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Data Article

Dataset linking free polyunsaturated fatty acid concentrations in erythrocytes with chronic pain conditions in adults

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ABSTRACT

Circulating polyunsaturated fatty acids (PUFAs) and lipid mediators were extracted from human red blood cells and quantified using liquid chromatography-tandem mass spectrometry (LC-MS/MS). The method encompassed 13 different PUFAs and lipid mediators, however, due to instrument capability only five were confidently quantified (EPA, ALA, AA, DHA, and LA). The extraction focused on free polyunsaturated fatty acids since they have a strong correlation with health in humans. The study design was a secondary analysis of the OPPERA-2 study of chronic overlapping pain conditions in adults. The data included are: a) raw LC-MS/MS data (.raw); b) processed data (.xlsx) including chromatographic peak area for each compound and a concentration (ng/mL) based on external calibration with internal standardization using pure analytical grade standards and heavy-isotope labeled internal standards; c) study participant demographics and phenotypes (.xlsx). This dataset consisting of circulating PUFA quantities measured in 605 humans has been made publicly available for analysis and interpretation.

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Specifications Table

Subject	Health and medical sciences
Specific subject area	These data describe associations between omega-3 and omega-6 PUFAs and chronic pain conditions in adults. Liquid chromatography-tandem mass spectrometry and external calibration with internal standardization was used to quantify the amount of PUFAs present in human erythrocytes.
Type of data	Thermo Raw LC-MS/MS data acquired on a Thermo Triple Quadrupole utilizing multiple reaction monitoring (MRM) (repository) Table Figure Excel Spreadsheet with chromatographic peak areas and quantitation results (repository) Excel Spreadsheets with demographic and phenotypic characteristics of study participants (repository)
How the data were acquired	Data were acquired via LC-MS/MS using a Thermo triple quadrupole mass spectrometer (TSQ Vantage) and a Waters Acquity UPLC. Separations were performed on a 150 mm x 2.1 mm BEH C18 with an LC flow rate of 0.25 mL/min and a sample injection volume of 10 µL. Selected reaction monitoring (SRM) was performed in negative mode heated electrospray ionization in three segments based on chromatographic retention time. The first segment is 0-3.7 min and includes Resolvin 1 and Prostaglandin E2. The second segment takes place between 3.7-8 min and includes 9-HODE, 18-HEPE, 17-HDHA, Maresin 2, Maresin 1, Protectin D1, and Maresin 1-D5. The last segment is 8-16 min and includes EPA, ALA, LA, AA, DHA, EPA-D5, DHA-D5, and LA-D4 (Table 1). Compounds were quantified over a range of 1000 ng/mL to 0.975 ng/mL with an internal standard concentration of 50 ng/mL.
Data format	Raw LC-MS/MS files: .raw Processed LC-MS/MS data: .xlsx OPPERA2 study participant demographics: .xlsx OPPERA2 study participant phenotypes: .xlsx
Description of data collection	Data were normalized via deuterated internal standards. The sample of 605 adults were characterized based on the presence/absence of 5 common chronic pain conditions: temporomandibular disorder, headache, low back pain, irritable bowel syndrome and fibromyalgia. Liquid chromatography tandem mass spectroscopy quantified erythrocyte PUFAs.
Data source location	Institution: University of North Carolina at Chapel Hill City/Town/Region: Chapel Hill, NC Country: USA
Data accessibility	Repository name: Mendeley Data Data identification number: 10.17632/gpptkyynwr.3 Direct URL to data: https://data.mendeley.com/datasets/gpptkyynwr/3
Related research article	A.E. Sanders, E.D. Weatherspoon, B.M. Ehrmann, P.S. Soma, S.R. Shaikh, J.S. Pressier, R. Ohrbach, R.B. Fillingim, G.D. Slade. Polyunsaturated fatty acids, pressure pain thresholds, and nociplastic pain conditions. Prostaglandins Leukot Essent Fatty Acids. 2022 Sept;184:102476. https://doi.org/10.1016/j.plefa.2022.102476

Value of the Data

- These data are useful for determining quantities of free PUFAs in erythrocytes. Metadata can be used to create correlations between pain conditions and PUFAs.
- Persons studying PUFAs and/or their correlation with pain conditions can benefit from studying this data.
- These data can be used to determine future experiments by looking at concentrations of PUFAs present in different sexes, ages, and pain conditions.
- This dataset contains quantitative values of free PUFAs in erythrocytes from approximately 600 humans. Though this study focused on associations between PUFAs and chronic pain, there are many other comparisons that can be examined (such as sex, age, etc.).

- The processed and raw data have been included in a data repository. This allows other researchers to process/interpret the raw and processed data in novel ways.

1. Data Description

The files included in the repository allow for full reprocessing/viewing of the data. All Xcalibur raw files are included, with 7 different calibration curves, 28 quality controls, and all 605 erythrocyte extracts. The OPPERA2 study participant demographics spreadsheet consists of numerical identifications, age, sex, and race for all 605 participants. The OPPERA2 study participant phenotypes spreadsheet includes age, sex, race, and numerical values corresponding to 5 pain conditions: temporomandibular myalgia (TMD), headache, irritable bowel syndrome (IBS), low back pain (LBP), and fibromyalgia.

Table 1 shows detailed information about the LC-MS/MS methodology including retention time (min), precursor ion (*m/z*), product ion (*m/z*), and collision energy (V) for each compound. These parameters were used in the companion article to measure quantities of circulating PUFAs in human erythrocytes [1]. Though the companion article focused on EPA, ALA, DHA, ARA, and LA; the data for all 13 compounds are included in the data repository [2]. The erythrocytes extracted and analyzed originated from the OPPERA2 study and were categorized by the following pain conditions: temporomandibular disorder, headache, low back pain, irritable bowel syndrome and fibromyalgia [3].

The limit of detection (LOD) and limit of quantitation (LOQ) are listed in Table 2 for each compound on the LC-MS/MS system used for analysis (Thermo TSQ Vantage coupled to a Waters Acquity UPLC). Any value below the LOQ should not be used as an accurate estimation of quantity since it cannot accurately be estimated by the system/calibration curve. Values under the LOD may result in negative value estimations, these should not be regarded as true values. Treat values under the LOD as not present. Eight compounds were below the limit of detection or quantitation, likely in part because the extraction focused on free PUFAs versus total (circulating and glycerophospholipid bound). The circulating PUFAs have been indicated to correlate with health impacts in humans [4–6], though future analyses will focus on total PUFAs to increase the potential measurement of the analysis.

The chromatography is demonstrated in Fig. 1. Lipid mediators (PUFA metabolites) were fully resolved and separated from similar metabolites as well as their PUFA predecessors. There may

Table 1
Fatty acids with corresponding SRM transitions (quadrupole 1 m/z, quadrupole 3 m/z, and collision energy).

Analyte	Retention Time (min)	Q1 (m/z)	Q3 (m/z)	Collision Energy (V)
Eicosapentaenoic acid (EPA)	9.44	301.3	257.2	16
α-linolenic acid (ALA)	9.53	277.2	233.1	15
Docosahexaenoic acid (DHA)	9.72	327.3	283.4	14
Arachidonic acid (ARA)	9.92	303.0	259.0	17
Linolenic acid (LA)	10.20	279.2	261.1	20
Resolvin 1 (RVE1)	2.02	349.2	205.1	20
Prostaglandin E2 (PGE2)	2.76	351.2	271.2	20
Protectin D1 (PD1)	4.05	359.2	206.1	19
Maresin 1 (MR1)	4.26	359.2	250.3	19
Maresin 2 (mr2)	5.04	359.2	147.1	18
18-HEPE	6.17	317.1	215.1	15
9-HODE	7.21	295.3	171.2	20
17-HDHA	7.26	343.2	281.2	15
Maresin 1-d5*	4.26	364.1	302.3	18
EPA-d5*	9.44	306.1	262.3	14
DHA-d5*	9.72	332.1	288.4	14
LA-d4*	10.2	283.1	265.3	14

* Functioned as a deuterated internal standard.

Table 2
Polyunsaturated fatty acids with their limit of detection (LOD), and limit of quantitation (LOQ) according to LC-MS/MS analysis.

Analyte	Limit of Detection[1](ng/mL)	Limit of Quantitation[2](ng/mL)
Prostaglandin E2	0.060	1.9
Protectin D1	0.060	1.9
Maresin 1	0.060	3.9
Maresin 2	0.11	3.9
Eicosapentaenoic acid	0.67	7.8
α-linolenic acid	7.8 *	15
Docosahexaenoic acid	0.25	1.9
Arachidonic acid	1.5	3.9
Linolenic acid	0.97 *	7.8
Resolvin E1	0.13	3.9
18-HEPE	0.65	1.9
17-HDHA	0.60	0.98
9-HODE	0.70	1.9

[1] Limit of detection was calculated using the formula $LOD = 3s \div m$ where s is the standard deviation of the control and m is the slope from the linear regression. Values denoted with a * are observed limited of detections instead of calculated.
[2] Limit of quantitation was determined as the lowest concentration of standard in the calibration curve that provided a residual of less than 15%.

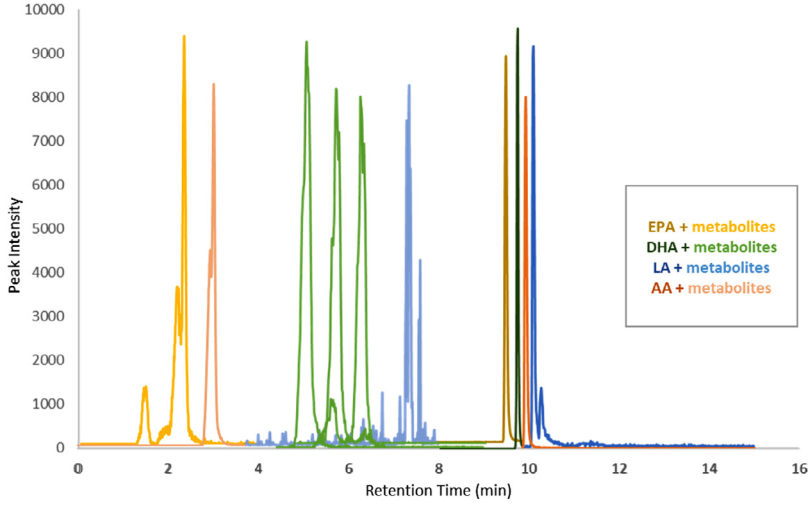

Fig. 1. A standard mixture showcasing the chromatagraphic separation of PUFA standards. Eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), arachidonic acid (AA), and linoleic acid (LA) are pictured in dark colors with their metabolites pictured in lighter colors. All of the metabolites elute prior to the original poly unsaturated fatty acids. Peak intensity has been normalized to 100% relative intensity.

be co-elution between similar mediators, only the compounds listed in Table 2 were monitored. An example of this would be co-elution of Protectin D1 and Protectin D2. Since the other forms of the mediators were not analyzed we are not certain whether co-elution is present or not. This methodology can be implemented on many different LC-MS/MS systems for PUFA quantification.

2. Experimental Design, Materials and Methods

This study used data from OPPERA-II, the second phase of the Orofacial Pain Prospective Evaluation and Research Assessment (OPPERA) study. OPPERA-II was conducted between 2014 and

2016 as a follow-up of 543 OPPERA participants along with an additional 127 adults aged 18-74 years with TMD. The main objective of OPPERA-II was to study the overlap of TMD with other idiopathic pain conditions. Participants underwent clinical examinations and completed standardized questionnaires and a venous non-fasting blood draw. This study used meta data and biospecimens from OPPERA-II participants.

From each participant, a 20 mL sample of circulating blood was obtained by venipuncture and collected into tubes containing EDTA that were promptly centrifuged for 10 min at 4°C. Erythrocytes were washed with sodium perborate, vortexed and again centrifuged. After removing the sodium perborate supernatant, erythrocytes were aliquoted into 400 µL cryotubes and stored at -80°C.

Red blood cells were stored at -80°C until extraction. For each sample 150 µL of red blood cells were extracted with 1 mL of 90:10 methanol to water. Samples were vortexed then centrifuged at 20,000 rcf for 10 minutes. The supernatant was dried down and resuspended in 150 µL of 90:10 methanol to water containing deuterated internal standards (50 ng/mL). Two quality control standards with known concentrations (20 and 500 ng/mL) as well as the deuterated internal standard mixture were analyzed twice per batch of 96 samples to ensure accuracy and reproducibility. The calibration curve was analyzed twice per batch of 96 samples and averaged to minimize error across the analysis, using standard deviation as error bars.

Analysis was conducted using a Waters Acquity Ultra-Performance Liquid Chromatography system tandem to a ThermoScientific TSQ Vantage as published [1].

Ethics Statements

This current study used data and biospecimens from OPPERA-II participants. The study was reviewed and approved by the UNC Office of Human Research Ethics (study 13-2232). All study participants verbally agreed to a screening interview done by telephone and provided informed, signed consent for all other study procedures. The study was completed in accordance of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

Dataset linking free polyunsaturated fatty acid concentrations in erythrocytes with chronic pa in conditions in adults (Original data) (Mendeley Data)

CRediT Author Statement

Paul S. Soma: Methodology, Validation, Writing – review & editing; **Brandie M. Ehrmann:** Methodology, Resources, Supervision; **Gary D. Slade:** Conceptualization, Resources; **Anne E. Sanders:** Conceptualization, Formal analysis, Data curation, Visualization; **E. Diane Weatherspoon:** Methodology, Validation, Investigation, Formal analysis, Writing – original draft.

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