Dietary Linolenic Acid Is Associated With a Lower Prevalence of Hypertension in the NHLBI Family Heart Study

Luc Djousse, Donna K. Arnett, James S. Pankow, Paul N. Hopkins, Michael A. Province, R. Curtis Ellison

Abstract—Dietary linolenic acid has been shown to be associated with coronary artery disease. However, limited data are available on its effects on blood pressure. We used data from 4594 white participants (aged 25 to 93 years) in the National Heart, Lung, and Blood Institute (NHLBI) Family Heart Study to evaluate whether dietary linolenic acid was associated with prevalent hypertension and resting blood pressure. We used generalized estimating equations to determine the prevalence odds ratios (ORs) of hypertension and adjusted means of systolic and diastolic blood pressure across quartiles of linolenic acid. Mean dietary linolenic acid intake was 0.81 ± 0.35 g per day for men and 0.69 ± 0.29 g per day for women. From the lowest to the highest quartile of linolenic acid, multivariable adjusted ORs (95% confidence interval [CI]) for hypertension were 1.0 (reference), 0.73 (0.56 to 0.95), 0.71 (0.53 to 0.95), and 0.67 (0.47 to 0.96), respectively (P for trend 0.04), controlling for age, sex, energy intake, body mass index, risk group, study site, education, smoking, alcohol intake, exercise, and history of coronary artery disease and diabetes mellitus. Dietary linolenic acid was related inversely to resting systolic (P for trend 0.03) but not diastolic blood pressure (P for trend 0.43). Linoleic acid, an omega-6 fatty acid, was not associated with prevalent hypertension or blood pressure. These data suggest that dietary linolenic acid is associated with a lower prevalence of hypertension and lower systolic blood pressure in white subjects. (Hypertension. 2005;45:368-373.)

Key Words: fatty acids ■ blood pressure

Coronary artery disease (CAD) remains the leading cause of death in the United States and other industrialized nations. Although several studies have demonstrated that dietary linolenic acid is associated with lower risk of fatal and nonfatal myocardial infarction,1-5 limited data are available on its effects on hypertension among subjects in a community setting. Animal and human studies on the association between linolenic acid and blood pressure have been inconsistent. Rupp et al6 showed that a diet supplemented with α-linolenic acid lowered systolic blood pressure (SBP) by 6 mm Hg after 7 weeks in 28 spontaneous hypertensive rats. In a cross-sectional study of 399 male subjects aged 20 to 78 years, a 1% higher adipose tissue α-linolenic acid was associated with a 5 mm Hg lower SBP and diastolic blood pressure (DBP).7 In the Kuopio Ischemic Heart Disease Risk Factor Study,8 dietary intake of linolenic acid, assessed by a 4-day food record, was associated inversely with SBP and mean blood pressure but not with DBP. Physiological mechanisms by which dietary linolenic acid might lower blood pressure are not well understood. However, it has been suggested that the hypotensive effects of linolenic acid could be mediated through its influence on arachidonic acid and eicosanoids synthesis, leading to an anti-inflammatory response and to vasodilation.6,9

We used data collected on 4594 white participants of the National Heart, Lung, and Blood Institute (NHLBI) Family Heart Study to assess whether dietary consumption of higher amounts of total linolenic acid (α-linolenic and γ-linolenic acid) was associated with a lower prevalence of hypertension and lower resting blood pressure.

Subjects and Methods

Study Population

Participants in this project were members of the NHLBI Family Heart Study, which is a multicenter, population-based study designed to identify and evaluate genetic and nongenetic determinants of CAD, preclinical atherosclerosis, and cardiovascular risk factors. A detailed description of the NHLBI Family Heart Study has been published.10 Briefly, families in the study had been chosen randomly (a random group) or based on a higher-than-expected risk of CAD (a high-risk group) from previously established population-based co-
hort studies. A family risk score, which related the family’s age- and sex-specific incidence of CAD to that expected in the general population, was used to identify families for the high-risk group. During a clinic visit at one of the study centers, a detailed medical and lifestyle history was obtained through interview, and laboratory measurements were done. Of the 5710 whites, 1116 were excluded because of probable errors on food frequency questionnaires: (1) answers on the food frequency questionnaire judged by the interviewer as unreliable or >18 items left blank on the dietary questionnaires (n = 152), or (2) energy intake outside a priori ranges (acceptance range 3347.2 to 17 572.8 kJ for men and 2510.4 to 14 644 kJ for women [n = 964]). The current analyses are based on 4594 white participants (from random and high-risk groups) with complete data on diet and blood pressure. The total number of nonwhites with available data (n = 265) was inadequate for ethnicity-specific analyses, so they were not included in the main analyses. Each participant gave informed consent, and the study protocol was reviewed and approved by each of the participating institutions.

Dietary Assessment
A staff-administered semiquantitative food frequency questionnaire was used to collect data on the intake of dietary linolenic acid and other dietary information. The reproducibility and validity of this food frequency questionnaire have been documented previously. The intake of specific nutrients was computed by multiplying the frequency of consumption of an item by the nutrient content of specified portions. Composition values for total linolenic acid and other nutrients were obtained from the Harvard University Food Composition Database derived from US Department of Agriculture sources and manufacturer information.

Blood Pressure Measurement and Prevalent Hypertension
Resting blood pressure was measured 3× on seated participants after a 5-minute rest using a random zero sphygmomanometer by trained and certified technicians. The appropriate cuff size was determined by the arm circumference. For arm circumference <240 mm, 240 to 320 mm, 321 to 240 mm, and >240 mm, a pediatric, regular, large, and thigh cuff sizes were used, respectively. For analyses, the average SBP and DBP from the second and third measurements were used. We used the Joint National Committee (JNC) VII classification to define hypertension (stages 1 or 2, SBP of 140 mm Hg or DBP of 90 mm Hg) or if the subject reported that he/she was currently taking medications for hypertension.

Other Variables
Information on cigarette smoking, alcohol intake, education, and level of physical activity during the previous year was obtained by interview during the clinic visit. The type of salad dressing consumed and the frequency of fish intake and fruit and vegetable consumption were obtained from the food frequency questionnaire. Diabetes mellitus was present if a subject was taking hypoglycemic agents or if a physician had told him/her that he/she has diabetes mellitus or if fasting glucose levels were >7.0 mmol/L. Prevalent CAD was assessed by self-reported history of myocardial infarction, percutaneous transluminal coronary angioplasty, or coronary artery bypass graft.

Statistical Analyses
Because energy intake and dietary patterns differ between men and women, we created sex-specific quartiles of linolenic acid. We conducted sex-specific analyses, but because we observed an inverse association in both sexes and there was no statistical interaction between gender and linolenic acid (P = 0.3), we present combined data using sex-specific quartiles of linolenic acid. We used generalized estimating equations to compute adjusted ORs for prevalent hypertension and adjusted mean blood pressure across quartiles of linolenic acid. The multivariable model controlled for age, sex, energy intake, body mass index, risk group for CAD, study site, education, alcohol intake (0, ≤1, and >1 drink per day), smoking, physical activity, and history of CAD and diabetes mellitus. Because linolenic acid and linolenic acid compete as substrates for desaturase enzymes and linoleic acid is highly prevalent in Western diets, it has been suggested that a lower ratio of linoleic acid/linolenic acid might be optimal for the effects of linoleic acid in humans. Thus, we also assessed independent effects of both fatty acids and their interaction on prevalent hypertension. We evaluated 3-way and 2-way interactions between linoleic acid, linolenic acid, and long-chain fatty acids (P values ranging from 0.13 to 0.89). To assess residual confounding by energy intake, we used residuals of dietary linolenic acid controlling for energy as independent variable. We repeated SBP/DBP analyses restricted to 3918 subjects who were not being treated for hypertension or whose SBP and DBP were <140 mm Hg and 90 mm Hg, respectively.

Results

Participant Characteristics
Of the 4594 white participants included in the analyses, 2113 were men and 2481 were women. The mean age was 52.4 ± 13.7 years for men and 51.8 ± 14.0 years for women. The average daily consumption of total dietary linolenic acid was 0.81 ± 0.35 g for men (range 0.19 to 3.48 g per day) and 0.69 ± 0.29 g for women (range 0.13 to 2.45 g per day). Tables 1 and 2 present the baseline characteristics by quartiles of dietary linolenic acid for men and women, respectively. A higher intake of dietary linolenic acid was associated with younger age, higher body mass index and waist-to-hip ratio, higher energy intake, higher fruit and vegetable consumption, higher intake of linoleic acid and eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), use of creamy salad dressing, and current smoking. In addition, higher intake of linolenic acid was associated with a lower percentage of subjects with a college education and current use of antihypertensive drugs in men.

Association Between Dietary Linolenic Acid and Prevalent Hypertension
There was suggestive evidence for an association between dietary linolenic acid and prevalent hypertension in men (β-coefficient [SE] –0.5214 [0.3217]) and women (β-coefficient [SE] –0.4153 [0.3575]) in a multivariable model. There was no statistically significant interaction between gender and linolenic acid (P = 0.3). Compared with subjects in the lowest quartile, being in the highest quartile of linolenic acid was associated with 37% lower odds of hypertension in a multivariable model (model 2) controlling for age, sex, energy intake, risk group (high versus normal CAD risk), and body mass index (Table 3). Additional adjustment for study center, education, smoking, alcohol intake, physical activity, history of CAD and diabetes (model 3) did not change the results (Table 3). Although the number of black subjects was insufficient for separate analyses, we found evidence for a nonsignificant association between dietary linolenic acid and prevalent hypertension in blacks (OR [95% CI], 1.0, 0.89 [0.33 to 2.37], and 0.57 [0.15 to 0.22], from the lowest to the highest tertile of linolenic acid; P for trend 0.42), and combining both races did not change the results (OR [95% CI] 1.0, 0.72 [0.56 to 0.93], 0.70 [0.52 to 0.93], and 0.66 [0.49 to 0.94], from the lowest to the highest quartile of linolenic acid, respectively; P for trend 0.04). Using energy-adjusted residuals of linolenic acid as exposure, the observed association remained (β-coefficient –0.0790; SE 0.0384; P value
of 0.039 in the full model). Linoleic acid was not associated with prevalent hypertension and there was no evidence for interaction between linoleic and linolenic acid on hypertension \(P\) for interaction 0.41).

**Association Between Dietary Linolenic Acid and Blood Pressure**

Dietary linolenic acid was related inversely to lower resting SBP but not DBP in a model controlling for age, sex, energy intake, study site, body mass index, risk group, education, smoking, alcohol intake, physical activity, antihypertensive medications, and prevalent CAD and diabetes mellitus \(P\) for trend 0.03; Table 4). This association was borderline significant after exclusion of 676 subjects who were stage 1 or stage 2 of the JNC VII classification for hypertension or who reported current treatment for hypertension \(P\) for linear trend 0.07; Table 4).

**Discussion**

Hypertension is highly prevalent in the United States and is a risk factor for stroke and CAD.\(^{17,18}\) Data on the association between essential fatty acids and hypertension or blood pressure have been inconsistent. In this cross-sectional study, we demonstrated that higher intake of dietary linolenic acid (\(\alpha\)-linolenic and \(\gamma\)-linolenic acid) was associated with a lower prevalence of hypertension, with only modest evidence for a dose-response relationship. In addition, we found that total linolenic acid was associated with lower resting SBP (\(=2.0\) mm Hg lower in the highest compared with the lowest quartile of linolenic acid). Linoleic acid was not associated with hypertension, and we did not find evidence for a significant interaction between linoleic and linolenic acid.

**n-3 Fatty Acids and Cardiovascular Disease and Blood Pressure**

Although several epidemiologic studies have shown the beneficial effects of linolenic acid on fatal and nonfatal CAD,\(^{2–4}\) triglycerides,\(^{19}\) and carotid wall thickness,\(^{20}\) limited data are available on the effect of linolenic acid on hypertension or resting blood pressure in a community setting. Previous trials have focused on long-chain omega-3 fatty acid (such as those found in fish) and have yielded inconsistent results;\(^{21,22}\) considerable reduction in blood pressure was observed mostly either in hypertensive subjects or in subjects with a higher dose of omega-3 fatty acids (eg, >3 g per day).\(^{21}\) In a randomized trial of subjects with high-normal DBP, a dietary supplement containing 0.48 g of EPA and 0.12 g of \(\gamma\)-linolenic acid per capsule did lower SBP and DBP after 12 weeks of intervention.\(^{23}\) In a trial of 33 normotensive men with slightly elevated cholesterol, a diet supplemented with EPA and DHA (3.4 g per day) was associated with a 5 mm Hg reduction of SBP after 6 weeks of intervention, but a daily intake of 9.2 g of \(\alpha\)-linolenic acid did not influence SBP during the same period of follow-up.\(^{24}\) Data from a cross-sectional study\(^{7}\) have shown an inverse association between adipose linolenic acid and SBP, DBP, and mean arterial pressure (=5 mm Hg decrease per 1% increase of adipose linolenic acid each) in 399 male subjects. In another
cross-sectional study, dietary linolenic acid was related inversely to SBP ($P$ for trend 0.041) but not DBP ($P$ for trend 0.08) among 722 normotensive Finnish men; in that study, the magnitude of SBP reduction between the extreme quartiles of linolenic acid was larger than that observed in our study (4.7 mm Hg versus 1.9 mm Hg, respectively). Of note, subjects in the highest quartile of linolenic acid in that study consumed considerably more linolenic acid than the subjects in our study.

Delta-5 desaturase is an important enzyme for the metabolism of linoleic and linolenic acid. Because both fatty acids compete for this enzyme, it has been suggested that a lower ratio of linoleic/linolenic might improve the conversion of linolenic to EPA. We demonstrated previously that the association between linolenic acid and CAD was stronger in the lowest tertile of the ratio of linoleic-to-linolenic acid. In the present study, there was no evidence for interaction between linoleic and linolenic acid on hypertension.

### Physiological Mechanisms

Little is known about biological mechanisms by which dietary linolenic acid might lower blood pressure.

| TABLE 2. Characteristics of the 2481 White Female Participants in the NHLBI Family Heart Study |
|-----------------------------------------------|----------------|----------------|----------------|----------------|----------------|
| Characteristics                              | Q1             | Q2             | Q3             | Q4             | P*             |
| Mean (range)                                 | (n=636)        | (n=590)        | (n=635)        | (n=620)        | 0.04           |
| Age, years                                   | 53.1±12.9      | 54.0±13.8      | 51.3±13.6      | 51.2±14.2      |                |
| Waist-to-hip ratio                           | 0.88±0.10      | 0.88±0.08      | 0.88±0.09      | 0.89±0.09      | 0.06           |
| Body mass index, kg/m²                       | 26.6±5.6       | 26.7±5.6       | 27.4±6.3       | 28.1±6.8       | 0.07           |
| Exercise minutes, per day                    | 23.7±27.3      | 25.1±38.4      | 25.3±32.8      | 24.2±33.9      | 0.27           |
| LDL-cholesterol, mmol/L                      | 3.2±0.9        | 3.2±1.0        | 3.2±1.0        | 3.2±0.9        | 0.78           |
| HDL-cholesterol, mmol/L                      | 1.0±0.17       | 0.22±0.21      | 0.24±0.21      | 0.29±0.27      | <0.0001        |
| LDL-cholesterol ratio                        | 4.2±2.1        | 5.7±2.2        | 7.1±2.8        | 10.0±3.7       | <0.0001        |
| Fruits and vegetables, servings per day      | 3.0±1.5        | 3.5±1.8        | 3.7±1.7        | 3.9±2.0        | <0.0001        |
| Energy intake kJ, per day                    | 4626.3±1227.2  | 5976.2±1284.2  | 7159.0±1480.5  | 9214.7±2102.2  | <0.0001        |

*P value obtained from ANOVA and $\chi^2$ for continuous and categorical variables, respectively.

### Physiological Mechanisms

Little is known about biological mechanisms by which dietary linolenic acid might lower blood pressure. α-Linolenic acid competes for this enzyme, suggesting that a lower ratio of linoleic/linolenic might improve the conversion of linolenic to EPA. We demonstrated previously that the association between linolenic acid and CAD was stronger in the lowest tertile of the ratio of linoleic-to-linolenic acid. In the present study, there was no evidence for interaction between linoleic and linolenic acid on hypertension.

### Table 3. Prevalence ORs (95% CIs) of Hypertension by Quartiles of Linolenic Acid for 4594 Participants in the NHLBI Family Heart Study*

<table>
<thead>
<tr>
<th>Quartiles (Q1–Q4) of Linolenic Acid</th>
<th>Cases/n</th>
<th>Model 1†</th>
<th>Model 2‡</th>
<th>Model 3¶</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q1 (low)</td>
<td>188/1168</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Q2</td>
<td>159/1101</td>
<td>0.73 (0.57–0.95)</td>
<td>0.71 (0.55–0.93)</td>
<td>0.73 (0.56–0.95)</td>
</tr>
<tr>
<td>Q3</td>
<td>159/1169</td>
<td>0.74 (0.56–0.99)</td>
<td>0.70 (0.53–0.94)</td>
<td>0.71 (0.53–0.95)</td>
</tr>
<tr>
<td>Q4 (high)</td>
<td>170/1156</td>
<td>0.68 (0.48–0.96)</td>
<td>0.63 (0.44–0.89)</td>
<td>0.67 (0.47–0.96)</td>
</tr>
</tbody>
</table>

*Hypertension was defined as stages 1 and 2 of JNC 7 or current treatment for high blood pressure. Sex-specific means and ranges of dietary linolenic acid are shown in Tables 1 and 2.†Adjusted for age, sex, and energy intake using generalized estimating equations.‡Variables in model 1 plus additional adjustment for body mass index and risk group (random vs high risk).¶Variables in model 2 plus additional adjustment for study site (4 categories), education (3 groups), alcohol consumption (0, <=1, and >1 drink per day), current smoking (yes/no), physical activity, and history of coronary heart disease and diabetes mellitus.
nic acid and γ-linolenic acid are precursors of eicosanoids that can generate prostaglandins (PGs) and leukotrienes. Specifically, α-linolenic acid is precursor of PG I₂ (a vasodilator) and thromboxane A₂, reported to be less active.\(^8\) Other investigators have suggested that a diet rich in n-3 fatty acids could suppress plasma levels of metabolites of linoleic acid such as thromboxane A₂, which stimulates vasoconstriction and platelet aggregation.\(^2\) In animal models, renomedul-ary production of PG F₂α, which stimulates vascular con-striction and smooth muscle contraction, was significantly reduced in animals fed diets rich in α-linolenic and γ-linolenic acids.\(^9\) Thus, it is possible that a diet rich in linolenic acid might reduce blood pressure through reduction of vascular tone. It is also possible that the effects of linolenic acid on blood pressure might be mediated through its anti-inflammatory effects.\(^2\) Dietary linolenic acid has been shown to decrease C-reactive protein, interleukin-6, and serum amyloid A.\(^2\) The anti-inflammatory hypothesis is consistent with our previous findings showing that dietary linolenic acid is inversely related to (1) the intima-media thickness of the carotid arteries\(^2\) and (2) calcified atherosclerotic plaque in the coronary arteries (Djoussé et al, manuscript under re-view). In addition, the effects of linolenic acid on blood pressure could be indirect through effects of its metabolites on cell membrane structure and function.

**Study Limitations and Strengths**

In the present study, nutrients were derived from a food frequency questionnaire shown to underestimate energy in-take when compared with the doubly labeled water tech-nique.\(^2\) Therefore, our estimate of daily intake of linolenic acid and other nutrients might have been biased. We were not able to separate γ-form and α-form of linolenic acid. However, it has been reported that the main sources of γ-linolenic acid are beef fats and other animal fats and that γ-linolenic acid concentration in these fats is small.\(^3\) Furthermore, the relation of α-linolenic acid to CAD has been shown to be similar to that of total linolenic acid to CAD.\(^1\) The cross-sectional design of our study limits our ability to infer causality between linolenic acid intake and blood pressure. However, the large sample size, the availability of data on several risk factors, the wide range of age and linolenic acid intake, the consistency of our findings with other published reports, and the multicenter design are strengths of our study.

**Perspectives**

Our findings indicate that a higher intake of dietary linolenic acid is associated with a lower prevalence of hypertension and lower SBP in whites. In most previous short-term trials, fish oil dietary supplements have been used to increase daily intake of omega-3 fatty acids. It is possible that dietary intake of linolenic acid, a plant-based omega-3, through foods consumed regularly might be acceptable and sustainable. Such approach provides the ability to choose from a variety of foods rich in plant-based omega-3 fatty acids. Future studies are needed to investigate prospectively the effects of dietary linolenic acid on blood pressure as well as the underlying physiological mechanisms.

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**TABLE 4. Adjusted Means of SBP and DBP by Quartiles of Linolenic Acid in the NHLBI Family Heart Study***

<table>
<thead>
<tr>
<th>Quartiles (Q1–Q4) of Linolenic Acid</th>
<th>SBP (mm Hg)</th>
<th>DBP (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Model 1†</td>
</tr>
<tr>
<td>Q1 (low)</td>
<td>1168</td>
<td>118.2±0.6</td>
</tr>
<tr>
<td>Q2</td>
<td>1101</td>
<td>117.8±0.5</td>
</tr>
<tr>
<td>Q3</td>
<td>1169</td>
<td>116.8±0.5</td>
</tr>
<tr>
<td>Q4 (high)</td>
<td>1156</td>
<td>116.3±0.6</td>
</tr>
<tr>
<td>P for linear trend</td>
<td>0.03</td>
<td>0.07</td>
</tr>
</tbody>
</table>

*All models are adjusted for age, sex, energy intake, study site (4 categories), body mass index, risk group (random vs high risk for CHD), education (3 groups), alcohol consumption (0, ≤1, and >1 drink per day), antihypertensive medication (yes/no), current smoking (yes/no), physical activity, and history of coronary heart disease and diabetes mellitus using generalized estimating equations.
†Model 1 includes all subjects (n=4594).
‡Model 2 is restricted to subjects without current or recent use of hypotensive medications (n=3918).
References


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