High erythrocyte levels of the n-6 polyunsaturated fatty acid linoleic acid are associated with lower risk of subsequent rheumatoid arthritis in a Southern European nested case-control study.

Paola de Pablo,[1] Dora Romaguera,[2,3] Helena L Fisk,[4] Philip C Calder,[4] Anne-Marie Quirke,[5] Alison J Cartwright,[5] Salvatore Panico,[6] Amalia Mattiello,[6] Diana Gavrila,[7,8] Carmen Navarro,[7,8,9] Carlotta Sacerdote,[10] Paolo Vineis,[11,12] Rosario Tumino,[13] William E Ollier,[14] Dominique S Michaud,[2,15] Elio Riboli,[2] Patrick J Venables,[5] Benjamin A Fisher.[1]

[1] Rheumatology Research Group and Arthritis Research UK Rheumatoid Arthritis Pathogenesis Centre of Excellence (RACE), Institute of Inflammation and Ageing, University of Birmingham, Birmingham, UK

[2] School of Public Health, Imperial College London, London, UK

[3] CIBER-OBN (Fisiopatología de la Obesidad y Nutrición), and IdISBa, University Hospital Son Espases, Palma, Spain

[4] Faculty of Medicine, University of Southampton, outhampton UK and NIHR Southampton Biomedical Research Centre, University Hospital Southampton NHS Foundation Trust and University of Southampton, Southampton, UK

[5] Kennedy Institute of Rheumatology, University of Oxford, Oxford, UK

[6] Department of Clinical and Experimental Medicine, Federico II University of Naples, Naples, Italy

[7] Department of Epidemiology, Murcia Regional Health Council, IMIB-Arrixaca, Murcia, Spain

[8] CIBER Epidemiología y Salud Pública (CIBERESP), Spain

[9] Department of Health and Social Sciences, Universidad de Murcia, Murcia, Spain

[10] Unit of Cancer Epidemiology, Città della Salute e della Scienza University-Hospital and Center for Cancer Prevention (CPO), Turin, Italy

[11] Human Genetics Foundation, Turin, Italy

[12] MRC-PHE Centre for Environment and Health, School of Public Health, Imperial College London, London, UK

[13] Cancer Registry and Histopathology Unit, "Civic - M.P.Arezzo" Hospital, ASP Ragusa, Italy

[14] Centre for Integrated Genomic Medical Research, Division of Population Health, Faculty of Biology, Medicine and Health, University of Manchester, Manchester, UK

[15] Department of Public Health and Community Medicine, Tufts University Medical School, Boston, MA, USA

Corresponding author: Dr Benjamin Fisher, Centre for Translational Inflammation Research, Queen Elizabeth Hospital Birmingham, Birmingham, B15 2WB, UK

b.fisher@bham.ac.uk

Online Supplementary Table 1. Multivariate negative binomial regression models on the association between serum cytokines and erythrocyte membrane linoleic acid (LA), total n-3 PUFA, n-6 PUFA, and the n-3/n-6 PUFA ratio in the control population.

	TNF	IL-1	IL-2	IL-4	IL-5	IL-6	IL-10	IL-12	IL-13	IFN-γ
	RR 95% CI*	RR 95% CI	RR 95% CI	RR 95% CI	RR 95% CI	RR 95% CI	RR 95% CI	RR 95% CI	RR 95% CI	RR 95% CI
Fatty acids										
LA										
Model 1	**1.09 (1.04-1.15)**	1.0 (0.94-1.19)	0.99 (0.89-1.10)	**0.84 (0.78-0.91)**	**0.55 (0.48-0.62)**	**1.07 (1.02-1.12)**	**0.62 (0.56-.68)**	**0.76 (0.65-0.88)**	**0.53 (0.45-0.62)**	1.06 (0.98-1.14)
Model 2	**1.11 (1.06-1.17)**	1.03 (0.93-1.15)	0.90 (0.78-1.04)	**0.88 (0.81-0.95)**	**0.78 (0.69-0.89)**	**1.08 (1.03-1.14)**	**0.87 (0.78-0.96)**	**0.84 (0.71-0.99)**	**0.78 (0.66-0.91)**	**0.90 (0.82-0.98)**
n-3PUFA										
Model 1	**1.12 (1.00-1.26)**	0.89 (0.75-1.06)	**1.51 (1.16-1.96)**	0.93 (0.77-1.11)	0.30 (0.22-0.43)	0.99 (0.89-1.10)	**0.32 (0.24-0.42)**	0.74 (0.52-1.05)	**0.27 (0.18-0.41)**	0.95 (0.77, 1.16)
Model 2	1.09 (0.97-1.23)	0.86 (0.72-1.01)	**1.45 (1.10-1.93)**	1.01 (0.84-1.21)	0.88 (0.67-1.16)	0.96 (0.87-1.07)	0.88 (0.71-1.09)	0.91 (0.62-1.34)	0.85 (0.60-1.19)	0.78 (0.64-0.95)
n-6 PUFA										
Model 1	**1.06 (1.02-1.10)**	**1.07 (1.00-1.15)**	0.99 (0.88-1.12)	0.88 (0.82-0.93)	**0.63 (0.59-0.67)**	**1.05 (1.02-1.09)**	**0.69 (0.66-0.73)**	**0.77 (0.71-0.85)**	**0.61 (0.56-0.66)**	**1.11 (1.05-1.17)**
Model 2	**1.06 (1.01-1.10)**	**1.12 (1.04-1.19)**	0.99 (0.88-1.12)	0.92 (0.86-0.98)	**0.81 (0.75-0.88)**	**1.06 (1.02-1.10)**	**0.87 (0.81-0.92)**	**0.80 (0.73-0.88)**	**0.81 (0.73-0.90)**	0.99 (0.93, 1.06)
Ratio n-3/n-6**										
Model 1	1.15 (0.64-2.07)	**0.38 (0.16-0.92)**	**4.70 (1.27-17.3)**	**3.07 (1.22-7.68)**	**228 67-777)**	0.67 (0.40-1.12)	**244 (83-720)**	**10.9 (2.30-51.45)**	**339 (75-1539)**	**0.31 (0.11-0.87)**
Model 2	1.04 (0.57-1.90)	**0.24 (0.10-0.57)**	**5.54 (1.30-23.5)**	2.43 (0.97-6.08)	**6.12 (1.70-22)**	0.62 (0.37-1.06)	**3.54 (1.27-9.83)**	**11.7 (2.65-51.55)**	**7.06 (1.41-35.24)**	0.48 (0.18-1.27)

* The exponentiated regression coefficients (relative risk [RR]) have interpretation as a ratio of means. Model 1: Age- and sex-adjusted; Model 2: Model 1 with further adjustment for BMI, country of origin and smoking status; ** Log-transformed for analyses. Results in bold indicate p<0.05.

Online Supplementary Table 2. Multivariate negative binomial regression models on the association between serum cytokines and erythrocyte membrane linoleic acid (LA), total n-3 PUFA, n-6 PUFA, and the n-3/n-6 PUFA ratio in the pre-RA group.

	TNF	IL-1	IL-2	IL-4	IL-5	IL-6	IL-10	IL-12	IL-13	IFN-γ
	RR 95% CI*	RR 95% CI	RR 95% CI	RR 95% CI	RR 95% CI	RR 95% CI	RR 95% CI	RR 95% CI	RR 95% CI	RR 95% CI
Fatty acids										
LA										
Model 1	**1.12 (1.05-1.18)**	1.03 (0.88-1.21)	1.04 (0.90-1.20)	0.97 (0.85-1.11)	0.99 (0.87-1.13)	**0.84 (0.78-0.91)**	0.99 (0.89-1.09)	0.91 (0.77-1.06)	1.01 (0.86-1.18)	1.08 (0.98-1.19)
Model 2	**1.13 (1.05-1.22)**	**1.21 (1.02-1.43)**	1.02 (0.85-1.23)	1.03 (0.88-1.22)	**0.84 (0.71-0.98)**	**0.86 (0.78-0.95)**	0.93 (0.83-1.05)	**0.79 (0.64-0.97)**	**0.80 (0.66-0.97)**	1.07 (0.95-1.21)
n-3 PUFA										
Model 1	0.92 (0.77-1.08)	0.84 (0.57-1.26)	0.92 (0.63-1.35)	0.93 (0.65-1.32)	1.04 (0.73-1.46)	1.16 (0.95-1.43)	0.93 (0.73-1.20)	0.97 (0.65-1.42)	1.16 (0.77-1.75)	0.95 (0.73-1.22)
Model 2	0.87 (0.73-1.02)	0.81 (0.54-1.23)	0.85 (0.55-1.32)	0.87 (0.60-1.26)	0.93 (0.65-1.34)	1.09 (0.89-1.34)	0.89 (0.67-1.17)	0.99 (0.64-1.55)	1.00 (0.64-1.56)	0.90 (0.68-1.19)
n-6 PUFA										
Model 1	1.05 (0.99-1.10)	1.07 (0.96-1.20)	1.08 (0.96-1.22)	1.03 (0.92-1.14)	0.99 (0.89-1.10)	0.97 (0.91-1.03)	1.01 (0.93-1.08)	0.98 (0.87-1.11)	1.00 (0.88-1.14)	1.06 (0.98-1.15)
Model 2	1.03 (0.97-1.09)	**1.19 (1.05-1.35)**	1.06 (0.92-1.21)	1.05 (0.93-1.19)	0.95 (0.86-1.06)	1.00 (0.944-1.07)	0.99 (0.91-1.07)	0.93 (0.80-1.07)	0.94 (0.83-1.08)	1.05 (0.96-1.15)
Ratio n-3/n-6**										
Model 1	**0.36 (0.15-0.86)**	**0.15 (0.02-1.27)**	0.22 (0.02-1.95)	0.52 (0.07-3.77)	1.32 (0.21-7.93)	3.23 (0.97-10.7)	0.68 (0.18-2.55)	1.12 (0.12-10.25)	1.98 (0.22-17.6)	0.33 (0.08-1.37)
Model 2	**0.33 (0.14-0.82)**	**0.06 (0.01-0.53)**	0.25 (0.02-2.54)	0.32 (0.04-2.50)	1.45 (0.24-8.87)	1.49 (0.42-5.20)	0.69 (0.17-2.74)	2.05 (0.18-22.44)	1.82 (0.20-16.3)	0.34 (0.08-1.51)

* The exponentiated regression coefficients (relative risk [RR]) have interpretation as a ratio of means. Model 1: Age- and sex-adjusted; Model 2: Model 1 with further adjustment for BMI, country of origin and smoking status. ** Log-transformed for analyses. Results in bold indicate p<0.05.