Homocysteine may play a causal role in cognitive decline. The authors analyzed the 5,10-methylenetetrahydrofolate reductase (MTHFR) C677T genotype, a correlate of plasma homocysteine levels, among 6,653 participants in the Study of Osteoporotic Fractures, a community-based, prospective cohort study of older women in four US states. During the years 1986–1998, the authors assessed whether the distribution of MTHFR C677T genotypes was independent of potential confounders and whether persons with the TT genotype had lower baseline performance or showed greater longitudinal declines on standard cognitive tests. Although ethnicity was associated with MTHFR genotype distribution within the entire cohort ($p < 0.001$), all measured confounders appeared independent of MTHFR genotype within the largest ethnically homogenous subgroup, persons of Northern and/or Central European ancestry ($n = 5,668$) (Kolmogorov-Smirnov $p = 0.97$). In this subgroup, the TT genotype was associated with lower scores on the Digit Symbol Substitution Test ($p = 0.034$) and the Trails B test ($p = 0.020$) and with a small excess annual decline on a modified version of the Mini-Mental State Examination ($p = 0.035$). Although the strength of the observed associations was modest, these results lend some support to the theory that an elevated homocysteine level contributes to cognitive decline.

Abbreviations: CI, confidence interval; DSST, Digit Symbol Substitution Test; mMMSE, modified Mini-Mental State Examination; MTHFR, 5,10-methylenetetrahydrofolate reductase (NADPH2); random allocation
Genetic association studies have been proposed as an alternative means of testing the effects of a biologic factor such as homocysteine on complex human phenotypes like cognition (7–9). The basic argument is that the independent assortment of genes may create a natural randomization in which individuals are assigned to different exposures of a downstream biologic factor based on the genotype they have inherited at a particular locus. This concept has recently been called “Mendelian randomization,” and it represents an instrumental-variables analysis for which the basic theoretical principles have long been established (10). A key tenet underlying the concept of Mendelian randomization (and one that cannot be proven empirically) is that the instrumental variable, in this case a genotype, is related to the outcome exclusively through its association with the biologic factor of interest and not, for example, through an unidentified biologic pathway or a larger genetic structure within a cohort.

A common missense polymorphism in the 5,10-methylene-tetrahydrofolate reductase (MTHFR) gene, a C→T change at nucleotide 667, causes a valine-to-alanine substitution which produces a thermolabile variant of the enzyme and is associated with higher levels of plasma total homocysteine, particularly in persons with the TT genotype (11). For example, in a recent meta-analysis, persons with the TT genotype had homocysteine levels that were 2.7 μmol/liter higher, on average, than those of persons with the CC genotype, while persons with the CT genotype had homocysteine levels that were 0.3 μmol/liter higher than those of persons with the CC genotype (12). In the largest cohort study carried out to date, the C677T polymorphism explained approximately 6 percent of the overall phenotypic variance in plasma homocysteine levels (13). Although this estimated effect size is small and implies that large samples would be required for adequate research, the C677T polymorphism is one of the most commonly cited examples of a genetic variant relevant to Mendelian randomization, because its effect on a modifiable metabolic pathway is widely accepted (7, 14). Therefore, we used a large, community-based cohort to assess whether MTHFR C677T genotype was associated with decreased cognitive function or prospectively measured cognitive decline and whether the distribution of potentially confounding variables was consistent with the assumptions of Mendelian randomization.

MATERIALS AND METHODS

The Study of Osteoporotic Fractures is a prospective study of risk factors for fracture and physical and cognitive decline among community-dwelling older women in four US states. Details on the study cohort and procedures have been published previously (15). Briefly, between 1986 and 1988, 9,704 primarily White, community-dwelling women were recruited, irrespective of osteoporosis status, from population-based lists in Baltimore, Maryland; Minneapolis, Minnesota; Portland, Oregon; and the Monongahela Valley in Pennsylvania. Subjects were between the ages of 65 and 99 years, were able to walk without the assistance of another person, and were not institutionalized. Interviews, questionnaires, and examinations were completed at study enrollment and at follow-up visits scheduled approximately every 2 years. The study is still ongoing.

Blood samples were collected from 6,975 participants at either the second study visit (1989–1990) or the sixth study visit (1997–1998). Genotyping for the MTHFR C677T polymorphism was performed in all subjects who had given informed consent and who had adequate specimens. Multiplex polymerase chain reaction was used to amplify the region encompassing the MTHFR C677T polymorphism, and detection of allelic variants for the MTHFR C677T single nucleotide polymorphism was performed by hybridization of biotinylated polymerase chain reaction products to immobilized sequence-specific probes using standard protocols (16).

Cognitive function was measured in the Study of Osteoporotic Fractures using three tests: a modified version of the Mini-Mental State Examination (mMMSE) (17), the Digit Symbol Substitution Test (DSST), (18), and the Trails B test (19). The mMMSE is similar to the standard Mini-Mental State Examination but has fewer questions regarding orientation and has a total score of 26 points instead of 30. The Trails B test is a timed test in which the subject connects an alternating sequence of letters and numbers in ascending order. The person’s score on the test, which is based on the time required to complete the sequence, is a measure of executive function, attention, and visual scanning abilities. The DSST is a timed, written test that requires the subject to translate numbers into symbols using a key. DSST performance reflects psychomotor speed, attention, and perceptual organization. The mMMSE was given at study visits 1, 4, 5, and 6; the DSST was given at visits 2 and 4; and the Trails B test was given at visits 2, 4, and 6.

Extensive data on demographic factors, lifestyle, and medical history were collected from all study participants. Subjects were asked to select from the following categories up to two that best described their ethnic origin or nationality: 1) Northern European (Canadian, English, Irish, Scandinavian, Scottish, or Welsh); 2) Central European (French Canadian, Czech, Dutch, French, German, Polish, Serbo-Croatian, or Swiss); 3) Southern European (Greek, Italian, Portuguese, or Spanish); 4) Native American; 5) Jewish; 6) Russian; 7) Black; or 8) other. Based on all combinations of observed participant responses, 35 mutually exclusive ethnic groupings were defined. Information about education, tobacco use, and vascular risk factors was abstracted from the baseline study visit. Diabetes mellitus was defined by a self-report of physician-diagnosed diabetes and/or insulin use. Hypertension was defined as a systolic blood pressure >140 mmHg, a diastolic blood pressure >90 mmHg, or use of a thiazide diuretic. Average daily folate consumption was calculated at visit 6 from the Block food frequency questionnaire (20).

Statistical methods

Differences in baseline characteristics by genotype were assessed using the chi-squared test for categorical variables
or the Kruskal-Wallis test for continuous variables. In order to assess whether the distribution of MTHFR C677T genotypes was consistent with natural randomization, we plotted ordered $p$ values from the tests for baseline differences by genotype against quantiles of the uniform distribution. Departure from a uniform distribution was assessed visually and quantitatively using a one-sample Kolmogorov-Smirnov test. We considered genetic structure due to racial or ethnic variations in gene frequencies to be a major potential reason for a nonrandom distribution of the MTHFR C677T genotype within the cohort (21). Therefore, we excluded subjects for whom information on race and ethnicity was not available. We performed restricted analyses in the largest ethnically homogenous subgroup in an attempt to avoid bias from population stratification.

We evaluated baseline differences in cognitive test performance by MTHFR C677T genotype using multivariable linear regression. Since Trails B scores were right-skewed, we used log-transformed score as the dependent variable. In unadjusted models, we verified analyses that used the log-transformed scores by comparing raw Trails B scores across genotypes with the Wilcoxon rank-sum test. Since mMMSE scores have a limited distribution that is approximately normal until the ceiling is reached at 26 points, we modeled differences using Tobit regression, which assumes that values at the upper limit are censored and could represent either 26 or a higher value if the test did not have a ceiling effect. In the longitudinal analyses, we modeled individual change in cognitive test performance over time using a linear, mixed-effects model wherein individual change over time was modeled as a random slope. In all longitudinal models for which results are reported, we adjusted for baseline cognitive test performance to account for ceiling effects and regression to the mean (22). Results were similar in random-intercept models that did not adjust for baseline performance. Since prior studies have established that the most salient elevation in plasma homocysteine levels occurs in persons with the TT genotype and that there is minimal, if any, difference in plasma homocysteine levels between the CT and CC genotypes (13), the primary hypothesis tested in these analyses was that of a phenotypically recessive model (i.e., comparison of the TT genotype with the CT/CC genotype). We also used linear contrast methods to test for a linear trend in cognitive test scores associated with having zero, one, or two $T$ alleles, as would be expected on the basis of a codominant genetic model (23).

The primary results were the unadjusted association between MTHFR C677T genotype and cognitive function, as would be appropriate if Mendelian randomization were adequate to balance both measured and unmeasured confounders. We also created multivariable models that added covariates for ethnicity, age, education, and vascular risk factors in order to increase power in the regression analyses and to protect against the possibility of chance or other residual confounding of the instrumental variable. Hardy-Weinberg equilibrium was assessed using a chi-squared test. All tests of significance were two-sided. Analyses were performed using the Stata statistical package (version 8; Stata Corporation, College Station, Texas).

### RESULTS

MTHFR C677T genotype was determined in 6,653 members of the Study of Osteoporotic Fractures cohort for whom complete data on race and ethnicity had been recorded. This represents 69 percent of the total cohort ($n = 9,704$) and 95 percent of all subjects for whom genetic material was collected ($n = 6,975$) (figure 1). Among cohort members who completed the sixth follow-up visit (when the last DNA specimens were obtained), there was no difference in subsequent mortality between cohort members with and without genotype information (15.3 percent vs. 14.3 percent; $p = 0.31$).

Although more than 99 percent of the cohort ($n = 6,630$) identified their race/ethnicity as White, we found strong associations between MTHFR C677T genotype and ethnicity, indicating a nonrandom distribution of genotypes. For example, among ethnic groupings ($n = 8$) with more than 50 subjects, the frequency of the TT genotype ranged from 23.5 percent among subjects who identified themselves as Jewish to 8.8 percent among subjects who identified themselves as Russian ($p < 0.001$). Since 85 percent ($n = 5,668$) of the cohort identified their ethnicity as Northern European only ($n = 2,542$), Central European only ($n = 1,525$), or both Northern and Central European ($n = 1,601$), we performed a restricted analysis in this ethnically homogenous group. The results excluded from this restricted analysis were 320 women who identified themselves as Southern European and 665 other subjects who were distributed among 32 other ethnic groups, averaging 35 subjects per group.

Among cohort members who identified their ancestry as Northern and/or Central European ($n = 5,668$), the frequency of the $T$ allele was 32.7 percent and there was no apparent deviation from Hardy-Weinberg equilibrium ($p = 0.61$). The frequency of the $T$ allele was 32.8 percent in women who reported Northern European ancestry only, 32.4 percent in women who reported Central European ancestry.
ancestry only, and 33.0 percent in women who reported both
Central and Northern European ancestry ($p = 0.87$). Baseline
characteristics such as age, ethnicity, hypertension, dia-
betes, and tobacco use appeared equally distributed across
the MTHFR C677T genotypes (table 1). The distribution of
all $p$ values generated by the tests of baseline characteristics
closely approximated the expected distribution assuming
that genotype was randomly distributed within the cohort
(Kolmogorov-Smirnov $p = 0.97$) (figure 2).

Among the Northern and Central European subjects, per-
sons with the $TT$ genotype required 4.6 percent more time to
complete the baseline Trails B test than did subjects with the
$CT$ and $CC$ genotypes (95 percent confidence interval (CI): 0.7, 8.6; $p = 0.020$). The median time to completion was
119.5 seconds versus 115 seconds (Wilcoxon $p = 0.02$). This
result was only minimally changed in a fully adjusted
model that included terms for age, ethnicity, education, and
vascular risk factors (table 2). Similar findings were also
seen for baseline DSST performance (difference in number of
correct symbols = −1.1, 95 percent CI: −2.2, −0.1; $p = 0.034$), but there was no apparent relation between MTHFR
C677T genotype and baseline mMMSE score ($p = 0.98$)
(table 2). The association between the $TT$ genotype and
lower baseline Trails B and DSST performance did not ap-
pear to be attenuated among persons who reported a higher
folate intake at visit 6 (for interaction between $TT$ genotype
and folate consumption (mg/day), $p = 0.16$ in the Trails B
model and $p = 0.95$ in the DSST model).

There were no apparent differences in baseline cognitive
test performance between the $CT$ and $CC$ genotypes in the
Northern and Central European cohort members ($p > 0.5$
for all cognitive tests). When a trend across genotypes was
considered, both Trails B performance ($p$ for trend $= 0.044$) and DSST score ($p$ for trend $= 0.049$) declined with
increasing numbers of $T$ alleles. The decline in performance,
however, did not appear to represent a linear trend (Trails B
departure from linear trend: $p = 0.033$), indicating that the
observed relation between genotype and cognitive perfor-
mance was most consistent with a phenotypically recessive
model as opposed to a co-dominant model.

In the longitudinal analysis, follow-up data were most
extensive for mMMSE performance: 5,641 Northern and

| TABLE 1. Baseline characteristics of cohort members of Northern and Central European ethnicity ($n = 5,668$), by 5,10-methylenetetrahydrofolate reductase C677T genotype, Study of Osteoprotic Fractures, 1986–1998* |
|------------------|------------------|------------------|------------------|------------------|------------------|
| Characteristic   | Genotype         | Genotype         | Genotype         | $p$ value        |
|                  | $CC$             | $CT$             | $TT$             |                  |
|                  | ($n = 2,558$)    | ($n = 2,512$)    | ($n = 598$)      |                  |
| Age (years)      | 71.3 (5.1)       | 71.5 (5.2)       | 71.4 (5.0)       | 0.31             |
| Ethnicity        |                  |                  |                  |                  |
| Northern European only | 44.7            | 45.1            | 44.5            | 0.94             |
| Central European only | 26.9            | 27.4            | 25.1            | 0.53             |
| Central and Northern European | 28.4          | 27.6            | 30.4            | 0.36             |
| Educational level|                  |                  |                  |                  |
| Less than high school completion | 20.4         | 18.1            | 18.2            | 0.10             |
| High school only | 41.2            | 38.8            | 41.0            | 0.21             |
| Some college     | 20.5            | 23.0            | 21.1            | 0.08             |
| College graduation or more | 17.9        | 19.8            | 19.7            | 0.17             |
| Husband's educational level |                  |                  |                  |                  |
| Less than high school completion | 27.6         | 24.4            | 23.4            | 0.01             |
| High school only | 31.1            | 32.3            | 31.6            | 0.67             |
| Some college     | 26.8            | 28.0            | 30.1            | 0.25             |
| College graduation or more | 26.9        | 28.0            | 28.3            | 0.63             |
| Diabetes mellitus† | 6.3             | 6.5             | 6.4             | 0.98             |
| Active smoker    | 9.4             | 8.5             | 9.1             | 0.51             |
| Hypertension‡   | 61.1            | 60.9            | 62.9            | 0.67             |
| Systolic blood pressure (mmHg) | 142.2       | 142.5           | 142.8           | 0.90             |
| Diastolic blood pressure (mmHg) | 77.0         | 76.8            | 77.0            | 0.83             |
| Daily folate consumption (g)§ | 253.2       | 252.7           | 257.1           | 0.53             |

* Values are expressed as either means (with standard deviations) or percentages.
† Diabetes was defined by self-report of physician-diagnosed diabetes and/or insulin use.
‡ Hypertension was defined as systolic blood pressure >140 mmHg, diastolic blood pressure >90 mmHg, or use of a thiazide diuretic.
§ Based on the visit 6 Block food frequency questionnaire ($n = 3,508$).

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Central European subjects completed an average of 3.2 follow-up examinations, corresponding to an average total time from the baseline examination to the last available examination of 9.2 years (range, 4.5–12.1 years). In contrast, subjects completed an average of 2.4 Trails B tests over an average total follow-up period of 7.0 years and 1.8 DSST tests over an average total follow-up period of 3.5 years. The TT genotype was not associated with either death before visit 6 (odds ratio = 1.1, 95 percent CI: 0.9, 1.4; \( p = 0.26 \)) or the average total duration of follow-up for the mMmMSE (\( p = 0.62 \)), the Trails B test (\( p = 0.70 \)), or the DSST (\( p = 0.84 \)). The TT genotype was associated with a small increase in the average annual decline in mMmMSE performance in comparison with the CT or CC genotype (an excess average decline of 0.03 points per year (95 percent CI: 0.00, 0.05); \( p = 0.035 \)). However, similar findings were not apparent when change in Trails B or DSST performance was considered. Adjustment for potential confounders did not meaningfully affect the findings (table 3).

**DISCUSSION**

This study provides evidence that *MTHFR* C677T genotype is associated with cognitive test performance in a large cohort of older women. Furthermore, the distribution of *MTHFR* C677T genotypes with respect to other baseline variables was consistent with the theory of Mendelian randomization, as long as the analysis was restricted to the majority of the cohort with genetically similar ethnicities. Although the relation between genotype and cognitive test performance was statistically significant, the magnitude of the association was small. Since prior studies have found that differences in homocysteine levels by genotype are comparable to what has been achieved in clinical trials of folate supplementation (24), our results argue against a large clinical benefit from routine folate supplementation for the prevention of cognitive decline, but they do lend support to the underlying biologic hypotheses that motivated such trials.

Our ability to use an association between *MTHFR* genotype and cognitive function to draw conclusions about the effect of homocysteine level on cognitive test performance is based on two main assumptions. The first is that *MTHFR* C677T genotype was associated with different exposures to plasma homocysteine over the course of the subjects’ lifetime. We believe that this assumption is reasonable based on multiple prior studies (12, 13), and prospective measurement of homocysteine in cohort members would have provided information about only a small fraction of total-life homocysteine exposure potentially attributable to genotype. Secondly, we must assume that *MTHFR* C677T genotype is associated with cognitive test performance exclusively through its influence on homocysteine levels. The possibility that an alternative, unidentified biologic pathway

![Figure 2](https://academic.oup.com/aje/article-abstract/166/6/672/89013)

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<table>
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<th>Adjusted*</th>
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* Adjusted for ethnicity, age, education, hypertension, diabetes, and smoking. Because of missing values for some covariates, the sample size in the adjusted model was lower.
† Values represent the average difference in cognitive test performance associated with the TT genotype as compared with the CT/CC genotype. For each test, negative values represent worse performance.
‡ CI, confidence interval; mMmMSE, modified Mini-Mental State Examination; DSST, Digit Symbol Substitution Test.
§ Log-transformed time to completion. Values approximate the average percent difference in amount of time needed to complete the Trails B test.
mediates the association between MTHFR and cognitive function is an untestable possibility that always threatens the validity of Mendelian randomization analyses. However, a major strength of this study is that its large size and detailed characterization of ethnicity provided substantial statistical power to assess whether MTHFR C677T genotype was associated with cognition because of an association with demographic factors or vascular risk factors—variables which frequently confound observational analyses of homocysteine and cognitive function. Since MTHFR genotype appears to be inherited independently of multiple traits known to affect cognition, the assumption that other, unmeasured confounders are also balanced across genotypes, a fundamental implication of natural randomization and the independent assortment of genes, is at least plausible within our ethnically homogenous cohort.

In spite of our findings, it is still reasonable to question whether genotype at an individual locus represents a random event. Certainly, partner selection and mating, which are the proximate determinants of genotype, are not random processes. The real question, however, is whether mating decisions are influenced by factors that also affect genotype distributions. Clearly ethnicity would be one such factor, although recent reports have found little evidence for genome-wide structure within the major self-identified racial groups (25). We found strong associations between MTHFR C677T genotype and ethnicity among White cohort members, but this finding may have been due to chance selection, as many ethnic groups were represented by small numbers of persons, and the association was not apparent in the large majority who identified themselves as being of Central and/or Northern European ancestry. Other geographic or cultural differences that could affect both mating decisions and differences in genotype distributions could also undermine the randomization assumption. At least in the United States, however, geographic differences in genotype distributions appear to be minimal (25, 26).

Our findings are weakened somewhat by the lack of consistency across the cognitive tests and differences between the cross-sectional and longitudinal analyses. We believe that the results of the cross-sectional analysis represent a more sensitive and accurate test of the association between MTHFR C677T genotype and cognitive function than the results of the longitudinal analysis. The cross-sectional results captured the impact of lifetime exposure to the MTHFR C677T genotype, whereas the longitudinal results reflected the impact of genotype exposure over several years in late life, when the association between MTHFR genotype and homocysteine level is weakest (13). The shorter duration of homocysteine lowering that has been achieved in randomized, controlled trials (when compared with the potentially lifelong differences in homocysteine levels that may result from MTHFR genotype variation) may also explain the differences in results of these trials as compared with our analysis (5). Finally, informative censoring due to an association between not completing follow-up testing and the progression of cognitive impairment could have introduced additional biases into the longitudinal results (27). The power of the mMMSE to detect differences in score by genotype would be expected to be lowest in the cross-sectional and longitudinal analysis because of its strong ceiling effect. However, duration of follow-up was greatest for mMMSE in the longitudinal analysis, and this may have increased our power to observe an effect on this cognitive test as compared with the others.

With the caveats described above, the results of our study provide some support for elevated homocysteine level as an etiologic factor in the decline in cognitive test performance that is common with advanced age. It is not possible to infer from this study whether this decline is clinically meaningful from the standpoint of incident dementia or mild cognitive impairment, although lower cognitive test scores are generally strong predictors of these clinical entities and represent an important goal for prevention (28–31). Furthermore, while the effects of intervention with vitamins, such as folic acid, are believed to be mediated primarily through changes in homocysteine levels, they may have pleiotropic effects. Therefore, it would be problematic to use our findings to

### TABLE 3. Association of 5,10-methylene tetrahydrofolate reductase TT genotype with longitudinal change in cognitive test performance among cohort members of Northern and Central European ethnicity, Study of Osteoporotic Fractures, 1986–1998

<table>
<thead>
<tr>
<th>Cognitive test</th>
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<td>0.26</td>
</tr>
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</table>

* Model 1 results were adjusted for baseline score. Model 2 results were adjusted for baseline score, ethnicity, age, education, hypertension, diabetes, and smoking. Because of missing values for some covariates, the sample size in model 2 was lower.
† Values represent the average difference in annual change in cognitive test performance associated with the TT genotype as compared with the CT/CC genotype. For each test, negative values represent worse performance.
‡ CI, confidence interval; mMMSE, modified Mini-Mental State Examination; DSST, Digit Symbol Substitution Test.
§ Log-transformed time to completion. Values approximate the average percent difference in amount of time needed to complete the Trails B test.
extrapolate the potential benefits of a therapy based solely on its effect on homocysteine levels. Randomized trials of specific therapies will always be necessary to make such determinations. Nevertheless, this study strengthens the rationale for continued, large-scale testing of interventions that modulate homocysteine levels in order to prevent cognitive impairment in the elderly.

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REFERENCES


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