Plasma Homocysteine, Hypertension Incidence, and Blood Pressure Tracking

The Framingham Heart Study


Abstract—Plasma homocysteine is cross-sectionally associated with blood pressure in large, community-based studies. It is unknown whether elevated plasma homocysteine predicts hypertension incidence. We investigated the relations of baseline plasma total homocysteine levels to hypertension incidence and blood pressure tracking in 2104 Framingham Heart Study participants (mean age, 57 years; 58% women), who were free of hypertension, myocardial infarction, heart failure, atrial fibrillation, or renal failure at baseline. Baseline mean±SD plasma homocysteine was 10.1±3.7 μmol/L. On follow-up 4 years from baseline, 360 persons (17.1%) had developed hypertension, and 878 persons (41.7%) had progressed to a higher blood pressure stage. In unadjusted analyses, a 1-SD higher log homocysteine value was associated with increased odds of developing hypertension (odds ratio [OR], 1.18; 95% confidence interval [CI], 1.05 to 1.32) and increased odds of blood pressure progression (OR, 1.17; 95% CI, 1.07 to 1.27). The relations of plasma homocysteine to the incidence of hypertension or blood pressure progression were statistically nonsignificant in age- and sex-adjusted logistic regression models (OR, 0.98; 95% CI, 0.87 to 1.11 and OR, 1.05; 95% CI, 0.96 to 1.16, respectively) and in multivariable models adjusted for age, sex, body mass index, diabetes, interim weight change, smoking, serum creatinine, baseline blood pressure, and blood pressure category (OR, 0.92; 95% CI, 0.81 to 1.06 and OR, 1.07; 95% CI, 0.97 to 1.18, respectively). In conclusion, we found no major relation of baseline plasma homocysteine levels to hypertension incidence or longitudinal blood pressure progression in a large, community-based cohort of nonhypertensive individuals after adjustment for age, sex, and other important covariates. (Hypertension. 2003;42:G55–G62.)

Key Words: hypertension, detection and control ■ blood pressure ■ homocysteine ■ metabolism ■ epidemiology ■ longitudinal studies

Several epidemiologic studies have demonstrated that elevated plasma total homocysteine has a modest effect on the risk of cardiovascular disease.1 The vascular risk associated with hyperhomocysteinemia has been observed to be stronger in hypertensive individuals.3 More recently, attention has been focused on the direct relations of plasma homocysteine to blood pressure and hypertension4–7 because of the suggestion that the adverse risk associated with hyperhomocysteinemia might be mediated in part by the positive association of homocysteine with hypertension. In the third National Health and Nutrition Examination Survey (NHANES III), persons in the highest quintile of plasma homocysteine had a 2- to 3-fold increased prevalence of hypertension relative to those in the lowest quintile.5 These observations have been confirmed in other cross-sectional reports6 and in experimental studies.8 Additionally, a potential causal role for homocysteine in the pathogenesis of elevated blood pressure is raised by the demonstration that homocysteine-lowering treatment is associated with a reduction in systolic and diastolic blood pressures.9,10 Thus, a considerable body of evidence suggests a role for plasma homocysteine in the pathogenesis of hypertension.7

No prior study has examined prospectively the relation of plasma homocysteine to hypertension incidence. It is possible that the cross-sectional relation of plasma homocysteine to blood pressure might be due to hyperhomocysteinemia being

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From the Framingham Heart Study (J.S., D.L., P.W.F.W., R.S.V.), Framingham, Mass; the Department of Preventive Medicine (D.L., R.S.V.), Cardiology Section (R.S.V.), and Endocrinology Division (P.W.F.W.), Boston University School of Medicine, Boston, Mass; the Department of Mathematics (L.S., R.B.D.), Boston University, Boston, Mass; the Jean Mayer US Department of Agriculture Human Nutrition Research Center on Aging (P.F.J., I.H.R.), Tufts University, Boston, Mass; and the National Heart, Lung, and Blood Institute (NHBLI; D.L.), Bethesda, Md.

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Correspondence to Ramachandran S. Vasan, MD, Framingham Heart Study, 73 Mt Wayte Ave, Framingham, MA 01702-5803. E-mail vasan@fram.nhlbi.nih.gov

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a marker for nephrosclerosis and mild renal dysfunction.12 Hence, a prospective, longitudinal study investigating the relation of homocysteine to blood pressure tracking is required to clarify whether plasma homocysteine truly has a causal role in hypertension.13 Accordingly, we tested the hypothesis that hyperhomocysteinemia is related to the development of hypertension and blood pressure tracking in a community-based cohort of nonhypertensive individuals.

Methods

Study Sample
The design and selection criteria of the original Framingham Heart Study and the Framingham Offspring Study have been described previously.14,15 Participants were eligible for inclusion in the present study if they had attended original cohort examination 16 (1979–1982) or offspring cohort examination 5 (1991–1995) and a follow-up examination 4 years later. There were 6150 attendees at the 2 examinations.

Subjects were excluded for the following reasons: prevalent hypertension at baseline, as defined by the sixth report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI)16 and the World Health Organization–International Society of Hypertension,17 i.e., systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or use of antihypertensive medication (n=2813); history of recognized myocardial infarction or heart failure (n=108); atrial fibrillation (n=44); serum creatinine >2.0 mg/dL (n=5); missing covariates at baseline examination (n=654); heart failure or recognized myocardial infarction on follow-up examination (n=50); or nonattendance or missing blood pressure information at follow-up examination (n=372). Subjects with myocardial infarction or heart failure were excluded because these conditions influence blood pressure. After these exclusions, 2104 individuals (mean age, 57 years; 58% women), all of whom were followed up for 4 years, remained eligible. Informed consent was obtained, and the Boston University School of Medicine institutional review board approved the study.

Baseline Examinations
Participants underwent a standardized medical history and physical examination, anthropometric measurements, laboratory tests, and a 12-lead ECG. Using a mercury column sphygmomanometer and a standardized protocol, a physician measured systolic and diastolic blood pressures twice in the left arm of seated subjects who had been resting for at least 5 minutes. The mean of these 2 readings was used for classification of blood pressure according to JNC VI criteria into the following categories: optimal (systolic <120 mm Hg and diastolic <80 mm Hg), normal (systolic 120 to 129 mm Hg or diastolic 80 to 84 mm Hg), or high-normal (systolic 130 to 139 mm Hg or diastolic 85 to 89 mm Hg) blood pressure at the baseline examination.18 When systolic and diastolic blood pressure readings belonged to different categories, the higher of the 2 categories was used. Diabetes was defined according to current American Diabetes Association guidelines.18 A panel of 3 physicians determined the prevalence of various cardiovascular diseases.19

Plasma Homocysteine
At the baseline examinations, plasma specimens obtained from attendees were refrigerated immediately after phlebotomy and stored at or below −20°C. Plasma total homocysteine levels were measured subsequently (multiple runs over a period of a few months between late 1996 and early 1997) by high-performance liquid chromatography with fluorometric detection.20 The coefficient of variation for homocysteine assays for samples from these examinations was 8%. The stability of plasma homocysteine in samples stored at temperatures below −20°C has been reported previously.21

Outcome Measures
At the follow-up examinations 4 years from baseline, participants underwent routine assessment of their blood pressure by the same standardized protocol and were reclassified according to their blood pressure category as defined by JNC VI criteria.16 The outcomes examined were incidence of hypertension and increase of blood pressure by 1 or more JNC VI blood pressure stage.22

Statistical Analysis
The goal was to investigate the relation of baseline plasma homocysteine to incidence of hypertension and blood pressure tracking over a 4-year follow-up. Before the formal tests, a series of univariate analyses were conducted to assess the distributional properties of plasma homocysteine and of important covariates in the total sample and then stratified by sex. Because plasma homocysteine was skewed, we used a logarithmic transformation to promote normality and also considered sex-specific quartiles of homocysteine in our modeling. Multiple logistic regression models were developed to investigate relations between baseline plasma homocysteine levels and blood pressure outcomes on follow-up. Plasma homocysteine was analyzed as a continuous variable (natural logarithm), as sex-specific quartiles, and as an indicator of hyperhomocysteinemia (plasma homocysteine >14 μmol/L) in each model. Unadjusted models, age- and sex-adjusted models, and multivariable adjusted models were examined. The latter included age, sex, body mass index, diabetes, interim weight change, smoking, serum creatinine, baseline systolic and diastolic blood pressures, blood pressure category, and baseline use of cardiac medication for indications other than hypertension. These covariates have been previously reported to influence blood pressure tracking.22 Because no effect modification by sex was noted, sex-pooled analyses were performed.

We also investigated interaction terms to evaluate variation in the relation of plasma homocysteine to blood pressure outcomes according to baseline age, body mass index, smoking status, and systolic blood pressure. In additional analyses, examination cycle and examination date (before/after mandatory folate fortification of cereal was introduced23) were investigated as covariates.

We also performed secondary analyses examining the relations of plasma homocysteine to longitudinal systolic and diastolic blood pressure change analyzed as continuous variables in a subgroup of 1912 individuals (91% of sample) who were not on antihypertensive medications at the follow-up examination. Linear regression models were constructed with changes in systolic and diastolic blood pressure as dependent variables (separate models for each blood pressure variable). These models were analogous to the primary analyses (unadjusted, age- and sex-adjusted, and multivariable models, with plasma homocysteine modeled as a continuous variable, as sex-specific quartiles, and as a dichotomous variable).

Results
The baseline characteristics of our study participants are displayed in Table 1. Ranges of plasma homocysteine in the quartiles are given in Table 2 and were similar in men and women.

At the follow-up examinations 4 years from baseline, 360 persons (17.1%, 55% women) had developed hypertension. Rates of progression to hypertension were similar in men and women and are presented by baseline plasma homocysteine category in Table 2. In unadjusted analyses, a 1-SD higher log-normal homocysteine value was associated with increased odds of developing hypertension (odds ratio [OR], 1.18; 95% confidence interval [CI], 1.05 to 1.32), and there was an increasing incidence of hypertension across plasma homocysteine quartiles and in persons with plasma homocysteine >14 μmol/L (Table 3). In the age- and sex-adjusted models and in the multivariable models, the relations of
plasma homocysteine to the incidence of hypertension were not statistically significant (Table 3).

On follow-up, 878 persons (41.7%, 56% women) experienced an increase to a higher JNC VI blood pressure stage. Rates of blood pressure progression were similar in men and women and are shown according to baseline plasma homocysteine category in Table 2. In unadjusted analyses, a 1-SD higher log homocysteine value was associated with increased odds of blood pressure progression (OR, 1.17; 95% CI, 1.07 to 1.27), and there was an increasing proportion of blood pressure progression across plasma homocysteine quartiles and in persons with plasma homocysteine >14 μmol/L (Table 3). However, the association of plasma homocysteine with blood pressure progression was no longer statistically significant after adjustment for age and sex in multivariable models (Table 3). None of the investigated statistical interaction terms were significant. Adjustment for examination cycle and date of examination did not alter the findings.

In secondary analyses evaluating longitudinal blood pressure as a continuous measure, mean systolic blood pressure increased by 6 mm Hg (SD, 13), whereas diastolic blood pressure increased by 2 mm Hg (SD, 8) among study participants not on antihypertensive medications at follow-up. Plasma homocysteine was not related to change in systolic blood pressure in any of the models (all probability values exceeded 0.20). An inverse association of plasma homocysteine to change in diastolic blood pressure was observed in unadjusted analyses (a decrease of 0.3 mm Hg per quartile of plasma homocysteine; P=0.055) but was not statistically significant after adjustment (all probability values exceeded 0.10).

**Statistical Power**

Because we found no association of plasma homocysteine with blood pressure outcomes but the NHANES III study reported a 2- to 3-fold cross-sectional risk for having hypertension after comparing the highest and lowest plasma homocysteine quintiles, we assessed our statistical power to detect such a relation. We had 94% power to detect an OR of 1.50 for development of hypertension in tests for trend across quartiles of plasma homocysteine. Likewise, we had 99% statistical power to detect an OR of 1.50 for progression of blood pressure stage across quartiles of plasma homocysteine. For analyses evaluating change in blood pressure as a continuous variable, we had >80% power to detect increments of systolic and diastolic blood pressure of 1.7 and 1.0 mm Hg, respectively, for trend across quartiles of plasma homocysteine.

**Discussion**

**Principal Findings**

We investigated for the first time in a community-based setting the relations of plasma homocysteine levels to hypertension incidence and blood pressure tracking. In unadjusted analyses, plasma homocysteine was positively associated with hypertension incidence and blood pressure progression. However, in age- and sex-adjusted and in multivariable adjusted models, the association was no longer statistically significant. In light of our observations, it is likely that the increased plasma homocysteine levels previously reported in hypertensive persons are concomitant rather than a precursor of hypertension.12,13

**Comparison With Prior Reports**

Experimental investigations evaluating the association of homocysteine and blood pressure have not yielded consistent results; diet-induced hyperhomocysteinemia has been demonstrated to elevate blood pressure in some investigations6 but lowered blood pressure in others.24 Several clinical...
It is important to note that the sample size in the NHANES III investigation was 3 times as large as ours, and in that investigation, such as intake of caffeine, alcohol, folate, or vitamin B supplements. 4

**Perspectives**

Mechanisms by which homocysteine could promote hypertension include increased arterial stiffness,29-31 impaired endothelial integrity,29,32 reduced vasodilatory capacity,32,33 and insulin resistance.7 If hyperhomocysteinemia were a risk factor for hypertension, then it would be of public health importance because elevated levels can be lowered through relatively simple nutritional measures, such as increased use of folic acid supplements or fortification of foods with folic acid.5,23

<table>
<thead>
<tr>
<th>Independent Variable/Model</th>
<th>OR (95% CI) for Developing Hypertension</th>
<th>OR (95% CI) for ≥1 BP Stage Increase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma homocysteine as a continuous variable (1-SD higher ln[homocysteine])</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crude</td>
<td>1.18 (1.05–1.32)*</td>
<td>1.17 (1.07–1.27)*</td>
</tr>
<tr>
<td>Age- and sex-adjusted</td>
<td>0.98 (0.87–1.11)</td>
<td>1.05 (0.96–1.16)</td>
</tr>
<tr>
<td>Multivariable†</td>
<td>0.92 (0.81–1.06)</td>
<td>1.07 (0.97–1.18)</td>
</tr>
<tr>
<td>Plasma homocysteine as a categorical variable (trend across homocysteine quartiles)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crude</td>
<td>1.13 (1.02–1.26)*</td>
<td>1.12 (1.04–1.21)*</td>
</tr>
<tr>
<td>Age- and sex-adjusted</td>
<td>0.97 (0.87–1.08)</td>
<td>1.03 (0.95–1.12)</td>
</tr>
<tr>
<td>Multivariable†</td>
<td>0.92 (0.82–1.04)</td>
<td>1.03 (0.95–1.13)</td>
</tr>
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<td>Homocysteine &gt; vs ≤14 μmol/L</td>
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<td></td>
</tr>
<tr>
<td>Crude</td>
<td>1.45 (1.03–2.05)*</td>
<td>1.44 (1.08–1.91)*</td>
</tr>
<tr>
<td>Age- and sex-adjusted</td>
<td>1.08 (0.75–1.55)</td>
<td>1.21 (0.90–1.61)</td>
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<tr>
<td>Multivariable†</td>
<td>0.91 (0.62–1.33)</td>
<td>1.29 (0.95–1.75)</td>
</tr>
</tbody>
</table>

*P < 0.05. All other P values exceeded 0.10. Blood pressure stages as in Table 1.
†Multivariable models adjusted for age, sex, body mass index, diabetes, interim weight change, smoking, serum creatinine, baseline blood pressure category, baseline use of cardiac medication for indications other than hypertension, and baseline systolic and diastolic blood pressure.

TABLE 3. Risk of Blood Pressure Outcomes According to Plasma Homocysteine Level at Baseline

In our study, the relations of plasma homocysteine to blood pressure outcomes were attenuated by adjustment for age. Because age is an important determinant of plasma homocysteine,4 it is possible that plasma homocysteine is a marker for age and age-related mild, subclinical renal dysfunction.12 In most previous cross-sectional studies, antihypertensive medication use has been a stronger correlate of plasma homocysteine than have blood pressure levels.4,5,6 Some antihypertensive drugs might have homocysteine-elevating effects,28 which might have contributed to previously observed associations.

**Strengths and Limitations**

Strengths of the present investigation include the large, community-based sample of nonhypertensive persons, the standardized blood pressure measurement at baseline and on follow-up, and the multivariable analyses adjusting for factors known to influence plasma homocysteine levels and blood pressure progression.22 Limitations include the predominantly white sample, with unknown generalizability to other ethnic groups. In addition, several factors that might influence plasma homocysteine levels were not assessed in our investigation, such as intake of caffeine, alcohol, folate, or vitamin B supplements.4

Perspectives by which homocysteine could promote hypertension include increased arterial stiffness, impaired endothelial integrity, reduced vasodilatory capacity, and insulin resistance. If hyperhomocysteinemia were a risk factor for hypertension, then it would be of public health importance because elevated levels can be lowered through relatively simple nutritional measures, such as increased use of folic acid supplements or fortification of foods with folic acid.
Cross-sectional investigations cannot clarify the temporal sequence between increased plasma homocysteine levels and presence of elevated blood pressure; such an association might arise if high blood pressure results in subclinical renal dysfunction (reverse causality). It is important to underscore that even in longitudinal studies (such as ours), within-subject variability in both plasma homocysteine and blood pressure measurements might result in an underestimation of a true association (regression-dilution bias). Larger prospective investigations of both young and middle-aged individuals relating plasma homocysteine (preferably average of multiple measurements) to changes in blood pressure would be required to exclude modest effects of homocysteine on blood pressure. Ongoing clinical trials of homocysteine lowering might provide an opportunity to examine blood pressure changes in treatment groups in relation to variations in plasma homocysteine levels. It is important to note that it might not be possible to prove the “homocysteine–high blood pressure” hypothesis even in clinical trials of folate supplementation because the antihypertensive effects of folate might be independent of its homocysteine-lowering properties; it might not be possible to distinguish the effects of folate from those of a lower plasma homocysteine.

Conclusions
Baseline plasma homocysteine level was not a major risk factor for hypertension incidence or blood pressure tracking in our large, community-based sample. Our longitudinal observations do not support the hypothesis that plasma homocysteine is causally related to elevated blood pressure. Additional prospective investigations are warranted to confirm these findings.

Acknowledgments
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