Myeloperoxidase Polymorphism and Cognitive Decline in Older Adults in the Health, Aging, and Body Composition Study

Sandra K. Pope\(^1\), Stephen B. Kritchevsky\(^2\), Christine Ambrosone\(^3\), Kristine Yaffe\(^4\), Frances Tylavsky\(^5\), Eleanor M. Simonsick\(^6\), Caterina Rosano\(^7\), Scott Stewart\(^8\), and Tamara Harris\(^9\) for the Health ABC Study

\(^1\) Department of Geriatrics, College of Medicine, University of Arkansas for Medical Sciences, Little Rock, AR.
\(^2\) J. Paul Sticht Center on Aging, Wake Forest University Health Sciences, School of Medicine, Winston-Salem, NC.
\(^3\) Division of Cancer Prevention and Population Science, Roswell Park Cancer Institute, Buffalo, NY.
\(^4\) Department of Psychiatry, Neurology and Epidemiology, University of California, San Francisco, San Francisco, CA.
\(^5\) Department of Preventive Medicine, University of Tennessee Health Science Center, Memphis, TN.
\(^6\) Intramural Research Program, National Institute on Aging, Bethesda, MD.
\(^7\) Department of Epidemiology, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, PA.
\(^8\) Department of Biostatistics, College of Medicine, University of Arkansas for Medical Sciences, Little Rock, AR.
\(^9\) Clinical Research Branch, National Institute on Aging, Baltimore, MD.

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Myeloperoxidase, an antimicrobial enzyme, produces oxidative free radicals. Rarely found in normal brain tissue, myeloperoxidase has been detected in microglia associated with Alzheimer’s disease plaques. The authors examined a G-463A polymorphism in the promoter region of the myeloperoxidase gene (MPO) to determine the relation of MPO variants to cognitive decline over 4 years in a cohort of adults, aged 70–79 years at baseline (1997–1998), recruited from Memphis, Tennessee, and Pittsburgh, Pennsylvania, into the Health, Aging, and Body Composition Study. In this sample, 8% of the participants had the AA, 36.9% the AG, and 55.2% the GG genotype of MPO. The frequency of AA and AG genotypes was higher in Blacks than Whites (11.2% vs. 5.9%, and 44.1% vs. 32.9%, respectively). Multivariate logistic regression analyses showed that, for participants with the MPO AA genotype, cognitive decline was 1.58 (95% confidence interval: 1.07, 2.35) times more likely than for participants with the AG genotype and 1.96 (95% confidence interval: 1.33, 2.88) times more likely than for those with the GG genotype. Interactions between MPO and race, sex, or the apolipoprotein gene were not significant. In this sample, MPO AA, associated with decreased production of myeloperoxidase, was found to be a risk factor for cognitive decline.

Abbreviations: APOE, apolipoprotein E gene; Health ABC, Health, Aging, and Body Composition; MPO, myeloperoxidase gene; 3MS, Modified Mini-Mental State Examination.

Oxidative damage is implicated in the development of Alzheimer’s disease, and activated microglia, the resident brain macrophages, are a primary source for oxidative damage. Amyloid beta deposition, one of the hallmark signs of Alzheimer’s disease, increases under oxidative conditions. Although normally quiescent, microglia activated in response...
to neuronal damage or other stimuli can cause inflammatory and immune responses that can result in further oxidative damage (1). For example, amyloid beta aggregates can stimulate microglia to phagocytose amyloid beta particles, releasing oxidizing species such as superoxide, hydroxyl radicals, hydrogen peroxide, and nitric acid (2, 3).

Myeloperoxidase is a myeloid-specific enzyme present in high levels in neutrophils, monocytes, and some classes of macrophages, including microglia (4). It is strongly antimicrobial, defending the body against bacteria by generating free radical species that promote oxidative damage (4).

Myeloperoxidase may contribute to cognitive decline and Alzheimer’s disease by producing reactive radicals. Recent research indicates that myeloperoxidase is both expressed and enzymatically active in the human brain, although the absolute levels are very low in normal brain tissue (5). However, myeloperoxidase is increased in brain tissue that exhibits the typical Alzheimer’s disease pathology of amyloid beta deposition and neurofibrillary tangles (6), and several oxidative products of myeloperoxidase are elevated in the brain tissue of persons with Alzheimer’s disease (5). Myeloperoxidase is present in some of the activated microglia in Alzheimer’s brains and appears to localize with plaques and tangles and with neuronal cells of the hippocampus. Additionally, myeloperoxidase is present in the scattered amyloid plaques and neurofibrillary tangles of normal brain tissue (5).

A functional G-463A polymorphism of the myeloperoxidase gene (MPO) (17q23) is associated with a number of diseases with inflammatory components, including Alzheimer’s disease (6). The G-463A MPO polymorphism is a G-to-A substitution in the promoter region of the gene. The more common G allele increases expression of myeloperoxidase, whereas the less common A allele decreases myeloperoxidase expression, apparently by destroying a binding site for the transcription factor (7).

Research on the relation of MPO genotypes and Alzheimer’s disease is mixed, with some studies finding that the GG genotype is associated with an increased risk for women but a decreased risk for men (6). Another study found that the GG genotypes increased Alzheimer’s disease risk for Caucasians but not Hispanics (8), while yet another found that the presence of at least one A allele and at least one apolipoprotein gene (APOE) e4 allele, the most important known genetic risk factor for late-onset Alzheimer’s disease (9), interacted to increase risk for men but not for women (10). A recent study and meta-analysis found no association of the GG genotype with risk of Alzheimer’s disease (11).

Little research has examined the prevalence of MPO alleles in a sample of healthy older adults or in a population large enough to evaluate the risk of each genotype separately. Because of small sample sizes, especially for persons with the AA genotype, all of the studies described above combined data on participants with AA or AG genotypes and compared this group with participants with the GG genotype. To our knowledge, the relation of MPO polymorphisms with cognitive decline has not been studied, nor has the prevalence of MPO genotypes in Black populations been ascertained. In this study, we examined the prevalence of MPO genotypes and the relation of the MPO genotype with cognitive decline over 4 years in a large biracial sample of older adults.

**MATERIALS AND METHODS**

**Study population**

The study participants were adults recruited into the Health, Aging, and Body Composition (Health ABC) Study in 1997 and 1998. This clinical research study, sponsored by the National Institute on Aging, is designed to increase the understanding of functional decline in well-functioning older adults. The Health ABC sample includes 3,075 Medicare-eligible adults, aged 70–79 years at baseline, and consists of approximately equal numbers of men and women; Blacks constitute 41 percent of the participants. Eligible participants were community-dwelling elders in the Memphis, Tennessee, and Pittsburgh, Pennsylvania, areas who were free of difficulties in performing basic activities of daily living, mobility limitations, and life-threatening cancer at the time of study entry. Sampling details have been described previously (12, 13). Although dementia was not a specified exclusion, all participants were functionally independent at baseline and were able to complete a comprehensive 90-minute interview at intake.

These analyses were conducted by using data for all participants enrolled in the Health ABC Study, excluding those who were 1) missing year 1 cognitive data (n = 14); 2) coded by interviewers at baseline as being illiterate (n = 50); 3) considered to have mild cognitive impairment at baseline, as defined by scoring two standard deviations below the age-education-specific means on the Modified Mini-Mental State Examination (3MS) (n = 146) (14); 4) missing APOE or MPO genotype (n = 145); or 5) missing cognitive data for both years 3 and 5 (n = 349). These exclusions resulted in a final sample of 2,350 for the analyses presented in this paper. Participants included in these analyses, compared with those who were not, were more likely to be White (64 percent vs. 40 percent), be female (53 percent vs. 47 percent), have higher baseline 3MS scores (92 vs. 84), score higher on the Rapid Assessment of Adult Literacy in Medicine (58 vs. 21), and have a high school degree or higher educational level (80 percent vs. 58 percent). There were no age differences, nor were there differences in the presence of an e4 allele in the APOE genotyping between groups. Although there were no differences in the MPO AA genotype, those participants included in analyses, compared with those excluded, were less likely to be heterozygotes (AG; 37 percent vs. 43 percent) and more likely to have the GG genotype (55 percent vs. 50 percent; p = 0.04).

**Cognitive status assessment**

Cognitive status was assessed with the 3MS at the year 1 (baseline), year 3, and year 5 clinic visits. The 3MS, a widely used measure of global cognitive function, is an expanded 100-point version of the original Folstein Mini-Mental Status Examination, designed to increase the standardization, sensitivity, and specificity of the test as a screen for dementia (15, 16). The 3MS samples a wide range of cognitive abilities.
and provides a ceiling and floor that are greater than many other standard cognitive assessments, therefore enhancing the reliability and validity of test scores. Higher scores on the 3MS indicate better cognitive function. Cognitive decline was defined as a drop of five or more points in 3MS scores from year 1 to year 5, or, if year 5 data were not available, data from years 1 and 3 were used, with a drop of five or more points from year 1 to year 3 considered cognitive decline.

To further examine the characteristics of those excluded from the analyses, we compared those excluded because they met criteria for mild cognitive impairment with those excluded for all other reasons. Findings revealed that those with mild cognitive impairment were more likely to be Black and to have at least one APOE e4 allele. However, there were no differences in the two categories of excluded participants based on MPO genotype.

**Genotyping**

All participants provided informed consent for genotyping. MPO and APOE genotyping assays were performed by BioServe Biotechnologies, Ltd. in Laurel, Maryland, on DNA extracted from blood samples collected in year 1 by using standard extraction methodology. DNA samples, including 5 percent blinded duplicates, were shipped from the central Health ABC laboratory to BioServe, and genotyping was performed by using high-throughput matrix-assisted laser desorption time-of-flight mass spectrometry (MALDI-TOF; Sequenom, Inc., San Diego, California) utilizing the MassEXTEND reaction (Sequenom). Polymerase chain reaction primers and extension primers were designed with SpectroDESIGNER software (Sequenom) and were synthesized at BioServe. Oligonucleotide sequences of the primers and probes for the assays are described in the next two paragraphs.

For MPO (RS# 2333227), forward primer AGTGTACCTGCTAGGCTAGTC, reverse primer TGAGTGTATTTTTAGTGTACAGGTTCCA, and extension primer CTGACCTCAAAGTGTACCC were used. Blind duplicate assays conducted by BioServe on 5 percent of the samples were analyzed by the Health ABC coordinating site and indicated 100 percent concordance for the MPO duplicate assays. The polymorphism was in Hardy-Weinberg equilibrium, stratified by race. MPO was examined as a tri- or dichotomous variable using all three genotypes and as a dichotomous variable with AA genotype versus GG/AG genotypes. Additionally, we examined G/G versus A/A and A/G to compare our results with those from other studies.

For APOE (RS# 429358), forward primer CTGTTGAGA- TGTGGTACAGGAGCTGGCAGGC, reverse primer AGCT- GTGTGGATGACATGGCCTGGACCTGG, and extension primer CGGCCGTGCTTTGACA were used. Blind duplicate assays conducted by BioServe on 5 percent of the samples were analyzed by the Health ABC coordinating site and indicated 100 percent concordance for the APOE duplicate assays. The polymorphism was in Hardy-Weinberg equilibrium, stratified by race. APOE was in Hardy-Weinberg equilibrium, stratified by race. Participants were categorized according to the presence or absence of an e4 allele.

**Other participant characteristics**

In addition to study site (Pittsburgh vs. Memphis), participant characteristics used in these analyses included age as a continuous variable (range, 70–79 years at baseline), sex, race (Black vs. White), and education (<high school graduate, high school graduate, postgraduate education), all of which were determined through self-report. Literacy was evaluated with the Rapid Estimate of Adult Literacy in Medicine, an assessment of reading level, with higher scores indicating higher literacy (17). Baseline 3MS score was included to control for initial cognitive status.

Self-reported smoking and alcohol drinking were assessed at baseline and were categorized as never, former, and current. Lipid variables examined included high density lipoprotein cholesterol, low density lipoprotein cholesterol, triglycerides, and total cholesterol, all of which were measured in milligrams per deciliter. These assays were conducted on serum collected at the year 1 clinical visit.

Body mass index was calculated as weight in kilograms divided by height in meters squared. Cerebrovascular disease was determined by self-report of transient ischemic attack, stroke, or carotid endarterectomy. Heart disease was determined by self-report or use of antiangiogenesis medication. Diabetes was determined by self-report of use of diabetes medication.

**Statistical analyses**

We used chi-square analyses to compare the prevalence of MPO genotypes (A/A, A/G, G/G) stratified by race. The bivariate relations between cognitive decline, MPO genotype, and other variables were examined by using chi-square tests, t tests, and analyses of variance for the entire sample and were stratified by race. The required assumptions for the analyses of variance were tested by using Levene’s test (homogeneity of variance) and the Shapiro-Wilk test (normality) (18).

Unconditional logistic regression analyses examined the independent relation between cognitive decline (yes/no) and MPO genotype, controlling for potential confounding effects of other variables in the model. We computed unadjusted and adjusted odds ratios and corresponding 95 percent confidence intervals for cognitive decline relative to each genotype. To determine which variables to include in the multivariate regression model, we examined the bivariate relation of each potential predictor variable with the bivariate measure cognitive decline and included only those variables significant at the two-sided p < 0.25 level and those shown in scientific literature to be associated with either cognitive decline or myeloperoxidase production. Two-way interactions were then examined with cross-product terms, and, for continuous variables, linearity in the logit assumption was assessed by using the quartile method.

**RESULTS**

Of the 2,350 Health ABC participants included in these analyses, 2,081 had year 5 cognitive data; for the other 269, year 3 cognitive data were used since these participants did
not have a year 5 clinical assessment. All analyses were repeated by including and excluding the 269 adults with cognitive data for only years 1 and 3. Because the results were very similar, we show analyses for the combined cohort of 2,350 participants in the remainder of this paper.

Sample characteristics are shown in table 1. Slightly over half of the participants were female, the average age was 73.6 years, and participants had an average of 13.3 years of education. At the baseline assessment, almost half of the participants reported being former smokers (46.6 percent), with 8.5 percent reporting current smoking; 20.4 percent reported former alcohol drinking, with 51.6 percent reporting current drinking. Body mass index (weight (kg)/height (m)²) averaged 27.3. Diabetes was reported by 14.2 percent, definite or possible cerebrovascular disease was reported by 7.3 percent, and definite or possible heart disease was reported by 19.5 percent of study participants. The average baseline score on the 3MS was 91.8 points and on the Rapid Estimate of Adult Literacy in Medicine was 61.4 points. For more than 21.1 percent of the participants, their 3MS scores indicated cognitive decline. At least one e4 allele of the APOE gene was detected in 28.2 percent of the participants.

Stratification by race revealed that, in this study sample, Blacks were more likely than Whites to be female and to have lower educational attainment. Whites were more likely to drink and less likely to smoke than Blacks. Compared with Whites, Blacks had higher body mass index scores and higher high density lipoprotein cholesterol and low density lipoprotein cholesterol levels. However, Whites had higher triglyceride levels. Blacks were more likely to have at least one APOE e4 allele and to report diabetes, heart disease, and cerebrovascular disease. Compared with Whites, Blacks were also more likely to have lower baseline 3MS and Rapid Estimate of Adult Literacy in Medicine scores, as well as more cognitive decline.

The distribution of MPO genotypes in the Health ABC participants is shown in table 2. Almost 8 percent had the AA, 37.0 percent the AG, and 55.2 percent the GG genotype. The frequencies of the AA and AG genotypes were higher in Blacks than in Whites (AA: 11.2 percent vs. 5.9 percent; AG: 44.1 percent vs. 32.9 percent, respectively). To determine whether participant characteristics differed by MPO genotype, other than the differences in MPO distribution between Blacks and White, bivariate analyses were conducted, controlling for race. Results indicated no differences in any of the other variables examined, including gender, age, education, health conditions, baseline 3MS score, literacy, and APOE e4 status.

Bivariate analyses of MPO genotype and cognitive decline revealed that 31.5 percent of participants with the AA genotype had experienced cognitive decline, compared with 23.3 percent of those with the AG and 18.2 percent of those with the GG genotypes (p < 0.0001). This finding resulted in an unadjusted odds ratio of 2.07 (95 percent confidence interval: 1.47, 2.92) for cognitive decline when we compared

### Table 1. Sample characteristics of participants included in analyses of myeloperoxidase polymorphism and cognitive decline, stratified by race: Health, Aging, and Body Composition Study, Pennsylvania and Tennessee, 1997–2003

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total sample</th>
<th>Whites (n = 1,502)</th>
<th>Blacks (n = 848)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex: female*</td>
<td>52.9</td>
<td>48.4</td>
<td>60.7</td>
</tr>
<tr>
<td>Age (years)</td>
<td>73.6 (2.9)</td>
<td>73.7 (2.8)</td>
<td>73.5 (2.9)</td>
</tr>
<tr>
<td>Education (years)*</td>
<td>13.3 (3.0)</td>
<td>14.1 (2.5)</td>
<td>12.1 (3.3)</td>
</tr>
<tr>
<td>Smoker*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Former</td>
<td>46.6</td>
<td>49.7</td>
<td>40.9</td>
</tr>
<tr>
<td>Current</td>
<td>8.5</td>
<td>5.4</td>
<td>14.1</td>
</tr>
<tr>
<td>Alcohol drinker*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Former</td>
<td>20.4</td>
<td>15.6</td>
<td>28.7</td>
</tr>
<tr>
<td>Current</td>
<td>51.6</td>
<td>59.4</td>
<td>37.8</td>
</tr>
<tr>
<td>Body mass index (weight (kg)/height (m)²)*</td>
<td>27.3 (4.7)</td>
<td>26.6 (4.1)</td>
<td>28.7 (5.3)</td>
</tr>
<tr>
<td>High density lipoprotein cholesterol (mg/dl)*</td>
<td>54.1 (17.2)</td>
<td>52.7 (16.2)</td>
<td>57.4 (17.8)</td>
</tr>
<tr>
<td>Low density lipoprotein cholesterol (mg/dl)*</td>
<td>121.7 (34.5)</td>
<td>120.1 (33.4)</td>
<td>124.3 (36.2)</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)*</td>
<td>140.5 (84.7)</td>
<td>152.9 (87.4)</td>
<td>118.4 (74.7)</td>
</tr>
<tr>
<td>Diabetes*</td>
<td>14.2</td>
<td>10.5</td>
<td>20.7</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Definite</td>
<td>6.7</td>
<td>5.9</td>
<td>8.1</td>
</tr>
<tr>
<td>Possible</td>
<td>0.6</td>
<td>0.9</td>
<td>0.2</td>
</tr>
<tr>
<td>Heart disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Definite</td>
<td>16.0</td>
<td>16.9</td>
<td>14.3</td>
</tr>
<tr>
<td>Possible</td>
<td>3.5</td>
<td>2.8</td>
<td>4.9</td>
</tr>
<tr>
<td>Presence of the APOE e4 allele*</td>
<td>28.2</td>
<td>24.0</td>
<td>35.6</td>
</tr>
<tr>
<td>Baseline 3MS score*</td>
<td>91.8 (6.2)</td>
<td>93.5 (4.9)</td>
<td>88.8 (7.1)</td>
</tr>
<tr>
<td>REALM score*</td>
<td>61.4 (9.5)</td>
<td>63.9 (4.7)</td>
<td>56.6 (13.5)</td>
</tr>
<tr>
<td>Cognitive decline*</td>
<td>21.1</td>
<td>15.9</td>
<td>30.4</td>
</tr>
</tbody>
</table>

* p < 0.001.
† Values are expressed as either percent or mean (standard deviation).
‡ APOE: apolipoprotein E gene; 3MS, Modified Mini-Mental State Examination; REALM, Rapid Estimate of Adult Literacy in Medicine.
participants with the AA genotype with those with the GG genotype and an unadjusted odds ratio of 1.52 (95 percent confidence interval: 1.07, 2.15) when we compared participants with the AG genotype with those with the GG genotype.

In logistic regression analyses controlling for site, race, age, education, baseline 3MS score, literacy, diabetes, and APOE e4 status, cognitive decline was 1.96 (95 percent confidence interval: 1.33, 2.88) times more likely in participants with the MPO AA genotype compared with the GG genotype and 1.58 (95 percent confidence interval: 1.07, 2.35) times more likely in those with the MPO AA genotype compared with the AG genotype (table 3). The interactions between MPO and race, MPO and sex, and MPO and APOE were not significant.

Three sensitivity analyses were conducted: 1) excluding all those for whom year 5 cognitive data were missing; 2) excluding participants scoring below 80 on the 3MS rather than two standard deviations below the age-education-adjusted 3MS norms; and 3) not excluding participants scoring two standard deviations below the age-education-adjusted means on the 3MS. All three analyses produced very similar results, and the findings regarding the relation between MPO genotypes and cognitive decline were almost identical.

DISCUSSION

This study provides evidence of an association between the MPO AA genotype and cognitive decline in older Black adults and White adults enrolled in the Health ABC Study. This finding differs from those in some of the studies of patients with Alzheimer’s disease, where either the G allele has been found to increase the risk of Alzheimer’s disease or no association between MPO and Alzheimer’s disease was identified (11, 19). A small European study by Reynolds et al. (6) of 69 Alzheimer’s disease cases and controls who were autopsied found that the GG genotype, compared with the GA or AA genotype, increased the risk of Alzheimer’s disease for women but decreased the risk for men. Crawford et al. (8) found that the GG genotype increased the risk of Alzheimer’s disease 1.57 times for Caucasians (n = 392), whereas there was no effect of the MPO genotype on Alzheimer’s disease for Hispanics (n = 134). A recent study and a meta-analysis of several studies showed no association of the GG genotype with Alzheimer’s disease (11).

However, other studies have shown increased risk for the MPO A allele. A second study by Reynolds et al. (10) of 301 Finnish Alzheimer’s disease patients and controls indicated that the MPO A allele was associated with increased risk of Alzheimer’s disease in Finnish men with an APOE e4 allele, but not in women. The ApoEurope study found that the MPO A allele was associated with increased risk of Alzheimer’s disease in European women but not in men (20). Finally, a study of recovery from brain infarction found that the A allele was associated with poorer functional short-term outcome from brain infarction (21).

Numerous explanations are possible for the discrepant findings between the studies of persons with Alzheimer’s disease, including differences in selection criteria for study populations, differences in gender distribution between case and control groups, genetic differences between populations, and lack of statistical power (20). One study is of autopsy samples of Caucasians and Hispanics (6). One of the cohort studies is of Caucasians in Finland (10), whereas another is of Hispanics and Caucasians in Florida (8). Differing ages between cohorts is of note because a Finnish study found that the MPO AA genotype reduced male life expectancy (10); thus, the AA genotype may be depleted in men of advanced age. Many studies of MPO and Alzheimer’s disease are conducted in samples that are largely female, and in some studies the gender distribution of cases is quite different from that of controls (22). Furthermore, many studies do not include a large enough sample to stratify participants by all three genotypes, and therefore comparisons are often made between AA and AG combined versus GG genotypes. Most studies lack sufficient power to stratify by race.

Although this study examined cognitive decline rather than diagnosed Alzheimer’s disease, and adults with cognitive decline may or may not later develop Alzheimer’s disease, the risk factors for the two conditions may be similar. It is projected that each year, approximately 5 percent of those experiencing cognitive decline will advance to a diagnosis of Alzheimer’s disease (23). Cognitive decline and Alzheimer’s disease may represent a continuum of disease or they may partially overlap, but it is apparent that both conditions are complex, with additional risk factors being uncovered (24).

Since expression of myeloperoxidase is decreased with age, education baseline 3MS score, literacy, diabetes, and APOE e4 status, cognitive decline was 1.96 (95 percent confidence interval: 1.33, 2.88) times more likely in those with the MPO AA genotype compared with the AG genotype (table 3). The interactions between MPO and race, MPO and sex, and MPO and APOE were not significant.

Three sensitivity analyses were conducted: 1) excluding all those for whom year 5 cognitive data were missing; 2) excluding participants scoring below 80 on the 3MS rather than two standard deviations below the age-education-adjusted 3MS norms; and 3) not excluding participants scoring two standard deviations below the age-education-adjusted means on the 3MS. All three analyses produced very similar results, and the findings regarding the relation between MPO genotypes and cognitive decline were almost identical.

TABLE 3. Adjusted odds ratios* and 95% confidence intervals for cognitive decline in cohort participants (N = 2,350): Health, Aging, and Body Composition Study, Pennsylvania and Tennessee, 1997–2003

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Adjusted odds ratio</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Race: Black vs. White</td>
<td>1.88</td>
<td>1.45, 2.43</td>
</tr>
<tr>
<td>Sex: female vs. male</td>
<td>1.06</td>
<td>0.65, 1.34</td>
</tr>
<tr>
<td>Age: per year of age</td>
<td>1.09</td>
<td>1.05, 1.13</td>
</tr>
<tr>
<td>Education</td>
<td>1.69</td>
<td>1.29, 2.21</td>
</tr>
<tr>
<td>High school vs. postgraduate</td>
<td>2.74</td>
<td>1.96, 3.84</td>
</tr>
<tr>
<td>Diabetes (yes vs. no)</td>
<td>1.35</td>
<td>1.00, 1.82</td>
</tr>
<tr>
<td>Baseline 3MS† score</td>
<td>1.06</td>
<td>1.04, 1.09</td>
</tr>
<tr>
<td>REALM† score</td>
<td>0.97</td>
<td>0.96, 0.99</td>
</tr>
<tr>
<td>APOE† allele: e4 vs. others</td>
<td>1.61</td>
<td>1.27, 2.04</td>
</tr>
<tr>
<td>MPO‡ genotype</td>
<td>1.58</td>
<td>1.07, 2.35</td>
</tr>
<tr>
<td>A/A vs. A/G</td>
<td>1.96</td>
<td>1.33, 2.88</td>
</tr>
</tbody>
</table>

* All odds ratios were adjusted for site plus all other variables in this table.
† 3MS, Modified Mini-Mental State Examination; REALM, Rapid Estimate of Adult Literacy in Medicine; APOE, apolipoprotein E gene; MPO, myeloperoxidase gene.
decline may represent a more systemic aspect of the disease process than is seen when autopsied brains of Alzheimer’s disease patients are examined. Reduced myeloperoxidase activity may indicate a deficit of host protection against oxidative damage, whereas once Alzheimer’s disease pathology begins, the affinity of both amyloid plaques and neurofibrillary tangles for negatively charged glycoproteins may in turn interact with whatever myeloperoxidase is present to promote further protein oxidation (25).

Not normally detected in microglia of normal brain tissue, myeloperoxidase has been demonstrated in microglia associated with Alzheimer’s disease plaques (8). In addition, myeloperoxidase oxidizes APOE in vitro (20), which may impair the ability of APOE to bind to phospholipids in the brain and add to impaired brain lipid recycling. Although it is unclear how myeloperoxidase levels in serum relate to levels in the brain, we know that myeloperoxidase concentration in serum is not determined solely by genetics. Other factors, such as age, smoking, and oral contraception use, affect myeloperoxidase production, and the actual percentage of concentration variability explained by genetics may be small (21). Additionally, the A allele of MPO has been found to be associated with increased levels of several lipid parameters, such as total cholesterol, low density lipoprotein cholesterol, and triglyceride levels, all of which are risk factors for atherosclerosis and other vascular diseases (21). To complicate things further, genetic and environmental factors probably interact to affect serum concentrations.

The large sample size of the Health ABC Study provides prevalence estimates of the AA, AG, and GG genotypes in Blacks and Whites. The prevalence rates observed in this study are similar to what has been found in other studies for similar healthy populations (60.3 percent, 34.2 percent, and 5.5 percent for GG, AG, and AA, respectively). For example, prevalence rates for controls in the ApoEurope Study were 63.8 percent, 34.6 percent, and 2.0 percent for GG, AG, and AA, respectively (20). Other studies of MPO in Black populations indicate that up to 15 percent of Blacks have the AA genotype, which is similar to our finding of 10.2 percent.

A few study limitations merit consideration. The definition of cognitive decline was based on the 3MS, which does not examine cognitive function in depth, nor was it designed to capture cognitive change. This possibility of a ceiling effect for highly functioning adults cannot be ruled out, which limits interpretability of cognitive change scores in this population. However, feasibility issues in large studies such as this one necessitate use of a simple screener, such as the 3MS, and utilization of a screener that is relatively insensitive for measuring cognitive changes and that has potential ceiling effects biases the results toward the null hypothesis. Additionally, cognitive data were not available on about 20 percent of the Health ABC cohort, and participants who completed the year 5 assessment were more likely to be White, be female, be younger, have higher 3MS scores, and be more educated than those who did not attend the clinic visit. However, there were no differences in MPO or APOE genotypes among those with and without cognitive change data.

This study suggests that the AA allele, which decreases expression of myeloperoxidase, is a risk factor for cognitive decline in a cohort of Black adults and White adults who were healthy at baseline. The relation between the genotypes and actual myeloperoxidase expression during the disease process will provide valuable information for determining the role of the polymorphism in disease development and progression as well as for examining the interactions between MPO and environmental and behavioral factors. Further studies of inflammatory cytokines, oxidative stress measures, and genetic polymorphisms are needed to help confirm and explain these relations.

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