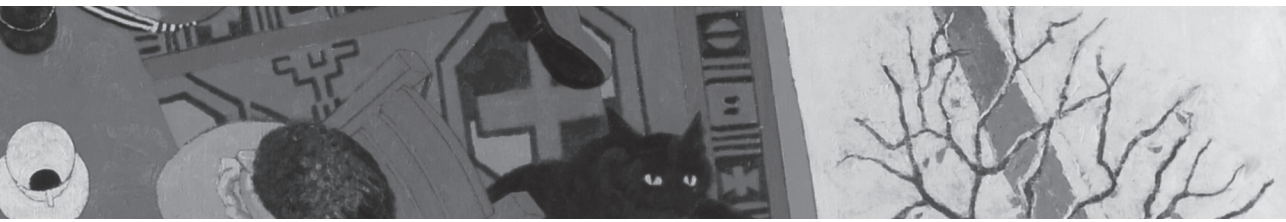


# CHAPTER

# 7

Summary, general discussion and  
recommendations for future research





IADL is an important aspect of the ability to function independently in society. One of the consequences of dementia is a growing inability to perform these essential daily tasks. This greatly reduces the patient's autonomy, which not only has a major influence on the patient, but also to caregivers and society.

The main objective of this thesis was to investigate the measurement of IADL functioning in patients with dementia. We investigated the role of problems in IADL for diagnosing dementia, we rated the quality of existing IADL informant-based questionnaire and we developed a new questionnaire for the measurement of IADL in patients with early dementia.

In this chapter we will provide a summary of the research findings, discuss the results in the general discussion section and present the conclusions of this thesis. We will conclude this chapter with the clinical implications of the findings and recommendations for future research.

## SUMMARY

### Measuring everyday cognitive functioning

In **chapter 2** we examined the usefulness of the informant questionnaire on cognitive decline in the elderly (IQCODE) for the distinction between AD, MCI and patients with subjective memory complaints in a memory clinic setting. The IQCODE is a questionnaire containing items related to everyday memory and intelligence and aimed at measuring everyday cognitive functioning.<sup>1</sup> In **chapter 2.1** we showed that AD patients had more problems with everyday cognitive functioning than patients with MCI or subjective memory complaints. Contrary to our expectations, we found no differences between patients with MCI and subjective memory complaints.

We hypothesized that groups of items within the IQCODE differed in their diagnostic ability and we investigated this in **chapter 2.2**. Based on the content of the items, we distinguished items measuring IADL and items measuring everyday memory. A two-dimensional graded response model confirmed the presence of both dimensions within the IQCODE. However, the high correlation between the two factors suggested unidimensionality. We therefore continued with a single dimension and showed that this dimension could distinguish between all patient groups. In an exploratory analysis we showed that of the two dimensions, IADL was able to differentiate between all patient groups, whereas memory was not.

## Measuring IADL

In **chapter 3** we further investigated the role of IADL in a European prospective cohort study. In this study, non-demented patients who visited a memory clinic were followed over time. We aimed to investigate whether IADL could predict a diagnosis of dementia at follow-up. Different IADL questionnaires were used in the study centers, so we pooled activities from these questionnaires to answer the research question. We showed that problems in IADL contributed to a diagnosis of dementia at one- and two-year follow-up, over other commonly used clinical measures.

As many IADL questionnaires are available, we conducted a systematic review of dementia-specific informant-based IADL questionnaires in **chapter 4**. We rated the psychometric properties of 12 questionnaires. Information on essential psychometric properties, such as the internal consistency, construct validity, agreement and responsiveness was missing for many questionnaires, underlining the need for improvements.

Following the conclusions of the systematic review and the widely observed need for better IADL questionnaires in dementia research and clinical practice <sup>2-5</sup>, we initiated the development of a new IADL questionnaire. In **chapter 5** we describe the development of the Amsterdam IADL Questionnaire®, aimed at detecting IADL problems in early and early-onset dementia for diagnostic use. For the development of this questionnaire we defined IADL in consensus with experts. Items were constructed based on theory, existing items and suggestions from experts and informants. In this chapter we showed that the questionnaire consisted of a single factor, had a high internal consistency and that the majority of the items had substantial to almost perfect test-retest reliability values. These results suggest that the Amsterdam IADL Questionnaire® is a promising new instrument.

In **chapter 6** we described the scoring and further validation of the Amsterdam IADL Questionnaire®. Due to the tailored approach we had many missing item scores, and we therefore used item response theory (IRT) to provide a latent trait estimate for scoring. We examined the construct validity by comparing the latent trait estimate with other clinical measurement instruments, such as depression and global cognition. The directions and magnitudes of the correlations were in concordance with our hypotheses. In addition, we compared scores between patient groups. We found differences between demented and non-demented patients. No differences were found between patients with early- and late-onset dementia, indicating the usefulness of the questionnaire for a broad age range. These results add support to the use of the Amsterdam IADL Questionnaire® in a memory clinic setting.

## GENERAL DISCUSSION

### Defining IADL

Before we are able to measure IADL, we first need to define what we see as IADL. IADL is a commonly used term in the medical nomenclature and is sporadically described as extended ADL<sup>6</sup>, complex ADL<sup>7</sup> or as everyday cognitive functioning.<sup>8,9</sup> In spite of its wide use, a clear and generally accepted definition of the construct is lacking.<sup>10,11</sup> Even though the description of IADL from Lawton & Brody provides a conceptual understanding, there is no agreement on the exact categories seen as IADL.<sup>11,12</sup>

To provide limits to the construct IADL, we composed a definition of IADL in which we incorporated several theories and research findings on cognitive complex everyday functioning in dementia.<sup>13-16</sup> This definition provides restrictions to the construct by excluding activities strictly related to mobility, single neuropsychological functions or BADL. These activities should be distinguished from IADL, as factor analytical studies showed distinctions between items related to IADL and items related to BADL, mobility or orientation.<sup>17,18</sup> However, it must be noted that our definition does not provide exact categories and absolute limits for IADL. As this definition of IADL has to apply to all people, it will set limits to the idiosyncratic evaluation of the construct. We think that this definition, though not perfect, is a first step towards clearly defined IADL.

The usefulness of IADL as a diagnostic and predictive measure In **chapter 2** we investigated the role of problems in everyday cognition in the diagnosis of AD and MCI in two studies. The findings of these two studies did not correspond. In **chapter 2.2** we found the IQCODE able to distinguish between all patients groups, whereas in **chapter 2.1** we only found an ability to distinguish AD from the other patients groups. How can we explain these contradicting findings? A difference between these studies is the correction for the MMSE. Correcting for the MMSE is subject to debate, as the MMSE and IQCODE are correlated. They are partly measuring the same, though several studies indicated that everyday functioning has an additional effect on cognitive measures in diagnosing dementia.<sup>19,20</sup> As the ability of the IQCODE to distinguish between SMC and MCI disappeared after correction for the MMSE, this is a plausible explanation. Moreover, we used different statistical techniques: In **chapter 2.1** we used logistic regression, whereas in **chapter 2.2** we used SEM modeling. The latter is more powerful and has the advantage that relations are corrected for measurement error.<sup>21</sup>

Our finding that the IADL items of the IQCODE could distinguish between all patient groups, whereas the memory items could not, is remarkable. Decline in cognition is generally thought to precede the decline in IADL.<sup>22,23</sup> Our findings

might reflect that memory problems are already present in MCI and AD patients. However, one would consequently expect that the memory items would distinguish between patients with subjective memory complaints and MCI, which we did not find. Another possible explanation for these findings would be the variation in complexity of the items. Memory items, such as ‘remembering his/her address and telephone number’ might be less complex than IADL items such as ‘learning to use a new gadget or machine around the house’.<sup>1</sup> In an informant questionnaire, complex activities might be more suited to distinguish between patients groups. This interpretation is supported by several studies in which the lack of sensitivity in informant-rated instruments is noted.<sup>3,24</sup>

A drawback of the studies in **chapter 2** is their cross-sectional nature. Even though diagnoses were made independently of the IQCODE, a diagnosis of dementia and an everyday functioning score are not entirely independent, as problems in everyday functioning are part of the diagnostic criteria of dementia.<sup>25</sup> This is referred to as an incorporation bias, which can lead to an overestimation of diagnostic accuracy.<sup>26</sup> This incorporation can be avoided in a longitudinal study, which we conducted in **chapter 3**. A unique aspect of this prospective cohort study is that we investigated the additional value of IADL over commonly used clinical measures for the prediction of dementia. The findings of this study correspond to longitudinal studies in community-based populations.<sup>27-31</sup> Moreover, they correspond to studies restricted to MCI patients, in which patients with MCI and IADL impairment were found to be a high-risk population for future dementia.<sup>5,32</sup>

One might argue that the patients with IADL problems at baseline were in fact already demented at that time. A majority of the patients met criteria for MCI, implying that they had cognitive problems, but these problems were not severe enough to cause interference in activities of daily living.<sup>23</sup> This contradicts the finding of problems in IADL in these non-demented patients. However, an important issue is that these patients did not meet the clinical criteria for dementia. One of the criteria for MCI is that the patient is ‘not demented’. Apparently, these patients had (slight) problems in IADL, but were clinically not demented.

Closely related is the question of how we should define interference in activities of daily living. This remains unclear, as some studies showed that patients with MCI experience difficulties performing complex daily activities, arguing for the inclusion of IADL problems in the definition of MCI.<sup>33-36</sup> There has been some controversy regarding the precise definition of MCI and its usefulness in clinical practice.<sup>37</sup> MCI has recently been defined with ‘generally preserved activities of daily living’.<sup>38</sup> This discussion point clearly illustrates the need for clear cut-off points in IADL functioning for MCI and dementia.

In general, our findings emphasize the importance of measuring IADL in a memory clinic setting.

### The development of a new IADL questionnaire

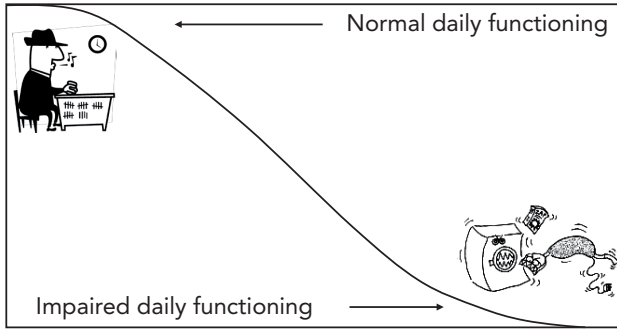
We developed a new dementia-specific informant-based IADL questionnaire, aimed at detecting IADL problems in early dementia for diagnostic use and useful for a broad age range. We did this despite the presence of a large number of (I) ADL informant-based questionnaires.<sup>3</sup> The development of a questionnaire is a long process and we therefore must ask ourselves whether the continuation of the validation of an existing questionnaire might have been a better idea. Perhaps, but we thought the new questionnaire would be able to handle some important measurement issues in IADL. We will discuss these issues below.

In **chapter 4** we showed that none of the existing IADL questionnaire had been developed for diagnostic use, despite the relevance of IADL problems for a diagnosis of dementia.<sup>27,29,39</sup> Most of the dementia-specific questionnaires were developed to measure change over time<sup>17,40-43</sup> or simply aimed to measure (I)ADL<sup>12,44-48</sup>. Even though most memory clinics use an IADL questionnaire, as can be seen in **chapter 3**, the diagnostic usefulness of these questionnaires remains unclear. We developed the Amsterdam IADL Questionnaire® for diagnostic use with the explicit intention to meet high psychometric standards.

In the developmental process we tried to include a broad range of IADL activities. IADL can consist of very complex tasks, such as working and doing finances. Activities such as using a vacuum cleaner or a washing machine are also considered IADL, but might be less complex as they rely to a lesser extent on controlled processing.<sup>13</sup> The proposed decline in IADL is depicted in Figure 1. Most questionnaires mainly included automated activities, and in consequence, the majority of patients will not show any deficits in the early stages of the disease.<sup>24</sup> When an instrument includes very complex IADL activities, one might see problems in IADL in very early stages of dementia. In the Amsterdam IADL Questionnaire®, we tried to include this entire spectrum of IADL activities.

Another important aspect of measuring IADL concerns the individual differences between patients. To measure decline in IADL, the activities each patient was doing before the onset of disease symptoms are highly relevant. Consider a patient who rarely cooks: Asking whether the patient has difficulty cooking might force the informant to answer ‘yes’, even though these difficulties do not reflect a change and are therefore not relevant for a diagnosis of dementia.

Existing questionnaires handled this issue of individual differences in several ways. The original Lawton IADL consists of separate questions for men and women.<sup>12</sup>



**Figure 1.** Decline in IADL functioning

They assumed that each man would be able to handle finances and each woman would be able to prepare food. However, changes in gender roles since the 1960s limit the usefulness of this method. Other questionnaires included a ‘non-applicable’ or ‘never did this activity before’ answer option.<sup>17,42,43,45,48,49</sup> A drawback of a non-applicable option is that it may reflect several answers. The informant might not have been able to make up his mind, the patient might never have done the activity or he might be no longer able to do the activity due to physical problems. Moreover, the non-applicable answer option might also be very important, for instance when a patient stopped managing the household budget due to cognitive problems. A non-applicable answer ignores the relevance of ceasing or not doing an activity and should therefore be avoided.

Another drawback of the non-applicable answer options in many questionnaires is that no clear guidelines are provided on how to deal with these answers.<sup>17,42,43,45,48</sup> In most cases, a total score excluding the non-applicable items is calculated by dividing the total score by the number of items rated. As a result, items not completed are replaced by the arithmetic mean for which difficulties were rated.<sup>50</sup> Disadvantages of this method are the assumed irrelevance of non-applicable items and the artificial reduction of variability within the population. The latter is of particular importance for research purposes.

In **chapter 5** we described how we handled the issue of individual differences in the Amsterdam IADL Questionnaire®, with most importantly the adaptive nature of the questionnaire and the item formulation. In the appendix an example of item formulation is given.

One might argue that when the individual decline in IADL is of particular importance in diagnosing dementia, a clinical interview might suffice. Even though a clinical interview is very important in diagnosing dementia, we think otherwise. A standardized measure has several advantages, including the assumed completeness.



A clinician might ask a general question about daily functioning, without detailed questions on specific activities. Moreover, the informant might feel restricted talking about problems in a clinical interview, in particular in the patient's presence. For research purposes, a standardized measure has numerous advantages; we can compare scores between different patients, between different study centers and between different countries. In addition, it allows for the measurement of change over time.

Another issue in the measurement of IADL is the informant-based measurement method. Using informant-ratings as measurement of IADL has several drawbacks. One of them is the influence of depressive symptoms and health status on the informant ratings.<sup>51</sup> In our study in **chapter 6** we did not find an influence of depressive symptoms of both informant and caregiver on the Amsterdam IADL scores. A possible explanation might be the item content and formulation as we included objective, observable phenomena, for which informants are known to provide fairly accurate information.<sup>52</sup> Subjective ratings, such as emotional states are prone to influences by the psychological status of the informant.<sup>52</sup> We did find a substantial correlation between caregiver burden and the scores on the Amsterdam IADL Questionnaire®, a finding which corresponds to findings in a previous study with the IQCODE.<sup>51</sup> However, studies into caregiver characteristics are scarce, which makes it difficult to indicate when an informant is 'reliable enough' to provide an IADL rating.

The type of informant might also influence IADL ratings. We might assume information provided by a spouse will be of more relevance than information provided by another relative. However, a study on the influence of type of informant on informant ratings showed substantial to almost perfect agreement between primary and secondary caregivers.<sup>53</sup>

Another important part of the questionnaire development is the item formulation. Consider the item depicted in Table 1. It is very difficult to answer this question when the patient has some difficulty handling the microwave, but does not have difficulty with any of the other appliances or the repairs. Item formulation is an essential part of test construction and we carried this out meticulously. We paid considerable attention to the wording of the items and were careful to avoid double-barreled questions, negative wording, jargon and value-laden words, all known to influence an informant's responses.<sup>52</sup> Extensive pilot-testing ensured that no such items were included.

In several chapters of this thesis we made use of IRT models. Due to the tailored approach of the Amsterdam IADL Questionnaire® we had a high number of missing

**Table 1.** IADL item (based on ADCS-ADL-PI).<sup>45</sup>

Item	Answer options
In the past 3 months, did he/she use an appliance such as a microwave, dishwasher, computer or vacuum cleaner or did he/she carry out household repairs?	With some difficulty With a lot of difficulty As well as usual

item scores. We therefore relied on IRT to estimate trait levels. IRT is a ‘strong’ modeling method because it has strong assumptions, such as unidimensionality, local independence and monotonicity of items.<sup>54</sup> We showed that the new questionnaire met these assumptions and we were able to use IRT, which has several advantages over commonly used scoring methods. For the measurement of IADL, it is relevant that IRT allows for a test-free measurement. That is, patients can be compared on the trait even if they completed different items. Second, the IRT is able to handle floor- and ceiling effects. This is also important as many (I)ADL measurement instruments show floor- and ceiling effects.<sup>2</sup> Another advantage is that shorter tests can be as reliable as long ones using IRT.<sup>52</sup>

However, estimation trait levels using IRT required advances numeric methods. Adding up raw item scores is clearly much easier. Is this added complexity of IRT really worth the trouble in term of test score validity? In general, high correlations between raw scores and trait level estimates are found.<sup>54,55</sup> However, considering the high number of missing items estimating trait levels is the only suitable method of scoring. Since many other IADL questionnaires also have to deal with missing non-applicable answers, one might even question the use of a total score for an IADL measurement.

The questionnaire has been developed to be suitable for patients living in modern society, in contrast to the existing questionnaires, often developed many years ago. The Amsterdam IADL Questionnaire® will not stay up-to-date though, as changes in technology and behaviors will continue. When we started the development of the questionnaire in 2007, e-readers or iPads were absent in common life. In the meantime however, we are administering the questionnaire on an iPad. This illustrates the ongoing changes in everyday technology, which will need constant adaptation. The adaptive nature of our new questionnaire and IRT will provide opportunities for these necessary adjustments.

## CONCLUSIONS

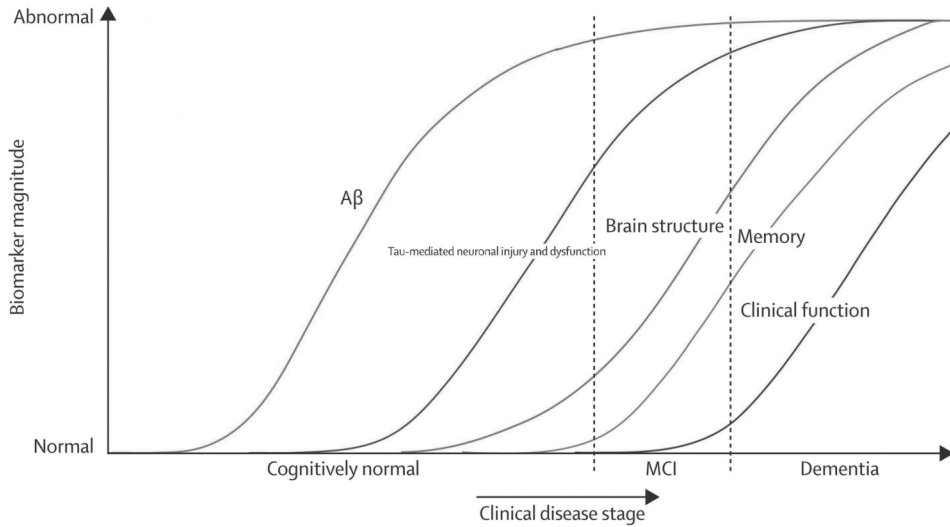
In this thesis we have showed that measuring IADL is useful in a memory clinic setting, for diagnostic use as well as the prediction of dementia at follow-up. Despite their usefulness, we demonstrated that the quality of the existing questionnaires was lacking. Due to controversies in the concept of IADL, we provided a new definition of IADL. With this definition, we started the development of the Amsterdam IADL Questionnaire®. The process of test construction ensured good content validity. Reliability and validation studies resulted in sufficient support for both reliability and construct validity. With the Amsterdam IADL Questionnaire®, reliable IADL estimates can be obtained for patients in a memory-clinic setting.

## RECOMMENDATIONS FOR FUTURE RESEARCH

The work presented in this thesis contributed to the overall understanding of IADL functioning in (early) dementia. Further validation of the results is necessary, and in this section we will provide some directions for future studies.

A point that needs further exploration is the need of IADL interference for a diagnosis of dementia. The onset of the cause of dementia occurs many years before the onset of dementia.<sup>22</sup> This has been investigated most thoroughly in AD, where the formation of  $\beta$ -amyloid plaques in the brain precedes the clinical disease onset.<sup>56</sup> In the pathological cascade of AD, clinical function or IADL is thought to be the last aspect declining in the disease process, as depicted in Figure 2. This model is contradicted by the findings that IADL problems can occur 10 years before the onset of dementia.<sup>27</sup> A recent study showed that patients with MCI and IADL impairment had a more widespread pattern of gray matter loss involving frontal and parietal regions suggesting IADL impairment in an early stage of AD.<sup>5</sup> To prevent the progression to dementia when disease-modifying drugs become available, the diagnosis of AD should be made at the start of slight IADL interference. Research criteria using biomarkers have been proposed, but a recent study showed that these criteria may be lacking in accuracy.<sup>22,57</sup> To better understand the role of IADL decline in these disease stages, relations between IADL and biomarkers should be further investigated.

In this thesis we focused on the diagnosis of dementia, but clinical criteria reflect that IADL interference might not be relevant for all types of dementia.<sup>58</sup> Two recent studies explored the relationship between problems in IADL and dementia subtypes. Patient with vascular dementia (vAD) were found to have more IADL impairments than patients with AD or other dementias.<sup>59</sup> Patients with the behavioral variant of



**Figure 2.** Biomarkers, memory, clinical function and progression to Alzheimer's disease.<sup>56</sup> Adapted from *The Lancet*, 9, Jack CR et al., Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade, 119-128, Copyright (2010), with permission from Elsevier.

FTD presented with moderate to severe ADL impairment, whereas patients with language variants of FTD tended to present with mild impairment in ADL.<sup>60,61</sup> Studies are limited though, and the relevance of IADL interference for different forms of dementia needs further exploration. In particular, the role of IADL functioning in the distinction between different types of dementia might be of interest.

For diagnostic studies, it is also relevant to know whether different types of informants are able to provide relevant information. Studies into different types of informants are limited and this topic needs further exploration. To investigate this, multiple informants should complete the IADL questionnaire for a single patient.

Moreover, no clear cut-off scores exist for impaired IADL functioning. In clinical practice, there is a great need for cut-off values, norms and guidelines on interpreting IADL scores. Future studies should focus on this. This topic will be addressed in the further validation of the Amsterdam IADL Questionnaire®.

Validation of a questionnaire is an ongoing process. The Amsterdam IADL Questionnaire® should therefore be validated in larger samples, other clinical populations and populations with different cultural backgrounds to confirm its usefulness. In general, large sample sizes are necessary for IRT analyses to obtain precise estimations of item difficulty and item discrimination characteristics. As some activities (such as using a Smartphone) were only performed by a limited number of patients, the questionnaire should be administered in more patients.

Other samples are also necessary, even though we used IRT analysis. An advantage of IRT is its invariance property, in other words, item characteristics are independent of the sample from which they were derived.<sup>52</sup> Since differences between populations have been found in previous IRT studies<sup>52</sup>, studies into the Amsterdam IADL Questionnaire® in other samples are necessary.

We assumed that we developed a sensitive IADL measurement instrument, by including a broad range of IADL activities. But we do not yet know whether this instrument is sensitive to early decline. Future studies are necessary to investigate for example whether IADL difficulties can be detected in MCI patients or in patients defined as prodromal AD.<sup>62</sup>

Further exploration is also necessary for item characteristics in different subgroups. Differential item functioning (DIF) or item bias occurs when the items response function of a particular item is different in two relevant subgroups. In other words, respondents from different subgroups who have the same level on the latent trait respond differently to the item. This is problematic, as theory assumes that the responses on items are dependent on the latent trait which the scale represents and not on other properties of the respondent. Of particular interest for future study are aspects such as gender, education and type of dementia. Cultural backgrounds should also be considered as daily activities relate to culture and lifestyle.<sup>63,64</sup>

Many questionnaires were developed to measure change over time.<sup>40-43,46</sup> In **chapter 4** we showed that none of these questionnaires received a positive rating on an important psychometric property for measuring change over time: responsiveness. The relevance of IADL makes it an important outcome measure for clinical trials.<sup>3</sup> Even though the Amsterdam IADL Questionnaire® was not primarily aimed at measuring change, it is an interesting and important topic for future study. IRT enables us to provide an estimation of a person's ability on the latent IADL trait. Since the scale that emerges from IRT analysis has interval-level properties, it would be very suitable for measuring change. As the Amsterdam IADL Questionnaire® was developed for patients with early and early onset dementia, this questionnaire will be of particular interest for clinical trials in these patients.

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