

# Symptoms of Preclinical Dementia in General Practice up to Five Years before Dementia Diagnosis

Inez H.G.B. Ramakers<sup>a</sup> Pieter Jelle Visser<sup>a,c</sup> Pauline Aalten<sup>a</sup> Jos H.M. Boesten<sup>b</sup>  
Job F.M. Metsemakers<sup>b</sup> Jelle Jolles<sup>a</sup> Frans R.J. Verhey<sup>a</sup>

<sup>a</sup>Department of Psychiatry and Neuropsychology, Institute of Brain and Behavior, and <sup>b</sup>Department of General Practice, Maastricht University, Maastricht, and <sup>c</sup>Department of Neurology, VU University Medical Centre, Amsterdam, The Netherlands

## Key Words

Preclinical dementia · General practice ·  
Contact frequency with general practitioner

## Abstract

**Objectives:** To investigate which symptoms are indicative of preclinical dementia in general practice and whether subjects with preclinical dementia have an increased contact frequency with their general practitioner (GP). **Methods:** Individuals with preclinical dementia (n = 75) and non-demented controls (n = 125) were selected from the Dutch GP registration network (RNH). Number of visits and odds ratio for the risk of subsequent dementia of various symptoms were analysed. Analyses were done separately for each 12-month period, in the 5 years prior to the diagnosis of dementia. **Results:** In the 5 years prior to diagnosis, subjects with preclinical dementia visited their GP more often than controls. Gait disturbances were the earliest predictor. Cognitive complaints were predictive for dementia in the 3 years before diagnosis. All other symptoms, except vascular symptoms, were predictive in the year prior to diagnosis. Sensitivity was highest for cognitive symptoms (0.58) and gait disturbances (0.47) in the year before diagnosis. **Conclusion:** Preclinical dementia is associated with an increased contact

frequency between patient and GP at least 5 years prior to the diagnosis of dementia. Gait disturbances and cognitive complaints are the earliest symptoms of preclinical dementia.

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## Introduction

Dementing disorders are often characterized by a preclinical stage in which the individual experiences impairments but is not yet demented. It is important to identify subjects with preclinical dementia so that early interventions can be applied and psychosocial support can be provided.

The general practitioner (GP) plays an important role in the identification of subjects with preclinical dementia given that these subjects or their relatives often contact the GP first with their complaints [1]. Additionally, GPs are able to detect gradual changes in cognition and behaviour, because they often know their patients for a long time. However, knowledge with respect to which symptoms are suggestive of preclinical dementia in general practice is very limited and this may cause an undesirable delay in time between the first symptoms and the diag-

**Table 1.** Baseline characteristics

	Preclinical dementia group (n = 74)	Control group (n = 125)
Mean age, years	79 (6.2)	79 (7.4)
Female, %	62	61
Married, %	53	46
Education low/middle/high, %	81/17/2	77/20/3
Hypertension, %	42	36
Coronary heart disease, %	22	24
Stroke, %	18	11
TIA, %	10	8

Educational level: low = Lower general and vocational education; middle = middle general and vocational education; high = higher general and vocational education. TIA = Transient ischaemic attack. Figures in parentheses indicate SD.

nosis [1]. Additionally, early recognition of potential dementing subjects can help GPs to select subjects that may benefit from referral to specialized facilities such as memory clinics for further diagnostics and prevention of disease progression.

The aim of the present study was to investigate how subjects with preclinical dementia present in general practice. We investigated these individuals' contact frequency with their GP in the 5 years prior to their diagnosis. Additionally, we investigated the symptoms with which these subjects presented in those 5 years. Contact frequency and symptoms of these subjects were compared with those of control subjects. We hypothesized that subjects with preclinical dementia would have a higher contact frequency with their GP and would also present more complaints that had previously been recognized as early symptoms of dementia or risk factors for dementia in the general population. These symptoms include cognitive impairment, affective symptoms, behavioural problems, vascular problems, gait disturbances, and changes in appetite and weight [2–7].

## Methods

### Subjects

Subjects were selected from the Dutch registration network of family practices (RNH). The RNH is a computerized and anonymous database that contains patient characteristics and all relevant health problems of subjects from 21 rural and urban GPs in the Southern region of the Netherlands [8]. The register offers a unique opportunity as a sample frame for research in a general

practice setting on which cross-sectional and longitudinal analyses can be performed [8]. When compared with the Dutch population, the RNH population showed a slightly higher mean age. Further, some differences with respect to the marital status were noted [8, 9].

The cases included in this study consisted of subjects who had a diagnosis of dementia registered in the RNH database between 1996 and 1999. During the study period, GPs in the Netherlands followed the Dutch Guidelines for General Practitioners [10] for the diagnosis of dementia, which included the DSM-III-R criteria for dementia [11]. For each demented subject, two control subjects were randomly selected from the same practice, after matching for age ( $\pm 5$  years) and sex. This resulted in 82 demented subjects and 150 control subjects. From this sample, we excluded 25 subjects, because insufficient data were available for the period of at least 3 years prior to diagnosis. We also excluded 8 control subjects who had been diagnosed with dementia in the time that passed between the index period and the date of analysis. This was done to prevent contamination of the control group. The final study population consisted of 74 demented patients and 125 non-demented controls (table 1). The study was approved by the Medical Ethics Committee of the University Hospital of Maastricht, the Netherlands.

### Data Collection

Data were collected on the contact frequency (including GP consultations, telephone consultations and visits) and symptoms presented during each contact. These were collected separately for each 12-month period over the course of the 5 years prior to the dementia diagnosis. For 1 control subject and 2 subjects with preclinical dementia, no data were available for the fourth year prior to diagnosis. For the fifth year prior to diagnosis, data were missing for 2 control subjects and 2 subjects with preclinical dementia.

All relevant health complaints presented during a contact (in person or by telephone) were entered in the practice file by the GP. We compiled the presenting symptoms at each contact from the anonymous raw data output for the general practice setting and thereby derived 136 different symptoms. We then classified these symptoms into the following 6 categories: (a) cognitive symptoms (including amnesia, forgetfulness, confusion, cognitive decline, orientation problems, language problems, problems with logical thinking, and loss of decorum); (b) affective symptoms (including fatigue, irritability, anxiety, sleep-related problems, depressive mood, being upset, loss of initiative, loss of interest, crying, complaining, sadness, hyperventilation, mood changes, and suicidal ideation); (c) behavioural symptoms (including restlessness, delusions/hallucinations, aggression/agitation, changes in character, and suspicion); (d) vascular symptoms (including chest pains, loss of speech, temporary paralysis, continuous paralysis, loss of strength, decline in vision, and thick tongue); (e) gait disturbances (including falls and problems with walking), and (f) changes in weight or appetite (including loss of appetite and other weight changes).

### Data Analyses

Statistical analyses were performed using the SPSS 11 for Macintosh. The difference in contact frequency between subjects with preclinical dementia and controls were analysed using independent t tests. The predictive accuracy of the symptoms for demen-

tia was determined using binary logistic regression analyses. The main outcome measure was the odds ratio (OR). Secondary outcome measures were the sensitivity (percentage of subjects with preclinical dementia who expressed the symptom) and the specificity (percentage of control subjects who did not express the symptom). Analyses were done separately for each 12-month period, in the 5 years prior to dementia diagnosis. All analyses were performed with a two-tailed alpha level of 0.05.

## Results

### Frequency of Contact

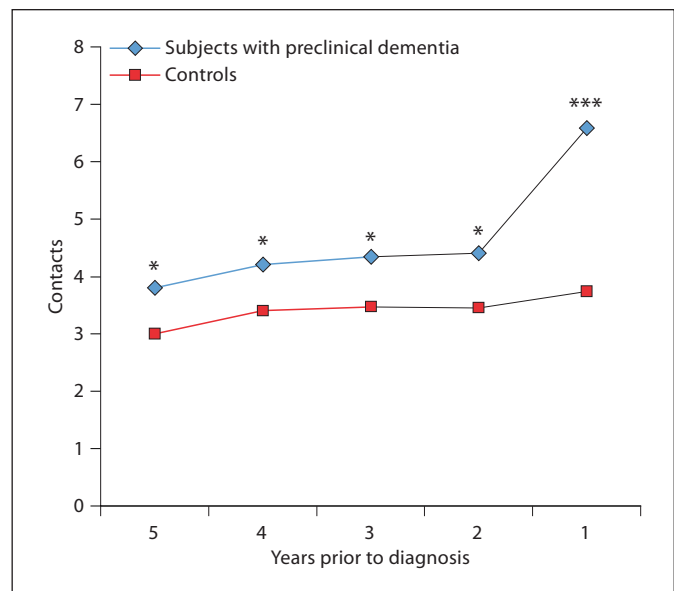
In total, 3,837 contacts with the GP were registered during the time period under investigation. In each of the 5 years, subjects with preclinical dementia showed a significantly higher contact frequency than subjects without preclinical dementia. A notably more pronounced difference between the two groups in the year prior to diagnosis was also demonstrated (fig. 1; 5 years prior: 3.8 vs. 3.0; 4 years prior: 4.2 vs. 3.4; 3 years prior: 4.4 vs. 3.5; 2 years prior: 4.4 vs. 3.5, and 1 year prior: 6.6 vs. 3.8).

### Predictors of Dementia

The earliest predictor was complaints about gait disturbances in the fifth year prior to diagnosis (OR = 3.5; table 2). Gait disturbances were also predictive in the third and final year before diagnosis (OR = 3.8 and 6.1, respectively). Cognitive complaints were associated with the highest risk for dementia, with ORs ranging from 5.3 5 years before diagnosis to 56 in the year before the diagnosis. Affective and behavioural symptoms and symptoms related to weight loss and appetite were predictive in the first year prior to diagnosis, with ORs ranging from 3 to 14. The ORs for all symptoms, except for vascular symptoms, increased progressively over the course of the 5 years prior to the diagnosis. The ORs of vascular symptoms did not change over time (table 2). Even after adjusting for age and sex, the significance of the results remained (data not shown).

Specificity was above 0.83 for all symptoms indicating that the control subjects did not frequently report these symptoms (table 2). Sensitivity for all symptoms increased over the course of the 5 years prior to diagnosis. The highest sensitivity noted was related to cognitive symptoms (0.58) and gait disturbances (0.47) in the year before diagnosis was made. This suggests that only a subset of subjects with preclinical dementia report these symptoms to their GP (table 2).

As gait disturbances could also result from a stroke, we performed post hoc analyses in which we excluded all



**Fig. 1.** Average number of contacts in the 5 years prior to diagnosis. \*  $p < 0.05$ ; \*\*\*  $p < 0.001$ .

subjects who had had a stroke in the past ( $n = 27$ ). The predictive accuracy of gait disturbances in subjects without a stroke remained essentially the same (first year prior: OR = 7.3,  $p < 0.001$ ; second year prior: OR = 2.5,  $p < 0.05$ ; third year prior: OR = 5.2,  $p < 0.01$ ; fourth year prior: OR = 1.3,  $p > 0.05$ , and fifth year prior: OR = 3.3,  $p < 0.05$ ).

## Discussion

Preclinical dementia is associated with increased contact frequency to the GP at least 5 years prior to the diagnosis of dementia. Symptoms that could best predict dementia in the general practice setting were cognitive symptoms and gait disturbances.

The observation that subjects with preclinical dementia had an increased contact frequency up to 5 years before the dementia diagnosis supports and extends the findings of a previous study in which an increased contact frequency 2 years before the diagnosis of dementia was found [12]. It is possible that the increase in contact frequency occurred because patients experienced symptoms related to the dementing disorder. Alternatively, subjects with preclinical dementia may more often have had control visits for conditions that are risk factors for dementia, such as hypertension or diabetes. However, a

**Table 2.** Predictive values of symptoms for the development of dementia

Symptoms	Years prior to diagnosis				
	fifth	fourth	third	second	first
<b>Cognitive symptoms</b>					
OR (95% CI)	5.3 (0.5–51.8)	2.9 (0.9–9.5)	5.4 (1.1–28)*	13 (3.7–46)***	56 (16–194)***
Sensitivity	0.04	0.11	0.08	0.24	0.58
Specificity	0.99	0.96	0.98	0.98	0.98
<b>Affective symptoms</b>					
OR (95% CI)	1.5 (0.6–3.7)	0.7 (0.3–1.8)	1.0 (0.4–2.2)	1.1 (0.5–2.3)	3.0 (1.5–6.2)**
Sensitivity	0.14	0.11	0.15	0.18	0.32
Specificity	0.9	0.85	0.85	0.83	0.86
<b>Behavioural symptoms</b>					
OR (95% CI)	1.1 (0.2–7.0)	0.9 (0.2–4.8)	3.5 (0.6–20)	2.4 (0.8–7.2)	14 (3.2–65)**
Sensitivity	0.03	0.03	0.05	0.11	0.19
Specificity	0.98	0.97	0.98	0.95	0.98
<b>Vascular symptoms</b>					
OR (95% CI)	0.7 (0.3–1.9)	0.9 (0.4–2.1)	1.4 (0.6–3.2)	0.96 (0.4–2.4)	1.6 (0.7–3.5)
Sensitivity	0.08	0.13	0.16	0.11	0.18
Specificity	0.89	0.86	0.88	0.89	0.88
<b>Gait disturbances</b>					
OR (95% CI)	3.5 (1.2–10)*	1.5 (0.6–3.6)	3.8 (1.4–11)*	2.2 (0.98–4.9)	6.1 (3.1–12)***
Sensitivity	0.15	0.14	0.16	0.2	0.47
Specificity	0.95	0.9	0.95	0.9	0.87
<b>Changes in weight and appetite</b>					
OR (95% CI)	0.6 (0.1–2.8)	0.8 (0.2–3.5)	1.1 (0.4–3.0)	1.8 (0.5–5.6)	5.9 (2.2–16)***
Sensitivity	0.03	0.04	0.09	0.08	0.23
Specificity	0.95	0.95	0.91	0.95	0.95

CI = Confidence interval. \*  $p < 0.05$ ; \*\*  $p < 0.01$ ; \*\*\*  $p < 0.001$ .

post hoc analysis indicated that control visits were equally common in both groups (data not shown). The increase in contact frequency for subjects with preclinical dementia in the year prior to diagnosis may have been the result of the patients entering the diagnostic phase in which the dementia was established.

The earliest predictor of dementia was gait disturbances. This was already predictive in the fifth year prior to diagnosis. It is also important to note that cognitive complaints were associated with the highest risk for dementia. For most predictors included in this study, the OR increased over the course of 5 years prior to diagnosis. As expected, the predictors were most notable in the final year before diagnosis. The high ORs for the symptoms in the final year may be partly explained by circularity since the presence of some of the symptoms likely initiated the process by which the diagnosis of dementia could be made.

Complaints about everyday memory problems have been associated with cognitive impairment and dementia

in several clinical and population-based studies [6]. Although cognitive symptoms are a key feature of dementing disorders, in our study, cognitive complaints are indicative of preclinical dementia only in the final 2 years prior to diagnosis. In all other years, a low predictive accuracy was found. Further, cognitive symptoms were not expressed in the entire sample but only in a subgroup of subjects with preclinical dementia and ranged from 4% 5 years prior to diagnosis to 58% in the year before diagnosis. A possible explanation for this finding is that many subjects with preclinical dementia considered cognitive impairments normal for their age. Alternatively, they may have been ashamed of their impairments and thus chose not to report them. It is also possible that, as a result of the dementing process, subjects were unaware of cognitive changes [13]. A final option is that, especially in the fourth and fifth year prior to diagnosis, preclinical subjects simply did not experience any cognitive impairment. Our findings with respect to the low predictive accuracy of cognitive impairments for the group with pre-

clinical dementia corresponds with previous studies in which many subjects with preclinical dementia did not express cognitive complaints [13–15]. However, because our findings are based on contact notes of the GP and because it is possible that the GPs did not take sufficiently detailed notes during their contacts with patients, we may have underestimated the frequency of cognitive symptoms.

Our finding that gait disturbances predict dementia is in agreement with recent research that suggests that gait disturbances in aging may be indicative of a cognitive impairment that can be objectified several years later [7, 16]. A population-based study demonstrated that subjects with gait abnormalities had an increased risk of developing dementia, especially non-Alzheimer's dementia [7]. In addition, another study noted that fall events occurred in 42% of the participating mild-to-moderate dementia subjects [17]. The present study indicated that gait disturbances were reported long before the diagnosis was made and that these disturbances were quite frequent even 5 years prior to the diagnosis. In this fifth year prior to diagnosis, gait disturbances (15%) were much more frequent than cognitive symptoms (4%). This finding is similar to the study of Ganguli et al. [14] who, using primary care charts, established that falls occurred in 15% of subjects with a Clinical Dementia Rating total box score of 0.5, compared to memory complaints in only 8% of subjects. The specificity of gait disturbances for dementia in our study was high (above 0.87). Whether this high specificity translates to a high positive predictive value depends on the incidence of dementia, which could not be investigated in this study because of the case-control design.

The finding that gait disturbances are a sign of early dementia is in line with recent research, summarized by Scherder et al. [16]. They concluded that there is a strong relationship between gait and cognition, gait and gait-related motor disturbances being present in all subtypes of dementia, even in the early and preclinical stages. Neural support for this relationship was based on recent studies that found a strong involvement of the hippocampus in gait because of its connections with the prefrontal cortex and the striatum [16].

A decline in gait and balance is not only associated with vascular white matter lesion [18], but also with Alzheimer's disease, which is consistent with our post hoc analyses, in which we showed that after exclusion of subjects with stroke, gait disturbances were still predictive of dementia. Waite et al. [19] found that subjects with cognitive impairment in combination with impaired motor

control were at higher risk for developing dementia than subjects with cognitive impairment alone.

Affective symptoms were a marker of preclinical dementia only in the year prior to diagnosis. In the other years, affective symptoms were equally common among subjects with preclinical dementia and the control subjects. This finding does not correspond with a recent meta-analysis in which the conclusion presented was that a history of depression may be an independent risk factor for Alzheimer's disease [20]. Our findings also fail to support another conducted study in a general practice setting in which a significant relationship between old-age depression and subsequent dementia was found [21]. If we had conducted a depression diagnosis, rather than merely documenting affective symptoms, we might possibly have been able to demonstrate greater predictive power of affective symptoms and, more especially, depression. Another possible explanation for this lack of predictive power is that the present study included only subjects who visited the GP. It is possible that affective symptoms have more discriminative power in the general population.

Behavioural symptoms and changes in weight and appetite were only predictive in the year preceding diagnosis. This suggests that these symptoms develop later in the neurodegenerative process or, alternatively, that these symptoms only became severe enough to report to the GP in the final year prior to diagnosis.

In contrast to our expectations, the frequency of contact with the GP as a result of vascular symptoms did not differ significantly between subjects who developed dementia and subjects who did not. The prevalence in both groups was approximately 15%. A possible explanation for this is that the vascular complaints that patients presented to their GP in this study may not have been specific for underlying vascular pathology. When we excluded symptoms that were thought not to be related to a vascular disorder, results were essentially the same.

In the RNH database, dementia is used as a diagnostic entity rather than dementia subtypes. Still, because the RNH database registered all relevant health care problems, an indicator for vascular causes of dementia could be inferred. Of the 74 patients with dementia, 13 subjects (18%) had experienced a stroke before the diagnosis of dementia and 31 subjects (42%) were known with hypertension. Thus, dementia might have had resulted from stroke in about 20% of the subjects, while small vessel disease might have contributed to the dementia syndrome in about 40%.

Dementia was diagnosed according to DSM-III-R criteria [11]. The GP, however, might have missed the diag-

nosis at earlier visits, because demented subjects may have been unaware of their cognitive impairment, especially when an informant was absent. Therefore, in some subjects, symptoms considered to reflect preclinical dementia might have been symptoms of dementia. Cognitive tests might have been useful to identify subjects with dementia in an earlier stage, but such tests were not used for screening purposes on a routine basis, only when cognitive impairment was suspected.

One of the strengths of our study was the large size of our study population. A second strength was our use of a matched control design in which subjects were included from both rural and urban general practices. In doing this, we were able to increase the generalizability of our findings. Our inclusion of 5 years worth of data is an additional strength. Lastly, by following up on control subjects after the index date, we were able to exclude control subjects that had developed dementia in the period between the index date and date of analyses, and thereby avoided contamination in so far as was possible.

Our study also had several limitations. Our reliance on reports written by GPs can be considered a limitation. Despite continuous note-taking training [22], it is possible that some of the reports were incomplete. Additionally, we were not able to obtain data on the type of dementia the preclinical subjects developed. An additional limitation worthy of attention is the broad confidence intervals of some of the predictors that were noted during the regression analyses. It is possible that these broad confidence intervals were caused by the relative infre-

quency of several of the reported complaints. The classification of some symptoms might be arbitrary as some symptoms could be classified in more than one category, especially for symptoms classified as cognitive, affective, or behavioural symptoms. However, when loss of decorum (classified into the cognitive category) and irritability (classified into the affective category) were classified as behavioural symptoms, the results did not change. Finally, our findings may not be applicable in different settings and in younger subjects.

The GP plays a crucial role in the timely recognition and early identification of subjects at risk for dementia [1, 23, 24]. The present study showed that complaints of cognitive performance and gait should alert the GP for incipient dementia. If these symptoms are expressed, the GP may do a formal assessment of cognition, refer the patient for further diagnostic evaluation, or keep the patient under clinical supervision. Given that almost half of the subjects did not actively report cognitive symptoms in the year prior to the diagnosis, we contend that the GP must play an active role in identifying subjects at risk for dementia by bringing together all the available information related to the medical, cognitive, and daily functioning of their patients. By referring to symptoms that present during consultations, GPs are not only in a position whereby they can identify subjects at risk for developing dementia, they can also start a process by which additional diagnostic testing can be conducted, and follow these subjects over time.

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