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Mild Parkinsonian Signs are Associated with Lower Olfactory Test Scores in the Community-dwelling Elderly

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Abstract

Background—Mild Parkinsonian signs (MPS, impaired gait, rigidity, bradykinesia, rest tremor) are commonly found during the clinical examination of older people and may be a precursor to Parkinson's disease (PD) or Alzheimer's disease (AD). Marked deficits in olfaction occur in PD and AD.

Objective—To determine whether University of Pennsylvania Smell Test (UPSIT) scores were lower in non-demented community-dwelling elderly with vs. without MPS.

Methods—Non-demented persons age ≥65 years without PD in Washington Heights-Inwood, NY were evaluated with an abbreviated motor Unified Parkinson's Disease Rating Scale and a 40-item UPSIT. Lower UPSIT and higher transformed UPSIT score (square root [UPSIT — 41]) indicated greater olfactory dysfunction.

Results—One-hundred-seventy-seven (16.4%) of 1,078 participants had MPS. Mean UPSIT scores (MPS vs. without MPS) were 24.3±7.1 vs. 26.4±6.8, $p < 0.001$. In a logistic regression analysis adjusting for age and education, transformed UPSIT score was associated with MPS (OR 1.25, 95% CI 1.04 – 1.52, $p = 0.02$). In an adjusted logistic regression analysis, participants with higher transformed UPSIT scores (based on a median split) were 1.55 times more likely to have MPS than were those with lower scores ($p = 0.01$). Within transformed UPSIT score quartiles, the odds of having MPS were 1.0 (reference), 1.35, 2.02, and 2.20 ($p < 0.05$). The association with transformed UPSIT scores was similar across MPS sub-types (axial dysfunction, rigidity, tremor).

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Conclusions—MPS were associated with a mild reduction in olfactory function. These observations further support the view of MPS as a marker of emerging degenerative brain pathologies.

Keywords

Mild parkinsonian signs; olfaction; elderly; population; epidemiology

Introduction

Deficits in odor identification (i.e., lower University of Pennsylvania Smell Test [UPSIT] scores[1]) have been observed in patients with Parkinson's disease (PD)[2,3] and Alzheimer's disease (AD).[4-7] The olfactory deficit in both disorders occurs early in the disease process.[2,4,7]

Mild Parkinsonian signs (MPS) are commonly found during the clinical examination of otherwise normal older people, with the most common of these being impaired gait and balance, followed by rigidity and bradykinesia, and least commonly rest tremor.[8-12] MPS, which may be defined as the mild presence of at least two cardinal signs or the moderate presence of one sign, are associated with functional disability,[13,14] and increased risks for dementia and mortality.[9,12,15] The mechanistic basis for MPS is not clear; however, MPS may represent the early development of neurodegenerative (Lewy body or Alzheimer's type) pathologies in the basal ganglia.[16] Given this possibility, and that PD and AD are associated with olfactory dysfunction, it seemed logical to also examine UPSIT scores in persons with MPS. We studied a sample of non-demented elderly persons living in Washington Heights-Inwood, New York and hypothesized that UPSIT scores would be slightly lower in the elderly with MPS vs. without MPS. If so, this would further support the notion of MPS as an early marker of emerging degenerative brain pathologies.

Methods

Study Population

Study participants were drawn by random sampling of healthy Medicare beneficiaries aged ≥65 years, and resided within a geographically-defined area of northern Manhattan, New York.[17] The cohort represents a combination of continuing members of a cohort originally recruited in 1992 and members of a new cohort recruited between 1999 and 2001; approximately one-quarter of the sample was from the original 1992 cohort and three-quarters from the new cohort. Recruitment of all participants was initially achieved by contacting a stratified random sample of 50% of all persons age 65 years and older obtained from the Health Care Finance Administration (CMS: Center for Medicare Services).[17] As of February 23, 2007, data were available on 1,511 participants who were evaluated between 2004 and 2006 (for the original 1992 cohort this represented their fifth follow-up assessment and for the new cohort this represented their third follow-up assessment).[17] This assessment was chosen for these analyses because it was during this assessment that the UPSIT was administered.

A trained research assistant administered a structured interview of health. Each participant also underwent a standardized neurological examination, which included an abbreviated (ten-item) version of the motor portion of the Unified Parkinson's Disease Rating Scale (UPDRS).[18] We assigned a diagnosis of PD or Parkinson Plus syndrome based on research criteria[19] and participants were considered to have PD or Parkinson Plus syndrome if (1) they had previously received these diagnoses, or (2) they had two or more cardinal signs of parkinsonism (UPDRS rating was ≥ 2) on the standardized neurological examination. Seventeen (1.1%) participants had a diagnosis of PD or Parkinson Plus syndrome, which is consistent with the reported

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prevalence of PD in persons ≥65 years of age in northern Manhattan.[20] These 17 participants were excluded. The study was approved by our Institution's Internal Review Board and written consent was obtained from all participants.

Neurological Evaluation

The ten-item version of the motor portion of the UPDRS included evaluations of speech, facial expression, tremor at rest (in any body region), rigidity (rated separately in the neck and each limb), changes in posture, and body (axial) bradykinesia.[17] Each of the ten items was rated from 0 – 4 (total MPS score = 0 – 40). The general medical doctors who administered the modified motor portion of the UPDRS were trained using a structured protocol.[17] Inter-rater reliability of their ratings was in the substantial to excellent range (weighted kappa statistics for ratings of speech, facial expression, tremor at rest, posture, and axial bradykinesia = 0.65 - 0.90) and agreement (percent concordance) with a movement disorder neurologist's ratings (E.D.L.) was 79%.[17]

As in previous analyses,[17] MPS were defined as present when any one of the following conditions was met: (1) two or more UPDRS ratings = 1 or (2) one UPDRS rating ≥ 2 or (3) the UPDRS rest tremor rating = 1. Based on a factor analysis, MPS was stratified into three MPS subscores: axial function (changes in speech, facial expression, changes in posture, and axial bradykinesia), rigidity, and tremor.[11,17] An abnormality in axial function was considered present when the participants had either: (1) UPDRS ratings = 1 in two or more items assessing axial function or (2) one UPDRS axial function rating ≥ 2. Rigidity was considered present when the participants had either: (1) UPDRS ratings = 1 in two or more items assessing rigidity or (2) one UPDRS rigidity rating ≥ 2. Tremor was considered present when the participants had a UPDRS rest tremor rating = 1.[17]

All participants underwent a standardized neuropsychological battery[21] designed to assess cognitive functions that are typically affected in dementia[21] and including measures of learning and memory, orientation, abstract reasoning, language, and visuospatial ability. Participants were considered demented if they met established criteria,[22] and the 213 participants who met inclusion criteria for dementia were excluded.

Depressive symptoms were assessed with a 9-item version of the Center for Epidemiological Study Depression (CESD) scale,[25] in which individuals reported symptoms of depression (0 [no depressive symptoms] - 9 [maximal depressive symptoms]). Based on a previously established cut point,[26] a score of 4 or higher was coded as depressed.

Olfactory Testing

Odor identification testing was performed with the UPSIT (Sensonics Inc., Haddon Heights NJ) in which 40 microencapsulated odors were presented using a four-item forced choice word format.[1-3] Testing was not performed if participants had active upper respiratory tract infections or allergies. The UPSIT is highly reliable[1] and sensitive to a variety of olfactory deficits. The scores range from 0 to 40 (all odors correctly identified).[1]

Final Sample

There were 1,511 participants (mean age = 81.6 ± 6.3 years, 1,062 [70.3%] women, 432 [28.6%] white, mean education = 10.1 ± 4.9 years). We excluded 213 participants with dementia (mean UPSIT score = 17.8 ± 6.5), 17 with PD (mean UPSIT score = 19.1 ± 6.5), 13 with incomplete MPS evaluations, and 190 without UPSIT evaluations. This left 1,078 participants in our final sample (mean age = 80.6 ± 5.7 years, 741 [68.7%] women, 340 [31.5%] white, mean education = 10.8 ± 4.7 years). None of the 1,078 participants in our final sample had dementia or PD or was taking a neuroleptic medication.

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Statistical Analyses

Analyses on these 1,078 non-demented participants were conducted in SPSS Version 15.0. Chi-square (χ^2) and t tests were used. The UPSIT score was not normally distributed (Kolmogorov-Smirnov $z = 2.52$, $p < 0.001$). In an initial analysis, we compared UPSIT scores in participants with vs. without MPS using a Mann-Whitney test. We also created UPSIT score quartiles, with each quartile comprised of approximately 25% of participants. The quartiles were ≤ 22, 23 – 27, 28 – 31, and 32 – 40. We then used the published formula (41 - UPSIT), which has been suggested for analysis of UPSIT data.[25] While some authors further log transform this score, in this sample, the square root of this score better normalized the distribution of UPSIT scores than did the log transformation. Hence, we used the formula *square root (41 — UPSIT)*, referring to this as the transformed UPSIT score. While a lower UPSIT score was indicative of greater olfactory dysfunction, a higher transformed UPSIT score was indicative of greater olfactory dysfunction.

In unadjusted logistic regression analyses, MPS was the dependent variable (present vs. absent) and transformed UPSIT score was the independent variable; this yielded odds ratios (OR) with 95% Confidence Intervals (CIs). MPS was treated as a binary variable rather than a continuous measure because the total MPS score was 0 in 822 (76.3%) of 1,078 participants and, even after log transformation, was not normally distributed; hence use of this continuous measure would have violated one of the assumptions of linear regression modeling. We then considered possible covariates that could be confounders: age in years, gender, race (white, African-American, Hispanic, other), years of education, Blessed score (as a measure of general cognitive function),[26] cigarette smoker (ever vs. never), current cigarette smoker (yes vs. no) and depression (based on CESD score). These analyses identified two variables (age and education) that were possible confounders because they were associated both with MPS score and transformed UPSIT scores. In adjusted logistic regression analyses, we then controlled for age and education. In addition, we identified three variables (gender, Blessed score, ever smoker) that were associated either with MPS or transformed UPSIT scores. In additional adjusted models, we considered these covariates as well. In one analysis, we also adjusted for a greater number of memory measures (i.e., an index comprised of six items: total recall, long term recall, delayed recall, long term storage, consistent ling-term retrieval, and delayed recognition) and, in another analysis, for the 15-item Boston Naming Test.[27] In several analyses, we stratified the transformed UPSIT score into higher vs. lower scores (based on the median score) and also into quartiles. The association between MPS and quartiles of transformed UPSIT score was assessed with a linear test for trend (i.e., a logistic regression analysis in which quartile was treated as a continuous variable rather than as a categorical variable). Also, we examined the associations between presence of MPS subtypes (axial dysfunction, rigidity, and tremor) and transformed UPSIT scores.

Results

MPS were present in 177 (16.4%) of 1,078 participants, who were older, had marginally fewer years of education and were marginally more likely to have been smokers (ever) than the 901 participants without MPS (Table 1).

Poorer olfaction (higher transformed UPSIT score) was associated with greater age in years (Spearman's rho = 0.25, $p < 0.001$), male gender (men = 3.96 ± 0.93, women = 3.67 ± 0.89, $t = 4.83$, $p < 0.001$), fewer years of education (Spearman's rho = -0.18, $p < 0.001$), and higher Blessed score (Spearman's rho = 0.25, $p < 0.001$), but not with smoking (ever vs. never), smoking (current yes vs. no), depression, or race.

The mean UPSIT score was 24.3 ± 7.1 in participants with MPS vs. 26.4 ± 6.8 in participants without MPS (Mann Whitney $z = 3.80$, $p < 0.001$)(Table 1) and total MPS score was inversely

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associated with the UPSIT score (Spearman's rho = -0.13, $p < 0.001$). The mean UPSIT score in participants with MPS was higher than that of the 17 participants with PD who had been excluded (Mann Whitney z = 2.69, p = 0.007). In one analysis, in addition to excluding 17 participants with PD, we further excluded 5% of participants with the highest MPS scores, to address the possibility that conceivably we may have failed to diagnose PD in some of our participants with MPS; in the remaining participants, the mean UPSIT scores were 24.1 ± 7.3 (MPS) vs. 26.4 ± 6.8 (without MPS)(Mann Whitney z = 3.44, p = 0.001). The UPSIT score was also divided into quartiles. Participants with MPS differed from those without MPS with regard to their distribution within these four quartiles ($X^2 = 15.78$, $p = 0.001$). More participants with MPS (66.7%) than without MPS (5.13%) were in the lower two UPSIT score quartiles ($X^2 = 14.10$, $p < 0.001$). Similarly, 36.2% of participants with MPS were in the lowest quartile vs. 26.4% of participants without MPS ($X^2 = 6.96$, $p = 0.008$).

In an unadjusted logistic regression analysis, transformed UPSIT score was associated with MPS (dependent variable): OR = 1.40, 95% CI = 1.17 – 1.68, $p < 0.001$)(i.e., with each one point increase in the transformed UPSIT score [declining olfaction], the odds of MPS increased by 40%). In a model that adjusted for age and education, OR = 1.25, 95% CI = 1.04 – 1.52, p = 0.02. In a model that adjusted for age, education, gender, Blessed score, and ever smoker, OR = 1.22, 95% CI = 1.00 – 1.48, p = 0.05. Also, adjusting for current cigarette use (yes. vs. no) did not change the results. Although history of diabetes mellitus, hypertension, peripheral vascular disease, and stroke were not associated with UPSIT scores, diabetes (p = 0.07), peripheral vascular disease ($p < 0.001$) and stroke ($p < 0.001$) were more prevalent in participants with than without MPS; when these three variables were placed in a model that also adjusted for age and education, OR = 1.27, 95% CI = 1.04 – 1.54, p = 0.017. In addition to excluding participants with dementia and then further adjusting for Blessed score, we took several additional steps to control for cognition. First, we adjusted for a greater number of memory measures (i.e., an index comprised of six items: total recall, long term recall, delayed recall, long term storage, consistent ling-term retrieval, and delayed recognition) along with age and education, and OR = 1.23, 95% CI = 1.01 – 1.50, p = 0.038. Second, after adjusting for the 15-item Boston Naming Test, which is a specific measure of naming, along with age and education, OR = 1.22, 95% CI = 1.01 – 1.49, p = 0.04).

We stratified the transformed UPSIT score into higher (at or above the median) vs. lower (below the median) scores and, in an unadjusted logistic regression analysis, participants with a higher transformed UPSIT score (i.e., poorer olfaction) were 1.84 times more likely to have MPS than were those with a lower score ($p < 0.001$, Table 2). In a model that adjusted for age and education, participants with a higher transformed UPSIT score were 1.55 times more likely to have MPS than were those with a lower score (p = 0.01, Table 2). In a model that further adjusted for age, education, gender, Blessed score, and ever smoker, OR = 1.46, 95% CI = 1.03 – 2.08, p = 0.03.

We also stratified the transformed UPSIT score into quartiles and, in an unadjusted logistic regression analysis, participants in the highest transformed UPSIT score quartile (i.e., poorest olfaction quartile) were 2.20 times more likely to have MPS than were those in the lowest transformed UPSIT score quartile (p = 0.001, Table 2). Also, there was a dose-effect, with each successive transformed UPSIT score quartile having a higher odds of MPS than the prior quartile (1.0 [reference], 1.35 [second quartile], 2.02 [third quartile], 2.20 [fourth quartile], linear test for trend $p < 0.001$, Table 2). Analyses that adjusted for age and education yielded similar results (Table 2), as did analyses that further adjusted for gender, Blessed score, and ever smoker.

The association with transformed UPSIT scores seemed to be similar across sub-types of MPS (axial dysfunction, rigidity, tremor, Table 3).

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Discussion

The non-demented community-dwelling elderly with MPS had poorer olfaction (i.e., lower UPSIT scores and higher transformed UPSIT scores) than did their counterparts without MPS. The association seemed to be similar for each MPS subtype (i.e., axial dysfunction, rigidity, tremor). Furthermore, when transformed UPSIT scores were stratified into quartiles, there was a dose-effect, with successive quartiles (i.e., poorer olfaction) having higher odds of MPS than did prior quartiles.

Marked deficits in olfaction occur in PD and AD. Published data suggest that MPS may be a precursor to AD or PD, although the mechanistic basis of MPS is not well understood.[12,16,17,28] It therefore seemed logical to also examine UPSIT scores in persons with MPS. We confirmed our hypothesis that UPSIT scores would be mildly yet significantly reduced in the elderly with vs. without MPS. This observation adds to our knowledge of the clinical correlates of MPS and serves as additional support for the view that MPS may be an early marker of emerging degenerative brain pathologies.

In PD a severe olfactory deficit occurs early in the disease process.[1] Ross et al.[29] recently reported that olfactory dysfunction is associated with incidental Lewy bodies in the elderly; in that study, the elderly with incidental Lewy bodies had lower UPSIT scores than those without incidental Lewy bodies. Mean UPSIT scores in patients with PD are often in the range of 20 - 21,[2,3] with the majority (approximately 70%) scoring below 24.[2] Our excluded PD cases similarly had low scores.

Deficits in olfaction also have been observed in AD[4-7] and early in the disease process.[2,4,7] Patients with mild cognitive impairment were examined prospectively in one study; baseline UPSIT scores among those who converted to AD were 26.1 ± 8.0 compared with 33.0 ± 4.7 among those who had not converted,[5] suggesting that an olfactory deficit appears early in AD, probably as a result of neurofibrillary tangles and amyloid plaques, which have been observed in the olfactory epithelium, olfactory bulb, entorhinal cortex and amygdala.[30-32] In the Rush Memory and Aging Project,[33] odor identification was inversely associated with a composite measure of plaques and tangles in persons of old age.

MPS are progressive and they are associated with a variety of adverse health outcomes, including neurological diseases, after controlling for age.[8-10,12-14,16,17,28] The current data are one further indicator that MPS represent more than a non-specific, non-neurological marker of aging.

Our data should not be over-interpreted. While UPSIT scores in the lowest quartile (≤ 22) occurred in approximately one-third of participants with MPS, they also occurred in 26.4% of elderly participants without MPS. It is not clear that a low UPSIT score in an elderly person with MPS is necessarily a harbinger of early PD or AD in that person (i.e., its diagnostic value in this setting remains uncertain).

One issue is whether some of the participants with MPS actually had PD (i.e., diagnostic mis-classification). While this is possible, each of these individuals, examined by a trained physician who administered the motor portion of the UPDRS, did not meet diagnostic criteria for PD (two or more cardinal signs of PD). Second, the prevalence of PD that we observed in our cohort was similar to the expected prevalence of PD in northern Manhattan[20] and in other elderly population-based samples (i.e., approximately 1%),[34] indicating that it is unlikely that we failed to diagnose/detect very many cases of PD. Finally, even when we further excluded the 5% of participants with the highest MPS scores (thereby assuming a prevalence of PD > 6%), participants with MPS had lower UPSIT scores than did those without MPS.

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One limitation of these analyses is that they were cross-sectional. Longitudinal follow-up of our participants is planned in future years, so we will be able to determine whether lower UPSIT score in combination with MPS increases the risk of developing incident PD or AD. In addition, while we excluded participants with active upper respiratory infections and allergies, we did not perform a thorough nasal evaluation (nasal examination or endoscopy) to rule out other potential causes for olfactory dysfunction. This study also had a number of strengths including the community-based design and the standardized ratings of MPS. It is the only study, to our knowledge, to examine MPS and their association with UPSIT scores in a large cohort of community-dwelling elderly.

In conclusion, MPS were associated with a mild yet significant reduction in olfactory function. The current data are one further indicator that MPS represent more than a non-specific, non-neurological marker of aging and they further support the view of MPS as a marker of emerging degenerative brain pathologies.

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Table 1

Characteristics of participants with MPS vs. participants without MPS

Characteristic	MPS N = 177	No MPS N = 901
Age in years****	82.8 ± 5.7	80.1 ± 5.6
Female gender	115 (65.0%)	626 (69.5%)
Race		
White	49 (27.7%)	291 (32.3%)
African-American	57 (32.2%)	280 (31.1%)
Hispanic	69 (39.0%)	317 (35.2%)
Other	2 (1.1%)	13 (1.4%)
Education in years*	10.2 ± 4.7	10.9 ± 4.7
Smoker (ever)*	93 (52.5%)	406 (45.1%)
Smoker (current)	12 (6.8%)	61 (6.8%)
Depression	25 (14.5%)	102 (11.5%)
Blessed score	1.6 ± 2.1	1.4 ± 1.8
UPSIT score	24.3 ± 7.1	26.4 ± 6.8

For several variables, data were available on fewer than 1,078 participants.

* $p < 0.10$

** $p < 0.05$

*** $p < 0.01$

**** $p < 0.001$

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Table 2

Association between strata of transformed UPSIT score and MPS

	Unadjusted logistic regression analysis (MPS = dependent variable)	Adjusted logistic regression analysis^ (MPS = dependent variable)
Transformed UPSIT score		
Below median	1 (reference)	1 (reference)
At or above median	1.84 (1.33 – 2.57), p < 0.001	1.55 (1.10 – 2.18), p = 0.01
Transformed UPSIT score		
Lowest quartile	1 (reference)	1 (reference)
Second quartile	1.35 (0.81 – 2.26), p = 0.24	1.24 (0.74 – 2.09), p = 0.42
Third quartile	2.02 (1.28 – 3.18), p = 0.002	1.74 (1.09 – 2.78), p = 0.02
Highest quartile	2.20 (1.39 – 3.48), p = 0.001 *	1.67 (1.03 – 2.72), p = 0.04 **

^ Adjusted for age and education.

* In a test for trend, p < 0.001.

** In a test for trend, p < 0.05.

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Table 3

Association between strata of transformed UPSIT score and axial dysfunction, rigidity, and tremor

	Unadjusted logistic regression (axial dysfunction = dependent variable)	**Adjusted^ logistic regression (axial dysfunction = dependent variable)**
Transformed UPSIT score		
Below median	1 (reference)	1 (reference)
At or above median	1.81 (1.15 – 2.85), p = 0.01	1.41 (0.88 – 2.26), p = 0.15
Transformed UPSIT score		
Lowest quartile	1 (reference)	1 (reference)
Second quartile	1.50 (0.74 – 3.07), p = 0.26	1.29 (0.62 – 2.66), p =0.50
Third quartile	2.16 (1.14 – 4.08), p = 0.02	1.70 (0.88 – 3.27), p = 0.11
Highest quartile	2.18 (1.14 – 4.18), p = 0.02	1.48 (0.75 – 2.91), p = 0.26
	Unadjusted logistic regression (**rigidity** = dependent variable)	Adjusted^ logistic regression (**rigidity** = dependent variable)
Transformed UPSIT score		
Below median	1 (reference)	1 (reference)
At or above median	1.79 (1.22 – 2.62), p = 0.03	1.56 (1.05 – 2.32), p = 0.03
Transform ed UPSIT score		
Lowest quartile	1 (reference)	1 (reference)
Second quartile	1.27 (0.70 – 2.30), p = 0.44	1.20 (0.66 – 2.20), p = 0.55
Third quartile	1.76 (1.04 – 2.99), p = 0.04	1.58 (0.91 – 2.73), p = 0.10
Highest quartile	2.23 (1.32 – 3.76), p = 0.003	1.84 (1.06 – 3.19), p = 0.03
	Unadjusted logistic regression (**tremor** = dependent variable)	Adjusted^ logistic regression (**tremor** = dependent variable)
Transformed UPSIT score		
Below median	1 (reference)	1 (reference)
At or above median	1.91 (1.06 – 3.44), p = 0.03	1.70 (0.92 – 3.17), p = 0.09
Transformed UPSIT score		
Lowest quartile	1 (reference)	1 (reference)
Second quartile	1.18 (0.46 – 3.04), p = 0.73	1.20 (0.45 – 3.21), p = 0.79
Third quartile	1.54 (0.67 – 3.58), p = 0.31	1.51 (0.63 – 3.67), p = 0.36
Highest quartile	2.63 (1.20 – 5.76), p = 0.02	2.23 (0.96 – 5.18), p = 0.06

^Adjusted for age and education.