UNIVERSITY OF TURKU

METABOLOMICS AND METAGENOMICS IN HYPERTENSION

Joonatan Palmu

List of Original Publications

This dissertation is based on the following original publications, which are referred to in the text by their Roman numerals:

I   Palmu J, Lahti L, Niiranen TJ. Targeting Gut Microbiota to Treat Hypertension: A Systematic Review. *International Journal of Environmental Research and Public Health*, 2021, 18: 1248.

II   Palmu J, Salosensaari A, Havulinna AS, Cheng S, Inouye M, Jain M, Salido RA, Sanders JG, Brennan C, Humphrey GC, Sanders JG, Vartiainen E, Laatikainen T, Jousilahti P, Salomaa V, Knight R, Lahti L, Niiranen TJ. Association Between the Gut Microbiota and Blood Pressure in a Population Cohort of 6953 Individuals. *Journal of the American Heart Association*, 2020, 9: e016641.

III   Palmu J, Watrous JD, Mercader K, Havulinna AS, Lagerborg KA, Salosensaari A, Inouye M, Larson MG, Rong J, Vasan RS, Lahti L, Allen A, Cheng S, Jousilahti P, Salomaa V, Jain M, Niiranen TJ. Eicosanoid Inflammatory Mediators Are Robustly Associated With Blood Pressure in the General Population. *Journal of the American Heart Association*, 2020, 9: e017598.

IV   Palmu J, Tikkanen E, Havulinna AS, Vartiainen E, Lundqvist A, Ruuskanen MO, Perola M, Ala-Korpela M, Jousilahti P, Würtz P, Salomaa V, Lahti L, Niiranen T. Comprehensive biomarker profiling of hypertension in 36 985 Finnish individuals. *Journal of Hypertension*, 2021.

Supplement Figures in
Original Publications

Palmu J, **Salosensaari A, Havulinna AS, Cheng S,
Inouye M, Jain M, Salido RA, Sanders K, Brennan C,
Humphrey GC, Sanders JG, Vartiainen E, Laatikainen T,
Jousilahti P, Salomaa V, Knight R, Lahti L, Niiranen TJ (2020)
Association Between the Gut Microbiota and Blood Pressure in a
Population Cohort of 6953 Individuals.**
Journal of the American Heart Association

II

Figure S1. Associations between *Lactobacilli* and blood pressure by sex.
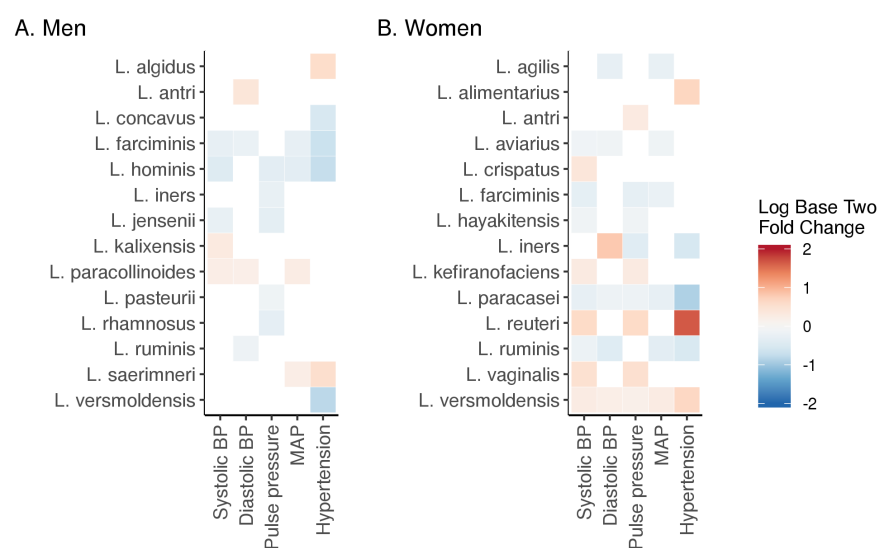

The models are adjusted for age, BMI, smoking, exercise, diuretics, beta blockers, calcium channel blockers, and renin–angiotensin system blockers. N=3 819 for women and N=3 134 for men. BP, Blood pressure; MAP, Mean arterial pressure.

Figure S2. Associations between *Lactobacilli* and blood pressure by antihypertensive medication use.
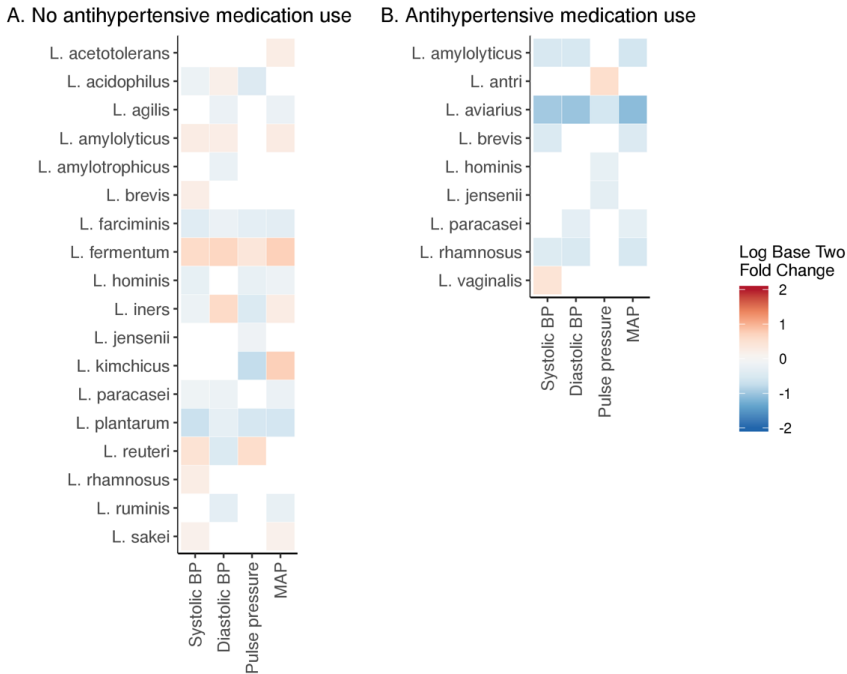
The models are adjusted for age, sex, BMI, smoking, exercise, diuretics, beta blockers, calcium channel blockers, and renin–angiotensin system blockers. Association with bacterial plasmid is denoted using asterisk. N=1 253 for antihypertensive medication users and N=5 700 for non-users. BP, Blood pressure; MAP, Mean arterial pressure.

Figure S3. Functional pathways associated with systolic BP.
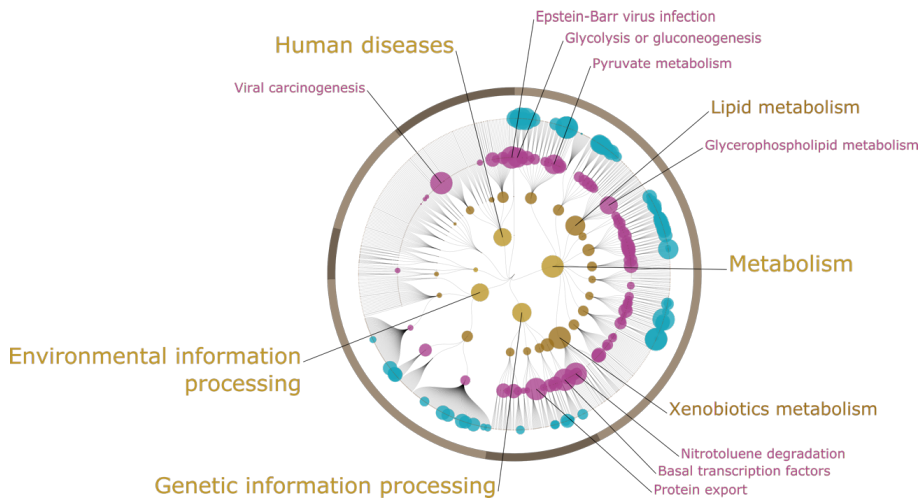
For the module (cyan), pathway (purple), biological process (dark brown), and biological category (light brown) functional layers, node size corresponds to the average inverse P value of the KO group assigned to that node. Only KO groups that were negatively associated with systolic BP were included. Node titles are shown for nodes in the three highest layers with a size > 200.

**Palmu J, Watrous JD, Mercader K, Havulinna AS,
Lagerborg KA, Salosensaari A, Inouye M, Larson MG,
Rong J, Vasan RS, Lahti L, Andres A, Cheng S,
Jousilahti P, Salomaa V, Jain M, Niiranen TJ (2020)
Eicosanoid Inflammatory Mediators Are Robustly Associated
With Blood Pressure in the General Population.**
Journal of the American Heart

III

Figure S1. Correlation matrix with labels for the 187 plasma eicosanoids related to systolic blood pressure in FINRISK 2002.
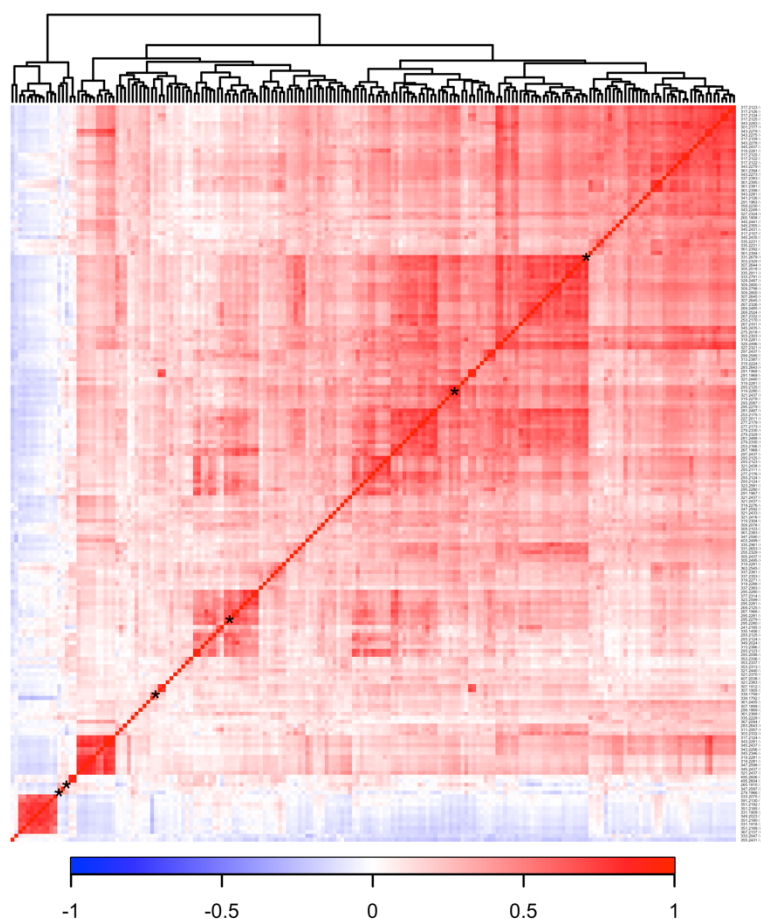

Relations between eicosanoids were calculated using Spearman correlation and ordered using hierarchical cluster analysis with complete linkage method. Only eicosanoids related to systolic blood pressure were included in the correlation matrix. Asterisk denotes the six eicosanoids species in our eicosanoid profile.

Figure S2. The subgroup analyses for the association of eicosanoid risk score with systolic BP.
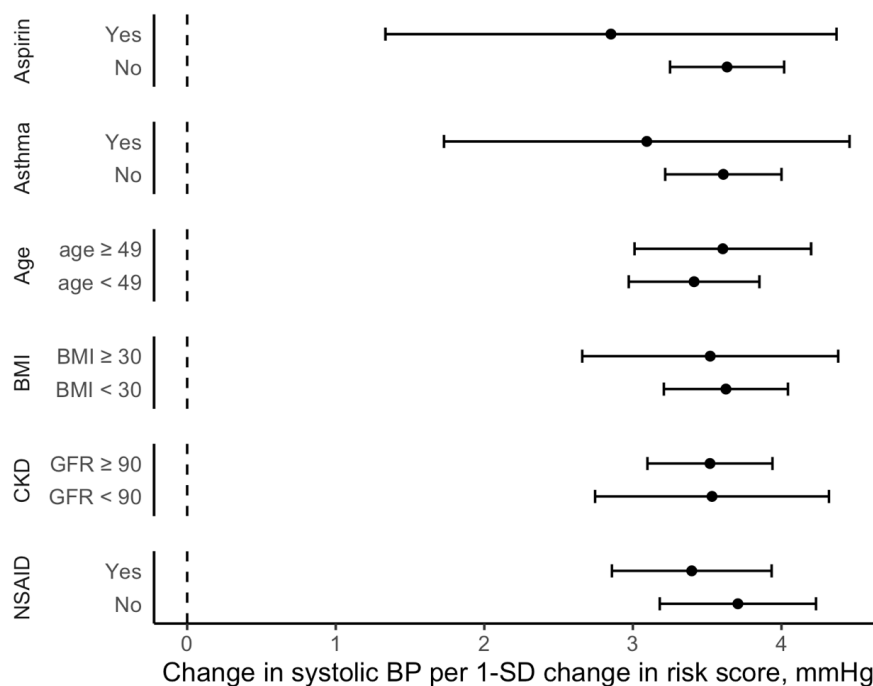

The association are adjusted for age, sex, BMI, smoking, diabetes, antihypertensive medication, and batch. The number of individuals with aspirin, asthma, age ≥49 years, BMI ≥30, GFR ≥90, and NSAIDs was 795, 653, 3963, 1720, 5572, and 4032, respectively. BMI, body mass index; CKD, chronic kidney disease; GFR, glomerular filtration rate; NSAID, nonsteroidal anti-inflammatory drugs.

Figure S3. Manhattan plot for the genome-wide association study.
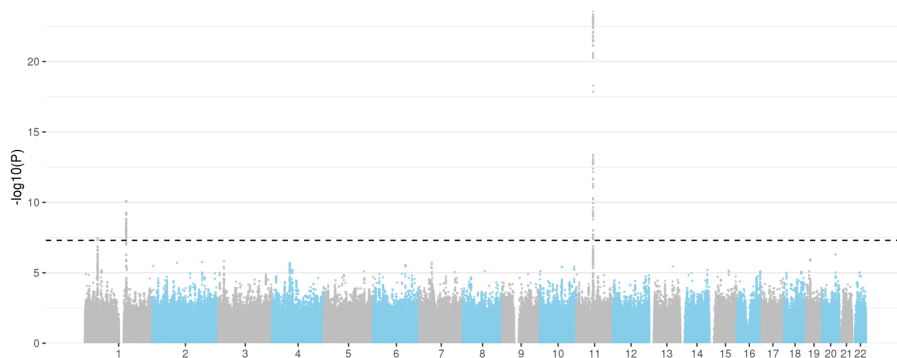
We performed genome-wide association study (GWAS) for eicosanoid risk score observing three distinct windows with significant single nucleotide polymorphism (SNP). The alternating coloring denotes different chromosomes and SNPs are ordered according their location in chromosomes. The dotted line marks the level of significance (P < 5E-8).

Palmu J, Tikkanen E, Havulinna AS, Vartiainen E, Lundqvist A, Ruuskanen MO, Perola M, Ala-Korpela M, Jousilahti P, Würtz P, Salomaa V, Lahti L, Niiranen T (2021)
Comprehensive biomarker profiling of hypertension in 36 985 Finnish individuals.
Journal of Hypertension

IV

Figure S1. Flow diagram for selection of cross-sectional and longitudinal samples.
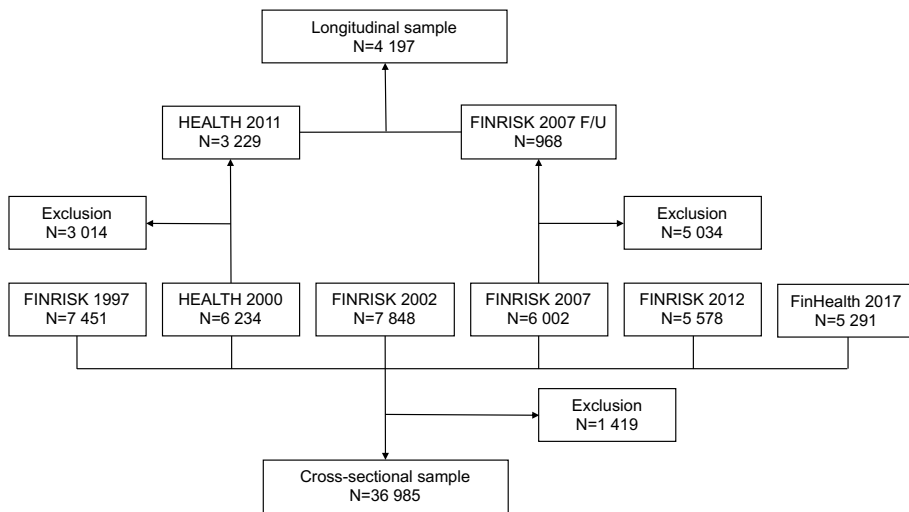

The cross-sectional sample is combined from four independent FINRISK cohorts between 1997-2012 and HEALTH 2000. Longitudinal samples combined for the two cohorts with follow-up data: Health 2000-2011 and DILGOM.

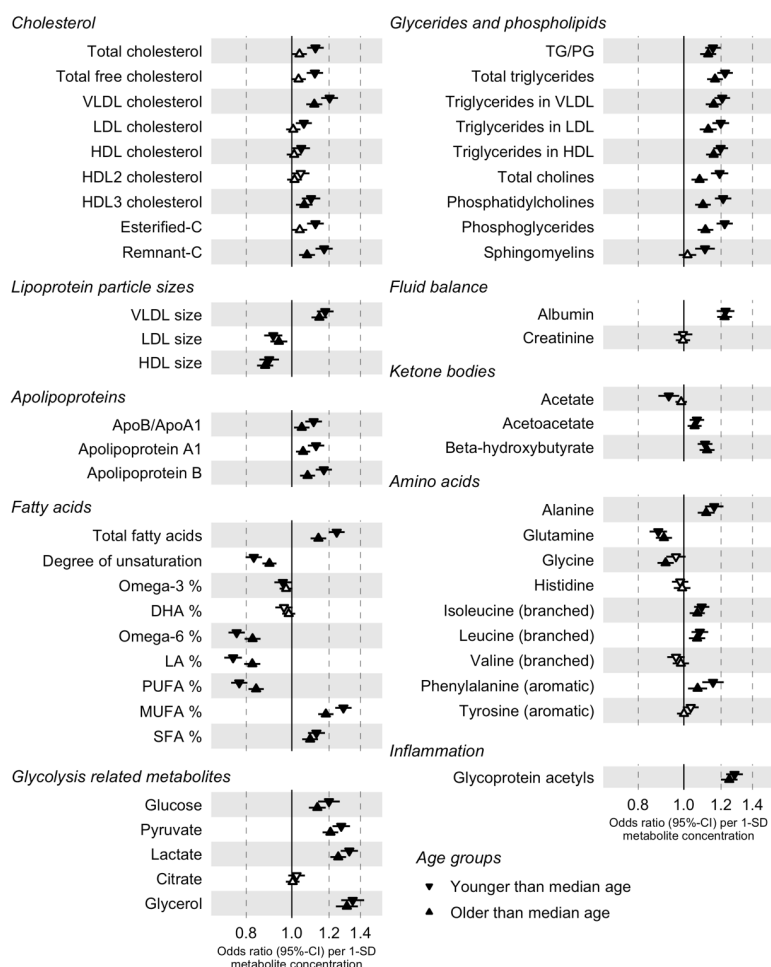**Figure S2.** Cross-sectional associations between the metabolites and hypertension (N=36985).
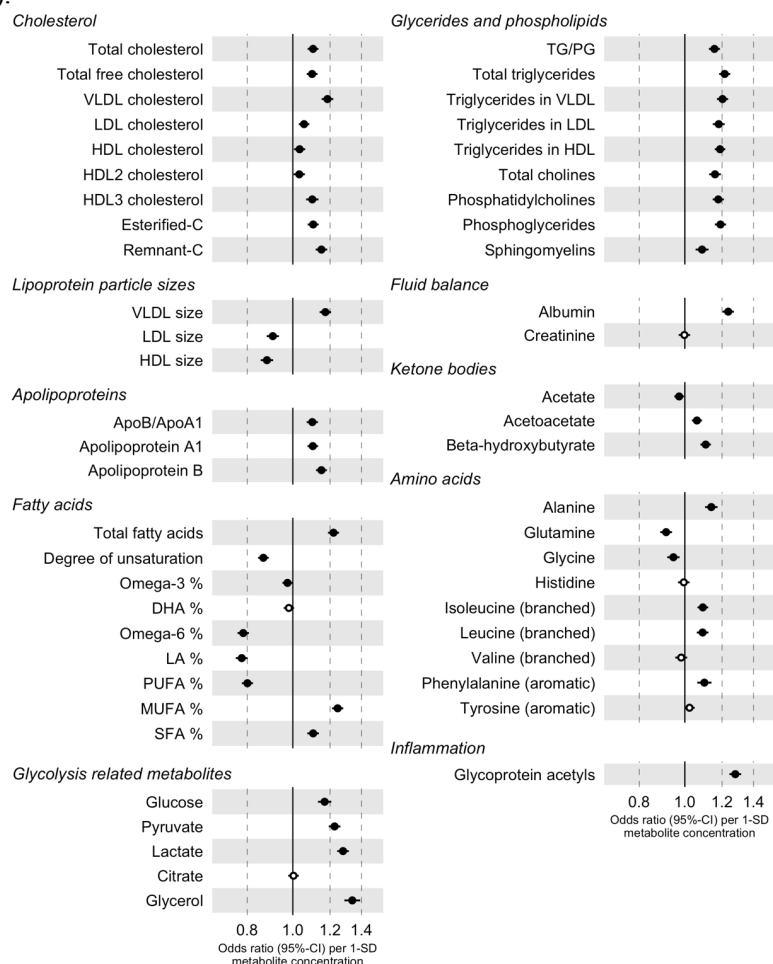
Filled circle signifies FDR-corrected *P*<0.05. Associations are adjusted for age, sex, BMI, current smoking, diabetes, exercise, lipid medication, and cohort. MUFA, monounsaturated fatty acids; SFA, saturated fatty acids; TG, triglycerides; PG, phosphoglycerides; VLDL, very low density lipoprotein; LDL, low density lipoprotein; HDL, high density lipoprotein Apo, apolipoprotein; C, cholesterol; DHA, docosahexaenoic acid; PUFA, polyunsaturated fatty acids; LA, linoleic acid.

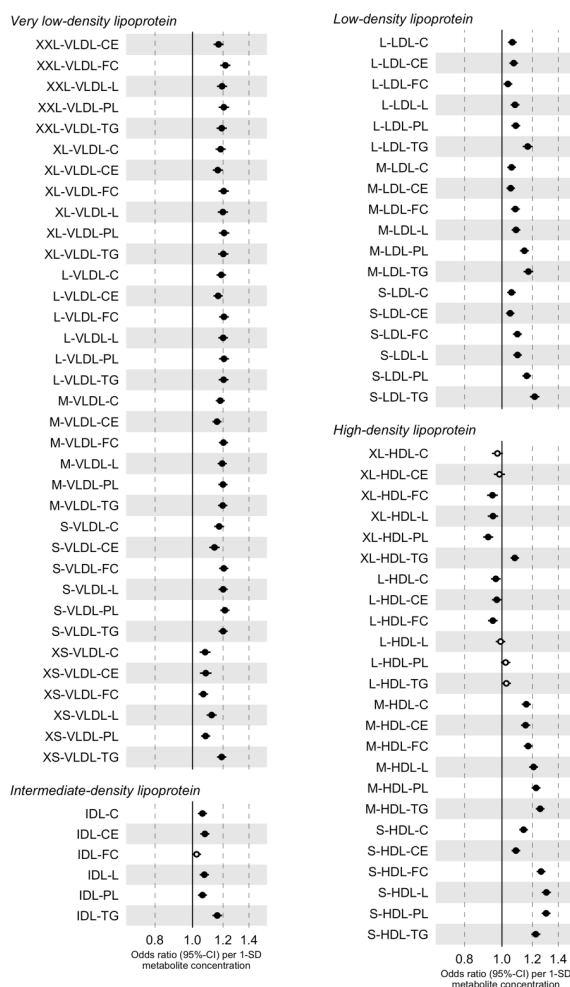**Figure S3.** Cross-sectional associations between metabolic measures and hypertension by sex.
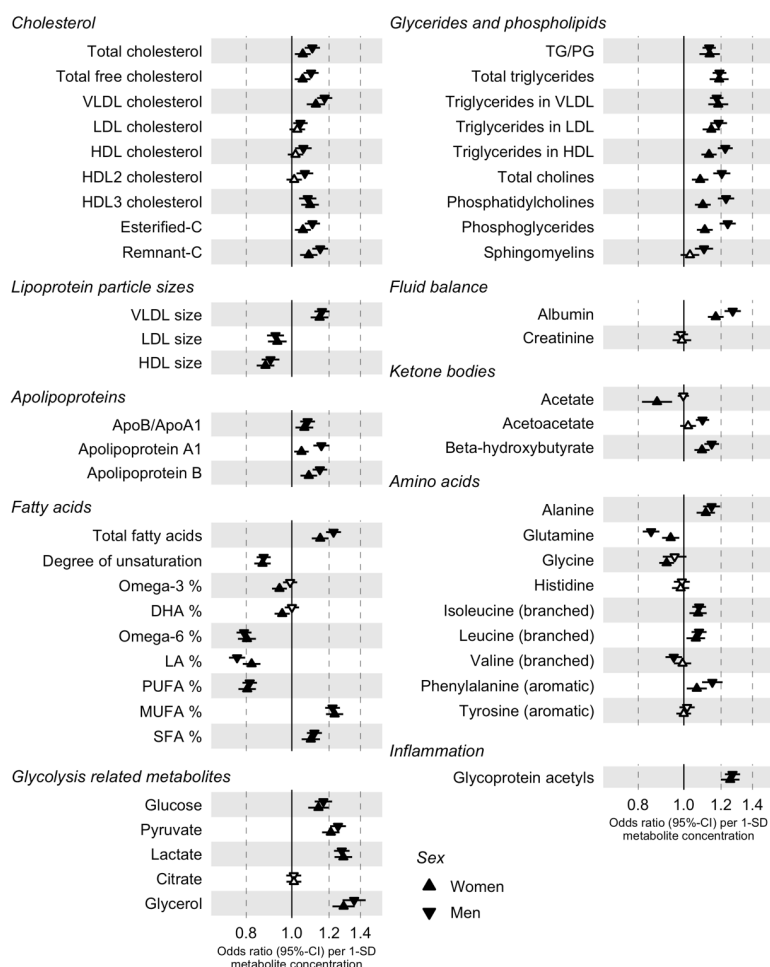
Filled triangle signifies FDR-corrected *P*<0.05. Associations are adjusted for age, sex, BMI, current smoking, diabetes, exercise, lipid medication, and cohort. MUFA, monounsaturated fatty acids; SFA, saturated fatty acids; TG, triglycerides; PG, phosphoglycerides; VLDL, very low density lipoprotein; LDL, low density lipoprotein; HDL, high density lipoprotein; Apo, apolipoprotein; C, cholesterol; DHA, docosahexaenoic acid; PUFA, polyunsaturated fatty acids; LA, linoleic acid.

Figure S4. Cross-sectional associations between metabolites and hypertension in younger and older participants.
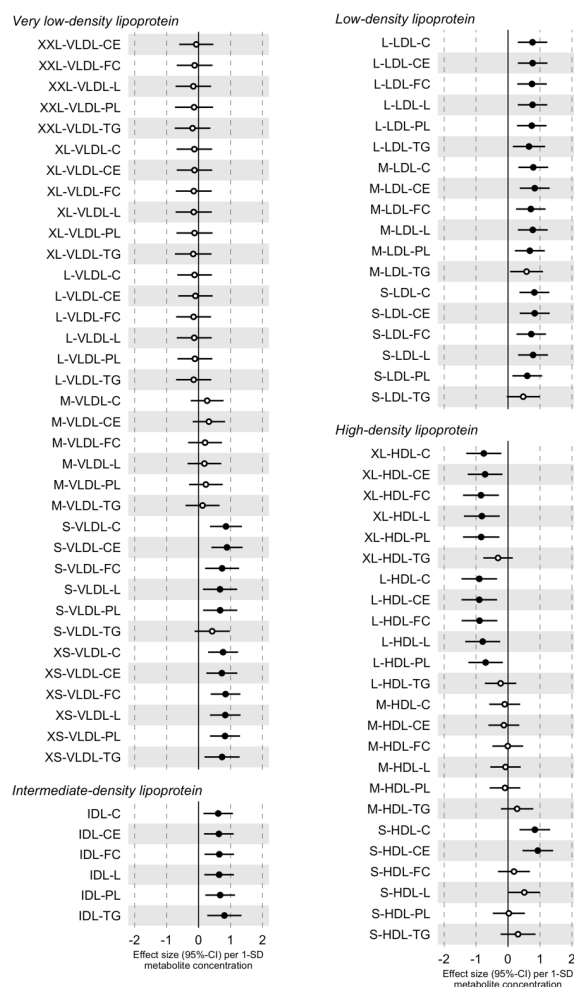

Filled triangle signifies FDR-corrected *P*<0.05. Associations are adjusted for age, sex, BMI, current smoking, diabetes, exercise, lipid medication, and cohort. MUFA, monounsaturated fatty acids; SFA, saturated fatty acids; TG, triglycerides; PG, phosphoglycerides; VLDL, very low density lipoprotein; LDL, low density lipoprotein; HDL, high density lipoprotein; Apo, apolipoprotein; C, cholesterol; DHA, docosahexaenoic acid; PUFA, polyunsaturated fatty acids; LA, linoleic acid.

Figure S5. Cross-sectional associations between lipoprotein measures related to 14 lipoprotein subclasses and hypertension.
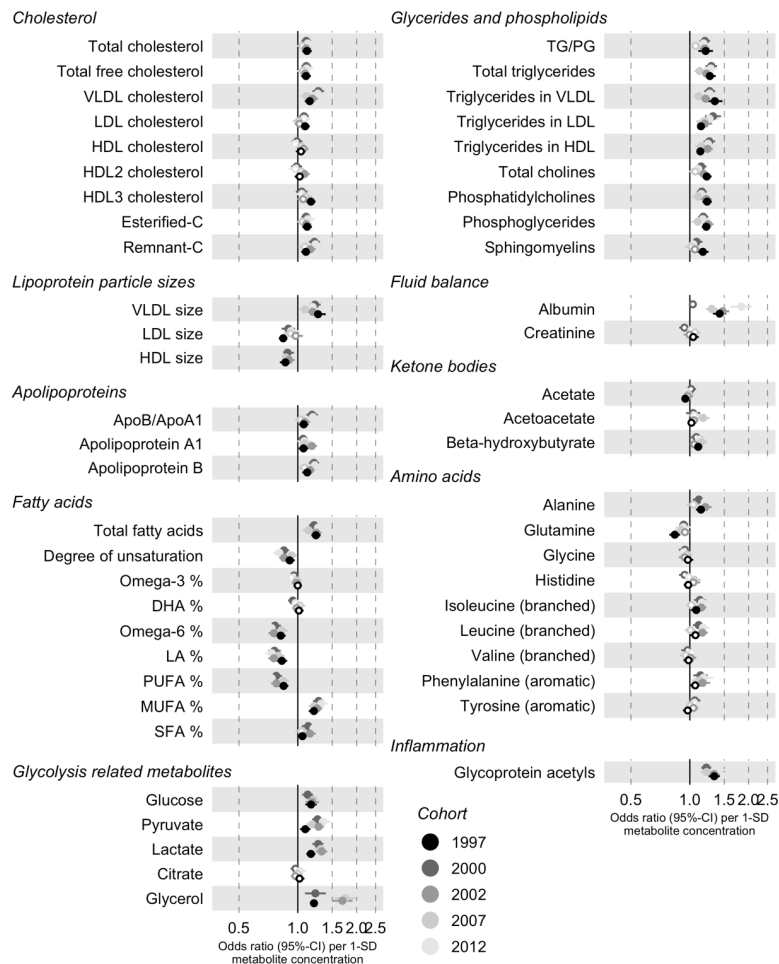

Filled circle signifies FDR-corrected P<0.05. Associations are adjusted for age, sex, BMI, current smoking, diabetes, antihypertensive medication, exercise, lipid medication, and cohort. C, Total cholesterol in lipoproteins; CE, Cholesterol esters in lipoproteins; FC, Free cholesterol in lipoproteins; HDL, high density lipoprotein; ILDL, intermediate-density lipoproteins; L, Total lipids in lipoproteins; LDL, low density lipoprotein; PL, Phospholipids in lipoproteins; TG, Triglycerides in lipoproteins. VLDL, very low density lipoprotein.

Figure S6. Longitudinal associations between baseline lipoprotein measures related to 14 lipoprotein subclasses and systolic blood pressure change (N=4197).
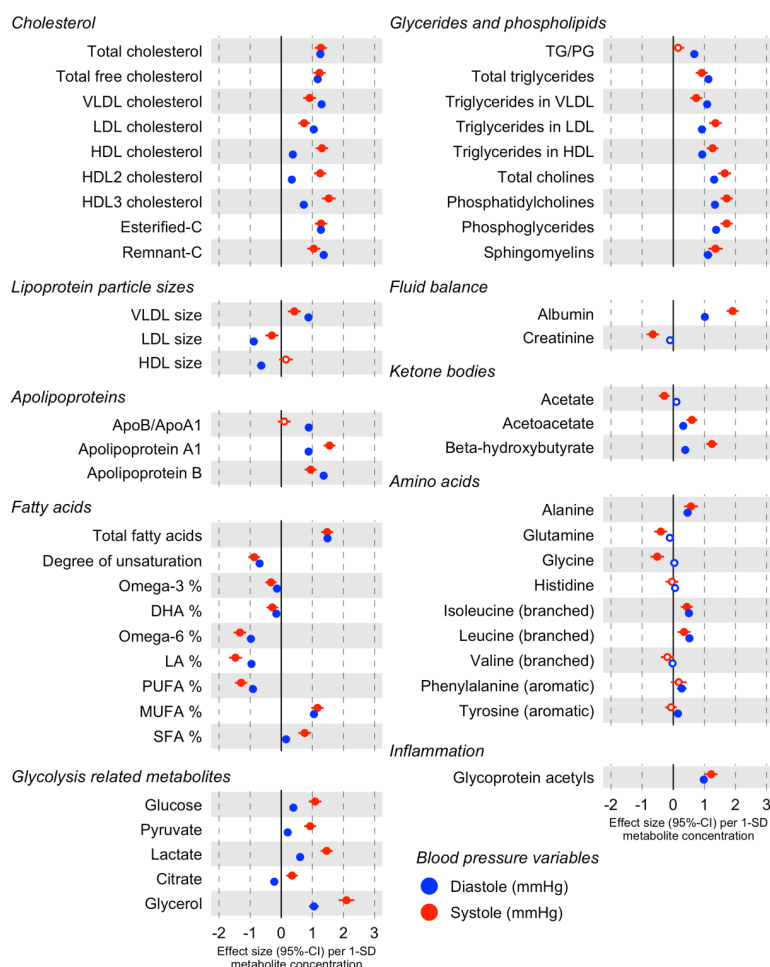

Filled circle signifies FDR-corrected *P*<0.05. Associations are adjusted for baseline systolic BP, age, sex, BMI, current smoking, diabetes, antihypertensive medication, exercise, lipid medication, and cohort. C, total cholesterol in lipoproteins; CE, cholesterol esters in lipoproteins; FC, free cholesterol in lipoproteins; HDL, high density lipoprotein; ILDL, intermediate-density lipoproteins; L, total lipids in lipoproteins; LDL, low density lipoprotein; PL, phospholipids in lipoproteins; TG, triglycerides in lipoproteins. VLDL, very low density lipoprotein.

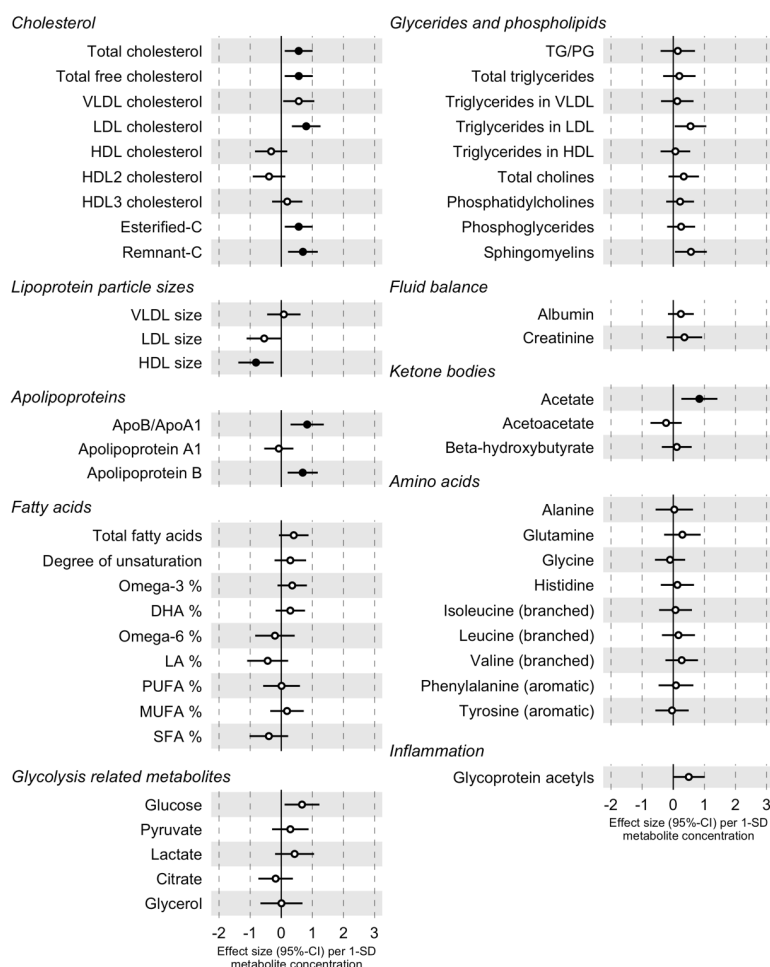**Figure S7.** Cross-sectional associations between metabolic measures and hypertension by cohort.

Filled circle signifies FDR-corrected *P*<0.05. Associations are adjusted for age, sex, BMI, current smoking, diabetes, exercise, and lipid medication. MUFA, monounsaturated fatty acids; SFA, saturated fatty acids; TG, triglycerides; PG, phosphoglycerides; VLDL, very low density lipoprotein; LDL, low density lipoprotein; HDL, high density lipoprotein; Apo, apolipoprotein; C, cholesterol; DHA, docosahexaenoic acid; PUFA, polyunsaturated fatty acids; LA, linoleic acid.

Figure S8. Meta-analysis for the cross-sectional associations between metabolic measures and continuous blood pressure variables.

Filled circle signifies FDR-corrected *P*<0.05. Associations are adjusted for age, sex, BMI, current smoking, diabetes, antihypertensive medication, exercise, and lipid medication. MUFA, monounsaturated fatty acids; SFA, saturated fatty acids; TG, triglycerides; PG, phosphoglycerides; VLDL, very low density lipoprotein; LDL, low density lipoprotein; HDL, high density lipoprotein; Apo, apolipoprotein; C, cholesterol; DHA, docosahexaenoic acid; PUFA, polyunsaturated fatty acids; LA, linoleic acid.

Figure S9. Meta-analysis for the longitudinal associations between metabolic measures and continuous blood pressure variables.

Filled circle signifies FDR-corrected *P*<0.05. Associations are adjusted for baseline systolic BP, age, sex, BMI, current smoking, diabetes, antihypertensive medication, exercise, lipid medication, and cohort. MUFA, monounsaturated fatty acids; SFA, saturated fatty acids; TG, triglycerides; PG, phosphoglycerides; VLDL, very low density lipoprotein; LDL, low density lipoprotein; HDL, high density lipoprotein; Apo, apolipoprotein; C, cholesterol; DHA, docosahexaenoic acid; PUFA, polyunsaturated fatty acids; LA, linoleic acid.