Nutrition, Metabolism & Cardiovascular Diseases (2014) **24**, 1234–1239

Available online at www.sciencedirect.com

Nutrition, Metabolism & Cardiovascular Diseases

journal homepage: www.elsevier.com/locate/nmcd

Omega-3 fatty acids and the genetic risk of early onset acute coronary syndrome

S.S.L. Leung Yinko [a,b], G. Thanassoulis [b,c], K.D. Stark [d], M. Avgil Tsadok [b], J.C. Engert [e,f,1], L. Pilote [a,b,g,*,1], for the GENESIS-PRAXY investigators[2]

[a] Department of Epidemiology, Biostatistics and Occupational Health, McGill University, Montreal, Quebec, Canada
[b] Division of Clinical Epidemiology, Research Institute of McGill University Health Centre, Montreal, Quebec, Canada
[c] Division of Cardiology, McGill University Health Centre, Montreal, Quebec, Canada
[d] Department of Kinesiology, University of Waterloo, Waterloo, Ontario, Canada
[e] Department of Medicine, McGill University, Montreal, Quebec, Canada
[f] Department of Human Genetics, McGill University, Montreal, Quebec, Canada
[g] Division of General Internal Medicine, McGill University Health Centre, Montreal, Quebec, Canada

Received 12 February 2014; received in revised form 30 May 2014; accepted 3 June 2014
Available online 13 June 2014

KEYWORDS
Diet;
Genes;
Genetics;
Lipids;
Nutrition

Abstract *Background and aims:* Recent gene-environment interaction studies suggest that diet may influence an individual's genetic predisposition to cardiovascular risk. We evaluated whether omega-3 fatty acid intake may influence the risk for acute coronary syndrome (ACS) conferred by genetic polymorphisms among patients with early onset ACS.
Methods and results: Our population consisted of 705 patients of white European descent enrolled in GENESIS-PRAXY, a multicenter cohort study of patients aged 18–55 years and hospitalized with ACS. We used a case-only design to investigate interactions between the omega-3 index (a validated biomarker of omega-3 fatty acid intake) and 30 single nucleotide polymorphisms (SNPs) robustly associated with ACS. We used logistic regression to assess the interaction between each SNP and the omega-3 index. Interaction was also assessed between the omega-3 index and a genetic risk score generated from the 30 SNPs. All models were adjusted for age and sex. An interaction for increased ACS risk was found between carriers of the chromosome 9p21 variant rs4977574 and low omega-3 index (OR 1.57, 95% CI 1.07–2.32, $p = 0.02$), but this was not significant after correction for multiple testing. Similar results were obtained in the adjusted model (OR 1.55, 95% CI 1.05–2.29, $p = 0.03$). We did not observe any interaction between the genetic risk score or any of the other SNPs and the omega-3 index.
Conclusion: Our results suggest that omega-3 fatty acid intake may modify the genetic risk conferred by chromosome 9p21 variation in the development of early onset ACS and requires independent replication.

List of acronyms: ACS, acute coronary syndrome; CAD, coronary artery disease; CI, confidence interval; CVD, cardiovascular diseases; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; GWAS, genome-wide association studies; HWE, Hardy–Weinberg equilibrium; MI, myocardial infarction; SNP, single nucleotide polymorphism; OR, odds ratio; IQR, interquartile range.

* Corresponding author. Division of Clinical Epidemiology, McGill University Health Centre, 687 Pine Avenue West V-Building, Montreal, Quebec H3A 1A1, Canada. Tel.: +1 514 934 1934x44722; fax: +1 514 934 8293.
E-mail address: louise.pilote@mcgill.ca (L. Pilote).

[1] Dr. Engert and Dr. Pilote are co-last authors and contributed equally to this work.
[2] See Appendix 1 and 2 for a list of GENESIS-PRAXY co-investigators and participating centers.

http://dx.doi.org/10.1016/j.numecd.2014.06.001
0939-4753/

Introduction

It is well-recognized that cardiovascular diseases (CVD) are complex multifactorial conditions involving genetic and environmental risk factors [1]. Although gene-environment interactions could be part of additional mechanisms that contribute to cardiovascular outcomes, little is known about how environmental factors, such as diet, interact with an individual's genetic predisposition to early onset acute coronary syndrome (ACS).

Recent gene-environment interaction studies of CVD, including gene–diet interaction studies [2,3], suggest that diet may influence an individual's genetic predisposition to CVD. Evidence also suggests a plausible interplay between an individual's genetic variation and omega-3 fatty acid intake [4,5]. An increased intake of omega-3 fatty acids, consisting of eicosapentaenoic acid (EPA; 20:5n-3) and docosahexaenoic acid (DHA; 22:6n-3), has been indicated to be cardioprotective [6]. The associations between omega-3 fatty acids and CVD risk have been demonstrated in many studies [7–9]. However, although omega-3 fatty acid intake has been suggested to increase survival following cardiovascular events, not all trials have shown an association between omega-3 fatty acid intake and cardiovascular risk [10–12].

The omega-3 index (i.e. the sum of the percentage of EPA and DHA in total erythrocyte fatty acids) is a well-validated biomarker that has been shown to be highly reliable for assessing usual omega-3 fatty acid intake over the long-term [13]. It is based on the fatty acid composition of the erythrocyte that has a lipid bilayer that reflects the fatty acids in cell membranes of tissues and organs such as the heart [12]. Additionally, the slower fatty acid remodeling of the erythrocyte better reflects long-term dietary habits as compared with plasma fatty acids [12]. The fatty acid composition of erythrocytes has also been demonstrated to be stable after myocardial infarction (MI) and after clinical intervention post-infarction [14]. Furthermore, in clinical trials, the omega-3 index has been demonstrated to be inversely associated with CVD [13,15] and studies have shown that a low level of erythrocyte EPA + DHA is an independent predictor of increased risk for ACS [16,17].

In this study, we aimed to evaluate whether omega-3 fatty acid levels, as measured by the omega-3 index, may influence the genetic risk conferred by genetic variants that predispose to ACS. We hypothesized that low omega-3 fatty acid levels will interact with the genetic predisposition to ACS to increase the risk for early onset ACS.

Methods

Study population

The study population consisted of patients enrolled in GENESIS-PRAXY (GENdEr and Sex determInantS of cardiovascular disease: from bench to beyond Premature Acute Coronary SYndrome), a multicenter prospective cohort study of adults hospitalized with early onset ACS. The protocol and methods of the GENESIS-PRAXY study have been previously described [18]. Briefly, eligible participants included patients aged 18–55 years, admitted with a diagnosis of ACS to a participating hospital, fluent in English and/or French, and able to provide informed consent. The study began in January 2009 and includes 24 sites across Canada, one in the US and one in Switzerland. In Quebec, a multicenter ethics review allowed for the McGill University Health Centre to act as the central review board and coordinate ethics approval for all centers. All other centers received ethics approval from their respective hospital ethics review boards.

For the present study, our population was restricted to patients of white European ethnicity, which made up more than 90% of enrolled participants. This was done as a means to avoid population stratification bias (i.e. confounding by ethnicity), an issue which can arise in genetic studies, including case-only studies.

Data collection

Study participants were approached by a trained research nurse within 48 h of hospital admission. After consent, personal and medical data were collected via self-administered questionnaires and medical chart reviews. Patients also provided a blood sample which was immediately centrifuged. Serum and plasma were distributed into aliquots, and then stored locally at −80 °C until being transported in dry ice to the McGill University Health Centre in Montreal, Canada.

Omega-3 index

The fatty acid composition of erythrocytes was determined using fast gas chromatography methods at the University of Waterloo [19]. Briefly, erythrocyte fatty acids were determined by isolating the lipids with a double extraction protocol, followed by transesterification with boron trifluoride in methanol with hexane to generate fatty acid methyl esters [20]. Thirty-two fatty acid methyl esters were consistently identified and quantitated, and data were expressed as absolute concentrations (μg fatty acid/mL erythrocytes). Individual fatty acids were also expressed as the relative weight percentage (relative %) of total fatty acids. The omega-3 index was calculated by adding the relative % of EPA and the relative % of DHA.

DNA extraction and genotyping

ACS includes MI and unstable angina. These conditions of coronary heart disease (CAD) share common etiology and pathology and represent a continuum of severity, with MI being the most severe. We considered the top 30 single nucleotide polymorphisms (SNPs) robustly associated with MI/CAD from recent genome-wide association studies (GWAS). These SNPs have strong evidence for a true association with MI (minimum p-value for association $<5 \times 10^{-8}$) and have all been replicated in at least one additional independent sample (see Supplementary Table 1 for references). A 30 SNP genetic risk score (GRS) was