ORIGINAL CONTRIBUTION

Mild Parkinsonian Signs and Plasma Homocysteine Concentration in Community-Dwelling Elderly Individuals

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Objective: To determine whether plasma homocysteine (Hcy) concentration is associated with mild parkinsonian signs (MPS) in community-dwelling elderly individuals.

Design: Cross-sectional analyses of a population-based cohort study.

Setting: Washington Heights–Inwood, New York.

Patients: Persons without dementia 65 years and older.

Main Outcome Measure: Participants underwent an abbreviated motor portion of the Unified Parkinson's Disease Rating Scale. Each participant was assigned an MPS score (range, 0-40). The Hcy concentration was measured from plasma. All analyses were cross-sectional.

Results: There were 369 participants (mean±SD age, 77.8±6.0 years; mean±SD MPS score, 1.51±2.55; mean±SD plasma Hcy concentration, 17.3±6.5 μmol/L). Mean±SD MPS scores in plasma Hcy concentration quintiles were as follows: lowest quintile, 1.15±1.77; second quintile, 1.18±1.88; third quintile, 1.64±2.93; fourth quintile, 1.45±2.17; and highest quintile, 2.12±3.49 (84.3% higher than 1.15) (P=.02). In an unadjusted linear regression model, plasma Hcy concentration was associated with log MPS score (dependent variable) (P=.008). In a linear regression model that adjusted for confounding variables, plasma Hcy concentration was associated with log MPS score (P=.04).

Conclusions: These data indicate that MPS are associated with higher plasma Hcy concentrations. Prospective neuroimaging as well as clinical-pathological studies would further our understanding of several mechanisms that could underlie the observed association.

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MILD PARKINSONIAN signs (MPS), which include impaired gait and balance, rigidity, bradykinesia, and rest tremor, are commonly found during the clinical examination of older people who do not have any diagnosed neurological disease.[1-7] These signs, which are highly prevalent, are associated with functional disability[8,9] and increased risks for dementia[5,7] and mortality.[2,10] The processes that underlie MPS are not clear but could include an age-associated decline in nigrostriatal dopaminergic activity, the development of degenerative (eg, Lewy body or Alzheimer type) pathological changes, or the accumulation of vascular pathological changes in the cerebral subcortical white matter or other brain regions. Elevated homocysteine (Hcy) concentration is a cerebrovascular risk factor but it has also been associated with treated and untreated Parkinson disease (PD).[11,12] With one possible exception,[12] to our knowledge plasma Hcy concentrations have not been assessed in elderly individuals with MPS nor have we previously assessed the association between these concentrations and MPS in our cohorts in northern Manhattan, New York. A recent cross-sectional study in 3 French cities demonstrated an association between elevated plasma Hcy concentration and slower walking speed in elderly individuals.[12] In that study,[12] however, investigators focused on gait speed rather than MPS. We studied a sample of elderly persons without dementia living in Washington Heights–Inwood, New York, to determine specifically whether plasma Hcy concentration is associated with MPS.

METHODS

STUDY SAMPLE

Participants in the Washington Heights–Inwood Columbia Aging Project cohort were drawn by random stratified sampling of healthy Medicare beneficiaries 65 years or older residing within a geographically defined area of northern Manhattan. The sampling procedures have

been described elsewhere.[1,13] The participants were recruited between 1992 and 1994, and 2126 were enrolled. Their mean ± SD age was 77.2 ± 7.2 years, mean ± SD education was 8.2 ± 4.9 years, 69.4% were women, and 20.7% were non-Hispanic white. Each participant underwent a structured interview of health and function at the time of study entry and, over the ensuing year, was referred for the same standardized neurological examination, which included an abbreviated, 10-item version of the motor portion of the Unified Parkinson's Disease Rating Scale (UPDRS).[14]

We excluded data on 1104 participants. First, we excluded data from 676 individuals who screened negative for dementia, PD, or stroke or who had died or were lost to follow-up and therefore did not receive the standardized neurological examination. Second, data on an additional 44 participants were excluded because of incomplete neurological examinations. Third, we excluded data from 53 participants who were taking a neuroleptic medication because parkinsonian signs can result from the use of these medications. Fourth, we assigned a diagnosis of PD or Parkinson plus syndrome based on research criteria[15] and participants were considered to have PD or Parkinson plus syndrome if (1) they had previously received a diagnosis of PD or Parkinson plus syndrome or (2) they had on the standardized neurological examination 2 or more cardinal signs of parkinsonism. Cardinal signs were bradykinesia, rigidity, postural changes, and rest tremor. A cardinal sign was considered to be present when 1 UPDRS rating was 2, 3, or 4. Fourteen (1.0%) of the remaining 1353 participants had a diagnosis of PD or a Parkinson plus syndrome, which is consistent with a prevalence of 0.7% to 1.2% for PD, which has been reported for persons 65 years and older in northern Manhattan.[16] These 14 participants were excluded because our intention was to study a community population of older people without these diseases. Fifth, all participants also underwent a standardized neuropsychological battery.[17] Using these test results as well as clinical information, a consensus diagnosis of dementia was assigned if participants met established criteria[18] and if functional difficulties could be attributed to cognitive rather than physical disability.[19] A Clinical Dementia Rating (CDR) score was assigned as well. We excluded 227 participants with dementia. After the exclusion of 1014 participants, the remaining sample comprised 1112 potential participants.

A sample of 909 participants from the original cohort of 2126 had been selected randomly at the time of their baseline assessment to conduct a study of Hcy concentration in elderly individuals.[20] Of the 1112 remaining potential participants, 369 (33.2%) had been selected for the plasma Hcy concentration study. Therefore, our final sample comprised these 369 participants. The study was approved by our institution's internal review board and written consent was obtained from all participants.

EVALUATION

As noted earlier, a standardized neurological examination was conducted by 1 of 3 neurologists, including an abbreviated, 10-item version of the motor portion of the UPDRS.[14] The 10 items included speech, facial expression, tremor at rest (1 item), rigidity (rated separately in the neck, right arm, left arm, right leg, and left leg), posture, and body (axial) bradykinesia.[1] Each of the 10 items was rated from 0 to 4. A rating of 1 indicated a mild abnormality and a rating of 2 or more indicated an abnormality of moderate or greater severity. Reliability of assessment of parkinsonian signs by 3 neurologists has been reported and was acceptable (intraclass correlation coefficient for total motor score = 0.82).[21] An MPS score (range, 0-40) was calculated for each participant.

Demographic data were collected, including age and sex. Ethnic group was based on self-report using the format of the 1990 US census.[22] Individuals were asked whether they were of Hispanic origin. Participants were then assigned to 1 of the following ethnic groups: non-Hispanic black, Hispanic, non-Hispanic white, and other. Number of years of education was obtained by self-report. Presence of a history of diabetes mellitus, hypertension, stroke, heart disease (myocardial infarction or congestive heart failure), or arthritis was assessed by self-report, as was use of nonsteroidal anti-inflammatory drugs (ever vs never). Participants were asked whether they smoked cigarettes (coded as ever [including current or past smokers] vs never) or regularly used ethanol (ever vs never).

PLASMA Hcy AND OTHER PLASMA AND SERUM CONCENTRATIONS

Fasting blood was drawn at baseline in EDTA tubes. Within 2 hours of collection, it was centrifuged, separated into plasma aliquots, and stored at −70°C. The Hcy concentration was measured from stored plasma using high-performance liquid chromatography with fluorescence detection.[23] Plasma concentrations of folate and vitamin B_{12} were determined by radioassay (Simultrac; ICN Pharmaceuticals, Costa Mesa, California). Serum creatinine concentration was measured by spectrophotometric assay (Sigma, St Louis, Missouri).

STATISTICAL ANALYSES

These cross-sectional statistical analyses were performed in SPSS (version 13.0; SPSS Inc, Chicago, Illinois). The MPS score had a value of 0 in 204 of 369 participants, which could violate one of the assumptions that justify the use of linear regression modeling. Therefore, for our linear regression models, we added the value 1.0 to the value in all 369 participants and then log transformed ($\log_{10}$) this modified MPS score.

In a linear regression model, we examined the association between MPS score categories (0, 1, 2, 3, 4, ≥5) and plasma Hcy concentration. In an additional analysis, plasma Hcy concentration was divided into quintiles (≤12.115 µmol/L, >12.115 to ≤14.080 µmol/L, >14.080 to ≤16.555 µmol/L, >16.555 to <20.111 µmol/L, and >20.111 µmol/L [to convert to milligrams per liter, divide by 7.397]), and in a linear regression model, we examined the association between plasma Hcy concentration quintile and log MPS score (dependent variable).

An unadjusted linear regression analysis was performed with log MPS score as the dependent variable and plasma Hcy concentration as the independent variable. We then considered possible covariates that were confounders or mediators; in these analyses, because MPS score was not normally distributed, Spearman correlation coefficients (r) were used to assess associations between the MPS score and continuous covariates (eg, age) and Mann-Whitney U tests or Kruskal-Wallis tests were used to assess associations between the MPS score and categorical covariates (eg, sex). Covariates that we considered were age in years; sex; ethnic group (non-Hispanic black, Hispanic, non-Hispanic white, and other); years of education; regular ethanol use (ever vs never); cigarette use (ever vs never); history of stroke, arthritis, diabetes, hypertension, or heart disease; nonsteroidal anti-inflammatory drug use (ever vs never); CDR score (0 or 0.5); plasma folate and vitamin B_{12} concentrations; and serum creatinine concentration. These analyses identified 4 variables that were associated with MPS score: age, diabetes mellitus, heart disease, and CDR score (**Table**). Each of these 4 variables was then placed in a linear regression model along with plasma Hcy concentration (log MPS score = dependent variable), and in these 4 models (each with 2 independent variables: plasma Hcy concentration and 1 of the 4 confounding variables), the association between plasma Hcy concentration

Table. Log MPS Score, Plasma Homocysteine Concentration, and Covariates

Covariate	Sample Size	Mean±SD	
		Log MPS Score	Plasma Homocysteine Concentration, μmol/L
Age	369	r=0.26[a]	r=.08
Sex			
M	94	0.23±0.34	18.5±7.8[b]
F	275	0.27±0.32	16.5±7.6
Race			
Non-Hispanic white	68	0.25±0.34	16.7±7.2
Non-Hispanic black	110	0.27±0.34	18.1±9.4
Hispanic	189	0.26±0.31	16.4±6.6
Other	2	0.00±0.00	16.3±4.9
Years of education	369	r=–0.07	r=–0.01
Arthritis			
No	117	0.23±0.33	17.1±6.7
Yes	252	0.27±0.32	16.9±8.1
Diabetes mellitus			
No	300	0.23±0.31[c]	16.8±7.4
Yes	69	0.37±0.37	17.5±8.9
Hypertension			
No	150	0.25±0.32	16.6±7.5
Yes	219	0.27±0.33	17.3±7.8
Heart disease			
No	286	0.23±0.31[c]	16.9±7.2
Yes	40	0.37±0.33	16.9±6.7
Stroke			
No	325	0.25±0.32	16.8±7.2
Yes	44	0.29±0.34	18.3±10.7
Regular ethanol use			
No	318	0.25±0.32	16.4±6.4[c]
Yes	51	0.29±0.34	20.4±12.8
Smoked cigarettes			
No	251	0.26±0.32	16.6±7.8
Yes	118	0.25±0.33	17.7±7.4
NSAID use			
No	327	0.25±0.33	17.1±7.9
Yes	42	0.30±0.30	15.8±5.5
CDR score			
0	292	0.21±0.30[a]	16.8±7.2
0.5	73	0.44±0.36	17.8±9.3
Plasma vitamin B_{12} concentration	301	r=–0.01	r=–0.24[a]
Plasma folate concentration	301	r=–0.04	r=–0.25[a]
Serum creatinine concentration	366	r=0.005	r=0.47[a]

Abbreviations: CDR, Clinical Dementia Rating; MPS, mild parkinsonian signs; NSAID, nonsteroidal anti-inflammatory drug.
[a] $P<.001$.
[b] $P<.05$.
[c] $P<.01$.

and log MPS score remained robust, indicating that these confounding variables were not likely to be mediators. We then performed linear regression analyses (log MPS score = dependent variable) that adjusted simultaneously for age, diabetes mellitus, heart disease, and CDR score. To further test whether vascular disorders (diabetes mellitus, heart disease, hypertension, and stroke) were mediators, in 4 linear regression analyses, we excluded participants with these vascular disorders and examined the association between plasma Hcy concentration and log MPS score. In some analyses, we also stratified by age into 4 strata.

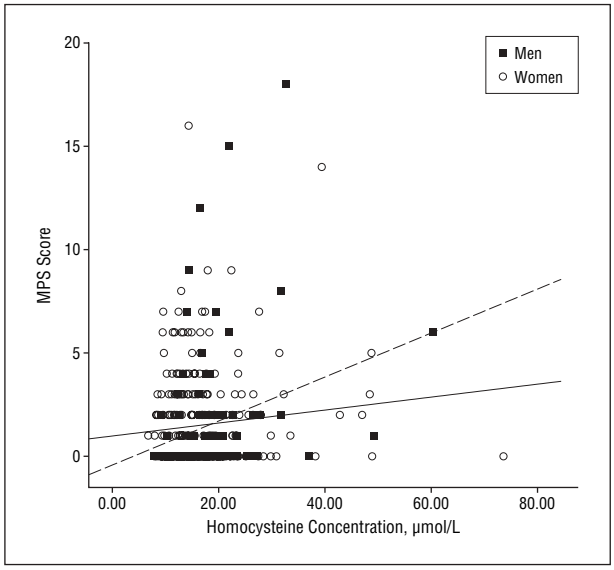

Figure 1. Scatter plot of mild parkinsonian signs (MPS) score by plasma homocysteine concentration in men and women. Fit line for men is depicted by a broken line; fit line for women is depicted by a solid line.

RESULTS

There were 369 participants. Their mean±SD age was 77.8±6.0 years, mean±SD education was 7.9±4.7 years, and 68 (18.4%) were non-Hispanic white, which was similar to the original cohort of 2126 from which they were derived. Two-hundred seventy-five (74.5%) were women, which is 5.1% higher than the original cohort (69.2%); because of the large size of the comparison groups, this modest difference reached marginal significance (P=.046). None had PD or dementia and none was receiving levodopa therapy. The mean±SD MPS score was 1.51±2.55 (range, 0-18). The MPS score was 0 in 204 participants (55.3%), 1 in 39 (10.6%), 2 in 45 (12.2%), 3 in 27 (7.3%), 4 in 18 (4.9%), and 5 or higher in the remaining 36 participants (9.8%). The mean±SD plasma Hcy concentration was 17.3±6.5 μmol/L (range, 8.3-54.1 μmol/L). The median latency between the 10-item version of the motor portion of the UPDRS and phlebotomy was 41 days (interquartile range, 18-71 days), indicating that the 2 events were separated by only a modest interval.

Log MPS score was associated with age and was higher in participants with diabetes mellitus, heart disease, or a CDR score of 0.5 (Table). Plasma Hcy concentration was higher in men and ethanol users; it was also associated with plasma concentrations of folate and vitamin B_{12} and serum creatinine concentration (Table).

Higher MPS score was associated with higher plasma Hcy concentration (**Figure 1**). For example, for an MPS score of 0, the mean±SD plasma Hcy concentration was 16.2±6.7 μmol/L; MPS score of 1, 17.3±7.7 μmol/L; MPS score of 2, 18.5±8.4 μmol/L; MPS score of 3, 17.0±8.3 μmol/L; MPS score of 4, 15.1±3.3 μmol/L; and MPS score of 5 or higher, 20.2±11.0 μmol/L (linear regression analysis, β=0.56; P=.02). Plasma Hcy concentration was stratified into quintiles (**Figure 2**); the mean±SD MPS score in each quintile was as follows: lowest plasma Hcy concentration quintile, 1.15±1.77; second quintile,

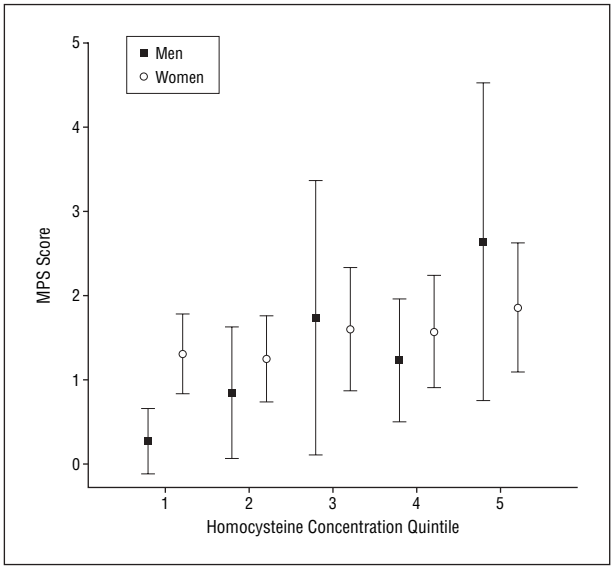

Figure 2. Mild parkinsonian signs (MPS) score by plasma homocysteine concentration quintile in men and women. Each bar represents 2 SEs and each box or circle represents the mean MPS score.

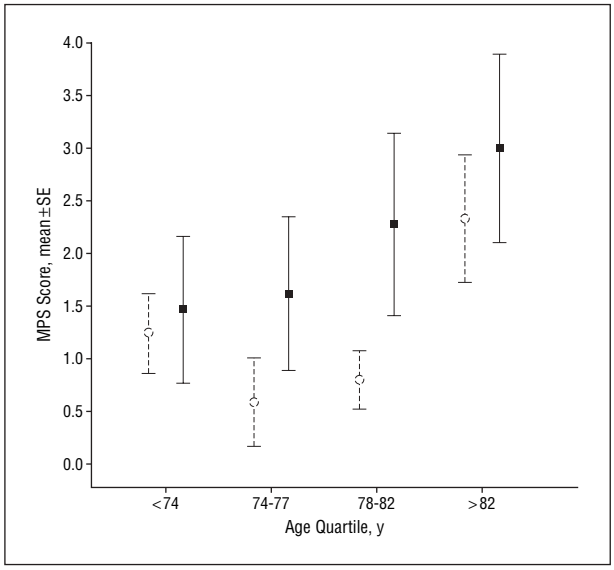

Figure 3. Within each of the 4 age strata (<74, 74-77, 78-82, and >82 years), mean±SD mild parkinsonian signs (MPS) scores in the lowest vs highest plasma homocysteine concentration quintile were: 1.25±1.80 vs 1.47±2.70 (17.3% difference) (<74 years), 0.59±1.73 vs 1.69±3.35 (175.3% difference) (age 74-77 years), 0.80±1.24 vs 2.28±3.68 (184.7% difference) (age 78-82 years), and 2.33±2.10 vs 3.00±4.00 (28.6% difference) (>82 years). Lowest quintiles are depicted by dashed bars and highest quintiles, by solid bars.

1.18±1.88; third quintile, 1.64±2.93; fourth quintile, 1.45±2.17; and highest quintile, 2.12±3.49 (84.3% higher than 1.15) (linear regression analysis for MPS score, β=0.022; $P=.02$ and linear regression analysis for log MPS score, β=0.025; $P=.03$). The mean±SD MPS scores in the highest vs lowest plasma Hcy concentration quintile were 2.12±3.49 vs 1.15±1.77 (84.3% difference). Within each of the 4 age strata (<74, 74-77, 78-82, and >82 years), MPS scores in the lowest vs highest plasma Hcy concentration quintile were 1.25±1.80 vs 1.47±2.70 (17.3% difference) (<74 years); 0.59±1.73 vs 1.69±3.35 (175.3% difference) (age 74-77 years); 0.80±1.24 vs 2.28±3.68 (184.7% difference) (age 78-82 years); and 2.33±2.10 vs 3.00±4.00 (28.6% difference) (>82 years) (**Figure 3**).

In an unadjusted linear regression model, plasma Hcy concentration was associated with log MPS score (dependent variable) (β=0.006; $P=.008$). In a linear regression model that adjusted for covariates that were associated with log MPS score at the $P<.10$ level (age, diabetes mellitus, heart disease, and CDR score [Table]), plasma Hcy concentration was associated with log MPS score (β=0.004; $P=.04$). In the adjusted model, 3 of the 4 covariates were also associated with log MPS score: age (β=0.011; $P<.001$), diabetes mellitus (β=0.135; $P=.001$), heart disease (β=0.006; $P=.30$), and CDR score (β=0.036; $P<.001$). In a model that adjusted simultaneously for age and CDR score as well as multiple vascular disorders (diabetes mellitus, heart disease, hypertension, and stroke), plasma Hcy concentration was associated with log MPS score (β=0.004; $P=.04$). Finally, in 4 linear regression analyses that excluded participants with each of the 4 vascular disorders (eg, analysis 1 excluded participants with diabetes mellitus and analysis 2 excluded participants with heart disease), the association between plasma Hcy concentration and log MPS score persisted (data not shown).

Besides adjusting for age in our linear regression models, we also stratified the sample based on age (<74, 74-77, 78-82, and >82 years). Within each of these 4 age strata, the β values for the association between plasma Hcy concentration and log MPS score remained unchanged, further indicating that the association was not due to the confounding effects of age.

COMMENT

We studied a group of community-dwelling elderly persons without dementia in northern Manhattan. None had PD or a Parkinson plus syndrome and none were using levodopa. Our data show that elevated plasma Hcy concentration was associated with MPS.

The mean difference in MPS score between the highest vs lowest plasma Hcy concentration quintile was 0.97 points (2.12 vs 1.15), which was an 84.3% increase. This difference is greater than the difference we have reported in the MPS scores of smokers vs nonsmokers (a 77.8% difference).[1] We have previously shown that an increase in MPS score from 1 to 2 is associated with a reduction in several functional measures (15% reduction in Active Life Expectancy Score and 10% increase in the timed chair stand test score), indicating that this small absolute difference in MPS score can have functional consequences.[8]

The mechanism that underlies the observed association is not clear but there are several possibilities. First, elevated plasma Hcy concentration could result in MPS. This could either be a direct cause or through an intermediate step (eg, vascular disease [strokes] or some other unknown factor). Arguing against strokes are our data, which suggest that vascular factors are not mediating this association. Second, MPS could result in elevated plasma Hcy concentrations. However, this scenario does not seem

biologically plausible. Third, elevated plasma Hcy concentration and MPS may be associated with one another yet one may not cause the other. For example, elevated plasma Hcy concentration and MPS could both be due to underlying vascular disease, Lewy bodies, or some other unknown factor. Possibilities 1 and 2 imply a causal connection between plasma Hcy concentrations and MPS, whereas possibility 3 suggests an association without causation (ie, elevated plasma Hcy concentrations and MPS may each be markers of a common underlying process).

Elevated plasma Hcy concentration is often viewed as a marker of cerebrovascular risk.[12] There are a variety of types of evidence for a vascular etiology for MPS. It is well known that more severe forms of parkinsonism, such as vascular parkinsonism, can occur in the setting of basal ganglia infarcts or deep white matter ischemic lesions.[24-28] With regard to normal elderly persons, there have been several epidemiological studies examining the associations between vascular risk factors or vascular disease and milder parkinsonian signs. In one study,[29] elderly individuals with rigidity and gait disturbance were compared with their counterparts without these signs, and they were more likely to have hypertension and reduced high-density lipoprotein levels. In a second study,[30] the relation between diabetes mellitus and MPS was assessed prospectively in older Catholic clergy without PD or dementia; the investigators found that diabetes was associated with progression of rigidity and gait disturbance. Finally, in a study of 2776 elderly residents of northern Manhattan enrolled between 1999 and 2001,[31] diabetes, heart disease, peripheral vascular disease, and stroke were more prevalent in participants with MPS than in those without MPS, whereas nonvascular diseases were no more prevalent; furthermore, the number of vascular diseases was associated with MPS (odds ratio, 1.31; 95% confidence interval, 1.18-1.46; $P < .001$). The combination of diabetes mellitus and heart diseases increased the odds of MPS by 70% and the combination of these with stroke increased the odds by 3-fold.[31]

Elevated plasma Hcy concentration has also been reported to occur in treated and untreated PD.[11] Hence, elevated plasma Hcy concentration may be a feature of patients with Lewy bodies. It is not known, however, to what extent MPS occur as a marker of underlying emerging Lewy bodies.

Our findings extend those of the recent French study that found that higher plasma Hcy concentrations were associated with slower walking speed.[12] While slow walking speed should not necessarily be equated with parkinsonism, patients with parkinsonism often manifest slow walking speed. In another study,[32] Hcy concentration was associated with a global measure of physical performance. That measure included a variety of tests of balance, gait, lower body strength and coordination, and manual dexterity, although not MPS per se.

Our findings raise the question as to whether MPS may be prevented by lowering plasma Hcy concentrations. Plasma Hcy concentration can be lowered with vitamin B_6, vitamin B_{12}, and folate supplementation, but results of a trial of these vitamin supplements to lower Hcy concentrations in the secondary prevention of stroke were negative.[33]

As discussed earlier, one of the potential mechanisms linking plasma Hcy concentration to MPS is cerebrovascular disease. Mean plasma Hcy concentration was 1.5 µmol/L higher in participants with a history of stroke vs those without such a history, but the difference was not significant ($P = .20$). We believe that the lack of statistical significance was due to the relatively small sample size and the use of clinical history rather than brain imaging data to ascertain cerebrovascular disease. This likely resulted in an underestimation of the true prevalence of cerebrovascular disease, thereby biasing our results toward the finding of a nonsignificant difference in plasma Hcy concentration between participants with vs without stroke. Ideally, our study should be replicated in a sample with brain imaging data to assess subclinical cerebrovascular disease.

This study had a number of limitations. First, our analyses were cross-sectional. This does not lessen the validity of the association we observed but places limitations on our ability to study its underlying mechanisms. More specifically, longitudinal analyses would have allowed us to assess whether higher plasma Hcy concentration is a risk factor for subsequent development of MPS, or conversely, whether MPS are a risk factor for subsequent development of elevated plasma Hcy concentration. Biologically, the former rather than latter explanation is more plausible but this cannot be directly addressed by the current analyses. Brain imaging studies (eg, magnetic resonance imaging) or postmortem studies would also allow one to further examine the possible biological bases (vascular vs Lewy body) for the association we observed. However, we do not have these types of data. Second, only about one-third of our sample of 1112 potential participants had had plasma Hcy concentration measurements, raising the issue of selection bias. Arguing most strongly against this is that the participants who underwent phlebotomy for Hcy concentration had been selected randomly. Furthermore, the age and educational characteristics of our final sample of 369 participants were similar to those of the initial sample of 2126. A small percentage difference in the proportion of women reached statistical significance in these large sample size comparisons. Sex, however, was not associated with our outcome variable, MPS. Women did have lower plasma Hcy concentrations (and less variance in these concentrations) than men. Hence, in a sample that was slightly enriched in women, as ours was, this lower variance in one of the primary variables (plasma Hcy concentration) may have made it more difficult for us to detect the association between Hcy concentrations and MPS. Third, our blood samples were centrifuged, aliquoted, and frozen within 2 hours rather than 30 minutes of collection. This 2-hour processing time could have resulted in elevated Hcy concentrations. However, we have no reason to suspect that processing time was differential across MPS strata. Finally, prior work has indicated that MPS comprise several discrete factors (eg, tremor, rigidity, bradykinesia).[6] While it would have been interesting to have examined the association between MPS and each of these factors, our study was not sufficiently powered for these analyses. Despite these limitations, this study is one of

few that have examined the associations between plasma Hcy concentrations and motor signs in elderly individuals. Its strengths include the population-based design, the careful assessment of MPS in several hundred elderly persons, the exclusion of participants with dementia and parkinsonism, and the adjustment for a variety of potential confounding variables.

In summary, we provide evidence of an association between MPS and elevated plasma Hcy concentrations. Prospective neuroimaging as well as clinical-pathological studies are now needed to further our understanding of mechanisms that may underlie this association.

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Author Contributions: Dr Louis had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Louis, Schupf, Marder, and Luchsinger. *Analysis and interpretation of data:* Louis, Schupf, Tang, Marder, and Luchsinger. *Drafting of the manuscript:* Louis and Luchsinger. *Critical revision of the manuscript for important intellectual content:* Louis, Schupf, Tang, Marder, and Luchsinger. *Statistical analysis:* Louis, Schupf, Tang, Marder, and Luchsinger. *Study supervision:* Schupf.
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