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Journal of Gerontology: Medical Sciences (Accepted Author's Copy)

Intraindividual stepping reaction time variability predicts falls in older adults with Mild Cognitive Impairment

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Running page headline: RT variability, falls and MCI

ABSTRACT

BACKGROUND: Reaction time measures have considerable potential to aid neuropsychological assessment in a variety of healthcare settings. One such measure, the intraindividual reaction time variability (IIV), is of particular interest as it is thought to reflect neurobiological disturbance. IIV is associated with a variety of age-related neurological disorders, as well as gait impairment and future falls in older adults. However, although persons diagnosed with Mild Cognitive Impairment (MCI) are at high risk of falling, the association between IIV and prospective falls is unknown.

METHODS: We conducted a longitudinal cohort study in cognitively intact (n=271) and MCI (n=154) community-dwelling adults aged 70-90 years. IIV was assessed through a variety of measures including simple and choice hand reaction time and choice stepping reaction time tasks (CSRT), the latter administered as a single task and also with a secondary working memory task.

RESULTS: Logistic regression did not show an association between IIV on the hand-held tasks and falls. Greater IIV in both CSRT tasks, however, did significantly increase the risk of future falls. This effect was specific to the MCI group, with a stronger effect in persons exhibiting gait, posture or physiological impairment.

CONCLUSIONS: The findings suggest that increased stepping IIV may indicate compromised neural circuitry involved in executive function, gait and posture in persons with MCI increasing their risk of falling. IIV measures have potential to assess neurobiological disturbance underlying physical and cognitive dysfunction in old age, and aid fall risk assessment and routine care in community and healthcare settings.

Key words: falls, mild cognitive impairment, intraindividual variability; reaction time

INTRODUCTION

Over a third of older adults experience a fall each year (1), half of whom experience multiple falls (2). Risk factors for falls in older adults are multifaceted and include impairment in both physiological (3) and cognitive domains (4). Regarding the latter, it is well established that dementia-related cognitive deficits increase the risk of falling (5). However, recent research suggests that Mild Cognitive Impairment (MCI) in the absence of dementia is also associated with falls (6, 7). As there is a need to prolong independence and quality of life in community-dwelling older adults living with MCI, it is important to better understand factors associated with falls in this vulnerable group. Moreover, identifying people in pre-Alzheimer's disease is increasingly seen as the target for disease-modifying drug trials and for non-pharmacological interventions.

The present study investigated a potential assessment tool in relation to falls that has received considerable attention in the broader cognitive aging and neuropsychology literature. Intraindividual variability (IIV) refers to within-person fluctuations in cognitive performance, which is commonly operationalized as the trial-to-trial reaction time (RT) variability for a speed-related task. Increased IIV is thought to reflect fluctuations in attentional or executive control (8-10), and has been proposed as a behavioral marker of neurobiological disturbance (11). Empirical studies have shown IIV increases with age (12) and various neuropathological conditions including MCI (e.g. 13, 14, 15) and dementia (16).

As IIV is quick to measure, requires little neuropsychological training and provides reliable predictions of potential neuropathology (17), it has potential for use in clinical and community contexts. Moreover, as it captures both cognitive and motor components of RT performance, there is reason to expect an association between IIV and falls in older age. Falls have been related to impaired executive function (4) and there is the aforementioned theoretical link between IIV and executive control. White matter hyperintensities (WMH), particularly in frontal and periventricular regions, have been implicated in balance, gait and mobility impairment (18) and associated with future falls in older people (19). IIV has also been associated with frontal WMH burden in midlife (17, 20) and older age (21). Together, this evidence suggests that similar neurobiological circuitry and disturbance may underlie both greater variability and falls. Indeed, a recent review (22) produced evidence suggesting that IIV significantly predicted falls in cognitively intact adults living in the community. However, as little work has directly investigated IIV and falls specifically in community-dwelling adults with MCI, the present study sought to provide insights into those associations in this important group relative to cognitively intact controls.

In order to understand whether the risk of falling and IIV varies according to MCI, we explored the relationship using four different tasks: Simple *hand* RT (SRT), choice *hand* RT (CRT), choice *stepping* RT (CSRT), and CSRT with a secondary visuospatial working memory task (CSRT-WM). Dual-task paradigms have been studied extensively in relation to fall risk, but their value over standard single tasks has been recently questioned (23). Although falls have been associated with mean RT on the CSRT (24) and the CSRT-WM (25) tasks, the association between falls and IIV on those tasks has not previously been assessed. This is of interest as, relative to variability on the hand-administered tasks, we hypothesized that the association between IIV and falls would be stronger in the stepping tasks as they capture the demands needed for avoiding many falls more directly (i.e., those requiring volitional steps).

Additionally, a number of motor factors that may influence the relationship between IIV and falls are captured by measures of gait, posture and physiological function. It is suggested that gait and executive or attentional control mechanisms share common underlying brain circuitry that is vulnerable to age-related neuropathology (26). Consistent with this view, differences exist between persons with MCI and controls on gait variability measures, particularly in dual-task conditions (27). Impaired physiological function (e.g., poor visual acuity and proprioception) also increases the risk of falling (28). Although this has not previously been linked with IIV, associations between physiological function and cognition in predicting multiple falls have been shown (29). Given this body of work, we additionally hypothesized that associations between IIV and falls would vary according to gait, posture and physiological function.

METHODS

Participants

Participants of English-speaking background were drawn from Wave 1 of the Sydney Memory and Aging Study (MAS), a cohort of 1037 community-dwelling adults aged 70 years and over in Eastern Sydney (30). The first 500 recruits were invited to participate in a falls and balance sub-study (see 6, 31). Participants from the sub-study were included here if they also performed the RT tasks described below. There were no differences in demographic or health-related variables between this subsample and the main cohort.

MCI classification

Participants were classified for MCI according to international consensus criteria (32) where all of the following were met: (i) Subjective or informant complaint of cognitive decline, (ii) cognitive impairment on objective testing, (iii) normal or minimally impaired function according to the Bayer-Activities of Daily Living Scale (33), and (iv) no dementia as determined by a consensus diagnosis from a team of old age psychiatrists, neuropsychiatrists and neuropsychologists (see 30). MCI prevalence in the present sample (36.2%) was consistent with the full MAS sample (30, 34).

Falls

Falls were assessed over a one year follow-up period using monthly falls diaries and telephone calls where needed. A fall was defined as “an unexpected event in which the person comes to rest on the ground, floor, or lower level” (35). Following previous studies (6, 31), participants were classified as fallers if they experienced two or more falls during the follow-up period, or one injurious fall.

Simple and choice hand-administered RT tasks

Participants completed hand-administered SRT and CRT tasks employing touch screen technology. For the SRT task, participants responded as quickly as possible to 36 trials over two sessions where a yellow square appeared against a grey background (interstimulus interval either 1, 2 or 4 s). For the CRT task, 40 trials were administered across two sessions, in which two squares appeared vertically in one of four pseudorandomised configurations (red-red, yellow-yellow, red-yellow, yellow-red). Participants pressed the upper square if the colors were the same, or the bottom square if they were different, as quickly and as accurately as possible (interstimulus interval, 3 s). Prior to testing, practice trials were administered until participants made four correct responses.

Prior to calculating variability metrics, we removed error trials for the CRT task, and trimmed unusually fast RTs as these were likely to represent accidental screen presses (SRT, <250 ms; CRT, <400 ms) and following previous studies (12), RTs greater than 3 *SD*s above the age group task mean. Missing trials were replaced by imputing values using a regression procedure (replaced trials = <1% for SRT, <4% for CRT). Intraindividual *SD*s and mean RT metrics were then computed. To obtain the most reliable estimates, metrics were averaged across the two sessions.

Choice Stepping Reaction Time

The CSRT task used a non-slip black platform (0.8 x 0.8 cm) containing four rectangular panels (32 x 13 cm). Participants stood with their feet 12 cm apart with one panel in front, and to the side of each foot (see 24). For each trial, participants stepped onto a single illuminated panel as quickly as possible using the appropriate foot. Two RT measures were recorded: Trial *total-RT* represented the time from the panel illumination to foot contact with the correct panel; *response-RT* was the time from panel illumination to lifting the appropriate leg prior to stepping. The CSRT task was completed under single- and dual-task conditions, the latter involving a concurrent visuospatial working memory task (CSRT-WM: see 25). For both conditions, participants completed four to eight practice trials, followed by 20 test trials. Here, the intraindividual *SD* and mean RT were computed using total-RTs and response-RTs for both CSRT and CSRT-WM tasks.

Gait and posture assessment

Gait and posture were assessed by trained researchers using items from the Unified Parkinson's Disease Rating Scale – Section III: Motor Section (36) performed during a 6 m walk. For *gait*, participants were classified as either "normal", "loss of arm-swing", "walks slowly", "walks with difficulty", "severe gait disturbance", or "cannot walk". Scores were recoded into two categories representing "normal gait" or "abnormal gait" (any category outside of normal). For *posture*, participants were coded as either "normal", "slightly stooped", "moderately stooped", "severely stooped" or "extremely stooped". Here, scores were recoded into either "normal posture" or "abnormal posture" (any category outside of normal). Correlations between these measures and the timed 6 m walk were between .32 and .43 (*p*s<.001).

Physiological Profile Assessment

The Physiological Profile Assessment (*PPA*) estimates physiological falls risk from five measures (visual contrast sensitivity, lower limb proprioception, quadriceps strength, simple RT, postural sway: see 3, 31). Following earlier work identifying the cut-off best distinguishing fallers from non-fallers (31), the PPA was recoded categorically where scores ≥0.60 were classed as high falls risk and scores <0.60 as low risk.

Statistical analyses

The data were analyzed using IBM SPSS version 20. Missing data for CSRT (1.6%), CSRT-WM (8.1%) and SRT and CRT tasks (0.9%) were imputed using the multiple imputation procedure. A series of logistic regression models were run with falls (yes/no) as the outcome measure and IIV or *M* RT as predictor variables. As the aim was to investigate the differential relationship between IIV and falls in the MCI and normal cognition groups, all models were run separately for MCI and non-MCI participants. We adjusted for years of education and sex at Step 1 of the regressions and added the cognitive measure at Step 2. To establish how far gait, posture or PPA accounted for associations between variability and falls, models were re-run separately with either gait, posture, or PPA added at Step 1, and their association with variability tested at Step 3 (using a cross-product interaction term). We did not adjust for age as our underlying premise was physiologically-based whereby the effects of age would manifest in one or more of the physiological measures assessed. Therefore, inclusion of age in the multivariate models may result in "over-adjusting" and dilution of important explanatory findings (37).

RESULTS

Demographic details of the current sample are presented in Table 1. As fallers and non-fallers differed on years of education, this variable was taken into account in analyses reported below.

Table 1 about here

Simple and choice hand-administered RT

For the hand-administered tasks, variability did not emerge as a significant predictor of falls for either SRT or CRT in both the MCI group or normal cognition groups (see Table 2, left column). Mean RT also failed to predict falls for either task[1]. Due to the nonsignificant findings, these tasks were not considered further in analyses.

Table 2 about here

Choice stepping RT

For the stepping tasks, in the MCI group, variability emerged as a significant predictor of falls (see Table 2, right column) for both response- and total-RT in the single- and dual-task conditions. By contrast in the normal cognition group, variability failed to predict falls using either measure. With respect to mean RT, only the single-task response-RT showed a significant relationship with falls[1]. As increases in variability may be related to general RT slowing (all variability-mean RT *r*s ≥.64, *p*s<.001), Model 1 was re-run controlling for mean RT. This did not affect the significant associations between variability and falls in the single-task condition, and for the dual-task condition, the predictive power of variability was attenuated (*p*=.090), although the trend remained the same.

Gait, posture and PPA

In the MCI group, adding gait, posture or PPA to the models did not affect the predictive utility of the variability measures (see Table 3). However, there was evidence that the strength of

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[1] We repeated the models adjusting for falls in the past 18 months. This made no difference to the reported analyses.

association varied as a function of these variables. For the single-task condition there was a significant Gait x IIV and Posture x IIV interaction. Within group analyses revealed that in participants with abnormal gait (n=50) or posture (n=64) variability was a significant predictor of falls, (Gait: total-RT, OR=6.84, p=.004; response-RT OR=8.34, p=.004; Posture: total-RT, OR=3.23, p=.001; response-RT, OR=3.57, p<.001) whereas in the participants with normal gait (n=88) or normal posture (n=74) variability failed to predict falls. For PPA scores, although the PPA x IIV interaction term was nonsignificant, a similar trend was observed. In the high falls risk group (n=95), variability predicted falls (total-RT, OR=1.79, p=.014; response-RT, OR=2.05, p=.004) whereas in the low falls risk group (n=45), it failed to predict falls. In respect to the non-MCI group, taking gait, posture or PPA into account did not influence the nonsignificant relationship between IIV and falls.

Finally, adjusting for age in the above analyses did not affect any of the findings.

DISCUSSION

This study extends previous research by investigating associations between IIV for hand and stepping RT tasks and falls in individuals with MCI and intact cognition. There were several interesting findings. First, the expectation of a relationship between falls and variability in the stepping task due to the weight and balance transfer demands captured by the task, was confirmed. Importantly, this effect was specific to participants with MCI whereas in cognitively intact persons, stepping variability failed to predict falls. Second, the strength of association between stepping IIV and falls in the MCI group was related to gait and posture, and PPA status. Finally, no significant associations were found between the hand-administered RT tasks and falls.

The findings suggest that IIV measures may provide useful insights into possible neurobiological disturbance underlying physical dysfunction and falls risk in old age. Variability has been theoretically linked to fluctuations in attentional or executive control (8-10) and is thought to be a behavioral marker of neurobiological decline (11). It has also been proposed that executive control and gait share common frontal brain circuitry that is vulnerable to age-related neuropathology (26). As gait abnormalities have been identified in individuals with MCI (e.g., 38) and there is work showing IIV is related to frontal white matter integrity in both healthy aging and early Alzheimer's disease (e.g., 21, 39), it is possible that IIV is capturing compromised neural circuitry in MCI that is also implicated in both executive control and gait. The present findings suggest that possible compromise to these brain structures captured by IIV may also contribute to falls in older adults with MCI. The nonsignificant findings for the stepping task in respect to the cognitively intact group is most likely due to IIV not reaching a sufficiently high level in this group to be predictive of falls. However, although requiring further research, these findings suggest that variability measures may supplement existing gait and walking assessment tools and help identify persons, particularly those with MCI, at risk of future falls.

The results contrast with previous research suggesting that IIV on hand-administered RT tasks is associated with falling (22). In the present study, significant associations between IIV and falls were only evident in the stepping task and not for the hand-administered RT tasks. This is not surprising as the stepping RT task captures the demands required in avoiding a fall more directly. Furthermore, the contrast with the hand-administered tasks may stem from earlier studies using variability measures that placed greater demands on higher-order executive control (e.g., go-no-go tasks). IIV in these measures may more directly tap the brain circuitry governing gait and posture, and relatedly, falls. It is also of note that for the CSRT task, the findings suggest that variability in both central processing and movement time was related to falls. Specifically, as response-RT draws upon central processing in deciding and initiating the appropriate motor output, while total-RT includes both central processing and the movement time (25), the results suggest that there are both cognitive and motor contributions to the overall variability associated with falls.

Previous work has related falls to mean RT in the single-condition CSRT task (24). Here we have extended this research by also investigating falls in relation to a dual-task condition. In line with a recent systematic review that found dual-task assessments of gait speed provided no additional value in predicting falls in older people, including those with cognitive impairment (23), the relationship between variability and falls was stronger for all measures in the MCI group in the single, as opposed to the dual-task condition. This likely indicates the single CSRT task appropriately assesses the ability to take quick and accurate steps for fall avoidance and is sufficient to discriminate between those with a low and high fall risk. Additionally, controlling for mean RT did not affect variability-falls associations in the single task, although they were attenuated in the dual-task condition. Although there are reports that mean RT is a stronger predictor of outcomes in old age than measures of within-person variability (e.g., 40), overall, the present findings suggest that the variability measure captured underlying processes that were independent of mean RT.

Although strengths of the study include the large community-based sample, use of a detailed diary procedure to prospectively measure falls, and diagnosis of MCI using recognized clinical criteria, there are some potential limitations. First, RT measures of variability were obtained from a single time-point and future research should investigate longitudinal associations between IIV and falls as this may give insights into the causal structure of relations in older persons with MCI. Additionally, errors in the CSRT task may represent a potential confound to the findings. As participants corrected step errors during the trial, it is possible that such errors increased RTs, thereby inflating the variability measure. However, when analyses were re-run adjusting for error rates, the original results were unaffected, suggesting that errors did not influence the relationship between IIV and falls.

To conclude, this study used a large community-based sample to investigate the relationship between within-person variability and prospective falls in older adults with MCI. Although previous studies have investigated the association between IIV and falls using computerized measures, this is the first study to contrast hand-administered and stepping RT tasks. In persons with MCI, there was a strong association between falls and variability in the stepping tasks, but not in the hand-administered tasks. The association was stronger in MCI sufferers with poorer gait, balance and PPA scores. The findings suggest that IIV may be sensitive to overlapping neural circuitry that is compromised in MCI and implicated in gait and posture deficits that may increase the risk of falling in old age. As such, IIV measures may not only provide valuable insights into the cognitive and motor factors underlying falls in old age, but also have the potential to supplement existing neuropsychological assessment measures in clinical contexts.

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Table 1. Descriptive Statistics

		Normal cognition		MCI	
		Fallers	Non-fallers	Fallers	Non-fallers
Sample size[a]		91 (76)	180 (154)	55 (53)	99 (87)
Age		80.0 (4.9)	77.4 (4.3)	78.5 (4.5)	78.6 (4.6)
Years in education		11.8 (3.4) *	11.0 (3.1)	12.3 (3.9) *	10.9 (3.3)
Sex (% male)		36.3	45.0	60.0	49.5
MMSE		28.5 (1.4)	28.3 (1.2)	27.8 (1.7)	27.4 (1.6)
Physiological measures					
Posture (% impaired)		29.9	29.9	46.2	46.5
Gait (% impaired)		27.6	24.0	28.8	47.7
PPA (% high risk)		73.7	54.5	73.6	64.4
Reaction time tasks (ms)					
SRT	IIV	320.1 (320.9)	318.1 (271.4)	313.0 (229.2)	393.9 (320.2)
	MRT	620.9 (201.6)	592.5 (161.4)	674.9 (218.5)	704.1 (287.6)
CRT	IIV	276.6 (126.5)	246.1 (102.4)	286.5 (108.4)	287.0 (118.8)
	MRT	945.3 (180.1)	911.9 (157.8)	1023.1 (247.5)	1040.2 (251.4)
CSRT					
Total-RT	IIV	307.0 (212.7)	331.8 (235.9)	459.9 (312.4) *	347.6 (308.5)
	MRT	966.8 (192.3)	974.7 (198.0)	1103.8 (264.9)	1081.5 (242.3)
Response-RT	IIV	271.1 (209.0)	301.2 (239.0)	433.1 (310.2) *	302.8 (301.1)
	MRT	632.9 (137.3)	642.0 (145.2)	747.7 (212.1)	701.3 (167.2)
CSRT-WM					
Total-RT	IIV	875.9 (539.2)	876.8 (747.0)	1338.3 (1192.4)	1036.8 (528.6)
	MRT	1654.3 (629.9)	1635.0 (710.5)	2208.8 (1025.7)	1984.1 (786.1)
Response-RT	IIV	853.9 (535.5)	813.8 (592.2)	1268.5 (1110.3)	990.8 (535.3)
	MRT	1280.1 (566.8)	1242.3 (660.3)	1763.4 (923.1)	1529.4 (731.4)

Notes: [a] Numbers in parentheses= participants with CSRT data. PPA= Physiological Profile Assessment; SRT= Simple Reaction Time; CRT= Choice Reaction Time; CSRT(-WM)= Choice Stepping Reaction Time (with working memory task); MRT= Mean RT; *p<.05

Table 2. Logistic Regression Predicting Falls Status from Variability in the MCI Group.

Hand-administered				Stepping			
Step	Condition	B (SE)	Odds ratio	Step	Condition	B (SE)	Odds ratio
1	Education	0.10 (0.05)	**1.11* (1.01-1.22)**	1	Education	0.10 (0.05)	**1.11* (1.01-1.22)**
	Sex	0.32 (0.35)	1.37 (0.69-2.72)		Sex	0.28 (0.36)	1.33 (0.65-2.70)
SRT				CSRT Total-RT			
2a	IIV	0.28 (0.17)	1.32 (0.94-1.86)	2a	IIV	0.44 (0.19)	**1.56* (1.07-2.25)**
2b	MRT	0.14 (0.17)	1.14 (0.82-1.59)	2b	MRT	0.19 (0.18)	1.21 (0.84-1.73)
CRT				CSRT Response-RT			
2c	IIV	0.04 (0.17)	1.04 (0.74-1.46)	2c	IIV	0.52 (0.19)	**1.68** (1.15-2.45)**
2d	MRT	0.10 (0.17)	1.11 (0.79-1.55)	2d	MRT	0.38 (0.19)	**1.46* (1.01-2.10)**
				CSRT-WM Total-RT			
				2e	IIV	0.42 (0.19)	**1.52* (1.03-2.22)**
				2f	MRT	0.26 (0.18)	1.30 (0.92-1.84)
				CSRT-WM Response-RT			
				2g	IIV	0.40 (0.20)	**1.50* (1.02-2.19)**
				2h	MRT	0.19 (0.18)	1.21 (0.84-1.73)

Notes: SRT= Simple Reaction Time; CRT= Choice Reaction Time; CSRT(-WM)= Choice Stepping Reaction Time (with working memory task); MRT= Mean RT. *p<.05,**p<.01. MRT and IIV models run separately. All models adjusted for education and sex.

Table 3. Logistic Regression Predicting Falls Status from CSRT Variability in the MCI group.

		Gait		**Posture**		**PPA**	
Step	Condition	B (SE)	Odds ratio	B (SE)	Odds ratio	B (SE)	Odds ratio
1	Education	0.10 (0.05)	**1.11* (1.00-1.22)**	0.10 (0.05)	**1.11* (1.00-1.22)**	0.10 (0.05)	**1.11* (1.00-1.22)**
	Sex	0.40 (0.37)	1.49 (0.72-3.07)	0.36 (0.37)	1.43 (0.70-2.96)	0.33 (0.37)	1.39 (0.68-2.84)
	Physiological measure	-0.55 (0.39)	0.58 (0.27-1.23)	-0.05 (0.36)	0.95 (0.47-1.93)	0.47 (0.39)	1.60 (0.74-3.46)
	CSRT						
2a	Total-RT IIV	0.42 (0.19)	**1.52* (1.04-2.21)**	0.46 (0.20)	**1.58* (1.08-2.33)**	0.43 (0.19)	**1.55* (1.07-2.24)**
3a	Interaction[a]	1.07 (0.49)	**2.90* (1.11-7.61)**	1.32 (0.43)	**3.73** (1.59-8.72)**	0.43 (0.38)	1.53 (0.73-3.22)
2b	Response-RT IIV	0.48 (0.20)	**1.62* (1.10-2.37)**	0.53 (0.22)	**1.70** (1.15-2.50)**	0.52 (0.19)	**1.68**(1.15-2.45)**
3b	Interaction[a]	1.31 (0.56)	**3.71* (1.25-11.01)**	1.32 (0.43)	**3.76** (1.61-8.78)**	0.55 (0.39)	1.74 (0.82-3.70)
	CSRT-WM						
2c	Total-RT IIV	0.46 (0.20)	**1.58* (1.07-2.33)**	0.46 (0.20)	**1.58* (1.07-2.35)**	0.42 (0.19)	**1.52*(1.04-2.23)**
3c	Interaction[a]	0.39 (0.43)	1.47 (0.63-3.41)	0.80 (0.46)	2.21 (0.91-5.40)	0.14 (0.39)	1.14 (0.53-2.46)
2d	Response-RT IIV	0.45 (0.20)	**1.57* (1.06-2.32)**	0.44(0.20)	**1.55* (1.05-2.31)**	0.41 (0.19)	**1.50*(1.03-2.20)**
3d	Interaction[a]	0.36 (0.42)	1.43 (0.62-3.24)	0.78 (0.44)	2.18 (0.92-5.18)	0.20 (0.38)	1.22 (0.58-2.55)

Notes: [a]This refers to the IIV x Gait or Posture or PPA interaction; CSRT(-WM)= Choice Stepping Reaction Time (with working memory task); PPA= Physiological Profile Assessment; * *p*<.05,***p*<.01. All models adjusted for education and sex.