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published in
Journal of the American Medical Directors Association
2019

DOI (link to publisher)
10.1016/j.jamda.2018.06.019

document version
Publisher's PDF, also known as Version of record

JAMDA 20 (2019) 14–21

JAMDA

journal homepage: www.jamda.com

Review Article

Energy and Protein Intake of Alzheimer's Disease Patients Compared to Cognitively Normal Controls: Systematic Review

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Keywords:
Older adults
malnutrition
mild cognitive impairment

A B S T R A C T

Objectives: Protein and energy malnutrition and unintended weight loss are frequently reported in patients with mild cognitive impairment (MCI) and Alzheimer's disease (AD). Possible underlying mechanisms include increased energy expenditure, altered uptake of nutrients, a reduced nutritional intake, or a combination of these 3. We aimed at systematically reviewing the literature to examine potential differences in energy and protein intake in patients with MCI and AD compared to controls as a possible mechanism for unintended weight loss.
Design: Systematic review and meta-analysis.
Setting: PubMed and Cochrane Electronic databases were searched from inception to September 2017 for case control studies.
Participants: Patients with MCI or AD compared to cognitive healthy controls, all adhering to a Western dietary pattern.
Measurements: Energy and protein intake.
Results: The search resulted in 7 articles on patients with AD versus controls, and none on patients with MCI. Four articles found no differences in energy and protein intakes, 1 found higher intakes in patients with AD, and 1 article found lower intakes in patients with AD compared to controls. One article reported on intakes, but did not test differences. A meta-analysis of the results indicated no difference between patients with AD and controls in energy [−8 kcal/d, 95% confidence interval (CI): −97, 81; $P = .85$], or protein intake (2 g/d, 95% CI: −4, 9; $P = .47$). However, heterogeneity was high ($I^2 > 70\%$), and study methodology was generally poor or moderate.
Conclusion: Contrary to frequently reported unintended weight loss, our systematic review does not provide evidence for a lower energy or protein intake in patients with AD compared to controls. High heterogeneity of the results as well as of participant characteristics, setting, and study methods was observed. High-quality studies are needed to study energy and protein intake as a possible mechanism for unintended weight loss and malnutrition in both patients with MCI and AD.

This work was supported by a grant from NWO-FCB (project number 057-14-004), the Netherlands. Research of the VUmc Alzheimer Center is part of the neurodegeneration research program of Amsterdam Neuroscience (www.amsterdamresearch.org). The VUmc Alzheimer Center is supported by Stichting Alzheimer Nederland and Stichting VUmc fonds. Astrid Doorduijn is appointed on a NWO-FCB grant, NUDAD (project number 057-14-004).

The authors declare no conflicts of interest.

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https://doi.org/10.1016/j.jamda.2018.06.019
1525-8610/

Alzheimer's disease (AD) is a progressive neurodegenerative disease, characterized by progressive deterioration in cognitive functioning resulting in interference with daily functioning.[1] In the early stage of the disease, patients experience cognitive complaints in (most often) 1 or 2 functions, while the ability to take care of themselves remains intact. With progression of the disease, patients become more and more dependent on their caregivers, and in the final stage institutionalization is almost unavoidable.

An estimated number of almost 50 million people worldwide suffer from dementia and the World Health Organization predicts that the number of people will reach 131 million in 2050.[2] To date, there is neither an effective curative treatment, nor one that slows down the progression of the disease.

AD is the cause of more than 70% of dementia cases.[2] The phase between cognitive changes due to normal aging and the first clinical features of dementia is called mild cognitive impairment (MCI). Patients with MCI experience a decline in cognition, mostly memory, but their daily functioning is still intact.[3]

Patients with MCI and AD often suffer from weight loss and protein and energy malnutrition, with reported prevalence ranging between 20% and 50%,[4–8] depending on the methods used and the severity of the disease stage. Patients in more advanced stages of AD are more often unable to feed themselves and/or might suffer from dysphagia, hindering adequate intake.[9] Unintended weight loss and malnutrition have been associated with an accelerated progression of the disease, a higher rate of institutionalization, and increased mortality.[10,11] The mechanisms underlying unintended weight loss and increased risk of malnutrition are not yet clear.

Several mechanisms that could contribute to the observed malnutrition and weight loss have been proposed.[12,13] The first mechanism could be a disbalance between energy expenditure and energy intake, because of an increased energy expenditure in the patient with AD.[13] However, no differences between patients with AD and healthy older adults in measured daily energy expenditure, adjusted for body composition, were observed in a previous study.[14] Another study found no differences in physical activity between patients with AD compared to healthy control subjects matched for age, gender, and body mass index (BMI).[15] An increased energy expenditure as possible mechanism underlying weight loss and malnutrition seems unlikely based on these 2 studies; however, more research is clearly needed. As a second proposed mechanism, patients with AD might have a less efficient uptake of nutrients, leading to malnutrition.[13] This mechanism has rarely been studied and is mostly related to deficiencies in vitamins and minerals rather than protein and energy malnutrition.[12,16] Lastly, patients with AD might have a lower nutritional intake, caused by reduced appetite, smell, or taste. Little is known about the nutritional intake of patients with MCI and AD compared to controls. Therefore, we systematically reviewed the literature for observational studies providing data on the actual energy and protein intake of patients with MCI and AD compared to cognitively normal controls.

Methods

Search Strategy

A systematic literature search was performed in accordance with Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA).[17] The bibliographic database PubMed and the Cochrane database were searched from inception to September 5, 2017. We searched for articles that reported the actual energy and protein intake in patients with MCI or AD compared to controls, using a combination of MeSH and text-based terms.

("Dementia" [MeSH] OR "Alzheimer" [MeSH] OR "mild cognitive impairment" [MeSH]) AND ("energy intake" [Title/Abstract] OR "protein intake" [Title/Abstract] "nutritional intake" [Title/Abstract] OR "nutrition*" [Title/Abstract] OR "dietary intake" [Title/Abstract] OR "food intake" [Title/Abstract] OR "eating habit" [Title/Abstract] OR "diet" [Title/Abstract]) AND ("Adult"[Mesh] OR adult*[Title/Abstract]).

Additionally, reference lists of identified manuscripts and reviews were checked manually.

Criteria for Inclusion

Only articles with a case-control design reporting on energy and/or protein intake in patients with MCI or AD compared with cognitively normal controls were included. Participants should adhere to a Western dietary pattern, and publications had to be written in English and to be available in full-text.

Criteria for Exclusion

Articles were excluded if they focused on specific subgroups of patients with MCI or AD, for example, those with significant weight loss or those on a semisolid or liquid diet. Articles that focused on the role of nutrition in the development of dementia were also excluded.

Study Selection Process

The search strategy identified 800 articles, which were screened on title and abstract by 2 authors independently. Screening resulted in 136 articles eligible for full-text screening. One additional article was found via the reference list of an included article.[15] Finally, 7 articles were included based on abstract and full text (Figure 1).

Quality Assessment of the Studies

The Newcastle-Ottawa Scale (NOS) for case-control studies[18] was used to assess the methodological quality of the included papers. The following criteria were scored: definition of cases, representativeness of cases, selection of controls, definition of controls, comparability of cases and controls on age and gender, nutritional intake method, and using the same methodology in both groups.[18] The more criteria were met, the higher the score and the better the methodological quality. Two authors independently assessed the quality of the studies; disagreements were solved by a third author. A study was considered to have poor methodological quality when the score of the scale was below 5 of 8 criteria.

Data Extraction

From the selected articles, the following information was extracted: number of participants per group, selection criteria for control group, diagnostic criteria used, study setting, Mini-Mental State Examination (MMSE[19]) score, mean age, percentage female, anthropometry (BMI or body weight), feeding difficulties, nutritional status, nutritional intake assessment method, results of energy (kilocalories per day) and protein (grams per day) intake per group.

Of 3 articles using a different unit of energy intake, energy intake was recalculated to kilocalories per day.[15,20,21] Two studies[20,21] reported the energy and protein intake per kilogram body weight. As we were unable to contact the authors, we recalculated the intake by multiplying the reported intake in kilocalories or grams per kilogram body weight by the mean body weight of the study sample.

Meta-analysis

Random effects meta-analyses were performed to estimate the mean energy and protein intakes across the selected articles.[22] Results are presented as forest plots. The Cochrane χ^2 was used to test the

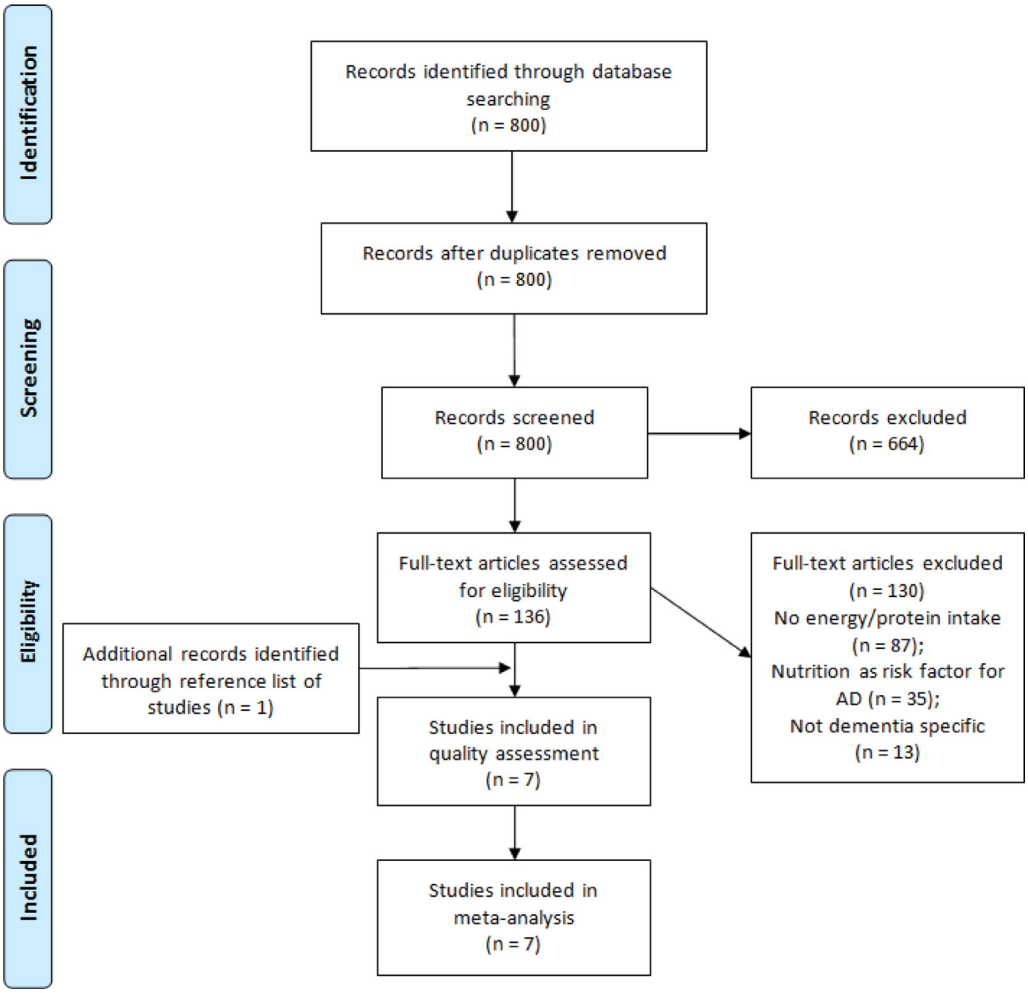

Fig. 1. Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) flow diagram for the study selection process.

presence of heterogeneity across the included articles, a $P < .05$ was considered as indicative of heterogeneity. The degree of heterogeneity was evaluated using I^2, with values of 25%, 50% and 75% indicating low, moderate and high degrees of heterogeneity respectively.[23] The analyses were performed using Review Manager 5 (version 5.3, The Cochrane Collaboration, Copenhagen, Denmark). Six studies were included in the meta-analysis on energy intake, Spindler[20] could not be included since only median values and interquartile ranges were reported. Five studies reported on protein intake and were included in the meta-analysis on protein intake. The meta-analyses was stratified by disease severity; severe dementia (MMSE score ≤18) versus mild dementia (MMSE score >18).[24] Stratification was also performed using 3 groups: severe dementia (MMSE score 0-7), moderate dementia (MMSE score 8-14), and mild dementia (MMSE score 15-23).[25]

Results

Table 1 summarizes the 7 articles included in this review. Four articles were based on data collected in European countries (United Kingdom,[27] Finland,[28] Italy,[21] and France[29]), 2 collected data in the USA,[15,20] and 1 in Canada.[26] Four articles were based on data from community-dwelling patients with AD,[15,26–28] and 3 on data from institutionalized patients with AD.[20,21,29] No articles focusing on patients with MCI were found. Sample size ranged from 40[20] to 346[29] participants. The mean MMSE score of the cases ranged from 11[21] to 24,[26] and of the controls from 25[21] to 30.[26,27] The mean age of the participants ranged from 72[20] to 88[21] years, with 31%[28] to 91%[21] women. In the study population of Franzoni,[21] 45% needed total assistance with feeding; in all other articles, cases and controls did not have problems with feeding themselves. In the study of Jesus,[29] both cases and controls had nutritional difficulties (changes in weight or appetite) as assessed by a General Practitioner, and both groups were at risk for malnutrition. The patients with AD in the study of Shatenstein[26] were more likely to be at moderate risk for malnutrition compared to controls. The patients with AD in the study of Dvorak[15] had lost on average 4.1 kg body weight, in the past year and in the study of Puranen, 51% of the female and 40% of the male AD patients were at risk for malnutrition. The other 2 articles[20,27] did not provide information on the nutritional status of their participants. Two articles did not specify the type of dementia.[21,29] Controls consisted of spouses,[27,28] residents who did not have dementia,[21,29] or age- and BMI-matched community-dwelling individuals.[15,20,26] Four studies used a 3- or 4-day food diary to estimate nutritional intake,[15,20,27,28] 1 used 2 nonconsecutive 24-hour recalls,[26] 2 studies weighed the food that was consumed by the participants,[20,21] and 1 used a 3-day survey of food intake by paramedical personnel.[29] Except for Spindler,[20] all studies used the same nutritional intake assessment method in both groups.

Quality Assessment of the Studies

Table 2 presents the assessment of methodological quality. Two studies had a high methodological quality, scoring 7 of 8 points,[15,21]

Table 1
Summary of Characteristics and Energy and Protein Intake per Day of Patients With AD and Controls From the 7 Included Articles in This Review

Author, year, Country	Groups	Diagnostic Criteria	Setting	MMSE Score	Age (years)	Female, %	Anthropometry	Feeding Difficulties	Nutritional Status	Nutritional Intake Assessment Method	Energy (kcal)	Protein (g)
Shatenstein, 2007[26] Canada	36 patients with AD	DSM IV	Community	24 ± 4	78 ± 5	61	BMI: 25.8 ± 4.5	Inclusion criterion: "were physically well with no significant weight loss (defined as <4.5 kg during a 6-month period or <2.2 kg during a 1-month period) during the previous year"	Moderate risk of malnutrition based on ENS[‡] 3.9 ± 1.8	2 nonconsecutive 24-h recalls	1527 ± 364	64 ± 19
	58 age-matched controls			30 ± 1[†]	74 ± 6[†]	77	BMI: 25.9 ± 3.2	No information	Low risk of malnutrition based on ENS[‡] 2.1 ± 1.3[*]		1781 ± 419[*]	74 ± 17[*]
Dvorak, 1998[15] USA	30 patients with AD	NINCDS-ADRDA	Community	17 ± 8	74 ± 8	57	Body weight: 64.9 ± 11.4 kg	No information	Mean weight loss 4.1 ± 1 kg in the past year	3-d food diary (1 weekend, 2 weekdays)	*1799 ± 404* (7.53 ± 1.69 MJ)	–
	30 age- and BMI-matched controls			29 ± 2[†]	73 ± 7	57	Body weight: 66.4 ± 10.6 kg	No information	No information		*1810 ± 370* (7.58 ± 1.55 MJ)	–
Spindler, 1996[20] USA	17 patients with AD	NINCDS-ADRDA	Institution	–	M 77 ± 8 F 81 ± 6	65	BMI M 25.8 ± 2.8 BMI F 22.0 ± 2.8	Inclusion criterion: able to feed themselves	No information	Weighing 2 consecutive days	*2256* (34 kcal/kg BW)	*93 ± 20* (1.4 ± 0.3 g/kg BW)
	23 controls		Community	–	M 73 ± 6 F 72 ± 7[*]	61	BMI M 25.5 ± 4.0 BMI F 25.3 ± 5.7	No information	No information	4-d food diary (1 weekend, 3 weekdays)	*1643* (24 kcal/kg BW[†])	*75 ± 27* (1.1 ± 0.4 g/kg BW[†])
Tabet, 2005,[27] UK	26 patients with AD	NINCDS-ADRDA	Community	21 [19-23]	77 [75-80]	42	–	"No subjects had any physical disorder as to interfere with normal food intake or its absorption"	No information	3-d food diary (1 weekend, 2 weekdays)	1636 [1336-1936]	–
	26 controls (spouses)			30 [29-30][†]	74 [72-76]	58	–	No information	No information		1629 [1467-1782]	–
Puranen, 2014,[28] Finland	99 patients with AD	NINCDS-ADRDA	Community	19 ± 5	77 ± 6	31	–	No information	51.6% of female and 39.7 of male AD at risk of malnutrition based on MNA[§]	3-d food diary	1714 ± 392	73 ± 22
	99 controls (spouses)			28 ± 2	75 ± 7	69	–	No information	No information		1558 ± 420	68 ± 19

(*continued on next page*)

Table 1 (*continued*)

Author, year, Country	Groups	Diagnostic Criteria	Setting	MMSE Score	Age (years)	Female, %	Anthropometry	Feeding Difficulties	Nutritional Status	Nutritional Intake Assessment Method	Energy (kcal)	Protein (g)
Franzoni, 1996,[21] Italy	33 residents with dementia not AD specific	DSM IIIR	Institution	11 ± 6	86 ± 6	91	BMI: 22.8 ± 4.6	"55% of total population able to feed themselves, others required total assistance"	"our patients had overall good nutritional status, as supported by the observation that no patient had cholesterol levels lower than 120 mg/dL or albumin levels lower than 3.0 g/dL"	Weighing 3 d	*1458 ± 408* (28.2 ± 7.9 kcal/kg BW)	*62 ± 21* (1.2 ± 0.4 g/kg BW)
	25 residents without dementia equalized by age			25 ± 4†	85 ± 6	88	BMI: 23.3 ± 3.8				*1560 ± 440* (28.0 ± 7.9 kcal/kg BW)	*61 ± 22* (1.1 ± 0.4 g/kg BW)
Jesus, 2012,[29] France	223 residents with dementia not AD specific	MMSE <24 or history of dementia	Institution	14 ± 6	88 ± 7	83	BMI: 25.0 ± 5.9	Inclusion criterion: "All residents considered by their General Practitioner to have nutritional difficulties as manifested by alterations in general condition and changes in weight, appetite, etc (at the practitioner's discretion)"	Poor to moderate nutritional status, based on MNA§ score: 17.9 ± 4.4	3-d survey of food intake by paramedical personnel	1526 ± 390 (27.1 ± 8.7 kcal/kg BW)	62 ± 18 (1.1 ± 0.4 g/kg BW)
	123 residents without dementia			26 ± 3†	88 ± 7	83	BMI: 26.3 ± 7.5		Poor to moderate nutritional status, based on MNA§ score: 18.5 ± 4.2		1487 ± 332 (25.0 ± 8.9 kcal/kg BW*)	58 ± 17 (1.0 ± 0.4 g/kg BW*)

−, not in text; BW, body weight; DSM, Diagnostic and Statistical Manual of Mental Disorders; F, female; M, male; MJ, megajoules; NINCDS-ADRDA, National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association.

All data are in mean ± SD or median [95% CI], Numbers in italic were recalculated.

*$P < .01$ vs AD.

†$P < .001$ vs AD.

‡ENS = Elderly Nutrition Screening (0-2 = low risk; 3-5 = moderate risk; 6+ = high risk).

§MNA = mini nutritional assessment (range 0-30; ≤17.5 = malnourished; 17.5-23.5 = at risk of malnutrition; ≥23.5 = no nutritional problems).

Table 2
Methodological Quality of the 7 Included Articles Assessed Using the Newcastle Ottawa Scale for Case Control Studies[17]

Author	Selection				Comparability		Exposure		Score
	Definition of Cases	Representative Cases	Selection of Controls	Definition of Controls	Age	Gender	Nutritional Intake*	Same Method	Total (Max 8)
Shatenstein[26]	+	−	+	+	−	−	+	+	5
Dvorak[15]	+	+	+	−	+	+	+	+	7
Spindler[20]	+	+	−	−	−	−	+	−	3
Tabet[27]	+	+	−	+	+	+	−	+	6
Puranen[28]	+	+	−	−	−	−	−	+	3
Franzoni[21]	+	+	+	−	+	+	+	+	7
Jesus[29]	−	−	+	−	+	+	−	+	4

+, quality criterion met; −, quality criterion not met.
*Quality of the nutritional intake assessment method used.

and 2 studies had a moderate methodological quality,[26,27] scoring 5 and 6 points. The 3 studies[20,28,29] with poor methodological quality (less than 5 points) particularly performed poorly on control selection, definition of controls, and the comparability of cases and controls.

Quantitative Analysis

Three articles found no difference in energy and protein intake between patients with AD and controls. Tabet[27] found no differences in total energy and protein intake, but did observe differences in intakes expressed per kilogram of body weight. One article found a lower energy and protein intake in patients with AD compared to controls,[26] whereas another article found a higher energy and protein intake in patients with AD.[20] Puranen reported energy and protein intake in patients with AD compared to their spouses, but did not test the differences.[28] In patients with or at risk of malnutrition, 1 study found a higher nutritional intake,[28] 2 studies found no difference in intake,[15,29] and another study reported a lower nutritional intake[26] compared to controls.

Meta-analysis was used to combine study results. Forest plots (Figure 2) indicate mean differences in energy (A) and protein (B) intake between patients with AD and controls.

The overall mean intakes did not differ between patients with AD and controls for energy [6 studies, mean difference (MD): −8 kcal/d, 95% confidence interval (CI): −97, 81; $P = .85$], and protein (5 studies, MD: 2 g/d, 95% CI: −4, 9; $P = .47$). Heterogeneity was high for both outcome measures ($I^2 = 73\%$, $P = .003$; $I^2 = 75\%$, $P = .003$, respectively). Leaving out the 3 studies with poor methodological quality did not significantly change the results of both energy (4 studies, MD: −81 kcal/d, 95% CI: −213, 51; $P = .23$) and protein intake (2 studies, MD: −5 g/d, 95% CI: −16, 5; $P = .30$), with moderate to high heterogeneity (I^2 of 69% and 58%, respectively).

Stratification of the results by disease severity based on the review of Tombaugh (severe dementia: mean MMSE score ≤17, 3 studies for energy and protein and moderate dementia: mean MMSE score >18, 3 studies for energy and 2 studies for protein) did not significantly change the results of energy intake (severe dementia: MD: 19 kcal/d, 95% CI: −49, 88; $P = .58$; moderate dementia: MD: −20 kcal/d, 95% CI: −195, 155; $P = .83$) and protein intake (severe dementia: MD: 6 g/d, 95% CI: −2, 13; $P = .12$; moderate dementia: MD: −2 g/d, 95% CI: −17, 13; $P = .77$). Stratification of the results by disease severity based on the article of Kreamer [severe dementia (MMSE score 0-7), no studies, moderate dementia (MMSE score 8-14), 2 studies for energy and protein and mild dementia (MMSE score 15-23), 3 studies for energy

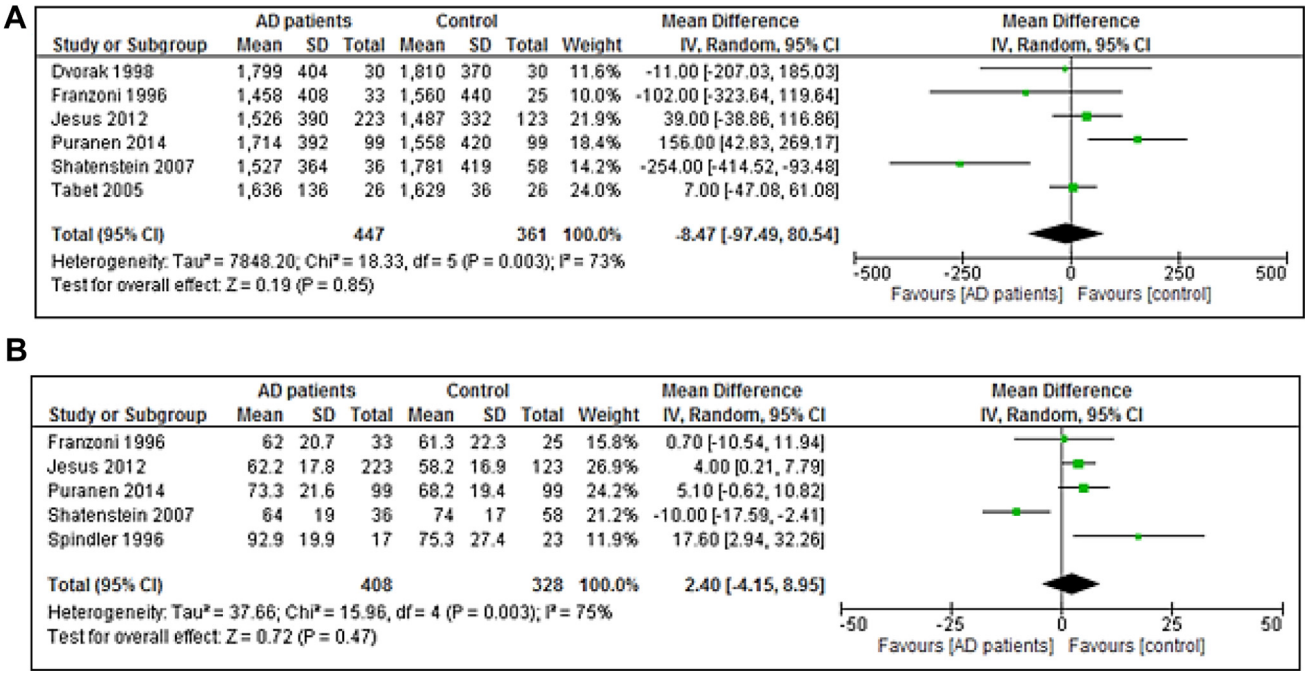

Fig. 2. Forest plots of energy intake in kilocalories per day (A) and protein (B) intake in grams per day of AD patients compared to cognitively normal controls.

and 1 study for protein] did not significantly change the results of energy intake (moderate dementia: MD: 8 kcal/d, 95% CI: −106, 122; $P = .89$; mild dementia: MD: 54 kcal/d, 95% CI: −54, 161; $P = .23$) and protein intake (moderate dementia: MD: 4 g/d, 95% CI: 0, 7; $P = .05$; mild dementia not possible, only 1 study).

Stratification of the results by study setting did not significantly change the results of either energy (institution, 2 studies, MD: 8 kcal/d, 95% CI: −106, 122; $P = .89$; community, 4 studies, MD: −16 kcal/d, 95% CI: −156, 124; $P = .82$) or protein intake (institution, 3 studies, MD: 6 g/d, 95% CI: −2, 13; $P = .12$; community, 2 studies, MD: −2 g/d, 95% CI: −17, 13; $P = .77$).

Discussion

We found 7 articles in this literature search reporting energy and/or protein intake of patients with AD versus controls, but none reporting the intakes of patients with MCI. The studies varied in participant characteristics, selection of controls, setting and nutritional intake assessment method, and often were of poor or moderate methodological quality. The main finding of this study is that the available literature does not provide evidence for a lower energy and protein intake of patients with AD versus controls.

The included articles differed in participant characteristics (age, gender, MMSE score), study setting, and nutritional intake assessment method. For example, the MMSE scores in the patients with AD and controls varied but overlapped between the groups, which may have influenced the results. The MMSE score of patients with AD ranged from 11 to 24, covering both moderate and severe disease stages. Stratification of the meta-analyses in 2 subgroups by disease stage did not significantly change the results and suggests there is no difference in nutritional intake between different disease stages. Stratification of the meta-analyses in 3 subgroups was difficult to interpret because of the limited number of studies in each stratum. In 2 articles,[27,28] patients were compared with their spouses and were therefore always compared with someone from the opposite gender. As men are likely to eat more energy and protein per day than women,[30] such a comparison might introduce bias. Because of the high degree of heterogeneity across articles, results of our meta-analysis should be interpreted with caution.

In the studies conducted in institutionalized patients, consumed food was weighed[20,21] or the food intake was recorded by care professionals during 3 days, requiring no participation of the patients or controls.[29] In the studies conducted in community-dwelling patients, the most commonly used method to assess nutritional intake was a 3- or 4-day food diary, or two 24-hour recalls.[15,20,26,27] These methods rely on the memory of the participant. It is not known how valid a food diary or two 24-hour recalls are to estimate nutritional intake in populations with dementia. There is a clear need for validation of nutritional assessment methods in this particular group of patients.[31–33]

This study has some limitations. First of all, the high heterogeneity across articles makes it hard to compare studies and to draw conclusions. Across the articles, different units of energy and protein intake were used. As the majority of the results was expressed in absolute numbers and not all articles described the mean body weight of their participants, we decided to recalculate nutritional intake by multiplying the reported intake in kilocalories or grams per kilogram body weight by the mean body weight of the study sample. We are, however, aware of the limitations by reporting data on nutritional intake this way, and adjustment for body weight and/or physical activity level would have been preferred. Only 1 study reported data on activity level, which made it impossible to consider physical activity level in the comparison of nutritional intakes between patients and controls. Because of the observational design of the studies, where food intake was measured at one moment in time, we were not able to study a possible decline in food intake or changes in nutritional status or body weight over time. Furthermore, cases and controls were not always comparable, especially not in the study of Spindler, because cases and controls lived in different settings. No difference in nutritional intake was found after stratification of the meta-analysis by study setting, that is, institution versus community. However, the number of studies included per group after stratification was very small.

Only 2 studies scored 7 of 8 points on the Newcastle Ottawa Scale for quality assessment for case-control studies, indicating good methodologic quality. Both studies, 1 in community-dwelling patients with energy intake expressed in kilocalories per day and 1 in institutionalized patients with energy and protein expressed per kilogram body weight, found no differences in intake between patients and controls.[15,21] Other articles scored lower on methodologic quality, most often because the controls were not comparable to the cases.

Summarizing, results of this review based on 7 articles suggest no lower energy and protein intake of patients with AD compared to controls. No articles comparing the intakes of patients with MCI versus controls were found. Because of the high degree of heterogeneity across studies, the limited number of included studies, and their poor to moderate methodologic quality, these results should be interpreted with caution. High-quality research is needed to obtain more insight into the role of low protein and energy intake as a possible mechanism for weight loss and malnutrition in patients with AD. Furthermore, we recommend studies in patients with MCI, as this might give useful information on the earliest changes in nutritional intake, even before the diagnosis of AD.

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