Nutritional care in old age:

the effect of supplementation on nutritional status and performance

Marleen Manders

Promotoren

Prof. dr. W.A. van Staveren
Hoogleraar Voeding van de Oudere Mens, Afdeling Humane Voeding, Wageningen Universiteit

Prof. dr. W.H.L. Hoefnagels
Hoogleraar Klinische Geriatrie, Kenniscentrum Geriatrie, Radboud Universiteit Nijmegen

Copromotor

Prof. dr. ir. C.P.G.M. de Groot
Hoogleraar Voedingsfysiologie met bijzondere aandacht voor het Verouderingsproces en de Oudere Mens, Afdeling Humane Voeding, Wageningen Universiteit

Samenstelling promotiecommissie

Dr. M.G. Wilson
Saint Louis University School of Medicine, USA

Prof. dr. J.M.G.A. Schols
Universiteit Maastricht en Universiteit van Tilburg

Prof. dr. J.J. van Binsbergen
Radboud Universiteit Nijmegen

Prof. dr. E.G. Schouten
Wageningen Universiteit

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Voeding van de oudere mens:

het effect van supplementen op de voedingstoestand en op de functionaliteit

Marleen Manders

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Voor Ralf

Je bent een kanjer!

Abstract

Malnutrition is frequently observed in elderly people living in nursing homes and homes for the elderly. Anorexia resulting in inadequate dietary intake is often a cause of malnutrition. Malnutrition in old age affects several aspects of functioning. Earlier research has shown that a complete supplement improves nutritional status. These studies were however not sufficiently powerful to investigate an effect of such a supplement on functioning. Yet, positive results of a pilot study pointed in that direction. In this thesis we assumed that improving nutritional status by nutritional supplementation could lead to improvement in functioning, following improved total dietary intake, without affecting habitual intakes.

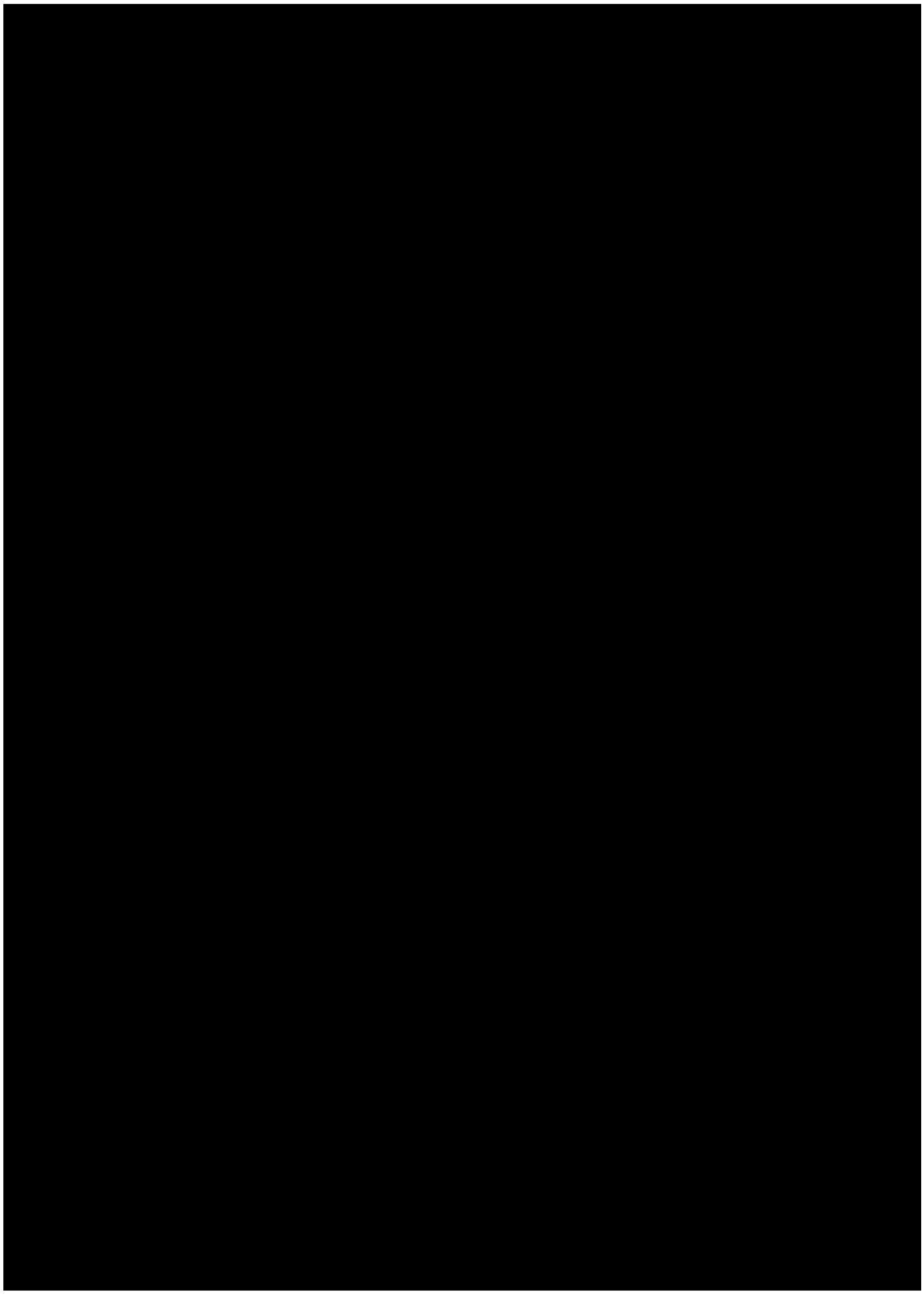
In the current study residents of nursing homes and homes for the elderly were participating in a 24-week, randomised, double-blind, placebo-controlled intervention trial (n=176). They randomly received either a nutrient dense drink or a placebo drink twice a day in addition to their usual diet. Two packages of the nutrient dense drink contained 250 kcal and vitamins, minerals and trace elements at the level of 25 to 175% of the Dutch RDA. The placebo drink contained no energy and no vitamins and minerals.

Using the complete supplement appeared to have a beneficial effect on dietary intake. The change in total energy intake was some 0.8 MJ/day higher in the supplement group than that in the control group ($p=0.166$). Moreover, a significantly favourable effect ($p<0.001$) was observed for the intake of vitamins and minerals. Hereby the supplement group did not appear to compensate their regular intakes for the energy content of the provided supplements. The positive effect on dietary intake was supported by changes in nutritional status, because markers of nutritional status of the intervention group compared favourably with those of the placebo group. These changes showed amongst others a positive effect of the intervention drink on body weight (1.6 kg difference in change; $p=0.035$), calf circumference (0.9 cm difference in change; $p=0.048$), and blood values (e.g. Hcy decreased from 16.8 to 11.2 μmol/L in the supplement group). In the study population no significant effect was found on functionality outcomes, including cognitive function, mood, physical performance and the ability to perform activities of daily living. However, a subgroup of participants with BMI at baseline below 24.4 kg/m² performed better on the cognitive subscale of the Alzheimer's Disease Assessment Scale ($p=0.09$), and its language sub score ($p=0.01$) after 24 weeks of intervention.

To prevent serious malnutrition it is advocated to regularly weigh institutionalised elderly and use a short questionnaire for decreased appetite. With these instruments the development of malnutrition can be detected early and if indicated preventive action can be taken. Future research should be focused on efficient implementation of the used food supplement in every day practice. Nutrition policy should be focused on improvement of usual diet as well as temporarily providing nutritional supplements if indicated. From the findings of our intervention trial we conclude that the applied supplement is effective for counteracting the development of malnutrition in this population. Furthermore, the results of this trial suggest that it is effective as treatment for decreasing function in a subgroup of institutionalized elderly people with low BMI.

Contents

Chapter 1	Introduction	11
Chapter 2	Effectiveness of nutritional supplements on cognitive functioning in elderly persons: a systematic review	25
Chapter 3	Effect of a nutrient enriched drink on dietary intake and nutritional status in institutionalised elderly	43
Chapter 4	The effect of a nutrient dense drink on mental and physical function in institutionalized elderly people	67
Chapter 5	Homocysteine and cognitive function in institutionalised elderly: a cross-sectional analysis	87
Chapter 6	General discussion	103
Samenvatting		119
Dankwoord		125
About the author		131



1 Introduction

Disability is a complex phenomenon which is the outcome of interactions between health conditions (diseases, disorders and injuries) and contextual factors, like internal personal factors and external environmental factors. The impact of health and disability on day-to-day-life can be assessed by the International Classification of Functioning, Disability and Health (ICF) published by the World Health Organization (WHO). Human functioning is classified by ICF at the following three levels: body or body part, the whole person, and the whole person in a social context.[1] Disability therefore involves dysfunctioning at one or more of these same levels: impairments, activity limitations and participation restrictions. In elderly people impairment of body functions could be present as decreased muscle function, a decline in impaired immune function, bone health, loss in sensory aspects like vision and hearing or impaired cognitive performance. Institutionalised elderly people are the most vulnerable group of the elderly population. Besides the process of biological aging they suffer from a variety of chronic medical conditions and experience unfavourable contextual factors both leading to disabilities, and can therefore be classified as frail elderly.[2] In frail elderly multisystem impairment is likely and might lead to difficulties in executing activities: in the WHO framework defined as activity limitations. Dependency on health care might be increased and quality of life decreased when these limitations are present. Reductions in the incidence and severity of disability in elderly people could have a positive influence on both population and individual level. On the population level providing sufficient and suitable care to elderly people is demanding for health professionals and family caregivers and is accompanied by high costs for (public) health care. Moreover, on the individual level an improvement in quality of life could be very important. Therefore, an important aim in gerontologic research is to reduce disability in old age.

Causes of disability are besides biological aging and chronic diseases, modifiable factors such as malnutrition and decreased physical activity (figure 1). This PhD thesis will focus on possibilities to counteract a decline in physical and mental functioning in institutionalised elderly by combating malnutrition, through improvement of nutritional intake. In this chapter we first describe the population of institutionalised elderly in the Netherlands and the risk factors of malnutrition and inadequate nutritional intake. Subsequently we will describe the relation between malnutrition and decreased

functioning and different possibilities for interventions counteracting this decrease. In figure 1 a simplified overview of these relations is depicted.

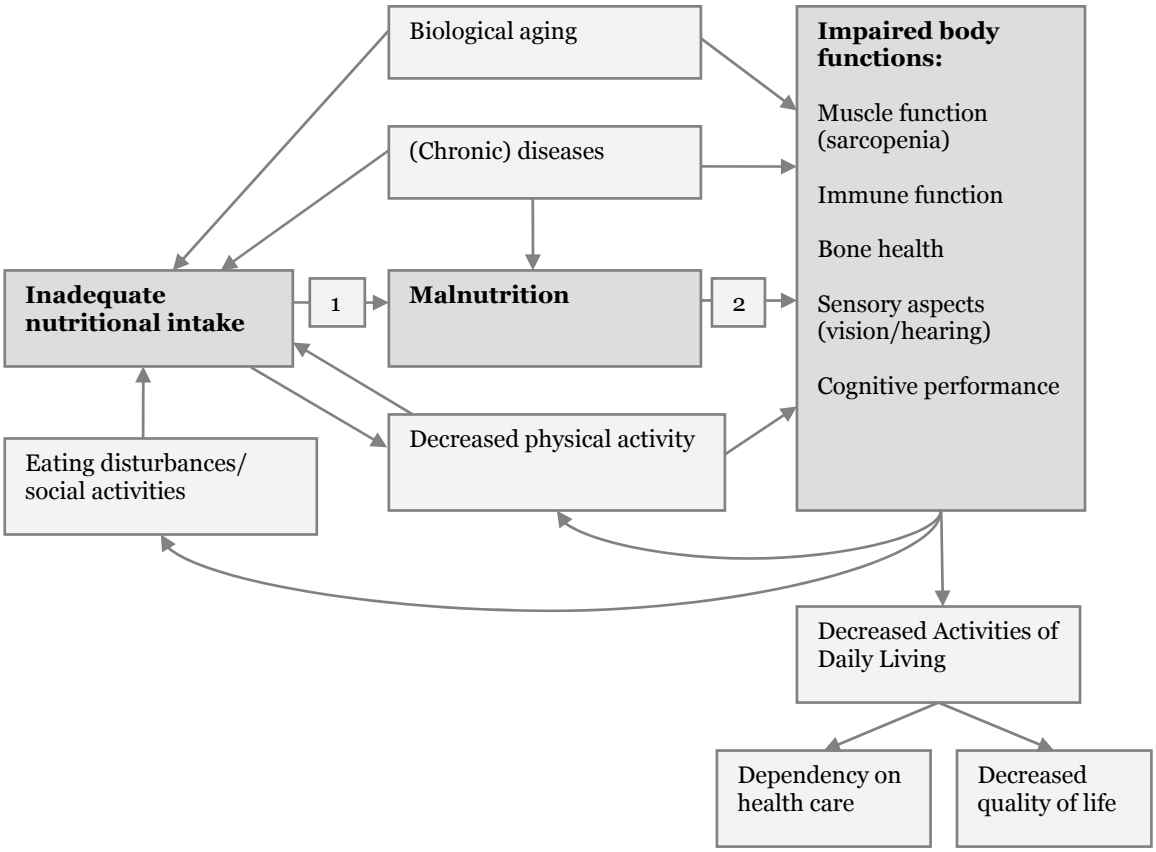


Figure 1 **Simplified overview of possible relations on different levels of the development of dependency on health care and decreased quality of life, hypotheses investigated in this thesis are indicated by numbers (1, 2)**

Institutionalised elderly in the Netherlands

If elderly people require more care than merely family care, assistance by home care services and assist-living facilities is indicated. In case people cannot live any longer independently, admission to an institute for chronic care is inevitable. In the Netherlands two types of chronic care institutes exist: homes for the elderly and nursing homes. In both types of institutes professional care is available for 24 hours a day. This includes nursing service and social assistance for activities of daily living and household management, central meal preparation and distribution of drugs. In homes for the elderly a family physician is responsible for medical care in contrast to the nursing homes where medical care is provided by a nursing home physician. Nursing homes only provide continuous long-term care to elderly people if it is not possible to provide

adequate informal and formal care to elderly people at home.[3] In 2003 over 100,000 Dutch elderly people lived permanently in homes for the elderly (n=574). In nursing homes (n=335) almost 58,000 beds are available for elderly people. Of the Dutch elderly people aged 65-79 years in 2003 (n=1,676,486), 2% was living in an institute for chronic care. In the group of elderly people aged 80 years and over (n=543,970) this percentage increased to 18%.[4]

Prevalence of chronic diseases and disorders among institutionalised elderly is higher than among free-living elderly people. Furthermore, mobility is limited and malnutrition (see Box) is a common and serious problem in elderly people.[5] These factors all affect functioning (figure 1).

In summary, a considerable part of the Dutch elderly people is institutionalised and this population is vulnerable. Research to reduce disability is important, because this reduction will lead to less dependency on health care and better quality of life.

Definition of malnutrition and its causes

Malnutrition could be defined as different deviations from the normal nutritional state.[6] Prevalence of malnutrition depends on which definition is used. In this thesis malnutrition refers to a state of undernutrition. Possible definitions of undernutrition are given in the box below.

Often used definitions of malnutrition reflecting undereating:[7]

- Historical unintentional weight loss (e.g. 10% in last 6 months or 5% in last month);
- Biochemical deficiencies of nutritional indicators (e.g. serum albumin, cholesterol, vitamins);
- Low score on screening instruments (specially developed for geriatric patients) for protein-energy malnutrition (e.g. MiniNutritional Assessment (MNA) or Sadness, low Cholesterol, low Albumin, Loss of weight, Eating problems, Shopping problems (SCALES)).

The prevalence of malnutrition as defined by MNA in European institutionalised elderly is about 37%.[8]

In the Netherlands institutionalised elderly are far more often malnourished (defined by biochemical variables in blood) than free-living elderly people[9] and they have often an inadequate nutritional intake: low intake of energy (5.9-6.6. MJ/day) and micronutrients (e.g. thiamine, riboflavin, vitamin B_6, vitamin C).[10-12] These intakes are much lower than in independently living older people especially for energy, vitamin C and vitamin B_6 intake.[10,13] In the Netherlands multidisciplinary guidelines have been developed for fluid and food supply to improve the nutritional status of patients indicated for nursing home care; however the impact of this guideline on the prevalence of malnutrition is not yet known.[14]

Inadequate nutritional intake is the predominant cause of malnutrition in older persons (figure 1).[15,16] Other causes of malnutrition are impaired digestion (caused by medical conditions e.g. atrophic gastritis or gastrointestinal tumours) and increased requirements during chronic diseases like dementia and acute diseases like infections.

Malnutrition as a result of inadequate nutritional intake (quantity and/or quality) during aging could be a consequence of decreased physical activity (lower need for energy from food), anatomical changes (loss of tooth, swallow or chewing problems), physiological changes (diminished smell and taste performance), satiety related hormonal changes (e.g. leptin), medicine use, malignancies, dementia and depression, and social causes (isolation, stressful life event, poverty) (figure 1).[7,16]

In summary, malnutrition is a common problem in institutionalised elderly and has many different causes. Inadequate nutritional intake is a cause, often observed.[13,15,16]

Malnutrition and its consequences for functioning

Inadequate nutritional intake and a fragile condition in elderly people may lead to increased morbidity and mortality.[17-19] Furthermore, in general a marginal nutritional status and physical inactivity are positively associated with a decline in functioning, followed by an increase in dependency on health care in performing activities of daily

living (figure 1).[20,21] More specifically, deficiencies of several micronutrients are related to different aspects of functioning.[22]

Physical functioning

The biological aging process results in body composition changes (e.g. less muscle mass) and impairs body functions, which might lead to disability. As pointed out in figure 1, physical activity and dietary habits have an additional influence on the decrease in functioning. Institutionalised elderly often have a sedentary lifestyle and consequently this results in loss of fat free mass (muscle mass), muscle strength and therefore in functional disorders and frailty.[23] For full muscle function physical activity and a proper diet with adequate amounts of proteins, minerals and vitamins is required.[22,24] Especially circulating vitamin D levels (via calcium and phosphorus) are associated with muscle function.[22,25] Decreased physical activity will also influence the immune system, which is associated with dietary intakes of protein, vitamin B_6, zinc and the anti-oxidants vitamin E and vitamin C.[26] For two other body functions, bone health and sensory aspects (vision and hearing), an effect of malnutrition has also been suggested. Several nutrients are associated with these determinants and nutritional deficiencies may lead to a decrease in functioning.[27-29]

Mental functioning

Another important determinant of functioning is cognitive performance. Cross-sectional studies have shown that low blood levels of certain nutrients are associated with impaired cognitive performance in elderly people.[30-32] Longitudinal studies have shown that persons with suboptimal nutritional status appear to be at a higher risk for development of cognitive impairment.[33-35] Jorissen and Riedel[36] and Gonzalez-Gross and colleagues[37] reviewed nutrition-related risk factors for cognitive impairment. They found that nutritional factors such as amino acids, antioxidants, lipids, and B vitamins appear to be related to cognitive decline. Recent studies in Alzheimer's disease patients[38,39] and healthy, community-dwelling elderly[40,41] did not find an effect of nutritional supplementation on cognitive outcome measures. However, a recent study in frail elderly by Wouters-Wesseling and colleagues[42] did show that nutritional intervention for 6 months significantly improved scores on a word learning test and a category fluency test.

In this thesis special attention is given to the amino acid homocysteine. The homocysteine level in blood will rise if the intake and/or level of vitamin B_{12}, folate and/or vitamin B_6 is too low and is therefore directly linked to malnutrition. An elevated plasma homocysteine level has been suggested as one of the possible, modifiable risk factors for neuropsychiatric disorders, such as cognitive impairment.[32,43,44]

There are some plausible biological mechanisms that might explain the relation between homocysteine and cognitive performance. One of the hypotheses is that cognitive impairment is caused by hypomethylation of methyl-acceptors like myelin, neurotransmitters and membrane-phospholipids.[22,45] Besides that, a methyl donor deficiency may disturb the repair of DNA damage by oxidative stress.[46] Another effect of hyperhomocysteinemia on cognitive performance might be the neurotoxicity of homocysteine.[22,45,47] In this thesis the relation between homocysteine level and cognitive performance will be further explored.

Downward health spiral

As pointed out in figure 1 malnutrition and decreased physical activity have an effect on body functions such as muscle function, immune function, bone health, vision and hearing and cognitive performance. Because a decline in these determinants might influence eating behaviour, social activities and physical activity, which consequently influence dietary intake, a downward health spiral with more nutritional deficiencies and more functional problems is likely to develop.[48] The question is how to counteract this downward health spiral.

In summary, malnutrition in old age affects different aspects of functioning and counteracting it is therefore an important aim in research.

Interventions

Based on figure 1, our hypothesis is that changes in lifestyle (e.g. physical activity, dietary habits) might counteract a decrease in functioning. In this thesis we choose to intervene on nutrition (indicated as 2 in figure 1), because earlier controlled studies with multinutrient supplementation in institutionalised elderly people showed that it is possible to improve nutritional status, whereby improvement of functioning was

inconsistent.[11,49-51] Increasing physical activity in this population is difficult because of functional limitations of elderly people.

One of the possible interventions to counteract the development of malnutrition in elderly people might be accomplished by providing nutritional supplementation (indicated as 1 in figure 1). In this thesis, we define nutritional supplementation as any nutritional intervention aimed at improving the quantity (macronutrients) or quality (micronutrients) of the dietary intake of the participants. This supplementation is possible as enriched drinks on the basis of juice or milk. Another possibility is to provide multivitamin tablets or vitamin injections. In our intervention study we choose to use an enriched milk drink with both macronutrients and micronutrients in physiological doses. In an institutionalised population this combination of nutrients is preferable to only vitamin pills for two reasons: 1) besides the micronutrients added to the supplements they supply energy and macronutrients of which the intake is low in many elderly people, 2) a synthetic preparation is unattractive as it is yet another tablet in addition to regular medication. An extra pill every day may affect compliance of other prescribed medicines.[52] One of the disadvantages of multinutrient supplements is that people could compensate for the energy content of the supplement by replacing items from their usual diet. It is therefore important that a multinutrient supplement is used in addition to the normal diet to ensure that voluntary intake from foods would remain the same and that a supplement will not reduce subsequent food intake. The risk for this energy compensation is considered low, because of an earlier shown impaired ability to regulate food intake by elderly people.[53,54] For elderly people a multinutrient supplement seems to be an appropriate measure to improve their dietary intake and therefore to counteract the development of malnutrition and possibly the consequent decline in functioning. In the last chapter of this thesis we will position our intervention in the context of guidelines for fluid and food supply in Dutch nursing homes which have been developed in 2001 and the implementation of which is strongly encouraged.[14]

In summary, a complete supplement improves nutritional status and is therefore used to reduce disability in the intervention trial described in this thesis.

Rationale of the study

A number of studies have been performed to test the effect of nutritional supplementation on health status. In a recent review Milne and colleagues[55] described almost 50 studies focussing on the effect of oral dietary supplements on nutritional status and clinical outcomes in elderly people. In older people supplementation turned out to produce weight gain. Milne and colleagues concluded that more large-scale trials with better research design are required to investigate the functional benefits of dietary supplementation. In institutionalised elderly the effect of nutritional intervention on functioning has scarcely been studied[11,49-51] and results are inconsistent. In a small randomized, placebo-controlled Dutch pilot study of 12 weeks a complete nutrient-enriched low-volume liquid nutrition supplement improved both body weight and biochemical indicators of nutritional status in nursing home residents (n=42) but no improvement in physical performance was demonstrated due to the small number of participants and probably a too short duration.[12] The positive results from the pilot study and the feasibility of the applied design made us decide to conduct a larger intervention with more participants and a longer period of supplementation. We hypothesized that in this larger study improvement of the nutritional status will lead to an improvement in functioning.

Outline of the thesis

The aim of the randomized, placebo-controlled intervention described in this thesis is to investigate the effect of nutritional supplementation on dietary intake, nutritional status and physical and mental functioning in institutionalised elderly people.

Chapter 2 includes a systematic review in which the existing evidence, based on studies on the effectiveness of nutritional supplementation in improving cognitive function in elderly people is discussed.

Chapter 3 evaluates the effect of a nutrient dense drink on dietary intake of institutionalised elderly, besides a positive effect on body weight and biochemical indicators of nutritional status. Furthermore, we investigate if subjects tend to change their voluntary dietary intake to compensate the energy content of the intervention product.

Chapter 4 reports the effect of a nutrient dense product on physical functioning. Furthermore, we simultaneously investigated the effect of a combination of macronutrients and micronutrients on mental functioning in institutionalised elderly people.

In **Chapter 5** we test the hypothesis of an inverse association between homocysteine and cognitive function in institutionalised elderly.

In the General Discussion (**Chapter 6**) the main findings of our studies are summarized, methodological considerations are portrayed and implications for health care will be given.

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Abstract

Background: The effectiveness of nutritional supplementation in improving cognitive functioning is evaluated in elderly people.

Methods: The authors systematically reviewed randomized controlled trials that compared nutritional supplementation with a placebo treatment. Trials were identified from a MEDLINE search and from reference lists of identified studies and review articles. From each trial, information was gathered on the number and age of persons studied; the type, dosage, and duration of the intervention; and the assessed outcome measures.

Results: From 1086 titles, 571 articles were excluded based on their titles. Of the remaining 467 articles, the abstracts were read and 422 articles were excluded based on information found there. The remaining articles were screened for quality aspects of the study design, leaving 21 proper randomized, controlled trials. These trials are discussed in three groups according to the type of supplementation: multinutrient intervention or single components with or without a putative mechanism. Twelve studies, which were evenly distributed among the three supplement groups, found significantly positive effects of nutritional intervention on cognitive functioning, whereas nine studies did not. None of the studies found a significantly negative effect of nutritional intervention.

Conclusions: Shortcomings in methodology varying from the duration of intervention to outcome measures partly explain discrepancies in findings. Despite the heterogeneity in trial design, the results of this review suggest that nutritional supplements may improve the cognitive functioning of elderly persons and do no harm. Further well-designed studies are needed to support these findings.

2

Effectiveness of nutritional supplements on cognitive functioning in elderly persons: a systematic review

Marleen Manders, Lisette CPGM de Groot, Wija A van Staveren,
Wendeline Wouters-Wesseling, Ans JMJ Mulders,
Jos MGA Schols, Willibrord HL Hoefnagels

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Introduction

The aging population is increasing and the risks for malnutrition and impaired cognitive functioning increase with advancing age. Cognitive problems influence behavior, social activities, and independence, especially in elderly people. Therefore, it is important to evaluate the cognitive functioning of this population. Because malnutrition might influence cognition and a decline in cognitive functioning might influence eating behavior, a vicious cycle with more nutritional deficiencies and more cognitive problems is likely to develop.

The relation between malnutrition and cognitive functioning is complicated. Besides being a cause of cognitive impairment, malnutrition might also be a consequence of it. Cross-sectional studies have shown that low blood levels of certain nutrients are associated with impaired cognitive functioning in elderly persons.[1-4] Longitudinal studies have shown that persons with suboptimal nutritional status seem to be at a higher risk for development of cognitive impairment.[5-7] For this reason, it is important to determine whether cognitive functioning of elderly people would be improved by consumption of a nutritional supplement.

According to the literature, a few factors influence the effectiveness of a nutritional intervention on cognitive functioning: the stage of cognitive decline or nutritional deficiency of the investigated population, the applied nutrient and its dose, and the duration of intervention

Most likely, benefits of nutritional supplementation can be expected mainly early after the onset of cognitive impairment. In later stages, the process of demyelination becomes irreversible and existing neuronal damage is not likely to be reversed.[4,8] It is also hypothesized that the effects will be smaller in apparently healthy persons or those with a more advanced impairment of cognitive status. Therefore, the selection of the target group is important in intervention trials. Based on findings from the literature, it is not clear in which groups of elderly people improvement by nutritional intervention is most effective. Therefore, for this review, we wanted to evaluate studies in healthy elderly volunteers and in elderly patients. In our literature search, we did not select studies for the stage of cognitive decline of the target group they investigated.

In addition, we wanted to determine whether a single nutrient can improve cognitive functioning or whether a combination of more nutrients is needed. Table 1 presents single and mixtures of nutrients with their possible mechanisms in affecting cognition. Jorissen and Riedel[9] and Gonzalez-Gross and colleagues[4] have reviewed nutrition-related risk factors for cognitive impairment. Nutritional factors such as amino acids, antioxidants, lipids, and vitamins seem to have a relation to cognitive decline. The applied doses of the supplemented nutrients also might influence the effectiveness. For this review, we defined nutritional supplements as any nutritional intervention aimed at improving the dietary intake of participants. Therefore, we did not include trials that provided their participants with medication.

Table 1 **Possible mechanisms of food components improving cognitive functioning**

Food Component	Supposed Mechanism
Single and Combined Factors	
B vitamins (folic acid, vitamins B_{12} and B_6)	Hypomethylation hypothesis (direct and possibly acute effect); aberrations in the (B_{12} dependent) trans-methylation reactions[4,31]
	Homocysteine hypothesis (indirect and longer term effect); hypovitaminosis could contribute to hyperhomocysteinaemia → excitotoxicity; high homocysteine → homocysteic acid and cysteine sulphinic acid; endogenous agonists of N-methyl-D-aspartate receptors;[9] this results in neuronal injury and death through excessive glutamate receptor activation[31]
Antioxidants (β-carotene, vitamins C and E)	Oxidative damage on neurites by disturbance in antioxidant balance; antioxidants act synergistically as free-radical scavengers[4,9] Vitamins C and E: protect the muscarinic acetycholine receptor from irreversible inhibition by the endogenous inhibitor or haem[4]
Fatty acids	By altering the membrane fluidity, membrane receptor formation and function, membrane signalling, and surface membrane activity, phospholipids and fatty acids affect the activity of the blood-brain barrier, neurotransmitters, hormones and cytokines[9]
Amino acids	Tryptophan affects serotonine and noradrenaline-dopamine synthesis in the central nervous system[4] Methionine influences transmethylation processes[4]
Foods	
Olive oil and fish[32,33]	Antioxidant compounds (tocopheroles and polyphenoles) in olive oil Fatty acids maintain the structural integrity of neuronal membranes[33]
Complete food	Malnutrition leads to multiple deficiencies; a well-balanced diet, rather than the quantity of individual components or foods, may result in good cognitive function[34]

Furthermore, in studying the relationship between nutritional supplementation and cognitive functioning, besides population selection and diet factors, the duration of the intervention also influences the effectiveness of treatment.

Regarding the fact that cognitive problems are diverse, it is also interesting to know which domain of cognitive functioning is impaired and in which domain improvement by nutrition is possible. Outcome measurements should be selected with care in studies relating diet to cognitive functioning, because of the complexity and multiplicity of cognitive functioning and the impossibility of measuring all cognitive functions using a single study design.

The purpose of our systematic review was to evaluate the existing evidence based on studies on the effectiveness of nutritional supplementation in improving cognitive functioning in elderly persons. We selected only randomized controlled trials of high quality. Therefore, we used a priori defined criteria for selection. Our hypothesis was that cognitive functioning would be improved in elderly people by a complete supplement, as combined factors in the diet cause cognitive decline. The factors we have noted already may influence the effect. We performed a MEDLINE search for articles describing intervention studies on this subject.

Methods

Identification of trials

We conducted a MEDLINE search (using SilverPlatter software, version 3.11; SilverPlatter International, N.V.) from January 1980 to September 2003. Starting with the key words "elderly," "nutrition," and "cognition," we constructed three groups of Medical Subject Headings (MeSH) combined with key words to define our topic. We used another group of MeSH terms and key words to identify only trials. The search strategy was restricted to English, German, French, or Dutch language citations. We also used the check tag "human." In addition, we manually checked the references of selected articles and of some reviews on nutritional supplementation and cognitive functioning.

Inclusion criteria

We identified 1038 potentially eligible trials. If, according to the title, articles did not report on human elderly subjects, an intervention trial, nutritional supplementation, or cognitive function or nutritional status as primary outcomes, we did not consider the studies for our review. We excluded 571 studies accordingly. We further explored the

467 remaining articles by reviewing the abstract. We used the same criteria as for the title screen to exclude abstracts from our review, which ultimately resulted in 47 potentially eligible trials. We scored these articles on quality aspects using a checklist for randomized controlled trials of the Dutch Cochrane Centre, extended with items from the Delphi list.[10] Considering the quality aspects, we excluded 26 articles from the review: 3 were not an intervention study, 14 did not use a placebo treatment, 4 were not double blind, and 4 did not describe a randomization procedure. Later, in Results, we evaluate only the 21 best-conducted trials (randomized, double-blind, placebo-controlled studies).

Data extraction

From each trial we gathered information on the number and age of the persons examined; the description of the investigated population; the type, dosage, and duration of the intervention; and the assessed outcome measures. Our tables summarize this information.

Results

As a result of the literature search, we identified 47 intervention trials. Only 21 of them were randomized, double-blind, placebo-controlled studies. We divided the trials into three groups (multinutrient intervention, single components with putative mechanisms, and single components without putative mechanisms). One group of interventions was performed with multinutrient supplements (table 2). Two of these studies did not find a significant effect although the other two studies did. The second group consisted of interventions with single active components (table 3). In three of these studies, no significant effects were present, and in the other four studies, a positive effect was found on one or more cognitive outcome measures. The trials with specific components with an unknown mechanism in view of cognitive functioning comprise the third group (table 4). Four of the 10 reviewed studies showed no significant effect.

In summary, nine studies found no significant effect of nutritional intervention on cognitive functioning. The 12 remaining studies found significantly positive results. None of the studies found a significantly negative effect of nutritional intervention.

Table 2 **Randomized, double-blind, placebo-controlled, intervention trials (parallel or cross-over) on the effect of multinutrient food supplements on cognitive functioning**

Study	N	Study population	Age (y)	Intervention	Duration	Outcome measures	Results
No sign. effect							
de Jong et al., 2001	130	Free-living frail elderly	≥70 y mean = 78 y	Multiple micronutrient enriched foods*, or placebo	Daily for 17 weeks	2 neuropsychological tests (block-transfer test and reaction time test)	No significant effect of the enriched foods was observed on the 2 neuropsychological tests
Hogarth et al., 1996	87	Elderly medical in-patients	Mean = 83.2 y (energy) Mean = 84.3 y (vitamin) Mean = 81.8 y (E+vit) Mean = 81.3 y (placebo)	750 ml energy (540 kcal) (n = 22), multivitamin supplementation† (n = 20), both energy and vitamin† (n = 24) or placebo (n = 21)	4 weeks	Hodkinson's abbreviated mental test score (MTS)	No significant differences in mental test score between the groups for energy and vitamin supplementation
Positive							
Bryan et al., 2002	211	Healthy younger, middle-aged, and older women	20–30 y (n = 56) 45–55 y (n = 80) 65–92 y (n = 75)	750 µg of folate, 15 µg of vitamin B_{12}, 75 mg of vitamin B_6, or a placebo	Daily for 5 weeks	Alternate forms of standardized tests of cognitive processing resources, memory, executive function, verbal ability, and self-report mood measures	Significant positive effect on some measures of memory performance only, and no effect on mood
Chandra, 2001	86	Apparently healthy, independently living elderly subjects	> 65 y Mean = 75 y (supplement) Mean = 74 y (placebo)	Supplement of trace elements and vitamins‡ (n = 45) or a placebo (n = 41)	Daily for 1 year	Cognitive function consisting of immediate and long-term memory, abstract thinking, problem-solving ability, and attention	Significant improvement in all cognitive tests ($p < 0.001$ to 0.05) except long-term memory recall ($p > 0.1$)

* Supplement contains ≈100% of the Dutch RDA of the vitamins D, E, thiamine, riboflavin, B6, folic acid, B12, and C, and ≈25–100% of the Dutch RDA of calcium, magnesium, zinc, iron, and iodine.
† Supplement contains vitamins A (8000 U), B1 (15 mg), B2 (15 mg), B3 (50 mg), B6 (10 mg), and C (500 mg).
‡ Supplement contains vitamin A (400 RE), β-carotene (16 mg), thiamine (2.2 mg), riboflavin (1.5 mg), niacin (16 mg), vitamin B6 (3.0 mg), folate (400 µg), vitamin B12 (4.0 µg), vitamin C (80 mg), vitamin D (4.0 µg), vitamin E (44 mg), iron (16 mg), zinc (14 mg), copper (1.4 mg), selenium (20 µg), and iodine (0.2 mg).

In each group of studies, we first searched for an overall explanation for the lack of effect. If such an explanation was missing, we further explored the characteristics of the studies without positive effects.

The first group of studies consisted of four trials that addressed the effect of a multinutrient supplement (table 2). Except for the study of Hogarth and colleagues,[11] all participants in these four studies were community-dwelling elderly people. In none of the studies were participants screened for existing vitamin deficiencies or impaired cognitive functioning before the intervention. The interventions in the study by Hogarth and colleagues[11] and the study by Bryan and colleagues[12] were short and involved a mega-dose of vitamins. Conversely, de Jong and colleagues[13] and Chandra[14] investigated a multivitamin supplement during 17 weeks and 1 year, respectively, and did not use high doses. Differences in population, doses, or duration could not explain the difference in effectiveness of the supplements. Typically, the studies that did not show a significant effect used simple, general tests for cognitive functioning. In contrast, positive effects were noted in the studies in which different domains of cognitive functioning were specifically measured. This suggests that the difference in result could be explained in part by the choice of outcome measures. None of the studies in table 2 reported adverse effects of supplementation.

Table 3 lists studies that evaluated the effect of supplying a single nutrient rather than multinutrients. In total, 7 studies of the 21 randomized, double-blind, placebo-controlled trials investigated 1 active component. In four intervention studies, B vitamins (B_1, B_6, and B_{12}) were supplied. In one study, guarana (a Brazilian medicinal plant) was given, in one alpha-tocopherol, and in one inositol. In three of the four positive studies, patients with Alzheimer's disease were examined, and in another study, apparently healthy elderly persons were enrolled. In all studies, participants were on average older than 70 years, except for the study of Galduroz and Carlini[15] in which they were younger. One of the significantly positive studies[16] was a long-term investigation with a supplementation period of 2 years. The period of supplementation in the other three positive studies was 4 or 12 weeks. In the vitamin studies (B vitamins and alpha-tocopherol), a high dose was used (4 to 3000 times the recommended daily allowance). Sano and colleagues[16] used no neuropsychological test battery, in contrast to the outcome measures in the other significantly positive studies. The nutrients that showed

Table 3 **Randomized, double-blind, placebo-controlled intervention trials (parallel or cross-over) on the effect of one single nutrient on cognitive functioning**

Study	N	Study population	Age (y)	Intervention	Duration	Outcome measures	Results
No sign. effect							
Seal et al., 2002	31	Inpatients with serum vitamin B_{12} levels between 100 and 150 pmol/L, without pernicious anemia, other malabsorption disorders, or progressive neurological or terminal illness	Mean = 81.4 y	Oral cyanocobalamin 10 µg (n = 10) and 50 µg (n = 10) or placebo (n = 11)	Daily for 4 weeks	MMSE	There were no significant changes in MMSE
Galduroz and Carlini, 1996	45	Normal, elderly volunteers	> 60 y Mean = 65 y	500 mg brown sugar (placebo) (n = 15), 12.5 mg caffeine (n = 15), and 500 mg guarana (Paulinia cupana is a Brazilian plant) (n = 15)	21 weeks	Cognitive evaluation (Digital Span, free recall, Digital Symbol, cancellation tests, Mosaic test)	No significant cognitive alterations in these volunteers
Nolan et al., 1991	10	Patients with probable or possible Alzheimer's disease (NINCDS-ADRDA criteria)	Mean = 76.3 y	Thiamine at 3 g/d or (lactose) placebo	1 year	MMSE, CERAD neuropsychological battery	No significant differences were found between the placebo and thiamine groups at any point during the study; in both groups, overall means for the MMSE, verbal learning, and naming scores decreased significantly over the 12-month study period
Positive							
Sano et al., 1997	341	Patients with probable Alzheimer's disease of moderate severity (CDR = 2)	Mean = 72.7 y (S) Mean = 73.4 y (AT) Mean = 73.9 y (S+AT) Mean = 73.5 y (placebo)	Selegiline (10 mg a day) (n = 84), alpha-tocopherol (vitamin E, 2000 IU a day) (n = 87), both selegiline and alpha-tocopherol (n = 85), or placebo (n = 85)	Daily for 2 years	Time to the occurrence of any of the following: death, institutionalization, loss of the ability to perform basic activities of daily living, or severe dementia (defined as a CDR of 3)	In patients with moderately severe impairment from Alzheimer's disease, treatment with selegiline or alphatocopherol slows the progression of disease
Barak et al., 1996*	11	Hospitalized Alzheimer patients	Mean = 81.6 y	6 g of inositol or dextrose	Daily for 4 weeks	CAMCOG scores	Language and orientation improved significantly more on inositol than on placebo
Meador et al., 1993*	18	Patients with probable Alzheimer's disease	Mean = 71 y	3 g/day thiamine administered orally or placebo	4 weeks	ADAS, MMSE, CGIC	Thiamine may have a mild beneficial effect in dementia of Alzheimer's type
Deijen et al., 1992	76	Apparently healthy, self-supporting healthy male controls matched for age, plasma pyridoxal-5'-phosphateconcentration, and intelligence score	70–79 y Mean = 73 y	20 mg pyridoxine HCL (n = 38) or placebo (n = 38)	Daily for 12 weeks	Cognitive performance	Positive effects of vitamin B_6 supplementation were only found with respect to memory, especially concerning long-term memory

MMSE = Mini-Mental State Examination; NINCDS = National Institute of Neurological and Communicative Disorders and Stroke; ADRDA = Alzheimer's Disease and Related Disorders Association; CERAD = Consortium to Establish a Registry for Alzheimer's Disease; CDR = Clinical Dementia Rating; CAMCOG = Cambridge Cognitive Examination; ADAS = Alzheimer's Disease Assessment Scale; CGIC = Clinical Global Impression of Change. * Cross-over study.

a positive effect were alphatocopherol, inositol, thiamine, and pyridoxine. However, the study by Nolan and colleagues[17] did not show a positive effect of thiamine. Overall, no clear pattern explains the difference in results between the studies.

In the study of Seal and colleagues,[18] which was a small study population, the short period of intervention or the use of the Mini-Mental State Examination as primary outcome might explain the lack of effect. Galduroz and Carlini[15] investigated apparently healthy, elderly volunteers who were not screened for vitamin deficiencies. This might explain why they did not find any significant alteration in cognitive functioning. The only factor that might explain the lack of effect in the study by Nolan and colleagues[17] is that the study was insufficiently powered, because they included only 10 patients. None of the suggested factors completely explains the difference in effectiveness of the studies.

Galduroz and Carlini[15] used guarana, which was not completely free of adverse effects, because four volunteers showed some discomfort. Overall, in the study by Sano and colleagues,[16] no statistically significant differences occurred in adverse event categories among the four treatment groups. Barak and colleagues[19] reported adverse effects of inositol such as mild insomnia and flatus during the treatment period. Meador and colleagues[20] noted no adverse systemic effects of thiamine. Seal and colleagues,[18] Nolan and colleagues,[17] and Deijen and colleagues[21] reported no data concerning adverse effects.

Table 4 summarizes the findings of the 10 studies performed to investigate the effect of acetyl-L-carnitine (ALCAR). All studies addressed the effect of ALCAR supplementation in persons with mild or moderate cognitive impairment. Here we evaluate the most remarkable characteristics of those studies. One of the six studies with positive findings included participants who were aged 40 years or older. The most recent significantly positive studies were long-term ones that had an intervention period between 6 months and 1 year. The three earlier studies had a much shorter intervention period (4, 6, or 12 weeks). The supplemented dose in all studies ranged from 1 to 3 g/day. Extensive cognitive tests were used as outcome measures in all studies, except for the study by Herrmann and colleagues.[22] For the difference in results in the 10 ALCAR studies, no unambiguous reason can be given.

Table 4 Randomized, double-blind, placebo-controlled, intervention trials (parallel or cross-over) on the effect of ALCAR on cognitive functioning

Study	N	Study population	Age (y)	Intervention	Duration	Outcome measures	Results
No sign. effect							
Thal et al., 2000	197	Subjects with a diagnosis of probable Alzheimer's disease (NINCDS-ADRDA criteria) MMSE 12–26	45–65 y Mean = 58 y	3 g/day acetyl-L-carnitine (ALCAR) (n = 95) or placebo (n = 102)	Daily for 1 year	Primary outcome measures were the Alzheimer's Disease Assessment Scale (ADAS) Cognitive Component and the Clinical Dementia Rating Scale. Secondary measures included the ADAS Non-Cognitive Subscale, the MMSE, an Activities of Daily Living Scale (ADL), and a Clinician-Based Impression of Change (CIBIC)	There were no significant differences between the treatment groups on the change from baseline to endpoint in the intent-to-treat analysis
Thal et al., 1996	419	Subjects with mild to moderate probable Alzheimer's disease (NINCDS-ADRDA criteria) MMSE 13–26	> 50 y Mean = 71 y (placebo), Mean = 72 y (ALCAR)	3 g/day of ALCAR (n = 207) or placebo (n = 212)	Daily for 1 year	ADAS cognitive component and the Clinical Dementia Rating Scale	Overall, both ALCAR- and placebotreated patients declined at the same rate on primary measures during the trial
Rai et al., 1990	36	Patients with dementia of the Alzheimer type	> 60 y Mean = 79.0 y	1 g acetyl-L-carnitine twice daily and placebo	6 months	Battery of neuropsychological tests	Trends for greater improvement in the ALCAR group in relation to the Names Learning Test and a computerized Digit Recall Test, both related to aspects of short-term memory
Herrmann et al., 1990	187	Elderly outpatients with a clinical diagnosis of mild to moderate cognitive decline	60–80 y	1.5 g/day acetyl-L-carnitine (n = 94) or placebo (n = 93)	12 weeks	Clinical global impression Digital symbol substitution test	Statistically significant effects after 12 weeks of treatment on the physician's clinical global impression, not on digital symbol substitution test
Positive							
Brooks et al., 1998 [35]	334	Subjects diagnosed with probable Alzheimer's disease (NINCDS-ADRDA criteria)	Mean = 70.8 y (placebo) Mean = 71.3 y (ALC)	3 g/day acetyl-L-carnitine (ALC) (n = 165) or placebo (n = 169)	Daily for 1 year	Cognitive subscale of ADAS	ALC slows the progression of Alzheimer's disease in younger subjects (< 65 y)
Sano et al., 1992	27	Mild to moderately demented patients with probable Alzheimer's disease (NINCDS-ADRDA criteria)	60–80 y Mean = 71.2 y (placebo) Mean = 67.6 y (ALH)	Acetyl levocarnitine hydrochloride (2.5 g/d for 3 months followed by 3 g/d for 3 months) (n = 13) or placebo (n = 14)	6 months	Tests of memory, attention, language, visuospatial, and constructional abilities	Acetyl levocarnitine group demonstrated significantly less deterioration in timed cancellation tasks and Digit Span (forward) and a trend toward less deterioration in a timed verbal fluency task

NINCDS-ADRDA = National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association; MMSE = Mini-Mental State Examination
* Cross-over study.

Table 4 **Randomized, double-blind, placebo-controlled, intervention trials (parallel or cross-over) on the effect of ALCAR on cognitive functioning (continued)**

Study	N	Study population	Age (y)	Intervention	Duration	Outcome measures	Results
Spagnoli et al., 1991	130	Patients with a clinical diagnosis of Alzheimer's disease	> 40 y Mean = 75.7 y (ALCAR) Mean = 74.7 y (placebo)	Acetyl-L-carnitine 2 g/day (n = 63) or placebo (n = 67)	1 year	14 outcome measures to assess functional and cognitive impairment	Treated group showed a slower rate of deterioration in 13 of the 14 outcome measures, reaching statistical significance for the Blessed Dementia Scale, logical intelligence, verbal critical abilities, long-term verbal memory, and selective attention
Arrigo et al., 1990*	12	Elderly subjects with chronic cerebral lesions	58–65 y Mean = 61.1 y	1.5 g/day acetyl-L-carnitine or placebo	Daily for 4 weeks	Mini-Mental Test, STAI, memory for numbers, memory for words, non-verbal performance, motor performance	Significant differences between drug and placebo were found in memory (number and word tests) and in responses to simple stimuli and the performance of the maze test
Passeri et al., 1990 [36]	60	Elderly suffering from mild mental impairment	> 65 y Mean = 75.1 y (placebo) Mean = 74.0 y (ALCAR)	2 g/day acetyl-L-carnitine (n = 30) or placebo (n = 30)	12 weeks	Complete battery of rating scales and psychometric tests	Acetyl-L-carnitine-treated patients showed statistically significant improvement in the behavioral scales, in the memory tests, in the attention barrage test, and in the Verbal Fluency test
Bonavita, 1986	40	Patients showing neuropsychic signs and/or symptoms of slight–medium intensity, which were consistent with clinical identification of the senile brain	> 65 y 66–85 y Mean = 74.5 y	1 g/day L-acetylcarnitine or placebo	6 weeks	Mental parameters of the senile brain	Short-term, intensive L-acetylcarnitine treatment can determine a significant improvement of the main mental parameters of the senile brain

NINCDS-ADRDA = National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association; MMSE = Mini-Mental State Examination
* Cross-over study.

Thal and colleagues[23] reported 20 different treatment-related adverse effects, but they noted no difference in the number of serious adverse effects between the treatment groups. Thal and colleagues[24] noted no clinically significant supplement-related adverse effects in their earlier study. Herrmann and colleagues[22] found that some central nervous symptoms, such as headache and dizziness, occurred slightly more frequently under the supplement condition than under the placebo condition. Sano and colleagues[25] reported a few adverse effects possibly related to ALCAR treatment (nausea, vomiting, and abdominal discomfort). In their study, Spagnoli and colleagues[26] observed no significant difference either in the incidence rate or severity of adverse effects (agitation was the most common adverse effect) between the experimental and control groups. Rai and colleagues[27] reported nausea and vomiting as adverse effects that may have been related to ALCAR therapy. None of the patients in Arrigo's study reported adverse effects.[28] In the earliest study, adverse effects (insomnia, epigastralgia, and pruritus) were limited in both incidence and intensity and did not cause discontinuation of treatment.[29]

Discussion

We evaluated the existing evidence on the effectiveness of nutritional supplements in improving cognitive functioning of elderly people. Most of the 21 studies included in our review showed significantly positive effects of nutritional supplementation on cognitive functioning. Some adverse effects of guarana, inositol, and ALCAR were reported. These may be clinically irrelevant. Our findings suggest that nutritional supplements may improve and not harm the cognitive functioning of elderly persons and that some supplements may have a positive effect in selected groups of patients.

A weakness of all the reviews concerning the effectiveness of treatment is publication bias as a result of the selective nonpublication of null or negative trials. For this systematic review, we performed a MEDLINE search of the literature. We used carefully determined key words and selection criteria to define our topic. We used the criteria at different stages in the selection procedure of articles for our review. In addition to the MEDLINE search, we manually checked the references of selected articles and some reviews on nutritional supplements and cognitive functioning to yield the best possible literature search.

We reviewed all potentially eligible articles using a checklist for randomized controlled trials by the Dutch Cochrane Centre, extended with items from the Delphi list[10] to select only trials with high-quality designs. In most excluded articles, the methodologic aspects, such as randomization, blindness of treatment, and placebo treatment, were not clearly described. As a result of the selection, we found a wide variety in participants, intervention dose and duration, and applied outcome measures in the performed trials.

Because of the wide variety in the study designs, it is difficult to draw a firm conclusion about which nutrient or combination of nutrients supplied would have a positive effect on which domain of cognitive functioning. No clear pattern emerged to explain the observed positive effects.

The clearest finding was that in the multinutrient studies that did not show positive effects, cognitive functioning was tested using simple, general tests. Conversely, significantly positive effects were found in the multinutrient studies in which functioning was specifically measured on different aspects of cognitive functioning. Martin and colleagues[30] also noted this phenomenon in their review. A possible explanation is the difference between fluid and crystallized abilities. Cognition has two aspects: one is the capacity to apply information learned during the life span (crystallized abilities) and the other reflects information-processing capacities (fluid abilities). The latter are more vulnerable to changes in nutritional status and could be influenced more by B vitamin supplementation.[31] Results of intervention studies, therefore, depend in part on which of the two aspects of cognition is tested. Another aspect influencing the effect is that changes in cognitive functioning by nutrition are subtle. The outcome measures included in intervention trials should be able to detect small changes over time. The use of several different outcome measures in the studies reviewed makes it difficult to interpret the results.

Another interesting aspect of the trials reviewed is the large number of articles on ALCAR, mostly funded by Sigma-Tau Pharmaceuticals (Gaithersburg, MD). A variety of nutritional components may positively influence cognitive functioning. Table 1 lists the putative mechanisms behind these results. In this review, alpha-tocopherol, inositol, and some B vitamins (thiamine, pyridoxine, folate, and B_{12}) had a positive effect on cognitive functioning in some studies. In other studies, vitamin B_{12} and thiamine did not

show this positive effect. In the group of ALCAR studies, six trials found significantly positive effects but the other four did not. Thal and colleagues[23,24] suggest a possible mechanism for the effects of ALCAR. ALCAR's most common function is to shuttle acetyl groups across the inner mitochondrial membrane to be available for oxidation, thereby participating in cellular energy production. In addition, ALCAR appears to play a role in the removal of toxic accumulations of fatty acids from mitochondria. Furthermore, ALCAR functions as a membrane-stabilizing agent. The best way to improve cognitive functioning in elderly persons might be to combine all positive effects of different nutrients, as we hypothesized in the introduction of this review. A proper supply of nutrients is probably more important for cognitive functioning than the availability of a single component.

Besides the selection of outcome measures, other factors that might explain the absence of effect are the size of the study population, the age of the participants, the presence of Alzheimer's disease, and the dose and duration of the intervention. Because of the heterogeneity of the trials and the lack of a clear pattern of explanatory factors, it is difficult to draw a conclusion about the effectiveness of single nutrients in improving cognitive functioning or preventing impairment in elderly persons. Therefore, we conclude that additional high-quality trials are needed to cluster the results in different components of the diet and to suggest firm conclusions about single nutrients. Future trials should be conducted in patients with mild cognitive impairment, because the window of opportunity for effective intervention may be as short as 1 year from the onset of medical symptoms, as Martin and colleagues[8] suggested. The duration of administration of the nutrient should be long enough to counteract reversible damage processes to the brain. In designing a trial, researchers should keep in mind which possible nutritional mechanism underlies their study. For the outcome measures, the most ideal situation would be that researchers in the field would use one standard neuropsychological battery of sensitive tests. Comparing studies would become easier and more accurate. Finally, dose–response relationships of nutrients should be investigated to determine an optimal dose for improving cognitive functioning.

Our results suggest that nutritional supplements may improve the cognitive functioning of elderly persons and do no harm. A great opportunity exists to conduct well-designed studies to support these findings.

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Abstract

Objective: To determine whether nutritional supplementation (energy and micronutrients) in institutionalised elderly has a positive effect on dietary intake and nutritional status. Subsequently, we investigated if subjects tended to compensate the energy content of the intervention product by decreasing their habitual food consumption.

Design: A 24-week, randomised, double-blind, placebo-controlled, intervention trial.

Setting: Homes for the elderly and nursing homes in the Netherlands.

Subjects: Institutionalised elderly people older than 60 years, with a BMI ≤ 30 kg/m² and a Mini-Mental State Examination score of ten points or higher.

Interventions: In addition to their usual diet the participants (n=176) randomly received either a nutrient enriched drink or a placebo drink twice a day during 24 weeks. Allocation to treatment took into account sex, MMSE score and blood levels of homocysteine in order to limit differences in indicators of health status at baseline in both groups.

Main outcome measures: Anthropometrical measurements were performed and fasting blood samples were collected. Dietary intake data were collected in a sub sample (n=66).

Results: A significantly favourable effect ($p<0.001$) was observed of the intervention drink on vitamin intake, mineral intake and vitamin status in blood (e.g. Hcy decreased from 14.7 to 9.5 µmol/L in the supplement group) as compared to the placebo group for the entire 24-week period. The difference in change in total energy intake between the two treatment groups was 0.8 MJ/day ($p=0.166$). Voluntary energy intake decreased in both groups to the same extent (-0.5 MJ/day), therefore the decrease in intake of the supplement group cannot be considered as compensation for the energy content of the product.

Conclusions: The results of our trial show that this group of institutionalised elderly people do not compensate the energy content of a concentrated nutritional supplement. Therefore, this supplement is effective for counteracting the development of malnutrition in this population.

3

Effect of a nutrient enriched drink on dietary intake and nutritional status in institutionalised elderly

Marleen Manders, Lisette CPGM de Groot, Ybel H Blauw,
Liesbeth van Hoeckel-Prüst, Jacques G Bindels,
Els Siebelink, Wija A van Staveren

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Introduction

Malnutrition is a common and serious problem in elderly people. The prevalence of malnutrition (as defined by MNA) in European institutionalised elderly is about 37%[1] Malnutrition or inadequate nutritional intake in elderly may lead to increased morbidity and mortality.[2,3] Furthermore, a marginal nutritional status is associated with a decrease in functionality and an increase of dependency on care in performing activities of daily living.[4,5]

Weight loss in older persons is predominantly caused by a decline in food intake.[6] The direct cause of (protein-energy) malnutrition in elderly is a lower intake of food rather than higher energy expenditure.[7] Institutionalised elderly people often have a low intake of energy and micronutrients,[8-10] which also leads to micronutrient deficiencies.

Development of malnutrition in the elderly might be counteracted by improvement of dietary intake, e.g. by providing enriched nutritional supplements. A prerequisite for this strategy is that these multinutrient supplements are used in addition to the normal diet and that a supplement will not reduce subsequent food intake and consequently total energy intake. However, short-term (30-90 min) energy regulation in healthy elderly is found to be normal[11] or only slightly impaired[12] compared to young adults. In the study of Zandstra and colleagues[11] incomplete short-term energy compensation (17% to 23%) was found in healthy elderly, which means that at least part of the supplement will be used as extra. After longer periods (three weeks) of over- or underfeeding elderly men did not adjust their voluntary energy intake.[13] Thus, it seems possible to increase energy intake using dietary supplementation.

Studies conducted so far in institutionalised elderly on the effect of nutrient dense products are indicative for increment of dietary intake given the observed improvements in body weight and biochemical indicators of nutritional status.[8,9,14,15] In those studies dietary intake was not assessed[14,15] or only at baseline.[8,9]

Controlled trials on the effect of supplementation on dietary intake are mostly conducted in free-living individuals and either of short duration[16] or without a placebo treatment in the control group.[17-19] Placebo-controlled interventions of 17 to 24 weeks in frail participants by Wouters-Wesseling et al.[20] and De Jong and colleagues[21] did not find a significant effect of nutrient dense products on energy intake.

Three recent studies in free-living as well as institutionalised Alzheimer patients did not use a proper placebo and found contradictory results.[22-24] The three studies that are conducted so far in nursing home residents also showed contradictory results, lacking placebo treatment and/or lack a supplementation period long enough to signal change in energy intake.[25-27]

As part of a larger placebo-controlled study we investigated during 24 weeks, if using a nutrient dense drink has a positive effect on dietary intake of institutionalised elderly, and consequently on body weight and biochemical indicators of nutritional status. Furthermore, we investigated in the present study if subjects tended to change their voluntary dietary intake to compensate for the energy content of the intervention product.

Methods

Study design

The study was a 24-week, randomized, double-blind, placebo-controlled, parallel-group, intervention trial. The study was performed from May 2000 until December 2003, with a phased onset of the study in different institutes for chronic care. At the start and at the end of the intervention period anthropometrical and dietary measurements were performed and fasting blood samples were collected.

Study population

Institutionalised elderly were recruited from nine different institutes for chronic care in the southern part of the Netherlands. The management teams, client councils and Medical Ethics Committees of three nursing home corporations gave their approval. An invitation letter and information on the study protocol was sent to the residents and one of their relatives. For all participants written informed consent was obtained from the participants themselves and/or from one of their legal representatives. The Medical Ethics Committee of Wageningen University approved the study protocol.

Of the 1 050 residents contacted, 265 residents were willing to participate and were actually screened for their eligibility (figure 1).

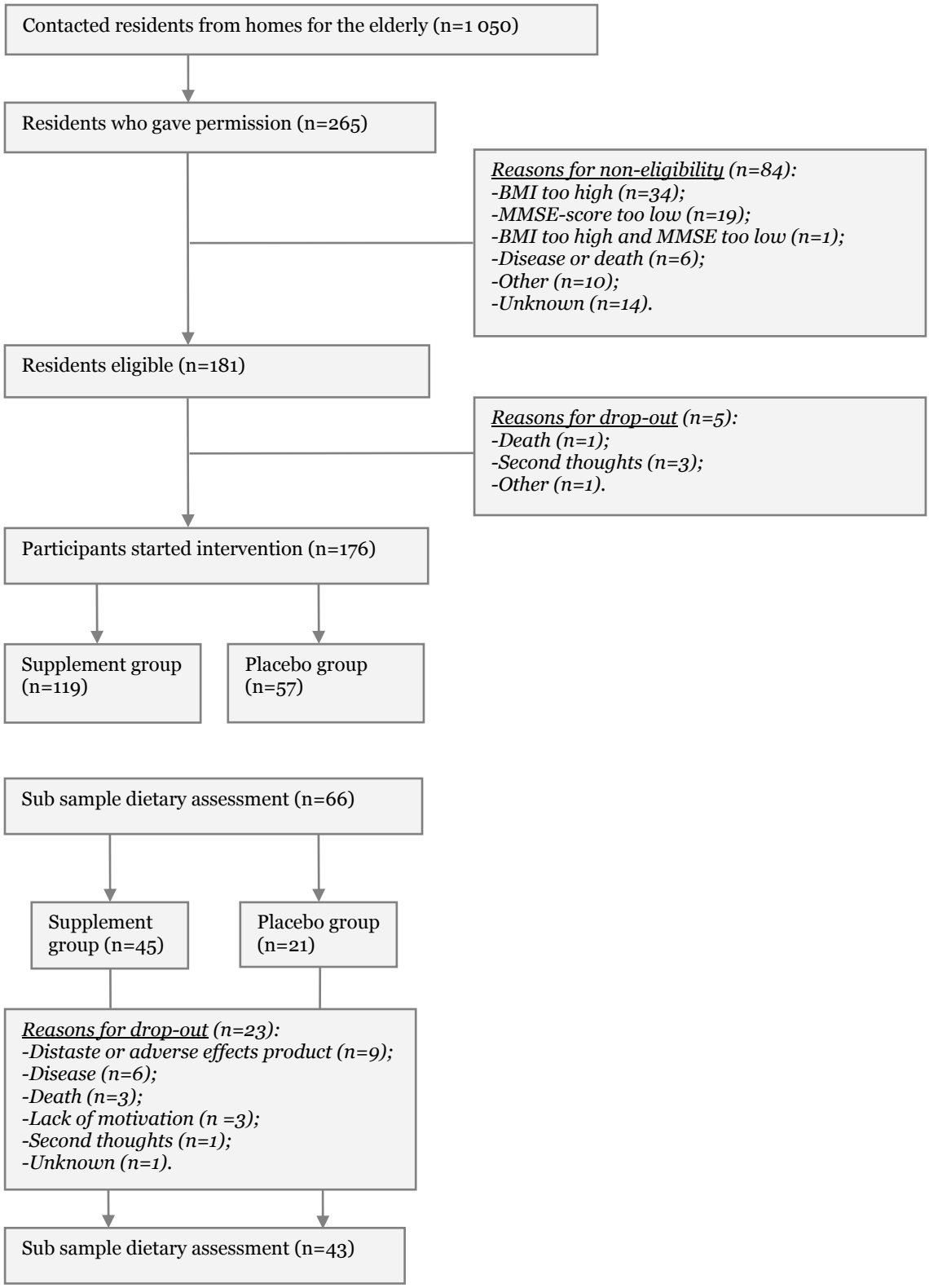

Figure 1 **Flow chart of participants of an intervention trial in Dutch institutionalised elderly people (with an enriched product) and reasons for drop-out**

Subjects meeting the following criteria were included: (1) age ≥ 60 years; (2) institutionalised for at least two months at the start of the intervention; (3) Mini-Mental State Examination (MMSE) score higher or equal to ten points; (4) Body Mass Index (BMI) lower or equal to 30 kg/m^2.

Exclusion criteria were: (1) presence of serious morbidity overruling the study assessments (malignant cancer, severe infectious diseases, use of parenteral food or structural use of tube feeding, disorders of the gastro-intestinal tract, terminal care); (2) presence of interfering co-interventions, in particular medication or supplements with a debilitating influence on the safe administration of the intervention drink.

After screening, 176 participants were randomly allocated to one of two regimens: nutrient dense drink or placebo drink. Allocation to treatment took into account sex, MMSE score (cut-off value for strata: 19 points), and blood levels of homocysteine (cut-off value for strata: 19 μmol/L) in order to limit differences in health status and functioning at baseline in both groups. Two-thirds of the participants used the nutrient dense drink (n=119) and one-third used the placebo drink (n=57). We based this unequal distribution of participants between the two treatment groups on the results of a pilot study in which a positive effect of a comparable intervention drink on nutritional status was found.[9]

In a because of practical reasons not randomly selected sub sample of 66 participants (supplement group: n=45, placebo group: n=21) in the first five institutions dietary intake was assessed by observation.

Intervention

The experimental intervention consisted of the supply of two packages of 125 ml of a complete nutrient enriched dairy drink or a placebo drink during 24 weeks (table 1).

Two packages of enriched drink contained 1.05 MJ (250 kcal). Vitamins, minerals and trace elements were added in amounts of approximately 25 to 175% of Dutch Recommended Daily Allowance (RDA)[28-30] with enhanced amounts of antioxidants.

The placebo drink (125 ml/package) contained no energy or vitamins or minerals but contained water, cloudifier, thickener, flavouring, colorant, and non-caloric sweetener.

Table 1 Composition of the dietary supplement per daily dose

Nutrient		250 ml
Energy	MJ (kcal)	1.05 (250)
Protein	g	8.75
Fat	g	11.25
Carbohydrates	g	28.5
Dietary Fibre	g	4.5
Vitamins		
vit A	µg	240
vit D	µg	13
vit E	mg	70
vit K	µg	80
vit C	mg	250
thiamine	mg	1.9
riboflavin	mg	1.9
niacin	mg NE	14
pyridoxine	mg	2.5
folate	µg	480
vit B_{12}	µg	5.3
pantothenic acid	mg	4.5
biotin	µg	70
Minerals		
Na	mg	80
K	mg	550
Cl	mg	40
Ca	mg	400
P	mg	400
Fe	mg	9
Zn	mg	18
Mg	mg	100
Trace elements		
Cu	mg	3
Mn	mg	4
Se	µg	85
Mo	µg	40
Cr	µg	35
I	µg	150
F	µg	75
Others		
Carotenoids	mg	3
Flavonoids	mg	19
Coenzyme Q10	mg	3

Special efforts were made to improve the comparability of intervention and placebo drinks with respect to their appearance and taste.

Both treatment drinks were available in two different flavours: 'summer fruit' and 'spring fruit'. Numico Research BV (the Netherlands) developed the drinks especially for this and a previous study.[20] One of the researchers (MM) visited the subjects every two weeks to provide them with the drinks. Study participants took their daily dose in addition to their usual diet and were instructed to drink it between meals. Compliance with the study supplement was registered by counting leftovers during the two-weekly home visits. Compliance percentage was quantified as (number of supplements provided – number of supplements returned) / number of supplements provided * 100%.

Data collection

Baseline characteristics

General characteristics

Information on sex, age, length of stay in the (nursing/elderly) home, percentage living alone, percentage currently smoking, educational level (low; completed primary education or

lower vocational education, medium; intermediate vocational or general education, and high; higher vocational training, college or university) and supplement use was collected from the personal file kept for each participant at the institution. Information on the number of chronic diseases was derived from the medical file.

Physical and mental functioning

Nursing personnel scored the activities of daily living (ADL) according to the Barthel Index. The Barthel Index is developed to measure ability to perform ADL and uses a scale from zero to 20; a higher score indicates better functional capacity.

Trained interviewers collected data regarding mental functioning by structured interviews. Mental function questionnaires (MMSE and GDS) were administered by the same interviewer and were conducted at the subject's room, with no other people but the participant and the interviewer around.

The MMSE is based exclusively on the cognitive components of dementia and is considered to have a high reliability and validity.[31] The score ranges from 0 to 30 points.

The Geriatric Depression Scale-15 (GDS) is a short, 15-item instrument specifically developed for the assessment of mood in geriatric populations. It is a reliable and valid self-rating depression screening scale for elderly populations. Questions can be answered with "yes" or "no", with a total score ranging from 0 to 15. Higher scores on GDS indicate the presence of severe depressive symptoms.[32,33]

Dietary intake

Dietary data were collected from the subjects during two weekdays at the start and the end of the intervention period. Trained dieticians used an observation including weighing-back method. For the cooked meal individual menus and recipes of the two days of dietary assessment were obtained from the kitchen staff in advance. In each institute portion sizes of the cooked meal were determined by weighing the separate components of three standard meals. Food consumption at the cooked meal was registered by keeping records of foods and portion sizes served; after the meal leftovers were weighed. The intake from other meals during the day was observed and recorded in terms of household measures and standard portion sizes. Portion sizes of common-consumed items during other meals (like bread and coffee) were determined for each

institute. All foods and beverages consumed outside regular mealtimes were also carefully observed. Dieticians observed the intake of the intervention drinks during dietary assessment days at the end of the intervention period and dietary intake was calculated with the nutrient content of the intervention drink included.

Intake of energy, macronutrients, dietary fibre, vitamins (B-complex, C, D, E and A) and minerals was calculated using the VBS food calculation system (BAS Nutrition Software) based on the Dutch Nutrient Database.[34]

Nutritional status

Anthropometrical assessment

Body weight (kg) was measured to the nearest 0.5 kg before breakfast, with subjects dressed in light clothing and without shoes. Participants who were able to stand were measured with a calibrated mechanical balance (Seca). We used a sitting weighing scale or a calibrated stretcher scale for persons who were not able to stand upright.

Knee-to-floor height (KFH) (cm) of the left leg was measured to the nearest 0.1 cm with the subject in a sitting position. KFH was measured from the anterior surface of the thigh to the floor with ankle and knee each flexed at a 90° angle against the metallic help of a stadiometer. Body height was derived using the following formula: height (in cm)=3.16*KFH (in cm).[35]

With a measuring tape the calf circumference (cm) at the widest part of the left leg was obtained with the subject in a sitting position. Knee and ankle were in an angle of 90 degrees and the calf was relaxed. The calf circumference of some subjects was measured in a lying position; in this situation only the knee was in an angle of 90 degrees. Calf circumference was measured to the nearest 0.1 cm.

Biochemical assessment

Blood samples (one 10 ml gel tube, two 3 ml EDTA tubes and two 5 ml lithium heparin tubes) were collected from subjects in fasting state at the start and the end of the intervention period. Albumin, pre-albumin and C-reactive protein (CRP) concentrations were analyzed with the Dimension® clinical chemistry system. Creatinine was determined by a Synchron LX20. After extraction of vitamin 25-OH-D and other hydroxylated metabolites serum 25-OH-vitamin D was analyzed on basis of

immunoassay with a DiaSorin. Folate and vitamin B_{12} were analyzed with immunoassay (with the Beckman Coulter Access2). Total plasma homocysteine concentration was measured using HPLC (high performance liquid chromatography) with fluorescence detection. Haemoglobin and hematocrit were analyzed within 24 hours at the laboratory in an HmX hematologyanalyzer (Beckman Coulter). Plasma methyl malonic acid (MMA) concentrations were measured with use of the LC-MS-MS method. Vitamin B_6 was determined after storage with HPLC with fluorometric detection.

Analyses were performed at the laboratory of the Division of Human Nutrition at Wageningen University, the Netherlands (homocysteine), the Laboratory of Paediatrics and Neurology, University Medical Centre Nijmegen, the Netherlands (MMA) and Stichting Huisartsenlaboratorium Oost in Velp, the Netherlands.

Statistical analysis

First, the distribution of all variables was examined and normality was tested. The distributions of skewed variables were normalized by transformation to the logarithm. Sex, living alone, currently smoking, educational level and supplement use were categorical variables. "Length of stay in (nursing/elderly) home" was normalized after log-transformation and data are reported as geometric means ± SD. Age, number of diseases, Barthel Index score, MMSE score, GDS, CRP, creatinine, vitamin D, homocysteine, serum folate, vitamin B_{12}, MMA and vitamin B_6 were not normally distributed and could not be normalized and were therefore tested with non-parametric test statistics (data shown as medians (p_{10} - p_{90})). All other variables were normally distributed.

Baseline data and data after 24 weeks of dietary intake were compared with Dutch RDA data.[28-30] Two-thirds of the Dutch RDA was taken as cut-off value for an adequate diet and percentages below this cut-off value are presented. For blood values the percentage below reference values are also shown.[8,36-40]

For each of the treatment groups we calculated the means and standard deviations or medians and p_{10} and p_{90} of the changes in score on the dietary intake and nutritional status. Student's t-test or Mann-Whitney U tests were used to compare the 0 to 24-week changes in outcome measures between the treatment groups receiving either

intervention drinks or placebo drinks. Results of all subjects in the dietary assessment sub sample who completed the full protocol were included in this analysis.

Data were analyzed using the statistical program SPSS, version 11.0 for Windows (SPSS Inc, Chicago, IL, USA).

Results

Subjects

In the sub sample in which dietary assessment took place 43 of 66 subjects completed the full protocol. In the placebo group there were relatively more drop-outs (38%) than in the supplement group (33%). Distaste or adverse effects of the intervention product, occurrence of disease and death, lack of motivation to continue were registered most as reasons for withdrawal (figure 1). Drop-outs had the same general characteristics at baseline as the participants who completed the full protocol except for the number of diseases (drop-outs: 5 and compliers: 3 (p=0.017)). Furthermore, they differed in their MMSE score (26 in drop-outs compared to 22 in compliers; p=0.001), energy intake, macronutrient intake, dietary fibre intake, thiamine intake, vitamin D intake and iron intake (drop-outs had significantly lower intakes than compliers; p between 0.002 and 0.04) and their homocysteine level in blood (20.9 μmol/L in drop-outs compared to 15.0 μmol/L in compliers; p=0.013). In the group of participants who completed the full protocol median compliance was 79.5% (range: 18.5 – 94.4%).

Table 2 shows the baseline characteristics of the supplement group and the placebo group of the sub sample in which dietary assessment took place. Median age of the subjects (81 years) was comparable with other nursing home populations. Mean BMI was 25.8 kg/m^2 and higher than in other institutionalised populations, because we did not focus on low BMI in this study. Based on a MMSE score of 23.5 points (p_{10}-p_{90}: 10.7-27.3) and Barthel Index of 16 we may characterize our population of 80'ers on average as an institutionalised, borderline demented population, but reasonably independent for activities of daily living.

None of the baseline characteristics differed significantly between the two treatment groups.

Table 2 **Baseline characteristics of a sub sample of Dutch institutionalised elderly participating in a 24-week intervention trial (n=66)**
Data shown as mean ± SD*, median (p_{10} - p_{90}) or as percentage

Variable	Supplement group (n=45)	Placebo group (n=21)
General characteristics		
Sex (female/male)	32/13	17/4
Age (years)	81.0 (65.0 – 89.4)	81.0 (68.4 – 87.6)
Length of stay in (nursing/elderly) home (months)*	16.4 ± 2.5	19.7 ± 2.9
Living alone (%)	60	81
Currently smoking (%)	38	36
Educational level (%)		
Low	49	48
Medium	11	19
High	16	10
Missing	24	24
Diseases (number)	3.0 (1.0 – 6.6)	4.0 (1.2 – 7.8)
Supplement use (%)	11.6	19.0
Anthropometrical assessment		
BMI (kg/m²)	26.1 ± 3.7	25.0 ± 3.5
Calf circumference (cm)	33.7 ± 3.5	33.3 ± 3.5
Physical and mental functioning		
Barthel Index (points)	15.5 (6.0 – 19.5)	16.0 (3.2 – 19.8)
MMSE (points)	23.0 (9.6 – 27.4)	24.0 (11.2 – 27.8)
GDS	4.0 (1.0 – 10.0)	5.0 (0.2 – 11.0)
Drop-outs (%)	33	38

* geometric mean ± SD

Dietary intake and nutritional status

Data on dietary intake and nutritional status before and after the intervention period of 24 weeks are presented in table 3: nutritional intake and percentage of subjects below two-thirds of the Dutch recommended dietary intakes[28-30] and table 4: body weight and blood values and percentage of subjects below the reference deficiency levels.[8,36-40]

Baseline mean energy, protein and fat intake as well as the intakes of vitamins and minerals of our population are much lower than that of independently living Dutch elderly.[41,42]

Table 3 **Effect of 24 weeks nutritional intervention on dietary intake in Dutch institutionalised elderly people**
Data shown as mean ± SD

	Supplement group (n=30)			Placebo group (n=13)			
Variable	**Week 0**	**Week 24**	**Change**	**Week 0**	**Week 24**	**Change**	**p-value[a]**
Energy intake (MJ/day)	7.17 ± 1.83	7.58 ± 1.57	**0.23 ± 1.83**	7.15 ± 1.39	6.59 ± 1.71	**-0.56 ± 1.60**	0.193
< reference, %	30	15		38	38		
Protein (g/day)	59.9 ± 15.5	67.5 ± 14.6	**6.3 ± 14.7**	58.8 ± 15.4	56.7 ± 13.3	**-2.1 ± 11.8**	0.079
< reference, %	6	4		8	8		
Fat (g/day)	61.4 ± 19.7	68.1 ± 17.6	**4.6 ± 19.8**	60.2 ± 18.8	58.0 ± 18.3	**-2.2 ± 22.4**	0.338
Carbohydrate (g/day)	213.4 ± 56.3	219.1 ± 48.3	**1.0 ± 62.0**	223.8 ± 38.8	199.5 ± 55.7	**-24.3 ± 39.2**	0.186
Dietary fibre (g/day)	16.3 ± 5.9	18.2 ± 4.4	**1.4 ± 6.5**	14.8 ± 2.4	12.9 ± 5.1	**-1.9 ± 4.5**	0.108
Calcium (mg/day)	840.5 ± 306.4	1114.2 ± 322.2	**262.5 ± 253.7**	896.6 ± 281.4	862.1 ± 214.7	**-34.5 ± 213.4**	**0.001**
< reference, %	50	19		38	46		
Iron (mg/day)	8.0 ± 2.3	14.8 ± 3.0	**6.6 ± 3.3**	7.7 ± 1.5	7.1 ± 2.3	**-0.7 ± 2.0**	**<0.001**
< reference, %	23	4		31	46		
Vitamin A RE (mg/day)	0.7 ± 0.8	1.1 ± 0.9	**0.4 ± 1.2**	0.5 ± 0.2	0.7 ± 0.4	**0.2 ± 0.4**	0.513
< reference, %	53	30		69	54		
Thiamine (mg/day)	0.7 ± 0.2	2.2 ± 0.6	**1.5 ± 0.6**	0.7 ± 0.2	0.6 ± 0.2	**-0.1 ± 0.2**	**<0.001**
< reference, %	57	4		62	69		
Riboflavin (mg/day)	1.2 ± 0.4	2.7 ± 0.7	**1.5 ± 0.6**	1.3 ± 0.4	1.2 ± 0.3	**-0.1 ± 0.2**	**<0.001**
< reference, %	13	0		15	8		
Vitamin B_6 (mg/day)	1.0 ± 0.2	2.9 ± 0.6	**1.9 ± 0.7**	0.9 ± 0.2	0.8 ± 0.3	**-0.1 ± 0.2**	**<0.001**
< reference, %	60	4		62	77		
Folate (µg/day)	180.1 ± 63.1	490.5 ± 109.8	**306.1 ± 120.5**	170.1 ± 44.2	168.8 ± 35.3	**-1.3 ± 35.6**	**<0.001**
< reference, %	63	4		69	77		
Vitamin B_{12} (µg/day)	3.2 ± 1.4	6.1 ± 2.2	**2.8 ± 2.2**	2.8 ± 1.1	2.6 ± 1.1	**-0.2 ± 0.8**	**<0.001**
< reference, %	17	4		23	23		
Vitamin C (mg/day)	50.1 ± 31.4	221.0 ± 64.6	**169.3 ± 67.9**	63.7 ± 43.7	50.8 ± 41.2	**-12.9 ± 49.6**	**<0.001**
< reference, %	47	4		38	62		
Vitamin D (µg/day)	3.4 ± 1.8	11.3 ± 3.3	**7.8 ± 3.5**	2.7 ± 1.0	2.7 ± 1.0	**0.0 ± 0.8**	**<0.001**
< reference, %	100	33		100	100		
Vitamin E (mg/day)	9.9 ± 4.2	52.4 ± 14.8	**42.2 ± 14.5**	9.7 ± 3.9	7.4 ± 3.2	**-2.3 ± 4.6**	**<0.001**
< reference, %	10	0		0	38		

a differences between changes during 24 weeks in supplement group and placebo group
reference value for vitamins and minerals is two-thirds of the Dutch RDA [28-30]; energy: % below 6.3 MJ/day [43]

In taking two-thirds of the Dutch RDA as cut-off value for an adequate diet, most of our participants had an adequate intake of protein and most of the vitamins and minerals. Exceptions (>50% below cut-off value) were thiamine, vitamin B_6, folate, vitamin D and vitamin A.

If baseline blood values were compared to reference values for blood, the percentage of especially deficiencies in vitamin D and prevalence of hyperhomocysteinemia is high. For vitamin D more than 80% of the participants were deficient at baseline.

Changes in dietary intake

After 24 weeks of treatment, statistically significant effects in favour of the intervention drink were found for nutritional intake (table 3). Energy intake, intake of macronutrients, vitamins and minerals increased in the supplement group and decreased or remained stable in the placebo group. Changes in vitamin and mineral intakes except for vitamin A intake were significantly different between the treatment groups ($p=0.001$). Dietary intake including the nutrient content of the intervention drink improved for the supplement group if dietary intake was compared to the placebo group. We observed that the energy intake from regular food (without the nutrient content of the drink) decreased in the supplement group with 0.53 MJ/day and in the placebo group with 0.56 MJ/day. These decreases were not significantly different from each other. Therefore, no energy compensation of the supplement had occurred.

Changes in nutritional status

Body weight increased with 1.4 kg in the supplement group and decreased by 0.6 kg in the placebo group. This difference in change did not reach statistical significance ($p=0.123$).

Albumin and prealbumin improved in the supplement group and decreased in the placebo group after 24 weeks of treatment. Average levels of haemoglobin, hematocrit, CRP and creatinine remained all within the ranges accepted as normal. Changes in blood proteins and biochemical indicators of general health did not differ significantly between the two treatment groups. Vitamin D, homocysteine, serum folate, vitamin B_{12} and vitamin B_6 changed significantly in favour of the intervention drink ($p<0.01$).

Table 4 **Effect of 24 weeks nutritional intervention on nutritional status in Dutch institutionalised elderly people**
Data shown as mean ± SD or as median (p_{10} - p_{90})

	Supplement group (n=30)			Placebo group (n=13)			
Variable	**Week 0**	**Week 24**	**Change**	**Week 0**	**Week 24**	**Change**	**p-value[a]**
Body weight (kg)	70.3 ± 10.2	71.6 ± 10.7	**1.4 ± 3.8**	66.1 ± 11.6	65.5 ± 11.1	**-0.6 ± 3.8**	0.123
Albumin (g/L)	35.9 ± 3.5	36.4 ± 3.0	**0.3 ± 2.7**	36.3 ± 4.0	34.8 ± 4.0	**-1.5 ± 3.1**	0.063
< 35.0 g/L, %[36]	27	24		38	31		
Prealbumin (mg/L)	245.5 ± 65.1	245.8 ± 61.6	**0.6 ± 50.9**	243.1 ± 51.1	229.2 ± 52.4	**-13.9 ± 32.4**	0.352
< 100 mg/L, %[8]	0	0		0	0		
Hemoglobin (mmol/L)	8.52 ± 0.84	8.37 ± 0.83	**-0.19 ± 0.57**	8.41 ± 0.88	8.44 ± 0.97	**0.03 ± 0.78**	0.303
Hematocrit (L/L)	0.41 ± 0.04	0.40 ± 0.04	**-0.01 ± 0.03**	0.40 ± 0.04	0.41 ± 0.05	**0.01 ± 0.04**	0.084
CRP (mg/L)	11.0	16.0	**1.0**	9.0	9.0	**-0.5**	0.394
	(5.0 – 42.6)	(5.0 – 32.8)	(-44.0 – 21.2)	(6.0 –)	(5.0 –)	(-5.0 –)	
Creatinine (µmol/L)	93.5	96.0	**1.0**	87.0	84.0	**-2.0**	0.205
	(59.7 – 134.6)	(63.0 – 152.0)	(-9.0 – 46.0)	(51.6 – 125.4)	(67.4 – 126.6)	(-10.6 – 26.0)	
Vitamin D (nmol/L)	21.5	49.2	**28.7**	20.3	18.1	**2.5**	**<0.001**
	(13.1 – 34.5)	(28.7 – 73.4)	(11.7 – 50.4)	(8.6 – 93.7)	(10.4 – 112.5)	(-6.4 – 22.8)	
< 30.0 nmol/L, %[37]	87	10		83	75		
Homocysteine (µmol/L)	14.7	9.5	**-3.9**	17.2	15.9	**0.8**	**<0.001**
> 19.1 µmol/L (♂);	(10.4 – 24.4)	(6.6 – 17.6)	(-9.6 – -0.3)	(8.7 – 25.4)	(8.2 – 28.4)	(-4.7 – 9.1)	
18.3 µmol/L (♀), %[38]	30	7		31	38		
Serum folate (nmol/L)	8.8	33.6	**24.7**	8.4	9.3	**0.5**	**<0.001**
	(5.5 – 11.6)	(22.9 – 42.2)	(15.0 – 33.4)	(5.2 – 24.9)	(5.3 – 25.0)	(-6.5 – 8.4)	
< 6.8 nmol/L, %[39]	23	0		23	31		
Vitamin B_{12} (pmol/L)	220.0	321.0	**75.0**	233.0	246.5	**11.5**	**0.007**
	(127.3 – 497.7)	(169.0 – 882.0)	(-19.2 – 281.8)	(135.4 – 713.2)	(134.8 – 680.6)	(-61.9 – 268.8)	
< 160 pmol/L, %[40]	14	7		8	8		
MMA (µmol/L)	0.27	0.26	**-0.02**	0.21	0.19	**-0.01**	0.272
	(0.17 – 0.59)	(0.17 – 0.47)	(-0.14 – 0.07)	(0.12 – 0.93)	(0.11 – 0.85)	(-0.05 – 0.18)	
> 0.32 µmol/L, %[40]	39	18		9	31		
Vitamin B_6 (nmol/L)	53.0	99.0	**41.0**	50.0	51.0	**0.0**	**<0.001**
	(36.1 – 80.1)	(65.0 – 175.0)	(11.0 – 126.0)	(28.8 – 159.2)	(31.8 – 124.6)	(-34.6 – 27.4)	
< 20 nmol/L, %[39]	0	0		0	0		

a differences between changes during 24 weeks in supplement group and placebo group

The beneficial effects of supplementation for vitamin levels are also reflected in the changes of percentages of subjects outside the reference values. In the supplement group most of the deficiencies were normalized. The effect was most obvious for deficiencies in vitamin D levels. Before the intervention vitamin D deficiency was present in 83 to 87% of the subjects; after the intervention in the supplement group only 10% remained deficient, meanwhile in the placebo group still 75% had a vitamin D deficiency.

Discussion

Our trial in institutionalised elderly people for 24 weeks showed a statistically significant effect of nutritional supplementation on the intake of vitamins and minerals and on plasma vitamin status (vitamin D, homocysteine, serum folate, vitamin B_{12}, vitamin B_6). Positive effects on the intake of macronutrients and body weight were found, although these effects were not statistically significant. Energy intake from regular food decreased in the supplement group and in the placebo group to the same extent. Energy compensation possibly induced by the supplement did not occur.

We have chosen to investigate a population of institutionalised elderly because they have an elevated risk on malnutrition, given their low intake of energy and micronutrients. We indeed selected a population prone to undernutrition. Dutch free-living elderly people of the SENECA (Survey in Europe on Nutrition and the Elderly, a Concerted Action) study had higher intake of energy, protein, fat and vitamins and minerals than our institutionalised elderly.[41,42] The intakes of our institutionalised elderly confirmed low intakes earlier observed in Dutch nursing home residents.[8,9] One third of our subjects had an energy intake below 6.3 MJ/day and this is one of the indicators to be at risk for inadequate micronutrient intakes.[43] In our population a high prevalence of deficiency in some micronutrients was found. Especially, a high prevalence of >80% vitamin D deficiency was found. This prevalence would even be higher with an optimal vitamin D level between 50 and 80 nmol/L as recently suggested by Dawson-Hughes and colleagues.[44] Vitamin D supplementation therefore needs special attention in institutionalised elderly.

For practical reasons we could not select randomly the sub sample of elderly for the dietary assessment. The 66 participants in the sub sample were significantly younger

(three years) and had higher MMSE score (23.5 vs. 20 points) and calf circumference (33.6 vs. 32.5 cm) than the other participants of the total study population. It is not likely that the selection of the group influenced the results on change in nutritional status, because this is a physiologic process. Energy compensation is more likely in a younger population, but both the total study population and our dietary sub sample (median age: 81 years) were old enough to have impaired energy compensation. Our conclusions on energy compensation would presumably not have been different with a randomly selected dietary sub sample.

We experienced a drop-out rate of 35%. The drop-outs performed cognitively better and had lower intakes of certain nutrients and higher level of homocysteine in blood than participants who completed the full protocol. Probably, the subjects with better cognitive performance experienced the protocol as more intensive. Therefore, if the drop-outs had completed the full protocol the results would have been more outspoken because the drop-outs had a worse physical health status at baseline and would probably have profited most by supplementation. The number of drop-outs was distributed almost equally over the placebo group and the supplement group and reasons for drop-out were similar for both groups. Therefore, we expect that drop-out at most would have attenuated our conclusions.

We found favourable effects of nutritional supplementation on dietary intake and nutritional status despite a relatively low compliance (79.5% (range: 18.5 – 94.4%)) in our population. Insufficient compliance with the study treatment (less than 50% of the intervention products consumed) was registered in one fifth of the population. We tried to prevent this low compliance with stimulating measures, such as a distribution schedule provided to the nursing staff or participant, encouragement of drinking by the nursing staff and providing drinks in two different flavours (to counteract boredom in taste). Reason for low compliance might be that taste of the intervention drinks was not adjusted for our population of institutionalised, borderline demented elderly. An indication comes from a pilot study by Wouters-Wesseling and colleagues[9] where positive remarks were made about the intervention product. For the present study the nutrient dense drink was slightly changed and no such positive remarks were obtained during this study. Secondly, the proposed times to use the drink (between main meals) were probably not the best suitable for our population of elderly. Together with the time

constraints of the staff of the nursing homes this could have led to lower compliance. Further analysis by comparing results of participants with a compliance rate of 75% or higher did not show an effect of compliance on biochemical indicators and intake of vitamins and minerals. The decrease in intake of energy of the background diet was however relatively high in the high compliance group, suggesting that a higher compliance leads to energy compensation.

We were able to uncover the effect of supplementation on micronutrient intake and status. A reason for a difference in effect of the intervention on the intake of vitamins and minerals and the intake of macronutrients could have been that our dietary assessment was not accurate enough to detect a significant change in macronutrients. For this purpose a method covering a longer period or investigating dietary habits would be more suitable. Another reason might be that the supplement contained relatively more micronutrients than energy in comparison with the reference values (energy 20% and micronutrients 100%). In our trial we used an observation including weighing-back method to investigate the changes in dietary intake. In our population this was the most accurate method, because a food frequency questionnaire, 24-hour recalls or dietary history are less reliable in our population with impaired cognitive function.[45] For practical reasons we did not measure on weekend days, but since the diet of institutionalised elderly will not be that different from weekdays we do not expect this has influenced our results. Dieticians were previously trained to ensure an accurate and detailed measurement of the dietary intake. Therefore we do not expect that the choice of our method could have affected our results. Furthermore, like in Fiatarone's study[25] we did not find a significant effect of the supplement on energy intake, but in contrast there was an increase in body weight of 1.4 kg after 24 weeks of intervention in the supplement group. This contradicting finding might be explained by a high intraindividual coefficient of variation in energy intake[46] and thus lack of power to observe a significant difference. Therefore we expect that the macronutrient intake was effectively improved in this group. We considered a total follow-up period of 24 weeks long enough to observe differences in both dietary intake and nutritional status between the two groups. In free-living elderly, improvement in total dietary intake as well as in nutritional status was also shown in studies of 16 to 24 weeks of intervention.[18,20,21]

To reduce compensation during other meals we instructed the subjects to consume the intervention products between main meals. Wilson and colleagues[47] suggested that for a higher total energy intake it is important to administer the supplement at least 60 minutes before the meal. This was however not confirmed in a recent study by Boudville and colleagues.[48] Another way to reduce compensation was by limiting the volume of the intervention product and still including nutrients in amounts in the physiologic range. Despite our efforts to reduce compensation, we did observe that nutritional intake from regular food decreased in the supplement group (energy intake: -0.53 MJ/day), but that these decreases were nearly identical to the decreases found in the placebo group (energy intake: -0.56 MJ/day). Therefore this decline in intake is not related to the energy content of the intervention product. Probably the decrease in voluntary intake is related to the volume of the intervention products. Studies of Rolls and colleagues[12] and Roberts and colleagues[13] suggested that for elderly people it is more difficult than for younger people to regulate energy intake in case of changes in their diet. This is not confirmed in our study, because we did not find energy related compensation in our population. Regarding the basic diet it is remarkable that voluntary dietary fibre intake decreased in the supplement group with 3.2 g/day and in the placebo group with only 1.9 g/day. In addition folate intake decreased in the basic diet with respectively 8.4 µg/day and 1.3 µg/day. This may be the consequence of a lower intake of vegetables (supplement group: -25 g/day; placebo group: -21 g/day) and fruits (supplement group: -20 g/day; placebo group: -6 g/day) at the end of the intervention compared to baseline. Those differences did not reach statistical significance between the two treatment groups.

Data on dietary intake from placebo-controlled studies are scarce. In most studies only intake of macronutrients is measured. Our findings regarding energy intake differ from the results of the groups at risk of malnutrition in the study by Lauque and colleagues.[27] In the latter study one of the groups received oral supplementation and the other group did not receive supplementation. At the end of the study, the placebo group had not changed their intake in contrast to the supplement group who increased the intake with one MJ/day on average. In our study we found in both treatment groups a decrease in intake in the background diet. Our supplement was able to counteract this decline in energy intake. From the differences in results compared to other studies it can be concluded that higher baseline data lead to a higher decrease in macronutrient intake.[20]

Besides the effect on macronutrient also the effect on micronutrient intake is comparable to other research.[49]

In conclusion, we found a positive effect of the intervention on dietary intake and nutritional status in the supplement group. The results of our trial show that this group of institutionalised elderly people do not compensate the energy content of a concentrated nutritional supplement. Despite the fact that the consumption of both the watery placebo and the nutrient dense drink decreased intake of the background diet, the total daily intake of macronutrients and micronutrients was improved by supplementation. Therefore, the nutrient enriched drink used in this study is supposed to be able to counteract the development of malnutrition in institutionalised elderly.

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Abstract

Objectives: To determine whether in the current study the supply of a nutrient dense drink, besides improving the nutritional status of nursing home residents as demonstrated in a pilot study, also has a positive effect on mental and physical function of institutionalized elderly people.

Design: A 24-week, randomized, double-blind, placebo-controlled, parallel-group, intervention trial.

Setting: Homes for the elderly and nursing homes in the Netherlands.

Participants: Institutionalized elderly people older than 60 years, with a BMI ≤ 30 kg/m², and a Mini-Mental State Examination score of at least 10 points.

Intervention: In addition to their usual diet the participants (n=176) received either a nutrient dense drink or a placebo drink twice a day during 24 weeks.

Measurements: The functionality measures included cognitive function, mood, physical performance and the ability to perform activities of daily living.

Results: In the supplement group a favorable effect of the intervention drink on body weight (1.6 kg difference in change; p=0.035), calf circumference (0.9 cm difference in change; p=0.048), and blood values (e.g. Hcy decreased from 16.8 to 11.2 μmol/L in the supplement group) was found. In the total group no significant effect was found on functionality outcomes. However, a subgroup of participants with BMI at baseline below 24.4 kg/m² performed better on the cognitive subscale of Alzheimer's Disease Assessment Scale (p=0.09), and its language sub score (p=0.01) after 24 weeks of intervention.

Conclusion: The results in the total group of this trial suggest that the nutritional supplement used in this study improves nutritional status. Furthermore, the results of this trial suggest that it is effective as treatment for decreasing function in a subgroup of institutionalized elderly people with low BMI.

4

The effect of a nutrient dense drink on mental and physical function in institutionalized elderly people

Marleen Manders, Lisette CPGM de Groot,
Willibrord HL Hoefnagels, Wendeline Wouters-Wesseling,
Ans JMJ Mulders, Wija A van Staveren

Submitted for publication

Introduction

Institutionalized elderly people can in general be classified as “accelerated agers”, who carry a heavy burden of chronic medical conditions, and disabilities.[1,2] These elderly people often have a low intake of energy and micronutrients.[3,4] As a consequence malnutrition is diagnosed in about 37% of them.[5] A fragile condition, malnutrition and deficiencies of several micronutrients are connected with decreased functioning. Micronutrient supplementation may have a positive effect on nutritional status and physical and mental functioning, and with that on quality of life of elderly people, and the degree of dependence on care.

Earlier studies demonstrated improvement of nutritional status - body weight and/or biochemical parameters - by nutritional intervention not only in institutionalized elderly people[3,6-8] but also in free-living elderly people.[9-12]

Studies in institutionalized elderly people have not revealed an effect of multinutrient supplementation on physical function. The reason for this might be that the period of supplementation was too short[6,7,13,14] or that the number of participants was too low.[3,8]

Randomized, double-blind, placebo-controlled trials on the effect of daily multinutrient supplementation on cognitive performance - presented in a review by Manders and colleagues[15] - did not show unequivocal results. A more recent study in frail elderly people showed that nutritional intervention significantly improved scores on a word learning test and a category fluency test.[16] Other recent studies in Alzheimer’s disease patients[17,18] and healthy, community-dwelling elderly[19,20] could however not confirm this result.

In institutionalized elderly people a beneficial effect of multinutrient supplementation on physical and mental function is not yet shown. In a small pilot study of 12 weeks a complete nutrient enriched low-volume liquid nutrition supplement improved both body weight and biochemical indicators of nutritional status in nursing home residents but no improvement in physical performance could be demonstrated due to the “pilot” design of the study (small number, short duration).[4] Therefore, for this study the aim was to investigate the effect of this nutrient dense product on weight and plasma vitamin status (as indicators of nutritional status) and on physical function in a larger study of longer duration. Furthermore, simultaneously the effect of a combination of

macronutrients and micronutrients on mental function in institutionalized elderly people was investigated.

Methods

Study design

The study was a 24-week, randomized, double-blind, placebo-controlled, parallel-group, intervention trial. Before and after the intervention, anthropometric values, biochemical indicators and mental and physical function were measured. The study was performed from May 2000 until December 2003.

Participants

The study population was recruited from nine different homes for elderly persons. The management teams, client councils, and Medical Ethics Committees of three nursing home corporations and the Medical Ethics Committee of Wageningen University, the Netherlands approved the study protocol. Participants themselves and/or one of their legal representatives gave written informed consent.

Of the 1,050 residents contacted, 265 residents were willing to participate and were actually screened for their eligibility (figure 1). Enrolment criteria were: age ≥ 60 years; institutionalized for at least two months; Mini-Mental State Examination (MMSE) score ≥ 10 points[21,22] and BMI ≤ 30 kg/m^2. Persons with serious morbidity (malignant cancer, severe infectious diseases, use of parenteral food or structural use of tube feeding, absorption disorders, terminal care) or interfering co-interventions were not allowed to participate.

Randomization

After screening, 176 participants were stratified to their sex, MMSE score (cut-off value for strata: 19 points), and blood levels of homocysteine (cut-off value for strata: 19 μmol/L). Then two-thirds of the participants (n=119) were randomly allocated to receive 125 ml of a complete nutrient dense dairy drink twice daily between meals and one-third (n=57) to receive the placebo drink in addition to their usual diet.

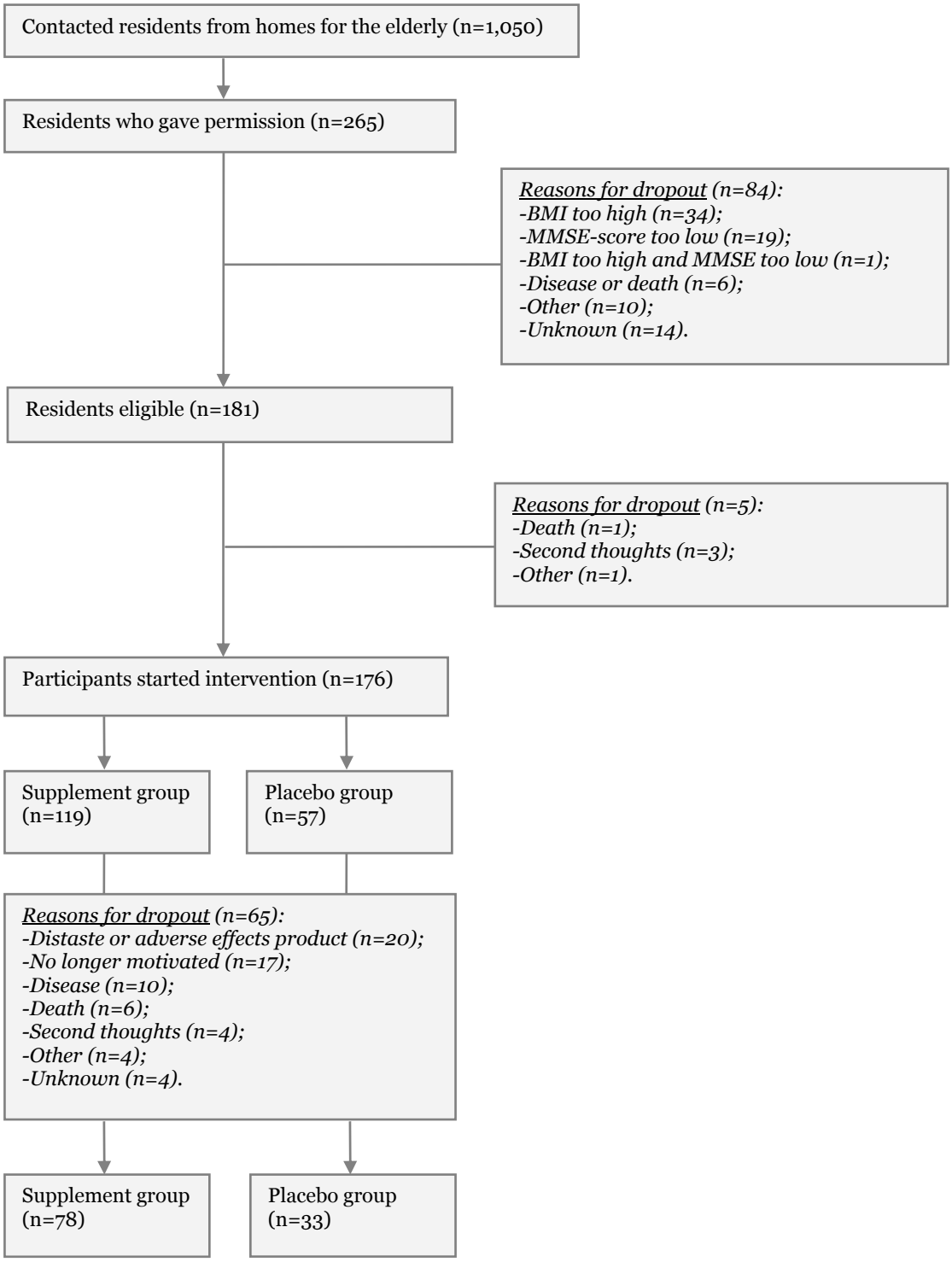

Figure 1 **Flow chart of participants of an intervention trial in Dutch institutionalized elderly people (with a nutrient dense drink) and reasons for dropout**

Interventions

The nutrient dense drink contained energy (250 kcal/day) and macronutrients with added vitamins (B vitamins, vitamin A, D, E, K, and C), minerals, and trace elements (in amounts of approximately 25 to 175% of U.S. Recommended Daily Allowance with enhanced amounts of antioxidants). The placebo drink contained neither energy nor vitamins or minerals, but contained water, cloudifier, thickener, flavoring, colorant, and non-caloric sweetener. One of the researchers (MM) visited the participants every two weeks at home to provide them with the drinks and to register compliance by counting leftovers. Compliance percentage was quantified as (number of supplements provided – number of supplements returned) / number of supplements provided * 100%.

Data collection

Baseline characteristics

Information on sex, age, length of stay in the (nursing) home, marital status, smoking habits, and educational level was collected. Information on presence of chronic diseases was derived from the medical file or identified by blood values.

Nutritional status

Anthropometrical assessment

Before breakfast, with participants dressed in light clothing without shoes, body weight (kg) was measured to the nearest 0.5 kg using a calibrated mechanical balance (Seca), a sitting weighing scale or a calibrated stretcher scale.

Knee-to-floor height (KFH) (cm) of the left leg was measured to the nearest 0.1 cm using a stadiometer with the subject in a sitting position. Body height (in cm) was calculated as 3.16*KFH (in cm).[23]

Using a measuring tape calf circumference (cm) of the left leg was obtained to the nearest 0.1 cm with the subject in a sitting position.

Biochemical assessment

Blood samples were collected in gel tubes (albumin, pre-albumin, C-reactive protein (CRP), creatinine, vitamin D, folate, and vitamin B_{12}), EDTA tubes (homocysteine, hemoglobin and hematocrit) or lithium heparin tubes (Methyl Malonic Acid (MMA), vitamin B_6) from participants in fasting state. The gel tube, one of the EDTA tubes and

one of the heparin tubes were centrifuged (2970 rpm) at a temperature of 4 °C for ten minutes and plasma or serum was stored at −80 °C till further analyses. The other EDTA tube was stored and hemoglobin and hematocrit were analyzed within 24 hours at the laboratory. The other heparin tube was stored in the dark and frozen at −80 °C for later vitamin B_6 determination with reversed-phase high performance liquid chromatography (HPLC) with fluorometric detection.

Albumin, pre-albumin, and CRP concentrations were analyzed using the Dimension® clinical chemistry system. Creatinine was determined by measuring absorption of the reaction product of creatinine and picric acid at 520 nm by a Synchron LX20. Serum 25-OH-vitamin D was analyzed on basis of immunoassay with a DiaSorin. Folate and vitamin B_{12} were analyzed using immunoassay (with the Beckman Coulter Access2). Total plasma homocysteine concentration was measured using HPLC with fluorescence detection. Plasma MMA concentrations were measured using the LC-MS-MS method.

Analyses were performed at the laboratory of the Division of Human Nutrition at Wageningen University, the Netherlands (homocysteine), the Laboratory of Pediatrics and Neurology, University Medical Centre Nijmegen, the Netherlands (MMA) and Stichting Huisartsenlaboratorium Oost in Velp, the Netherlands.

Physical performance

Three consecutive measures of handgrip strength (kgf) were recorded to the nearest 0.5 kg using a hand dynamometer (Lafayette Instrument Company, Lafayette, Indiana, USA). Maximum strength effort was used for data analysis.

Nursing personnel scored the activities of daily living (ADL) according to the Barthel Index which uses a scale from zero to 20; a higher score indicates better functional capacity. Items from the Frail Elderly Functional Assessment (FEFA) were added to the Barthel Index to be able to measure a lower level of daily activities.[24]

The Berkhout Index was also scored by the nursing personnel to determine the subject's possibilities to choose his own food, to bring the food to his mouth, and to chew and swallow.[25]

Mental functioning

Structured interviews to collect data regarding mental function were administered by trained interviewers and were conducted at the subject's home, with only the participant and the interviewer present in the room.

Cognitive function was measured using the Dutch revision of the Alzheimer's Disease Assessment Scale (ADAS). ADAS consists of a non-cognitive part rating emotional and behavioral symptoms with ten items and a cognitive part, used in this study and referred to as ADAS-cog, consisting of 12 items with a total score ranging from 0 (no impairment) to 75 (severe impairment). The items rate components of memory and orientation (total score=40), language (total score=25), and praxis (total score=10).[26,27]

In the Verbal Fluency test the participant was asked to name as many animals and professions as possible in 60 seconds.

The Geriatric Depression Scale-15 (GDS) is a short, 15-item instrument specifically developed for the assessment of mood in geriatric populations with a total score ranging from 0 to 15; higher scores indicate the presence of severe depressive symptoms.[28,29]

Sample size

To assess the required sample size a power calculation was performed before the start of the trial. For the ADAS-cog it was calculated that 165 evaluable participants would be sufficient to detect a clinically meaningful effect of 3 scale points after 24 weeks (assumptions: normal distribution, SD of 7.6 in supplement group, treatment allocation ratio = 2:1, α=0.05, 1-β=0.80). To account for the probability that 20% of the participants would not complete the study protocol, the aim was to random allocate 210 participants.

Statistical methods

Variables are shown as means ± SD if they were normally distributed. Variables which were normalized after log-transformation are reported as geometric means ± SD. Non-parametric test statistics were used if variables could not be normalized (data shown as medians (p_{10} - p_{90})).

Table 1 **General characteristics of Dutch institutionalized elderly people at baseline of a 24-week intervention trial (n=176)**
Data shown as mean ± SD*, median (p_{10} - p_{90}) or as percentage

Variable	Supplement group (n=119)	Placebo group (n=57)
Sex (female/male)	83/36	39/18
Age (years)	83.0 (72.9 – 92.0)	83.0 (70.8 – 91.4)
Length of stay in (nursing) home (months)*	21.8 ± 2.6	21.4 ± 2.6
Marital status (%)		
Married	24	12
Not married/single	9	14
Widow/widower	57	68
Divorced	5	5
Missing	5	0
Smoking habits (%)		
Never	31	32
Former	21	23
Current	20	14
Missing	28	32
Diseases (number)	3.0 (0.0 – 5.0)	3.0 (1.0 – 6.2)
History of CVD† (%)	39.0	54.4
Diabetes mellitus (%)	11.0	15.8
Impaired renal function‡ (%)	19.6	16.4
BMI (kg/m²)	25.3 ± 3.6	25.0 ± 3.5
Educational level (%)		
Low	60	61
Medium	17	18
High	9	7
Missing	14	14
MMSE§ (points: 0-30)	22.0 (12.0 – 27.0)	21.0 (11.8 – 26.2)
Albumin (g/L)	36.4 ± 3.9	37.3 ± 3.9
Prealbumin (mg/L)	235.8 ± 58.9	239.1 ± 55.8
Hemoglobin (mmol/L)	8.43 ± 0.87	8.44 ± 0.89
Hematocrit (L/L)	0.41 ± 0.04	0.40 ± 0.04
CRP|| (mg/L)	9.0 (5.0 – 40.0)	9.0 (5.7 – 18.2)
Creatinine (µmol/L)*	93.3 ± 1.4	91.8 ± 1.3

* geometric mean ± SD
† CVD: cardiovascular disease; difference in history of CVD (p=0.07)
‡ serum creatinine > 120 µmol/L
§ MMSE: Mini-Mental State Examination
|| CRP: C-reactive protein

For each of the treatment groups the means and standard deviations or medians and p_{10} and p_{90} were measured of the changes in score on the outcome parameters. Student t test or Mann-Whitney U tests were used to compare the 0 to 24-week changes in scores between the treatment groups receiving either intervention drinks or placebo drinks.

Data were analyzed using the statistical program SPSS, version 11.0 for Windows (SPSS Inc, Chicago, IL, USA).

Results

Participants

In total 65 participants withdrew from the study during the 24 weeks of intervention. Distaste or adverse effects of the drink, lack of motivation to continue, occurrence of disease and death were registered most as reasons for withdrawal (figure 1). Drop-outs had the same baseline characteristics as the participants who completed the full protocol, except for a better score on baseline MMSE, ADAS-cog and Verbal Fluency (p=0.01) and a higher score on GDS (p=0.02). In the group of participants who completed the full protocol median compliance was 66.7%, with two of the 111 subjects having compliance below 10%.

Baseline data

Table 1 shows baseline characteristics, which did not significantly differ between the two treatment groups. Median age of the participants was 83 years in both groups. Mean BMI of the participants was 25 kg/m^2. The median MMSE score of the total study population was 21, with 50% in the 17 to 25 range.

Changes in nutritional status

After 24 weeks of treatment, statistically significant effects in favor of the nutrient dense drink were found for nutritional status (table 2). Body weight increased with 0.8 kg in the supplement group and decreased by 0.8 kg in the placebo group (p=0.04, 95%-confidence interval (CI) =-3.11,-0.11). For calf circumference similar results were found (0.3 cm increase and 0.6 cm decrease respectively (p=0.05, 95%-CI=-1.82,-0.01)). Plasma vitamin status improved in the supplement group and remained similar in the placebo group (p<0.01).

Table 2 **Effect of 24 weeks nutritional intervention on nutritional status and blood values in Dutch institutionalized elderly people**

Data shown as mean ± SD or as median (p_{10} - p_{90})

	Supplement group (n=78)			Placebo group (n=33)			
Variable	**Week 0**	**Week 24**	**Change**	**Week 0**	**Week 24**	**Change**	**p-value[a]**
Body weight (kg)	66.3 ± 10.8	67.0 ± 11.0	**0.8 ± 3.6**	66.4 ± 11.9	65.7 ± 12.3	**-0.8 ± 3.3**	**0.035**
Calf circumference (cm)	32.9 ± 3.5	33.2 ± 3.3	**0.3 ± 2.1**	33.4 ± 3.7	32.9 ± 3.4	**-0.6 ± 2.4**	**0.048**
Vitamin D (nmol/L)	23.0 (14.7 – 44.3)	44.5 (25.8 – 80.6)	**21.0** (-2.7 – 57.9)	19.6 (12.1 – 52.5)	18.1 (11.0 – 65.0)	**-0.5** (-5.4 – 24.8)	**< 0.001**
Homocysteine (µmol/L)	16.8 (10.2 – 26.9)	11.2 (7.7 – 18.4)	**-3.9** (-13.5 – 0.5)	15.3 (8.7 – 27.4)	15.0 (9.8 – 27.5)	**0.3** (-6.5 – 7.6)	**< 0.001**
Serum folate (nmol/L)	8.8 (5.9 – 15.0)	31.1 (13.7 – 40.6)	**20.5** (6.0 – 31.4)	8.1 (5.0 – 19.7)	9.6 (5.3 – 27.5)	**0.0** (-3.4 – 9.3)	**< 0.001**
Vitamin B_{12} (pmol/L)	227.5 (132.4 – 484.4)	294.5 (168.3 – 612.4)	**65.0** (-18.2 – 184.4)	230.0 (111.6 – 638.2)	238.0 (109.2 – 551.1)	**7.5** (-73.5 – 120.1)	**< 0.001**
MMA[†] (µmol/L)	0.27 (0.16 – 0.69)	0.26 (0.17 – 0.53)	**-0.02** (-0.17 – 0.06)	0.25 (0.13 – 0.58)	0.28 (0.14 – 0.64)	**0.01** (-0.06 – 0.10)	**0.011**
Vitamin B_6 (nmol/L)	52.0 (31.7 – 93.5)	94.5 (62.8 – 149.0)	**40.0** (6.0 – 87.5)	52.0 (30.9 – 119.5)	59.0 (31.0 – 156.4)	**0.5** (-28.9 – 30.6)	**< 0.001**

* differences between changes during 24 weeks in supplement group and placebo group

† MMA: Methyl Malonic Acid

no significant differences between supplement group and placebo group at baseline

Table 3 **Effect of 24 weeks nutritional intervention on physical and mental functioning in Dutch institutionalized elderly people**

Data shown as mean ± SD or as median (p10 - p90)

	Supplement group (n=78)			Placebo group (n=33)			
Variable	**Week 0**	**Week 24**	**Change**	**Week 0**	**Week 24**	**Change**	**p-value[a]**
Grip strength (kgf)	16.2 ± 6.9	15.6 ± 6.8	**-0.5 ± 3.5**	15.7 ± 8.8	14.6 ± 7.5	**-1.5 ± 3.8**	0.233
Barthel Index score (points: 0-20)	15.5 (7.0 – 20.0)	15.0 (8.4 – 20.0)	**0.0** (-4.0 – 3.0)	15.0 (3.0 – 19.0)	15.0 (2.4 – 18.9)	**0.0** (-4.0 – 3.0)	0.745
FEFA[†] score (points: 0-10)	10.0 (6.0 – 10.0)	10.0 (6.7 – 10.0)	**0.0** (-1.0 – 1.0)	10.0 (5.3 – 10.0)	10.0 (5.4 – 10.0)	**0.0** (-1.9 – 1.0)	0.822
Berkhout Index score (points: 0-8)	8.0 (7.0 – 8.0)	8.0 (7.0 – 8.0)	**0.0** (-1.0 – 0.3)	8.0 (7.0 – 8.0)	8.0 (7.0 – 8.0)	**0.0** (-1.0 – 0.0)	0.360
ADAS-cog[‡] (points: 0-75)	18.0 (6.4 – 33.0)	16.0 (7.0 – 33.0)	**0.0** (-5.0 – 8.0)	19.0 (7.0 – 35.0)	18.0 (8.0 – 32.0)	**1.0** (-5.6 – 6.0)	0.845
Memory/orientation	13.0 (5.0 – 25.0)	10.0 (6.0 – 25.0)	**0.0** (-4.8 – 5.0)	12.0 (4.0 – 25.4)	13.0 (4.2 – 25.4)	**0.0** (-3.0 – 5.0)	0.792
Language	2.0 (0.5 – 5.5)	2.0 (0.0 – 6.6)	**0.0** (-1.0 – 2.7)	2.0 (1.0 – 6.2)	2.0 (0.4 – 5.6)	**0.0** (-2.6 – 3.0)	0.884
Praxis	2.0 (0.0 – 5.0)	2.0 (0.0 – 6.0)	**0.0** (-1.0 – 2.0)	3.0 (1.0 – 5.6)	3.0 (1.0 – 6.8)	**0.0** (-2.0 – 3.6)	0.703
Verbal Fluency animals	9.6 ± 4.5	10.3 ± 4.8	**0.6 ± 3.4**	9.9 ± 4.0	9.9 ± 4.5	**0.0 ± 3.2**	0.410
Verbal Fluency professions	6.3 ± 3.3	6.5 ± 3.9	**-0.1 ± 3.0**	6.6 ± 3.6	6.3 ± 3.7	**-0.3 ± 2.6**	0.687
GDS[§] (points: 0-15)	3.0 (1.0 – 9.0)	3.0 (1.0 – 9.3)	**0.0** (-3.0 – 3.0)	3.0 (0.0 – 9.6)	3.0 (1.0 – 9.2)	**0.0** (-4.0 – 3.0)	0.925

* differences between changes during 24 weeks in supplement group and placebo group

† FEFA: Frail Elderly Functional Assessment

‡ ADAS-cog: cognitive subscale of Alzheimer's Disease Assessment Scale

§ GDS: Geriatric Depression Scale

no significant differences between supplement group and placebo group at baseline

Changes in function

Median baseline score on ADAS-cog was 18 points in the supplement group and 19 points in the placebo group (table 3). Baseline GDS had a median value of 3 points in both groups. The changes in grip strength, ADAS-cog total score, and Verbal Fluency scores differed - not statistically significant - between the two treatment groups. Other parameters in table 3 remained similar during the 24-week intervention period.

Subgroup analyses

In a subgroup analysis we examined if elderly people at risk for malnutrition benefited more from supplementation. Low BMI and high plasma homocysteine concentrations were used as indicators of inadequate nutritional status. High homocysteine is related to low status of vitamin B_{12}, B_6 and folate. Probably intake of these vitamins is low and this might be accompanied by low intake of other micronutrients. Low BMI is related to low energy intake, which is a risk factor for malnutrition.

Therefore the two indicators were divided in tertiles for the total group of participants. Cut-off value for the lowest BMI tertile was 24.4 kg/m^2 and for the highest homocysteine tertile 19.2 μmol/L.

Results of these stratified analyses suggested that only function of the group of participants with low BMI at baseline benefited from the intervention product (n=20) as compared with placebo (n=9) (table 4). In mental function the favorable effect of the intervention was statistically (borderline) significant in ADAS-cog total score (p=0.09) and language sub score (p=0.01). Other mental functionality parameters also showed an improvement in comparison with the placebo. This differential treatment effect for different BMI tertiles was confirmed by a multiple regression analysis in which the interaction term between BMI tertile and treatment group turned out to be significant ($p<0.05$).

The results of the homocysteine subgroup analyses were approximately the same as for the total population (data not shown).

Table 4 **Effect of 24 weeks nutritional intervention on nutritional status, physical and mental functioning in a subgroup of Dutch institutionalized elderly people with marginal nutritional status at baseline (lowest tertile BMI; ≤ 24.4 kg/m²)**

Data shown as mean ± SD or as median (p_{10} - p_{90})

	Supplement group (n=20)		Placebo group (n=9)		
Variable	**Baseline**	**Change**	**Baseline**	**Change**	**p-value[a]**
Body weight (kg)	57.6 ± 10.8	0.3 ± 3.0	58.6 ± 9.7	-0.7 ± 4.7	0.512
Calf circumference (cm)	30.8 ± 2.6	0.3 ± 1.4	31.7 ± 2.6	0.0 ± 2.2	0.611
Grip strength (kgf)	17.6 ± 7.9	-0.9 ± 3.7	13.2 ± 6.2	-2.7 ± 4.7	0.285
Barthel Index score	16.0 (4.2 - 19.9)	0.0 (-3.9 - 7.0)	15.0 (1.0 -)	-1.0 (-6.0 –)	0.167
FEFA score	9.5 (6.0 - 10.0)	0.0 (-1.0 - 1.9)	10.0 (5.0 -)	0.0 (-4.0 –)	0.871
Berkhout Index score	8.0 (7.0 - 8.0)	0.0 (-1.0 - 0.9)	8.0 (7.0 -)	0.0 (-1.0 –)	0.532
ADAS-cog	21.0 (4.0 – 33.0)	-2.5 (-8.0 - 8.2)	19.0 (9.0 -)	1.0 (-4.0 –)	0.085
Memory/orientation	16.0 (3.0 – 25.0)	-1.0 (-7.0 – 5.0)	12.0 (5.0 -)	1.0 (-2.0 –)	0.169
Language	3.0 (0.0 - 4.0)	0.0 (-2.0 – 2.0)	2.0 (1.0 -)	1.0 (0.0 –)	**0.014**
Praxis	2.0 (0.0 - 4.4)	0.0 (-1.0 - 3.1)	2.0 (1.0 -)	1.0 (-2.0 –)	0.160
Verbal Fluency animals	10.0 ± 5.1	0.8 ± 3.9	9.9 ± 3.9	-0.6 ± 2.6	0.352
Verbal Fluency professions	6.5 ± 3.4	-0.3 ± 3.1	6.1 ± 3.1	-1.2 ± 2.7	0.449
GDS	4.0 (1.0 - 10.8)	0.0 (-2.0 - 2.9)	4.0 (0.0 -)	0.0 (-6.0 –)	0.594

* differences between changes during 24 weeks in supplement group and placebo group
no significant differences between supplement group and placebo group at baseline

Discussion

The current trial in institutionalized elderly people for 24 weeks showed a statistically significant and clinically relevant effect of supply of a nutrient dense drink, in particular on body weight, calf circumference, and plasma vitamin status. No such beneficial effects were found in the total group for measures of functionality. In a subgroup of participants with low BMI at baseline (≤ 24.4 kg/m²) favorable effects were found for the scores on the functionality measures ADAS-cog total score and language sub score.

The elderly population in this study is on average very old and suffers from several different chronic diseases and types of dementia. In this population one-third of the population was at risk for malnutrition according to their BMI. Accidentally, in this population the cut-off value for the lowest tertile of BMI (24.4 kg/m²) was the same as Beck and Ovesen[30] proposed as cut-off value for nutritional risk in their article.

In this study an intervention drink containing energy and vitamins and minerals was supplied. All nutrients were added in amounts in the physiologic range and were not considered as mega dose to be able to investigate the effect of a complete supplement in combination with the usual diet of the participants. We expected that a total follow-up period of 24 weeks would be adequate to observe subtle differences in mental and physical functioning between the two groups. However, in this respect one should be aware that neuropsychological improvements probably require more time to become manifest than physical function improvement. Remarkably, all earlier studies on the effect of nutritional supplements on function in institutionalized elderly people had shorter intervention periods, ranging from 4 weeks to 5 months.

We experienced a dropout rate of 37%, with a quite homogeneous distribution among the treatment groups (42% of the placebo group and 34% of the supplement group) and the reasons for dropout were the same for both groups. Therefore, we expect that dropout could not have influenced the results. Although high compliance was stimulated with a) a distribution schedule provided to the nursing staff or participant, b) intake encouraged by the nursing staff and c) intervention drinks provided in two different flavors (to counteract boredom in taste), mean compliance was low (67%) in comparison with the compliance (90%) in a comparable study by Wouters-Wesseling and colleagues.[31] However, in the supplement group plasma levels of micronutrients

rose significantly in comparison with the placebo group. Lack of such rise could indicate insufficient compliance, so mean compliance in the supplement group was probably sufficient to affect the outcome measures. In addition, an analysis with only participants with high compliance (> 75%) did not change the conclusions of the first analyses.

The current findings regarding the parameters of nutritional status are in agreement with earlier placebo-controlled studies on these parameters in institutionalized elderly people. In this study during 24 weeks we found a difference in body weight of 1.6 kg between the two treatment groups. Other studies found after 10-12 weeks of intervention a difference in change in body weight of 1.3 to 2.2 kg between the supplement group and the placebo group.[3,4,13] The fact that the difference in body weight change is lower than expected (additional 250 kcal/day for 24 weeks) might be the consequence of low compliance and compensation of the energy content of the product. Calf circumference was measured to assess muscle mass. In this study the significant changes in calf circumference were smaller than Gray-Donald and colleagues[9] found in their randomized trial, but they investigated free-living participants who are more physical active and have more possibilities for improving their muscle mass. Wouters-Wesseling and colleagues[31] could not confirm these results. In this study blood values of homocysteine, serum folate, vitamin B_{12}, MMA, and vitamin B_6 significantly improved in the supplement group compared with the placebo group. Some other placebo-controlled trials in frail elderly people found similar effects of nutritional supplementation on plasma vitamin status.[3,4,11]

In line with previous placebo-controlled trials in which the effect of nutritional supplementation was studied we failed to identify any (significant) changes in physical performance with the Barthel Index (as in[4,14]) nor by using handgrip strength (as in[3,7,9]). Though the placebo group diminished more in handgrip strength than the supplement group, this difference was not statistically significant. In the subgroup of participants with low BMI at baseline the effect of supplementation was more pronounced but not significant either. Possibly handgrip strength is not sensitive enough to find effects of nutritional intervention in this population.

The current study is, to our knowledge, the first randomized placebo-controlled trial to investigate the long-term effect of a complete supplement on mental function in

institutionalized elderly people. In frail elderly Wouters-Wesseling and colleagues[16] used tests for specific cognitive domains in a comparable study. On the contrary, we used ADAS-cog as the primary outcome measurement for general mental function. Clarke and colleagues[32] described the use of ADAS-cog in their article, but did not present their data on the effect of treatment. Placebo-controlled trials testing the efficacy of medicines also used the ADAS in some form as one of the endpoints.[21,33] Both medicine studies found a difference in change of around 3 points after 24 weeks of follow-up. This was higher than the change we found in our total population after 24 weeks. However, the level of ADAS-cog at baseline was higher in the studies by Imbimbo and colleagues ([21]; mean ADAS-cog 30.3) and Thal and colleagues ([33]; mean ADAS-cog around 26) than in this trial. In the subgroup analyses we found a borderline statistically significant difference in change of around 3 points between the supplement group and the placebo group. Power calculations (treatment allocation ratio = 2:1, α=0.05 (one-sided), 1-β=0.80) showed that if we would have had larger subgroups (>12 placebo and > 24 supplement) we would have observed significant results for ADAS-cog total score.

The results of the current trial confirm the positive effect of nutritional supplementation on nutritional status from a number of previous studies among healthy elderly people and nursing home residents. It seems to be possible to counteract the development of malnutrition. Subjective observations of functional improvement in the pilot study prompted us to study the effect of nutritional supplementation on functional outcome measures.[4] Although our efforts improved the design of the study, we were not able to find clear effects of a complete supplement on the physical performance of institutionalized elderly people. In the total group of participants no significant effects on cognitive function were found. However, in a subgroup of the participants with low BMI at baseline the intervention drink appear to have a positive effect on cognitive function parameters, which indicates that for people with a marginal nutritional status or at risk of malnutrition nutritional supplementation might be advisable. In the future, research could possibly confirm these positive results in populations with worse nutritional status at baseline or in younger populations with slightly diminished functionality.

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Abstract

Background: Several cross-sectional, case-control and prospective studies revealed a relation between homocysteine and cognitive function or dementia. These studies included either patient populations or healthy, community- dwelling elderly people.

Aim of the study: In this study we tested the hypothesis that homocysteine was inversely associated with cognitive function in a population of institutionalised elderly (aged ≥ 60 y; n=157).

Methods: For testing this hypothesis baseline data of a recently conducted intervention study in institutionalised elderly (median age 83 years) were used. Cognitive function was evaluated by the cognitive subscale of the Alzheimer's disease Assessment Scale (ADAS-cog). The association between fasting plasma homocysteine level and cognitive function was investigated by multiple linear regression analysis.

Results: In the crude model homocysteine concentration was not significantly related to ADAS-cog score (β=0.061; p=0.45). Age was found to be related to ADAS-cog score (β=0.161; $p<0.05$). Adjusting for age did however not result in a relation between homocysteine and cognitive function.

Conclusions: In our study no association was found between homocysteine and cognitive function in a population of very old institutionalised subjects.

Homocysteine and cognitive function in institutionalised elderly: a cross-sectional analysis

5

Marleen Manders, Emmelyne Vasse, Lisette CPGM de Groot,
Wija A van Staveren, Jacques G Bindels, Henk J Blom,
Willibrord HL Hoefnagels

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Introduction

Vascular diseases and dementia are common disorders in old age and important predisposing factors of mortality.[1,2] An elevated plasma homocysteine level has been suggested as one of the possible, modifiable risk factors for cardiovascular diseases.[3-5] An association between vascular diseases and decreased cognitive performance is also suspected.[6] Furthermore, it has been suggested that elevated plasma homocysteine levels as such are associated with neuropsychiatric disorders, such as cognitive impairment.[7-9] Therefore, homocysteine levels and cognitive function might be related either indirectly or directly.

There are some plausible biological mechanisms that might explain the relation between homocysteine and cognitive function. One of the hypotheses is that cognitive impairment is caused by hypomethylation of methyl-acceptors like myelin, neurotransmitters and membrane-phospholipids.[10,11] Besides that a methyl donor deficiency may disturb the repair of DNA damage by oxidative stress.[12] Another effect of hyperhomocysteinemia on cognitive function is the neurotoxicity of homocysteine.[10,11,13] There is evidence showing that elevated homocysteine levels are associated with neuropsychiatric disorders including cognitive decline.

Table 1 presents a summary of earlier studies that investigated the relation between homocysteine and cognitive function or dementia. In several case-control studies patients with a diagnosis of dementia had significantly higher mean total homocysteine levels than controls.[14-17] Ravaglia and colleagues did however not confirm this difference in homocysteine level.[18]

In the non-demented, healthy elderly population, hyperhomocysteinemia has been shown to be associated with poor performance on neuropsychological tests measuring specific cognitive abilities.[19-22] Furthermore, in recent studies elevated homocysteine was significantly associated with poor performance on more general cognitive tests or composite cognitive scores.[23-27] Longitudinal studies on a relation between cognitive performance and homocysteine showed less unequivocal results.[28-30]

Most earlier studies found an association between homocysteine and cognitive function or dementia either in a specific patient population or in healthy, community-dwelling elderly. No such association study has been conducted so far in the group of

institutionalised elderly. Therefore we decided to test the hypothesis that homocysteine was inversely associated with cognitive function in institutionalised elderly, hereby taking several confounding factors into account.

Material and methods

For testing our hypothesis we used baseline data on cognitive assessment and the biochemical assessment of homocysteine of a recently conducted intervention study. In this trial we investigated the effect of a nutrient dense dairy drink on physical and mental functioning in institutionalised elderly people. The drink was enriched with vitamins, minerals and trace elements added in amounts of approximately 25 to 175% of US RDA.

Subjects

Elderly who were dependent on professional care because of diminished cognitive function or deteriorated physical health were recruited from nine institutions in the southern part of the Netherlands. In the Netherlands two different kinds of institutionalisation exist; homes for the elderly and nursing homes. For activities of daily living and household management elderly in both types of institution are dependent on professional care, in nursing homes additional medical care is required. In both institutions central meal preparation and distribution of medicines is present. With permission of the board of the (nursing) homes, an invitation letter with information about the study protocol was sent to the residents and to one of their relatives. For all participants written informed consent was obtained from the participants themselves and/or from one of their legal representatives.

Subjects (n=265) were included in a screening procedure to assess if they met the following inclusion criteria: age ≥ 60 years, Body Mass Index (BMI) ≤ 30 kg/m^2, MMSE (Mini Mental State Examination) score ≥ 10 and institutionalised for at least two months at the start of the study.

Exclusion criteria were: tumours, with unstable body weight at the time of the measurements, terminal care, severe infectious diseases, disorders of the gastro-intestinal tract, use of parenteral food or structural use of tube feeding, intolerant or allergic to one of the ingredients of the intervention product and use of medication or

Table 1 Earlier studies that investigated the relation between homocysteine and cognitive function or dementia

Case-control studies in groups of patients with a diagnosis of dementia			
Study	**Subjects**		**Conclusion**
	Cases	**Controls**	
Nilsson et al., 1996 [14]	psycho geriatric patients (n = 510) demented and non-demented subgroup	reference population (n = 163)	Plasma homocysteine concentrations were significantly increased in both the demented and the non-demented patients compared to control subjects.
Joosten et al., 1997 [15]	patients with Alzheimer's disease (n = 52)	non-demented hospitalized controls (n = 50) healthy elderly subjects living at home (n = 49)	Mean homocysteine level is significantly higher in patients with Alzheimer's disease as compared to non-demented patients or subjects living at home.
Clarke et al., 1998 [16]	hospital clinic patients, aged 55 years or older, with a clinical diagnosis of dementia of Alzheimer type, including 76 patients with histologically confirmed Alzheimer's disease (n = 164)	elderly volunteer controls without symptoms of memory impairment (n = 108)	The odds ratio of histologically confirmed Alzheimer's disease associated with serum homocysteine concentrations ≥ 14 µmol/L (top third of the control distribution) compared to individuals with low serum homocysteine (≤ 11 µmol/L) was 4.5.
McCaddon et al., 1998 [17]	patients of a psycho geriatric assessment centre, aged 65 or over, seen with features compatible with DSM-III-R criteria for primary degenerative dementia of Alzheimer type (n = 30)	cognitively intact age-matched control subjects from a local general practice (n = 30)	Patients had a highly significant elevation of homocysteine compared with controls.
Ravaglia et al. 2000 [18]	demented centenarians with a clinical diagnosis of Alzheimer's disease (n = 34)	cognitively impaired not-demented centenarians (n = 10) cognitively normal centenarians (n = 13)	No significant difference was found for plasma homocysteine levels among the three diagnostic groups.
Cross-sectional studies in community-dwelling, non-demented, healthy elderly			
Study	**Subjects**		**Conclusion**
Riggs et al., 1996 [19]	male participants from the Normative Aging Study (n = 70)		Higher concentrations of homocysteine were strongly associated with poorer spatial copying skills, but not with the performance of tests on any of the other cognitive domains (memory, language, perceptual speed, or spatial reasoning)
Morris et al., 2001 [20]	elderly men and women participated in phase 2 of NHANES III (aged ≥ 60 y, ≥ 8 years of education, no previous stroke, atp test in one try) (n = 1270 and 1200)		Hyperhomocysteinemia was associated with poorer performance on measures of recall.
Prins et al., 2002 [21]	population-based study of non-demented elderly (n = 1077)		Elevated homocysteine levels are associated with decreased cognitive performance in non-demented elderly people, and the relation was most marked for psychomotor speed.

Table 1 Earlier studies that investigated the relation between homocysteine and cognitive function or dementia (continued)

Cross-sectional studies in community-dwelling, non-demented, healthy elderly		
Study	**Subject**	**Conclusion**
Budge et al., 2002 [22]	community-dwelling volunteers aged 60 to 91 (n = 158)	Homocysteine was negatively associated with total CAMCOG score. Higher homocysteine levels were associated with poorer performance on the memory and perception sub scores of CAMCOG but not with the other cognitive subscales or MMSE score.
Stewart et al., 2002 [23]	individuals aged 55 to 75 who were born in a Caribbean nation and living in community accommodation (from registration lists for primary care services) (n = 248)	Raised homocysteine (highest quartile: > 13.85 μmol/L) was significantly associated with cognitive impairment.
Duthie et al., 2002 [24]	survivors of the Scottish Mental Surveys, which surveyed childhood intelligence quotient. Cohort of children born in 1921 or 1936; 183 ABC21 and 148 ABC36, living independently in the local community	In the ABC21 but not the ABC36, homocysteine accounted for approximately 7–8 % of the variance in cognitive performance.
Miller et al., 2003 [25]	community-dwelling elderly Latinos (aged ≥ 60 y) (n = 1789)	Homocysteine is a modest independent predictor of cognitive function in community-dwelling elderly Latinos.
Ravaglia et al., 2003 [26]	healthy, cognitively normal Italian community dwellers aged ≥ 65 y (n = 650)	Elevated plasma homocysteine has an independent, graded association with concurrent cognitive impairment as measured with the MMSE in healthy elderly community dwellers.
Garcia et al., 2004 [27]	cognitively normal, community-dwelling participants aged 65 and older (n = 281)	Significant correlations between levels of homocysteine and the Stroop score and homocysteine and some scores of the California Verbal Learning Test were found.
Prospective community-based studies		
Study	**Subjects**	**Conclusion**
Kalmijn et al., 1999 [28]	community-dwelling respondents aged 55 years or over (n = 702)	No inverse association between elevated plasma homocysteine levels and concurrent cognitive impairment or subsequent cognitive decline over a 3-y follow-up was found.
Seshadri et al., 2002 [29]	subjects without dementia (667 women and 425 men) from the Framingham Heart Study (n = 1092)	An increased baseline plasma homocysteine concentration was a strong, independent risk factor for the development of dementia and Alzheimer's disease over an 8-y period.
Teunissen et al., 2003 [30]	normal aging individuals aged 30–80 years (n = 93)	An association between elevated homocysteine concentrations and prolonged lower cognitive performance has been observed after six years of follow-up.

supplements that could influence safe administration of the intervention product. The Medical Ethical Committee of Wageningen University approved the study protocol.

Measurements

In total 176 subjects were eligible and willing to participate. Subjects with both data on ADAS-cog score and homocysteine concentration were included in the analyses described in this article (n=157). From these subjects we gathered information on general characteristics to describe our population. Furthermore, all subjects underwent anthropometrical and cognitive assessments. Weight and knee-to-floor height[31] were measured and BMI calculated. The cognitive part of the Alzheimer's disease Assessment Scale (ADAS-cog)[32] and Geriatric Depression Scale (GDS)[33] were administered. Fasting blood samples were collected to determine homocysteine levels in plasma.

General characteristics

Information on age, sex, length of stay in (nursing) home, smoking habits (never, former and current), and educational level (low; completed primary education or lower vocational education, medium; intermediate vocational or general education and high; higher vocational training, college or university) was collected from personal files, available at the institution. Information on presence of several chronic diseases, like history of CVD (cardiovascular disease) and diabetes, was collected from medical files, also available at the institution. To assess the presence of chronic renal failure, creatinine levels in blood were measured.

Cognitive assessment

Mental function was measured using the following questionnaires: MMSE for the screening procedure, ADAS-cog score and GDS as baseline and outcome measure of the intervention. The MMSE is a questionnaire with 12 questions concerning orientation, memory, attention, and the ability to name and to follow verbal and written commands. MMSE is considered to have a high interrater reliability and validity.[34]

The ADAS was originally designed as a rating scale for severity of dysfunction in cognitive and non-cognitive behaviour characteristics of persons with Alzheimer's disease (AD). The scale is composed of items with significant interrater and test-retest reliability for Alzheimer patients. Since the symptoms of AD and other dementias

overlap to some extent, the ADAS may be applicable to other dementias. The ADAS consists of a non-cognitive part rating emotional and behavioural symptoms with ten items and a cognitive part, used in this study and referred to as ADAS-cog, consisting of 12 items with a total score ranging from 0 (no impairment) to 75 (severe impairment). The target symptoms are supposed to represent several domains of impaired cognitive function. The items rate components of memory and orientation (total score=40), language (total score=25), and praxis (total score=10).[32,35]

The Geriatric Depression Scale-15 is a short, 15-item instrument specifically developed to assess depression in geriatric populations. It is a reliable and valid self-rating depression screening scale for elderly populations. Questions can be answered with "yes" or "no", with a total score ranging from 0 to 15.Higher scores on GDS indicate the presence of severe depressive symptoms.[33,36]

Biochemical assessment

Blood samples were collected from fasting subjects in a gel tube and an EDTA-containing tube. These tubes were centrifuged (2970 rpm) at a temperature of 4 °C during 10 minutes within 1 hour of blood collection. The serum and plasma samples were stored at –80 °C till further analyses of homocysteine and creatinine.

Total plasma homocysteine concentration was measured using high performance liquid chromatography with fluorescence detection. The lower limit of sensitivity of this method is 0.22 μmol/L in plasma and the method is highly reproducible (intra- and interassay coefficients of variation=5.0 and 4.5%, respectively).[37] Creatinine was determined by measuring absorption of the reaction product of creatinine and picric acid at 520 nm by a Synchron LX20, with a CV below 3% and a lowest detectable level of 8.84 μmol/L (modified Jaffé method). The laboratory of the Division of Human Nutrition at Wageningen University, the Netherlands performed the homocysteine analyses. The creatinine analyses were performed at Stichting Huisartsenlaboratorium Oost in Velp, the Netherlands.

Confounders

Factors that could potentially influence the relation between plasma homocysteine and cognitive performance were taken into account. In the present analyses age, sex,

vascular diseases, diabetes mellitus, chronic renal failure, educational level, smoking habits, BMI and depression were considered as potential confounders.[20,25,28,29]

Statistical analyses

Because the variables ADAS-cog score and homocysteine concentration were not normally distributed we performed a log-transformation of those variables and calculated the geometric mean and standard deviation. For the normally distributed confounder BMI, the mean and standard deviation were calculated. For the not normally distributed confounders (age and GDS) the median and 10th and 90th percentile were calculated.

Multiple linear regression was performed to investigate the relation between homocysteine concentration and ADAS-cog score. Age, sex, history of CVD, diabetes, chronic renal failure, educational level, smoking habits, BMI and GDS were tested as potential confounders, but hardly affect the results. The interaction between homocysteine concentration and all potential confounders was not statistically significant.

Statistical significance was defined for all analyses as $p < 0.05$. Data were analysed using the statistical program SPSS, version 11.0 for Windows.

Results

Characteristics of the population

Table 2 presents the characteristics of the study population. The median age of the participants was 83 years. The participants were institutionalised for an average of 21.6 months at the time of the measurements. Eighteen percent of the participants were current smokers. Of the participants, 14% had diabetes, 20% had chronic renal failure and 45% history of CVD. Mean BMI of the participants was 25.3 kg/m^2. Mean plasma homocysteine level was 16.9 µmol/L (table 2). The educational level of most participants (60%) was low. The mean score on the ADAS-cog measurement was 14.8 points. The memory and orientation sub score of the ADAS-cog was on average 10.8 points. GDS had a median of 4 points. Differences in general characteristics between men and

women were significant for smoking habits and presence of chronic renal failure ($p<0.001$) (table 2).

Table 2 **General health characteristics of a subgroup of Dutch institutionalised elderly (n=157)**

Variable	Total population	Women (n=108)	Men (n=49)
Age (years)[c]	83.0 (72.0;91.3)	83.0 (72.8;93.0)	83.0 (67.0;89.0)
Length of stay in (nursing) home (months)[b]	21.6 ± 2.5	20.3 ± 2.5	24.8 ± 2.5
Smoking habits (%)*			
Never	32	44	4
Former	22	10	49
Current	18	15	24
Missing	28	31	22
History of CVD[d] (%)	45	40	55
Diabetes (%)	14	13	14
Chronic renal failure[e] (%)*	20	12	38
BMI (kg/m²)[a]	25.3 ± 3.5	25.4 ± 3.6	25.1 ± 3.3
Homocysteine concentration (µmol/L)[b]	16.9 ± 1.5	16.4 ± 1.5	18.0 ± 1.4
Educational level (%)			
Low	60	57	65
Medium	20	19	20
High	7	7	6
Missing	13	16	8
MMSE[c]	21 (12;27)	21 (12;27)	22 (14;28)
ADAS-cog score[b]	14.8 ± 1.8	15.5 ± 1.8	13.5 ± 1.7
Memory and orientation[b]	10.8 ± 1.8	11.3 ± 1.8	9.8 ± 1.7
Language[c]	2 (0;5)	2 (0;5)	2 (0;5)
Praxis[c]	2 (0;5)	2 (0;5)	2 (0;4)
GDS[c]	4 (1;9)	3 (1;9)	4 (1;8)

a mean ± SD; b geometric mean ± SD; c median (p_{10};p_{90})
d CVD cardiovascular disease
e serum creatinine > 120 µmol/L
* $p < 0.001$ difference between men and women

Relation between homocysteine and cognitive function

To examine the relation between homocysteine concentration and ADAS-cog score, first a regression model without adjustment for confounders was analysed (table 3). In this model homocysteine concentration was not significantly related to ADAS-cog score. Of the confounders considered only age turned out to be significantly related to the ADAS-cog score. If age was added as explanatory variable (Model 2 in table 3), this analysis did

not result in a significant relation between homocysteine concentration and ADAS-cog score.

Table 3 **Multiple linear regression models for homocysteine concentration (independent variable) versus ADAS-cog score (dependent variable) in a subgroup of Dutch institutionalised elderly (β (p-value))**

ADAS-cog score			
Model	**Homocysteine concentration**	**Age**	**Adj. R^2**
1	0.061 (0.448)		-0.003
2	0.057 (0.472)	0.159 (0.047)	0.016

Model 1 homocysteine concentration alone; Model 2 model 1 + age

Discussion

We hypothesized that there would be a relation between plasma homocysteine level and cognitive function in institutionalised elderly. The cross-sectional analysis in our study did not show such an association in our population.

In the existing literature either specific patient populations or healthy, community-dwelling elderly have been investigated. The reason that in this study no relation was found might be that we investigated a population of institutionalised elderly, which is classified in the literature as "accelerated agers".[38,39] This group of subjects may suffer from several different chronic diseases and types of dementia. Therefore, the elderly population in our study was very heterogeneous with respect to diseases and comorbidity. This could have confounded the relation between homocysteine and cognitive function but when we adjusted for the presence of history of CVD, diabetes and impaired renal function in the multiple regression model the relation between homocysteine concentration and ADAS-cog score was still not significant. Residual confounding caused by comorbidity is still possible, although we adjusted the analyses for the most important chronic diseases.

In contrast with the heterogeneity in disease, our population might have been too homogenous for two other factors, both the outcome measure (ADAS-cog score) and the main determinant (homocysteine concentration). The reason that we did not find an association between homocysteine concentration and ADAS-cog score might be that a large part of the population had a low ADAS-cog score. Approximately 60% of the

participants had an ADAS-cog score below 20 points (ADAS-cog range 0–75), indicating a homogenous population with a low range of ADAS-cog score. None of the other recent cross-sectional studies on homocysteine and cognitive function used ADAS-cog to assess cognitive function. Therefore, it was not possible to compare the level of and variance in ADAS-cog scores with other studies. The MMSE level (median 21: indicating that the subjects on average had dementia), however, was lower than in four other studies that included MMSE as an outcome measure and did find an association. Prins and colleagues[21] used in their study participants with a mean MMSE of 27.5±2.1. In the studies of Budge and colleagues,[22] Duthie and colleagues[24] and Ravaglia and colleagues[26] the mean MMSE of the participants was around 29 points. Based on MMSE score we could consider that too few people with a good cognitive status were present in our population.

Furthermore, the homocysteine levels that were observed (mean: 16.9±1.5 μmol/L) were relatively high in comparison to other studies. In four other cross-sectional studies fasting homocysteine levels were determined: Riggs and colleagues,[19] Ravaglia and colleagues,[26] Morris and colleagues[20] and Miller and colleagues[25] found a homocysteine level of 11.9 μmol/L,12.3 μmol/L, 10.4 μmol/L and 9.8 μmol/L respectively. Prins and colleagues,[21] Budge and colleagues[22] and Stewart and colleagues[23] used non-fasting homocysteine levels of 11.5 μmol/L, 12.6 μmol/L and 12.3 μmol/L respectively. The mean age in these seven studies ranged from 65 to 74 years. For elderly people higher cut-off values for hyperhomocysteinemia have been put forward. In the reference population used by the Dutch Heart Foundation a cut-off value of 17.4 μmol/L for men between 60 and 70 years old and 15.2 μmol/L for women (60–70 years old) is used. For men and women above the age of 70 this cut-off value is respectively 19.1 μmol/L and 18.3 μmol/L. Meaning that the mean level in our population (median age of 83 years) could be considered as normal. Besides the higher level of homocysteine, the variation in homocysteine levels in our population was comparable to other fasting ranges, but was less than in studies using non-fasting levels. Thus the reason that we did not find an association between homocysteine concentration and ADAS-cog score most likely is that there were too few people with low homocysteine levels among the participants.

So in our population relatively low cognitive function (measured as MMSE) and high homocysteine levels were found in rather small ranges. In the literature both factors are

related to age. The fact that our population is older (median: 83 years) than in most other cross-sectional studies (mean age between 65 and 74 years) might be an explanation for our findings. In most cross-sectional studies among healthy elderly an inverse association between homocysteine and cognitive function was found (table 1). Duthie and colleagues[24] found in a cross-sectional analysis among survivors of the Scottish Mental Surveys (ABC21 and ABC36) that homocysteine was associated with cognitive variation in the older cohort (around 78 years old), but surprisingly not in the younger cohort (around 63 years old). The age of the oldest cohort was however lower than the age of our population. In a case-control study of Ravaglia and colleagues[18] in Italian centenarians no significant difference was found between homocysteine levels in a demented group and a cognitively normal group. These results suggest that a possible association between homocysteine and cognitive function disappears when getting into the oldest old (above the age of 80 years). One possible explanation could be that selective survival occurs and that only elderly who are less susceptible to elevated levels of homocysteine survive. Furthermore, it is of course also possible that the relation between homocysteine and cognitive function changes with age.

Age was considered as one of the confounding factors in our multiple regression model. Adding age did however not result in a relation between homocysteine and cognitive function. All confounders that were considered in our analyses (age, sex, vascular diseases, diabetes mellitus, chronic renal failure, educational level, smoking habits, BMI and depression) were used in other population-based studies as well.[25] Other factors that could have influenced the relation between homocysteine and cognitive function were levels of blood folate, serum vitamin B_{12} and plasma vitamin B_6. These factors were not adjusted for in our analyses because they are highly related to homocysteine levels and could have over adjusted the relation between homocysteine and cognitive function. Factors like hypertension, genetic factors, alcohol consumption, cholesterol and several other blood values are also potential confounders but unfortunately we did not have information on these variables.

In conclusion, in our study no association was found between homocysteine and cognitive function in a population of elderly institutionalised subjects. Despite possible biological mechanisms and the offered methodological explanations, the hypothesis that homocysteine is related to cognitive function in our population of very old

institutionalised elderly is rejected. Studies with more heterogeneous (in respect of homocysteine and cognitive function), very old populations and prospective studies that focus on old age are needed to investigate the possibility that such a relation still exists in the oldest old.

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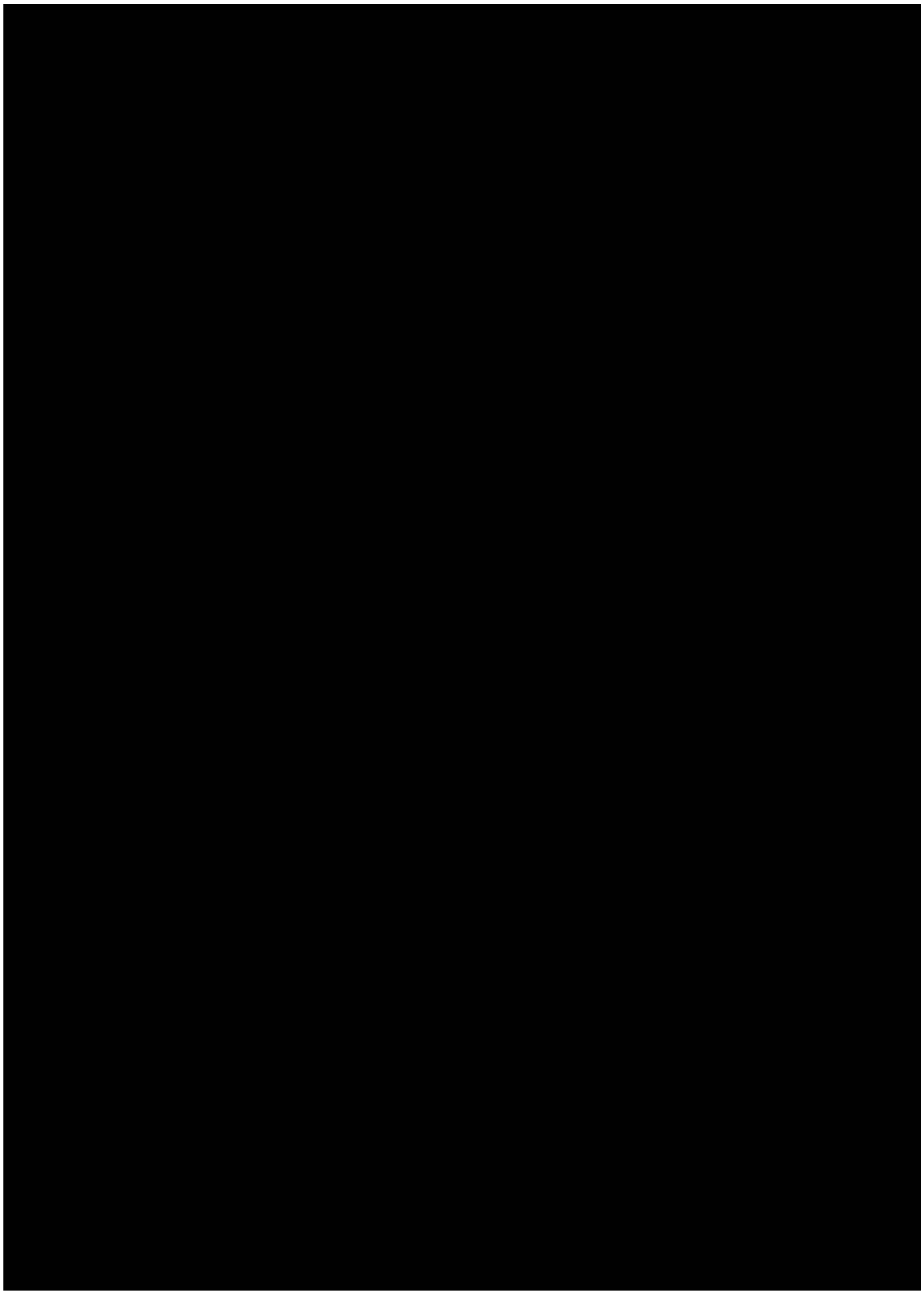

6 General discussion

Main findings from the intervention study

As described in Chapter 1, the objective of this thesis was to investigate the effect of nutritional supplementation on dietary intake, nutritional status and mental and physical functioning in institutionalised elderly people. Results of our 24 weeks covering trial involving institutionalised elderly people show that nutritional supplementation significantly improves the intake of vitamins and minerals and as expected had a positive effect on nutritional status; body weight, calf circumference and plasma vitamin status. We were not able to demonstrate general effects of our intervention on physical performance. Cognitive function parameters, such as ADAS-cog total score and language sub score, were positively affected in a subgroup of participants with low BMI at baseline (below or equal to 24.4 kg/m^2). In this chapter we will reflect on the validity of our findings, extrapolations to other groups and the impact for nutritional care in elderly people.

Methodological considerations

Study population

Malnutrition is one of the factors which contribute to the progression of functional decline. In later stages of this process towards disability, functional impairment may even contribute to the development of poor nutritional status. So, a vicious circle might develop. To test if refeeding can prevent, stop or revert this down spiralling process, a careful selection of the study population is needed: prone to undernutrition and not in the end stages of functional decline.

Because of their low intake of energy and micronutrients and associated elevated risk on malnutrition,[1,2] we chose to investigate a population of institutionalised older persons. Our study population was indeed at risk for undernutrition in view of the following facts. The intakes of energy, protein, fat and vitamins and minerals were lower in our institutionalised elderly people, as compared to healthy Dutch elderly people of the SENECA study[3,4] but comparable to other studies in Dutch nursing home residents.[5,6] One third of our subjects had an energy intake below 6.3 MJ/day and with this level of intake it is difficult to obtain sufficient amounts of micronutrients.[7] Furthermore, one third of the population was at risk for malnutrition according to their BMI, when using

the cut-off value of 24 kg/m² for nutritional risk as proposed in an article by Beck and Ovesen.[8] All these findings indicate that our population was indeed at risk of malnutrition.

Given the fact that the group of institutionalised elderly suffers from several different chronic diseases, it is not unexpected that their performance level is diminished. We did not select subjects with subnormal levels of physical and mental performance at baseline. Based on their Barthel Index score at baseline (15 points) our population was better able to perform activities of daily living than a comparable institutionalised population in a study by Wouters-Wesseling and colleagues (Barthel Index score: 5 points).[6] On the other hand our participants had a lower level of performance than healthy, free-living individuals as investigated in the Seneca study. We excluded people with a too low cognitive performance, because the decline in functioning might then be irreversible. Besides that patients with dementia are not able to respond to study questionnaires. Such a procedure was also used in a study by Wouters-Wesseling and colleagues.[9]

Recruitment of institutionalised elderly people

The recruitment of an elderly population from institutes for chronic care takes a long time because approval has to be given by different sections of the organisations and cooperation is needed from professional and family care givers. In this study the recruitment took us from May 2000 until December 2003. We could only approach the elderly individual in these institutes with the permission of the management team, client council, and Medical Ethics Committee of the nursing home corporations. We then sent an invitation letter and information on the study protocol to the residents and one of their relatives. For all participants written informed consent was obtained from the participants themselves and/or from one of their legal representatives.

It turned out to be very tough to find enough subjects because the institutionalised elderly were not willing to become involved. The most reported reason for this was lack of motivation. Therefore our population consists of people who were motivated to take the supplements for half a year and to participate in the measurements.

It is unlikely that this selective participation affected our outcomes as the hypothesis we investigated is based on physiological processes of aging. Therefore we assume that our

conclusions can be extrapolated to all institutionalised elderly people with a marginal nutritional status and diminished functioning.

Study design

We investigated our hypothesis in a randomized, placebo-controlled, double-blind intervention trial. The strong points from our study were the design and methods used. Furthermore, we were able to obtain a specially designed placebo product. Special efforts were made to improve the comparability of intervention and placebo drinks with respect to their appearance and taste. The type of studies applied, compliance and compensation will be described in the next paragraphs.

Intervention

There are several methods to improve nutritional status, such as appetite stimulating interventions like drugs or meal ambiance. We selected a relatively undemanding method, by providing nutritional supplements and showed that the nutritional status could be improved in elderly people.

For this nutritional supplement we choose to intervene by a combination of macronutrients and micronutrients, because the elderly in our population are prone to malnutrition and could benefit more from a complete supplement.[10,11] Macronutrients in a complete supplement may lead to improvement of the energy balance and by including micronutrients at the same time the deficiencies of specific micronutrients can be solved. In this study we added micronutrients in amounts up to recommended daily intakes. For a more outspoken effect on functioning possibly higher doses of some of the nutrients added to our product (like B vitamins, antioxidants and n-3 fatty acids) would have been required. Evidence of beneficial effects on cognitive performance of such higher doses is still lacking as follows from our review of Chapter 2 in which we did not find an unambiguous result of specific nutrients on cognitive function.

Compliance

Given the inclusion of subjects who turned out to be highly motivated, good compliance could be expected. Nevertheless due attention was given to encourage compliance, which was stimulated with a) a distribution schedule provided to the nursing staff or participant, b) intake encouraged by the nursing staff and c) intervention drinks

provided in two different flavours (to counteract boredom in taste). Despite these efforts, compliance was rather low (median: 67% of the provided supplements consumed) in comparison with the compliance in a study by Wouters-Wesseling and colleagues (90%),[12] but better than the compliance experienced by Hogarth and colleagues, with two thirds of the participants consuming less than 50% of the supplements.[13] In our study this was experienced in one third of the participants. Yet, the clear favourable effects we demonstrated on blood levels indicated that the compliance was on average sufficient to improve nutritional status. It could be argued that with better compliance we might have found positive effects on physical and mental function as well and effects on nutritional status would have been more pronounced. However, an analysis including only participants with high compliance (> 75%) did not reveal a stronger effect of the intervention. Therefore, we assume that better compliance would not have led to other conclusions.

Compensation

We found beneficial effects of the nutrient dense drink on total daily intake of macronutrients and micronutrients despite an unintended decline in voluntary dietary intake during the rest of the day. To prevent compensation during other meals we instructed the subjects to consume the intervention products between main meals and we provided a nutrient dense product with low volume (125ml). We observed in our study that the decrease in energy intake from regular food in the supplement group (Δ energy intake: -0.53 MJ/d) was on average not significantly different from that in the placebo group (Δ energy intake: -0.56 MJ/d). Therefore we conclude that the supplement group did not compensate during the meals for the energy content of the supplement. Both groups partly compensated the volume of the product. Therefore it is important to use intervention products with a low volume.

Internal and external validity of the measurements

Dietary intake

Trained dieticians measured dietary intake using an observation including weighing-back method on two weekdays, at the start and the end of the intervention period. This method is more suitable for the subjects in this type of study as compared to a food frequency questionnaire, 24-hour recalls or dietary history.[14] Because of memory problems (MMSE median: 21 points) a retrospective method is not useful and due to

their physical and mental conditions institutionalised elderly people are not able to record their own intake.

Data on dietary intake from other placebo-controlled studies in institutionalised elderly are scarce. In a review about the effect of protein and energy supplementation in malnourished elderly by Milne and colleagues many studies were included in medical patients (acute or chronic disease) or free-living elderly. In addition the habitual diet was used as the control treatment.[15] In most studies only intake of macronutrients is measured. In our study we did not find a significant difference in change in energy intake between the two treatments groups. These findings differ from the results of a study in a group of persons at risk of malnutrition by Lauque and colleagues who found pronounced increases in energy intake (including intervention products) after an intervention with Clinutren products (energy and nutrients in a small volume).[16] The reason could be that their participants had a lower mean energy intake (6.5 MJ/day) than our institutionalised elderly (mean energy intake at baseline: 7.2 MJ/day). Modest changes in energy intake were found in a study by Fiatarone and colleagues.[17] Experimental subjects increased their total energy intake (diet plus research supplement) by 0.21 MJ/day over 10 weeks. The total energy intake decreased in control subjects by 0.3 MJ/day. Like in our study the difference in change between the two treatment groups was not significant.

Nutritional status

Body weight, calf circumference and plasma levels of micronutrients were used to determine the effect of the intervention on nutritional status. Calf circumference was measured to assess muscle mass. Our results confirm the positive effect of nutritional supplementation on nutritional status found in a number of previous studies among healthy elderly people and nursing home residents.[5,16,18-22]

In our study with a duration of 24 weeks we found a difference in body weight of 1.6 kg between the two treatment groups. The difference in energy intake between the two treatment groups (0.8 MJ/day) would theoretically have increased body weight by 4.6 kg.[23] The found effect could be lower because of modest changes in energy expenditure. We did however not measure physical activity levels and therefore this can not be checked. Comparable results on body weight were found in shorter interventions (10-12

weeks) by van der Wielen and colleagues,[5] Fiatarone and colleagues[24] and by Wouters-Wesseling and colleagues.[6] Furthermore, in our study a significant difference in change in calf circumference between treatment groups was found. In studies by Gray-Donald and colleagues[18] and Wouters-Wesseling and colleagues[12] no significant differences in calf circumference were found between two treatment groups of frail elderly people.

As expected, in our study blood values of homocysteine, serum folate, vitamin B_{12}, MMA, and vitamin B_6 improved significantly in the supplement group compared to the placebo group. Some other placebo-controlled trials in frail elderly people found similar effects of nutritional supplementation on plasma vitamin status.[5,6,25]

One striking finding in our study was the very low vitamin D status. Vitamin D deficiency is very common in this population. We experienced a prevalence of >80% below reference value (30 nmol/L). In an editorial of Dawson-Hughes and colleagues[26] it was mentioned that there is no common definition of optimal vitamin D status and they agreed that this level should be between 50 and 80 nmol/L. Prevalence of vitamin D insufficiency is therefore much higher than previously believed. Vitamin D deficiency is caused by low exposure to sunshine, decreased synthesis of vitamin D in the skin and low dietary intake (in our study: 100% below reference). The Health Council of the Netherlands advised an adequate intake of 15 µg/day for people older than 70 years and hereby took into account that elderly people were not exposed to sunlight.[27] In our population none of the participants even reached an intake of 10 µg/day. In institutionalised elderly prescription of vitamin D supplements should be considered, because deficiency could possibly be related to physical functioning such as muscle strength which is a risk factor for falling and therefore also for fractures.[28,29] However, Lips and colleagues[30] were not able to find an effect of 400 IU/day vitamin D supplements in a RCT on fracture incidence in a group of independently living Dutch elderly. In a recent meta-analysis Bischoff-Ferrari and colleagues[29] suggest an intake of more than 700 to 800 IU/day of vitamin D (the biological activity of 1 µg vitamin D is equal to 40 IUs) for optimal fracture prevention in populations with low baseline 25-OH-vitamin D levels. In institutionalised elderly fracture incidence is high and therefore due attention is needed for vitamin D status of this population and adequate measures should be taken in case of low sunlight exposure and/or low dietary intake.

Physical functioning

Physical function should ideally be assessed by sensitive tools covering a wide range. We choose to use Barthel Index to evaluate the effect of nutritional supplementation on performance of Activities of Daily Living (ADL) as the Barthel Index is easy to administer and only takes a few minutes to fill out. During the study the score of our participants on Barthel Index turned out to be high reflecting a reasonable level of independency in activities of daily living. The addition of items from the Frail Elderly Functional Assessment (FEFA) did not affect the outcomes, because from the FEFA we added questions related to lower activity levels. So according to both methods the physical performance level of our participants was high. Barthel Index was used in two previous placebo-controlled trials in which the effect of nutritional supplementation was studied.[6,13] In accordance with their results, we also failed to identify any significant changes in physical performance with the Barthel Index. The results of our trial on performance of ADL would probably be more pronounced if a measurement tool with a wider range of functioning was used, because with Barthel Index we experienced a ceiling effect in our study population. Possibly the use of a specifically designed tool such as the Bristol Activities of Daily Living Scale[31] would have been more appropriate.

Besides ADL we measured changes in muscle function as indicator of physical function by measuring handgrip strength. The handgrip strength seemed more diminished in the placebo group in our trial than in the supplement group, but this difference was not statistically significant. In the subgroup of participants with low BMI at baseline the effect of supplementation seemed more pronounced but was not significant either. Other studies also failed to show a significant effect on grip strength.[5,16,18] These studies had however a shorter duration (8.5 - 12 weeks) than our study. Possibly handgrip strength is not sensitive enough to find effects of nutritional intervention in this population.

The methods we used to measure physical performance were easy to administer, but turned out not to be sensitive enough to detect an effect even after 24 weeks of intervention. Perhaps we should have used other outcome measures like functional performance tests (balance, gait, standing up).[32] Our data give the impression that the supplement can counteract a decrease in functional decline. Based on earlier studies we hypothesize that a combination with exercise will show a more pronounced effect[32,33]

and therefore possible combined interventions in institutionalised elderly should be investigated.

Mental functioning

Prior to our study we paid due attention to the assessment of changes in mental functioning. We choose cognitive function established by ADAS-cog as the primary outcome measurement to investigate the effect of nutritional supplementation on general mental function. This test is specifically designed to examine cognitive and behavioural disorders in Alzheimer's disease. Because of the applicability of the ADAS to other dementias, we used it as a measurement tool for mental functioning in our trial. In placebo-controlled trials testing the efficacy of medicines the cognitive subscale of the ADAS was used as primary outcome measure.[34,35] These pharmacological studies found a significant difference in change after 24 weeks of follow-up. This indicates that ADAS-cog is sensitive enough to detect an effect of intervention.

Our study is, to our knowledge, the first randomized placebo-controlled trial to investigate the effect of a complete supplement on mental function in institutionalised elderly people. Clarke and colleagues[36] described the use of ADAS-cog in their article, but did not present their data on the effect of treatment. Our study failed to show an effect on ADAS-cog in the total group of participants. In our subgroup analyses participants with low BMI at baseline in the supplement group had a difference in change of around 3 points compared to the placebo group, which was borderline statistically significant. This indicates that a decrease in mental function could possibly be counteracted in elderly people with deficiencies of certain nutrients.

Another study in institutionalised elderly people investigating the effect of nutritional intervention on cognitive function did find a negative effect on MMSE. This study had however a relatively small sample size (n=33) and did not use a placebo treatment.[21] Also in frail independently living individuals de Jong and colleagues[25] did not find a positive effect on neuropsychological functioning. A recent study in frail elderly by Wouters-Wesseling and colleagues[9] showed however that nutritional intervention for 6 months significantly improved scores on a word learning test and a category fluency test.

Power calculations (treatment allocation ratio = 2:1, α=0.05 (one-sided), 1-β=0.80) showed that we needed larger subgroups (>12 placebo and > 24 supplement) to observe significant results for ADAS-cog total score.

In this thesis we focused on the mental and physical part of decreased functioning. These parameters are not the only outcome measures to be affected by nutritional supplements. Dietary intake has also influence on factors like bone health, immune function and hearing. For those factors it is also important to have an adequate nutritional intake, which could be reached by improving dietary intake or using supplements.

Implications for health care

The findings as described in this thesis can contribute to nutrition policy in institutes for chronic care. We do not advocate that a complete supplement is indicated for all institutionalised elderly. However, as shown also in earlier Dutch studies, a large proportion of the elderly people in our study turned out to be prone to malnutrition. Due attention is needed to adequate intakes and to efforts to improve these intakes.

As already recommended in the Dutch guideline for fluid and food supply in nursing homes body weight should be measured in elderly people at admission to an institute for chronic care.[37] We suggest that BMI is calculated and that for every individual with BMI below 24 kg/m^2 (Chapter 4) usual weight (before onset of morbidity) and recent weight loss should be checked. Possible reasons for this low BMI should be identified and a strategy must be decided to improve dietary intake. Besides that, regularly, e.g. every 3 months, weighing institutionalised elderly might prevent serious malnutrition with taking adequate measures to improve food and nutrient intake. However, detecting weight loss is already late in the prevention of malnutrition; care takers might want an earlier warning signal. Early detection and treatment of diminished food consumption is important and therefore in institutes for chronic care residents should be regularly screened for decreased appetite. On the “observation card fluid and food” that is suggested in the Dutch guideline for fluid and food supply in nursing homes one of the questions is about decreased appetite.[37] Wilson and colleagues[38] developed a short questionnaire to identify persons at risk of significant weight loss (sensitivity for 5% weight loss in 6 months = 81.6% and specificity for 5% weight loss in 6 months =

84.6%). For these persons an accurate and quick measure should be taken to improve their usual diet. In case risk for malnutrition is present or expected shortly, e.g. because of illness or stress, efforts to increase energy and micronutrients intake might be indicated.

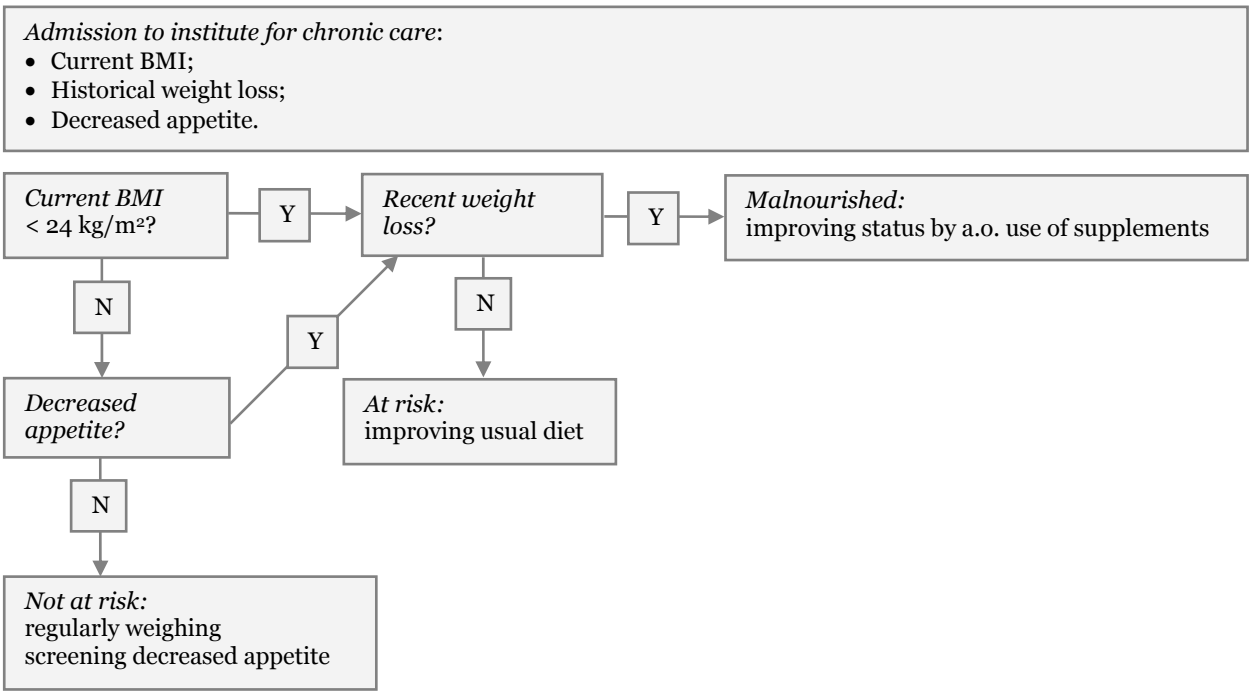

Figure 1 **Proposed flow chart to monitor risk of malnutrition/weight loss in institutionalised elderly (based on the findings of this study, not yet checked in practice)**

Recommendations for future research

In this thesis the positive effects of the applied intervention product are portrayed. The supplement had a positive influence on both the total study population and a specific sub group. Therefore future research should be focused on an efficient implementation in every day practice and the position of nutritional supplements in the Dutch guideline for fluid and food supply in nursing homes. For this implementation a few issues should be taken into account: which residents of the institutes are at risk for malnutrition, who is responsible for designing an adequate strategy to improve dietary intake if necessary and how can other risk factors for undernutrition be identified. One possibility to classify for "dietary risk" is to screen all residents for decreased appetite, recent weight loss and current BMI. Depending on the outcome of these screening, efforts should be made to improve usual diet (e.g. by solving the possible causes of the nutritional

problem as suggested by the Dutch guideline for fluid and food supply in nursing homes) or otherwise to temporarily provide nutritional supplements with physiological doses of several vitamins and minerals. The different decisions are indicated in figure 1. An implementation protocol needs to be developed by a team of different professionals in the institutes, because many persons are involved in dietary care of the residents. There are several ways to improve dietary intake and providing a nutritional supplement is one of them. In the future, efforts should be made to design a feasible and cost effective procedure in every day practice of improving dietary intake and providing nutritional supplements when indicated. In this procedure attention should be paid to monitoring and evaluation of supplement use. During our intervention trial use of the supplements was monitored in two weekly home visits to all participants. In institutes a better way could be to involve the monitoring in the report of usual daily care. For the evaluation of supplement use the procedure should be clear about who is responsible to decide about starting and stopping use of nutritional supplements.

In our trial we used several ways to evaluate the performance level of the participants. The existing indicators that we used for physical function turned out to be too insensitive in this study design. Therefore, in the future an appropriate way should be developed to get an overview of a person's functioning. Therefore more sensitive measures of functioning especially developed for institutionalised elderly people are needed to evaluate intervention strategies.

In our research it is not possible to determine which of the added nutrients was able to counteract the decline in function. Future research may focus on unravelling the processes involved in the relation between nutrition and function. By that it will be possible to develop a supplement that is applicable to certain disabilities. B-vitamins and n-3 fatty acids are very promising in the field of cognition. Vitamin D may have an important role in the improvement of physical functioning.

We are convinced that the group of institutionalised elderly is vulnerable and prone to malnutrition and adequate measures should be taken to improve their dietary intake to prevent and/or counteract functional decline. The Dutch multidisciplinary guidelines for fluid and food supply are an important step to improve the situation in institutes for

chronic care. We concluded from the findings of our study that our intervention improved nutritional status and in a subgroup also functional status.

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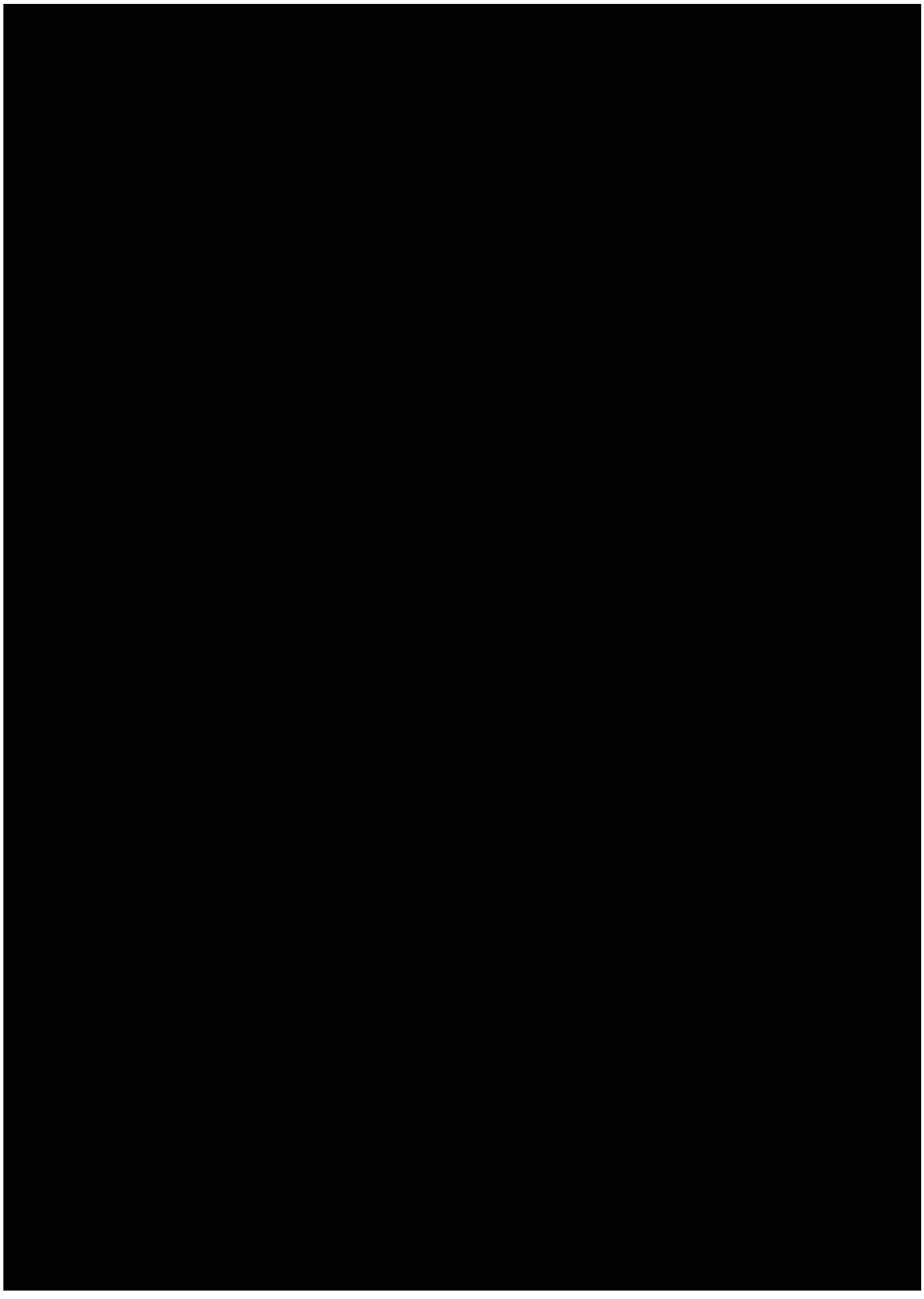


Samenvatting

Inleiding

Ondervoeding komt veel voor bij ouderen, die in verpleeghuizen of verzorgingshuizen wonen. Men schat de prevalentie op ongeveer 40%, maar het exacte percentage is afhankelijk van de definitie van ondervoeding. Hoewel de oorzaak van ondervoeding gelegen kan zijn in ziekteprocessen of absorptiestoornissen is deze bij ouderen dikwijls toe te schrijven aan anorexie met als gevolg een inadequate voedingsinname. Ondervoeding tast verschillende aspecten van functioneren aan en men heeft daarom naar methoden gezocht om ondervoeding te voorkomen en/of te behandelen, bijvoorbeeld door middel van suppletie met een compleet voedingssupplement. Onder een dergelijk compleet voedingssupplement wordt verstaan een verrijkte drank, bijv. sap of melk, met zowel een hoge macro- als micronutriëntendichtheid. Eerder onderzoek heeft aangetoond dat een compleet voedingssupplement de voedingstoestand verbetert, maar de studies waren te beperkt om het effect van een dergelijk supplement op het functioneren van ouderen te onderzoeken. Daarom hebben wij een interventiestudie uitgevoerd met een compleet voedingssupplement ten einde na te gaan of bij een studieduur van 6 maanden en een groot aantal deelnemers (n=176) een effect op het functioneren aantoonbaar is. De positieve resultaten van de pilotstudie wezen in die richting. We veronderstelden dat in deze langere studie verbetering van de voedingstoestand zou leiden tot een verbetering in functioneren (hoofdstuk 4), in vervolg op het verbeteren van de totale voedingsinname, zonder daarbij de gebruikelijke consumptie van de deelnemers te beïnvloeden (hoofdstuk 3).

Studieopzet

De studie was opgezet als een randomised controlled trial (RCT). We hebben negen verschillende verpleeg- en verzorgingshuizen in het zuiden van Nederland bezocht om deelnemers te werven voor ons onderzoek. Van de 1050 bewoners waarmee we in contact kwamen, waren 265 bewoners bereid te participeren. Vervolgens moest nagegaan worden of zij voldeden aan alle criteria. Bewoners waren geschikt om deel te nemen als ze 60 jaar of ouder waren, als ze langer dan 2 maanden woonachtig waren in de instelling, een BMI hadden van 30 kg/m^2 of lager en een Mini-Mental State Examination Score van 10 punten of hoger. Ouderen met ernstige co-morbiditeit (kanker, ernstige infectieziekten, gebruik van parenterale voeding of structureel gebruik

van sondevoeding, absorptiestoornissen, terminale zorg) of verstorende behandelingen konden niet deelnemen. In aanvulling op hun gebruikelijke voedingspatroon ontvingen de deelnemers (n=176) willekeurig een nutriëntdichte melkdrank of een placebodrank twee keer per dag gedurende 24 weken. Twee verpakkingen van de nutriëntdichte melkdrank leverden samen 250 kcal en vitaminen, mineralen en spoorelementen waren toegevoegd in ongeveer 25 tot 175% van de Nederlandse aanbevelingen. De placebodrank bevatte geen energie en vitaminen en mineralen. Toewijzing aan de behandeling hield rekening met het geslacht, de MMSE score en het niveau van homocysteine in het bloed om de verschillen in gezondheidstoestand en functionaliteit aan het begin van de studie tussen de beide groepen te verminderen. Twee derde van de deelnemers gebruikte de nutriëntdichte melkdrank (n=119) en een derde de placebodrank (n=57). De antropometrische waarden (gewicht, kniehoogte en kuitomtrek) en nuchtere bloedwaarden (albumine, pre-albumine, CRP, vitamine D, B-vitaminen homocysteine en MMA) werden bepaald als uitkomstmaten. Voedselconsumptiegegevens werden nagegaan in een subgroep (n=66; supplementgroep: n=45, placebogroep: n=21). Verder werden lichamelijk en psychisch functioneren gemeten met verschillende vragenlijsten en testen (knijpkracht, Barthel Index, FEFA, ADAS-cog, verbal fluency en GDS).

Resultaten

Het gebruik van het complete voedingssupplement had een gunstig effect op de kwaliteit van de voeding (hoofdstuk 3). Er was bijvoorbeeld een significant ($p<0,001$) positief effect op de inname van vitaminen en mineralen. Daarnaast was er een duidelijk verschil in verandering in totale energie-inname tussen de twee behandelingsgroepen ter hoogte van 0,8 MJ/dag ($p=0,166$). Vrijwillige energie-inname verminderde in beide groepen even sterk (-0,5 MJ/dag), zodat gesteld kan worden dat de deelnemers niet compenseerden voor de energie-inhoud van het product.

Dit positieve effect wordt ondersteund door de veranderingen in de voedingstoestand (hoofdstuk 4), waarbij de resultaten van de interventiegroep gunstig afstaken ten opzichte van de controlegroep. Deze veranderingen hielden onder andere verbeteringen in van: 1) lichaamsgewicht (1,6 kg verschil in verandering; $p=0,035$), 2) kuitomtrek (0,9

cm verschil in verandering; p=0,048) en 3) vitaminestatus in het bloed (bijv. Hcy daalde van 16,8 tot 11,2 µmol/L in de supplementgroep).

In de onderzoeksgroep werden geen algemene effecten van de interventie gevonden op lichamelijk functioneren. In een subgroep van deelnemers met een lage BMI (<24,4 kg/m^2) bij aanvang van de studie werd wel een positieve invloed gevonden op het cognitief functioneren (ADAS-cog (p=0,09) en taal subscore (p=0,01)).

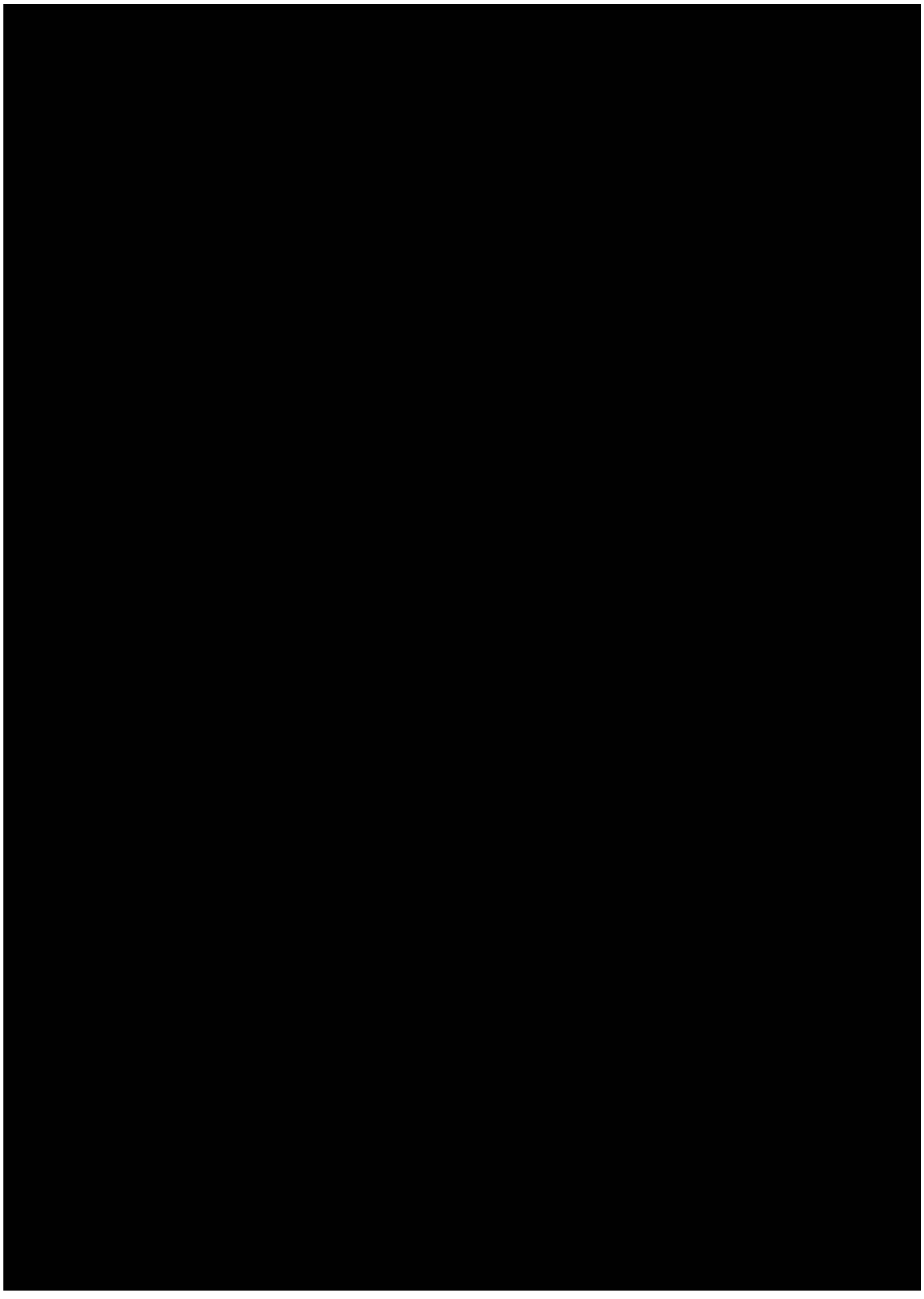
Discussie en conclusie

In de algemene discussie in hoofdstuk 6 zijn de belangrijkste bevindingen van de interventiestudie bediscussieerd. Allereerst hebben we de selectie van de onderzoekspopulatie besproken en daarbij geconcludeerd dat het ons gelukt is een populatie te selecteren die vatbaar was voor ondervoeding en kleine functionele problemen had. We hebben in deze studie een product gebruikt met fysiologische doses van micronutriënten. Mogelijk was het effect op functioneren meer uitgesproken geweest als hogere doses waren gebruikt. Ondanks onze zeer gemotiveerde deelnemers hebben we helaas moeten constateren dat het niveau van compliance laag was, maar betere compliance had waarschijnlijk niet geleid tot andere conclusies. In hoofdstuk 6 is verder besproken dat niet voor de energie-inhoud, maar wel voor het volume van de nutriëntdichte melkdrank is gecompenseerd en kan geconcludeerd worden dat in voedingsinterventies supplementen met een laag volume het meest geschikt zijn. De gebruikte uitkomstmaten zijn de beste uit de beschikbare instrumenten voor onze populatie. Resultaten zijn vergelijkbaar met eerdere studies in vergelijkbare populaties. Een opmerkelijke bevinding is de hoge prevalentie van vitamine D deficiëntie. Adequate maatregelen moeten worden genomen indien geïnstitutionaliseerde ouderen weinig worden blootgesteld aan zonlicht en/of als zij een lage inname van vitamine D hebben.

De resultaten van het onderzoek kunnen gebruikt worden bij het opstellen van voedingsbeleid in de verpleeg- en verzorgingshuizen. In hoofdstuk 6 doen wij een voorstel voor een flowchart. Hiermee kan tijdig het ontstaan van ondervoeding gesignaleerd worden en kan zo mogelijk preventief ingegrepen worden. Adviezen daarin zijn onder andere het regelmatig (iedere 3 maanden) wegen van bewoners en het gebruik van een screeningsvragenlijst voor verminderde eetlust. Onderzoek zou in de toekomst gericht moeten zijn op een efficiënte implementatie van het gebruikte

supplement in de dagelijkse praktijk, waarbij beleid gericht moet zijn op zowel het verbeteren van het dagelijkse voedselpakket als het verschaffen van voedingssupplementen zodra dit gewenst is.

We concluderen uit de bevindingen van onze interventiestudie dat de interventie die we hebben gebruikt de voedingstoestand verbetert en in een subgroep mogelijk ook de functionele status.



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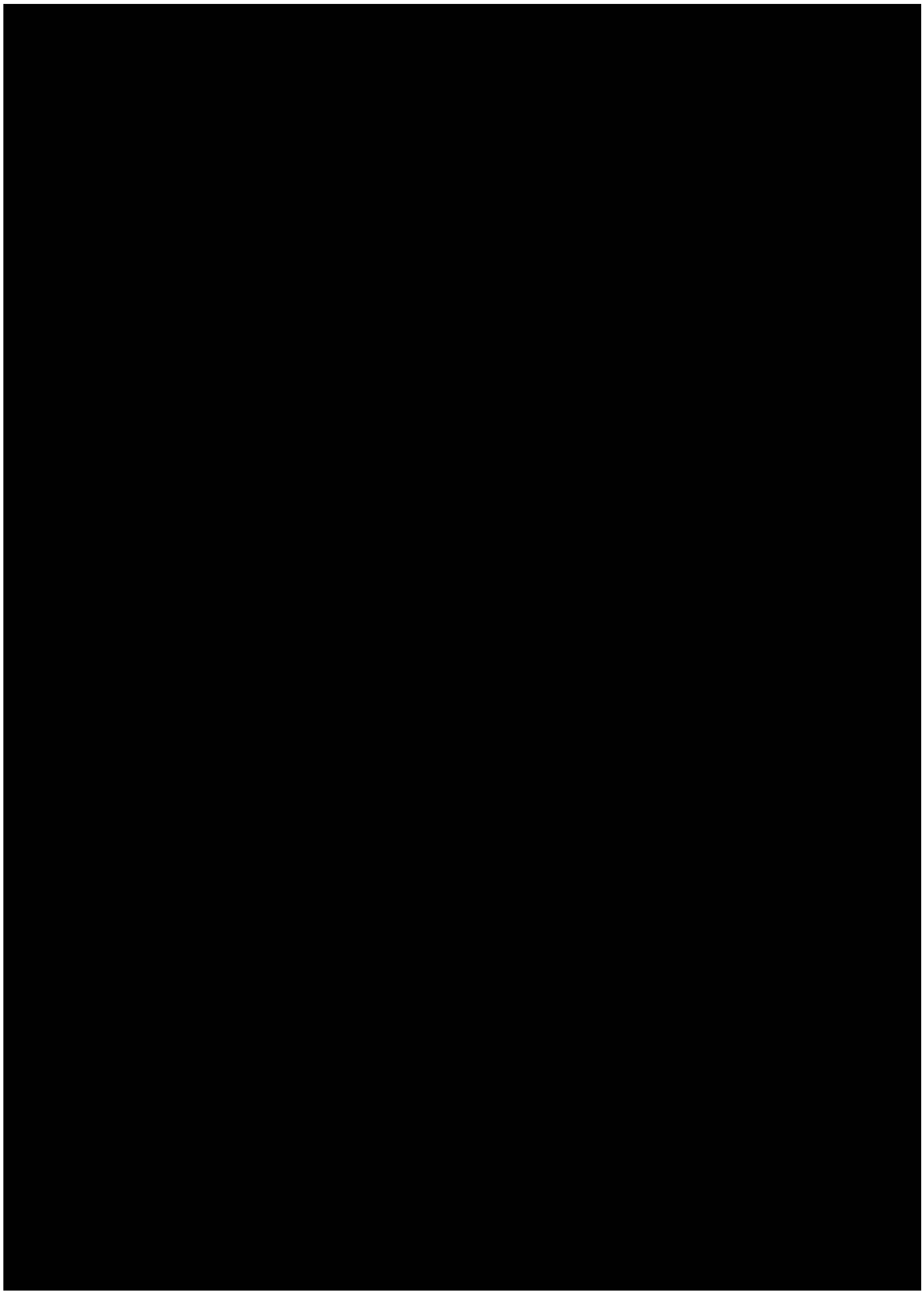
Marleen



About the author

Curriculum vitae

Marleen Manders was born on the 8th of April 1976 in Veldhoven, the Netherlands. After completing secondary school (VWO) at the "Anton van Duinkerkencollege" in Veldhoven in 1994, she started studying Human Nutrition at the former Wageningen Agricultural University. As part of that study she conducted a research project on falling in frail elderly at the Division of Human Nutrition and Epidemiology, Wageningen Agricultural University. She spent a 5 months training period at the Research Department of Human Nutrition, The Royal Veterinary and Agricultural University, Copenhagen, Denmark. Subsequently she conducted a research project on energy metabolism and body composition in young children with Prader-Willi syndrome at the Department of Human Biology, Maastricht University. Finally, she spent a 5 months training period at the Regional Health Service Nijmegen. In 1999 she received her MSc degree with majors in human nutrition, physiology and communication and innovation. In October 1999 Wageningen University, Division of Human Nutrition and Epidemiology, appointed her as a PhD-fellow to conduct a trial on the effect of daily intake of a nutrient dense product on physical and psychical functioning in elderly people as described in this thesis. She joined several conferences and followed courses on nutrition and geriatrics within the framework of the educational programme of the Graduate School VLAG (Food Technology, Agrobiotechnology, Nutrition and Health Sciences). She participated in several discussion groups of the Division of Human Nutrition. She is currently working as Senior Scientist Nutrition at Masterfoods, Veghel, the Netherlands.

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Manders M, de Groot CPGM, Blauw YH, van Hoeckel-Prüst L, Bindels JG, Siebelink E, van Staveren WA. Effect of a nutrient enriched drink on dietary intake and nutritional status in institutionalised elderly. *Submitted for publication*

Abstract in scientific journal or proceedings

Manders M, de Groot L, Hoefnagels W, Bindels J, van Staveren W. Institutionalized elderly and the effect of a nutrient dense supplement on health status. *Journal of Nutrition, Health & Aging*. 2003;7(4):213-4 [abstract]

Peer reviewed book chapter

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Educational programme (selection)

Discipline specific activities

- Meetings NWO Nutrition, Arnhem, 1999-2004
- Symposium “De voeding van Nederland in de twintigste eeuw”, NVVL, Ede, 1999
- Najaarscongres “Voeding in het verpleeghuis, een kwestie van smaak?”, NVVA, Ede, 1999
- Symposium “Geriatriedagen: Continuïteit van zorg(en), VVVG & NVvG, Ede, 2000
- Symposium “Ouder worden in Nederland: 10 jaar LASA”, VU Amsterdam, 2000
- Third European Congress on Nutrition and Health in the Elderly People, Madrid, Spain, 2000
- Advanced course “Nutritional and Lifestyle Epidemiology”, VLAG, Wageningen, 2001
- Symposium “Homocysteine, folate and vitamin B12 in cardiovascular and neurological diseases”, UMC St Radboud, Ravenstein, 2001
- Symposium “Cognitieve veroudering: performance, determinanten en interventie”, IHG, Maastricht, 2003
- Second International Meeting IANA, Albuquerque, USA, 2003
- Forumdag “Dementie nader bekeken”, FOVV, Utrecht, 2003
- Masterclass “Geriatric Nutrition: diet, functionality and disease”, VLAG, Wageningen, 2004
- Fourth European Congress on Nutrition and Health in the Elderly People, Toulouse, France, 2004

General courses

- VLAG PhD week, Bilthoven, 1999
- Systematic literature search: identification, extraction and analysis, NUTRIM, Maastricht, 2000
- Organising and supervising thesis work, Wageningen University, Wageningen, 2001
- Scientific Writing, Wageningen University, Wageningen, 2003
- Talentendag “Werken aan een carrière in de wetenschap”, NWO, Zeist, 2003
- VLAG Successful functioning in organisations, Wageningen, 2003

Optional courses and activities

- Preparation PhD research proposal, Wageningen University, 1999
- PhD Study Tour to Switzerland, Italy and Germany, Wageningen University, 2001
- Oldsmobiles Club, Wageningen University, 1999-2005
- Journal Club, Wageningen University, 1999-2001
- Homocysteine Club, Wageningen University, 2001-2004

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