

# Gait slowing as a predictor of incident dementia: 6-year longitudinal data from the Sydney Older Persons Study

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## Abstract

Current definitions for the preclinical phase of dementia focus predominantly on cognitive measures, with particular emphasis on memory and the prediction of Alzheimer's disease. Incorporation of non-cognitive, clinical markers into preclinical definitions may improve their predictive power. The Sydney Older Persons Study examined 6-year outcomes of 630 community-dwelling participants aged 75 or over at recruitment. At baseline, participants were defined as demented, cognitively intact or having a syndrome possibly representing the preclinical phase of Alzheimer's disease, vascular dementia, an extrapyramidal dementia or various combinations of the three. Those with cognitive impairment in combination with gait and motor slowing were the most likely to dement over the 6-year period (OR 5.6; 95% CI 2.5–12.6). This group was also the most likely to die (OR 3.3; 95% CI 1.6–6.9). White matter indices on MRI scanning were not consistently correlated with gait abnormalities. Simple measures of gait may provide useful clinical tools, assisting in the prediction of dementia. However, the underlying nature of these deficits is not yet known.

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## 1. Introduction

Identifying states that will predict the subsequent development of dementia has important implications for future therapeutic interventions. Much current focus is upon the entity of Mild Cognitive Impairment (MCI) [1,2]. However, it is argued that MCI may be a heterogeneous entity, with possible subtypes existing for the non-Alzheimer dementias [2,3]. Furthermore, there may be non-cognitive markers that predict the progression of MCI to dementia. Extrapyramidal signs in non-demented subjects are associated with higher mortality, increased functional impairment and the subsequent development of dementia [4–10]. Gait abnormalities have been found to precede the onset of dementia by many years. In the Bronx

Aging Study of community living participants aged 75 and over, abnormalities of gait including unsteadiness, frontal gait disorders and hemiparetic gaits predicted the development of non-Alzheimer dementias over a median period of 6.6 years [11]. Over a 6-year period, the Oregon Brain Ageing study of initially well participants aged 65 and over, found that a longer time to complete a 30-ft walk was an independent predictor of persistent cognitive deficits [12].

Therefore, signs of extrapyramidalism and slowing of gait may act as clinical markers for the increased likelihood of progressing to dementia. This study aims to examine the predictive role of extrapyramidalism and slowing of gait in the development of incident dementia and mortality in a sample of individuals who were community dwellers and aged 75 and over at baseline. It was hypothesised that gait abnormalities would prove to be a useful adjunct in predicting those participants who would subsequently dement or die within the 6-year study period.

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## 2. Materials and methods

A sample of 630 non-institutionalised men and women aged 75 years or older residing in the Central Sydney Area Health Service participated in the Sydney Older Persons Study from 1991 to 1993 [13–15]. Participants were assessed at baseline and on a further three occasions—at 3 years, at 5 years for collection of blood samples including DNA and at 6 years for further reassessment. Data from baseline, 3- and 6-year follow-ups are presented in these analyses. By the 6-year follow-up, 226 (35.9%) participants had died, 33 (5.2%) were lost to follow-up and a further 64 (10.2%) refused to be interviewed. An additional 8 (1.3%) participants were alive but due to ill-health or distance were not seen. Those who died were older, more likely to be male and more likely to be cognitively impaired at baseline. Refusals and non-contacts did not differ in age or Mini-Mental State Examination (MMSE) score at baseline [16]. At all assessments, participants gave written informed consent and the study had institutional ethics approval.

Of the 630 participants at baseline, 522 participated in a medical assessment which included; a standardised medical history examining past and current health and medication usage; a neuropsychological battery and physical examination. Diagnoses of dementia using this baseline information were assigned by the clinician using DSM-III-R criteria [17]. As this study aims to examine the predictors of dementia, only participants not demented at baseline are included in analyses. Diagnoses of dementia at 3- and 6-year follow-ups fulfilled the general DSM-IV criteria (criteria A and B) [18]. Regular meetings were held reviewing dementia diagnoses over the course of the study to ensure consistency. In those participants at 3- and 6-year follow-ups where no assessment was possible or where participants had died, an informant questionnaire [19] which examined the six domains of the Clinical Dementia Rating (CDR) was used to identify incident dementia cases in order to achieve more complete case ascertainment (sensitivity 80%, specificity 98%). Participants assessed by the informant questionnaire were diagnosed as demented if they were rated as mildly, moderately or severely demented according to the informant CDR. Thus, in using both the clinical and informant data, we were able to include 394 (91.6%) of the 430 participants not demented at baseline in analyses examining incident dementia at 3 and 6 years. For mortality analyses, 428 participants not demented at baseline are included at 3 years and 417 at 6 years.

Preclinical syndromes for the three main dementias, Alzheimer's disease (AD), Vascular dementia (VaD) and the extrapyramidal dementias (EPD) were defined [9]. It was also necessary to define multi-pathology preclinical syndromes as 34% of dementia cases were found to be multi-aetiological at baseline [14]. As vascular and extrapyramidal features may be present initially without evidence of cognitive deficits, distinct sets of preclinical syndromes

for VaD and EPD with or without cognitive deficits were defined.

Participants were hypothesised to have preclinical AD if they showed cognitive impairment without vascular or extrapyramidal features, termed here CI. Participants were clinically defined as having cognitive impairment if they displayed mild to moderate deficits in one or more areas of cognition (memory, language, visuospatial or executive function) but did not reach DSM-III-R criteria for dementia.

VaD is characterised by dementia with historical or clinical evidence of stroke in association with other vascular disease and the presence of vascular risk factors. At a pre-dementia syndromal stage, any of these characteristics may be expected. Participants met the pre-vascular criterion if they had experienced either a transient ischaemic attack or stroke or they had three or more vascular risks (atrial fibrillation, diabetes, hypertension, heart disease, claudication, self-reported hypercholesterolaemia or smoking). TIA and stroke were diagnosed according to history and clinical evaluation. Neuroimaging was not available at baseline assessment. Diabetes and hypertension were diagnosed from medical history, including review of relevant medications for treatment of these conditions. Heart disease was inclusive of all types of heart disease including both ischaemic and valvular. The pre-vascular group, termed preVasc, included participants with vascular features exclusively. Another group, CI+preVasc, included participants with additional cognitive impairment.

The extrapyramidal (EP) features associated with EPD include bradykinesia, rigidity and tremor. At a pre-dementia stage, such features, of lesser severity, would be expected to occur in association with varying levels of cognitive deficits. Two components comprised the EP measure. The first component was an EP score. This EP score included severity graded measures of tone (rigidity, cogwheeling, nuchal rigidity), bradykinesia (slowed fine finger movements, reduced arm swing and an overall clinical assessment of the presence of bradykinesia), resting tremor, postural flexion and the glabella tap. A cutoff of one or more in the EP score was used corresponding to either one severe sign, one moderate and one mild sign or three mild signs. The second component was an objective measure of extrapyramidal gait changes as assessed by the time to complete the 5-m returned walk, controlled for causes of mechanical slowing such as arthritis. Participants who had either a slowed 5-m returned walk or scored one or more in the EP score were included in the EP prodromal group. The EP groups were termed preEP and CI+preEP when occurring without or with cognitive deficits, respectively.

As both vascular and extrapyramidal features may co-exist, two groups termed preVasc+preEP and CI+preVasc+preEP were also created. Thus, a total of seven preclinical groups were created: three denoting a single underlying pathology: CI, preVasc and preEP; and four denoting multiple underlying pathologies: CI+preVasc, CI+preEP, preVasc+preEP and CI+preVasc+preEP.

Table 1  
Distribution and odds ratios of preclinical syndromes progressing to dementia at 3 and 6 years

Clinical status	n (%)	Demented (%)		OR (95% CI)	
		Baseline	3 years	6 years	3 years
Well	126 (32.8)	6 (4.8)	22 (17.5)	1 <sup>a</sup>	1 <sup>a</sup>
CI	72 (17.3)	15 (20.8)	29 (40.3)	5.3 (1.9–14.3)	3.2 (1.6–6.2)
PreVasc	50 (12.4)	2 (4.0)	9 (18.0)	0.8 (0.2–4.3)	1.0 (0.4–2.4)
CI+preVasc	24 (5.6)	5 (20.8)	8 (33.3)	5.3 (1.5–19.0)	2.4 (0.9–6.2)
PreEP	40 (10.1)	5 (12.5)	9 (22.5)	2.9 (0.8–9.9)	1.4 (0.6–3.2)
CI+preEP	35 (9.4)	12 (34.3)	19 (54.3)	10.4 (3.6–30.6)	5.6 (2.5–12.6)
PreVasc+preEP	26 (7.0)	5 (19.2)	7 (26.9)	4.8 (1.3–17.0)	1.7 (0.6–4.6)
CI+preVasc+preEP	21 (5.4)	8 (38.1)	9 (42.9)	12.3 (3.7–41.0)	3.6 (1.3–9.4)

<sup>a</sup> Reference group.

Using well participants as the reference group, a logistic regression model examined whether the preclinical syndromes (both as a group and as individual syndromes) were predictive of dementia and death at 3 and 6 years.

At the 6-year evaluation, participants were invited to participate in an MRI scan. Participants needed to be able to give informed consent and be well enough to be transported to the MRI scanner. This procedure therefore excluded those with more significant cognitive or functional impairment resulting in a healthy survivor cohort. MRI assessments were carried out on a G.E. Signa 1.5T scanner and periventricular and deep white matter changes were rated [20]. Size (mm) of periventricular white matter lesions (WML) was recorded in three regions; frontal caps, lateral bands and occipital caps. Deep WML were rated in four regions; frontal, occipital, temporal, and parietal. In each region, the lesions were rated according to number and size and WML volume (cm<sup>3</sup>) ascertained. Periventricular and deep WML measures were correlated with the EP score and timed walk as measured at the 6-year review.

### 3. Results

The odds of any preclinical syndrome resulting in dementia at 3 years was 4.8 (95% CI 2.0–11.5,  $p < 0.001$ ) and at 6 years was 1.7 (95% CI 1.1–2.6,  $p < 0.05$ ). The prevalence of the preclinical syndromes is shown in Table 1. The percentage of patients developing dementia

and the odds of each preclinical syndrome resulting in dementia at both 3 and 6 years is also shown in Table 1.

Preclinical syndromes affected approximately two-thirds of the non-demented study population. Those with CI were the most prevalent. At the 3-year assessment, all preclinical syndromes were at greater risk of progressing to dementia with the exception of the preVasc and preEP groups. The risk was maximal in the CI+preVasc+preEP group. At 6 years, the odds ratios for the prediction of dementia are less pronounced. Those groups that combine motor slowing and cognitive deficits were most likely to progress to dementia (CI+preEP, CI+preVasc+preEP). At the 6-year follow-up, the vascular measure had little impact, with no significant associations identified.

The odds of death for each preclinical syndrome at 3 and 6 years are shown in Table 2. Similar findings are identified with those having cognitive impairment and motor slowing being the most likely to die during the 6-year study period.

In both the examination of dementia incidence and death, the CI and preEP groups appeared to exert the greatest impact. To explore the relationship between CI and preEP with dementia and death further, we collapsed the preclinical syndromes and calculated the odds ratios for dementia and death at 3 and 6 years. All participants who had cognitive impairment in the absence EP features formed the CI–no-preEP group and therefore included those with CI and CI+preVasc. All those who had no cognitive impairment but had EP features formed the preEP–no-CI group and therefore included those with preEP and preVasc+preEP. Those who had cognitive impairment and EP

Table 2  
Odds ratios of preclinical syndromes resulting in death at 3 and 6 years

Clinical status	Deceased, n (%)		OR (95% CI)	
	3 years	6 years	3 years	6 years
Well	19 (13.7)	36 (26.9)	1 <sup>a</sup>	1 <sup>a</sup>
CI	13 (17.3)	24 (33.3)	1.3 (0.6–2.9)	1.4 (0.7–2.5)
PreVasc	8 (14.8)	14 (25.9)	1.1 (0.5–2.7)	0.9 (0.5–1.9)
CI+preVasc	4 (16.7)	6 (25.0)	1.3 (0.4–4.1)	0.9 (0.3–2.5)
PreEP	13 (29.5)	18 (41.9)	2.7 (1.2–5.9)	2.0 (0.9–4.0)
CI+preEP	12 (29.3)	22 (55.0)	2.6 (1.1–6.0)	3.3 (1.6–6.9)
PreVasc+preEP	4 (13.8)	11 (39.3)	1.0 (0.3–3.2)	1.8 (0.8–4.1)
CI+preVasc+preEP	8 (36.4)	12 (54.5)	3.6 (1.3–9.8)	3.3 (1.3–8.2)

<sup>a</sup> Reference group.

Table 3

Odds ratios of cognitive impairment (CI) and extrapyramidal (EP) syndromes progressing to dementia at 3 and 6 years

Clinical status	Demented, <i>n</i> (%)		OR (95% CI)	
	3 years	6 years	3 years	6 years
Baseline				
Well	6 (4.8)	22 (17.5)	1 <sup>a</sup>	1 <sup>a</sup>
CI no preEP	20 (20.8)	37 (38.5)	5.3 (2.0–13.7)	3.0 (1.6–5.5)
PreEP no CI	10 (15.2)	16 (24.2)	3.6 (1.2–10.3)	1.5 (0.7–3.1)
CI and PreEP	20 (35.7)	28 (50.0)	11.1 (4.2–29.8)	4.7 (2.4–9.5)

<sup>a</sup> Reference group.

features formed the CI-and-preEP group and therefore included those with CI+preEP and CI+preVasc+preEP. As the preVasc group had little impact on dementia they have not been included in these analyses. The odds for these collapsed groups progressing to dementia at 3 and 6 years are presented in Table 3, and for death in Table 4.

While those with either cognitive impairment or EP features were at greater odds of dementing at 3 years, at both 3 and 6 years it was those who had concurrent cognitive impairment and EP features who did most poorly, with 50% dementing by 6 years. Those with extrapyramidalism in the absence of cognitive impairment were not at greater odds of dementing at 6 years but were at 3 years. A similar pattern is seen with death where again it is those with cognitive impairment and motor slowing who are most likely to die at both 3 and 6 years.

At 3 years, 52 of 58 incident dementias had a preclinical syndrome at baseline, yielding a sensitivity of 89.7%. At 6 years, 90 of 112 incident dementias had a preclinical syndrome at baseline (sensitivity 80.4%) However, at 3 years, 216 of 268 preclinical participants did not dement (positive predictive value 19.4%, specificity 35.7%) and at 6 years, 178 of 268 preclinical participants did not dement (positive predictive value 33.6%, specificity 36.9%).

In the MRI group subjects had a mean arteriopathy score of 1.8 (S.D. 1.2) while 43% of participants reported or had been diagnosed with a lifetime history of TIA or stroke. Periventricular WMLs were present in all regions. Lateral bands correlated with the timed walk ( $r=0.31$ ,  $p<0.001$ ) and EP score ( $r=0.19$ ,  $p<0.05$ ). Parietal deep WMLs were significantly associated with the timed walk ( $r=0.33$ ,  $p<0.001$ ) and the EP score correlated with temporal deep WMLs ( $r=0.23$ ,  $p<0.05$ ) [20]. No other significant correlations were identified.

Table 4

Odds ratios of cognitive impairment (CI) and extrapyramidal (EP) syndromes resulting in death at 3 and 6 years

Clinical status	Deceased, <i>n</i> (%)		OR (95% CI)	
	3 years	6 years	3 years	6 years
Baseline				
Well	19 (13.7)	36 (26.9)	1 <sup>a</sup>	1
CI no preEP	17(17.2)	30 (31.2)	1.3 (0.6–2.7)	1.2 (0.7–2.0)
PreEP no CI	17 (23.3)	29 (40.8)	1.9 (0.9–4.0)	1.9 (1.0–2.8)
CI and PreEP	20 (31.7)	34 (54.8)	2.9 (1.4–6.0)	3.3 (1.8–5.8)

<sup>a</sup> Reference group.

#### 4. Discussion

Participants exhibiting preclinical syndromes were at greater odds of developing dementia, with the coexistence of cognitive deficits and EP features predicting most strongly those who would either dement or die. The presence of both had an additive effect, suggesting that the incorporation of clinical gait and motor measures may improve current MCI definitions and have important prognostic implications. The increased mortality of those with parkinsonism is consistent with previous studies [4,5].

The conceptual framework for this study was the definition of preclinical syndromes for the three main dementia subtypes of AD, VaD and the EPDs. Therefore, those with motor slowing or neurological signs often associated with extrapyramidal disorders, were termed the preEP group with the hypothesis that this group would progress to the EPDs. Considerable confusion exists as to the nosology used in defining the motor syndromes associated with dementia [21], and it is recognised that, although the clinical features and syndromes overlap, they may represent quite distinct underlying pathologies. White matter changes have previously been associated with gait abnormalities [22–24], hence the term vascular parkinsonism as distinct from parkinsonism associated with Lewy Body pathology. However, neuroimaging in this study did not identify consistent white matter changes. Neuropathological studies of participants with mild extrapyramidalism and gait changes are required to elucidate the underlying pathological processes, as is currently in progress with this study.

The preVasc group was not at increased risk for progression to dementia. In part, the definition of this group was based upon the presence of current vascular risk factors. Studies have identified that it is mid-life vascular risk factors that are important in the prediction of dementia [25]. Further refinement of an appropriate vascular measure, reflecting the presence of cerebrovascular disease is therefore required.

The preclinical syndromes were sensitive tools in the prediction of dementia. However, they had poor specificity, with many not progressing to dementia over the 6-year period. They therefore cannot be applied in the clinical setting. The diagnosis of cognitive impairment in this study was clinically based, encompassing non-amnesic cognitive deficits in comparison to the more stringently defined MCI. It is reported that MCI progresses to dementia at a rate of

15% per annum with 80% being demented by 6 years [26]. The rate of progression to dementia in this community-based study was therefore less, indicating that the definition of MCI is more stringent. However, despite these definitional limitations, this study has identified that the presence of gait abnormalities in combination with cognitive deficits resulted in a marked increased odds of progression to dementia than either condition alone at both 3 and 6 years. Incorporation of simple gait measures may act as a useful adjunct to cognitive measures in the prediction of dementia.

The odds ratios for dementia declined between the 3- and the 6-year review, although they remained fairly stable for death. Subjects who died between assessments were included in analyses, using diagnostic information from the informant interview and it is therefore unlikely that the drop is due to subject attrition. The greater odds of the preclinical syndromes progressing to dementia at 3 years possibly indicates that they have a “toxic”, more rapid effect. This would be supported by the more rapid progression in demented subjects with AD who have EP findings [27].

In conclusion, incorporating measures of gait into definitions of preclinical dementia states may assist in increasing the predictive power of these clinical paradigms. The aetiology of the gait and motor changes is yet to be elucidated.

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