EFFECT OF A MEDICAL FOOD ON BODY MASS INDEX AND ACTIVITIES OF DAILY LIVING IN PATIENTS WITH ALZHEIMER'S DISEASE: SECONDARY ANALYSES FROM A RANDOMIZED, CONTROLLED TRIAL

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Abstract: *Objectives:* To investigate the effect of a medical food (Souvenaid) on body mass index (BMI) and functional abilities in patients with mild Alzheimer's disease (AD). *Design/setting/participants/intervention/measurements:* These analyses were performed on data from a 12-week, double-blind, randomized, controlled, multicenter, proof-of-concept study with a similarly designed and exploratory 12-week extension period. Patients with mild AD (Mini-Mental State Examination score of 20–26) were randomized to receive either the active product or an iso-caloric control product. While primary outcomes included measures of cognition, the 23-item Alzheimer's Disease Cooperative Study-Activities of Daily Living (ADCS-ADL) scale was included as a secondary outcome. Both ADCS-ADL and BMI were assessed at baseline and Weeks 6, 12 and 24. Data were analyzed using a repeated-measures mixed model. *Results:* Overall, data suggested an increased BMI in the active versus the control group at Week 24 (ITT: $p = 0.07$; PP: $p = 0.03$), but no treatment effect on ADCS-ADL was observed. However, baseline BMI was found to be a significant treatment effect modifier (ITT: $p = 0.04$; PP: $p = 0.05$), and an increase in ADCS-ADL was observed at Week 12 in patients with a 'low' baseline BMI (ITT: $p = 0.02$; PP: $p = 0.04$). *Conclusions:* These data indicate that baseline BMI significantly impacts the effect of Souvenaid on functional abilities. In addition, there was a suggestion that Souvenaid increased BMI.

Key words: Alzheimer's disease, activities of daily living, treatment outcome, nutrition, BMI.

Introduction

One of the characteristic hallmarks of Alzheimer's disease (AD) is a progressive deterioration in the ability to perform activities of daily living (ADL), as well as impairments in cognition, visuospatial function and memory (1). One of the primary causes of AD symptomatology is believed to be synaptic loss, particularly in the hippocampal and cortical synapses (2, 3).

Preclinical research has suggested that the ingestion of certain nutrients may help to improve the formation of new synapses in the brain. Specifically, these include the rate-limiting precursors uridine, choline, and docosahexaenoic acid (DHA), involved in the synthesis of the synaptic membrane phosphatides essential for neuronal formation and function (4-6). B-vitamins, phospholipids and antioxidants also serve as co-factors by enhancing the availability of these precursors (7). Combined dietary enrichment with these nutrients has also been shown to influence membrane-dependent processes, e.g. reducing amyloid precursor processing pathways and receptor function. This, in turn, could result in reduced amyloid-beta production, plaque burden and amyloid-beta toxicity (8). In support of this, epidemiological and cohort studies suggest that a diet rich in omega-3 fatty acids, B-vitamins, and antioxidants decreases the risk of AD (9, 10), while other studies suggest

that patients with AD have lower plasma levels of these nutrients when compared with cognitively intact age-matched controls (11).

These observations led to the development of Souvenaid®, a multi-nutrient drink designed to deliver the supporting nutrients to improve synaptic membrane formation and function in patients with AD. This medical food contains a specific formulation of nutrients registered as Fortasyn™ Connect (including DHA, eicosapentanoic acid, phospholipids, choline, uridine monophosphate, vitamins B12, B6, and folate, vitamins C and E and selenium), along with other vitamins, minerals, trace elements and macronutrients (12). The efficacy and tolerability of Souvenaid in mild AD was investigated in a 24-week, multicenter, controlled, proof-of-concept study (12). Memory performance was significantly improved in the group that received Souvenaid versus the control group (12).

In the early course of AD, the more complex instrumental ADL such as shopping, preparing a meal and handling finances have already begun to deteriorate (13). At the same time, AD patients face a risk of malnutrition and weight loss that is thought to influence the evolution and worsening of the condition and predict mortality (14-16). Poor nutritional status has also been shown to be closely related to the occurrence of functional deficits, even at the initial stages of AD (17, 18). Body mass index (BMI) is a widely accepted indicator of

nutritional status (19), and was used in the current study.

The relationship between BMI and functional abilities formed the rationale for the analyses presented here. These investigated whether baseline BMI impacts the effect of Souvenaid on functional abilities in patients with mild AD. In addition, the influence of the medical food on BMI was assessed.

Methods

Study design

The proof-of-concept study with Souvenaid was a 12-week, double-blind, randomized, controlled, multicenter study with a similarly designed, exploratory, optional 12-week extension period. The detailed methodology and primary results of the study have been described previously (12). Briefly, 225 patients with mild AD (Mini-Mental State Examination [MMSE] score of 20–26) were recruited and randomized 1:1 to receive either the active (Souvenaid®, Nutricia N.V., Zoetermeer, The Netherlands) or iso-caloric control product as a 125 ml drink to be taken every day (12). In line with current guidelines for clinical trials in AD (20), the study included measures of cognition (modified Alzheimer's Disease Assessment Scale-cognitive subscale, primary outcome) (21) and functional abilities (23-item Alzheimer's Disease Cooperative Study-ADL [ADCS-ADL], secondary outcome) (22). The ADCS-ADL scale is rated by the caregiver and ranges from 0 (need for extensive help) to 78 (independent performance). Baseline height and weight measurements were used to calculate BMI (kg/m^2). Both ADCS-ADL and body weight were assessed at baseline, Week 6, 12 and 24 (height was measured at baseline only).

The study was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use / WHO Good Clinical Practice (ICH-GCP) guidelines, as appropriate to the legislation of the countries participating in the study. The clinical trial registration number is ISRCTN72254645.

Modeling analysis

The primary analysis population was the intent-to-treat (ITT) efficacy population, defined as all patients who received at least one dose of study product and one post-baseline assessment. The per-protocol (PP) efficacy population consisted of all patients who completed the study without major protocol deviations. Patients who did not receive any study product for > 25% of days, and/or patients who received < 70% of the prescribed dosage overall, were excluded from the PP group.

Data were analyzed with a linear repeated-measures mixed (RMM) model, using SAS® software version 9.2. The current data showed the best fit with the RMM model and Heterogeneous Compound Symmetry variance–covariance structure where time was treated as a categorical variable and represented by dummy codes. Exploratory additional comparisons were performed using contrast statements.

Prior to the modeling analyses, the ADCS-ADL data were transformed using a quadratic transformation to adjust for the skewed nature of the data. Similarly, a square-root transformation was applied to BMI data.

Results

In the initial proof-of-concept study, 225 patients were randomized to treatment, of whom 112 received active product and 113 received control product. Overall, 161 patients completed the 24-week study (12). Of the 212 patients in the ITT efficacy population (12), 144 were included in the PP analysis population. No statistically significant differences between active or control groups were reported for any baseline characteristic (Table 1).

Table 1
Baseline characteristics for the ITT population (12)

Characteristics	Control product	Active product
Total patient population	(n = 106)	(n = 106)
Men, n (%)	52 (49)	54 (51)
Age (yr)		
Mean ± SD	73.3 ± 7.8	74.1 ± 7.2
MMSE		
Mean ± SD	24.0 ± 2.5	23.8 ± 2.7
Total ADCS-ADL		
Mean ± SD	61.9 ± 10.9	61.1 ± 10.5
Median [range]	64.5 [10 – 77]	63.0 [28 – 78]
BMI		
Mean ± SD	26.2 ± 3.5	26.2 ± 4.8
Median [range]	26.0 [18 – 37]	25.5 [15 – 41]
'low' baseline BMI group	(n = 52)	(n = 60)
Men, n (%)	28 (54)	31 (52)
Age (yr)		
Mean ± SD	72.2 ± 8.4	74.9 ± 7.0
MMSE		
Mean ± SD	24.4 ± 2.4	23.9 ± 2.5
Total ADCS-ADL		
Mean ± SD	62.3 ± 11.5	60.7 ± 10.4
Median [range]	65.0 [10 – 77]	63.0 [28 – 78]
BMI		
Mean ± SD	23.4 ± 1.7	23.2 ± 2.6
Median [range]	23.8 [18 – 26]	23.6 [15 – 27]
'high' baseline BMI group	(n = 51)	(n = 40)
Men, n (%)	23 (45)	20 (50)
Age (yr)		
Mean ± SD	74.3 ± 7.1	73.0 ± 7.5
MMSE		
Mean ± SD	23.5 ± 2.6	23.6 ± 2.5
Total ADCS-ADL		
Mean ± SD	61.9 ± 10.5	61.8 ± 11.2
Median [range]	62.0 [36 – 77]	63.0 [29 – 78]
BMI		
Mean ± SD	29.0 ± 2.4	30.8 ± 3.5
Median [range]	28.4 [26 – 37]	30.1 [26 – 41]

ADCS-ADL = Alzheimer's Disease Cooperative Study-Activities of Daily Living (0–78; higher scores indicate greater functioning); BMI = Body mass index; MMSE = Mini-Mental State Examination (0–30; lower scores indicate greater cognitive dysfunction).

Treatment effect on BMI

In the entire study population, data suggested an increased BMI in the active study group versus the control group at Week 24 (ITT: $p = 0.07$; PP: $p = 0.03$), but not at Week 12 (ITT: $p = 0.39$; PP: $p = 0.42$; Figure 1, Table 2).

Table 2

Estimated marginal mean (95% confidence interval) BMI values over 24 weeks for patients receiving active or control product

	Estimated marginal mean BMI in entire study population (ITT)			
	n*	**Control**	**n**	**Active**
Baseline	103	26.1 (25.3 – 26.9)	100	26.0 (25.2 – 26.8)
Week 6	97	26.2 (25.4 – 27.0)	96	26.2 (25.4 – 27.0)
Week 12	97	26.2 (25.4 – 27.0)	98	26.3 (25.5 – 27.1)
Week 24	76	26.2 (25.4 – 27.0)	76	26.4 (25.6 – 27.2)

*Not all patients provided BMI data at all timepoints; BMI = Body mass index; ITT = Intention to treat. Data are back transformed; transformed [square-root] data were squared. 12-week, active versus control: ITT: $p = 0.39$; PP: $p = 0.42$. 24-week active versus control: ITT: $p = 0.07$; PP: $p = 0.03$.

Figure 1

Estimated marginal mean BMI change from baseline over 24 weeks. ITT; back-transformed data
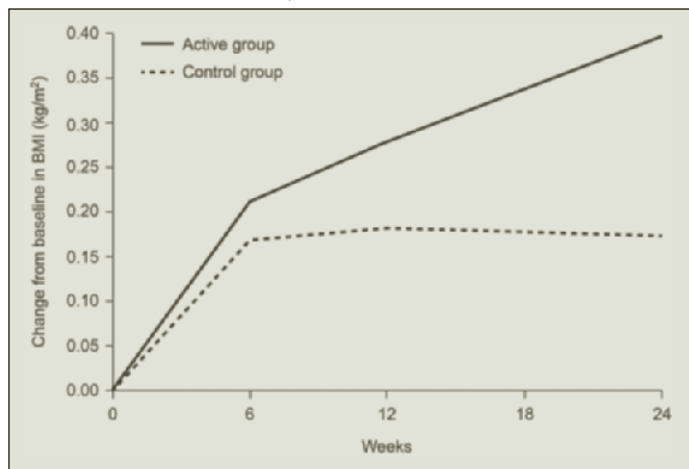
Treatment effect on ADL

Overall, no treatment effect on ADCS-ADL was observed. However, baseline BMI was found to be a significant treatment effect modifier (ITT: $p = 0.04$; PP: $p = 0.05$) indicating that BMI significantly affected the ADCS-ADL response of Souvenaid. In order to study whether this effect was predominantly driven by low or high BMI, patients were divided into two subgroups: those with a baseline BMI less than or equal to the mean (26.2 kg/m²) and those above the mean.

ADL effect in the subgroups of patients with 'high' or 'low' baseline BMI

No intervention effect on ADL outcome was observed in the subgroup of patients with 'high' baseline BMI (Week 12, ITT:

$p = 0.23$; PP: $p = 0.18$, Week 24, ITT: $p = 0.17$; PP: $p = 0.17$). Within the 'low' baseline BMI subgroup, the RMM model indicated an increase of ADCS-ADL scores at Week 12 in the active study group versus the control group (ITT: $p = 0.02$; PP: $p = 0.04$). However, no significant difference was observed at Week 24 (ITT: $p = 0.20$; PP: $p = 0.10$; Figure 2, Table 3).

Table 3

Estimated marginal mean (95% confidence interval) ADCS-ADL scores over 24 weeks for patients receiving active or control product with a 'low' (≤ mean) baseline BMI

	Estimated marginal mean ADCS-ADL in 'low' BMI subgroup (ITT)			
	n	**Control**	**n**	**Active**
Baseline	52	63.5 (60.6 – 66.2)	60	61.7 (58.8 – 62.4)
Week 6	50	64.5 (61.6 – 67.2)	57	63.4 (60.7 – 66.1)
Week 12	49	62.7 (59.7 – 65.6)	56	63.9 (61.1 – 66.6)
Week 24	37	62.5 (59.1 – 65.7)	45	62.6 (59.4 – 65.6)

ADCS-ADL = Alzheimer's Disease Cooperative Study-Activities of Daily Living (0–78; higher scores indicate greater functioning); BMI = Body mass index; ITT = Intention to treat. 12-week active versus control: ITT: $p = 0.02$; PP: $p = 0.04$; 24-week active versus control: ITT: $p = 0.20$; PP: $p = 0.10$. Data are back transformed; transformed [squared] data underwent a square-root calculation.

Figure 2

Estimated marginal mean ADCS-ADL change from baseline over 24 weeks in the subgroup of patients with 'low' (≤ mean) baseline BMI. ITT; back-transformed data
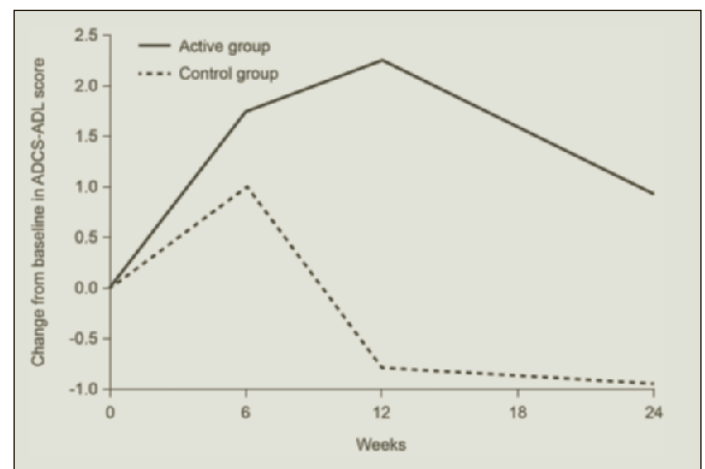
Exploratory analyses using contrast statements were conducted to further investigate the effect of treatment on ADL response in patients with 'low' baseline BMI. When baseline ADCS-ADL was contrasted against all post-baseline assessments, no significant treatment effect was observed (ITT: $p = 0.08$, PP: $p = 0.13$). There was an apparent placebo effect observed at Week 6 on the ADCS-ADL (illustrated in Figure 2). To adjust for this, the baseline and Week 6 ADCS-ADL scores were combined and contrasted against the Week 12 and Week 24 ADCS-ADL scores (combined). This exploratory analysis showed a significant treatment effect (ITT: $p = 0.03$,

PP: p = 0.01) suggesting that the effect of Souvenaid versus control on ADL performance within the 'low' BMI subgroup may only be observable after at least 6 weeks of treatment.

Sensitivity analyses showed that the results were independent of transformation used and type of covariance structure chosen.

Discussion

In addition to the effects of Souvenaid on memory performance described previously (12), this report presents the positive effect of the multi-nutrient product on BMI. In addition, the modeling analyses presented here indicated that baseline BMI significantly influenced the effect of Souvenaid on ADCS-ADL performance, and that Souvenaid improved ADCS-ADL in a subgroup of mild AD patients with 'low' baseline BMI.

This is the first study to suggest that increased BMI can be achieved with a specific combination of nutrients, independent of the energy content of the product, in patients with mild AD. The influence of omega-3 fatty acids on body weight and BMI in patients with mild to moderate AD has been previously reported (23). However, weight loss is more likely to occur in patients with mild to moderate AD versus a mild AD population (14). A study conducted by Faxén-Irving et al. (23) showed that an increase in body weight correlated with an increase in Neuropsychiatric Inventory (NPI) appetite score, although food intake data were not collected (23).

There was insufficient variance in the NPI appetite scores in the current study to investigate the correlation with BMI. Food intake was not measured and so the extent to which this factor may have contributed to the improved BMI is not known. Unpublished preclinical studies of iso-caloric diets with and without the specific nutrient mixture Fortasyn™ Connect have shown that body weight increases as a result of this nutrient combination. These results suggest that the observed increase in BMI may be independent of energy intake. The mechanism by which Fortasyn™ Connect contributes to improved BMI warrants clarification in future research. At present we can only speculate: it may be that changes in the basal metabolic rate or activation of biochemical pathways contribute to an increase in BMI. Alternatively, improved lifestyle and eating habits may also have resulted in increased BMI. Methods to investigate these hypotheses should be incorporated into future clinical studies.

ADCS-ADL performance was significantly improved in a subgroup of patients with 'low' baseline BMI. Additional analyses showed that the treatment effect appeared to be primarily driven by an improvement in instrumental ADL rather than basic ADL (data not shown). Deficits in instrumental ADL are known to occur in the early stage of AD (13) and have been associated with disease progression (24).

Previous research has demonstrated that among community-dwelling patients with AD, those with a lower BMI and nutritional status exhibit a faster decline in functional capability (25, 26). The impact of Souvenaid on ADL performance in the 'low' BMI subgroup may therefore be due to the faster natural decline in this subgroup presenting a greater opportunity for improvements in functional performance. Furthermore, decreased activity, reduced metabolic cell mass, and lower energy expenditure in the elderly result in reduced dietary intake and a lower intake of nutrients (27). This may also help to explain the functional treatment effect bestowed by the nutrient formulation (Fortasyn™ Connect) in Souvenaid. However, it should be noted that the statistical phenomenon of linear regression to the mean could also have contributed to the apparent treatment effect. This effect should therefore be regarded as an exploratory finding.

The mean BMI for the 'low' baseline BMI subgroup was 23.3 kg/m^2, which can be regarded as suboptimal, as previous research has shown a BMI < 23 kg/m^2 to be associated with poorer 7-year survival in patients with AD (23, 28). In addition, a BMI of ≤ 23.5 kg/m^2 has been defined as one of the contributing factors to frailty in elderly people (29). However, BMI itself should not be considered a complete measure of nutritional status, and the follow-up studies with Souvenaid will include other parameters to obtain a more comprehensive overview of the patient's nutritional status.

The results presented here suggest that baseline BMI is a predictor of ADL outcome. The data indicated that patients with lower BMI at baseline may benefit more from Souvenaid, with respect to functional outcome, than those with higher baseline BMI. In addition, there was a suggestion that Souvenaid improved BMI in the entire study population. The current observations may be important for clinical care.

These findings warrant confirmation in larger, more highly powered, controlled clinical studies in which subgroups of patients with worsening nutritional status receive further attention. These studies will include measures to confirm and extend the observed BMI-dependent effects of Souvenaid on ADL performance and will provide more data on the nutritional status of the patients.

References

1. Rosenstein LD. Differential diagnosis of the major progressive dementias and depression in middle and late adulthood: a summary of the literature of the early 1990s. Neuropsychol Rev. 1998 Sep;8(3):109-67.
2. Selkoe DJ. Alzheimer's disease is a synaptic failure. Science 2002;298:789-91.
3. Terry RD. Alzheimer's disease and the aging brain. J Geriatr Psychiatry Neurol. 2006 Sep;19(3):125-8.
4. Wurtman RJ, Ulus IH, Cansev M, et al. Synaptic proteins and phospholipids are increased in gerbil brain by administering uridine plus docosahexaenoic acid orally. Brain Res. 2006 May 9;1088(1):83-92.
5. Cansev M, Wurtman RJ, Sakamoto T, et al. Oral administration of circulating

precursors for membrane phosphatides can promote the synthesis of new brain synapses. Alzheimers Dement. 2008 Jan;4(1 Suppl 1):S153-68.

6. Cansev M, Wurtman RJ. Chronic administration of docosahexaenoic acid or eicosapentaenoic acid, but not arachidonic acid, alone or in combination with uridine, increases brain phosphatide and synaptic protein levels in gerbils. Neuroscience. 2007 Aug 24;148(2):421-31.

7. Van Wijk NW, Böhlke M, Maher TJ, et al. Combined dietary vitamins B6, B12, and folate increase plasma choline levels in rats. Abstract. 2011;10th International Conference of Alzheimer's and Parkinson's Diseases (AD/PD), Spain, Barcelona:Program number: 194.

8. Broersen LM, De Wilde M, I. L, et al. Reduced beta-amyloid plaque burden and neurodegeneration in APP/PS1 transgenic mice following multi-nutrient dietary intervention. Society for Neuroscience (San Diego, CA). 2007;Programme number 157.116/U127.

9. Barberger-Gateau P, Raffaitin C, Letenneur L, et al. Dietary patterns and risk of dementia: the Three-City cohort study. Neurology. 2007 Nov 13;69(20):1921-30.

10. Luchsinger JA, Tang MX, Miller J, et al. Relation of higher folate intake to lower risk of Alzheimer disease in the elderly. Arch Neurol. 2007 Jan;64(1):86-92.

11. Shatenstein B, Kergoat MJ, Reid I. Poor nutrient intakes during 1-year follow-up with community-dwelling older adults with early-stage Alzheimer dementia compared to cognitively intact matched controls. J Am Diet Assoc. 2007 Dec;107(12):2091-9.

12. Scheltens P, Kamphuis PJ, Verhey FR, et al. Efficacy of a medical food in mild Alzheimer's disease: A randomized, controlled trial. Alzheimers Dement. 2010 Jan;6(1):1-10 e1.

13. Barberger-Gateau P, Commenges D, Gagnon M, et al. Instrumental activities of daily living as a screening tool for cognitive impairment and dementia in elderly community dwellers. J Am Geriatr Soc. 1992 Nov;40(11):1129-34.

14. White H, Pieper C, Schmader K. The association of weight change in Alzheimer's disease with severity of disease and mortality: a longitudinal analysis. J Am Geriatr Soc. 1998 Oct;46(10):1223-7.

15. Guerin O, Andrieu S, Schneider SM, et al. Different modes of weight loss in Alzheimer disease: a prospective study of 395 patients. Am J Clin Nutr. 2005 Aug;82(2):435-41.

16. Faxen-Irving G, Basun H, Cederholm T. Nutritional and cognitive relationships and long-term mortality in patients with various dementia disorders. Age and Ageing. 2005 Mar;34(2):136-41.

17. Spaccavento S, Del Prete M, Craca A, et al. Influence of nutritional status on cognitive, functional and neuropsychiatric deficits in Alzheimer's disease. Arch Gerontol Geriatr. 2009 May-Jun;48(3):356-60.

18. Ousset PJ, Nourhashemi F, Reynish E, et al. Nutritional status is associated with disease progression in very mild Alzheimer disease. Alzheimer Dis Assoc Disord. 2008 Jan-Mar;22(1):66-71.

19. Cook Z, Kirk S, Lawrenson S, et al. Use of BMI in the assessment of undernutrition in older subjects: reflecting on practice. Proc Nutr Soc. 2005 Aug;64(3):313-7.

20. (CHMP) CfMPfHU. Guideline on Medicinal Products for the Treatment of Alzheimer's Disease and Other Dementias (Document CPMP/EWP/553/95 Rev 1). London, UK: European Medicines Agency; 2009.

21. Mohs RC, Knopman D, Petersen RC, et al. Development of cognitive instruments for use in clinical trials of antidementia drugs: additions to the Alzheimer's Disease Assessment Scale that broaden its scope. The Alzheimer's Disease Cooperative Study. Alzheimer Dis Assoc Disord. 1997;11 Suppl 2:S13-21.

22. Galasko D, Bennett D, Sano M, et al. An inventory to assess activities of daily living for clinical trials in Alzheimer's disease. The Alzheimer's Disease Cooperative Study. Alzheimer Dis Assoc Disord. 1997;11 Suppl 2:S33-9.

23. Irving GF, Freund-Levi Y, Eriksdotter-Jonhagen M, et al. Omega-3 fatty acid supplementation effects on weight and appetite in patients with Alzheimer's disease: the omega-3 Alzheimer's disease study. J Am Geriatr Soc. 2009 Jan;57(1):11-7.

24. Gauthier S, Lopez OL, Waldemar G, et al. Effects of donepezil on activities of daily living: integrated analysis of patient data from studies in mild, moderate and severe Alzheimer's disease. Int Psychogeriatr. 2010 Sep;22(6):973-83.

25. Galanos AN, Pieper CF, Cornoni-Huntley JC, et al. Nutrition and function: is there a relationship between body mass index and the functional capabilities of community-dwelling elderly? J Am Geriatr Soc. 1994 Apr;42(4):368-73.

26. Guerin O, Soto ME, Brocker P, et al. Nutritional status assessment during Alzheimer's disease: results after one year (the REAL French Study Group). J Nutr Health Aging. 2005;9(2):81-4.

27. de Jong N, Chin APMJ, de Groot LC, et al. Functional biochemical and nutrient indices in frail elderly people are partly affected by dietary supplements but not by exercise. J Nutr. 1999 Nov;129(11):2028-36.

28. Faxen-Irving G, Basun H, Cederholm T. Nutritional and cognitive relationships and long-term mortality in patients with various dementia disorders. Age Ageing. 2005 Mar;34(2):136-41.

29. Chin A Paw MJ, Dekker JM, Feskens EJ, et al. How to select a frail elderly population? A comparison of three working definitions. J Clin Epidemiol. 1999 Nov;52(11):1015-21.