

## RESEARCH ARTICLE

# Identifying relevant outcomes in the progression of Alzheimer's disease; what do patients and care partners want to know about prognosis?

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## Abstract

**Background:** Prognostic studies in the context of Alzheimer's disease (AD) mainly predicted time to dementia. However, it is questionable whether onset of dementia is the most relevant outcome along the AD disease trajectory from the perspective of patients and their care partners. Therefore, we aimed to identify the most relevant outcomes from the viewpoint of patients and care partners.

**Methods:** We used a two-step, mixed-methods approach. As a first step we conducted four focus groups in the Netherlands to elicit a comprehensive list of outcomes considered important by patients ( $n = 12$ ) and care partners ( $n = 14$ ) in the prognosis of AD. The focus groups resulted in a list of 59 items, divided into five categories. Next, in an online European survey, we asked participants ( $n = 232$ ; 99 patients, 133 care partners) to rate the importance of all 59 items (5-point Likert scale). As participants were likely to rate a large number of outcomes as "important" (4) or "very important" (5), we subsequently asked them to select the three items they considered most important.

**Results:** The top-10 lists of items most frequently mentioned as "most important" by patients and care partners were merged into one core outcome list, comprising 13 items. Both patients and care partners selected outcomes from the category "cognition" most often, followed by items in the categories "functioning and dependency" and "physical health." No items from the category "behavior and neuropsychiatry" and "social environment" ended up in our core list of relevant outcomes.

**Conclusion:** We identified a core list of outcomes relevant to patients and care partner, and found that prognostic information related to cognitive decline, dependency, and physical health are considered most relevant by both patients and their care partners.

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## RESEARCH IN CONTEXT

- 1. Systematic review:** The literature shows that most patients and their care partners desire prognostic information. However, prognostic studies mainly attempted to predict progression to dementia, and it is questionable whether this is the most relevant outcome from a patient's perspective. The few available studies that focused on patient-relevant outcomes were based on interviews in small samples.
- 2. Interpretation:** By using a two-step approach (Dutch focus groups and a European survey), this study resulted in a comprehensive list of 13 core outcomes in the AD trajectory that are relevant to both patients and care partners, for example, memory deterioration and life expectancy.
- 3. Future directions:** These core outcomes can be incorporated in research and clinical practice. Integration of these outcomes into disease progression models can help to provide patients and care partners with specific and personalized information on what they can expect to happen in the future when living with AD.

## 1 | INTRODUCTION

Alzheimer's disease (AD) is a progressive neurodegenerative disorder, characterized by cognitive decline and dementia.<sup>1</sup> Dementia is in fact a late stage of this disease that takes decades to develop. Pre-dementia stages of AD include preclinical AD, which may express as subjective cognitive decline (SCD) and mild cognitive impairment (MCI).<sup>1</sup> Advances in biomarker-based diagnostic testing allow for an AD diagnosis in pre-dementia stages.<sup>2</sup> However, the question asked immediately after "doctor, what is wrong with me?" is "what can I expect?"<sup>3</sup> The establishment of an individual prognosis is still challenging due to the high variability in disease course and phenotypic manifestation.<sup>1</sup> In addition, it is not fully known which information patients and care partners would value most about their course of the disease.

Until now, prognostic studies mainly attempted to predict progression to dementia. While the syndrome diagnosis of dementia is an important endpoint in research, it may be rather an arbitrary point along the entire disease trajectory from the perspective of patients and care partners.<sup>4,5</sup> Which endpoints are most relevant to patients has not yet been thoroughly assessed. In addition, factors that are important for patients to know about the future may differ from those of care partners. As care partners have a significant role when making (dementia) care-related decisions, it is important to identify both patient- and care partner-relevant outcomes in the prognosis of AD.<sup>6,7</sup>

In addition, it can be debated whether the data we collect at memory clinics during routine follow-up cover the prognostic information most relevant to patients and care partners. There is increasing inter-

est in so-called patient-reported outcomes (PROs).<sup>8</sup> These include aspects such as (health-related) quality of life, activities of daily living, and interpersonal functioning from the perspective of patients and care partners, which may be missed during our current, routine check-ups. Some existing outcome instruments, such as TOPICS-MDS, are already based on patient report.<sup>9,10</sup> These outcome sets however have mostly been developed without consulting patients and caregivers about what is relevant to them. A few former studies that took into account patients' perspectives mostly focused on specific disease outcomes or on experiences with specific treatments.<sup>11,12</sup> The few available studies that focused on relevant outcomes from the perspective of patients were based on interviews in small samples.<sup>13,14</sup> In the current study, taking the viewpoints of patients and care partners as the starting point, we aimed to identify outcomes in the disease course of AD relevant to patients and care partners from multiple European countries.

## 2 | METHODS

### 2.1 | Design

In this mixed-method, multicenter study, we used a two-step approach with four focus groups followed by an online survey that was distributed in multiple European countries. Written informed consent was obtained from participants of the focus groups and digital informed consent was obtained from participants of the online survey. Local boards of the medical ethics committee reviewed and approved this study.

### 2.2 | Focus groups (step 1)

We took on a qualitative, bottom-up approach, using focus groups to elicit a comprehensive list of patient- and care partner-relevant outcomes in the progression of AD to serve as input for the online survey (step 2).

#### 2.2.1 | Participants

We conducted four focus groups. Three focus groups were conducted in an academic hospital (Alzheimer Centre Amsterdam, Amsterdam UMC) and one focus group in a local hospital (Alrijne Hospital Leiden) between July 2019 and October 2019. Participants were recruited from the memory clinics in both hospitals. We purposefully selected participants to compose heterogeneous groups in terms of sex, age, education, and disease stage (AD dementia, MCI, or SCD). Patients were eligible if they were diagnosed with AD dementia, MCI, or SCD at the memory clinic. Patients were not eligible if (1) their Mini-Mental State Examination (MMSE) score was less than 18, (2) they had a psychiatric disorder, (3) they reported hallucinations, or (4) they did not speak or understand Dutch. Care partners were eligible if they were a relative or loved one involved in care for someone with a diagnosis of AD dementia, MCI, or SCD. Care partners were not eligible if they

were younger than 18 years old or if they did not speak or understand Dutch.

## 2.2.2 | Procedures

Each focus group consisted of two parts. In the first part, we used a photo elicitation method, aimed at stimulating participants to think about and express what is most important to them in life. We showed the participants 13 pictures related to everyday situations and activities. We asked the participants to select one or more pictures that reflected what is important to them in life. Then, we asked them to explain why they selected this picture. The photo elicitation method was only used to prompt thoughts and feelings relevant to the goal of the focus groups, and data of this part was therefore not analyzed. The second part of the focus groups was aimed at obtaining a comprehensive list of concrete outcomes. We therefore asked the participants to formulate as many answers as possible to two main questions:

1. What do you want to know about the course of the symptoms?
2. If there was a treatment for Alzheimer's disease, on which specific aspect should this have an effect?

For each question, participants were first given 5 minutes to write their answers on individual sticky notes. Then, one by one participants were asked to read out loud and explain one of the outcomes they had written down. We collected and placed the sticky notes on large paper sheets, broadly clustering them into categories. In subsequent rounds, the participants expanded these lists with outcomes that had not yet been mentioned. After all outcomes had been read out loud and broadly categorized, participants were asked if they could think of any additional outcomes of relevance to them, which were then added. Audio recordings were made of all focus groups, and the sticky notes on the paper sheets were also saved.

## 2.2.3 | Analysis

One author (AM) transcribed the audiotaped focus groups using intelligent verbatim transcription. A second author (EDB) checked the transcripts for completeness. The transcripts were analyzed in MAXQDA software<sup>15</sup> using a process of inductive and deductive thematic analysis (directed content analysis). One author (AM) generated a "start list" of codes based on literature, prior to coding. Subsequently, two authors (AM and LNCV) coded the transcripts independently, adding, adjusting, and categorizing the codes based on the transcripts and the answers from the sticky notes. Afterward, they compared and discussed the differences in coding until consensus was reached. After the fourth focus groups, data saturation was achieved, that is, no new outcomes were identified based on the data from the fourth focus group compared to the previous three focus groups.

The final list consisted of 60 outcomes, which were subdivided into five categories. The item "How long am I able to decide whether I want

euthanasia?" is only relevant in the Netherlands, because euthanasia is not legally permitted in the other European countries, and the final list used in the European survey thus included 59 items.

## 2.3 | Online survey (step 2)

Subsequently, we used a quantitative, online European survey to determine the most relevant items among the outcomes identified in the focus groups.

### 2.3.1 | Participants

Participants were recruited via multiple routes. We recruited patients and care partners through memory clinics in the Netherlands, Slovenia, and Slovakia, who were then sent a link to the online survey. In addition, the online survey was sent to members (patients and care partners) of the dementia association Demensförbundet in Sweden. Finally, Alzheimer Europe sent a link to the online survey to members (patients and care partners) of its European Working group of People with Dementia. Alzheimer Europe also invited three of its member associations (i.e., national AD associations) to share this link with members of other similar English-speaking national working groups of people with dementia and care partners.

Patients were eligible to participate if they had a diagnosis of SCD, MCI, or mild dementia. Because we were interested in outcomes that participants want to know at the beginning of the disease process, severe dementia was not our target group. Care partners were eligible if they were a relative or loved one involved in caring for someone with a diagnosis of dementia, MCI, or SCD. Care partners were not eligible if they were younger than 18 years old.

### 2.3.2 | Design

The survey was created in the online survey tool Survalyzer.<sup>16</sup> We translated the survey into five different languages (Dutch, English, Slovak, Slovenian, and Swedish) and created separate versions for patients and care partners. Both versions consisted of two parts. In part 1, we collected background information about the participants, including age, sex, ethnicity, education, disease stage, and year of diagnosis. In part 2, we first asked participants to rate their importance of all 59 items (1-unimportant, 2-not very important, 3-neutral, 4-important, 5-very important). Participants also had the option to add additional missing items. As we anticipated that participants would rank many items as (very) important, we subsequently provided them with the items that they rated as "important" or "very important" and asked them to select the three most important items. This stepped approach facilitated the identification of the most relevant items out of the long list of 59 items that resulted from the focus groups.

### 2.3.3 | Analysis

Data was analyzed using version 22.0 of SPSS for Windows. Frequencies and percentages were calculated, resulting in two lists of the 10 items most frequently rated as most relevant by patients and care partners, respectively. We assessed concordance of these two lists between patients and care partners and subsequently compiled a final list of important items merging the top-10 lists of both patients and care partners. We compared the frequency of patients and care partners who selected at least one item as important from the category using a chi-squared test (see Appendix A in supporting information).

## 3 | RESULTS

### 3.1 | Focus groups

In total, 12 patients and 14 care partners participated in the focus groups. Median age (interquartile range [IQR]) of the patients was 66 (61–72) years and  $n = 6$  (50%) were female. There were  $n = 5$  (41%) patients with AD dementia,  $n = 3$  (25%) with MCI, and  $n = 4$  (33%) with SCD. Mean  $\pm$  standard deviation (SD) time since diagnosis was  $3 \pm 1$  years. Care partners had a median (IQR) age of 69 (54–74) years and  $n = 9$  (64%) were female;  $N = 11$  (79%) were care partner of a patient with AD dementia and  $n = 3$  (21%) of a person with MCI. Mean time since diagnosis was  $3 \pm 1$  years. Most care partners were a life partner (spouse) of the patient ( $n = 9$ ; 64%) and living with the patient ( $n = 9$ ; 64%). Seven care partners participated as a couple in the focus groups. Two life partners participated without the patient.

The focus groups revealed 59 outcomes of relevance, which we subdivided into five broad categories: (1) cognition (12 items); (2) functioning and dependency (18 items); (3) behavior and neuropsychiatry (14 items); (4) social environment (8 items); (5) Physical health (7 items). The supporting information provides an overview of the list of 59 outcomes, ordered by five major categories.

#### 3.1.1 | Cognition

This category included outcomes such as learning, recognizing loved ones, planning, and organizing. The following quote is a concrete example of an AD dementia patient who wants to know how the memory symptoms will progress.

Quote 1: *“How quickly does my memory deteriorate?”*

#### 3.1.2 | Functioning and dependency

Patients with AD dementia gradually lose the ability to make important decisions and eventually become legally incapacitated. The following quote of an AD dementia care partner illustrates how patients and care partners expressed an interest in predicting the patient's independence and ability to make decisions.

Quote 2: *“My mother has always been an independent woman who does not accept help from others. So the first thing that came to my mind was: when is she no longer able to make decisions on her own?”*

Closely related to dependency, patients and care partners mentioned outcomes related to everyday functioning and activities. The following quote by an individual with SCD illustrates the importance of the ability to perform hobbies and other enjoyable activities.

Quote 3: *“Singing, gardening, attending workshops. At this moment, I am able to do my hobbies. If I am no longer able to do my hobbies, then it is a great loss. I think it is important that I am able to do the things that I enjoy.”*

#### 3.1.3 | Behavior and neuropsychiatry

This category comprises outcomes such as anxiety and depressive symptoms, living in accordance with personal values and beliefs, and behavioral changes. Many participants pointed out the importance of maintaining, and being able to predict changes in, their personality and identity, as illustrated by the quote below by an individual with SCD.

Quote 4: *“My personality is important to me. I am always happy, that is what I am known for. I would like to know: when am I no longer myself?”*

#### 3.1.4 | Social environment

The category social environment includes outcomes such as patient and care partner quality of life and having meaningful moments with loved ones. The following quote of an AD dementia care partner shows the financial importance of knowing how long you are able to do activities together.

Quote 5: *“We consciously decided to make memories and do activities together as long as we are able to. And sometimes that costs money. If you know how long you can do meaningful activities together, then you can take that into account financially.”*

#### 3.1.5 | Physical health

This category comprises outcomes such as the progression of problems regarding motor skills and biomarkers in the brain, as illustrated by the quote below by an AD dementia care partner.

Quote 6: *“How long is he able to cycle?”*

Also, some participants experience AD as a hopeless process, and they therefore want to know what their life expectancy is, like this AD dementia patient:

Quote 7: *“It is a hopeless and long process. When can I expect the end?”*

For most participants, it appeared to be important to know more about the progression of the symptoms. However, a few participants expressed not being interested in the course of the symptoms, as illustrated by this quote from an AD dementia care partner.

Quote 8: *“We live our lives from day to day. So, I do not want to know anything about symptom progression.”*

**TABLE 1** Sample descriptives of patients and care partners who participated in the online survey

	Patients (n = 99)	Care partners (n = 133)
Age, median (IQR)	67 (61–73)	62 (52–72)
Female, n (%)	58 (59%)	78 (59%)
Country, n (%)	The Netherlands: 50 (51%) Slovakia: 16 (16%) Slovenia: 13 (13%) Sweden: 3 (3%) Other: 17 (17%)*	The Netherlands: 50 (38%) Slovakia: 37 (28%) Slovenia: 10 (8%) Sweden: 21 (16%) Other: 15 (11%)**
Years of education, median (IQR)	16 (13–18)	15 (13–17)
Diagnosis of patient, n (%)		
Dementia	42 (42%)	103 (77%)
MCI	29 (29%)	23 (17%)
SCD	28 (29%)	7 (5%)
Time since diagnosis (years), mean $\pm$ SD	4 $\pm$ 5	3 $\pm$ 3
Relation to patient, n (%)		
Partner/spouse	NA	76 (57%)
Child	NA	44 (33%)
Grandchild	NA	5 (4%)
Sister/brother (in law)	NA	3 (2%)
Other	NA	5 (4%)
Living with patient, n (%)	NA	83 (62%)

**Notes.**

\*Ireland: 5 (5), United Kingdom: 4 (4), Switzerland: 2 (2), Belgium: 1 (1), Finland: 1 (1), Germany: 1 (1), Austria: 1 (1), Portugal: 1 (1), Czech Republic: 1 (1).

\*\*Ireland: 6 (5), Switzerland: 3 (2), United Kingdom: 1 (1), Belgium: 1 (1), Finland: 1 (1), Germany: 1 (1), Austria: 1 (1), Portugal: 1 (1).

Abbreviations: IQR, interquartile range; MCI, mild cognitive impairment; SCD, subjective cognitive impairment; SD, standard deviation.

### 3.2 | Online survey

Table 1 presents the sample descriptives of the 232 participants from 13 European countries who completed the online survey. Figure 1 and Appendix A display how frequent every item, grouped by category, was selected as one of the three most important outcomes by patients and care partners. For both patients and care partners, cognition-related items were most frequently selected, followed by functioning and dependency. Compared to patients, care partners more often selected at least one of the items from the categories “behavior and neuropsychiatry” (13 [13%] vs. 38 [29%];  $P < .01$ ) and “physical health” (11 [11%] vs. 36 [27%];  $P < .01$ ) as important. Seven patients (7%) and three care partners (2%) indicated they did not want to know anything about the progression of the symptoms.

The top-10 lists of items most frequently mentioned as most important by patients and care partners were quite concordant, as seven items (70%) were selected by both groups. We merged the seven matching items and the six non-matching items into a core outcome list of 13 most important items as shown in Table 2. The majority (9 items) of these 13 items is part of the category “cognition,” followed by three items in the category “functioning and dependency” and one item in the category “physical health.” There were no items from the

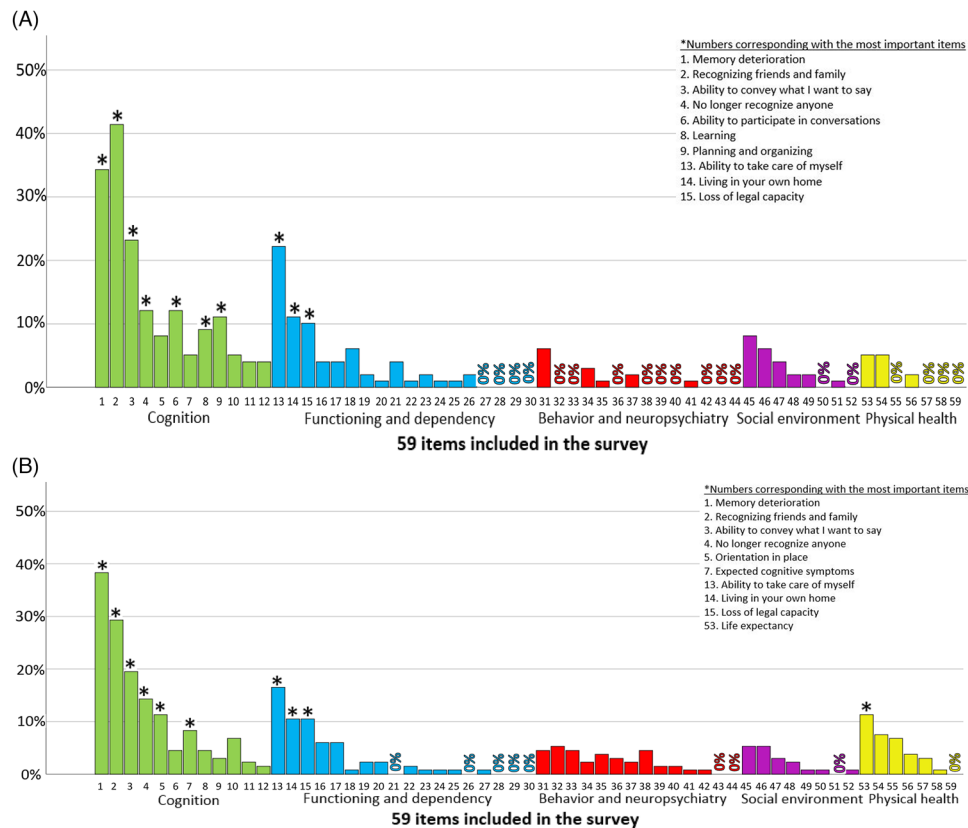
category “behavior and neuropsychiatry” and “social environment” in the core outcome list.

Of note, the item “How long am I able to decide whether I want euthanasia?,” which was only included in the Dutch survey, was the 5th most important outcome in the Dutch sample, selected by six (16%) of the Dutch participants. In addition, the item regarding loss of legal incapacitation was considered more important by the Dutch population compared to participants in other European countries (18 [18%] vs. 6 [5%]). We did not find other important differences comparing subgroups based on country (comparing the Netherlands vs. other European countries; Appendix B in supporting information). In addition, we found no differences in selected important outcomes comparing participants in pre-dementia stages to participants in dementia stage (Appendix B). Furthermore, participants had the option to add any outcomes they considered relevant in the online survey. This resulted in five new items only, which were not mentioned frequently (see Appendix A).

## 4 | DISCUSSION

In this pan-European study, we identified a core list with outcomes relevant to patients and care partners in the disease trajectory of AD.





**FIGURE 1** Percentage of participants who selected the item as important. A, Patients ( $n = 99$ ). B, Care partners ( $n = 133$ ). Figures show how frequently every item, grouped by category, was selected as one of the three most important outcomes by patients (A) and care partners (B). The items corresponding to each number can be found in the supporting information. The asterisks indicate the 10 items most frequently identified as most important by patients and by care partners, included in the core item list. Because seven items overlap, the core list comprises of 13 items

Patients and care partners largely identified similar outcomes as most important, including memory deterioration; loss of legal capacity; no longer recognizing (significant) others; and the patient's ability to convey what they want to say, take care of themselves, and live in their own home. Most selected outcomes were from the category "cognition," followed by items in the categories "functioning and dependency" and "physical health."

Many patients perceive the neuropsychological examination as stressful, yet our results show that they highly value a prognosis in terms of cognitive outcomes. Patients and care partners are keen to know about the (expected) course of the cognitive outcomes.<sup>17</sup> The current study underlines that we should bridge the gap between cognitive test scores and daily functioning, by making an effort to translate numerical cognitive test results to cognitive outcomes such as mentioned in this study, that is, better reflecting problems with cognition as experienced in daily life.

Contrary to our expectation, outcomes from the category "behavior and neuropsychiatry," such as anxiety and apathy, were not often selected by our participants as most important. This finding is in correspondence with results from a previous study, reporting that anxiety and depressive symptoms were not highly prioritized by patients with MCI and their care partners.<sup>11</sup> Nonetheless, behavioral and psychological symptoms are highly prevalent across the entire spectrum of AD,

with 96% of the patients showing at least one symptom.<sup>18,19</sup> Former studies reported that these symptoms were associated with increased risk of institutionalization, difficulties in daily functioning, and caregiver burden.<sup>20,21</sup> We could speculate that symptoms from the category "behavior and neuropsychiatry" may be more relevant at a later stage, or that patients and care partners may not have realized that these symptoms are related to AD. Alternatively, these symptoms may not be the most striking aspect of managing AD in everyday life, and this could be different in other types of dementia such as dementia with Lewy bodies or frontotemporal dementia, in which behavioral and psychological signs and symptoms are more in the foreground.<sup>22,23</sup> More research is needed regarding the causes of these symptoms, to better understand and explain their relevance.

We observed large variability in the importance rating of individual items, as 33 out of the list of 59 were rated as "most important" by at least one patient or caregiver. When scrutinizing the individual items, some showed some overlap with other items from the same category. For example, the items "How long am I able to recognize my family and friends?" and "When do I no longer recognize anyone?" from the category cognition showed resemblance as they both focused on the ability to recognize others. Nevertheless, on a category level, it was clear that most patients and care partners identified items related to cognitive decline and functional dependence as most important. In view of

**TABLE 2** Core outcome list

Outcomes	Category	Frequency	
		Patients (n = 99)	Care partner (n = 133)
<b>Memory deterioration</b> <i>How quickly does my memory deteriorate?</i>	Cognition	34 (34%)	51 (38%)
<b>Recognizing friends and family</b> <i>How long am I able to recognize my family and friends?</i>	Cognition	41 (41%)	39 (29%)
<b>Ability to convey what I want to say</b> <i>How long am I able to convey what I want to say?</i>	Cognition	23 (23%)	26 (19%)
<b>Ability to take care of myself</b> <i>How long am I able to take care of myself?</i>	Functioning and dependency	22 (22%)	22 (16%)
<b>No longer recognize anyone</b> <i>When do I no longer recognize anyone?</i>	Cognition	12 (12.1%)	19 (14%)
<b>Loss of legal capacity</b> <i>When are discussions underway about the (possible) need for legal incapacitation?</i>	Functioning and dependency	10 (10%)	14 (11%)
<b>Living in your own home</b> <i>How long am I able to live in my own home?</i>	Functioning and dependency	11 (11%)	14 (11%)
<b>Orientation in place**</b> <i>How long am I able to find my way back home?</i>	Cognition	8 (8%)	15 (11%)
<b>Life expectancy**</b> <i>What is my life expectancy?</i>	Physical health	5 (5%)	15 (11%)
<b>Ability to participate in conversations*</b> <i>How long am I able to participate in conversations?</i>	Cognition	12 (12%)	6 (5%)
<b>Expected cognitive symptoms**</b> <i>Which cognitive symptoms should I expect?</i>	Cognition	5 (5%)	11 (8%)
<b>Learning*</b> <i>How long am I able to learn new things?</i>	Cognition	9 (9%)	6 (5%)
<b>Planning and organizing*</b> <i>How long am I able to plan and organize everyday activities?</i>	Cognition	11 (11%)	4 (3%)

\*Item only mentioned in the list of the 10 items most frequently rated as most important to patients.

\*\*Item only mentioned in the list of the 10 items most frequently rated as most important to care partners.

The top 10 lists of both patients and care partners were merged into one core outcome list, comprising of 13 items.

the large variability in items selected as most important, it was even more remarkable that outcomes deemed relevant by patients and care partners were very similar. Seven out of 10 items in both the patient and care partner top-10 lists were concordant, justifying us merging these lists into one core outcome list of 13 items. However, the differences are also interesting. Care partners, for example, indicated a strong wish to know the patient's life expectancy. Patients on the other hand emphasized the importance of maintaining their ability to participate meaningfully in conversations. By merging the top-10 lists of both patients and care partners into one core outcome list, the perspectives of both stakeholder groups are equally well represented.

To our knowledge, this is the first study that has investigated outcomes of relevance to patients and care partners in the disease trajectory of AD (AD dementia, MCI, and SCD) in multiple European countries, using a mixed-methods approach. A former review reported comparable results in relevant outcomes of patients with MCI or AD and their care partners and health-care providers.<sup>24</sup> This review identified some outcomes mentioned in our study, for example, memory, mental health, activities of daily living, and maintenance of identity. Outcomes

that we did not replicate are eating behaviors, apathy, and self-efficacy in the ability to manage memory impairment. In addition, a recent qualitative study examined what matters most to patients and care partners across the AD continuum, by means of interviews only.<sup>25</sup> They also observed that memory (e.g., forgetting friends/family) was reported as one of the most challenging issues by the majority of the participants. In addition, they reported that the impact of AD varies across the disease-severity spectrum. Emotional impact (e.g., more frustrated) and social impacts (e.g., decreased social activities) were most commonly reported in the early stages of AD. However, care partners of patients with mild to severe AD reported impact on their own daily responsibilities as most important.

One of the strengths of our study is the two-stepp, mixed-methods approach, whereby we first used a qualitative bottom-up strategy to generate a comprehensive list of outcomes, and then a quantitative approach to provide a selection of most important outcomes from the perspectives of a large sample of patients and care partners. Also, we included participants from 13 different European countries, which is a very heterogenous representation of European countries, which also

greatly enhances generalizability. Among the potential limitations is our use of an online survey, which may have led to an underrepresentation of computer-illiterate individuals and patients with severe cognitive symptoms. However, one might argue that with the diagnosis of AD being made in an increasingly early stage, the preferences and wishes with respect to prognosis of individuals without severe symptoms are most relevant in this context. Another potential limitation is that identifying the most important items in the online survey was challenging for participants. To support participants in identifying what mattered most to them, we used a stepped approach that made it easier for the participants to select the three items they considered most important. Another potential limitation is that focus groups were conducted in the Netherlands only. However, participants had the option to add any outcomes they considered relevant in the online survey. This resulted in five new items only, which were not mentioned frequently (see Appendix A). In addition, a relatively larger proportion of survey participants were from the Netherlands. However, the most important items selected by the Dutch participants were similar to the ones selected by participants from the other European countries (Appendix B). Only the items regarding euthanasia and legal incapacitation were considered important by the Dutch population.

The current findings have implications for research and clinical practice. Because information on individual disease trajectories can support patients, care partners, and health-care providers to plan and organize care, we will use the results of the current study to collect PROs in the context of the European ADDITION project. Subsequently, we will integrate these PROs into a disease progression model. A previous study constructed biomarker-based models for prediction of progression to dementia in MCI patients.<sup>26</sup> The next step is to predict other outcomes relevant to patients and care partners, and subsequently stimulate the use of this prognostic information in clinical practice, for example, by providing patients and care partners with personalized information on their expected disease course.

In addition, based on our results, it can be debated whether the data we routinely collect during follow-up at the memory clinic (i.e., medical exam, cognitive testing) sufficiently reflect the outcomes that are most relevant. We should bridge the gap between the relatively abstract medical/cognitive test scores on the one hand and concrete daily life experiences/problems of patients and care partners on the other hand, for example by focusing more on data collection of PROs, such as identified in the current study. The following outcomes should be better represented in routine data collection: quality of life, mental health, activities of daily living, and social interactions, from the perspectives of both patients and care partners. These data can be used to provide insight into these outcomes over time, and possibly, to support the conversations between clinicians and care partners about these important topics, for example during follow-up.

Moreover, previous studies investigated the views of health-care professionals regarding important outcomes in AD, and reported driving,<sup>13</sup> patient and care partner quality of life,<sup>13,27</sup> maintaining personality and identity,<sup>13</sup> and behavior changes<sup>13,28</sup> as relevant. These did not, however, end up in our core outcome list from the perspec-

tive of patients and care partners. This would suggest that important outcomes from the perspective of health-care professionals are additionally relevant and could also be taken into account when investigating PROs in AD studies. Of note, seven (7.1%) patients and three (2.3%) care partners in our study reported that they did not want to know anything about the progression of the symptoms. Therefore, it is important to adopt a process of shared decision-making in memory clinics,<sup>29</sup> in which patients, care partners, and clinician decide together which prognostic information about the course of AD is most relevant.

To follow patients more efficiently, we could make more use of online opportunities, and this has particularly become relevant in the current times with COVID-19-related regulations that hamper physical visits. We will therefore incorporate our core outcome list in a large-scale online data-collection of PROs, supplemented with outcomes that are deemed relevant from the perspective of the professionals (e.g., quality of life and behavior changes). In our online data collection, in addition to questionnaires on quality of life and activities of daily living, we include questions about social environment, and patients' ability to participate in conversations, to recognize loved ones, and to keep up hobbies. Some outcomes identified in our study are too abstract or otherwise impossible to inquire about by means of a questionnaire (e.g., how long am I able to convey what I want to say?). Still, acknowledging these uncertainties and the impossibility to adequately answer these questions in a conversation with the clinician might help them cope.<sup>30</sup>

In conclusion, this study resulted in a comprehensive core list of 13 outcomes in the AD trajectory relevant to both patients and care partners. These outcomes can be incorporated in patient care and research, for example, via online survey. Integration of these outcomes into a disease progression model can help to provide patients and care partners with personalized information on prognosis of AD.

#### ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was evaluated on ethical grounds and approved by the local boards of the Medical Ethics Committee (Amsterdam UMC (approval no.2019.282), Karolinska Institutet Stockholm, University Medical Centre Ljubjana, and Institute of Neuroimmunology AD center Slovakia). All participants provided informed consent.

#### AVAILABILITY OF DATA AND MATERIALS

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

#### CONFLICTS OF INTEREST

The authors declare that they have no competing interests.

#### AUTHOR CONTRIBUTIONS

AM, LNCV, WMvdF designed the study. AM, EDB, EMMG, LJ, MGK, PN, AD, DG collected the data. AM, LNCV, EDB conducted the data analysis. AM, LNCV, WMvdF interpreted the data and drafted the article. All authors revised the manuscript. AM had full access to all data in the study. LNCV and WMF were responsible for study supervision.



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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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