Does Elevated Plasma Fibrinogen Increase the Risk of Coronary Heart Disease?
Evidence from a Meta-Analysis of Genetic Association Studies

George Davey Smith, Roger Harbord, Julie Milton, Shah Ebrahim, Jonathan A.C. Sterne

Objective—The purpose of this study was to assess whether a genetic variant associated with higher fibrinogen levels is associated with increased coronary heart disease (CHD) risk, as a test of the causal influence of fibrinogen on CHD.

Methods and Results—We performed a meta-analysis of case-control and prospective studies of the G-455→A and C-148→T β-fibrinogen promoter region variants, in relation to CHD risk. The 19 studies found included 12,393 cases and 21,649 controls. Fibrinogen levels were robustly related to the genetic variants (mean increase per allele, 0.117 g/L; 95% CI, 0.091–0.142 g/L). However, the genetic variants were unrelated to CHD risk (odds ratio per allele, 0.976; 95% CI, 0.916–1.040). The predicted causal odds ratio for a 1 g/L higher plasma fibrinogen level, given the genetic variant–fibrinogen and genetic variant–CHD associations, was 0.81 (95% CI, 0.46–1.40).

Conclusions—Although imprecise, the predicted causal effect of fibrinogen on CHD is clearly different from the odds ratio of 1.8 (95% CI, 1.6–2.0) for an increase of 1 g/L derived from a meta-analysis of observational studies. This evidence suggests that lowering the fibrinogen level may not, in itself, reduce CHD risk. (Arterioscler Thromb Vasc Biol. 2005;25:2228-2233.)

Key Words: Mendelian randomization ■ fibrinogen ■ coronary heart disease

The status of plasma fibrinogen as a cardiovascular risk factor remains controversial.1–7 In prospective observational studies and case-control studies, fibrinogen level is predictive of coronary heart disease (CHD) risk, a meta-analysis reporting a relative risk of 1.8 (95% CI, 1.6–2.0) for the top to the bottom third of the fibrinogen distribution.8 However, existing atherosclerosis may increase fibrinogen levels, and, thus, reverse causation will lead fibrinogen to predict future CHD events. There is also substantial confounding, with higher fibrinogen levels being seen in several population subgroups known to have increased CHD risk, for example, cigarette smokers, people from less favorable socioeconomic backgrounds, nondrinkers, and people who engage in less leisure time activity.9 Certain members of the fibrate class of drugs, including clofibrate and bezafibrate, lower fibrinogen levels, and, if fibrinogen were causally related to CHD, should reduce CHD risk to a greater extent than predicted by their cholesterol lowering effect. This has not been seen in randomized, controlled trials.10,11 Thus, it is unclear whether fibrinogen is a causal factor for CHD or merely serves as a marker of both preexisting disease status and other causal factors.

Several authors have explicitly suggested that genetic polymorphisms related to differences in fibrinogen levels could be used to examine whether fibrinogen is a causal factor with respect to CHD.5,6,12 The association between CHD risk and a polymorphism related to increased circulating fibrinogen levels is not susceptible to reverse causation or confounding, because atherosclerosis will not change genetic make-up, nor is it likely that behavioral and socioeconomic confounding factors will be related to the distribution of the polymorphism in question. These properties, that have been referred to as those of “Mendelian randomisation,”13 mean that the association between a genetic polymorphism and a disease outcome provides robust evidence of the causal nature of the factor influenced by the polymorphism, such as circulating fibrinogen level in the present case. The sustained differences in fibrinogen level related to the polymorphism should translate into differences in CHD risk if there is a causal association between fibrinogen and CHD. In studies that relate the polymorphism to fibrinogen level and to CHD risk, if fibrinogen is a causal factor, the polymorphism should be related to CHD risk to the degree predicted by the joint associations of the polymorphism with fibrinogen level and of fibrinogen level with CHD risk.12,13 The most common polymorphism that has been studied in this regard is the G-455→A polymorphism in the promoter region of the β-fibrinogen gene. This polymorphism is consistently associated with differences in fibrinogen levels and, therefore, should be associated with CHD risk if fibrinogen is a causal

Original received April 28, 2005; final version accepted July 13, 2005.
From the Department of Social Medicine, Bristol, UK.
Correspondence to George Davey Smith, Department of Social Medicine, Canynge Hall, Whiteladies Rd, Bristol BS8 2PR, United Kingdom. E-mail zetkin@bristol.ac.uk
© 2005 American Heart Association, Inc.
Arterioscler Thromb Vasc Biol. is available at http://www.atvbaha.org
DOI: 10.1161/01.ATV.0000183937.65887.9e

2228
factor. A second variant, C-148→T, is essentially in complete linkage disequilibrium with the G-455→A variant in European-origin and Indian subcontinent origin populations. We have, therefore, analyzed these 2 variants together.

Individual studies of the G-455→A polymorphism that have explicitly related this polymorphism to both fibrinogen levels and CHD risk as a test of the causal nature of the fibrinogen–CHD association have been grossly underpowered. For example, in a report of a case-control study provocatively titled “Elevated plasma fibrinogen. Cause or consequence of cardiovascular disease?”, a 1 g/L increase in fibrinogen level was associated with a relative risk of myocardial infarction (MI) of 1.45 (95% CI, 1.12–1.88), whereas the association between genotype and MI risk was essentially null. The authors interpreted these results as indicating that fibrinogen was not a cause of MI. However, the predicted risk according to genotype, given the observed associations of fibrinogen with MI and of genotype with fibrinogen, could not be reliably distinguished from the observed relative risk.

Given the inadequate sample sizes of individual studies, we have performed a meta-analysis of the associations of this polymorphism with CHD risk, examining the polymorphism–CHD and polymorphism–fibrinogen associations and testing these against the expectation based on a causal link between fibrinogen and CHD.

Methods

Search Strategy for Identification of Studies

MEDLINE and EMBASE were searched for articles that might describe association studies of β-fibrinogen and cardiovascular diseases. The following keywords were used in the search: “genotype fibrinogen locus,” “beta gene,” “genotype,” “β-fibrinogen,” “β-fibrinogen gene,” “polymorphism (genetics),” “β-chain gene,” “polymorphisms,” “g-455-a,” “fibrinogen,” “fibrinogen,” “blood coagulation factors,” “cardiovascular diseases,” “heart diseases,” “coronary diseases,” “myocardial infarction,” “ischemia,” “atherosclerosis,” “-455G>A,” “-455T>A,” “cardiovascular risk,” and “risk factors”. The search was rerun with C-148-T in place of G-455-A.

Studies were defined as eligible if they were case-control or prospective cohort studies relating fibrinogen polymorphisms (ascertained via genotyping) to CHD, including CHD, angina, MI, coronary atheroma, atherosclerosis, coronary artery disease, ischemic heart disease, and coronary stenosis. Family studies or studies of disease progression were excluded. The title and abstract of each article were scanned, and full article copies of potentially eligible studies or reviews that might contain references to such studies were retrieved. The reference lists of these articles were scanned for additional potentially eligible studies. Where necessary, articles were translated into English.

For each eligible study, we extracted (where available) details of the association between the genotype and end point of interest, genotype and intermediate phenotype (plasma fibrinogen), and intermediate phenotype and end point (CHD). We also recorded study design, case definition, whether cases were incident or prevalent, exclusion criteria, whether the study was restricted to patients with a particular disease and how controls were selected, variables used to adjust estimated associations, whether those doing the genotyping were blind to participants’ disease status, geographic location of the study, details of the gender, age, body mass index, smoking patterns, alcohol consumption of cases and controls, and whether subgroup analyses had been performed.

Because we have combined studies of 2 variants essentially in complete linkage disequilibrium, we used the terminology H1 (haplotype 1) to refer to the G allele of the G-455→A variant or the C allele for the C-148→T variant. H2 refers to the A and T alleles.

Where the numbers of cases and controls in the 3 categories of genotype (H1H1, H1H2, and H2H2) were reported, these were recorded and used for analyses. Studies that did not report all of the categories (because they combined H1H2 with H2H2) contributed only to the meta-analyses for their reported comparison. For all of the studies providing usable data, we derived the mean and SD of fibrinogen levels in cases and controls. All of the units were standardized to grams per liter. Where studies reported geometric means with associated CIs, means and SDs were derived on the assumption that plasma fibrinogen has a log-normal distribution.

A test for Hardy-Weinberg equilibrium was performed on the control group genotype data when this was provided in full, using an exact test. We meta-analyzed the mean difference in fibrinogen between H1H1 and H1H2 controls and also between H1H1 and H2H2 controls. We also analyzed the mean fibrinogen difference per H2 allele assuming a codominant mode of transmission by first fitting a per-allele model to the data from each study using variance-weighted least squares, in which the genotype was coded as 0 (H1H1), 1 (H1H2), or 2 (H2H2), and meta-analyzing the resulting slopes.

We conducted a meta-analysis of the genotype–CHD association corresponding with a codominant mode of transmission. This was derived from the log odds ratio and corresponding SE from a logistic regression analysis of the results from each study with the genotype coded as above. Both fixed-effect meta-analysis (inverse-variance method) and random-effects meta-analysis (Der Simonian and Laird method) were used. As well as deriving tests for heterogeneity, we quantified the amount of heterogeneity in each meta-analysis using I² statistics. Funnel plots of effect size against its SE were examined visually for signs of asymmetry, and formal tests of small-study effects were performed using rank correlation and regression tests.

Results

Characteristics of Included Studies

Table 1 shows the study design, genotype information, and availability of plasma fibrinogen measurements for the 19 included studies.5–7,12,21–35 None of the genotype frequencies showed notable departure from Hardy-Weinberg equilibrium after allowing for the multiplicity of tests.

Association of β-Fibrinogen Genotypes With Plasma Fibrinogen

We examined the difference in mean plasma fibrinogen between genotypes in control participants. Thirteen of the 19 studies measured plasma fibrinogen. However, 4 of these did not present the results by genotype in controls in extractable form (we attempted to contact the authors but with limited success). Of the remaining 9 studies, 2 small studies presented plasma fibrinogen in H1H2 and H2H2 subjects combined, but these 2 studies contributed only 4% of the remaining 10,656 control subjects. Figure 1 shows the results for the 7 studies that presented extractable plasma fibrinogen data for each genotype. The results are homogeneous with the exception of 1 study,22 with only 1 H2H2 control subject, that gave results incompatible with the others, and in which all of the plasma fibrinogen results appeared anomalously high. If we exclude this anomalous study, compared with control subjects with H1H1 genotypes, mean fibrinogen levels are higher by 0.12 g/L (95% CI, 0.08–0.15 g/L) in H1H2 controls and by 0.24 g/L (95% CI, 0.16–0.31 g/L) in H2H2 controls. This gives evidence that the
\(\text{H9252}\) fibrinogen gene is codominant, with the difference in mean plasma fibrinogen between those with H2H2 and H1H1 genotypes being twice that between H1H2 and H1H1 genotypes. By fitting such a per-allele model within each of the 6 homogeneous studies and meta-analyzing the results (\(I^2\) of 0\%), fixed-effect and random-effects models equivalent), we obtained a final estimate that each H2 allele gives a mean increase in plasma fibrinogen of 0.117 g/L (95% CI, 0.091–0.142 g/L). There was no indication of funnel plot asymmetry from visual inspection or formal tests (\(P=0.71\) by rank correlation test and \(P=0.74\) by regression test).

**Association of H\(9252\)-Fibrinogen Genotype With CHD**

In light of the above evidence that H\(9252\)-fibrinogen has a codominant effect on plasma fibrinogen levels, it was assumed that a “per-allele” model also applies to the association of H\(9252\)-fibrinogen genotype with cardiovascular disease, that is, that the odds ratios for comparison of H1H2 to H1H1 and H2H2 to H1H1 genotypes should be essentially the same. The study characteristics, genotype information, and availability of plasma fibrinogen measurements are shown in Table 1.

### Table 1. Study Characteristics, Genotype Information, and Availability of Plasma Fibrinogen Measurements

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Design</th>
<th>Cases</th>
<th>Controls</th>
<th>Polymorphism</th>
<th>Genotype Cases</th>
<th>Controls</th>
<th>Prevalence of H1H1 Genotype</th>
<th>H-W Equilibrium Test P</th>
<th>Extractable by Genotype in Controls?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Green 1993?</td>
<td>Case-control</td>
<td>123</td>
<td>86</td>
<td>G455A</td>
<td>69 47 7</td>
<td>49 31 6</td>
<td>H1H1: 57% H1H2: 63% H2H2: 63%</td>
<td>0.773</td>
<td>Yes†</td>
</tr>
<tr>
<td>Behague 1996?</td>
<td>Case-control</td>
<td>565</td>
<td>668</td>
<td>G455A</td>
<td>368 174 23</td>
<td>419 212 37</td>
<td>H1H1: 63% H1H2: 63% H2H2: 63%</td>
<td>0.136</td>
<td>Yes</td>
</tr>
<tr>
<td>Yu 1996?</td>
<td>Case-control</td>
<td>192</td>
<td>331</td>
<td>G455A</td>
<td>137 48 7</td>
<td>180 139 12</td>
<td>H1H1: 54% H1H2: 60% H2H2: 60%</td>
<td>0.018</td>
<td>No</td>
</tr>
<tr>
<td>Gardemann 1997?</td>
<td>Retrospective cohort</td>
<td>450</td>
<td>473</td>
<td>G455A</td>
<td>275 155 20</td>
<td>282 157 34</td>
<td>H1H1: 60% H1H2: 60% H2H2: 60%</td>
<td>0.075</td>
<td>Yes</td>
</tr>
<tr>
<td>Tybjærg-Hansen 1997?</td>
<td>Cohort</td>
<td>489</td>
<td>6852</td>
<td>G455A</td>
<td>305 168 16</td>
<td>4344 2236 272</td>
<td>H1H1: 63% H1H2: 63% H2H2: 63%</td>
<td>0.478</td>
<td>No</td>
</tr>
<tr>
<td>Van der Born 1998?</td>
<td>Case-control</td>
<td>139</td>
<td>287</td>
<td>G455A</td>
<td>86 ——— S3 ———</td>
<td>183 ——— T04 ———</td>
<td>H1H1: 64% H1H2: 64% H2H2: 64%</td>
<td>——</td>
<td>Yes†</td>
</tr>
<tr>
<td>Lee 1999?</td>
<td>Cohort</td>
<td>195</td>
<td>423</td>
<td>G455A</td>
<td>123 47 8</td>
<td>276 102 15</td>
<td>H1H1: 65% H1H2: 65% H2H2: 65%</td>
<td>0.151</td>
<td>Yes</td>
</tr>
<tr>
<td>Ma 1999?</td>
<td>Case-control</td>
<td>66</td>
<td>53</td>
<td>G455A</td>
<td>36 26 4</td>
<td>41 11 1</td>
<td>H1H1: 77% H1H2: 77% H2H2: 77%</td>
<td>0.567</td>
<td>Yes‡</td>
</tr>
<tr>
<td>Doggen 2000?</td>
<td>Case-control</td>
<td>560</td>
<td>646</td>
<td>G455A</td>
<td>343 199 18</td>
<td>404 211 31</td>
<td>H1H1: 63% H1H2: 63% H2H2: 63%</td>
<td>0.637</td>
<td>Yes</td>
</tr>
<tr>
<td>Youngman 2000?</td>
<td>Case-control</td>
<td>4685</td>
<td>6002</td>
<td>C148T</td>
<td>——Information not available——</td>
<td>——</td>
<td>——</td>
<td>——</td>
<td>Yes†</td>
</tr>
<tr>
<td>Blake 2001?</td>
<td>Nested case-control</td>
<td>386</td>
<td>751</td>
<td>C148T</td>
<td>235 127 24</td>
<td>468 243 40</td>
<td>H1H1: 62% H1H2: 62% H2H2: 62%</td>
<td>0.279</td>
<td>No</td>
</tr>
<tr>
<td>Folson 2001?</td>
<td>Nested case-control</td>
<td>398</td>
<td>481</td>
<td>G455A</td>
<td>275 111 12</td>
<td>323 134 24</td>
<td>H1H1: 67% H1H2: 67% H2H2: 67%</td>
<td>0.052</td>
<td>Yes‡</td>
</tr>
<tr>
<td>Lee 2001?</td>
<td>Case-control</td>
<td>305</td>
<td>215</td>
<td>G455A</td>
<td>204 90 11</td>
<td>148 63 4</td>
<td>H1H1: 69% H1H2: 69% H2H2: 69%</td>
<td>0.463</td>
<td>Yes</td>
</tr>
<tr>
<td>Leander 2002?</td>
<td>Case-control</td>
<td>1180</td>
<td>1528</td>
<td>G455A</td>
<td>744 377 48</td>
<td>940 509 68</td>
<td>H1H1: 62% H1H2: 62% H2H2: 62%</td>
<td>1.000</td>
<td>Yes</td>
</tr>
<tr>
<td>Yamada 2002?</td>
<td>Case-control</td>
<td>445</td>
<td>464</td>
<td>G455A</td>
<td>346 96 3</td>
<td>353 104 7</td>
<td>H1H1: 76% H1H2: 76% H2H2: 76%</td>
<td>1.000</td>
<td>No</td>
</tr>
<tr>
<td>ATVBSIG 2003?</td>
<td>Case-control</td>
<td>1210</td>
<td>1210</td>
<td>G455A</td>
<td>732 425 53</td>
<td>744 398 68</td>
<td>H1H1: 61% H1H2: 61% H2H2: 61%</td>
<td>0.132</td>
<td>No</td>
</tr>
<tr>
<td>Völzke 2003?</td>
<td>Cohort</td>
<td>26</td>
<td>184</td>
<td>G455A</td>
<td>11 12 3</td>
<td>99 77 8</td>
<td>H1H1: 54% H1H2: 54% H2H2: 54%</td>
<td>0.175</td>
<td>Yes</td>
</tr>
<tr>
<td>Magzhal 2003?</td>
<td>Case-control</td>
<td>432</td>
<td>490</td>
<td>G455A</td>
<td>258 156 18</td>
<td>311 156 23</td>
<td>H1H1: 60% H1H2: 60% H2H2: 60%</td>
<td>0.560</td>
<td>No</td>
</tr>
<tr>
<td>Tobin 2004?</td>
<td>Case-control</td>
<td>547</td>
<td>505</td>
<td>G455A</td>
<td>381 150 15</td>
<td>339 148 18</td>
<td>H1H1: 67% H1H2: 67% H2H2: 67%</td>
<td>0.657</td>
<td>No</td>
</tr>
</tbody>
</table>

The total no. of cases and controls with genotype data in some studies are slightly lower than the total no. of cases and controls because of genotyping failure.

*Only combined H1H2+H2H2 numbers given.
†Plasma fibrinogen results presented with H1H2+H2H2 combined.
‡Only 1 H2H2 control so SD of plasma fibrinogen cannot be computed for this genotype.
H2H2 to H1H2 individuals are the same. Of the 19 studies, 16 combined H1H1 and H1H2 subjects in their results and, thus, cannot be included in this analysis. Results for the other 18 studies are presented in Figure 2. Nearly all of the studies are consistent with the null hypothesis that the polymorphism has no effect on CHD risk, with the possible exception of 2 studies,22,30 1 of which22 also gave anomalous results for the association with plasma fibrinogen. The other30 gives an association in the opposite direction from that which might be expected. As a sensitivity analysis, Table 2 shows the results of random-effects meta-analyses excluding 1 or both of these studies. There was no impression of asymmetry in the funnel plot, nor formal evidence of small study effects (P = 0.41 by rank correlation test and P = 0.93 by regression test, with all of the studies included). The 2 studies of the C-148→T variant produced a per-allele OR of 1.03 (95% CI, 0.97–1.10), whereas the 16 studies of the G-455→A variant produced an equivalent OR of 0.96 (95% CI, 0.89–1.04). There is no strong statistical evidence to suggest these are different (P = 0.27, permutation test).

**Predicted Association of Plasma Fibrinogen With CHD From Mendelian Randomization**

Table 2 shows the predicted OR for a 1 g/L increase in plasma fibrinogen, calculated assuming a linear-logistic relationship between plasma fibrinogen level and odds of CHD and that each H2 allele gives an increase in plasma fibrinogen of 0.117 g/L by raising the odds ratio per H2 allele to the power of 0.117. Allowing for the uncertainty in the association between genotype and plasma fibrinogen makes little difference to the width of the CIs (maximum increase in width of CIs for log odds ratios is 3.2%, in model 3), because the uncertainty in this estimate is small compared with the uncertainty in the association between genotype and CHD. The predicted odds ratio for a 1 g/L increase in plasma fibrinogen is 0.81 (95% CI, 0.46–1.40) for model 1, which includes all of the studies.

**Discussion**

In this meta-analysis, we demonstrate that a common variant in the promoter region of the β-fibrinogen gene is associated
with a robust difference in circulating fibrinogen levels. If fibrinogen were a causal factor for CHD, the expectation would be that carriers of such a variant would be at increased risk of CHD. However, there is no strong evidence of any association between carriage of the variant and CHD risk, and when the joint associations of variant with fibrinogen and variant with CHD risk were combined to yield a predicted estimate of the causal influence of fibrinogen on CHD, the odds ratio was less than unity, although with relatively wide CIs. A meta-analysis of prospective observational studies of the association between fibrinogen and CHD found that an increase of 1.0 g/L in long-term usual mean fibrinogen was associated with a risk ratio of 1.8 (95% CI, 1.6–2.0). Comparing this with our predicted estimate from all studies of 0.81 (95% CI, 0.46–1.40) shows strong evidence that the estimates differ (P=0.005, 2-sample z-test).

It has been suggested that methods for reducing fibrinogen levels should be sought, because they may have the potential to reduce CHD risk. However, these data cast doubt on this proposition. This is in line with findings from randomized, controlled trials of those fibrates that reduce fibrinogen level but do not have a greater effect on CHD than that predicted by their cholesterol-lowering action. Furthermore, although CHD risk factors, such as cholesterol level, blood pressure, and smoking, are associated with CHD risk both within populations and between populations, the same is not consistently true for fibrinogen. Although 1 study within Europe suggests a positive ecological association between nephelometric fibrinogen levels and CHD rates, another study found higher fibrinogen levels in a low-CHD risk African country than in countries with much higher rates of CHD. Finally, 1 study finding a positive association between fibrinogen and CHD risk demonstrated that adjustment for a wide range of confounding factors essentially abolished this association.

One study carried out in China reported an order of magnitude greater effect of genotype on fibrinogen and a nominally significant association between genotype and CHD risk. Linkage disequilibrium between the G-455→A and C-148→T variants may be lower in this population. However, it is the C-148→T variant that has been shown to be more directly associated with fibrinogen than the G-455→A variant, and, thus, in a population where there is less linkage disequilibrium between the variants, the G-455→A variant would be expected to be less strongly related to outcomes, rather than more strongly related. The small sample size of the Chinese study, or particular methodological issues, may have generated this markedly outlying finding. A study carried out in South Korea generated findings similar to those of the overall meta-analysis. More data from non-European origin populations would be of value, however.

Limitations of the “Mendelian randomization” approach illustrated in this article need to be considered. Confounding of the genotype–CHD association could occur if the genotype were in linkage disequilibrium with other genetic variants that influenced CHD risk through processes other than fibrinogen level. If this were the case, then the genotype would be expected to be related to other CHD risk factors, but the studies that examined this found it not to be the case. A second possibility is that the variant associated with fibrinogen has pleiotropic effects on other metabolic or physiological systems that influence CHD risk. Again, this would be expected to reveal itself through an association between the variant and other CHD risk factors. Such pleiotropic effects may, however, occur through mechanisms that have not been investigated in these studies.

Publication bias could influence evidence on genetic variant–disease associations, but this would be expected to lead to overestimates, rather than underestimates, of any effects. We found no evidence of an association between study size and the strength of either genotype–CHD or genotype–fibrinogen associations, although such tests have limited power when the number of studies is modest.

Canalization, in which there is compensation to altered gene expression during development, could occur such that elevated fibrinogen levels expressed throughout the developmental period may not have the same biological effects on the cardiovascular system as fibrinogen levels that become elevated during later stages of life. This proposition is difficult to test outside animal models, and we know of no evidence to either support or refute it.

Perhaps the most serious drawback to the Mendelian randomization approach applied in this article is the need for very large sample sizes. Even in this meta-analysis, which included 12,393 cases and 21,649 controls, CIs around the estimated association between plasma fibrinogen and CHD risk, given the joint associations of genetic variant and fibrinogen and genetic variant and CHD risk, were wide. We have estimated previously that 30,000 cases and 30,000 controls would be required to produce an appropriately precise estimate. Given this, the central effect estimate is the best available, and it suggests that there may be no causal association between fibrinogen and CHD risk.

References

2. Kamath S, Lip GYH. Fibrinogen: biochemistry, epidemiology and deter-
fibrinogen to predict stroke and myocardial infarction. Arterioscler
4. Hackam DG, Anand SS. Emerging risk factors for atherosclerotic
5. Tybjærg-Hansen A, Agerholm-Larsen B, Humphries SE, Abildgaard S,
Schnohr P, Nordestgaard BG. A common mutation (G455→A) in the
α-fibrinogen promoter is an independent predictor of plasma fibrinogen,
6. Van der Bom JG, De Maat MPM, Bots ML, Haverkate F, De Jong
Cause or consequence of cardiovascular disease? Arterioscler Thromb
7. Doggen CJM, Bertina RM, Manger Cats V, Roosendaal FR. Fibrinogen
polyphenotypes are not associated with the risk of myocardial infarc-
carbonic anhydrase protein or leucocyte count with coronary heart
J. Childhood social circumstances and psychosocial and behavioural
factors as determinants of plasma fibrinogen. Lancet. 1996;347:
1008–1013.
10. The Coronary Drug Project Research Group. Clofibrate and niacin in
11. Meade T, Zuhrie R, Cook C, Cooper J. Bezafibrate in men with lower
fibrinogen to predict stroke and myocardial infarction. QJM
13. Meade T, Zuhrie R, Cook C, Cooper J. Bezafibrate in men with lower
fibrinogen to predict stroke and myocardial infarction. QJM
19. Meade T, Zuhrie R, Cook C, Cooper J. Bezafibrate in men with lower
fibrinogen to predict stroke and myocardial infarction. QJM
23. Lee AJ, Fowkes FGR, Lowe GDO, Connor JM, Rumley A. Fibrinogen,
polymorphism of the fibrinogen Bβ-gene relates to plasma fibrinogen
in male cases, but does not interact with environmental factors in
causing myocardial infarction in either men or women. J Int Med.
25. Folsom AR, Aleksic N, Ahn C, Boerwinkle E, Wu KK. β-fibrinogen gene
−455G/A polymorphism and coronary heart disease incidence: The
27. Blake GJ, Schmitz C, Lindpaintner K, Ridker PM. Mutation in the
promoter region of the β-fibrinogen gene and the risk of future
myocardial infarction, stroke and venous thrombosis. Eur Heart J.
H, Heehrle NW, Waas W, Eberbach A. Positive association of the beta
fibrinogen H1/H2 gene variation to basal fibrinogen levels and to
the increase in fibrinogen concentration during acute phase reaction but
not to coronary artery disease and myocardial infarction. Thromb Haemost.
29. Yu Q, Safavi F, Roberts R, Marijan AJ. A variant of β fibrinogen is a genetic
risk factor for coronary artery disease and myocardial infarction. 
30. Tobin MD, Braun RS, Burton PR, Thompson JR, Steeds R, Channer K,
31. Meade T, Zuhrie R, Cook C, Cooper J. Bezafibrate in men with lower
fibrinogen to predict stroke and myocardial infarction. QJM
32. Volzke H, Robinson DM, Kleine V, Hertwig S, Schwahn C, Grimm R,
33. Atherosclerosis, Thrombosis and Vascular Biology Italian Study Group. 
No evidence of association between prothrombotic gene polymorphisms
and the development of acute myocardial infarction at a young age.
34. Lee WH, Hwang TH, Oh GT, Kwon SU, Choi YH, Park JE. Genetic
factors associated with endothelial dysfunction affect the early onset of
35. Maghazli GI, Brennan SO, George PM. Fibrinogen α beta polymorphisms
do not directly contribute to an altered in vitro clot structure in humans.
36. Higgins JPT, Thompson SG. Controlling the risk of spurious findings
diseases: Part I. general considerations, the epidemiologic transition,
diseases: Part II: variations in cardiovascular disease by specific ethnic
groups nad geographic regions and prevention strategies. Circulation.
2001;104:2855–2864.
39. Beaglehole R, Magnus P. The search for new risk factors for coronary
40. Yarnell J, McCrum E, Rumley A, Patterson C, Salomaa V, Lowe G,
and interregional comparison of haemostatic variables in the study of
42. Lawlor DA, Davey Smith G, Rumley A, Lowe GDO. Ebrahim S. Asso-
ciations of fibrinogen and C-reactive protein with prevalent and incident
coronary heart disease are attenuated by adjustment for confounding
43. Davey Smith G, Ebrahim S. Mendelian randomization: prospects,
44. Colhoun HM, McKiige PM, Davey Smith G. Problems of reporting
Does Elevated Plasma Fibrinogen Increase the Risk of Coronary Heart Disease?: Evidence from a Meta-Analysis of Genetic Association Studies
George Davey Smith, Roger Harbord, Julie Milton, Shah Ebrahim and Jonathan A.C. Sterne

Arterioscler Thromb Vasc Biol. 2005;25:2228-2233; originally published online August 25, 2005;
doi: 10.1161/01.ATV.0000183937.65887.9c
Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2005 American Heart Association, Inc. All rights reserved.
Print ISSN: 1079-5642. Online ISSN: 1524-4636

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://atvb.ahajournals.org/content/25/10/2228

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Arteriosclerosis, Thrombosis, and Vascular Biology can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Arteriosclerosis, Thrombosis, and Vascular Biology is online at:
http://atvb.ahajournals.org//subscriptions/