

## Biomarkers (non-neuroimaging) / novel biomarkers

# Docosahexaenoic acid oxylipins are associated with white matter microstructural integrity in a cohort of cognitively normal, hypertensive young-old

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**Abstract**

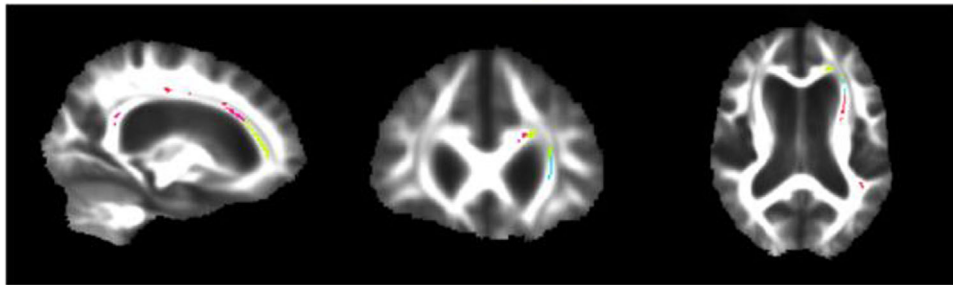
**Background:** Previous studies investigating potential beneficial effects of Omega-3 Polyunsaturated Fatty Acids (PUFA) on vascular health have shown inconsistent results. Oxylipins, produced from the oxidation of PUFAs, have potent vascular effects shown to be relevant to human disease. We have previously reported the cytochrome P450-derived Omega-3 PUFA Docosahexaenoic acid (DHA) oxylipin 16,17-EpDPE to be associated with less cerebral white matter hyperintensities (WMH), while a ratio of its soluble epoxide hydrolase (sEH) products, 19,20-DiHDPE/19,20-EpDPE were associated with higher WMH. Relationships between DHA and its oxylipin products and microstructural white matter integrity is unknown.

**Method:** 36 cognitively intact subjects with low blood omega-3 levels, controlled hypertension, 55 years or older, enrolled in a study investigating fish oil and lipoic acid on preserving cognitive function, underwent baseline MRI and plasma PUFA oxylipins measured by liquid chromatography tandem mass spectrometry. Voxel-wise associations between Diffusion Tensor Imaging (DTI) metrics, including fractional anisotropy (FA), radial (RD) and axial (AD) diffusivity, and DHA and oxylipins were examined using Tract-Based Spatial Statistics, adjusted for age and sex.

**Result:** Higher DHA oxylipin 16, 17-EpDPE was associated with increased FA clusters within the inferior frontal-occipital fasciculus, and the cingulate and anterior thalamic radiation tracts. Higher DHA oxylipin ratio 19, 20-DiHDPE/19, 20-EpDPE was associated with decreased FA in those same regions, as well as in the superior and inferior longitudinal fasciculi and corticospinal tract. Increased RD clusters were observed in some corresponding regions in relation to 19, 20-DiHDPE/19, 20-EpDPE. DHA was not related to DTI measures.

**Conclusion:** The oxylipin 16,17-EpDPE, an epoxide, is associated with greater DTI white matter integrity, while a ratio of 19,20-DiHDPE/19,20-EpDPE, is associated with decreased DTI white matter integrity, in a hypertensive young-old cohort. Protective epoxides are converted to diols by sEH, the ratio of diol/epoxide is an indirect measure of sEH activity. Affected areas were found largely in long-range association fibers, important for intrahemispheric cortical connectivity, with extension beyond areas of macrostructural WMH lesions. DHA-derived cytochrome P450 oxylipins, not DHA, are associated with DTI white matter integrity with differential effects observed. Targeting specific DHA oxylipin products is warranted for the effective prevention of cerebrovascular disease.

**Figure 1.** Significant White Matter Tract Clusters: FA and 19,20-DiHDPA/19,20-EpDPE  $p < 0.05$



**FIGURE 1**

**TABLE 1**

**Table 1.** Subject Characteristics

Variable (units)	Mean (SD or %)
Age (years)	65.6 (7.1)
Female	22/36 (61.1)
Race (White)	32/36 (88.9)
College or greater	28/36 (77.8)
Systolic BP (mmHg)	133.1 (14.3)
Diastolic BP (mmHg)	74.1 (10.6)
White Matter Hyperintensity (cc)*	6.0 (10.0)
Linoleic Acid (mcg/ml)	386.3 (78.2)
Arachidonic Acid (mcg/ml)	245.1 (66.1)
Eicosapentaenoic Acid (mcg/ml)	27.0 (11.6)
Docosahexaenoic Acid (mcg/ml)	52.5 (22.7)

TABLE 2

Table 2. TBSS metrics in relation to PUFA, Oxylipin, and Epoxide/Diol

PUFA and Oxylipins	FA p value	AD p value	RD p value
DHA	0.357	0.242	0.287
16,17-EpDPE	0.032	0.191	0.075
19,20-DiHDPE/19,20-EpDPE	0.016	0.088	0.042

TABLE 3

Table 3. White Matter Tract Clusters in which higher FA is associated with higher 16,17-EPDPE ( $p < 0.05$ )

Regional Tract	Total significant voxels
Inferior fronto-occipital fasciculus L	199
Inferior fronto-occipital fasciculus R	160
Cingulum (cingulate gyrus) R	102
Anterior thalamic radiation R	58

TABLE 4

Table 4. White Matter Tract Clusters in which lower FA is associated with higher 19,20-DiHDPA/19,20-EpDPE ( $p < 0.05$ )

Regional Tract	Total significant voxels
Superior longitudinal fasciculus R	662
Inferior fronto-occipital fasciculus L	302
Cingulum (cingulate gyrus) R	247
Inferior fronto-occipital fasciculus R	246
Inferior longitudinal fasciculus R	120
Anterior thalamic radiation R	87
Corticospinal tract R	64
Cingulum (hippocampus) L	20
Uncinate fasciculus R	8

TABLE 5

**Table 5.** White Matter Tract Clusters in which higher RD is associated with higher 19,20-DiHDP/19,20-EpDPE  $p < 0.05$

Regional Tract	Total significant voxels
Superior longitudinal fasciculus R	187
Inferior fronto-occipital fasciculus R	89
Corticospinal tract R	24
Anterior thalamic radiation R	13