Chapter 3.4

Nutritional interventions in community-dwelling Alzheimer patients with (risk of) undernutrition: a systematic review

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Int Psychogeriatr. 2014 May 20:1-9
ABSTRACT

Background: Weight loss and undernutrition are common in patients with Alzheimer's disease (AD) and associated with negative health outcomes. In the current guidelines on diagnosis and treatment of AD, no recommendations for treatment of (risk of) undernutrition in community-dwelling AD patients are given.

Methods: We conducted a systematic review on the effect of nutritional interventions in community-dwelling AD patients with (risk of) undernutrition, according to the methods outlined by the Cochrane Collaboration. Three electronic databases and three trial registers were searched from inception till April 2013.

Results: Literature search in the electronic databases yielded 546 records of which one was relevant for this review. This study, with a high risk of bias, demonstrated that oral nutritional supplements improved nutritional outcomes without effect on clinical and biochemical outcomes. The search in the trial registers yielded 369 records of which two were relevant. One trial was terminated because of failing inclusion, the other is ongoing.

Conclusion: This systematic review on the effect of nutritional interventions in community-dwelling AD patients with (risk of) undernutrition, reveals a serious lack of evidence. Therefore, it is not possible to state what the best approach is.
**INTRODUCTION**

In 1907, Alois Alzheimer described weight loss in his first patient\(^1\) and weight loss is currently recognized as a clinical feature of AD\(^2\). Weight loss, a characteristic of undernutrition\(^3\), has been described in approximately 20% to 45% of community-dwelling AD patients\(^4-9\). In our own recent publication, one in seven community-dwelling elderly with newly diagnosed AD was at risk of undernutrition according to the Mini Nutritional Assessment (MNA)\(^10\). Other studies in community-dwelling AD patients reported even higher rates of prevalence of at risk of undernutrition (evaluated with the MNA), ranging from 26% to 80%\(^6,11-17\). Weight loss and (risk of) undernutrition have been associated with an accelerated progression of AD\(^6,7,12,18\), a higher rate of institutionalization\(^19\) and increased mortality\(^20-22\).

Thus, the prevalence of weight loss and risk of undernutrition in community-dwelling AD patients is high and associated with negative health outcomes. Nevertheless, in the current guidelines on diagnosis and treatment of AD\(^23-25\), no attention is given to what clinicians should do in case of poor nutritional status in community-dwelling AD patients. There are several guidelines and studies on the treatment of (risk of) undernutrition in older people without AD\(^26,27\). However, in our opinion, these results can not be extrapolated to AD patients. Firstly, because the mechanism of weight loss and undernutrition in AD patients is probably not the same as in individuals without AD. This is supported by studies showing that the prevalence of weight loss is higher in patients with AD compared to controls without AD\(^4,5,28\). Secondly, because of expected differences in adherence to the nutritional interventions. Due to their cognitive impairment, AD patients may forget to take an oral nutritional supplement (ONS).

Given the adverse outcomes of weight loss and (risk of) undernutrition, there is a need for evidence-based nutritional interventions for community-dwelling AD patients with a poor nutritional status. A systematic review (type 1 in the hierarchy of evidence) is considered the best way of assessing the evidence base for interventions\(^29\). We conducted a systematic review with the aim to critically assess the current evidence regarding the effect of nutritional interventions in community-dwelling AD patients with (risk of) undernutrition.

**METHODS**

This systematic review was conducted according to the methods outlined by the Cochrane Collaboration\(^29\).

**Review question and eligibility criteria**

We defined eligibility criteria based on the PICO framework\(^29\) and types of studies (table 1). Our PICO was: what is the effect of nutritional interventions (I) in community-dwelling AD patients with (risk of) undernutrition (P) compared to an inactive or active control intervention (C) on clinical,
Table 1. Inclusion and exclusion criteria for selection of studies based on the PICO framework and study types

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
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<tbody>
<tr>
<td><strong>Participants</strong></td>
<td></td>
</tr>
<tr>
<td>● Probable Alzheimer’s disease according to accepted criteria such as the NINCDS-ADRDA (2)</td>
<td>● Patients without Alzheimer’s disease</td>
</tr>
<tr>
<td>● Community-dwelling</td>
<td>● Institutionalized, e.g. nursing home</td>
</tr>
<tr>
<td>● Undernourished or at risk of undernutrition according to accepted criteria such as the MNA59</td>
<td>● Well-nourished</td>
</tr>
<tr>
<td></td>
<td>● Animal studies</td>
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<tr>
<td><strong>Intervention</strong></td>
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<tr>
<td>● Nutritional intervention, i.e. any intervention provided with the aim to improve nutritional status (e.g. weight, upper arm anthropometry), such as oral nutritional supplements, dietary advice, food fortification, nutritional education programs</td>
<td>● Studies using specially designed supplements or supplements containing only specific amino acids or micronutrients, not given with the aim to improve nutritional status but, for example, to influence specific brain processes</td>
</tr>
<tr>
<td><strong>Comparison</strong></td>
<td></td>
</tr>
<tr>
<td>● Inactive control intervention (e.g. placebo, no treatment, care as usual), or an active control intervention (e.g. a different kind of therapy, a different variant of the same intervention)</td>
<td>● None</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td></td>
</tr>
<tr>
<td>● Clinical outcomes (e.g. mortality, cognitive function, functional status, behavior, quality of live)</td>
<td>● None</td>
</tr>
<tr>
<td>● Nutritional outcomes (e.g. weight, upper arm anthropometry, energy intake, protein intake)</td>
<td></td>
</tr>
<tr>
<td><strong>Study types</strong></td>
<td></td>
</tr>
<tr>
<td>● RCTs, non-RCTs</td>
<td>● Case reports, retrospective observational studies</td>
</tr>
</tbody>
</table>

Abbreviations: PICO: Population, Intervention, Comparison, Outcomes, NINCDS-ADRDA: National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer’s Disease and Related Disorders Association, MNA: Mini Nutritional Assessment, RCT: Randomized Controlled Trial

nutritional and economic outcomes (O)? Studies were eligible for inclusion if they met the predetermined inclusion criteria (table 1). Although their evidence is less robust, non-randomized controlled trials (RCTs) were included to ensure capture of all of the available information. Studies in all languages were included to prevent bias. There were no restrictions with regard to publication year.
Search methods
Assisted by information specialists, three electronic databases, including Pubmed, Embase and the Cochrane Central Register of Controlled Trials, were searched from inception till April 24 2013. In addition, three trial registers, including Clinicaltrials.gov (an American trial register), Clinicaltrialregister.eu (an European trial register) and Trialregister.nl (a Dutch trial register) were searched in order to identify unpublished trials. Search terms (Medical Subject Headings (MeSH), Emtree, keywords and title and abstract words) for Alzheimer’s disease, undernourished or at risk of undernutrition and nutritional intervention were combined (table 2). Initially, we combined the terms with search terms for community-dwelling. Though, this search provided only 10 records.

Data selection and data extraction
Studies were selected based on eligibility criteria (table 1) in two steps. The first step involved screening of the studies by title and abstract. Potential relevant studies identified in the first step, were subsequently assessed for eligibility based on the full-text. If necessary, authors of studies were contacted to obtain information. The data selection was done independently by two reviewers (ED and DA). The agreement between the two reviewers was measured by calculating the kappa value\(^2\)\(^9\). Data of eligible studies were extracted by one reviewer (ED) and confirmed independently by the other reviewer (DA).

Assessment of risk of bias
Two investigators independently (ED and DA) assessed the risk of bias of the included studies following the instructions given in the Cochrane handbook\(^2\)\(^9\). This handbook recommends assessing the risk of bias for seven domains. Each domain was judged by categorizing it as low, high or unclear risk of bias\(^2\)\(^9\).

Quality assessment
We planned to assess the quality of evidence for each outcome using the Grades of Recommendation, Assessment, Development and Evaluation Working Group (GRADE) system\(^2\)\(^9\)-\(^3\)\(^1\). Quality assessment was performed if there were at least two studies on the same intervention and on the same outcome, because consistency (i.e. the degree of heterogeneity) of results cannot be assessed with only one study. The quality assessment was planned to be done by two reviewers, independently.

Data analysis
We planned to perform a meta-analysis according to the recommendations of the Cochrane Collaboration\(^2\)\(^9\). Heterogeneity would be explored by the \(\chi^2\) test and with \(P\) statistics. If a meta-analysis was not suitable, we planned to perform a narrative analysis.
### Table 2. Search terms used in Pubmed

<table>
<thead>
<tr>
<th>Category</th>
<th>Search Terms</th>
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The search may be reproduced by adding the boolean operator AND in between the different search sets.

**Abbreviations:** MUST: Malnutrition Universal Screening Tool, SNAQ: Simplified Nutritional Appetite Questionnaire, NSI: Nutrition Screening Initiative, ANSI: Australian Nutritional Screening Initiative, SCREEN: Seniors in the Community: Risk Evaluation for Eating and Nutrition, MNA: Mini Nutritional Assessment (the MUST, SNAQ, NSI, ANSI, SCREEN and MNA are nutrition screening tools for older adults living in the community), PNI: Prognostic Nutritional Index, ONS: Oral Nutritional Supplements, MeSH: Medical Subject Headings, tiab: title and abstract, noexp: Do not include MeSH terms found below this term in the MeSH hierarchy

* Truncation was used to find word variants. For example: a search for alzheimer* finds citations with the word alzheimers.

**N.a. 1:** The search terms in Embase and the Cochrane Central Register of Controlled Trials were derived from the search terms used in Pubmed and are available on request from the author.

**N.a.2:** In the trial registers the following search terms were used: alzheimer, senile dementia, presenile dementia, pre senile dementia, dementia, nutritional treatment, nutrition treatment, nutritional management, nutrition therapy, nutritional therapy, dietary management, diet advice, dietary advice, fortified food, enriched food, nutrition education, food education, diet education, nutritional education, dietary education, health education.
Results of the search

Literature search yielded 546 records. After removal of duplicates, 473 studies remained for screening of title and abstract after which 451 were excluded. The full-text of three articles could not be obtained, leaving 19 articles for full-text review. Of these, six were excluded because the study participants were not undernourished or at risk of undernutrition32-37. Three were excluded because the participants were not community-dwelling38-40. Another five studies were excluded because it involved a description of a study protocol41-45 and four studies were excluded because of other reasons (see figure 1)6,46-48, leaving one study relevant for the purpose of this review49. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart in figure 1 outlines the study selection process50. The agreement between the two reviewers with regard to the data selection was fair (i.e. a kappa value of 0.49)29.

The search in the trial registers yielded 369 records, of which 207 were found in the American trial register, 134 in the European trial register and 28 in the Dutch trial register. After screening of the titles and the abstracts, two trials were considered relevant51,52.

Table 3. Assessment of risk of bias

<table>
<thead>
<tr>
<th>Domain</th>
<th>Judgement</th>
<th>Support for judgement</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation</td>
<td>Low risk</td>
<td>The investigators describe a random component in the sequence generation process: the subjects were randomized into two groups by drawing numbers with sealed envelopes.</td>
<td></td>
</tr>
<tr>
<td>Allocation concealment</td>
<td>High risk</td>
<td>It is not stated whether the envelopes were sequentially numbered or whether they were opaque.</td>
<td></td>
</tr>
<tr>
<td>Blinding of participants and personnel</td>
<td>High risk</td>
<td>No placebo was used, so participants were not be blinded for the intervention. In addition, the dietician was not blinded which may have influenced the outcomes.</td>
<td></td>
</tr>
<tr>
<td>Blinding of outcome assessment</td>
<td>High risk</td>
<td>The outcome measurement is potentially to be influenced by lack of blinding of the dietician.</td>
<td></td>
</tr>
<tr>
<td>Incomplete outcome data</td>
<td>High risk</td>
<td>In the intervention group, two participants died and seven were excluded (i.e. 20% of the patients from the intervention group dropped out after three months). In the control group, only two patients were excluded after three months (i.e. this is a drop-out rate of 4%). This imbalance may have influenced the outcomes.</td>
<td></td>
</tr>
<tr>
<td>Selective reporting</td>
<td>High risk</td>
<td>Not all of the study’s pre-specified outcomes have been reported, for example compliance of the oral nutritional supplements.</td>
<td></td>
</tr>
<tr>
<td>Other bias</td>
<td>Unclear</td>
<td>There is insufficient information to assess whether an important other risk of bias exist.</td>
<td></td>
</tr>
</tbody>
</table>

Assessed study: Lauque et al., 200449

N.a.: Each domain was judged by categorizing it as 'low risk of bias' (i.e. plausible bias unlikely to seriously alter the results), ‘high risk of bias’ (i.e. plausible bias that seriously weakens confidence in the results) or ‘unclear risk of bias’ (i.e. plausible bias that raises some doubt about the results)29

Results
Study characteristics

The study relevant for the present review is the study of Lauque et al., published in 2004. It was a prospective, randomized, controlled study on the effect of ONS on clinical (cognition, Activities of Daily Living (ADL), fractures, pressure ulcers, hospitalization), nutritional (weight, Body Mass Index (BMI), MNA, eating behavior, energy intake, protein intake, fat-free mass) and biochemical (albumin, C-reactive protein) outcomes in community-dwelling AD patients at risk of undernutrition, as evaluated with the MNA. The ONS used contained between 300 and 500 kcal in addition to the patients’ spontaneous food intake and was enriched with proteins, vitamins and minerals. 46 Patients received three months ONS (intervention group) and 45 patients received care as usual (control group). Three months daily ONS significantly improved nutritional outcomes in the intervention group. The nutritional status of the control group also improved after three months. Although, the intervention group improved significantly more than the control group. No significant changes were found on the clinical and biochemical outcomes.

Two trials were considered relevant for the purpose of the present review. One trial, still ongoing, aims to evaluate a diet (i.e. ‘T-Diet plus’; a high protein and moderated high energy ONS, indicated
for patients with neurodegenerative diseases and related malnutrition) in patients with senile dementia at risk of malnutrition. It is not clear if the patients are community-dwelling. The other trial aimed to evaluate the effect of megestrol acetate in outpatients with dementia and weight loss. This trial was prematurely terminated because of insufficient recruitment.

**Risk of bias**
The outcome of the assessment of risk of bias in the study of Lauque et al. (2004) is presented in table 3. The overall risk of bias was judged as ‘high’, because five of the seven domains were judged as ‘high risk of bias’ (table 3).

**Quality assessment and data analysis**
It was not possible to perform a quality assessment or meta-analysis, because only one study was included.

**Discussion**
This is the first systematic review on the effect of nutritional interventions in community-dwelling AD patients with (risk of) undernutrition. Surprisingly, only one study was eligible for the purpose of this review. In this study, Lauque et al. showed that ONS significantly improved nutritional outcomes in community-dwelling AD patients at risk of undernutrition. However, no effect was found on clinical and biochemical outcomes. In addition, the risk of bias in the study of Lauque et al. was high. What does the lack of evidence mean?

It may mean that undernutrition in community-dwelling AD patients is not such an important issue as postulated. This is supported by the fact that one of the retrieved trials in the present systematic review was terminated because of difficulties in the recruitment of patients meeting the inclusion criteria, including undernutrition. In addition, a recent study showed that community-dwelling patients with moderate AD did not lose weight during four years of follow-up. Moreover, in our own recent published investigation, the prevalence of undernutrition in community-dwelling, newly diagnosed AD patients was 0%. This low number of undernourished patients is in line with other studies, where the prevalence of undernutrition in community-dwelling AD patients ranged from 0% to 9% (as evaluated with the MNA). Although, frank undernutrition may be a non-issue in community-dwelling AD patients, one in seven community-dwelling elderly with newly diagnosed AD was at risk of undernutrition in our recent published investigation and other studies reported even higher rates, ranging from 26% to 80%. Given the adverse outcomes of weight loss and (risk of) undernutrition, it is important to know what the best approach is to community-dwelling AD patients with a risk of developing a poor nutritional status. Unfortunately, based on the results of the present systematic review, it is not possible to state what the best approach is. Several studies investigated the effect
of nutritional interventions in institutionalized patients with an advanced stage of dementia\textsuperscript{54-56}. However, these results cannot be extrapolated to community-dwelling AD patients, because for example the compliance in institutionalized patients may be better than in community-dwelling patients, i.e. community-dwelling patients have no professional caregiver who ensures that the patient is adherent to therapy. More research is needed to be conclusive about the best approach to community-dwelling AD patients with risk of undernutrition. In addition, research should focus on establishing its risk factors in order to design targeted (nutritional) interventions. Moreover, future trials should focus on outcomes of relevance to patients and caregivers, such as improvements in function and quality of life.

Another explanation for the lack of evidence may be our strict eligibility criteria. However, we have consciously chosen for these criteria. We focused on community-dwelling AD patients because most of the AD patients are community-dwelling (i.e. in the Netherlands for example 70\%)\textsuperscript{57}. Moreover, by focussing on community-dwelling patients, it is possible to figure out if a nutritional intervention can delay institutionalisation. We focused on patients with a poor nutritional status because they benefit the most from nutritional interventions\textsuperscript{58}.

Unfortunately, despite our comprehensive literature search, only one study was relevant for the purpose of this review. Hence, it was not possible to perform a meta-analysis and to give firm conclusions about the effect of nutritional interventions in community-dwelling AD patients with (risk of) undernutrition. A strength of the present study is that the data selection was done by two reviewers, independently. The agreement between the two reviewers was fair. Another strength includes that studies in all languages were retrieved. Moreover, three trial registers were searched.

In conclusion, the present systematic review on the effect of nutritional interventions in community-dwelling AD patients with (risk of) undernutrition, reveals a serious lack of evidence. As a result, it is not possible to state what the best approach is. Frank undernutrition in community-dwelling AD patients appears to be an infrequent condition. Many patients however are at risk of undernutrition. Therefore, research should focus on establishing its risk factors in order to design targeted (nutritional) interventions.
References


