Unawareness of motor phenoconversion in Huntington disease

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ABSTRACT

Objective: To determine whether Huntington disease (HD) mutation carriers have motor symptoms (complaints) when definite motor onset (motor phenoconversion) is diagnosed and document differences between the groups with and without unawareness of motor signs.

Methods: We analyzed data from 550 HD mutation carriers participating in the multicenter PREDICT-HD Study followed through the HD prodrome. Data analysis included demographics, the Unified Huntington's Disease Rating Scale (UHDRS) and the Participant HD History of symptoms, self-report of progression, and cognitive, behavioral, and imaging measures. Unawareness was identified when no motor symptoms were self-reported but when definite motor HD was diagnosed.

Results: Of 38 (6.91%) with onset of motor HD, almost half (18/38 = 47.36%) had no motor symptoms despite signs of disease on the UHDRS motor rating and consistent with unawareness. A group with motor symptoms and signs was similar on a range of measures to the unaware group. Those with unawareness of HD signs reported less depression. Patients with symptoms had more striatal atrophy on imaging measures.

Conclusions: Only half of the patients with newly diagnosed motor HD had motor symptoms. Unaware patients were less likely to be depressed. Self-report of symptoms may be inaccurate in HD at the earliest stage. *Neurology*® 2013;81:1141-1147

GLOSSARY

ANCOVA = analysis of covariance; **BDI-II** = Beck Depression Inventory-II; **CAP** = CAG-Age Product; **DCL** = diagnostic confidence level; **FrSBs** = Frontal Systems Behavior Scale; **HD** = Huntington disease; **HDHX** = Participant Huntington Disease History; **UHDRS** = Unified Huntington's Disease Rating Scale.

Patient unawareness of disease manifestations is documented in neurodegenerative diseases associated with cognitive impairment.¹ Unawareness or anosognosia, the pathologic unawareness of a neurologic or functional deficit,² is measured as “the discrepancy between the patient's self-report and the report of a natural caregiver or the clinical rating of a health professional.”³ Clearly, affected patients may have no complaints (symptoms), deny difficulty, and display lack of concern (anosodiaphoria) and insight into disease impact and, importantly, the need for care.^{4,5}

Evidence of unawareness in Huntington disease (HD) in the following studies focused mainly on individuals with a clinical diagnosis. Patients with HD have difficulty identifying their chorea, as contrasted with findings on an objective neurologic examination.⁶ Impaired self-awareness of the movement disorder is greater in HD than in Parkinson disease.⁷ Patients with HD have impaired awareness of their cognitive, emotional, and functional capacity compared with companion ratings and objective assessments.^{7,8}

The PREDICT-HD Study is a longitudinal observational investigation of those with the HD mutation but who do not meet criteria for a diagnosis of HD at study entry.⁹ In an earlier study of a subset of the PREDICT-HD sample, mutation carriers had significantly more frontal behaviors than noncarriers and a greater discrepancy in reporting frontal behaviors from the companion report in those closest to phenoconversion, consistent with unawareness.¹⁰

Supplemental data at
www.neurology.org

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PREDICT-HD coinvestigators are listed on the *Neurology*® Web site at www.neurology.org.

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Unawareness could influence accuracy of information about disease course when there is reliance on self-report alone. We analyzed the PREDICT-HD data at the third annual study visit to:

1. Examine whether patients with HD have motor symptoms at the time the rater records a motor diagnosis (phenoconversion) based on the findings of unequivocal signs on motor examination.
2. Document differences between the groups with unawareness of motor phenoconversion and without.
3. Determine whether there is a group with increased vigilance for possible HD symptoms and signs.

METHODS **Standard protocol approvals, registrations, and patient consents.** Five hundred fifty HD mutation carriers and 163 noncarriers (controls) from the PREDICT-HD Study (clinicaltrials.gov registry identifier NCT00051324) were included. All participants provided written informed consent as approved by their individual sites' Institutional Review Boards.

Participants. The participants did not know of this study hypothesis when they consented to join the PREDICT-HD Study. The study was not conceived at the time of data collection by motor raters. Observations at the third annual study visit provided a reasonable sample size for the grouping of interest. Demographics and data on a variety of domains were collected at each visit, including the Unified Huntington's Disease Rating Scale (UHDRS) and the Participant HD History (HDHX). Table 1 shows the 4 groups (A–D) identified by responses to 1) the self-report HDHX item 1 (“Since your last visit, have you noticed any symptoms that you feel are suggestive of HD?”), and 2) the motor examiner report UHDRS item 17 (“To what degree are you confident that this participant meets the operational definition of the unequivocal presence of an otherwise unexplained extrapyramidal movement disorder in a participant at risk for HD?”). Motor diagnosis is defined as a rating of 4 (≥99% rater confidence) on UHDRS item 17, known as the diagnostic confidence level (DCL). Those diagnosed at baseline or visit 2 were excluded, and because UHDRS item 17 refers to motor signs, participants reporting symptoms other than “Motor,” “Oculomotor,” or “Mixed” on HDHX item 3 (“Describe the symptom[s] that

you noticed since your last visit: Motor, Cognitive, Psychiatric, Oculomotor, Other, Mixed”) were also excluded. Unawareness was identified when no motor symptoms were self-reported but when a diagnosis of definite motor HD was made.

As seen in table 1, group A reported no symptoms and did not have a motor diagnosis. Group B reported symptoms but did not have a motor diagnosis. Group C reported no symptoms but had a motor diagnosis. Finally, group D reported symptoms and had a motor diagnosis.

Measures. Clinical. Trained examiners administered the UHDRS motor examination,¹¹ consisting of 15 primary items. The examiner rates the DCL based on the UHDRS motor examination that conveys the degree of likelihood that the participant has manifest HD ranging from 0 = no abnormalities to 4 = motor abnormalities that are unequivocal signs of HD (≥99% confidence). The UHDRS also includes the Total Functional Capacity score and a participant assessment of HD progression (UHDRS item 79: “Since your last assessment, do you feel improved, worsened, or about the same?”). At the first study visit, examiners record whether they are blinded to the participant's HD mutation status. For this sample, data were available for all participants except for one mutation carrier. Motor raters knew the gene status for 74% of the HD mutation carriers, and 71% of the noncarriers.

Self-report questionnaires. Frontal/executive dysfunction was rated using an adaptation of the Frontal Systems Behavior Scale (FrSBe),¹² a 24-item scale on which both participants and their companions (informants) rate the participant's severity and level of distress on a number of frontal/dysexecutive behaviors. Mood was assessed with the Beck Depression Inventory–II (BDI-II).¹³

Cognitive measures. Because they are robust clinical indicators of the disease process,¹⁴ motor speed was assessed using the Speeded Tapping Test¹⁵ and verbal memory using the Delayed Trial of the Hopkins Verbal Learning Test–Revised.¹⁶ Measures of executive functioning included a computerized tower task to assess planning and reasoning (similar to that used by Saint-Cyr et al.¹⁷) and the Interference task from the Stroop Interference Test.¹⁸

Imaging measures. MRI scans were obtained at the same visit as the clinical measures and acquired and analyzed using a standard protocol described in previous PREDICT-HD studies.^{19–24}

Data analysis. Two main methods of analysis were used: the χ^2 test of association for contingency tables, and analysis of covariance (ANCOVA) for comparisons between the groups. A χ^2 test of association was used to examine awareness group (groups A–D) responses to UHDRS item 79 (see above). For a comparison of symptoms reported by participant group (groups B and D), a χ^2 test was used. Analysis groups were compared on clinical, self-report, cognitive, and imaging measures by ANCOVA models, adjusting for age, sex, and education. Pairwise group comparisons were made with follow-up *t* tests.

RESULTS Table 2 presents demographic variables for the groups. The groups did not differ for female preponderance or education levels. Age difference was not statistically significant between the mutation carrier groups (groups A–D). Baseline progression was indexed by the CAG-Age Product or CAP score,²⁵ which is computed as CAP = (Age at entry) × (CAG – 33.66). CAP scores can be converted to a scaled CAP score (CAP_s) based on a 5-year probability of diagnosis from study entry.²⁵ While group D's CAP score was

Table 1 Definition of 4 awareness groups (A–D) for participants with HD mutation

UHDRS item 17	HDHX item 1: Since your last visit, have you noticed any symptoms that you feel are suggestive of HD?	
	No symptoms	Symptoms
DCL		
No Dx (rating of 0–3)	A (n = 427)	B (n = 85)
Dx (rating of 4)	C (n = 18)	D (n = 20)

Abbreviations: DCL = diagnostic confidence level; Dx = diagnosis; HD = Huntington disease; HDHX = Participant HD History; UHDRS = Unified Huntington's Disease Rating Scale.

Table 2 Demographics

	Group				
	A (no Sym, no Dx)	B (Sym, no Dx)	C (no Sym, Dx)	D (Sym, Dx)	E (control)
No.	427	85	18	20	163
Sex, % female	62.30	65.88	72.22	70.00	65.64
Age, y, mean (SD)	42.87 (10.01)	44.79 (9.43)	44.83 (11.28)	43.99 (8.05)	46.69 (10.98)
Education, y, mean (SD)	14.48 (2.73)	14.69 (2.78)	13.89 (2.81)	13.75 (2.00)	14.73 (2.61)
CAP, mean (SD)^a	337.98 (75.51)	349.66 (78.94)	387.99 (66.66)	460.30 (114.50)	NA

Abbreviations: CAP = CAG-Age Product; Dx = diagnosis; NA = not applicable; Sym = symptoms.

^aCAP = (Age at entry) × (CAG – 33.66).

significantly higher than that in other groups, the CAP score for the other diagnosed group (group C) was significantly higher than for groups A and B, indicating that these undiagnosed groups were further from estimated diagnosis.

Table 3 shows the frequency and percentage of responses to UHDRS item 79 by awareness groups. There was a statistically significant group effect, $\chi^2(6) = 155.52$, $p < 0.0001$, with a greater frequency of group D (symptoms, diagnosis) participants reporting decline than participants from other groups (63.2% vs 43.4% for group B, 11.8% for group C, and 3.6% for group A). The comparison between groups B and D was not statistically significant, $\chi^2(1) = 1.03$, $p = 0.3098$, indicating no evidence of a difference of symptom perception among the groups.

Table 4 shows the frequency and percentage of HDHX item 3 for the subcomparison of the symptomatic groups B and D. More than half of the participants in each group reported a decline of motor functioning relative to their previous visit.

Table 5 presents results for clinical, self-report, cognitive, and imaging variables. Analysis group means and SDs are displayed along with ANCOVA model results. Pairwise group comparisons are shown in the last column.

The ANCOVA results column indicates a statistically significant group effect for all variables. The group

comparison column shows the details of the inequalities. For every outcome, the control group had the best performance (e.g., smallest mean total motor score). Group C or D (i.e., manifest HD) or both had the worst performance or most negative mean score on most of the outcomes. However, groups reporting HD symptoms, group B (no diagnosis) along with D (diagnosis), had the most negative mean score on the BDI-II and the FrSBe. For most variables, group A (no symptoms, no diagnosis) had the second-best performance/positive mean score after the control group.

Comparison of groups C and D. Table 5 shows the group means and differences on the clinical, questionnaire, cognitive, and imaging measures between the 2 groups with a diagnosis, one group of patients with impaired awareness of motor symptoms (group C) and another without (group D). These 2 groups did not differ on their total motor score on the UHDRS or any cognitive measures, although they performed worse on these measures than the 2 other patient groups and the control group. Group C had significantly (albeit slightly) better functional capacity, less depressive symptoms, performed faster on a motor speed task, and had greater striatal and white matter volumes. Companions in group C reported significantly lower levels of dysexecutive behaviors on the FrSBe compared with group D; there was no statistically significant

Table 3 Participant self-ratings of HD progression (UHDRS item 79)

	Group				Total
	A (no Sym, no Dx)	B (Sym, no Dx)	C (no Sym, Dx)	D (Sym, Dx)	
HD progression					
Worsened	15 (3.6)	36 (43.4)	2 (11.8)	12 (63.2)	65
About the same	347 (82.2)	39 (47.0)	14 (82.4)	4 (21.1)	404
Improved	60 (14.2)	8 (9.6)	1 (5.9)	3 (15.8)	72
Total	422	83	17	19	541

Abbreviations: Dx = diagnosis; HD = Huntington disease; Sym = symptoms; UHDRS = Unified Huntington's Disease Rating Scale.

Data are n (%) by awareness group ($p < 0.0001$).

Table 4 Frequency (%) of symptoms reported (HDHX item 3) by group (B and D)

Symptom type	Group		Total
	B (Sym, no Dx)	D (Sym, Dx)	
Motor only	57 (67)	11 (55)	68
Mixed motor	28 (33)	9 (45)	37
Total	85	20	105

Abbreviations: Dx = diagnosis; Sym = symptoms; HDHX = Participant Huntington Disease History.

difference in FrSBe participant ratings between these groups.

Comparison of groups A and B. Table 5 also shows the group means and differences on the clinical, questionnaire, cognitive, and imaging measures between the 2 groups that did not have a diagnosis, one reporting symptoms (group B) and one without symptoms (group A). Group B participants returned a significantly higher motor score on the UHDRS, reported less functional capacity, had a higher level of depressive symptoms

(similar to group D), and were slower on the speeded tapping task. Participants and companions of group B reported greater dysexecutive behaviors compared with group A. These 2 prodromal groups did not differ on any of the cognitive or imaging measures. However, compared with the control group, both performed significantly worse on Verbal Memory and Stroop Interference and had smaller magnetic resonance volumes.

Post hoc correlation analyses. Examination of the results in table 5 suggested a relationship between dysexecutive behaviors (FrSBe) and depressive symptoms (BDI-II). To explore this possibility, correlations between these 2 measures for each of the groups were analyzed (table e-1 on the *Neurology*[®] Web site at www.neurology.org). In all groups, participants with increasing BDI-II scores also had significantly higher FrSBe scores. Similar significant results in the same direction were observed for companion ratings in groups A, B, C, and the controls. Companions had no significant correlation in group D.

DISCUSSION The main findings in this study were that half of the patients with newly diagnosed motor

Table 5 Mean (SD) for analysis groups

Measure	Group					ANCOVA result	Group comparison ^a
	A (no Sym, no Dx)	B (Sym, no Dx)	C (no Sym, Dx)	D (Sym, Dx)	Control		
UHDRS motor score	4.70 (5.2)	9.02 (6.6)	20.89 (6.9)	23.20 (11.1)	2.66 (2.8)	$F_{4,705} = 117.46$; $p < 0.0001$	C, D > B > A > Cont
UHDRS TFC	12.85 (0.7)	12.27 (1.2)	12.00 (1.9)	11.20 (2.0)	12.98 (0.2)	$F_{4,705} = 34.57$; $p < 0.0001$	D < B, C < A, Cont
FrSBe total-participant ^b	55.6 (16.4)	66.7 (23.7)	59.3 (24.2)	68.8 (25.6)	54.3 (14.8)	$F_{4,691} = 10.47$; $p < 0.0001$	B, D > A, Cont
FrSBe total-companion ^b	53.1 (17.9)	62.1 (23.0)	60.7 (22.0)	73.7 (29.4)	47.1 (13.0)	$F_{4,619} = 15.19$; $p < 0.0001$	D > B > A > Cont; D > C > Cont
BDI-II	5.71 (7.0)	12.86 (11.7)	7.39 (11.4)	14.55 (12.3)	4.40 (5.8)	$F_{4,703} = 23.51$; $p < 0.0001$	B, D > A, C, Cont
Speeded Tapping-nondominant index	253.1 (48.8)	274.9 (63.5)	308.9 (70.1)	380.3 (122.7)	232.9 (28.9)	$F_{4,684} = 45.70$; $p < 0.0001$	D > C > B > A > Cont
HVLT delayed recall	9.80 (2.1)	9.81 (1.8)	8.13 (2.3)	7.40 (3.4)	10.61 (1.7)	$F_{4,628} = 14.39$; $p < 0.0001$	C, D < A, B < Cont
Tower task	25.37 (6.5)	24.82 (6.0)	30.05 (8.6)	29.61 (7.3)	24.84 (5.5)	$F_{4,603} = 3.94$; $p = 0.0036$	C, D > A, B, Cont
Stroop Interference	47.00 (10.6)	44.72 (9.8)	36.18 (8.7)	32.25 (9.1)	48.43 (9.4)	$F_{4,695} = 18.01$; $p < 0.0001$	C, D < A, B < Cont
Striatum/ICV ratio	0.010 (0.002)	0.010 (0.001)	0.009 (0.001)	0.006 (0.001)	0.011 (0.001)	$F_{4,348} = 31.62$; $p < 0.0001$	D < A, B, C < Cont
White matter/ICV ratio	0.28 (0.03)	0.28 (0.03)	0.29 (0.03)	0.27 (0.03)	0.30 (0.03)	$F_{4,348} = 8.30$; $p < 0.0001$	D < A < Cont; B < Cont; D < C

Abbreviations: ANCOVA = analysis of covariance; BDI = Beck Depression Inventory-II; Cont = control; Dx = diagnosis; FrSBe = Frontal Systems Behavior Scale; HVLT = Hopkins Verbal Learning Test; ICV = intracranial volume; Sym = symptoms; TFC = Total Functional Capacity; UHDRS = Unified Huntington's Disease Rating Scale.

The less than (<) and greater than (>) symbols indicate a statistically significant group difference in the stated direction. A group that is not statistically different from any of the others is not listed. For example, on the FrSBe participant measure, groups B and D are not statistically different from each other but they are higher than group A and control, while group C is omitted because it is not statistically different from any other group.

^aResults of ANCOVA adjusting for age, sex, and education.

^bThe FrSBe total score is calculated by summing the products of the frequency and distress scores for items 1-18.

HD had unawareness and were without motor symptoms. These unaware patients were less likely to be depressed or to report progression. However, paradoxically aware patients had more striatal atrophy. The unaware group (group C) was similar on a range of measures—memory and executive functioning and motor score—to the group who reported symptoms and had a motor diagnosis (group D). Group B reported motor symptoms but had no motor diagnosis.

An unexpected finding was that groups C and D differed significantly on FrSBe companion scores ($D > C$; see table 5). This questionnaire may not be an accurate measure of frontal dysfunction associated with unawareness and may reflect a degree of depressive symptomatology. A relationship between depressive symptoms and reporting of dysexecutive behaviors on the FrSBe is shown in the supplementary material. The reliability of these subjective reports of frontal dysfunction is also questionable in the group with unawareness. In other studies, impairment on the Wisconsin Card Sorting Test correlated better with lack of awareness.⁸

Group C had significantly lower scores on the BDI-II than group D. The other symptomatic group, group B, also had a higher depression rating. Depression is unlikely to account for the motor symptoms in groups B and D. Depression may be reactive and related to awareness of onset of motor dysfunction. Greater insight and awareness would be expected to be associated with more depression.²⁶ The finding of less depression in group C suggests lack of insight in this asymptomatic group. In a recent review of suicide in dementia, preserved insight was a putative risk factor.²⁷

Participants in the PREDICT-HD Study are not informed of the HD diagnosis/phenoconversion by the research team, but some with more symptoms may have been given a formal diagnosis of HD onset by their treating HD specialist. Because group D had slightly more progression of HD, more symptoms would be expected, but group B although undiagnosed was symptomatic as well. In group B, there were more motor signs recorded on the UHDRS compared with group A. Group A participants (without a diagnosis or symptoms) had very subtle motor signs, were younger, and had a lower CAP score, being furthest from predicted onset. Symptoms reported in group B, although undiagnosed and with a lower motor rating than groups C and D, may represent hypervigilance but some may have had activities that required fine motor skills that are more sensitive to changes. Considering the range of overlap between the motor scores for groups B (9.02 ± 6.6) and C (20.89 ± 6.9), earlier diagnosis could have been given to some in group B but the DCL rating of 4 is a conservative assessment that there can be no doubt about the diagnosis.

Group C differed in other ways from the groups with symptoms (groups B and D). Group C was more likely to report no change or improvement since the visit the year before, again consistent with unawareness with 88% feeling the same or better and only 12% reporting decline. The participants in the symptomatic groups D and B were much more likely to report that they were the same or worse. There are other possible reasons for unawareness. With a very gradual change over many years, onset might not be noticed. Better knowledge of the disease including seeing an affected relative could influence symptom report. Some motor signs may not be associated with symptoms, i.e., eye-movement impairment. However, the UHDRS mean score in these groups is such that some signs would be expected to produce symptoms. If these individuals whose symptom report is at variance with findings on examination are included in a clinical trial, efficacy measures, based on self-report for an intervention, could be inaccurate. For participants classified as still prodromal, those with motor symptoms of HD (group B) had similar cognitive functioning on most measures to the asymptomatic, undiagnosed younger group A participants. Group B participants had significantly higher ratings of depression and more frontal/executive dysfunction compared with those who were “symptom-free” (group A). Interestingly, group B had similar ratings on some measures to the groups with an HD diagnosis (C and D) despite fewer signs of disease. Earlier care or intervention could be offered to a group of individuals identified with apparently heightened awareness in the prodromal stages.

There is clearly a group unaware of manifestations (group C). In addition, there is a group whose participants were more aware of motor symptoms (group B) even before a definitive diagnosis. Looking at the groups identified in this analysis, it appears that there is the expected progression of motor signs in the prodrome leading up to HD diagnosis but not a parallel progression of symptoms.

There were no significant differences in striatal volumes between the groups other than group D, who had a significant reduction of striatal volumes. In previous studies, patient self-reported ratings of “frontal” behaviors have not correlated with measures of striatal atrophy.¹⁰ Striatal and white matter volumes may be irrelevant in the study of unawareness but correlate better with motor manifestations and other measures of cognitive function. Imaging studies that target the likely area of pathology in unawareness have not been reported in HD. In other neurodegenerations, including Alzheimer disease, using a range of imaging modalities, the predominant changes were in the right dorsolateral prefrontal region.^{4,28–31} Orbito-frontal-limbic pathology is suggested as the likely trigger

for anosognosia/anosodiaphoria in HD.⁷ Neuroimaging in extrastriatal areas may be more informative.

This study addressed only the motor phenoconverters. There is increased recognition of cognitive/behavioral phenotypes.^{32–36} A more comprehensive study would include these other HD manifestations.

There is approximately 20% uptake of predictive testing.^{37,38} The PREDICT-HD participants are a select group of volunteers. Because pretest and posttest counseling programs are a requirement of predictive genetic testing, greater awareness of HD symptoms and signs would be expected in these tested participants. Unawareness in this group and unreliable symptom report could be more marked in the general population of those at risk. Unawareness has major implications for better defining the disease process, time of presentation for diagnosis and assistance, measures of progression, the impact of impaired function in daily activities including driving and in the workplace, as well as perception of possible discrimination and caregiver burden. Treatment, when available or for symptomatic disease features, could be delayed if the person fails to notice the changes taking place and to present for care.

Methods of measurement and documentation of unawareness in this earliest disease stage need further study. Possible measures in established HD and in frontotemporal dementia and Alzheimer disease are reported that include an anosognosia rating scale³⁹ as well as several neuropsychological measures of impairment in the anosognosia group, the Wisconsin Card Sorting Test and tests of visual-spatial ability on the Wechsler Adult Intelligence Scale–revised. Patients with HD studied using the Dysexecutive Questionnaire⁴⁰ rated their carer accurately but underrated their own executive dysfunction. Patients with HD self-reported higher ratings on a competency rating scale than their collateral's rating and disease severity correlated with measures of executive function.⁸ In particular, the collateral's rating of the patient's behavioral and functional competency correlated with the patient's number of Wisconsin Card Sorting Test perseverative responses and scores on the Dementia Rating Scale Initiation and Perseveration subscales and the Symbol Digit Modalities Test.

Although the numbers in this study are small, these results suggest that unawareness of HD motor changes occurs in a significant number of participants converting from the prodromal to the early stages of HD and that self-report of symptoms can be unreliable. Another group may overreport symptoms, or rater scores for diagnosis including use of the DCL rating are too conservative or not sufficiently accurate and objective to reflect subtle but definite HD signs.

These findings in this unique group of participants in the PREDICT-HD Study evolving to very early HD have implications for other neurodegenerations.

AUTHOR CONTRIBUTIONS

Elizabeth McCusker: concept and design, data acquisition, analysis and interpretation, and critical revisions. David Gunn and Eric Epping: data acquisition, analysis and interpretation, and critical revisions. Clement Loy and Kylie Radford: concept and design, data acquisition, analysis and interpretation, and critical revisions. Jane Griffith: data acquisition and critical revisions. James Mills: analysis and interpretation. Jeffery Long: analysis and interpretation and critical revisions. Jane Paulsen: funding, analysis and interpretation, and critical revisions.

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