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A Screening Tool to Detect Clinical Manganese Neurotoxicity

Brad A. Racette^{a,b}, Anat Gross^a, Susan R. Criswell^a, Harvey Checkoway^{c,d}, and Susan Searles Nielsen^a

^aDepartment of Neurology, Washington University in St. Louis School of Medicine, 660 South Euclid Avenue, St. Louis, MO 63110, USA

^bSchool of Public Health, Faculty of Health Sciences, University of the Witwatersrand, 27 St. Andrews Road, Parktown 2193, South Africa; University of California, San Diego

^cDepartment of Family Medicine and Public Health, Department of Neurosciences, La Jolla, CA, USA

Abstract

Manganese (Mn) over-exposure in occupational settings is associated with basal ganglia toxicity and a movement disorder characterized by parkinsonism (i.e., the signs and symptoms of Parkinson disease). A simple test to help non-neurologists identify workers with clinical Mn neurotoxicity represents an unmet need. In a cohort of Mn-exposed workers from welding worksites, with extensive clinical data, we developed a linear regression model to predict the Unified Parkinson Disease Rating Scale motor subsection part 3 (UPDRS3) score. We primarily considered factors easily obtained in a primary care or occupational medicine clinic, specifically easily assessed signs of parkinsonism and factors likely to be associated with UPDRS3 such as age, timed motor task results, and selected symptoms/conditions. Secondly we considered other demographic variables and welding exposure. We based the model on 596 examined workers age 65 years and with timed motor task data. We selected the model based on simplicity for clinical application, biologic plausibility, and statistical significance and magnitude of regression coefficients. The model contained age, timed motor task scores for each hand, and indicators of action tremor, speech difficulty, anxiety, depression, loneliness, pain and current cigarette smoking. When we examined how well the model identified workers with clinically significant parkinsonism (UPDRS3 ≥ 15) the Receiver Operating Characteristic Area Under the Curve (AUC) was 0.72 (95% confidence interval 0.67, 0.77). With a cut point that provided 80% sensitivity, specificity was 52.0%, the positive predictive value in our cohort was 29%, and the negative predictive value was 92%. Using the same cut point for predicted UPDRS3, the AUC was nearly identical for UPDRS3 ≥ 10, and 0.83 (95% CI 0.76, 0.90) for UPDRS3 ≥ 20. Since welding exposure data was not required after including its putative effects, this model may help identify workers with clinically significant Mn neurotoxicity in a variety of settings as a first step in a tiered occupational screening program.

Corresponding author: Brad A. Racette, M.D., Washington University School of Medicine, 660 South Euclid Ave., Box 8111, St. Louis, MO 63110, USA, Telephone -1-(314)747-0532, Fax -1-(314)362-0168, racetteb@wustl.edu.

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Keywords

Manganese; Welding; Predictive Model; Parkinsonism

Introduction

Chronic occupational exposure to manganese (Mn) has been associated historically with a severe, atypical neurologic disorder characterized by parkinsonism, dystonia, cognitive dysfunction, and behavioral dysfunction.(Rodier, 1955; Wang et al., 1989) The exposures causing this phenotype were as high as 1,000,000 $\mu\text{g Mn/m}^3$.(Rodier, 1955; Wang et al., 1989) In workers with lower occupational exposures, typical of the modern workplace, the phenotype of occupational Mn exposure is substantially different from phenotype associated with historical, high exposures. In fact, exposures at or below the current Occupational Safety and Health Administration (OSHA) exposure limit of 5000 $\mu\text{g Mn/m}^3$ have also been associated with clinical neurotoxicity.(Roels et al., 1987; Roels et al., 1985) In particular, we have previously described that Mn-exposed welders have a phenotype that is predominantly characterized by symmetric parkinsonism that includes rigidity and bradykinesia, and cognitive control dysfunction.(Racette et al., 2012) These neurologic abnormalities are associated with reductions in Parkinson-specific quality of life and appear to be progressive. (Harris et al., 2011; Racette et al., 2017)

There have been several attempts to develop an operational definition of manganism to inform clinical criteria to identify those with clinical Mn neurotoxicity.(Calne et al., 1994; Jankovic, 2005) These criteria are based on the classic phenotype associated with very high Mn exposures and were focused on distinguishing manganism from Parkinson disease (PD). However, these criteria have never been updated to reflect the distinct phenotypic differences between historic and modern Mn exposures. Given our previous findings, suggesting that more than 15% of Mn-exposed welders have clinically relevant parkinsonism,(Racette et al., 2012) we sought to fill this knowledge gap by developing clinical criteria that could serve as an initial screening tool for Mn-exposed workers to identify those experiencing clinically relevant Mn neurotoxicity.

Materials and Methods

Study design and clinical assessment- We identified participants from a union membership list and recruited from one indoor fabrication shop and two shipyards in the Midwestern U.S. between the years 2006 and 2016, as detailed previously.(Racette et al., 2017) Workers on the list had to have been employed at one of these welding worksites for at least 90 days. No workers or retirees from these worksites were excluded from participation, except as noted below. Two movement disorders trained neurologists (B.A.R, S.R.C.) performed neurologic exams that included the Unified Parkinson Disease Rating Scale motor subsection part 3 (UPDRS3),(Fahn et al., 1987) blinded to workers' exposure history and validated with timed motor testing data.(Racette et al., 2017) Examinations were conducted in local union halls near each worksite. The study neurologists completed 1537 exams, and after excluding 45 exams in workers with a history of stroke, brain tumor, or other medical

condition that would compromise the UPDRS3 score, 1492 exams in 886 individuals were available. (Racette et al., 2017)

Subjects also completed a timed motor task using a counter with two levers spaced 20 cm apart, as previously described.(Criswell et al., 2010) Scores were reported for each of three trials for each hand, and we calculated the mean of the trials for the dominant hand and non-dominant hand. Lower values indicate poorer performance, and are strongly positively associated with UPDRS3 scores in this cohort ($p < 0.0005$). (Racette et al., 2017) For the present study, we focused on workers who had both a complete UPDRS3 exam and at least one trial of the timed motor task per hand. We also restricted this analysis to workers exposed to welding fume (Mn) and of working age (≥ 65 years) to ensure the model could be applied to current Mn-exposed workers. If subjects had more than one exam with a timed motor task, we only included the earliest exam. In total, we included 596 (67%) workers in the present analysis. The most common reason for exclusion was a lack of the timed motor task, which was only administered from 2006–2013.

In addition to the clinical motor assessments, workers completed a PD specific quality of life questionnaire(Jenkinson et al., 1997) and a PD symptom questionnaire.(Duarte et al., 1995; Tanner et al., 1990) We also obtained detailed demographic and lifestyle information from a questionnaire,(Hobson et al., 2009) including medical conditions, the use of medications, and common PD risk factors such as cigarette smoking, and consumption of other types of tobacco, caffeine and alcohol.(Checkoway et al., 2002) Finally, all subjects completed a comprehensive welding exposure questionnaire,(Hobson et al., 2011a; Hobson et al., 2009) which we used to determine duration and intensity of welding fume exposure and hence cumulative Mn exposure.(Racette et al., 2012; Racette et al., 2017) We validated these measures in a subset of 38 workers with pallidal index data from T1-weighted magnetic resonance imaging.(Racette et al., 2017)

Statistical analysis- We performed statistical analyses in R (version 3.3.2, R Core Team, Vienna, Austria) and Stata version 11.0. We built a predictive model of parkinsonism, with simple linear regression, using the UPDRS3 score as a continuous measure as our outcome variable. Given that UPDRS3 scores were rated by two examiners over several years, we first adjusted UPDRS3 subscores for examiner and examiner by time differences, and then summed these subscores to obtain the total (adjusted) UPDRS3 score as previously.(Racette et al., 2017) We included age and timed motor task data *a priori* as predictors because of their strong associations with UPDRS3,(Racette et al., 2017) while using locally weighted scatterplot smoothing (LOWESS) to inform how to model these continuous measures. We then individually introduced additional potential predictors into the model to identify those with a biologically plausible direction of association at $p \leq 0.1$ (one-sided alpha of 0.05) and/or with a clinically meaningful difference (approximately 1 point difference in UPDRS3 score) and sufficiently narrow 95% confidence intervals (CIs). The primary potential predictors of interest were factors that could be determined by a non-neurologist to further (i.e. beyond the objective timed motor test results) capture the motor and associated non-motor effects of Mn overexposure. We also examined some of the UPDRS3 subscores that directly contribute to the UPDRS3 score, specifically, those that reasonably might be assessed by a non-neurologist clinician: action tremor, arising from chair, gait, posture, and

speech. For this we dichotomized the respective subscores to indicate presence (1) of the sign rather than retaining them on the 1–4 scale, which would likely require neurologist expertise. We also examined whether the model would be improved by inclusion of factors from the PD symptom questionnaire, the PDQ39, and selected self-reported medical conditions and medications, namely depression and anxiety, which have been associated with Mn overexposure. (Bowler et al., 2006; Bowler et al., 1999; Mergler et al., 1994)

Secondary predictors we considered included other selected medical conditions: asthma, diabetes, heart disease, high blood pressure, pain, rheumatoid arthritis in particular, and history of head injury which required hospitalization. We also examined sex, race/ethnicity, education, handedness, body mass index (BMI), family history of PD in a first degree relative, consumption of tobacco, caffeine and alcohol as potential predictors. Finally, we assessed the potential contribution of several welding exposure variables including percent of time spent working in confined spaces, job category (welder, welder helper, around welding) and/or flux core arc welding, whether the subject had worked at the site within the last year (retiree status), total duration of welding work, and weighted welding years. (Hobson et al., 2011b; Racette et al., 2012)

In selecting the final model, we assessed the consistency of results for primary predictors that were similar (e.g. self-reported depression and use of medications used for depression), and when their coefficients were sufficiently similar, we combined these variables to improve precision and to simplify the model before selecting the final model. Finally, we entered age, timed motor task data, and the additional identified predictors simultaneously into a multivariable linear regression model to identify the strongest independent predictors. For those variables that remained, we tested for interactions on the multiplicative scale, while initially including all main effects terms when obtaining the interaction p-value. We then verified model fit and checked for multicollinearity and influential data points.

Results

Most (97%) of the examined workers were non-Hispanic Caucasian men who still worked around welding or had done so in the past year. (Table 1) The mean age at exam was 44.7 years (SD 11.8). A majority (69%) had ever smoked cigarettes, and 42% of all workers still smoked. UPDRS3 scores ranged from 0 to 31, with a mean score of 8.5 (SD 5.8). There was a linear, positive association between age and UPDRS3, with a 0.081 (95% CI 0.044, 0.119) greater UPDRS3 score with each additional year of age. (Table 2) This association was not attenuated by adjustment for the total number of years occupationally exposed to welding fume.

The timed motor task score for the dominant hand was largely linearly associated with UPDRS3 in LOWESS. Somewhat in contrast, the score for the non-dominant hand was not linearly associated with UPDRS3 and we fit a linear spline with a knot at a non-dominant hand timed motor task score of 35, as suggested by LOWESS. We only retained one spline, for scores <35, in the model, to allow for a (linear) effect of the non-dominant hand timed motor task if the non-dominant hand score was sufficiently poor (<35). The second spline, for scores ≥ 35, was not significantly associated with UPDRS3, when the other non-

dominant hand spline and the linear term for the dominant hand was included, indicating little further influence on the UPDRS3 score once subjects reached a score of 35 in the non-dominant hand. Both timed motor task score variables, for the dominant and non-dominant hand, were significantly inversely associated with UPDRS3, when placed in the model together despite their strong correlation ($r = 0.77$).

Most of the primary predictor variables (UPDRS3 subscores, PD symptom questionnaire, PDQ39 questionnaire, depression and anxiety) were significantly associated with UPDRS3, even after accounting for age and timed motor task scores. The primary predictor variables were generally all positively correlated, and in a multivariable model the following variables remained independently predictive: upper limb action tremor/self-reported shaking of arms or legs, speech difficulty, dressing difficulty, anxiety, depression, and loneliness. (Table 2) Secondary predictors that contributed further to a predictive model with the above primary predictors were pain, current cigarette smoking and sex. However, given small numbers of women and inconsistent direction of results for sex in models stratified on other factors, we did not retain sex in the model. Dichotomous variables for pain, anxiety, loneliness and depression were individually significant and had similar effect sizes. As such, we formed a variable capturing pain, anxiety, loneliness, and depression (PALD) based on the total number of these conditions present (0, 1, 2 or 3+). We also observed an interaction between current cigarette smoking status and this PALD category on the UPDRS3 score, such that PALD only clearly suggested a higher UPDRS3 score among workers who were not currently smoking cigarettes. We included this interaction, but for simpler application of this predictive model, we did not include the main effect term for current smoking in the final model. (Table 2) The magnitude of the estimated coefficient for smoking status among those without PALD was fairly modest (0.35 reduction in UPDRS3 score) and removal of this term from the model had little impact on remaining terms, the predicted scores, or model performance. We made further simplifications to allow ultimately easier clinical application, i.e. a one-page screening form based on the most simplified model. (Table 2, Figure 1)

The adjusted R-squared of the model was 0.25 ($p < 2.2 \times 10^{-16}$). No variance inflation factor values exceeded ten and the mean was < 2 indicating no collinearity in the model. A residual plot suggested that a linear fit was appropriate. Using a UPDRS3 ≥ 15 as the threshold for clinically significant parkinsonism, (Racette et al., 2012) the Receiver Operating Characteristic (ROC) Area Under the Curve (AUC) was 0.72 (95% CI 0.67, 0.77). (Figure 2) In order to achieve 80% sensitivity, a cut point of 9.88 for the predicted UPDRS3 score was required, resulting in 52% specificity (Table 3). The positive predictive value in our cohort using this cut point was 29% and the negative predictive value was 92% (not shown in tables). The overall performance of the model as measured by the AUC was essentially the same if we used UPDRS3 ≥ 10 as the threshold for clinical significance (AUC=0.72, 95% CI 0.68, 0.76). Model performance was improved substantially when using UPDRS3 ≥ 20 as the threshold (AUC=0.83, 95% CI 0.76, 0.90).

Discussion

We developed a predictive model of UPDRS3 score, using a large worksite-based cohort of Mn-exposed welders that identified those with parkinsonism markedly better than chance. In

our cohort, in which parkinsonism (UPDRS3 = 15) is fairly common, only 8% of the workers who are told that they do not have parkinsonism would be incorrectly categorized. Application of this predictive model can be altered to increase sensitivity or specificity for parkinsonism, depending on the needs of the clinician. For example, we used a cut point of a predicted UPDRS3 of 9.88 to achieve a sensitivity of 80% to identify workers with parkinsonism, but a lower cut point would increase sensitivity and a higher cut point would increase specificity. We assumed that clinicians would use a definition of parkinsonism of UPDRS3 = 15, because this score is similar to that observed in PD patients at diagnosis. (Rascol et al., 2011; The Parkinson's Study, 1996) However, using a higher or lower UPDRS3 score does not affect the model, only the assessment of its performance. For example, the model's performance was substantially better when using a UPDRS3 threshold of = 20. In addition, it is possible that the predictive model could be enhanced through the addition of biomarker data. Blood Mn did not improve our model, but other measurements in blood, urine or saliva may ultimately prove useful. Finally, as detailed later below, we anticipate that this would only be the first step in a tiered screening program, as conceived previously.(Myers et al., 2009)

A key strength of this study is the use of a large cohort that was examined by a movement disorders specialist. The use of a movement disorders trained physician exam as the gold standard is unique in reports describing clinical manganism criteria. Our comprehensive model-building approach is also a strength. We emphasized questions and clinical tests that could be administered by ancillary staff in an occupational medicine physician's office, while also recognizing the challenges of the additional burden of screening for neurologic diseases in a busy clinical practice. We used the parameter estimates from the model to create a simple form for clinicians to predict a UPDRS3 score. Each variable from the final simplified predictive model is represented by a question or combination of questions on the form. Responses should be recorded and used to compute a score for each question to contribute to the final predicted UPDRS3 score. Specifically, the predicted UPDRS3 score is the sum of all the question scores with the base (intercept) score. Most importantly, the application of these criteria does not require focused neurologic training such as a neurology residency or movement disorders fellowship.

We developed these clinical criteria with an emphasis on usability in resource poor environments and modeled this approach based upon a previous tiered, Mn-screening program.(Myers et al., 2009) In that study, the authors used occupational health nurses to perform an initial screening of workers, followed by examination by a physician for those identified as having evidence of neurologic abnormalities. While this is a cost-effective approach, the nurses performing this screening did not have comparable neurologic expertise of the movement disorders specialists who performed the examinations in our study. Moreover, the brief neurologic examination they employed required considerable subjective interpretation. In contrast, we designed a screening tool that could be administered consistently by an ancillary staff person in a physician's office. Nevertheless, we modeled our proposed manganism screening on their tiered-screening protocol and recommend that workers identified undergo magnetic resonance imaging (MRI) of the brain to measure T1 relaxation time(Lee et al., 2015; Lewis et al., 2016) or pallidal index.(Criswell et al., 2012; Nelson et al., 1993) We recommend that those workers identified as having parkinsonism

and who have a shortened T1 relaxation time or high pallidal index, should have an evaluation by a neurologist, preferably one with movement disorders training, in order to confirm clinical status. The threshold for the imaging screening step will require further research. While our proposed manganese clinical criteria require neurologic expertise for the final confirmation, we used an evidence-based approach of the critical first step.

The variables included in our screening form provide a unique insight into the pathophysiology of Mn neurotoxicity. For example, motor abnormalities included in our predictive model, tremor, hand dexterity, and speech impairment were included, consistent with our recent study demonstrating that progression of upper extremity bradykinesia, tremor, and speech impairment were associated with cumulative Mn exposure.(Racette et al., 2017) Interestingly, current tobacco use, associated with reduced risk for idiopathic PD, (Searles Nielsen et al., 2012) appeared to strongly influence whether depression, and especially pain, anxiety and loneliness were indicative of parkinsonism. The inclusion of pain, anxiety, loneliness, and depression in the model are consistent with numerous occupational and environmental Mn studies that identified Mn-exposure as associated with mood abnormalities.(Bowler et al., 2006; Bowler et al., 2007) The significance of pain in the predictive model is unclear. Pain may be associated with rigidity or dystonia in PD patients; although, we found dystonia in only a few of our subjects.(Racette et al., 2017) The pain questions also may be more fully capturing depression.

As with any study, there are some limitations to this work. Although the predictive model ROC had modest sensitivity and specificity at the peak of the AUC, we proposed a predicted UPDRS3 that is somewhat lower than our case definition of parkinsonism (UPDRS3 = 15) to achieve a sensitivity of 80%. While this will result in more false positives, we believe that this cutoff is prudent if the goal is to identify the majority of those with clinically relevant Mn neurotoxicity. It is important to note that without these criteria, there are no evidence-based clinical criteria to guide the primary care or occupational medicine physician. Ultimately, the addition of inexpensive biomarkers (blood, urine, saliva) of parkinsonism to this protocol could provide much greater sensitivity and specificity. This approach has proven to be useful in some studies of prodromal Parkinson disease. (Nalls et al., 2015; Schrag et al., 2017) While these criteria were designed in a Mn-exposed welding cohort, further studies will be needed to confirm that these will apply to other occupational settings. Welding exposure is the most common source of occupational Mn exposure worldwide, but use of this predictive model to identify those with clinical Mn neurotoxicity in other settings would broaden the impact of this work. Unfortunately, we were not able to design a simple questionnaire that would eliminate the need for a specialist examination at a later stage, likely reflecting the complexity of the neurologic clinical phenotype. Nevertheless, the screening approach we outlined should serve as a starting point on which we and others can develop a single assessment tool to identify those Mn-exposed workers experiencing the neurotoxic effects of their occupational exposure.

Conclusion

This predictive model of UPDRS3 score and resulting screening tool may help identify workers with clinically significant Mn neurotoxicity and may be particularly useful in

occupational medicine or primary care settings in which a movement disorders specialist or other neurologist is not available. The proposed screening tool might be applied as a first step in a tiered occupational screening program that can be implemented in a wide variety of settings.

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Section 1: Timed Motor Task					
Question	Mean Number of Clicks	Instructions	Value		Section Score
Dominant Clicker Score	Hand _____ mean clicks in 30 seconds trials	Multiply by 0.13	→		
Non-Dominant Clicker Score	Hand _____ mean clicks in 30 seconds trials	If less than 35: Multiply by 0.40 If 35 or more: The score is 14	→		
			Sum up the clicker question scores	→	subtract from 25.9
					Section 1 Score: →
Section 2: Age					
Patient Age	_____ years	Multiply by 0.037	→		Section 2 Score: →
Section 3: Speech					
Have you experienced at least one of the following? 1. People telling you your voice is softer than it once was 2. Speech difficulty more than occasionally in the last month	Yes	No	If no to both, the section score is 0 Otherwise the section score is 3	→	Section 3 Score: →
Observable Speech Impairment	Yes	No			(This value should be 3 or 0)
Section 4: Tremor					
Do your arms and legs shake?	Yes	No	If no to both, the section score is 0 Otherwise the section score is 2.5	→	Section 4 Score: →
Observable Action Tremor	Yes	No			(This value should be 2.5 or 0)
Section 5: Smoking Status and PALD (Pain/Anxiety/Loneliness/Depression)					
Do you currently smoke cigarettes?	Yes	No	If yes, the section score is 0 If no, proceed to the next question to assess PALD	→	Section 5 Score: →
In the past month have you felt lonely, depressed, or anxious more than occasionally?	Yes	No	If no to both, the section score is 0 Otherwise the section score is 2.9	→	
Is the patient currently taking medication for pain, anxiety, or depression?	Yes	No			(This value should be 2.9 or 0)
Predicted UPDRS3 Score			Sum all section scores	→	

Figure 1.

Figure 2. Receiver operator characteristic curve for UPDRS3 15

The area under the receiver operator characteristic curve was 0.72 (95% confidence interval 0.67, 0.77) indicating that the final simplified predictive model for UPDRS3 performed significantly better than chance.

Table 1

Characteristics of subjects with timed motor task data at exam, U.S. Midwestern Welders Cohort

	N = 596 n (%)
Recruitment site	
Worksite 1	235 (39)
Worksite 2	251 (42)
Worksite 3	110 (18)
Most welding fume intensive job at time of exam	
Welder	215 (36)
Welder helper	71 (12)
Other worker exposed to welding	310 (52)
Male	567 (95)
Non-Hispanic Caucasian	578 (97)
Ever smoked cigarettes	411 (69)
Currently smoke cigarettes	249 (42)
Worked at worksite in past year	582 (98)
	Mean (SD)
Age, years	
Mean (SD)	44.7 (11.8)
Minimum	18
Median	48
Maximum	65
UPDRS3	
Mean (SD)	8.5 (5.8)
Minimum	0
Median	8
Maximum	31
Timed motor task score, ^a dominant hand	
Mean (SD)	38.4 (5.5)
Minimum	25
Median	38
Maximum	57
Timed motor task score, ^a non-dominant hand	
Mean (SD)	35.7 (5.2)
Minimum	21
Median	36
Maximum	52

^aMean count from three 30 second trials for each hand. Lower mean counts represent worse performance. Abbreviations: UPDRS3 = Unified Parkinson Disease Rating Scale motor subsection 3

Table 2

Linear regression coefficients and 95% confidence intervals for predicting UPDRS3, U.S. Midwestern Welders Cohort

	N = 596 n (%)	Unadjusted Model	Adjusted for Age and Timed Motor Task	Final Model (Mutually Adjusted)	Simplified Final Model (Mutually Adjusted)
Age, per year		0.081 (0.044, 0.119)	0.059 (0.024, 0.094)	0.033 (-0.0014, 0.067)	0.037 (0.003, 0.071)
Timed motor task score, ^a dominant hand, per point		-0.34 (-0.41, -0.26)	-0.17 (-0.27, -0.07)	-0.14 (-0.23, -0.044)	-0.13 (-0.22, -0.036)
Timed motor task score, ^a non-dominant hand, per point, up to a maximum score of 35 ^b		-0.70 (-0.84, -0.55)	-0.46 (-0.65, -0.27)	-0.40 (-0.58, -0.21)	-0.40 (-0.58, -0.22)
Difficulty speaking	116 (20)	3.65 (2.6, 4.7)	2.96 (1.9, 4.0)	2.70 (1.7, 3.7)	2.98 (2.0, 4.0)
Difficulty dressing	22 (4)	2.98 (0.62, 5.3)	1.32 (-0.89, 3.5)	0.88 (-1.3, 3.1)	N/A ^c
Arms and legs shake	53 (9)	2.18 (0.62, 3.7)	1.65 (0.20, 3.1)	1.02 (-0.40, 2.4)	2.54 (1.6, 3.5) ^d
Upper limb action tremor	102 (17)	3.27 (2.1, 4.4)	2.53 (1.4, 3.6)	2.34 (1.3, 3.4)	
Current cigarette smoking and number of conditions present (pain, anxiety, loneliness, depression [PALD]) ^e					
Non-smoker with 1 condition	47 (8)	3.61 (2.0, 5.2)	2.62 (1.1, 4.1)	2.60 (1.1, 4.1)	5 (1.3, 4.6) ^f
Non-smoker with 2 conditions	18 (3)	4.85 (2.3, 7.4)	4.25 (1.9, 6.6)	3.16 (0.85, 5.5)	
Non-smoker with 3+ conditions	9 (1)	4.28 (0.71, 7.8)	3.09 (-0.23, 6.4)	1.33 (-1.9, 4.6)	
Smoker with 1 condition	39 (7)	-3.07 (-5.4, -0.78)	-3.07 (-5.2, -0.93)	-3.31 (-5.4, -1.2)	g
Smoker with 2 conditions	14 (2)	-2.46 (-6.2, 1.3)	-3.91 (-7.4, -0.38)	-3.33 (-6.8, 0.10)	
Smoker with 3+ conditions	8 (1)	1.61 (-3.5, 6.7)	1.49 (-3.3, 6.3)	1.97 (-2.6, 6.6)	

^aMean of three 30 second trials of a time motor task as described previously.(Criswell et al., 2010) A lower score indicates poorer performance.

^bTimed motor task scores(Criswell et al., 2010) for the non-dominant hand were modeled using a linear spline such that scores above 35 were treated as 35 and scores below 35 were modeled linearly.

^cDifficulty dressing was removed because an influential point contributed to the magnitude of the positive association.

^dArms and legs shake (self-reported) was assumed to be an action tremor and was combined with action tremor (as assessed by a neurologist) because rest tremor (as assessed by a neurologist) was relatively uncommon (0.7%) in this worker sample.

^eSingle variable to capture pain, anxiety, loneliness, and/or depression (PALD). Pain was considered present if the individual was taking pain medications. Anxiety was considered present if the individual was taking anxiety medication and/or reported having anxiety in the PDQ39. Loneliness was determined using the PDQ39. Depression was considered present if the individual was taking medication for depression and/or reported having depression on the main questionnaire or PDQ39.

^fAny pain, anxiety, loneliness and/or depression (PALD) dichotomized.

^gExcluded due to inconsistency of results for PALD among current cigarette smokers.

Abbreviations: UPDRS3 = Unified Parkinson Disease Rating Scale motor subsection 3

Table 3

Sensitivity (%) and Specificity (%) of the Final Simplified UPDRS3 Predictive Model (Form), by Selected Cut Points for Predicted and Neurologist Assessed UPDRS3 Scores^a

Neurologist Assessed UPDRS3						
	UPDRS3 10		UPDRS3 15		UPDRS3 20	
	Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity
Predicted UPDRS3						
8.81	81	46	90	38	95	35
9.88	70	61	80	52	92	49
12.10	40	88	49	80	74	78
15.75	11	99	20	98	38	96

^a Selected cut points for the predicted UPDRS3 score are those that respectively yield a 90% sensitivity, 80% sensitivity, 80% specificity, or maximizes the total percent classified correctly for a UPDRS3 15 by neurologist assessment. These or other cut points can be applied to the score predicted by the model (form).

Abbreviations: UPDRS3 = Unified Parkinson Disease Rating Scale motor subsection 3