Common Methylene Tetrahydrofolate Reductase Gene Mutation Leads to Hyperhomocysteinemia but Not to Vascular Disease
The Result of a Meta-Analysis

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Background—The results of retrospective and prospective case-control studies have clearly established that mild elevations of the plasma homocysteine level are associated with increased risk of coronary, cerebral, and peripheral vascular disease. Recently, a mutation (677C→T) was identified in the methylenetetrahydrofolate reductase (MTHFR) gene that results in reduced folate-dependent enzyme activity and reduced remethylation of homocysteine to methionine. Mutant homozygotes (TT genotype) constitute ≈12% of the white population and frequently have mildly elevated circulating homocysteine. Therefore, it seems likely that they would also be at increased risk of vascular disease. A number of studies have investigated this during the past 3 years, and the present article evaluates the results in a meta-analysis.

Methods and Results—We identified 13 studies in which there were measurements of plasma homocysteine in relation to the 3 genotypes (TT, CT, and CC) and 23 case-control studies comprising 5869 genotyped cardiovascular disease patients (mostly coronary artery disease) and 6644 genotyped control subjects. Those bearing the TT genotype had plasma homocysteine concentrations 2.6 µmol/L (25%) higher than those with the CC genotype. However, there was no difference between patients and control subjects either in the frequency of mutant alleles (T) (34.3% versus 33.8%) or the TT genotype (11.9% versus 11.7%). In the analysis of the 23 studies, the relative risk (OR) of vascular disease associated with the TT genotype was 1.12 (95% CI, 0.92 to 1.37).

Conclusions—We conclude that although the C677T/MTHFR mutation is a major cause of mild hyperhomocysteinemia, the mutation does not increase cardiovascular risk. Our findings suggest that the mild hyperhomocysteinemia found frequently in vascular disease patients is not causally related to the pathogenesis of the vascular disease. (Circulation. 1998;98:2520-2526.)

Key Words: homocysteine • methylenetetrahydrofolate reductase • risk factors • coronary disease

There is increased interest in mild hyperhomocysteinemia as an important common risk factor for cardiovascular disease that can easily be normalized with folic acid therapy. The basis of this interest stems from the knowledge that certain rare inborn errors of metabolism, generally called homocystinurias, lead to severe hyperhomocysteinemia (>150 µmol/L), arteriosclerosis, and life-threatening arterial and venous thromboembolic events in the very young. This has led to many studies of mild homocysteine elevation in the adult general population, and the results of these suggest that even slight elevations of total plasma homocysteine (>15 µmol/L) concentrations are associated with increased risk of myocardial infarction, stroke, peripheral arterial disease, and venous thrombosis. Furthermore, results of cross-sectional and retrospective and prospective case-control studies have found a graded relationship between plasma homocysteine levels and the risk or severity of cardiovascular disease, suggesting that the relationship is causal.

Homocysteine is methylated to methionine by the transfer of the methyl group of methylenetetrahydrofolate, which is formed by reduction of the methylene-tetrahydrofolate in a reaction catalyzed by methylenetetrahydrofolate reductase (MTHFR). Genetic deficiency of MTHFR is one of the rare homocystinurias leading to severe hyperhomocysteinemia and cardiovascular disease in the very young. In 1988, Kang et al described a thermolabile variant of MTHFR that is associated with decreased enzyme activity.
and mildly elevated plasma homocysteine levels. The responsible mutation in the MTHFR gene, a C→T substitution at base pair 677 leading to the exchange of an alanine to a valine, was identified by Frosst et al in 1995. They found that the mutation was present in ~35% of alleles and that mutant homoyzgotes (TT genotype, ~12% of the population) had significantly higher mean plasma homocysteine concentrations than those not carrying the mutant allele (CC genotype). Consequently, this common C677T/MTHFR mutation was considered likely to be a common genetic risk factor for cardiovascular disease, and a number of studies were undertaken to explore this possibility.

In the present study, we present a meta-analysis of the combined results of the first 13 studies that have documented plasma homocysteine concentrations in relation to the 3 genotypes TT, CT, and CC and of the first 23 studies that have explored the risk of cardiovascular disease in the TT versus the CC genotypes.

### Methods

Through Medline, Current Contents, and abstracts books from congresses, we identified 25 reports on the frequency of the C677T/MTHFR mutation in cardiovascular disease patients and control subjects. Eighteen of these studies have been published as full articles, 6 as letters to editors, and 1 as an abstract. Two of these reports were not included in the meta-analysis, 1 because of uncertainty regarding the ethnic origin of patients and control subjects and 1 because of lack of an adequate control group. The numbers of C677T/MTHFR mutant homozygotes (TT genotype), mutant heterozygotes (CT genotype), and normal homozygotes (CC genotype = wild type) in patients and control subjects from each study are shown in Table 1. In 2 studies, the genotype frequency was not reported, and we obtained these data from the authors.

We used the data shown in the tables to estimate the relative risks for cardiovascular disease by calculating the ORs and CI.
ORS and 95% CIs estimating relative risk of cardiovascular disease in C677T/MTHFR homozygotes (TT genotype) versus normal homozygotes (CC genotype) in 23 different studies (Reference No.) of patients with cardiovascular disease and control subjects. Summary OR is adjusted for heterogeneity between studies.

corresponding 95% CIs. In each study, the ORs were calculated for cardiovascular disease in the TT versus CC genotype of use of formulas published elsewhere. The ORs for the 23 studies were tested for homogeneity by the Breslow-Day test. The result was highly significant (P<0.0001), indicating heterogeneity between studies. To allow for heterogeneity between studies, a random-effect model was assessed as follows. Let $\Psi_i$ denote the true log OR for study $i$. Then an unbiased estimate of $\Psi_i$ is $\hat{\Psi}_i = \log \left( \frac{a_i d_i}{b_i c_i} \right)$, where $a_i$, $b_i$, $c_i$, and $d_i$ are the number of TT cases, TT controls, CC cases, and CC controls, respectively, in study $i$. The asymptotic variance of $\hat{\Psi}_i$ is given by $\text{Var}(\hat{\Psi}_i) = 1/\left( a_i + b_i + c_i + d_i \right)$. Assume that the $\Psi_i$'s are normally distributed with mean $\Psi$ and variance $\tau^2$. The between-study variance $\tau^2$ is estimated as $\hat{\tau}^2 = \max(0, (\psi - (k-1))/\left( \sum w_i - \sum w_i^* \right))$, where $k$ is the number of studies, $w_i = 1/\text{Var}(\hat{\Psi}_i)$, and $\psi = \sum w_i \hat{\Psi}/\left( \sum w_i \hat{\Psi} \right)$. The common OR, exp($\psi$), can now be estimated as exp($\psi$), where $\hat{\Psi} = \sum w_i \hat{\Psi} / \sum w_i$ and $w_i^* = 1/\text{Var}(\hat{\Psi}_i + \hat{\tau}^2)$. Because the asymptotic variance of $\hat{\Psi}$ is $\text{Var}(\hat{\Psi}) = 1/\sum w_i^*$, an approximate 95% CI for the common OR is given by $[\exp(\hat{\Psi} - 1.96/\sqrt{\sum w_i^*}), \exp(\hat{\Psi} + 1.96/\sqrt{\sum w_i^*})]$. 

### Results

In the 23 studies included in the meta-analysis, the C677T/MTHFR genotype was available in a total of 5869 patients with cardiovascular disease and in 6644 control subjects (Table 1). The prevalence of the TT genotype varied between 5.4% and 16.0% in the different groups of control subjects and between 6.5% and 29.7% in the different groups of patients. In all studies combined, the distributions of the different genotypes and the allele frequency were almost identical in patients and control subjects (Table 1). The TT genotype was present in 11.9% of the patients and in 11.7% of the control subjects.

The OR as an estimate of relative cardiovascular risk in the TT versus CC genotypes was $>1.0$ in 11 and $<1.0$ in 12 studies (Figure). In 4 studies, both the ORs and the 95% CIs were $>1.0$. In two of these 4, the TT genotype frequencies in control subjects were only 5.4% (6 of 111) and 6.7% (7 of 105). These frequencies are considerably lower than those found in other larger groups from the same populations: 8.5% (106 of 1250, Dutch) and 11.5% (72 of 625, Irish), respectively. There was a considerable heterogeneity of the ORs of the 23 studies. After adjustment for heterogeneity, the combined OR of all 23 studies for relative vascular risk in TT homozygotes versus normal CC homozygotes was 1.12 (95% CI, 0.92 to 1.37) (Figure). The corresponding combined OR for the 17 studies that included only patients with coronary heart disease (CHD in Table 1) was 1.11 (95% CI, 0.91 to 1.37).

The results of 13 studies of total plasma homocysteine concentrations in the different C677T/MTHFR genotypes are shown in Table 2. They establish that the TT genotype has significantly higher mean homocysteine concentration than the CT and CC genotypes. On average, those with the TT genotype have $\approx 2.6 \mu mol/L$ or 25% higher mean total plasma homocysteine concentration than those with the CC genotype. Table 3 shows that the TT genotype is considerably more frequent among those with elevated total plasma homocysteine than in the whole population.

Finally, Table 4 shows that the phenotypic expression of elevated total plasma homocysteine in those with the TT genotype was most pronounced in homozygotes with folate levels below the median or in the lowest quartile of serum folate. In subjects with higher folate levels, total plasma homocysteine concentrations between the different genotypes are not different.

### Discussion

This meta-analysis of the distribution of the common C677T/MTHFR gene mutation genotypes in patients with cardiovascular disease and in control subjects shows that although those bearing the TT genotype have on average 25% higher mean total plasma homocysteine concentration than the normal wild CC genotype, they have no overall increased risk of cardiovascular disease generally or of coronary heart disease in particular. The power of this analysis is such that any important increased risk would have been detected. Moreover, in developed countries, cardiovascular disease is the main cause of death. Yet, in a meta-analysis of 4 studies of the C677T/MTHFR mutation in elderly and newborn or young subjects, the OR representing the likelihood of those with the TT genotype attaining old age relative to those with the CC genotype was 0.87 (95% CI, 0.69 to 1.11). This is not compatible with the mutation being a major risk factor for premature cardiovascular death and is in accord with the findings of the present meta-analysis.

There is strong evidence that mild hyperhomocysteinemia, in the range found in the TT genotype, is a risk factor for atherosclerotic and thrombotic cardiovascular disease. The relationship has been considered to be causal, and homocysteine-lowering therapy with folic acid proposed to reduce the risk. If mild hyperhomocysteinemia itself causes vascular injury and cardiovascular disease, it would be logical...
to consider that any cause of long-standing mild hyperhomocysteinemia (ie, TT genotype) would also increase cardiovascular risk. This led to the studies included in the present meta-analysis. As an explanation for the negative results found in many of these studies, it was argued that because increased plasma homocysteine in TT homozygotes is folate-dependent, caution is warranted in drawing conclusions from reports lacking adequate information on folate and homocysteine levels. Therefore, we assessed published data on homocysteine and the homocysteine-folate relationship in relation to C677T/MTHFR genotypes (Tables 2 through 4).

These combined data clearly establish that the TT genotype is associated with elevated mean plasma homocysteine levels in probably well-nourished groups of American, Canadian, Dutch, Norwegian, Italian, and Irish subjects and that high homocysteine levels are confined primarily to those TT homozygotes with folate levels below the median or in the lowest quartile of serum or plasma folate. Depending on the chosen cutoff point for hyperhomocysteinemia, the combined data also show that 21% to 73% of hyperhomocysteinemic subjects are TT homozygotes. Thus, the TT genotype is a major cause of mild hyperhomocysteinemia in these populations.

The frequently quoted prospective US Physicians Health Study provides an example of the discrepancy between cardiovascular risk attributable to homocysteine and the C677T/MTHFR mutation. It showed a minimal but significant excess (0.6 \mu mol/L) of plasma homocysteine in those who subsequently developed myocardial infarction compared with matched control subjects (11.1 versus 10.5 \mu mol/L). The relative risk for myocardial infarction for the highest 5% of the homocyst(e)ine distribution (>15.8 \mu mol/L) versus the bottom 90% was significant: 3.4 (95% CI, 1.3 to 8.8). In a later report on essentially the same patients and control subjects, the TT genotype was present in 21% of hyperhomocysteinemic subjects (>15.8 \mu mol/L) and in 12% of normohomocysteinemic subjects, and the mean plasma homocysteine was 2.0 \mu mol/L higher in TT homozygotes than in CC homozygotes (12.6 versus 10.6 \mu mol/L). Nonetheless, the TT genotype was found less frequently in patients than in control subjects.

| Study (Reference No.) | TT Genotype (n) | CT Genotype (n) | CC Genotype (n) |
|-----------------------|----------------|----------------|----------------|
| Froist et al 1995 (14) | 22.4±2.9 (12) | 13.8±1.0 (9) | 12.6±1.1 (19) |
| van der Put et al 1995 (15) | 17.1±1.5 (34) | 13.2±3.1 (164) | 13.4±3.4 (194) |
| Jacques et al 1996 (16) | 9.9 (45) | 8.4 (170) | 8.7 (150) |
| Harmon et al 1996 (17) | 9.5 (72) | 7.1 (273) | 6.8 (280) |
| Kluijmans et al 1996 (18) | 16.3±8.3 (15) | 13.4±4.0 (61) | 12.3±3.6 (93) |
| Schmitz et al 1996 (19) | 9.1±2.3 (14) | 10.6±3.8 (46) | 9.9±2.7 (67) |
| Ma et al 1996 (20) | 12.6±0.58 (72) | 10.9±0.37 (240) | 10.6±0.36 (271) |
| Deloughery et al 1996 (21) | 17.2±13 (22) | 13.6±6.9 (111) | 13.0±5.5 (114) |
| Verhoef et al 1997 (22) | 15.5 (30) | 12.3 (150) | 11.4 (138) |
| Kluijmans et al 1997 (23) | 15.4 (51) | 13.4 (233) | 12.6 (231) |
| Christensen et al 1997 (24) | 12.8±4.1 (22) | 11.0±3.9 (98) | 10.3±3.6 (89) |
| Schwartz et al 1997 (25) | 13.5±7.0 (43) | 10.8±3.9 (141) | 10.9±3.8 (154) |
| Legnani et al 1997 (26) | 13.0±6.9 (12) | 7.8±2.3 (31) | 7.4±2.1 (20) |
| Approximate means of all studies | 13.3 (444) | 10.9 (1727) | 10.7 (1820) |
| Elevation compared with CC genotype | 2.6 (24%) | 0.2 (2%) |
control subjects (11.3% versus 13.4%), and it was not associated with risk of myocardial infarction (OR, 0.84; 95% CI, 0.50 to 1.42). In the Health Professionals Follow-up Study,17 the TT genotype was present in 12.2% of men with coronary artery disease (n=280) or myocardial infarction (n=220) and in 14.2% of 500 male control subjects. For the TT genotype, the OR of coronary artery disease was 1.04 (95% CI, 0.67 to 1.62) and, surprisingly, the OR for myocardial infarction was significantly reduced (OR, 0.49; 95% CI, 0.28 to 0.87). Moreover, the TT genotype was not positively associated with risk of coronary heart disease among men with low intake of folate.

As an extension of the results of this meta-analysis, which excludes an association between increased cardiovascular risk and the TT genotype, itself a major cause of mild homocysteinemia, our findings argue against there being a causal relationship between mildly elevated plasma homocysteine and increased cardiovascular risk. What, then, is the explanation for the frequent finding of mild hyperhomocysteinemia in patients who have or will develop cardiovascular disease? The Hordaland Study,49 the largest population-based study (7591 men and 8585 women, 40 to 67 years of age) of the relationship between plasma homocysteine and established risk factors for cardiovascular disease, has provided important data relevant to this question. The study showed that elevated plasma homocysteine was strongly and positively associated with major components of the cardiovascular risk profile, ie, male sex, age, smoking, blood pressure, elevated total cholesterol, and lack of exercise. Such relationships may well account for the frequent finding of elevated plasma homocysteine in patients with cardiovascular disease. Relatively small case-control studies may not have the statistical power to adjust for and fully eliminate the effects of these other risk factors on plasma homocysteine concentration.

Another possible cause of elevated plasma homocysteine in cardiovascular disease is mildly impaired renal function resulting from both hypertension and atherosclerosis. Under physiological conditions, the kidneys are estimated to be responsible for ≥70% of plasma homocysteine clearance, and in renal insufficiency, when clearance is reduced, plasma homocysteine concentration is considerably increased.50,51 Renal function is a major determinant of plasma homocysteine concentration, because there is a strong positive correlation between the levels of plasma homocysteine and serum creatinine in both healthy subjects and patients with cardiovascular disease.1,10,52,53 The likelihood is that patients with both subclinical and clinical atherosclerotic vascular disease on average have renal function that is slightly reduced compared with that of control subjects. This may also contribute to the finding of higher plasma homocysteine concentrations in patients than in normal control subjects in both prospective nested and retrospective case-control studies and of a graded relationship between plasma homocysteine and severity of atherosclerosis.

In conclusion, although the markedly elevated homocysteine levels (>150 μmol/L) found in the inborn errors leading to homocystinuria undoubtedly are associated with vascular disease and reducing these high concentrations reduces cardiovascular risk,54,55 it is very doubtful whether the small homocysteine elevations (>15 μmol/L) found in cardiovascular disease patients have directly contributed to the development of their disease. The common MTHFR mutation is accompanied by the small homocysteine elevations also found in vascular patients, but the present analysis establishes that the mutation is not associated with increased cardiovascular risk. We suggest that the modest homocysteine increase found in patients with cardiovascular disease is an epiphenomenon, a consequence of the effects of the well-established standard risk factors for vascular disease and renal function, and that it is not directly causal.

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Circulation. 1998;98:2520-2526
doi: 10.1161/01.CIR.98.23.2520

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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