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Associations of Plasma Fibrinogen Levels with Established Cardiovascular Disease Risk Factors, Inflammatory Markers, and Other Characteristics: Individual Participant Meta-Analysis of 154,211 Adults in 31 Prospective Studies

The Fibrinogen Studies Collaboration

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Long-term increases in plasma fibrinogen levels of 1 g/liter are associated with an approximate doubling of risk of major cardiovascular disease outcomes, but causality remains uncertain. To quantify cross-sectional associations of fibrinogen levels with established risk factors and other characteristics, the investigators combined individual data on 154,211 apparently healthy adults from 31 prospective studies conducted between 1967 and 2003, using a linear mixed model that included random effects at the cohort level. Fibrinogen levels increased with age and showed continuous, approximately linear relations with several risk markers and slightly curvilinear associations with log triglycerides, albumin, and tobacco and alcohol consumption. Female sex, Black ethnicity, lower socio-economic status, and alcohol abstinence were each associated with modestly higher fibrinogen levels. Approximately one third of the variation in fibrinogen levels was explained by cohort, age, and sex. An additional 7% was explained by established risk factors (notably, positive associations with smoking and body mass index and an inverse association with high density lipoprotein cholesterol), and a further 10% was explained by inflammatory markers (notably, a positive association with C-reactive protein). The association with body mass index was twice as strong in women as in men, whereas the association with smoking was much stronger in men. These findings substantially advance understanding of the correlates and possible determinants of fibrinogen levels.

association; cohort studies; fibrinogen; meta-analysis; prospective studies; risk factors

Abbreviations: BMI, body mass index; FSC, Fibrinogen Studies Collaboration; HDL, high density lipoprotein; LDL, low density lipoprotein.

Fibrinogen is the major coagulation protein in blood by mass; it is the precursor of fibrin and an important determinant of blood viscosity and platelet aggregation (1). The Fibrinogen Studies Collaboration (FSC) involves combined analyses of individual data from 31 prospective studies of plasma fibrinogen levels in 154,211 adults without known cardiovascular diseases at an initial baseline examination. FSC investigators have previously reported that a long-term increase of 1 g/liter in plasma fibrinogen level is associated with an approximate doubling in risk of major cardiovascular disease outcomes (such as coronary heart disease and stroke) and of aggregate nonvascular mortality (mainly comprising cancer deaths) (2); causality, however, remains uncertain (3). Associations of fibrinogen levels with coronary heart disease or stroke were reduced substantially in the FSC after adjustments were made for measured levels of several established cardiovascular disease risk factors (2), and genotypes that influence fibrinogen levels are not strongly related to coronary heart disease risk (4, 5). However, because selective fibrinogen-lowering agents are not yet available, the issue of causality (or, at least, reversibility of risk) has not been specifically addressed in randomized trials (6, 7).

To conduct a comprehensive and powerful quantitative assessment of the correlates of fibrinogen level, we analyzed cross-sectional associations of fibrinogen levels with biochemical, lifestyle, and other characteristics in 154,211 adults without known cardiovascular disease at baseline from 31 largely population-based prospective studies (1, 2).
The size and detail of the FSC data set permitted precise estimates of the age- and sex-specific associations of plasma fibrinogen with several established and emerging cardiovascular disease risk factors under different circumstances, thereby advancing understanding of the possible determinants of fibrinogen level (particularly behavioral and lifestyle correlates that could represent nonpharmacologic ways of lowering fibrinogen level) and of the scope of potential confounding in epidemiologic studies. To limit possible biases, the present meta-analysis involved only within-study comparisons.

MATERIALS AND METHODS

Study participants

The FSC has been described in detail previously (1, 2). Long-term (mostly population-based) prospective studies that recorded fibrinogen levels and cardiovascular disease outcomes in essentially healthy populations were identified through database searches and discussions with authors of relevant reports. Individual data on fibrinogen levels, age, sex, a range of other covariates, major incident cardiovascular morbidity, and cause-specific mortality were supplied on 155,827 adults without known cardiovascular disease from 31 studies conducted between 1967 and 2003. As in previous FSC reports (2, 8), the primary analyses were restricted to 154,211 participants with baseline fibrinogen values less than or equal to 5.62 g/liter, in order to avoid possible distortions arising from acute-phase reactions among persons with fibrinogen values in the highest 1 percent of levels (9) (although supplementary analyses also included these participants). Data cleaning and harmonization procedures maximized the comparability of coding across studies (particularly for categorical variables for which data were collected in different ways, such as physical activity and socioeconomic status). Any queries arising were referred back to the collaborators before the common database was finalized. Contributing studies were all based in the Northern Hemisphere, so calendar seasons, calculated from the dates of baseline blood collection, were defined as follows: winter, December–February; spring, March–May; summer, June–August; and autumn, September–November. As in previous reports (2, 8), fibrinogen assay methods were grouped as follows: 1) clotting time (i.e., Clauss assays: 18 cohorts); 2) clot weight (i.e., clot weight, Swain, or Blomback assays: three cohorts); or 3) nonclot methods using various immunologic assays (i.e., nephelometry, turbidometry, or electroimmunoassay: 10 cohorts).

The FSC has received institutional review board approval from the Cambridgeshire Research Ethics Committee (Cambridgeshire, United Kingdom). In addition, each of the 31 studies included has been previously published, and each received local institutional review board approval and consent from participants.

Statistical analysis

Unadjusted Pearson correlation coefficients pooled across cohorts by random-effects meta-analysis of Fisher’s z-transformed cohort- and sex-specific correlation coefficients were initially used for descriptive summaries. Thereafter, changes in coefficients of determination ($r^2$) in multivariable adjusted models (described below) were used to quantify the proportion of variance in fibrinogen explained by risk factor(s) over and above the effects of cohort, age, and sex. Because only one type of assay was used to measure fibrinogen levels in each cohort, it was not possible to directly assess the effect of assay method independently of any cohort effects. Hence, the extent to which assay method contributed to variation in fibrinogen levels was assessed using a nested analysis-of-variance model, testing whether differences in mean fibrinogen levels were greater within a group of studies using similar assay methods than across studies using different assay methods (i.e., cohort effect nested within assay). Associations of fibrinogen levels with other characteristics were then assessed using a linear mixed model that included random effects at the cohort level. The main effect of cohort was modeled as a separate fixed effect. Continuous variables were divided into tenths based on the overall distribution in males and females combined. This approach allowed assessment of the shape of any association with fibrinogen without imposing any particular shape on the association a priori. The fixed effects in each model were: cohort, age, age$^2$, sex, age$^2 \times$ sex, risk-factor tenth, risk-factor tenth $\times$ sex, and risk-factor tenth $\times$ age (where $\times$ denotes an interaction). Coefficients that were allowed to vary randomly across cohorts were: age, age$^2$, sex, and risk-factor tenth (entered as a continuous variable). The latter allows for an arbitrary overall shape of the association but constrains individual cohort departures from the overall shape to depend linearly on the level of the risk factor. Natural logarithms were used to achieve approximately symmetrical distributions for positively skewed variables. Categorical variables were modeled similarly to the risk-factor tenths, except that dummy variables were also used in the random part, since there was no natural monotonic ordering of the categories.

From each fitted mixed model, overall adjusted mean values and 95 percent confidence intervals for fibrinogen level by sex within tenths of continuous markers, or within category for categorical variables, were obtained with age fixed at 50 years (with supplementary analyses adjusted to ages 65 and 80 years). We used these adjusted mean values to assess the shape of the association by plotting the mean fibrinogen level against the mean marker value within each tenth. An inverse-variance weighted polynomial was superimposed across the adjusted means to assess whether the overall association was consistent with a linear shape or a quadratic shape. To assess associations with fibrinogen levels after adjustment for measured levels of risk factors and other characteristics, we fitted a multiple linear mixed regression model. Because of missing data, it was not possible to simultaneously assess the multivariable adjusted associations with all of the characteristics listed in table 1. Therefore, we fitted two models: 1) a model using data sets from 18 cohorts with complete data for fibrinogen, age, sex, body mass index (BMI; weight (kg)/height (m)$^2$), systolic blood pressure, total cholesterol, high density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL) cholesterol, cholesterol, low density lipoprotein (LDL) cholesterol,
smoking status, season, ethnic group, diabetes history, and alcohol consumption \((n = 89,226)\); and 2) a model using data from four cohorts with information on C-reactive protein level in addition to the above variables \((n = 5,569)\), created because C-reactive protein appeared to be the strongest correlate in univariate models. Analyses were restricted to characteristics recorded in at least 5,000 participants.

**RESULTS**

Table 1 summarizes characteristics of the 154,211 persons without known cardiovascular diseases at baseline, including sex-specific summaries derived only from cohorts involving both men and women, to avoid any confounding by study (cohort-specific summaries are provided in Web table 1, which is posted on the Journal’s website (http://www.aje.oxfordjournals.org)). All participants had full data on fibrinogen, age, sex, BMI, systolic blood pressure, total cholesterol, smoking history, and season. A total of 89,226 participants (from 18 studies) had data on these core variables plus full data on diastolic blood pressure, HDL cholesterol, LDL cholesterol, ethnic group, diabetes history, and alcohol consumption. Of those with data on all of the above variables, the numbers with additional data on either triglycerides, leukocyte count, albumin, lipoprotein(a), or history of hypertension were between 39,054 and 75,219. Data on C-reactive protein were available for 7,010 participants from six cohorts.

Figure 1 shows sex-specific overall mean fibrinogen levels by cohort and assay method, as well as sex-specific mean levels in 5-year age bands adjusted for cohort and then further adjusted for BMI. There was almost twofold variation in the cohorts in relation to the highest (4.14 g/liter) and lowest (2.32 g/liter) mean fibrinogen values. Mean fibrinogen levels, however, were just as diverse within studies that used similar assay methods as across studies that used different assay methods (nested analysis of variance: \(p = 0.29\) for test of assay mean differences relative to variation between cohorts within assay), underscoring the contribution of other study-level characteristics to this heterogeneity. Fibrinogen levels increased with age and were higher in females than in males, with the mean difference, adjusted to age 50 years, being 0.12 g/liter (figure 1). C-reactive protein was the strongest correlate of fibrinogen among the continuous variables (Pearson correlation: \(r = 0.49\)), with Pearson correlation coefficients for other characteristics ranging between −0.13 for HDL cholesterol and 0.22 for leukocyte count (table 1).

Figures 2 and 3 plot mean fibrinogen levels by sex, adjusted to age 50 years, against mean values within tenths of several established cardiovascular disease risk factors and inflammatory markers, generally demonstrating continuous and approximately linear associations, apart from slightly curvilinear relations with log triglycerides, albumin, amount of smoking (number of cigarettes smoked per day), and amount of alcohol drinking (number of drinks consumed per day) (Web table 2, posted on the Journal’s website (http://www.aje.oxfordjournals.org)), provides numerical details). Among males, the differences in fibrinogen values in the extreme tenths of these continuous characteristics ranged from as little as 0.08 g/liter for lipoprotein(a) to 1.19 g/liter for C-reactive protein; among females, such differences ranged from 0.10 g/liter for lipoprotein(a) to 0.92 g/liter for C-reactive protein. The shapes of these associations were similar in analyses adjusted to age 65 years (see Web figures 1 and 2, posted on the Journal’s website (http://www.aje.oxfordjournals.org)), although the trends were less distinct in analyses adjusted to age 80 years because of smaller numbers (see Web figures 3 and 4, posted on the Journal’s website (http://www.aje.oxfordjournals.org)).

Figure 4 plots mean fibrinogen values by sex, adjusted to age 50 years, against levels of several categorical characteristics. The figure demonstrates modestly higher fibrinogen values in smokers than in nonsmokers (0.27 g/liter higher in men and 0.14 g/liter higher in women, even after adjustment for numbers of cigarettes smoked per day), in participants who provided samples during winter than in those who provided samples in other seasons (0.03 g/liter higher in men and 0.01 g/liter higher in women), in non-Blacks than in Whites (for men: 0.14 g/liter higher in Asians and 0.15 g/liter higher in Blacks; for women: 0.15 g/liter higher in Asians and 0.26 g/liter higher in Blacks), in people with diabetes than in those without diabetes (0.09 g/liter higher in men and 0.17 g/liter higher in women), and in alcohol abstainers than in alcohol drinkers (0.11 g/liter higher in men and 0.15 g/liter higher in women). Fibrinogen levels were also somewhat higher in unemployed people (0.09 g/liter higher in men without a job and 0.02 g/liter higher in women without a job than among those in manual or nonmanual employment), in people with less education (0.15 g/liter higher in men and 0.20 g/liter higher in women without a job than among those in manual or nonmanual employment), in people with only primary schooling compared with those with a university education), in less physically active people (0.16 g/liter higher in men and 0.15 g/liter higher in women compared with physically active persons), and in people with a history of hypertension (0.09 g/liter higher in men and 0.17 g/liter higher in women) (numerical details are provided in Web table 3, posted on the Journal’s website (http://www.aje.oxfordjournals.org)). Web figures 5 and 6, posted on the Journal’s website (http://www.aje.oxfordjournals.org), plot similar findings in analyses adjusted to ages 65 and 80 years, respectively, though the differences tended to become attenuated with increasing age. In these models, adjusted for associations with cohort, age, and sex (which explained approximately one third of the variation in fibrinogen), even the strongest correlates of fibrinogen level each accounted for only a relatively small increment in the percent-age of variation explained—such as C-reactive protein (14.9 percent), leukocyte count (4.5 percent), cigarette smoking (2.5 percent), BMI (1.4 percent), and HDL cholesterol (1.4 percent) (see Web table 4, posted on the Journal’s website (http://www.aje.oxfordjournals.org)).

Table 2 extends the above analyses by displaying results from a multivariable model assessing the mutually adjusted associations with fibrinogen level using data on 89,226 participants from 18 studies. These participants had complete data on fibrinogen, age, sex, BMI, systolic blood pressure, total cholesterol, HDL cholesterol, LDL cholesterol, smoking,
<table>
<thead>
<tr>
<th>Variable</th>
<th>Total</th>
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<tr>
<td></td>
<td>No. of cohorts</td>
<td>Total no. of subjects</td>
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<td>Mean fibrinogen level (g/liter)</td>
<td>31</td>
<td>154,211</td>
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<tr>
<td>Questionnaire</td>
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<td>154,211</td>
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<tr>
<td>Smoking§ (yes) (no. (%))</td>
<td>31</td>
<td>154,211</td>
</tr>
<tr>
<td>Season (no. (%))</td>
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<td>154,211</td>
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<tr>
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<td>Alcohol drinking§ (yes) (no. (%))</td>
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<td>Occupation (no. (%))</td>
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<td>54,455</td>
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<tr>
<td>History of hypertension (yes) (no. (%))</td>
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<td>39,598</td>
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</table>

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<table>
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<th>Physical measurements</th>
<th>Mean body mass index ($\text{kg}/\text{m}^2$)</th>
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<th>26.06 (4.17)</th>
<th>0.15</th>
<th>0.12, 0.18</th>
<th>16</th>
<th>49,101</th>
<th>25.88 (3.89)</th>
<th>0.10</th>
<th>0.07, 0.13</th>
<th>16</th>
<th>41,428</th>
<th>26.11 (5.29)</th>
<th>0.27</th>
<th>0.23, 0.31</th>
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<tbody>
<tr>
<td>Mean systolic blood pressure (mmHg)</td>
<td>31 154,211</td>
<td>133.2 (21.0)</td>
<td>0.12</td>
<td>0.10, 0.14</td>
<td>16</td>
<td>49,101</td>
<td>130.51 (19.29)</td>
<td>0.12</td>
<td>0.09, 0.14</td>
<td>16</td>
<td>41,428</td>
<td>129.17 (21.4)</td>
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<td>0.14, 0.21</td>
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<tr>
<td>Mean diastolic blood pressure (mmHg)</td>
<td>31 154,170</td>
<td>81.98 (12.35)</td>
<td>0.06</td>
<td>0.05, 0.08</td>
<td>16</td>
<td>49,083</td>
<td>81.39 (11.9)</td>
<td>0.05</td>
<td>0.03, 0.07</td>
<td>16</td>
<td>41,409</td>
<td>77.78 (11.9)</td>
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<td>0.08, 0.13</td>
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<td>Mean lipid levels (mmol/liter)</td>
<td>Total cholesterol</td>
<td>31 154,211</td>
<td>5.90 (1.16)</td>
<td>0.11</td>
<td>0.09, 0.13</td>
<td>16</td>
<td>49,101</td>
<td>5.77 (1.16)</td>
<td>0.08</td>
<td>0.06, 0.10</td>
<td>16</td>
<td>41,428</td>
<td>5.91 (1.23)</td>
<td>0.17</td>
<td>0.12, 0.21</td>
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<tr>
<td>High density lipoprotein cholesterol</td>
<td>24 114,006</td>
<td>1.35 (0.41)</td>
<td>$-0.13$</td>
<td>$-0.14, -0.11$</td>
<td>14</td>
<td>44,448</td>
<td>1.28 (0.37)</td>
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<td>$-0.13, -0.10$</td>
<td>14</td>
<td>38,691</td>
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<td>Low density lipoprotein cholesterol</td>
<td>21 101,176</td>
<td>3.74 (1.06)</td>
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<td>39,021</td>
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<td>34,043</td>
<td>3.66 (1.11)</td>
<td>0.19</td>
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<td>Log triglycerides</td>
<td>18 94,900</td>
<td>0.32 (0.53)</td>
<td>0.09</td>
<td>0.06, 0.12</td>
<td>11</td>
<td>36,915</td>
<td>0.35 (0.56)</td>
<td>0.06</td>
<td>0.03, 0.09</td>
<td>11</td>
<td>31,174</td>
<td>0.20 (0.51)</td>
<td>0.15</td>
<td>0.10, 0.20</td>
<td></td>
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<tr>
<td>Inflammatory markers</td>
<td>Log leukocyte count ($&gt;10^9$ cells/liter)</td>
<td>14 52,072</td>
<td>1.78 (0.30)</td>
<td>0.22</td>
<td>0.19, 0.26</td>
<td>7</td>
<td>15,705</td>
<td>1.79 (0.30)</td>
<td>0.25</td>
<td>0.21, 0.28</td>
<td>7</td>
<td>17,870</td>
<td>1.74 (0.31)</td>
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<td>0.15, 0.24</td>
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<td>Mean albumin level (g/liter)</td>
<td>9 49,804</td>
<td>42.97 (4.51)</td>
<td>$-0.10$</td>
<td>$-0.13, -0.07$</td>
<td>6</td>
<td>21,002</td>
<td>43.44 (4.45)</td>
<td>$-0.14$</td>
<td>$-0.18, -0.11$</td>
<td>6</td>
<td>20,778</td>
<td>41.88 (4.63)</td>
<td>$-0.08$</td>
<td>$-0.14, -0.02$</td>
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<td>Log lipoprotein(a) level (mg/dl)</td>
<td>8 30,440</td>
<td>3.02 (1.21)</td>
<td>0.08</td>
<td>0.02, 0.15</td>
<td>4</td>
<td>5,453</td>
<td>2.79 (1.41)</td>
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<td>0.08, 0.13</td>
<td>4</td>
<td>7,477</td>
<td>2.95 (1.39)</td>
<td>0.14</td>
<td>0.12, 0.17</td>
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<tr>
<td>Log C-reactive protein level (mg/dl)</td>
<td>6 7,010</td>
<td>0.45 (1.07)</td>
<td>0.49</td>
<td>0.46, 0.52</td>
<td>2</td>
<td>2,734</td>
<td>0.41 (1.07)</td>
<td>0.51</td>
<td>0.48, 0.53</td>
<td>2</td>
<td>1,576</td>
<td>0.45 (1.11)</td>
<td>0.45</td>
<td>0.41, 0.49</td>
<td></td>
</tr>
</tbody>
</table>

* To avoid confounding by cohort when comparing estimates for males and females, the sex-specific summaries were calculated using only data from cohorts that included both sexes.
† SD, standard deviation; CI, confidence interval.
‡ Pearson correlation coefficient for the correlation between fibrinogen level and the row variable, pooled across cohorts by random-effects meta-analysis. For calculation of $r$, ethnic group was coded as White vs. non-White; season was coded as winter vs. all other seasons; occupation was coded as not working vs. all other statuses; and education was coded as primary schooling vs. secondary and university schooling.
§ For the variables smoking history and alcohol drinking, yes = current use and no = never or former use.
¶ Weight (kg)/height (m)$^2$.
# Geometric mean values for these log-transformed variables in the total sample were: triglycerides, 1.37 mmol/liter; leukocyte count, $5.91 \times 10^9$ cells/liter; lipoprotein(a), 20.5 mg/dl; and C-reactive protein, 1.57 mg/dl. For the sex-specific summaries using data from cohorts that included both sexes, the geometric mean values (males vs. females) were: triglycerides, 1.42 vs. 1.22 mmol/liter; leukocyte count, 5.99 vs. 5.67 cells $\times 10^9$/liter; lipoprotein(a), 16.2 vs. 19.1 mg/dl; and C-reactive protein, 1.51 vs. 1.57 mg/dl.
season, ethnic group, diabetes history, and alcohol consumption. Fibrinogen was highly significantly associated with all measured variables, except for total cholesterol ($p = 0.25$) and history of diabetes ($p = 0.18$). The combined association with all of the above characteristics explained 42 percent of the variation in fibrinogen level, of which 36 percent was attributable to cohort, age, and sex and the remaining 6 percent was attributable to associations with BMI, HDL cholesterol, LDL cholesterol, systolic blood pressure, smoking, season, ethnic group, alcohol consumption, and diabetes history. When HDL cholesterol and LDL cholesterol were excluded from the model, total cholesterol was significantly positively associated with fibrinogen level. Similarly, diastolic blood pressure was positively associated with fibrinogen level when systolic blood pressure was excluded. BMI was almost twice as strongly associated with fibrinogen level in women as in men ($p < 0.0001$), but any differential associations by sex were not so convincing for systolic blood pressure or HDL cholesterol. The final column in table 2 provides the standard deviation of the cohort random effect, a summary of the variability across cohorts in associations between fibrinogen levels and particular characteristics. For example, the average association with BMI across cohorts in men was an increase in fibrinogen of $0.013 \pm 1.96 \times 0.010$, which is $-0.007$ to $0.033$, suggesting that some such associations in single large

![FIGURE 1. Mean fibrinogen levels in males (black diamonds) and females (gray squares) according to cohort and assay method (part a) and within 5-year age bands, adjusted for cohort (part b) and adjusted for cohort and to BMI of 25 (part c). SHHS, Scottish Heart Health Study; WHITE2, Whitehall II Study; BRUN, Bruneck Study; PROCAM, Prospective Cardiovascular Münster Study; OSAKA, Osaka Study; NPHSII, Northwick Park Heart Study II; STRONG, Strong Heart Study; TPT, Thrombosis Prevention Trial; ARIC, Atherosclerosis Risk in Communities Study; KIHD, Kuopio Ischaemic Heart Disease Study; HONOL, Honolulu Heart Program; GOTO33, Göteborg 1933 Study; CHS, Cardiovascular Health Study; PRIME, Prospective Epidemiological Study of Myocardial Infarction; CAER, Caerphilly Prospective Study; ZUTE, Zutphen Elderly Study; PAIS, Platelet Activation and Inflammation Study; QUEBEC, Quebec Cardiovascular Study; FRAM, Framingham Heart Study; NPHSI, Northwick Park Heart Study I; GOTO, Göteborg 1913 Study; EAS, Edinburgh Artery Study; VITA, Vicenza Thrombophilia and Atherosclerosis Project; KORA, S3, MONICA/KORA-Augsburg Study, Survey 3; COPEN, Copenhagen City Heart Study; FINRISK, Finish National Risk Factor Survey 1992; MALMO, Malmö Study; SPEED, Speedwell Study; GRIPS, Göttingen Risk Incidence and Prevalence Study; KORA, S2, MONICA/KORA-Augsburg Study, Survey 2; WOSCOPS, West of Scotland Coronary Prevention Study. Bars, 95% confidence interval.](image)
cohorts might be observed as inverse. For women, the 95 percent range of values would be 0.025 /C6 1.96 3 0.010, which is 0.005 to 0.045, suggesting that it would be unlikely to observe an inverse association of fibrinogen with BMI in a single large cohort.

When log C-reactive protein was added to the multivariable model in table 2 (using data on 5,569 persons from four cohorts who had full information on all of these variables), the model explained 53 percent of the variance in fibrinogen level, of which 36 percent was attributable to associations with cohort, age, and sex; 7 percent to associations with BMI, HDL cholesterol, LDL cholesterol, systolic blood pressure, smoking, season, ethnic group, alcohol consumption, total cholesterol, and diabetes history; and a further 10 percent to C-reactive protein. Alternatively expressed, non-modifiable factors (i.e., cohort, age, sex, ethnic group, and season) explained 37 percent of the variation in fibrinogen levels, while potentially modifiable factors (i.e., BMI, HDL cholesterol, LDL cholesterol, systolic blood pressure, smoking, alcohol consumption, total cholesterol, diabetes history, and C-reactive protein) explained a further 16 percent of the variation after adjustment for nonmodifiable factors. Thus,

**FIGURE 2.** Mean fibrinogen levels, adjusted to age 50 years, within tenths of cardiovascular disease risk factors (continuous variables) in males (black diamonds) and females (gray squares), plotted against the mean of the risk factor values in each tenth for assessment of the shape of the association with fibrinogen. Tenths of each risk factor were defined on the basis of the distribution in males and females combined to allow for comparison between sexes with the same levels of the risk factor. Note that the overall mean fibrinogen value in each graph depends on which cohorts were included in the analysis that provided data for the relevant risk factor (see Web table 1, which is posted on the Journal’s website (http://www.aje.oxfordjournals.org)). BMI, body mass index (weight (kg)/height (m)2); BP, blood pressure; HDL, high density lipoprotein; LDL, low density lipoprotein; cig, cigarettes. Bars, 95% confidence interval.
approximately 70 percent of the explained variation in fibrinogen levels was attributable to nonmodifiable factors and approximately 30 percent to potentially modifiable factors.

DISCUSSION

This meta-analysis of individual data on 154,211 adults without known cardiovascular diseases from 31 prospective studies precisely quantified cross-sectional associations of fibrinogen levels with several established and emerging cardiovascular disease risk factors and other characteristics under different circumstances (e.g., in men and women, at different ages, and at different fibrinogen levels). Approximately one third of the variation in fibrinogen levels was accounted for by age, sex, and cohort (with the latter being a proxy for differences in population characteristics and fibrinogen assay methods). An additional 7 percent of the variation was explained by several risk factors (notably cigarette smoking, BMI, and HDL cholesterol), and a further 10 percent was explained by inflammatory markers (notably C-reactive protein). Inflammatory markers accounted for a somewhat larger fraction of the variation in fibrinogen levels than did other characteristics, partly because levels of fibrinogen and C-reactive protein vary together in people in response to acute-phase reactions, whereas most noninflammatory markers principally have only long-term average associations with fibrinogen. Fibrinogen levels showed continuous, approximately linear relations with most measured continuous variables, except for slightly curvilinear

**FIGURE 3.** Mean fibrinogen levels, adjusted to age 50 years, within tenths of inflammatory markers (continuous variables) in males (black diamonds) and females (gray squares), plotted against the mean of the risk factor values in each tenth for assessment of the shape of the association with fibrinogen. Tenths of each risk factor were defined on the basis of the distribution in males and females combined to allow for comparison between sexes with the same levels of the risk factor. Note that the overall mean fibrinogen value in each graph depends on which cohorts were included in the analysis that provided data for the relevant risk factor (see Web table 1, posted on the Journal’s website [http://www.aje.oxfordjournals.org](http://www.aje.oxfordjournals.org)). Because of tied values, the second and third tenths and the fourth, fifth, and sixth tenths of leukocyte count coincided, yielding missing values for adjusted means in the figure. Bars, 95% confidence interval.
associations with log triglycerides, albumin, and amount of tobacco or alcohol used. Female sex, low socioeconomic status, Black ethnicity, and alcohol abstinence were each associated with modestly higher fibrinogen levels. The present findings substantially advance our understanding of the correlates and possible determinants of fibrinogen levels.

Age, sex, and cohort

The present data demonstrate that fibrinogen levels increase with age, in both middle-aged and elderly participants, perhaps because they are indicators of increasing atherothrombotic activity (10, 11). Although the present data indicate that mean fibrinogen levels are approximately 0.16 g/liter higher in women than in men after adjustment for several established risk factors (10, 12–15), it has been suggested that at least part of this apparent sex difference is due to greater dilution of citrated blood samples in men (who tend to have higher hematocrit values than women) (9, 16). In preliminary studies that have used dry potassium edetate as an anticoagulant (which should help to avoid dilution by liquid sodium citrate), investigators have reported no discernible differences in fibrinogen levels by sex (9, 17); it was not possible to test this possibility in the FSC, because hematocrit values were generally not available. Since we observed that the diversity in fibrinogen levels was just as great within studies.

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<table>
<thead>
<tr>
<th>Variable</th>
<th>Males ((n = 60,092))</th>
<th>Females ((n = 29,134))</th>
<th>Female – male slope</th>
<th>p value for sex interaction</th>
<th>Cohort random effect</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Slope</strong></td>
<td><strong>95% CI</strong></td>
<td><strong>Slope</strong></td>
<td><strong>95% CI</strong></td>
<td><strong>Difference</strong></td>
<td><strong>95% CI</strong></td>
</tr>
<tr>
<td>Age (per 1 year)</td>
<td>0.018</td>
<td>0.013, 0.022</td>
<td>0.015</td>
<td>0.011, 0.019</td>
<td>–0.003</td>
</tr>
<tr>
<td>Body mass index (\dagger) (per 1 kg/m(^2))</td>
<td>0.013</td>
<td>0.008, 0.018</td>
<td>0.025</td>
<td>0.020, 0.030</td>
<td>0.012</td>
</tr>
<tr>
<td>Smoking history (current vs. never/former)</td>
<td>0.290</td>
<td>0.245, 0.335</td>
<td>0.150</td>
<td>0.102, 0.197</td>
<td>–0.140</td>
</tr>
<tr>
<td>High density lipoprotein cholesterol (per 1 mmol/liter)</td>
<td>–0.150</td>
<td>–0.187, –0.114</td>
<td>–0.101</td>
<td>–0.144, –0.058</td>
<td>0.050</td>
</tr>
<tr>
<td>Systolic blood pressure (per 10 mmHg)</td>
<td>0.014</td>
<td>0.009, 0.019</td>
<td>0.009</td>
<td>0.002, 0.015</td>
<td>–0.005</td>
</tr>
<tr>
<td><strong>Season</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spring vs. winter</td>
<td>0.010</td>
<td>–0.024, 0.045</td>
<td>0.000</td>
<td>–0.038, 0.038</td>
<td>–0.011</td>
</tr>
<tr>
<td>Summer vs. winter</td>
<td>–0.034</td>
<td>–0.086, 0.020</td>
<td>–0.023</td>
<td>–0.080, 0.034</td>
<td>0.011</td>
</tr>
<tr>
<td>Autumn vs. winter</td>
<td>–0.056</td>
<td>–0.091, –0.021</td>
<td>–0.031</td>
<td>–0.069, 0.008</td>
<td>0.025</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black vs. White</td>
<td>0.086</td>
<td>0.051, 0.120</td>
<td>0.124</td>
<td>0.094, 0.153</td>
<td>0.038</td>
</tr>
<tr>
<td>Asian/Oriental vs. White</td>
<td>0.040</td>
<td>–0.060, 0.140</td>
<td>0.041</td>
<td>–0.069, 0.151</td>
<td>0.001</td>
</tr>
<tr>
<td>Other vs. White</td>
<td>0.000</td>
<td>–0.093, 0.094</td>
<td>0.006</td>
<td>–0.105, 0.118</td>
<td>0.006</td>
</tr>
<tr>
<td>Low density lipoprotein cholesterol (per 1 mmol/liter)</td>
<td>0.075</td>
<td>0.043, 0.107</td>
<td>0.100</td>
<td>0.061, 0.140</td>
<td>0.025</td>
</tr>
<tr>
<td>Alcohol consumption (current vs. never/former)</td>
<td>–0.081</td>
<td>–0.120, –0.043</td>
<td>–0.089</td>
<td>–0.130, –0.049</td>
<td>–0.008</td>
</tr>
<tr>
<td>Total cholesterol (per 1 mmol/liter)</td>
<td>–0.011</td>
<td>–0.040, 0.018</td>
<td>–0.031</td>
<td>–0.067, 0.006</td>
<td>–0.020</td>
</tr>
<tr>
<td>History of diabetes (yes vs. no)</td>
<td>0.041</td>
<td>–0.003, 0.085</td>
<td>0.029</td>
<td>–0.023, 0.080</td>
<td>–0.012</td>
</tr>
</tbody>
</table>

* Each slope was adjusted for the other factors included in the model.
† CI, confidence interval; SD, standard deviation.
‡ Because of rounding, the female – male differences in slope shown may not be exactly the same as those obtained by direct subtraction of the rounded-off slope coefficients for females and males.
§ The cohort random-effect standard deviation summarizes the variability of the risk factor association with fibrinogen across cohorts. For example, the average effect of body mass index across men in an increase in fibrinogen of 0.013 g/liter per 1-kg/m\(^2\) increase in body mass index, and the 95% range of values expected for individual cohorts can be estimated to be 0.013 ± 1.96 × 0.010, which is –0.007 to 0.033.
¶ Weight (kg)/height (m\(^2\)).
# The between-cohort standard deviation for the effect of ethnic group was not estimated, since the model did not converge when a random effect for ethnic group was included in the model (most cohorts were homogeneous with respect to ethnic group).
using similar assay methods as across studies using different assay methods, the heterogeneity in fibrinogen levels in the FSC probably chiefly reflects differences in population characteristics (17–19) and the lack of an agreed-upon fibrinogen standard (9) prior to its introduction by the World Health Organization in 1992 (20–22). (A previous FSC study found that associations of fibrinogen levels with risk of coronary heart disease or stroke did not vary importantly by assay method used (2).) The current analyses were stratified by (or adjusted for) cohort, thereby accounting for any effect of fibrinogen assay methods on age, sex, or risk factor associations.

**Inflammatory markers**

C-reactive protein was the strongest correlate of fibrinogen levels; there were somewhat weaker associations with other inflammatory markers, such as leucocyte count and, inversely, albumin (a negative acute-phase reactant). Like fibrinogen levels, levels of these other “downstream” markers of inflammation (23, 24) are governed by proximal mediators of inflammatory cascades, such as the cytokine interleukin-6 (25, 26). Therefore, the present data are consistent with suggestions that variability in fibrinogen levels is partly explained by low-grade inflammatory responses to environmental stimuli (such as the behavioral and lifestyle characteristics described below) (3).

**Tobacco and alcohol use and physical activity**

The present data demonstrate that overall mean fibrinogen levels were higher in current smokers than in other persons after multivariate adjustment, with the impact of smoking on fibrinogen in men (0.29 g/liter higher) being approximately double that in women (0.15 g/liter higher), even after adjustment for numbers of cigarettes smoked per day (27). Smoke-induced inflammation of the lungs and other organs, mediated by proinflammatory cytokines, results in a generalized, dose-dependent increase in circulating inflammatory markers (28–30), a process which is slowly reversible after years of smoking cessation (28–30). It is likely, therefore, that active tobacco smoking is a causal mechanism for increased fibrinogen levels in the general population. The present data do not, however, address the separate issue of passive smoking. Overall fibrinogen levels were approximately 0.08 g/liter lower in alcohol drinkers than in alcohol abstainers after multivariate adjustment, with a curvilinear association being observed with increasing consumption. Overall fibrinogen levels were approximately 0.16 g/liter higher in less physically active people than in active participants. It has been suggested that the association of fibrinogen with alcohol consumption and physical activity might also be mediated by inflammatory cascades (31, 32).

**Obesity, blood lipids, diabetes, and hypertension**

Fibrinogen levels were positively correlated with BMI, other components of the “metabolic syndrome” (such as blood pressure, triglycerides, and low HDL cholesterol), and a history of diabetes or hypertension. The association of BMI with fibrinogen levels in women was approximately twice as strong as that in men. It is proposed that proinflammatory cytokines (such as interleukin-6, tumor necrosis factor α, and leptin) mediate these associations through low-grade inflammatory responses to central adiposity (33, 34)—processes which may be reversed by increasing physical activity (32).

**Ethnicity, socioeconomic status, and season**

Adjusted mean fibrinogen levels were approximately 0.12 g/liter higher in Blacks than in Whites (35). Fibrinogen levels tended to be higher in persons without employment and persons with lower levels of education. Contrary to previous suggestions (13, 36), the winter season was only weakly correlated with fibrinogen levels in the present analysis, perhaps partly because the timing of the onset of winter varied among different cohorts (despite all studies’ being from the Northern Hemisphere). The large variation among cohorts in the present analysis in associations of fibrinogen with the winter season is consistent with such a source of heterogeneity.

**Strengths and limitations**

The present report provides precise, reliable, and comprehensive assessments of several cross-sectional correlates of fibrinogen levels through meta-analysis of individual data on 154,211 adults from 31 largely population-based prospective cohorts. To our knowledge, the FSC includes data from all long-term prospective studies that have reported on fibrinogen levels and cardiovascular disease outcomes in essentially healthy populations (i.e., studies that did not select participants on the basis of preexisting diseases), and it encompasses and builds on relevant previously published studies on the correlates of fibrinogen (12–15, 35, 37–41). In contrast with some previous investigations, the present meta-analysis should have minimized any impact of preexisting cardiovascular diseases, because it involved only participants without known cardiovascular disease. Subsidiary findings in participants who remained free of cardiovascular disease for at least 5 years after the baseline examination were very similar to the overall results (data available upon request), further reducing the scope of any possible “reverse association” biases. Findings were also very similar in subsidiary analyses including the 1,616 (1 percent) participants with fibrinogen values greater than 5.62 g/liter (data available upon request). However, because the present analyses were restricted to characteristics for which there were available data on at least 5,000 participants, we could not investigate proximal inflammatory mediators, hemostatic factors, markers of glycemic status, dietary factors, or psychological characteristics in this study (42). Moreover, information on genetic factors, which have been suggested to explain at least 15 percent of the variation in fibrinogen levels (42–44), was not recorded in the FSC. Measurement error in both fibrinogen levels and correlates could contribute to part of the unexplained variation in the present analysis, but the impact of correction for measurement error could not be appropriately assessed because...
repeat measurements were available for only a narrow range of covariates.

Conclusions

Fibrinogen levels are correlated with several established cardiovascular disease risk factors, but modifiable lifestyle characteristics (such as smoking, alcohol consumption, physical activity, and obesity) together explain only a few percent of the total variation in fibrinogen levels. Even in aggregate, all of the variables considered in this review explained only about one half of the total variation in fibrinogen levels. This suggests that 1) the potential for altering fibrinogen levels through known lifestyle modifications is probably modest and 2) the scope of confounding in observational studies of fibrinogen levels and chronic disease outcomes appears to be considerable, as suggested by the many known correlates of fibrinogen (only some of which are typically measured and adjusted for) and the likely existence of as-yet-unrecognized determinants. These considerations underscore the need for approaches in the etiologic assessment of fibrinogen levels that can minimize residual biases, including the use of appropriately adjusted models in studies assessing fibrinogen as a risk factor.

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Conflict of interest: none declared.

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