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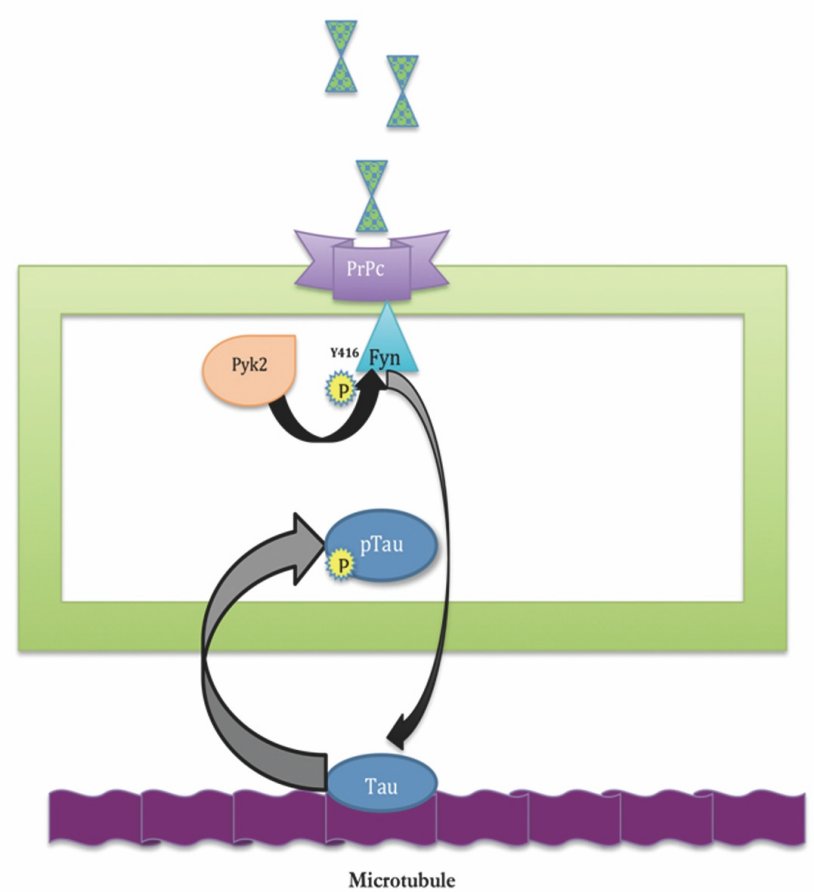
Scientific Research

# Advances in Alzheimer's Disease

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# Options for Evaluating Treatment Benefit in MCI and Prodromal Alzheimer's Disease: Content Validity of the Perceived Deficits Questionnaire (PDQ) in Patients with Early Symptoms of Cognitive Decline*

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## Abstract

**Background: Many instruments used to assess outcomes of treatment for Alzheimer's disease (AD) have no published evidence of their relevance and content validity in earlier stages of the disease, *i.e.*, mild cognitive impairment, or prodromal AD (pAD). The objective of this project was to evaluate the applicability and usefulness of the Perceived Deficits Questionnaire (PDQ) as an outcome measure in this population using qualitative methodology to support content validity. Method: Two waves of qualitative interviews were conducted in patients with MCI and pAD. Results: Evidence for content validity and usefulness of the instrument was demonstrated in the patient interviews. Minor modifications to the wording of several items were suggested for the PDQ and the recall period was changed. Conclusion: With these modifications, the PDQ has improved content validity and relevance. It is therefore a potentially useful outcome measure to evaluate therapeutic benefit in interventional studies of patients in the early stages of AD.**

## Keywords

**MCI; Prodromal AD; Content Validity; Perceived Deficits Questionnaire**

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## 1. Introduction

The value of patient-reported outcomes (PRO) in measuring the treatment effects in patients with mild cognitive impairment (MCI) and prodromal Alzheimer's disease (pAD) is increasingly recognized. However, the availability of PRO instruments with established reliability and validity for this early part of the Alzheimer's disease continuum is so far limited [1]. Furthermore, there is ongoing debate about how to diagnose those patients with cognitive impairment who are most likely to progress to AD, and various terms, such as MCI due to AD [2], amnestic MCI [3], and prodromal AD [4], have all been proposed, all with subtle differences in their definition. For example, Albert *et al*. [2] propose both clinical criteria and research criteria for MCI due to AD, the latter of which incorporate biomarkers to increase the predictive validity of the diagnosis. Prodromal AD is described as an amnestic syndrome of the hippocampal type and can be identified clinically by 1) a very poor free recall; and 2) a decreased total recall due to an insufficient effect of cueing with a high sensitivity of 79.7% and a specificity of 89.9% [4]. Clearly, the various MCI diagnostic criteria are closely related, and there is a need for clinically relevant instruments that are applicable across categories. To underscore this point, Ganguli and colleagues recently conducted a one-year study looking at various approaches to diagnosing MCI and their ability to predict disease progression, and found few differences in predictive utility, proposing that research criteria be validated at the community level before being incorporated into clinical practice [5].

PROs represent the voice of the patient in treatment development [6]; therefore, as more studies focus on treatments for MCI and pAD, there is a growing need for validated instruments for this part of the AD disease spectrum. One PRO that has previously been used in this population for evaluating medical treatments is the Perceived Deficit Questionnaire (PDQ) [7]. Originally designed to capture the decline in cognitive function among multiple sclerosis and traumatic brain injury patients [7], the PDQ provides a way to measure the patient's own perception of his or her cognition in specific domains: attention and concentration, retrospective memory, prospective memory, and planning and organizing [7]. One major study of MCI found that the PDQ was able to distinguish differences in treatment better than other well-established measures used in this population [8]. Assessing the relevance and content validity of a self-reported outcome instrument has recently been mandated by the United States (US) Food and Drug Administration (FDA) to obtain labeling claims on the same instrument [9] [10]. The FDA guidance recommends the use of qualitative research methods, typically cognitive interviews with patients, in ensuring PRO content validity [9]. Interviews are usually conducted among patients with the condition to ensure that the instrument is comprehensible and relevant to the patient population of interest, However, the relevance and hence content validity of the PDQ was never formally established with MCI or pAD patients, thereby limiting our understanding of whether the instrument is able to accurately measure patient relevant concepts of interest in this population.

Therefore, the primary objective of this study was to assess the relevance and content validity of the PDQ (in patients) using qualitative interviewing methodology (Wave 1). A secondary objective of this study was to adapt the measures to improve content validity based on the patients' evaluations and, subsequently, to evaluate the revised instrument using the same methodological approach (Wave 2). The comprehensibility of the items, appropriateness of the recall period, and the response options of the modified measure were also evaluated. These steps were undertaken to ensure that the PDQ was fit for use in clinical trials with MCI and/or pAD populations, so that the patients did not encounter questions that they clearly did not understand or could not answer. The project was designed to enable confident use of the PDQ in populations with early symptoms of cognitive decline in clinical practice and clinical trials in order to provide a better evaluation of treatment benefit in patients with these symptoms.

## 2. Methods

### 2.1. Study Design

This was a cross-sectional, qualitative research study conducted at two clinical sites in the continental United States (California and Vermont). As discussed above, the study was conducted in two waves in order to test the measure modifications made after the first wave of interviews. Wave 1 took place in October and November 2011; Wave 2 took place in June 2012. In accordance with the FDA guidance on qualitative research, one-on-one in-person cognitive interviews were conducted during which participants completed the PDQ while providing feedback on the content of each item. The sample size of each wave was defined by the saturation of concepts as previously defined. Institutional review board (IRB) approval was obtained prior to the start of the study

and after instrument modification, and the study was conducted in accordance with the Helsinki Declaration of 1975, as revised in 1983. All participants provided written informed consent prior to the start of the interview.

## 2.2. Participants

Potential subjects were identified from patient databases or medical records at each site. Eligible patients included subjects at least age 50, with a diagnosis of MCI or pAD and a Mini-Mental State Examinations (MMSE) score between 24 and 30 within the past three months. For Wave 1, participants with an MCI diagnosis were specifically recruited and had to meet criteria based on neuropsychological testing (cognitive testing one and a half standard deviations below normal for age and education) as outlined by Albert and colleagues [2]. During Wave 2, participants were screened for pAD with a clinical dementia rating (CDR) of 0.5 within the last six months of study baseline and a subjective complaint of worsening memory over the previous 12 months. We identified this population in order to specifically target a population of individuals more likely to progress to AD. Although the diagnoses of MCI due to AD and pAD differ in some respects, from a symptomatic perspective, there is considerable overlap, and we consider the results of these interviews generalizable to both MCI and pAD. Subjects were excluded from participating in Waves 1 and 2 if they were clinically depressed, had a history of alcohol or substance abuse, had experienced a negative life event, had taken drugs that affected cognition, or were mentally incapable of participating in the interview.

We have listed all patient inclusion and exclusion criteria in Appendix A1 (supplementary material).

Overall, 19 pAD or MCI patients participated in the two waves of interviews. Wave 1 included 11 subjects for patients diagnosed with MCI, and Wave 2 included eight subjects for patients diagnosed with pAD. **Table 1** provides a full list of the sociodemographic characteristics of all subjects for both waves.

## 2.3. Instruments

The PDQ is a 20-item questionnaire that covers four domains of cognitive function: attention and concentration, retrospective memory, prospective memory, and planning and organizing. The items were rationally derived or selected from a similar questionnaire developed for head-injured individuals [11]. The response options are answered on a five-point Likert scale, with 0 = never, 1 = rarely, 2 = sometimes, 3 = often, and 4 = almost always. A recall period of four weeks is traditionally used for each item. Subscales can be calculated by summing raw scores for the relevant five items (subscale range is 0 - 20), and the total score is calculated by summing raw scores for all of the PDQ items (scale range is 0 - 80). A higher score indicates greater perceived cognitive impairment.

## 2.4. Data Collection Procedure

Prior to participating in the interviews, each participant completed an eligibility form, the Patient Health Questionnaire-9 (PHQ-9), and the MMSE administered by the clinical site or an Evidera staff member. During the interviews, subjects completed a version of the PDQ (slight modifications were made between waves) followed by a cognitive debrief of the instrument where patients report their thoughts and feelings with regard to each item and their understanding of each item is assessed. While participants completed the PDQ measure, pauses were taken between questions for interviewers to ask questions and debrief each item.

The interview began with open-ended questions about symptoms of memory impairment then moved to questions about the instructions of the questionnaires—for example, "*Were there any words or phrases in the instructions that were difficult to understand*?" The interview then transitioned to the participant's understanding and interpretation of each item, including whether: 1) the questions were clear and easy to understand; 2) the response options were clear and appropriate; 3) the recall period was appropriate for the concepts being addressed, and 4) individual concepts could be expressed in alternative ways.

Interviews were conducted using a semi-structured interview guide. All interviews were conducted in English and took approximately 90 - 120 minutes to complete. Upon completion of the interview, each participant completed a basic sociodemographic information form. Clinical sites also completed a clinical form about the subjects' MCI/pAD and recorded patient medications.

## 2.5. Data Analysis

Descriptive summary statistics were used to characterize the sociodemographic and clinical characteristics of the

**Table 1.** Sociodemographic characteristics.

| Characteristics | Patient Characteristics | | |
|---|---|---|---|
| | **Wave 1 (n = 11)** | **Wave 2 (n = 8)** | **Total Sample (N = 19)** |
| **Age, Mean (SD) [Range]** | 72.1 (7.8) [56-82] | 72.5 (7.6) [63-84] | 72.7 (7.6) [56-84] |
| **Gender N (%)** | | | |
| Male | 8 (72.7%) | 7 (87.5%) | 15 (78.9%) |
| Female | 3 (27.3%) | 1 (12.5%) | 4 (21.1%) |
| **Ethnicity N (%)** | | | |
| Not Hispanic or Latino | 10 (90.9%) | 6 (75.0%) | 16 (84.2%) |
| Hispanic or Latino | 1 (9.1%) | 2 (25.0%) | 3 (15.8%) |
| **Race N (%)*** | | | |
| White | 11 (100%) | 6 (75.0%) | 17 (89.5%) |
| American Indian or Alaska Native | 1 (9.1%) | 1 (12.5%) | 2 (10.5%) |
| Other (Mexican) | -- | 1 (12.5%) | 1 (5.3%) |
| **Domestic Situation N (%)** | | | |
| Living with a partner or spouse, family, or friends | 10 (90.9%) | 7 (87.5%) | 17 (89.5%) |
| Living alone | 1 (9.1%) | 1 (12.5%) | 2 (10.5%) |
| **Employment N (%)** | | | |
| Retired | 9 (81.8%) | 6 (75.0%) | 15 (78.9%) |
| Employed, full-time | 1 (9.1%) | 1 (12.5%) | 2 (10.5%) |
| Employed, part-time | -- | 1 (12.5%) | 1 (5.3%) |
| Other–self-employed | 1 (9.1%) | -- | 1 (5.3%) |
| **Education N (%)** | | | |
| Elementary/primary School | 1 (9.1%) | -- | 1 (5.3%) |
| Secondary/high school | 1 (9.1%) | 3 (37.5%) | 4 (21.1%) |
| Some college | 3 (27.3%) | 2 (25.0%) | 5 (26.3%) |
| College degree | 3 (27.3%) | 3 (37.5%) | 6 (31.6%) |
| Postgraduate degree | 3 (27.3%) | -- | 3 (15.8%) |
| **Health Conditions**** | | | |
| Arthritis | 5 (45.5) | 4 (50.0%) | 9 (47.4%) |
| Cancer | 1 (9.1%) | -- | 1 (5.3%) |
| Hypertension | 2 (18.2) | 1 (12.5%) | 3 (15.8%) |
| Chronic obstructive pulmonary disease | -- | 2 (25.0%) | 2 (10.5%) |
| Other | | | |
| High cholesterol | 1 (9.1%) | -- | 1 (3.5%) |
| Heart surgery | 1 (9.1%) | -- | 1 (3.5%) |
| Diabetes | 2 (18.2) | 2 (25.0%) | 4 (21.2%) |

**Continued**

| | | | |
|---|---|---|---|
| High blood pressure | -- | 1 (12.5%) | 1 (5.3%) |
| **Relation to Participant** | **N/A** | **N/A** | **N/A** |
| Spouse | -- | -- | -- |
| Child | -- | -- | -- |
| Other family relation | -- | -- | -- |
| Friend | -- | -- | -- |
| Number of years known patient, Mean (SD) [Range] | -- | -- | -- |
| Hours/Day in contact with patient, Mean (SD) [Range] | -- | -- | -- |

*One participant selected both "White" and "American Indian or Alaska Native."; **Participants checked all that applied.

subject. Content analysis was used to evaluate the information gathered during the qualitative interviews. A qualitative analysis software program, ATLAS.ti [12], was used as a tool to systematically organize and categorize the text in the interview transcripts. The research team developed a coding dictionary to organize feedback provided by the participants about specific items or sections in the measures, and words and phrases were coded into groupings of feedback for items and sections of the measures. The output created from the ATLAS.ti coding included participant quotes linked to key concepts from the cognitive interviews. The conceptual quotes from each wave were analyzed and used to summarize the results.

## 3. Results

The demographic characteristics of participants in Wave 1 and 2 were similar. There were more men than women, the most commonly reported employment status was "retired," and the majority reported more than one comorbid condition. **Table 1** includes the full description of subject and informant sociodemographic information.

**Table 2** provides the information obtained from the medical chart review. On average, subjects in Wave 1 reported symptoms of cognitive impairment and a diagnosis of MCI more recently than participants in Wave 2 reported a diagnosis of pAD; however, the difference was not statistically significant. The mean MMSE score for both samples averaged 28.2 out of 30, indicating very mild impairment. During the cognitive interviews, each patient completed a version of the PDQ, either in its original form (Wave 1) or the amended version (Wave 2).

### 3.1. Wave 1 PDQ Results

We assessed participants' understanding of an item's intent and the timeframe used in the questionnaire. All participants understood 15 of 20 items. The five items that were partially misunderstood or misinterpreted by one or more participants included Items 6, 10, 12, 13, and 15. Of the five items that were misunderstood, three items (6, 10, and 13) were misunderstood by only one participant, and two items (12 and 15) were misunderstood by two participants. For Item 12 "*have trouble getting started, even if you had a lot of things to do*?" participants suggested that they did not have generally a lot to do.

"*It, it—to me 'getting started,' and 'lots of things to do' didn't relate and that's why I reread it. Uh, I have trouble getting started, uh, started doing what, you know? Even if I have a lot of things to do, uh, that—the different parts of that question was confusing to me.* ***Is there a different way that we could word it that you can think of?*** *I, I, I think I would say 'having trouble getting started when you have lots of things to do'*. [*Participant* 01-02-109, *Item* 12]"

Regarding Item 15, participants said that forgetting to turn on the alarm clock and forgetting to turn off the stove were not the same in terms of their consequences.

"*No, I don't. Yeah, I don't. But in my case it was okay because, um, you know, I don't rely on that alarm clock. So, I don't have to answer yes or no to that. To me that's an immediate no and the stove is an immediate no. But maybe had it been stove and oven, you know, or a water faucet, you know, then to me those are danger things. The alarm to me is not danger. That's just, you'll be late to work if you don't do that.* [*Participant* 01-02-107]"

**Table 2.** Patient clinical characteristics.

| Patient Clinical Characteristics | Wave 1 (n = 11) | Wave 2 (n = 8) | Total Sample (N = 19) |
|---|---|---|---|
| First Reported Symptoms, Mean Years Ago (SD) [range] | 3.5 (3.2) [0.0-10.0] | 4.8 (1.8) [2.0-8.0] | 4.0 (2.7) [0.0-10.0] |
| MCI Diagnosis, Mean Years Ago (SD) [range] | 0.9 (1.6) [0.0-4.0] | 2.0 (1.7) [0.0-5.0] | 1.4 (1.67) [0.0-5.0] |
| MMSE score, Mean (SD) [range] | 28.3 (0.8) [27.0-30.0] | 28.1 (2.0) [24.0-30.0] | 28.2 (1.4) [24.0-30.0] |
| Time Since Last MMSE, Mean Months Ago (SD) [range] | 1.7 (1.1) [0.3-3.4] | 7.5 (11.5) [0.7-27.1] | 3.63 (7.62) [0.0-27.1] |

The PDQ asks patients to consider the previous four weeks when answering the questions. We asked what actual timeframe participants were considering while answering the question; their responses varied between and within items. For only three of the 20 items, one or more participants indicated that they were using a four-week timeframe, and four participants indicated that Item 4 did not require a timeframe at all, since they had always been organized or disorganized. All other item responses ranged from days to weeks to a lifetime. In other words, rather than simply considering the four-week recall period, participants seemed to think back to the last example of the behavior or symptom described in the item. We discussed this issue with the author of the PDQ, and a decision was made to narrow the recall period to provide a more reasonable timeframe for subjects to consider when answering the questions. The new timeframe would also provide ample recall to evaluate treatments.

Overall, Wave 1 results showed the PDQ was a relevant, well-understood questionnaire for MCI patients. Based on the cognitive interviews and a discussion with the PDQ's author, two changes were made to the instrument between Wave 1 and Wave 2. They included the following:

1) Changing Item 15 to "*forget to do things like turn off the stove, or lock the door*?"
2) Changing the recall period from four weeks to one week.

## 3.2. Wave 2 PDQ Results

The interview guide used included similar questions to the prior cognitive interviews, as well as questions on item relevance and item response options. **Figures 1** and **2** provide a graphic visualization of participant understanding and relevance by PDQ item, recall period, and response options by PDQ item.

### 3.2.1. Understanding

Of the 20 items debriefed during the interviews, 17 items were interpreted as the author intended by at least 70% of the patients. The three items which caused the greatest difficulty for participants were Items 5, 8, and 12.

Item 8 "*have difficulty planning what to do in the day*?" was the most difficult to interpret, with only 38% (n = 3) of participants demonstrating an interpretation of its meaning that matched the intent of the item. The reasons why participants found this item difficult related to variations in scheduling or reliance on a calendar to dictate their plans. Two participants said it was not relevant because they did not have many plans to make. It was decided to keep this item in the instrument as some people did experience this difficulty, and hence we felt that it was best to keep measuring this effect.

Close to half of the participants (n = 3) had problems with Item 5 "*have trouble concentrating on what people are saying during a conversation*?" The main reason was misinterpretation of the question relating to the importance of a particular conversation, instead of the act of forgetting.

"*Well, there's two variables, one, depending on who I'm talking to and two, whether I'm interested in what they are having to say or what the topic is about I should say*. [*Participant* 001-104]"

We found similar difficulties as in Wave 1 for Item 12 '*have trouble getting started, even if you had a lot of things to do*?' Item 12 was equated to laziness or procrastination for the participants who did not understand the intent of the question.

"*It means that, um, I know I have these things that are uh, have to be completed, but I'm procrastinating and, uh, making, rationals of why I shouldn't do it, shouldn't do them. And, uh, being lazy, you know, and no—no account.* [*Participant* 001-104]"

As suggested during the first wave of the interview, we amended the item to say "*have trouble getting started, when you had a lot of things to do*?"

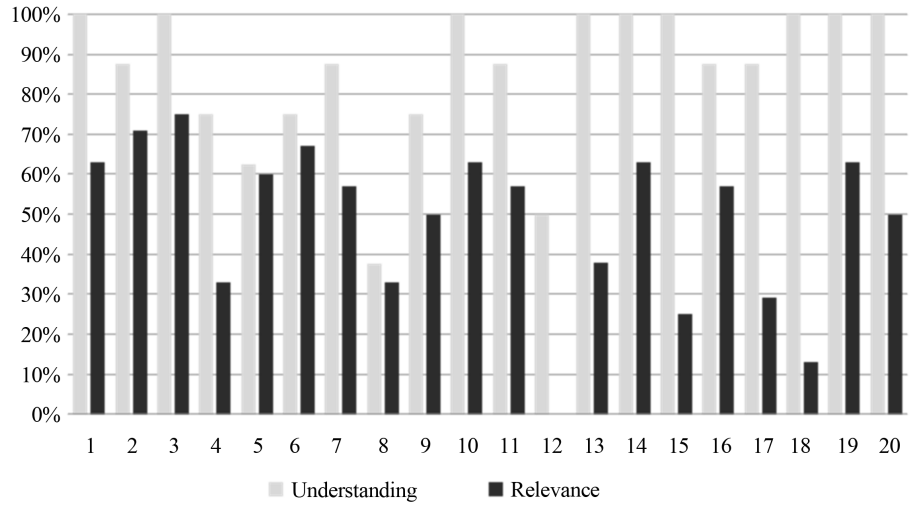


**Figure 1.** Percent of participants who understood an item or found the item relevant in the PDQ (Wave 2, n = 8).

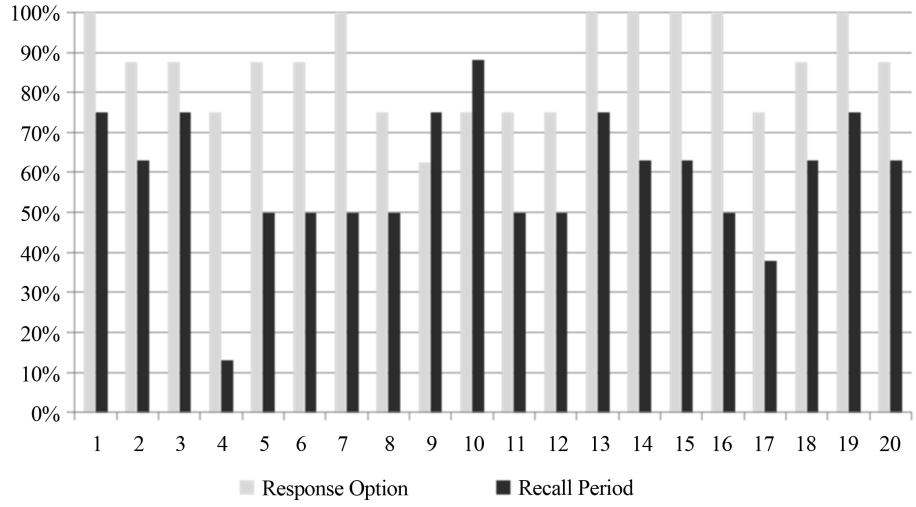


**Figure 2.** Percent of participants who understood the response options and recall period for the PDQ (Wave 2, n = 8).

We also noted that Item 11 "*forget the date unless you looked it up*?" was answered correctly by most participants (n = 7); however, the responses indicated a misinterpretation of the question. At least three participants referred to using a calendar or phone to help them keep track of the date, not understanding the relationship to thinking and memory associated with the item. We again decided to keep the item in the revised item list as it is useful to keep an account of this effect for some patients.

### 3.2.2. Relevance

We asked participants whether an item was relevant to their memory issues or thinking problems; many participants indicated that an item was not relevant if they personally did not face the issue. For example, Item 12 "*have trouble getting started, even if you had a lot of things to do*?" was rated as the least relevant, with no participants indicating relevance to their memory problems. However, the reasons included statements such as "*Because I have zero occurrences*" [Participant 001-107] and "*Because it would only—if—if there are things that I have to do, um, they're going to be put on my, uh, calendar*" [Participant 001-102].

Item 18 "*forget what you did last weekend*?" had one (13%) participant indicate the item was relevant. All others gave reasons such as "*I remember what I did the whole weekend*" [Participant 001-101]. One participant

said it wasn't applicable to him, but he could see how it would be relevant for someone else.

"*If the weekend wasn't somewhat special, it might be a little bit more difficult to remember.* [*Participant* 001-102]"

Item 15, "*forget to do things like turn off the stove, or lock the door*?" and Item 17, "*have trouble holding phone numbers in your head, even for a few seconds*?" were identified as relevant to the participant by less than 30% of the sample. Item 3, "*forget what you came into the room for*?" was the most relevant item based on participant responses, with six of the eight participants indicating it was relevant.

### 3.2.3. Recall Period

On average, five of the eight participants indicated that they were thinking about the last week on any given item. This was a higher rate than the four-week recall period considered in Wave 1. Item 4, "*have trouble getting things organized*?" had only one participant indicate that he was thinking about the last week while answering the question, whereas for Item 10, "*forget what you did the night before*?" almost all participants indicated that they were thinking of "last week" (n = 7). Other timeframes commonly reported by participants included the past in general; longer than a week; specific timeframes like a month, a year, last year; a couple weeks; and not applicable or never happened.

### 3.2.4. Response Options

The response options were generally well understood by participants. When asked to explain why a certain response was selected compared to adjacent options, patients were able to provide a clear reasoning for their choice 92.5% of the time. On average, seven of the eight participants were able to differentiate between the response options on any given question. For seven of the 20 questions, all the participants were able to select a response option and identify why they had selected it. Item 9, "*have trouble concentrating on things like watching a television program or reading a book*?" gave the most participants trouble in choosing the response options, with three participants unable to explain why they had selected their choice over another.

"*And, uh, when I'm reading a book because I like to read so much I don't usually having concentrating on telling—on—on what is—the content of the book is. So, I—I really don't know how to answer that. Uh, I would say—I wouldn't say never, but I would—I wouldn't say—uh, so—uh, so I probably would have to say sometimes.* [*Participant* 001-106, *SIC*]"

## 4. Discussion

The PDQ was cognitively debriefed in MCI and pAD samples to establish the relevance and content validity of the instrument where there was limited prior evidence. Overall, the items in the PDQ were largely well understood by most patients with MCI and/or pAD during Wave 1 and Wave 2, and although only a small sample of participants were included in each wave of the study, there was overall consensus across the concepts and questions reviewed. Only one item (Item 15) was modified between waves, in order to equate the severity of memory failure consequences between the examples used in the item. In other words, the example of setting the alarm was changed to locking the door, as setting an alarm was not relevant to this mostly retired population and the consequences of oversleeping were less severe than leaving the stove on. The timeframe was also modified from four weeks to one week as a consequence of the first wave of debriefings, which enhanced participants' ability to justify and explain their response choices. These modifications were well-accepted during Wave 2 interviews. During the interviews, the majority of the items (12 out of 20) were seen as relevant to the majority of patients with pAD. Eight items were identified by participants as not relevant to their current experience; these items were mostly part of the planning and organizing domain of the PDQ (three of five items). After further examination of the transcripts, this seemed largely due to participants reporting relevance of a particular item to their own lives, rather than considering the relevance of a particular item to all patients with early signs of AD. However, in the context of use as an outcome measure this may not be considered irrelevant for the person who has experienced problems in this area and an improvement in score could identify a beneficial treatment.

While the recall period for the PDQ was shortened from four weeks to one week to improve validity, there is still debate about what constitutes the most appropriate recall period for this patient population. When the recall period was set at four weeks, there was considerable variation in the actual recall period used. To some extent, that pattern was less observed when the recall period was only one week, as subjects could conform to the one-

week recall period much more easily. Nevertheless, when participants did not have an experience or a memory difficulty during the past week, they would simply go back to their last experience of the event and answer accordingly.

Our study also raised the issue of denial and potential lack of insight by participants struggling with early symptoms of a debilitating illness. For example, some respondents indicated that items were not relevant because they did not want to acknowledge that they were experiencing such symptoms, or they lacked some insight when they had found alternative strategies such as looking at their phone to remember the date.

In addition, we want to raise awareness that many pharmaceutical companies are currently contributing to the development of another MCI specific patient reported outcome measure to evaluate the therapeutic benefit of their drugs in the MCI population via the PRO Consortium of the Critical Path Institute (C-Path). The PDQ tested here measures a different concept (cognitive impairment) than the other instrument, which is focused on the measurement of complex activities of daily living (CADL) and interpersonal functioning (IF).

In conclusion, we found that the patient insights were valuable in improving the tool, and given that the PDQ has demonstrated content validity, we would advocate its further use to evaluate therapeutic benefit in clinical trials of patients with MCI or pAD. Our results suggest that items in the planning and organization sub-domain may be less of an issue (low relevance) for some of these patients, but improvements or lack of deterioration in the scores of this domain would be valuable for these patients. The modifications made to the PDQ improved the instrument's content validity and relevance in this population, therefore making the instrument more suitable for administration in clinical trials.

## Conflict of Interest

The project described in this paper was sponsored by Pfizer Inc and Janssen Alzheimer Immunotherapy Research and Development, LLC. Katja Rüdell is an employee of Pfizer Inc., and Maren Gaudig is an employee of Janssen Alzheimer's Immunotherapy. The study sponsor was involved in all aspects of the research except for actual data collection and data analysis.

**Description of authors' roles:** William R. Lenderking, PhD, was the Principal Investigator of the study, was involved in all aspects of the study, and helped draft the paper. Anna Steenrod, MPH, participated in the data collection and data analysis and helped draft the paper. Katja Rüdell, PhD, CPsychol, participated in the formulation of the research question for Wave 2 and participated in the interpretation of the data. Stephanie Klapper, BA, participated in the data collection for Wave 1 and helped draft the paper. Kellee Howard, MSc, MA, oversaw the data collection for Wave 1. Maren Gaudig, MSc, participated in the formulation of the research question for Wave 2 and participated in the interpretation of the data.

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Scientific Research

# Prevalence of Mild Cognitive Impairment in Individuals Aged over 65 in a Rural Area in North Greece

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## Abstract

**There are no data available on the prevalence of Mild Cognitive Impairment (MCI) in Greece, and the existing information about dementia shows important variations depending on the geographical setting as well as the methodology employed. The aim of this study was to determine the prevalence of MCI in individuals aged over 65 in a rural area in the north part of Greece. From 1428 residents, 678 were finally examined, with a mean age of 73.35 years. Assessments, including neuropsychological testing, neurological examination and medical history, were used to assign a diagnosis of normal cognition, mild cognitive impairment (MCI), with or without depression, depression or dementia according to suitable criteria. A questionnaire was also used to obtain social and demographic data. The 26.3% were classified as Mild Cognitive Impaired without depression, the 8.8% as Mild Cognitive Impaired due to depression, 5.9% had sole depression, the 2.4% were diagnosed with dementia and 56.6% had normal mental status. The observed prevalence for MCI with and without depression implies a total of 35.1% of all people aged over 65 with MCI in the study area. Mild cognitive impairment is more prevalent in Greece than dementia, and its subtypes vary in prevalence.**

## Keywords

**Mild Cognitive Impairment; Prevalence; Epidemiology; Greece**

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## 1. Introduction

Subjects with Mild Cognitive Impairment (MCI) constitute a risk population of developing disability, increased health care costs and progression to dementia and thus a population of big clinical interest. Better characterization of the preclinical stage of Alzheimer's Disease (AD) has been a crucial challenge for research over the past 10 years. Biological markers are used in different research projects. MCI appears to be the stage at which prevention strategies should prove most efficient in delaying or even avoiding further cognitive decline.

The prevalence of MCI is increasing in the developing as well as in the developed world in tandem with the ageing population [1]. Greece is among the countries with the oldest residents and the speed of aging in the Greek population is considered to be one of the fastest in the world [2]. As a result of this ageing process, a significant increase in the prevalence of cognitive impairment is to be expected.

The prevalence of MCI cannot be easily estimated precisely at present, mainly due to differences in the definition. There are wide variations between studies which have been held in Europe and worldwide [3]-[6] which can be also explained if we take into consideration the different design used each time and the characteristics of the samples which greatly vary from study to study. Direct age-adjusted comparisons have been made but other variables, such as life style or educational level have also an important impact. Additionally, the diagnostic criteria for MCI are neither objective nor stable, as they are constantly changing [7].

Up to now, few studies have explored MCI in healthy people from the general population, and the most recent results have shown the difficulty in approaching the MCI prevalence, which vary considerably according to the criteria applied [8].

We previously reported our estimates of the prevalence of dementia in Greece [9]. The aim of the present study was to contribute to epidemiological studies to Cognitive Impairment knowledge in Greece by estimating the prevalence of MCI in a rural population over 65 years of age in the north part of the country.

## 2. Materials and Method

### 2.1. Study Design

This is a door to door, home questionnaire-based study. It lasted from March 2009 to September 2009.

### 2.2. Setting-Participants.

The municipality of Alexander the Great is a rural area in the north of Greece and consists of seven small villages. From 1428 residents over 65 in the municipality list, 678 were finally examined while 423 subjects denied to participate in the study and 327 subjects had moved out of the villages and could not be detected. The most common cause for refusal was lack of interest (41.4%). Other reasons for non participation or refusal included: no available time (27.3%) illnesses (23.1%), suspicion (10.6%), fatigue (2.9%), lack of proxy from husband or children (2%) and finally bereavement (1%).

### 2.3. Study Procedure

This study was carried out by three research assistants, students of the Department of Social Work, Crete, after an intensive three-month training, in collaboration with a neurologist, specialist in dementia, who assessed the patients and who is working at the 3rd Department of Neurology Aristotle University of Thessaloniki.

Lists of residents were obtained from the municipal registry office. All registered individuals 65 years or older residing in the municipality were eligible for the study. Firstly, we came in contact with the mayor of the municipality of Alexander the Great, to take permission to carry out our research and seek for support in possible situations that would emerge. To encourage participation in the study, wall posters were sent to each village and were put at key points of each village. The study protocol was explained and discussed in meetings with general practitioners, local health authorities and the resident population. In addition, relevant brochures were handed out. We contacted also local authorities (presidents, priests, rural doctors) of each village and asked their help in raising awareness among residents.

All participants were assessed in-person in their residence. Firstly, a questionnaire on demographics was administered and included questions about gender, age, education, occupation, marital status, health problems (illness, medication), self care, use of leisure time, lifestyle habits (smoking, alcohol use, exercise) and aware-

ness/perceptions about AD. After that point, the neuropsychological battery described below was administered and recorded. The scores and results were provided to the neurologist-specialist in dementia, who assessed the patients and who was responsible for the final diagnosis.

## 2.4. Ethical Considerations

The study protocol was approved by the Research Ethics Committee of Aristotle university of Thessaloniki. The researchers informed the participants about the procedures of the study and discussed thoroughly different areas of concern, including data protection. Patients who agreed to participate in the study signed the consent document and were provided with the researchers' contact details.

## 2.5. Neuropsychological Assessment

Neuropsychological assessment of patient cognitive status was carried out with Mini - Mental State Examination or Hindi Mental State Examination for illiterates, the Instrumental Activity of Daily Living and finally, the Geriatric Depression Scale

1) In our study Mini-Mental State Examination (MMSE) [10] was administered to people who had completed at least 5 years of basic education. In those with fewer years of education we used HINDI test instead [11].

2) The Instrumental Activity of Daily Living (IADL) test describes tasks in a person's everyday life and is used to assess the functional status; using telephone, going shopping, preparing own meals, doing housework, laundering, use of transportation, managing medicine, and handling money. However in our study we evaluated only 4 of the 8 questions. Specifically, the questions had to do with the ability to use telephone, use of transportation, medication and financial behavior. The reason we evaluated only these specific questions is that the male population in Greece is not usually involved in housework [12] [13].

3) The short form of Geriatric Depression Scale (GDS) with 15 closed questions. To assess the mood and emotions of the elderly was also used. Scores of 0 - 6 are considered normal while scores of 7 - 15 indicate depressive symptoms [14].

## 2.6. Diagnosis

The participants of our study had either normal mental status, or MCI with or without depression, depression or dementia according suitable criteria.

We used Petersen's criteria [15] for **MCI** diagnosis. **1)** Memory impairment: Memory domain composite score >1.0 SD below the mean for age/sex/education. **2)** Memory complaint: 2 or more items endorsed from the first 16 subjective cognitive symptoms. **3)** Normal mental status: MMSE ≥ 21 (standard MMSE without age-education correction); non-memory domain composite scores within 1.0 SD of their means. **4)** No functional impairment: all IADL items reported as able to perform independently or with some help. **v.** Absence of dementia: CDR < 1.

Patients with **MCI with depression** met the criteria above, but the presence of depressive symptoms (GDS > 6) implied possible MCI due to depression.

**Depression** diagnosis was made according DSM-IV [16] criteria, with a final score of MMSE greater than 28, no functional problems, or if any they were due to coexisting health problems. In all these patients the total score of the GDS was greater than 6.

**Dementia** diagnosis was based on DSM-IV criteria; In order to establish the diagnosis, we also took into account all available information that was collected. Specifically, apart from the three screening tools performed (Mini Mental State Examination/Hindi Mental State Examination, Instrumental Activity of Daily Living, Geriatric Depression Scale), we took into consideration factors such as the age of the responder, gender, current employment, marital status, care, health problems, how they live, the municipal district. Emphasis was given on the ability of the individual to take medications, since it is the most reliable question of this test.

To establish this diagnosis according to the NINCDS-ADRDA [17] criteria we took into consideration functional problems not caused by other health problems. Some participants were found with functional problems although no health problems were reported. These findings, in combination with the low score in the MMSE and the absence of depression led us to the diagnosis of dementia.

Finally, responders not included in any of the above categories, had **normal mental level.** They had high score in the MMSE (>28), no functional problems and absence of depression.

### 2.7. Statistical Analysis

The raw prevalence of MCI with and without depression was calculated with respect to the total sample of the study. Global prevalence was calculated along with prevalence according to the age group and sex. Global and age specific prevalence was also calculated adjusted for age and sex according to the European standard population. For each prevalence estimate, 95% confidence intervals (95% CI) were also calculated. Chi-squared goodness of fit test was used to check the uniformity MCI with and without depression among age groups. Pearson chi-squared test was used to check the independence between categorical variables such as diagnosis and sex. Odds ratio was used to quantify the effect size of the relationship between MCI with or without depression and sex. One way analysis of variance with Tukey post hoc tests was used to check differences between means of continuous variables for the different diagnostic groups. P values less than 0.05 were considered statistically significant. Statistical analysis was performed using SPSS v20.0 (IBM Corp, Armonk, NY).

## 3. Results

**Table 1** shows the crude, age-adjusted and age-and sex-adjusted according to the European standard population prevalence of MCI without depression (178 participants, 26.3%) and MCI with depression (60 participants, 8.8%). In total, 238 of the individuals studied (35.1%) were diagnosed with MCI (with and without depression). On standardizing for age, the MCI prevalence decreased in both men and women-the estimated prevalence when adjusted for age was 30.8% (95% CI: 27.3 - 34.3), versus 30.1% (95% CI: 26.6 - 33.5) when adjusted for age and sex. The prevalence of MCI and the prevalence of the subtypes MCI with depression and MCI without depression increased with age ($p < 0.001$), (**Figure 1**) and women were seen to predominate among the individuals in all three categories.

Overall, prevalence of MCI differs among the age categories, both in males ($p = 0.032$) and in females ($p = 0.045$). (**Table 2**) Prevalence of MCI with depression does not differ among the different categories neither in men ($p = 0.626$) nor in women ($p = 0.512$). Finally, prevalence of MCI without depression differs among the age categories in men ($p = 0.010$) but not in women ($p = 0.104$). Compared with men, women are significantly more likely to develop MCI with depression (OR = 2.44, $p = 0.007$, 95% CI = 1.27 - 4.71).

**Table 3** shows the characteristics of the study participants, stratified by cognitive status. Results from one-way ANOVA showed that the mean age of individuals was significantly different between the diagnosis categories ($p = 0.001$). It did not show any significant differences in the mean age of male individuals among diagnosis categories ($p = 0.055$). However there are statistically significant differences in the mean age of women between the categories of cognitive status ($p < 0.001$). Chi-squared test results showed that there is dependence between gender and diagnosis categories ($\chi^2 = 23.9$, df = 4, $p < 0.001$) and a dependency between diagnosis categories and years of education ($\chi^2 = 18.54$, df = 8, $p = 0.018$).

## 4. Discussion

In our study, the observed prevalence of 26.3% for MCI without depression and 8.8% for MCI with depression implies a total of 35.1% of all residents aged over 65 with MCI in the municipality of Alexander the Great.

MCI has been variably described according to different assessments, diagnostic criteria and reference populations. In comparison with worldwide studies our MCI results are within the higher range. Ranaglia *et al*. in Italy,

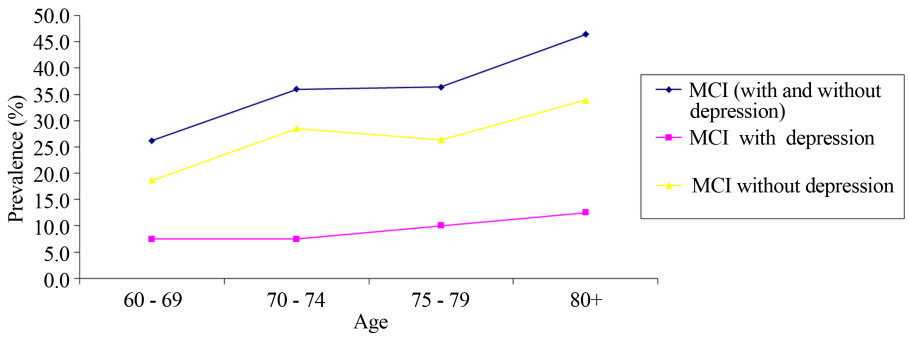


**Figure 1.** Prevalence of MCI in different age groups.

**Table 1.** Crude, age-adjusted and age-and sex-adjusted prevalence of MCI according to the European standard population prevalence of MCI.

| | Crude | | Age adjusted | | Age and sex adjusted | |
|---|---|---|---|---|---|---|
| | N (%) | 95% CI | Percentage (%) | 95%CI | Percentage (%) | 95%CI |
| **MCI (with and without depression)** | | | | | | |
| **Male** | 95 (32.3) | 26.9 - 37.6 | 24.4 | 19.5 - 29.4 | | |
| **Female** | 143 (37.2) | 32.4 - 42.1 | 35.7 | 30.8 - 40.4 | | |
| **Both** | 238 (35.1) | 31.5 - 38.7 | 30.8 | 27.3 - 34.3 | 30.1 | 26.6 - 33.5 |
| **Age group** | | | | | | |
| **65 - 69** | 49 (26.2) | 19.9 - 32.5 | | | | |
| **70 - 74** | 86 (36.0) | 29.8 - 42.1 | | | | |
| **75 - 79** | 51 (36.4) | 28.4 - 44.4 | | | | |
| **80+** | 52 (46.4) | 37.2 - 55.6 | | | | |
| **MCI (with depression)** | | | | | | |
| **Male** | 15 (5.1) | 2.6 - 7.6 | 4.0 | 1.8 - 6.3 | | |
| **Female** | 45 (11.7) | 8.5 - 14.9 | 11.2 | 8.0 - 14.3 | | |
| **Both** | 60 (8.8) | 6.7 - 10.9 | 8.1 | 6.1 - 10.1 | 7.6 | 5.6 - 9.6 |
| **Age group** | | | | | | |
| **65 - 69** | 14 (7.5) | 3.7 - 11.2 | | | | |
| **70 - 74** | 18 (7.5) | 4.2 - 10.9 | | | | |
| **75 - 79** | 14 (10.0) | 5.0 - 14.9 | | | | |
| **80+** | 14 (12.5) | 6.4 - 18.6 | | | | |
| **MCI (without depression)** | | | | | | |
| **Male** | 80 (27.2) | 22.1 - 32.2 | 20.5 | 15.8 - 25.0 | | |
| **Female** | 98 (25.5) | 21.1 - 29.9 | 24.8 | 20.5 - 28.7 | | |
| **Both** | 178 (26.3) | 22.9 - 29.5 | 22.7 | 19.5 - 25.8 | 22.7 | 29.5 - 25.8 |
| **Age group** | | | | | | |
| **65 - 69** | 35 (18.7) | 13.1 - 24.3 | | | | |
| **70 - 74** | 68 (28.5) | 22.7 - 34.1 | | | | |
| **75 - 79** | 37 (26.4) | 19.1 - 33.7 | | | | |
| **80+** | 38 (33.9) | 25.1 - 42.7 | | | | |

estimated the MCI prevalence about 7.7% [18] while Juarez-Cedillo et al in Mexico reported 6.45% [19] Similarly, another study showed that the prevalence of MCI of 1313 subjects older than 65 years was 28.3% in the United States [20] Also, Guo *et al.* in China estimated MCI prevalence to be 13.3% [21] while Wada-Isoe *et al.* reported 23.4% for Japan [22].

Recent findings from neighbor countries are also available and the results provided are also lower than ours. In Bulgaria, MCI prevalence was found to be 6.7%. Totally 607 subjects over 65 years old, a sample very similar to ours, were included; MCI diagnosis was made according to Petersen criteria, modified by Portet *et al.* [23] In Italy, MCI prevalence was 6% among a sample of 6921 subjects assessed using an operational definition according to MMSE score, but much higher almost 24.5% when psychometrically derived criteria of MCI were

**Table 2.** Age and sex prevalence of MCI and its subtypes.

| MCI (with and without depression) | Male | | Female | |
|---|---|---|---|---|
| **Age group** | **N (%)** | **CI** | **N (%)** | **CI** |
| **65 - 69** | 21 (42.9) | 28.8 - 47.7 | 28 (57.1) | 42.2 - 71.1 |
| **70 - 74** | 36 (41.9) | 31.3 - 51.9 | 50 (58.1) | 47.0 - 68.7 |
| **75 - 79** | 17 (33.3) | 20.7 - 47.9 | 34 (66.7) | 52.1 - 79.2 |
| **80+** | 21 (40.4) | 27.0 - 54.9 | 31 (59.6) | 45.1 - 72.9 |
| **MCI (with depression)** | | | | |
| **Age group** | | | | |
| **65 - 69** | 5 (10.2) | 3.3 - 22.2 | 9 (18.3) | 8.8 - 32.0 |
| **70 - 74** | 3 (3.5) | 0.7 - 9.8 | 15 (17.4) | 10.1 - 27.1 |
| **75 - 79** | 2 (3.9) | 0.4 - 13.4 | 12 (23.5) | 12.8 - 37.5 |
| **80+** | 5 (9.6) | 3.2 - 21.0 | 9 (17.3) | 8.2 - 30.3 |
| **MCI (without depression)** | | | | |
| **Age group** | | | | |
| **65 - 69** | 16 (32.7) | 19.9 - 47.5 | 19 (38.8) | 25.2 - 53.7 |
| **70 - 74** | 33 (38.4) | 28.1 - 49.5 | 35 (40.7) | 30.2 - 51.8 |
| **75 - 79** | 15 (29.4) | 17.5 - 43.8 | 22 (43.2) | 29.3 - 57.7 |
| **80+** | 16 (30.8) | 18.7 - 45.1 | 22 (42.3) | 28.7 - 56.8 |

**Table 3.** Sociodemographic, functional, clinical and neuropsychological characteristics of the participants according to cognitive impairment.

| | | Normal subjects N (%) | Subjects with depression N (%) | Subjects with MCI due to depression N (%) | Subjects with MCI without depression N (%) | Subjects with dementia N (%) | p |
|---|---|---|---|---|---|---|---|
| **Number of subjects = 678** | | 384 (56.6) | 40 (5.9) | 60 (8.8) | 178 (26.3) | 16 (2.4) | |
| **Age (mean ± sd)** | | 72.5 ± 5.4 | 74.5 ± 6.1 | 74.3 ± 6.1 | 74.3 ± 5.7 | 75.8 ± 5.9 | 0.001 |
| | Male | 73.4 ± 5.4 | 79.0 ± 7.3 | 74.5 ± 6.6 | 74.2 ± 5.6 | 73.7 ± 8.5 | 0.055 |
| | Female | 71.7 ± 5.4 | 73.3 ± 5.2 | 74.3 ± 5.9 | 74.4 ± 5.7 | 76.3 ± 5.4 | <0.001 |
| **Sex N (%)** | | | | | | | <0.001 |
| | Male | 187 (63.6) | 9 (3.1) | 15 (5.1) | 80 (27.2) | 3 (1.0) | |
| | Female | 197 (51.3) | 31 (8.1) | 45 (11.7) | 98 (25.5) | 13 (3.4) | |
| **Years of education N (%)** | | | | | | | 0.018 |
| | 0-4 | 104 (48.1) | 18 (8.3) | 26 (12.0) | 62 (28.7) | 6 (2.8) | |
| | 5-8 | 264 (59.7) | 22 (5.0) | 31 (7.0) | 115 (26.0) | 10 (2.3) | |
| | 9-12 | 16 (84.2) | 0 (0.0) | 2 (10.5) | 1 (5.3) | 0 (0.0) | |

used [24]. On the contrary, in northern Israel, a high prevalence of MCI, 32.1%, was observed among 944 participants [25].

However, the prevalence of MCI found in our study is lower than the one reported for France (42%) [26] ac-

cording to revised MCI criteria, with the aid of the following tests: Benton Visual Retention Test, Trail Making Test, Isaacs' Set Test in a large sample of 6892 subjects over 65 years old and similar to a study from Nigeria where cognitive impairment no dementia (CIND) prevalence was 35.9% in a community of 2487 residents over 65 according specific criteria [27].

There is no other study in the field of prevalence of MCI in Greece and therefore reliable conclusions are difficult to draw. We believe that the high prevalence of MCI we reported is connected with the low prevalence rates we have for dementia.

There have been only two studies which estimated the prevalence of dementia in Greece and this is the third one. The first Greek study about prevalence and incidence of dementia was conducted in the municipality of Pylea, Thessaloniki (1993-1997) [9] The age specific prevalence of dementia in Greece was 4.24% between 70 - 74 years, 10,7 % between 75 - 79 years, 10.64% between 80 - 84 years, 11.8% between 85 - 89 and 36.7% over 90 years old. In this study, the prevalence of dementia by age groups is: 1.6% between ages 65 - 69, 1.7% between 70 - 74 years, 4.3% between 75 - 79 years, and in those aged over 80 years was 2.7%. One possible explanation for these findings, which are lower from the previous study, may be that the municipality of Alexander the Great is a rural area while Pylea is an urban area and another one is the unknown age of 9 patients we found with dementia.

The third survey carried out in Greece, estimated the prevalence of dementia in Greek Orthodox monasteries [28]. The monks and nuns who live in these monasteries live far from the community, most of them are not married, their mind is always active as they are constantly praying and their diet is poor in lipids. The study reports that dementia is not present in ages between 60 to 75 years in monasteries. The prevalence of dementia is 9% over 80 years old while in Pylea is 9% over 70 years old. Also the prevalence rate in 80 - 84 ages in monasteries is half of the rate in the community. Diet was suggested as a contributor factor to these special findings indicating that nutritional habits could be a keystone. Lifestyle holds a great role as well.

Concerning the prevalence of dementia, it does not follow global prevalence rates, as our findings in all three studies are lower than in any other study in Europe or worldwide [29]-[33].

Lifestyle, the Mediterranean diet, the social network and the constant occupation with activities, even after years of retirement could contribute to these findings. The majority of the subjects are farmers and fishermen, who continue their activities several times per week for some years after retirement helping themselves being active. Indeed, several studies highlight the neuroprotective impact of physical activity, which could probably delay the onset of dementia [34] [35]. Also, the important role of family which takes care of their relatives and helps them to remain active is of great value. Attending a day center for elderly as well as attending church services is popular habits for the elderly in Greek countryside indicating that people passing from midlife to late life may have also a rather high social engagement.

Many studies have described the association of the Mediterranean diet with a slower cognitive decline [36] [37]. The Mediterranean diet is popular among Greeks.

Our study is the first mild cognitive impairment prevalence study in Greece. It shows that mild cognitive impairment affects a large percentage of the elderly we study. The prevalence rates of MCI vary widely, and possible risk factors for incident MCI are analyzed only to a limited extent. Our data are within the higher range of worldwide studies. The findings call for an agreement concerning the criteria used for MCI, use of biomarkers and the operationalization of these criteria.

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# Mapping It Out: A Novel Signaling Pathway Linking A$\beta$-PrP$^c$-Fyn Complex to Cognitive Impairment in Alzheimer's Disease

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## Abstract

**Understanding the signaling cascade that leads to the rapid memory and cognitive breakdown in Alzheimer's disease is the key to finding a potential treatment method for the disease. Recently, Larson *et al*. connect the roles of major proteins implicated in the disease progression and propose targeting of cellular prion protein (PrP$^c$) as a way of someday rescuing synaptic plasticity in humans with Alzheimer's, as it has been done on mice.**

## Keywords

**Alzheimer's; PrP$^c$; A$\beta$; Fyn; Tau; Microtubule**

## 1. Introduction

Alzheimer's disease (AD), an often times-fatal form of dementia, is among the most prevalent neurodegenerative disorders alongside Parkinson's disease and Amyotrophic Lateral Sclerosis. Two of the most prominent characteristics that define Alzheimer's disease are amyloid plaques, which are solid deposits of beta-amyloid (A$\beta$) protein, and neurofibrillary tangles, comprised of insoluble aggregates of tau protein along with collapsed microtubules. For the past few decades, many have sought to understand the biological mechanisms underlying Alzheimer's disease, and although much research has gone into deciphering the roles of the key players at work, up until recently, a detailed molecular pathway leading to Alzheimer's disease had not yet been mapped out.

Some of these key players in AD include A$\beta$ oligomers, cellular prion protein (PrP$^c$), tau protein, and Fyn kinase. Working in conjunction with cellular prion protein (PrP$^c$), A$\beta$ dimmers are largely responsible for inhibit-

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ing long-term potentiation (LTP) and inducing dendritic spine loss in hippocampal neurons [1], thus causing synaptic plasticity impairment in AD patients [2]. In other AD studies, hyperphosphorylation of tau (a microtubule-associated protein) caused tau mislocalization in dendritic spines, which disrupts synaptic plasticity and cognitive function [3]. Furthermore, cognitive impairment is not only associated with heightened levels of phosphorylated tau, but it is also linked to overexpression of the protein Fyn [4], a postsynaptic protein kinase implicated in the integrin signaling pathway [5]. Therefore, evidence from previous studies suggests that A$\beta$, $PrP^c$, tau, and Fyn somehow all contribute to the synaptic impairment and cognitive decline in AD patients. However, the link between the A$\beta$-$PrP^c$-Fyn complex and tau hyperphosphorylation and how it leads to dementia in AD remains unclear.

## 2. Role of $PrP^c$-Dimeric A$\beta$ Signaling

A primary goal of this paper by Larson *et al*. is to elucidate the molecular mechanism (**Figure 1**) by which oligomeric A$\beta$, coupled with $PrP^c$ receptor, phosphorylates the tyrosine kinase Fyn and produces neurofibrillary tangles in AD [5]. Through confocal immunofluorescence, Larson *et al*. observed that colocalization of $PrP^c$ and A$\beta$ occurred predominantly on synaptic sites, providing evidence that $PrP^c$ serves as a membrane receptor for

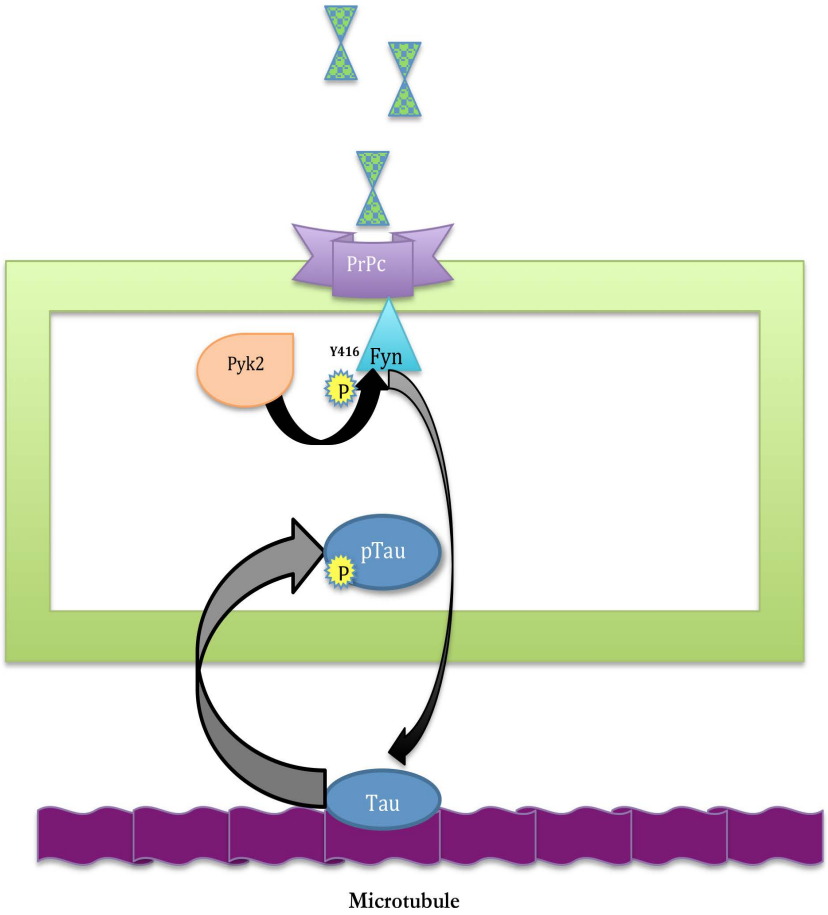


**Figure 1.** A schematic of the signaling cascade described by Larson *et al*. (2012), starting with A$\beta$ dimer- PrPc binding to the disruption of tau function. (From top to bottom): (I) Endogenous A$\beta$ dimers bind to $PrP^c$ receptors on cell surface; (II) Once A$\beta$ binds $PrP^c$, a signaling cascade is triggered in which Pyk2 (an integrin subunit) phosphorylates Fyn at the Y416 site (a tyrosine protein kinase to which $PrP^c$ is coupled) and activates Fyn; (III) Phosphorylated Fyn moves to the dendritic spine where microtubules are mediated by the protein tau; (IV) Fyn acts on tau to hyperphosphorylate it, leading to tau dysfunction, microtubule destabilization, and impairment of synaptic plasticity.

the A$\beta$ ligand (**Figure 1(I)**). Ultimately, Larson *et al*. characterize a signaling cascade in AD, through which dimeric A$\beta$ acts as a ligand for the $PrP^c$ receptor and activates intracellular Fyn through phosphorylation (**Figure 1(II)**). Fyn activation in turn hyperphosphorylates and mislocalizes tau protein in the dendritic spines, leading to destabilized microtubules, which produce neurofibrillary tangles and the cognitive impairment characteristic of AD patients (**Figures 1(III)** and **(IV)**). The authors found that AD brain tissue contained greater levels of cellular prion protein ($PrP^c$) expression, which was positively correlated with Fyn phosphorylation. These observations support previous studies pointing to Fyn's role in mediating cognitive defects associated with AD [5]. But here, Larson *et al*. draws a novel connection between $PrP^c$ and Fyn, suggesting that their interaction in conjunction with the presence of A$\beta$ oligomers may be bringing about the neurological impairments in AD.

## 3. Discussion

However, in opposition to Larson *et al*.'s findings asserting the necessity of $PrP^c$ in mediating synaptic toxicity, several other studies produced results that are not consistent to this claim. Notably, in two studies done in 2010, APP-expressing transgenic mice displayed no significant difference in cognitive performance regardless of $PrP^c$ overexpression or ablation [6] [7]. These studies that failed to show synaptic impairment in AD as dependent upon $PrP^c$ overexpression [7] stand in direct opposition to Larson *et al*.'s findings.

Yet, in defense of Larson *et al*.'s conclusion, we must consider that, whereas the research conflicting with Larson *et al*.'s results experimented with 2-to-4-month-old Prnp transgenic mice, the age at which amyloid plaques actually begin forming in mice brains is no earlier than 10 - 14 months old [5]. Since these beta-amyloid plaques found only in older mice comprise A$\beta$ dimers, and since A$\beta$ dimers are the only beta-amyloid species to bind $PrP^c$ receptors, only in the AD mice older than 10 months can we see the effect that $PrP^c$ receptor exerts on synaptic plasticity impairment once it binds dimeric A$\beta$ [5]. Therefore, these studies [6] [7] failed to observe $PrP^c$'s effects on LTP impairment as reported by Larson *et al*., not because $PrP^c$ is not implicated in the signaling pathway, but rather because the mice they experimented with were too young to have actually developed the A$\beta$ dimers that bind $PrP^c$ to initiate the signaling cascade.

### 3.1. Significance of Tau Mislocalization in Alzheimer's Disease

The paper by Larson *et al*. is essentially the first to characterize the signaling cascade linking endogenous A$\beta$ dimer with the mislocalization and hyperphosphorylation of tau in Alzheimer's disease [5]. It consolidates evidence from previous papers illustrating the roles that various molecules play to produce neuronal dysfunction in AD. This paper pieces together the bits of information gathered from research over the decades so that this proposed pathway has logical flow throughout.

Previous studies have documented the consequences of $PrP^c$ and A$\beta$ interaction on LTP impairment [1], reversal of synaptotoxic effects by A$\beta$ due to genetic ablation of Fyn [4], and neurofibrillary tangles resulting from tau hyperphosphorylation [3]. But prior to this paper, it was unclear how these phenomena were related to produce Alzheimer's disease. Therefore, Larson *et al*. were the first to draw a link among these findings and prove a logical signaling cascade in which A$\beta$ dimer binds to the $PrP^c$ receptor to activate Fyn, which then goes on to phosphorylate tau and cause tau missorting in the dendritic spine, and this tau mislocalization eventually leads to synaptic plasticity inhibition.

### 3.2. Potential Treatment Methods Targeting $PrP^c$-A$\beta$ Dimer Binding

In addition, Larson *et al*. cites $PrP^c$ targeting as a potentially viable method for slowing down the progression of Alzheimer's disease in humans, since blocking $PrP^c$-A$\beta$ dimer binding using the antibody 6D11 in AD mice resulted in the reversal of LTP impairment [5], or LTP rescue. Furthermore, the authors add that since $PrP^c$ receptors located on the cell membranes are readily accessible, targeting them as a possible treatment method is entirely feasible to do in the near future. Finally, this paper allows us to see why neurofibrillary tangles and amyloid-beta plaques appear simultaneously in AD brain tissue: the A$\beta$ dimers that comprise plaques directly influence phoshporylated tau aggregation into neurofibrillary tangles.

### 3.3. Future Directions

To build upon the knowledge that Larson *et al*. have presented, future research may strive to find a safe and ef-

fective way to block $PrP^c$-A$\beta$ dimer binding in humans so as to potentially rescue LTP in Alzheimer's patients. Furthermore, one may try to find any link between the integrin signaling cascade and the proposed pathway, both of which involve the Fyn kinase, as such knowledge may allow us to gain a broader perspective of how interconnected the various molecules and pathways are in the AD neuron.

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# Mutations of *TP*53 Gene and Oxidative Stress in Alzheimer's Disease Patients

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## Abstract

**Alzheimer's disease (AD) leads to the generation of *β*-amyloid (A*β*), which may damage DNA and thus lead to apoptosis induction by the p53 pathway. Dysfunction of the p53 protein may then be connected with the development of AD. Studies were conducted on 28 AD patients and 30 non-AD controls. Analysis of *TP*53 mutations in exon 7 was performed on DNA isolated from whole blood and biochemical parameters in the peripheral lymphocytes of these individuals. Our study showed a silent mutation *TP*53 C708T (21%) [p < 0.05] and a missense mutation *TP*53 C748A (4%) only in the AD patients. Moreover, in AD patients with the *TP*53 C748A mutation, the level of 8-oxo-2'-deoxyguanosine (8-oxo2dG) was more than 5 times higher than the average level in this study group. In AD patients with the wild-type *TP*53 gene, the level of 8-oxo2dG was correlated with the level of protein p53 (R = +0.7388, p < 0.05). The level of the oxoguanine DNA glycosylase 1 (OGG1) protein was similar in AD patients with the silent mutation and the wild-type gene *TP*53 (p < 0.05) and lower than in the controls. It appears that mutations in exon 7 of *TP*53 (C748A, C708T) may be associated with pathogenesis of AD.**

## Keywords

***TP*53; 8-oxo2dG; p53; OGG1; AD**

## 1. Introduction

Alzheimer's disease (AD) is one of the most important neurodegenerative diseases. A number of factors are in-

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volved in the pathogenesis of AD, e.g. amyloid precursor protein (APP). Mutations in the *APP* gene account for familial AD (FAD) which is caused by changes which result in an increase of the *β*-amyloid (A*β*) level in the processing of this gene [1]. An elevated level of A*β* may generate free radicals, which may then oxidize macromolecules, such as DNA [2]-[5].

Among the markers of oxidative DNA modifications, 8-oxo-2'-deoxyguanosine (8-oxo2dG) is the most abundant product of hydroxyl-induced oxidation in the purine bases of nucleic acids. Variable levels of 8-oxo2dG have been shown in both the brain [6] [7] and peripheral blood lymphocytes of AD patients [8] [9]. Furthermore, it has been demonstrated that in humans, 8-oxoguanine DNA glycosylase 1 (OGG1) is the main DNA repair enzyme that excises 8-oxo2dG from DNA [9]. A study by Dorszewska *et al.* [9] showed that the expression of three isoforms of OGG-1a, 1b, and 1c changes to the levels of 8-oxo2dG in the peripheral blood lymphocytes of AD patients.

It was postulated that decreased expression of OGG1 may lead to higher background mutation frequency, e.g. GC → AT [10]. This type of mutation is commonly observed in the tumor suppressor *TP*53 gene [10]. According to De la Monte and Wands [11], the p53 protein can be involved in neuronal death in AD patients, and its transcription is up-regulated at the early stages of the disease and down-regulated during the neurodegenerative process. *TP*53 gene mutants have also been found in various cancers. There is accumulating evidence pointing to the contribution of oxidative stress in both AD and cancer [12]. Postmortem studies have shown underreported signs of AD in patients diagnosed with brain tumors, thus disclosing a putative crosslink between the p53 pathway and degeneration [13].

The purpose of this study was to analyze of the *TP*53 gene mutations in exon 7 and the extent of oxidative DNA damage (8-oxo2dG) as well as expression of p53 and OGG1 protein levels in the peripheral lymphocytes of AD patients and controls.

## 2. Materials and Methods

### 2.1. Patients and Control Subjects

The studies were conducted on 28 patients with AD, including 15 women and 13 men aged 52 - 85 years. Patients with AD were diagnosed according to the criteria of the National Institute of Neurological and Communicative Disorders–Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) [14]. The patients were not screened for the presence of known mutations in the *APP* or *PSEN* genes.

The control group included 30 non-AD individuals, 17 women and 13 men aged 40 - 83 years. None of the control subjects had verifiable symptoms of dementia or any other neurological disorders.

A local ethical committee approved the study and written consent of all the patients or their caregivers was obtained.

### 2.2. Mutation Analysis of the *TP*53 Gene in Exon 7

DNA for genotyping was isolated from whole blood by standard procedure. *TP*53 mutation analysis was carried out on DNA using PCR and DNA sequencing with the use of primers targeting exon 7, designed with Primer 3+ software. The following primers were used: *TP*53*F:* GCGCACTGGCCTCATCTT and *TP*53*R*: AGGGTGGCAAGTGGCTC. PCR was carried out in 20 µl of mixture containing: 11.6 µl of Mili-Q water, 2.0 µl of 10x PCR buffer without $MgCl_2$ (Novazym, Poland), 0.8 µl of $MgCl_2$ solution (25 mM, Novazym, Poland), 2.2 µl of primer solution, 1.1 µl dNTPs (Novazym, Poland), 0.3 µl Allegro Taq polymerase (Novazym, Poland), and 2 µl of the tested DNA. The annealing temperature was optimized to 62˚C and the PCR was performed for 35 cycles. Quality of the product was analyzed by standard gel electrophoresis.

The PCR product (see **Figure 1**) was purified and sequenced according to a standard protocol at the Laboratory of Molecular Biology Techniques at the Faculty of Biology, Adam Mickiewicz University, Poznan, Poland. The samples were analyzed with sequencer 3130xl Genetic Analyzer (Applied Biosystems HITACHI, USA). All samples showing the presence of mutations were re-analyzed to confirm the presence of specific changes. The sequencing results were analyzed using BioEdit software based on a reference sequence.

### 2.3. Determination of 8-oxo2dG

*Isolation of DNA.* DNA was isolated from peripheral blood lymphocytes by five-fold centrifugation in a lytic

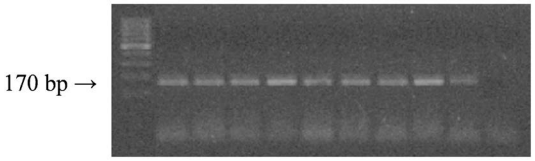


**Figure 1.** Results of agarose gel electrophoresis of the PCR product of the *TP*53 gene in exon 7.

buffer containing 155 mM $NH_4Cl$, 10 mM $KHCO_3$, 0.1 mM $Na_2EDTA$, and pH 7.4 in the presence of a buffer containing 75 mM NaCl, 9 mM $Na_2EDTA$, pH 8.0, sodium dodecyl sulfate and proteinase K (Sigma, St. Louis, MO). Subsequently, NaCl was added, the lysate was centrifuged, and DNA present in the upper layer was precipitated with 98% ethanol.

*Enzymatic hydrolysis of DNA to nucleosides*. DNA was hydrolyzed to nucleosides using $P_1$ nuclease (Sigma) for 2 h at 37˚C in 10 mM NaOAc, pH 4.5. The solution was buffered with 100 mM Tris-HCl, pH 7.5. Subsequently, the DNA was hydrolyzed with alkaline phosphatase (1U/µl; Roche, Germany) for 1 h at 37˚C and the obtained nucleoside mixture was applied to a high performance liquid chromatography system with both electrochemical and ultraviolet detection (HPLC/EC/UV).

*Estimation of* 8-*oxo2dG*. To determine the 8-oxo2dG levels the nucleoside mixture was applied to the HPLC/UV system (P580A; Dionex, Germany), coupled to an electrochemical detector (CoulArray 5600; ESA, USA). Nucleosides were separated in a Thermo Hypersil BDS C18 (250 mm × 4.6 mm × 5 µm) column (Germany). The system was controlled and data were collected and processed using Chromeleon software (Dionex, Germany). The results were expressed as a ratio of oxidized nucleosides in the form of 8-oxo2dG to unmodified 2'dG [15].

## 2.4. Estimation of OGG1 and p53 Proteins Levels

*Isolation of protein.* Blood was gradiated onto gradisol L at a 1:1 ratio and centrifuged, followed by collection of the interphase which was then rinsed in PBS buffer (0.9% NaCl in phosphate buffer) and centrifuged. The obtained lymphocyte precipitate was rinsed with radioimmunoprotein assay (RIPA) buffer (50 mM Tris-HCl, pH 7.2, 150 mM NaCl, 1% IGEPAL CA-630, 0.05% SDS, and 1% sodium deoxycholate), supplemented with a protease inhibitor cocktail (Sigma), homogenized in a mixture of RIPA with protease inhibitor cocktail (16:1) and 0.5 µl PSMF (Sigma) in isopropanol (10 mg/100 µl), and centrifuged. The obtained supernatant then underwent further analysis [16].

*Western blot.* The OGG1 protein was analyzed in 12% and the p53 protein was analyzed in 7.5% polyacrylamide gel. Equivalent amounts of protein (30 µg protein/lane) were loaded to the wells. The gel-separated proteins were electrotransferred to a nitrocellulose filter in a semidry Western Blot analysis apparatus (Apelex, France). To estimate the levels of the OGG1 protein, the filters were exposed first to an anti-OGG1/2 goat polyclonal antibody (G-20, IgG, 200 µg/1.0 ml; Santa Cruz, USA), and for the p53 protein, anti-p53 mouse monoclonal antibody (IgG-2a, 200 µg/1.0 ml; Santa Cruz, USA) diluted 1:500.

Subsequently, individual sheets of nitrocellulose filter were incubated with the second antibody; for the OGG1 protein this was mouse anti-goat IgG-HRP (200 µg/0.5 ml; Santa Cruz, USA) and for p53 protein this was goat anti-mouse IgG-HRP (200 µg/0.5 ml; Santa Cruz, USA) at a dilution of 1:2000. Peroxidase BMB was added (BM blue POD substrate precipitation; Roche, Germany) to stain the immunoreactive bands. The surface area of the immunoreactive bands was registered using a densitometer (GS-710; Bio-Rad, Hercules, CA) in the Quantity One System [9] [17].

## 2.5. Statistical Analysis of the Results

The obtained data were evaluated using Kruskal-Wallis and Fischer exact tests. Correlations between the obtained results were tested using the Spearman test.

GraphPad (Instant, USA) and Statistica for Windows (Stat Soft, USA) were used to perform statistical analyses of the results.

## 3. Results

Our studies revealed the presence of two different mutations only in AD patients, a silent mutation *TP*53 C708T (Y236Y) in six patients (21%) [Fischer's exact test, $p < 0.05$] and a missense mutation *TP*53 C748A (P250T) in one patient (4%) (see **Table 1**, **Figures 2(a)** and **(b)**).

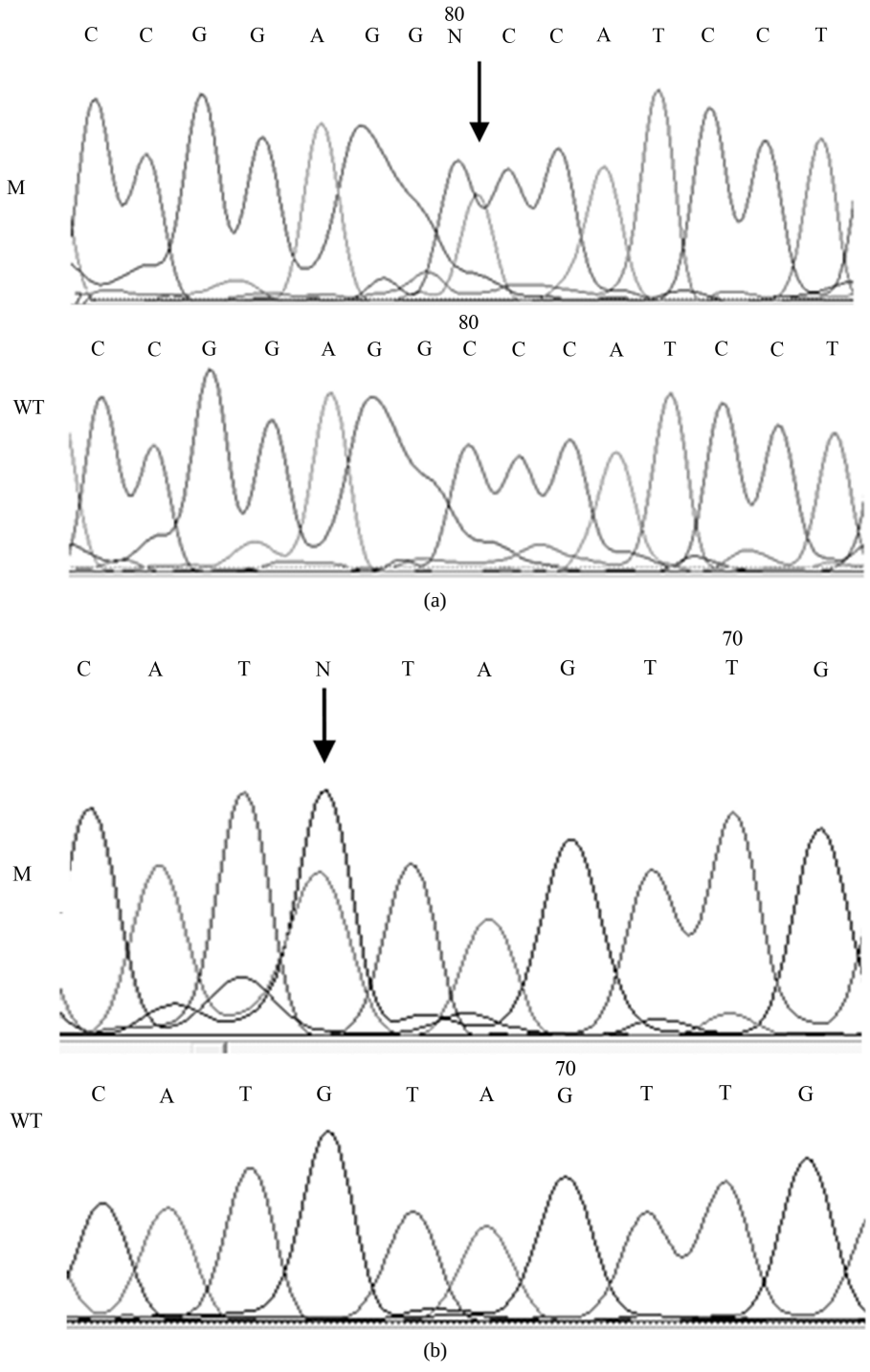


**Figure 2.** Mutations of the *TP*53 gene in exon 7 in AD patients; 2A, *TP*53 C748A (P250T) missense mutation (M) and wild-type (WT); 2B, *TP*53 C708T (Y236Y) [reverse strand] silent mutation (M) and wild-type (WT).

**Table 1.** Identified *TP*53 mutation in exon 7 in AD patients.

| Subject | DNA mutation | Amino acid substitution | Mutation frequency n/% |
|---|---|---|---|
| AD patients | C748A | P250T | 1/4 |
| AD patients | C708T | Y236Y | 6/21* |
| Controls | None | None | - |

n-Number of patients with mutations. Fischer's exact test, *$p < 0.05$.

In the AD patient with the *TP*53 C748A missense mutation was shown that the level of 8-oxo2dG was more than 5 times higher ($298.0 \times 10^{-5}$) than the average level in the AD group (see **Table 2**). However, in this AD patient the level of the p53 (87.1) and OGG1 (12.2) proteins was similar to the average level in patients with AD (see **Table 2**).

In the AD patients with the *TP*53 C708T silent mutation, slightly elevated levels were shown of the 8-oxo2dG and p53 proteins as compared to patients with the wild-type *TP*53 gene and controls (see **Table 2**, **Figure 3**). However, the OGG1 protein level was similar in AD patients with and without the *TP*53 C708T mutation and at the same time in these patients was about two times lower than in the controls. This study also demonstrates that in AD patients with the wild-type *TP*53 gene the level of 8-oxo2dG correlated with the level of the p53 protein (Spearman test, R +0.7388, $p < 0.05$, see **Table 2**, **Figure 3**).

## 4. Discussion

In AD various factors, e.g. elevated level of A*β* [2]-[5], may lead to the generation of oxidative stress and oxidative DNA damage [18]. It was shown that the neurotoxic 42 - 43 amino-acid-long A*β* peptide is a breakdown product of a much larger protein, *i.e.* the A*β*/A4 protein precursor—APP [19]. Moreover, the 4 - 4.5 kDa A*β*/A4 polypeptide is probably the major protein component of senile plaques (SPs) [20]. It was also shown that A*β*/A4-related peptides may occur in both AD and normal subjects, while their production is increased in FAD [20] [21]. Moreover, it has been indicated that intraneuronal A*β* may be the cause of mitochondrial [22], lysosomal [23] [24] and synaptic [25] dysfunctions which possibly lead to apoptosis [26] and oxidative degeneration.

8-Oxo-2dG or its nucleoside is one of the markers of oxidative DNA modification. Moreover, 8-oxo2dG is considered to be a marker of oxidative DNA damage in degenerative diseases, cancer and aging process. As has been shown in the literature, oxidative DNA damage in AD (8-oxo2dG) may occur both in the central nervous system [6] [7] as well as in the peripheral lymphocytes [8] [9] [27] [28]. Studies by Dorszewska *et al.* [8] [9] [27], Dezor *et al*. [17] as well as this study on the peripheral lymphocytes of AD patients have demonstrated elevated 8-oxo2dG levels.

Studies by Dezor *et al*. [17], Dorszewska *et al*. [9] [29] and this study have also shown that nucleotide oxidation, reflected by an elevated 8-oxo2dG level in AD patients, may be associated with a decrease in the level of the OGG1 protein and/or by a decrease in the mitochondrial OGG1-1b isoform's expression. Further studies by Iida *et al*. [30] indicated that the reduction in OGG1 expression in the brains of patients with AD was accompanied by the formation of neurofibrillary tangles (NFTs), axonal dystrophy and reactive astrocytes. However, Mao *et al*. [31] demonstrated that the decreased excision activity of OGG1 in patients with AD may be affected by mutations in the gene encoding OGG1. In Mao *et al*.'s study, the presence of mutations was shown in 4 out of 14 patients with AD, where two patients possessed C796 deletions that completely eliminated the activity of the OGG1 enzyme and two patients carried single point mutations that led to distinctly decreased activity of the OGG1. Moreover, literature data indicated that oxidative DNA damage may induce different types of transversions in genes coding DNA repair (OGG1) [10] [30].

It has also been shown that oxidized guanine in DNA induces GC-to-AT transversion-type point mutations. The same type of mutation and the loss of heterozygosity have also been observed in the tumor suppressor *TP*53 gene and are commonly associated with a wide variety of tumors in humans and in experimental animals [10] [32]-[34]. Mutations abrogating of p53 function and allelic loss of its locus were among the first genetic lesions identified in glioblastoma multiforme [35]. *TP*53 mutations are also present in all grades of human astrocytoma [36] and in the murine model of astrocytoma [37].

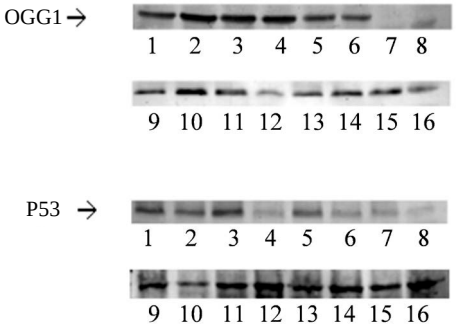


**Figure 3.** Western blot analysis of OGG1 and p53 protein levels, 1 - 8 controls and 9 - 16 AD patients.

**Table 2.** Level of 8-oxo2dG (8-oxo2dG/dG × $10^{-5}$), p53 and OGG1 proteins (% area immunoreactive bands) in AD patients with and without the detected *TP*53 C708T mutation and controls.

| Parameters | Controls | AD patients | | | p |
|---|---|---|---|---|---|
| | | ***TP*53 C708T** | **Wild-type *TP*53** | **With and without *TP*53 mutations** | |
| 8-oxo2dG | 37.3 ± 20.4 | 51.8 ± 35.3 | 38.7 ± 31.8 | 52.9 ± 63.0 | 0.8765 |
| p53 | 71.5 ± 22.6 | 89.7 ± 8.8 | 77.5 ± 15.6 | 80.9 ± 14.5 | 0.6047 |
| OGG1 | 29.8 ± 25.2 | 12.9 ± 5.1 | 12.7 ± 2.1 | 12.7 ± 3.0 | 0.8240 |

Mean ± SD. No significant differences in the Kruskal-Wallis test. AD patients with the wild-type *TP*53 gene, Spearman coefficient +0.7388 between 8-oxo2dG and p53 protein levels ($p < 0.05$).

Furthermore, the mutations in AD patients that were shown in this study turned out to be similar to mutations that were previously described in various cancers. Simultaneously, as in this study, in exon 7 of the *TP*53 gene of AD patients with no history of cancer the synonymous variant *TP*53 C708T was reported by Zhang *et al.* [38] to be present in rectal cancer. Moreover, the missense mutation *TP*53 C748A was found by Boersma *et al.* [39] in breast cancer. A *TP*53 missense mutation in exon 7 was also found in an adrenocortical carcinoma patient. Although the phenotype was not clinically distinct, the authors suspected a hereditary background due to early onset of the disease [40].

It seems that in AD the missense *TP*53 C748A mutation may be associated with an increase in oxidative stress, as in this study the tendency for a significant increase in the 8-oxo2dG level was observed only in the patient with this mutation. It also appears that in this AD patient elevated level of 8-oxo2dG could have induced the repair system of oxidative DNA damage by a tendency to increase the p53 protein level.

P53 is a key regulator of multiple cellular processes, and depending on the cell type it is activated by different stressors to induce apoptosis or autophagic cell death; but is also responsible for reversible and irreversible cell cycle arrest, or senescence [41]. The induction of cellular aging by elevated p53 levels in response to stress is designed to prevent proliferation of damaged cells. Two main groups of signals influence the p53 pathway. These include DNA damage and oncogenic stress as a result of cancer and/or aging which may be induced by p53 mutation [13].

There have been reports in the literature indicating that the p53 protein participates in neuronal apoptosis in the brains of AD patients [11] and can typically be associated with increased expression of p53. An increase in the p53 protein level has been shown both in the cultures of human and rat neurons and astrocytes as well as in the peripheral blood lymphocytes and brains of patients with AD [17] [29].

A study by Ohyagi *et al.* [26] suggested that in AD patients, p53-dependent apoptosis leads directly to neuronal loss through A$\beta$42 binding and activation of the p53 promoter. The accumulation of both A$\beta$42 and p53 is manifested in some degenerating-shape neurons in AD.

A study by Dorszewska *et al.* 2013, unpublished data] demonstrated the presence of A$\beta$ in PS/APP mice along with a high p53 level as compared to younger mice, which may indicate the possible induction of apoptosis. It has been shown that p53-dependent neuronal apoptosis may also result from decreased activity of anti-

apoptotic PS1 caused by p53 protein-protein interactions or by pro-apoptotic presenilin-2 (PS2), which down-regulates PS1 expression [18] [42]. It seems that the elevated p53 level influences PS1-mediated abnormalities of intracellular calcium levels [43]. On the other hand, it seems that in this study the silent mutation C708T in the *TP*53 gene causes a slight (although varied) increase in p53 protein levels in AD patients. However, p53 protein levels were more varied in patients without the mutation than in patients with the mutation, probably due to the impact of other factors.

It is known that mutations in DNA cause a change of the sequence in the corresponding mRNA and may influence its stability, thus affecting the number of mRNA copies translated into protein (e.g. p53). At the same time, the presence of SNPs has been associated with changes of methylation pattern affecting the genes expression [44]. Moreover, has been suggested that the change in mRNA may alter the target of expression modulating factors which would result in misbalanced expression of p53.

However, a study by Uberti *et al*. [45] on fibroblasts from seven sporadic AD patients did not reveal the presence of mutations in exons 1 - 11 of the *TP*53 gene. This difference might be explained by the small number of studied AD patients.

In conclusion, it seems that both of the analyzed mutations of *TP*53 (C748A, C708T) gene in exon 7 may be involved in neurodegenerative processes in this study in AD patients. It is possible that the missense mutation, C748A, may be responsible for generating oxidative stress, which is represented by an elevated level of 8-oxo2dG. Moreover, the synonymous mutation, *TP*53 C708T, may lead to modification of p53 protein activity.

However, the suggested action mechanisms of both variants in AD require further studies, an analysis of both exons 1 - 11 of the *TP*53 gene and the biochemical parameters of oxidative stress on a cohort of AD patients with varying degrees of dementia. *In vitro* point mutation studies are also required.

## Acknowledgements

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Scientific Research

# Caring for Individuals with Early-Onset Dementia and Their Family Caregivers: The Perspective of Health Care Professionals

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## Abstract

**The phenomenon of early-onset dementia remains an under-researched subject from the perspective of health care professionals. The aim of this qualitative study was to document the experiences and service needs of patients and their family caregivers for optimal clinical management of early-onset dementia from the perspective of health care professionals. A sample of 13 health care professionals from various disciplines, who worked with individuals who suffered from Alzheimer's disease or related disorders and their family caregivers, took part in focus groups or semi-structured individual interviews, based on a life course perspective. Three recurrent themes emerged from the data collected from health care professionals and are related to: 1) identification with the difficult experiences of caregivers and powerlessness in view of the lack of services; 2) gaps in the care and services offered, including the lack of clinical tools to ensure that patients under age 65 were diagnosed and received follow-up care, and 3) solutions for care and services that were tailored to the needs of the caregiver-patient dyads and health care professionals, the most important being that the residual abilities of younger patients be taken into account, that flexible forms of respite be offered to family caregivers and that training be provided to health care professionals. The results of this study provided some innovative guidelines for optimal clinical management of early-onset dementia in terms of the caregiver-patient dyad.**

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## Keywords

**Early-Onset Dementia; Family Caregivers; Perspective of Health Care Professionals; Service Needs**

## 1. Introduction

Advances in the development of diagnostic tools have resulted in more cases of dementia being identified in younger people. Considered by the American Alzheimer's Association [1] to be a national challenge, early-onset dementia is raising questions about the quality of life of the family system affected by the illness at a younger age.

Distinctions can be made between younger persons and older persons suffering from dementia. The most important differences between early- and late-onset forms of the disease are: a broader spectrum of clinical profiles (Alzheimer's disease, frontotemporal lobe degeneration, focal atrophy, subcortical vascular dementia and Lewy body dementia); pervasiveness of certain cognitive symptoms; severity of neuropsychiatric signs and changes in character and behaviour [2].

The experiences of family caregivers of early-onset dementia patients have been explored and described in several qualitative studies over the last decade [3]-[6]. These studies show that family caregivers of individuals suffering from early-onset dementia are often their spouse, in their 50 s, who still have children at home and are also looking after an elderly parent suffering from gradual loss of autonomy [7]. Their life partner's illness has multiple repercussions on the socio-professional, financial and psychological aspects of family life and studies show that the burden of these caregivers is even greater than that of caregivers of elderly individuals with the same illnesses [8]-[10]. Specific factors undermining quality of life of the caregiver-patient dyad identified in a previous study include: problems managing the behavioural and psychological symptoms associated with the illness, which are often more significant at a younger age; a longer quest for diagnosis, as the signs and symptoms observed are often attributed to other conditions; non-disclosure to others and denial of diagnosis, as the illness is mainly associated with old age and younger people who have it are marginalized; grief for loss of mid-life projects, difficulty assuming an unexpected role and planning for the future [4].

In spite of this knowledge about the experiences of patients and family caregivers, the phenomenon of early-onset dementia remains an under-researched subject from the perspective of health care providers. Specifically, the experience of health care providers in caring for persons with early-onset dementia and their caregivers is unknown, as is their perception of optimal clinical management for this emergent population in the health care system. As pointed out over a decade ago, recommendations on dementia services for younger people and their families are not based on scientific evidence [11] and research is needed to gain a more in-depth understanding of the experience of these professionals so services tailored to the needs of patients and their caregivers can be developed. The services used by families of older patients are still not geared toward younger patients and their caregivers, and what is being decried is the lack of programs developed specifically for younger patients and their families [12] [13].

Against this backdrop, we undertook a project to document the experiences of patients and family caregivers and their service needs for optimal clinical management of early-onset dementia from the perspective of health care professionals.

## 2. Methods

### 2.1. Design

In view of the lack of empirical research on the subject, a qualitative design was selected to explore the perceptions of health care professionals.

### 2.2. Setting, Sample and Recruitment

Health care professionals were recruited from memory clinics associated with a centre of excellence in cognitive health of an integrated university network, including hospitals and local community health and social services centres in a large metropolitan centre in Quebec (Canada). Neurologists, psychiatrists and geriatricians at these

clinics regularly diagnose dementia. Other participants were recruited from Alzheimer societies that provide support to young patients and their family caregivers.

Participants had to meet the following selection criteria: be a health care professional with a minimum of one year's experience working with patients age 65 or under who suffer from Alzheimer's disease or related disorder and their family caregivers.

The health care professionals were approached by the project coordinator to assess their interest in participating in focus groups to share their perceptions of the experiences of patients and their family caregivers, and to give suggestions on what services could help optimize the provision of care. A focus group was formed once 4 to 6 participants were interested. The number of groups was determined by data saturation or redundancy emerging from the participants' discourse [14] [15].

Two focus groups were thereby formed consisting of 5 and 6 participants respectively (n = 11). As two health care professionals who had pertinent expertise were not available to participate in either of the two groups, the study coordinator conducted two individual interviews using the same interview guide, thereby bringing the total number of participating health care professionals to 13.

These professionals (all women) had different disciplinary backgrounds: nursing, psychology, social work, medicine. Some perform coordination or advisory functions (case managers) at memory clinics or Alzheimer societies. The participants had a mean age of 46.4 years (S.D. = 10.5), had several years' experience in the health care system (X = 17.3, S.D. = 9.8), specifically 8.9 years' (S.D. = 7.5) experience working with dementia patients, including diverse experience with young people. Specifically, all the health care professionals who participated worked occasionally (82%), fairly often (23%) or often (15%) with this population in their recent years of practice. The vast majority were university educated (92%) (see **Table 1** for the key characteristics of the participants).

**Table 1.** Socio-demographic characteristics of the health care professionals (N = 13).

| Variable | N (%) | Mean (SD) |
|---|---|---|
| | **Gender** | |
| Female | 13 (100) | |
| **Age** (years) | | 46.4 (10.5) |
| | **Education** | |
| College | 1 (7.7) | |
| Bachelor's | 6 (46.1) | |
| Master's | 4 (30.8) | |
| Doctorate | 2 (15.4) | |
| | **Occupation** | |
| Nurse | 5 (38.4) | |
| Psychologist | 1 (7.7) | |
| Social worker | 2 (15.4) | |
| Physician | 1 (7.7) | |
| Manager | 4 (30.8) | |
| | **Work experience** (years) | |
| Health care system | | 7.3 (9.8) |
| With people suffering from dementia | | 8.9 (7.4) |

## 2.3. Data Collection Tool

A group interview guide was designed taking into account the care trajectory of patients and their family caregivers, namely with reference to the current and potential offer of services to support them. Like Rosenthal-Gelman and Greer [16], we drew inspiration from pertinent conceptual frameworks in designing the interview guide, namely a life course perspective [17] and a family systems approach [18]. The life course perspective emphasizes the importance of the timing of the events affecting the individuals and their families. Receiving a diagnosis of early-onset Alzheimer's disease or related disorder is a non-normative event and gives rise to particular needs and unforeseen difficulties in life trajectory. With a family systems approach, the focus is on the interaction and interdependence among family members and emphasizes that any change, such as a health problem, in one of its members will have repercussions on all the others. This approach involves not only considering the person suffering from early-onset dementia but also his primary family caregiver and family network.

The guide included open-ended questions divided into four main sections. The first covered the health care professionals' overall experience with early-onset dementia (e.g., *Please indicate how you are involved in the care of early-onset dementia patients and their caregivers in your workplace*?). The second section dealt with the care trajectory of patients and their families (e.g., *How does it work when you have to help and support a young person diagnosed with dementia and his/her caregivers in the care trajectory*?). The expected responses pertained to the professionals perceptions regarding early-onset dementia and the problems encountered by patients, family caregivers and the family network, and those encountered by themselves as members of the formal support system for patients and their families.

In order to further operationalize the comments collected from participants, the third section asked each professional to present two opposite cases, namely a complex case where they felt that a follow-up went well, and another where it didn't based on their individual assessment (*Can you each tell me about at least one complex case where you felt that the follow-up was satisfactory*? *And another complex case where it wasn't*?). The aim of the exercise was to specifically identify the resources and means used to support patients and their families, among others, their primary family caregiver. In this last part of the discussion, participants were asked to imagine the ideal situation for addressing the problems identified, namely how the services could be evolved so that the unique needs and problems of these patients and their families be better taken into account for the purposes of optimal clinical management (*Regarding the case follow-up problems you identified, what changes could be made so that the needs and resources be better taken into account young patients and their families be better supported*?). This part of the discussion allowed us to identify innovative solutions and proposals to evolve the care and support practices. The session ended with a sociodemographic questionnaire that participants answered on their own.

On average, the group discussions lasted for 120 minutes, including an initial period for signing the consent form to participate in the study and a final period for collecting the socio-demographic and descriptive information.

## 2.4. Data Collection Procedure

The project was approved by the ethics review boards of the recruitment sites (CER IUGM 10-11-018). The study coordinator contacted professionals from the memory clinics associated with the centre of excellence for cognitive health and Alzheimer societies by telephone to explain the purpose of the study, verify the inclusion criteria and ask if they were interested in participating in a focus group, outside of work hours, at a location close to their workplace. A lump sum to cover their transportation and parking expenses was offered.

The focus groups were held in a central location, in a comfortable room in one of the facilities associated with the centre of excellence. The date of the focus group was determined at the convenience of the participants and the interview guide was sent by email one week prior to the session to allow participants to reflect on the various topics and clinical situations of their case load. On the day of the focus group, the participants signed the consent form on arrival.

The discussion was led by a trained group facilitator along with an observer who ensured the proper conduct of the session, namely that all the topics were covered and that each participant had the chance to speak. This person also ensured the quality of the audio recording of the group sessions and took notes on the non-verbal behaviour of the participants or made other observations related to the climate of the interview [19].

### 2.5. Data Analysis

The data from the recordings of the group discussions were fully transcribed in electronic format and analyzed by group [19], and were then combined with the recordings of the qualitative data from the two additional individual interviews. Content analysis was performed using QDA Miner, version 4.0, a qualitative data analysis software. The analysis consisted of coding the transcripts using the Huberman and Miles approach [15], namely identifying the units of meaning to which a code was assigned. After having read the transcript of the first discussion group, two members of the team developed an initial coding scheme by noting the statements deemed to be significant in relation to the purpose of the study and the various topics covered. Inter subjective verification was performed and consensuses were established in this first round of coding, which were then used to analyze the thematic content of subsequent data, namely the second discussion group and the two individual interviews. The recurring themes from the transcripts and the communalities of the participants comments (convergence of discourse) were sought. The analysis was also used to index the opposite clinical cases, namely those regarding the successes and failures of case follow-ups.

## 3. Results

The recurring themes from the comments collected from the health care professionals pertain to three main aspects, namely: 1) identification with the difficult experiences of caregivers and powerlessness in view of the lack of services; 2) gaps in the care and services offered and 3) solutions for care and services that are better tailored to the needs of the caregiver-patient dyads and health care professionals. The results are presented based on these themes and are illustrated by excerpts from the transcripts.

### 3.1. Identification with the Difficult Experiences of Caregivers and Powerlessness in View of the Lack of Services

All the health care professionals pointed out the problem they had in dealing with the caregivers' difficult experiences, a problem that seems to be linked to identifying with these people who were often in their same age group. The issue of working with these young family caregivers, the fact that they are marginalized and are often in a situation of being double caregivers, namely caring for their spouse and for an elderly relative, are aspects that particularly affected the professionals, who seem to project themselves into the world of these caregivers, and one that is in the realm of possibility at their age:

… it's like sitting in front of a mirror with the thought that it could be me… it affects me particularly in view of their age, because it's their spouse who is 52 - 53 years old and the caregiver is still working…. The reality is that she has to keep working, just like us. It's difficult to give them the support they need (Participant 08/FG2, p.3-4).

… People age 48, 53, 58 are coming to see me and they're my age, and like me, their parents are still around!…. (Participant 07/FG2, p.3).

The health care professionals also feel extremely powerless in view of the lack of services and support programs tailored to the needs of these patients. Where do we refer these people who are suffering from cognitive impairment at a young age? What services can we offer these patients and their families? The health care professionals interviewed indicated that they felt extremely helpless in view of this situation, as eloquently expressed in many of the excerpts from the transcripts:

"No case file is opened and there are waiting lists everywhere… I really feel powerless… and I get calls from nurses from the clinics who say: we'd like to do something, but what can we offer them while waiting for the diagnosis?… there's something missing in the system… but what? (Participant 04/FG1/p.41).

… I'm often troubled. I feel like thre's a "box" missing for these young people… to refer them to the right place… it doubles the stigma of an illness that already has one attached.… there's nothing we can do… (Participant 10/FG2/p.5, 35).

In their comments, the health care professionals constantly indicated having problems managing this population as there were important gaps in the care and services offered in the current context.

### 3.2. Gaps in the Care and Services

There was a consensus on the scarcity or complete lack of facilities and clinical tools to provide care to those under age 65, both for a diagnosis and follow-up:

… no care is generally provided in memory clinics to those under age 65… (Participant 01/FG1/p.46).

There aren't a lot of resources. I think about the people I've had to turn away… I can't help them. When I call and tell them they have to be age 65 to get services, they understand, but they then ask me, so where do we go? (Participant 02/FG1/p.44).

… we have some great screening tools for our elderly patients, but would my colleagues know how to screen young people who turn up at the hospital with problems like this? They're beautiful and young, and you can't tell by looking at them (Participant 04/FG1/p.24).

We know that frontotemporal dementia often occurs at a younger age with all the behaviour disorders… these are needs that require specific services, especially if their behaviour is affected… and we don't have the skills or resources (Participant 02/FG1/p.33).

Specifically, the health care professionals noted a lack of coordination in the services offered to young people and their families and a need for psychosocial support:

We have a "silo mentality" when it comes to what is being offered to people. We have to start thinking outside the box (Participant 11/FG2/p.6).

The social workers at the community centre don't have the time to provide psychosocial support. They're increasingly becoming administrators and service managers of home support services… and don't have any time to provide psychosocial support… (Participant 13/individual interview).

Faced with their powerlessness and the gaps in the care and services that they identified, the health care professionals indicated what needs to be changed and proposed some innovative solutions regarding the preferred services model to meet the needs of the caregiver-patient dyads and those of health care professionals.

## 3.3. Solutions for Care and Services Tailored to the Needs of the Caregiver-Patient Dyads and Health Care Professionals

The solutions proposed by the health care professionals relate to patients and their family caregivers, as well as their own problems dealing with this population. In terms of the patients, the early detection of the illness and a more diversified and flexible offer of services to ensure quality of follow-up were proposed. From a systemic perspective, this offer of services should not only take into account the respect of the patients' residual abilities, but also the unique needs of their caregivers, particularly their need for respite.

### 3.3.1. Detection of the Disease and More Diversified and Flexible Offer of Services

For health care professionals, earlier detection of the disease in young people is a priority concern that needs to be addressed:

How do we detect this, something's missing in the system… there could be screening, people could be prioritized to get access to this screening and they could more readily referred to the right resources (Participant 04/FG1/p.41).

In the resources indicated, the health care professionals mentioned the need to develop new diversified and more flexible services for the caregiver-patient dyads, including psychosocial services at home and to have a phone line and services that use information and communication technologies taking into account the age of the dyads:

… equip them psychologically so they're more confident in their daily lives and with their own resources at home (Participant 08/FG2/p.57).

When the illness evolves… have a hotline for family caregivers… a place that is accessible, for example, at the Alzheimer society (Participant 04/FG1/p.72)

In the future, perhaps organize a forum of some kind, like online training… that would give everyone access and where people could get answers to their questions at any time (Participant 03/FG1/p.76).

For health care professionals, respite is a priority need for caregivers, which also requires more flexible, creative and different solutions than those usually offered. The health care professionals spoke of "tailored respite" that would allow caregivers to stay in the workforce and let them have more time for their personal and family activities with children or teenagers who are often still living at home and other family members:

… more creative ideas… perhaps going into a centre is not really for them (young people)… maybe have someone at home with them doing an activity they enjoy while the caregiver goes to work (Participant 09/FG2/p.60).

For caregivers, it would be great if they could be given a respite passport… (Participant 01/FG1/p.13).

That respite be given right from the start… as a package. As soon as the diagnosis is made, this could be a first approach… they would be given a coupon entitling them to a weekend or a week at a given date… caregivers wouldn't thereby feel like they're asking for the service (Participant 03/FG1/p.79).

Or, we could set up a respite model that allows a spouse to get away for a weekend with the kids to an outdoor activity centre and someone could look after the patient at home… (Participant 04/FG1/p.79).

Taking into account the physical and residual cognitive abilities of patients, among others things, their ability to work and the development of systemic family interventions were also part of the recurring innovative solutions proposed by the health care professionals.

### 3.3.2. Taking into Account Young Patients' Residual Abilities

The health care professionals indicated the importance of developing activities tailored to the residual potential of these young patients:

Give lots of information, especially on the abilities… cognitive stimulation… physical exercise… fun activities (Participant 01/FG1/p.69).

… set up different groups for younger patients and older patients, because the needs are different (Participant 09/FG2/p.39).

In view of the evolution of the illness, the importance of having a smooth transition in the services offered to patients was indicated. For example, young people could take part in support groups specifically designed for them in the early stages of the illness, and then volunteer at recreation centres for seniors where they could offer their expertise and skills and, finally, they could take part in the activities organized at these same centres once their loss of autonomy becomes more severe:

The illness evolves, so they're no longer able to attend this type of group (group for people in the early stages of the illness)… they could be taken to a recreation centre that is mainly for seniors… where they recently volunteered… and then they feel really valued … and slowly get into the centre… this is a model that could also be used in day centres (Participant 05/FG1/p. 63).

For the health care professionals, preserving the young people's ability to work is essential for maintaining their self-esteem and sense of being useful:

… young people want to stay physically active… they need to exert themselves physically and there's nothing better than doing something productive, therefore having a job that's adapted to young people suffering from dementia because they want to feel useful, even if it involves doing a repetitive task (Participant 07/FG2/p.15).

… depending on the type of work they used to do, I feel they can still work. But often, they stop working when the diagnosis is made, it's devastating, so they stop doing everything… we can find them something suitable to do at the onset of the illness, it helps them to keep going… (Participant 03/FG1/p.30).

Lastly, the health care professionals acknowledge the importance of using a more systemic approach to the care and services, namely to not consider the patient and the illness in isolation, but rather as part of a family system.

### 3.3.3. A more Systemic Approach to the Care and Services Taking into Account the Family

A systemic approach where the family is taken more into consideration is favoured by the health care professionals:

… thinking of the caregivers for whom things are really difficult, for example, when the behaviour of those suffering from frontotemporal dementia changes drastically. It's really hard for the caregivers… thinking about the caregivers and the whole family in the intervention, in terms of psychosocial support, and not just about the patient (Participant 02/FG1/p.70).

The kids… meeting with them also helps them to deal with things (Participant 01/FG1/p.61).

In terms of the necessity of this more systemic approach that takes into account the family as a whole, the participants specifically mentioned that not only the patients should be considered as clients of the health care system, but so should their primary family caregivers, in view of their high needs and the impact of their role on their own health. The possibility of opening a file in the name of the caregiver was mentioned so their own need for care and services is recognized:

A file could be open for family caregivers, as they might also require services (Participant 04/FG1/p.15).

Solutions were proposed regarding the needs of the health care professionals who work every day with patients and their families. In view of their powerlessness, the health care professionals confess their lack of training to

intervene with this specific population and the need to acquire knowledge to help them improve their feeling of competence and control.

#### 3.3.4. Training that Takes into Account the Particular Characteristics of the Young People and Their Family Caregivers

All the participants pointed out the need for better training so they can have innovative intervention strategies for young patients and their families, strategies that are different from those used with older people. To accomplish this, the expertise of mental health specialists was mentioned many times as being a precious resource that could be used more and taken advantage of:

… we need training… mental health workers could let us know some of their approaches… (Participant 07/FG2/p.61).

As we have very little to offer in terms of medication, the idea is to support people in relation to their symptoms… we need to learn what to do. We should combine the skills of health care professionals with those of mental health workers to deal with situations like these (Participant 11/FG2/p.38).

Training in medical clinics… I get calls from doctors and hear comments… but most of the comments I get is that they don't feel well equipped: we need staff who have better mental health training… they are mainly trained for physical care… and dementia isn't covered in the training (Participant 08/FG2/p.38).

In short, the health care professionals are sensitive to the unique experiences of the dyads who are living with early-onset Alzheimer's disease or related disorders, experiences with which they seem to identify. Faced with their feeling of powerlessness due to the lack of resources, they point out the importance of developing services geared toward the specific needs of the dyads. In this regard, many proposals based on their experience were made to promote quality care practices and improve their expertise, which they feel is lacking with this specific population. In the next section, we will discuss these results.

## 4. Discussion

The perceptions of the health care professionals regarding the experiences and preoccupations of family caregivers of people suffering from early-onset dementia are consistent with those mentioned by the family caregivers themselves and documented in the literature [4] [20]. These professionals also told us about specific elements of their own experience that need to be taken into account in the training they are asking for, so as to better intervene with this specific population. In particular, their identification with and projection they made relating to the lived experience of the caregivers and their feeling of powerlessness should not be overlooked. The health care professionals are often the same age as the family caregivers they meet and thereby identify with the difficult situation and suffering they are going through on a daily basis. From this perspective, the training of these professionals should not just include aspects surrounding the distinctive signs and symptoms of early-onset dementia. As the stigma associated with the disease influences perception, more predominantly at a younger age [21], the training should also include the perceptions the professionals have of the illness, and any associated myths and taboos. Discussing uncertainties, values and beliefs about the illness, as well as having the opportunity to share clinical stories with patients and their families is part of a narrative pedagogy that might help reduce the phenomenon of identification and increase the sense of control of practitioners [22].

As for the learned powerlessness from having contact with individuals who suffer from early-onset dementia and their family caregivers and relating to the lack of resources, it could very likely be limited or reduced if the suggestions from the health care professionals, based on their experience and expertise, were taken into account by managers in developing care and services in line with the specific needs of this population. Like patients and families, health care professionals are important stakeholders in the design of tailored interventions. This approach could help not only reduce the feeling of helplessness but also empower the health care professionals [23]. Among other things, the interest in exploring existing interventions in the field of mental health and referring to the expertise of mental health professionals, as mentioned by the participants, is particularly interesting.

The data collected in this study underscore the importance of having faster access to screening and diagnosis in terms of the care and services to offer the caregiver-patient dyads. The long quest for diagnosis has often been mentioned in studies on family caregivers of young patients to be a source of suffering [4] [24]. The relationships between family physicians and second-line specialists need to be tightened so that faster screening is possible. However, it is not just faster access to diagnosis that is important for the quality of life of patients and

their family members, but also that required services be offered as soon as the diagnosis is made and that the uncertainty and powerlessness [25] for both professionals and the caregiver-patient dyads be reduced. In this perspective, better coordination between memory clinics and the various community organizations is required.

As mentioned above, being diagnosed with early-onset Alzheimer's or related disorder is, based on a life course perspective, a non-normative event that gives rise to particular needs and unforeseen difficulties in life trajectory. In this context, our study clearly underscores the need for specific measures of support further to the diagnosis. This is why the health care professionals noted other elements to be considered in the services to offer this particular population. The fact that the majority of these younger people are still active and generally have fewer chronic health problems is one of these specific elements, which means that different activities than those offered to seniors are needed. The day centres, as currently designed, do not meet the needs of these more active young patients who often have just left the workforce and still have residual skills that could be put to use.

As suggested in the literature [11], some of the support interventions required by family caregivers of persons with dementia are generic. These include support at time of diagnostic disclosure, help managing changes, learning to assume the caregiver role, and juggling other responsibilities [26]-[28]. From the perspective of the health care professionals, the results of our study underscore that other more specific support measures are needed for caregivers of patients with early-onset dementia. More diversified forms of care and support, offered in various forms (psychosocial intervention at home, telephone or online intervention) were proposed to meet the varied needs of these younger patients and avoid the "one-size-fits-all" formula that, according to the studies, only has modest effects on the quality of life of caregivers [26]. The considerable need for respite that requires the development of innovative forms to take into account caregivers in the workforce and children, who often are still living at home, was also mentioned.

By recognizing several specific needs of caregivers, health care professionals thereby propose that caregivers are considered as clients of the services and, as such, that a clinical file is opened for them. In a broader sense, in light of the numerous losses experienced by the young patients, their family caregivers and their entire families, the health care professionals suggest that a care and service model that uses a more systemic approach, namely one that takes into account the family system, is developed. This care and services model is certainly relevant in the current context but needs a paradigm shift towards a family-centered approach. An expert case manager or, as suggested by Beattie and his colleagues, an expert in dementia care [11], could be assigned to the family following diagnostic disclosure in order to assess specific support needs collaboratively. Such an approach will have to be offered using a realistic and feasible approach to avoid overburdening the caregiver-care receiver dyads.

Lastly, the results of this study and its underlying theoretical perspectives, namely the life course perspective [17] and family systems theory [18], offer some innovative guidelines for developing professional interventions for optimal clinical management of early-onset dementia, guidelines that take into account not only the patients and their illness, but also the caregiver-patient dyad, and the impact of the illness on the entire family system. It is important to note that, in spite of its small size, data saturation was achieved with the sample of this study. Obviously, other studies conducted in various contexts will ensure the transferability of these initial findings that provide knowledge about a recent care and service problem, namely with the advent of tools to identify the disease earlier and earlier.

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Scientific Research

# Association between Caregiver Quality of Life and the Care Provided to Persons with Alzheimer's Disease: Systematic Review

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## Abstract

**We reviewed the literature to examine whether an association exists between the quality of life (QoL) of primary informal Alzheimer's disease (AD) caregivers and the level and quality of care that these caregivers provide to their loved ones with AD. We obtained studies focusing on the care that these caregivers provide for their family members with AD. Our outcome of interest was level or quality of care and the independent variable was caregiver QoL. We extracted data in tabular form and used a narrative synthesis approach to describe our findings. Only one relevant study was included in the review. Overall, the evidence was equivocal regarding the associations between caregiver QoL and the level/quality of care in AD.**

## Keywords

**Alzheimer's Disease Caregiver; Quality of Life; Level of Care; Quality of Care**

## 1. Introduction

Alzheimer's disease (AD) is a type of dementia characterized by progressive declines in cognitive and functional abilities [1]. Its symptoms often begin with memory loss and progress to an inability to perform basic activities of daily living (e.g., dressing, feeding); persons with AD eventually become completely reliant on third-party care [2].

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The impact of AD is global. An estimated 5.4 million people in the United States had AD in 2012, including 5.2 million people aged 65 and older [3]. In Canada, projections show the number of cases of AD could increase to 509,000 in 2031 from the current figure of 300,000 [4] [5]. Also, the proportion of people living with dementia in North America will increase to 63% over the next twenty years [6]. About 36 million people world-wide were living with AD in 2010 and this figure is set to top 115 million people by 2050 [4]. Further estimates suggest that AD will affect nearly 1 in every 85 people around the world over the next 40 years [6].

Caregivers provide critically needed care for persons with AD because cognitive decline ultimately prevents people diagnosed with AD from functioning independently. Primary informal caregivers (e.g., spouses, children) are generally not paid for the care they provide. These caregivers perform comprehensive duties such as shopping for groceries, helping with medications, managing finances and legal affairs, guarding against wandering and other unsafe practices, bathing, dressing, and making arrangements for medical care [7]. Even when persons with AD move to assisted living facilities, most primary caregivers continue to provide help with grooming [8] [9].

Due to the many tasks required of AD caregivers, the emotional and physical demands of caregiving are high. Consequently, unpaid family caregivers in AD usually have lower QoL than caregivers for persons who have not been diagnosed with AD [10]. Since lower QoL has been shown to increase work absenteeism and reduce productivity in workplace settings [11], it is possible that the demands of caregiving might also lead to declining "caregiver productivity" in care provision. We hypothesized that caregiver QoL might affect caregivers' ability to provide care. Indeed, the strain of performing caregiver tasks has been cited as one of the leading reasons why caregivers institutionalize their loved ones [12] [13].

The current review investigated the association between the QoL of primary informal AD caregivers and the level and quality of care that these caregivers provide to their loved ones with AD. We addressed the following research questions:

What is the relationship between caregiver QoL and level of care?

What is the relationship between caregiver QoL and quality of care?

## 2. Methods

### 2.1. Data Sources and Selection

A protocol detailing the methods for this systematic review has been previously published (PROSPERO registration number: CRD42013003613) [14]. Briefly, we searched CINAHL, Cochrane Central-OVID, Embase-OVID, Medline-OVID, PsycINFO-OVID and Business Source Complete from database inception through December 2012. The search strategy was adjusted for the specific nuances of each database. Internet searches were also performed in order to identify grey literature. An experienced medical librarian conducted the literature search (databases and internet) and uploaded the results to DistillerSR. DistillerSR is an online application specifically designed for conducting the screening and data extraction phases of systematic reviews. Standardized screening forms were developed for this study and uploaded onto Distiller. All screening and data extraction were done on DistillerSR.

Titles and abstracts of studies identified in the literature search were independently screened by two reviewers. Studies meeting the eligibility criteria, or studies whose titles and abstracts did not provide sufficient information to assess eligibility, advanced to full-text screening. During full-text screening, two reviewers independently read each entire paper and assessed eligibility. Conflicts were resolved through reviewer consensus or by the involvement of a third reviewer.

### 2.2. Criteria for Considering Studies for This Review

We included studies dealing with *primary informal caregivers* of community-dwelling persons with AD. We included studies with QoL as the independent variable and outcomes pertaining to level or quality of care.

#### Quality-of-Life (QoL)

The concept of QoL may be defined in several ways. The World Health Organization defines QoL to refer to a person's state of complete physical, mental, and social well-being [15]. Though complex to describe, QoL has often been defined as "the degree to which a person enjoys the important possibilities of his or her life" [16].

QoL may be measured using scales, several of which have been developed for healthcare research [17]. Other

generic, health-related QoL scales include the Short Form 36 (SF-36) [18], Euro QoL Group's EQ-5D [19], and the World Health Organization Quality of Life-BREF [20].

We included any study measuring caregiver QoL, regardless of how the construct was defined or measured. In addition to QoL, studies examining the impact of constructs that are closely related to QoL (e.g., well-being, social support, caregiver burden, depression) were treated as if they measured QoL.

## 2.3. Definition of Concepts Related to QoL

### 2.3.1. Caregiver Well-Being

The concept of well-being is closely related to QoL. In the context of care giving, it is concerned with caregivers' basic human needs and their satisfaction with activities of daily living. Caregiver well-being has several components including social, physical, emotional, and spiritual [15]. In health research, well-being is generally measured by asking respondents to evaluate their state over a given period of time.

### 2.3.2. Social Support

Social support is a multidimensional construct of the extent to which individuals receive emotional support, assistance, information, guidance and feedback, personal support, and companionship from family members, friends, co-workers, other persons (for example, acquaintances, religious leaders, therapists), or organizations (for example, caregiver support groups) [21].

### 2.3.3. Caregiver Burden

Caregiver burden is an important component of QoL. It is operationalized by any construct representing the physical, emotional, and financial strain of providing care for a loved one with AD. The Zarit Burden Interview (ZBI) is a widely used instrument for measuring caregiver burden [10] [22].

### 2.3.4. Caregiver Depression

Although depression is a key element of QoL, it is also an important construct on its own. Indeed, depression is one of the common side effects of long-term care giving [23]. Depression can be measured by several instruments, including the Center for Epidemiologic Studies-Depression (CES-D) scale [24] [25].

### 2.3.5. Caregiver Sleep

There is a strong association between sleep disturbances and depression which impacts quality of life [26]. Caregivers of persons with AD generally report high level of sleep problems, and the Caregiver Sleep Questionnaire is a common way to measure the quality, quantity, and the frequency of seven sleep problems during the past month [27].

## 2.4. Definition of Level/Quality of Care

### 2.4.1. Level of Care

Level of care outcomes were measured as total hours per day that caregivers were doing things for care recipients (CR) and total hours per day that caregivers were helping CR with Instrumental Activities of Daily Living (IADLs) ("About how many hours a day do you estimate that you are actually doing things for care recipient?").

### 2.4.2. Quality of Care

Quality of care outcomes were measured as caregiver proficiency in care giving. Proficiency included caregiver mastery ("How often do you feel you should be doing more for care recipient?") and skill enhancement as measured by the Task Management Strategy Index or TMSI ("To what extent were positive care giving strategies used to manage activities of daily living [ADL], dependence and problem behaviors?").

## 2.5. Assessment of Risk of Bias and Grade

Each included study was assessed for risk of bias by two raters using the Cochrane Risk of Bias Tool v5.1 [28]-[30]. We rated risk of bias on the three domains identified in the tool, namely blinding of outcome assessment, incomplete outcome data, and selective reporting. The overall risk of bias was judged by using the ratings on the

individual domains and any instructions for overall assessment that the tool might contain. The overall risk of bias was classified as "low", "high", or "unclear".

In addition to assessing the risk of bias, we also used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) to rate the level of evidence and to make judgements regarding whether the evidence is convincing enough already, such that future evidence is unlikely to change our conclusions. Studies were rated on the type of evidence (for example, RCT or observational), consistency, directness, precision and quality. The overall GRADE score, which reflects the average of the ratings on each of the dimensions above, was categorized as "high", "moderate", "low", and "very low" [31].

### 2.6. Data Extraction

A data extraction form was developed to collect the following information from included articles: study characteristics, participant characteristics (e.g., type and number of caregivers and care recipients, caregiver relationship to care recipient, living situation, age, AD diagnostic criteria), and results (e.g., quality of life, quality of care, level of care).

The data extraction form was piloted by two reviewers and further refined as necessary. Two reviewers independently extracted all data and met to resolve discrepancies by consensus. Whenever consensus could not be reached, a third reviewer was asked to adjudicate. In cases where studies reported outcome results over different time periods, we extracted data from each time period to examine the impact of the intervention over time. We followed the PRISMA guidelines in completing this systematic review [32].

## 3. Results

**Figure 1** shows the flow of studies through the screening process. Nine hundred thirty-eight articles were captured during the initial literature search, of which 902 (96%) were excluded at the title and abstract screening stage. Full text screening was performed on 36 articles, of which only one was found to meet all the inclusion criteria. The reason for exclusion at the full-text screening stage was non-relevance of the article to our research objective (e.g., the outcomes of interest were not measured). **Table 1** shows detailed study information for the only included study [33].

### 3.1. Methodological Quality Assessment

The included study, by Gitlin *et al*. [33], is an RCT in which outcome data were completely presented and no issues were evident with respect to selective reporting or any other type of bias. Overall, the study was rated as having a "low risk" of bias.

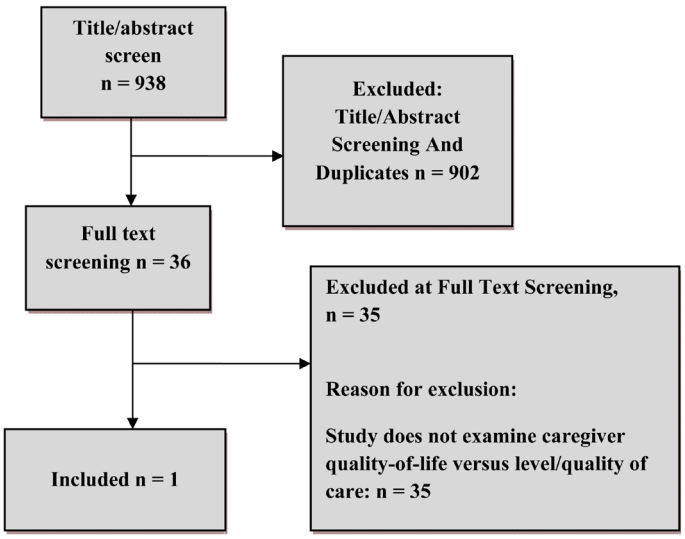


**Figure 1.** Study flow diagram.

**Table 1.** Basic study description and data.

| Study Information | Population Description | Intervention | Outcomes |
|---|---|---|---|
| Gitlin (2003)<br>USA<br>RCT<br>Purpose:<br>ESP–2 phases–active (first 6 months); maintenance (next 6 months) | Baseline = 255<br>Participants at 6 months:<br>Int n = 89; Cntrl n = 101<br>**Population Description at Baseline:**<br>Caregivers:<br>Mean Age (SD):<br>Int: 60.4 yrs (13.6)<br>Cntrl: 60.5 yrs (13.6)<br>% Male: Int 25%; Cntrl 23%<br>Care Recipient:<br>Mean Age (SD):<br>Int: 80.2 yrs (8.0)<br>Cntrl: 81.5 yrs (8.0)<br>% Male: Int 28%; Cntrl 37%<br>Mean MMSE (SD):<br>Int 11.6 (7.3); Cntrl 12.5 (7.1) | Follow-ups:<br>6, 12 and 18 months post-baseline | CR:<br>behavioral problems; dependence in ADLs; dependence in IADLs<br>CG: Caregiver well-being<br>Mastery: Caregiving Mastery Index<br>Skill enhancement:<br>Task Management Strategy Index |

CG = caregiver; CR = care recipient; ESP = environmental skill-building program; NH = nursing home; Int = intervention; Cntrl = control; MMSE = mini-mental state examination; ADL = Activities of daily living; IADL; Instrumental activities of daily living.

## 3.2. Summary of Extracted Study

Although the included study was not specifically designed to answer our research questions, the data contained in the study did indirectly address whether caregiver QoL impacts the level or quality of care that caregivers provide to loved ones with AD. The Gitlin et al paper was primarily designed to examine the effect of an intervention (skills building program versus usual care) on caregiver well-being and care recipient functioning but contains sufficient information to examine the relationship between QoL and level/quality of care within groups of caregivers randomized into intervention and usual care control groups.

**Table 1** presents demographic information from the Gitlin *et al*. [33] paper that is relevant to the research questions in the current study. The population examined by Gitlin *et al*. consisted of 255 primary informal AD caregivers who were providing care for at least four hours per day for 6 months or more. The authors evaluated the impact of a Home Environmental Skill-Building Program (ESP) compared to a usual care control group. The ESP was designed to provide caregivers with education, problem-solving skills, and adaptive equipment to manage daily care challenges effectively and to reduce burdensome environmental stressors (e.g., CR behaviors) [33]. One hundred ninety caregivers completed six months of follow-up.

As part of the study, the authors collected information about caregiver overall well-being, an important component of QoL [15] [33]. Caregiver overall well-being was measured with a 13-item scale (the Perceived Change Index [PCI]). On the PCI, caregivers used a 5-point scale to rate whether their situation (e.g., ability to manage difficult behaviors) ranged from "becoming worse" to "improving a lot" over the past month.

The relevant level of care measure in the Gitlin *et al*. paper was caregiver time (the *amount of time* devoted to providing care and total hours of IADL help). The quality of care measures included caregiver mastery and skill enhancement. Caregiver mastery was measured with the Caregiving Mastery Index (CMI) [33]. The CMI is a six-item scale evaluating the caregiver's appraisal of his or her ability to provide care to the CR (e.g., "How often do you feel you should be doing more for care recipient?). The scale uses a 5-point Likert format ranging from 1 (never) to 5 (always). A higher score means greater mastery of the care giving role. Skill enhancement was measured with the Task Management Strategy Index (TMSI), which is a 19-item scale that measures the extent to which positive care giving strategies were used to manage ADL dependence and problem behaviors in care recipients. The scale uses a 5-point Likert format from 1 (never) to 5 (always) [33].

### 3.2.1. What Is the Relationship between Caregiver QoL and Level or Quality of Care Provided to Persons with AD?

**Table 2** shows the summary of data extracted from the included study. Overall, results from this study are

**Table 2.** Association between QoL and level/quality of care.

| Type of variable | Measure | Experimental | | | Control | | |
|---|---|---|---|---|---|---|---|
| | | BE | 6ME | Diff E | BC | 6MC | Diff C |
| QoL (Overall well-being) | PCI | 2.84 | 3.00 | 0.16 | 2.94 | 2.89 | −0.05 |
| Level of care | Hours doing things for CR | 12.23 | 11.51 | −0.79 | 12.13 | 11.66 | −0.47 |
| Level of care | Hours helping with IADLs | 5.25 | 5.50 | 0.25 | 6.03 | 5.62 | −0.41 |
| Quality of care | TMSI | 2.91 | 3.05 | 0.14 | 2.92 | 2.93 | 0.01 |
| Quality of care | CMI | 3.74 | 3.88 | 0.14 | 3.87 | 3.84 | −0.03 |

E = Experimental; C = Control; CR = Care Recipient; QoL = Quality of Life; IADL = Instrumental Activities of Daily Living; PCI = Perceived Change Index; TMSI = Task Management Strategy Index; CMI = Care giving Mastery Index; B = Baseline; 6M = 6 month follow-up; Diff = Difference.

mixed. We are primarily interested in whether changes in QoL are associated with changes in level or quality of care, within the experimental and the control group. Comparisons are described below:

### 3.2.2. Experimental vs Control Group: Baseline and 6-Month Follow-up

Comparing the experimental group to the control group on outcomes related to level of care at baseline, results related to hours doing things for the CR are consistent with the hypothesis since lower QoL at baseline (before any intervention is given) is associated with higher number of hours spent caring for the CR (someone spending a lot of time providing care will have lower QoL). However, results for hours helping with IADLs do not support the hypothesis. Results for the quality of care variables (TMSI and CMI) are also consistent with the hypothesis. Compared to caregivers in the control group, lower QoL among caregivers in the intervention group is consistent with the lower quality of care that these caregivers provide at baseline.

After 6 months of follow-up, there was an increase in the mean QoL among caregivers in the experimental group. On the other hand, there was a decrease in the mean QoL of caregivers in the control group over this period of time. Consistent with the hypothesis, there was an increase in the level (Hours helping with IADLs) and quality of care (TMSI and CMI) provided by caregivers in the intervention group compared to caregivers in the control group. The only exception to this trend is “hours doing things for CR”, which decreased among intervention group caregivers.

### 3.2.3. Experimental Group: Baseline to 6-Month Follow up

Among caregivers in the experimental group, the QoL (PCI) variable increased over time. The overall results for this group from baseline to 6-months show that the experimental group QoL and quality of care measures increased over the follow-up period. On the other hand, results for the level of care variables are mixed, with hours doing things for CR showing a reduction over time, and hours helping with IADLs showing an increase over the same time period.

The overall trend is consistent with the hypothesis since higher QoL at 6-month follow-up is related to higher level of care and quality of care. This means that caregivers with higher QoL are more likely to provide higher level of care and better quality of care.

### 3.2.4. Control: Baseline to 6-Month Follow up

For caregivers in the control group, the QoL decreased over time from baseline to follow-up. The level of care and quality of care variables also decreased over time, with the only exception being TMSI which remains fairly constant over time. The observed trend is also consistent with the hypothesis since caregivers with lower QoL are likely to provide lower level and quality of care.

Compared to caregivers in the control group, caregivers in the experimental group provided better care overall after 6-months follow-up.

### 3.3. Grade

Results from the GRADE assessment are presented in **Table 3**. For both the level and quality of care outcomes, the type of evidence presented received the highest rating because the included study (Gitlin *et al.*) is an RCT and there were no serious issues with the quality of the study. However, the consistency, directness, and precision scores for both outcomes are affected by different factors, resulting in reduced scores on some of these domains. Consistency and directness points were deducted from both outcomes because the study was not designed to answer our research questions and results only indirectly addressed the questions. Finally, the precision scores were unchanged because the measures of effect were not statistically significant as reported in the included study [34].

## 4. Discussion

We were interested in evaluating how caregiver QoL impacts the level or quality of care that primary informal caregivers provide to their loved ones with AD. The included paper looks at level of care outcomes such as hours doing things for the CR and hours helping with IADLs. The paper also examine quality of care outcomes such as skill enhancement and caregiver mastery. Overall, the evidence was equivocal regarding the relationship between caregiver QoL and the level/quality of care provided to persons with AD. This is also the reason why the overall GRADE ratings for the outcomes from these studies are "moderate" This means that further research is likely to have an important impact on our confidence in this result [34].

Although the overall results were mixed, this study shows that higher caregiver QoL is related to higher level and quality of care provided to persons with AD. Among a group of 255 primary informal AD caregivers who were providing care for at least four hours per day for 6 months or more, findings at baseline show that caregivers spending a lot of time providing care were more likely to have lower QoL. This supports previous studies that have shown that caregiving in AD is stressful and has serious implications for the well-being of unpaid family caregivers [7]-[10].

In order to shed light on the relationship between QoL and level/quality of care provided to persons with AD, results for intervention and control group caregivers were analyzed after 6-months of follow-up. While there was an increase in the mean QoL among caregivers in the intervention group over the 6-month follow-up period, there was a decrease in the mean QoL of caregivers in the control group. As the QoL of intervention group caregivers increases over time, there was an increase in the level of care (Hours helping with IADLs) among these caregivers relative to caregivers in the control group. However, there was a decrease in the other level of care (Hours doing things for the CR) variable after 6-month of follow-up. It should be noted that "hours helping with IADLs" is a component of "total hours doing things for the CR" [33]. It is possible that "hours helping with IADLs" captures the important duties that AD caregivers perform for their loved ones better than "hours doing things for the CR". At the same time, there was an increase in the quality of care (TMSI and CMI) provided by caregivers in the intervention group compared to those in the control group after 6-month follow-up. Although some specific results were mixed, the overall results supports the hypothesis that better caregiver QoL may lead to better level/quality of care for the CR.

The mixed evidence from this systematic review suggests that research is needed to examine the relationship between caregiver QoL and the care provided to persons with AD. It is important to understand this relationship because our healthcare system places great responsibility on AD caregivers and we already know that AD caregivers' QoL is lower than other caregivers' QoL. Considering the critical duties that caregivers of persons with

**Table 3.** Grade results.

| Outcome | Type of evidence | Quality | Consistency | Directness | Precision | GRADE | Notes |
|---|---|---|---|---|---|---|---|
| Level of care (hours helping care recipient, hours helping with IADLs) | 4 | 0 | −1 | −1 | 0 | Moderate | Directness point deducted because results indirectly address review questions |
| Quality of care (TMSI, CMI) | 4 | 0 | −1 | −1 | 0 | Moderate | Consistency point deducted because only one trial examined the intervention |

IADL = Instrumental Activities of Daily Living; TMSI = Task Management Strategy Index; CMI = Care giving Mastery Index.

AD perform, the current systematic review shows an urgent need for studies examining the relationships between caregiver QoL and the level/quality of care.

The ideal type of primary study to address our research questions is a longitudinal cohort study measuring QoL, level of care, and quality of care in AD caregivers. If such a study were to be conducted, the longitudinal component will show how the relationship between variables changes as caregiver QoL deteriorates over time. The Canadian Longitudinal Study on Aging (CLSA) is a model for the types of studies that could be used to collect the data needed to answer our research questions [35] [36].

If the results from a longitudinal study show that caregivers' QoL does indeed affect their ability to provide care for their loved ones with AD, then this issue needs to be addressed through additional support programs that improve caregiver QoL. For example, respite care and similar alternative care options could be made more available to relieve caregivers of persons with AD from their care giving duties. Further, programs could be designed to help caregivers address day-to-day challenges such as financial and legal planning, stress management, and behavioural interventions. Access to educational interventions that help caregivers acquire valuable skills would also improve the care giving experience.

## 5. Limitations

One limitation of this systematic review is that the only study that met the inclusion criteria provided indirect evidence to answer the research questions. Also, because primary data were not available, it was not possible to determine if the observed relationships between caregiver QoL and level/quality of care are statistically significant or not.

However, this systematic review makes an important contribution to the literature because it shows that very little research has been conducted into the relation between QoL and level/quality of care. The review highlights the need for additional research in this area.

## 6. Conclusion

As population aging continues to occupy a more prominent role in research and policy discussions, more attention needs to be given to the situation of unpaid family caregivers of persons with AD. Family caregivers play an important role in the management of AD and several studies have shown that these caregivers experience lower QoL compared to the QoL experienced by caregivers of persons who do not have AD. This systematic review shows that there is insufficient evidence regarding the nature of the relationship between unpaid family caregiver QoL and level/quality of care provided to persons with AD. Considering the important duties that caregivers of persons with AD perform, additional research should be conducted to examine this relationship.

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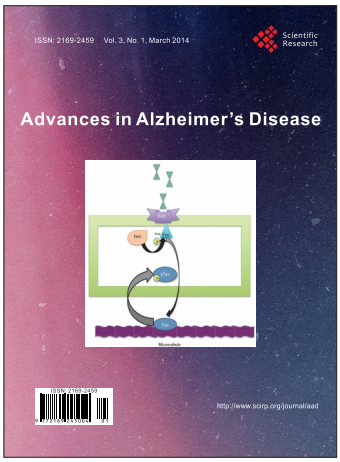


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