Plasma Fatty Acid Composition and 6-Year Incidence of Hypertension in Middle-aged Adults

The Atherosclerosis Risk In Communities (ARIC) Study

Zhi-Jie Zheng,1 Aaron R. Folsom,2 Jing Ma,3 Donna K. Arnett,2 Paul G. McGovern,2 and John H. Eckfeldt,* for the ARIC Study Investigators

The association of baseline fatty acid composition in plasma cholesterol esters with 6-year incidence of hypertension was examined in middle-aged Minneapolis participants of the Atherosclerosis Risk in Communities (ARIC) Study (1987–1995). Compared with those who were never hypertensive (n = 1,975), incident hypertensives (n = 413) had statistically significantly higher baseline levels of palmitic (16:0) and palmitoleic (16:1n7) acids but lower levels of linoleic (18:2n6) acid and the polyunsaturated/saturated fatty acids ratio (P/S ratio). Among polyunsaturated fatty acids, levels of dihomo-γ-linolenic (20:3n6) and arachidonic (20:4n6) acids were statistically significantly higher in incident hypertensives, compared with normotensives. After adjustment for age, sex, body mass index, waist/hip ratio, smoking status, ethanol intake, education level, physical activity, and baseline systolic blood pressure in separate models, the odds ratio estimates of incident hypertension for an interquartile increment of a fatty acid in cholesterol esters were 1.26 (95% confidence interval (CI): 1.05, 1.51) for 16:0, 1.11 (95% CI: 0.96, 1.28) for 16:1n7, 1.01 (95% CI: 0.85, 1.21) for 20:3n6, 1.14 (95% CI: 1.03, 1.27) for 20:5n3, 0.81 (95% CI: 0.68, 0.96) for 18:2n6, and 0.83 (95% CI: 0.70, 0.99) for the P/S ratio. The authors conclude that reduced levels of linoleic acid and the P/S ratio and elevated levels of palmitic and arachidonic acids are associated with a higher risk of hypertension. Am J Epidemiol 1999;150:492–500.

Fatty acid intake and metabolism may play a role in the pathogenesis of essential hypertension (1–4). Animal experiments have demonstrated that dietary fat composition affects blood pressure regulation: higher saturated fatty acid intake increases blood pressure, while polyunsaturated fatty acids, particularly linoleic acid and the n-3 series, decrease blood pressure (4–7). Human population-based epidemiologic studies, however, have been less consistent on the association of dietary fatty acid intake with blood pressure. In cross-sectional studies of the Finnish population, the mean blood pressure was positively associated with dietary intake of saturated fats (8, 9) and inversely associated with dietary intake of linolenic acid (9); others, however, found no cross-sectional associations (10–14). In the prospective Nurses’ Health Study (15) and Health Professionals Follow-up Study (16), dietary saturated, monounsaturated, and polyunsaturated fatty acids were not significantly associated with incident hypertension, once adjusted for other hypertension risk factors.

Received for publication January 12, 1998, and accepted for publication July 17, 1998.

Abbreviations: ARIC, Atherosclerosis Risk in Communities; CI, confidence interval; P/S ratio, polyunsaturated/saturated fatty acids ratio.

1 Division of Cardiovascular Medicine and Department of Preventive Medicine, University of Kentucky Chandler Medical Center, Lexington, KY.
2 Division of Epidemiology, School of Public Health, University of Minnesota, Minneapolis, MN.
3 Department of Medicine, Channing Laboratory, Brigham and Women’s Hospital, Harvard Medical School, Boston, MA.
4 Department of Laboratory Medicine and Pathology, University of Minnesota, Minneapolis, MN.

Reprint requests to Dr. Aaron Folsom, Division of Epidemiology, School of Public Health, University of Minnesota, 1300 South Second Street, Suite 300, Minneapolis, MN 55454-1015.

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are consistent with cross-sectional data, we also report the association of plasma fatty acid composition with prevalent hypertension at the baseline examination.

MATERIALS AND METHODS

The ARIC Study is a longitudinal study designed to investigate the natural history and etiology of preclinical and clinical atherosclerotic disease by ethnicity, sex, age, and location. The Study includes community surveillance and cohort components. Detailed descriptions of the study design and objectives have been published elsewhere (20, 21). Briefly, the cohort was sampled from four US communities: Forsyth County, North Carolina; Jackson, Mississippi; suburban Minneapolis, Minnesota; and Washington County, Maryland. Participants constituted a probability sample of eligible adults, aged 45–64 years. A total of 15,800 men and women underwent a comprehensive baseline (visit 1) clinical examination from 1987 to 1989. Participants were contacted by annual telephone calls and asked to come back every 3 years for follow-up examinations (visit 2: 1990–1992; visit 3: 1993–1995). Plasma cholesterol ester and phospholipid fatty acid composition were measured in nearly 4,000 participants in the Minneapolis ARIC Study field center at the baseline examination.

Fasting blood (12 hours) was collected using standardized ARIC Study protocols. Blood was drawn into vacuum tubes containing ethylenediaminetetraacetic acid, with less than 2 minutes’ tourniquet time. Plasma was then separated and dispensed into two 1.5-ml aliquots and frozen at −70°C for approximately 2 years before analysis for fatty acid content by a single technician at the University of Minnesota.

A detailed description of plasma fatty acid analysis has been published previously (19, 22). Briefly, 0.5 ml of plasma were extracted under a nitrogen atmosphere with 0.5 ml of methanol followed by 1.0 ml of chloroform. The lipid extract was filtered to remove protein. The cholesterol ester and phospholipid fractions were separated by thin-layer chromatography by using a silica-gel plate (Silica Gel H; Analtech, Newark, Delaware) and a two-stage mobile-phase development, using 80:20:1 (by volume) and 40:60:1 (by volume) mixtures of petroleum ether, diethyl ether, and glacial acetic acid, respectively. The plate was dried between development solvents, and the second mobile phase was allowed to migrate only half the plate length. After redrying, one lane was sprayed with dichlorofluorescein to visualize the cholesterol ester, phospholipid, triglyceride, and free fatty acid bands under ultraviolet light. The cholesterol ester and phospholipid bands were scraped into separate test tubes, and the lipids were converted to methyl esters of fatty acids by boron trifluoride catalysis. The methyl esters were then separated and measured on a Hewlett-Packard 5890 gas chromatograph (Hewlett Packard, Avondale, Pennsylvania) equipped with a 50-m FFAP WCOT glass capillary column (J & W Scientific, Folsom, California) and a flame ionization detector. The identity of each fatty acid peak was ascertained by comparison of the peak’s retention time with a previously characterized standard. The relative amount of each fatty acid (percent of total fatty acid) was quantified by integration of the area under the peak and dividing the result by the total area for all fatty acids.

Groupings of saturated, monounsaturated, and polyunsaturated fatty acids were calculated by summing all the respective fatty acid peaks with 12- to 24-carbon atom chains. The P/S ratio was also calculated. Test-retest reliability coefficients (intraclass correlations), based on individuals sampled three times, 2 weeks apart, ranged from 0.50 to 0.93 for cholesterol ester fatty acids and from 0.31 to 0.89 for phospholipid fatty acids (23).

Sitting blood pressures were measured after a 5-minute rest in the right arm using random zero sphygmomanometers by trained and certified ARIC Study technicians. Systolic and diastolic blood pressures were calculated as the average of the second and third of three consecutive measurements. Hypertension was defined as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg or by the use of anti-hypertensive medications. Prevalent hypertensives were defined as those who had hypertension at the baseline examination. Incident hypertensives were defined as normotensives at baseline who had hypertension at the 3-year or 6-year follow-up examinations.

Body mass index was defined as weight in kilograms, divided by height in meters squared. The waist/hip ratio was calculated as waist (umbilical) circumference divided by hip (maximum) circumference. Smoking status, education level, and usual alcohol consumption were determined by interview. A sports participation index was obtained through the leisure time physical activity questionnaire of Baechle et al. (24). The use of fish oil in the prior 2 weeks was obtained from a medication survey. A detailed description of these measurements is in the ARIC Study Manuals of Operation (21).

Statistical analysis

Of the 4,009 Minneapolis ARIC Study participants, 3,497 completed the 6-year examination. Participants who were non-Whites (n = 28), had prevalent cardiovascular disease at baseline (n = 168) and missing fatty acids measurements (n =186), were taking cholesterol-lowering medications, were on special diets, or fasted
less than 12 hours \((n = 26)\) were excluded from the analysis. The exclusions for baseline clinical cardiovascular disease were made because symptomatic patients may have altered their diet as a result of their disease. Thus, the final sample size was 2,378 (413 incident hypertensive cases, 1,066 men and 1,312 women) for the incidence analysis and 3,081 (698 prevalent hypertensive cases, 1,409 men and 1,672 women) for the prevalence analysis. The SAS package was used for analysis (25). The mean levels of proportionate plasma fatty acid composition were compared between incident or prevalent hypertensives and nonhypertensives using \(t\) tests. Pearson’s correlation coefficients between plasma fatty acids and baseline variables (systolic blood pressure, diastolic blood pressure, body mass index, waist/hip ratio, ethanol intake, cigarette-years of smoking, and sport index) were calculated among participants free of clinical cardiovascular disease and hypertension at baseline. Multivariate logistic regression models were used to examine the independence of associations, using individual or grouped fatty acid as a separate independent variable, with adjustment, partly or fully, for sex, baseline age (continuous variable), body mass index (continuous variable), waist/hip ratio (continuous variable), cigarette-years of smoking (continuous variable), ethanol intake (continuous variable), education level (\(<\) high school, \(\geq\) high school), the sports index (continuous variable), baseline systolic blood pressure (continuous variable), and family history of hypertension (yes, no). Odds ratio estimates of prevalent or incident hypertension for an increment of fatty acid in percentage points equal to the total sample’s interquartile range (i.e., from the 25th to the 75th percentile) were calculated for each grouped or individual fatty acid. Because conclusions for cholesterol ester and phospholipid fatty acid composition were identical, we chose to present cholesterol ester results only. The phospholipid data may be obtained by request.

**RESULTS**

Compared with nonhypertensives, incident hypertensives \((n = 413)\) and prevalent hypertensives \((n = 698)\) were older at baseline and had statistically significantly higher age-adjusted baseline mean levels of body mass index, waist/hip ratio, and systolic and diastolic blood pressures (table 1). Prevalent hypertensives also reported a statistically significantly higher mean ethanol intake, a lower mean sport index, and a lower prevalence of current smoking. The mean cigarette-years of smoking were higher in both incident and prevalent hypertensives than in their nonhypertensive counterparts, although the difference was not statistically significant. The prevalences of low education and family history of hypertension were higher in incident and prevalent hypertensives. There was no difference in the prevalence of fish oil use in any group.

Table 2 shows the mean values and standard deviations of plasma cholesterol ester fatty acids by hypertension status. Compared with nonhypertensives, both

<table>
<thead>
<tr>
<th>Baseline variable</th>
<th>Baseline (\text{age (years)})</th>
<th>Men (%)</th>
<th>(&lt;\text{high school education} &gt;)</th>
<th>Current smoking (%)</th>
<th>Fish oil user (%)</th>
<th>Family history of hypertension (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incident hypertensives</td>
<td>No ((n = 1,965))</td>
<td>52.8 (5.3)***</td>
<td>44</td>
<td>5</td>
<td>22</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Yes ((n = 413))</td>
<td>54.2 (5.8)***</td>
<td>49*</td>
<td>6*</td>
<td>19</td>
<td>3</td>
</tr>
<tr>
<td>Prevalent hypertensives</td>
<td>No ((n = 2,383))</td>
<td>53.0 (5.4)</td>
<td>45</td>
<td>5</td>
<td>22</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Yes ((n = 698))</td>
<td>55.9 (5.3)***</td>
<td>48</td>
<td>8***</td>
<td>15***</td>
<td>3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Baseline variable</th>
<th>BMIf ((\text{kg/m}^2))</th>
<th>Waist/hip ratio</th>
<th>SBPf ((\text{mmHg}))</th>
<th>DBPf ((\text{mmHg}))</th>
<th>Sport Index</th>
<th>Ethanol intake ((\text{g/week}))</th>
<th>Cigarette-years of smoking</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incident hypertensives</td>
<td>No ((n = 1,965))</td>
<td>Mean</td>
<td>SE</td>
<td>Mean</td>
<td>SE</td>
<td>Mean</td>
<td>SE</td>
</tr>
<tr>
<td></td>
<td>Yes ((n = 413))</td>
<td>26.2</td>
<td>0.90</td>
<td>0.002</td>
<td>111.4</td>
<td>0.24</td>
<td>70.3</td>
</tr>
<tr>
<td>Prevalent hypertensives</td>
<td>No ((n = 2,383))</td>
<td>26.4</td>
<td>0.29***</td>
<td>0.002</td>
<td>113.9</td>
<td>0.26</td>
<td>71.3</td>
</tr>
<tr>
<td></td>
<td>Yes ((n = 698))</td>
<td>28.8</td>
<td>0.17***</td>
<td>0.002</td>
<td>133.5</td>
<td>0.40***</td>
<td>81.8</td>
</tr>
</tbody>
</table>

\* \(p < 0.05, ** p < 0.01, *** p < 0.001\) (comparisons based on \(t\) tests).  
† ARIC, Atherosclerosis Risk in Communities; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; SE, standard error.  
‡ Numbers in parentheses, standard deviation.
prevalent and incident hypertensives had statistically significantly higher levels of saturated fatty acids, mainly palmitic acid (16:0), and monounsaturated fatty acids, mainly palmitoleic acid (16:1n7), but lower levels of polyunsaturated fatty acids and the P/S ratio. Among polyunsaturated fatty acids, levels of linoleic acid (18:2n6) were statistically significantly lower, while levels of dihomo-γ-linolenic (20:3n6), arachidonic (20:4n6), and eicosapentaenoic (20:5n3) acids were statistically significantly higher in both incident and prevalent hypertensives compared with nonhypertensives. Incident hypertensives also had a higher level of oleic acid (18:1n9).

Table 3 shows Pearson's correlation coefficients of cholesterol ester fatty acids with systolic blood pressure, body mass index, waist/hip ratio, ethanol intake, cigarette-years of smoking, and the sports index among participants free of hypertension and cardiovascular disease at the baseline examination. Systolic blood pressure was positively associated with 16:0 (r = 0.11), 16:1n7 (r = 0.15), and 20:3n6 (r = 0.17) and negatively correlated with linoleic acid (r = -0.13) and the P/S ratio (r = -0.13). The correlations of fatty acids with diastolic blood pressure were slightly weaker (data not shown). Similarly, body mass index, waist/hip ratio, ethanol intake, and cigarette smoking were positively correlated with saturated and monounsaturated fatty acids and 20:3n6 and negatively correlated with polyunsaturated fatty acids and the P/S ratio. For example, the correlation coefficient was 0.39 between body mass index and 20:3n6, 0.29 between the waist/hip ratio and 20:3n6, 0.23 between the waist/hip ratio and saturated fatty acids, 0.26 between ethanol intake and palmitic acid, 0.34 between ethanol intake and 16:1n7, 0.22 between cigarette-years of smoking and oleic acid (18:1n9), and -0.24 between the waist/hip ratio and the P/S ratio. The sports index was weakly negatively correlated with saturated fatty acids (r = -0.02), monounsaturated fatty acids (r = -0.10), and 20:3n6 (r = -0.13) and positively correlated with the P/S ratio (r = 0.06).

Table 4 presents the adjusted odds ratio estimates and their 95 percent confidence intervals of incident and prevalent hypertension in relation to an interquartile increment of grouped and individual cholesterol ester fatty acids. Saturated fatty acids (mainly 16:0), monounsaturated fatty acids (both 16:1n7 and 18:1n9), 20:2n3, 20:4n6, and 20:5n3 were positively, while 18:2n6 and the P/S ratio were inversely, associated with incident hypertension, after adjustment for age and sex (model 1). The associations were slightly attenuated but remained statistically significant (except for 20:3n6) after further adjustment for body mass index, the waist/hip ratio, smoking status, ethanol intake, education level, and the sports index (model 2). For example, after adjustment for the above variables, the odds ratio estimate of incident hypertension for an interquartile increment of a fatty acid in cholesterol esters was 1.28 (95 percent confidence interval (CI): 1.09, 1.50) for 16:0, 1.26 (95 percent confidence interval (CI): 1.09, 1.50) for 18:2n6, and 1.26 (95 percent confidence interval (CI): 1.09, 1.50) for 20:3n6.
TABLE 3. Pearson's correlation coefficients of plasma cholesterol ester fatty acids with systolic blood pressure, body mass index, waist/hip ratio, ethanol intake, cigarette-years of smoking, and sport index, ARIC Study Minneapolis Field Center, 1987–1995

<table>
<thead>
<tr>
<th>Fatty acids</th>
<th>Systolic blood pressure</th>
<th>Body mass index</th>
<th>Waist/hip ratio</th>
<th>Ethanol intake</th>
<th>Cigarette-years of smoking</th>
<th>Sport index</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saturated fatty acids</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16:0</td>
<td>0.10</td>
<td>0.14</td>
<td>0.23</td>
<td>0.19</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18:0</td>
<td>0.11</td>
<td>0.11</td>
<td>0.20</td>
<td>0.26</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monounsaturated fatty acids</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16:1n7</td>
<td>0.12</td>
<td>0.16</td>
<td>0.30</td>
<td>0.21</td>
<td>-0.10</td>
<td></td>
</tr>
<tr>
<td>18:1n9</td>
<td>0.15</td>
<td>0.13</td>
<td>0.11</td>
<td>0.34</td>
<td>-0.11</td>
<td></td>
</tr>
<tr>
<td>Polyunsaturated fatty acids</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18:2n6</td>
<td>-0.13</td>
<td>-0.12</td>
<td>-0.20</td>
<td>-0.26</td>
<td>-0.19</td>
<td></td>
</tr>
<tr>
<td>18:3n3</td>
<td>-0.13</td>
<td>-0.14</td>
<td>-0.19</td>
<td>-0.25</td>
<td>-0.14</td>
<td></td>
</tr>
<tr>
<td>20:3n6</td>
<td>0.17</td>
<td>0.39</td>
<td>0.28</td>
<td></td>
<td>-0.13</td>
<td></td>
</tr>
<tr>
<td>20:4n6</td>
<td>0.11</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20:5n3</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>22:6n3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polyunsaturated/saturated fatty acids ratio</td>
<td>-0.13</td>
<td>-0.15</td>
<td>-0.24</td>
<td>-0.24</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

† Only correlation coefficients of 0.10 or above are included in the table.
‡ ARIC, Atherosclerosis Risk in Communities.

A further adjustment for baseline systolic blood pressure (model 3) attenuated the associations of fatty acids with incident hypertension. Palmitic (16:0), arachidonic (20:4n6), and eicosapentaenoic (20:5n3) acids remained positively and statistically significantly

TABLE 4. Adjusted odds ratios of incident hypertension and prevalent hypertension in relation to an interquartile increment of plasma cholesterol ester fatty acids, ARIC Study Minneapolis Field Center, 1987–1995

<table>
<thead>
<tr>
<th>Fatty acids</th>
<th>Incident hypertension analysis</th>
<th>Prevalent hypertension analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Model 1§</td>
<td>Model 2¶</td>
</tr>
<tr>
<td>Saturated fatty acids</td>
<td>1.28 (1.19, 1.46)**</td>
<td>1.21 (1.04, 1.41)*</td>
</tr>
<tr>
<td>16:0</td>
<td>1.08 (1.13, 1.26)**</td>
<td>1.28 (1.09, 1.50)**</td>
</tr>
<tr>
<td>18:0</td>
<td>0.24 (0.23, 1.10)</td>
<td>0.81 (0.69, 0.98)**</td>
</tr>
<tr>
<td>Monounsaturated fatty acids</td>
<td>3.38 (2.51, 4.40)**</td>
<td>1.21 (1.06, 1.38)**</td>
</tr>
<tr>
<td>16:1n7</td>
<td>1.26 (1.09, 1.44)**</td>
<td>1.26 (1.11, 1.42)**</td>
</tr>
<tr>
<td>18:1n9</td>
<td>2.48 (1.94, 3.15)**</td>
<td>1.16 (1.01, 1.33)**</td>
</tr>
<tr>
<td>Polyunsaturated fatty acids</td>
<td>4.72 (0.78, 0.88)**</td>
<td>0.80 (0.69, 0.92)**</td>
</tr>
<tr>
<td>18:2n6</td>
<td>6.07 (0.72, 0.85)**</td>
<td>0.76 (0.65, 0.88)**</td>
</tr>
<tr>
<td>18:3n3</td>
<td>0.14 (0.13, 1.19)</td>
<td>1.05 (0.91, 1.21)</td>
</tr>
<tr>
<td>20:3n6</td>
<td>0.22 (0.12, 0.47)**</td>
<td>1.11 (0.95, 1.29)</td>
</tr>
<tr>
<td>20:4n6</td>
<td>2.26 (1.05, 1.40)**</td>
<td>1.17 (1.01, 1.36)**</td>
</tr>
<tr>
<td>20:5n3</td>
<td>0.26 (1.01, 1.21)*</td>
<td>1.10 (1.00, 1.21)*</td>
</tr>
<tr>
<td>22:6n3</td>
<td>0.18 (1.00, 1.16)</td>
<td>1.08 (0.95, 1.22)</td>
</tr>
<tr>
<td>Polyunsaturated/saturated fatty acids ratio</td>
<td>0.97</td>
<td>0.75 (0.65, 0.87)**</td>
</tr>
</tbody>
</table>

* p < 0.05, ** p < 0.01, *** p < 0.001.
† ARIC, Atherosclerosis Risk in Communities.
‡ Fatty acid increment in percentage points equal to the total sample's interquartile range (i.e., from the 25th to 75th percentile). Each fatty acid (continuous variable) entered into the model separately.
§ Model 1, adjusted for age and sex.
¶ Model 2, adjusted for age, sex, body mass index, waist/hip ratio, smoking status, ethanol intake, education level, and sport index.
# Model 3, adjusted for all variables in model 2 plus baseline systolic blood pressure.
†† Numbers in parentheses, 95% confidence interval.
associated with incident hypertension, while linoleic acid (18:2n6) and the P/S ratio were inversely associated with incident hypertension. The direction and magnitude of the associations of fatty acid composition with incident hypertension did not change when further adjusting for the family history of hypertension, total fatty acid intake, or weight change (data not shown).

In general, the direction and magnitude of the association of fatty acid composition with incident hypertension were similar to those for prevalent hypertension (except for stearic acid) (table 4). For example, in relation to an interquartile increment of cholesterol ester 18:2n6, the monounsaturated fatty acid estimate was 0.81 (95 percent CI: 0.72, 0.92) for prevalent hypertension and 0.76 (95 percent CI: 0.65, 0.88) for incident hypertension, after adjustment for age, sex, body mass index, the waist/hip ratio, smoking status, ethanol intake, education level, and the sports index (model 2). The monounsaturated fatty acid estimate in relation to an interquartile increase of the cholesterol ester P/S ratio was 0.77 (95 percent CI: 0.67, 0.87) for prevalent hypertension and 0.79 (95 percent CI: 0.67, 0.92) for incident hypertension after multivariate adjustment (model 2). Fish oil use was not associated with either prevalent or incident hypertension. No sex interaction was observed in the associations of major plasma fatty acids with prevalent or incident hypertension.

In addition, we ran several supplemental analyses. First, adjustment of model 3 of table 4 for low density lipoprotein cholesterol did not alter the estimates of risk. Second, analyses using absolute concentrations, instead of percentage composition, of plasma fatty acids also did not materially alter our conclusions. Finally, we eliminated users of antihypertensive medications (43 percent of incident hypertensives) and examined change in systolic blood pressure level as the dependent variable in a linear regression model (with the same covariates as model 3 of table 4). Although associations of fatty acids with blood pressure change were uniformly in the same direction as for model 3, few were statistically significant, perhaps because removing users of antihypertensive medication decreased the sample size by 8 percent and particularly removed many participants with the highest blood pressure levels.

DISCUSSION

The fatty acid composition of lipid fractions is influenced by three major factors: 1) dietary intake of fatty acids, 2) metabolic regulation of fatty acid synthesis, and 3) preferential incorporation of some fatty acids into different fat classes (26). The fatty acid composition of plasma cholesterol esters and phospholipids is fairly reproducible over the short-term (weeks) and long-term (years) (23) and to some degree reflects the fatty acid composition of the diet and a certain dietary pattern, particularly the essential fatty acids, such as linoleic acid (17–19). It may also reflect an individual’s metabolic processing of fatty acids independent of dietary fat intake (1). In the ARIC Study (19), the correlation of fatty acid composition measured in cholesterol esters with that measured by a food frequency questionnaire (percent of total fat) was 0.31 for polyunsaturated fatty acids (0.28 for linoleic acid) and 0.23 for saturated fatty acids (0.19 for palmitic acid), but only 0.01 for monounsaturated fatty acids.

Among nine major case-control and cross-sectional studies (27–35) in the literature that have examined the association of blood pressure with tissue fatty acids, four studies (one measured plasma phospholipids, three adipose tissue) found an inverse association of linoleic acid with blood pressure (27–30). One study found that the concentration of adipose tissue linolenic acid, but not of linoleic acid, was inversely correlated with blood pressure (31). Adipose palmitic acid was directly correlated with blood pressure in relatively small samples from Helsinki and southern Italy (28, 32), while an inverse relation was found between saturated fatty acids and blood pressure in eastern and southwestern Finland (30). The discordant findings among these small studies could have been caused by a lack of multivariate analyses that included other potentially confounding variables affecting fatty acid content, such as alcohol intake, cigarette smoking, and obesity (1, 36).

In the Paris Prospective Study II (34), one of the largest and thoroughly analyzed cross-sectional investigations to date, only palmitoleic acid measured in serum cholesterol esters was independently and positively associated with blood pressure after adjustment for age, body mass index, alcohol intake, and cigarette smoking. The Paris study and other cross-sectional studies analyzed blood pressure as a continuous variable without adjustment or stratification for antihypertensive medication use. Their results could be biased toward the null if there were many treated hypertensives with a normal blood pressure level. In a recent cross-sectional study of 156 middle-aged healthy men who were enrolled in the Multiple Risk Factor Intervention Trial, free of coronary heart disease and stroke and not taking antihypertensive medications, Simon et al. (35) reported that serum levels of stearic acid (18:0), 16:1n7, n-9 eicosatetraenoic acid, and 20:3n6 were significantly associated with systolic or diastolic blood pressure, after adjustment for age, body mass index, smoking, plasma cholesterol level, alcohol consumption, annual family income, energy intake, and dietary intake of cholesterol, sodium, and fatty acids.
In this large population sample of middle-aged adults, we demonstrated that, in both plasma fractions, a lower relative proportion of polyunsaturated fatty acids (particularly linoleic acid) and a higher relative proportion of saturated fatty acids (particularly palmitic acid) and monounsaturated fatty acids (particularly palmitoleic acid) were associated with increased risk of hypertension. The associations were moderately strong, even after adjustment for body mass index, cigarette smoking, alcohol intake, physical activity, and other variables.

It has been hypothesized that the relation between polyunsaturated fatty acids and blood pressure may be mediated through changes in eicosanoid/prostaglandin metabolism (37, 38). These changes may affect the balance between thromboxane \( A_2 \), which causes vasoconstriction, and prostacyclin \( I_2 \), a vasodilatory agent. Our data showed that lower levels of linoleic acid and the \( P/S \) ratio in plasma cholesterol esters and phospholipids were associated with a higher risk of developing hypertension. Since linoleic acid is an essential fatty acid, the lower levels in those who later developed hypertension may mirror a significantly lower intake of linoleic acid-rich food. In this population, plasma n-3 fatty acids were either not statistically significantly (e.g., linolenic and docosahexaenoic) or positively (eicosapentaenoic) associated with hypertension. This is in contrast to several reports from clinical trials (39, 40) that dietary supplementation with fish oil (mainly n-3 polyunsaturated fatty acids) reduces blood pressure in individuals with untreated hypertension, as well as numerous clinical and experimental studies (37, 38, 41), which have shown that n-3 fatty acids (particularly eicosapentaenoic and docosahexaenoic acid) decrease thromboxane \( A_2 \) production, thus shifting in the balance between thromboxane \( A_2 \) and prostacyclin \( I_2 \) toward a more favorable vasodilatory condition. The homogeneity of the diet and the relatively low intake of fish and marine foods in this population may partly explain the null association.

Hypertension was positively associated with the relative proportion of 20:3n6 and 20:4n6 in this population, although the association was no longer statistically significant for 20:3n6 after further adjustment for body mass index, waist/hip ratio, smoking, and other variables. Both 20:3n6 and 20:4n6 are synthesized from linoleic acid through the desaturation and elongation processes by \( \Delta-6 \)-desaturase, elongase, and \( \Delta-5 \)-desaturase (38). It has been reported that insulin stimulates fatty acid desaturation under experimental conditions (42); thus, higher levels of 20:3n6 and 20:4n6 in hypertensives could be related to insulin level. In our analysis, the direction and magnitude of the associations of 20:3n6 and 20:4n6 with incident hypertension remain unchanged even after further adjustment for fasting insulin level in the multivariate logistic regression models. The levels of 20:4n6 measured in plasma fractions may actually reflect animal fat consumption. One study (43) reported that the serum arachidonic acid concentration was positively correlated with dietary intake of total fat (\( r = 0.29 \)), saturated fat (\( r = 0.37 \)), oleic acid (\( r = 0.34 \)), cholesterol (\( r = 0.40 \)), and total energy (\( r = 0.29 \)). However, proportional arachidonic acid was not statistically significantly correlated with dietary intake of the above nutrients in this ARIC Study population.

Consistent with several other reports (34, 35), our study showed that higher proportional levels of palmitic (16:0) and palmitoleic (16:1n7) acids were associated with higher risk of hypertension. Palmitic acid is the main saturated fatty acid in most diets, and its consumption is known to raise total and low-density lipoprotein cholesterol levels (38). As shown in table 3, palmitic acid was highly correlated with the waist/hip ratio and ethanol intake, and its role in the etiology of hypertension could be via the development of obesity (44). However, the association for saturated fatty acids remains statistically significant, even after adjustment for body mass index, waist/hip ratio, and ethanol intake, suggesting that other mechanisms may also be involved. In addition, in this population plasma monounsaturated fatty acid levels do not reflect dietary monounsaturated fatty acid intake but, rather, saturated fatty acid intake (\( r = 0.26 \)) (19), given considerable endogenous synthesis of monounsaturated fatty acids from saturated fatty acids; thus, an association of hypertension with plasma monounsaturated fatty acids may actually reflect that for dietary saturated fatty acids. Furthermore, it is possible that the association attributed to saturated fatty acids is a result of competing effects of nutrients on blood pressure regulation, since plasma fatty acid composition also reflects a certain dietary pattern. For example, individuals who eat more saturated fat may also have a higher total fat intake and a lower dietary intake of carbohydrate, fiber, polyunsaturated fatty acids, and antioxidants.

There are a few limitations to this study. Though the expression of fatty acid composition as "proportions" has some advantages over absolute "concentration" (45), there may be difficulties in the interpretation of differences in proportions because of the mathematic and biologic interdependence of the fatty acid constituents. Since total fatty acids must sum to 100 percent, the proportions of minor components change as a result of changes in the proportion of major components. It is possible that positive associations of some polyunsaturated fatty acids with hypertension are the result of this problem. It may also prevent us from discerning...
whether some fatty acids are associated with hypertension independently of other fatty acids. However, analyses using absolute concentrations of plasma fatty acids did not materially alter the results from those using proportional composition. Nevertheless, the grouped fatty acids and major individual fatty acids were associated with hypertension in directions and magnitudes similar to reports on coronary heart disease, stroke, and peripheral arterial disease (46–48). In addition, hypertension was defined primarily by three readings on one occasion (clinical examination) and by information on antihypertensive medication use. Thus, some misclassifications likely occurred.

The authors conclude that reduced levels of linoleic acid and the P/S ratio and elevated levels of palmitic acid are associated with higher risk of hypertension, independent of the body mass index, waist/hip ratio, ethanol intake, cigarette smoking, physical activity, and baseline blood pressure. More investigations are needed to clarify the positive associations of dihomo-γ-linoleic (20:3n6), arachidonic (20:4n6), eicosapentaenoic (20:5n3), and docosahexaenoic (22:6n3) acids with hypertension. To our knowledge, this is the first prospective population study to demonstrate with biochemical markers that fatty acid metabolism may be involved in the etiology and pathogenesis of hypertension.

ACKNOWLEDGMENTS

The ARIC Study is supported by contracts NO1-HC-550515, NO1-HC-55016, NO1-HC-55018, NO1-HC-55019, NO1-HC-55020, NO1-HC-55021, and NO1-HC-55022 from the US National Heart, Lung, and Blood Institute, National Institutes of Health. Dr. Zheng was supported by an institutional National Research Service Award (I-T32-HL-07779) from the US National Institutes of Health.

The authors thank Linda Lewis for analyzing the plasma fatty acids.

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