RESEARCH ARTICLE

Self-Reported Motor and Nonmotor Symptoms, Prodromal Parkinson's Disease Probability, and Incident Parkinson's Disease in US Farmers

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ABSTRACT: Background: Few studies have assessed motor and nonmotor symptoms and the prodromal probability of Parkinson's disease (PD) among farming populations.

Objective: The aim was to assess self-reported nonmotor and motor symptoms and the prodromal PD probability in relation to incident PD among US farmers.

Methods: The study included 16,059 farmers (aged 65.6 ± 10.8 years) from the Agricultural Health Study, with a median of 6.2 years of follow-up. We assessed associations using multivariable logistic regression and presented odds ratios (OR) and 95% confidence intervals (CI).

Results: At baseline, the prevalence of individual symptoms ranged from 2.0% for arm/leg tremor to 21.1% for excessive daytime sleepiness. We identified 127 incident PD patients during follow-up. Except for depression, all symptoms were significantly associated with future PD diagnosis, with OR (95% CI) ranging from 1.6 (1.1–2.2) for excessive daytime sleepiness to 3.9 (2.3–6.8) for arm/leg tremor. The prodromal PD probability, calculated based on limited available self-reported prodromal and PD risk markers, was low. Using the Movement Disorder Society's prodromal PD criteria, the median (interquartile range) at baseline was 4.4% (7.2%) for incident PD patients and 2.3% (3.4%) for participants free of PD. Further, it exhibited low sensitivity and positive predictive value in identifying incident PD patients in this farming population.

Conclusions: Self-reported prodromal PD symptoms were relatively common in US farmers. They were associated with incident PD diagnosis but had limited values in predicting disease risk.

Key Words: MDS prodromal criteria; motor symptoms; nonmotor symptoms; Parkinson's disease; prodromal

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Late-onset Parkinson's disease (PD) often takes decades to develop. There is a substantial interest in characterizing the period of prodromal PD, during which various nonmotor symptoms (NMS) and subtle motor symptoms (MS) may develop.[1] The best-studied prodromal NMSs include olfactory impairment,[2] dream-enacting behaviors,[3,4] and constipation,[5] each associated with a two to fivefold higher risk of PD. Further, clinically confirmed idiopathic rapid eye movement sleep behavior disorder (RBD) is likely a subtype of prodromal PD and related synucleinopathy.[3,4] This line of research, along with advances in understanding PD risk factors and prodromal markers, led the International Movement Disorder Society (MDS) to develop research criteria for prodromal PD,[6,7] with the primary goal of screening high-risk individuals for clinical trial inclusion. This concept may also greatly facilitate the study of PD natural history and etiology in large population-based epidemiological studies.[8] Although the MDS definition showed satisfactory to excellent performance in high-risk populations of RBD patients[9] or LRRK2 mutation carriers,[10] evidence for its performance in the general populations is limited and various.[11-15]

Compared to the general population, farmers are at a higher PD risk, likely due to their occupational use of pesticides.[16] We have previously reported the cross-sectional relationships of six self-reported NMSs to PD among farmers in the Agricultural Health Study (AHS).[17] We now report the association of these NMSs, six MSs, and the prodromal probability with incident PD over ~6 years of follow-up. We further calculate the probability of prodromal PD according to the MDS 2019 research criteria[7] and evaluate performance in predicting incident PD in this unique occupational cohort.

Patients and Methods

Study Population

From 1993 to 1997 (phase 1), AHS recruited 52,394 licensed private pesticide applicators (hereafter referred to as farmers) from Iowa and North Carolina who completed the enrollment questionnaire.[18] The survey collected information on farming activities, including lifetime use of pesticides, sociodemographics, and medical history. Follow-up interviews were conducted during 1999 to 2003 (phase 2), 2005 to 2010 (phase 3), 2013 to 2015 (phase 4), and most recently 2018 to 2020 (phase 5). In the current analysis, we used AHS phase 4 as the baseline when NMS questions were first asked. Of the 21,782 AHS phase 4 participants free of PD (97.0% whites and 97.1% men), we excluded 583 with proxy respondents and 5140 censored in post-phase 4 PD determination due to either non-participation in phase 5 (n = 4998) or missing data on the PD question (n = 142), leaving 16,059 for the current analyses (Fig. S1). Compared to our analytic sample, the excluded participants were more likely to be under age 55, from North Carolina, and less likely to be married or have regular pesticide exposure. However, they had a similar distribution in other PD risk markers, NMSs, MSs, and major health conditions (Table S1). All participants consented by completing and returning study materials. The study protocol was approved by the institutional review boards at the National Institutes of Health and Michigan State University.

Self-Reported MSs and NMSs

The AHS surveys are available at https://aghealth.nih.gov/collaboration/questionnaires.html. At AHS phase 4, participants were asked to report whether they had the following six MSs: hand tremor, arm/leg tremor, small handwriting, soft speaking, shuffling gate, and trouble rising from chairs, with "yes" or "no" answer choices. We considered two or more symptoms as motor impairment.

We also assessed the presence of six NMS. Specifically, poor olfaction was self-reported as a loss or significantly decreased sense of smell. Although self-report of olfaction status is often inaccurate as compared to smell test results, when endorsed, it strongly predicts future risks of PD.[19] For dream-enacting behavior, we used the one-item RBD screener that was developed and validated for use in large epidemiological studies.[20] For constipation, our definition was infrequent bowel movement (less than or equal to three to four times a week), similar to approaches used in other studies.[5,21] We defined excessive daytime sleepiness as feeling sleepy most of the day for ≥1 to 2 days a week.[21] We defined depression as a score ≥3 on the two-item Patient Health Questionnaire[22] and anxiety as a score ≥3 on the two-item Generalized Anxiety Disorder scale.[23] We adopted a conservative approach by including an uncertain category for MSs and NMSs that were ambiguously present/absent or had borderline values, as recommended by the MDS 2019 criteria.[7] Symptom definitions are presented in Table S2. A few participants were missing on NMSs and MSs, ranging from 1.4% to 2.3%. Age-specific distribution details are further provided in Figure S2.

Other Covariates

In addition to MS and NMS, we obtained information on PD risk markers included in the MDS 2019 criteria and other covariates related to missingness in post-phase 4 PD status. We defined age at phase 4 in 5-year groups and various risk/prodromal markers as detailed in Table S2. Briefly, cigarette smoking was defined as never, former, or current smokers. The history of type 2 diabetes was self-reported as diagnosed by a doctor. The family history of PD was defined as

PD in any first-degree biological relative. For pesticides, we calculated the cumulative days of any pesticide use as the product of self-reported years and average days of use per year. Regular pesticide exposure was defined as cumulative use of any pesticide ≥200 days or between 50 and 200 days with use reported for ≥10 years. Other relevant covariates included sex, state, education, marital status, alcohol use, acres of working farm, use of chemical-resistant gloves when applying or mixing pesticides, body mass index (BMI), history of head injury, and history of various health conditions such as asthma, chronic lung diseases, cardiovascular diseases, and hypertension. For sex, state, and protective equipment usage when applying/mixing pesticides, we used data from phase 1. All other covariates were assessed in the phase 4 survey. Missing values in covariates were imputed with the mode.

Posttest Prodromal PD Probability

In this large study of rural farmers, we collected data via self-reports without assessing the several most predictive items of the MDS prodromal PD criteria (eg, polysomnogram (PSG)-proven RBD and abnormal dopaminergic PET/SPECT [positron emission tomography/single-photon emission computed tomography] scan). We calculated the age-adjusted posttest prodromal PD probability using the updated MDS criteria, customized to AHS data availability.[6,7] The calculation included information on 5 of 10 risk markers and 4 of 13 prodromal markers. Detailed definitions of these markers, their corresponding likelihood ratios (LR), and the calculation steps are provided in Tables S2 and S3. In calculating the prodromal PD probability, we excluded self-reported olfactory and motor impairment because the MDS criteria require objectively tested olfaction and motor function. In secondary analyses, we included these two items in the calculation as the data may be useful for populations where remote self-assessment is more feasible. This approach comes with the caveat that the MDS LRs overestimated the LRs of these two measures. Because no pretest probability was provided for participants <50 years (n = 981), we used the 0.4% pretest probability for the 50 to 54 age group. As recommended by the protocol, missing values or uncertain exposure status was given an LR of 1.

Outcome Determination

In all AHS surveys and an olfaction substudy conducted during 2020 to 2021, we asked participants whether they had ever been diagnosed with PD by a physician and the age at diagnosis. Further, in AHS phases 2 to 4 and the olfaction substudy, we asked about the presence of MS using questions adapted from the nine-item PD screener, symptom asymmetry, and the use of PD medications and response to medications. In AHS phase 5, we asked about only PD diagnosis, age of diagnosis, and ever use of PD medications and responses. In all surveys, whereas MSs were asked for the entire cohort, PD diagnostic and treatment information was sought only from participants who reported a diagnosis. Vital status through December 31, 2019, was determined via linkage to the National Death Index. The underlying cause of death was recorded along with up to 20 contributing causes. Potential PD patients were identified if a physician-made PD diagnosis was reported at any of the study's follow-up contacts, or PD was listed as the underlying or contributing cause of death on the death certificate (International Disease Classification Version 10, G20).

In 2023, we conducted a retrospective PD adjudication for all potential patients identified earlier. For each, we compiled an Excel file with longitudinal data on MSs and PD diagnosis available for up to five time points spanning up to 28 years from study enrollment to the olfaction substudy or phase 5 survey and the listed causes of death if available. Because we did not conduct clinical exams, we could not apply standard PD diagnostic criteria in PD adjudication.[24,25] Rather, we considered self-reported data for and against PD diagnosis and the consistency of information within each survey and over time. We adjudicated PD patients as if there were multiple consistent reports of PD diagnosis, supported by MSs *and* evidence of responsiveness to dopaminergic treatment; if the report(s) of PD diagnosis was supported by consistent MSs over years *or* evidence of responsiveness to dopaminergic treatment, without contradictory evidence; or if there were multiple reports of PD diagnosis but the evidence for MSs and/or responsiveness to PD medication was insufficient, or there was only one report of PD diagnosis, supported by the presence of MSs and/or responsiveness to PD medication.

In adjudication, we considered the following as non-PD: if self-reported PD diagnosis was denied in later survey(s), alternative neurodegenerative diseases were noted on the death certificate, or there was only one report without consistent, supportive information of MS or responsiveness to medications; or if there were indications of error in filling out the questionnaire. We have applied similar approaches in other large population-based cohorts with proven validity.[26-28] Of the 904 potential patients identified, we adjudicated 778 as having PD and excluded the 126 for whom PD was not confirmed from the study. The current analyses included 127 incident patients after phase 4 and 15,932 controls who never reported a PD diagnosis up to AHS phase 5.

Statistical Analysis

In our primary analysis, we used weighted logistic regression to extrapolate data to all eligible PD-free

participants of the AHS phase 4 survey (n = 21,782), assuming the associations between NMSs and MSs with incident PD were not influenced by missing data, given the observed covariates. For each symptom, we estimated the conditional probability of nonmissing PD status and the symptom being evaluated, and not having proxy respondents, using multivariable logistic regression (the missingness model). This model adjusted for all NMSs and MSs (excluding the symptom being assessed, with missing values imputed by mode), all available risk markers, age, state, education, marital status, smoking status, alcohol use, acres of working farm, use of chemical-resistant gloves when applying or mixing pesticides, BMI, history of head injury, and history of various health conditions such as asthma, chronic lung diseases, cardiovascular diseases, and hypertension. Weights for each participant were calculated as the inverse of this probability, and weighted logistic regression (the outcome model) was then used to evaluate the association between each symptom and incident PD. Outcome models were adjusted for two different sets of covariates. Model 1 calculated the odds ratios (OR) and 95% confidence intervals (CI) for each symptom with PD, adjusting for linear and quadratic terms of age, state, education, marital status, and smoking status. In model 2, all individual symptoms within the same category (NMS or MS) were mutually adjusted for each other in addition to covariates in model 1.

We further examined the association between the post-test probability of prodromal PD and incident PD using the same weighted logistic regression approach, accounting for proxy respondents and missingness in PD status. The missingness model adjusted for the same covariates as those used for NMS/MS. The outcome model adjusted for linear and quadratic terms of age, state, education, and marital status. We reported ORs and 95% CI for each prodromal PD probability group compared to the lowest probability group (<10%). Additionally, we calculated the sensitivity, specificity, positive predictive value (PPV), and negative predictive value. We used the exposure-participant-specific weights mentioned earlier to extrapolate calculations to all eligible PD-free participants of AHS phase 4. We used AHS data releases AHSREL20150600, P1REL201209_00, P2REL20120900, P3REL20120900, and Final_06172015. All statistical tests were 2-tailed with $\alpha = 0.05$. Statistical analyses were performed using SAS version 9.3 (SAS Institute Inc., Cary, NC).

Results

Of the 16,059 participants free of PD at AHS phase 4, 127 received a PD diagnosis during a median of 6.2 years of follow-up. Table 1 presents population characteristics. Compared to participants who remained PD free during the follow-up, those who were diagnosed with PD were older and more likely to endorse NMSs and MSs and to have a higher prodromal probability.

The Prevalence of NMSs and MSs among At-Risk Population at AHS Phase 4

Excessive daytime sleepiness was the most common NMS endorsed by the farmers (21.1%), followed by olfactory impairment (9.6%), depression (6.4%), infrequent bowel movement (5.6%), dream-enacting behavior (4.5%), and anxiety (3.3%) (Table 1). Of the MSs, trouble rising from chairs was most frequently reported (18.6%), followed by soft speaking (11.3%), small handwriting (8.8%), shuffling gait (7.4%), hand tremor (7.2%), and arm/leg tremor (2.0%). Without exception, MS prevalence increased monotonically with age (Fig. 1). In contrast, of the NMSs, only olfactory impairment and infrequent bowel movements exhibited modest age dependency. Dream-enacting behavior, the other NMS strongly associated with PD, exhibited no age variation.

Association between NMSs and MSs Reported at AHS Phase 4 with Incident PD

Except for depression, all NMS were significantly associated with higher PD risk, with ORs ranging from 1.6 (95% CI: 1.1, 2.2) for excessive daytime sleepiness to 3.1 (95% CI: 1.9, 5.0) for dream-enacting behavior (Table 2). Mutual adjustment for other NMSs moderately attenuated the associations, but dream-enacting behavior, olfactory impairment, infrequent bowel movements, and anxiety remained statistically significant with ORs of ≥2.0. All MSs were associated with higher PD risk, with ORs ranging from 1.6 (95% CI: 1.1, 2.2) for trouble rising from chairs to 3.9 (95% CI: 2.3, 6.8) for arm/leg tremor (Table 2). Their individual associations with PD, however, were substantially attenuated when other MSs were simultaneously adjusted for. Nevertheless, ORs for hand tremor, soft speaking, and shuffling gait remained statistically significant.

Prodromal PD Probability at AHS Phase 4 and Incident PD

The median MDS prodromal probability (interquartile range) was 4.4% (7.2%) for incident PD patients and 2.3% (3.4%) for those who remained PD free during the follow-up (Table 1). Notably, only 27 incident patients had a prodromal PD probability between 10% and 30% and 3 patients 30% or higher. Compared to farmers with a probability of less than 10%, the multivariable OR was 2.3 (95% CI: 1.6, 3.5) and 2.5 (95% CI: 0.9, 6.6), respectively (Table 3). We did not use cut-offs beyond 30% due to sample size concerns. In

TABLE 1 *Population characteristics by incident PD status*

Characteristics*	Overall (N = 16,059)**	PD status**		P-value***
		Incident patients N = 127	Participants free of PD N = 15,932	
Baseline age in years				
Mean ± SD	65.6 ± 10.8	71.8 ± 8.30	65.5 ± 10.8	<0.001
<55	2490 (15.5)	5 (3.9)	2485 (15.5)	
55–<60	2493 (15.5)	5 (3.9)	2488 (15.6)	
60–<65	2825 (17.6)	13 (10.2)	2812 (17.7)	
65–<70	2383 (14.8)	20 (15.7)	2363 (14.8)	
70–<75	2158 (13.4)	31 (24.4)	2127 (13.4)	
75–<80	1897 (11.8)	37 (29.1)	1860 (11.7)	
≥80	1813 (11.3)	16 (12.6)	1797 (11.3)	
State				
Iowa	11,428 (71.2)	85 (66.9)	11,343 (71.2)	0.34
North Carolina	4631 (28.8)	42 (33.1)	4589 (28.8)	
Education				
High school and lower	7503 (46.7)	69 (54.3)	7434 (46.7)	0.31
Beyond high school	5278 (32.9)	33 (26.0)	5245 (32.9)	
Bachelor's degree and above	3101 (19.3)	24 (18.9)	3077 (19.3)	
Missing	177 (1.1)	1 (0.8)	176 (1.1)	
Marital status				
Living as married	13,621 (84.8)	107 (84.3)	13,514 (84.8)	0.64
Single	900 (5.6)	5 (3.9)	895 (5.6)	
Divorced/widowed	1375 (8.6)	14 (11.0)	1361 (8.5)	
Missing	163 (1.0)	1 (0.8)	162 (1.0)	
PD risk markers with customized definition consistent with prodromal PD MDS 2019 criteria[a]				
Sex				
Male	15,604 (97.2)	124 (97.6)	15,480 (97.2)	1
Female	455 (2.8)	3 (2.4)	452 (2.8)	
Regular pesticide exposure				
Yes	9997 (62.3)	81 (63.8)	9916 (62.2)	0.24
No	3359 (20.9)	32 (25.2)	3327 (20.9)	
Uncertain[b]	1845 (11.5)	8 (6.3)	1837 (11.5)	
Missing	858 (5.3)	6 (4.7)	852 (5.3)	
Smoking status				
Current smoker	802 (5.0)	3 (2.4)	799 (5.0)	0.23
Former smoker	3963 (24.7)	39 (30.7)	3924 (24.6)	
Never smoker	9494 (59.1)	68 (53.5)	9426 (59.2)	
Uncertain[b]	1627 (10.1)	15 (11.8)	1612 (10.1)	

(Continues)

TABLE 1 *Continued*

Characteristics*	Overall (N = 16,059)**	PD status**		*P*-value***
		Incident patients N = 127	Participants free of PD N = 15,932	
Missing	173 (1.1)	2 (1.6)	171 (1.1)	
First-degree relative with PD				
Yes	1149 (7.2)	8 (6.3)	1141 (7.2)	0.69
No	14,731 (91.7)	119 (93.7)	14,612 (91.7)	
Missing	179 (1.1)	0 (0)	179 (1.1)	
Diabetes mellitus (type II)				
Yes	2421 (15.1)	24 (18.9)	2397 (15.0)	0.35
No	13,501 (84.1)	103 (81.1)	13,398 (84.1)	
Missing	137 (0.9)	0 (0)	137 (0.9)	
PD prodromal markers with customized definitions according to MDS 2019 criteria[a]				
Dream-enacting behavior				
Yes	727 (4.5)	14 (11.0)	713 (4.5)	<0.001
No	14,597 (90.9)	101 (79.5)	14,496 (91.0)	
Uncertain[b]	503 (3.1)	11 (8.7)	492 (3.1)	
Missing	232 (1.4)	1 (0.8)	231 (1.5)	
Olfactory impairment				
Yes	1544 (9.6)	29 (22.8)	1515 (9.5)	<0.001
No	14,263 (88.8)	96 (75.6)	14,167 (88.9)	
Missing	252 (1.6)	2 (1.6)	250 (1.6)	
Infrequent bowel movements				
Yes	899 (5.6)	17 (13.4)	882 (5.5)	0.004
No	13,905 (86.6)	98 (77.2)	13,807 (86.7)	
Uncertain[b]	1005 (6.3)	10 (7.9)	995 (6.2)	
Missing	250 (1.6)	2 (1.6)	248 (1.6)	
Excessive daytime sleepiness				
Yes	3389 (21.1)	35 (27.6)	3354 (21.1)	0.27
No	9053 (56.4)	64 (50.4)	8989 (56.4)	
Uncertain[b]	3314 (20.6)	25 (19.7)	3289 (20.6)	
Missing	303 (1.9)	3 (2.4)	300 (1.9)	
Depression				
Yes	1027 (6.4)	12 (9.4)	1015 (6.4)	0.34
No	14,748 (91.8)	113 (89.0)	14,635 (91.9)	
Missing	284 (1.8)	2 (1.6)	282 (1.8)	
Anxiety				
Yes	537 (3.3)	11 (8.7)	526 (3.3)	0.01
No	15,215 (94.7)	114 (89.8)	15,101 (94.8)	

(Continues)

TABLE 1 *Continued*

Characteristics*	Overall (N = 16,059)**	PD status**		*P*-value***
		Incident patients N = 127	Participants free of PD N = 15,932	
Missing	307 (1.9)	2 (1.6)	305 (1.9)	
Hand tremor				
Yes	1163 (7.2)	25 (19.7)	1138 (7.1)	<0.001
No	14,672 (91.4)	101 (79.5)	14,571 (91.5)	
Missing	224 (1.4)	1 (0.8)	223 (1.4)	
Arm/leg tremor				
Yes	326 (2.0)	11 (8.7)	315 (2.0)	<0.001
No	15,504 (96.5)	115 (90.6)	15,389 (96.6)	
Missing	229 (1.4)	1 (0.8)	228 (1.4)	
Small handwriting				
Yes	1407 (8.8)	28 (22.0)	1379 (8.7)	<0.001
No	14,335 (89.3)	98 (77.2)	14,237 (89.4)	
Missing	317 (2.0)	1 (0.8)	316 (2.0)	
Soft speaking				
Yes	1820 (11.3)	37 (29.1)	1783 (11.2)	<0.001
No	13,865 (86.3)	88 (69.3)	13,777 (86.5)	
Missing	374 (2.3)	2 (1.6)	372 (2.3)	
Shuffling gait				
Yes	1189 (7.4)	27 (21.3)	1162 (7.3)	<0.001
No	14,600 (90.9)	98 (77.2)	14,502 (91.0)	
Missing	270 (1.7)	2 (1.6)	268 (1.7)	
Trouble rising from chairs				
Yes	2982 (18.6)	42 (33.1)	2940 (18.5)	<0.001
No	12,823 (79.8)	84 (66.1)	12,739 (80.0)	
Missing	254 (1.6)	1 (0.8)	253 (1.6)	
Motor impairment (≥2 motor symptoms)				
Yes	2188 (13.6)	43 (33.9)	2145 (13.5)	<0.001
No	10,567 (65.8)	50 (39.4)	10,517 (66.0)	
Uncertain[b]	3110 (19.4)	33 (26.0)	3077 (19.3)	
Missing	194 (1.2)	1 (0.8)	193 (1.2)	
Parameters for the MDS 2019 prodromal PD criteria				
Pretest probability (%)				
Mean ± SD	1.9 ± 1.2	2.6 ± 1.0	1.9 ± 1.2	<0.001
Median (IQR)	2.0 (1.8)	2.5 (1.5)	2.0 (1.8)	
LR from self-reported risk markers				

(Continues)

TABLE 1 *Continued*

Characteristics*	Overall (N = 16,059)**	PD status**		P-value***
		Incident patients N = 127	Participants free of PD N = 15,932	
Mean ± SD	1.9 ± 0.9	2.0 ± 0.9	1.9 ± 0.9	0.67
Median (IQR)	1.8 (0.7)	1.8 (0.7)	1.8 (0.7)	
LR from self-reported prodromal markers				
Mean ± SD	1.2 ± 1.4	1.8 ± 2.1	1.2 ± 1.4	<0.001
Median (IQR)	0.6 (1.2)	0.7 (1.2)	0.6 (1.2)	
LR based on all available self-reported markers				
Mean ± SD	2.3 ± 3.5	3.4 ± 4.5	2.3 ± 3.5	<0.001
Median (IQR)	1.2 (1.5)	1.6 (2.6)	1.2 (1.5)	
Posttest prodromal PD probability (%)				
Mean ± SD	3.9 ± 5.5	7.5 ± 8.6	3.9 ± 5.5	<0.001
Median (IQR)	2.3 (3.4)	4.4 (7.2)	2.3 (3.4)	
0–10	14,685 (91.4%)	97 (76.4%)	14,588 (91.6%)	
10–<30	1236 (7.7%)	27 (21.3%)	1209 (7.6%)	
≥50	138 (0.9%)	3 (2.4%)	135 (0.8%)	

Abbreviations: PD, Parkinson's disease; SD, standard deviation; MDS, Movement Disorder Society; IQR, interquartile range; LR, likelihood ratio.
*State was obtained from phase 1 survey (1993–1997). All other characteristics were assessed in the phase 4 survey (2013–2015).
**N (column %) values are presented unless otherwise specified.
***P-values were calculated using the Mann-Whitney *U* test for continuous variables and the χ^2 or Fisher's exact test for categorical variables, as appropriate.
[a]Detailed definitions are provided in Table S2. Self-reported olfactory and motor impairments were listed in lieu of objectively tested olfaction and motor function. They were not used in the calculation of the posttest probability.
[b]We adopted a conservative approach by including an uncertain category if markers were ambiguously present/absent or had borderline values, as recommended by the MDS 2019 criteria. Details are provided in Table S2.

secondary analyses, adding self-reported motor and olfactory impairments increased the prodromal probabilities and demonstrated a monotonic association between the posttest probability and PD. However, the sensitivity and PPV were very low in both primary and secondary analyses (Table 4).

Discussion

In this study, we assessed the prevalence of major NMSs and MSs of PD in US farmers via self-reports. We further calculated the prodromal PD probability based on the limited marker information collected in the study with and without considering self-reported motor and olfactory impairment. Although these symptoms and the prodromal PD probability were evidently associated with incident PD, they likely have limited potential for predicting future PD diagnosis in this population of older farmers.

In the past two decades, it has been increasingly recognized that late-onset PD has a prolonged prodromal stage, during which many nonspecific NMSs and MSs may arise at various time points.[29,30] These symptoms robustly predict future PD risk and are integral to the MDS prodromal PD research criteria. The criteria estimate individuals' probability of developing PD in coming years based on their age and the presence or absence of various PD risk and prodromal markers. Using a Bayesian approach, they aim to identify individuals at a high probability of impending PD clinical diagnosis to facilitate the design and efficiency of PD interventional trials.[31] This effort is equally valuable for epidemiological research to dissect the complex natural history of PD prodromal development and to identify contributions from genetic and nongenetic risk factors, as detailed elsewhere.[8] Therefore, a few epidemiological studies have begun to use this and similar concepts to investigate risk factors that may contribute to early PD development.[32-38] However, this line of research requires establishing the facile validity of these intermediate PD prodromal phenotypes across diverse populations.

The performance of the MDS criteria in predicting incident PD risk has been evaluated in several cohorts,[9-15,39] as summarized in Table S4. Although data are still limited, the MDS prodromal criteria perform reasonably well in high-risk individuals with idiopathic RBD[9] and LRRK2 mutation,[10] but their performance in general population studies varies significantly.[11-15,39] For example, using the

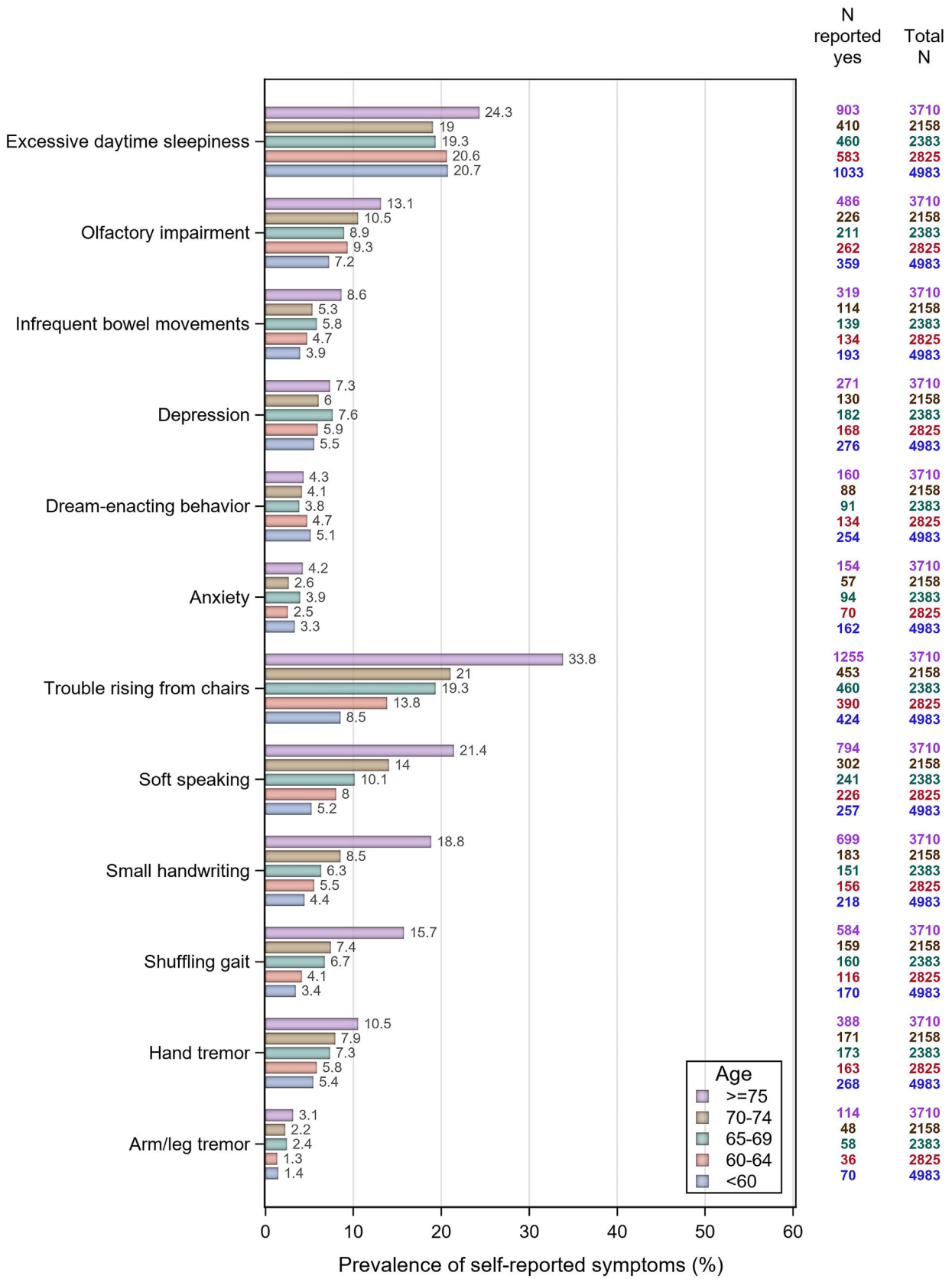

FIG. 1. Prevalence of nonmotor and motor symptoms of baseline population by age groups.

TABLE 2 *Baseline presence of nonmotor and motor symptoms in relation to incident PD*

		OR (95% CI)*	
	N, PD/non-PD	Model 1	Model 2
Olfactory impairment			
No	96/14,167	1 (reference)	1 (reference)
Yes	29/1515	2.6 (1.8, 3.8)	2.2 (1.5, 3.1)
Missing	2/250	–[a]	–[a]
Dream-enacting behavior			
No	101/14,496	1 (reference)	1 (reference)
Yes	14/713	3.1 (1.9, 5.0)	2.5 (1.5, 4.1)
Uncertain	11/492	3.3 (1.9, 5.6)	2.9 (1.7, 5.0)
Missing	1/231	–[a]	–[a]
Infrequent bowel movements			
No	98/13,807	1 (reference)	1 (reference)
Yes	17/882	2.4 (1.6, 3.8)	2.1 (1.3, 3.3)
Uncertain	10/995	1.2 (0.7, 2.1)	1.1 (0.6, 2.0)
Missing	2/248	–[a]	–[a]
Excessive daytime sleepiness			
No	64/8989	1 (reference)	1 (reference)
Yes	35/3354	1.6 (1.1, 2.2)	1.2 (0.8, 1.7)
Uncertain	25/3289	1.3 (0.8, 1.9)	1.1 (0.8, 1.7)
Missing	3/300	–[a]	–[a]
Depression			
No	113/14,635	1 (reference)	1 (reference)
Yes	12/1015	1.5 (0.9, 2.5)	0.9 (0.5, 1.7)
Missing	2/282	–[a]	–[a]
Anxiety			
No	114/15,101	1 (reference)	1 (reference)
Yes	11/526	2.7 (1.6, 4.6)	2.0 (1.1, 3.7)
Missing	2/305	–[a]	–[a]
Hand tremor			
No	101/14,571	1 (reference)	1 (reference)
Yes	25/1138	2.8 (1.9, 4.1)	1.8 (1.2, 2.9)
Missing	1/223	–[a]	–[a]
Arm/leg tremor			
No	115/15,389	1 (reference)	1 (reference)
Yes	11/315	3.9 (2.2, 6.8)	1.6 (0.9, 3.1)
Missing	1/228	–[a]	–[a]
Small handwriting			
No	98/14,237	1 (reference)	1 (reference)

(Continues)

TABLE 2 *Continued*

	N, PD/non-PD	OR (95% CI)*	
		Model 1	Model 2
Yes	28/1379	2.3 (1.6, 3.4)	1.3 (0.8, 2.0)
Missing	1/316	–[a]	–[a]
Soft speaking			
No	88/13,777	1 (reference)	1 (reference)
Yes	37/1783	2.4 (1.7, 3.4)	1.7 (1.2, 2.5)
Missing	2/372	–[a]	–[a]
Shuffling gait			
No	98/14,502	1 (reference)	1 (reference)
Yes	27/1162	2.6 (1.8, 3.8)	1.7 (1.1, 2.7)
Missing	2/268	–[a]	–[a]
Trouble rising from chairs			
No	84/12,739	1 (reference)	1 (reference)
Yes	42/2940	1.6 (1.2, 2.2)	1.1 (0.7, 1.5)
Missing	1/253	–[a]	–[a]
Motor impairment (≥2 motor symptoms)			
No	50/10,517	1 (reference)	1 (reference)
Yes	43/2145	3.1 (2.1, 4.5)	–[a]
Uncertain	33/3077	1.9 (1.3, 2.7)	–[a]
Missing	1/193	–[a]	–[a]

Abbreviations: PD, Parkinson's disease; OR, odds ratio; CI, confidence interval.
*Model 1 adjusted for linear and quadratic terms of age, state, education, marital status, and smoking status; model 2 additionally adjusted for all other individual symptoms within the same category (NMS [nonmotor] or MS [motor]) as the symptom under evaluation; accounting for proxy respondents and missingness in both PD status and the evaluated symptom, allowing inferences for all eligible PD-free participants in the AHS (Agricultural Health Study) phase 4 survey (N = 21,782).
[a]Calculation not needed.

cutoff as 50% or higher, the Hellenic Longitudinal Investigation of Aging and Diet (HELIAD) study[15] reported a low sensitivity (4.5%) and PPV (5.9%) of the MDS prodromal PD probability for predicting 3-year PD risk, whereas the Tübingen Evaluation of Risk Factors for Early Detection of Neurodegeneration cohort (TREND study)[11] showed moderate sensitivity (30%) and PPV (18.8%) in predicting 5-year PD risk. Unlike previous studies, our study participants were older farmers who might be at higher risk for PD due to environmental reasons. We assessed multiple PD prodromal NMSs and MSs along with various PD risk factors. However, the assessments relied entirely on self-reporting due to field feasibility. Nevertheless, we used symptom screening questions that are commonly used in other population-based studies,[5,20,21,40] and we confirmed their individual associations with incident PD risk in the expected direction and strengths. We further calculated the prodromal PD probability to the extent our data collection allowed, with and without considering the self-reported olfactory and motor impairment. Either way, the probability demonstrated little value in predicting future PD risk in this farming population with low sensitivity and PPVs.

Our results must be interpreted within the context of the study. Due to the remote nature of the study, we could not assess several markers with the highest LR+ values, such as PSG-proven RBD, subthreshold parkinsonism, tested olfactory loss, dopaminergic PET/SPECT scan, and orthostatic hypotension. This could significantly underestimate the probability of having prodromal PD in farmers who actually had these markers while potentially overestimating the probability for those who did not. However, these measures require clinical assessments that are often infeasible in large-scale screening. Our approach explores the potential of utilizing remotely accessible markers to estimate prodromal PD probability, potentially informing future large-scale PD studies where clinical assessments are not feasible.

It is challenging to identify prodromal PD in populations that are not genetically predisposed or

TABLE 3 *Baseline posttest prodromal PD probability in relation to incident PD*

Posttest probability (%)	MDS definition* PD (N = 127)	MDS definition* Non-PD (N = 15,932)	MDS definition* OR (95% CI)***	Secondary definition** PD (N = 127)	Secondary definition** Non-PD (N = 15,932)	Secondary definition** OR (95% CI)***
0–10	97	14,588	1 (reference)	85	14,261	1 (reference)
10–<30	27	1209	*2.3 (1.6, 3.5)*	19	1052	*2.1 (1.4, 3.4)*
≥30	3	135	2.5 (0.9, 6.6)	23	619	*4.7 (3.1, 7.2)*
30–<50	–[a]	–[a]	–[a]	*8*	*287*	*3.5 (1.8, 6.7)*
50–80	–[a]	–[a]	–[a]	*8*	*254*	*4.1 (2.2, 7.9)*
80–100	–[a]	–[a]	–[a]	7	*78*	*11.9 (5.7, 24.7)*
≥80% cutoff						
No	–[a]	–[a]	–[a]	120	15,854	1 (reference)
Yes	–[a]	–[a]	–[a]	7	78	*8.6 (4.2, 17.7)*
≥50% cutoff						
No	–[a]	–[a]	–[a]	112	15,600	1 (reference)
Yes	–[a]	–[a]	–[a]	15	332	*4.7 (2.9, 7.7)*
≥30% cutoff						
No	124	15,797	1 (reference)	104	15,313	1 (reference)
Yes	3	135	2.0 (0.7, 5.2)	23	619	*4.1 (2.7, 6.3)*
≥10% cutoff						
No	97	14,588	1 (reference)	85	14,261	1 (reference)
Yes	30	1344	*2.4 (1.6, 3.4)*	42	1671	*3.0 (2.1, 4.3)*

Abbreviations: PD, Parkinson's disease; MDS, Movement Disorder Society; OR, odds ratio; CI, confidence interval.
*Included all available risk markers and four prodromal markers (dream-enacting behavior, infrequent bowel movements, daytime sleepiness, and depression) in the calculation.
**Additionally included self-reported olfactory and motor impairments.
***Model adjusted for age (both linear and quadratic terms), state, education, marital status; accounting for proxy respondents and missingness in PD status, allowing inferences for all eligible PD-free participants in the AHS (Agricultural Health Study) phase 4 survey (N = 21,782).
[a]Data are not provided for analyses due to the small sample size.

TABLE 4 *Sensitivity, specificity, PPV, and NPV of prodromal PD probability in predicting incident PD*

	Sensitivity (%, 95% CI)*	Specificity (%, 95% CI)*	PPV (%, 95% CI)*	NPV (%, 95% CI)*
Posttest prodromal PD probability[a]				
≥30%	2.6 (0.9, 7.1)	99.1 (99.0, 99.3)	2.3 (0.8, 6.4)	99.2 (99.1, 99.4)
≥10%	24.5 (17.8, 32.6)	91.6 (91.1, 92.0)	2.2 (1.6, 3.1)	99.4 (99.2, 99.5)
Secondary definition[b]				
≥80%	5.6 (2.7, 11.0)	99.5 (99.4, 99.6)	8.1 (4.0,15.9)	99.3 (99.1, 99.4)
≥50%	12.2 (7.6,19.1)	98.0 (97.8, 98.2)	4.5 (2.8,7.2)	99.3 (99.2, 99.4)
≥30%	18.2 (12.5, 25.9)	96.2 (95.9, 96.5)	3.7 (2.5, 5.4)	99.3 (99.2, 99.5)
≥10%	32.9 (25.3, 41.4)	89.7 (89.3, 90.2)	2.4 (1.8, 3.3)	99.4 (99.3, 99.5)

Abbreviations: PPV, positive predictive value; NPV, negative predictive value; PD, Parkinson's disease; CI, confidence interval.
*Accounting for proxy respondents and missing data in PD status to extrapolate estimates back to all eligible PD-free participants of AHS (Agricultural Health Study) phase 4 survey (N = 21,782).
[a]Included all available risk markers and four prodromal markers (dream-enacting behavior, infrequent bowel movements, daytime sleepiness, and depression) in the calculation. No calculations beyond 30% due to small sample size.
[b]Additionally included self-reported olfactory and motor impairment.

otherwise highly susceptible. First, the risk of developing incident PD is relatively low in the general population. Further, PD prodromal development is inherently complex and heterogeneous and may span over 10 to 20 years, further complicating reliable identification and characterization of disease markers at any single time point.[41,42] With a few exceptions, markers used in the MDS criteria are not specific to PD, making it difficult to differentiate PD-relevant symptoms from those due to aging or other health reasons. Therefore, with the current evidence, the identification of prodromal PD candidates for interventional trials is still most promising in risk-enriched populations such as individuals with clinical RBD or an LRRK2 mutation.[9,10] The notion of identifying prodromal PD patients from the general population remains appealing but requires further research using novel ideas and approaches, including possible blood biomarkers.

Strengths of our study include the relatively large sample size, prospective study design, and assessment of a range of PD MSs and NMSs in a select occupational population. Our study also has limitations. First, study participants are older US farmers, predominantly white men, and thus, study findings may not be readily generalizable to populations with different demographics. Second, as detailed earlier, both NMSs and MSs are self-reported, and we were not able to assess many PD markers with high predictive values. Therefore, although our data provide important information on the lack of validity of this simplified approach to assess prodromal PD in population-based studies, it does not invalidate the importance of the MDS prodromal criteria, particularly for research in risk-enriched populations. Third, although the AHS cohort was not designed for PD research, it has systematically collected information on PD diagnoses, treatments, and relevant symptoms over several decades. Although we systematically adjudicated PD diagnosis in these longitudinal data using established protocols, this process did not incorporate in-person exams needed for clinical diagnosis.

In this large cohort of US farmers, although we confirmed the associations of NMSs and MSs with future PD risk, the MDS prodromal PD probability exhibited suboptimal performance in identifying prodromal PD patients, highlighting the practical difficulties of applying this approach in population-based studies without assessing the markers of high LR values. ■

Author Roles: (1) Research project: A. Conception, B. Organization, C. Execution; (2) Statistical analysis: A. Design, B. Execution, C. Review and critique; (3) Manuscript preparation: A. Writing of the first draft, B. Review and critique.
S.S. (Shengfang Song): 1A, 1C, 2A, 2B, 2C, 3A, 3B
Z.L.: 2A, 2B, 2C, 3B
B.L.P: 1B, 2C, 3B
X.H: 2C, 3B
Y.Y.: 2A, 2B, 2C, 3B
S.S. (Srishti Shrestha): 2C, 3B
C.G.P: 1B, 2C, 3B
J.N.H: 1B, 2C, 3B
L.E.B.F.: 1B, 2C, 3B
D.P.S.: 1B, 2C, 3B
H.C.: 1A, 1B, 1C, 2A, 2B, 2C, 3A, 3B

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Data Availability Statement

Requests for data, including the data used in this manuscript, are welcome as described on the study website (https://www. aghealth.nih.gov/collaboration/process.html). Data requests may be made directly at www.aghealthstars.com; registration is required. The Agricultural Health Study is an ongoing prospective study. The data sharing policy was developed to protect the privacy of study participants and is consistent with study informed consent documents as approved by the NIH Institutional Review Board.

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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.