=15°, slice thickness=3mm, and resolution 0.9mm × 0.9mm | plasma | >8h | Biocrates Absolute IDQ p180, $N_{metabolites}$=183; Bruker B.I.-LISA, $N_{metabolites}$=117; Metabolon (2014), $N_{metabolites}$=290 |
| SHIP-2 | 1.5 T Siemens Magnetom Avanto | In-house[88] | T1 and T2-FLAIR | T1: orientation=axial plane, TR=1900ms, TE=3.37ms, flip angle=15°, slice thickness=1mm, and resolution 1mm x 1mm, FLAIR: orientation=axial plane, TR=5000ms, TE=325ms, flip angle=15°, slice thickness=3mm, and resolution 0.9mm × 0.9mm | plasma | <4h | Biocrates Absolute IDQ p180, $N_{metabolites}$=177; Bruker B.I.-LISA, $N_{metabolites}$=115 |
| SYS | 1.5 T Siemens Magnetom Avanto | FreeSurfer (5.1.0) | T1 | T1W, 1-mm, isotropic resolution images acquired with a 3D fast radio frequency (RF)-spoiled gradient-echo scan. | serum | overnight | Nightingale Health (2016), $N_{metabolites}$=230; Metabolon Complex Lipids, $N_{metabolites}$=662 |

**Table S2. A summary of the population-specific characteristics.**

| *Sample* | Cohort | N | Males (%) | Smokers (%) | Age (years) | BMI (kg/m2) | logWMH* | Time** | Total-TG (mmol/L) | Total-C (mmol/L) | LDL-C (mmol/L) | HDL-C (mmol/L) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *Combined* | AGES | 561 | 43.3 | 11.2 | 76.2 ± 4.3 | 27.2 ± 4.0 | 2.65 ± 0.79 | 0 | n.a. | n.a. | n.a. | n.a. |
| | FHS-GEN2 | 1,492 | 46.8 | 16.6 | 54.1 ± 9.4 | 27.3 ± 4.8 | 0.67 ± 0.59 | 8.3 ± 2.9 | n.a. | n.a. | n.a. | n.a. |
| | FHS-GEN3 | 621 | 48.1 | 14.7 | 39.9 ± 9.0 | 26.6 ± 5.1 | 0.45 ± 0.41 | 8.4 ± 1.6 | n.a. | n.a. | n.a. | n.a. |
| | Insight46 | 428 | 52.6 | 5.4 | 63.3 ± 1.1 | 27.4 ± 4.0 | 1.51 ± 0.73 | 7.3 ± 1.3 | n.a. | n.a. | n.a. | n.a. |
| | LBC1936 | 482 | 53.5 | 7.3 | 72.6 ± 0.7 | 27.7 ± 4.3 | 8.49 ± 1.94 | 0.2 ± 0.1 | 1.44 ± 0.55 | 5.59 ± 1.18 | 3.05 ± 0.82 | 1.50 ± 0.33 |
| | RS-I-3 | 95 | 49.5 | 6.3 | 80.6 ± 4.8 | 25.9 ± 3.2 | 9.08 ± 0.95 | n.a. | n.a. | n.a. | n.a. | n.a. |
| | RS-I-4 | 1,086 | 43.4 | 11.0 | 77.6 ± 6.9 | 27.2 ± 3.9 | 8.91 ± 1.01 | 5.7 ± 2.1 | 1.38 ± 0.57 | 4.72 ± 0.86 | 1.65 ± 0.44 | 1.41 ± 0.28 |
| | RS-II-3 | 540 | 43.9 | 9.1 | 67.7 ± 5.9 | 27.6 ± 4.0 | 8.29 ± 0.88 | 0.6 ± 1.3 | 1.52 ± 0.82 | 4.97 ± 1.00 | 1.86 ± 0.57 | 1.48 ± 0.39 |
| | RS-III-2 | 1,294 | 57.0 | 13.7 | 62.1 ± 5.9 | 27.3 ± 4.3 | 7.83 ± 0.87 | 0.8 ± 1.5 | 1.30 ± 0.57 | 4.45 ± 0.93 | 1.76 ± 0.50 | 1.38 ± 0.35 |
| | SABRE-EUR | 239 | 79.9 | 5.9 | 67.4 ± 5.2 | 27.9 ± 4.1 | 8.28 ± 1.04 | 6.2 ± 0.7 | 1.42 ± 0.65 | 4.95 ± 1.21 | 1.79 ± 0.66 | 1.55 ± 0.39 |
| | SABRE-SA | 165 | 84.8 | 3.6 | 66.7 ± 5.0 | 26.2 ± 3.7 | 8.10 ± 1.10 | 6.0 ± 0.6 | 1.38 ± 0.78 | 4.35 ± 1.15 | 1.56 ± 0.65 | 1.38 ± 0.32 |
| | SABRE-CARIB | 69 | 50.7 | 4.3 | 68.4 ± 5.2 | 29.3 ± 4.9 | 8.47 ± 1.09 | 6.2 ± 0.6 | 0.95 ± 0.45 | 4.66 ± 1.04 | 1.63 ± 0.60 | 1.60 ± 0.34 |
| | SHIP-TREND | 726 | 42.0 | 20.9 | 50.5 ± 13.3 | 27.2 ± 4.3 | 5.21 ± 1.47 | 0.1 ± 0.2 | 1.43 ± 0.80 | 6.50 ± 1.21 | 3.87 ± 0.95 | 1.74 ± 0.41 |
| | SHIP-2 | 902 | 46.1 | 19.4 | 55.8 ± 16.6 | 27.7 ± 4.4 | 5.64 ± 1.54 | 0.1 ± 0.2 | n.a. | n.a. | 3.87 ± 1.05 | 1.74 ± 0.42 |
| | SYS | 590 | 46.9 | 18.1 | 49.3 ± 5.0 | 27.9 ± 5.2 | 7.29 ± 0.35 | 0 | 1.38 ± 0.66 | 4.18 ± 0.87 | 1.54 ± 0.48 | 1.34 ± 0.35 |
| *Females* | AGES | 318 | 0 | 12.6 | 76.4 ± 4.3 | 27.5 ± 4.2 | 2.60 ± 0.80 | 0 | n.a. | n.a. | n.a. | n.a. |
| | FHS-GEN2 | 794 | 0 | 16.0 | 53.9 ± 9.4 | 26.5 ± 5.3 | 0.65 ± 0.58 | 8.3 ± 2.8 | n.a. | n.a. | n.a. | n.a. |
| | FHS-GEN3 | 322 | 0 | 13.4 | 39.9 ± 9.0 | 25.6 ± 5.4 | 0.45 ± 0.41 | 8.4 ± 1.7 | n.a. | n.a. | n.a. | n.a. |
| | Insight46 | 203 | 0 | 5.4 | 63.3 ± 1.1 | 27.2 ± 4.5 | 1.56 ± 0.76 | 7.4 ± 1.3 | n.a. | n.a. | n.a. | n.a. |
| | LBC1936 | 224 | 0 | 6.7 | 72.7 ± 0.73 | 27.6 ± 4.6 | 8.54 ± 1.79 | 0.2 ± 0.1 | 1.45 ± 0.51 | 6.01 ± 1.15 | 3.30 ± 0.81 | 1.60 ± 0.34 |
| | RS-I-3 | 48 | 0 | 2.1 | 80.7 ± 4.8 | 26.3 ± 3.8 | 9.10 ± 0.91 | n.a. | n.a. | n.a. | n.a. | n.a. |
| | RS-I-4 | 615 | 0 | 10.4 | 77.7 ± 6.8 | 27.5 ± 4.3 | 8.92 ± 0.99 | 5.9 ± 2.0 | 1.39 ± 0.60 | 4.93 ± 0.87 | 1.72 ± 0.46 | 1.50 ± 0.28 |
| | RS-II-3 | 303 | 0 | 10.9 | 67.3 ± 5.9 | 27.7 ± 4.2 | 8.27 ± 0.85 | 0.6 ± 1.3 | 1.43 ± 0.61 | 5.27 ± 0.92 | 1.97 ± 0.53 | 1.63 ± 0.36 |
| | RS-III-2 | 557 | 0 | 14.5 | 62.2 ± 5.9 | 27.4 ± 3.5 | 7.78 ± 0.87 | 0.8 ± 1.5 | 1.40 ± 0.63 | 4.14 ± 0.91 | 1.68 ± 0.51 | 1.19 ± 0.27 |
| | SABRE-EUR | 48 | 0 | 8.3 | 67.0 ± 5.5 | 27.3 ± 4.7 | 8.47 ± 1.03 | 6.2 ± 0.5 | 1.41 ± 0.57 | 5.66 ± 1.14 | 2.09 ± 0.61 | 1.76 ± 0.43 |
| | SABRE-SA | 25 | 0 | 4.0 | 65.6 ± 5.1 | 28.9 ± 5.4 | 7.92 ± 0.78 | 6.0 ± 0.6 | 1.64 ± 1.01 | 4.98 ± 1.17 | 1.80 ± 0.69 | 1.54 ± 0.32 |
| | SABRE-CARIB | 34 | 0 | 2.9 | 68.0 ± 5.6 | 30.7 ± 4.6 | 8.37 ± 0.94 | 6.4 ± 0.7 | 0.94 ± 0.42 | 4.68 ± 1.08 | 1.59 ± 0.64 | 1.67 ± 0.35 |
| | SHIP-TREND | 422 | 0 | 20.7 | 50.7 ± 12.7 | 26.7 ± 4.8 | 5.02 ± 1.49 | 0.1 ± 0.2 | 1.34 ± 0.71 | 6.64 ± 1.23 | 3.93 ± 0.96 | 1.88 ± 0.41 |
| | SHIP-2 | 486 | 0 | 19.1 | 55.1 ± 12.1 | 27.3 ± 5.1 | 5.42 ± 1.56 | 0.1 ± 0.1 | n.a. | n.a. | 3.88± 1.03 | 1.89 ± 0.42 |
| | SYS | 313 | 0 | 19.2 | 47.8 ± 4.7 | 27.6 ± 5.8 | 7.21 ± 0.37 | 0 | 1.25 ± 0.60 | 4.18 ± 0.78 | 1.48 ± 0.43 | 1.46 ± 0.35 |

| *Sample* | Cohort | N | Males (%) | Smokers (%) | Age (years) | BMI (kg/m2) | logWMH* | Time** | Total-TG (mmol/L) | Total-C (mmol/L) | LDL-C (mmol/L) | HDL-C (mmol/L) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *Males* | AGES | 243 | 100 | 9.5 | 75.9 ± 4.3 | 26.9 ± 3.7 | 2.70 ± 0.77 | 0 | n.a. | n.a. | n.a. | n.a. |
| | FHS-GEN2 | 698 | 100 | 17.3 | 54.5 ± 9.4 | 28.1 ± 4.1 | 0.70 ±0.60 | 8.4 ± 2.9 | n.a. | n.a. | n.a. | n.a. |
| | FHS-GEN3 | 299 | 100 | 16.1 | 39.9 ± 8.9 | 27.6 ± 4.5 | 0.45 ± 0.41 | 8.4 ± 1.4 | n.a. | n.a. | n.a. | n.a. |
| | Insight46 | 225 | 100 | 5.3 | 63.4 ± 1.1 | 27.6 ± 3.5 | 1.46 ± 0.71 | 7.3 ± 1.3 | n.a. | n.a. | n.a. | n.a. |
| | LBC1936 | 258 | 100 | 7.8 | 72.6 ± 0.7 | 27.7 ± 4.1 | 8.44 ± 2.07 | 0.2 ± 0.1 | 1.42 ± 0.57 | 5.22 ± 1.08 | 2.84 ± 0.77 | 1.41 ± 0.31 |
| | RS-I-3 | 47 | 100 | 10.6 | 80.4 ± 5.0 | 25.5 ± 2.5 | 9.05 ± 1.00 | n.a. | n.a. | n.a. | n.a. | n.a. |
| | RS-I-4 | 417 | 100 | 11.7 | 77.4 ± 7.1 | 26.8 ± 3.1 | 8.88 ± 1.04 | 5.6 ± 2.1 | 1.36 ± 0.53 | 4.44 ± 0.77 | 1.56 ± 0.41 | 1.28 ± 0.24 |
| | RS-II-3 | 237 | 100 | 6.8 | 68.2 ± 5.9 | 27.4 ± 3.7 | 8.32 ± 0.91 | 0.6 ± 1.4 | 1.64 ± 1.01 | 4.59 ± 0.97 | 1.71 ± 0.57 | 1.28 ± 0.32 |
| | RS-III-2 | 737 | 100 | 13.0 | 62.1 ± 5.9 | 27.3 ± 4.9 | 7.87 ± 0.86 | 0.9 ± 1.6 | 1.22 ± 0.51 | 4.68 ± 0.88 | 1.83 ± 0.49 | 1.53 ± 0.32 |
| | SABRE-EUR | 191 | 100 | 5.2 | 67.5 ± 5.2 | 27.5 ± 3.9 | 8.23 ± 1.04 | 6.2 ± 0.7 | 1.42 ± 0.67 | 4.77 ± 1.16 | 1.71 ± 0.65 | 1.50 ± 0.37 |
| | SABRE-SA | 140 | 100 | 3.6 | 67.0 ± 5.0 | 25.7 ± 3.1 | 8.13 ± 1.15 | 6.1 ± 0.6 | 1.34 ± 0.73 | 4.24 ± 1.12 | 1.51 ± 0.63 | 1.35 ± 0.31 |
| | SABRE-CARIB | 35 | 100 | 5.7 | 68.7 ± 4.7 | 28.0 ± 4.9 | 8.57 ± 1.22 | 6.0 ± 0.3 | 0.97 ± 0.48 | 4.63 ± 1.01 | 1.67 ± 0.55 | 1.53 ± 0.33 |
| | SHIP-TREND | 305 | 100 | 21.3 | 50.1 ± 14.1 | 27.7 ± 3.6 | 5.48 ± 1.42 | 0.1 ± 0.1 | 1.56 ± 0.89 | 6.31 ± 1.15 | 3.80 ± 0.92 | 1.54 ± 0.33 |
| | SHIP-2 | 416 | 100 | 19.7 | 56.5 ± 13.2 | 28.1 ± 3.5 | 5.89 ± 1.49 | 0.1 ± 0.2 | n.a. | n.a. | 3.87 ± 1.08 | 1.56 ± 0.34 |
| | SYS | 277 | 100 | 17.0 | 51.0 ± 4.7 | 28.2 ± 4.3 | 7.38 ± 0.31 | 0 | 1.53 ± 0.71 | 4.19 ± 0.97 | 1.61 ± 0.53 | 1.21 ± 0.30 |
| *On statin* | AGES | 121 | 54.5 | 11.6 | 76.4 ± 4.2 | 27.8 ± 3.5 | 2.67 ± 0.79 | 0 | n.a. | n.a. | n.a. | n.a. |
| | FHS-GEN2 | 91 | 59.3 | 15.4 | 59.6 ± 8.1 | 29.1 ± 4.6 | 0.75 ± 0.67 | 7.5 ± 1.6 | n.a. | n.a. | n.a. | n.a. |
| | FHS-GEN3 | 46 | 76.1 | 13.0 | 47.6 ± 8.3 | 27.5 ± 4.8 | 0.65 ± 0.60 | 8.3 ± 1.1 | n.a. | n.a. | n.a. | n.a. |
| | Insight46 | 74 | 68.9 | 5.4 | 63.0 ± 1.3 | 28.3 ± 3.6 | 1.68 ± 0.75 | 7.6 ± 1.5 | n.a. | n.a. | n.a. | n.a. |
| | LBC1936 | 146 | 65.1 | 6.2 | 72.6 ± 0.7 | 28.9 ± 4.8 | 8.43 ± 2.15 | 0.2 ± 0.1 | 1.42 ± 0.58 | 4.70 ± 0.90 | 2.40 ± 0.62 | 1.42 ± 0.29 |
| | RS-I-3 | 10 | 50.0 | n.a. | 79.7 ± 3.1 | 26.9 ± 3.4 | 9.35 ± 1.06 | n.a. | n.a. | n.a. | n.a. | n.a. |
| | RS-I-4 | 248 | 46.0 | 10.5 | 77.4 ± 6.4 | 27.6 ± 3.8 | 8.93 ± 1.00 | 5.7 ± 2.2 | 1.43 ± 0.62 | 4.16 ± 0.82 | 1.37 ± 0.43 | 1.31 ± 0.27 |
| | RS-II-3 | 168 | 51.2 | 10.1 | 68.5 ± 5.7 | 28.0 ± 4.3 | 8.43 ± 0.91 | 0.7 ± 1.6 | 1.61 ± 0.88 | 4.29 ± 0.90 | 1.49 ± 0.51 | 1.36 ± 0.35 |
| | RS-III-2 | 274 | 49.3 | 14.6 | 63.9 ± 6.4 | 28.4 ± 3.9 | 7.95 ± 0.93 | 0.9 ± 1.5 | 1.43 ± 0.67 | 3.70 ± 0.78 | 1.36 ± 0.39 | 1.25 ± 0.34 |
| | SABRE-EUR | 94 | 88.3 | 3.2 | 68.7 ± 5.5 | 28.1 ± 3.9 | 8.43 ± 1.01 | 6.2 ± 0.7 | 1.52 ± 0.72 | 4.25 ± 1.13 | 1.39 ± 0.59 | 1.47 ± 0.38 |
| | SABRE-SA | 108 | 87.0 | 3.7 | 67.6 ± 5.2 | 26.5 ± 3.4 | 8.14 ± 1.08 | 6.1 ± 0.6 | 1.37 ± 0.84 | 3.89 ± 1.00 | 1.30 ± 0.55 | 1.33 ± 0.29 |
| | SABRE-CARIB | 26 | 46.2 | n.a. | 69.6 ± 5.2 | 28.7 ± 4.2 | 8.29 ± 1.15 | 6.3 ± 0.7 | 0.98 ± 0.43 | 4.25 ± 1.03 | 1.42 ± 0.58 | 1.52 ± 0.32 |
| | SHIP-TREND | 46 | 52.2 | 10.9 | 63.8 ± 8.8 | 29.0 ± 3.7 | 6.03 ± 1.39 | 0.1 ± 0.1 | 1.56 ± 0.65 | 6.05 ± 1.13 | 3.36 ± 0.92 | 1.79 ± 0.42 |
| | SHIP-2 | 125 | 53.6 | 8.8 | 66.7 ± 8.6 | 29.2 ± 4.3 | 6.47 ± 1.66 | 0.1 ± 0.2 | n.a. | n.a. | 3.23 ± 0.90 | 1.73 ± 0.41 |
| | SYS | 56 | 66.1 | 23.2 | 52.2 ± 5.2 | 29.1 ± 4.5 | 7.41 ± 0.33 | 0 | 1.35 ± 0.62 | 3.53 ± 0.81 | 1.20 ± 0.39 | 1.27 ± 0.33 |

| *Sample* | Cohort | N | Males (%) | Smokers (%) | Age (years) | BMI (kg/m2) | logWMH* | Time** | Total-TG (mmol/L) | Total-C (mmol/L) | LDL-C (mmol/L) | HDL-C (mmol/L) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *Not on statin* | AGES | 437 | 40.3 | 11.2 | 76.0 ± 4.3 | 27.1 ± 4.1 | 2.64 ± 0.79 | 0 | n.a. | n.a. | n.a. | n.a. |
| | FHS-GEN2 | 1,401 | 46.0 | 16.7 | 53.8 ± 9.3 | 27.1 ± 4.8 | 0.67 ± 0.58 | 8.4 ± 2.9 | n.a. | n.a. | n.a. | n.a. |
| | FHS-GEN3 | 575 | 45.9 | 14.8 | 39.3 ± 8.7 | 26.5 ± 5.1 | 0.44 ± 0.39 | 8.4 ± 1.6 | n.a. | n.a. | n.a. | n.a. |
| | Insight46 | 323 | 47.7 | 5.9 | 63.3 ± 1.0 | 27.1 ± 4.1 | 1.46 ± 0.73 | 7.3 ± 1.2 | n.a. | n.a. | n.a. | n.a. |
| | LBC1936 | 331 | 48.6 | 7.9 | 72.6 ± 0.7 | 27.1 ± 4.0 | 8.51 ± 1.85 | 0.2 ± 0.1 | 1.45 ± 0.54 | 5.99 ± 1.07 | 3.35 ± 0.72 | 1.53 ± 0.35 |
| | RS-I-3 | 83 | 50.6 | 6.0 | 80.6 ± 5.0 | 25.8 ± 3.2 | 9.02 ± 0.90 | n.a. | n.a. | n.a. | n.a. | n.a. |
| | RS-I-4 | 837 | 42.7 | 11.0 | 77.6 ± 7.0 | 27.1 ± 3.9 | 8.90 ± 1.02 | 5.8 ± 2.0 | 1.36 ± 0.56 | 4.88 ± 0.80 | 1.73 ± 0.41 | 1.44 ± 0.28 |
| | RS-II-3 | 372 | 40.6 | 8.6 | 67.3 ± 6.0 | 27.4 ± 3.9 | 8.23 ± 0.86 | 0.6 ± 1.2 | 1.48 ± 0.79 | 5.28 ± 0.89 | 2.02 ± 0.51 | 1.53 ± 0.39 |
| | RS-III-2 | 1,020 | 59.0 | 13.4 | 61.7 ± 5.7 | 27.0 ± 4.4 | 7.80 ± 0.85 | 0.8 ± 1.5 | 1.26 ± 0.54 | 4.65 ± 0.86 | 1.88 ± 0.47 | 1.42 ± 0.34 |
| | SABRE-EUR | 145 | 74.5 | 7.6 | 66.5 ± 4.8 | 27.1 ± 4.2 | 8.18 ± 1.05 | 6.2 ± 0.6 | 1.35 ± 0.59 | 5.40 ± 1.03 | 2.04 ± 0.58 | 1.61 ± 0.39 |
| | SABRE-SA | 57 | 80.7 | 3.5 | 65.2 ± 4.3 | 25.6 ± 4.2 | 8.02 ± 1.13 | 6.0 ± 0.7 | 1.41 ± 0.67 | 5.23 ± 0.89 | 2.04 ± 0.51 | 1.45 ± 0.35 |
| | SABRE-CARIB | 43 | 53.5 | 7.0 | 67.6 ± 5.1 | 29.7 ± 5.3 | 8.59 ± 1.04 | 6.2 ± 0.5 | 0.93 ± 0.46 | 4.90 ± 0.98 | 1.76 ± 0.57 | 1.64 ± 0.35 |
| | SHIP-TREND | 679 | 41.4 | 21.6 | 49.6 ± 13.1 | 27.0 ± 4.3 | 5.15 ± 1.46 | 0.1 ± 0.2 | 1.42 ± 0.81 | 6.53 ± 1.21 | 3.91 ± 0.94 | 1.74 ± 0.41 |
| | SHIP-2 | 766 | 44.6 | 21.3 | 53.9 ± 12.3 | 27.4 ± 4.4 | 5.50 ± 1.48 | 0.1 ± 0.2 | n.a. | n.a. | 3.98 ±1.04 | 1.74 ± 0.42 |
| | SYS | 496 | 44.6 | 18.3 | 49.0 ± 4.8 | 27.7 ± 5.2 | 7.27 ± 0.34 | 0 | 1.36 ± 0.66 | 4.26 ± 0.83 | 1.58 ± 0.46 | 1.36 ± 0.35 |

* Multiple different quantification methods (Table S1) provide values on different scales and a direct comparison of the numerical values between cohorts is not meaningful.
** 'Time' indicates the years between blood sampling for metabolomic quantifications and brain MRI: blood for metabolomic quantifications was always drawn before or at the time of MRI in all studies except RS in which there is inter-individual variation in whether blood sampling was prior to MRI or vice versa.
n.a., not available.

**Table S3. Relative importance metrics for the fully adjusted hydroxyphenylpyruvate model**

The values are relative importance metrics ($R^2$) estimated in the two cohorts, the 3rd Generation of the Framingham Heart Study and Insight46, that provided results for the hydroxyphenylpyruvate in the fully adjusted model.

| | FHS-GEN3 | | | Insight46 | | |
|---|---|---|---|---|---|---|
| **Variable** | **Pooled sample** | **Females** | **Males** | **Pooled sample** | **Females** | **Males** |
| Hydroxyphenylpyruvate | 0.0569 | 0.0003 | 0.1428 | 0.0049 | 0.0001 | 0.0327 |
| Age | 0.2010 | 0.1953 | 0.1871 | 0.0054 | 0.0086 | 0.0053 |
| Sex | 0.0030 | *n.a.* | *n.a.* | 0.0133 | *n.a.* | *n.a.* |
| Age-by-sex interaction | 0.0001 | *n.a.* | *n.a.* | 0.0020 | *n.a.* | *n.a.* |
| Hypertension | 0.0078 | 0.0095 | 0.0112 | 0.0050 | 0.0165 | 0.0010 |
| Diabetes | 0.0105 | 0.0145 | 0.0098 | 0.0163 | 0.0063 | 0.0291 |
| Smoking | 0.0001 | 0.0005 | 0.0010 | 0.0005 | 0.0035 | 0.0003 |
| BMI | 0.0021 | 0.0015 | 0.0103 | 0.0031 | 0.0023 | 0.0047 |
| eGFR | 0.0099 | 0.0078 | 0.0091 | 0.0042 | 0.0001 | 0.0149 |
| Statin use | 0.0033 | 0.0033 | 0.0061 | 0.0078 | 0.0005 | 0.0263 |
| ICV or brain size | 0.0111 | 0.0120 | 0.0138 | 0.0130 | 0.0173 | 0.0203 |
| Time* | 0.0043 | 0.0026 | 0.0066 | 0.0101 | 0.0054 | 0.0134 |
| Batch | 0.0039 | 0.0094 | 0.0017 | *n.a.* | *n.a.* | *n.a.* |
| Fasting duration | *n.a.* | *n.a.* | *n.a.* | 0.0011 | 0.0005 | 0.0031 |

* 'Time' indicates the years between blood sampling for metabolomic quantifications and brain MRI.

n.a., not applicable

## Supplemental Figures

**Figure S1. Distributions of the key metabolomic traits across the cohorts and the 5 analytical sub-samples.**

Cohort and sub-sample specific means (points) and standard deviations (vertical lines) are plotted for the 3 metabolomic measures showing FDR-significant association with white matter hyperintensities in the fully adjusted models and nominally significant sex-difference. SM (OH) C22:2 and hydroxyphenylpyruvate were quantified using multiple platforms and the original distributions were reported in varying units and, therefore, distributions are plotted relative to the mean value in the combined sample. * $p<0.05$ for difference (t-test); ns, not significant.

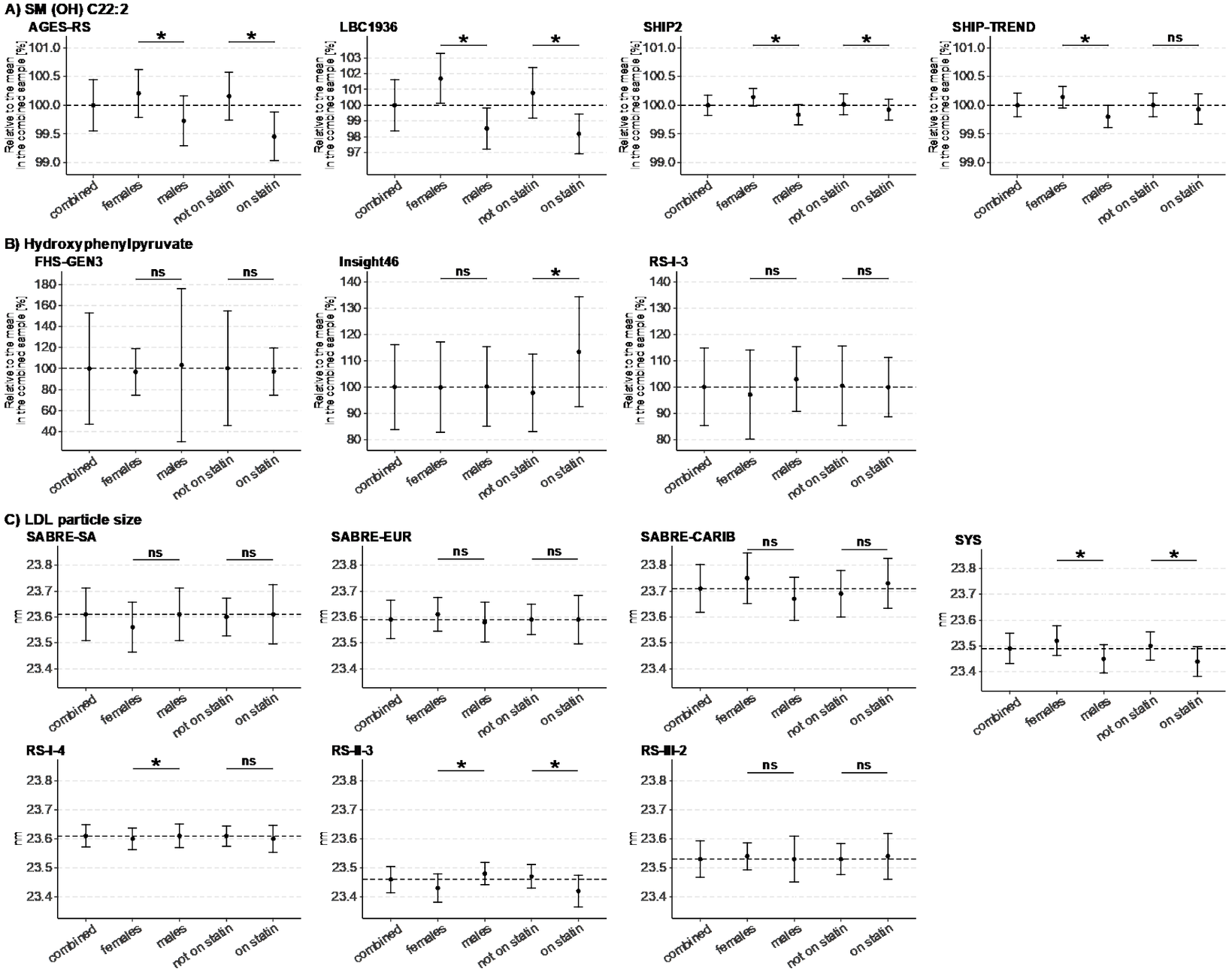

**Figure S2. Distributions of logWMH in females and males.**

*Figure S2 A) AGES*

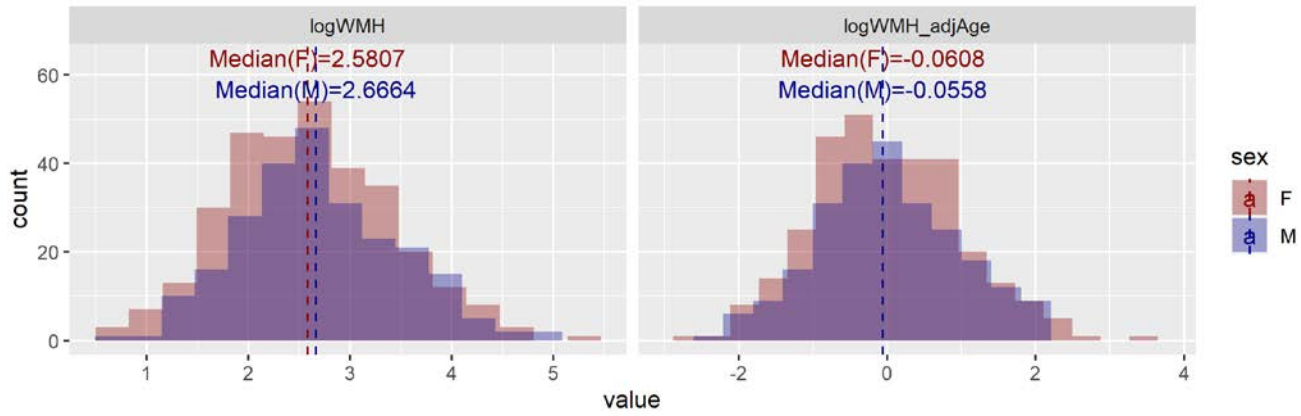


*Figure S2 B) FHS-GEN2*

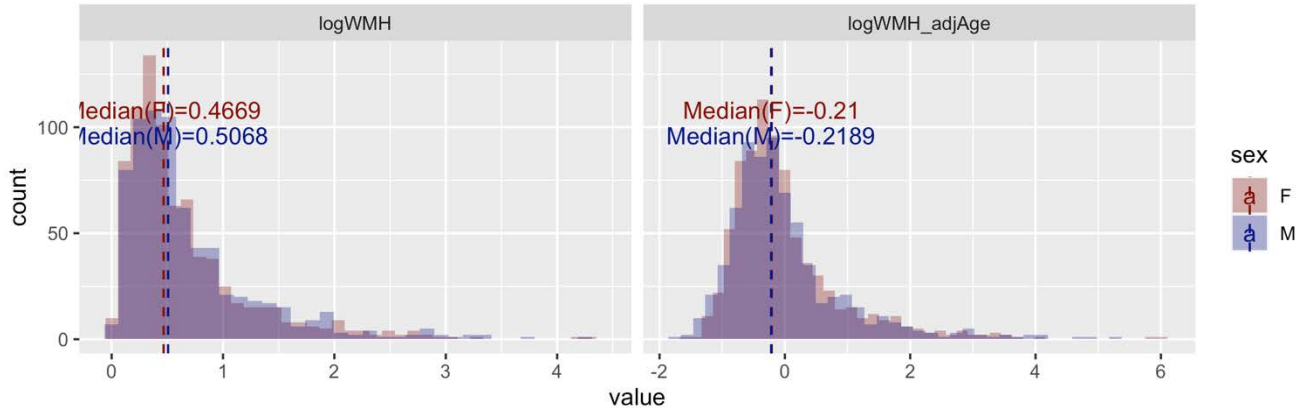


*Figure S2 C) FHS-GEN3*

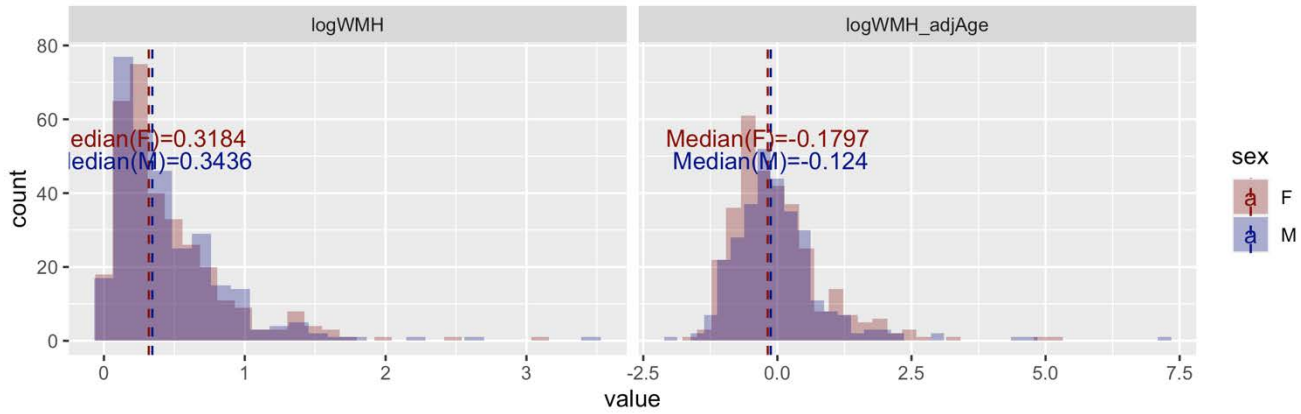


*Figure S2 D) Insight46*

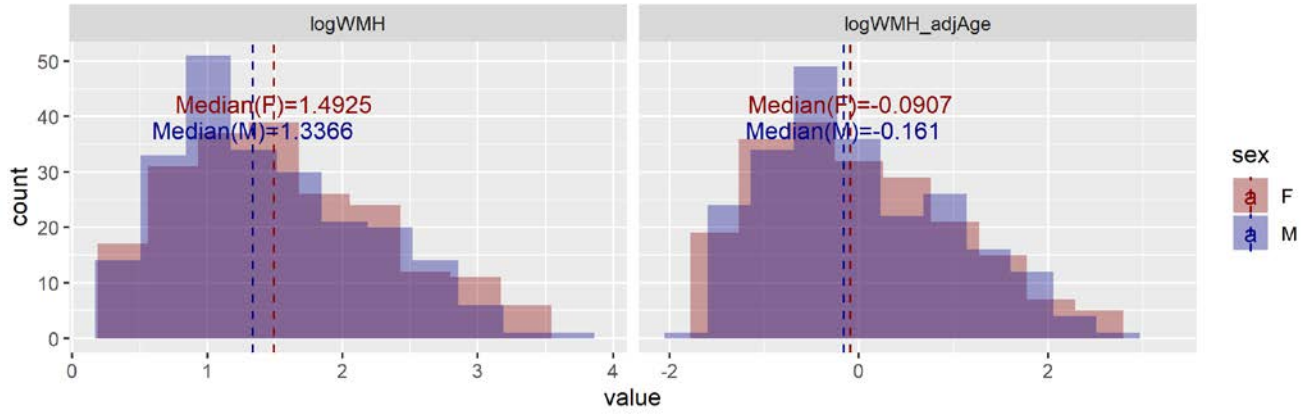

*Figure S2 E) LBC1936*

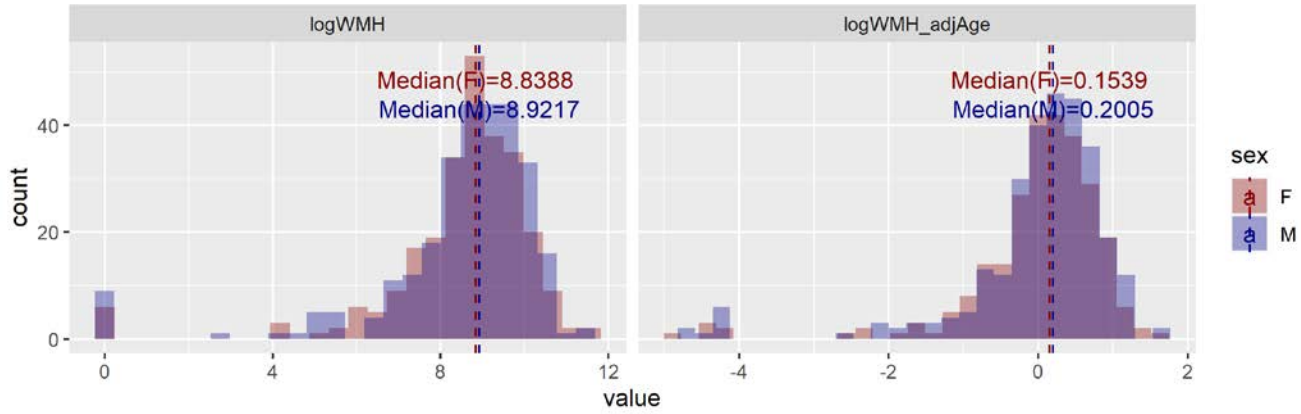


*Figure S2 F) RS-1-4*

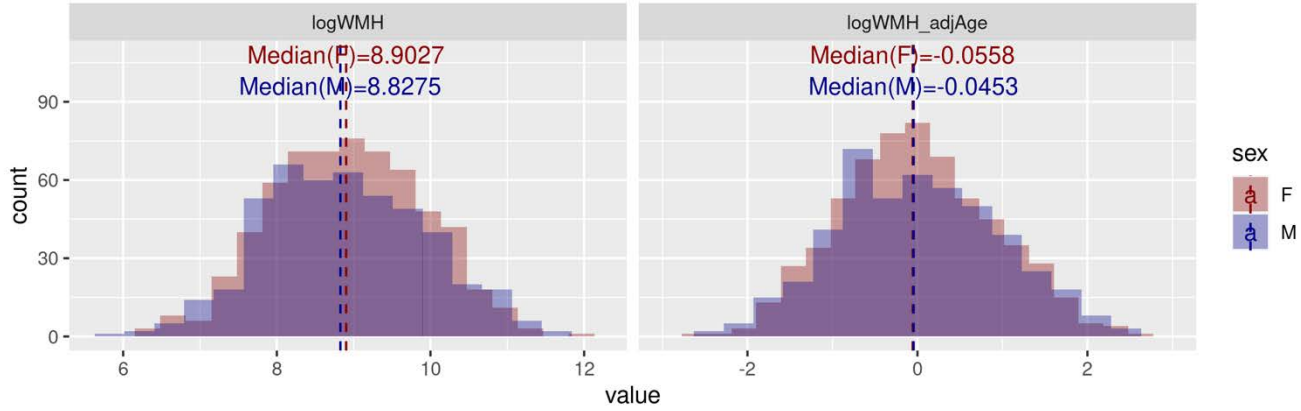


*Figure S2 G) RS-II-3*

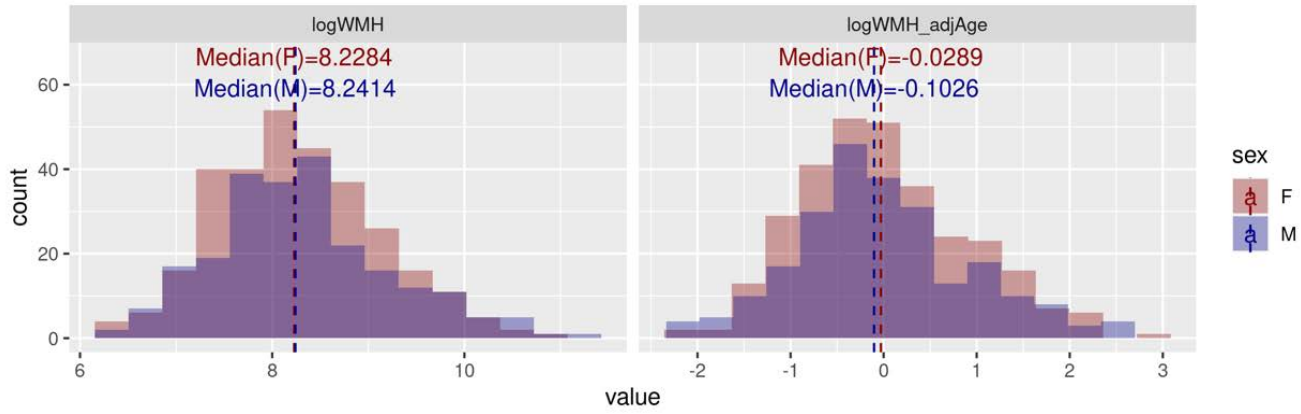


*Figure S2 H) RS-III-2*

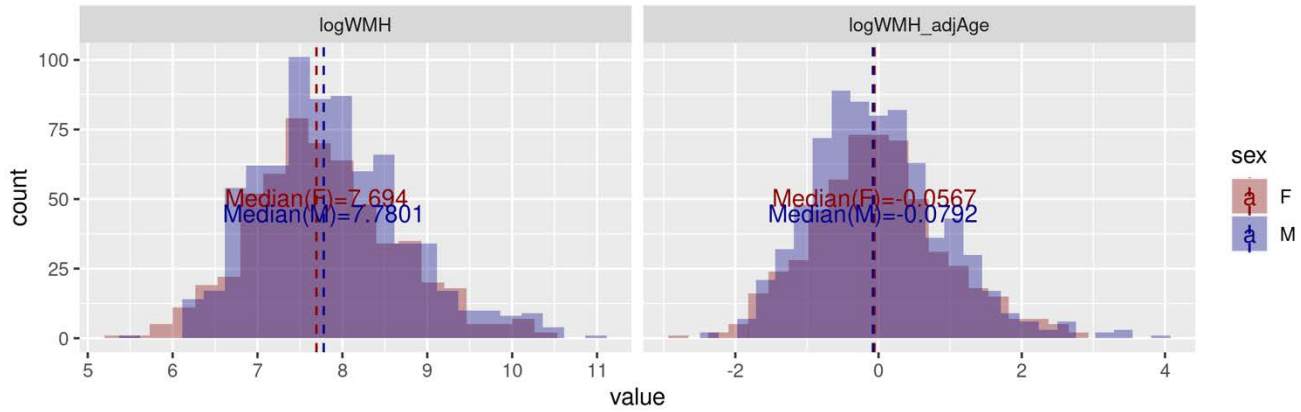

*Figure S2 I) SABRE-CARIB*

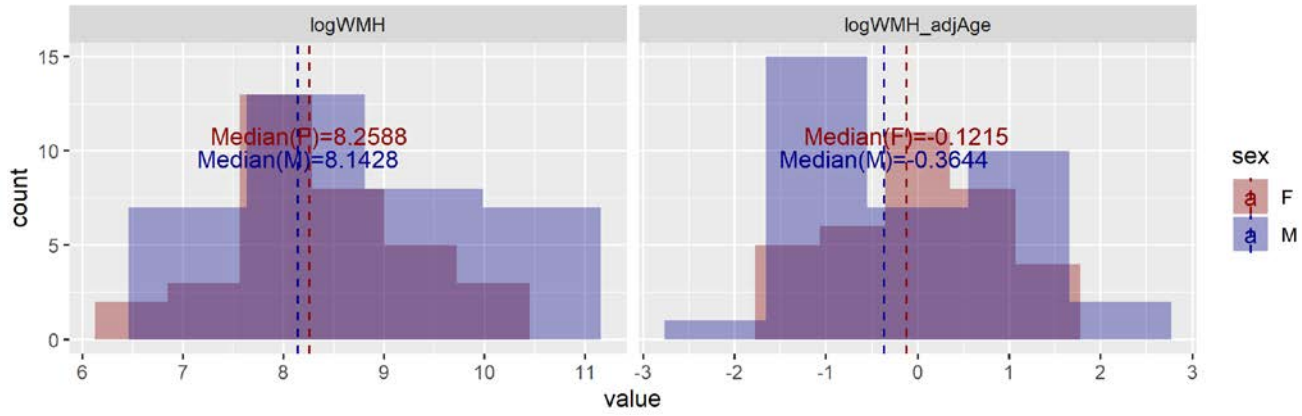


*Figure S2 J) SABRE-EUR*

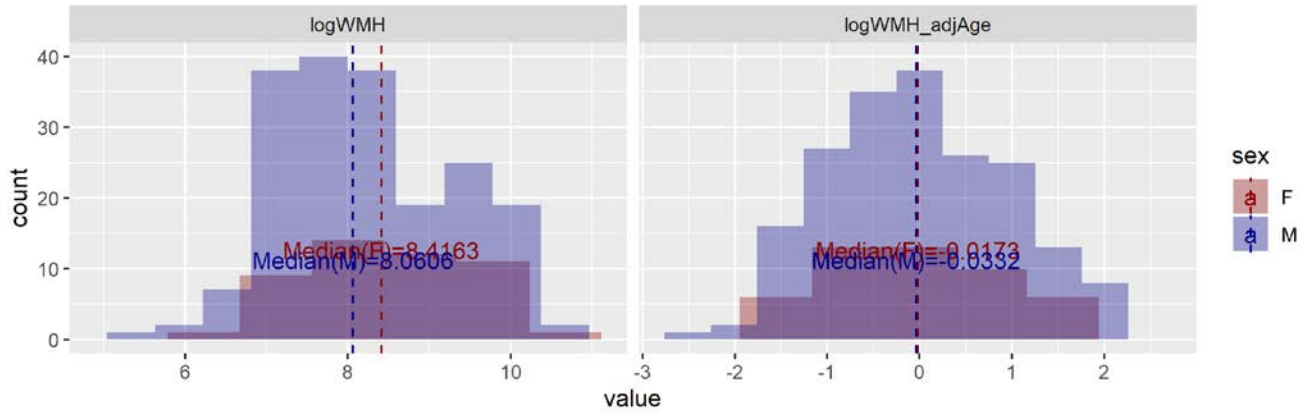


*Figure S2 K) SABRE-SA*

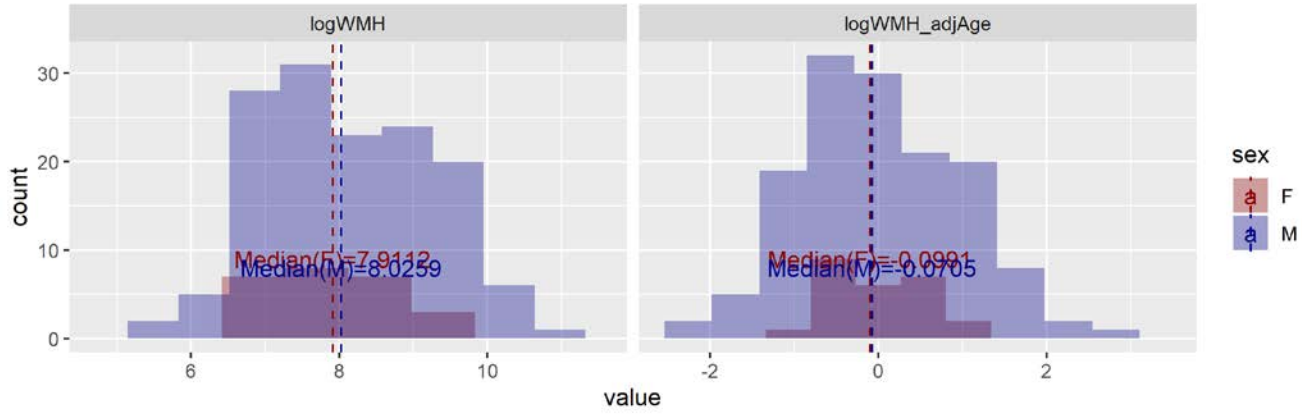


*Figure S2 L) SHIP-2*

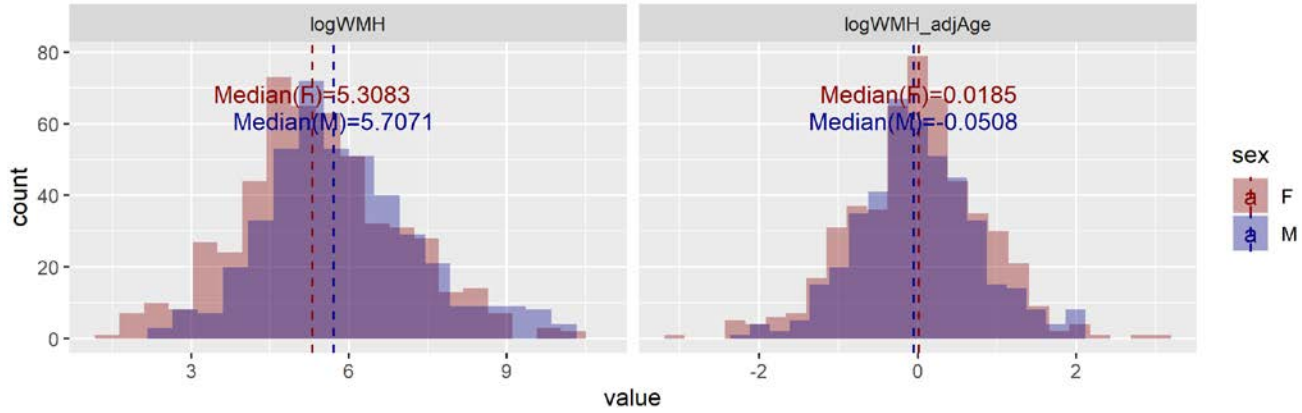

*Figure S2 M) SHIP-TREND*

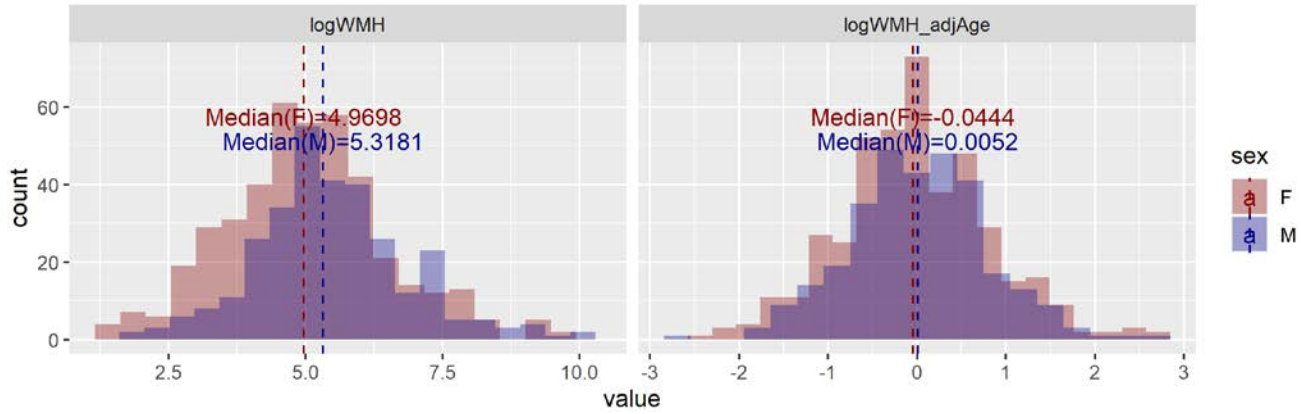


*Figure S2 N) SYS*

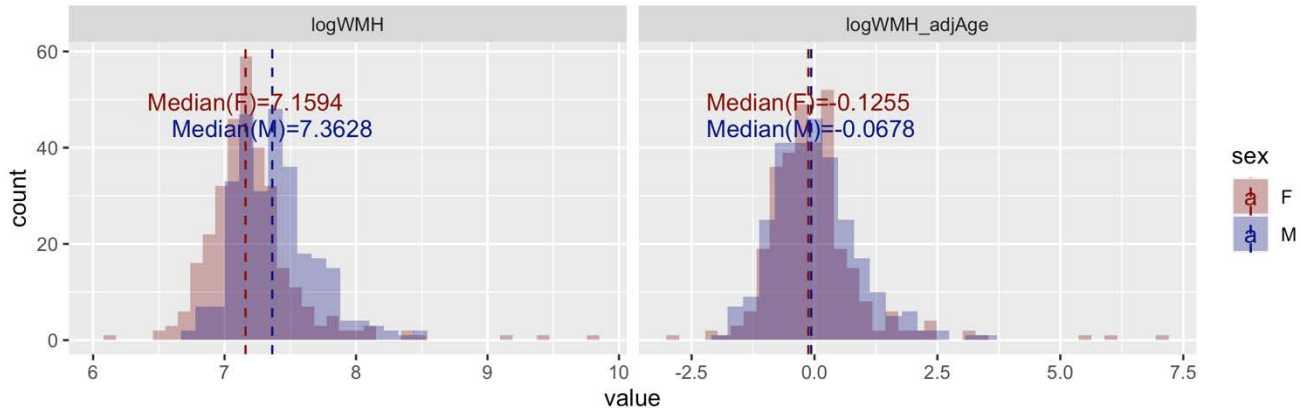

**Figure S3. Cohort-specific association results for the 31 metabolic measures showing significant association with WMH in the meta-analyzed results of at least one of the study models.**

The associations between WMH and circulating metabolic measures were determined using linear regression. In the combined sample and in statin-use stratified sub-samples, *the primary study models* ("basic"; left) were adjusted for age, sex, age-by-sex interaction and intracranial volume or brain size, and, in the sex-stratified samples, for age and intracranial volume or brain size. *The fully adjusted models* ("full"; right) were additionally adjusted for hypertension, type 2 diabetes, body mass index, current smoking status, estimated glomerular filtration rate, and hypertension, and, in the combined sample and in sex-stratified sub-samples, also for statin use. Where relevant, all models were adjusted for fasting duration, time between blood sampling and brain MRI, and possible cohort-specific covariates. Error bars indicate 95% confidence intervals. P-value for heterogeneity ($P_{HET}$) is obtained using Cochran's Q test. Plots for each metabolic measure are given in alphabetical order. The same data are tabulated in Tables S3-S21.

*Figure S3 I) Carnitine-C16:2-OH*

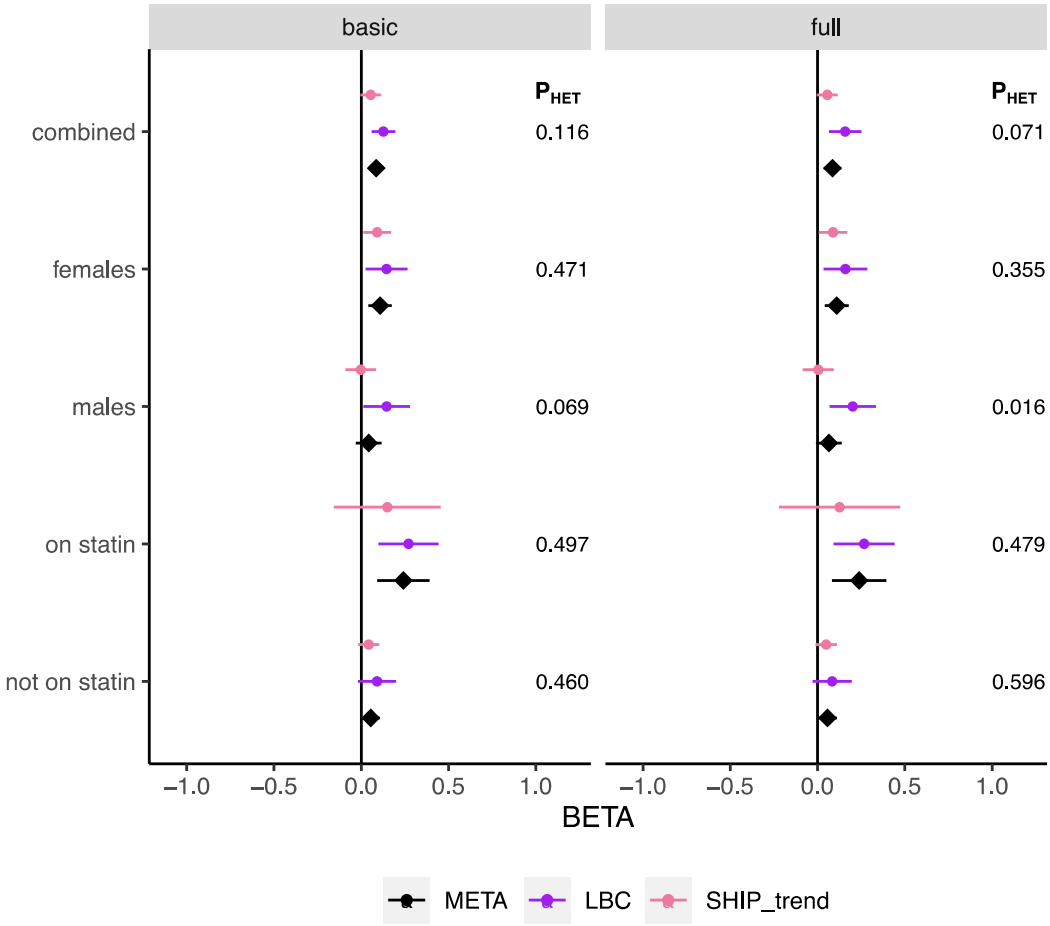

*Figure S3 II) CE(20:3)*

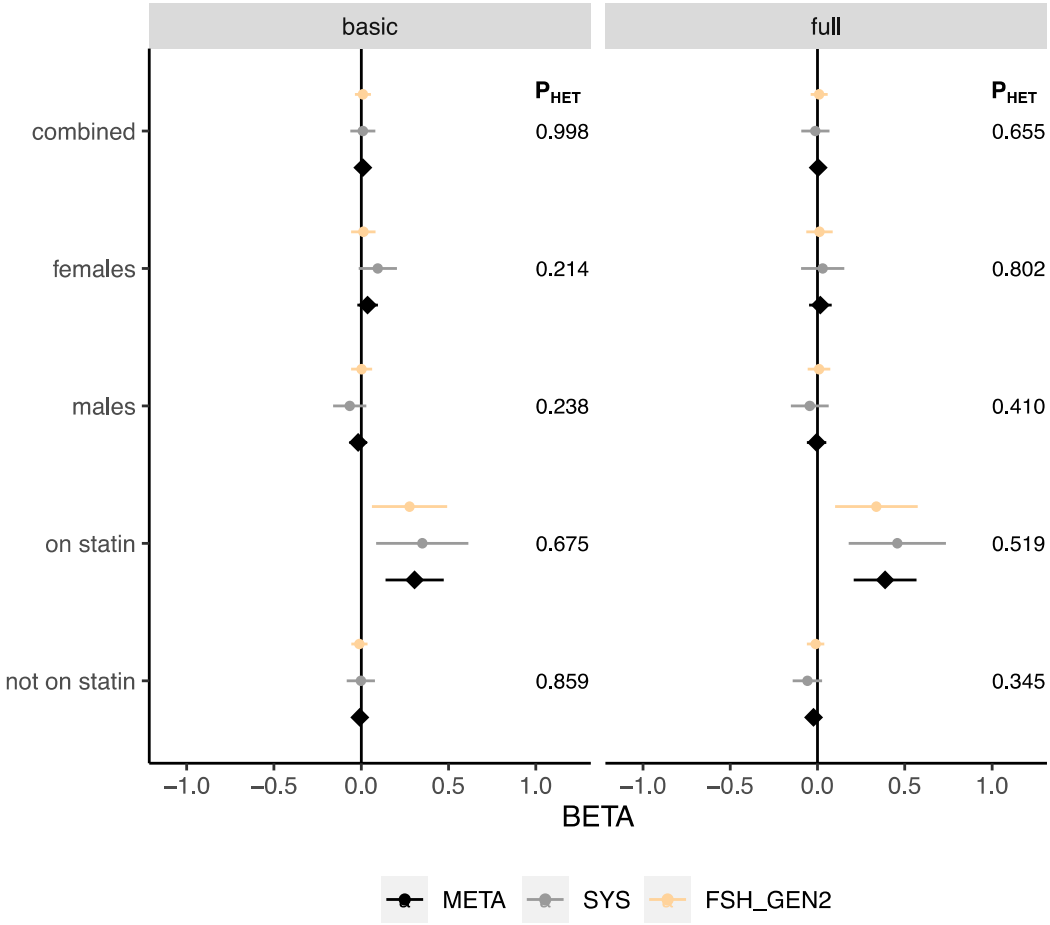


*Figure S3 III) Glucuronate*

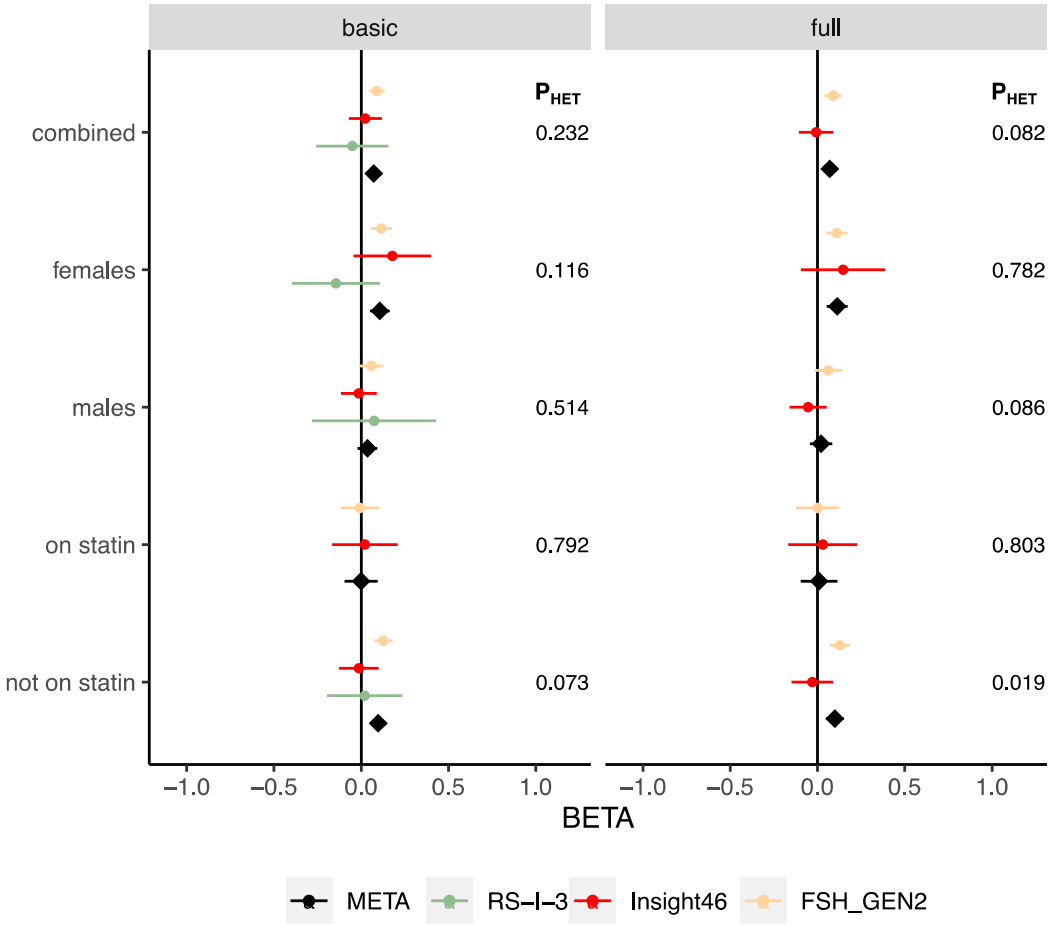

*Figure S3 IV) Hydroxyphenylpyruvate*

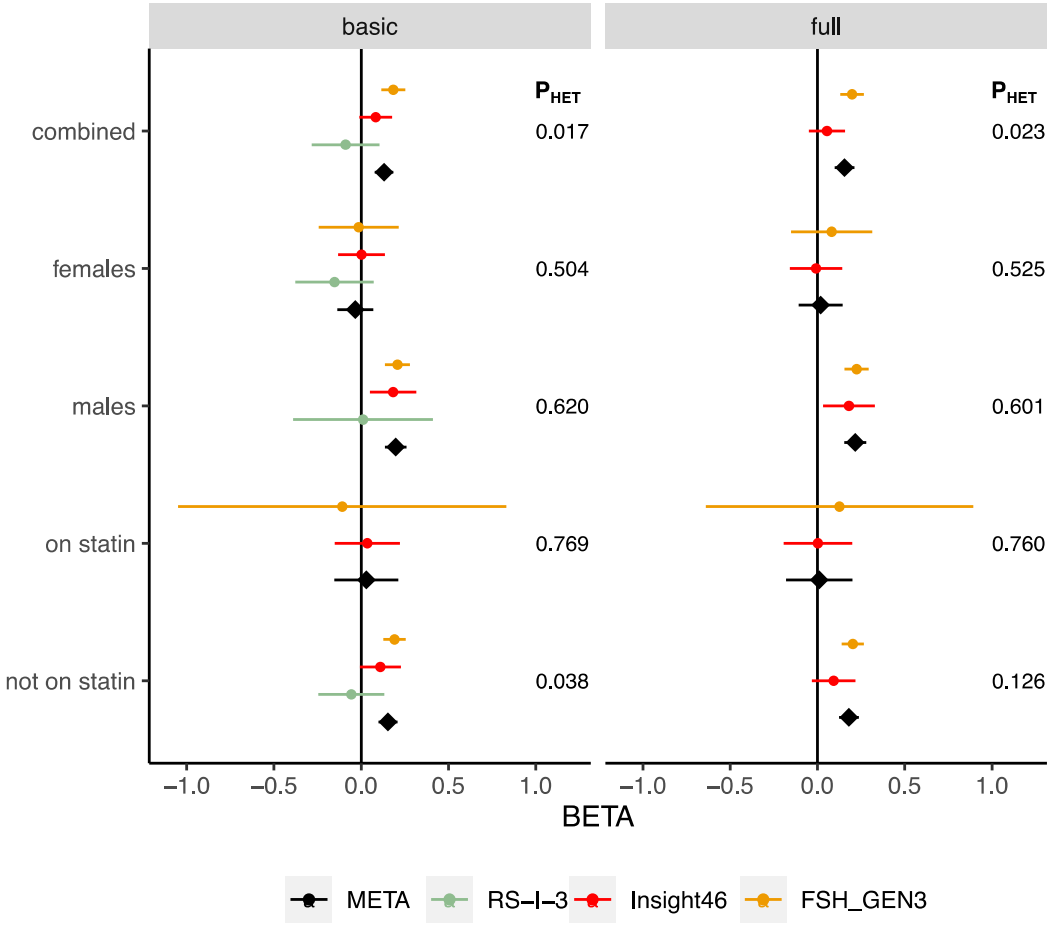


*Figure S3 V) IDL-C %*

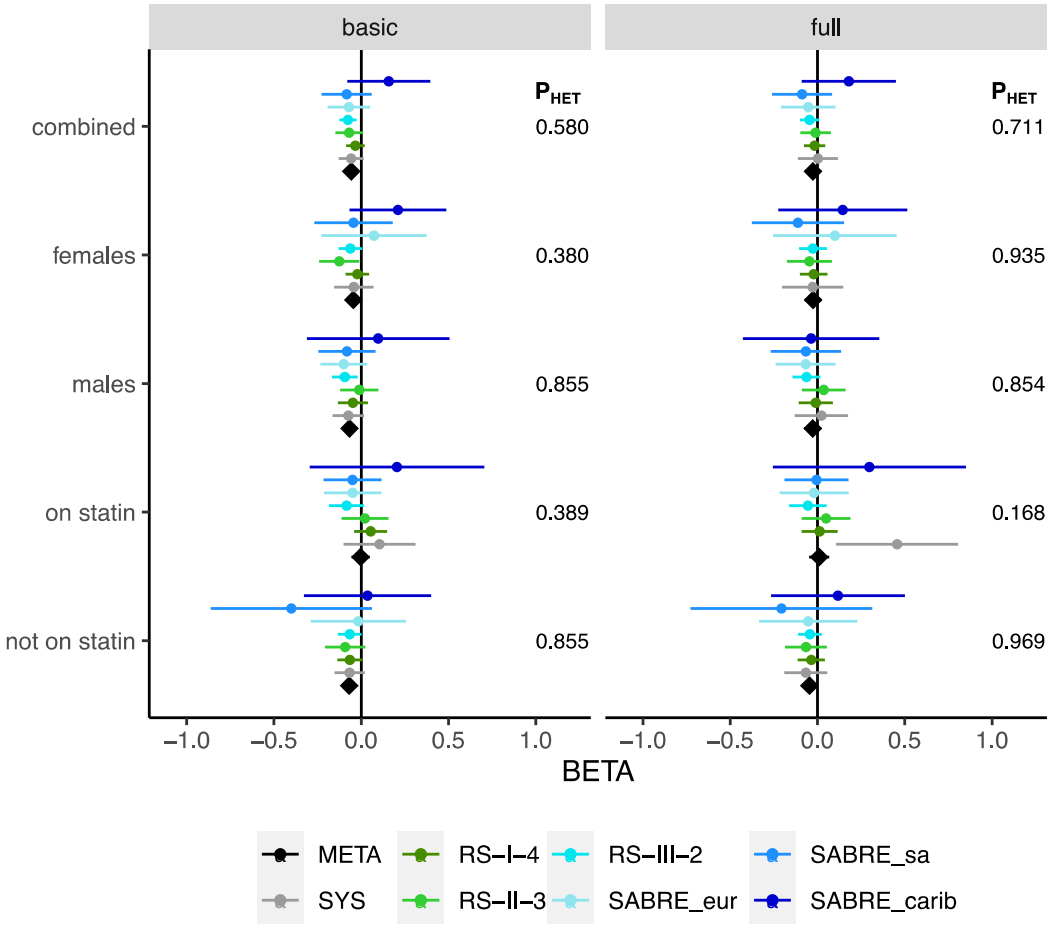

*Figure S3 VI) IDL-FC %*

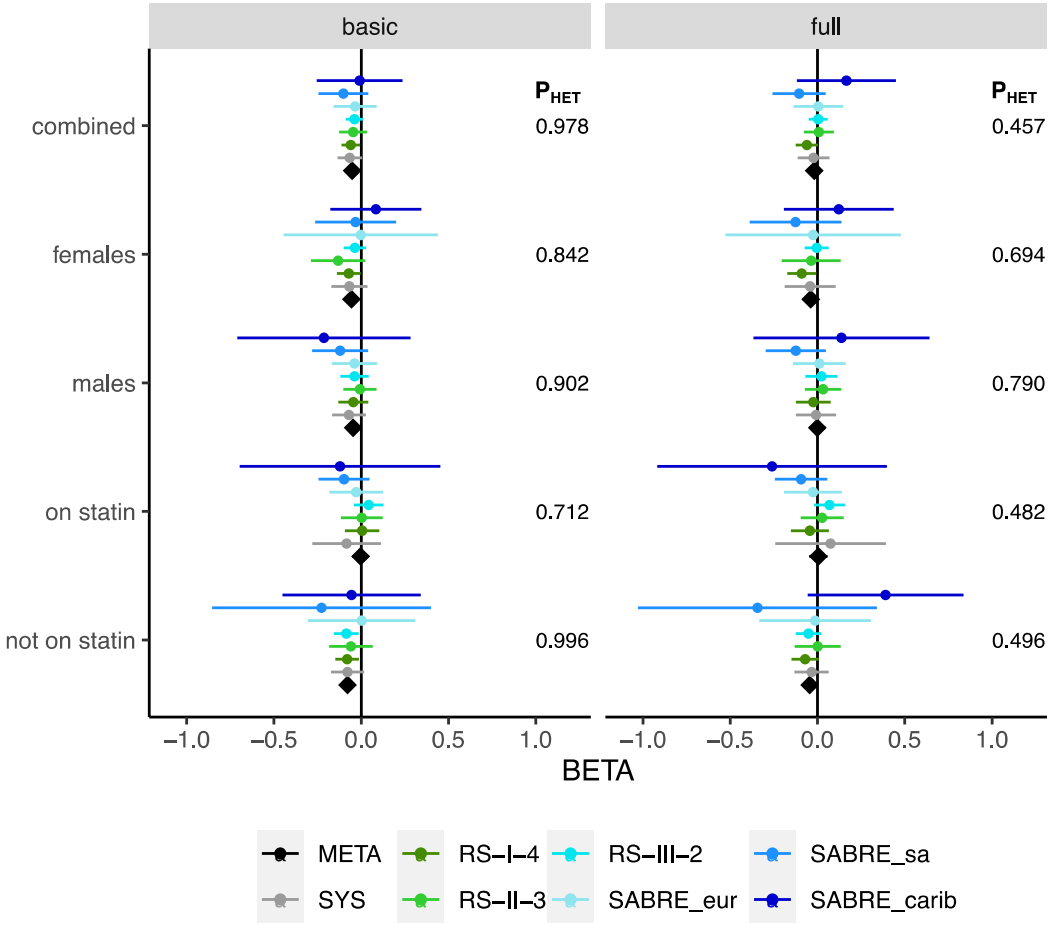


*Figure S3 VII) IDL-TG %*

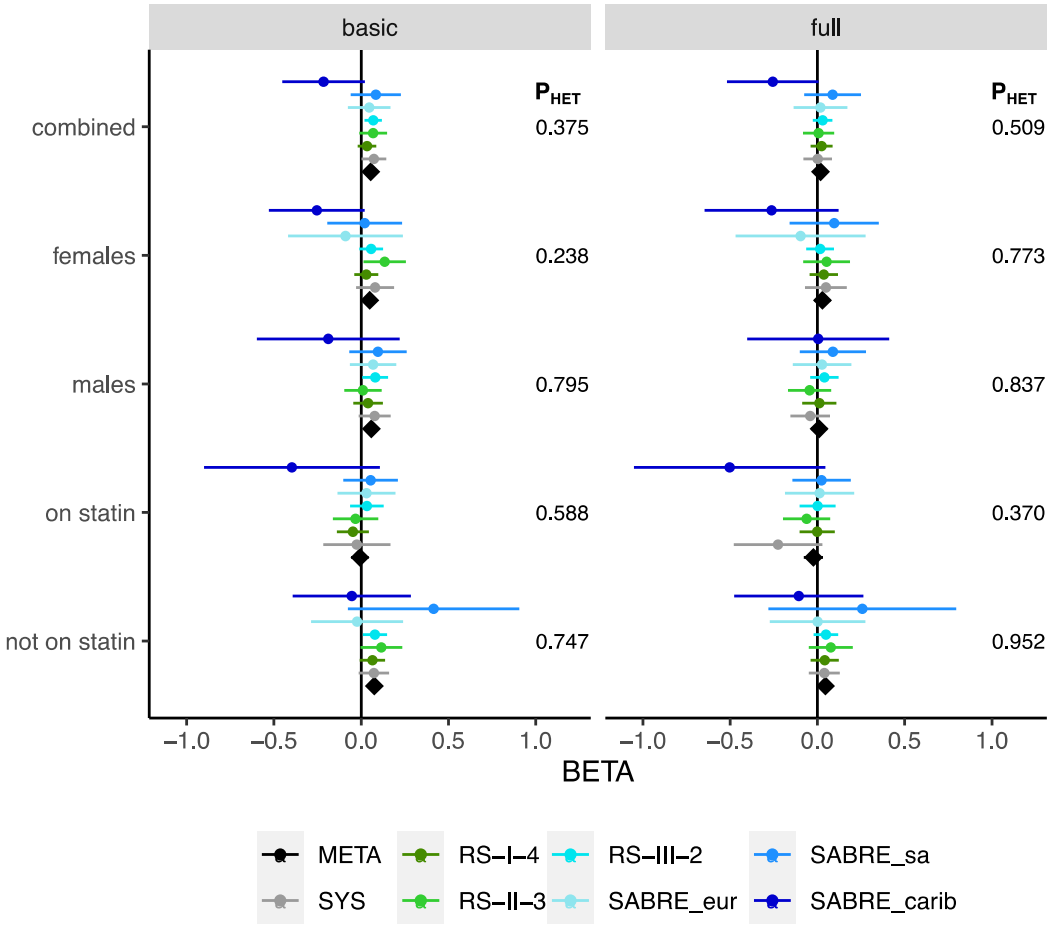

*Figure S3 VIII) L-LDL-CE %*

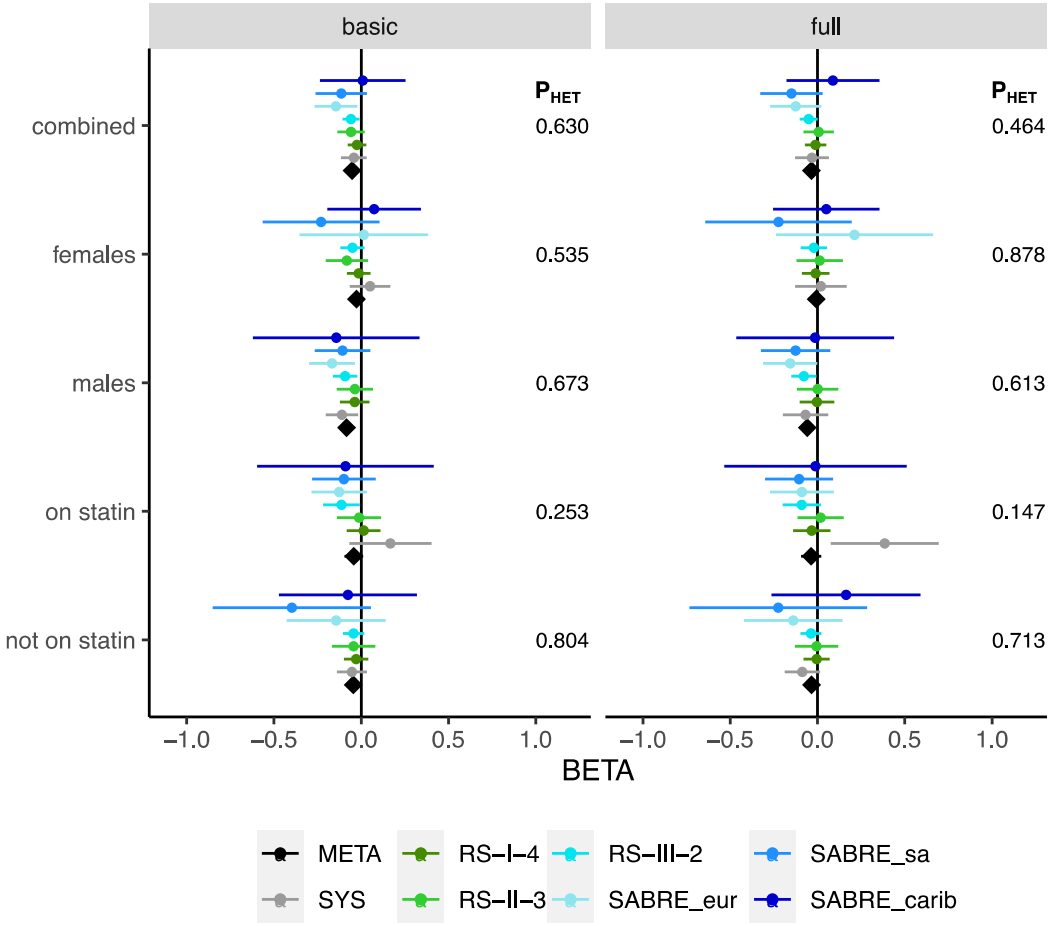


*Figure S3 IX) L-LDL-C %*

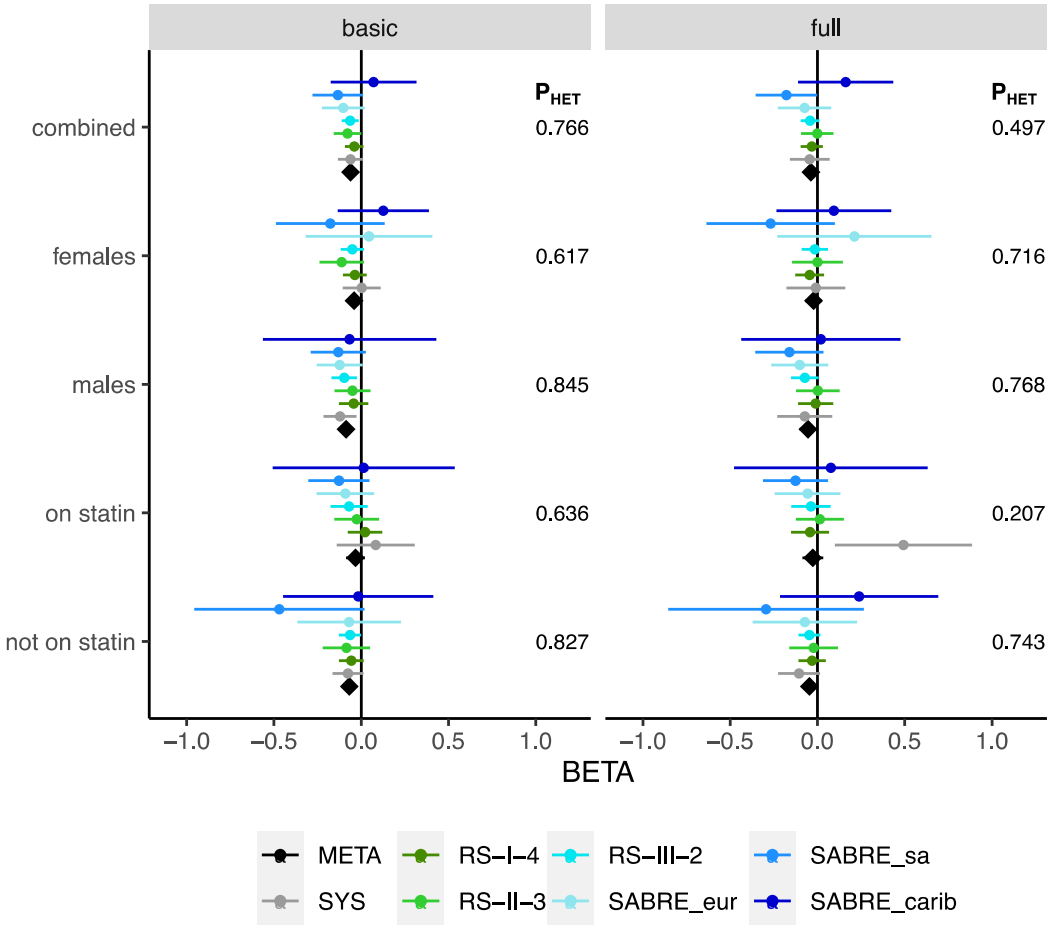

*Figure S3 X) L-LDL-TG %*

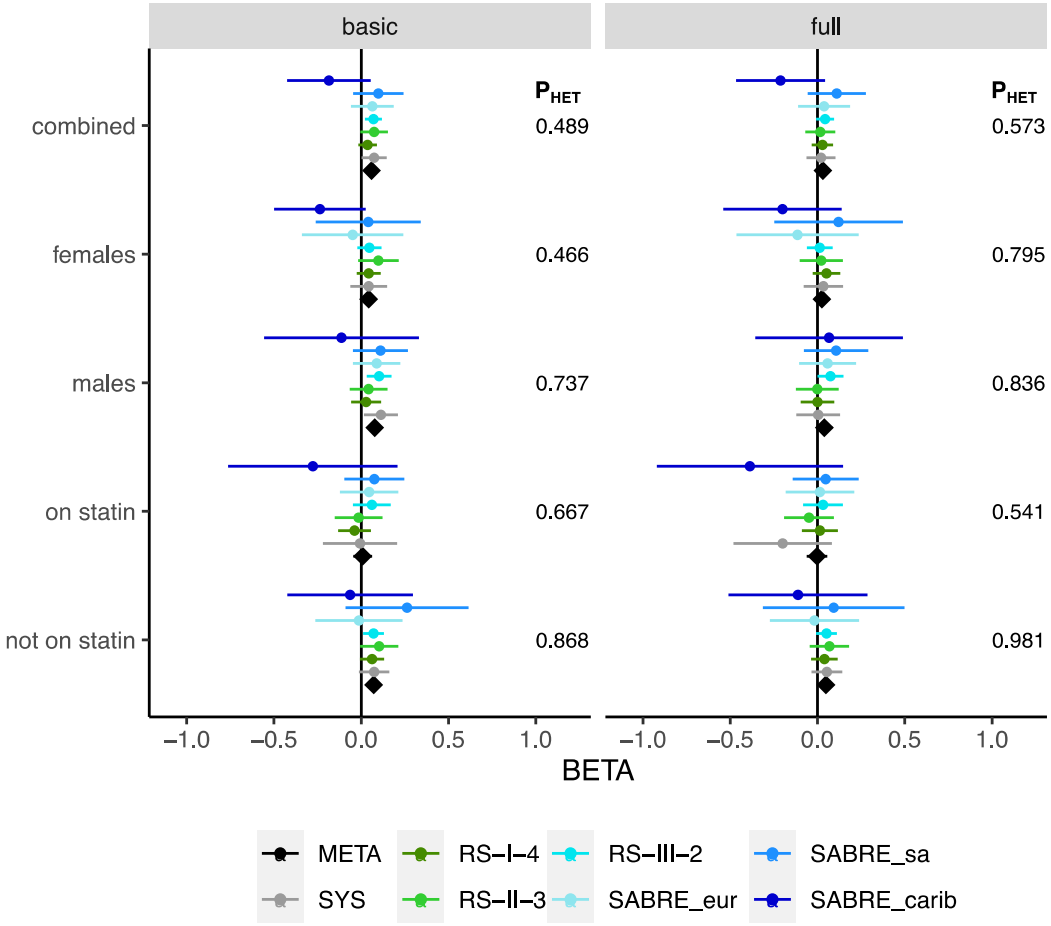


*Figure S3 XI) LDL-D*

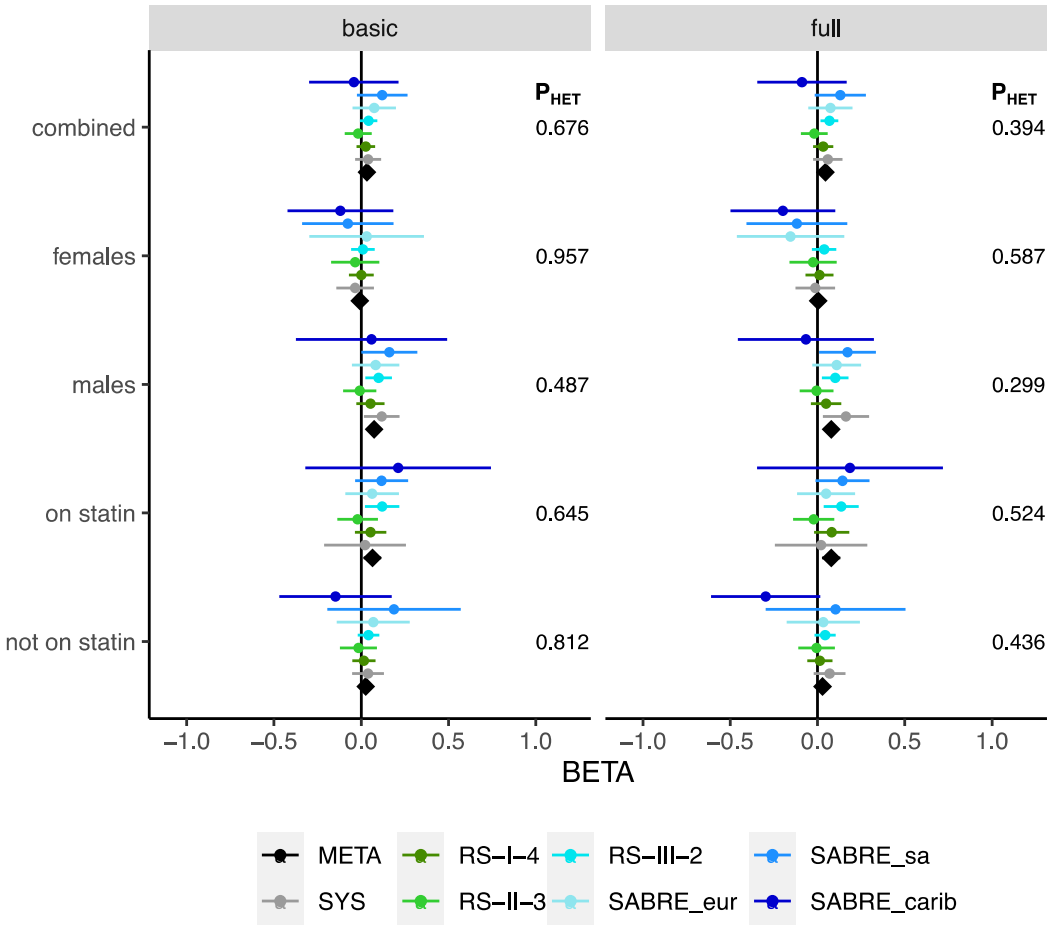

*Figure S3 XII) LPC(17:0)*

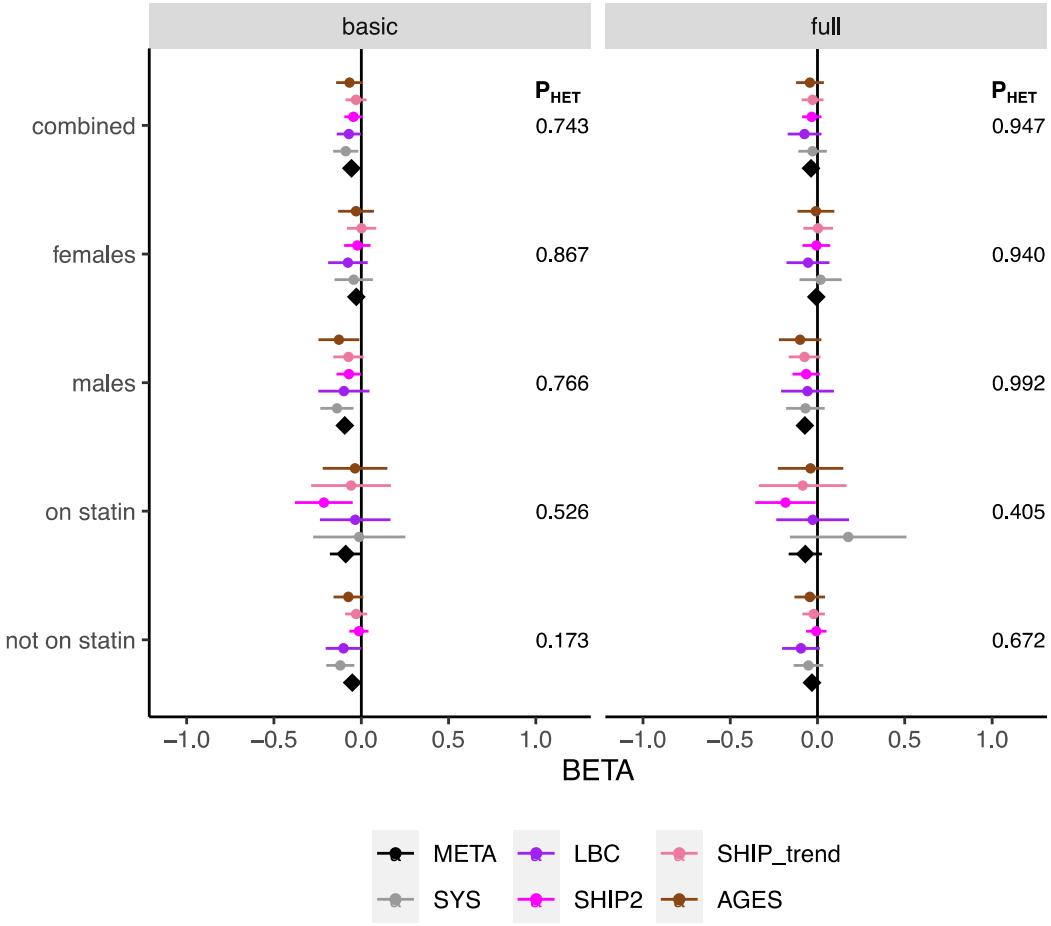


*Figure S3 XIII) LPC(18:2)*

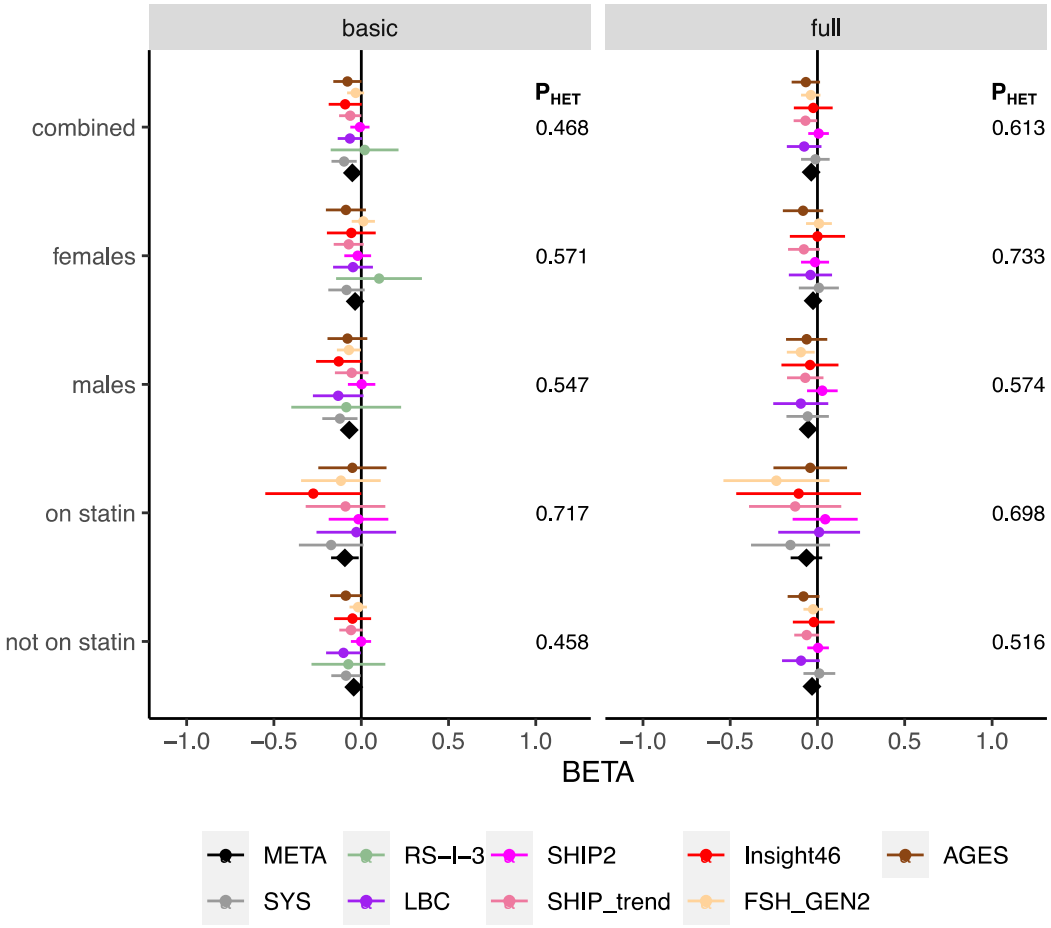

*Figure S3 XIV) LPC(22:6)*

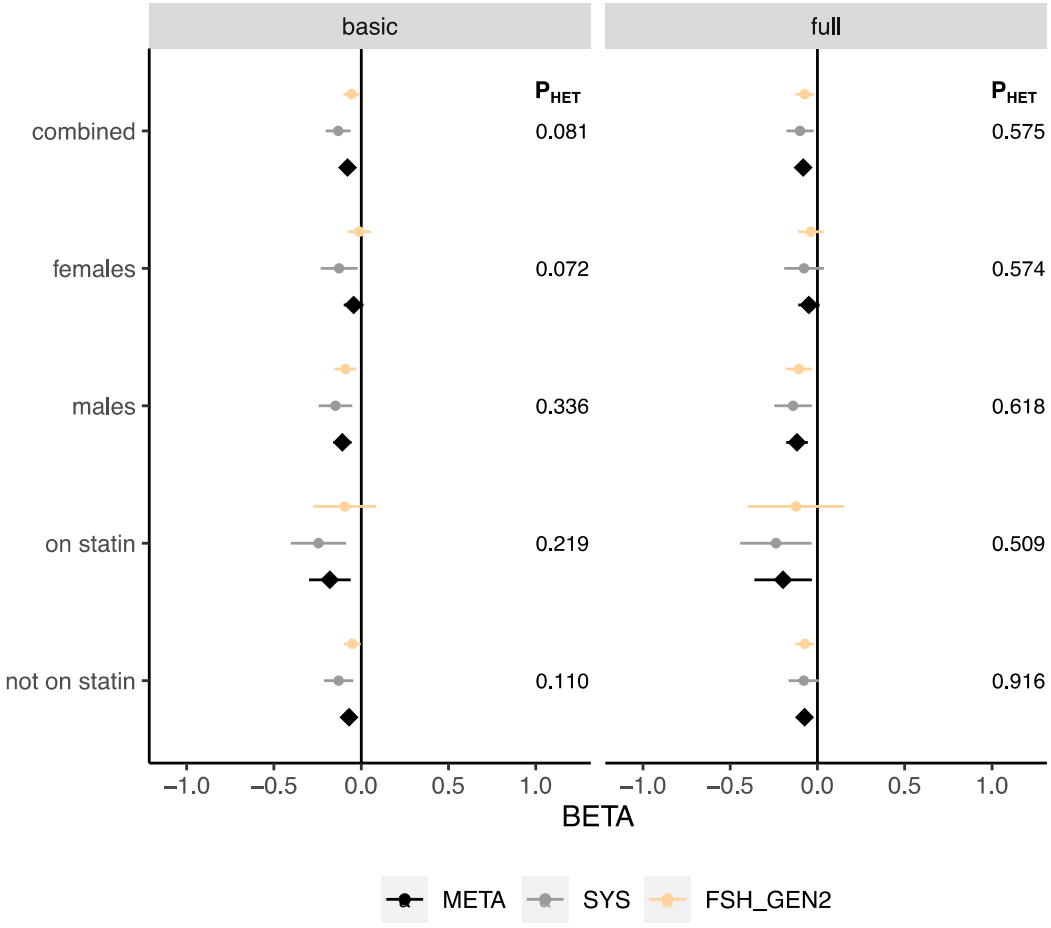


*Figure S3 XV) M-LDL-C*

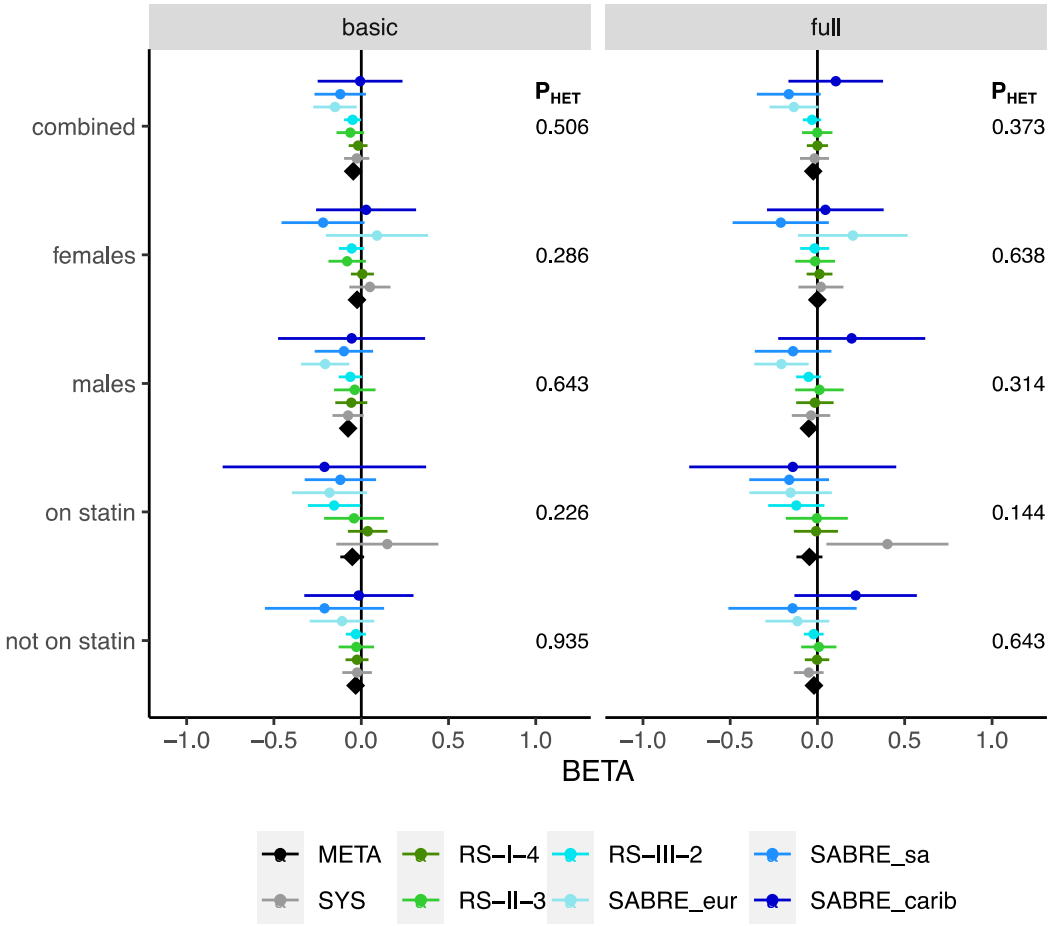

*Figure S3 XVI) M-LDL-CE*

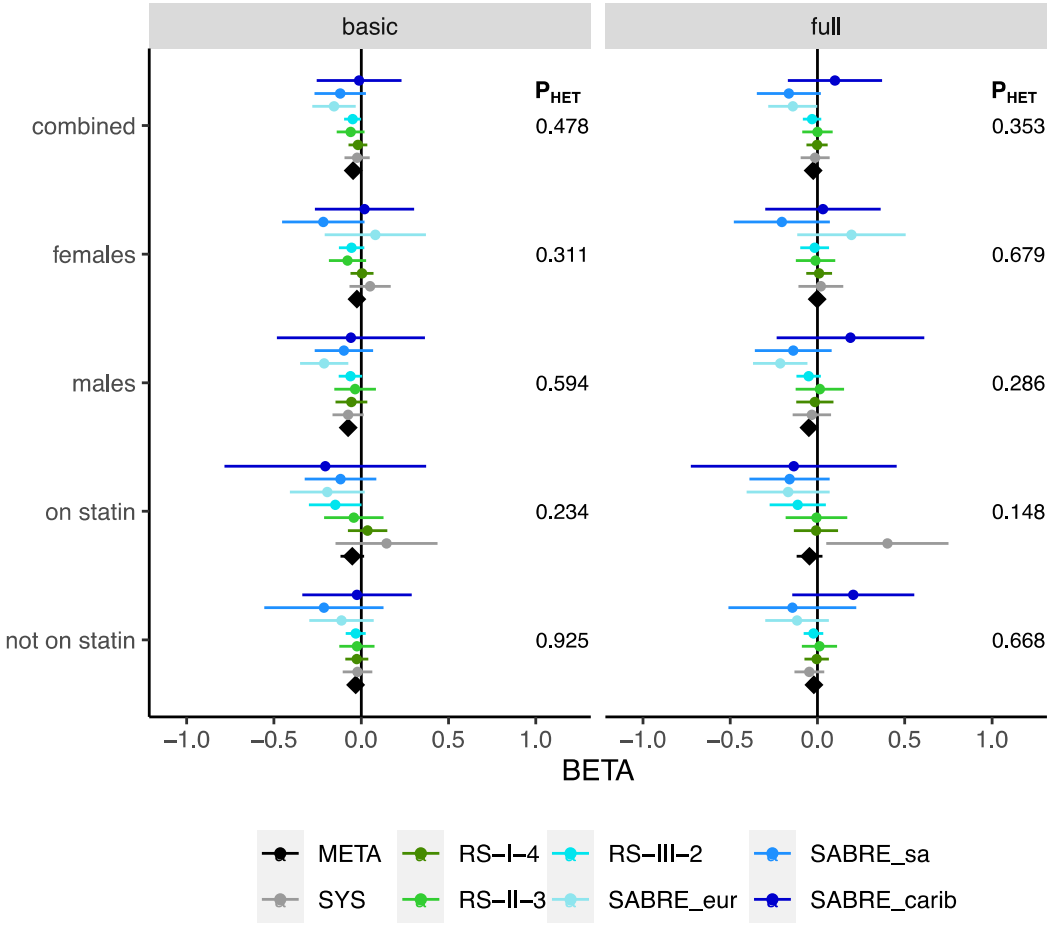


*Figure S3 XVII) M-LDL-CE %*

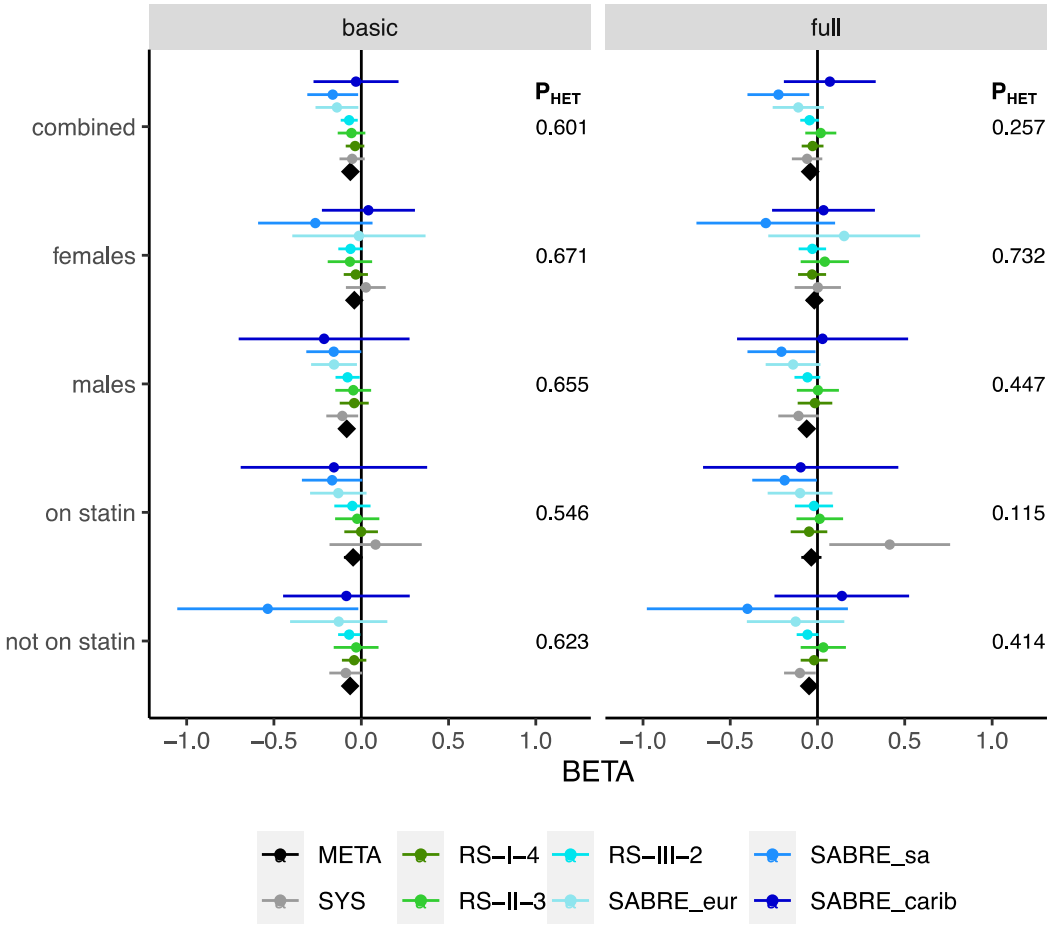

*Figure S3 XVIII) M-LDL-C %*

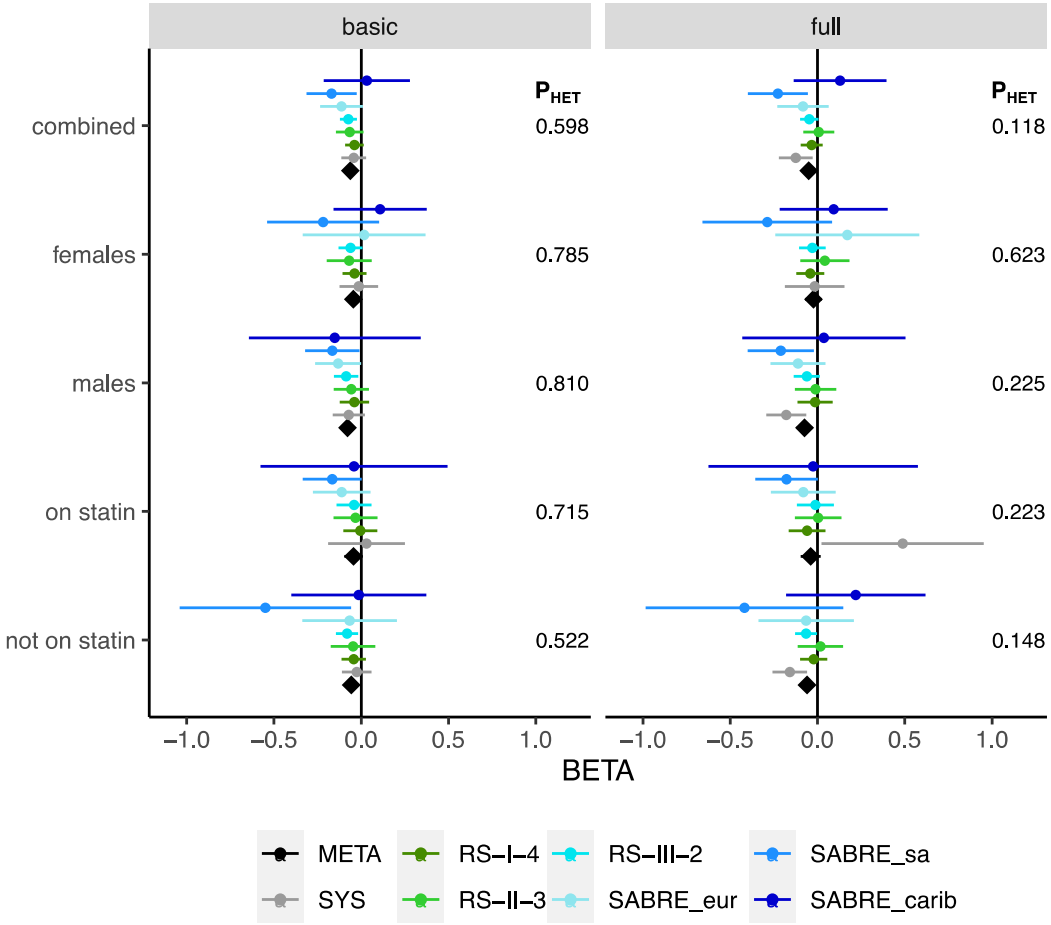


*Figure S3 XIX) M-LDL-FC*

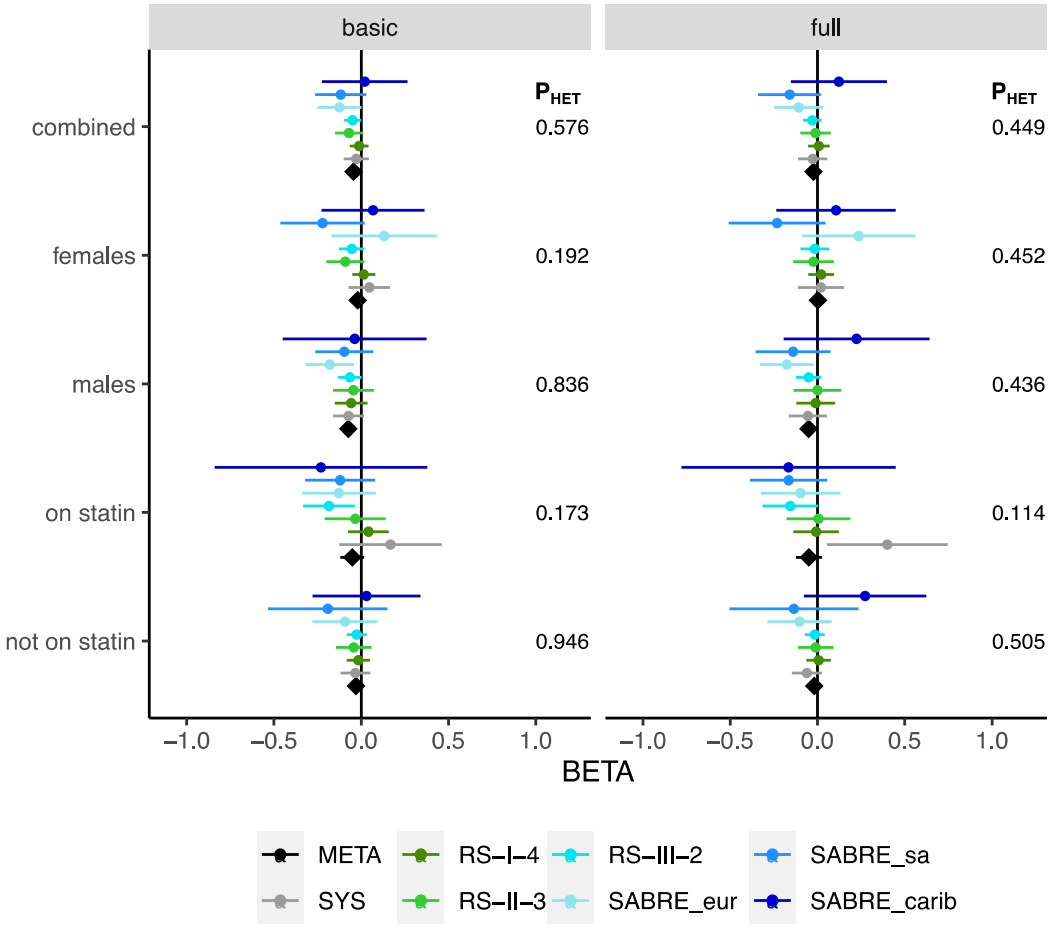

*Figure S3 XX) M-LDL-TG %*

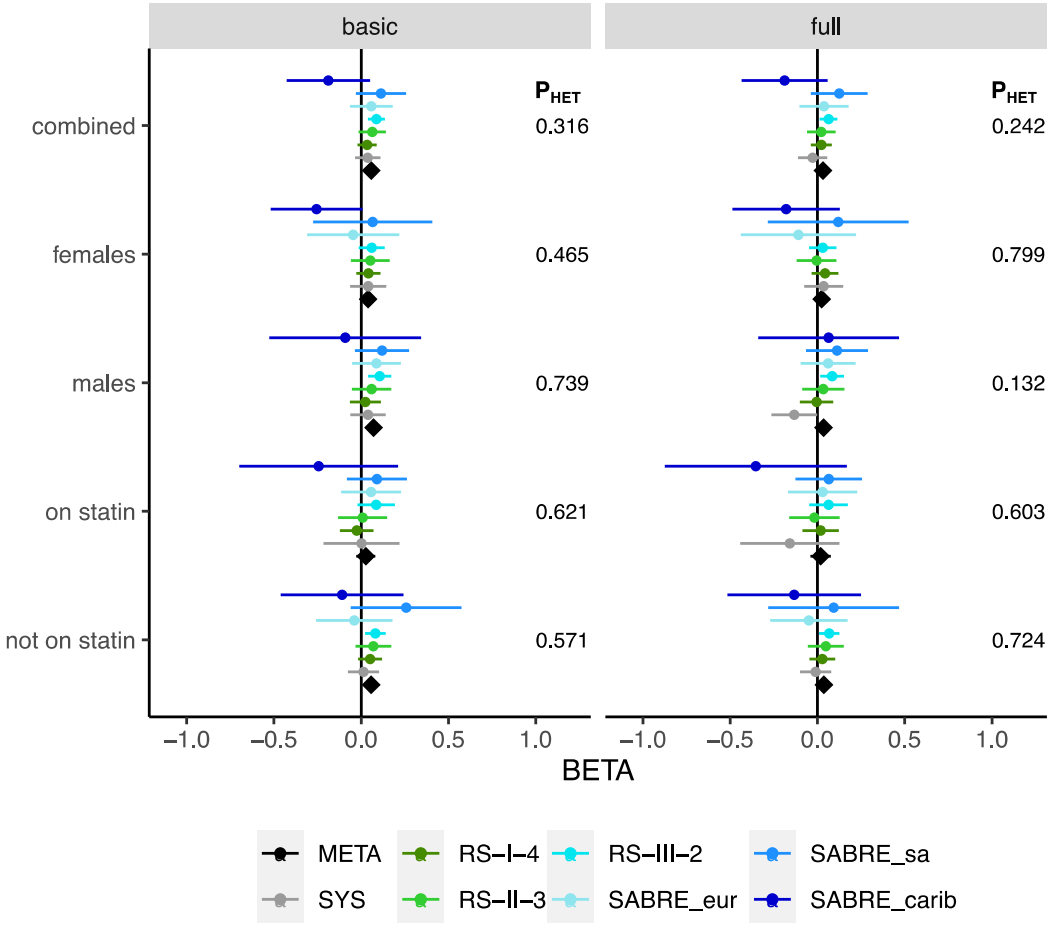


*Figure S3 XXI) M-VLDL-FC %*

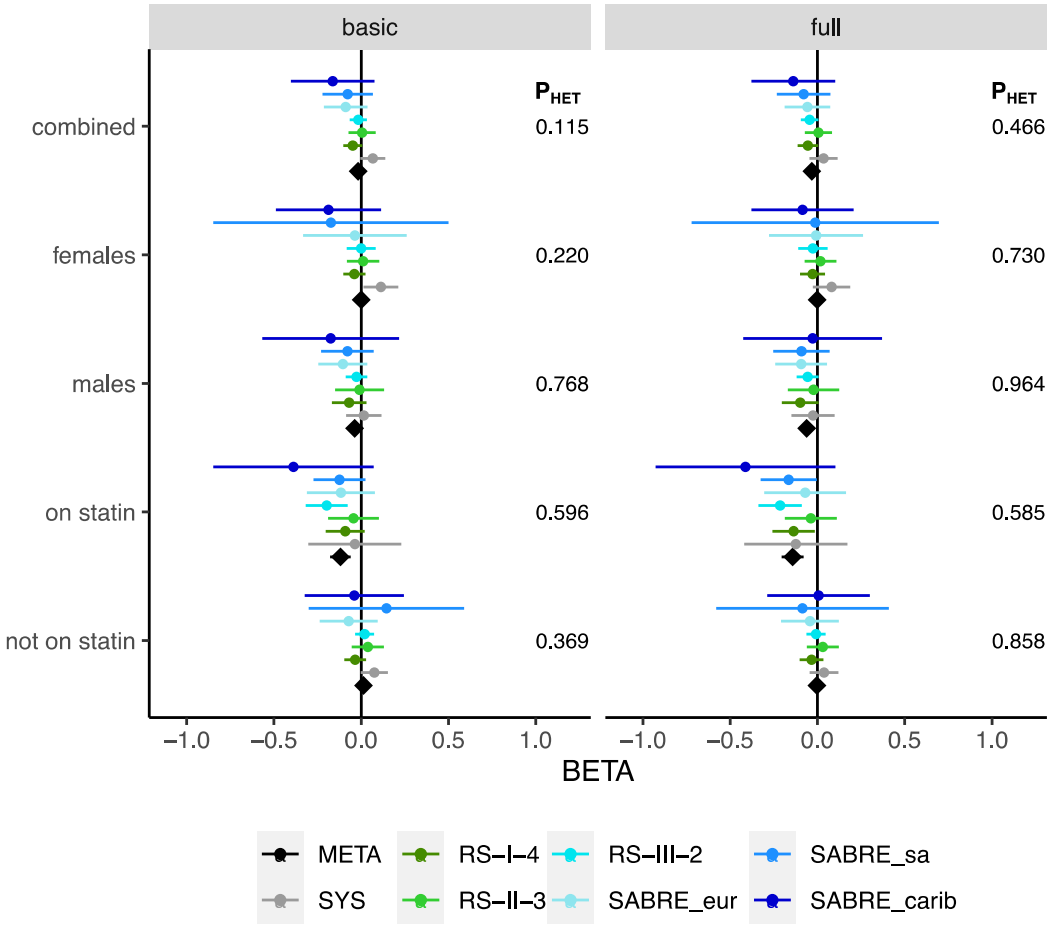

*Figure S3 XXII) MUFA %*

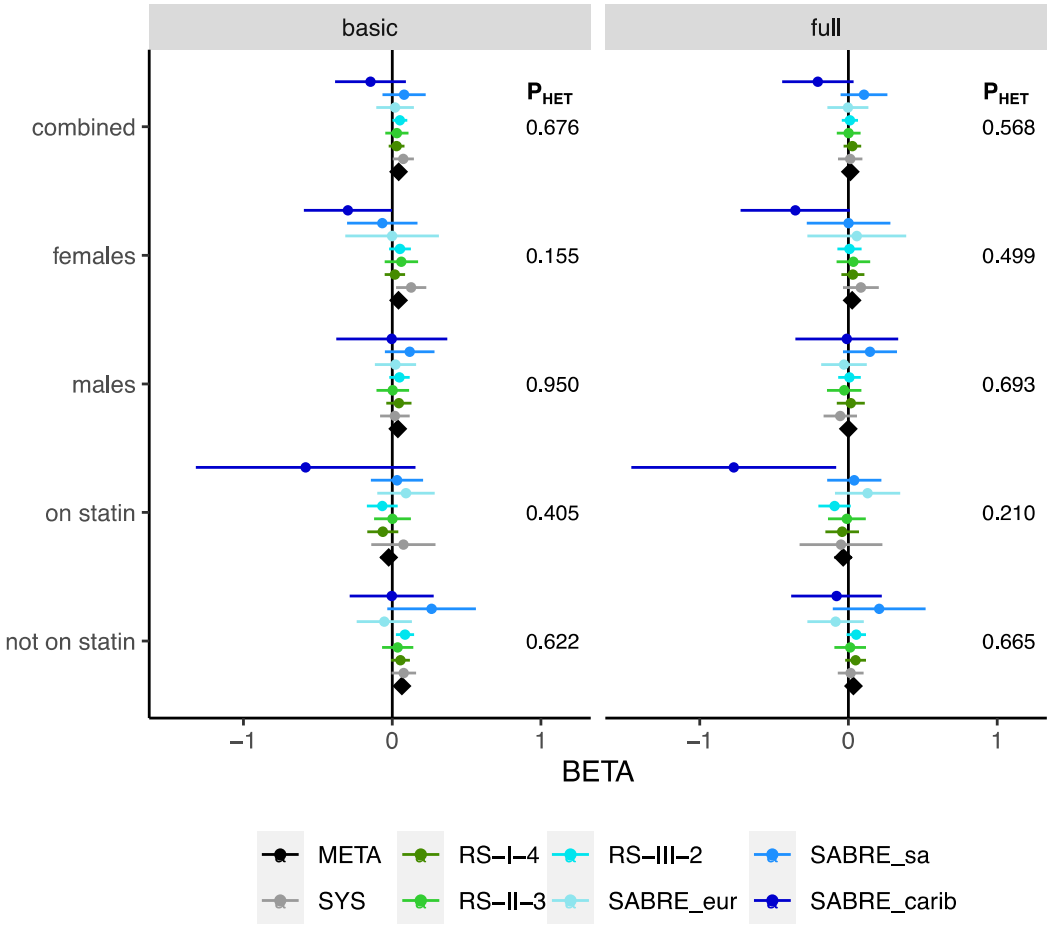


*Figure S3 XXIII) PC aa C32:1*

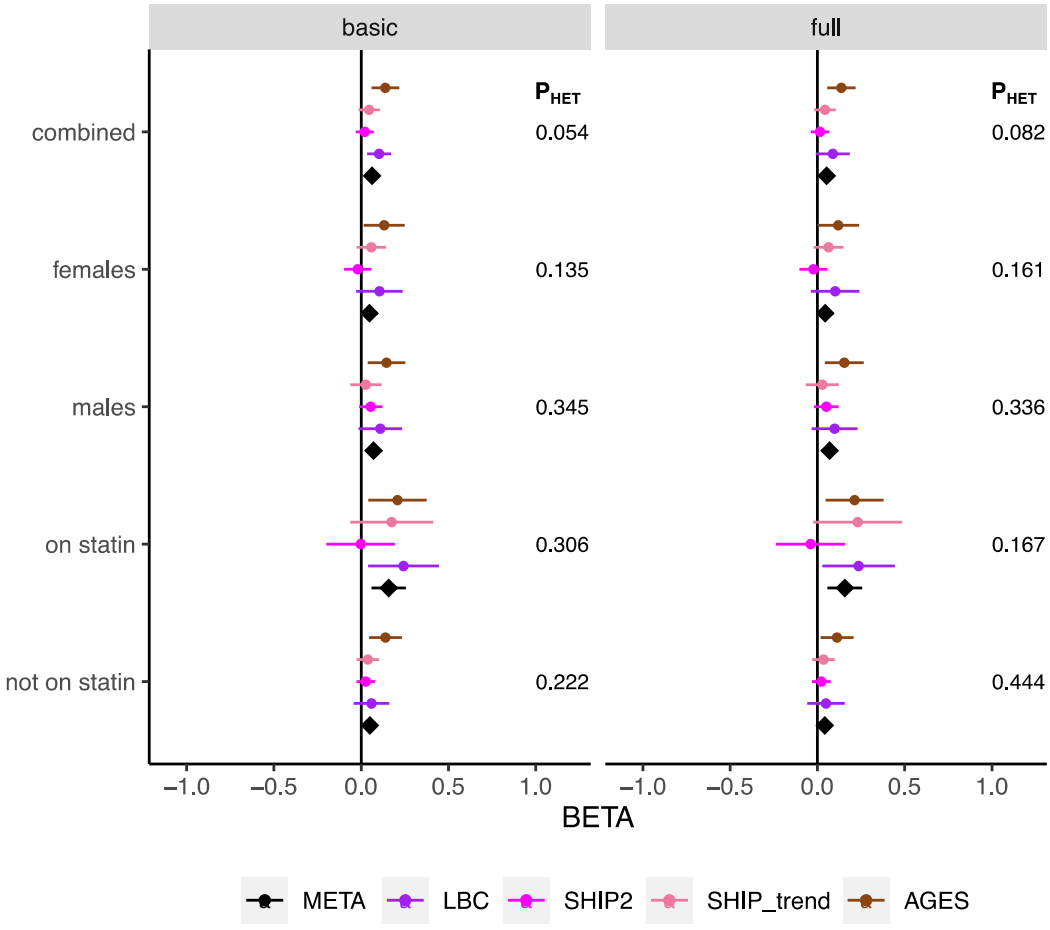

*Figure S3 XXIV) S-LDL-C*

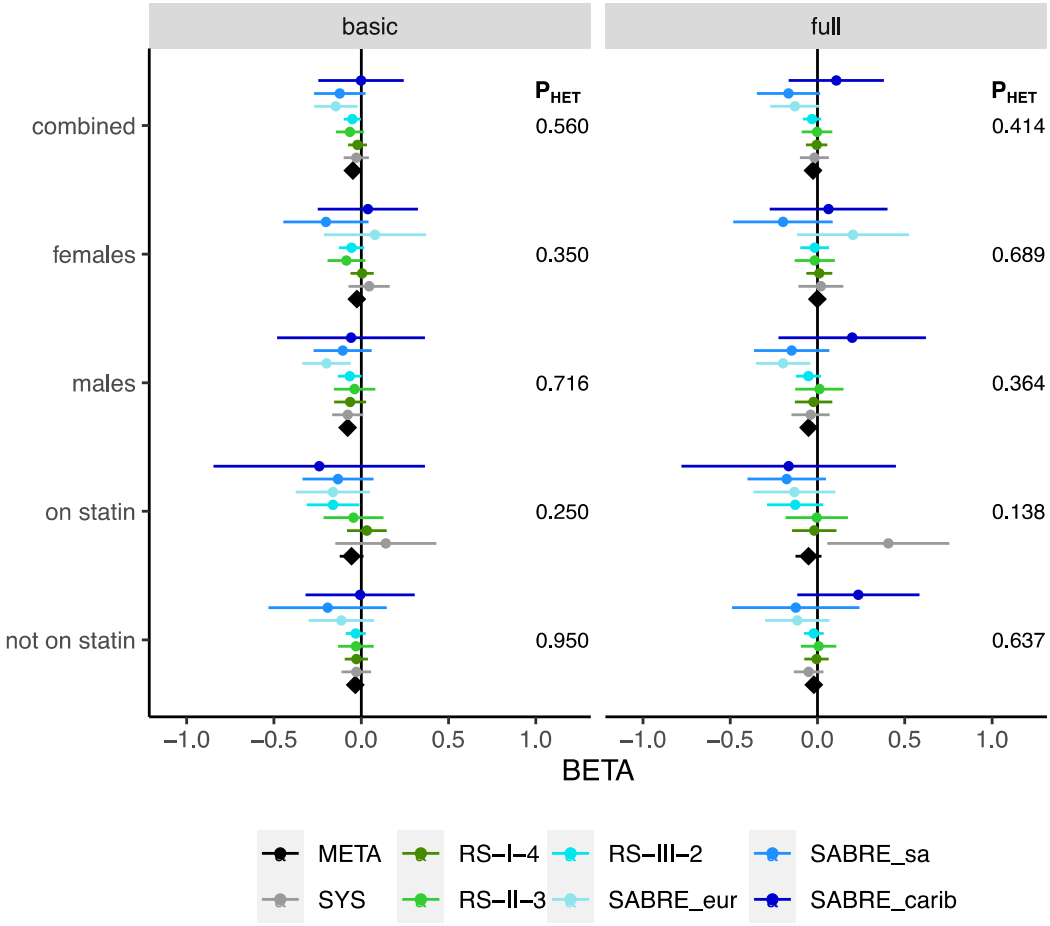


*Figure S3 XXV) S-LDL-CE*

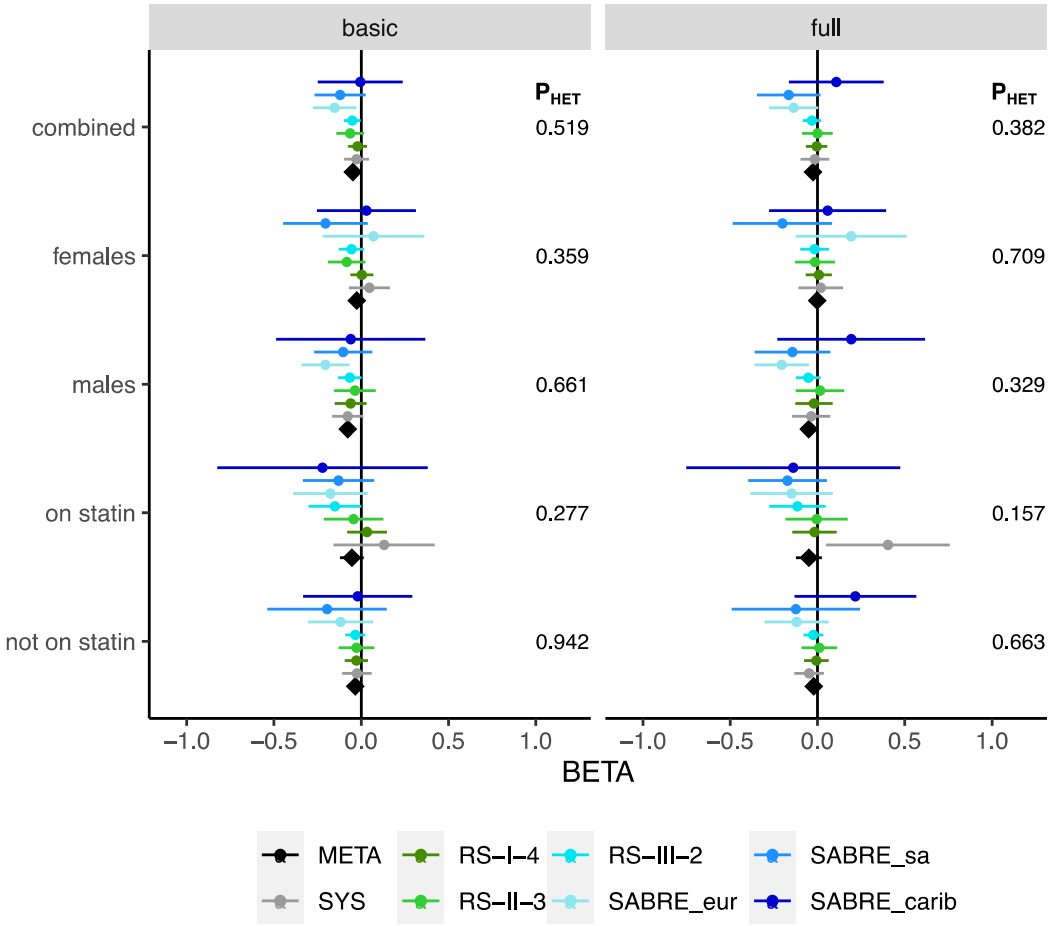

*Figure S3 XXVI) S-LDL-CE %*

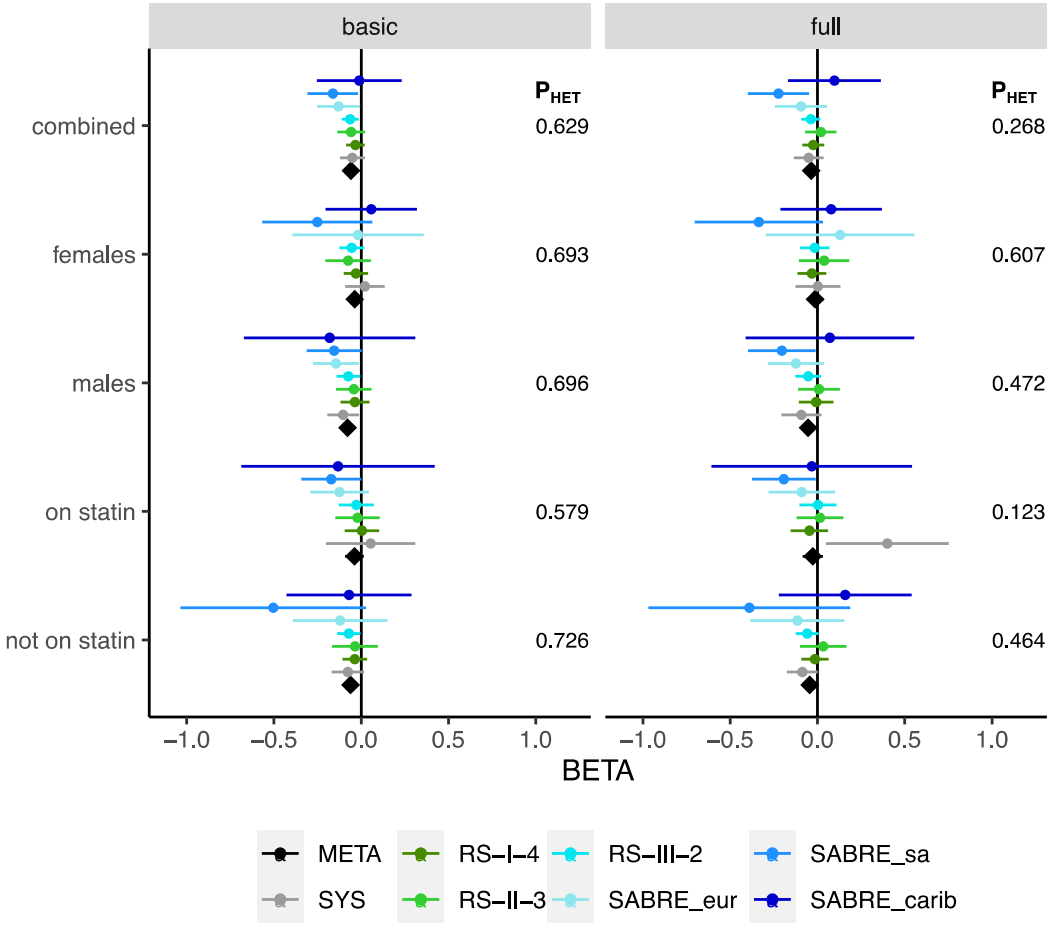


*Figure S3 XXVII) S-LDL-C %*

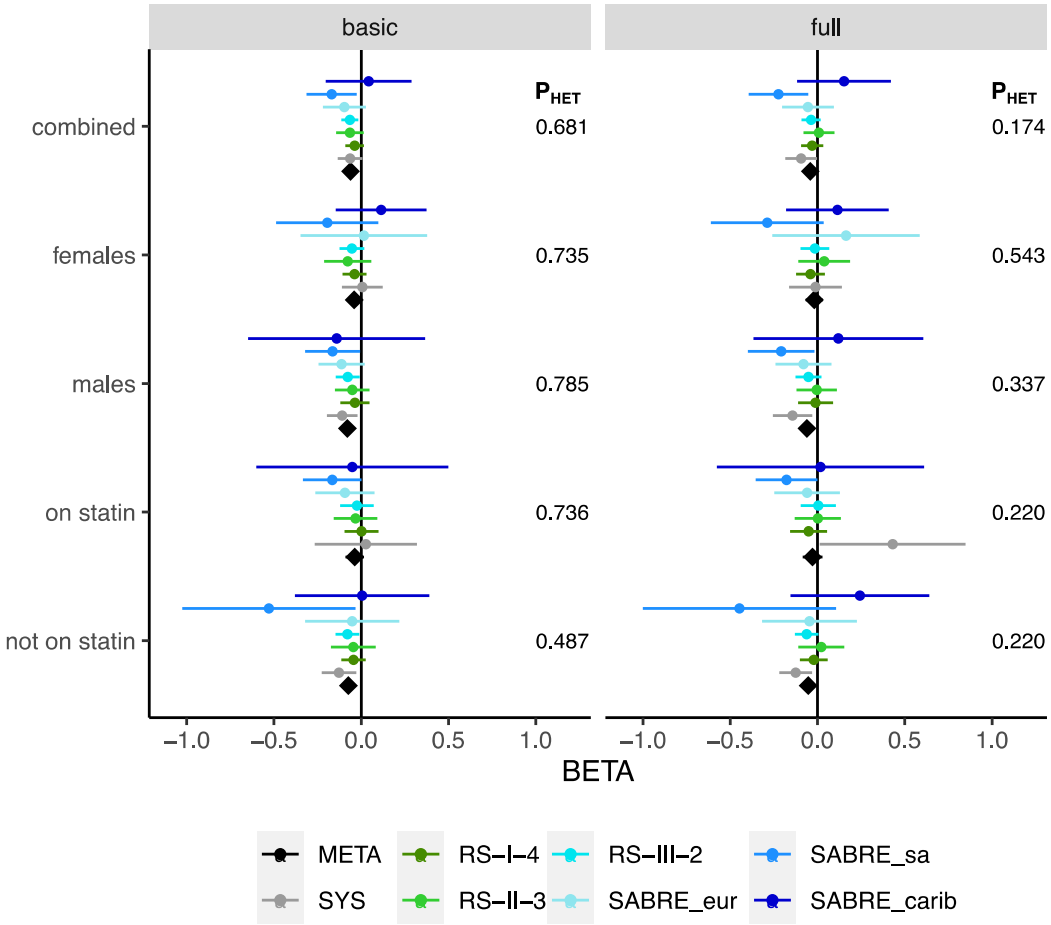

*Figure S3 XXVIII) S-LDL-FC*

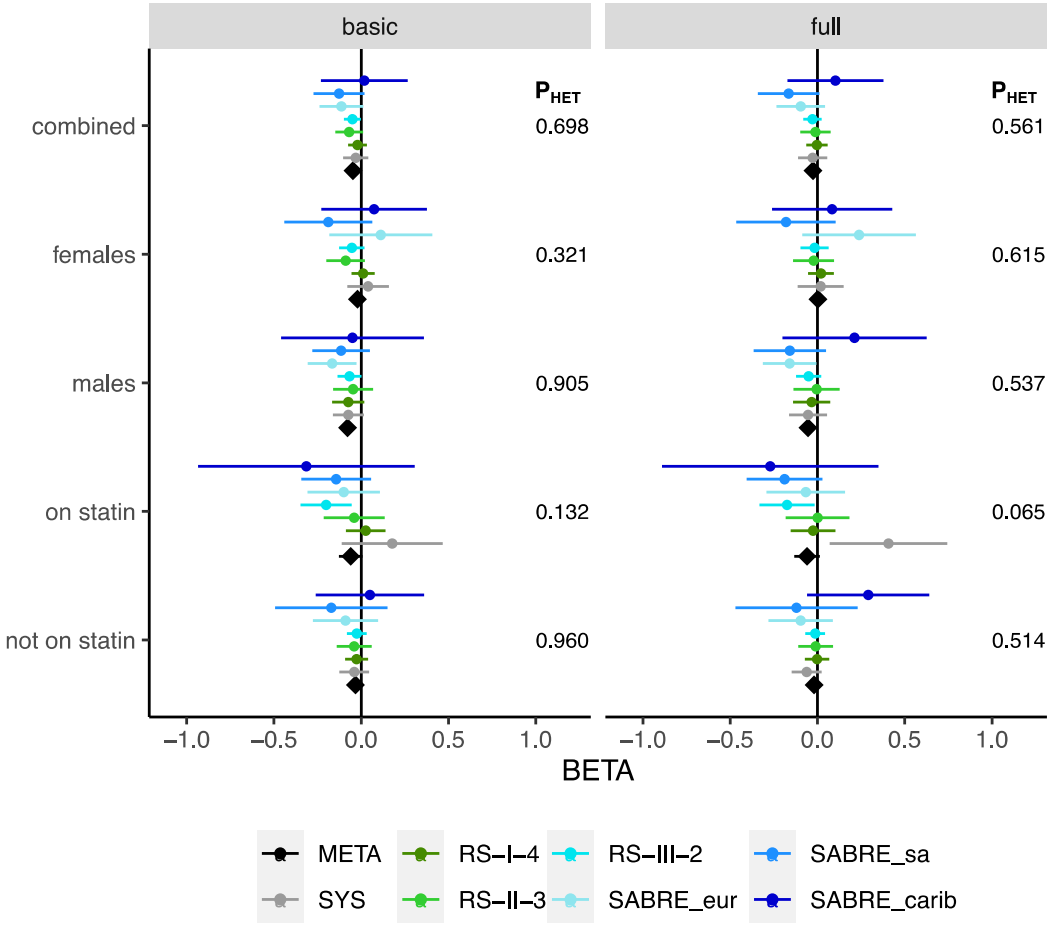


*Figure S3 XXIX) S-LDL-L*

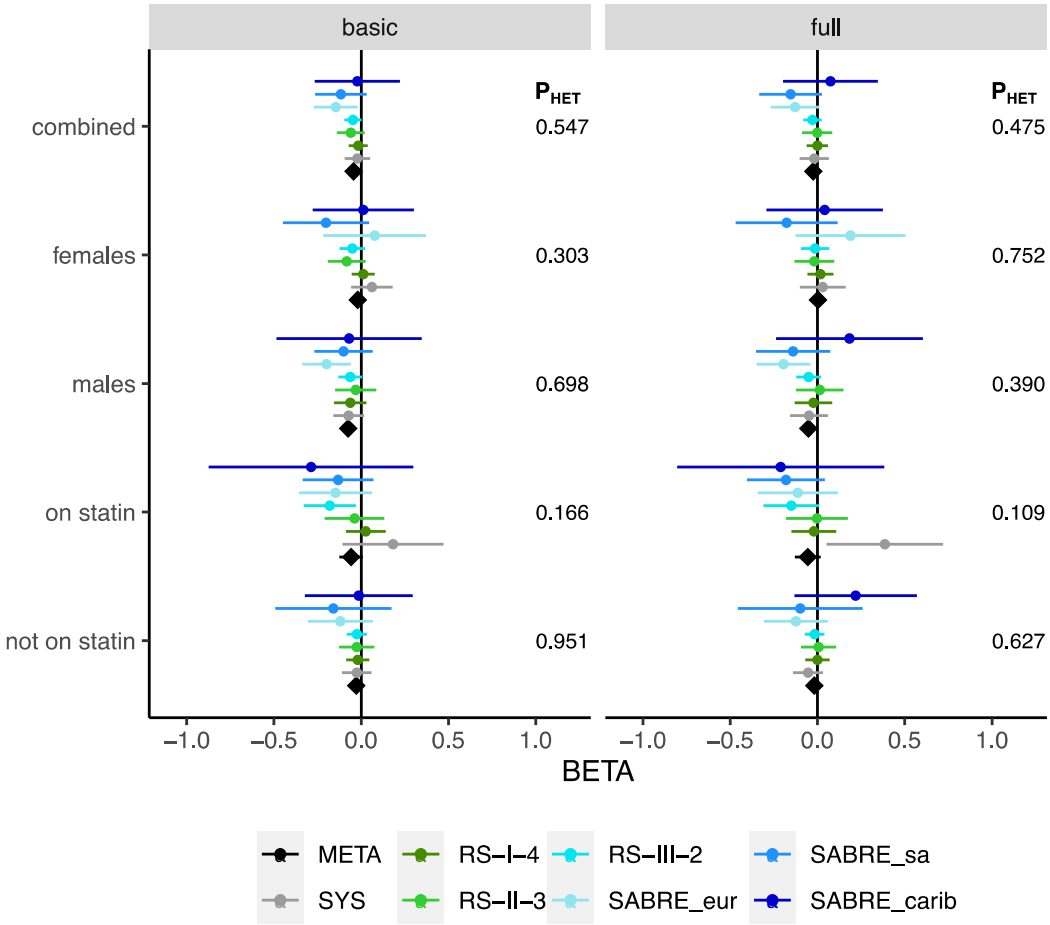

*Figure S3 XXX) S-LDL-P*

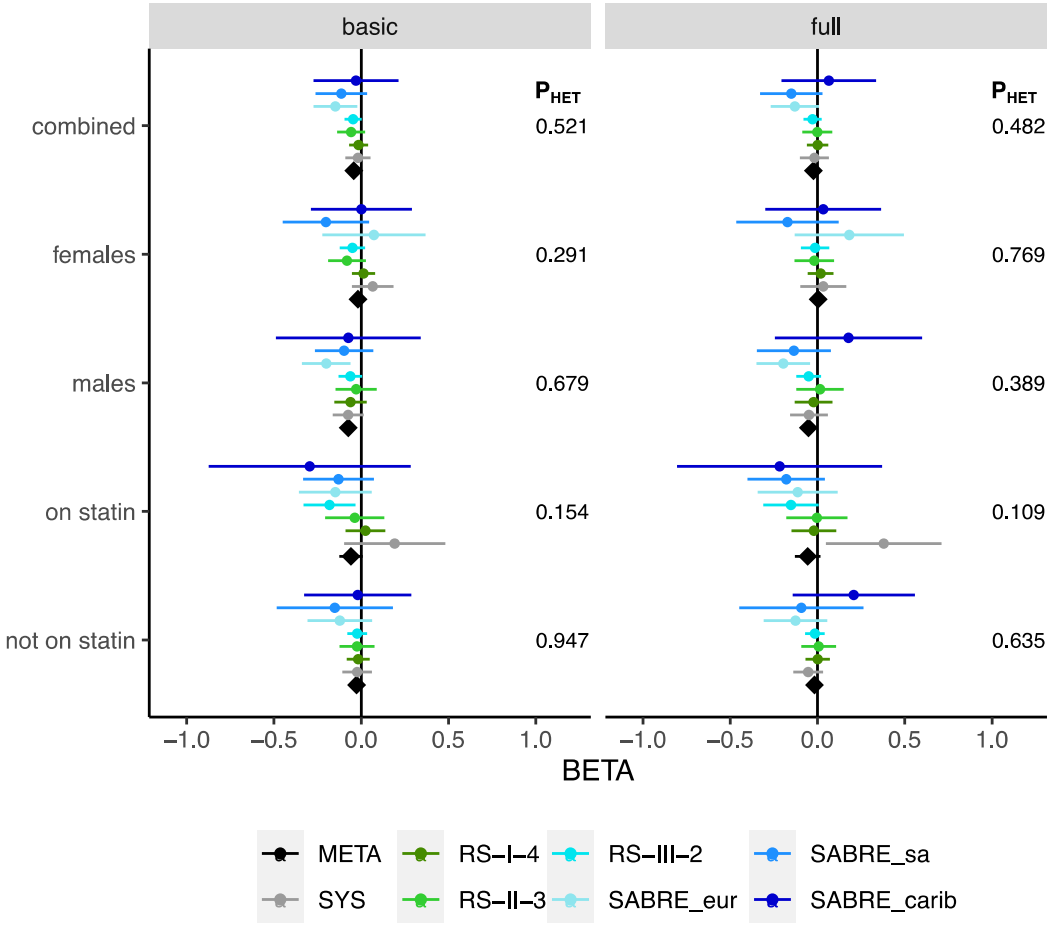


*Figure S3 XXXXI) SM-OH-C22:2*

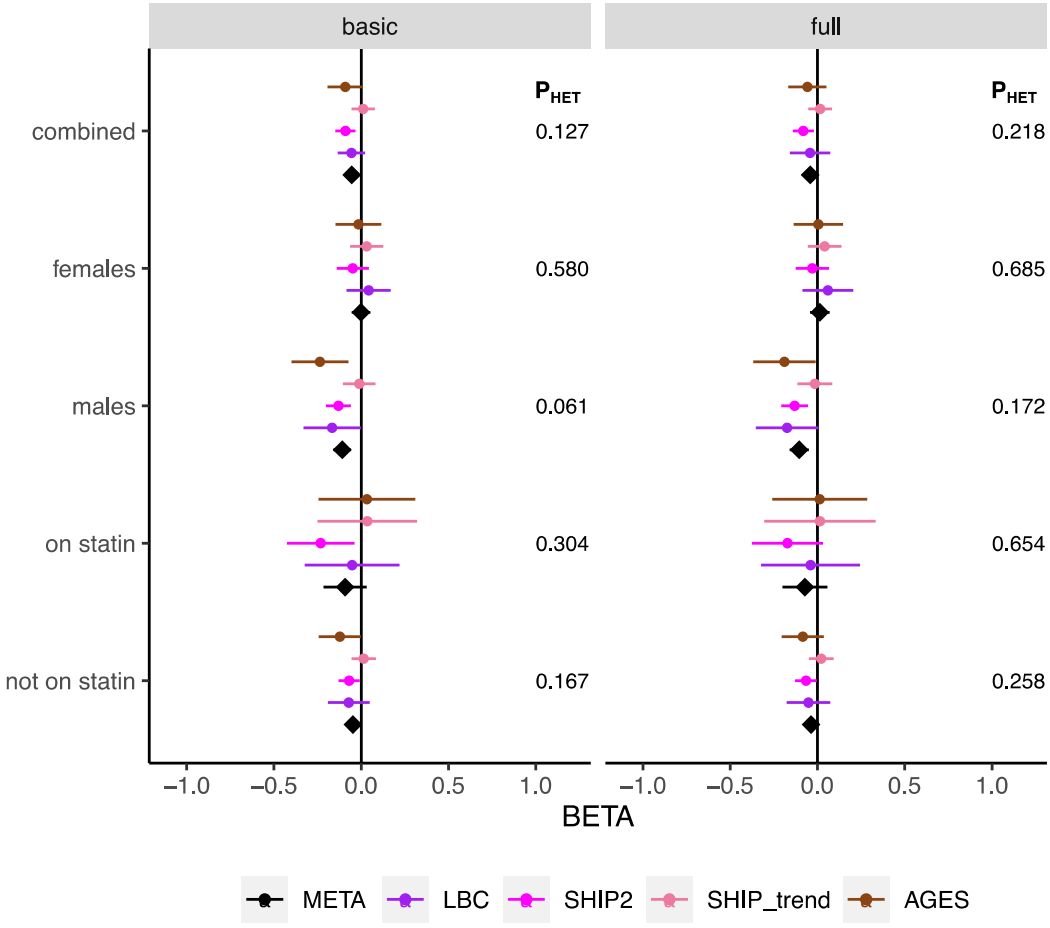

**Figure S4. Meta-analysis in populations with European ancestry only**

In sensitivity analyses, we compared metabolomic associations of WMH obtained by meta-analyzing cohort-specific results of all study populations (i.e., the results reported in this work) with results in European populations only. Inverse variance-weighted fixed effect meta-analysis was used on both occasions. The plot shows the effect estimates and corresponding 95% confidence intervals for 22 metabolic measures that 1) showed significant association with WMH in the primary analysis and 2) had a contribution from South Asian and Caribbean populations. The results from the basic study models are shown on the top row ("basic") and the results from the fully adjusted models are shown on the bottom row ("full").