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Adipose tissue arachidonic acid content is associated with the risk of myocardial infarction: A Danish case-cohort study

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ABSTRACT

Objective: The primary aim of the study was to evaluate the association between adipose tissue arachidonic acid (AA) content and the risk of myocardial infarction (MI). The secondary aim was to assess the correlation between adipose tissue AA and dietary intake of AA and linoleic acid (LA).
Methods: We conducted a case-cohort study nested within the Danish prospective Diet, Cancer and Health (DCH) study. After appropriate exclusions, the study included 2134 incident MI cases. Gluteal adipose tissue biopsies were collected at recruitment, and the fatty acid composition was determined by gas chromatography. A weighted Cox proportional hazards model was used to evaluate the association between adipose tissue AA content and the risk of MI.
Results: After adjusting for confounders we found a positive association between adipose tissue AA content and the risk of MI. Hazard ratios (HR) of MI relative to the lowest quintile of adipose tissue AA content, increased across quintiles; second quintile (HR 1.19 95%CI: 0.97–1.45), third (HR 1.24 95%CI: 1.02–1.52), fourth (HR 1.28 95%CI: 1.03–1.60), and fifth quintile (HR 1.39 95%CI: 1.10–1.77). Adipose tissue AA levels were not correlated with dietary intake of AA ($r = 0.03$, 95%CI: −0.01, 0.06) and weakly negatively correlated with dietary intake of LA ($r = -0.12$, 95%CI: −0.15, −0.08).
Conclusions: The adipose tissue content of AA was positively associated with the risk of MI but did not correlate with dietary intake of neither AA nor LA.

1. Introduction

The incidence of coronary heart disease (CHD) has been reduced substantially through the intense focus on the prevention and treatment of traditional modifiable risk factors for CHD like hypercholesterolemia, hypertension, tobacco smoking, diabetes mellitus, and obesity [1]. Despite this, the CHD burden remains unacceptably high, and this urgently calls for more knowledge on alternative biological pathways that might be important in the development of this disease.

Arachidonic acid (AA) is an $n-6$ polyunsaturated fatty acid (PUFA) and the precursor of pro-thrombotic and pro-inflammatory eicosanoids, including the 4-series leukotrienes which have been linked to atherosclerosis and plaque instability [2–5]. Interestingly, a positive association between dietary intake of AA and carotid intima media thickness has been observed although apparently restricted to a genetic subgroup [6]. Previous studies evaluating adipose tissue AA and the risk of CHD have been heterogeneous and relatively small in size [7–14] and some [7–9,14], but not all [10–13], studies have found a positive association between the content of AA in adipose tissue and the risk of CHD. Therefore, it remains uncertain whether adipose tissue AA is independently associated with the risk of MI. Also worth noting, the AA content in adipose tissue does not seem to reflect the dietary intake of neither AA nor the endogenous source of AA, linoleic acid (LA), as assessed from validated food frequency questionnaires (FFQs) [7].

The primary aim of this study was to assess the association between adipose tissue AA content and the risk of incident MI. Secondary aims were to quantify the correlation of adipose tissue AA with dietary intake of AA and LA, as well as the correlation of adipose tissue AA with adipose tissue LA.

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2. Methods

2.1. Study population

The Diet, Cancer and Health (DCH) study is a Danish prospective cohort study which has previously been described in detail [15]. Briefly, from November 1993 to May 1997, 160,725 men and women aged 50–64 years, born in Denmark, living in the urban areas of Copenhagen or Aarhus, and with no previous cancer diagnosis registered in the Danish Cancer Registry were invited to participate in the study; 57,053 (35%) accepted the invitation. At inclusion, participants filled in a questionnaire concerning lifestyle and medical history, including information on smoking habits, alcohol consumption, physical activity, education, history of diabetes mellitus, and (for women) hormone replacement therapy. Further, a validated 192-item food frequency questionnaire was completed and used to calculate daily intake of *n*−6 PUFA (AA and LA) by using the software FoodCalc (www.ibt.ku.dk/jesper/foodcalc) based on Danish food composition tables. The questionnaires were checked by a trained interviewer during a clinical visit. At the same visit, body weight, height, waist circumference, and blood pressure were measured, and biological material including an adipose tissue biopsy was collected. If participants had a cancer diagnosis at baseline that was not already recorded in the cancer registry at the time of inclusion due to, for example, processing delays, they were excluded since this was an exclusion criterion in the DCH study. Also, participants with a diagnosis of MI (only primary end point diagnoses, see below) before entry were excluded as were participants with missing information on one or more confounders (Fig. 1). All participants gave written informed consent, and the study was approved by the relevant Scientific Ethical Committees and the Danish Data Protection Agency.

2.2. Adipose tissue fatty acids

An adipose tissue biopsy was taken from the buttock of all participants using a luer lock system (Terumo, Terumo Corp, Tokyo, Japan) consisting of a needle, a venoject multi-sample luer adaptor, and an evacuated blood tube, according to the method of Beynen and Katan [16]. Samples were flushed with nitrogen and stored at −150 °C until analysis. When analyzed, biopsies were thawed, and approximately 3 mg of adipose tissue were removed to a glass and preheated at 50 °C for 10 min. Subsequently, the fat was dissolved in heptane at 50 °C, and fatty acids were transesterified by

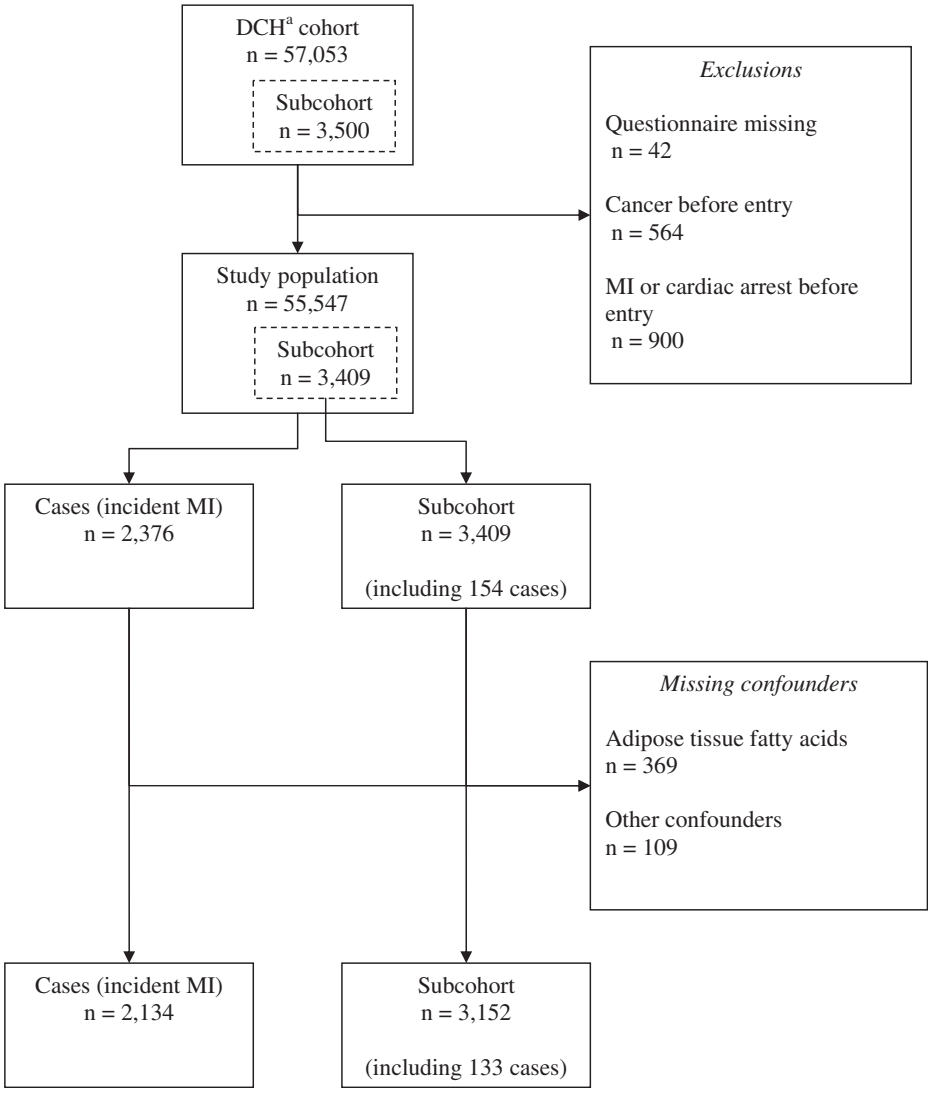

Fig. 1. Flowchart for the inclusion of case and subcohort participants. [a]Diet, Cancer and Health study.