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Erythrocyte omega-3 polyunsaturated fatty acid levels are associated with biomarkers of inflammation in older Australians

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ABSTRACT

Background: Elevated levels of pro-inflammatory mediators heighten the risk of developing or aggravating a spectrum of chronic diseases and are a strong predictor of mortality in elderly cohorts. Omega-3 polyunsaturated fatty acids (n-3PUFA), including eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are known to possess anti-inflammatory properties. However, the relationship between erythrocyte membrane n-3PUFA and inflammation biomarkers has not been well established.

Objective: This study aimed to determine if n-3PUFA status, together with the omega-3 index (O3I, erythrocyte membrane % EPA plus DHA), is associated with pro-inflammatory mediators in older Australians.

Methods: The study was a cross-sectional analysis of randomly selected older men and women aged ≥65 years (n = 620) recruited from the Central Coast of NSW, Australia. Fasted blood samples were analysed for C-reactive protein (CRP), fibrinogen and full blood count using standardised laboratory methods. The fatty acid composition of erythrocyte membranes was analysed via gas chromatography to determine n-3PUFA levels. The relationships between n-3PUFA and inflammatory mediators were evaluated in multivariate regression models after adjusting for known inflammatory confounders.

Results: After excluding participants who had an inflammatory disease, CRP levels >10 mg/L, or who were taking anti-inflammatory medications or n-3PUFA supplements, 126 participants (age 77.6 ± 7.3 years; females, 46%) were included in the analysis. After multivariate adjustments, O3I was inversely associated with CRP ($\beta = -0.209$, $p < 0.05$) and monocyte cell counts ($\beta = -0.205$, $p < 0.05$), and total n-3PUFA was inversely related to WBC ($\beta = -0.238$, $p < 0.05$), neutrophils ($\beta = -0.212$, $p < 0.05$) and monocytes ($\beta = -0.246$, $p < 0.05$). However no association between fibrinogen and O3I or total n-3PUFA was detected.

Conclusions: This study demonstrated a negative association between O3I and biomarkers of inflammation in an older population. The findings support a potential role for n-3PUFA supplementation in the management of inflammatory diseases.

1. Introduction

Pro-inflammatory mediators (including cytokines and eicosanoids) have been shown to be elevated in elderly people by as much as two-to four-fold, when compared to a younger population [1]. Sustained low grade inflammation indicated by increased circulating levels of C-reactive protein (CRP) is a strong predictor of mortality in elderly cohorts irrespective of concurrent morbidities or other known risk factors such as smoking or high blood pressure [1]. The inflammatory process is designed to help fight infection, remove harmful substances and repair damaged tissue and organ systems [2]. Although this process is generally protective, failure to resolve the inflammatory response can result in chronic inflammation, which may lead to the development and progression of a

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spectrum of chronic diseases including coronary vascular disease, Alzheimer's disease, depression, rheumatoid arthritis, cancer, sarcopenia and reduced physical functioning [1,3–5].

Elevated levels of acute phase proteins, C-reactive protein (CRP) and fibrinogen are reliable markers of sustained low grade systemic inflammation [6–8]. CRP and fibrinogen are released by hepatocytes in response to elevated cytokine levels during the acute inflammatory response. Fibrinogen is also a principal protein involved in blood clotting [7].

Omega-3 polyunsaturated fatty acids (n-3PUFA) of marine origin have attracted attention due to their anti-inflammatory effects [9]. The proposed mechanisms by which n-3PUFA mediates these effects include preferential incorporation of n-3PUFA into phospholipids resulting in the production of 3-series eicosanoids with lower biological activity, production of inflammation resolving lipid mediators (resolvins and protectins) and altered cytokine gene expression [2].

Most epidemiological and experimental studies have shown an association between higher plasma n-3PUFA levels and reductions in circulating plasma inflammatory mediators; interleukin-6 (IL-6), tumour necrosis factor-alpha (TNF-α) and CRP [10–13]. However, randomised controlled trials involving n-3PUFA supplementation have produced inconsistent results. Rangel-Heurta et al. were unable to draw a clear conclusion on the association between plasma n-3PUFA levels and reductions in inflammatory mediators, due to heterogeneity in study methodologies that include variations in study population, supplement dosage, study length, and sample size [14]. The strongest associations between plasma n-3PUFA levels and inflammatory mediators have been found in older populations, and in populations with elevated inflammatory biomarkers [15,16]. More recently a meta-analysis of randomised controlled trials by Li et al. reported a reduction in inflammatory mediators upon n-3PUFA supplementation in healthy and diseased populations [17].

The omega-3 index (O3I) is defined as the sum of EPA and DHA expressed as a percentage of total erythrocyte fatty acids [18]. O3I has been shown to correlate with n-3PUFA levels in body tissues [18] and is considered a reliable biomarker of long term n-3PUFA intake. The determination of O3I provides an opportunity to examine potential associations between n-3PUFA dietary intake and reductions in inflammatory biomarkers such as CRP and fibrinogen. To date, the association of O3I levels and inflammatory biomarkers has only been explored within unhealthy or moderately hypertriglyceridemic populations and has produced inconsistent results [12,19,20]. The aim of this project was to determine if n-3PUFA status, and in particular O3I, is associated with inflammatory mediators in older Australians. Our recent studies have demonstrated that the association between n-3PUFA status and chronic disease risk factors is sex-dependent [21,22], therefore, we examined the relationship between n-3PUFA and inflammation mediators separately in older men and women.

2. Materials and methods

2.1. Study population and design

This study is a cross-sectional analysis of data collected as part of the Retirement Health and Lifestyle Study (RHLS); a study of the health and lifestyle of older Australians (65 years and older) residing in retirement villages or within the community in the Central Coast region of NSW, Australia. Participants were eligible for the RHLS if they: were $\geq$65 years of age; their primary residence was located within the Wyong or Gosford Local Government Areas; and they had been living at their current address for $\geq$12 months. Participants were not eligible if: they were not living independently or were residing in a communal setting other than a retirement village; another member of their household was taking part in the study; they had language and/or other communicative difficulties that limited participation; or they were cognitively impaired and/or were unable to provide informed consent. Those who were eligible and chose to participate in the study (n = 831) took part in an interviewer-administered questionnaire (IAQ) adapted from validated lifestyle surveys [21–24]. A subset of eligible participants completed a clinical assessment (n = 670) and provided a blood sample (n = 649). Participants were included in the present study if they had erythrocyte samples available for fatty acid analyses (n = 620) and valid anthropometric and inflammatory marker measurements. Participants with CRP levels $\geq$10 mg/L (indicative of acute inflammation), and/or who reported inflammatory disease (e.g. arthritis), and/or that they were taking anti-inflammatory medication or n-3PUFA supplements [25] were excluded from the analyses. All subjects provided written informed consent, and the study was approved by the University of Newcastle Human Research Ethics Committee (H-2008-0431) and the Northern Sydney Central Coast Health Human Research Ethics Committee (Reference No. 1001-031M). The participant recruitment process is summarised in Fig. 1.

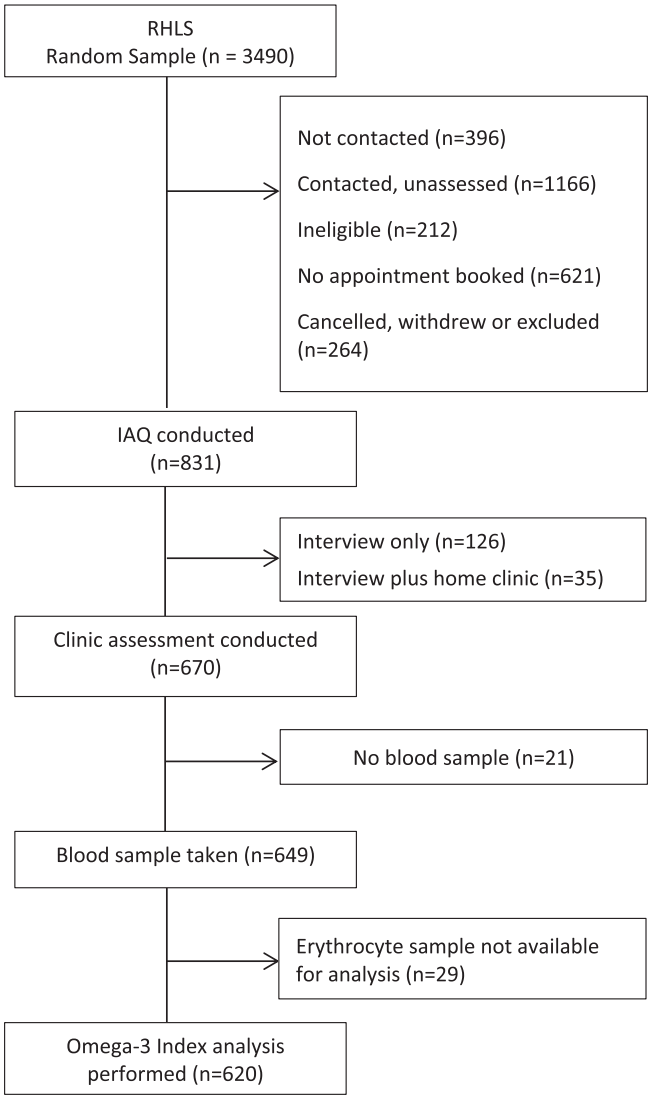

Fig. 1. Overview of participant recruitment.