Omega-6 fatty acids and risk of heart failure in the Physicians’ Health Study¹–³

Andrew B Petrone, Natalie Weir, Naomi Q Hanson, Robert Glynn, Michael Y Tsai, J Michael Gaziano, and Luc Djoussé

ABSTRACT
Background: Although 1 in 5 adults will develop heart failure (HF) in their lifetime, data on the effect of plasma omega-6 (n-3) PUFAs on risk of HF are currently sparse.

Objectives: We investigated whether plasma phospholipid omega-6 concentrations are associated with risk of HF in US male physicians. In a secondary analysis, we evaluated whether such an association differs between HF with and without previous myocardial infarction (MI).

Design: With the use of a nested case-control design, this ancillary study comprised 788 cases and 788 matched controls from the Physicians’ Health Study. Plasma omega-6 PUFAs were measured by using gas chromatography.

Results: The mean age of subjects was 58.7 y with a mean follow-up time of 17.1 y. We did not show any evidence of a statistically significant relation between total omega-6 PUFAs and HF (OR (95% CI): 1.00; 0.85 (0.63, 1.14); 0.84 (0.63, 1.13); and 0.87 (0.63, 1.20) across consecutive quartiles of omega-6 PUFAs; P-linear trend = 0.39). Results were similar for HF with and without previous MI.

Conclusion: Our data showed no significant association between total plasma omega-6 PUFAs and risk of developing HF.

INTRODUCTION

In 2010, ~6.6 million US adults had heart failure (HF)¹ (1), and lifetime risk of developing HF at 40 y of age is estimated to be 1 in 5 (2). With costs of HF at just under $40 billion/y and mortality ranging from 20% to 50%, the prevention of HF remains both a clinical and a public health issue (3–6). Major risk factors for HF include advanced age, hypertension, diabetes, obesity, valvular heart disease, and myocardial infarction (MI) (7, 8). Conversely, healthy lifestyle factors, including regular exercise, moderate alcohol intake, and consumption of fruits, vegetables, and breakfast cereals, are related to lower risk of HF (9). In addition, the consumption of fish high in omega-3 PUFAs and supplementation with omega-3 PUFAs have been shown to be inversely associated with risk of HF (10–13).

Several studies have assessed the effect of omega-6 PUFAs on hypertension, acute MI, cardiovascular mortality, and ischemic heart disease with mixed results dependent on the class of omega-6 and whether dietary or plasma omega-6 was measured (14–24). However, to our knowledge, only one study has analyzed risk of HF and omega-6 fatty acids. The Atherosclerosis Risk in Communities (ARIC) study showed a nonsignificant inverse relation between total omega-6 PUFAs and risk of HF (25). Nonetheless, there was an inverse association between both plasma cholesterol ester and phospholipid linoleic acid (LA) and arachidonic acid with risk of HF in women and a positive association with dihomo-γ-linolenic acid (DGLA) (25). However, these associations were attenuated once adjusted for covariates (25). This result is important because over the course of the 20th century, the consumption of LA, which is the primary dietary omega-6, has increased, whereas the percentage of omega-3 in tissue has decreased (26). Thus, it is important to understand whether omega-6 plasma concentrations confer lower or higher risk of HF.

In the current study, we sought to assess whether higher plasma phospholipid omega-6 concentrations are associated with lower risk of HF in US male physicians. In a secondary aim, we examined whether the relation between plasma omega-6 and risk of HF differs by individual omega-6 fatty acids and between HF with and without antecedent MI.

SUBJECTS AND METHODS

Study population

This ancillary study was a nested, case-control study that used data from the Physicians’ Health Study (PHS), which is a completed randomized, double-blind, placebo-controlled trial de-

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⁴ Abbreviations used: ARIC, Atherosclerosis Risk in Communities; CRP, C-reactive protein; DGLA, dihomo-γ-linolenic acid; HF, heart failure; LA, linoleic acid; MI, myocardial infarction; PHS, Physicians’ Health Study.

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signed to study low-dose aspirin and β carotene for the primary prevention of cardiovascular disease and cancer in US male physicians. A detailed description of the PHS has been previously published (27). Of the total 22,071 participants, 788 incident HF cases that occurred after a baseline blood collection were identified. We used a risk-set technique to match each new HF case to a control. Specifically, we matched each control subject to the index case for age at random assignment (±1 y), race (white compared with nonwhite), year of birth (±1 y), and time of blood collection (±288 d). For one pair, we had to loosen matching criteria on age to find a suitable control subject within 2 y of age. Each case was eligible to serve as a control before HF diagnosis. Similarly, each control subject was eligible to later become an HF case to ensure that controls were representative of the total population that gave rise to HF cases. Each participant gave written and informed consent, and the Institutional Review Board at Brigham and Women’s Hospital approved the study protocol.

Phospholipid fatty acid profile

The fatty acid profile was measured in plasma by using a method previously described (28). For the extraction of plasma phospholipid fatty acids, 0.3 mL plasma was mixed with 0.7 mL 0.9% saline. Lipids were extracted with a mixture of chloroform:methanol (2:1, vol:vol), and cholesterol, triglyceride, and phospholipid fractions were separated on a silica thin-layer chromatography plate in a solvent mixture of petroleum ether, diethyl ether, and glacial acetic acid (80:20:1, vol:vol:vol). The chromatography plate in a solvent mixture of petroleum ether, and phospholipid fractions were separated on a silica thin-layer chromatography plate in a solvent mixture of petroleum ether, diethyl ether, and glacial acetic acid (80:20:1, vol:vol:vol). The band of phospholipids was harvested for the formation of methyl esters. Fatty acid methyl esters were prepared with 1.5 mL 14% boron trifluoride in methanol, incubated at 80°C for 90 min, and extracted with petroleum ether. The final product was dissolved in heptane and injected onto a capillary Varian CP7420 (Agilent Technologies) 100-m column with a Hewlett-Packard 5890 gas chromatograph equipped with an HP6890A autosampler (Hewlett-Packard). The gas chromatograph was configured for a single capillary column with a flame-ionization detector and interfaced with HP ChemStation software (version G1701BA; Hewlett-Packard). An adequate separation of fatty acid methyl esters was obtained over an 80-min period with an initial temperature of 190°C for 25 min. The temperature was increased to 240°C at a rate of 2°C/min and held for 5 min. Fatty acid methyl esters from 14:0 through 24:1n−9 were separated, identified, and expressed as the percentage of total fatty acids. The following coefficients of variations were obtained on 30 blind duplicates—LA: 1.7%; α-linolenic acid: 3.0%; arachidonic acid: 3.2%; 16:1n−7cis: 1.8%; and 18:1n−7: 2.9%.

Ascertainment of HF in the PHS

HF outcomes in the PHS were determined with the use of annual follow-up questionnaires. Specifically, a questionnaire was mailed to each participant every 6 mo during the first year and annually thereafter to obtain information on compliance with the intervention and the occurrence of new medical diagnoses, including HF. A detailed description of HF validation in the PHS by using a review of medical records in a subsample has been published elsewhere (29, 30).

Other variables

Information on demographic variables, cigarette smoking, exercise, alcohol consumption, BMI, and history of diabetes, atrial fibrillation, coronary artery bypass surgery, hypertension, and hypercholesterolemia were collected at baseline. Information on incident comorbidities (ie atrial fibrillation, MI, and diabetes) was collected through annual follow-up questionnaires as previously described.

Statistical analysis

We used conditional logistic regression (whereby each matched pair was considered a stratum) to calculate ORs with corresponding 95% CIs. To assess risk of HF in the entire sample, quartiles of total omega-6 PUFAs were created on the basis of the distribution in the control series. For all analyses, the lowest quartile of omega-6 PUFAs was used as the reference group.

We assessed confounding by aspirin and β-carotene random assignment, BMI (continuous), smoking (never, past, or current), alcohol intake (rarely, monthly, weekly, or daily), exercise to sweat weekly or more (yes or no); hypercholesterolemia (reported total cholesterol ≥240 mg/dL or taking cholesterol-lowering medication); hypertension (reported systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or taking hypertension medication), and previous diabetes (yes or no), atrial fibrillation (yes or no), and coronary artery bypass surgery (yes or no). A variable was considered a confounder if its adjustment led to a ≥10% change in the regression coefficient for any omega-6 PUFA quartile. Finally, we evaluated possible interactions between total omega-6 PUFAs and confounding variables in each model.

We obtained a P-linear trend value by creating a new variable that was assigned the median omega-6 PUFA value from the control series in each quartile and used that new variable in the conditional logistic regression model.

The initial model accounted for matching factors only (age, date of blood collection, race, and year of birth). A parsimonious model adjusted for BMI, smoking, and history of atrial fibrillation. Because omega-6 PUFAs have been shown to be associated with blood pressure and CHD, we examined potential mediation of omega-6-HF associations by history of both hypertension and coronary artery bypass surgery. Finally, phospholipid omega-6 PUFA was examined as a continuous variable (OR per increase in SD). For each categorical variable except smoking, we created indicator variables for missing observations. Two individuals with missing values for smoking status were not included in the adjusted models.

In secondary analyses, we repeated the analysis for individual omega-6 PUFAs (LA, γ-linolenic acid, eicosadienoic acid, DGLA, arachidonic acid, and adrenic acid). In addition, we analyzed HF preceded by MI (n = 88) separately from HF without antecedent MI (n = 700). All analyses were completed with SAS software (version 9.2; SAS Institute). All P values were 2-tailed, and the significance level was set at α = 0.05 (0.008 with Bonferroni correction for 6 main exposures in a secondary analysis).

RESULTS

Characteristics of the 1576 US male physicians obtained at baseline are presented in Tables 1 and 2 according to total
phospholipid omega-6 PUFAs and status of cases and controls, respectively. The mean age of study participants at the baseline blood test was 58.7 ± 8.0 y (range: 40–82 y). The mean follow-up from baseline to incident HF in cases was 17.1 ± 6.1 y (range: 0.4–27.1 y). Compared with the lowest quartile, the highest quartile of phospholipid omega-6 fatty acid was associated with the lower prevalence of hypertension and diabetes and a higher prevalence of weekly exercisers. Compared with controls, cases had a higher BMI, a higher prevalence of atrial fibrillation, coronary artery bypass graft, diabetes, current smokers, and hypertension and a lower prevalence of current exercisers.

In a conditional logistic regression model with matching factors, BMI, smoking, and atrial fibrillation controlled for, there was no significant association between total phospholipid omega-6 fatty acids and risk of HF with ORs (95% CIs) of 1.00 (reference), 0.85 (0.63, 1.14), 0.84 (0.63, 1.13), and 0.87 (0.63, 1.20) across consecutive quartiles of total omega-6 PUFAs (P-linear trend = 0.39) (Table 3). When analyzed as a continuous variable, the OR associated with each SD increment of omega-6 PUFAs was 0.96 (95% CI: 0.86, 1.08) (Table 3).

In a secondary analysis, we examined the relation of total phospholipid omega-6 fatty acid with risk of HF with and without antecedent MI and showed no significant association [OR per SD for HF with previous MI: 0.84 (95% CI: 0.57, 1.25); OR per SD for HF without antecedent MI: 0.98 (95% CI: 0.87, 1.11)]. Last, we showed no evidence of a meaningful relation between individual omega-6 and HF (see the Table under “Supplemental data” in the online issue).

DISCUSSION

In this next case-control study, we showed no association between total omega-6 fatty acids and odds of HF. These findings did not differ for HF with and without antecedent MI.

The modern-day Western diet has increasingly been characterized by an increase in omega-6 intake (11–13, 26, 31). The average US intake of LA, which accounts for 85–90% of dietary omega-6, is 13.8 g/d, which on the basis of an average intake of 2000 kcal/d is 6.7% of energy (32). Our study measured plasma phospholipid PUFAs, which have been shown to be moderately correlated with dietary intake (33). In addition, mean plasma phospholipid concentrations observed in our study are comparable with those in other cohort studies (25, 34). In the Multi-Ethnic Study of Atherosclerosis, the mean LA and mean DGLA for white men were 20.93% and 3.39% total fatty acid, respectively (34), and in the ARIC cohort, mean LA and DGLA were 21.99 and 3.33% of total fatty acids, respectively (25).

### TABLE 1

Characteristics of the 1576 US male physicians according to quartiles of total plasma phospholipid omega-6 PUFAs

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Quartile 1 [33.80 (22.58, 34.76)]</th>
<th>Quartile 2 [35.49 (34.76, 36.13)]</th>
<th>Quartile 3 [36.80 (36.14, 37.53)]</th>
<th>Quartile 4 [38.56 (37.53, 43.04)]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n</strong></td>
<td>414</td>
<td>392</td>
<td>390</td>
<td>380</td>
</tr>
<tr>
<td><strong>BMI (kg/m²)</strong></td>
<td>25.21 ± 3.08²</td>
<td>25.54 ± 2.87</td>
<td>25.08 ± 2.77</td>
<td>25.12 ± 2.93</td>
</tr>
<tr>
<td><strong>Age (y)</strong></td>
<td>60.08 ± 8.30</td>
<td>58.54 ± 8.08</td>
<td>58.34 ± 7.90</td>
<td>57.83 ± 7.68</td>
</tr>
<tr>
<td>History of atrial fibrillation (%)</td>
<td>4.11</td>
<td>3.83</td>
<td>3.59</td>
<td>4.21</td>
</tr>
<tr>
<td>History of CABG (%)</td>
<td>2.42</td>
<td>1.53</td>
<td>1.28</td>
<td>1.32</td>
</tr>
<tr>
<td>History of diabetes (%)</td>
<td>6.04</td>
<td>5.61</td>
<td>5.90</td>
<td>4.74</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>36.96</td>
<td>31.63</td>
<td>28.46</td>
<td>26.32</td>
</tr>
<tr>
<td>High cholesterol (%)</td>
<td>13.77</td>
<td>16.33</td>
<td>11.28</td>
<td>12.11</td>
</tr>
<tr>
<td>Exercise (%)</td>
<td>68.84</td>
<td>70.66</td>
<td>74.10</td>
<td>79.47</td>
</tr>
<tr>
<td>Smoking status (%)</td>
<td>No</td>
<td>42.51</td>
<td>41.33</td>
<td>45.38</td>
</tr>
<tr>
<td>Past</td>
<td>44.20</td>
<td>47.45</td>
<td>42.05</td>
<td>40.26</td>
</tr>
<tr>
<td>Current</td>
<td>13.04</td>
<td>10.97</td>
<td>12.56</td>
<td>8.16</td>
</tr>
<tr>
<td>Alcohol use (%)</td>
<td>Rarely</td>
<td>13.29</td>
<td>11.73</td>
<td>19.74</td>
</tr>
<tr>
<td>Monthly</td>
<td>8.21</td>
<td>9.18</td>
<td>9.74</td>
<td>12.11</td>
</tr>
<tr>
<td>Weekly</td>
<td>43.24</td>
<td>49.49</td>
<td>45.90</td>
<td>44.47</td>
</tr>
<tr>
<td>Daily</td>
<td>35.27</td>
<td>28.83</td>
<td>23.85</td>
<td>24.21</td>
</tr>
</tbody>
</table>

18:2n-6 (linoleic acid) (percentage of total fatty acids) | 18.71 (17.09, 20.04)⁴ | 20.24 (19.12, 21.70) | 21.84 (20.50, 23.24) | 23.74 (22.20, 25.05) |

18:3n-6 (γ-linolenic acid) (percentage of total fatty acids) | 0.12 (0.09, 0.16) | 0.13 (0.10, 0.17) | 0.13 (0.10, 0.17) | 0.13 (0.11, 0.16) |

20:2n-6 (eicosadienoic acid) (percentage of total fatty acids) | 0.31 (0.28, 0.35) | 0.32 (0.28, 0.35) | 0.32 (0.29, 0.35) | 0.32 (0.28, 0.36) |

20:3n-6 (dihomo-γ-linolenic acid) (percentage of total fatty acids) | 2.83 (2.42, 3.30) | 2.86 (2.47, 3.39) | 2.83 (2.44, 3.20) | 2.76 (2.32, 3.24) |

20:4n-6 (arachidonic acid) (percentage of total fatty acids) | 10.93 (9.74, 12.09) | 11.27 (10.05, 12.32) | 11.17 (9.96, 12.28) | 11.41 (10.00, 12.69) |

22:4n-6 (adrenic acid) (percentage of total fatty acids) | 0.44 (0.38, 0.54) | 0.47 (0.40, 0.54) | 0.48 (0.42, 0.55) | 0.46 (0.40, 0.53) |

² Except for BMI and age, data for other characteristics were not provided by all individuals.
³ Quartiles of total plasma phospholipid omega-6 PUFAs are expressed as the median (range) of percentage of total fatty acids.
⁴ Mean ± SD (all such values).
⁵ CABG, coronary artery bypass graft.
⁶ Median; interquartile range in parentheses (all such values).
The ARIC cohort reported that plasma concentrations of phospholipid omega-6 PUFAs in the highest quintile compared with the lowest quintile was associated with nonsignificant lower risk of HF (HR: 0.69; 95% CI: 0.43, 1.09), LA with lower risk of HF (HR: 0.57; 95% CI: 0.36, 0.92), arachidonic with lower risk of HF in women (HR: 0.38; 95% CI: 0.16, 0.91) but not men (HR: 1.34; 95% CI: 0.79, 2.27), and DGLA with higher risk of HF (HR: 2.26; 95% CI: 1.38, 3.70) in models adjusted for age and sex (25).

In fully adjusted models, with the exception of arachidonic acid in women, each association was attenuated. Our results were consistent with the findings from the ARIC study. However, unlike the ARIC analysis, our study is the first, to our knowledge, to examine HF with and without antecedent MI. There are several biological mechanisms to explain the suggestive inverse association between LA and HF and a positive association between DGLA and HF. Major risk factors for HF include advanced age, hypertension, diabetes, obesity, valvular heart disease, and MI (7, 8). Evidence has suggested that LA could reduce the prevalence of certain risk factors for HF. In a meta-analysis of 25 studies, LA had a significant protective effect for nonfatal cardiovascular endpoints, including acute MI, coronary artery disease, and nonfatal ischemic heart disease.

### TABLE 2

Characteristics of the 1576 US male physicians according to heart failure status

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Cases (n = 788)</th>
<th>Controls (n = 788)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI (kg/m²)</td>
<td>25.77 ± 3.19²</td>
<td>24.60 ± 2.49</td>
</tr>
<tr>
<td>Age (y)</td>
<td>58.73 ± 8.02</td>
<td>58.71 ± 8.06</td>
</tr>
<tr>
<td>History of atrial fibrillation (%)</td>
<td>5.46</td>
<td>2.41</td>
</tr>
<tr>
<td>History of CABG (%)</td>
<td>2.41</td>
<td>0.89</td>
</tr>
<tr>
<td>History of diabetes (%)</td>
<td>7.87</td>
<td>3.30</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>37.31</td>
<td>24.62</td>
</tr>
<tr>
<td>High cholesterol (%)</td>
<td>14.34</td>
<td>12.44</td>
</tr>
<tr>
<td>Exercise (%)</td>
<td>71.07</td>
<td>75.25</td>
</tr>
<tr>
<td>Smoking status (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>40.99</td>
<td>49.24</td>
</tr>
<tr>
<td>Past</td>
<td>45.43</td>
<td>41.62</td>
</tr>
<tr>
<td>Current</td>
<td>13.58</td>
<td>8.88</td>
</tr>
<tr>
<td>Alcohol use (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rarely</td>
<td>17.01</td>
<td>14.85</td>
</tr>
<tr>
<td>Monthly</td>
<td>11.42</td>
<td>8.12</td>
</tr>
<tr>
<td>Weekly</td>
<td>44.67</td>
<td>46.83</td>
</tr>
<tr>
<td>Daily</td>
<td>26.40</td>
<td>29.95</td>
</tr>
<tr>
<td>18:2n-6 (linoleic acid)</td>
<td>21.20 (19.49, 23.17)²</td>
<td>20.82 (18.97, 22.68)</td>
</tr>
<tr>
<td>18:3n-6 (γ-linolenic acid)</td>
<td>0.13 (0.10, 0.16)</td>
<td>0.13 (0.10, 0.17)</td>
</tr>
<tr>
<td>20:2n-6 (eicosadienoic acid)</td>
<td>0.32 (0.28, 0.35)</td>
<td>0.32 (0.28, 0.35)</td>
</tr>
<tr>
<td>20:3n-6 (dihomo-γ-linolenic acid)</td>
<td>2.75 (2.34, 3.21)</td>
<td>2.91 (2.47, 3.37)</td>
</tr>
<tr>
<td>20:4n-6 (arachidonic acid)</td>
<td>11.07 (9.86, 12.34)</td>
<td>11.22 (9.99, 12.34)</td>
</tr>
<tr>
<td>22:4n-6 (adrenic acid)</td>
<td>0.46 (0.39, 0.54)</td>
<td>0.47 (0.40, 0.55)</td>
</tr>
</tbody>
</table>

¹Except for BMI and age, data for other characteristics were not provided by all individuals.
²Mean ± SD (all such values).
³CABG, coronary artery bypass graft.
⁴Median; interquartile range in parentheses (all such values).

### TABLE 3

ORs (95% CIs) of heart failure according to quartiles of total plasma phospholipid omega-6 PUFAs

<table>
<thead>
<tr>
<th>Omega-6 PUFA quartiles²</th>
<th>No. of cases</th>
<th>Unadjusted model</th>
<th>Model 1</th>
<th>Model 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>33.80 (22.58, 34.76)</td>
<td>218</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>35.49 (34.76, 36.1)</td>
<td>194</td>
<td>0.87 (0.66, 1.16)</td>
<td>0.85 (0.63, 1.14)</td>
<td>0.87 (0.64, 1.18)</td>
</tr>
<tr>
<td>36.80 (35.14, 37.53)</td>
<td>193</td>
<td>0.87 (0.66, 1.15)</td>
<td>0.84 (0.63, 1.13)</td>
<td>0.89 (0.66, 1.20)</td>
</tr>
<tr>
<td>38.56 (37.53, 43.04)</td>
<td>183</td>
<td>0.81 (0.60, 1.10)</td>
<td>0.87 (0.63, 1.20)</td>
<td>0.90 (0.65, 1.24)</td>
</tr>
<tr>
<td>F-linear trend</td>
<td>—</td>
<td>0.19</td>
<td>0.53</td>
<td>0.53</td>
</tr>
</tbody>
</table>

⁴Model 1 was assessed by using conditional logistic regression adjusted for smoking, BMI, and history of atrial fibrillation. Model 2 was adjusted as for model 1 and for hypertension status and history of coronary artery bypass surgery.
⁵Median (range) of percentage of total fatty acids.
⁶OR per SD increase in omega-6 PUFA (2.21% of total fatty acids).
and wrote the manuscript; ABP, NQH, RG, MYT, JMG, and LD: critically
reviewed the manuscript; and all authors: read and approved the
final manuscript. None of the authors had any conflicts of interest.

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