Genetic analyses of circulating PUFA-derived mediators identifies heritable dihydroxyeicosatrienoic acid species

Kathryn A. McGurk [a,b,1], Laura Farrell [b], Alexandra C. Kendall [b], Bernard D. Keavney [c,2], Anna Nicolaou [b,*,2]

[a] *Division of Cardiovascular Sciences, Faculty of Biology, Medicine and Health, University of Manchester, Manchester Academic Health Science Centre, Manchester, UK*
[b] *Laboratory for Lipidomics and Lipid Research, Division of Pharmacy and Optometry, Faculty of Biology, Medicine and Health, University of Manchester, Manchester Academic Health Science Centre, Manchester, UK*
[c] *Manchester Heart Centre, Manchester University NHS Foundation Trust, UK*

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ABSTRACT

Estimates of heritability are the first step in identifying a trait with substantial variation due to genetic factors. Large-scale genetic analyses can identify the DNA variants that influence the levels of circulating lipid species and the statistical technique Mendelian randomisation can use these DNA variants to address potential causality of these lipids in disease. We estimated the heritability of plasma eicosanoids, octadecanoids and docosanoids to identify those lipid species with substantial heritability. We analysed plasma lipid mediators in 31 White British families (196 participants) ascertained for high blood pressure and deeply clinically and biochemically phenotyped over a 25-year period. We found that the dihydroxyeicosatrienoic acid (DHET) species, 11,12-DHET and 14,15-DHET, products of arachidonic acid metabolism by cytochrome P450 (CYP) monooxygenase and soluble epoxide hydrolase (sEH), exhibited substantial heritability (h^2 = 33%−37%; P_{adj}<0.05). Identification of these two heritable bioactive lipid species allows for future large-scale, targeted, lipidomics-genomics analyses to address causality in cardiovascular and other diseases.

1. Introduction

Polyunsaturated fatty acids (PUFA) of the n-3 and n-6 families are derived from elongation and desaturation of the essential fatty acids linoleic (LA) and α-linolenic acid (ALA), as well as nutritional uptake. When metabolised via cyclooxygenases (*PTGS* genes), lipoxygenases (*ALOX* genes), and cytochrome P450 monooxygenases (*CYP1A, −2B, −2 C, −2D, −2 G, −2 J, −2 N, −4A* genes; including epoxygenases, mid-chain and terminal monooxygenases), the PUFA produce an array of lipid metabolites, many of which are known mediators of inflammation and immunity (Fig. 1) [1].

Circulating lipid mediators reflect production of the vascular endothelium, platelets and white blood cells, as well as systemic tissue production. Oxygenation of n-3 and n-6 PUFA results in the production of an array of species including: (i) eicosanoids, derivatives of the 20-carbon (C) n-6 PUFAs arachidonic acid (AA) and dihomo-γ-linolenic acid, and the n-3 PUFA eicosapentaenoic acid (EPA); (ii) docosanoids,

derivatives of the 22-C n-3 PUFA docosahexaenoic acid (DHA), and (iii) octadecanoids, derivatives of the 18-C n-6 PUFA LA and n-3 PUFA ALA [2–5].

These bioactive lipids have potent roles as signalling molecules of inflammation and immunity [6], are vasoactive [7], and their levels have been associated with cardiovascular disease (CVD) [8–14]. Numerous small-scale studies have found PUFA-derived lipid mediators at increased concentration in the blood of CVD patients, compared with healthy controls [10,15–18]. Examples include the AA-derived dihydroxyeicosatrienoic acid (DHET) species that have anti-inflammatory properties and play a role in vasodilation through hyperpolarising vascular smooth muscle cells [19,20] and dilation of human coronary arterioles [21]; the LA-derived hydroxyoctadecanoic acid (HODE) species that have been identified as major components of oxidised LDL [14] and 12,13-DiHOME that mediates cardiac function [22] and the AA-derived hydroxyeicosatetraenoic acid (HETE) species that have been shown to remodel the vasculature during hypertension [23,24].

Furthermore, the hydrolysis of the CYP-derived epoxyeicosatrienoic acid (EET) species by the enzyme soluble epoxide hydrolase (sEH) to generate the less potent DHET species, has been implicated in the regulation of vasoconstriction caused by EET [25].

Given the wide array of lipids that could potentially influence cardiovascular function to varying degrees, identifying lipids that are heritable within a population at risk of cardiovascular disease (CVD) is a useful tool to narrow down potential target species; this will allow for future analytical, biochemical and pharmacological studies to focus on specific lipids with a link to CVD risk. Although lipids are not encoded, DNA variants of the genes of the enzymes involved in their metabolism may reveal specific, heritable, lipid biomarkers of cardiovascular disease. Heritability is defined as the portion of phenotypic variance due to genetic factors; the heritability of plasma lipoproteins is known to vary substantially with lipoprotein (a), for example, being subject to substantial single-locus genetic influence [26]. Narrow-sense heritability (h^2) estimated in the present study is the variance in a phenotype attributable to additive genetic variance, i.e. that specified by a simple allele dosage model. Heritability can be estimated by partitioning the observed variation in a phenotype (e.g. varying measures of plasma lipids between individuals) into genetic and environmental factors. Some PUFA species (e.g., AA, eicosadienoic acid, DHA, and EPA) have been subject to genetic analyses, and 12%– 59% of the variance in the blood levels of those fatty acid studied to-date has been estimated to be due to genetic factors [28,29]. Recent studies have started the systematic genetic characterisation of PUFA-derived oxygenated mediator derivatives [30–32].

Aiming to estimate the heritability of circulating bioactive lipid species, we used targeted lipidomics to measure plasma eicosanoid, octadecanoid, and docosanoid species in 196 members of 31 White British families ascertained between 1993 and 1996 on the basis of high blood pressure, and deeply phenotyped at intervals thereafter. The families contributing to this study are a subset of a larger cohort (the HTO study), which has been previously identified genetic associations with cardiovascular phenotypes [33–37].

The identification of two substantially heritable DHET species, products of AA metabolism via the CYP/sEH axis, allows for future targeted assessment of a causal role for heritable signalling lipid species in CVD risk.

2. Methods

2.1. Family recruitment

Families contributing to this study are a subset of a larger cohort, which has previously yielded generalisable genetic associations with cardiovascular-relevant phenotypes [33–37]. The families consisted of 1–24 members (median of 5 members); participant characteristics are listed in Table 1 and Fig. S1. In detail: 31 families (196 individuals) were included in this study from a cohort recruited for a quantitative genetic study of hypertension and other cardiovascular risk factors, and selected via a proband with essential hypertension [38]. Included family members were UK residents of self-reported White ethnicity and were required to consist of three or more siblings quantitatively assessable for blood pressure if one parent of the sibship was available for blood sampling, or four or more siblings if no parent was available. First, second and third degree relatives were then recruited to assemble a series of extended British families with sufficient power to detect modest genetic influences on heritable quantitative traits, as previously shown [33,34,38–41]. Non-fasting blood samples collected in EDTA tubes was used to prepare plasma; aliquots were stored at − 80 °C. DNA was

Table 1
Summary characteristics of the study participants.

Trait	Mean (SD)
Gender	52% Male
Hypertensive	34%
Mean blood pressure	133/80 mmHg
Age (years)	46 (16)
BMI	25.97 (4.61)
WHR	0.86 (0.09)
Cholesterol (mmol/L)	5.46 (1.10)

Data is shown as mean and standard deviation (SD) or percentage (%); BMI, body mass index; WHR, waist-hip ratio; Mean blood pressure, the mean of three readings taken in the clinic.
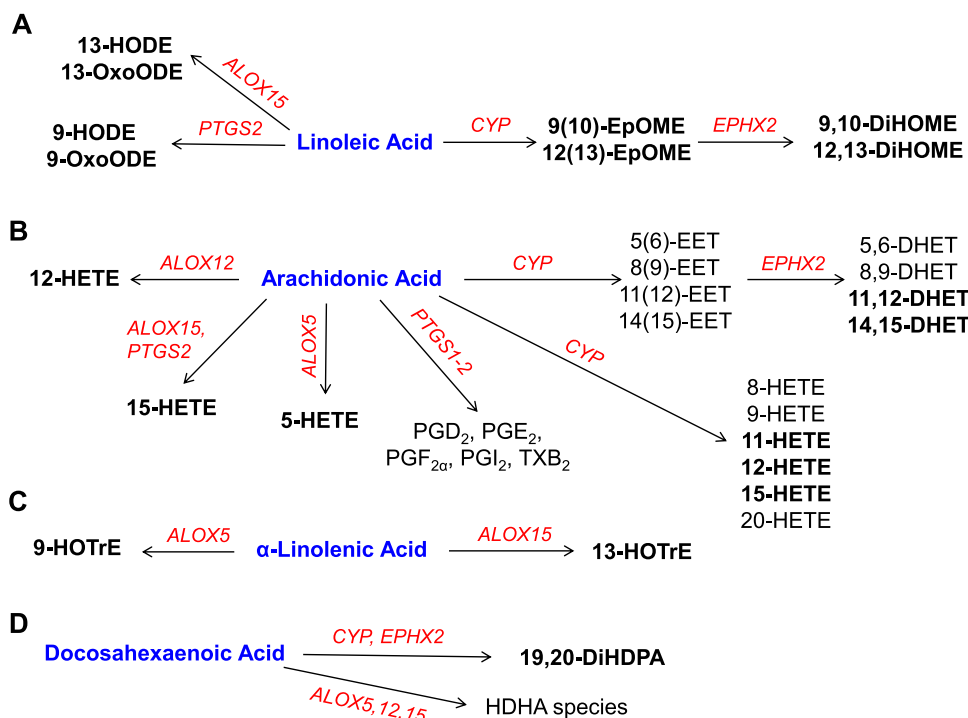

Fig. 1. Schematic biochemical pathways of eicosanoids, octadecanoids, and docosanoids. Linoleic acid (LA) metabolism via lipoxygenases (*ALOX*), CYP450 monooxygenases (*CYP*), and epoxide hydrolase (*EPHX2*). B) Arachidonic acid (AA) metabolism via cyclooxygenases (*PTGS*), lipoxygenases (*ALOX*), CYP450 monooxygenases (*CYP*), epoxide hydrolase (*EPHX2*), and glutathione peroxidase (*GPX*). C) Alpha-linolenic acid (ALA) metabolism via lipoxygenases (*ALOX*). D) Docosahexaenoic acid (DHA) metabolism via lipoxygenases (*ALOX*) CYP450 monooxygenase (*CYP*) and epoxide hydrolase (*EPHX2*). Lipid species that were detectable in the samples analysed are shown in bold.

extracted from whole blood as previously described [42]. Genotyping was performed using the Illumina 660 W-Quad chip that includes 557, 124 SNPs (single nucleotide polymorphisms). The collection protocol obtained ethical clearance from the Central Oxford Research Ethics Committee (06/Q1605/113) and it corresponds with the principles of the Declaration of Helsinki. Written informed consent was obtained from all participants.

2.2. Plasma mediator lipidomics

Plasma samples (1 ml) were spiked with deuterated internal standards (20 ng each; 12-HETE-*d*8, PGB$_2$-*d*4, 8,9-EET-*d*11, and 8,9-DHET-*d*11; Cayman Chemicals, Ann Arbor, MI, USA), extracted with acidified methanol (15% v/v), and semi-purified by solid phase extraction (C18-E; Phenomenex, Macclesfield, UK), as described previously [43,44]. Lipid mediators were analysed using ultra performance liquid chromatography (UPLC) with tandem mass spectrometry (MS/MS) on a Acquity UPLC pump (Waters, UK) coupled to a triple quadrupole mass spectrometer (Xevo TQS, Waters, UK) with an electrospray ionisation (ESI) probe (UPLC/ESI-MS/MS). Lipids were separated on a C18 column (2.1 × 50 mm; Acquity UPLC BEH, 1.7 μm, Waters, UK), fragmented using argon gas and monitored in the negative ion mode by multiple reaction monitoring. Plasma samples were analysed for the presence of 65 fatty acid derivatives of the COX, LOX and CYP pathways, as described in Camacho-Muñoz et al. (2021) [44]. 17 lipid species were consistently present in all samples and could be quantitated using a signal to noise ratio of 10. MRM transitions and other details for the UPLC/ESI-MS/MS analysis of these species are provided in Supplementary Table S1 and Fig. S2. Calibration lines of commercially available standards were used to quantitate the lipid mediators (Cayman Chemicals); data are presented as pg/ml plasma. Pooled plasma samples were used to create quality control samples that were extracted and analysed blindly alongside the samples (a further assessment of variation is presented in Supplementary methods **SM1)**.

2.3. Statistical analyses

2.3.1. Covariate adjustment

Systematic error was considered from a variety of sources, as previously published [33] (Supplementary Table S2). The lipid measurements were assessed for effect of potential covariates using stepwise multiple linear regression to identify the best set of predictors, using the caret package and 'leapSeq' method in R (version 3.5.2). Multiple linear regression of the best predictors was undertaken using the 'lm' function. Residuals from the covariate-adjusted regression models were standardised to have a mean of 0 and a variance of 1. Relationship between species was explored via correlation using rquery.cormat.

2.3.2. Genome-wide genotyping quality control

Genotyping was performed using the Illumina 660 W-Quad chip for 557,124 SNPs and the quality control has been previously described [33]. Routine quality control [45] was undertaken using PLINK [46] (version 1.9). SNPs with low genotyping rates (–geno 0.05), low minor allele frequency (–maf 0.05), and those that failed checks of Hardy-Weinberg Equilibrium (–hwe 1e-8) were excluded. Individuals with low genotype rates (–mind 0.05) and outlying heterozygosity were removed (0.31–0.33 included). Relatedness was assessed by high levels of IBD sharing (–genome and –rel-check) and by visualisation of pairs of individuals' degree of relatedness, and two outlier individuals were removed. Ethnicity was assessed via principal components analysis with genotype data from the 1000 Genome Project [47], and confirmed all participants were of European/CEU origin. GWAS were undertaken for the lipids using the GCTA software, specifying the —mlma command for mixed linear model association analyses. As anticipated given the numbers of participants studied, no locus attained GWAS significance.

2.3.3. Heritability estimates

Traditionally, heritability is estimated by regressing offspring phenotype values onto mean parental values. This can be extended to estimate pedigree-based heritability, by analysing phenotype correlations between pairs of blood relatives, using the expected resemblance of the known pedigree structure (the kinship coefficient) in the absence of any genotype information [48]. However, this analysis tends to be low-powered if there are relatively few controls; all founders in a family must be unrelated, sharing no alleles identical by descent. Therefore, we present pedigree-based heritability estimates using the QTDT software (version 2.6.1) [48], by specifying the -we and -veg options to compare an environmental only variance model with a polygenic and environmental variances model, as well as a complementary heritability estimate, using a linear mixed model (LMM) approach to estimate SNP-based heritability partitioned by measured SNPs using GCTA software (version 1.26.0) [49,50]. A genetic relationship matrix was created from the quality controlled genotyping data and the –reml command was used to estimate variance of the traits explained by the genotyped SNPs. LMM models within-family correlations to separate fixed-effect factors (e.g., gender or age) from random-effects (genomic and environmental factors unique to each individual). A key assumption of heritability estimates is that they depend on the population under study whenever genetic or environmental factors are population-specific, for instance allele frequencies or diet [51]. The statistical properties of heritability analysis methods are well described elsewhere [52]. The P-values presented are adjusted via Bonferroni Correction for 17 tests.

3. Results

3.1. Plasma mediator profiles

Plasma concentrations (pg/ml) of the 17 lipid mediators assessed in this study are shown in Table S3. 13-HODE, a derivative of the n-6 PUFA LA, was the most abundant mediator (7.32 ± 6.63 ng/ml), in agreement with previous reports [4,44]. Assessment of the relationships between the various lipid mediators identified two groups of relationships, mainly between the LA and ALA-derived species DiHOME, OxoODE, HODE, EpOME and HOTrE, and the AA derivatives DHET and HETE (Fig. 2). This finding may reflect the relationship of the parent PUFAs, as the essential fatty acids LA and ALA are precursors of the n-6 and n-3 PUFA families.

3.2. Heritability estimates

Two lipid species were estimated as significantly heritable (P$_{adj}$<0.05), namely the AA metabolites 11,12-DHET and 14,15-DHET (Fig. 3). The heritability estimated for these two species ranged from 33%− 37%. This suggests that about a third of the variance in the levels of these plasma lipids is due to genetic factors, with the remainder influenced by environmental or other non-genetic factors (Table S4).

4. Discussion

The lipid mediators 11,12-DHET and 14,15-DHET were identified as significantly heritable ($h^2 = 33\%-37\%$; P$_{adj}$<0.05) in a cohort of White British families. Heritability estimates can identify those lipid species whose variation in plasma is more controlled by genetic factors, in comparison to lipid species with lower estimates of heritability whose concentrations are more influenced by non-genetic, environmental factors. Therefore, the variation in plasma 11,12- and 14,15- DHET species, produced by AA metabolism via the CYP/sEH axis, is substantially influenced by genetic factors.

A recent study reported in serum samples that 12-HETE was heritable ($h^2 = 22\%-28\%$) [32]. However, the levels of eicosanoids and related lipid mediators can be affected by the process of coagulation and platelet aggregation [53], and lipoxygenase products such as 12-HETE
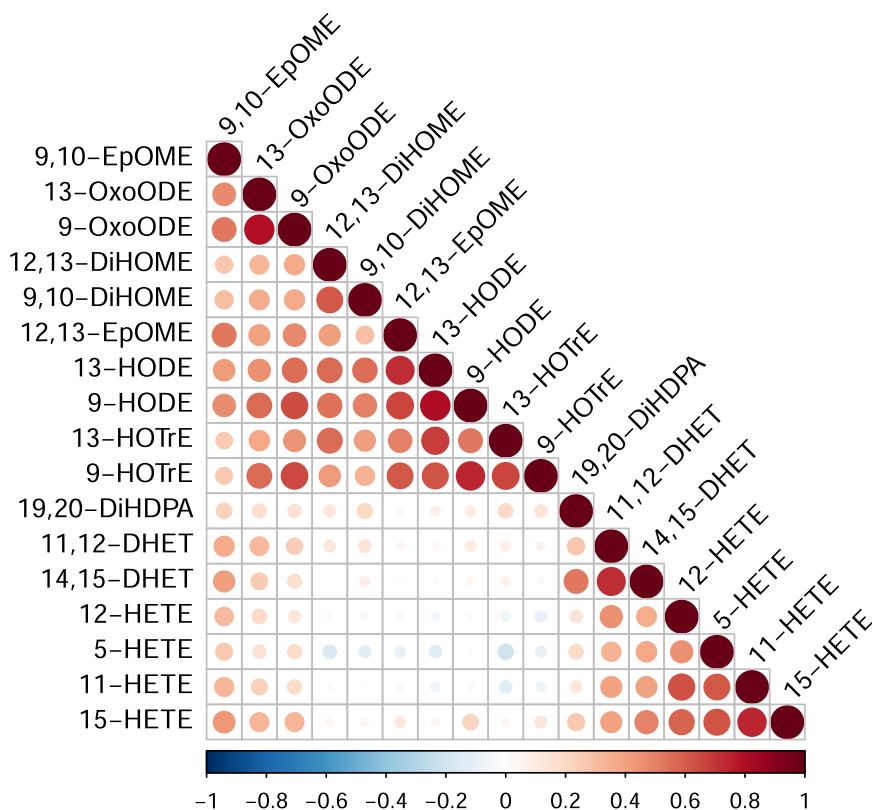
Fig. 2. Relationships between plasma lipid mediators identify significant correlations between linoleic and α-linolenic metabolites. The strength of the relationship (correlation coefficient) is depicted as a scale of colours; P-values are shown as size of circle produced (Further details provided in supplementary Table S5).
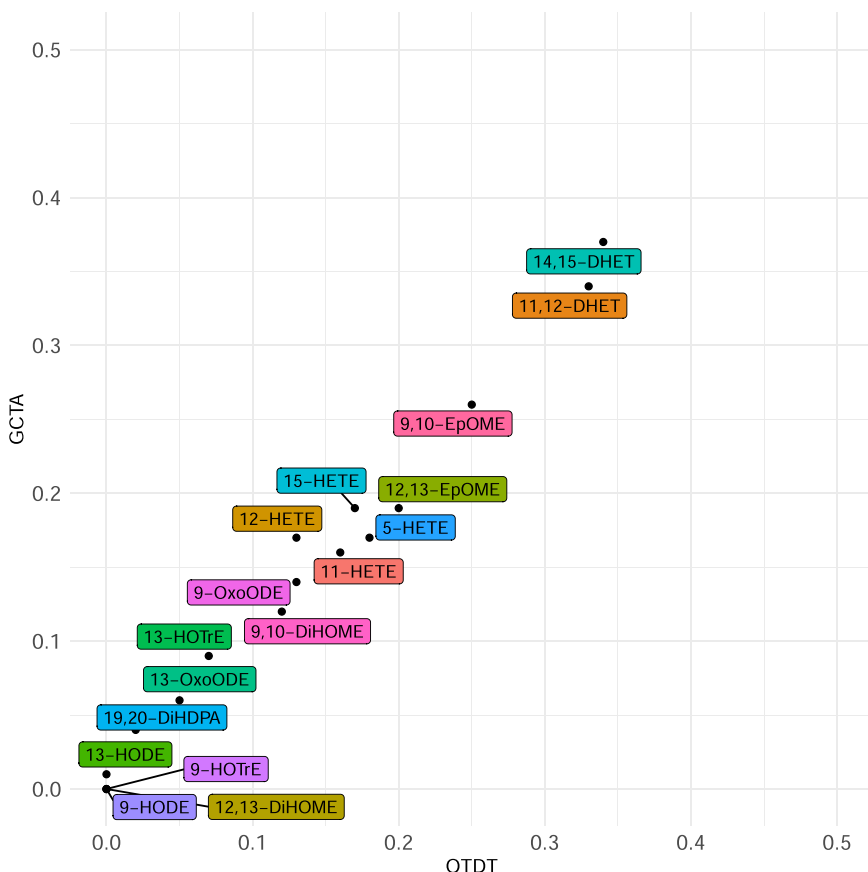

Fig. 3. Heritability estimates for the plasma lipid mediators. The estimates were performed using SNP-based GCTA software (y-axis) and reported pedigree-based QTDT software (x-axis). Heritability, the proportion of variation observed in lipid levels that is due to genetic factors, is estimated between the interval [0,1]. 11,12-DHET and 14,14-DHET were identified to be significantly heritable. GCTA software uses genotyped SNPs to estimate heritability of a trait and QTDT software uses the reported family pedigree to estimate heritability.

which is produced primarily from platelets, are found at much higher concentrations in serum samples than plasma [54,55]. In our study we estimated the heritability of lipid mediators in plasma, not serum, and 12-HETE was not significantly heritable.

The formation of DHET species, produced from the hydrolysis of EETs via sEH, is thought to attenuate the hypotensive, vasorelaxatory properties of the EET species through metabolism to the less bioactive DHET species [56]. The genetic influence over the levels of DHET species may therefore be a regulatory mechanism to control the functional activities of EETs [57]. sEH inhibitors are currently being trialled as treatments for hypertension, insulin resistance and impaired glucose tolerance, and subarachnoid haemorrhage [ClinicalTrials.gov; June 2021].

Patient carriers of specific DNA variants in CYP450 genes present with adverse responses to the usual recommended reference dosages of multiple drugs, including the anticoagulant Warfarin [58]. This may be a research area of therapeutic interest, where measurement of plasma EET and DHET species and future large cohort genetic-lipidomic studies of these species, will uncover the specific genetic variants influencing them.

Correlation analysis showed that the plasma lipids assessed in this study, were separated into two groups: the derivatives of the essential fatty acids LA- and ALA (DiHOME, OxoODE, HODE, EpOME and HOTrE) and the AA-derived DHET and HETE species. This suggests that the levels of lipid mediators in plasma depend upon the availability of the parent PUFA, due to the grouping of the lipid mediators by substrate, rather than genetic variability in the enzymes involved in the reaction. The most abundant of the plasma lipid species examined, 13-HODE, has been shown to be changed in concentration postprandially [59], which may be the reason why it was not estimated to be significantly influenced by genetic factors.

Heritability has been estimated for free fatty acids from plasma; AA has been estimated previously to have higher heritability (38–58% [28, 29]) than that of the other PUFAs, EPA (24% [29]) and DHA (12% [29]), which was congruent with our results, through the fatty-acid derived metabolites produced from them.

In the present study, we estimated the heritability of two of the four AA-derived DHET species, as the less abundant 5,6-DHET and 8,9-DHET [43,44] were not detected above the limit of quantitation of our assay. Similarly, the plasma levels of the DHET precursors 5,6-, 8,9-, 11,12- and 14,15-EET were not detectable. Therefore, further studies assessing the levels and heritability of all DHET and EET species are needed to confirm the contribution of the CYP/sEH axis in CVD. Such studies might also reveal the impact of genetic variations of CYPs and/or sEH on lipid heritability.

Another limitation of this study is its size, which limits the power to detect genetic influences. However, our study of 196 participants is the largest of which we are aware that has analysed this range of plasma PUFA derivatives to date. The significant heritability of AA derivatives of the CYP/sEH axis suggests the potential involvement of genetic variants of these two enzymes that may influence circulating lipid species, and further research is needed before their involvement in CVD can be concluded. Large-scale biobank studies combining genomics and lipidomics analyses could identify lipid biomarkers of disease risk as well as support the development stratified medicine and pharmacogenomics applications.

Conflicts of interest

Nothing to declare.

Data availability

Data will be made available on request.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.prostaglandins.2022.106638.

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A. Borodina, M. Lienhard, F. Mertes, M. Sultan, B. Timmermann, M.-L. Yaspo, E. R. Mardis (Co-Principal Investigator), R.K. Wilson (Co-Principal Investigator), L. Fulton, R. Fulton, S.T. Sherry (Principal Investigator), V. Ananiev, Z. Belaia, D. Beloslyudtsev, N. Bouk, C. Chen, D. Church, R. Cohen, C. Cook, J. Garner, T. Hefferon, M. Kimelman, C. Liu, J. Lopez, P. Meric, C. O'Sullivan, Y. Ostapchuk, L. Phan, S. Ponomarov, V. Schneider, E. Shekhtman, K. Sirotkin, D. Slotta, H. Zhang, G.A. McVean (Principal Investigator), R.M. Durbin (Principal Investigator), S. Balasubramaniam, J. Burton, P. Danecek, T.M. Keane, A. Kolb-Kokocinski, S. McCarthy, J. Stalker, M. Quail, J.P. Schmidt (Principal Investigator), C.J. Davies, J. Gollub, T. Webster, B. Wong, Y. Zhan, A. Auton (Principal Investigator), C.L. Campbell, Y. Kong, A. Marcketta, R.A. Gibbs (Principal Investigator), F. Yu (Project Leader), L. Antunes, M. Bainbridge, D. Muzny, A. Sabo, Z. Huang, J. Wang (Principal Investigator), L.J.M. 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Shlyakhter, S. F. Schaffner, J. Vitti, D.N. Cooper (Principal Investigator), E.V. Ball, P.D. Stenson, D.R. Bentley (Principal Investigator), B. Barnes, M. Bauer, R. Keira Cheetham, A. Cox, M. Eberle, S. Humphray, S. Kahn, L. Murray, J. Peden, R. Shaw, E.E. Kenny (Principal Investigator), M.A. Batzer (Principal Investigator), M.K. Konkel, J. A. Walker, D.G. MacArthur (Principal Investigator), M. Lek, R. Sudbrak (Project Leader), V.S. Amstislavskiy, R. Herwig, E.R. Mardis (Co-Principal Investigator), L. Ding, D.C. Koboldt, D. Larson, K. Ye, S. Gravel, A. Swaroop, E. Chew, T. Lappalainen (Principal Investigator), Y. Erlich (Principal Investigator), M. Gymrek, T. Frederick Willems, J.T. Simpson, M.D. Shriver (Principal Investigator), J.A. Rosenfeld (Principal Investigator), C.D. Bustamante (Principal Investigator), S.B. Montgomery (Principal Investigator), F.M. De La Vega (Principal Investigator), J.K. Byrnes, A.W. Carroll, M.K. DeGorter, P. Lacroute, B.K. Maples, A. R. Martin, A. Moreno-Estrada, S.S. Shringarpure, F. Zakharia, E. Halperin (Principal Investigator), Y. Baran, C. Lee (Principal Investigator), E. Cerveira, J. Hwang, A. Malhotra (Co-Project Lead), D. Plewczynski, K. Radew, M. Romanovitch, C. Zhang (Co-Project Lead), F.C.L. Hyland, D.W. Craig (Principal Investigator), A. Christoforides, N. Homer, T. Izatt, A.A. Kurdoglu, S.A. Sinari, K. Squire, S.T. Sherry (Principal Investigator), C. Xiao, J. Sebat (Principal Investigator), D. Antaki, M. Gujral, A. Noor, K. Ye, E.G. Burchard (Principal Investigator), R.D. Hernandez (Principal Investigator), C.R. Gignoux, D. Haussler (Principal Investigator), S.J. Katzman, W. James Kent, B. Howie, A. Ruiz-Linares (Principal Investigator), E.T. Dermitzakis (Principal Investigator), S.E. Devine (Principal Investigator), G.R. Abecasis (Principal Investigator), H. Min Kang (Project Leader), J.M. Kidd (Principal Investigator), T. Blackwell, S. Caron, W. Chen, S. Emery, L. Fritsche, C. Fuchsberger, G. Jun, B. Li, R. Lyons, C. Scheller, C. Sidore, S. Song, E. Sliwerska, A. Taliun, A. Tan, R. Welch, M. Kate Wing, X. Zhan, P. Awadalla (Principal Investigator), A. Hodgkinson, Y. Li, X. Shi (Principal Investigator), A. Quitadamo, G. Lunter (Principal Investigator), G. A. McVean (Principal Investigator) (Co-Chair), J.L. Marchini (Principal Investigator), S. Myers (Principal Investigator), C. Churchhouse, O. Delaneau, A. Gupta-Hinch, W. Kretzschmar, Z. Iqbal, I. Mathieson, A. Menelaou, A. Rimmer, D.K. Xifara, T.K. Oleksyk (Principal Investigator), Y. Fu (Principal Investigator), X. Liu, M. Xiong, L. Jorde, D. Witherspoon, J. Xing, E. E. Eichler (Principal Investigator), B.L. Browning (Principal Investigator), S. R. Browning (Principal Investigator), F. Hormozdiari, P.H. Sudmant, E. Khurana (Principal Investigator), R.M. Durbin (Principal Investigator), M.E. Hurles (Principal Investigator), C. Tyler-Smith (Principal Investigator), C.A. Albers, Q. Ayub, S. Balasubramaniam, Y. Chen, V. Colonna, P. Danecek, L. Jostins, T. M. Keane, S. McCarthy, K. Walter, Y. Xue, M.B. Gerstein (Principal Investigator), A. Abyzov, S. Balasubramanian, J. Chen, D. Clarke, Y. Fu, A.O. Harmanci, M. Jin, D. Lee, J. Liu, X. Jasmine Mu, J. Zhang, Y. Zhang, Y. Li, R. Luo, H. Zhu, C. Alkan, E. Dal, F. Kahveci, G.T. Marth (Principal Investigator), E.P. Garrison, D. Kural, W.-P. Lee, A.N. Ward, J. Wu, M. Zhang, S.A. McCarroll (Principal Investigator), R. E. Handsaker (Project Leader), D.M. Altshuler, E. Banks, G. del Angel, G. Genovese, C. Hartl, H. Li, S. Kashin, J.C. Nemesh, K. Shakir, S.C. Yoon (Principal Investigator), J. Lihm, V. Makarov, J. Degenhardt, J.O. Korbel (Principal Investigator) (Co-Chair), M.H. Fritz, S. Meiers, B. Raeder, T. Rausch, A.M. Stütz, P. Flicek (Principal Investigator), F. Paolo Casale, L. Clarke, R.E. Smith, O. Stegle, X. Zheng-Bradley, D.R. Bentley (Principal Investigator), B. Barnes, R. Keira Cheetham, M. Eberle, S. Humphray, S. Kahn, L. Murray, R. Shaw, E.-W. Lameijer, M.A. Batzer (Principal Investigator), M.K. Konkel, J.A. Walker, L. Ding (Principal Investigator), I. Hall, K. Ye, P. Lacroute, C. Lee (Principal Investigator) (Co-Chair), E. Cerveira, A. Malhotra, J. Hwang, D. Plewczynski, K. Radew, M. Romanovitch, C. Zhang, D.W. Craig (Principal Investigator), N. Homer, D. Church, C. Xiao, J. Sebat (Principal Investigator), D. Antaki, V. Bafna, J. Michaelson, K. Ye, S. E. Devine (Principal Investigator), E.J. Gardner (Project Leader), G.R. Abecasis (Principal Investigator), J.M. Kidd (Principal Investigator), R.E. Mills (Principal Investigator), G. Dayama, S. Emery, G. Jun, X. Shi (Principal Investigator), A. Quitadamo, G. Lunter, G.A. McVean (Principal Investigator), K. Chen (Principle Investigator), X. Fan, Z. Chong, T. Chen, D. Witherspoon, J. Xing, E.E. Eichler (Principal Investigator) (Co-Chair), M.

J. Chaisson, F. Hormozdiari, J. Huddleston, M. Malig, B.J. Nelson, P.H. Sudmant, N.F. Parrish, E. Khurana (Principal Investigator), M.E. Hurles (Principal Investigator), B. Blackburne, S.J. Lindsay, Z. Ning, K. Walter, Y. Zhang, M. B. Gerstein (Principal Investigator), A. Abyzov, J. Chen, D. Clarke, H. Lam, X. Jasmine Mu, C. Sisu, J. Zhang, Y. Zhang, R.A. Gibbs (Principal Investigator) (Co-Chair), F. Yu (Project Leader), M. Bainbridge, D. Challis, U.S. Evani, C. Kovar, J. Lu, D. Muzny, U. Nagaswamy, J.G. Reid, A. Sabo, J. Yu, X. Guo, W. Li, Y. Li, R. Wu, G. T. Marth (Principal Investigator) (Co-Chair), E.P. Garrison, W. Fung Leong, A. N. Ward, G. del Angel, M.A. DePristo, S.B. Gabriel, N. Gupta, C. Hartl, R.E. Poplin, A.G. Clark (Principal Investigator), J.L. Rodriguez-Flores, P. Flicek (Principal Investigator), L. Clarke, R.E. Smith, X. Zheng-Bradley, D.G. MacArthur (Principal Investigator), E.R. Mardis (Principal Investigator), R. Fulton, D.C. Koboldt, S. Gravel, C.D. Bustamante (Principal Investigator), D.W. Craig (Principal Investigator), A. Christoforides, N. Homer, T. Izatt, S.T. Sherry (Principal Investigator), C. Xiao, E.T. Dermitzakis (Principal Investigator), G.R. Abecasis (Principal Investigator), H. Min Kang, G.A. McVean (Principal Investigator), M. B. Gerstein (Principal Investigator), S. Balasubramanian, L. Habegger, H. Yu (Principal Investigator), P. Flicek (Principal Investigator), L. Clarke, F. Cunningham, I. Dunham, D. Zerbino, X. Zheng-Bradley, K. Lage (Principal Investigator), J. Berg Jespersen, H. Horn, S.B. Montgomery (Principal Investigator), M.K. DeGorter, E. Khurana (Principal Investigator), C. Tyler-Smith (Principal Investigator) (Co-Chair), Y. Chen, V. Colonna, Y. Xue, M.B. Gerstein (Principal Investigator) (Co-Chair), S. Balasubramanian, Y. Fu, D. Kim, A. Auton (Principal Investigator), A. Marcketta, R. Desalle, A. Narechania, M.A. Wilson Sayres, E.P. Garrison, R.E. Handsaker, S. Kashin, S.A. McCarroll, J.L. Rodriguez-Flores, P. Flicek (Principal Investigator), L. Clarke, X. Zheng-Bradley, Y. Erlich, M. Gymrek, T. Frederick Willems, C.D. Bustamante (Principal Investigator) (Co-Chair), F.L. Mendez, G. David Poznik, P.A. Underhill, C. Lee, E. Cerveira, A. Malhotra, M. Romanovitch, C. Zhang, G.R. Abecasis (Principal Investigator), L. Coin (Principal Investigator), H. Shao, D. Mittelman, C. Tyler-Smith (Principal Investigator) (Co-Chair), Q. Ayub, R. Banerjee, M. Cerezo, Y. Chen, T. W. Fitzgerald, S. Louzada, A. Massaia, S. McCarthy, G.R. Ritchie, Y. Xue, F. Yang, R.A. Gibbs (Principal Investigator), C. Kovar, D. Kalra, W. Hale, D. Muzny, J. G. Reid, J. Wang (Principal Investigator), X. Dan, X. Guo, G. Li, Y. Li, C. Ye, X. Zheng, D.M. Altshuler, P. Flicek (Principal Investigator) (Co-Chair), L. Clarke (Project Lead), X. Zheng-Bradley, D.R. Bentley (Principal Investigator), A. Cox, S. Humphray, S. Kahn, R. Sudbrak (Project Lead), M.W. Albrecht, M. Lienhard, D. Larson, D.W. Craig (Principal Investigator), T. Izatt, A.A. Kurdoglu, S.T. Sherry (Principal Investigator) (Co-Chair), C. Xiao, D. Haussler (Principal Investigator), G. R. Abecasis (Principal Investigator), G.A. McVean (Principal Investigator), R. M. Durbin (Principal Investigator), S. Balasubramaniam, T.M. Keane, S. McCarthy, J. Stalker, A. Chakravarti (Co-Chair), B.M. Knoppers (Co-Chair), G.R. Abecasis, K. C. Barnes, C. Beiswanger, E.G. Burchard, C.D. Bustamante, H. Cai, H. Cao, R. M. Durbin, N.P. Gerry, N. Gharani, R.A. Gibbs, C.R. Gignoux, S. Gravel, B. Henn, D. Jones, L. Jorde, J.S. Kaye, A. Keinan, A. Kent, A. Kerasidou, Y. Li, R. Mathias, G. A. McVean, A. Moreno-Estrada, P.N. Ossorio, M. Parker, A.M. Resch, C.N. Rotimi, C.D. Royal, K. Sandoval, Y. Su, R. Sudbrak, Z. Tian, S. Tishkoff, L.H. Toji, C. Tyler-Smith, M. Via, Y. Wang, H. Yang, L. Yang, J. Zhu, W. Bodmer, G. Bedoya, A. Ruiz-Linares, Z. Cai, Y. Gao, J. Chu, L. Peltonen, A. Garcia-Montero, A. Orfao, J. Dutil, J. C. Martinez-Cruzado, T.K. Oleksyk, K.C. Barnes, R.A. Mathias, A. Hennis, H. Watson, C. McKenzie, F. Qadri, R. LaRocque, P.C. Sabeti, J. Zhu, X. Deng, P. C. Sabeti, D. Asogun, O. Folarin, C. Happi, O. Omoniwa, M. Stremlau, R. Tariyal, M. Jallow, F. Sisay Joof, T. Corrah, K. Rockett, D. Kwiatkowski, J. Kooner, T. Tịnh Hiền, S.J. Dunstan, N. Thuy Hang, R. Fonnie, R. Garry, L. Kanneh, L. Moses, P. C. Sabeti, J. Schieffelin, D.S. Grant, C. Gallo, G. Poletti, D. Saleheen, A. Rasheed, L. D. Brooks, A.L. Felsenfeld, J.E. McEwen, Y. Vaydylevich, E.D. Green, A. Duncanson, M. Dunn, J.A. Schloss, J. Wang, H. Yang, A. Auton, L.D. Brooks, R. M. Durbin, E.P. Garrison, H. Min Kang, J.O. Korbel, J.L. Marchini, S. McCarthy, G. A. McVean, G.R. Abecasis, A global reference for human genetic variation, Nature 526 (2015) 68–74.

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