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ORIGINAL RESEARCH

Eicosanoid Inflammatory Mediators Are Robustly Associated With Blood Pressure in the General Population

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BACKGROUND: Epidemiological and animal studies have associated systemic inflammation with blood pressure (BP). However, the mechanistic factors linking inflammation and BP remain unknown. Fatty acid–derived eicosanoids serve as mediators of inflammation and have been suggested to regulate renal vascular tone, peripheral resistance, renin-angiotensin system, and endothelial function. We hypothesize that specific proinflammatory and anti-inflammatory eicosanoids are linked with BP.

METHODS AND RESULTS: We studied a population sample of 8099 FINRISK 2002 participants randomly drawn from the Finnish population register (53% women; mean age, 48±13 years) and, for external validation, a sample of 2859 FHS (Framingham Heart Study) Offspring study participants (55% women; mean age, 66±9 years). Using nontargeted liquid chromatography–mass spectrometry, we profiled 545 distinct high-quality eicosanoids and related oxylipin mediators in plasma. Adjusting for conventional hypertension risk factors, we observed 187 (34%) metabolites that were significantly associated with systolic BP (P<Bonferroni-corrected threshold of 0.05/545). We used forward selection linear regression modeling in FINRISK to define a general formula for individual eicosanoid risk score. Individuals of the top risk score quartile in FINRISK had a 9.0 (95% CI, 8.0–10.1) mm Hg higher systolic BP compared with individuals in the lowest quartile in fully adjusted models. Observed metabolite associations were consistent across FINRISK and FHS.

CONCLUSIONS: Plasma eicosanoids demonstrate strong associations with BP in the general population. As eicosanoid compounds affect numerous physiological processes that are central to BP regulation, they may offer new insights about the pathogenesis of hypertension, as well as serve as potential targets for therapeutic intervention.

Key Words: blood pressure ■ eicosanoids ■ hypertension ■ liquid chromatography–mass spectrometry ■ metabolite

A vast majority of patients with hypertension (>95%) are classified as having primary (essential) hypertension, a heterogeneous condition of hypertension that has no identifiable cause (by definition). Essential hypertension is most likely the consequence of an interaction between genetic factors and environmental factors (eg, obesity, insulin resistance, sedentary lifestyle, stress, and sodium intake).[1] Intriguingly, all of the aforementioned factors are also related to chronic low-grade inflammation, underscoring the need to further investigate inflammation as a potential mainstay pathologic mechanism underlying hypertension.[2]

The upstream initiation of inflammatory activity in humans is governed mainly by substrates and products of polyunsaturated fatty acids.[3] Termed

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CLINICAL PERSPECTIVE

What Is New?

- Fatty acid–derived eicosanoids serve as mediators of inflammation and have been suggested to regulate renal vascular tone, peripheral resistance, renin-angiotensin system, and endothelial function.
- We assayed a comprehensive panel of >500 distinct high-quality eicosanoids and related oxylipin mediators in community-based samples of >10 000 individuals using liquid chromatography–mass spectrometry and relate these eicosanoids and eicosanoid profiles to blood pressure traits.

What Are the Clinical Implications?

- We observed that 187 (34%) eicosanoids and related oxylipin mediators were significantly associated with systolic blood pressure.
- Individuals in the top quartile of a 6-metabolite risk score had a 9.0 mm Hg higher systolic blood pressure and 2-fold greater odds of hypertension compared with individuals in the bottom quartile.
- In conclusion, as eicosanoid species affect numerous physiological processes that are central to blood pressure regulation, they may offer new insights about the pathogenesis of hypertension, as well as serve as potential new targets for therapeutic intervention.

Nonstandard Abbreviations and Acronyms

12-HHTrE	12-hydroxyheptadecatrienoic acid
FHS	Framingham Heart Study
LC-MS	liquid chromatography–mass spectrometry
MS	mass spectrometry
TXA_2	thromboxane A2
TXB_2	thromboxane B2

eicosanoids, the small-molecule derivatives of arachidonic acid and other polyunsaturated fatty acids serve as both activators and suppressors of systemic inflammatory activity.[3] Data derived mainly from animal studies suggest that eicosanoid compounds affect renal vascular tone, urine sodium excretion, peripheral resistance, kidney disease, renin-angiotensin-aldosterone system, and endothelial function, factors that are central to blood pressure (BP) regulation itself.[4–9] Published data have also demonstrated that a few, select eicosanoids, such as 20-hydroxyeicosatetraenoic acid, and genetic polymorphisms that regulate the levels of these eicosanoids are altered in small samples of individuals and animals with hypertension.[10–12]

Until recently, sensitive methods for detecting and quantifying eicosanoids in large sample sizes were lacking. However, mass spectrometry (MS) based analytics now allow for the rapid large-scale quantification of several hundred upstream eicosanoids in human plasma.[13,14] Our goal was to gain a more detailed understanding of how upstream inflammatory mediators are related to an individual's prevalence for hypertension. We quantified a comprehensive panel of >500 distinct high-quality upstream eicosanoids and related oxylipin mediators in FINRISK 2002 (n=8099) and FHS (Framingham Heart Study) Offspring (n=2859) cohort participants using liquid chromatography–MS (LC-MS) and related these eicosanoids and eicosanoid profiles to BP traits.

METHODS

Availability of Data and Materials

The data that support the findings of this study are available from Finnish Institute for Health and Welfare Biobank (https://thl.fi/en/web/thl-biobank). The data are not publicly available because they contain information that could compromise research participant privacy/consent. The source code for the analyses is openly available at 10.5281/zenodo.3604123.

Cohorts

The FINRISK 2002 study used a random population sample of individuals, aged 25 to 74 years, from 6 geographical areas of Finland. The sampling was stratified by sex, region, and 10-year age group for a population sample of 13 500 individuals; the overall participation rate was 65.2% (n=8798). The sampling has been previously described in detail.[15] Plasma LC-MS was performed successfully on n=8292 participants. After excluding 193 participants with missing covariate data, n=8099 individuals were included in the analyses as the discovery cohort for the present investigation.

The first-generation (ie, the "original") cohort of the FHS included a random sample of two thirds of the adult population of Framingham, MA, who were enrolled in a longitudinal community-based cohort study in 1948. The FHS Offspring includes 5124 participants, children of the first-generation cohort and their spouses, who have been reexamined every 4 to 8 years since the first examination in 1971. The characteristics and study protocol of FHS Offspring cohort have been published.[16] For this study, we considered n=3002 individuals who participated in the 8

examination cycle of FHS Offspring in 2005 to 2008 and had assays for eicosanoids with LC-MS. After excluding 143 participants with missing covariates, we included n=2859 participants as the replication cohort.

Ethical Approval

The FINRISK 2002 study was approved by Coordinating Ethics Committee of the Helsinki University Hospital District. FHS Offspring was approved by Boston University Medical Center's Institutional Review Board. All participants in both studies provided written informed consent. Participants' consent to publication of information was not required because the participants remain unidentifiable.

Clinical Evaluation and Definitions

Participants of both cohorts provided a medical history, including information on medication use, and underwent a physical examination and laboratory assessment of cardiovascular risk factors at baseline. The methods of these examinations have been described previously in detail.[15,16] At all examinations, a healthcare professional performed 2 (FHS Offspring) or 3 (FINRISK) sequential BP measurements using a mercury column sphygmomanometer on seated participants, according to a standardized protocol. We defined the BP at a given examination as the mean of all sequentially measured BP values. We defined hypertension as BP ≥140/90 mm Hg or use of antihypertensive medication. Antihypertensive medication use was based on self-report in both studies. We defined pulse pressure as systolic minus diastolic BP and mean arterial pressure as [(2×diastolic BP)+systolic BP]/3. We defined body mass index (BMI) as weight (kg) divided by height (m) squared and current smoking as self-reported daily use of tobacco products. In FINRISK 2002, prevalent diabetes mellitus was defined as self-reported diabetes mellitus, a previous diagnostic code indicating diabetes mellitus in the nationwide Care Register for Health Care (*International Classification of Diseases, Tenth Revision* [*ICD-10*],[17] codes E10–E14; *International Classification of Diseases, Ninth Revision* [*ICD-9*], code 250; or *International Classification of Diseases, Eighth Revision* [*ICD-8*], code 250), a previous diabetes mellitus medication purchase (Anatomical Therapeutic Chemical code A10*) in the nationwide Prescribed Drug Purchase register, or a diabetes mellitus medication code in the nationwide Reimbursed Medication Register. In FHS Offspring, prevalent diabetes mellitus was defined as a fasting plasma glucose ≥7.0 mmol/L or self-reported use of glucose-lowering medications. Using data from the Hospital Discharge and Drug Reimbursement Registers, we defined asthma in FINRISK using diagnostic codes indicating asthma (*ICD-10* codes J45-J46 or *ICD-8/9* code 493), a previous asthma medication purchase (Anatomical Therapeutic Chemical codes R03BA, R03BC, R03DC, and R03AK), or having a special reimbursement for asthma medications. We estimated glomerular filtration rate using the Chronic Kidney Disease Epidemiology Collaboration formula.[18] We defined NSAID use by a prescription purchase of medication under Anatomical Therapeutic Chemical group M01A (excluding subgroup M01AX and self-care drug purchases).

Plasma Sampling

In FINRISK, blood samples were drawn after a minimum of 4 hours of fasting, the samples were kept at room temperature for 20 minutes before centrifugation, and the samples were stored at −70°C. In FHS, fasting samples were drawn, centrifuged for 22 minutes at 4°C, and separated plasma was stored at −80°C within 90 minutes of collection.

Eicosanoid Profiling

Using a directed nontargeted LC-MS approach in conjunction with computational chemical networking of spectral fragmentation patterns, we identified 545 eicosanoids and related oxylipins in the FINRISK. The methods of plasma eicosanoid profiling using LC-MS have been previously described in detail.[13,14] Metabolite data were adjusted for technical variation in off-plate pooled plasma samples and in spike-in internal standards. Missing values were replaced with minimum value for each eicosanoid abundance. The 6 eicosanoids and related oxylipin mediators included in the risk score were matched between FINRISK and FHS by comparing their LC-MS profiles. These metabolites were also identified, if possible, through comparisons with reference standards and online databases.

Genotyping

The methods of single-nucleotide polymorphism (SNP) genotyping and quality control have been previously described in detail.[19] In short, the participants of FINRISK were genotyped on Illumina CoreExome genotyping array. A reference panel of 1000 genomes was further used to impute genotypes.

Statistical Analysis

We used R version 3.6.1[20] for all analyses. The source code for the analyses is openly available at 10.5281/zenodo.3604123.[21] Unless otherwise noted, we adjusted all analyses for age, sex, BMI, current smoking, diabetes mellitus, antihypertensive medication, and MS batch. We normalized eicosanoid abundances using median absolute deviation; we calculated the median of the absolute difference from the median,

and used this value to scale all analyte values for a given assay plate. We used linear and logistic regression models to examine the associations between each eicosanoid molecule and BP traits (systolic BP, diastolic BP, pulse pressure, mean arterial pressure, and hypertension). We adjusted for multiple comparisons using Bonferroni correction to minimize the probability of type I error.[22] Relations between eicosanoids significantly associated with systolic blood arterial pressure were assessed using Spearman correlation and ordered using hierarchical cluster analysis with complete linkage method. We assessed the multivariable association between eicosanoids significantly related to systolic BP using stepwise linear regression modeling with forward selection and a Bonferroni-corrected inclusion threshold of P=0.05/545. For the 6 eicosanoids that remained in the models, we calculated eicosanoid risk scores according to the formula $\beta_1X_1+\beta_2X_2+...+\beta_nX_n$, with X_n denoting the standardized value for the nth eicosanoid abundance, and β_n denoting the regression coefficient from the regression model for systolic BP containing the statistically significant eicosanoids.[23] We assessed the odds of hypertension and increase in systolic BP by 1-SD increases and by quartiles of the risk scores using unadjusted and multivariable adjusted logistic and linear regression models. We replicated these analyses in FHS Offspring using the eicosanoid abundances in FHS and the regression coefficients from FINRISK.

We also assessed the association between the eicosanoid risk score and systolic BP in subgroups by aspirin use, asthma status, age (younger than versus older than the median age of 49 years), BMI (<30 versus ≥30 kg/m^2), glomerular filtration rate (<90 versus ≥90 mL/min), and NSAID use. We determined the association of the eicosanoid risk score with age, BMI, and estimated glomerular filtration rate using the Pearson correlation. We compared eicosanoid risk score levels between subgroups by aspirin use, asthma status, and NSAID use using the 2-sample t test. To analyze the causative role of the eicosanoid risk score, we performed genome-wide association study (GWAS) and 2-sample mendelian randomization (MR) in the study sample. To account for ordered patterns in genetic data, we calculated multidimensional scaling based on raw Hamming distances using PLINK[24] version 1.9. We performed the GWAS for the continuous eicosanoid risk scores and the autosomes using SNPTEST[25] version 2.5.2, adjusted for age, sex, batch, and first 10 multidimensional scaling axes. We included in the mendelian randomization the SNPs that had Hardy-Weinberg equilibrium >1E-6, P<5E-8, and minor allele frequencies >0.01 using TwoSampleMR.[26] For the outcome of the mendelian randomization, we used the GWAS results for automated systolic BP measurements in UK Biobank.[27,28] We estimated the causative roles using 5 distinct methods: inverse variance weighted,[29] weighted median,[30] weighted mode,[30] simple mode,[31] and MR-Egger.[32]

RESULTS

The characteristics of FINRISK (n=8099; mean age, 48.0±13.1 years; 53.1% women) and FHS (n=2859; mean age, 66.3±8.9 years; 54.7% women) cohorts are shown in the Table.

Association Between Eicosanoids and BP Traits

Of the eicosanoids and related oxylipin mediators, 187 (34.3%) were significantly associated with systolic BP, 124 (22.8%) with diastolic BP, 177 (32.5%) with mean arterial pressure, 161 (29.5%) with pulse pressure, and 155 (28.4%) with hypertension in FINRISK (Figure 1, Table S1). We selected systolic BP as our main outcome variable because of its strong association with cardiovascular diseases. We observed 175 (93.6%) positive and 12 (6.4%) negative associations for systolic BP (Figure 1, Table S1). The heat maps of pairwise correlations for the 187 metabolites related to systolic BP are shown in Figure 2 and Figure S1. This analysis revealed strong overall correlations, but only minor clustering of the eicosanoids.

Independent Determinants of BP and Hypertension

We used forward selection linear regression modeling with a Bonferroni-corrected inclusion threshold to define a set of metabolites that was independently

Table. Characteristics of the Discovery (FINRISK) and Replication (FHS) Samples

Characteristics	FINRISK 2002	FHS
No. of subjects	8099	2859
Age, mean (SD), y	48.0 (13.1)	66.3 (8.9)
Women, N (%)	4300 (53.1)	1564 (54.7)
BMI, mean (SD), kg/m^2	26.9 (4.7)	28.3 (5.4)
Systolic blood pressure, mean (SD), mm Hg	135.1 (20.0)	128.5 (17.2)
Diastolic blood pressure, mean (SD), mm Hg	79.0 (11.3)	73.4 (10.1)
Pulse pressure, mean (SD), mm Hg	56.1 (16.1)	55.1 (16.0)
Mean arterial pressure, mean (SD), mm Hg	97.7 (12.7)	91.8 (10.5)
Hypertension, N (%)	3567 (44.0)	1673 (58.5)
Antihypertensive medication, N (%)	1177 (14.5)	1389 (48.6)
Current smoker, N (%)	2097 (25.9)	256 (9.0)
Diabetes mellitus, N (%)	446 (5.5)	393 (13.7)

Continuous variables are presented as mean (SD). Categorical variables reported as absolute and relative frequencies. BMI indicates body mass index; and FHS, Framingham Heart Study.

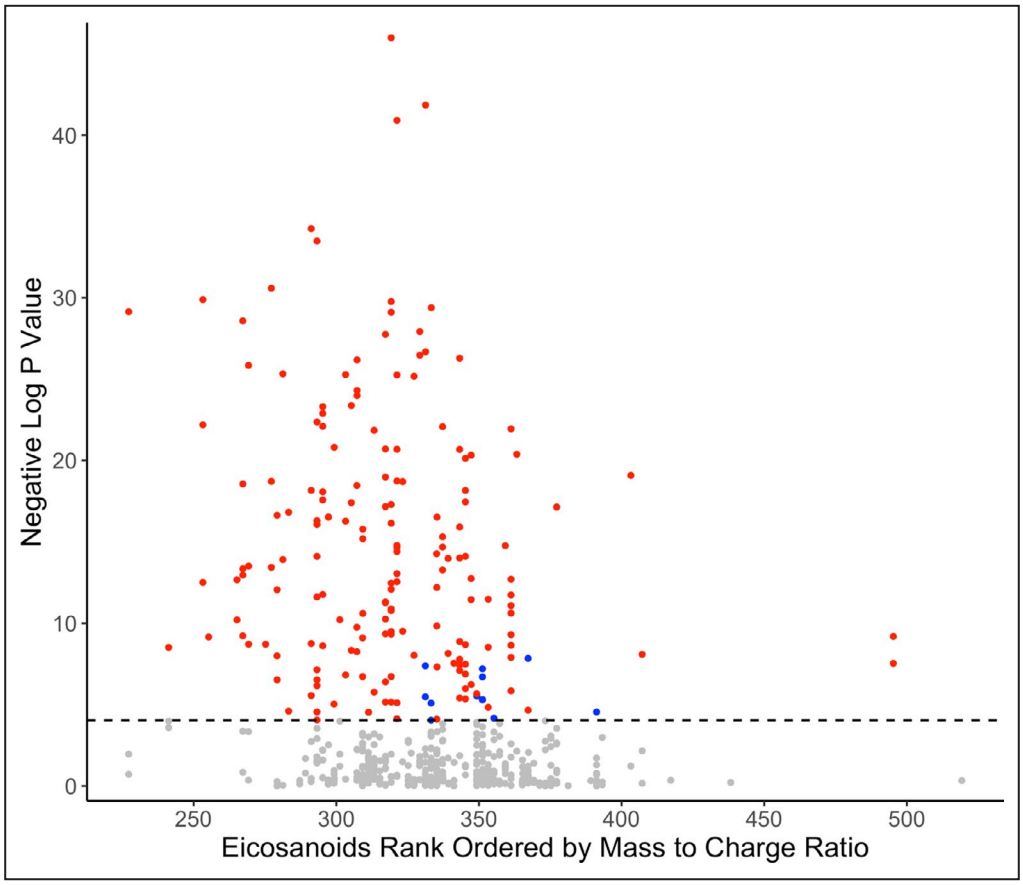

Figure 1. Manhattan plot for associations between metabolites and systolic blood pressure in FINRISK 2002.
A significant association was observed for 187 of the 545 eicosanoids. Positive correlations are denoted in red, negative in blue, and insignificant in gray. Eicosanoids are ordered by the value of mass/charge ratio. Dashed line represents the Bonferroni-corrected (P=0.05/545) level of significance. Analyses are adjusted for age, sex, body mass index, current smoking, diabetes mellitus, antihypertensive medication, and batch.

associated with systolic BP. In FINRISK, these 6 metabolites were 11-dehydro-2,3-dinor thromboxane B_2 (TXB_2), 12-hydroxyheptadecatrienoic acid (12-HHTrE), 265.1809/3.57 (putative eicosanoid), 295.2279/4.89 (putative eicosanoid), 319.2280/5.67 (unknown), and adrenic acid (Table S2). Of these 6 metabolites, 2 could not be detected in FHS plasma samples (11-dehydro-2,3-dinor-TXB_2 and 295.2279/4.89). Comparing single-metabolite associations, adjusted for relevant covariates, demonstrated that effect sizes between the metabolites were highly consistent across the 2 cohorts (Figure 3, Table S3).

Eicosanoid Risk Score

We defined an eicosanoid risk score using the effect sizes in FINRISK for the 6 previously mentioned metabolites (Table S2). The abundances of the 2 nondetected metabolites in FHS were treated as zero values. Individuals in the top risk quartile had 9.0 (95% CI, 8.0–10.1) mm Hg higher systolic BP in FINRISK and 6.8 (95% CI, 5.1–8.5) mm Hg higher systolic BP in FHS compared with individuals in the lowest quartile (Figures 4, 5 and Tables S4, S5, S6). The odds for hypertension were 2.3 (95% CI, 2.0–2.6) and 2.0 (95% CI, 1.6–2.5), respectively, for the top quartile compared with the lowest quartile (Figures 4 and 5). These associations were consistent across FINRISK and FHS. We observed no differences in these associations in subgroups by aspirin use, asthma status, age, BMI, kidney function, and NSAID use (Figure S2). The correlations of the eicosanoid risk score with age, BMI, and estimated glomerular filtration rate were 0.11 (P<0.001), 0.07 (P<0.001), and −0.02 (P=0.04), respectively. We observed no significant differences in the eicosanoid risk score levels in subgroups by aspirin use, asthma status, and NSAID use (P>0.5).

Two-Sample Mendelian Randomization

We observed 222 SNPs in 2 chromosomes significantly associated with the eicosanoid risk score (Figure S3, Table S7). To account for linkage-disequilibrium, in

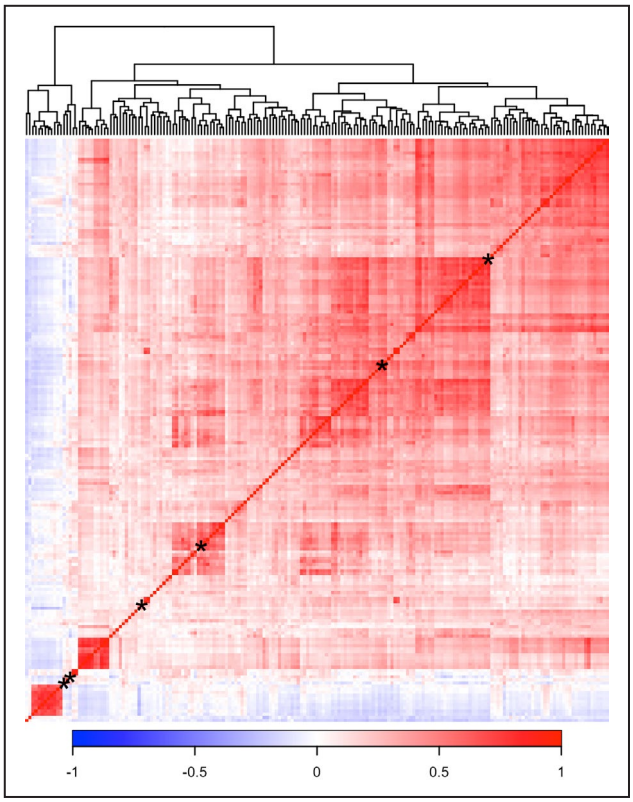

Figure 2. Correlation matrix for the 187 plasma metabolites related to systolic blood pressure in FINRISK 2002.
Relations between eicosanoids were calculated using Spearman correlation and ordered using hierarchical cluster analysis with complete linkage method. Only eicosanoids related to systolic blood pressure were included in the correlation matrix. Asterisk denotes position of the 6 metabolites in our eicosanoid risk score (Figure 3).

each 10-kb window (r^2<0.001) only the SNP with lowest *P* value was retained (Table S8). We used the (n=436 419) GWAS results for systolic BP in UK Biobank as the outcome variables.[27,28] The 2-sample mendelian randomization for the 3 SNPs and automated systolic BP measurement was nonsignificant (false discovery rate corrected *P*>0.26; Table S9).

DISCUSSION

Using a directed nontargeted LC-MS approach in well-phenotyped, large community-based cohorts, we identified 187 eicosanoids and related oxylipins that were associated with systolic BP. FINRISK 2002 participants in the top quartile of the eicosanoid risk score had 9.0 mm Hg greater systolic BP and a >2-fold odds of hypertension, compared with individuals in the lowest quartile. These findings were replicated in the FHS Offspring participants.

The upstream initiation of inflammatory activity in humans is governed mainly by substrates and products of polyunsaturated ω-3 and ω-6 20-carbon fatty acids.[7,33] The small-molecule derivatives of arachidonic acid and other polyunsaturated fatty acids, termed eicosanoids, serve as both activators and suppressors of systemic inflammatory activity.[34,35] Most research on systemic inflammation in humans has focused on downstream markers of inflammatory activity, such as cytokines and short-term phase reactants. Recent work by us and others has shown that long-term elevation in these downstream markers is associated with a variety of cardiovascular disease risk traits and outcomes.[36,37] In particular, several cross-sectional and prospective studies in humans have found an association of plasma concentrations of downstream low-grade inflammation markers, such as interleukin-6, intercellular adhesion molecule-1, CRP (C-reactive protein), and tumor necrosis factor-α, with arterial stiffness and hypertension.[38–44] Although downstream markers of inflammation are associated with hypertension and a variety of cardiovascular disease outcomes, evidence for a clinically important, causal role of these biomarkers has been mixed.[45] In addition, despite inflammation being pivotal in the development of atherosclerosis and certain medications with anti-inflammatory properties clearly reduce cardiovascular disease risk, the extent to which any given inflammatory pathway warrants attention as a direct putative target for therapy is unknown.[46] Such results have now led experts to suggest that, where inflammation is concerned, causal factors may be upstream.[45]

This study is the first to comprehensively examine the association between eicosanoids and BP in humans. Prior studies with study samples consisting of tens of hypertensive subjects with a panel of a few, mainly cytochrome P450 pathway eicosanoids have demonstrated that eicosanoids, in general, affect regulation of renal function, vascular tone, and the development of hypertension.[12,47–50] Our results from a large, population-based sample demonstrate that a large number of eicosanoid species are related to BP in both a positive and a negative way. In addition, we demonstrate that a distinct eicosanoid score is related to a >2-fold odds of hypertension. The subgroup analyses demonstrate that the association between our eicosanoid risk score and systolic BP was highly consistent, even in states that affect eicosanoid metabolism and excretion. Although the number of individuals in some subgroups was low, we observed no differences in the relation between the risk score and BP in subgroups by asthma status, age, aspirin use, BMI, and kidney function. Furthermore, the eicosanoid risk score demonstrated only weak correlations with these phenotypes, implying an independent role for eicosanoids in hypertension risk.

Eicosanoids are metabolized via 3 general pathways that involve cytochrome P450 monooxygenases, cyclooxygenases, and lipoxygenases. Several

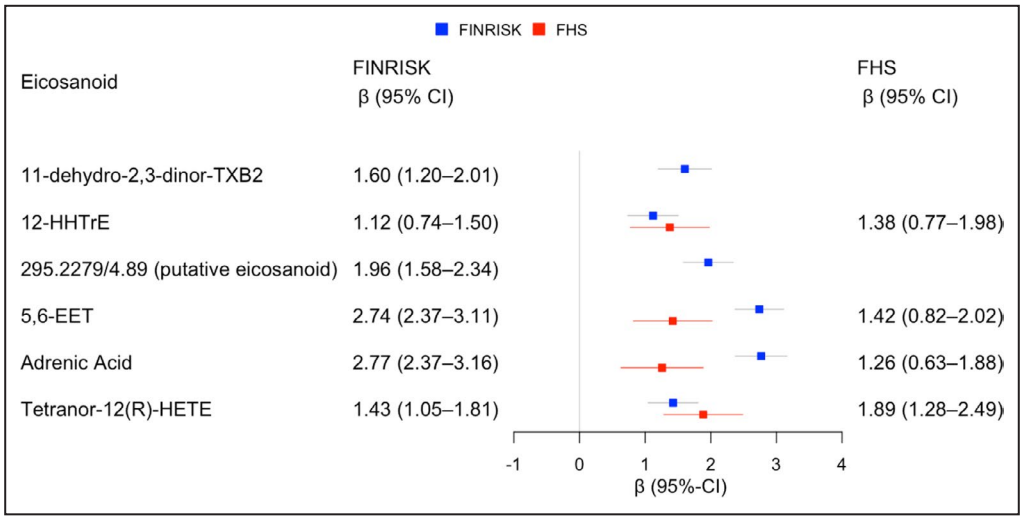

Figure 3. The associations between a subset of 6 metabolites and systolic blood pressure (BP) in FINRISK and replication of results in FHS (Framingham Heart Study).
The β coefficients are for the association between 1-SD increase in metabolite concentration and the absolute change of systolic BP (mm Hg) in the 2 study cohorts. All models were adjusted for age, sex, body mass index, current smoking, diabetes mellitus, antihypertensive medication, and batch. Of the 6 eicosanoids observed in FINRISK, 2 were not observed in FHS plasma samples. EET indicates epoxyeicosatrienoic acid; HETE, hexadecatrienoic acid; HHTrE, hydroxyheptadecatrenoic acid; and TXB_2, thromboxane B_2.

of the identified metabolites that remained in the 6-eicosanoid risk score are members of these pathways. In addition, the key metabolites included in the eicosanoid risk score include both intermediate (eg, adrenic acid and 12-HHTrE) and terminal (eg, 11-dehydro-2,3-dinor-TXB_2), potentially reflecting key eicosanoid pathways and species related to BP regulation. The cytochrome P450 pathway metabolizes arachidonic acid to several eicosanoids, including 20-hydroxyeicosatetraenoic acid and epoxyeicosatrienoic acids.[8] These metabolites are critical in BP regulation and provide cardioprotective and renoprotective effects in chronic kidney disease.[8] Cyclooxygenase pathway produced prostanoids are

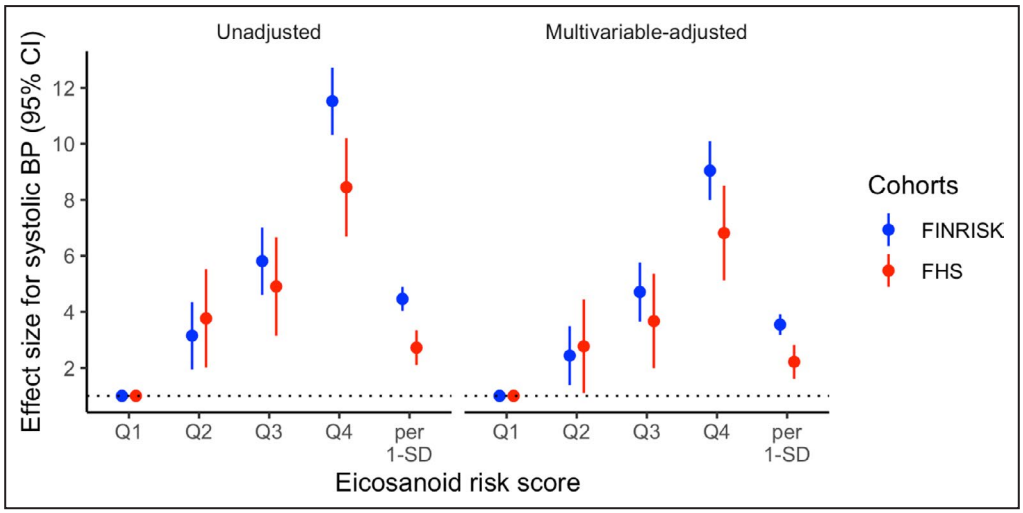

Figure 4. The association between the risk score and systolic blood pressure (BP) in FINRISK and FHS (Framingham Heart Study).
We calculated eicosanoid risk score for each participant according to the formula $\beta_1X_1+\beta_2X_2+...+\beta_nX_n$, with X_n denoting the standardized value for the nth eicosanoid abundance, and β_n denoting the regression coefficient from the regression model containing the indicated eicosanoids. Analyses are adjusted for age, sex, body mass index, current smoking, diabetes mellitus, antihypertensive medication, and batch. Q indicates quartile.

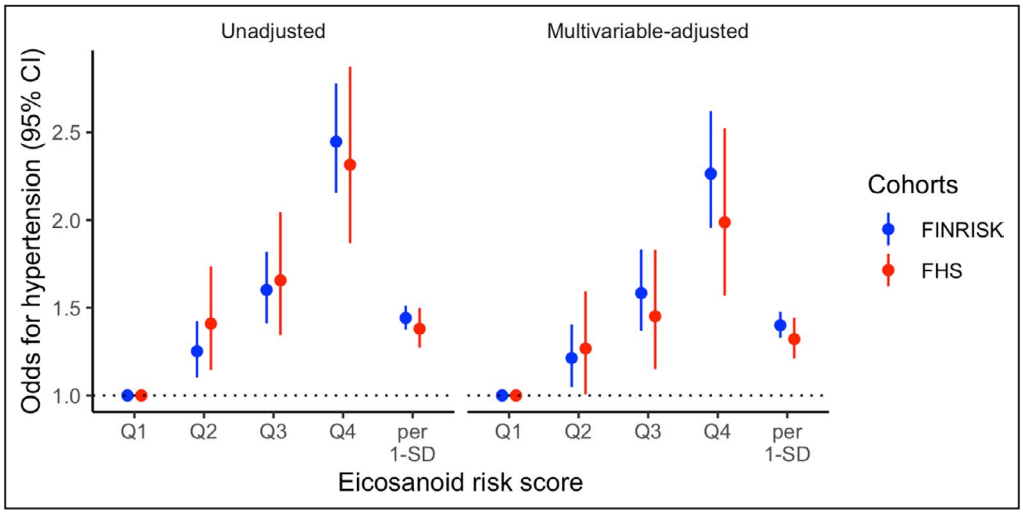

Figure 5. The association between the risk score and hypertension in FINRISK and FHS (Framingham Heart Study).
We calculated eicosanoid risk score for each participant according to the formula $\beta_1X_1+\beta_2X_2+...+\beta_nX_n$ with X_n denoting the standardized value for the nth eicosanoid abundance, and β_n denoting the regression coefficient from the regression model in FINRISK containing the indicated eicosanoids. Multivariable analyses are adjusted for age, sex, body mass index, current smoking, diabetes mellitus, antihypertensive medication, and batch. Q indicates quartile.

involved in BP homeostasis and, in particular, short-lived thromboxane A_2 (TXA_2; half-life, 30 seconds) has important role in various cardiovascular diseases through action on platelet aggregation, vasoconstriction, and proliferation.[51,52] TXA_2 is metabolized to inactive TXB_2, which is degraded through 2 major pathways (dehydrogenation and β-oxidation) and their combination, which results in the formation of 11-dehydro-2,3-dinor-TXB_2.[53,54] Currently, factors affecting the relative production of 11-dehydro-2,3-dinor-TXB_2 and analyte prognostic utility are not known.[52] However, 11-dehydro-2,3-dinor-TXB_2 may have a role in atherothrombosis.[54] Another metabolite included in our 6-eicosanoid risk score, 12-HHTrE, is a nonenzymatic degradation product of TXA_2 and prostaglandin H_2 (an important precursor for eicosanoids).[55] 12-HHTrE is a natural ligand for leukotriene B(4) receptor 2 and is linked to synthesis of prostacyclin (prostaglandin I_2), a potent vasodilator, and the main metabolite of 12-HHTrE has antagonist effect to TXA_2 receptor.[56,57] In addition to eicosanoid pathway products, adrenic acid was also included in our risk score. Adrenic acid is a polyunsaturated 22-carbon fatty acid and mainly a substrate for eicosanoid production, and it has been associated with the regulation of adrenal blood flow.[58] Given the findings from our study and from previous experimental trials, these results provide a strong biological basis for how eicosanoids could affect human BP regulation through several different mechanisms. In particular, elevated 11-dehydro-2,3-dinor-TXB_2 and 12-HHTrE levels may be result of elevated TXA_2 activity but their independent role and possible prognostic utility need to be evaluated in future research.

Our study has several strengths, such as unselected population sample, external replication of our results, and assays of a large number of eicosanoids. However, our results must be interpreted in the context of potential limitations. First, LC-MS is a highly sensitive method for assessing circulating metabolites. Particularly, of the 6 metabolites that remained in the final forward-selection regression model in FINRISK, only 4 were observed in FHS samples. This could in part be explained by the between-cohort age and smoking disparities. Second, the unambiguous metabolite classification and identification is still a challenge in high-throughput LC-MS. However, we have previously demonstrated that these signals are highly consistent with known and putative eicosanoids and related oxylipins in human plasma.[14] Third, many eicosanoids have short half-lives of <1 hour and the variance of the measured metabolites is expected to be highly affected by sample processing methods. However, our plasma samples were stored at –70 to 80°C on-site following a strict protocol, and we studied standardized, rather than absolute, metabolite concentrations. Finally, our study demonstrates a strong proof-of-concept association between eicosanoids and BP. Although much is known of eicosanoid physiology,[4–12] additional mechanistic and experimental studies are needed to assess the precise identities and functions of many of the observed metabolites. The eicosanoids included in the risk score are known to be produced in neuronal

tissues, platelets, leukocytes, and smooth muscle cells,[59] which could be used as starting points for in vitro experiments.

CONCLUSIONS

Plasma eicosanoids demonstrate strong associations with BP in the general population, and differences between eicosanoid profiles are observed between normotensive versus hypertensive participants. Intriguingly, although most of the associations were positive (harmful species), we observed protective molecules as well. In our mendelian randomization analysis, however, we were unable to demonstrate a causal association between eicosanoids and BP. However, this analysis could be limited by the small GWAS sample size. Additional preclinical analyses are therefore needed to examine the causality between eicosanoids and BP and to clarify whether eicosanoids could serve as potential targets for therapeutic intervention.

ARTICLE INFORMATION

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Supplementary Materials

Tables S1–S9
Figures S1–S3

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SUPPLEMENTAL MATERIAL

Table S1. Association of eicosanoids with mean arterial pressure, systolic blood pressure, diastolic blood pressure, pulse pressure and hypertension in FINRISK 2002.

		Systolic BP		Diastolic BP		MAP		Pulse pressure		Hypertension	
M/Z	RT	β±SE	p	β±SE	p	β±SE	p	β±SE	p	β±SE	p
227.2011	6.3517	2.27±0.20	7e-30	0.86±0.12	8e-13	1.33±0.13	2e-25	1.41±0.17	3e-16	1.27±0.03	2e-15
241.2185	6.4318	1.17±0.20	3e-09			0.64±0.13	4e-07	0.80±0.17	3e-06	1.14±0.03	9e-06
253.2166	6.4540	2.03±0.21	6e-23	0.94±0.12	3e-14	1.30±0.13	4e-23	1.09±0.18	7e-10	1.22±0.03	1e-10
253.2170	6.5120	1.48±0.20	3e-13	0.66±0.12	5e-08	0.93±0.13	5e-13	0.82±0.17	3e-06	1.18±0.03	3e-08
253.2175	6.5583	2.33±0.20	1e-30	0.96±0.12	2e-15	1.42±0.13	5e-28	1.37±0.17	5e-15	1.28±0.03	1e-15
255.2329	6.6107	1.23±0.20	7e-10			0.67±0.13	2e-07	0.84±0.17	9e-07	1.17±0.03	6e-08
265.1808	3.6322	1.27±0.19	6e-11	0.54±0.12	3e-06	0.78±0.12	3e-10	0.73±0.17	1e-05	1.14±0.03	1e-05
265.1810	3.5705	1.43±0.19	2e-13	0.64±0.12	3e-08	0.90±0.12	3e-13	0.78±0.17	3e-06	1.14±0.03	4e-06
267.1968	3.4410	1.24±0.20	6e-10			0.50±0.13	9e-05	1.10±0.17	1e-10		
267.1968	3.4780	2.18±0.19	3e-29	0.70±0.12	2e-09	1.19±0.12	7e-22	1.49±0.17	6e-19	1.29±0.03	4e-17
267.1968	3.5767							0.85±0.17	5e-07		
267.2326	6.6168	1.84±0.20	3e-19	0.67±0.12	4e-08	1.06±0.13	5e-16	1.17±0.18	4e-11	1.23±0.03	1e-11
267.2331	6.5490	1.50±0.20	4e-14	0.63±0.12	1e-07	0.92±0.13	4e-13	0.87±0.17	4e-07	1.16±0.03	4e-07
267.2332	6.4997	1.53±0.21	1e-13	0.75±0.12	1e-09	1.01±0.13	2e-14	0.78±0.18	1e-05	1.19±0.03	2e-08
269.2125	4.7668	2.10±0.20	1e-26	0.85±0.12	8e-13	1.26±0.13	9e-24	1.26±0.17	1e-13	1.26±0.03	2e-15
269.2485	6.6847	1.19±0.20	2e-09			0.61±0.13	1e-06	0.87±0.17	4e-07	1.15±0.03	4e-06
269.2524	6.5937	1.57±0.21	3e-14	0.53±0.12	2e-05	0.87±0.13	3e-11	1.04±0.18	5e-09	1.19±0.03	1e-08
275.2018	5.8892	1.16±0.19	2e-09			0.65±0.12	2e-07	0.77±0.17	4e-06	1.15±0.03	2e-05
277.2173	6.3486	1.79±0.20	2e-19	0.76±0.12	2e-10	1.10±0.13	4e-18	1.03±0.17	1e-09	1.21±0.03	6e-11
277.2176	6.2962	1.49±0.20	4e-14	0.53±0.12	7e-06	0.85±0.13	1e-11	0.96±0.17	1e-08	1.18±0.03	2e-08
277.2179	6.4056	2.39±0.20	3e-31	0.96±0.12	6e-15	1.44±0.13	6e-28	1.43±0.18	6e-16	1.25±0.03	2e-13
279.1966	3.7247	1.12±0.20	1e-08	0.52±0.12	8e-06	0.72±0.12	7e-09			1.13±0.03	2e-05
279.2329	6.5058	1.45±0.20	9e-13	0.57±0.12	2e-06	0.87±0.13	2e-11	0.88±0.17	5e-07	1.15±0.03	5e-06
279.2330	6.4750	1.02±0.20	3e-07			0.59±0.13	3e-06				
279.2330	6.5552	1.70±0.20	2e-17	0.60±0.12	5e-07	0.97±0.13	4e-14	1.10±0.17	2e-10	1.16±0.03	7e-07
281.2487	6.6847	2.11±0.20	5e-26	0.92±0.12	2e-14	1.32±0.13	7e-25	1.20±0.17	4e-12	1.29±0.03	4e-17
281.2488	6.5613	1.51±0.20	1e-14	0.62±0.12	1e-07	0.92±0.12	2e-13	0.89±0.17	1e-07	1.20±0.03	3e-10
283.2643	6.6168	0.82±0.19	3e-05			0.54±0.12	1e-05				
283.2643	6.7124	2.02±0.24	1e-17	0.73±0.14	3e-07	1.16±0.15	2e-14	1.29±0.20	2e-10	1.22±0.03	2e-08
291.1963	4.2427	0.94±0.20	3e-06			0.57±0.13	9e-06				
291.1967	3.9898	1.17±0.19	2e-09					1.03±0.17	8e-10		
291.1968	4.7360	2.35±0.19	6e-35	0.98±0.11	8e-18	1.44±0.12	3e-32	1.37±0.16	8e-17	1.27±0.03	2e-16
291.1969	4.6805	1.70±0.19	7e-19	0.62±0.11	7e-08	0.98±0.12	1e-15	1.08±0.16	5e-11	1.15±0.03	7e-07
293.2087	5.1060	1.49±0.19	8e-15	0.68±0.11	3e-09	0.95±0.12	7e-15	0.81±0.17	1e-06	1.17±0.03	3e-08
293.2098	4.0577	0.81±0.19	3e-05					0.71±0.17	2e-05		
293.2109	4.3136							0.80±0.17	1e-06		
293.2111	4.6898	1.60±0.19	9e-17	0.48±0.11	2e-05	0.86±0.12	3e-12	1.11±0.16	2e-11	1.16±0.03	1e-07
293.2123	3.8603							0.70±0.17	2e-05		
293.2123	3.9837	0.96±0.19	7e-07					0.79±0.17	2e-06	1.13±0.03	2e-05
293.2123	4.8100	1.62±0.19	5e-17			0.82±0.12	3e-11	1.20±0.17	5e-13	1.16±0.03	2e-07
293.2124	3.9343	1.39±0.20	2e-12			0.74±0.13	6e-09	0.98±0.17	9e-09	1.16±0.03	7e-07
293.2124	4.1687							0.66±0.17	6e-05		
293.2124	4.4030							0.78±0.17	2e-06		
293.2124	4.4585	0.75±0.19	9e-05					0.72±0.16	1e-05		

		Systolic BP		Diastolic BP		MAP		Pulse pressure		Hypertension	
M/Z	RT	β±SE	p	β±SE	p	β±SE	p	β±SE	p	β±SE	p
293.2124	4.5017	1.06±0.20	7e-08			0.50±0.13	6e-05	0.83±0.17	9e-07		
293.2125	4.3537	1.00±0.19	3e-07					1.03±0.17	8e-10	1.12±0.03	4e-05
293.2125	4.7607	1.91±0.19	4e-23	0.54±0.12	3e-06	1.00±0.12	7e-16	1.38±0.17	1e-16	1.20±0.03	2e-10
293.2125	5.0382	2.35±0.19	3e-34	1.03±0.12	6e-19	1.47±0.12	8e-33	1.32±0.17	2e-15	1.29±0.03	1e-18
295.2279	4.8902	1.96±0.19	5e-24			0.95±0.12	1e-14	1.51±0.17	1e-19	1.25±0.03	5e-15
295.2279	5.6055	1.68±0.19	3e-18	0.48±0.12	3e-05	0.88±0.12	9e-13	1.20±0.17	4e-13	1.19±0.03	4e-10
295.2280	3.9312	1.70±0.19	8e-19			0.78±0.12	2e-10	1.39±0.17	6e-17	1.21±0.03	2e-11
295.2280	4.4400							0.68±0.17	5e-05		
295.2280	4.5017	1.91±0.19	8e-23	0.57±0.12	1e-06	1.01±0.12	3e-16	1.34±0.17	9e-16	1.26±0.03	2e-15
295.2280	5.0690	1.36±0.19	2e-12					1.32±0.16	1e-15	1.16±0.03	5e-08
295.2281	4.6188	1.16±0.19	2e-09					1.07±0.17	2e-10		
295.2281	4.6682	1.94±0.19	1e-23	0.72±0.12	6e-10	1.12±0.12	9e-20	1.22±0.17	2e-13	1.22±0.03	7e-13
297.2437	4.6404	1.61±0.19	3e-17	0.70±0.11	1e-09	1.00±0.12	2e-16	0.92±0.16	3e-08	1.18±0.03	3e-09
297.2437	4.7237	1.76±0.21	3e-17	0.74±0.12	3e-09	1.08±0.13	4e-16	1.02±0.18	1e-08	1.20±0.03	1e-08
299.1869	2.6578	0.86±0.19	9e-06			0.55±0.12	8e-06				
299.2595	5.3974	1.83±0.19	2e-21	0.78±0.11	1e-11	1.13±0.12	3e-20	1.05±0.16	2e-10	1.22±0.03	3e-12
301.2177	6.2530	1.32±0.20	6e-11	0.57±0.12	3e-06	0.82±0.13	2e-10	0.76±0.17	1e-05	1.16±0.03	7e-07
303.2303	6.3933	1.67±0.20	5e-17	0.79±0.12	4e-11	1.08±0.13	2e-17	0.88±0.17	3e-07	1.22±0.03	7e-10
303.2329	6.4442	2.07±0.20	5e-26	0.77±0.12	5e-11	1.20±0.12	7e-22	1.30±0.17	2e-14	1.25±0.03	3e-14
303.2332	6.5367	1.05±0.20	2e-07			0.57±0.13	6e-06	0.71±0.17	3e-05	1.13±0.03	1e-05
305.2437	6.4627	1.18±0.20	5e-09			0.62±0.13	1e-06	0.84±0.17	1e-06	1.13±0.03	3e-05
305.2495	6.6137	1.74±0.20	4e-18	0.70±0.12	7e-09	1.04±0.13	3e-16	1.05±0.17	1e-09	1.21±0.03	2e-10
305.2518	6.4997	2.05±0.20	4e-24	0.76±0.12	4e-10	1.19±0.13	4e-20	1.29±0.17	1e-13	1.26±0.03	2e-14
307.1890	2.6208			0.52±0.12	1e-05	0.53±0.13	3e-05				
307.1899	2.3279	1.24±0.21	6e-09			0.59±0.14	1e-05	0.97±0.18	1e-07	1.15±0.03	8e-06
307.1905	2.4852	1.23±0.19	2e-10	0.51±0.12	1e-05	0.75±0.12	1e-09	0.73±0.17	1e-05		
307.1912	2.5222	1.74±0.19	3e-19	0.82±0.12	2e-12	1.12±0.12	1e-19	0.93±0.17	3e-08	1.18±0.03	5e-09
307.2644	6.5675	2.17±0.20	7e-27	0.74±0.12	1e-09	1.22±0.13	4e-21	1.43±0.17	2e-16	1.27±0.03	2e-15
307.2645	6.6168	2.01±0.20	1e-24	0.78±0.12	3e-11	1.19±0.12	2e-21	1.23±0.17	3e-13	1.25±0.03	3e-14
307.2645	6.6785	2.04±0.20	5e-25	0.76±0.12	1e-10	1.19±0.13	5e-21	1.28±0.17	5e-14	1.26±0.03	3e-15
309.2071	3.1327			-0.55±0.12	2e-06						
309.2074	4.2797					-0.52±0.12	3e-05				
309.2078	3.3238	1.19±0.19	8e-10			0.67±0.12	6e-08	0.78±0.17	3e-06	1.13±0.03	8e-06
309.2094	3.1851			-0.51±0.12	1e-05						
309.2103	2.8120	1.00±0.19	2e-07					0.80±0.16	1e-06		
309.2798	6.6353	1.66±0.20	2e-16	0.63±0.12	2e-07	0.97±0.13	4e-14	1.03±0.17	3e-09	1.20±0.03	2e-09
309.2800	6.6662	1.30±0.20	2e-11	0.51±0.12	1e-05	0.78±0.12	4e-10	0.79±0.17	3e-06	1.17±0.03	4e-08
309.2800	6.6970	1.59±0.20	6e-16	0.67±0.12	1e-08	0.98±0.13	7e-15	0.92±0.17	6e-08	1.22±0.03	1e-11
311.2231	2.9230			-0.60±0.11	2e-07			0.68±0.17	4e-05		
311.2231	2.9600			-0.47±0.11	3e-05						
311.2957	6.6908	0.82±0.19	3e-05								
311.2957	6.7217									1.14±0.03	5e-06
313.2386	3.5643	0.92±0.19	2e-06					0.75±0.16	6e-06		
313.2387	3.2313	1.88±0.19	1e-22	0.48±0.11	3e-05	0.94±0.12	1e-14	1.40±0.16	3e-17	1.24±0.03	2e-10
313.2388	3.3300							0.80±0.17	2e-06		
317.2109	4.3413	0.88±0.20	7e-06	0.49±0.12	3e-05	0.62±0.13	7e-07				
317.2122	3.6753	1.77±0.19	1e-19	0.61±0.12	2e-07	0.99±0.12	1e-15	1.16±0.17	5e-12	1.19±0.03	2e-09
317.2122	4.0145	1.32±0.19	5e-12			0.71±0.12	9e-09	0.93±0.17	2e-08	1.18±0.03	3e-07
317.2123	4.9148	1.39±0.20	5e-12	0.58±0.12	1e-06	0.85±0.13	3e-11	0.81±0.17	3e-06	1.16±0.03	4e-07

		Systolic BP		Diastolic BP		MAP		Pulse pressure		Hypertension	
M/Z	RT	β±SE	p	β±SE	p	β±SE	p	β±SE	p	β±SE	p
317.2124	4.1378	1.20±0.19	4e-10			0.68±0.12	3e-08	0.78±0.17	2e-06	1.15±0.03	7e-07
317.2124	5.3342	1.89±0.20	2e-21	0.83±0.12	3e-12	1.19±0.13	1e-20	1.06±0.17	6e-10	1.22±0.03	3e-11
317.2125	3.7185	1.68±0.19	7e-18	0.61±0.12	2e-07	0.96±0.12	8e-15	1.07±0.17	2e-10	1.18±0.03	4e-09
317.2125	5.2663	2.21±0.20	2e-28	1.07±0.12	3e-19	1.45±0.13	4e-30	1.14±0.17	4e-11	1.30±0.03	4e-18
317.2126	4.9580	1.01±0.20	4e-07	0.50±0.12	2e-05	0.67±0.13	1e-07				
317.2157	5.3897	1.28±0.20	6e-11	0.50±0.12	2e-05	0.76±0.12	1e-09	0.78±0.17	3e-06	1.18±0.03	6e-08
319.2224	4.0577	1.60±0.19	7e-17	0.50±0.11	1e-05	0.87±0.12	1e-12	1.10±0.16	3e-11	1.18±0.03	1e-09
319.2271	4.5818	1.21±0.19	5e-10			0.70±0.12	2e-08	0.77±0.17	5e-06	1.14±0.03	4e-06
319.2276	4.5017	1.20±0.19	3e-10	0.66±0.11	9e-09	0.84±0.12	6e-12				
319.2279	5.7288	2.20±0.19	2e-30	0.98±0.11	1e-17	1.39±0.12	7e-30	1.22±0.16	2e-13	1.29±0.03	2e-19
319.2280	5.6733	2.74±0.19	1e-46	1.19±0.11	3e-25	1.71±0.12	1e-44	1.55±0.16	5e-21	1.35±0.03	7e-25
319.2281	4.1070	1.70±0.20	5e-18	0.64±0.12	6e-08	0.99±0.13	3e-15	1.06±0.17	3e-10	1.20±0.03	2e-10
319.2281	4.6558	2.23±0.20	8e-30	1.05±0.12	4e-19	1.45±0.12	1e-30	1.18±0.17	4e-12	1.28±0.03	4e-17
319.2281	4.7730	1.37±0.19	8e-13	0.49±0.11	2e-05	0.78±0.12	2e-10	0.88±0.16	8e-08	1.16±0.03	5e-08
319.2281	4.8285	1.29±0.19	2e-11			0.73±0.12	3e-09	0.84±0.16	3e-07	1.14±0.03	2e-06
319.2281	5.0382	1.00±0.19	2e-07	0.49±0.11	2e-05	0.66±0.12	7e-08				
319.2281	5.2910	0.89±0.20	7e-06	0.61±0.12	2e-07	0.70±0.13	2e-08				
319.2288	5.1523	1.41±0.19	3e-13			0.74±0.12	3e-09	1.01±0.17	1e-09	1.19±0.03	2e-10
319.2304	4.8840	1.30±0.19	1e-11	0.61±0.11	1e-07	0.84±0.12	7e-12	0.69±0.16	3e-05	1.16±0.04	2e-05
321.2370	5.6795	1.81±0.25	3e-13	0.63±0.15	2e-05	1.03±0.16	9e-11	1.18±0.21	3e-08	1.23±0.04	4e-08
321.2383	5.1923	0.76±0.19	7e-05								
321.2416	5.7998	1.54±0.19	2e-15	0.96±0.12	7e-17	1.16±0.12	7e-21			1.24±0.03	7e-14
321.2433	4.8593	1.44±0.19	9e-14	0.75±0.12	8e-11	0.98±0.12	2e-15	0.69±0.17	3e-05	1.15±0.03	1e-06
321.2437	4.9025	1.54±0.19	2e-15	0.74±0.12	1e-10	1.01±0.12	4e-16	0.80±0.17	2e-06	1.21±0.03	8e-10
321.2437	4.9827	1.51±0.19	4e-15	0.70±0.11	1e-09	0.97±0.12	3e-15	0.82±0.17	8e-07	1.19±0.04	9e-07
321.2437	5.0813	1.82±0.19	2e-21	0.69±0.11	2e-09	1.07±0.12	3e-18	1.13±0.16	6e-12	1.23±0.03	3e-13
321.2437	6.0526	2.02±0.19	6e-26	0.98±0.11	2e-17	1.32±0.12	2e-27	1.04±0.16	3e-10	1.27±0.03	1e-16
321.2438	5.9508	1.73±0.19	2e-19	0.64±0.11	3e-08	1.00±0.12	3e-16	1.09±0.16	4e-11	1.20±0.03	2e-10
321.2440	4.4153	0.88±0.20	8e-06			0.57±0.13	6e-06				
321.2440	5.3958	2.60±0.19	1e-41	1.21±0.11	1e-25	1.67±0.12	3e-42	1.39±0.17	5e-17	1.31±0.03	8e-22
323.2581	5.4945	1.23±0.19	3e-10			0.56±0.12	8e-06	1.01±0.17	2e-09	1.16±0.03	5e-07
323.2599	5.6733	1.76±0.19	2e-19	0.51±0.12	1e-05	0.93±0.12	9e-14	1.24±0.17	1e-13	1.23±0.03	3e-12
325.2386	5.0258					-0.50±0.12	6e-05				
327.2321	6.4287	2.18±0.21	7e-26	0.97±0.12	5e-15	1.37±0.13	2e-25	1.21±0.18	1e-11	1.27±0.03	3e-14
327.2324	6.4966	1.15±0.20	9e-09			0.66±0.13	3e-07	0.73±0.17	2e-05	1.13±0.03	3e-05
329.2336	2.4235			-0.62±0.11	7e-08	-0.55±0.12	7e-06				
329.2341	2.5653			-0.59±0.12	3e-07	-0.54±0.12	1e-05				
329.2487	6.5058	2.21±0.20	1e-28	0.77±0.12	9e-11	1.25±0.13	7e-23	1.44±0.17	5e-17	1.23±0.03	4e-12
329.2496	6.4596	2.22±0.20	3e-27	0.85±0.12	6e-12	1.31±0.13	3e-23	1.38±0.18	9e-15	1.25±0.03	1e-12
331.1909	2.9766	-1.07±0.19	4e-08			-0.56±0.12	7e-06	-0.76±0.17	5e-06	0.87±0.03	3e-05
331.1918	2.6763	-0.91±0.20	3e-06			-0.60±0.12	2e-06			0.88±0.03	3e-05
331.2653	6.5737	2.14±0.20	2e-27	0.72±0.12	9e-10	1.20±0.13	2e-21	1.42±0.17	8e-17	1.28±0.03	4e-16
331.2679	6.5274	2.77±0.20	1e-42	1.04±0.12	1e-17	1.62±0.13	7e-36	1.73±0.17	4e-23	1.34±0.03	1e-21
333.2047	4.6312	-1.04±0.23	8e-06	-0.75±0.14	7e-08	-0.85±0.15	1e-08			0.86±0.04	8e-05
333.2051	4.3537			-0.48±0.12	4e-05						
333.2075	2.8613									0.84±0.04	8e-05
333.2075	3.2807	-0.76±0.20	9e-05			-0.49±0.12	9e-05				
333.2791	6.6269	2.26±0.20	4e-30	0.95±0.12	2e-15	1.38±0.13	8e-28	1.32±0.17	1e-14	1.30±0.03	1e-17
335.1456	3.8048	1.53±0.20	5e-15			0.70±0.13	3e-08	1.26±0.17	9e-14	1.16±0.03	4e-07

		Systolic BP		Diastolic BP		MAP		Pulse pressure		Hypertension	
M/Z	RT	β±SE	p	β±SE	p	β±SE	p	β±SE	p	β±SE	p
335.2229	3.0710	0.76±0.19	8e-05	0.58±0.12	5e-07	0.64±0.12	2e-07				
335.2231	3.3423	1.23±0.19	1e-10	0.53±0.11	5e-06	0.76±0.12	5e-10	0.71±0.17	2e-05	1.18±0.03	1e-08
335.2231	3.5643	1.40±0.19	6e-13	0.65±0.12	2e-08	0.90±0.12	4e-13	0.74±0.17	8e-06	1.21±0.03	2e-11
335.2911	6.6137	1.66±0.20	3e-17	0.71±0.12	1e-09	1.03±0.12	2e-16	0.94±0.17	2e-08	1.23±0.03	6e-10
335.2961	6.6847	1.05±0.19	5e-08	0.51±0.12	1e-05	0.69±0.12	2e-08			1.19±0.04	5e-06
337.2341	3.0093					0.49±0.12	5e-05				
337.2353	3.9158	1.52±0.19	2e-15	0.47±0.11	5e-05	0.82±0.12	2e-11	1.05±0.16	2e-10	1.17±0.03	2e-08
337.2371	3.0340					0.52±0.12	3e-05				
337.2381	3.5458	1.95±0.20	8e-23	0.47±0.12	8e-05	0.96±0.13	3e-14	1.48±0.17	4e-18	1.25±0.03	2e-13
337.2383	3.6260	1.60±0.20	5e-16	0.47±0.12	8e-05	0.84±0.13	2e-11	1.13±0.17	2e-11	1.21±0.03	9e-11
337.2383	4.1872	1.44±0.19	5e-14	0.53±0.11	4e-06	0.84±0.12	9e-12	0.91±0.16	3e-08	1.18±0.03	7e-09
339.1792	1.7883	1.16±0.20	7e-09					1.10±0.17	2e-10		
339.1799	1.7205	1.60±0.21	1e-14			0.61±0.13	4e-06	1.49±0.18	6e-17	1.16±0.03	2e-06
341.2126	5.2848	1.13±0.20	3e-08			0.51±0.13	8e-05	0.93±0.17	1e-07		
343.2248	4.4400	1.07±0.20	8e-08			0.60±0.13	2e-06	0.70±0.17	5e-05	1.15±0.03	3e-06
343.2256	4.6065	1.09±0.20	3e-08	0.53±0.12	7e-06	0.72±0.13	1e-08				
343.2273	5.3095	1.85±0.19	2e-21			0.90±0.12	5e-13	1.43±0.17	2e-17	1.24±0.03	7e-13
343.2275	4.5263	1.08±0.20	4e-08			0.61±0.12	9e-07	0.70±0.17	4e-05	1.13±0.03	1e-05
343.2278	5.1985	1.11±0.20	2e-08			0.64±0.13	3e-07	0.70±0.17	4e-05	1.15±0.03	6e-06
343.2279	4.7545	1.62±0.19	1e-16	0.56±0.12	2e-06	0.91±0.12	2e-13	1.06±0.17	3e-10	1.22±0.03	7e-12
343.2279	4.9950	2.09±0.19	5e-27	0.58±0.12	8e-07	1.08±0.12	3e-18	1.51±0.17	1e-19	1.27±0.03	4e-15
343.2281	4.6712	1.17±0.19	1e-09			0.66±0.12	8e-08	0.76±0.17	4e-06	1.16±0.03	5e-07
343.2281	5.0752	0.91±0.20	4e-06					0.84±0.17	7e-07		
343.2283	4.3012	1.53±0.20	1e-14	0.61±0.12	3e-07	0.92±0.13	4e-13	0.92±0.17	6e-08	1.18±0.03	9e-09
345.2346	4.6497	1.04±0.20	1e-07			0.61±0.13	1e-06			1.14±0.03	2e-05
345.2355	4.7607	0.90±0.20	4e-06			0.54±0.12	2e-05			1.15±0.03	2e-06
345.2431	4.7113	1.26±0.21	2e-09	0.56±0.13	9e-06	0.79±0.13	3e-09			1.17±0.03	6e-07
345.2435	4.5510	1.85±0.20	7e-21	0.74±0.12	5e-10	1.11±0.13	2e-18	1.12±0.17	6e-11	1.21±0.03	5e-11
345.2435	5.4698	1.68±0.19	4e-18	0.76±0.12	5e-11	1.07±0.12	6e-18	0.92±0.17	3e-08	1.21±0.04	8e-08
345.2437	4.8408	1.08±0.19	3e-08	0.55±0.12	3e-06	0.72±0.12	6e-09			1.12±0.03	6e-05
345.2437	4.9518	1.49±0.19	8e-15	0.59±0.11	3e-07	0.89±0.12	4e-13	0.91±0.17	4e-08	1.19±0.03	7e-10
345.2437	5.3033	1.70±0.19	7e-19	0.56±0.11	1e-06	0.94±0.12	2e-14	1.14±0.16	5e-12	1.21±0.03	1e-10
345.2441	5.0505	0.96±0.20	1e-06					0.74±0.17	1e-05		
347.2590	5.3835	1.54±0.21	2e-13	0.63±0.12	4e-07	0.93±0.13	2e-12	0.90±0.18	5e-07	1.20±0.03	4e-09
347.2592	5.7103	1.37±0.20	3e-12	0.58±0.12	9e-07	0.84±0.13	2e-11	0.79±0.17	3e-06	1.15±0.03	2e-06
347.2597	5.2972	0.99±0.20	6e-07			0.59±0.13	4e-06			1.13±0.03	2e-05
347.2598	5.6209	1.81±0.19	5e-21	0.73±0.11	2e-10	1.09±0.12	5e-19	1.08±0.17	8e-11	1.25±0.03	1e-13
349.2006	3.5705							0.78±0.17	2e-06		
349.2022	2.3032					0.52±0.13	4e-05				
349.2023	1.5047									0.88±0.03	3e-05
349.2023	1.5602	-0.91±0.19	3e-06			-0.49±0.12	7e-05			0.87±0.03	1e-05
349.2024	3.4472	0.93±0.20	2e-06					0.90±0.17	8e-08		
351.2173	2.3865			0.55±0.12	3e-06	0.56±0.12	8e-06				
351.2180	1.3937	-1.07±0.20	6e-08			-0.58±0.13	5e-06	-0.74±0.17	1e-05	0.85±0.03	1e-07
351.2184	2.8182					0.50±0.12	5e-05				
351.2185	1.2518	-0.89±0.20	5e-06			-0.53±0.12	2e-05			0.85±0.04	9e-06
351.2189	0.9743	-0.89±0.20	5e-06								
351.2192	1.9733	-1.02±0.20	2e-07			-0.49±0.12	9e-05	-0.79±0.17	2e-06	0.86±0.03	2e-07
353.2313	2.6671	0.83±0.19	1e-05	0.49±0.11	2e-05	0.60±0.12	8e-07				

		Systolic BP		Diastolic BP		MAP		Pulse pressure		Hypertension	
M/Z	RT	β±SE	p	β±SE	p	β±SE	p	β±SE	p	β±SE	p
353.2336	2.3927	1.36±0.20	3e-12	0.76±0.12	8e-11	0.96±0.12	1e-14			1.19±0.03	4e-09
353.2337	1.9487	1.21±0.20	3e-09	0.77±0.12	4e-10	0.91±0.13	2e-12			1.16±0.03	5e-07
355.2431	2.0658	-0.76±0.19	7e-05								
359.2230	3.2128	1.53±0.19	2e-15	0.60±0.11	2e-07	0.91±0.12	1e-13	0.93±0.17	2e-08	1.20±0.03	4e-10
361.2368	3.1142	1.39±0.20	2e-12	0.59±0.12	7e-07	0.86±0.13	1e-11	0.80±0.17	2e-06	1.15±0.03	3e-06
361.2381	3.6445	1.17±0.20	2e-09			0.55±0.13	1e-05	0.93±0.17	3e-08	1.14±0.03	5e-06
361.2383	3.4040	1.34±0.20	2e-11	0.48±0.12	7e-05	0.76±0.13	2e-09	0.87±0.17	6e-07	1.14±0.03	9e-06
361.2392	3.3454	1.32±0.19	8e-12	0.58±0.12	6e-07	0.82±0.12	2e-11	0.75±0.17	7e-06	1.15±0.03	5e-07
361.2394	3.4718	0.95±0.20	1e-06			0.52±0.13	3e-05				
361.2394	3.8141	1.90±0.19	1e-22	0.66±0.12	1e-08	1.07±0.12	5e-18	1.24±0.17	1e-13	1.25±0.03	3e-13
361.2395	3.4996	1.24±0.20	5e-10			0.52±0.13	4e-05	1.08±0.17	3e-10	1.13±0.03	2e-05
361.2398	3.7062	1.43±0.19	2e-13			0.71±0.12	1e-08	1.08±0.17	1e-10	1.16±0.03	3e-07
361.2405	4.0762	1.10±0.19	1e-08			0.55±0.12	1e-05	0.83±0.17	6e-07	1.13±0.03	2e-05
363.2545	3.8048	1.95±0.21	4e-21	0.61±0.12	7e-07	1.06±0.13	1e-15	1.34±0.18	6e-14	1.23±0.03	6e-12
367.2094	1.6897	0.82±0.19	2e-05								
367.2137	0.9003	-1.16±0.20	1e-08			-0.60±0.13	4e-06	-0.83±0.18	2e-06	0.84±0.04	4e-07
375.2184	3.7709			-0.56±0.11	9e-07						
377.2314	4.5140	1.67±0.19	7e-18	0.49±0.12	3e-05	0.88±0.12	1e-12	1.18±0.17	1e-12	1.23±0.03	3e-13
391.2130	1.7082	-0.81±0.19	3e-05							0.87±0.03	5e-06
403.2499	5.0782	1.91±0.21	8e-20			0.96±0.13	8e-13	1.43±0.18	3e-15	1.23±0.03	4e-11
407.2038	3.4472	1.19±0.21	8e-09			0.64±0.13	1e-06	0.83±0.18	3e-06		
495.2604	3.0248	1.08±0.20	3e-08					0.95±0.17	2e-08	1.13±0.03	2e-05
495.2606	3.0587	1.20±0.19	6e-10			0.63±0.12	4e-07	0.86±0.17	3e-07	1.15±0.03	9e-07

The relation between each eicosanoid and blood pressure variables was analyzed in separate linear regression models with age, sex, BMI, current smoking, diabetes, antihypertensive medication, and batch as covariates. The metabolites in our risk score are 265.1810/3.57 (putative eicosanoid), 279.1966/3.72 (12-HHTrE), 295.2279/4.89 (putative eicosanoid), 319.2280/5.67 (unknown), 331.2679/6.53 (Adrenic acid), and 339.1799/1.72 (11-dehydro-2,3-dinor-TXB2).

LQ/MS, liquid chromatography-mass spectrometry; MAP, mean arterial pressure; BP, blood pressure; M/Z, mass-to-charge ratio; RT, liquid chromatography retention time; β, effect size; SE, standard error.

Table S2. The six metabolites from forward selection regression model and the effect sizes that were used to define the eicosanoid risk profile.

Metabolite	M/Z	RT	β (95% CI)	p
11-dehydro-2,3-dinor-TXB2	339.1799	1.7205	0.88 (0.47–1.30)	3.25e-05
12-HHTrE	279.1966	3.7247	0.91 (0.52–1.30)	5.73e-06
295.2279/4.89 (putative eicosanoid)	295.2279	4.8902	1.00 (0.60–1.39)	8.45e-07
5,6-EET	319.2280	5.6733	1.32 (0.81–1.83)	4.35e-07
Adrenic Acid	331.2679	6.5274	1.35 (0.81–1.89)	9.15e-07
Tetranor-12(R)-HETE	265.1810	3.5705	0.83 (0.44–1.23)	3.36e-05

We used forward selection linear regression modeling with a Bonferroni-corrected inclusion threshold to define a set of metabolites that were independently associated with systolic BP. LQ/MS, liquid chromatography-mass spectrometry; M/Z, mass-to-charge ratio; RT, liquid chromatography retention time; β, effect size.

Table S3. The single metabolite associations with systolic BP for the six metabolites in our eicosanoid risk profile.

	FINRISK		FHS	
Metabolite	β (95% CI)	p	β (95% CI)	p
11-dehydro-2,3-dinor-TXB2	1.60 (1.20–2.01)	1.03e-14		
12-HHTrE	1.12 (0.74–1.50)	1.01e-08	1.38 (0.77–1.98)	7.90e-06
295.2279/4.89 (putative eicosanoid)	1.96 (1.58–2.34)	4.95e-24		
5,6-EET	2.74 (2.37–3.11)	1.05e-46	1.42 (0.82–2.02)	3.60e-06
Adrenic Acid	2.77 (2.37–3.16)	1.43e-42	1.26 (0.63–1.88)	8.31e-05
Tetranor-12(R)-HETE	1.43 (1.05–1.81)	2.11e-13	1.89 (1.28–2.49)	8.91e-10

Comparing single metabolite associations, adjusted for relevant covariates, demonstrated that effect sizes between the metabolites were highly consistent across the two cohorts. LQ/MS, liquid chromatography-mass spectrometry; M/Z, mass-to-charge ratio; RT, liquid chromatography retention time; β, effect size.

Table S4. The association between the six-eicosanoid risk score with systolic BP and hypertension in the discovery cohort (FINRISK).

			Effect size for systolic blood pressure		Odds for hypertension	
	N of individuals	N with HTN	Unadjusted β (95% CI)	Adjusted β (95% CI)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Per 1-SD			4.46 (4.04–4.88)	3.55 (3.17–3.92)	1.44 (1.38–1.51)	1.40 (1.33–1.48)
p			<0.001	<0.001	<0.001	<0.001
Quartile						
Q1	2025	698	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)
Q2	2025	804	3.15 (1.95–4.35)	2.44 (1.39–3.49)	1.25 (1.10–1.42)	1.21 (1.05–1.40)
Q3	2025	926	5.81 (4.61–7.01)	4.71 (3.66–5.76)	1.60 (1.41–1.82)	1.58 (1.37–1.83)
Q4	2024	1139	11.52 (10.32–12.73)	9.04 (7.98–10.10)	2.45 (2.16–2.78)	2.26 (1.96–2.62)

We calculated eicosanoid risk score for each participant according to the formula $\beta_1X_1 + \beta_2X_2 + ... + \beta_nX_n$, with X_n denoting the standardized value for the nth eicosanoid abundance, and β_n denoting the regression coefficient from the regression model containing the indicated eicosanoids. Analyses are adjusted for age, sex, BMI, current smoking, diabetes, antihypertensive medication and batch. HTN, hypertension; OR, odds ratio; CI, confidence interval.

Table S5. **Effect sizes for all the covariates in the fully adjusted models between the six-eicosanoid risk score with systolic BP and hypertension in the discovery cohort (FINRISK).**

	Odds for hypertension		Effect size for systolic blood pressure	
	OR (95% CI)	p	β (95% CI)	p
Age	0.59 (0.56–0.62)	3.02E-306	1.07 (1.07–1.08)	1.31E-216
BMI	0.75 (0.67–0.83)	2.98E-68	1.12 (1.10–1.13)	1.84E-70
Diabetes	-1.04 (-2.69–0.62)	2.19E-01	1.33 (1.05–1.68)	1.79E-02
Female sex	-4.16 (-4.91–-3.41)	3.21E-27	0.59 (0.53–0.66)	6.83E-23
Risk score	3.55 (3.17–3.92)	7.33E-76	1.40 (1.33–1.48)	9.21E-36
Smoking	0.23 (-0.63–1.10)	5.96E-01	0.99 (0.88–1.12)	9.11E-01

We calculated eicosanoid risk score for each participant according to the formula $\beta_1X_1 + \beta_2X_2 + ... + \beta_nX_n$, with X_n denoting the standardized value for the nth eicosanoid abundance, and β_n denoting the regression coefficient from the regression model containing the indicated eicosanoids. Analyses are adjusted for age, sex, BMI, current smoking, diabetes, antihypertensive medication and batch. HTN, hypertension; OR, odds ratio; CI, confidence interval.

Table S6. The association between a six-eicosanoid risk score with systolic BP and hypertension in the discovery cohort (Framingham Offspring Study).

			Effect size for systolic blood pressure		Odds for hypertension	
	N of individuals	N with HTN	Unadjusted β (95% CI)	Adjusted β (95% CI)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Per 1-SD			2.72 (2.10–3.35)	2.22 (1.62–2.82)	1.38 (1.27–1.50)	1.32 (1.21–1.44)
p			<0.001	<0.001	<0.001	<0.001
Quartile						
Q1	715	345	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)
Q2	715	406	3.77 (2.01–5.52)	2.77 (1.09–4.45)	1.41 (1.14–1.74)	1.27 (1.01–1.59)
Q3	715	434	4.90 (3.15–6.66)	3.67 (1.99–5.35)	1.66 (1.34–2.04)	1.45 (1.15–1.83)
Q4	714	488	8.45 (6.69–10.21)	6.81 (5.11–8.51)	2.32 (1.87–2.87)	1.99 (1.57–2.52)

We calculated eicosanoid risk score for each participant according to the formula $\beta_1X_1 + \beta_2X_2 + ... + \beta_nX_n$, with X_n denoting the standardized value for the nth eicosanoid abundance, and β_n denoting the regression coefficient from the regression model containing the indicated eicosanoids in FINRISK. Analyses are adjusted for age, sex, BMI, current smoking, diabetes, antihypertensive medication and batch. HTN, hypertension; OR, odds ratio; CI, confidence interval.

Table S7. **The SNPs associated with eicosanoid risk score in genome-wide association study.**

SNP	Chromosome	Effective allele	Non-effective allele	Minor allele frequency	Effect size	SE	p
rs72681939	1	A	G	0.136	0.136	0.025	3.5e-08
rs12566735	1	C	T	0.136	0.136	0.025	3.6e-08
rs3863632	1	C	T	0.136	0.136	0.025	3.6e-08
rs11584320	1	G	A	0.136	0.136	0.025	3.6e-08
rs11584834	1	G	A	0.136	0.136	0.025	3.6e-08
rs148839121	1	G	A	0.136	0.136	0.025	3.6e-08
rs4417002	1	C	T	0.136	0.136	0.025	3.6e-08
rs11211381	1	G	C	0.136	0.136	0.025	3.6e-08
rs2405337	1	G	A	0.136	0.136	0.025	3.6e-08
rs11584591	1	A	T	0.136	0.136	0.025	3.6e-08
rs11211386	1	C	A	0.136	0.136	0.025	3.7e-08
rs56028913	1	G	C	0.248	-0.111	0.020	1.4e-08
rs7541453	1	C	T	0.343	0.116	0.018	8.2e-11
rs11204906	1	G	A	0.248	-0.111	0.019	1.2e-08
rs10888445	1	A	T	0.343	0.116	0.018	8.8e-11
rs6684312	1	G	A	0.248	-0.110	0.019	1.4e-08
rs2338201	1	G	C	0.343	0.116	0.018	8.3e-11
rs7523082	1	A	T	0.343	0.116	0.018	8.1e-11
rs6685187	1	A	G	0.355	0.110	0.018	5.3e-10
rs6698740	1	G	A	0.355	0.109	0.018	6.4e-10
rs6690449	1	T	C	0.248	-0.111	0.019	1.2e-08
rs1060870	1	G	A	0.355	0.109	0.018	6.1e-10
rs12067594	1	G	A	0.355	0.109	0.018	6.1e-10
rs7542137	1	C	T	0.355	0.109	0.018	6.1e-10
rs57674198	1	T	C	0.248	-0.111	0.019	1.2e-08
rs9943281	1	G	T	0.355	0.109	0.018	6.1e-10
rs61817695	1	G	T	0.248	-0.111	0.019	1.2e-08
rs28415528	1	G	A	0.267	-0.115	0.019	1.5e-09
rs11204914	1	G	A	0.355	0.109	0.018	6.1e-10
rs11204915	1	C	T	0.355	0.109	0.018	6.2e-10
rs10788817	1	C	G	0.355	0.109	0.018	6.1e-10
rs6672064	1	A	G	0.248	-0.111	0.019	1.2e-08
rs6659662	1	C	G	0.248	-0.111	0.019	1.2e-08
rs10788818	1	T	C	0.335	0.105	0.018	5.5e-09
rs2338206	1	A	G	0.248	-0.111	0.019	1.2e-08
rs4845409	1	C	T	0.343	0.100	0.018	1.9e-08
rs4845713	1	G	A	0.343	0.100	0.018	1.9e-08
rs10788820	1	C	T	0.343	0.100	0.018	1.9e-08
rs3007711	1	G	T	0.343	0.100	0.018	1.9e-08
rs3007670	1	T	G	0.343	0.100	0.018	1.9e-08
rs56078223	1	T	G	0.256	-0.105	0.019	4.9e-08
rs12562586	1	C	G	0.343	0.100	0.018	1.9e-08
rs56000812	1	A	G	0.256	-0.105	0.019	4.9e-08
rs9435963	1	C	G	0.342	0.100	0.018	2.2e-08

SNP	Chromosome	Effective allele	Non-effective allele	Minor allele frequency	Effect size	SE	p
rs2932565	1	G	C	0.342	0.100	0.018	2.1e-08
rs9435964	1	G	A	0.342	0.100	0.018	2.1e-08
rs1907040	1	G	A	0.342	0.100	0.018	2.1e-08
rs2999544	1	G	A	0.334	0.104	0.018	5.9e-09
rs6701374	1	A	G	0.248	-0.111	0.019	1.2e-08
rs56313205	1	C	T	0.248	-0.111	0.019	1.2e-08
rs2999545	1	A	T	0.353	0.109	0.018	6.5e-10
rs72694840	1	T	A	0.248	-0.111	0.019	1.2e-08
rs1387833	1	T	G	0.332	0.103	0.018	1.0e-08
rs10494270	1	A	G	0.247	-0.112	0.019	9.0e-09
rs61817719	1	A	T	0.247	-0.112	0.019	9.1e-09
rs61817720	1	A	G	0.247	-0.112	0.019	9.1e-09
rs2999546	1	G	T	0.332	0.103	0.018	1.0e-08
rs6703448	1	A	C	0.247	-0.112	0.019	9.1e-09
rs2932577	1	T	C	0.332	0.103	0.018	1.0e-08
rs1844543	1	G	A	0.247	-0.112	0.019	8.8e-09
rs1490189	1	G	T	0.332	0.103	0.018	1.0e-08
rs6587632	1	A	G	0.247	-0.112	0.019	9.1e-09
rs2999506	1	G	C	0.332	0.103	0.018	1.0e-08
rs6587633	1	G	A	0.247	-0.112	0.019	9.1e-09
rs2932579	1	G	A	0.332	0.103	0.018	9.9e-09
rs9943221	1	G	A	0.247	-0.113	0.019	7.6e-09
rs6662602	1	C	T	0.232	-0.111	0.020	3.0e-08
rs6663064	1	C	T	0.247	-0.113	0.019	6.0e-09
rs6686874	1	G	A	0.247	-0.113	0.019	5.9e-09
rs7535002	1	T	A	0.247	-0.113	0.019	5.9e-09
rs9943251	1	G	A	0.267	-0.117	0.019	7.7e-10
rs2279501	1	G	C	0.361	0.102	0.018	5.5e-09
rs2279502	1	G	A	0.361	0.102	0.018	5.5e-09
rs16833668	1	C	A	0.267	-0.118	0.019	6.9e-10
rs12116923	1	G	A	0.362	0.103	0.018	4.2e-09
rs7538652	1	G	T	0.267	-0.118	0.019	6.9e-10
rs16833669	1	A	T	0.267	-0.118	0.019	6.8e-10
rs61817722	1	C	T	0.247	-0.113	0.019	5.8e-09
rs61817723	1	G	A	0.251	-0.114	0.019	4.1e-09
rs61817724	1	A	C	0.267	-0.118	0.019	6.8e-10
rs16833670	1	A	G	0.267	-0.118	0.019	6.8e-10
rs2932586	1	C	T	0.356	0.102	0.018	6.1e-09
rs61817725	1	G	A	0.247	-0.114	0.019	5.8e-09
rs2337685	1	C	T	0.267	-0.118	0.019	6.8e-10
rs6675930	1	C	T	0.267	-0.118	0.019	6.8e-10
rs6693901	1	T	C	0.267	-0.118	0.019	6.8e-10
rs6682605	1	C	T	0.262	-0.114	0.019	3.3e-09
rs6695324	1	A	T	0.262	-0.114	0.019	3.3e-09
rs57785325	1	A	G	0.262	-0.114	0.019	3.3e-09
rs6684114	1	A	G	0.262	-0.114	0.019	3.3e-09
rs6587634	1	G	T	0.262	-0.114	0.019	3.3e-09
rs6693388	1	T	C	0.263	-0.114	0.019	3.2e-09

SNP	Chromosome	Effective allele	Non-effective allele	Minor allele frequency	Effect size	SE	p
rs6693396	1	T	G	0.263	-0.114	0.019	3.2e-09
rs2932583	1	C	G	0.356	0.102	0.018	5.9e-09
rs4845719	1	C	G	0.266	-0.115	0.019	1.7e-09
rs11204919	1	T	G	0.266	-0.115	0.019	1.7e-09
rs11204920	1	T	C	0.266	-0.115	0.019	1.6e-09
rs2932581	1	G	C	0.360	0.104	0.018	3.1e-09
rs2932580	1	C	G	0.266	-0.115	0.019	1.7e-09
rs2999508	1	A	C	0.360	0.104	0.018	3.1e-09
rs11582739	1	C	A	0.246	-0.112	0.020	1.1e-08
rs902313	1	T	A	0.266	-0.115	0.019	1.7e-09
rs6662611	1	A	G	0.266	-0.115	0.019	1.7e-09
rs7554859	1	C	T	0.246	-0.112	0.020	1.1e-08
rs6587635	1	T	C	0.266	-0.115	0.019	1.7e-09
rs6587636	1	A	G	0.266	-0.115	0.019	1.7e-09
rs6587637	1	A	G	0.266	-0.115	0.019	1.7e-09
rs6587638	1	G	A	0.266	-0.115	0.019	1.7e-09
rs7541099	1	C	T	0.266	-0.115	0.019	1.7e-09
rs6703465	1	A	G	0.266	-0.115	0.019	1.7e-09
rs6657658	1	T	C	0.266	-0.115	0.019	1.7e-09
rs1038747	1	G	T	0.360	0.104	0.018	3.0e-09
rs971887	1	G	A	0.266	-0.116	0.019	1.5e-09
rs16833728	1	G	C	0.266	-0.115	0.019	1.7e-09
rs2999512	1	G	A	0.360	0.104	0.018	3.0e-09
rs2999526	1	G	A	0.363	0.100	0.018	1.1e-08
rs2999528	1	C	T	0.363	0.100	0.018	1.1e-08
rs2932590	1	C	T	0.363	0.100	0.018	1.1e-08
rs6678672	1	C	T	0.246	-0.112	0.020	1.1e-08
rs6587640	1	C	T	0.270	-0.110	0.019	7.8e-09
rs2338019	1	C	T	0.363	0.100	0.018	1.1e-08
rs3791153	1	A	G	0.246	-0.112	0.020	1.1e-08
rs16833743	1	T	C	0.246	-0.112	0.020	1.1e-08
rs112770825	1	G	A	0.246	-0.112	0.020	1.1e-08
rs3007708	1	G	T	0.363	0.100	0.018	1.0e-08
rs61814883	1	G	A	0.246	-0.112	0.020	1.2e-08
rs2999531	1	C	T	0.363	0.100	0.018	1.1e-08
rs12239945	1	A	G	0.247	-0.108	0.020	3.3e-08
rs6587643	1	A	G	0.247	-0.108	0.020	3.6e-08
rs6587644	1	G	A	0.247	-0.109	0.020	2.9e-08
rs6677973	1	C	T	0.247	-0.109	0.020	2.6e-08
rs61814891	1	C	T	0.247	-0.108	0.020	3.6e-08
rs174528	11	T	C	0.435	-0.169	0.017	4.4e-23
rs174529	11	T	C	0.434	-0.170	0.017	2.2e-23
rs174530	11	A	G	0.438	-0.172	0.017	1.2e-23
rs108499	11	C	T	0.357	-0.127	0.018	6.8e-13
rs509360	11	A	G	0.348	-0.112	0.018	3.6e-10
rs174533	11	G	A	0.429	-0.173	0.017	5.5e-24
rs174534	11	A	G	0.364	-0.130	0.018	1.3e-13
rs174535	11	T	C	0.429	-0.172	0.017	9.3e-24

SNP	Chromosome	Effective allele	Non-effective allele	Minor allele frequency	Effect size	SE	p
rs174536	11	A	C	0.428	-0.174	0.017	2.6e-24
rs174537	11	G	T	0.428	-0.174	0.017	2.6e-24
rs102275	11	T	C	0.430	-0.171	0.017	1.4e-23
rs102274	11	T	C	0.429	-0.173	0.017	6.4e-24
rs174541	11	T	C	0.457	-0.150	0.017	1.4e-18
rs174544	11	C	A	0.402	-0.169	0.017	3.0e-22
rs174545	11	C	G	0.428	-0.172	0.017	9.3e-24
rs174546	11	C	T	0.428	-0.172	0.017	1.0e-23
rs174547	11	T	C	0.429	-0.172	0.017	9.7e-24
rs174549	11	G	A	0.404	-0.168	0.017	3.8e-22
rs174550	11	T	C	0.429	-0.172	0.017	1.1e-23
rs4564341	11	C	T	0.197	-0.155	0.021	4.1e-13
rs174551	11	T	C	0.426	-0.172	0.017	8.2e-24
rs174553	11	A	G	0.428	-0.172	0.017	8.1e-24
rs116878346	11	T	G	0.075	-0.177	0.032	4.0e-08
rs174554	11	A	G	0.427	-0.171	0.017	1.9e-23
rs174556	11	C	T	0.402	-0.168	0.017	3.1e-22
rs174560	11	T	C	0.404	-0.168	0.017	3.0e-22
rs75810419	11	C	A	0.075	-0.177	0.032	4.0e-08
rs174561	11	T	C	0.403	-0.170	0.017	1.4e-22
rs116980792	11	G	A	0.075	-0.177	0.032	4.0e-08
rs174562	11	A	G	0.428	-0.172	0.017	8.7e-24
rs174564	11	A	G	0.429	-0.171	0.017	1.9e-23
rs28456	11	A	G	0.404	-0.167	0.017	7.2e-22
rs174565	11	C	G	0.241	-0.146	0.020	1.5e-13
rs174566	11	A	G	0.428	-0.172	0.017	8.5e-24
rs174568	11	C	T	0.426	-0.172	0.017	9.4e-24
rs99780	11	C	T	0.429	-0.171	0.017	1.0e-23
rs174570	11	C	T	0.241	-0.145	0.020	1.9e-13
rs1535	11	A	G	0.428	-0.173	0.017	4.6e-24
rs79976480	11	A	G	0.075	-0.177	0.032	4.1e-08
rs117553420	11	G	T	0.075	-0.177	0.032	4.1e-08
rs174574	11	A	C	0.429	0.172	0.017	8.6e-24
rs76498378	11	G	A	0.077	-0.179	0.032	2.1e-08
rs2524296	11	C	T	0.201	-0.158	0.021	8.8e-14
rs2845574	11	C	T	0.200	-0.157	0.021	1.4e-13
rs2845573	11	A	G	0.201	-0.158	0.021	9.3e-14
rs2727270	11	C	T	0.281	-0.185	0.019	9.1e-23
rs174576	11	C	A	0.428	-0.171	0.017	1.5e-23
rs2524299	11	A	T	0.282	-0.184	0.019	1.9e-22
rs174577	11	C	A	0.428	-0.171	0.017	1.4e-23
rs2072113	11	C	T	0.281	-0.186	0.019	8.1e-23
rs2072114	11	A	G	0.284	-0.181	0.019	7.5e-22
rs174578	11	T	A	0.429	-0.171	0.017	1.4e-23
rs174580	11	A	G	0.430	-0.170	0.017	3.4e-23
rs174581	11	G	A	0.430	-0.170	0.017	3.4e-23
rs174583	11	C	T	0.429	-0.171	0.017	1.7e-23
rs174584	11	G	A	0.429	-0.170	0.017	3.0e-23

SNP	Chromosome	Effective allele	Non-effective allele	Minor allele frequency	Effect size	SE	p
rs2526680	11	C	T	0.200	-0.156	0.021	1.9e-13
rs2845572	11	G	A	0.206	-0.159	0.021	4.2e-14
rs2851682	11	A	G	0.208	-0.157	0.021	5.7e-14
rs2727263	11	C	T	0.164	-0.158	0.023	6.8e-12
rs174592	11	A	G	0.440	-0.161	0.017	2.7e-21
rs174594	11	C	A	0.440	0.162	0.017	2.6e-21
rs174598	11	G	A	0.359	-0.122	0.018	4.8e-12
rs174599	11	G	C	0.441	-0.160	0.017	5.5e-21
rs73487492	11	A	G	0.123	-0.146	0.026	2.0e-08
rs174600	11	T	C	0.360	-0.123	0.018	2.4e-12
rs174601	11	C	T	0.441	-0.161	0.017	4.6e-21
rs2526678	11	G	A	0.194	-0.161	0.022	9.0e-14
rs97384	11	T	C	0.440	0.162	0.017	3.4e-21
rs174603	11	G	A	0.320	-0.113	0.018	5.4e-10
rs174604	11	C	G	0.391	-0.128	0.017	1.8e-13
rs174606	11	G	T	0.447	-0.105	0.017	8.0e-10
rs174609	11	T	C	0.448	-0.105	0.017	6.7e-10
rs174610	11	A	G	0.448	-0.106	0.017	5.4e-10
rs174612	11	C	G	0.448	-0.105	0.017	6.7e-10
rs174613	11	G	A	0.448	-0.105	0.017	6.7e-10
rs174614	11	T	C	0.446	-0.103	0.017	1.6e-09
rs174616	11	G	A	0.446	-0.104	0.017	9.7e-10
rs174617	11	A	G	0.447	-0.104	0.017	1.0e-09
rs174618	11	T	C	0.396	-0.096	0.017	2.2e-08
rs174619	11	A	G	0.446	0.108	0.017	2.3e-10
rs174623	11	G	A	0.447	0.098	0.017	9.5e-09
rs174626	11	G	A	0.445	0.098	0.017	1.0e-08
rs422249	11	T	C	0.343	0.115	0.018	1.2e-10
rs174448	11	G	A	0.385	0.114	0.017	4.9e-11
rs174449	11	G	A	0.372	0.115	0.018	6.2e-11
rs174455	11	G	A	0.377	0.119	0.017	8.8e-12
rs174458	11	C	T	0.296	0.104	0.019	2.0e-08
rs174460	11	C	T	0.293	0.103	0.019	3.0e-08
rs174465	11	C	T	0.303	0.102	0.018	3.3e-08

Table S8. The SNPs associated with eicosanoid risk score in genome-wide association study after adjusting forlinkage-disequilibrium.

SNP	Chromosome	Effective allele	Non-effective allele	Minor allele frequency	Effect size	SE	p
rs72681939	1	A	G	0.136166	0.136	0.025	3.5e-08
rs7523082	1	A	T	0.342975	0.116	0.018	8.1e-11
rs174536	11	A	C	0.428461	-0.174	0.017	2.6e-24

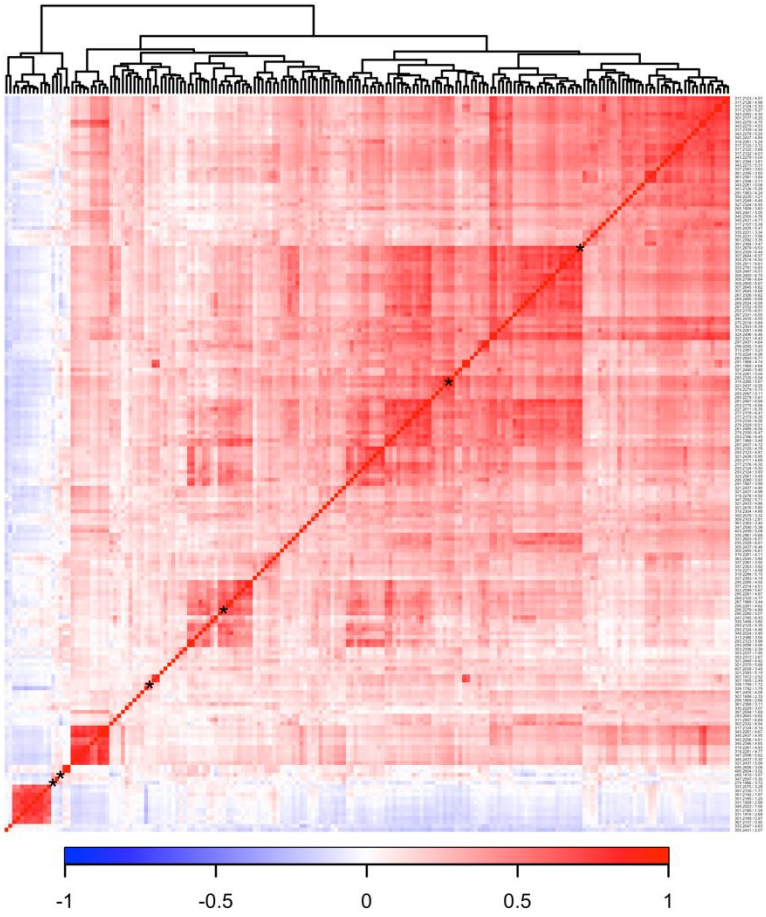
We performed genome-wide association study (GWAS) for eicosanoid risk score observing three significant single nucleotide polymorphism (SNP). SNPs were pruned for linkage-disequilibrium: in each 10kb window (r^2<0.001) only the SNP with the lowest p-value was retained. SNP, single nucleotide polymorphism.

Table S9. The results for two-sample Mendelian randomization for eicosanoid risk score and systolic BP.

Mendelian Randomization method	Effect size	p	FDR
Inverse variance weighted	-0.018	0.051	0.255
Weighted median	-0.015	0.141	0.353
Weighted mode	-0.014	0.345	0.465
Simple mode	-0.015	0.372	0.465
MR Egger	0.010	0.880	0.880

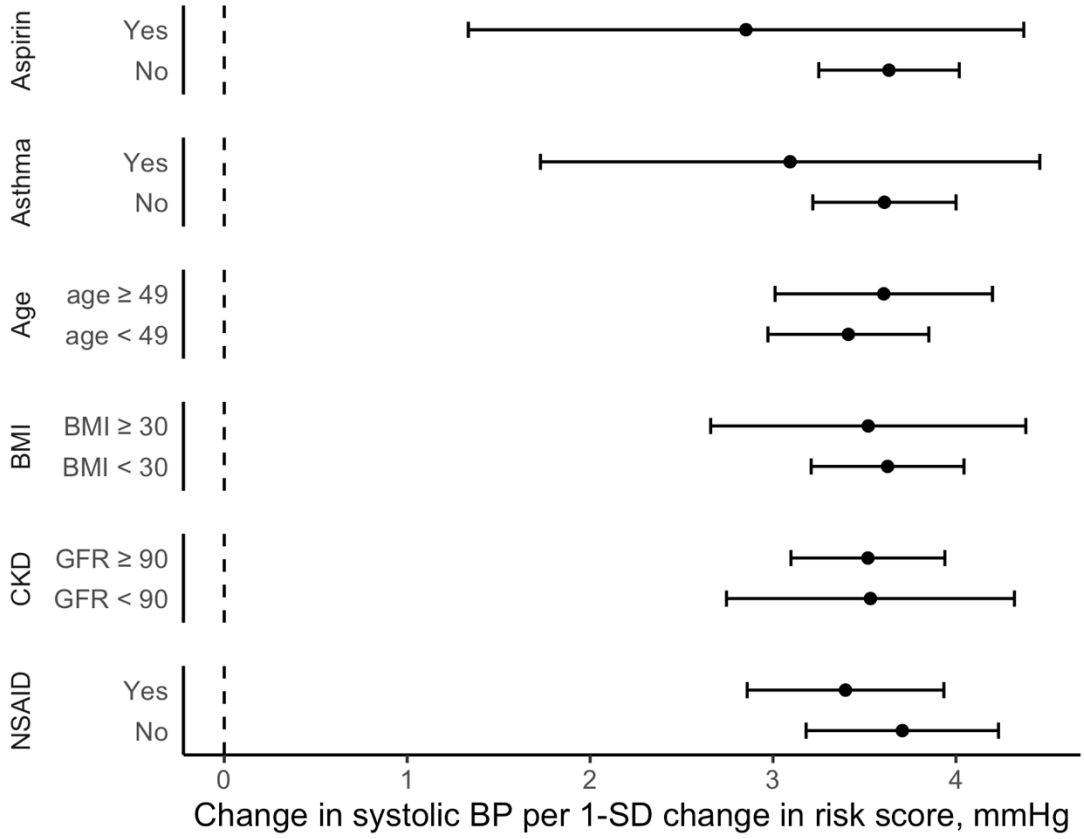
FDR, false discovery rate; MR, Mendelian randomization.

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



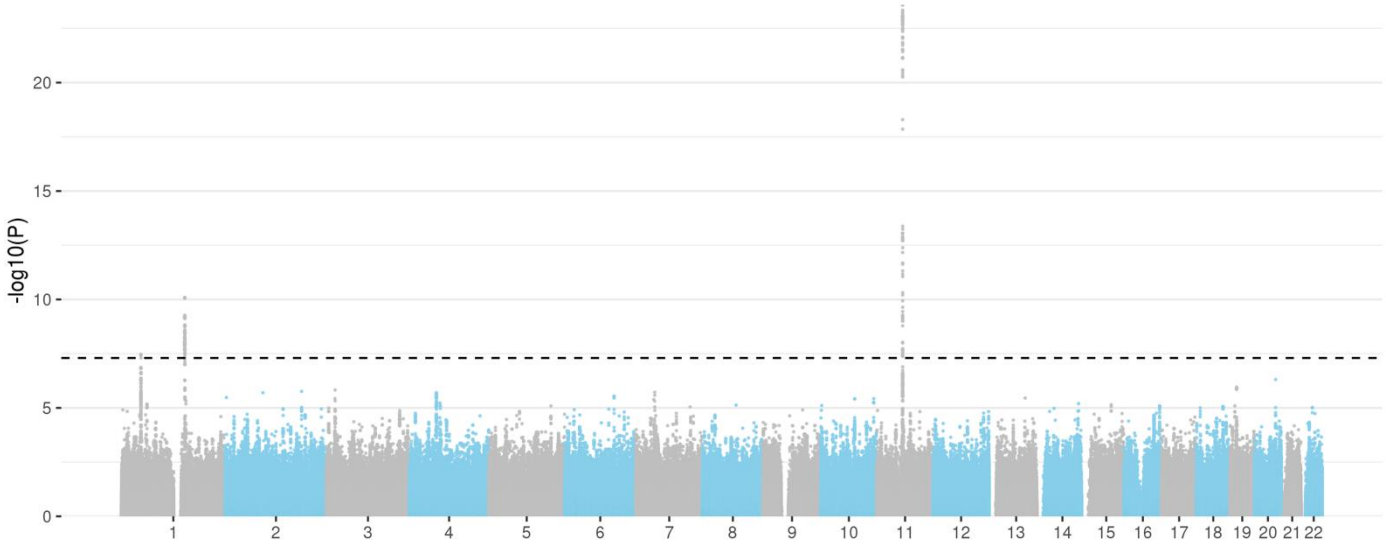
Relations between eicosanoids were calculated using Spearman correlation and ordered using hierarchical cluster analysis with complete linkage method. Only eicosanoids related to systolic blood pressure were included in the correlation matrix. Asterisk denotes the six eicosanoids species in our eicosanoid profile (**Table S2**).

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).