Plasma Homocysteine and Parental Myocardial Infarction in Young Adults in Jerusalem

J.D. Kark, MD, PhD; R. Sinnreich, PhD; I.H. Rosenberg, MD; P.F. Jacques, ScD; J. Selhub, PhD

Background—A causal role for mildly elevated plasma homocysteine (tHcy) in cardiovascular disease remains undetermined. To address the unresolved issue of the antecedent-consequent directionality of the relationship, we assessed the familial association of tHcy with parental myocardial infarction (MI) in young Israeli men and women. We also compared tHcy concentrations in Jerusalem, where rates of coronary heart disease (CHD) are high, with the United States Third National Health and Examination Survey (NHANES III).

Methods and Results—A total of 8646 17-year-olds and 6952 parents were examined from 1976 to 1979 in Jerusalem. At ages 28 to 32 years, offspring of parents who experienced a documented MI during a 10-year follow-up (n=133 men, 62 women; 72% response) and offspring of CHD-free parents (n=389 men, 208 women; 71% response) were reexamined. tHcy levels were determined by the same laboratory for the NHANES non-Hispanic white population aged 25 to 34 years (n=379) and the Jerusalem population sample (n=858). Men from Jerusalem, but not women, had clearly higher tHcy levels than the sample from the United States (90th percentile, 23 versus 14 μmol/L). This difference was largely attributable to lower plasma vitamin B_{12} levels in the Israeli population. Male case offspring had higher adjusted tHcy than did controls (1.9 μmol/L, P=0.002). Logistic modeling revealed a graded increase in risk of parental MI across quintiles of offspring tHcy, with an adjusted odds ratio of 2.7 in the 5th quintile (P=0.0026 for trend).

Conclusions—The higher tHcy in young male offspring of parents with CHD suggests that elevated tHcy precedes manifestation of CHD. The elevated population tHcy in men may contribute to the high incidence of CHD in Israel. (Circulation. 2002;105:2725-2729)

Key Words: myocardial infarction ■ coronary disease ■ epidemiology ■ homocysteine

Although mildly elevated total plasma homocysteine (tHcy) has repeatedly been shown to be associated with cardiovascular disease\(^1,2\) and with all-cause mortality,\(^3,4\) its role as a causal risk factor remains to be established. The implications are potentially far reaching in light of the simple intervention available, B vitamin fortification or supplementation. Included among the plausible noncausal mechanisms for the reported associations is the explanation that tHcy elevation is a marker of tissue damage and repair and is secondary to existing cardiovascular disease.\(^5\) Cohort studies are less convincing in showing a relationship than are cross-sectional case-control designs.\(^1\) Furthermore, there is some evidence that a tHcy–coronary heart disease (CHD) association is accentuated in, or limited to, patients who have preexisting CHD.\(^6\)

A potentially informative observational approach to unraveling the issue of the temporal (antecedent-consequent) directionality of relationships is a two-generational study of the familial association of tHcy with CHD in first-degree relatives. Fasting tHcy levels are partly genetically determined.\(^7-9\) Important enzymes that affect tHcy levels include methionine synthase and methylentetrahydrofolate reductase (MTHFR) in the remethylation pathway and cystathionine synthase in the trans-sulfuration pathway. Recent studies with the thermolabile MTHFR C677T polymorphism and its interaction with folate status demonstrate gene-environment contributions to tHcy variation.\(^10\) CHD shows consistently strong familial aggregation that has not yet been fully explained. A decade ago, Genest et al\(^9\) suggested that tHcy may play a role in this regard. Several studies have indicated that offspring of patients seem to have higher tHcy levels.\(^11-14\) Inference was limited by the generally small number of parental events involved, by the fact that parental events were usually reported rather than independently documented, and by the lack of control for potential confounders in most of the studies.

We assessed the familial association of tHcy with acute myocardial infarction (MI) in young Jewish residents of Jerusalem by comparing adult offspring of parents with a documented MI and offspring who had no parental history of CHD. We examined the dose-response relation and independence from the B vitamins, creatinine, and conventional predictors of MI. Furthermore, we compared tHcy concentrations in Jerusalem with those measured in Third National...
Health and Examination Survey (NHANES III). We have previously shown that tHcy predicted all-cause and cardiovascular mortality in the Jerusalem population.1,4,5

Methods
Sample
The Jerusalem Lipid Research Clinic study initially examined 8646 17-year-olds from Jerusalem between 1976 and 1979 and a sample comprising 6952 parents. The 17-year-olds, consisting of full age cohorts, were sequentially sampled at their obligatory induction medical examination for military service. The design and response were reported.16

In a follow-up study we drew a sex-stratified random sample comprising 1093 men and 753 women from the original 8646 participants, as previously reported.17 Excluded from the study were people who were not residents of Jerusalem (according to the national population registry); women who were pregnant, had given birth within 3 months, or were breast feeding up to 6 months; institutionalized people; and those unable to provide informed consent. Nine percent of eligible men and women could not be located, and 18% of men and 23% of women refused. A total of 570 consent. Nine percent of eligible men and women could not be notifications and confirmed according to MONICA criteria.18 Eligibility criteria for the case offspring were as for the controls; 200 eligible offspring participated (74% response in men and 68% response in women). Five people had missing tHcy determinations, leaving 195 (133 men and 62 women) for analysis (control group).

In addition, 6952 parents of the 17-year-olds were also examined in 1976 to 1979.19 During an average 10-year follow-up period, 366 and 208 women remained for analysis (control group).

manifestations of CHD including sudden death (n/H11005 26) or reported parental MI or other

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Laboratory Methods
In the Jerusalem sample, after an overnight fast, blood was drawn (with the patient seated) with minimal venous constricttion into EDTA-containing vacuum tubes, immediately placed on ice, refrigerator-centrifuged within 30 minutes at 2300g for 20 minutes, aliquotted into cryotubes, and stored at −80°C for 8 to 10 years until examination at the United States Department of Agriculture Human Nutrition Research Center in Boston in 1999. Coded and identically stored plasma samples of case and control offspring had been thawed once or twice for other tests before tHcy determination and once more before the B vitamins were measured. Total homocysteine in plasma was determined by HPLC with fluorometric detection,19 plasma vitamin B₁₂ (B₁₂), folate by microbial assay, and pyridoxal-5’-phosphate by the tyrosine decarboxylase apoenzyme method.20 Intra-assay and interassay coefficients of variation range across the range of values were, respectively, 4% to 7% and 3% to 4% for tHcy, 12% to 14% and 5% to 10% for folate, 7% to 8% and 2% to 6% for B₁₂, and 6% to 7% and

TABLE 1. Blood Homocysteine Levels (μmol/L) in Israel (Jerusalem) and the United States (NHANES III), Percentile Distribution

<table>
<thead>
<tr>
<th></th>
<th>10</th>
<th>15</th>
<th>25</th>
<th>50</th>
<th>75</th>
<th>85</th>
<th>90</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Jerusalem</td>
<td>7.2</td>
<td>7.7</td>
<td>8.6</td>
<td>10.6</td>
<td>13.6</td>
<td>16.4</td>
<td>22.7</td>
</tr>
<tr>
<td>NHANES</td>
<td>6.5</td>
<td>6.9</td>
<td>7.9</td>
<td>9.1</td>
<td>10.8</td>
<td>11.8</td>
<td>13.8</td>
</tr>
<tr>
<td>NHANES*</td>
<td>6.8</td>
<td>7.6</td>
<td>8.1</td>
<td>9.3</td>
<td>11.0</td>
<td>12.8</td>
<td>14.1</td>
</tr>
<tr>
<td>Women</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jerusalem</td>
<td>5.6</td>
<td>6.1</td>
<td>6.6</td>
<td>8.2</td>
<td>10.0</td>
<td>11.4</td>
<td>12.5</td>
</tr>
<tr>
<td>NHANES</td>
<td>4.9</td>
<td>5.2</td>
<td>5.9</td>
<td>7.3</td>
<td>9.6</td>
<td>11.5</td>
<td>12.4</td>
</tr>
<tr>
<td>NHANES*</td>
<td>5.2</td>
<td>5.7</td>
<td>6.4</td>
<td>8.3</td>
<td>10.7</td>
<td>12.1</td>
<td>13.2</td>
</tr>
</tbody>
</table>


*No use of vitamin supplements, 129 men and 167 women.

3% to 7% for vitamin B₁₂ (B₁₂). Plasma creatinine was measured by a kinetic modification of the Jaffe method (Roche reagent). Methods for plasma lipids have been reported.17

In NHANES III, blood was centrifuged after being allowed to clot at room temperature for 30 to 60 minutes, and serum was stored at −20°C. Measurements of tHcy in both NHANES III and the Israeli sample were conducted in the same laboratory using identical methods. In NHANES III, serum samples had been thawed 1 to 4 times for previous measurements. tHcy values measured in serum tend to be higher on average by 0.64 μmol/L than in plasma but are not affected by freeze-thaw cycles.21

Statistical Methods
tHcy values were log-transformed to approximately normalize the skewed distribution. For the United States–Israel comparison, percentile distributions of tHcy were obtained, and geometric means, estimated standard errors, and confidence intervals were computed, in NHANES both including and excluding vitamin users. Vitamin supplementation was practically nonexistent in young Israelis at the time. For NHANES III, SUDAAN statistical software was used to adjust for the sampling scheme.22

Geometric mean tHcy differences by parental MI status, adjusted for covariates, were tested by ANOVA. Statistical power to detect a geometric mean case-control difference of 1, 1.5, and 2 μmol/L, was 0.39, 0.70, and 0.90 in men and 0.36, 0.65, and 0.87 for the same relative difference in women, respectively. We also predicted parental events according to quintiles of tHcy in men, adjusting for covariates by use of logistic regression. We tested for trend by introduction of the natural logarithm of tHcy as a continuous variable.

Results
Jerusalem men, but not women, had substantially higher tHcy than did the United States sample, particularly evident in the upper end of the distribution. This difference persisted when users of vitamin supplements were excluded from the NHANES sample (Table 1) and is underestimated because tHcy is lower by 0.64 μmol/L in plasma (Jerusalem) than in serum (NHANES).22 The 90th percentile tHcy value in men was 23 μmol/L in Jerusalem versus 14 μmol/L in NHANES III. Geometric mean tHcy values also discriminated sharply in men (11.7 μmol/L [95% CI, 11.2 to 12.2] in Jerusalem versus 9.3 μmol/L [9.0 to 9.7] in NHANES) but less so in women (8.4 μmol/L [8.1 to 8.7] in Jerusalem versus 7.6 μmol/L [7.3 to 8.0] in NHANES).
Salient characteristics of the young Israeli adults are the extremely low alcohol intake and low HDL-cholesterol (Table 2) and apolipoprotein A-I concentrations. Male case offspring had higher total cholesterol and LDL-cholesterol levels than did controls.

The geometric mean tHcy was higher in male case offspring than control offspring (Table 2), and B 12 was lower. No differences were noted for plasma levels of B 6 , folate, or creatinine. Case-control comparisons of tHcy in women, for whom no association was noted, are not additionally reported.

In the control group, Spearman correlations of tHcy with folate, B12, B 6 , and creatinine were 0.45, 0.36, 0.21, and 0.15 in men and 0.48, 0.31, 0.18, and 0.25 in women, respectively.

The case-control difference in tHcy among men, evident throughout the distribution of tHcy (Mann-Whitney nonparametric test, P=0.005), was accentuated toward the upper tail (Figure).

In an ANOVA controlling for age and cholesterol, the geometric mean tHcy was higher in male cases than controls (difference of 1.9 μmol/L, P=0.002) and was weakened on control for the B vitamins (difference of 1.3 μmol/L, P=0.018). In a logistic regression restricted to male offspring with tHcy quintiles predicting parental MI (Table 3), there was a graded increase in risk across quintiles (model 1, age adjusted, P=0.003 for trend). Addition of plasma cholesterol slightly augmented the association, with odd ratios of 2.5 and 2.7 in the 4th and 5th quintiles, respectively (model 2, P=0.0026 for trend). Introduction of creatinine (not shown) did not affect the association. On addition of the B vitamins, a significant though modestly attenuated association persisted (model 3, P=0.016 for trend).

We examined the joint relationship of tHcy and cholesterol with parental MI (Table 4). Both variables, dichotomized at their median values, showed similar odds ratios for MI (OR, \( \approx 3 \)) in the stratum below the median of the other variable and weaker associations (OR, \( \approx 1.5 \)) in the stratum above the median of the other. The odds ratio when both variables were above their medians versus both below was less than multiplicative (OR, 4.6). A test for interaction was not significant (P=0.16).

### TABLE 2. Characteristics of Jerusalem LRC Young Adults (Aged 28–32 Years) by Parental Status (Case/Noncase) and by Sex

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th></th>
<th>Women</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Case Offspring (n=133)</td>
<td>Noncase</td>
<td>Case Offspring (n=62)</td>
<td>Noncase</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Offspring (n=389)</td>
<td></td>
<td>Offspring (n=208)</td>
</tr>
<tr>
<td></td>
<td>P</td>
<td></td>
<td>P</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>29.8 (0.8)</td>
<td>30.1 (0.9)</td>
<td>0.002</td>
<td>29.9 (0.8)</td>
</tr>
<tr>
<td>Present smoker, %</td>
<td>44</td>
<td>44</td>
<td>1.0</td>
<td>32</td>
</tr>
<tr>
<td>Alcohol daily, %</td>
<td>3.8</td>
<td>2.3</td>
<td>0.5</td>
<td>0</td>
</tr>
<tr>
<td>Strenuous exercise ≥ weekly, %</td>
<td>24</td>
<td>20</td>
<td>0.4</td>
<td>21</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>25.4 (3.5)</td>
<td>25.1 (3.7)</td>
<td>0.4</td>
<td>24.1 (3.5)</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>115 (9)</td>
<td>115 (9)</td>
<td>0.6</td>
<td>105 (9)</td>
</tr>
<tr>
<td>LDL-cholesterol, mmol/L</td>
<td>3.1 (0.8)</td>
<td>2.8 (0.8)</td>
<td>0.001</td>
<td>2.6 (0.6)</td>
</tr>
<tr>
<td>HDL-cholesterol, mmol/L</td>
<td>1.0 (0.3)</td>
<td>1.0 (0.3)</td>
<td>0.7</td>
<td>1.2 (0.3)</td>
</tr>
<tr>
<td>Glucose 2 h, mmol/L</td>
<td>5.1 (1.2)</td>
<td>5.0 (1.4)</td>
<td>0.25</td>
<td>5.0 (1.1)</td>
</tr>
<tr>
<td>Homocysteine, μmol/L</td>
<td>13.2 (7.1)</td>
<td>11.5 (5.5)</td>
<td>0.005</td>
<td>8.1 (2.8)</td>
</tr>
<tr>
<td>Creatinine, mmol/L</td>
<td>77 (16)</td>
<td>79 (14)</td>
<td>0.3</td>
<td>68 (11)</td>
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<tr>
<td>Vitamin B12, pmol/L</td>
<td>226 (64)</td>
<td>242 (76)</td>
<td>0.015</td>
<td>244 (67)</td>
</tr>
<tr>
<td>Vitamin B6, pmol/mL</td>
<td>49.8 (23.2)</td>
<td>49.8 (37.5)</td>
<td>0.99</td>
<td>44.5 (22.4)</td>
</tr>
<tr>
<td>Folate, nmol/L</td>
<td>5.58 (2.22)</td>
<td>5.78 (2.32)</td>
<td>0.4</td>
<td>7.15 (3.22)</td>
</tr>
</tbody>
</table>

*Geometric mean.

In the control group, Spearman correlations of tHcy with folate, B 12 , B 6 , and creatinine were −0.45, −0.36, −0.21, and 0.15 in men and −0.48, −0.31, −0.18, and 0.25 in women, respectively.

The case-control difference in tHcy among men, evident throughout the distribution of tHcy (Mann-Whitney nonparametric test, P=0.005), was accentuated toward the upper tail (Figure).

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Discussion

We found a positive association of tHcy with parental MI that was restricted to men and was not attributable to confounding by the classical risk factors for CHD or creatinine. Of the conventional risk factors, only total cholesterol and LDL-cholesterol were independent predictors of parental events. We infer from this result of higher tHcy in healthy young male offspring of parents with CHD (whether attributable to

Percentile distribution of plasma homocysteine in men by parental MI status. Black bars indicate infarction; gray bars, free of CHD. Mann-Whitney test, P=0.005.
TABLE 3. Association of Plasma Homocysteine in Male Offspring With Parental Acute MI Incidence

<table>
<thead>
<tr>
<th>tHcy Quintiles</th>
<th>Cutoff</th>
<th>Points</th>
<th>Model 1*</th>
<th>Model 2*</th>
<th>Model 3*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-8.11</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>-9.64</td>
<td>1.48</td>
<td>1.53</td>
<td>1.53</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>-11.35</td>
<td>1.99</td>
<td>2.13</td>
<td>2.06</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>-14.60</td>
<td>2.37</td>
<td>2.49</td>
<td>2.34</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>...</td>
<td>2.51</td>
<td>2.68</td>
<td>2.46</td>
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<tr>
<td>P†</td>
<td>...</td>
<td>0.003</td>
<td>0.0026</td>
<td>0.016</td>
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</tr>
</tbody>
</table>

*Model 1 was adjusted for age; model 2 was adjusted also for plasma total cholesterol; and model 3 was adjusted also for vitamin B12 and folate.
†Test for linear trend, ln tHcy introduced as a continuous variable.

The finding supports the view that elevated tHcy may play a pathogenic role, although it could also serve as a marker for other putatively causal variables, such as B vitamin status. This is also consistent with reports that vascular endothelial dysfunction shows a familial association, being impaired in offspring of patients with early onset CHD, and that endothelial function improved in response to folic acid and B12 supplementation, which lead to a reduction in tHcy levels. Although there was a strong relation of tHcy with the B vitamins in our study, control for folate, B12, and B6 attenuated but did not abolish the association of tHcy with parenteral events.

There is limited literature on familial prediction of cardiovascular disease by tHcy in clinically healthy first-degree relatives. tHcy in 8- to 12-year-old Norwegian children was associated with reported premature CHD death in male relatives (=age 55 years) but not with all events (fatal and nonfatal) in relatives. In Belgian 5- to 19-year-olds, tHcy above the 95th percentile was associated with cardiovascular disease in relatives. In the Bogalusa study, tHcy was associated with reported parental history of CHD in both black and white children. Among adolescent boys in the United States, serum tHcy was independently associated with documented parental CHD at ages ≥55 years.

The association of parental MI with offspring homocysteine in our study was limited to men. Although the absence of an association in women might reflect inadequate statistical power, it is also consistent with different age periods in the life course of men and women when tHcy becomes important in relation to CHD risk. The latter interpretation is supported by the fact that the sex difference in the tHcy–parental MI association was statistically significant (P<0.05). Similar sex differences in association were evident also for total cholesterol, LDL-cholesterol, and B12 (Table 2). tHcy concentrations were considerably higher in men than women, a disparity that is reduced around menopause.

This study design reduces the possibility that the rather consistent association of tHcy with CHD reported in the literature is secondary to CHD. Nevertheless, this argument cannot be totally dismissed, because mechanisms of tissue damage and repair may elevate plasma tHcy and case offspring at a mean age of 30 years may already have a greater subclinical burden of atherosclerosis or endothelial dysfunction, which might affect tHcy levels. However, the studies in children additionally support an inference that elevated tHcy precedes CHD. Although our study finding is consistent with the argument for a causal association, it does not eliminate the possibility that increased tHcy might be a noncausal familial marker of increased risk, whether attributable to shared genes or shared environment, including shared dietary intake of B vitamins. Controlling for the plasma B vitamins modestly attenuated the magnitude of the association. Such adjustment is justifiable, however, if tHcy serves solely as a risk marker, not if it is an intervening factor in the causal pathway.

A decade ago, Genest et al, who studied spouses and offspring of probands with CHD, concluded that elevated tHcy associated with CHD is in part genetically determined. An example of a genetic mechanism is the thermolabile MTHFR polymorphism with a folate-dependent effect on remethylation and hence on homocysteine levels. A study of patients with MI in Israel showed an increased risk associated with the mutant C677T MTHFR polymorphism that was limited to young patients (≤45 years of age). However, meta-analyses of MTHFR and CHD have provided conflicting results.

tHcy was substantially higher in Israeli than in NHANES III men. The absence of this finding in women, fortunate in light of the association of elevated tHcy with pregnancy outcomes, may reflect sex–dietary intake–gene interactions that result in sex differences in tHcy being larger in Israel than in the United States. The determinants, whether genetic or environmental, of the elevated levels in young Israeli men require consideration. In our study population, plasma folate and B12 were quite strongly associated with homocysteine in both sexes. Median serum B12 levels in NHANES III participants aged 20 to 39 years were higher than plasma B12 in Israel by 41% in men and 27% in women. Low serum B12 was confirmed in a separate Israeli study and may be an important contributor to the higher Israeli tHcy levels. On the basis of the regression association between B12 and homocysteine, an increase in B12 in Israel to NHANES III levels should lead to a reduction in tHcy by ~2.1 μmol/L in men and ~0.6 μmol/L in women, largely abolishing the excess tHcy levels in Israelis. Folate levels could not be similarly compared with NHANES III because of the effect of thawing and refreezing in the Jerusalem samples. Folate and B12 levels were higher and B6 lower in women than in men in our study.

An analysis controlling for plasma B vitamins reduced the sex difference in tHcy in Israelis from 3.3 to 2.5 μmol/L and to 1.9 μmol/L on adjustment for creatinine.
The United States–Israel tHcy difference might also have a genetic basis, for example attributable to MTHFR polymorphisms. The C677T polymorphism has been reported to be common in Ashkenazi Jews with an allele frequency of 40% to 45%. There is substantial heterogeneity in the mutant homozygote frequency within different ethnic groups in Israel. In our study, however, there was no evidence for ethnic variation in plasma homocysteine levels in parallel with the variation in MTHFR allele frequency (not shown).

The strong correlation of plasma B vitamins with tHcy and the high tHcy levels in men indicate that the impact of planned B vitamin fortification (folic acid and B12) in Israel on tHcy levels should be profound. National food balance data indicate a high intake of fruit and vegetables but apparently a relatively low consumption of B12-rich animal products, suggesting good folate but possible inadequate B12 intake.

In conclusion, the inference from our study is that elevated tHcy levels should be profound. National food balance data indicate a high intake of fruit and vegetables but apparently a relatively low consumption of B12-rich animal products, suggesting good folate but possible inadequate B12 intake.

Acknowledgment
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References
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