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**Title:** Low omega-3 fatty acid levels associate with frequent gout attacks – a case control study

**Authors:** A Abhishek<sup>1</sup>, Ana M Valdes<sup>1</sup>, Michael Doherty<sup>1</sup>

**Affiliation:** Academic Rheumatology, University of Nottingham, Clinical Sciences Building, Nottingham City Hospital, Nottingham NG5 1PB, UK

**Address for correspondence:**

Dr. A. Abhishek, PhD

Academic Rheumatology

University of Nottingham

Nottingham NG5 1PB

United Kingdom

Phone: +44 115 8231392

Fax: +44 115 8231757

Email: [Abhishek.abhishek@nottingham.ac.uk](mailto:Abhishek.abhishek@nottingham.ac.uk)

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Eicosapentaenoic acid and docosahexaenoic acid are omega-3 polyunsaturated fatty acids with anti-inflammatory effects. They inhibit several pathways like toll like receptor activation, NALP-3 inflammasome assembly, neutrophil chemotaxis, prostaglandin synthesis and nucleating factor-kB activity through which monosodium urate (MSU) crystals induce inflammation (1-6). In keeping with these findings, mice fed on diet rich in omega-3 fatty acids developed less inflammation after subcutaneous injection of MSU crystals than those on standard diets (1, 7). Thus, omega-3 fatty acids have the potential of preventing acute attacks of gout. However, the association between omega-3 fatty acid levels and frequency of gout attacks has not been examined in humans. The objective of this study was to examine if omega-3 fatty acid levels associate with frequent gout attacks.

This study was approved by the Nottinghamshire Research Ethics Committee-1. Data from 112 men with gout meeting the American College of Rheumatology classification criteria for gout and recruited from primary care were used (8). Patients were seen for one visit, had detailed metrologist assessments including height and weight measurement, self-reported their gout attack frequency in the previous 12 months, and had blood taken for measurement of omega-3 fatty acid and serum uric acid (SUA). For the present study, cases had >2 acute attacks while controls had ≤2 acute attacks of gout in the preceding 12 months. Odds ratio (OR) and 95% confidence intervals (95%CI) were calculated to examine the association between omega-3 fatty acid levels and gout attack frequency. This was adjusted for age, body mass index (kg/m<sup>2</sup>), disease duration and SUA (tertiles); and tophi, urate lowering treatment (absent or present) using binary logistic regression. Statistical analyses were carried out using Stata. Statistical significance was  $p < 0.05$ .

The characteristics of the study participants are described in Table 1. The mean (SD) omega-3 fatty acid level was 0.41 (0.11) mmol/L. There was a non-significant trend for a negative association between omega-3 fatty acid levels and >2 acute attacks of gout in the previous 12 months (OR (95%CI) 0.68 (0.46-1.02)  $p_{trend}$  0.06), however, it became significant after adjusting for covariates (aOR (95%CI) 0.62 (0.38 - 0.98),  $p_{trend}$  0.043) (Figure 1).

This is the first report of an association between high omega-3 fatty acid levels and infrequent acute attacks of gout. This novel finding raises the possibility that supplementation with omega-3 fatty acids may be used to prevent acute attacks of gout. However, there are several caveats to the study. Firstly, the frequency of gout attack was self-reported retrospectively, and may be affected by biased recall. However, self-reported gout attack frequency is unlikely to be affected by the omega-3 fatty acids levels, and will not result in a differential misclassification bias. Additionally, information about other factors that may affect gout attack frequency e.g. purine-rich alcohol consumption, red meat intake, and both gout attack frequency and omega-3 fatty acid levels e.g. sea-food intake were not available. Thus, the findings of this study should be confirmed in other studies in which information on lifestyle and dietary risk factors that affect gout attack frequency are collected.

**Competing Interests** None declared

**Contributorship** AA, AV and MD conceived the study. AA performed the data analysis. AA, AV and MD critically appraised the manuscript and approved the final version

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**Ethical approval information** Approved by the Nottinghamshire Research Ethics Committee-1

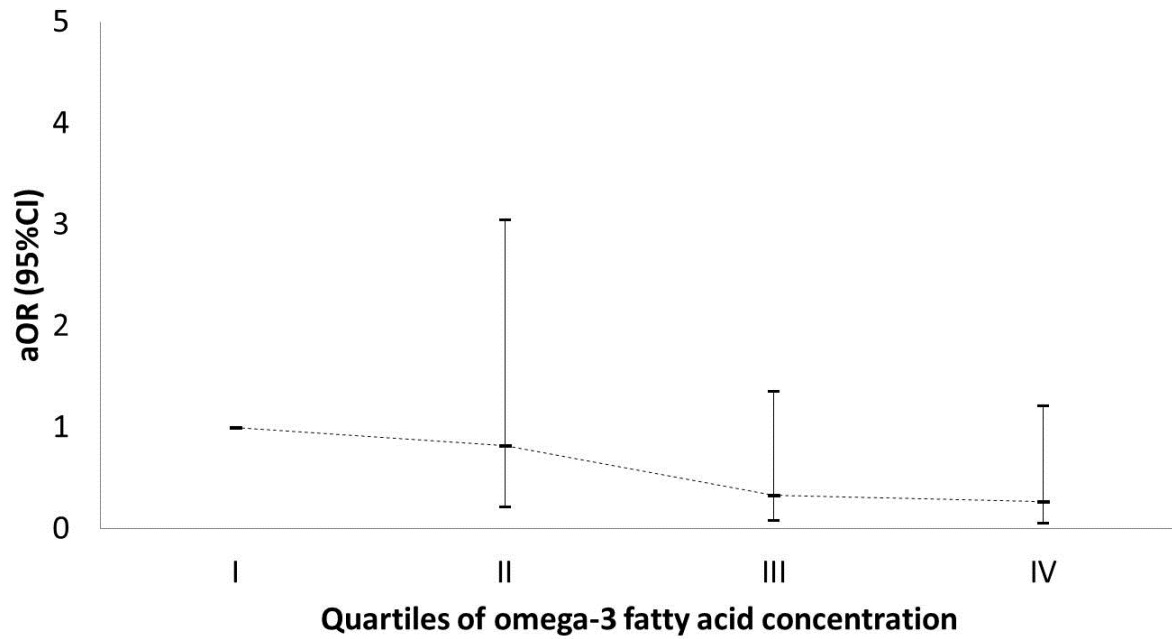
**Data sharing statement** Data used in this study are held in Academic Rheumatology, University of Nottingham, UK, under the custody of Prof. Michael Doherty and can be made available on request.

**Table 1** Disease and demographic characteristics of the study participants

	Cases (n= 31)	Controls (n=81)	<i>p</i> value
Age, mean (SD) <sup>1</sup>	59.67 (11.45)	64.44 (10.22)	0.03
BMI, mean (SD)	29.54 (5.32)	29.86 (4.57)	0.76
Disease duration, mean (SD)	9.53 (7.52)	12.93 (10.89)	0.11
Tophi, n (%) present	4 (12.9%)	4 (5.0%)	0.14
Serum uric acid, mean (SD)	424.52 (112.70)	391.77 (98.33)	0.13
n (%) on urate lowering treatment	11 (35.5%)	36 (44.44%)	0.74
Omega-3 fatty acid, range (mmol/L)			
≤0.355	9	18	
0.361 - 0.4025	10	16	
0.4067 – 0.4648	5	21	
≥ 0.4659	4	22	0.06 <sup>2</sup>

<sup>1</sup> SD (Standard Deviation); <sup>2</sup>p<sub>trend</sub>

Figure 1 Negative association between frequent gout attacks and increasing concentration of omega 3 fatty acid. The aOR for frequent gout attack reduces with increasing concentration of omega 3 fatty acid.



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