Supplementary Online Content

Cavus E, Karakas M, Ojeda FM, et al. Association of circulating metabolites with risk of coronary heart disease in a European population: results from the Biomarkers for Cardiovascular Risk Assessment in Europe (BiomarCaRE) consortium. *JAMA Cardiol*. Published online October 30, 2019. doi:10.1001/jamacardio.2019.4130

This supplementary material has been provided by the authors to give readers additional information about their work.

eAppendix 1. Description of the cohorts of the BiomarCaRE case-cohort study

This study used a case-cohort design within the BiomarCaRE cohorts, which involved a random subsample of the original cohort (subcohort), selected independently of the definition of cases, and all cases outside the subcohort (Kulathinal, Niemelä et al. 2005; Kulathinal, Karvanen et al. 2007; Zeller, Hughes et al. 2014).

FINRISK97: The FINRISK 1997 cohort study is based on a cardiovascular risk factor survey carried out in five districts of Finland, namely North Karelia, Kuopio Province, Helsinki, Turku/Loimaa, and Oulu Province. A stratified random sample was drawn from the national population register; the age-range was 25-74 years. All individuals enrolled in the study received a physical examination, a self-administered questionnaire, and a blood sample was drawn. The baseline survey was carried out in 1997. During follow-up the National Hospital Discharge Register, the National Causes of Death Register and the National Drug Reimbursement Register were used to identify endpoints. At the moment, the follow-up extends until Dec. 31st, 2010, i.e., 14 years for the FINRISK 1997 cohort. The maximum follow-up time was 13.9 years.

Funding: The FINRISK surveys were mainly funded by budgetary funds of THL. Additional funding has been obtained from numerous non-profit foundations. Dr. Salomaa (PI) has been supported by the Finnish Foundation for Cardiovascular Research and the Academy of Finland (grant number 139635).

Brianza: The MONICA-Brianza cohort study is a prospective observational study of 25-64 years old residents in Brianza, Italy. Gender- and 10-year age stratified samples were randomly drawn in 1986, 1990 and 1993, and baseline examinations were carried out accordingly in 1986-87, 1989-90, and 1993-1994. Cardiovascular risk factors were investigated at baseline and whole blood and serum samples were collected for all subjects. The protocol was approved by the Monza Hospital Ethical Committee. All study participants were enrolled and followed up for first coronary or stroke events, fatal and non-fatal, up to the end of 2008. The maximum follow-up time was 22.7 years.

Funding: The follow-up activities for the MONICA Brianza Study were funded by the Regione Lombardia Health Administration (grants 31737/1997, 17155/2004 and 10800/2009) as part of the Osservatorio Epidemiologico Cardiovascolare Regionale Lombardo. Key personnel: Ferrario MM and Cesana G (study PIs); F Gianfagna; G Veronesi; P Brambilla and S. Signorini (bio-banking activities).

Moli-sani: The Moli-sani study is an ongoing, prospective, population-based cohort of 24,325 individuals (48% men, aged ≥35 years, mean age ± SD: 55.8±12.0 years) living in the Molise region in south-central Italy. Participants were randomly enrolled from town registries between 2005 and 2010. Follow-up was performed through record linkage to national mortality registries and hospital discharge registers, while validation of events was achieved through hospital record linkage and doctors' medical records. The maximum follow-up time was 6.8 years.

Funding: The Moli-sani study was partially supported by research grants from Pfizer Foundation (Rome, Italy), the Italian Ministry of University and Research (MIUR, Rome, Italy)–Programma Triennale di Ricerca, Decreto n.1588 and Instrumentation Laboratory, Milan, Italy.

MONICA/KORA: The WHO Monitoring of Trends and Determinants in Cardiovascular Diseases (MONICA)/ Cooperative Health Research in the Region of Augsburg (KORA) cohort comprises data from the City of Augsburg and less urban Landkreis Augsburg and Landkreis Aichach-Friedberg in Germany. Representative samples were randomly collected from men and women aged 25-74 years. List of municipalities and population registers were used as sampling frames for the first and the second stage of two-stage sampling, respectively. The second stage of sampling was stratified by gender and 10-year age group. The BiomarCaRE project includes participants from the MONICA Augsburg Survey S3 carried out between 1994 to 1995 and the KORA Survey S4 carried out between 1999-2001, respectively. Coronary events occurring within the study area were identified through the MONICA/KORA Augsburg coronary event registry. Furthermore, follow-up questionnaires were sent out to all participants still alive in 2002 and 2009. The maximum follow-up time was 15.2 years.

Funding: The KORA research platform and the KORA Augsburg studies are financed by the Helmholtz Zentrum München, German Research Center for Environmental Health, which is funded by the German Federal Ministry of Science and Research (Berlin, Germany) and by the State of Bavaria. Furthermore, KORA research was supported within the Munich Center of Health Sciences (MC Health), Ludwig-Maximilians University München, as part of LMUinnovative.

DanMONICA: The DanMONICA cohort is a prospective population-based study which collected data from eleven municipalities in the urban county Glostrup of Copenhagen city, Denmark, from men and women of age of 30, 40, 50, 60, or 70 using a random sampling based on the national population register and stratified by gender and year of birth. The baseline survey was carried out between 1982 and 1992, and the follow-up was carried out until 2010. Follow-up was achieved through linkage to the National Cause of Death Register and National Hospital Discharge Register, with endpoint diagnoses based on MORGAM criteria and completed in 2010. The maximum follow-up time was 28.1 years.

Funding: The DanMONICA have been funded by the Danish Heart Foundation and the Danish Medical Research Council. Funding sources have also been acknowledged, where appropriate, in the original articles.

SHHEC: The SHHEC ("Scottish Heart Health Extended Cohort") consists of two overlapping studies, namely the Scottish Heart Health Study, which randomly recruited men and women across 22 Scottish districts in 1984-1987 (age 40 to 59), and the Scottish MONICA study, which similarly recruited men and women in Edinburgh and North Glasgow in 1986 (age 25 to 64), and in North Glasgow again in 1989 (age 25 to 64), 1992 (age 25 to 75), and in 1995 (age 25 to 64) as part of the WHO MONICA Project. Follow up was achieved through flagging for death certificates at the National Health Service Death Register and through the Scottish Record Linkage scheme for deaths and hospital discharge records run by Information Services Scotland. Risk factor and endpoint data were used to produce the ASSIGN cardiovascular risk score. The maximum follow-up time was 25.1 years. To save serum for other uses, the

cohort was halved for this metabolite study: each member of the cohort was selected with probability 0.5, and the case-cohort selection was done from this half of the cohort.

Funding: The Scottish Heart Health Extended Cohort (SHHEC) was funded by the Scottish Health Department Chief Scientist Organization; British Heart Foundation; FP Fleming Trust.

eAppendix 2. Samples preparation and measurement of metabolites

The Absolute*IDQ*® p180 Kit (BIOCRATES Life Sciences AG) was used for sample preparation according to the manufacturer's recommendation. 184 metabolites from six analyte groups (amino acids, biogenic amines, acylcarnitines, glycerophospholipids, sphingolipids and sugars) were quantified using liquid chromatography (LC) and flow injection analysis (FIA) mass spectrometry.

10µl of serum per sample were prepared on a 96-well plate including 72 samples, 7 standards and 3 control samples. For quantification, isotope-labeled internal standards and seven calibrators of different concentration levels were used. In addition, three different levels of quality controls were included (n=2 QC1, n=5 QC2, n=2 QC3), from which QC 2 was used for data normalization, containing metabolite levels most comparable to physiological levels. Measurements were performed on a TSQ Vantage (Thermo Fisher Scientific) connected to an UltiMate 3000 Pump/ Autosampler (Thermo Fisher Scientific). Amino acids and biogenic amines were measured by liquid chromatography (LC) assays and were quantified in relation to isotope-labeled internal standards. Metabolite identities were confirmed by the use of the internal standards. Raw data were processed with Xcalibur Version 2.2 SP1.48 (Thermo Fisher Scientific) and Met*IDQ*^{TM} (BIOCRATES Life Sciences AG). Acylcarnitines, glycerophospholipids, sphingolipids and sugars were injected directly into the mass spectrometer via flow injection analysis (FIA) without any previous separation.

eTable 1. Study characteristics according to center. Characteristics are presented for the overall case-cohort set as well as the individual centers separately. Characteristics are summarized by N (%) for categorical variables and median (25^{th} and 75^{th} percentile) for continuous variables.

Characteristics	Overall (N=10,741)	Brianza (N=511)	DanMONICA (N=3,432)	FINRISK (N=1,771)	MONICA/KORA (N=1,085)	Moli-sani (N=1,364)	SHHEC (N=2,578)
Age at baseline examination (years)	56.5 (49.2, 62.2)	55.7 (46.4, 61.3)	50.9 (41.1, 60.7)	59.0 (50.7, 65.4)	61.3 (52.2, 68.7)	66.6 (56.7, 74.5)	53.2 (47.5, 58.2)
Cardiovascular risk factors							
Body mass index (kg/m2)	26.2 (23.7, 29.1)	25.7 (23.8, 28.5)	24.9 (22.7, 27.8)	27.1 (24.6, 29.9)	27.7 (25.0, 30.3)	28.3 (25.6, 31.5)	25.7 (23.4, 28.4)
Systolic blood pressure (mm Hg)	135 (121, 150)	136 (124, 150)	126 (115, 139)	142 (129, 157)	138 (126, 154)	148 (135, 164)	133 (121, 149)
Diastolic blood pressure (mm Hg)	82 (75, 90)	86 (79, 94)	80 (72, 87)	85.0 (78, 92)	82 (74, 90)	83 (76, 90)	83 (75, 90)
Total cholesterol (mg/dL)	232 (201, 263)	227 (200, 254)	232 (201, 263)	220 (197, 248)	236 (213, 267)	214 (187, 240)	248 (217, 282)
HDL cholesterol (mg/dL)	53.0 (44.1, 64.2)	50.0 (43.0, 59.0)	54.5 (44.9, 66.1)	51.0 (42.9, 60.7)	51.8 (42.5, 62.3)	53.0 (45.0, 65.0)	54.0 (44.9, 65.0)
LDL cholesterol (mg/dL)	146 (122, 175)	148 (123, 171)	150 (124, 180)	140 (118, 166)	148 (123, 176)	131 (107, 154)	155 (128, 185)
Triglycerides (mg/dL)	123 (89, 180)	115 (84, 163)	106 (79, 149)	117 (87, 168)	148 (104, 220)	119 (86, 162)	152 (108, 233)
Daily smoking (%)	3,416 (31.8)	170 (33.3)	1,501 (43.7)	357 (20.2)	195 (18.0)	235 (17.2)	958 (37.2)
Diabetes mellitus (%)	562 (5.2)	40 (7.9)	96 (2.8)	132 (7.5)	86 (7.9)	151 (11.1)	57 (2.2)
Hypertension (%)	5,169 (48.1)	252 (49.3)	1,033 (30.1)	1,106 (62.5)	586 (54.0)	1,042 (76.4)	1,150 (44.6)

Characteristics	Overall (N=10,741)	Brianza (N=511)	DanMONICA (N=3,432)	FINRISK (N=1,771)	MONICA/KORA (N=1,085)	Moli-sani (N=1,364)	SHHEC (N=2,578)
Medication							
Anti-hypertensive medication (%)	1,795 (16.7)	80 (15.6)	307 (8.9)	334 (18.9)	226 (20.9)	607 (44.5)	240 (9.3)
Coronary heart disease endpoints							
CHD total cases (fatal, non-fatal) (%)	2,166 (20.2)	184 (36.0)	691 (20.1)	274 (15.5)	205 (18.9)	138 (10.1)	674 (26.1)
CHD fatal cases (%)	677 (6.3)	43 (8.4)	202 (5.9)	81 (4.6)	60 (5.5)	27 (2.0)	264 (10.2)
CHD non-fatal cases (%)	1,489 (13.9)	141 (27.6)	489 (14.2)	193 (10.9)	145 (13.4)	111 (8.1)	410 (15.9)

eTable 2. Study characteristics weighted to represent the full cohort of each center. To compute the weighted characteristics, the subcohort was used. Characteristics are presented as relative frequencies (%) for categorical variables, and median (25^{th} percentile, 75^{th} percentile) for continuous variables. Here, all characteristics are weighted by the inverse of the inclusion probability in the subcohort. (Kulathinal, Karvanen et al. 2007; Zeller, Hughes et al. 2014). In this table, N represents the full cohort (i.e. the sum of the weights).

Characteristics	Overall (N=52,415)	Brianza (N=4,544)	DanMONICA (N=6,468)	FINRISK (N=5,796)	MONICA/KORA (N=7,935)	Moli-sani (N=21,845)	SHHEC (N=5,828)
Age at baseline examination (years)	50.6 (41.4, 60.0)	44.4 (36.2, 53.8)	49.9 (39.8, 59.9)	47.5 (37.2, 58.1)	49.4 (38.3, 60.2)	53.8 (46.3, 62.8)	49.1 (43.0, 55.4)
Cardiovascular risk factors							
Body mass index (kg/m2)	26.5 (23.6, 29.8)	24.8 (22.8, 29.0)	24.3 (22.1, 27.1)	26.1 (23.7, 29.1)	26.4 (23.5, 29.5)	27.8 (24.7, 30.9)	25.5 (23.0, 28.3)
Systolic blood pressure (mm Hg)	133 (120, 148)	127 (119, 139)	121 (111, 133)	134 (121, 147)	129 (117, 143)	139 (127, 155)	129 (118, 142)
Diastolic blood pressure (mm Hg)	81 (74, 89)	82 (77, 90)	78 (70, 85)	82 (74, 89)	80 (72, 88)	83 (76, 90)	81 (73, 89)
Total cholesterol (mg/dL)	217 (190, 248)	199 (182, 232)	220 (190, 251)	210 (186, 240)	224 (201, 259)	214 (189, 244)	236 (209, 275)
HDL cholesterol (mg/dL)	54.5 (46.0, 65.0)	52.0 (45.0, 59.0)	55.7 (45.6, 66.9)	53.0 (44.9, 62.9)	55.5 (45.2, 67.9)	55.0 (47.0, 66.0)	54.4 (44.9, 66.1)
LDL cholesterol (mg/dL)	134 (111, 160)	124 (115, 152)	139 (113, 169)	131 (109, 156)	135 (106, 165)	132 (109, 155)	151 (123, 180)
Triglycerides (mg/dL)	112 (79, 159)	93 (73, 133)	96 (71, 135)	106 (75, 152)	127 (95, 193)	113 (79, 155)	140 (99, 212)
Daily smoking (%)	25.4	21.7	44.8	22.2	21.1	20.1	35.8
Diabetes mellitus (%)	4.4	3.6	2.2	5.4	3.4	6.0	1.5

Characteristics	Overall (N=52,415)	Brianza (N=4,544)	DanMONICA (N=6,468)	FINRISK (N=5,796)	MONICA/KORA (N=7,935)	Moli-sani (N=21,845)	SHHEC (N=5,828)
Hypertension (%)	43.8	31.1	22.2	46.2	34.9	57.3	36.4
Medication							
Anti-hypertensive medication (%)	17.3	9.9	6.5	11.4	12.4	28.2	6.8
Coronary heart disease endpoints							
CHD total cases (fatal, non-fatal) (%)	4.1	2.2	10.4	4.6	3.2	0.7	11.5
CHD fatal cases (%)	1.2	0.3	3.0	1.3	1.0	0.0	4.3
CHD non-fatal cases (%)	2.9	1.9	7.5	3.4	2.2	0.7	7.2

eTable 3. Comparative study characteristics of study participants before and after quality control. The quality control involved data processing and excluding of invalid samples and metabolites. Median (25^{th} percentile, 75^{th} percentile) are given for continuous variables, while absolute numbers (n) and percentages (%) are given for categorical variables. Raw characteristics are presented.

Characteristics	**Case-cohort set *before* quality control (N=12,928)**	**Case-cohort set *after* quality control (N=10,741)**
Age at baseline examinations (years)	56.8 (49.4, 62.8)	56.5 (49.2, 62.2)
Cardiovascular risk factors		
Body mass index (kg/m2)	26.2 (23.8, 29.1)	26.2 (23.7, 29.1)
Systolic blood pressure (mm Hg)	135 (122, 151)	135 (121, 150)
Diastolic blood pressure (mm Hg)	82 (75, 90)	82 (75, 90)
Total cholesterol (mg/dL)	232 (202, 263)	232 (201, 263)
HDL cholesterol (mg/dL)	52.6 (44.0, 63.8)	53.0 (44.1, 64.2)
LDL cholesterol (mg/dL)	147 (122, 176)	146 (122, 175)
Triglycerides (mg/dL)	124 (89, 184)	123 (89, 180)
Daily smoking (%)	4,216 (32.6)	3,416 (31.8)
Diabetes mellitus (%)	671 (5.2)	562 (5.2)
Medication		
Anti-hypertensive medication (%)	2,145 (16.6)	1,795 (16.7)
Coronary heart disease endpoints		
CHD fatal cases (%)	889 (6.9)	677 (6.3)
CHD non-fatal cases (%)	1,838 (14.2)	1,489 (13.9)
CHD total cases (fatal, non-fatal) (%)	2,727 (21.1)	2,166 (20.2)

eTable 4. Study characteristics weighted to represent the full cohort-. To compute the weighted characteristics, the subcohort was used. Characteristics are presented as relative frequencies (%) for categorical variables, and median (25^{th} and 75^{th} percentile) for continuous variables. The characteristics are weighted by the inverse of the inclusion probabilities in the subcohort of the case-cohort set (Kulathinal, Karvanen et al. 2007; Zeller, Hughes et al. 2014). In this table, N represents the full cohort (i.e. the sum of the weights).

Characteristics	**Overall (N=52,415)**	**Women (N=27,321)**	**Men (N=25,094)**
Age at baseline examination (years)	50.6 (41.4, 60)	50.7 (41.4, 59.9)	50.6 (41.4, 60)
Cardiovascular risk factors			
Body mass index (kg/m2)	26.5 (23.6, 29.8)	25.9 (22.8, 29.9)	26.9 (24.4, 29.7)
Systolic blood pressure (mm Hg)	132 (120, 148)	130 (117, 145)	136 (124, 150)
Diastolic blood pressure (mm Hg)	81 (74, 88)	80 (72, 87)	84 (77, 91)
Total cholesterol (mg/dL)	217 (190, 248)	220 (190, 251)	217 (190, 244)
HDL cholesterol (mg/dL)	54.5 (46, 65)	59.9 (51, 71.5)	49.0 (41, 58)
LDL cholesterol (mg/dL)	134 (111, 160)	134 (109, 160)	136 (114, 160)
Triglycerides (mg/dL)	112 (79, 159)	97 (73, 141)	126 (90, 186)
Daily smoking (%)	25.4	22.2	28.9
Diabetes mellitus (%)	4.4	3.1	5.7
Hypertension (%)	43.8	38.1	49.9
Medication			
Anti-hypertensive medication (%)	17.3	17.7	16.9
Coronary heart disease endpoints			
CHD total cases (fatal, non-fatal) (%)	4.1	2.4	5.9
CHD fatal cases (%)	1.2	0.7	1.7
CHD non-fatal cases (%)	2.9	1.7	4.2

eTable 5. Study characteristics of the overall cohort and males and females separately. Characteristics are presented for the overall case-cohort data set, as well as males and females separately. Characteristics are summarized by N (%) for categorical variables and median (25th and 75th percentile) for continuous variables.

Characteristics	Overall (N=10,741)	Women (N=4,157)	Men (N=6,584)
Age at baseline examination	56.5 (49.2, 62.2)	57.9 (50.2, 62.6)	55.8 (48.1, 61.8)
Cardiovascular risk factors			
Body mass index (kg/m2)	26.2 (23.7, 29.1)	25.8 (22.9, 29.3)	26.4 (24.2, 29)
Systolic blood pressure (mm	135 (121, 150)	134 (120, 150)	135 (123, 151)
Diastolic blood pressure (mm	82 (75, 90)	80 (73, 88)	83 (76, 91)
Total cholesterol (mg/dL)	232 (201, 263)	236 (209, 271)	226 (200, 255)
HDL cholesterol (mg/dL)	53.0 (44.1, 64.2)	60.6 (50.7, 71.5)	49.1 (41.4, 58.4)
LDL cholesterol (mg/dL)	146 (122, 175)	149 (123, 180)	144 (121, 171)
Triglycerides (mg/dL)	123 (89, 180)	112 (81, 157)	131 (93, 198)
Daily smoking (%)	3,416 (31.8)	1,203 (28.9)	2,213 (33.6)
Diabetes mellitus (%)	562 (5.2)	184 (4.4)	379 (5.8)
Hypertension (%)	5,169 (48.1)	1,898 (45.7)	3,271 (49.7)
Medication			
Anti-hypertensive medication	1,795 (16.7)	795 (19.1)	999 (15.2)
Coronary heart disease			
CHD total cases (fatal, non-	2,166 (20.2)	703 (16.9)	1,463 (22.2)
CHD fatal cases (%)	677 (6.3)	220 (5.3)	457 (6.9)
CHD non-fatal cases (%)	1,489 (13.9)	483 (11.6)	1,006 (15.3)

eTable 6. Levels of metabolites after normalization. Median (25th percentile, 75th percentile) levels (in µM) and % of valid measurement of 141 metabolites included in the analyses. aa, diacyl; ae, acyl-alkyl; PC, phosphatidylcholine, SM, sphingomyelin.

Metabolite Class	Metabolite	Median (25^{th} percentile, 75^{th} percentile) level [µM]	Valid Measurements (%)
Acylcarnitines	C0	36.07 (29.64, 43.74)	99.61
	C14:1	0.14 (0.11, 0.17)	99.27
	C14:2	0.03 (0.02, 0.05)	54.38
	C16:1	0.03 (0.02, 0.04)	61.17
	C18:1	0.12 (0.09, 0.15)	99.05
	C18:2	0.05 (0.03, 0.06)	85.02
	C2	3.32 (0.15, 5.32)	79.78
	C4-OH(C3-DC)	0.04 (0.01, 0.06)	48.74
	C8	0.14 (0.08, 0.18)	62.01
Amino Acids	Ala	426.30 (357.86, 514.00)	97.37
	Arg	164.36 (130.51, 204.18)	96.29
	Asn	36.97 (10.45, 48.22)	91.43
	Asp	55.23 (38.92, 79.26)	96.56
	Cit	34.46 (27.58, 43.26)	97.23
	Gln	477.65 (16.57, 650.67)	91.97
	Glu	280.10 (169.29, 536.11)	97.43
	Gly	326.26 (272.27, 393.15)	97.35
	His	96.33 (80.66, 115.70)	97.61
	Ile	84.26 (69.90, 104.24)	96.73
	Leu	165.17 (132.95, 208.38)	93.66
	Lys	252.67 (202.01, 317.63)	83.01
	Met	12.31 (1.56, 21.52)	75.62
	Orn	102.35 (78.11, 134.05)	88.02
	Phe	98.14 (79.97, 120.06)	97.61
	Pro	201.19 (159.29, 260.98)	97.61

Metabolite Class	Metabolite	Median (25th percentile, 75th percentile) level [µM]	Valid Measurements (%)
	Ser	185.78 (154.95, 219.68)	97.12
	Thr	129.97 (108.81, 155.55)	97.23
	Trp	63.29 (53.22, 76.46)	97.15
	Tyr	71.17 (58.64, 88.57)	97.15
	Val	252.31 (211.16, 305.54)	97.62
Biogenic Amines	ADMA	0.46 (0.37, 0.55)	96.52
	alpha-AAA	0.30 (0.05, 0.75)	53.97
	Creatinine	64.97 (54.64, 77.24)	97.60
	Kynurenine	1.14 (0.03, 2.18)	52.22
	Met-SO	11.63 (2.46, 21.29)	92.38
	Putrescine	0.04 (0.01, 0.11)	55.94
	Sarcosine	1.45 (1.03, 1.99)	92.66
	SDMA	0.44 (0.37, 0.52)	97.36
	Serotonin	0.41 (0.26, 0.60)	96.19
	Taurine	106.41 (82.78, 134.98)	96.99
	trans-OH-Pro	9.58 (7.03, 13.46)	97.29
Glycerophospholipids	lysoPC a C16:0	171.85 (132.00, 222.60)	99.99
	lysoPC a C16:1	4.94 (3.61, 6.67)	99.97
	lysoPC a C17:0	3.73 (2.58, 5.12)	99.99
	lysoPC a C18:0	46.52 (34.91, 62.56)	99.99
	lysoPC a C18:1	28.29 (22.19, 36.18)	100.00
	lysoPC a C18:2	27.81 (21.10, 35.70)	100.00
	lysoPC a C20:3	2.17 (1.73, 2.72)	99.73
	lysoPC a C20:4	5.72 (4.52, 7.22)	99.97
	lysoPC a C24:0	0.54 (0.35, 0.79)	72.05
	lysoPC a C26:0	0.38 (0.22, 0.65)	63.57
	lysoPC a C26:1	0.33 (0.19, 0.57)	47.63
	lysoPC a C28:0	0.49 (0.28, 0.78)	65.86

Metabolite Class	Metabolite	Median (25^{th} percentile, 75^{th} percentile) level [µM]	Valid Measurements (%)
	lysoPC a C28:1	0.54 (0.35, 0.82)	77.98
	diacyl-PC C24:0	0.18 (0.11, 0.27)	91.87
	diacyl-PC C28:1	2.39 (1.84, 3.06)	99.94
	diacyl-PC C30:0	3.29 (2.48, 4.37)	99.98
	diacyl-PC C32:0	9.25 (7.32, 11.47)	99.97
	diacyl-PC C32:1	10.18 (7.02, 15.11)	99.96
	diacyl-PC C32:2	1.83 (1.28, 2.60)	99.82
	diacyl-PC C32:3	0.45 (0.32, 0.62)	99.87
	diacyl-PC C34:1	167.17 (130.01, 216.50)	99.41
	diacyl-PC C34:2	275.24 (211.40, 353.80)	99.44
	diacyl-PC C34:3	15.76 (10.10, 23.75)	99.95
	diacyl-PC C34:4	1.22 (0.90, 1.65)	99.98
	diacyl-PC C36:0	3.61 (2.42, 5.43)	99.93
	diacyl-PC C36:1	42.63 (32.97, 55.30)	99.45
	diacyl-PC C36:2	178.84 (140.54, 226.54)	99.97
	diacyl-PC C36:3	105.75 (80.60, 134.05)	99.95
	diacyl-PC C36:4	100.98 (65.04, 145.60)	99.97
	diacyl-PC C36:5	15.32 (10.31, 22.38)	99.96
	diacyl-PC C36:6	1.24 (0.78, 1.81)	99.98
	diacyl-PC C38:0	3.40 (2.49, 4.74)	99.98
	diacyl-PC C38:3	34.52 (26.11, 44.82)	99.96
	diacyl-PC C38:4	59.81 (38.55, 87.13)	99.52
	diacyl-PC C38:5	34.83 (21.72, 47.49)	99.97
	diacyl-PC C38:6	49.30 (26.33, 72.90)	99.95
	diacyl-PC C40:1	0.68 (0.36, 1.04)	77.85
	diacyl-PC C40:2	1.52 (0.56, 2.65)	99.93
	diacyl-PC C40:3	2.12 (0.95, 3.45)	99.97
	diacyl-PC C40:4	3.81 (2.96, 5.01)	99.98

Metabolite Class	Metabolite	Median (25th percentile, 75th percentile) level [µM]	Valid Measurements (%)
	diacyl-PC C40:5	6.67 (4.45, 9.14)	99.97
	diacyl-PC C40:6	17.02 (9.57, 24.73)	99.97
	diacyl-PC C42:0	0.57 (0.44, 0.76)	99.96
	diacyl-PC C42:1	0.41 (0.29, 0.58)	99.77
	diacyl-PC C42:2	0.56 (0.32, 0.83)	99.19
	diacyl-PC C42:4	0.71 (0.31, 1.08)	98.84
	diacyl-PC C42:5	0.56 (0.38, 0.80)	99.88
	diacyl-PC C42:6	0.62 (0.46, 0.84)	88.73
	acyl-alkyl-PC C30:0	0.39 (0.29, 0.52)	95.62
	acyl-alkyl-PC C30:1	0.18 (0.10, 0.29)	77.37
	acyl-alkyl-PC C30:2	0.25 (0.16, 0.40)	87.38
	acyl-alkyl-PC C32:1	1.77 (1.39, 2.20)	99.97
	acyl-alkyl-PC C32:2	0.47 (0.37, 0.62)	99.93
	acyl-alkyl-PC C34:0	1.28 (0.97, 1.70)	99.95
	acyl-alkyl-PC C34:1	6.93 (5.47, 8.74)	99.97
	acyl-alkyl-PC C34:2	6.96 (5.40, 9.00)	99.95
	acyl-alkyl-PC C34:3	4.48 (3.42, 5.90)	99.96
	acyl-alkyl-PC C36:0	0.99 (0.59, 1.67)	93.00
	acyl-alkyl-PC C36:1	19.15 (9.88, 32.69)	99.97
	acyl-alkyl-PC C36:2	15.63 (10.92, 22.09)	99.96
	acyl-alkyl-PC C36:3	6.08 (4.76, 7.74)	99.98
	acyl-alkyl-PC C36:4	9.09 (6.02, 13.29)	99.97
	acyl-alkyl-PC C36:5	6.11 (3.81, 8.98)	99.94
	acyl-alkyl-PC C38:0	3.17 (2.10, 4.55)	99.94
	acyl-alkyl-PC C38:1	7.02 (1.65, 14.20)	99.12
	acyl-alkyl-PC C38:2	5.99 (2.52, 15.53)	99.44
	acyl-alkyl-PC C38:3	11.22 (6.12, 16.71)	99.95
	acyl-alkyl-PC C38:4	11.12 (8.78, 14.04)	99.96

Metabolite Class	Metabolite	Median (25th percentile, 75th percentile) level [µM]	Valid Measurements (%)
	acyl-alkyl-PC C38:5	10.61 (6.64, 15.12)	99.98
	acyl-alkyl-PC C38:6	4.67 (2.90, 6.50)	99.97
	acyl-alkyl-PC C40:1	1.73 (1.27, 2.44)	99.98
	acyl-alkyl-PC C40:2	3.84 (2.42, 5.69)	99.97
	acyl-alkyl-PC C40:3	5.52 (2.68, 8.39)	99.96
	acyl-alkyl-PC C40:4	5.19 (3.11, 7.48)	99.97
	acyl-alkyl-PC C40:5	5.95 (3.90, 8.91)	99.98
	acyl-alkyl-PC C40:6	3.99 (2.87, 5.35)	99.98
	acyl-alkyl-PC C42:1	0.75 (0.42, 1.17)	99.53
	acyl-alkyl-PC C42:2	1.03 (0.69, 1.51)	99.97
	acyl-alkyl-PC C42:3	1.26 (0.85, 1.80)	99.98
	acyl-alkyl-PC C42:4	1.22 (0.85, 1.69)	99.98
	acyl-alkyl-PC C42:5	2.42 (1.82, 3.30)	99.91
	acyl-alkyl-PC C44:3	0.31 (0.16, 0.48)	95.56
	acyl-alkyl-PC C44:4	0.41 (0.31, 0.55)	99.65
	acyl-alkyl-PC C44:5	0.95 (0.65, 1.31)	99.94
	acyl-alkyl-PC C44:6	0.67 (0.50, 0.88)	99.97
Monosaccharides	H1	4460.24	98.44
Sphingolipids	SM (OH) C14:1	4059.10 (3446.44, 4792.13)	98.32
	SM (OH) C16:1	6.53 (4.85, 8.55)	99.98
	SM (OH) C22:1	4.03 (3.02, 5.20)	99.98
	SM (OH) C22:2	16.68 (12.43, 23.37)	99.98
	SM (OH) C24:1	15.95 (11.48, 23.09)	99.42
	SM C16:0	123.66 (97.00, 154.50)	99.42
	SM C16:1	16.59 (13.06, 20.90)	99.94
	SM C18:0	27.77 (21.10, 36.14)	99.98
	SM C18:1	13.90 (10.60, 17.85)	99.94
	SM C20:2	0.51 (0.25, 0.99)	96.24

Metabolite Class	Metabolite	Median (25^{th} percentile, 75^{th} percentile) level [μM]	Valid Measurements (%)
	SM C24:0	28.23 (22.34, 35.46)	99.45
	SM C24:1	67.58 (51.99, 86.86)	99.27
	SM C26:0	0.14 (0.01, 0.28)	72.16
	SM C26:1	0.47 (0.32, 0.92)	98.74

eTable 7. Association of significant metabolites with future coronary heart disease adjusted for eGFR and non-HDL. Hazard ratios (HR) are per 1 standard deviation (SD) of log-transformed metabolite level and are adjusted for BMI, systolic blood pressure, antihypertensive treatment, diabetes, non-HDL cholesterol, estimated glomerular filtration rate, sex, daily smoking, study center and examination age. The log-metabolites levels were multiplied by -1 to obtain hazard ratios greater or equal than 1. Thus, HRs are described as HRs per 1 standard deviation decrease. CI, confidence interval; PC, phosphatidylcholine

Metabolite	HR per 1 SD (95% CI)	P-value
Acyl-alkyl-PC C40:6	1.13 (1.08, 1.19)	$2.60x10^{-6}$
Acyl-alkyl-PC C38:6	1.11 (1.06, 1.17)	$4.54x10^{-5}$
Diacyl-PC C38:5	1.11 (1.05, 1.17)	$1,29x10^{-4}$
Diacyl-PC C38:6	1.10 (1.05, 1.15)	$1.19x10^{-4}$
Diacyl-PC C40:6	1.11 (1.06, 1.17)	$7.14x10^{-5}$

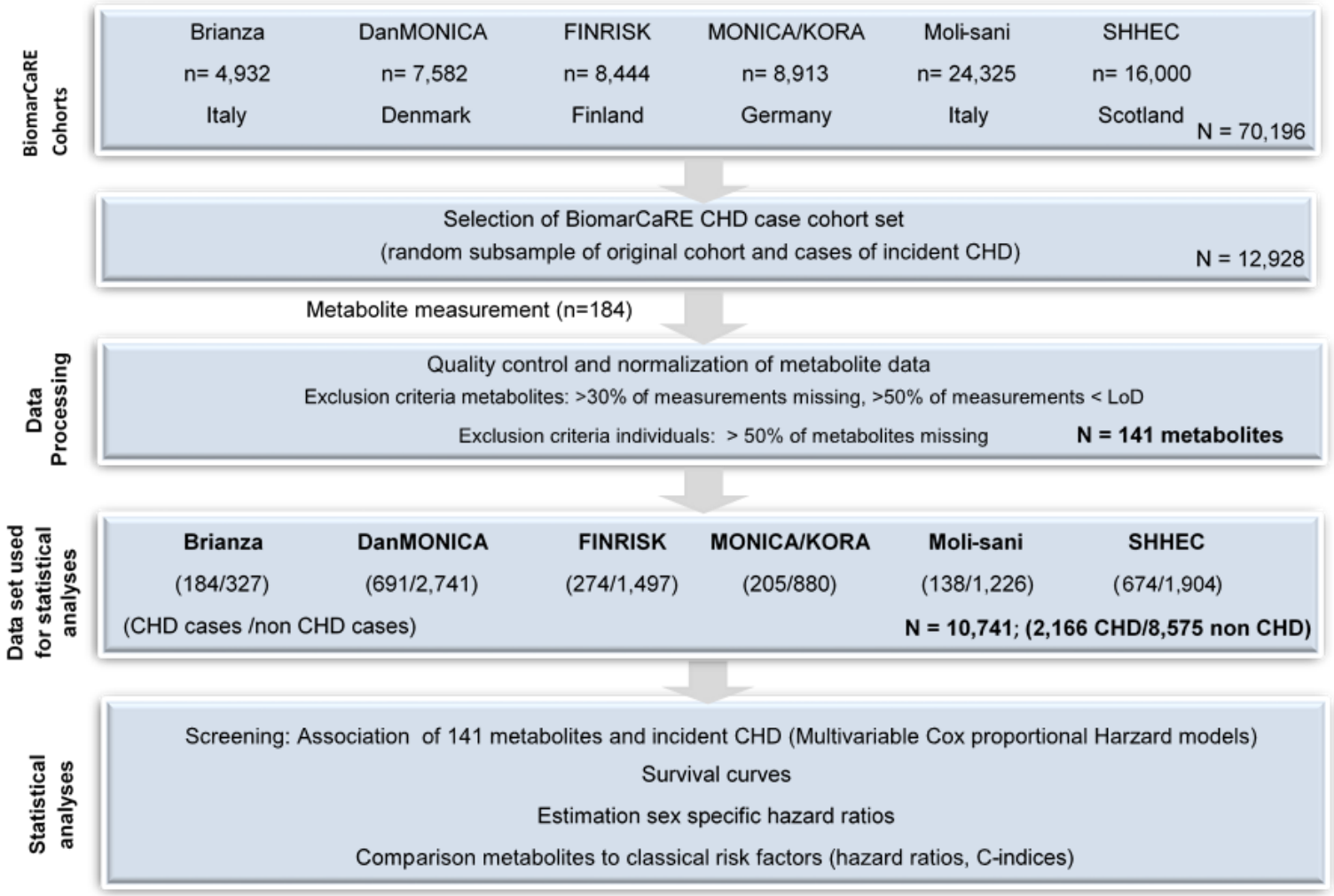
eTable 8. Results of interaction analyses between cholesterol-lowering medication and no cholesterol-lowering medication. Analyses were performed using a subset of the case-cohort set with available data on cholesterol-lowering medication, consisting of the Moli-sani and FINRISK subcohorts. The size of the Non-cholesterol-lowering medication group was 2,508 (with 326 events) and the size of the cholesterol-lowering medication group was 195 (with 21 events).

Metabolite	**Medication group**	**Interaction p-value**
acyl-alkyl-PC C40:6	No cholesterol lowering medication	0.438
	Cholesterol lowering medication	
acyl-alkyl-PC C38:6	No cholesterol lowering medication	0.899
	Cholesterol lowering medication	
diacyl-PC C38:5	No cholesterol lowering medication	0.685
	Cholesterol lowering medication	
diacyl-PC C38:6	No cholesterol lowering medication	0.372
	Cholesterol lowering medication	
diacyl-PC C40:6	No cholesterol lowering medication	0.865
	Cholesterol lowering medication	

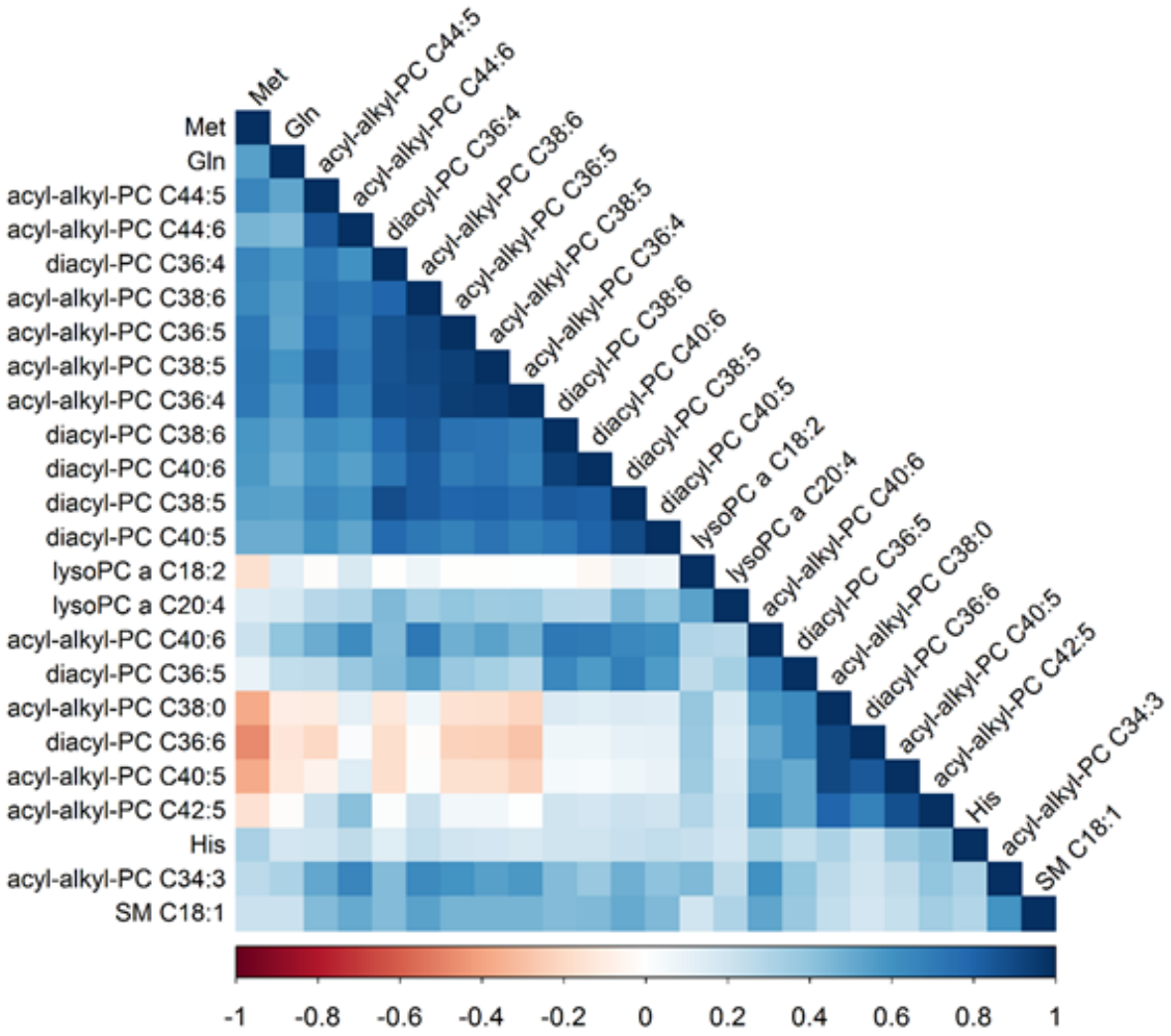
eTable 9. C-indices for 10-year prediction of coronary heart disease. Base model includes variables BMI, systolic BP, antihypertensive, diabetes, total cholesterol, sex, daily smoker, study center and age at examination. All Cox models used to compute the 10-year probabilities of CHD are adjusted for age and study center. Daily smoker and sex were used as stratification variables in those models that included them. PC, phosphatidylcholine. hsCRP, high-sensitivity assayed C-reactive protein; hsTnI, high-sensitivity assayed troponin I.

Model	C-index (95% CI)	C-Index difference (95% CI)	p-value
acyl-alkyl-PC C40:6	0.756 (0.738, 0.774)		
acyl-alkyl-PC C38:6	0.755 (0.736, 0.773)		
diacyl-PC C38:5	0.754 (0.736, 0.772)		
diacyl-PC C38:6	0.754 (0.736, 0.772)		
diacyl-PC C40:6	0.754 (0.736, 0.772)		
hsCRP	0.771 (0.752, 0.789)		
hsTnI	0.763 (0.745, 0.782)		
BMI	0.757 (0.738, 0.775)		
Diabetes	0.761 (0.743, 0.779)		
Total cholesterol	0.764 (0.746, 0.783)		
Systolic blood pressure + hypertensive medication	0.765 (0.747, 0.783)		
Daily smoker	0.785 (0.767, 0.803)		
Examination age	0.754 (0.736, 0.772)		
Sex	0.784 (0.766, 0.802)		
Base risk model	0.828 (0.809, 0.846)		
+ acyl-alkyl-PCC40:6	0.828 (0.810, 0.846)	0.0003 (-0.0009, 0.0015)	0.61
+ acyl-alkyl-PCC38:6	0.828 (0.810, 0.846)	0.0003 (-0.0006, 0.0012)	0.54
+ diacyl-PC C38:5	0.828 (0.810, 0.846)	0.0003 (-0.0006, 0.0012)	0.52
+ diacyl-PC C38:6	0.828 (0.810, 0.846)	0.0003 (-0.0006, 0.0012)	0.48
+ diacyl-PC C40:6	0.828 (0.809, 0.846)	-0.0001 (-0.0009, 0.0008)	0.90
+ all significant metabolites	0.828 (0.810, 0.846)	0.0003 (-0.0010, 0.0016)	0.64
+hsCRP	0.831 (0.813, 0.849)	0.0031 (0.0011, 0.0052)	0.0025
+hsTnI	0.829 (0.810, 0.847)	0.0010 (-0.0003, 0.0023)	0.13

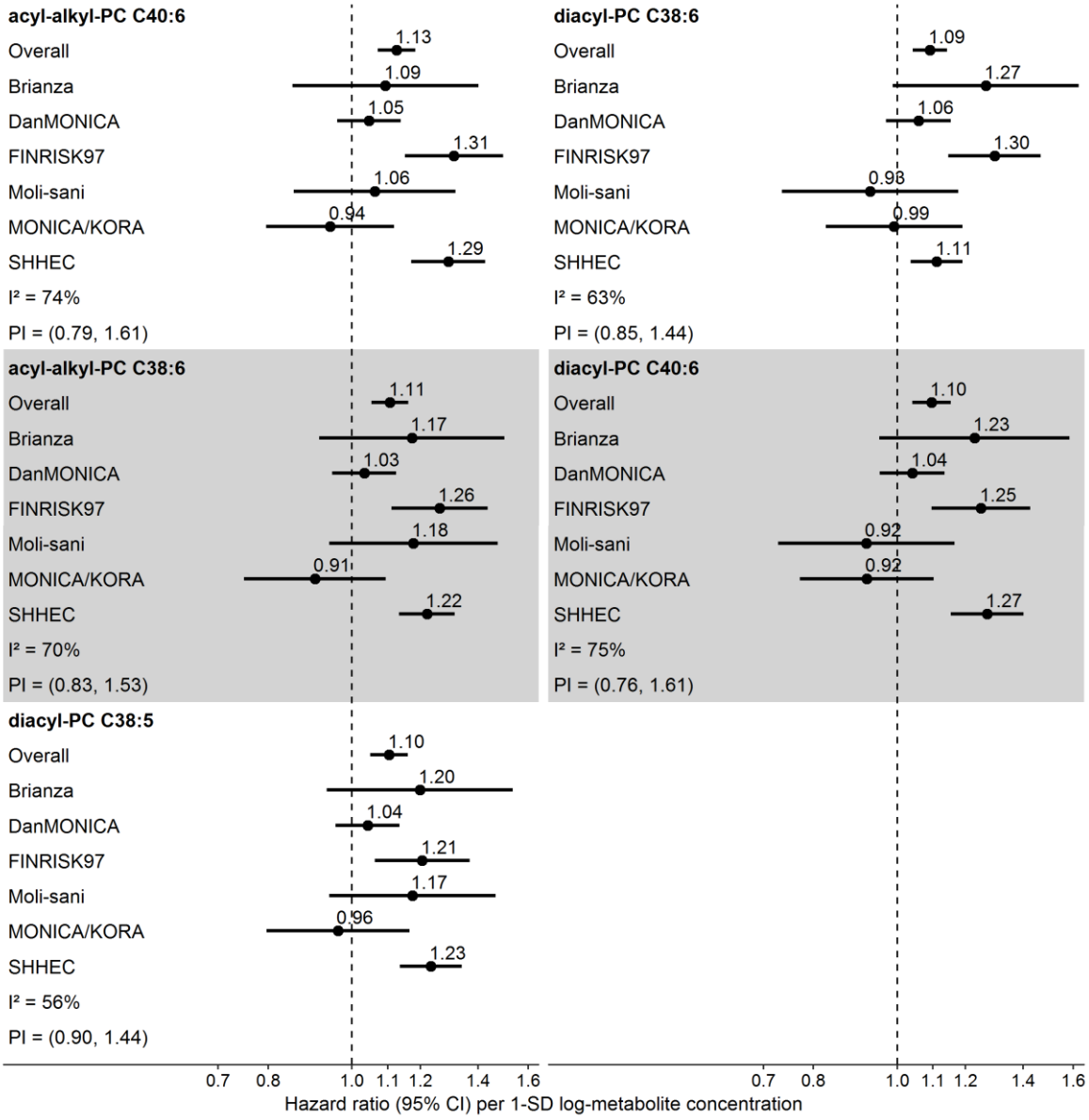
eFigure 1. Flow diagram of BiomarCaRE case cohort set, metabolite measurement and data processing.



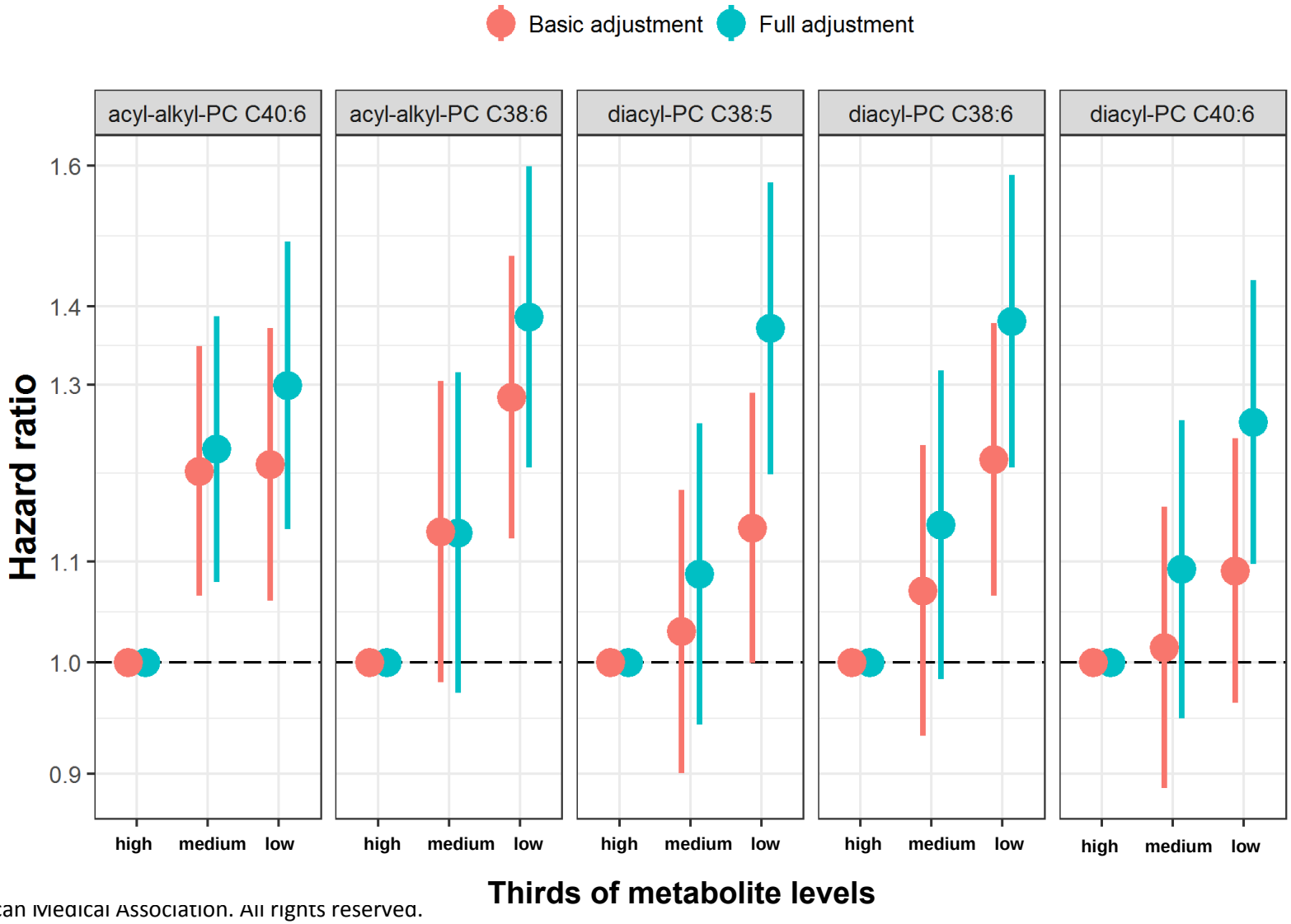
eFigure 2. Pearson correlation matrix for serum metabolite levels: Pearson correlation of the 24 log-transformed metabolites nominally significant with a p-value < 0.05. Correlations were weighted by the inverse of the inclusion probability. PC, phosphatidylcholine, Met, Methionine; Gln, Glutamine; His, Histidine; SM, sphingomyelin.



eFigure 3. Metabolite associations with future coronary heart disease per individuals study center. Hazard ratio (HR) are per 1 standard deviation log-transformed metabolite level and are adjusted for BMI, systolic blood pressure, antihypertensive treatment, diabetes, total cholesterol, male sex, daily smoking, study center and examination age. Error bars indicate 95% confidence intervals. The log-metabolite levels were multiplied by -1 before performing the computations. A logarithmic scale is used on the x-axis. PC, phosphatidylcholine; PI, predictive interval



eFigure 4. Hazard ratios across thirds (low, medium, high) of the significant phosphatidylcholine metabolites. Basic adjustment included age, sex and study center; full adjustment included BMI, systolic BP, antihypertensive, diabetes, total cholesterol, male sex, daily smoker, study center and examination age. A logarithmic scale is used on the y-axis.



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