Sensible Aging

Nutrient dense foods and physical exercise for the vulnerable elderly

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In herinnering aan de pakes
Voor beide beppes

Stellingen

1. Verrijkte voedingsmiddelen en lichamelijke activiteit lijken een complementair, gunstig, effect op de lichaamssamenstelling van ouderen te hebben. Het belang hiervan, ter verlichting van osteoporose en sarcopenie, wordt thans waarschijnlijk onderschat.
   O.a. dit proefschrift.

2. Voedingsmiddelen, verrijkt met een fysiologische dosis aan vitaminen en mineralen, zijn potentieel simpele, gebruiksvriendelijke en goedkope middelen om de voedingstoestand van fragiele ouderen te verbeteren.
   Dit proefschrift.

3. Zolang er geen duidelijke, uniforme criteria zijn voor fragiliteit, is onderlinge vergelijking van interventiestudies, uitgevoerd bij fragiele ouderen, moeilijk.
   O.a. dit proefschrift.

4. De opvatting van veel ouderen dat er vroeger meer smaak aan voedingsmiddelen zat dan tegenwoordig, kan verklaard worden uit een achteruitgang in geur- en smaakwaarneming met de leeftijd.

5. Beoordeling van de 'aangenaamheid' van gratis verstrekte voedingsmiddelen, door een generatie die de Tweede Wereldoorlog nog heeft meegemaakt, levert geen betrouwbare resultaten.

6. Onderzoek doen bij ouderen is dubbel investeren in de eigen toekomst.

7. Vervoer op tijd is beter dan vervoer op maat.

8. Voor onze kennisintensieve samenleving is vergrijzing een zegen.

9. De efficiëntie van een non-profit instelling is negatief gecorreleerd aan de gelaagdheid van haar organisatiestructuur.

10. Het vierjarige keurslijf van een promotie-onderzoek is achterhaald in een tijd van flexibiliteit.

11. 'Morgen zal alles anders zijn'. Dit is niet juist.
Bart Johannes Beers in 'De beste stellingen zijn van hout' – uitspraken van Delftse promovendi.

12. Minima verdienen evenveel aandacht als Maxima.
Ingeborg Brouwer en Nynke de Jong.

Stellingen behorend bij het proefschrift

Sensible Aging – Nutrient dense foods and physical exercise for the vulnerable elderly

Nynke de Jong
Wageningen, 19 oktober 1999

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1

General Introduction

The aging of the populations of developed as well as developing countries is well recognized. Demographic statistics show frequently increasing numbers of elderly over 65 years of age in the Netherlands (2.1 million to day) compared to numbers calculated in the seventies or eighties (1.6 million in 1980)[1;2]. Life expectancy has increased as well, but how much of this is 'disability free life expectancy' is a topic of much interest. Dutch men of 55 years of age have on average still 22.6 years to live of which 14 years should be healthy. For Dutch women this constitutes 16 healthy years of an expected total of 27.6 years[3].

As a consequence of present western health politics, the development of institutional care has been curtailed to limit governmental expenditure on health care. Less commonly mentioned is, for instance, the decreasing number of Dutch elderly homes and their inhabitants. In ten years time, approximately 175 homes have been closed, which was associated with a decline in the total number of residents from 0.14 to 0.11 million[1;2]. Consequently, an increasing number of elderly sustain an independent living in the community. Home-care services, social services and meals-on-wheels programs are of increasing value in assisting older people. Approximately, 90% of senior citizens visiting a general practitioner are experiencing minor or major functional disabilities[4]. The Dutch home-care registered 0.5 million clients in 1996 of which 75% were aged 65 years or older. A yearly increase of 3% in this age category was met. Similar statistics were found among the clientele of the meals-on-wheels services[5;6]. Hence, it is not surprising with clients and total costs rising, that a considerable burden and stress is placed upon these civil institutions and perhaps in the near future upon the total health care system[7]. The increase in societal costs and magnitude of elderly services, gives rise to discussions among politicians, administrators, researchers, care-givers and insurers. Elderly health promotion, ailment and disability prevention, meant to improve functional independence and quality of life, are given a high priority. In this respect nutritional research is acknowledged as an affirmative action.

The demographic statistics described above are based on classifications of elderly in order of chronological age. The aging population, however, is very heterogeneous within an individual (as organs and systems age differently), as well as between individuals due to different genetics, environment, social and economic circumstances[8]. In Figure 1.1 important determinants of aging are presented. The process of aging is based on a complex system with factors that can respond to feasible interventions, e.g. change in lifestyle factors, medication or perhaps environment. There are however also factors that are less susceptible to change, e.g. genetic factors. With the pace of aging differing from individual to individual, three categories of aging based on biological characteristics have been proposed. First, *successful agers* with little or no loss in functioning are noted; second *usual agers* who have a variety of chronic medical conditions and disabilities but are still living independently, and third *accelerated agers* who carry a heavy burden of chronic diseases and disabilities[9-11].

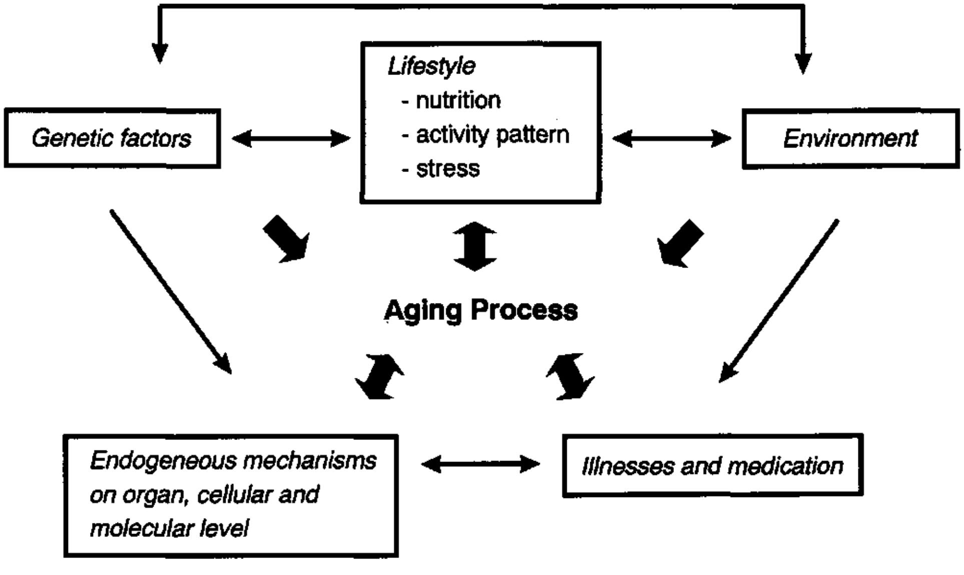

Figure 1.1: Determinants of aging, based on Eulderink et al. and Knook et al. [12;13]

Physical frailty

Among the three categories of aging, physical frailty may begin, leading eventually to a vulnerable status. Several definitions of frailty have been postulated in geriatric literature[14], but a practical explicit definition is still lacking[15]. Frailty may be regarded as a chronic disease[16] threatening the life expectancy, but may also be described as just part of the aging process[15]. An example supporting the latter statement is the broad definition of 'those elders who are neither too well, nor too disabled'[17]. Chronological age indications or living conditions are sometimes taken into account: 'frail elderly are individuals of more than 65 years of age who depend on others for the activities of daily living and who are often under institutional care'[18]. Finally, Buchner and Wagner (1992) tried a more physical approach in defining frailty as 'a state of reduced physiologic reserve, associated with an increased susceptibility of disability'[19]. The practical operation of the latter definition is, however, still indefinite. Propositions, directing to inactivity, medicine use, depression, feeding patterns, weight loss, low body weight or other low bodily measures like arm circumference and muscle strength have been made[19-22], but not thoroughly or appropriately tested in well-controlled intervention studies.

The assessment of functional status is an important decisive factor in defining physical frailty. Several domains of functioning have been proposed: i.e. physical, cognitive, emotional, sensory and/or social functioning[23]. Physical and cognitive dysfunction have the greatest impact on the overall burden, but emotional problems like depression, and sensory aspects like visual and hearing problems or even a declining taste and smell perception are known to contribute[24]. Widowhood is a good example of a mediating factor in social functioning. Consensus has been reached regarding frail elderly finding themselves in a precarious balance of assets and deficits. With passing time a continuous downward process will be established, leading to loss of physiologic reserves and finally to unfavorable institutionalization. Yet, physical frailty may be treatable or even preventable[14;15], thereby improving the quality of elderly life.

This latter belief was the starting point for the intervention trial in frail elderly described in this thesis. As shown in Figure 1.1, two important contributors to the process of aging, which may be susceptible to change, are nutrition and activity pattern. Since physiological reserves in the frail are reduced[19], we should aim on replenishment through improved food intake (with, for example, nutrient dense foods) and higher activity level. In assisting the frail elderly to remain autonomous and to enjoy a better life[25] minimizing the risk on (developing) nutritional deficiencies is emphasized [26;27].

Causes of the complex state of frailty

The adaptation of a sedentary lifestyle influences hunger, appetite, and consequently dietary intake. This is mainly induced by a lowering of the total daily energy expenditure. In sedentary individuals an important determinant of energy expenditure is the absolute amount of active metabolic tissue, i.e. fat-free mass and it is estimated that this tissue declines by about 15% between the third and eight decade of life[28-30]. The decline in fat-free mass and energy expenditure in the older individual will, at first, lead to excess storage of fat since energy intake is not reduced concomitantly. Energy intake exceeds requirements and results in an increased prevalence of obesity in middle-aged and younger-old individuals. However, in the oldest-old the amount of reduced physical activity, fat-free mass, and energy expenditure affects appetite and total dietary intake so that it becomes increasingly difficult to meet micronutrient requirements.

In addition, age-related decline in sensory perception, influencing the taste and smell of food, may limit food enjoyment[24;31;32]. Dietary intake may decline and the risk of developing nutrient deficiencies may be further increased. Along with this, a reduced absorption and utilization of several nutrients may escalate in the elderly. Adverse drug-nutrient interactions and altered drug metabolism in the frail may interfere as well[33-35], but controversy still exists with respect to the eventual influence of drugs on the nutritional status[36-39]. Synergistic actions of all modifiers may finally lead to detrimental blood nutrient levels and, perhaps, to adverse functional biochemical health indicator levels.

Another consequence of the disuse and wasting of muscle mass, by virtue of inactivity, is the related decline in bone mass and bone density[40-42]. The decrease in muscle mass is eventually responsible for a reduction in aerobic capacity, physical fitness and functioning[43-47]. A fear of falling may be developed and a further sequential deterioration in activity may result. Hereby a vicious circle is inevitably set. With the introduction of feasible exercises (to improve physical activity level) plus the preparation of enjoyable nutrient dense foods in small portions (to overcome the risk of nutritional deficiencies) an upward tendency, reversing the deteriorating process, may be introduced.

Aim of the study

A lot of research, performed on elderly until now, has focused on either apparently healthy elderly or institutional residents. The frail elderly, defined here as those who are trying to uphold their lives within their private homes in the community, have not been given much attention up to date. This is partly due to the fact that they do not easily respond to advertisements or calls to participate in trials, in contrast to healthy elderly. Research on the frail, is in the first place important because their nutritional and health status is likely to be different from healthy elderly. Many recommendations are based on research in the latter group and it is important to supplement our knowledge with data about the frail (less healthy) ones. The possibility of keeping them healthy and strong in their own surroundings and thus improving their quality of life, through relatively simple means seems a rather realistic and worthwhile goal. Supply of customary nutritious food and effective but moderate intense exercise programs may be examples of feasible interventions. Aiming for optimization of their quality of life while simultaneously reducing governmental expenses and stress placed upon the health care system should be key factors in current policy. Furthermore, valuable new data are needed to add to the current debate about the sense or nonsense of functional (enriched) foods for the elderly.

Research on the potential benefits of these types of interventions is important. However, a good appraisal of the newly developed interventions is a pre-requisite for future implementation. This point has been under-emphasized in most studies focusing on effectiveness.

Summarizing, the research questions addressed in this thesis are:

a. What is the nutritional status of Dutch frail elderly people?
b. What is the effect of specially developed nutrient dense foods and physical exercise on the nutritional and health status of the Dutch frail elderly?
c. What is the appraisal of nutrient dense foods by frail elderly?

Proposed interventions

nutrient dense foods

The risk of the frail elderly developing a suboptimal or deficient nutritional state is substantial. Underlying causes are diverse, as has already been outlined. Many intervention trials in elderly have focused on the effectiveness of a single nutrient on a single outcome parameter or have studied the application of highly dosed supplements. However, a suboptimal nutritional and health status which is caused by long term inactivity, low energy expenditure and, as it progresses, a deprived appetite and overall nutritional intake should be improved by a multiple nutrients approach. These elderly are most probably in need of a whole range of nutrients instead of a single isolated nutrient[48]. In addition the action of many nutrients may be complementary and, therefore, several balanced foods containing a range of vitamins and minerals, frequently characterized as deficient in elderly people, should be designed. Those with a poor appetite and low activity level may benefit most from an increase in the density of the diet instead of volume. Subsequently, small portions, palatable throughout the day and easy to include in all daily meals are needed. Inactive persons may achieve a new energy balance on a lower level, therefore, extra energy provided by the macronutrients fat or carbohydrate is questionable.

In addition to the information on isolated nutrients, research on pharmaceutical dosed supplements and lack of information on the distinction between sufficient and excessive use[35] should be noted. In our opinion, supply of physiological doses of nutrients, based on recommended daily allowances should be sufficient in order to overcome present deficiencies. The development of food products thereby is preferred above the use of tablets, since foods still contain other important nutrients as well as non-nutritive ingredients (e.g. dietary fiber). Furthermore, another tablet in addition to most probably frequently used prescribed medicines is unattractive. Details about the types of products used in our intervention trial, the exact amount of nutrients added to the products and the acceptance of the products by the subjects, can be found in *Chapters 3 to 7*, and the appendix of this thesis, moreover in our supplementary article describing the variability of the micronutrient content of the foods during the whole intervention period (de Jong et al., submitted).

physical exercise

Another important contributor to the downward process of frailty, which might be manipulated, is physical inactivity. A higher activity level might introduce a better appetite and nutritional intake and thus cause a beneficial effect on the nutritional and health status[49]. In this way synergy between both programs may even be established[50]. As skeletal muscle atrophy due to disuse is common, our exercise program aimed at altering muscle structure and mass. These alterations are likely to influence the functioning of essential and less important muscle groups. Physical activity will improve gait, postural control and functional mobility[50-52]. Maintenance or improvement of the performance of present daily activities by regular applicative exercise may prolong independent physical functioning in the elderly[28;45;53]. Until now several exercise programs have been developed and investigated on their effectiveness on health indicators[42;51;52;54], however, they mostly focus on resistance training.

In our all-round exercise program, emphasis has been placed on skill training, such as walking, stooping, lifting, and (chair) standing. Indirectly it, thereby, aimed at improving muscle strength, co-ordination, flexibility, speed and endurance. The program intended to be moderate intense and was gradually increasing. The all-round aspect due to a diversity of types of exercises and materials applied, instead of frequently repeated types of exercises was assumed to be appealing to frail elderly. Improvement of compliance but also testing of the feasibility of any of such program in daily elderly life were important goals of this diverse approach. Details about the design of the program can be found in the complementary thesis of Marijke Chin A Paw[55]. In the following section indicators of the nutritional and health status investigated in this thesis are briefly introduced.

Sensory factors and appetite

One of the domains influencing frailty is sensory aspects. Visual and hearing problems are essential elements but with respect to the nutrition intervention, taste and smell perception are also key factors. It is well established that sensory perception declines with age[32;56-58]. This decline is more evident in the sense of smell than the sense of taste and is often more distinct in men than in women[56]. Along with neurological changes during aging explanations such as diminished release of flavors due to impaired saliva flow combined with difficulties in chewing (bad fitting dentures) and swallowing, medications (causing a dry mouth or off-flavors) and smoking behavior have been investigated with mixed outcomes[35;56;59-63]. Reduced taste and smell perception may have a negative impact on appetite and hunger feelings, thereby reducing food enjoyment and finally total dietary intake[24].

However, while chronologic age-related decline has been well documented, the relation between a) sensory factors and other (age-related) contributors and b) sensory factors and food intake, through appetite and hunger feelings is less clear. In *Chapter 2* this topic is presented. Since food enjoyment is one of the stimuli which remains important until the very last end of life[64], a lot of work still needs to be carried out, gaining more insight into the declining sensory system, its impact on the quality of life and the way of dealing with it. The effectiveness of nutritional supplementation and physical exercise on sensory factors related to appetite, feelings of hunger and dietary intake in frail elderly has not been thoroughly investigated so far. *Chapter 3* deals with this topic.

Energy and nutrient intake

Total food intake may be related to the above mentioned taste and smell perception, but is more clearly associated with physical activity level, again for a substantial part through appetite. Inactivity leads to a decline in total energy expenditure. The age-related decrease in resting metabolic rate also accounts for this decline. Due to inactivity and the biological aging process, the total amount of active cell mass will be reduced, thereby preserving basal metabolic functions in first instance but reducing body reserves. The lower energy expenditure induces a poorer appetite and consequently a lower dietary intake. In terms of energy and its carriers (fat and carbohydrates), a new balance can be achieved since an inactive human being needs less 'fuel'. This is less clear for protein since extra protein may be needed for frequent repair of tissue. On the other hand renal function declines with age[65] and may affect the balance of elements whose main route of excretion is via the kidneys such as protein degradation substances. Caution, therefore, is warranted when supplying large amounts of protein to the elderly.

Apart from the macronutrients, a lot of bodily functions may need the same or perhaps an increased (due to diseases and dysfunctions) flow of micronutrients. However, special recommendations for elderly are frequently based on extrapolations of recommendations for younger adults. Hence, these recommendations need to be put forward in new and ongoing research[35;66;67]. Nevertheless, a multiple micronutrient deficiency is not a preferable state and elderly people with a poor appetite and low activity level may benefit from an increase in the density of the diet. Small portions of micronutrient dense foods should help in ensuring a constant micronutrient intake. Increasing the physical activity level, energy expenditure and indirectly dietary intake is another important opportunity, but is perhaps more difficult to achieve. A description of the intake of our frail elderly at baseline compared to healthy elderly and the effectiveness of our interventions in raising dietary intake are illustrated in *Chapters 3 and 4*.

Biochemical parameters of nutritional and health status

Dietary intake is not always predictive of the actual nutritional status. Other factors like diseases present and medicines may act as underlying causes for a different outcome of the nutritional status. Several studies on the elderly show correlation coefficients between intake data and biochemical indices of nutrients that vary between 0.0 to 0.6, depending on the type of nutrient, but also on the method of measuring[68;69]. Numerous biochemical indicators can be selected to define nutritional and health state but none is the absolute key descriptor on its own. It is important to select several indicators since they all vary in estimated half life, body pools and responsiveness to conditions related to malnutrition[48;70].

Until now, very few well-controlled trials investigating effects of both interventions have focused on biochemical evidence. It is expected, however, that especially frail elderly might suffer from suboptimal states and benefit from supplementation or exercise. Several direct measures of vitamins or derived functional tests indicative of vitamin status in blood have been performed to describe baseline vitamin state and change after intervention (*Chapter 4*). Checking compliance regarding the consumption of nutrient dense foods was an additional aim. Likewise, several other biochemical markers of malnutrition and/or illnesses have been measured to define nutritional and health status at baseline and after intervention. Emphasis has been placed on circulating proteins like albumin, pre-albumin, transferrin, ferritin and C-reactive protein. Hematological indicators such as hemoglobin, hematocrit, percentage lymphocytes and blood cell count have been described as well.

Homocysteine

An example of a functional measure of nutrition and health state is plasma homocysteine level. Interest in homocysteine level, as an independent risk factor for cardiovascular disease has grown eminently during the last decade. Deficiency in vitamins B_6, B_{12} and/or folate, all serving as co-enzymes in the metabolism of homocysteine, cause unfavorable elevated levels of this metabolite[71-74]. Frail elderly are at high risk for suboptimal or deficiency states and therefore have a serious elevated risk for high homocysteine levels. Another reason for outlining these B-vitamins is that deficiency in vitamin B_{12} and folate have been associated with neurological abnormalities[75-77]. *Chapter 5* describes the homocysteine state, the performance on two tests indicating neurological functioning, the vitamins involved, and the effectiveness of our interventions on these parameters.

Body and bone composition

Advancing age is associated with changes in body and bone composition. This is partly due to the direct effect of biological aging but is also due to diseases, inactivity and inadequate dietary intake. Changes in body composition have been differentiated in three categories: wasting (i.e. unintentional loss of total weight, including fat and fat-free mass), cachexia (i.e. loss of fat-free mass but little total weight loss) and sarcopenia (i.e. loss of skeletal muscle mass)[78]. Wasting may only develop at the far end of the 'life spectrum', but sarcopenia and cachexia may be pre-existing. Sarcopenia accounts for age-associated decreases in resting metabolic rate due to a decline in active cells and in activity levels, both, in turn, the cause of decreased energy requirements. Substantial additional effects of sarcopenia, due to disuse of muscles, on muscle strength, bone density (because of lack of regular substantial mechanical load) and functional capacity have been documented[28;43;45;46;79-81]. Although the effects of sarcopenia seem to be enormous, the public health significance of this process is still not fully appreciated.

Osteoporosis, on the contrary, has been recognized as one of the most important disorders associated with aging. It is characterized by a reduction in bone mass and an alteration of bone architecture leading to an increased susceptibility to fracture[82]. Causes should be sought in age-related factors and nutritional factors, with emphasis on vitamin D and calcium[83;84]. More recently, vitamin K[85] and cobalamin[86] have been mentioned. Controversy exists regarding the effect of dietary protein on bone. Extra protein may induce a higher urinary excretion of calcium, and may reflect a higher bone resorption, although not all studies support these findings[87].

The potential of osteoporosis to cause suffering is acknowledged. Maximizing the peak bone mass, its maintenance as long as possible and prevention of bone loss in old age are (therapeutic) objectives for the restoration of bone and prevention of osteoporotic-related fractures[88]. In our study we have investigated body composition (e.g. fat-free and fat mass) as well as bone mass and density. The changes due to the interventions are described in *Chapter 6*.

Design of the study

Subjects were recruited in Wageningen and surrounding municipalities. Several approaches were used: a) co-workers of home-care institutions were asked to encourage their clients to participate, b) letters, via meals-on-wheels services, were sent to ask customers to participate, c) letters, were distributed in elderly homes, as in d) social services centers for elderly, e) there was recruitment via general practitioners, and f) articles in local newspapers. After sending of the written information brochure, meetings with all initially interested were organized in order to explain the purpose of the study. Furthermore, the opportunity was provided to meet the investigators involved. During the meeting, it was emphasized that everything (including all transportation) would be arranged and that both intervention programs were especially designed for all elderly (even those not feeling too well). The design, selection criteria and subjects flow are presented in Figure 1.2. After assuring eligibility, subjects were randomized into one of four groups. Figure 1.2 shows that the study followed a 2x2 factorial design, which permitted us to investigate possible interaction between nutrient dense foods and exercise. In case of no interaction, we would be able to separate between both main effects.

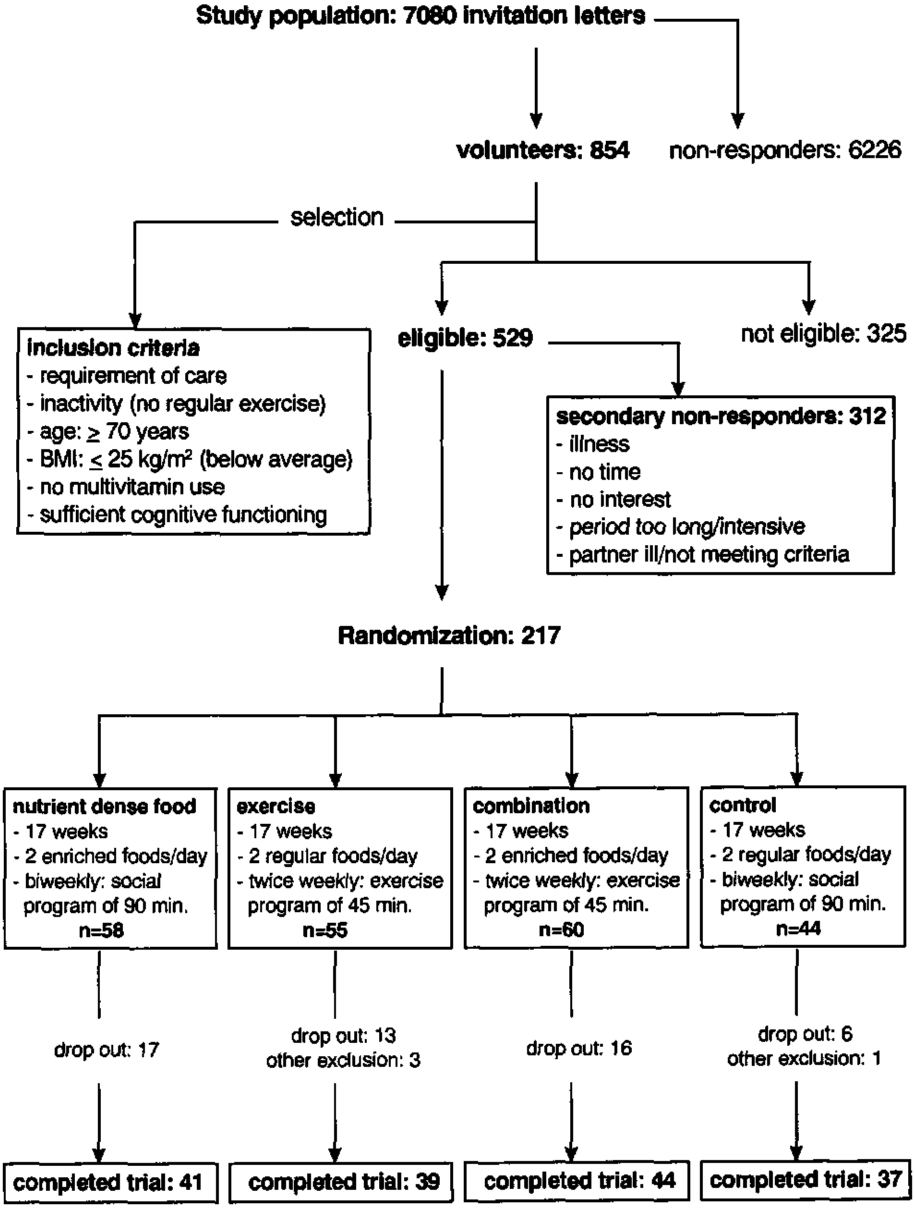

Figure 1.2: Outline of the design of the study and flow of subjects

Randomization is important for comparability of all factors (known or unknown to the investigator) that may affect the final results. A control group was added to investigate a possible placebo effect, i.e. the effect of just consuming regular foods and attention on the health and nutritional status. The purpose was to recruit 50 participants in all groups, because a substantial drop-out was expected. Before the actual start of the study all participants signed consent forms. Moreover, the subjects' general practitioners signed an agreement in which they agreed to their patients' participation.

The study period was 4 months (17 weeks). This period was based on evidence from earlier studies[51;89] which had demonstrated partial effects from exercise or nutrition on nutritional and health status indicators after only 10 or 12 weeks of intervention. Mann et al.[90] showed effects on the blood vitamin state after 4 months. In addition, red blood cells have a complete turnover period of approximately 16 weeks and the maximum possible biochemical effect should have been established by that time.

A longer intervention period would probably have negatively affected compliance and would have caused more problems with recruitment and logistics. At baseline (week 0) and after 17 weeks of intervention (week 18) data were collected. Exceptions were the collection of the energy and nutrient intake data, which were obtained in the last week of intervention. Information about the appraisal of the nutrient dense foods was gathered at the beginning (weeks 1 and 2) and during the last two weeks of intervention (weeks 16 and 17).

Outline of the thesis

In this thesis, the effectiveness of consuming multiple nutrient dense foods, containing a physiological dose of several micronutrients and an all-round moderate intense exercise program, both specifically designed for frail elderly, is described. Emphasis is placed on the following outcome parameters: sensory functioning, appetite, food intake, biochemical nutritional/health indicators and bone and body composition. The complementary thesis of Marijke Chin A Paw[55] focuses on several other health aspects: physical fitness and functioning, immune response and subjective well-being.

In *Chapter 2* a preliminary study is described. Two different elderly populations, i.e. free-living versus institutionalized are compared with respect to their taste and smell perception, possible determinants, appetite and food intake. By this, a reference with respect to sensory perception and appetite was created for our intervention population. *Chapters 3 to 6* focus on the effect of both interventions in a Dutch frail elderly population. *Chapter 3* mainly describes the effect on sensory perception, appetite, energy and macronutrient intake. Since (change in) intake is not always predictive for the (change in) nutrient and health status as indicated by biochemical parameters a separate *Chapter (4)* discusses this issue. An example of a functional biochemical indicator of health state is homocysteine, this is covered in *Chapter 5*. Interest in this indicator has grown markedly, since it is regarded as an important risk factor in cardiovascular disease. The vitamins involved in the metabolic process of homocysteine are also thought to be related to neurologic functioning. In *Chapter 6* we address the effect of our intervention programs on body composition (total body weight but also divided in fat and fat free mass), total bone mass and density. Following on from the effectiveness of the interventions, long-term feasibility is of major importance for future implementation. The appraisal of our nutrient dense foods is analyzed in *Chapter 7*, whereas the exercise program is described in Marijke Chin A Paw's thesis[55]. In *Chapter 8* the main results of the study are summarized and put into perspective and public health implications are considered.

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2

Impaired sensory functioning in elders: the relation with its potential determinants and nutritional intake

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This study assessed the relation of an impaired taste and smell perception with a) potential determinants and b) nutritional intake and status in elderly people. Determinants examined were age, gender, functional category (institutionalized vs independently living), dental state, illnesses, smoking behavior, drug usage, and saliva excretion and composition. Nutritional intake and status were measured by an 'appetite and hunger' questionnaire, a food frequency questionnaire and body mass index.

In order to have access to a large heterogeneous group, two different categories of elderly people were studied. We enrolled independently living elders (n=89) assumed to have a relatively good taste and smell perception, and institutionalized elders (n=67) with a potential poorer taste and smell perception. Scores at the smell identification (range: 0-10) and taste perception (range: 0-4) test were, respectively, 5.7 (independently living) vs 3.5 (institutionalized); $p<0.0001$ and 3.3 vs 3.0; $p<0.05$. Correlation between smell test scores and outcomes of the 'appetite and hunger' questionnaire ranged from r: 0.19 to 0.50; p-values<0.05. There was, however, no clear correlation of any sensory outcome with energy and food intake, nor with BMI. Regression analyses revealed that age and the functional category were the most important determinants of the scores on the taste perception and smell identification tests.

It is concluded that a poor performance on sensory tests is related to a poor appetite but not necessarily to low energy intake or low BMI. Age-related factors and smoking are important determinants of impaired sensory functioning.

INTRODUCTION

The process of aging may be accompanied by an increasingly poor nutritional and health status. A poor appetite and, consequently, a low food intake contribute to this phenomenon. One of the most important factors influencing food intake is enjoyment of food (e.g. because of its pleasant taste[1;2]). It is commonly known that a large part of our taste (in the general sense of the word) is determined by our sense of smell and that this smell perception is more affected by age than our taste perception[3-5]. It is estimated that half of the elderly population experience olfactory dysfunction[6]. Previous lab research has also shown that elderly people prefer a higher concentration of some specific food flavors[3;7-12].

Several factors may contribute to the decline in sensory functioning in elderly people (Figure 2.1): anatomical changes due to the aging process itself[4;13], a higher prevalence of illnesses, a higher drug usage[14-16]; wearing of dentures[17;18], a long history of smoking[19] and possibly a changed saliva production[20] and composition[21-23].

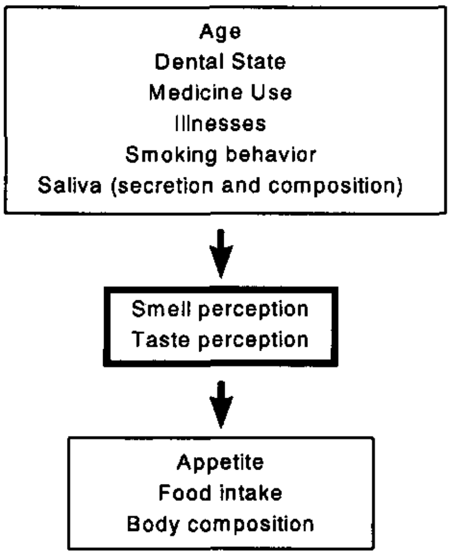

Figure 2.1: Model used to study relationships between sensory perception, potential determinants and nutritional factors

A variation in saliva composition might be caused by the saliva flow. This can be explained by the fact that water transport is driven by Cl^- fluxes and that this fluid driving mechanism is influenced by $Na^+/K^+/Cl^-$ cotransporters and a Ca^{2+} dependent Cl^- channel[23]. Elderly people with a poor sense of taste and smell may run a higher risk of developing a poor nutritional status[16].

Until now two hypotheses have been described that may explain the risk for developing a poor nutritional status. Duffy, Backstrand and Ferris[24] found that elders with olfactory dysfunction had difficulties in maintaining a healthy diet. This means that older adults may have a food pattern that consists of a *higher* intake of sweets and fats. On the other hand findings of Griep and colleagues[25] indicated that elderly adults with poor odor perception had a *lower* nutrient intake level than those with good odor perception. Both studies, however, were carried out in very special groups of community-living elders: Duffy and associates[24] performed her study in elders with known olfactory dysfunctioning, and Griep and colleagues[25] focused on extremely healthy elders.

The purpose of our trial was to investigate the relation between sensory dysfunctioning and nutritional intake in order to solve the apparent controversy raised in the literature. We studied those factors that might influence the taste and smell perception of elderly adults. In order to have access to a heterogeneous study population, we examined two groups of elders cross-sectionally: one independently living group and one institutionalized group.

METHODS

Subjects

A sample of 89 independently-living elders and 67 elders living in senior homes was recruited in the area of Wageningen, The Netherlands, through letters or by direct contact. The subjects had to be 70 years or older. Elderly adults with diabetes were excluded because of their inability to take the flavor test and their possible different food consumption pattern, fat distribution and possibly changed saliva composition. The study protocol was approved by the Medical Ethical Committee of the Division of Human Nutrition and Epidemiology of the Wageningen Agricultural University. Subjects received a study description, after which they signed a consent form.

Design of the study

Data were collected during two home visits in the period of December 1995 to January 1996. One hour before the start of the first home visit, subjects were asked not to eat, drink (with the exception of water), smoke, or brush their teeth (with respect to the collection of saliva and the taste and smell tests). After the collection of saliva, the assessment of the general questionnaire as well as the questionnaire concerning appetite, hunger feelings, and subjective feelings of taste and smell performance took place. The smell identification test and taste perception test were performed and, anthropometric measurements were conducted. The food frequency questionnaire was filled out during the second home visit.

Smell identification test

The smell identification test was based on the Connecticut Chemosensory Clinical Research Center (CCCRC) test[26]. The test comprised ten 40 ml plastic jars with 2 mm holes in their lids, containing the following stimuli: baby powder, chocolate, cinnamon, coffee, mothballs, peanut butter, soap, ammonia, onion (instead of the original item wintergreen, which is not familiar in the Netherlands), Vicks Vapo-Steam. Concentrations of the stimuli were set after pretesting with a group of 12 students, aged: 20-25 years; 73% of these students scored ≥ 8 items right. This result is in line with results obtained by the developing center[26]. Table 2.1 gives the concentrations of the stimuli.

Table 2.1: Concentration of stimuli used in the smell identification test (based on the CCCRC test)[26]

Item	Amount	Brandname
Ammonia	15 g (1:50) solution	EDAH ammonia, Helmond, The Netherlands
Chocolate	7 g	Droste cacao, Haarlem, The Netherlands
Cinnamon	4 g	't Zonnetje, Wageningen, The Netherlands
Coffee	3 g	Douwe Egberts, Utrecht, The Netherlands
Menthol	3 g	Vicks Vapo-Steam, Richardson Vicks BV, Rotterdam, The Netherlands
Mothballs	1 piece	Roxasect, Kali Chemie, Hannover, Germany
Peanut butter	10 g	PCD peanut butter, Swartberg, Rotterdam, The Netherlands
Baby powder	3 g	Zwitsal, Kortman Intradal, Veenendaal, The Netherlands
Onion	7.5 g	EDAH, Helmond, The Netherlands
Soap	6 g	Sanex, Kortman Intradal, Veenendaal, The Netherlands

To reduce cognitive bias, subjects selected the answer from a listing of the 10 test items and 10 distracters. The items were presented in random order. Subjects were allowed to smell with both nostrils. Repeated testing was not permitted. Scores were calculated as the number of correct answers (minimal 0, maximal 10), with answers like 'do not know' or 'smells nothing' coded as incorrect.

Taste perception test

The taste perception test comprised the four basic tastes: sweet, sour, salt, and bitter offered in food items that can be purchased in supermarkets, respectively: fruit yogurt (sweet taste), natural yogurt (sour taste), potato salad (salt taste), and five-fruit juice (bitter taste). Each item was offered in two different concentrations of the taste substances (Table 2.2).

Table 2.2: Concentrations of stimuli used in the taste perception test

Item	Flavor	Low concentration	High concentration
Potato salad[a]	salt	0 g NaCl	2.5 g NaCl
Natural yogurt[b]	sour	0 g citric acid	3 g citric acid
Fruit yogurt[c]	sweet	80 g sucrose	200 g sucrose
Five fruit juice[d]	bitter	0 g kininesulphate	0.05 g kininesulphate

[a] 500 g potato salad, Johma Nederland BV, Losser; 2.5 g NaCl, AKZO, Amsterdam, The Netherlands
[b] 1000 g skimmed yogurt, mild, Weilander, Den Haag, The Netherlands; 20 g sucrose, Suiker Unie, Breda, The Netherlands; 3 g citric acid dissolved in 6 ml water
[c] 200 g mixed berry pulp with flavor, Mona, Woerden, The Netherlands ; 800 g skimmed yogurt, mild, Weilander, Den Haag, The Netherlands; 80 or 200 g sucrose, Suiker Unie, Breda, The Netherlands
[d] 1.0 l five-fruit juice, EDAH Helmond, The Netherlands; 0.05 g kininesulphate

The stimuli were presented in polystyrene jars with a volume of 50 ml, at room temperature. Potato salad and both the natural and fruit yogurts were served with plastic teaspoons. Subjects were allowed to swallow the stimuli in order to imitate the realistic situation as much as possible. The order of presentation was random. Between tasting two stimuli, subjects rinsed their mouth with tap water. Subjects were asked to mark which of the two jars contained the highest concentration for each of the four different tastes. The minimal score was 0, the maximal score 4.

General questionnaire

Questions in the general questionnaire revealed information about age, sex, marital status, chronic illnesses, medicine use, dental state, chewing and swallowing problems, former and present smoking habits, and diets. Only medicines known to influence taste and smell perception were taken into account.

Saliva excretion and composition

Saliva was first collected in an unstimulated way to determine the spontaneous flow rate: subjects were asked to spit into a small plastic jar during exactly 5 minutes. Second, the saliva production was stimulated in order to get enough sample to determine the concentration of the minerals and protein. Production was stimulated with a piece of laboratory Parafilm of 5x5 cm. Subjects were asked to chew on this piece and spit the produced saliva in another plastic jar until a volume of 10 ml was reached. Both jars were kept on ice until further processing.

Weight of the unstimulated saliva was determined, after which the excretion rate in ml/min could be calculated with the assumption that 1 g of saliva should be equal to 1 ml. The pH was measured with a pH-electrode. The buffer capacity was determined with the measurement of the HCO_3^- content, through titration with acid. The stimulated saliva samples were kept at -20 °C until further analysis. The chloride content was determined with a chlorocounter type 77 (Marius, Utrecht, The Netherlands). Potassium, sodium, calcium, and magnesium contents were determined with the AAS (atomic absorption spectrometry) method (type 2380, Perkin Elmer, Norwalk, CT, USA). The total protein content was measured according to the method of Lowry and colleagues[27] with the standard protein: mucin type I from the bovine submandibulary glands (Sigma M4503).

Appetite, hunger, subjective taste, and smell questionnaire

The aim of this questionnaire was to provide descriptive data about the participants' own sensory impressions and their feelings of appetite and hunger. Subjects were asked to answer a total of 29 questions about their feelings of their present taste perception (8 questions), their present smell perception (3 questions), their present smell perception compared to their past perception (3 questions), their hunger feelings (9 questions) and appetite (6 questions). After reading the question the subjects had to score their answer on 5-point Likert scales with verbally labeled answering categories. An example of a 'question' is the following statement: *'In former days the taste of food was: 1. much better than nowadays, 2. better than nowadays, 3. the same as nowadays, 4. worse than nowadays, 5. much worse than nowadays'*. Every answer was coded from 1 to 5. A higher score corresponded to a more positive feeling about their taste and smell perception, appetite, and hunger. Five variables could be constructed:

1. subjective feelings of present taste perception (range: 8 - 40);
2. subjective feelings of present smell perception (range: 3 - 15);
3. appetite (range: 6 - 30);
4. daily feelings of hunger (range: 9 - 45);
5. present smell perception compared to the past (range 3 - 15).

Food and energy intake

A validated semi-quantitative food frequency questionnaire of 104 items[28] was carried out to estimate the intake of energy and the foods that contributed most to the intake of energy. The questionnaire was administered by trained interviewers. In a personal interview subjects were asked to recall the consumption of 104 items during the past month. The responses were coded as frequency per week, and energy, nutrient, and food intake was assessed with use of data from the 'Dutch Nutrient Data Base 1986/87'[29].

Anthropometry

Subjects were weighed on a mechanical weighing scale (Seca; Hamburg, Germany) to the nearest 0.5 kg. Height was measured to the nearest 0.001 m using a portable stadiometer. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Body circumferences were measured to the nearest 0.001 m with the subject standing upright in light clothing. The waist circumference was measured midway between the lower rib margin and the iliac crest around the abdomen at the level of the umbilicus. The hip circumference was measured at the level of the point yielding the maximum circumference over the buttocks. The waist-hip circumference ratio was calculated as waist circumference divided by hip circumference and was used as an index of body fat distribution[30].

Statistical analysis

Data analysis was conducted using the Statistical Analysis System (version 6; Cary, NC: SAS Institute Inc., 1990). To test whether the group was heterogeneous, differences between the two groups of elderly adults were tested with an unpaired t-test, a Pearson chi-squared test, or with the general linear model procedure. A Wilcoxon two-way rank order test was used when the response variables were not normally distributed. In order to test whether or not the group (independent vs institutionalized) differences were greater for smell than for taste, a repeated measures analysis was performed. For this, the taste score was multiplied by 2.5 to make both ranges more similar. Out of the taste and smell scores, one general sensory variable was constructed as repeated dependent measure; group and kind of test (smell or taste) were regarded as the independent variables. The interaction between the latter two indicated whether or not the group differences for smell were greater than the group differences for taste. Pearson correlation coefficients were used to test a) relationships between taste and smell perception and their possible mediating factors and b) taste and smell perception with energy intake, BMI, and fat distribution (see Figure 2.1). Pearson correlation coefficients were also used for quantifying the association between subjective feelings about taste and smell perception, appetite and hunger feelings and objective measurements of taste and smell perception. The internal validity of our appetite, hunger, subjective taste, and smell questionnaire was tested through the use of Cronbach's α. The level of $p<0.05$ was considered as statistically significant. In order to find out whether elderly subjects with a good sensory performance differed in food intake from those with a poor performance, we categorized elderly subjects into two groups: one distinct group of good smellers (high score on the smell test: 8–10) and one of poor smellers (score: 0–7 on smell test); cut off points were in line with boundary of normosmia of Cain and colleagues.[26]. Stepwise forward multiple regression technique was used to model which independent variables accounted most for the variation in the scores of the taste and smell tests (dependent variables). To compare the regression coefficients for the taste test and the smell variables directly, we constructed standardized coefficients within the regression procedure. Dummy variables were made for gender (men: 1, women: 2) and functional category (independently living: 1, institutionalized: 2).

RESULTS

Scores on taste and smell test

The mean scores (±sd) on the taste and smell tests are presented in Table 2.3. Differences between groups were obvious, with the institutionalized elders scoring lower on both tests. This difference held when men and women were studied separately. Overall, the female participants scored higher than the male participants, although these gender differences were not statistically significant (taste scores: $p=0.07$, smell scores: $p=0.10$). The differences between institutionalized and independently living subjects were more pronounced in the smell identification test. A repeated measures analysis of variance revealed a statistically significant interaction ($p<0.004$) between kind of test (smell vs taste) and group (institutionalized vs free-living).

Table 2.3: Mean scores (±sd) on smell identification and taste tests for the total group, for independently living versus institutionalized and for men and women separately. P-values represent the significance of the t-test between the institutionalized group and the independently living group

	Smell test (range 0 - 10) mean ± sd				Taste test (range 0 - 4) mean ± sd			
	total	independ[a]	institute[b]	p	total	independ[a]	institute[b]	p
Total	4.8 ± 2.7 (n=156)	5.7 ± 2.3 (n=89)	3.5 ± 2.6 (n=67)	<0.001	3.2 ± 0.8 (n=153)	3.3 ± 0.7 (n=89)	3.0 ± 0.9 (n=64)	<0.05
Men	4.3 ± 2.6 (n=48)	5.2 ± 2.5 (n=24)	3.3 ± 2.4 (n=24)	<0.05	3.0 ± 0.9 (n=47)	3.2 ± 0.8 (n=24)	2.8 ± 1.1 (n=23)	0.17
Women	5.0 ± 2.7 (n=108)	6.0 ± 2.2 (n=65)	3.6 ± 2.8 (n=43)	<0.001	3.3 ± 0.7 (n=106)	3.4 ± 0.7 (n=65)	3.1 ± 0.7 (n=41)	0.08

[a] independently living elderly people
[b] institutionalized elderly people

General characteristics

The general characteristics of the total group as well as both the independently living and the institutionalized subjects are shown in Table 2.4. Statistical analysis revealed that subjects in the institutionalized group were older ($p<0.001$), more people were wearing full dentures ($p<0.01$), more people used medicines ($p<0.05$) and their saliva excretion was lower ($p<0.01$). No clear differences were found in the groups' smoking behavior.

Table 2.4: General characteristics (expressed as means ± sd or percentages) of the total group and of independently living and institutionalized subjects separately

	Total group	Independently living			Institutionalized			
	n=156	men n=24	women n=65	total n=89	men n=24	women n=43	total n=67	difference between total groups (p)
Age (years)	79 ± 6	76 ± 4	77 ± 4	77 ± 4	82 ± 5	82 ± 6	82 ± 6	<0.001
Living alone (%)								
yes	63	17	32	55	56	84	74	<0.05
no	37	83	67	45	44	16	26	
Dental status (%)								
complete dentures	78	66	69	69	96	86	90	<0.01
partial dentures	10	17	12	13	4	7	6	
no dentures	12	17	19	18	0	7	4	
Smoking behavior (%)								
never smoked	57	13	72	56	17	82	58	0.80
stopped smoking	35	83	20	37	58	16	31	
still smoking	8	4	8	7	25	2	11	

Continued:

	Total group	Independently living			Institutionalized			
	n=156	men n=24	women n=65	total n=89	men n=24	women n=43	total n=67	difference between total groups (p)
Medicine use (%)								
yes	85	83	78	80	92	93	93	<0.05
no	15	17	22	20	8	7	7	
Illnesses (%)								
yes	77	58	82	75	79	79	79	0.58
no	23	42	18	25	21	21	21	
Dry mouth feeling (range: 1-5)	2.4±1.2	2.1±1.1	2.4±1.2	2.3±1.2	2.0±1.0	2.7±1.3	2.5±1.3	0.45
Saliva excretion (ml/min)	0.3±0.2	0.4 ± 0.2	0.3±0.2	0.4±0.2	0.3±0.2	0.2±0.2	0.3±0.2	<0.01
Energy intake (MJ/day)	8.8±1.8[a]	10.3±1.6[b]	8.7±1.6	9.1±1.7	9.0±1.8[b]	8.1±1.6[c]	8.4±1.7	<0.05
BMI (kg/m^2)	26.9±4.1	25.9±3.4	27.0±4.0	26.7±4.0	26.8±4.8	27.6±3.7	27.3±4.1	0.35
Waist/hip ratio	0.91±0.08	0.94±0.0	0.87±0.08	0.89±0.08	0.98±0.06	0.91±0.09	0.93± 0.09	<0.01

[a] n=152, [b] n=23, [c] n=41

Saliva production and composition

The saliva production was lower in institutionalized subjects (Table 2.4). Their dry mouth feeling was also slightly higher (not significant). The correlation coefficient between saliva production and the subjective dry mouth feeling in the total group was: -0.21 ($p<0.01$) ($n=155$). In Table 2.5, the concentration of protein and the most important minerals present in saliva as well as the buffering capacity and pH are shown. For protein and most of the minerals the concentration was slightly higher in the saliva of the institutionalized subjects. This was not true for pH and buffering capacity.

Table 2.5: Saliva composition (mean±sd) of independently living vs institutionalized elders

	Concentration (ppm)		
Components	independent (n=87)	institution (n=63)	p-value
HCO_3^- (buffering capacity)	3.9 ± 2.0	3.8 ± 1.6	0.93
pH	7.2 ± 0.5	6.9 ± 0.7	0.08
Protein (mg % of mucine)[a]	348.4 ± 184.0	420.5 ± 240.8	0.09
Calcium	3.9 ± 2.0	3.8 ± 1.6	0.72
Magnesium	3.6 ± 2.5	4.2 ± 3.3	0.25
Cloride	675.2 ± 251.7	814.1 ± 326.1	<0.01
Potassium	967.2 ± 238.7	1161.5 ± 288.6	<0.001
Sodium	148.8 ± 99.5	159.6 ± 113.8	0.54
Zinc	below detection limit[b]	below detection limit	

[a] numbers slightly lower

[b] values varied around 30ng/ml with a variation coefficient between 36%-49%

Appetite, hunger, subjective feelings of taste and smell questionnaire

The internal validity of this questionnaire was moderate to high; Cronbach's α was between 0.70 (present smell perception compared to the past) and 0.88 (appetite) for the five different variables. Institutionalized people rated significantly lower on all five variables of this questionnaire (Table 2.6); all 5 variables: $p<0.01$. This difference was most pronounced in the variable 'subjective feelings of taste perception' and least pronounced in the variable 'daily feelings of hunger'.

Table 2.6: Scores of the five variables (means±sd) derived from the appetite, hunger, taste and smell questionnaire for independently living vs institutionalized elders

Variable	possible range per item	Cronbach's α	Mean score ± sd total group (n=156)	independent (n=89)	institute (n=67)	p-value
Subjective feelings of present taste perception	8-40	0.80	23.6 ± 3.9	25.0 ± 3.0	21.7 ± 4.0	<0.001
Appetite	6-30	0.88	21.0 ± 4.4	21.8 ± 4.3	20.0 ± 4.4	<0.01
Subjective feelings of present smell perception	3-15	0.71	10.6 ± 2.5	11.1 ± 1.8	9.9 ± 3.0	<0.01
Present smell perception compared to the past	3-15	0.70	8.1 ± 2.1	8.6 ± 1.7	7.5 ± 2.5	<0.01
Daily feelings of hunger	9-45	0.73	34.9 ± 6.1	35.7 ± 5.0	33.7 ± 7.1	<0.05

Food and energy intake and anthropometry

Energy intake of the institutionalized group was significantly lower ($p<0.05$) compared to the independently living group, whereas their BMI (ns) and their waist-hip ratio ($p<0.05$) were higher (Table 2.4). With respect to fat and cholesterol intake, no large differences were found between the two groups (data not shown). To find out whether elderly people with a good sensory performance differed in food intake from those with a poor performance we categorized the subjects into two groups: one group of 'good smellers' and one of 'poor smellers'. In Table 2.7 food groups, that contributed a lot to total energy intake are shown. The classification of food groups into low, middle, and high fat content did not reveal a pronounced difference between the good and poor smellers. In general, the good smellers consumed more of the low fat items as well as the high fat items, with exception of the dairy and meat products. Statistically significant differences have been found with reference to the salty and sweet snacks, with the good smellers consuming more (high fat) snacks.

Analyses of possible relationships in the total group

The possible relationships of taste and smell perception with the potential determinants, and appetite, nutritional intake, and BMI were investigated through calculation of correlation coefficients and regression models. In Table 2.8 it can be seen that the subjective outcome of the appetite, hunger, taste, and smell questionnaire correlated well with the outcome of the more objective measure of the smell test. Energy intake and BMI did not correlate with any sensory outcome nor with outcomes of the 'appetite and hunger questionnaire'. An unfavorable waist-hip ratio was correlated with a poorer performance on the smell test. Also intake of cholesterol and unsaturated and saturated fatty acids was calculated; however, no correlation with the smell or taste tests appeared (data not shown).

An older age seemed to be the most predictive factor for a low score on the smell test ($p<0.001$), and saliva flow showed a significant correlation with both tests ($p<0.05$). None of the mineral concentrations correlated with scores on the taste and smell tests. When dental state was categorized into three variables i.e., no dentures, partial dentures, and full dentures no statistical differences in scores on taste and smell tests were found. To get more information about which factors accounted for the variation in the score on the taste and smell tests we performed regression analysis calculating standardized regression coefficients. Six percent of the variance in the taste score could be explained by the gender ($\beta=0.14$; $p=0.07$: borderline significant) and functional (independent vs institutionalized) categories ($\beta=-0.18$; $p=0.02$). If we adjusted the model for smoking behavior ($\beta=-0.08$; $p=0.38$), the contribution of gender was reduced ($\beta=0.10$; $p=0.32$) meaning that much of the gender difference was related to smoking behavior. The effect of functional category ($\beta=-0.19$; $p=0.02$) was equal in both models. With reference to the smell score, 26% of the variance could be explained by age ($\beta=-0.24$; $p<0.003$), functional category ($\beta=-0.30$; $p<0.001$), and smoking ($\beta=-0.19$; $p<0.01$). Saliva flow, gender, dental state, and medicine use did not contribute significantly.

Table 2.7: Mean (±sd) daily food intake (g) of low-scoring versus high-scoring subjects on the smell test

	Mean daily intake (g) ± sd		
Food group	low score (0-7) on smell test (n=121)	high score (8-10) on smell test (n=31)	p-value
Dairy	423.8 ± 256.6	436.3 ± 363.2	0.75
dairy low fat	114.1 ± 146.3	133.6 ± 143.2	0.29
dairy middle fat	232.9 ± 232.7	246.6 ± 284.4	0.93
dairy high fat	76.9 ± 127.3	56.1 ± 80.6	0.53
Meat	64.2 ± 27.4	59.7 ± 21.8	0.57
meat low fat	21.3 ± 16.4	22.9 ± 17.4	0.63
meat middle fat	21.9 ± 17.6	18.9 ± 14.6	0.54
meat high fat	21.1 ± 13.2	17.8 ± 11.9	0.25
Salty sandwich filling	40.9 ± 23.3	42.5 ± 23.0	0.71
salty sandwich filling low fat	6.3 ± 7.4	8.2 ± 10.6	0.75
salty sandwich filling middle fat	11.7 ± 15.3	8.6 ± 13.1	<0.05
salty sandwich filling high fat	23.0 ± 21.3	25.8 ± 17.5	0.19
Salty snacks	15.5 ± 15.9	25.3 ± 20.7	<0.001
salty snacks low fat	2.3 ± 4.4	4.1 ± 7.4	0.35
salty snacks middle fat	3.9 ± 5.1	6.6 ± 6.4	<0.001
salty snacks high fat	9.4 ± 11.8	14.6 ± 16.6	<0.05
Fish	18.8 ± 12.8	22.2 ± 12.8	0.19
fish low fat	4.8 ± 7.7	5.4 ± 7.5	0.46
fish middle fat	10.1 ± 8.8	11.6 ± 9.6	0.50
fish high fat	3.9 ± 5.5	5.2 ± 6.6	0.37
spread low SFA (saturated fatty acids)	23.3 ± 33.2	21.9 ± 32.3	0.49
spread middle SFA	23.3 ± 30.6	34.1 ± 42.2	0.16
spread high SFA	8.9 ± 15.5	12.4 ± 33.2	0.62
Sweet sandwich filling	16.0 ± 14.8	14.7 ± 11.2	0.83
sweet sandwich filling low fat	14.7 ± 13.6	13.4 ± 11.5	0.98
sweet sandwich filling middle fat	1.1 ± 3.5	0.8 ± 1.6	0.91
sweet sandwich filling high fat	0.2 ± 1.5	0.5 ± 1.2	0.08
Sweet snacks	36.8 ± 24.5	38.9 ± 17.9	0.29
sweet snacks low fat	3.8 ± 4.4	2.3 ± 4.0	<0.05
sweet snacks middle fat	20.0 ± 11.8	21.0 ± 11.0	0.58
sweet snacks high fat	13.0 ± 16.3	15.5 ± 10.3	<0.05
Nonalcoholic beverages	86.0 ± 144.7	69.8 ± 87.3	0.52

Table 2.8: Correlation coefficients between taste and smell perception, possible mediating factors and factors possibly influenced by taste and smell perception

	Taste score (n=153)		Smell score (n=156)	
	r	p	r	p
Independent variables				
age	-0.09	0.27	-0.40	<0.001
saliva secretion	0.16	<0.05	0.18	<0.05
pH	0.00	0.96	0.07	0.39
buffercapacity	0.00	0.98	-0.10	0.23
# medicines	-0.11	0.42	0.05	0.69
Dependent variables				
appetite	-0.06	0.50	0.19	<0.05
subjective taste perception	0.07	0.40	0.37	<0.001
subjective smell perception	0.10	0.22	0.50	<0.001
present smell perception compared to past	0.09	0.25	0.46	<0.001
daily feelings of hunger	-0.07	0.39	0.22	<0.01
energy intake	0.07[a]	0.41	0.06[b]	0.45
BMI (kg/m^2)	-0.05	0.60	0.01	0.32
waist-hip ratio	-0.04	0.76	-0.34	<0.001

[a]n=149, [b]n=152

DISCUSSION

This study did not reveal support for the hypothesis that a poor sensory perception in elderly adults influences the food and energy intake or BMI. In our elderly population we could not find evidence that a low score on the taste and/or smell tests either predicted a lower or a higher intake of any food or energy and fat. However, a poor smell perception was clearly associated with a poor appetite, less hunger feelings and a subjective judgment of a poor taste and smell perception. The factors that most influenced sensory perception were age, functional category, and smoking. Medicine use, dental state, and saliva composition were of less importance. Any gender effects were related to differences in smoking behavior.

Although it is widely assumed that smell and/or taste dysfunctions adversely influence dietary intake and nutritional status, fundamental relationships between chemosensory dysfunctioning and dietary behavior are lacking[31]. In Mattes and colleagues' studies[31;32], patients with chemosensory disorders were not automatically at substantial nutritional risk. However, the contrary also has been shown: studies of Schiffman (and Warwick[12;14;15]) revealed that especially sick elders with losses in taste and olfactory acuity showed a reduced intake of foods. Duffy and associates[24] found that olfactory dysfunction indicated a nutrient intake profile with a higher risk for cardiac disease, that is, higher intake of sweets and less intake of low-fat milk products and a lower preference for foods with a predominant sour/bitter taste or pungency. Griep et al.[25] indicated that lower serum levels of some parameters of nutritional status correlated with a poorer sense of smell.

Adding the results of our study to the present literature, we might now conclude that an impaired taste and smell perception in elderly adults probably influences the quality of life due to the loss of appetite, less hunger feelings, and the perception of a more bland taste of most foods. It does not automatically influence the nutritional intake or status. The group of sick elderly patients might be considered an exception.

In our study we used a food frequency questionnaire with a reference period of one month to measure food intake. This questionnaire, which focuses especially on energy, fats, fatty acids, cholesterol, and special food groups, has among others been validated in elderly subjects against a dietary history[28;33]. It was shown that this questionnaire only showed very small errors contributing to the total error and that individual means only differed between 0-10% of the reference means. Therefore, we think that this list is an appropriate tool in classifying elderly people according to their food intake.

We found a consistent distinction between the scores at the smell test and the taste test of the independently living subjects versus the institutionalized elders. This was expected, because the latter group is not only chronologically older but also seems to be biologically older. From literature we already know that a decline in taste and smell perception occurs as a part of the normal physiological aging process[4], partly due to degeneration of taste buds and nerves[16]. The influence of age and functional category on sensory perception reflected in the regression coefficients is more pronounced in the scores on the smell test. This finding is in line with findings in literature where smell deficits were mentioned as a more serious problem than taste deficits with increasing age[5;34;35]. In general, gender comparisons reveal that from childhood on, women score higher on sensory tests than men[6]. The mean outcomes of our smell and taste tests reveal differences between the two sexes, but the regression models show that gender differences in this study population are related to differences in smoking behavior between men and women.

Saliva composition, dental state, illnesses, and medicine use seemed to be of less influence on the smell and taste scores. Although evidence exists that medicines and illnesses can account for the loss in taste and smell perception[16], we did not find a clear relation. We especially coded the medicines known to influence taste and smell perception, and through this coding we even found a considerable number of people using these medicines. An explanation for no relation between medicine use and taste and smell perception could be the fact that we did not deal with (very) sick people and that therefore the dosages used were too low to influence sensory perception in a considerable way.

The influence of the dental state was also not proven, although the prevalence of people with full dentures was high in our study. Having full dentures does not of course automatically imply that dental problems exist. There is, however, abundant evidence that dentition state and chewing and swallowing ability are correlated in the sense that persons with full dentures are having more problems with chewing and swallowing. Moreover elderly people with these problems shift to dietary restrictions with respect to 'hard to chew' food items[17;36;37]. Reports in literature suggest that dentition influences taste perception[34]. In this study the number of elders with no dentures being so low, may create an analysis problem. The role of the dental state in chewing and swallowing abilities combined with the release of flavors should be investigated more extensively.

A correlation was found between the unstimulated saliva flow and both the subjective feeling of a dry mouth and the scores on the sensory tests. Also in literature it is stated that a reduced salivary flow goes together with a feeling of dryness, alterations in taste, and difficulty with chewing and swallowing[38].

Weiffenbach et al.[39] however question the search for a salivary factor responsible for the maintenance of taste. In the present study, no correlation was found between the scores on the sensory tests and the composition of saliva, although there seemed to be a trend for the institutionalized subjects to have a higher concentration of certain components. An explanation might be that, next to unstimulated saliva flow, the stimulated flow also is lower in institutionalized elders. This means a lower production of water and therefore a higher concentration of the components. Thorselius and colleagues[40] did not find any age-related alterations in the stimulated flow. Furthermore, mixed results have been found regarding a possible influence of the saliva composition on sensory aspects[21;23;41].

Next to the taste and smell scores institutionalized elders also scored lower on the questionnaire about appetite, hunger feelings and subjective judgment of taste and smell perception. Apart from the age-related factors involved, less physical activity and functioning could be an explanation. Physical functioning could be partially reflected by our division of subjects into two categories independently living and institutionalized. We unfortunately do not have any data on physical activity, but this will be investigated in our next study in a group of frail elders.

As far as we know, this is the first time that such an extended questionnaire assessing appetite, hunger, and subjective feelings about sensory perception has been used. A correlation of these items with smell perception was evident in the total group. The internal validity of the questionnaire was moderate to high, which supports the expectation that this questionnaire is a promising new measure in nutrition sciences. External validation of this questionnaire should take place in a future study.

In our study we used a slightly modified and translated identification part of the CCCRC test[26]. The other part of this test (threshold part) does have limitations in the reliability; the identification part may test some cognitive functioning. With respect to the latter we tried to overcome this with special answer forms that included all the answers next to some 'distracters'. From studies of Cain et al.[26;42] it was revealed that the identification part of this test had a slightly better resolution than the threshold part, meaning that identification may have a higher sensitivity. They furthermore argued that the identification part would generally be the choice on grounds of ease of use, speed of administration and resolution between patients. Since both threshold and identification may at least have equal limitations in reliability, we think that use of the identification test was sufficient. We adapted the test with respect to the smell 'wintergreen' which is not familiar in The Netherlands, and used onion instead. The original test correlated highly with the extensively validated UPSIT test[42]. We do not have evidence that the transition of wintergreen to onion (both prickling odorous) next to the translation to the Dutch language might have changed the test considerably.

Unfortunately, a validated simple taste test meeting our demands was not available. We therefore developed our own taste test and incorporated this test in the study after extensive pilot testing. With this test we did not aim to cover the whole spectrum of the taste perception field; we only aimed at distinguishing between elders with a good taste perception and elderly subjects with a poorer performance.

In order to study the determinants of sensory functioning and its impact on the nutritional intake in an apparently healthy elderly population we needed a heterogeneous group of elders with variation in the scores on the sensory tests, and with variation in the possible mediating factors and in nutritional and health status. The results show that our group of independently living elderly differed in quite some aspects of our group of institutionalized elders, despite the fact that an extremity of the distribution (sick people) was missing. Differences in taste and smell perception could be explained by age-related factors and smoking. A poor performance on the sensory tests was related to a poor appetite and less hunger feelings but not to a low energy intake or low BMI. The two latter variables might be more influenced by physical activity.

In future research, physical activity should be taken into account. Another next step should be a longitudinal study in which the direct consequences of a decline in taste and smell perception are investigated. Moreover, sources should be used on how to deal with a poor taste and smell perception and a (consequently) poor appetite, with the aim of improving the quality of elderly life, as the impact on the nutritional intake and nutritional state may not be alarming in apparently healthy elderly people.

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3

Effect of dietary supplements and physical exercise on sensory perception, appetite, intake and body weight in frail elderly?

Submitted

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This study investigated the effect of a 17-weeks intervention program with nutrient dense foods (enriched with vitamins and minerals at 25-100% of the Dutch RDA) and/or physical exercise in 159 frail elderly (46 men, 113 women, mean age: 78.7±5.6 years). Subjects were randomized over 4 groups: a) nutrition, b) exercise, c) both and d) control. Main outcome parameters were sensory perception (smell test and questionnaire), appetite (questionnaire), energy intake (3-day food record) and body weight (scale and DXA).
At baseline, moderate but significant correlations were found between appetite and energy intake (r=0.30, p<0.0001), between smell test and smell perception assessed by questionnaire (r=0.40, p<0.0001) and between lean body weight and energy intake (r=0.50, p<0.0001). Results after 17-weeks intervention revealed neither change in smell test scores (p=0.19) nor in appetite (p=0.17). A minimal positive effect of exercise compared to non-exercising groups on energy intake (difference: 0.5 MJ, p=0.05) was shown next to a preserving effect of exercise on lean body mass (+0.08 kg) compared to a decrease (-0.4 kg) in non-exercisers (p<0.02). Correlation between change in lean body mass and change in energy intake was 0.18 (p=0.05).
It is concluded that the preserving effect on lean body mass in frail elderly due to 17-weeks of exercise is related to changes in energy intake. Changes are however small. The effect on energy intake is not influenced by a change in reported appetite or sensory perception. Nutrient dense foods were not able to improve any of the outcome parameters in this study.

INTRODUCTION

Aging is often associated with an impairment of health and nutritional status. The onset and intensity of this process is not only determined by chronological age but also by biological factors. These factors differ for each individual and therefore lead to heterogeneity in the elderly population[1]. Researchers have made a distinction between successful, normal and accelerated aging[2;3]. Within all these categories the process of frailty may commence. Buchner and Wagner[4] define frailty as a state of reduced physiologic reserve associated with increased susceptibility to disability. However, other more extensive or more confined definitions have also been used[5]. Frailty is in most cases related to a diminished physical, cognitive, emotional, sensory and/or social functioning[6].

An impairment in sensory functioning, like a reduced taste and smell perception may have a negative impact on appetite and feelings of hunger, and thereby cause a decrease in energy intake. Clear evidence, however, for the relationship between an impaired taste and smell perception, a decreased appetite and food and energy intake has not been found so far. A few studies confirmed this relationship, especially in sick[7-9] but also in healthy elderly[10]. Others failed to detect associations between taste and smell perception, food acceptability and a substantial reduced energy or nutrient intake in apparently healthy elderly[11-13]. We were also not able to demonstrate a clear association between appetite and food intake in apparently healthy elderly people (*Chapter 2*).

Still, a good appetite is generally regarded as a sign of good health and a decreasing willingness or acceptance of food could be an early sign of the process of worsening health[14]. Since this process might be one of the indicators of frailty, attendance to this problem is, especially in the frail, of major importance. To improve or maintain the quality of 'the frail elderly life' it is important to maintain a sufficient appetite, and nutritional and health status or if necessary improve it. Adaptation of physical exercise, thereby increasing energy expenditure and hence appetite and total dietary intake, moreover assurance of a high nutritional quality of the diet of elderly people in order to combat any potential deficiencies are believed to be key factors in interfering in the process of frailty[15-17]. Changes in the taste and smell system with age may be interrelated to nutrient intake[18]. Only a few studies in frail elderly have been performed to investigate the effects of either physical exercise and/or nutritional supplements on several indicators of nutritional and health status[15;16;19-21]. However, none of these studies has focused on the effects of these interventions on sensory factors (in relation to), appetite, energy intake and (lean) body weight.

We hypothesized that frailty is (partially) mediated by an impaired sensory functioning, decreased appetite and hunger feelings and, therefore, a marginal nutritional intake. This in the end may result in a decreasing body weight. The current study is part of a large scale intervention trial in frail elderly and was designed to investigate the effect of the consumption of micronutrient dense products, a physical exercise program or a combination of the factors, mentioned. Emphasis is placed on the measurement of appetite and taste and smell perception as predictors for energy intake.

SUBJECTS AND METHODS

Subjects

A total of 7080 letters were sent to elderly living in the neighborhood of Wageningen, The Netherlands, resulting in a study population of 217 free-living frail elderly, who were interested and met the selection criteria. Figure 1.2 summarizes the process of subject selection for the trial. To fulfill the criteria 'frail' subjects should require a kind of health care, such as home care or meals-on-wheels. The main other selection criteria were: age (70 years or older), inactivity (not regularly participating in physical activities of moderate to high intensity), body mass index: BMI≤25 kg/m^2 (based on self-reported weight and length) or recent involuntary weight loss, no use of multivitamin supplements and ability to understand the study procedures.

Before the start of the baseline measurements subjects gave their written informed consent. The study protocol was approved by the external Medical Ethical Committee of the Division of Human Nutrition and Epidemiology of the Wageningen Agricultural University. Pre- and postmeasurement(s) were available of 165 subjects. Reasons for drop out (n=52, 24%) were mainly health problems, including (terminal) disease, hospital stay, recent falling and/or fracturing. Another four subjects were excluded because time between pre- and postmeasurement was less than 17 weeks due to hospitalization. Two subjects were hospitalized in the week of postmeasurements (sudden heart attack) and ended up with incomplete figures. This resulted in a population of 159 subjects.

Design

Enrollment took place between January (first starting group) and June 1997 (sixth starting group), depending on the area of residence. Within each starting group subjects were randomly assigned to one of the four intervention groups:

a. <u>nutrition</u>: nutrient dense products + social program;

b. <u>exercise</u>: regular products + exercise program;

c. <u>combination</u>: nutrient dense products + exercise program;

d. <u>control</u>: regular products + social program.

The intervention period was 17 weeks. The data were collected at baseline (week 0) and after 17 weeks (week 18).

Nutrient dense foods

The nutrient dense products as well as the regular products comprised of two categories: a fruit based category and a dairy category. All subjects were asked to consume daily one product out of each category (one dairy product and one fruit-based product per day). Within the two categories several products were developed. Availability of a variety of products was intended to help to prevent boredom and to increase acceptability of the enriched products. Since these foods had a limited shelf-life, each participant got weekly a new cooled container with fresh stock, containing the following:

<u>fruit based category</u> - 4 portions of apple/berry/grape juice (portion size: 100 grams);
- 4 portions orange/peach juice (100 grams);
- 2 portions of apple compote (100 grams);
- 2 portions of apple/peach compote (100 grams).

<u>dairy category</u> - 4 portions of vanilla custard (100 grams);
- 4 portions of strawberry yogurt (100 grams);
- 4 portions of vanilla/apple yogurt (100 grams);
- 4 portions of vanilla/mixed fruit quark (75 grams due to the 'satiating' effect of quark).

Due to daily consumption of two nutrient dense products, subjects in the nutrition group and combination group got ~100% of the Dutch RDA [22;23] of the vitamins D, E, B_1, B_2, B_6, folic acid, B_{12}, C and ~ 25-100% of the Dutch RDA of the following minerals: calcium (25%), magnesium (25%), zinc (50%), iron (50%), iodine (100%) on top of their normal intake (see also appendix). Subjects in the control group and the exercise group got the natural amount of the regular products on top of their normal intake (amount of vitamins and minerals in regular products negligible compared to the nutrient dense products). The energy content of the nutrient dense products was the same as the regular products. Consumption of two products a day delivered a mean energy intake of ~0.48 MJ/day.

Exercise program

The main objective of the exercise program was maintenance/improvement of mobility and performance of daily activities essential for independent functioning by maintenance of versatility in movement. Emphasis was placed on skill training; muscle strength, co-ordination, flexibility, speed and endurance were trained by exercises such as walking, stooping and chair stands thereby improving performance of daily activities. Different materials were used, for example balls, ropes, weights, dynabands. Group sessions were organized twice a week for 45 minutes and were of moderate, gradually increasing intensity. The sessions were co-ordinated by skilled teachers and supervised by one of the project leaders (MCAP). In order to guarantee uniformity all sessions were extensively rehearsed with all teachers together, moreover an instruction video and manual was made in advance. A social program was organized as a control for the exercise program, in order to check for possible effects of attention. Sessions of 90 minutes were organized once every two weeks by a skilled creative therapist. This program focused on creative activities, social activities and lectures about topics of interest for elderly. Transport to and from all the sessions was arranged.

General and activity questionnaires

Questions in the general questionnaire revealed information about age, sex, marital status, education, social activities, living conditions, illness, medicine use, dental state, chewing and swallowing problems and former and present smoking habits. Physical activity was assessed using a validated questionnaire based on the Physical Activity Scale for Elderly (PASE)[24;25].

Dietary intake

At baseline and in the last week of intervention a three day (two weekdays and one weekend day; non-consecutive) estimated dietary record was collected by three trained dietitians. Subjects having difficulties with writing could make use of a voice tape recorder. In home face-to-face interviews were organized before in order to explain and afterwards to revise and correct the diaries. Portion sizes were recorded in household measures, whereby frequently used household measures were weighed afterwards. Food consumption data were coded (with a frequent cross checking by all three dietitians) after which energy and nutrients were calculated with the computerized Dutch Food Composition Table of 1997[26]. The energy and macronutrient content of the intervention food products were included in the food consumption data.

Appetite, hunger, subjective taste and smell questionnaire

Subjects were asked to respond to a total of 29 questions about their feelings of appetite and hunger and about their taste and smell perception[27]. After reading the question subjects had to score on a 5 point Likert scale with verbally labeled answering categories. An example of a 'question' is the following statement: *'In former days my appetite was: 1. much better than nowadays, 2. better than nowadays, 3. the same as nowadays, 4. worse than nowadays, 5. much worse than nowadays'*. A higher score corresponded to a more positive feeling about their taste and smell perception, a better appetite and more feelings of hunger. Initially five variables were calculated:

1. present taste perception (8 items; range: 8 - 40);
2. present smell perception (3 items; range: 3 - 15);
3. appetite (6 items; range: 6 - 30);
4. daily feelings of hunger (9 items; range: 9 - 45);
5. present smell perception compared to the past (3 items; range: 3 - 15).

Smell identification test

The smell identification test, was based on the Connecticut Chemosensory Clinical Research Center (CCCRC) test[28;29]. The test comprised ten 40 ml plastic jars with 2 mm holes in their lids, containing the following stimuli: baby powder, chocolate, cinnamon, coffee, mothballs, peanut butter, soap, ammonia, onion (instead of the original item wintergreen, which is not familiar in the Netherlands), Vicks Vapo-Steam. To reduce cognitive bias, subjects selected the answer from a list which consisted of the 10 test items and 10 distracters. The items were presented in random order. Scores were calculated as the number of correct answers (minimal 0; maximal 10), with answers like 'do not know' or 'smells nothing' coded as incorrect.

Body weight and height

All anthropometric measurements were performed in the morning with subjects wearing underwear. Body weight was measured to the nearest 0.01 kg using a digital scale (ED-6-T; Berkel, Rotterdam, The Netherlands). Height was measured to the nearest 0.001 m using a wall-mounted stadiometer. Lean body mass data were obtained with DXA measurements (see also chapter 6). Body mass index was calculated as weight in kilograms divided by height in meters squared[30].

Statistical analysis

Data were analyzed using the statistical program SAS (Statistical Analysis Program, version 6, Cary, NC: SAS Institute Inc., 1990). Means ± standard deviations (sd) of baseline values were calculated per intervention group for the primary outcome variables. Absolute changes ± sd per intervention group were calculated and compared with each other by ANOVA (analysis of variance). Differences were tested with Tukey's procedure. A multiple regression model was used to determine the effect of both interventions and a possible interaction on the change in outcome variables. Since no interaction occurred between nutrition and exercise only these two independent variables were included in the model. Pearson correlation coefficients were used to calculate relationships in the baseline data between scores on the smell test, energy intake, body weight and outcomes of the questionnaire on appetite, hunger and sensory perception. The internal validity of this latter questionnaire was tested by calculating Cronbach's α. In order to investigate interrelationships among the questions on this list a principal components analysis with varimax rotation was used. Two-tailed p-values were considered statistically significant at $p<0.05$.

RESULTS

Baseline characteristics

In Table 3.1 baseline characteristics of the four intervention groups are presented. Approximately, 70% of the participants were women. Mean age of the study population was 79 years and mean BMI was 24.5 kg/m^2. One or more chronic diseases were present in at least 91% of the population. The majority was living alone. Only one quarter of the participants reported chewing problems, while at least three quarter complained of a dry mouth. Complete or partial dentures were found in 85% of the participants.

Table 3.1: Baseline characteristics of the study population according to intervention group

Parameter	Nutrition (n=41)	Exercise (n=39)	Combination (n=42)	Control (n=37)
% Women	73	73	72	68
Age (years) (mean ± sd)	79.6 ± 4.8	76.7 ± 4.4	79.2 ± 6.1	79.3 ± 6.6
BMI (kg/m^2) (mean ± sd)	24.4 ± 2.5	24.5 ± 3.0	25.0 ± 2.5	24.1 ± 3.2
Activity score (range PASE: 0-400) (median; P_{10}-P_{90})	59 (27-117)	63 (27-100)	59 (30-111)	59 (34-97)
Subjective health (range 0-10) (mean±sd)	6.9 ± 1.6	7.0 ± 1.2	6.9 ± 1.3	7.0 ± 1.4[a]
Current smokers (%)	12	10	7	16
Illness (%)	88	93	95	87
Prescribed medicines (%)	89	75	83	75
Living alone (%)	71	68	67	70
Problems with swallowing (%)	12	17	9	16
Problems with chewing (%)	24	25	28	27
Dry mouth feeling (%)	68	70	60	76
Dental state (%)				
complete dentures	54	48	52	68
partial dentures	29	34	29	27
no dentures	17	18	19	5

[a] n=36

Smell test, and appetite, hunger, taste and smell perception questionnaire

In Table 3.2 the mean scores (±sd) and absolute changes (±sd) on the smell identification test are shown. In general, no difference in the magnitude of change was observed relative to controls. On individual level improvement was found in 41 subjects, a decrease in 77 people and the remaining (n=37) scored equally. The distribution of increasing and decreasing subjects was equal over the four intervention groups. With respect to the five variables of the questionnaire on appetite, hunger feelings and taste and smell perception also no difference in change compared to the control group occurred after 17 weeks of intervention (Table 3.2).

Table 3.2: Mean baseline appetite, hunger, sensory perception and smell test scores (±sd) and changes (±sd) after 17 weeks of intervention in Dutch elderly[a]

Parameter	Nutrition (n=40)		Exercise (n=39)		Combination (n=40)		Control (n=36)	
	baseline ±sd	*change ±sd*	baseline ±sd	*change ±sd*	baseline ±sd	*change ±sd*	baseline ±sd	*change ±sd*
Smell test score (range: 0-10)	5.2 ± 2.7	*-0.5 ± 0.3*	5.6 ± 2.6	*-0.03 ± 0.3*	5.1 ± 2.7	*-0.7 ± 0.3*	4.7 ± 3.2	*-0.4 ± 0.3*
Appetite (range: 6-30)	20.9 ± 3.7	*-0.5 ± 0.4*	21.0 ± 3.9	*-0.08 ± 0.4*	20.5 ± 4.5	*-1.0 ± 0.6*	21.0 ± 4.3	*0.0 ± 0.6*
Present taste perception (range: 8-40)	25.6 ± 4.3	*0.2 ± 0.6*	27.4 ± 4.0	*-0.3 ± 0.4*	26.0 ± 4.8	*-0.9 ± 0.7*	26.3 ± 4.8	*-0.2 ± 0.6*
Present smell perception (range: 3-15)	11.2 ± 2.3	*-0.8 ± 0.3*	11.9 ± 2.3	*-1.9 ± 0.3*[b]	11.4 ± 2.2	*-1.3 ± 0.4*	11.1 ± 2.8	*-0.6 ± 0.4*
Present smell perception compared to the past (range: 3-15)	8.1 ± 2.0	*-0.4 ± 0.3*	8.5 ± 2.1	*-0.3 ± 0.3*	7.8 ± 2.4	*-0.2 ± 0.3*	8.5 ± 2.3	*-0.7 ± 0.3*
Daily feelings of hunger (range: 9-45)	33.3 ± 4.3	*-1.5 ± 0.7*	36.1 ± 5.8	*-0.8 ± 0.6*	34.3 ± 5.4	*-0.6 ± 0.8*	35.5 ± 5.1	*-0.3 ± 0.8*

[a] numbers vary slightly due to incomplete smell test or partially incomplete questionnaire

[b] $p < 0.05$, statistical difference with respect to the control group

In Table 3.3 the baseline score of the smell identification test is compared with the outcomes of the 'appetite, hunger and smell' questionnaire at baseline. The smell test score correlated ($p<0.0001$) with the answers on our smell perception variables. Furthermore, the answers on appetite and daily feelings of hunger were positively correlated ($p<0.0002$) with reported energy intake. No correlation appeared between smell test score and energy intake ($r=0.03$, $p=0.65$).

At baseline, appetite was negatively correlated with a dry mouth feeling ($r=-0.35$, $p<0.0001$) and problems with swallowing ($r=-0.19$, $p=0.007$). Problems with chewing were not directly related to appetite ($r=0.07$, $p=0.36$), however, correlation of appetite with number of teeth bordered on significance ($r=0.25$, $p=0.06$).

Table 3.3: Pearson correlation coefficients of baseline scores on appetite, hunger and sensory perception versus energy intake and smell test in Dutch elderly subjects

Parameter	Energy intake			Smell score		
	n	r	p	n	r	p
Appetite	158	0.30	0.0001	155	0.06	0.44
Perception of present taste	158	0.13	0.07	155	0.11	0.15
Perception of present smell	154	0.08	0.27	151	0.40	0.0000
Present smell perception compared to the past	156	0.09	0.23	154	0.32	0.0001
Daily feelings of hunger	156	0.27	0.0002	153	0.08	0.26

Dietary intake

In Table 3.4 the mean baseline energy and macronutrient intakes (±sd) and their 17-wk changes (±sd) are presented per intervention group. No statistically significant differences in baseline values nor in changes between the intervention groups compared to the control group were found. At baseline 66% (n=104) of the subjects had an energy intake below the Dutch Recommended Dietary Intakes [22;23]. Concerning micronutrients on average 58% had intakes below these recommendations.

Table 3.4: Mean baseline energy and macronutrient intake (±sd) and changes (±sd) after 17 weeks of intervention in Dutch elderly

Parameter	Nutrition (n=41)		Exercise (n=38)		Combination (n=42)		Control (n=37)	
	baseline ±sd	*change ±sd*	baseline ±sd	*change ±sd*	baseline ±sd	*change ±sd*	baseline ±sd	*change ±sd*
Energy intake (MJ)	7.8 ± 1.8	*-0.3 ± 0.2*	7.4 ± 1.7	*0.3 ± 0.2*	7.2 ± 1.5	*0.02 ± 0.2*	7.8 ± 2.3	*-0.4 ± 0.4*
Total protein (g)	66 ± 15	*-0.6 ± 2.2*	67 ± 19	*4.5 ± 2.6*	67 ± 16	*-1.3 ± 2.1*	69 ± 21	*0.3 ± 2.4*
protein of animal origin (g)	42 ± 13	*-0.3 ± 1.8*	42 ± 13	*5.0 ± 2.2*	44 ± 14	*-1.7 ± 1.9*	44 ± 17	*2.2 ± 2.0*
Total fat (g)	72 ± 22	*-1.5 ± 3.2*	70 ± 17	*2.3 ± 2.8*	68 ± 18	*-0.4 ± 2.8*	70 ± 27	*-4.3 ± 3.9*
Total cholesterol (mg)	194 ± 127	*17.5 ± 12.7*	163 ± 63	*23.7 ± 11.4*	191 ± 95	*-9.9 ± 11.7*	179 ± 84	*8.4 ± 14.3*
Total carbohydrates (g)	222 ± 57	*-14.7 ± 5.9*	212 ± 56	*3.5 ± 5.7*	200 ± 43	*5.3 ± 5.9*	221 ± 63	*-4.4 ± 10.7*
Total water (kg)	2.1 ± 0.5	*-0.1 ± 0.05*	2.2 ± 0.7	*-0.2 ± 0.08*	2.2 ± 0.7	*-0.1 ± 0.1*	2.2 ± 0.6	*0.03 ± 0.09*

Compared with two-thirds of the recommendations still 30% of the participants had energy intakes below 6.3 MJ. With respect to macro- and micronutrients intake percentages below two-third of the reference were varying from 3% for protein till 93% for vitamin D (in women; see also *Chapter 4*).

Since we found no evidence of an interaction between the two types of interventions we could analyze the effect of each intervention separately: exercise vs no-exercise and nutrient dense foods vs regular foods. In Table 3.5 the crude regression coefficients are presented with their p-values.

Table 3.5: Estimates of the mean difference in change between the group receiving nutrient dense products versus regular products, and the group receiving exercise versus no exercise

Parameter	Nutrient dense foods vs regular products		Exercise vs no exercise	
	difference	p	difference	p
Change in energy intake (MJ)	-0.09	0.72	0.48	0.05
Change in protein intake (g)	-3.40	0.15	1.61	0.49
Change in carbohydrate intake (g)	-4.17	0.56	14.23	0.05
Change in fat intake (g)	0.00	0.99	3.73	0.24
Change in score on smell test (range:0-10)	-0.39	0.19	0.06	0.84
Change in hunger feelings (range:9-45)	-0.48	0.51	0.24	0.75
Change in appetite (range:6-30)	-0.72	0.17	-0.27	0.61
Change in present taste perception (range:8-40)	-0.13	0.83	-0.63	0.27
Change in present smell perception (range:3-15)	0.20	0.52	-0.83	0.009

Exercise increased borderline significant energy intake and carbohydrate intake (p=0.05) towards the non-exercisers, although no clear effect is shown on the intake of the other macronutrients. When we corrected for baseline energy intake and age the regression coefficient for energy declined slightly to 0.4 MJ. The nutrient dense products compared to the group receiving regular products did not reveal significant differences on the intake variables. Furthermore no clear effect of the nutrition intervention nor of the exercise intervention was found on the changes in smell test score or items from the appetite, hunger and sensory perception questionnaire.

Body weight

At baseline the correlation between body weight and energy intake (n=156) was rather low 0.26 (p=0.0008), but this correlation coefficient was increased when only lean body weight as measure of metabolic tissue was taken into account: r=0.50, p=0.0001 (n=141). With respect to change in total body weight (measured by scale) due to the interventions a mean decline was found in the non-exercising groups of -0.3 kg, whereas a small increase of 0.2 kg was found in the exercising groups (estimate of the difference between exercisers and non-exercisers: 0.5 kg, p=0.041). Lean body mass (measured by DXA) declined even more in the non-exercising group (-0.4 kg) compared to a preserving effect of +0.08 kg in the exercisers (estimate of the difference between the two groups 0.5 kg; p=0.014), leaving room for a shift in lean body mass towards fat mass in the non-exercisers. Correlation between change in energy intake and change in both total body weight and lean body weight was moderate (r=0.18;p=0.02, respectively r=0.16; p=0.05).

DISCUSSION

This study revealed no relevant effect of the nutrition and exercise interventions on appetite and sensory perception, but a small effect of exercise was found on energy intake and lean body weight. A moderate but significant correlation between change in energy intake and change in (lean) body weight indicated that effects of interventions on these parameters may be related to each other. The small benefits of exercise on energy intake and body weight could not be attributed to an increase in reported appetite. The 17-weeks consumption of nutrient dense products did not result in an increment in energy and macronutrient intake or body weight.

Calculations of the sample size with a power of 80% and a two-sided significance level of 5% revealed that for detecting a mean change of 0.5±0.6MJ, 23 subjects per group were needed. This was certainly achieved in our study.

Effect of interventions on energy/food intake

In order to improve compliance the products were especially designed in small portions, moreover they should easily be included in the daily meals and palatable throughout the day. Consumption of two products revealed an extra 0.48 MJ per day, but we observed that total energy intake did not increase due to the nutritional intervention. The participants probably replaced their normal dessert or soft drink for a dairy product respectively a fruit juice supplied during the study, despite the possibility of consuming the products on top of their normal intake. This indicates that our supplements fitted remarkably well in the daily eating pattern of elderly and that they maintained their dietary pattern and regulated their food intake in this way.

With respect to subjects participating in the exercise program they might have been in need of extra energy or nutrients to maintain in energy balance. We found a small, borderline significant increase in energy intake of the exercising group towards a small decrease in the non-exercising group. Intake of macronutrients increased in the exercising vs the non-exercising group, although not very convincingly. We measured a preserving effect in (lean) body mass of the exercise compared to a decline in the non-exercising group, and we found a correlation between change in body mass and change in energy intake. In a supplementation study of Gray-Donald et al.[16], in which free-living frail elderly increased their total intake although not statistically significant, the observed weight gain was also compatible with the extra energy consumed.

The effect of adopting an exercise program on diet was only investigated in a few studies which showed inconsistent results (review)[31;32]. Figures on components of energy balance due to exercise in (frail) elderly have also not been intensively described in literature. Campbell et al.[33] studied the effect of a progressive resistance training program in healthy older adults and concluded that their program was effective in increasing energy requirements with 15%. Since their relatively intensive resistance training program is not comparable with our all-round exercise program designed for frail elderly we might perhaps expect an increase in the energy requirement of half of it, e.g. 7.5% = 0.5 MJ on a mean total of 7.4 MJ. In our exercising group the increase in energy intake was smaller: 0.2 MJ. Butterworth et al.[34] confirms the small effect of moderate amounts of exercise on enhanced dietary intake in elderly women. In the frail study population of Fiatarone et al.[15] total energy intake declined after the trial in the exercise and control group. In both the supplementation and combination group total energy intake increased but this was fully attributed to the energy dense supplement supplied. The same results have been found by Meredith et al.[20]. Their study clearly showed that the unsupplemented group tended to reduce their energy and macronutrient intake after training, the supplemented group increased their intake mainly due to the supplement itself.

Despite both environmental changes (nutrient dense foods supplied, exercise program) we observed that the elderly did not easily alter their food habits or intake. Whether this is an example of perfect regulation or that our intervention programs did not have enough power and intensity to establish a change or that this is a problem of (physiological) impairment of elderly to react on external changes is difficult to answer. Median attention rate at the exercise sessions was 90%, at the social sessions this was 80% thereby confirming the high compliance rate. Not many trials investigated long-term control of energy intake in elderly[35]. Results from Rolls et al.[36] and Roberts et al.[37] confirm that elderly are less capable of regulating energy intake despite changes in diet or activity level. Blundell et al.[38] point out that the human body may try as long as possible to deal with the higher physical activity levels with the same amount of nutrients. This is also stated by Rolls[39]. Schlettwein-Gsell[40] argues from a psychological and social point of view that a rapid change in food intake or altering familiar dietary habits might not be expected in elderly: 'they might notice their physical drawbacks, they however live in such strong regular life pattern that change might be threatening and consequently the will to change food intake might not be evident enough'.

Appetite, hunger feelings and sensory perception

With respect to the 'appetite, hunger and smell' questionnaire the internal validity was satisfactory (range: 0.69 till 0.89), moreover a poor appetite based on questionnaire predicted a lower energy intake. An explanation for the lack of effect on outcomes of our appetite, hunger and sensory perception questionnaire may be the intensity or duration of our intervention programs. Furthermore an interesting theory of De Castro[41] may apply: while aging, the ability of ingested nutrients to affect the subjective state of hunger in the individual is decreasing. In other words the internal state becomes less able to influence the subjective state as aging progresses. Because of this it may be extremely difficult to find a change on these subjective parameters.

Supplementation did not show an improvement on smell perception. This might also be extremely difficult to achieve since impairment of sensory perception may be mainly caused by age-related factors and smoking[42-44]. This is in agreement with conclusions from Schiffman's review[45] that the prognosis for recovery of smell and taste sensations is poor. On the other hand it has been postulated that several micronutrient deficiencies might influence taste and smell perception[18]. Especially zinc is mentioned within this respect, but also vitamin A, B_1, B_6, B_{12} and folic acid. Since all of these nutrients, with exception of vitamin A were added to the foods up to 50-100% of the Dutch RDA, it should have been possible to improve an impaired taste and smell perception caused by nutritional deficiencies with micronutrient supplementation. The fact that we did not find any change in smell perception may be explained by a) our participants did have a relatively low dietary intake when compared to healthy Dutch elderly and Dutch recommendations, but not low enough to establish effect (de Jong et al., manuscript submitted or *Chapter 4*) or b) subtle micronutrient deficiency is of minor importance compared to the (possibly irreversible) degenerative process in taste buds and nerves while ageing[46].

Type and duration of intervention

The difference between other supplementation/exercise studies[15;16;19;20;34] and our study is among others the type of the exercise program (an all-round program instead of only resistance training) and the supplement used. We strictly added only micronutrients, known to be frequently low in elderly, and no extra energy or macronutrients to the product since we had special interest in spontaneous changes in appetite and energy and macronutrient intake. Our time frame of 17 weeks might have been too short to measure effects of both the nutritional and exercise intervention on appetite, sensory perception or intake. These kind of intervention studies are however quite aggravating for frail elderly and it is therefore, difficult to implement interventions of longer duration.

Population

The question arising, is whether the population was really frail. One of the main criteria was BMI $\leq$ 25 kg/m^2 or recent uncontrolled weight loss. For practical reasons we had to rely on self-reported height and weight. Since elderly often overestimate their current height, their BMI turned out to be somewhat higher than initially calculated. However, comparing our population with healthy Dutch elderly our participants were less active (PASE score: 64 in our population vs 85 in the population of Schuit[25], the mean BMI of 24.5 kg/m^2 was lower compared with data from the European Seneca study (men: 26, women: 28 kg/m^2)[47] as well as the subjective rating of health on a 10-point scale: 7 in our population vs 8 in the healthy elderly population of Schuit[48]. The majority of our participants used medication and suffered from more than one disease. Furthermore, the mean energy intake is considerably lower compared to the intake of a representative group of Dutch apparently healthy elderly[49]. Summarizing this, means that our study group on average had a worse health profile compared to apparently healthy elderly.

Measurement methods

The internal validity of the questionnaire was moderate to high and since energy intake was clearly varying between groups scoring low or high on the appetite questions (data not shown) the questionnaire seems to be reliable. Furthermore, statistically significant correlation coefficients were found between the smell identification test and the measurement of smell perception with the questionnaire. The same was found between the 'gold standard' of appetite, namely total energy intake and the subjective measurements of appetite and feelings of hunger. Additional factor analysis revealed out of the 29 questions two factors: one for appetite in general and one for smell. We observed that the questions about taste were incorporated in the factor appetite. These two factors showed exactly the same statistical significant correlation coefficients with energy intake and score on the smell identification test respectively. And again also no absolute change with respect to the control group was observed in these two factors. This reinforces the results we initially found with the separate five constructed variables of the questionnaire. This questionnaire is a newly developed instrument which was tested in a population of institutionalized and free-living elderly[27]. Up till now a reliable extensive questionnaire with respect to appetite parameters is lacking. And although, the internal validity of this questionnaire is satisfying it would be very interesting to investigate whether or not ratings on the appetite scale could be related to physiological parameters.

We decided to use a 3-day dietary report instead of a food frequency questionnaire, 24-hour recalls or dietary history because short term memory in elderly may be impaired[50], and the burden on the participants was already quite high. We used a smell test as objective measurement of sensory perception since smell sensitivity declines more in elderly and is easier to measure compared to taste[51]. The smell identification test we used in this study was based on the validated CCCRC test[28;29] and we only adopted slight modifications.

Because appetite may be viewed as a sign of good health in the frail, it is important to focus on this topic, and not only through the difficult and intensive to measure 'gold standard' energy intake. Moreover, energy intake does not always reflect appetite because elderly may eat because they are used eating, although they do not feel like it. We were not able to improve either appetite, hunger feelings and sensory perception, and due to exercise we found only small effects on energy and nutrient intake. Changes in energy intake were neither convincingly correlated with appetite but slightly with body weight. This once more confirms the complexity of the whole system and the extremely difficult task to improve nutritional and health status of the frail elderly through increasing appetite by providing nutrient dense foods and exercise.

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4

Functional biochemical and nutrient indices in frail elderly people partly affected by dietary supplements but not by exercise

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Decline in dietary intake due to inactivity and hence development of a suboptimal nutritional status is a major problem in frail elderly people. However, benefits of micronutrient supplementation, all-round physical exercise, or a combination of both on functional biochemical and hematological indicators of nutritional and health status in frail elderly subjects have not been tested thoroughly.

A 17-wk randomized controlled trial was performed in 145 free-living frail elderly people (43 men, 102 women, mean age: 78±5.7 years). Based on a 2x2 factorial design, subjects were assigned to: a) nutrient dense foods, or b) exercise, or c) both, or d) control. Foods were enriched with micronutrients, frequently characterized as deficient in elderly people (25-100% of the RDA). Exercises focused on skill training including strength, endurance, coordination, flexibility. Dietary intake, blood vitamin levels and nutritional and health indicators, including (pre)albumin, ferritin, transferrin, C-reactive protein, hemoglobin and lymphocytes were measured.

At baseline, 28% of the total population had an energy intake below 6.3 MJ, up to a maximum of 93% having vitamin intakes below 2/3 of the Dutch RDA. Individual (blood)vitamin deficiencies, at baseline ranging from 3% for erythrocyte glutathione reductase-α to 39% for 25-hydroxy vitamin D and 42% for vitamin B_{12}, were corrected after 17-wks in the groups receiving the nutrient dense foods (groups a and c), whereas no significant changes were observed in the control or exercise group (b and d). Biochemical and hematological indicators at baseline were within the reference ranges (mean albumin: 46g/l, pre-albumin: 0.25g/l, hemoglobin: 8.6mmol/l) and not affected by any intervention.

Long term protective effects of nutrient supplementation and exercise by maintaining optimal nutrient levels and thereby reducing the initial chance of developing critical biochemical values needs further investigation. Other indicative functional variables for suboptimal nutritional state, next to exploration of the ones currently selected, should also be explored.

INTRODUCTION

Older adults are a heterogeneous group. Individuals differ with respect to the progress of aging due to several biological factors. Within this process of aging, physical frailty may commence. A more sedentary lifestyle, a reduction in metabolic cell mass and consequently a lower energy expenditure and dietary intake are important contributors to the downward process of frailty. A decline in intake is in turn associated with the risk of developing a suboptimal nutritional state or multiple micronutrient deficiencies. Although the small intestine, pancreas and liver are believed to undergo only few clinically relevant changes with normal aging due to their large reserve capacity[1;2], alterations in absorption and metabolism of several nutrients (including dietary vitamin B_6, vitamin B_{12}, folate, calcium, iron, zinc) accompany the frailty process. Various disease states, for example atrophic gastritis, and relatively high levels of medication also contribute to alterations in absorption and metabolism[2-4].

Blood concentrations of water-soluble vitamins often show the fastest decline in elderly people with inadequate dietary intake, since body reserves are limited[5], but marginal states of vitamin D and minerals like iron, magnesium and zinc are reported as well[3;6-9].

Until now, only a few studies have investigated the influence of nutrient supplementation and/or exercise on multiple indicators of nutritional status in elderly people, classified as frail or 'at risk'[10-13]. Physical exercise is reported to increase energy expenditure[14;15], resulting in a possible increment of total dietary intake[16]. Additionally, a slowing down or reversal of the overall age-related decline in physiological functioning may occur[17]. This may be reflected in the enhancement of a multitude of bodily processes including nutrient metabolism[18], organ system functioning[19], hormone secretion[20;21] and perhaps gastrointestinal nutrient absorption[22]. In an early study by Mann et al.[23], it was shown that multivitamin supplementation increased blood levels of the water soluble vitamins. This was not observed for fat soluble vitamins, thereby confirming the theory that greater storage pools of the fat soluble vitamins are present in the liver and fat tissue.

So far, well-controlled trials investigating possible benefits of all-round physical exercise and/or physiologically dosed micronutrient dense foods on functional biochemical indicators of nutritional status in frail elderly people, have not been published. Previous studies either investigated effects of nutritional supplements only, had access to just small samples, or focused on other outcomes.

For our present trial, we hypothesized that either supplementation of a physiological dose of micronutrients (due to a beneficial increase in nutrient status) or a progressive all-round exercise program (mainly by an increase in daily energy expenditure and dietary intake) would affect selected biochemical and hematological indicators of nutritional and health status in a group of community dwelling frail elderly people. As exercise might additionally result in a more efficient nutrient absorption and overall metabolism, a combination of both interventions may be even more beneficial. Nutrient intake, blood nutrient levels as indicators of available body pools[24], and functional biochemical indicators of overall nutritional and health status will be addressed.

MATERIAL AND METHODS

Subjects

The study population consisted of 217 free-living frail elderly Dutch people. Frailty was defined according to the following criteria: requirement of health care, such as home care or meals-on-wheels service; age (≥ 70 y); no regular exercise; body mass index below average (BMI ≤ 25 kg/m^2, based on self reported weight and height) or recent weight loss; no use of multivitamin supplements and ability to understand the study procedures.

All subjects gave their written informed consent. The study protocol was approved by the Medical Ethical Committee of the Division of Human Nutrition and Epidemiology of the Wageningen Agricultural University. Pre- and post-intervention measurement(s) were available for 165 subjects. Reasons for drop out (n=52, 24%) were mainly health problems, including (terminal) disease, hospital admittance, recent falling and/or fracturing. Valid (pre- and post) biochemical variables were available for 145 subjects. Four subjects were excluded because the time between pre- and post-intevention measurement was less than 13 wks due to hospitalization, three subjects were not able to visit our research center after intervention due to illness and therefore ended the trial with incomplete blood samples. Venipuncture did not succeed in one subject and 12 subjects were excluded from analyses because of multivitamin usage.

Design

Enrollment took place between January and June 1997. Subjects were randomly assigned to one of four intervention groups. The first group (nutrition) received nutrient dense products and a social program, the second group (exercise) received regular products and an exercise program, the third group (combination) received nutrient dense products with an exercise program and the fourth group, control (or placebo), received regular products and a social program. The intervention period was 17 wks and data were collected at baseline (week 0) and after 17 wks (in week 18). Dietary intake data were collected at baseline and during the last week of intervention (week 17).

Nutrient dense foods

Subjects were asked to consume two products a day: one from a series of fruit products and one from a series of dairy products. Availability of a variety of products was intended to avoid monotony and to increase acceptability of the products. Fresh 100 g servings of fruit based products (two types of both fruit juice and compote) and 100 g servings of dairy products (vanilla custard, two types of fruit yogurt and 75 g of cheese curd with fruits) were provided weekly. Daily consumption of two enriched products delivered ~100% of the Dutch RDA[9;25] of vitamins: D, E, B_1, B_2, B_6, folic acid, B_{12} and C and ~ 25-100% of the Dutch RDA of the minerals: calcium (25%), magnesium (25%), zinc (50%), iron (50%), iodine (100%). Subjects in the control and exercise group received the natural amount of the regular products (amount of vitamins and minerals in regular products at the highest 15% of the concentration in enriched products). Both the enriched and regular products had an energy content of ~0.48 MJ per two products.

Exercise program

The main objective of the exercise program was to maintain and/or improve mobility and performance of daily activities essential for independent functioning by maintaining versatility in movement. Perhaps via a more efficient nutrient absorption and metabolism, nutritional status could also be improved[18-20;22]. Emphasis was placed on skill training: muscle strength, coordination, flexibility, speed and endurance were trained by exercises such as walking, stooping and chair stands. Different materials were used, for example balls, ropes, weights and elastic bands. The second objective was to improve nutrient status, through increasing the daily activity level, overall energy expenditure and consequently dietary intake.

Group sessions were organized twice a week for 45 min and were of moderate, gradually increasing intensity. Since participants were assumed to be fairly inactive at baseline, sessions twice a week were considered the maximum amount in order to achieve sufficient compliance. From earlier studies we knew that with a twice-weekly-program beneficial effects could be determined on functional capacity and muscle strength[26;27]. Sessions were supervised by skilled teachers to improve safety and prevent wrong and harmful movements. In order to guarantee uniformity sessions were extensively rehearsed with all teachers together, and an instruction video and manual were made in advance. A social program served as a control (for attention) program for the exercise program. Sessions of 90 min were organized once every two weeks by a skilled creative therapist. This program focused on creative activities, social activities and lectures on interesting topics for elderly people. Transport to and from all sessions was arranged.

Questionnaires

A general questionnaire asked for information on age, sex, marital status, education, living conditions, illness, medicine and supplement use, and smoking habits. Physical activity was assessed using the validated Physical Activity Scale for Elderly (PASE)[28;29].

Anthropometry

All anthropometric measurements were performed with subjects wearing underclothes. Body weight was measured to the nearest 0.01 kg using a digital scale (ED-6-T; Berkel, Rotterdam, The Netherlands) and height was measured to the nearest 0.001 m using a wall-mounted stadiometer. Body mass index was calculated as weight in kilograms divided by height in meters squared[30].

Dietary intake

A three day (two weekdays and one weekend day; non-consecutive) estimated dietary record was obtained by three trained dietitians at baseline (week 0) and in the last week of intervention (week 17). During a home visit prior to the intervention, dietitians provided subjects with a clear explanation on how to record and estimate portion sizes in household measures. During a second visit, they checked the diary and weighed the portion sizes of the most frequently used foods in household measures. Subjects having difficulties with writing could use a voice tape recorder. In case of problems occurring during the three days of recording, subjects could telephone the dietitians at daytime and in the evening. Food consumption data were coded (with frequent cross checking by all three dietitians) after which energy and nutrients were calculated with the computerized Dutch Food Composition Table of 1997 and a supplement of 1995 for folate and vitamin B_{12}[31;32].

Biochemistry

Pre- and post-intervention blood samples were collected from fasting subjects between 07.00 and 09.00 for all indicators, except samples for complete blood count and vitamin C which for practical reasons were collected in our research center at noon and immediately put on ice before further processing. Within 1 h of collecting samples for vitamin C analysis 0.5 ml EDTA plasma was mixed with 2.0 mL metaphosphoric acid (50g/l, JT Baker Bakergrade) to deproteinize the vitamin C sample (analyzed with HPLC-fluorimetry, coefficient of variation between runs: 5-10%)[30;33]. A fresh 3 ml EDTA sample was used for complete blood count (Coulter Counter type T-860, Coulter Corporation, Miami, FL).

With respect to the fasting blood samples, 3 ml serum was used for analyses of the serum proteins: albumin (bromocresol-green), pre-albumin, C-reactive protein, transferrin, ferritin, thyroxine (T4) (immunoturbidimetric principle). A Hitachi-911 automatic analyzer, Hitachi Instrument Division, Japan and a AIA-600 Enzyme Immunoassay Analyzer, Tosoh Corporation, Japan were used with a CV between runs of 1-8%. For vitamins B_1 and B_2, erythrocyte transketolase activity (ETK) and erythrocyte glutathione reductase activity (EGR) were determined respectively (kinetic spectrophotometric enzyme determination), between-run-CV 7-9%[30;33]. Samples (3 ml) were hemolyzed after slow centrifugation and washed with an equal amount of 9 g/l NaCl. After three washing procedures the erythrocytes were diluted with an equal volume of Nonidet P40 (Boom, Meppel, The Netherlands). For vitamin B_6, serum pyridoxal-5'-phosphate (1 ml) was determined by HPLC-fluorimetry with a between-run-CV of 5-10%[30;33], for vitamin B_{12} a 0.5 ml plasma sample was analyzed with the IMx automated immunoassay system[34], and 25-hydroxy vitamin D values were analyzed in a 0.5 ml serum sample for vitamin D (CPB) with a between-run-CV of 5-10%[35]. All samples were stored at -80°C until analysis. Pre- and post-intervention samples were analyzed in the same batch. Analyses were performed by the TNO Nutrition and Food Research Institute, Zeist, The Netherlands, the Department of Clinical Chemistry, University Hospital Nijmegen, The Netherlands (B_{12}), and the Division of Human Nutrition and Epidemiology, Wageningen Agricultural University, The Netherlands (Coulter counter).

Statistical analysis

Data were analyzed using the statistical program SAS (Statistical Analysis Program, version 6, NC: SAS Institute Inc., 1990). Means ± sd, medians (10^{th}- 90^{th} percentiles) or percentages of (baseline) values were calculated for all intervention groups. The prevalence of subjects deviating from the reference were calculated as frequencies. Absolute changes ± sd per intervention group were calculated and compared with changes in the control group using an unpaired t-test. Since many subjects had a lower CRP level than the detection limit of 0.30 mg/l, we set those values at 0.15 mg/l in order to calculate changes on a continuous scale for the whole population. Multiple regression was used to determine the effect of both interventions and a possible interaction on the change in biochemical variables. Since no evidence of an interaction was observed between interventions a comparison was made between the supplemented group versus the non-supplemented group and the exercising group versus the non-exercising group respectively. For all the changes in the variables studied, confounding by baseline age, supplement use and corresponding baseline biochemical value was checked (e.g. for change in albumin the model was adjusted for baseline albumin and so forth). In the adjusted regression model only the corresponding baseline biochemical value was added as a confounder, since age and supplement use did not contribute significantly to the model. A p-value $\leq$0.05 was considered significant.

RESULTS

On average, 70% of the participants (mean age: 78 y) were women (Table 4.1). In general, none of the baseline variables differed considerably among the four intervention groups except age (exercise group slightly younger, p=0.20) and percentage of subjects using single nutrient supplements (combination group slightly higher, p=0.36).

Table 4.1: Baseline characteristics of the study population

Parameter	Nutrition (n=37)	Exercise (n=35)	Combination (n=39)	Control (n=34)
Women, %	70	71	72	68
Age, y[a]	78.9 ± 4.8	76.5 ± 4.5	78.8 ± 6.1	78.7 ± 6.8
Activity score[b,c]	59 (34-103)	59 (27-96)	62 (30-115)	59 (34-117)
Subjective health[a,d]	6.9 ± 1.7	7.0 ± 1.2	7.1 ± 1.2	7.0 ± 1.5[f]
Height[a], m	1.65 ± 0.10	1.65 ± 0.10	1.65 ± 0.08	1.64 ± 0.07
Weight[a], kg	66.1 ± 8.7	66.4 ± 12.1	67.7 ± 7.8	65.9 ± 10.8
Body Mass Index[a], kg/m^2	24.3 ± 2.3	24.3 ± 3.1	24.9 ± 2.5	24.1 ± 3.2
One or more diseases, %	86	91	95	85
Living alone, %	68	69	69	68
Falling experienced, %	51	51	46	41
Prescribed medicines[c], n	3.0 (0-6)	2.0 (0-6)	2.0 (0-5)	2.5 (0-7)
Supplement usage[e], %	22	29	38	24
Currently smoking, %	14	11	8	18
Outside daily during sunny periods, %	76	71	77	68
Avoidance of sunlight, %	27	23	36	32

[a] mean ± sd, [b] range PASE: 0-400, [c] median (P_{10};P_{90}), [d] range: 1-10, [e] subjects using multisupplements excluded from all analyses, [f] n=33

Most population characteristics did not change over the intervention, e.g. change in subjective health (range 1-10) varied between -0.2 and +0.2 points among the four groups (p=0.37). Only change in body weight showed a trend towards a decline in the control (-0.3 kg) and nutrition group (-0.1) and a small increase in both exercise (0.1 kg) and combination (0.2 kg) groups (p=0.33).

The baseline values of dietary intake for men and women and percentage of subjects below two-thirds of the Dutch recommended dietary intakes[9;25] are presented in Table 4.2. Comparing the mean intake data of our population with that of healthy Dutch elderly people[9;36-39], energy intake in our population was lower, as was protein and fat intake. With respect to the vitamins intakes of B_2, B_{12}, C, D and E were especially below the intake of healthy Dutch elderly people.

Table 4.2: Baseline daily dietary intake of the study population presented for men and women separately, percentages of subjects deviating from two-thirds of the Dutch RDA[a] and mean dietary intake of apparently healthy Dutch elderly[b]

Parameter	Men[c] (n=43)	Women[c] (n=102)	Percent below 2/3 of the Dutch RDA[a,d]		Dutch men of a healthy population[b,c]	Dutch women of a healthy population[b,c]
			%men	%women		
Energy intake, MJ/d	8.8 ± 2.0	6.9 ± 1.5	14	34	9.3 ± 2.0	7.7 ± 2.3
Carbohydrate, g/d	249 ± 71	196 ± 42	0	4	241 ± 37	204 ±35
Protein, g/d	76 ± 22	62 ± 15	0	3	79 ± 15	71 ±14
Fat, g/d	78 ± 23	65 ± 19			97 ± 15	80 ± 18
vitamin B_1, mg/d	1.37 ± 0.79	0.99 ± 0.55	5	16	1.19 ± 0.28	0.94 ± 0.27
vitamin B_2, mg/d	1.44 ± 0.58	1.26 ± 0.40	26	16	1.65 ± 0.44	1.63 ± 0.56
vitamin B_6, mg/d	1.52 ±0.58	1.33 ± 1.18	5	3	1.59 ± 0.40	1.29 ± 0.34
vitamin B_{12}, µg/d	4.1 ± 2.1	3.0 ± 1.2	5	11	5.8[e]	5.0[e]
vitamin C, mg/d	113 ± 59	92 ± 37	14	12	120 ± 58	118 ± 56
vitamin D, µg/d	3.6 ± 2.0	3.1 ± 1.7	79	93	6.4 ± 2.4	4.8 ± 1.8
vitamin E, mg α toc[f]/d	6.1 ± 3.0	4.8 ± 1.7	65	66	12.9[e]	10.5[e]
vitamin A, mg ret eq[g]/d	0.99 ± 0.73	0.79 ± 0.52	44	32	1.02[e]	0.86[e]

[a] see references: 9;25 [b] data based on various populations, see references: 9;36-39 [c] mean ± sd [d] energy: % below 6.3 MJ/day
[e] median values [f] alpha-tocopherol [g] retinol equivalents

When two-thirds of the Dutch RDA is taken as cut-off value, macronutrient intake was adequate in our population, whereas vitamin D, E and A in particular were below this cut-off value. With respect to energy intake 14% of the men and 34% of women had intakes below 6.3 MJ, the level at which several micronutrient deficiencies can be expected.

Mean intake data of each of the three intervention groups (i.e. nutrition, exercise and combination group) were compared with the control group (Table 4.3). Both the exercise and the combination group had a slightly lower energy (p=0.051) and carbohydrate intake (p<0.05) than the control group at baseline. At the end of intervention the combination and nutrition group significantly increased their intakes of those micronutrients which were added to the nutrient dense foods. No significant increases were found in the exercise group compared to the control group.

Table 4.3: Dietary intake, changes after 17-wks[a] and percentage of subjects below 2/3 of the Dutch RDA[b] presented for the all intervention groups separately[c]

Parameter	Nutrition (n=37)	Exercise (n=34)	Combination (n=38)	Control (n=34)
Energy intake, MJ/d				
baseline	7.8±1.8	7.2±1.8[d]	7.1±1.4[d]	7.7±2.2
change	-0.4±1.4	0.2±1.2	0.1±1.3	-0.4±2.1
pre/post-intervention < ref, %	22/30	32/21	34/34	21/38
Carbohydrate, g/d				
baseline	222±59	209±60*	196±43*	223±65
change	-16±39	2±34	9±38	-7±66
pre/post-intervention < ref, %	0/3	0/0	3/0	6/9
Protein, g/d				
baseline	66±15	65±20	67±16	68±22
change	-0.7±15	4±17	-0.8±14	0.8±14
pre/post-intervention < ref, %	0/0	0/0	3/0	3/6
Fat, g/d				
baseline	72±22	68±18	67±17	69±27
change	-2±21	2±18	0.9±18	-3±23
pre/post-intervention < ref, %	-	-	-	-

Continued:

Parameter	Nutrition (n=37)	Exercise (n=34)	Combination (n=38)	Control (n=34)
vitamin B_1, mg/d				
baseline	1.06±0.55	1.05±0.55	1.15±0.89	1.16±0.55
change	0.86±0.67***	-0.05±0.64	0.78±0.51***	-0.11±0.60
pre/post intervention < ref, %	8/5	15/6	16/0	9/21
vitamin B_2, mg/d				
baseline	1.38±0.40	1.19±0.46	1.33±0.47	1.34±0.52
change	1.34±0.71***	0.15±0.33	1.25±0.55***	0.16±0.45
pre/post intervention < ref, %	11/0	26/6	13/0	21/18
vitamin B_6, mg/d				
baseline	1.32±0.43	1.67±2.02	1.23±0.32	1.35±0.35
change	1.27±0.46***	-0.37±2.06	1.22±0.41***	0.03±0.36
pre/post intervention < ref, %	3/0	6/3	0/0	3/3
vitamin B_{12}, µg/d				
baseline	3.45±1.52	3.12±1.30	3.44±1.38	3.47±2.06[e]
change	3.42±4.24**	0.91±3.13	2.13±1.50**	0.72±2.34
pre/post intervention < ref, %	8/3	9/3	8/0	12/6
vitamin C, mg/d				
baseline	105.4±54.4	108.6±42.9	88.7±45.3	91.2±34.5
change	69.2±59.7***	-19.3±50.4	70.0±40.6***	3.1±42.1
pre/post intervention < ref, %	16/3	3/9	16/0	12/15
vitamin D, µg/d				
baseline	3.2±1.5	3.1±2.1	3.3±1.3	3.5±2.3
change	11.6±6.6***	-0.4±2.4	10.6±4.6***	0.2±1.6
pre/post intervention < ref, %	84/8	94/100	92/3	85/79
vitamin E, mg α tocopherol/d				
baseline	5.4±2.8	5.0±1.8	5.5±2.4	4.8±1.8
change	11.6±6.4***	-0.3±2.6	10.5±4.4***	0.2±2.3
pre/post intervention < ref, %	57/0	74/79	59/0	79/68
vitamin A , mg retinol eq/d				
baseline	0.93±0.79	0.86± .53	0.80±0.49	0.83±0.54
change	-0.03±0.63	0.02±0.74	-0.04±0.54	0.04±0.76
pre/post intervention < ref, %	32/32	29/24	42/37	35/32

[a] means ± sd [b] Recommended Daily Allowances [9;25] [c] 2 subjects excluded because of an incomplete post-intervention diary [d] p=0.05 compared to control group [e] n=33

* p< 0.05, ** p<0.01, *** p<0.001 compared to control group

With respect to blood levels of several selected vitamins and their 17-week changes (±sd), significant increases were detected in 25-hydroxyvitamin D, vitamin B_{12}, ascorbic acid and pyridoxal-5-phosphate in both the nutrition and combination group compared to the control group (Table 4.4). Erythrocyte transketolase factor α (as a measure for vitamin B_1) and glutathione factor α (as a measure for B_2) both decreased in the direction of 1.0. The change in ETK-α was borderline significant in the nutrition group ($p=0.07$) and the change in EGR-α was significant ($p<0.05$) in the combination group. Since values above 1.25 are unfavorable[6], this is considered a beneficial decrease. The beneficial effects of supplementation are also reflected in the percentages of subjects outside the reference values pre- and post-intervention (Table 4.4).

Overall, very few subjects in the supplemented groups (between 0% and 15%) were classified as deficient after intervention. No significant differences in change were found between the exercise group and the control group. Since no evidence of interaction was found we could focus on the main effects (i.e. the supplemented group vs the non-supplemented group and exercise vs non-exercise). For all micronutrients under study, we adjusted the models for the corresponding baseline values. Significant increases were calculated in micronutrient levels in the supplemented group compared to the non-supplemented group (all $p<0.003$), whereas no significant difference in change occurred in the exercisers vs non-exercisers (all $p>0.15$, data not shown).

In general, at baseline all mean values of the other selected biochemical and hematological indicators fell within or above the range of the reference values, meaning that no clinical deficiencies of any indices on group level were observed (Table 4.5). No statistically significant increases in the intervention groups compared to the control group were found. Only with respect to albumin, pre-albumin and thyroxine (T4) was a slight improvement in the nutrition compared to the control group noted. With respect to mean values of hemoglobin, hematocrit and number of red blood cells there was a tendency of decline in all groups, whereas the mean number of white blood cells and lymphocytes slightly increased.

Table 4.4: Blood vitamin levels and changes after 17-wks of the study population[a], values of a Dutch healthy elderly population[b] and reference values for deficiencies[b]

Parameter[a]	Nutrition (n=37)	Exercise (n=35)	Combination (n=39)	Control (n=34)	Dutch healthy elderly[2] men	Dutch healthy elderly[2] women	Reference values for deficiencies[2]
25-hydroxy vitamin D, nmol/l							
baseline	37 ± 20	40 ± 20	39 ± 16	36 ± 20	42	42	< 30
change	35 ± 18***	4 ± 12	31 ± 18***	5 ± 9			
pre/post-intervention < ref[b], %	51/0	29/26	33/0	44/38			
ETK-α[c]							
baseline	1.11 ± 0.12	1.13 ± 0.10	1.12 ± 0.13	1.15 ± 0.13	1.10	1.10	> 1.25
change	-0.03 ± 0.14[e]	0.01 ± 0.13	0.00 ± 0.14	0.04 ± 0.17			
pre/post-intervention < ref, %	8/3	11/11	15/15	24/18			
EGR-α[d]							
baseline	1.04 ± 0.06	1.08 ± 0.08	1.06 ± 0.09	1.08 ± 0.13	1.13	1.13	> 1.25
change	-0.05 ± 0.07	-0.03 ± 0.05	-0.07 ± 0.08*	-0.03 ± 0.08			
pre/post-intervention < ref, %	3/0	3/0	3/0	6/3			
pyridoxal-5-phosphate, nmol/l							
baseline	39 ± 25	34 ± 21	36 ± 29	33 ± 22	49	51	< 20
change	32 ± 29***	-0 ± 27	19 ± 26***	-3 ± 16			
pre/post-intervention < ref, %	14/0	23/17	26/3	24/24			
vitamin B_{12}, pmol/l							
baseline	280 ± 112	236 ± 94	299 ± 139	252 ± 136	277	280	<221
change	78 ± 66***	-5 ± 40	54 ± 75***	-8 ± 43			
pre/post-intervention < ref, %	41/11	54/51	28/15	47/44			
ascorbic acid[f], μmol/l							
baseline	67 ± 21	65 ± 19	60 ± 25	53 ± 27	90	61	< 23
change	12 ± 15**	-2 ± 20	18 ± 31**	-1 ± 20			
pre/post-intervention < ref, %	3/0	0/3	13/0	19/19			

[a] means ± sd [b] ref = references: 7;8;39;40;44;46;53 [c] Erythrocyte Transketolase alpha [d] Erythrocyte Glutathione alpha [e] p=0.07
[f] nutrition: n=34, exercise: n=34, combination: n=38, control: n=31 * p < 0.05, ** p < 0.01, *** p < 0.001 with respect to control group

Table 4.5: Biochemical and hematological indicators, changes after 17-wks[a] and references values

Parameter[a]	Nutrition (n=37)	Exercise (n=35)	Combination (n=39)	Control (n=34)	Reference values for clinical deficiencies[b,c]
Albumin, g/l					
baseline	46 ± 3	46 ± 2	46 ± 3	45 ± 3	< 35
change	0 ± 2[d]	-0 ± 2	-0 ± 2	-1 ± 2	
Pre-Albumin, g/l					
baseline	0.25 ± 0.06	0.25 ± 0.04	0.24 ± 0.05	0.24 ± 0.04	< 0.10
change	0.01 ± 0.02**	-0.00 ± 0.02	-0.00 ± 0.02	-0.01 ± 0.03	
C-reactive protein, mg/l					
baseline	1.3 ± 2.5	1.1 ± 2.5	3.2 ± 9.8	1.3 ± 2.5	> 10
change	-0.1 ± 1.7	-0.1 ± 1.9	-0.2 ± 13.4	0.9 ± 6.2	
Ferritin, μg/l					
baseline	99 ± 68	135 ± 96	153 ± 121	124 ± 86	<20.0 (M);
change	4 ± 24	-14 ± 28	-1 ± 35	3 ± 52	<10.0 (F)
Transferrin, g/l					
baseline	3.16 ± 0.59	2.96 ± 0.52	2.89 ± 0.42	2.99 ± 0.57	< 2.30
change	-0.02 ± 0.18	0.09 ± 0.35	-0.01 ± 0.21	-0.00 ± 0.23	
Thyroxine, 10^{-5}g/l					
baseline	7.4 ± 1.2	7.6 ± 1.5	7.4 ± 1.4	7.5 ± 1.6	< 4.0
change	0.4 ± 0.8*	-0.2 ± 0.6	-0.2 ± 1.3	-0.1 ± 0.7	
Hemoglobin, mmol/l					
baseline	8.6 ± 0.7	8.6 ± 0.7	8.8 ± 0.7	8.4 ± 0.7	< 8.7 (M);
change	-0.2 ± 0.3	-0.3 ± 0.3	-0.3 ± 0.3	-0.2 ± 0.4	< 7.5 (F)
Hematocrit					
baseline	0.42 ± 0.03	0.42 ± 0.03	0.43 ± 0.03	0.41 ± 0.03	< 0.43 (M);
change	-0.01 ± 0.02	-0.00 ± 0.01	-0.01 ± 0.01	-0.01 ± 0.02	< 0.36 (F)
Red blood cells x10^{12}/l					
baseline	4.53 ± 0.38	4.57 ± 0.37	4.69 ± 0.37	4.49 ± 0.43	<4.22x10^{12}(M);
change	-0.09 ± 0.17	-0.06 ± 0.16	-0.19 ± 0.13*	-0.09 ± 0.20	<3.77x10^{12} (F)
White blood cells x10^{9}/l					
baseline	7.18 ± 1.52	7.35 ± 1.66	8.11 ± 2.56	8.10 ± 1.98	<4.0 or >12.0x10^{9}
change	0.29 ± 1.14	0.20 ± 1.35	0.01 ± 1.49	0.04 ± 1.55	
Lymphocytes, %					
baseline	29.8 ± 5.6	27.8 ± 6.9	29.5 ± 7.2	27.3 ± 7.4	< 20 or > 50
change	0.2 ± 4.5	0.9 ± 5.4	1.3 ± 5.7	0.3 ± 5.8	

[a] mean ± sd, [b] reference values based on laboratory stated lower limits and studies from reference: 54
[c] M=men, F=women [d] p=0.05, * p< 0.05, ** p< 0.01 with respect to control group

For CRP (an indicator for acute phase proteins) statistical analyses were carried out for the total group in which values below detection rate were set at a fixed level of 0.15 mg/l. Additionally, analyses were only done with subjects who had measurable values (n=22). The mean change in the group receiving nutrient dense foods was -0.3±1.2 (n=6), in the exercise group -1.3±1.2 (n=5) and in the combination group -8.5±17.0 (n=5), versus an increase in the control group of 7.3±12.9 (n=6).

In Table 4.6 adjusted (for baseline values) differences in change in selected biochemical and hematological variables between the nutrient dense and regular food groups and the exercise versus non-exercise groups are shown respectively. Only the levels of albumin and pre-albumin were significantly improved after 17-wks of consuming nutrient dense foods. No meaningful differences were found in the other variables between either consumers of nutrient dense foods and regular foods, or between exercisers and non-exercisers.

Table 4.6: Adjusted (for baseline value) differences in the change (95% confidence intervals) of biochemical variables, according to type of intervention (n=145)

Parameter	Nutrient dense vs regular foods difference (95% CI)		Exercise vs no exercise difference (95% CI)	
Albumin, g/l	0.6	(0.0;1.2)	0.2	(-0.4;0.9)
Pre-albumin, g/l	0.01	(0.00;0.02)	-0.00	(-0.01;0.01)
C-reactive protein, mg/l[a]	0.4	(-1.5;2.3)	0.3	(-1.5;2.2)
Ferritin, μg/l	7	(-4;18)	-7	(-18;5)
Transferrin, g/l	-0.06	(-0.14;0.02)	0.04	(-0.04;0.13)
Thryoxine, 10^{-5} g/l	0.2	(-0.1;0.5)	-0.3	(-0.6;-0.0)
Hemoglobin, mmol/l	0.0	(-0.1;0.1)	-0.1	(-0.2;0.0)
Hematocrit	-0.00	(-0.01;0.00)	-0.00	(-0.01;0.00)
Red blood cell no. $x10^{12}$/l	-0.06	(-0.11;-0.00)	-0.03	(-0.08;0.03)
White blood cell no. $x10^{9}$/l	0.01	(-0.43;0.46)	-0.06	(-0.50;0.39)
Lymphocytes, %	0.5	(-1.2;2.2)	1.0	(-0.6;2.7)

[a] difference in C-reactive protein calculated only for subjects with measurable values: nutrient dense versus regular (n=11): -3.2 (-9.4;3.0), exercise versus no exercise (n=11): -4.1 (-10.3;2.1)

DISCUSSION

Nutrient dense foods containing a physiological dose of those micronutrients frequently characterized as deficient in frail elderly significantly improved blood vitamin levels and corrected present individual deficiencies. However, despite these individual vitamin deficiencies at baseline, mean values of selected biochemical and hematological indicators, were not found below reference values. Therefore, in our frail elders none of the selected indicators seemed to be considerably affected by either nutritional supplementation or the specifically designed all-round exercise program.

In affluent societies nutritional deficiencies are not common in healthy elderly people[40], but low dietary intakes and clinically relevant deficiencies are evident in institutionalized elderly people. This latter group is physically inactive, may have reduced energy needs and is deteriorating in health[41]. Our population of community-dwelling frail elderly people is, to a lesser extent, regarded as such a group. From several selected indicators it appeared that we studied an elderly group with indeed a worse health profile than apparently healthy Dutch elderly people. Their mean BMI was lower compared to Dutch elderly in the European Seneca study (24 kg/m^2 vs 26 kg/m^2 in men and 28 kg/m^2 in women)[42] and self rated health was lower (7.0 vs 7.7) as was their activity level (PASE score 64 vs 85)[29;43]. Mean scores on physical fitness tests were below average as well (Chin A Paw et al., submitted). In addition, we found that 34% of our female subjects had a substantially low energy intake (< 6.3 MJ) moreover relatively low intakes of several vitamins were calculated as well. Blood vitamin deficiency rates of the total group varied between 42% for vitamin B_{12} and 39% for serum 25-hydroxy vitamin D to 3% for EGR-α (a functional measure of vitamin B_2). For most vitamins mean blood values in our study population were lower compared to mean values in healthy Dutch elderly people[7;8;39;40;44-46].

On the mean group level, however, no clinically relevant deficiencies of functional variables were noted. Indicators of poor protein status or chronic or acute illnesses like low albumin, pre-albumin and transferrin levels, low lymphocyte count or high CRP levels were not notably prevalent in our frail population. This observation may act as the main explanation for the fact that despite the observed significant improvement in blood vitamin levels in the supplemented groups (which is a confirmation that indeed our nutrient dense foods had been consumed and that indeed the provided vitamins were circulating in blood) we did not detect many clinically relevant beneficial changes in the selected indicators. Only albumin and pre-albumin significantly improved after the 17 wks nutritional intervention, although levels were regarded as adequate at baseline. However, the relevance of these increases is equivocal: the change in (pre-) albumin, might only be attributed to chance. In a subgroup with measurable values of CRP, supplementation and exercise seemed to be beneficial, but due to a small sample size this finding should also be interpreted with caution.

In an early study by Mann et al.[23] it was observed that 4 months of daily multivitamin supplementation with tablets improved blood levels of the water soluble vitamins in elderly people. For the fat soluble vitamins this was not proven. In our supplemented groups the water soluble vitamins increased significantly. Since we only measured vitamin D, a fat soluble vitamin known to be frequently low in elderly, we cannot comment on improvement of fat soluble vitamins in general.

Until now clinical significance of improved vitamin levels as such have not been evaluated in well controlled intervention trials. Only very few studies have focused on the effects of both exercise and nutrition on several nutritional and health indicators in frail elderly people[10], and only very limited information is available about improvements in functional (biochemical and hematological) indicators by either intervention[12;13]. Also, as far as we know studies with an all-round progressive exercise program combined with provision of a physiological dose of micronutrients have not been performed in community-dwelling frail elderly people.

It was hypothesized that the physical exercise program would improve activity level, energy expenditure and hence dietary intake. In addition, other beneficial effects on a multitude of bodily processes may be attributed to exercise as well. Gastrointestinal dysmotility, for example, may be caused by hypothyroidism and may be enhanced by physical exercise[22]. Others have postulated that thyroid hormone levels[21;47] but also growth hormone[20], insulin/glucose dynamics and lipoprotein metabolism[18] can be affected by certain types of programmed exercise. Serum albumin has been positively associated with skeletal muscle mass[48], and may therefore be influenced by physical activity. Perhaps several other (still unknown) beneficial effects on the metabolism and organ functioning in aging persons may be induced by regular exercise. Our program may unintentionally have been of a too low intensity or short duration to induce any change in energy expenditure and dietary intake, or gastrointestinal absorption and metabolism. Hence, individual deficient nutrient blood levels were not corrected in the exercising group during the intervention period. Yet, the expected beneficial effects of exercise might be expressed in the long term as maintenance of bodily tissues, organ systems and biochemical variables. Additionally, significant favorable effects on biochemical indicators could only have been induced in more frail, bedridden, elderly people.

Our findings are in agreement with observations of Lipschitz et al.[13] who studied supplementation in a 'meals-on-wheels elderly population'. They observed no change in serum ferritin levels, hemoglobin levels (not even in persons with anemia) or lymphocyte count but found a modest rise in serum albumin and in several selected nutrient concentrations. Additionally, Meredith et al.[12] found normal nutritional biochemical values at baseline and no change in these variables after a refeeding program during physical rehabilitation in elderly men.

It has been suggested that the failure of most functional indicators to improve with nutritional support implies that abnormalities are age or disease related rather than nutrition related[13]. Other explanations may also be raised, such as possible slight alterations in (micro)nutrient metabolism due to organ dysfunctioning, thereby not profiting from the corrected blood nutrient levels. Another possibility is the occurrence of renewed blood plasma or red cell balances, due to resorption of other tissues in chronically deficient people. Regarding activity coefficients of ETK and EGR, long term deficiency may be masked by decreased synthesis or kinetic functions of the apoenzyme involved, thereby establishing a new balance[49-52]. Perhaps the reference values for clinically relevant deficiencies need some re-evaluation against recently postulated 'optimal nutrient levels'. A relatively short intervention period should also be mentioned within this respect. Long term protective effects of nutrient supplementation on biochemical and hematological variables may occur, due to maintenance of the optimal nutrient levels. But benefits from this maintenance may only be measurable after many years.

Alternatively, since no multiple clinically relevant deficiencies at baseline were found, no relevant improvements might be expected after 17 weeks of intervention. The fact that our variables did not change after intervention is consistent with earlier studies[12;13]. It suggests that improving these currently selected biochemical and hematological indicators in these specific community-dwelling frail elderly populations may not necessarily be the first aim. On the other hand, the risk of developing a 'delayed' suboptimal nutritional state in the long term due to exhausted body reserves may be present in these frail groups. This may not be determined immediately because a renewed but unfavorable balance through tissue resorption may be initiated in the first place. Long term effects of supplementation and also exercise should therefore be investigated, as well as the mechanisms settled within once deficient subjects. Additionally, the relationships between and effects on other functional indicators, for example incidence of (infectious) diseases, osteoporosis and physical fitness and functioning should be the topic of further research in this frail elderly community-dwelling population.

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5

Physiologically dosed nutrient dense foods and exercise in frail elderly: effect on B-vitamins, homocysteine and neuropsychological functioning

Submitted

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The objective was to determine the effect of enriched foods and physical exercise on blood vitamin concentrations, homocysteine level and neuropsychologic functioning in frail elderly. A 17-weeks randomized placebo controlled intervention trial, following a 2x2 factorial design was performed: a) group receiving enriched foods + social program, b) group receiving enriched foods + exercise program, c) group receiving regular foods + exercise program, d) group receiving regular foods + social program. Foods were enriched with a physiologically dosed cocktail of vitamins and minerals (25-100% of the Dutch RDA), the all-round exercise program focused on training of strength, coordination, flexibility and endurance. Plasma vitamin levels (cobalamin, folate and pyridoxine-5-phosphate(PLP)), red blood cell folate and homocysteine concentration were analyzed. In addition two neuropsychologic tests, i.e. reaction time and manual dexterity were performed.

Of 130 independently living frail elderly (mean age: 78±5 years) data were available. Vitamin levels were significantly ($p<0.001$) raised in the nutrient dense food groups compared to the non-enriched groups. Plasma cobalamin in the enriched groups was, with respect to baseline levels, raised with 22%, plasma folate with 101%, red cell folate with 87% and PLP with 68%. The non-enriched groups changed their levels with -2%, -6%,1% and -13% respectively. Homocysteine level deviated with -25% in the enriched groups, whereas a small increase of 2% in the non-enriched group was found ($p<0.002$). Compared to non-enriched subjects a mean (95% CI) decline of 5.0 μmol (-6.5;-3.5) was achieved in the nutrient dense group. Exercise did not affect vitamin or homocysteine level. No significant effect of both interventions was observed on the neuropsychologic tests.

In conclusion, the decrease in homocysteine level in frail elderly confirms a subclinical metabolic deficiency state and may reduce their risk of cardiovascular disease. Effects of B-vitamins on mental health have yet to be ascertained.

INTRODUCTION

Prevalence of low plasma cobalamin (vitamin B_{12}), folate and pyridoxal-5-phosphate (vitamin B_6) concentrations have been found with advancing age by several but not all investigators[1-7], thus demonstrating considerable controversy. Other clinical metabolic tests of functional intracellular vitamin deficiencies like plasma concentrations of homocysteine (Hcy) and methylmalonic acid (MMA) seem to be more functional[7;8]. These indicators suggest a substantially higher vitamin deficiency prevalence[7;9] and even metabolic evidence of vitamin deficiency in the presence of normal plasma vitamin levels have been reported[10].

Interest in elevated plasma Hcy, as a potential risk factor for cardiovascular disease has recently grown notably. Deficiency of either folate and/or cobalamin, and to a lesser extent vitamin B_6, all cofactors in the Hcy metabolizing enzymes, may cause elevated levels of Hcy. Deficiency of cobalamin as well as folate, are additionally associated with neurologic abnormalities[2;4;11-13].

Particularly frail elderly are at risk for suboptimal or deficient micronutrient states, functional decline and neurologic disorders. Primary or secondary factors influencing the nutritional and health state are biological aging, chronic diseases (e.g. atrophic gastritis) and physical inactivity resulting in less energy expenditure and inadequate dietary intake or uptake[14-18]. In the past decade research in frail elderly has demonstrated benefits of nutritional supplementation programs and/or exercise on some (but not all) indicators of nutritional and health status[19-22]. Nevertheless, influence of oral physiologically dosed multiple micronutrients on homocysteine levels have not been described in frail elderly. Likewise, the influence of exercise, aiming at a direct improvement of physical and neurologic functioning, but also aiming at improvement of physical activity, energy expenditure and hence total dietary intake, has not been taken into account.

For ethical reasons proposed public health programs for lowering homocysteine levels should not be based on unnecessarily high doses of folic acid or other B-vitamins[23]. To overcome any potential risk of over-exposure with adverse effects, research is needed for determination of optimal dosages for community based (frail) elderly with perhaps only mildly elevated homocysteine levels. In this intervention trial, we focus on the effects of multiple physiologically dosed nutrient dense foods and/or exercise on vitamin status, homocysteine levels and neuropsychological functioning in frail elderly.

MATERIAL AND METHODS

Subjects

The study population comprised of 217 free-living Dutch (frail) elderly. Frailty was defined according to the following criteria: requirement of health care (such as home care or meals-on-wheels service); age ≥ 70 years; no regular exercise; body mass index below average (BMI ≤ 25 kg/m^2, based on self reported weight and height) or recent weight loss; ability to understand the study procedures and no use of multivitamin supplements.

All subjects gave a written informed consent. The study protocol was approved by the external Medical Ethical Committee of the Division of Human Nutrition and Epidemiology of the Wageningen Agricultural University. Pre- and postintervention measurement(s) were available for 165 subjects. Reasons for this drop out (n=52, 24%) were mainly health problems, including (terminal) disease, hospital admittance, recent falling and/or fracturing. Valid (pre- and post) vitamin and homocysteine measures were available for 130 subjects. Four subjects were excluded because the time between pre- and postmeasurement was less than 13 weeks due to hospitalization, three subjects were not able to visit our research center after intervention due to illness. In one subject venipuncture was not successful and additionally 12 subjects were excluded from analyses, because of multivitamin usage. Another 14 subjects were excluded because of vitamin B-complex usage. Finally, one subject in the control group was dropped because of extremely high Hcy values (i.e. pre-intervention: 93.2 μmol/l, post-intervention: 84.3 μmol/l).

Design

Enrollment took place between January and June 1997. Subjects were randomly assigned to one of four intervention groups:

a. <u>nutrition</u>: nutrient dense products + social program;

b. <u>exercise</u>: regular products + exercise program;

c. <u>combination</u>: nutrient dense products + exercise program;

d. <u>control (or placebo)</u>: regular products + social program.

The intervention period was 17 weeks. At baseline (week 0) and after 17 weeks (in week 18) data were collected.

Nutrient dense foods

Subjects were asked to consume two products a day: one from a series of fruit products and one from a series of dairy products. Availability of a variety of products was intended to avoid boredom and to increase acceptability of the products. Fresh 100 g servings of fruit based products (two types of both fruit juice and compote) and 100 g servings of dairy products (vanilla custard, two types of fruit yogurt and cheese curd with fruits (75 g)) were provided weekly. Daily consumption of two enriched products delivered ~100% of the Dutch RDA [24;25] of the vitamins: D, E, B_1, B_2, B_6, folic acid, B_{12}, C and ~ 25-100% of the Dutch RDA of the minerals: calcium (25%), magnesium (25%), zinc (50%), iron (50%), iodine (100%). Details about the contents of the enriched products are described elsewhere (manuscript submitted) and in the appendix. Subjects in the control and exercise group received identical regular products (amount of vitamins and minerals at the highest 15% of the concentration in enriched products). Both the enriched and the regular products contained ~0.48 MJ of energy per two products.

Exercise program

The main objective of the exercise program was maintenance / improvement of mobility and performance of daily activities essential for independent functioning by maintenance of versatility in movement. Emphasis was placed on skill training: muscle strength, coordination, flexibility, speed and endurance were trained by exercises such as walking, stooping and chair stands. Different materials were used, for example balls, ropes, weights, elastic bands. Group sessions were organized twice a week for 45 minutes and were of moderate, gradually increasing intensity. The sessions were coördinated by skilled teachers and supervised by one of the project leaders (MCAP). In order to guarantee uniformity all sessions were extensively rehearsed with all teachers together, moreover an instruction video and manual were made in advance. A social program served as a control (for attention) program for the exercise program. Sessions of 90 minutes were organized once every two weeks by a skilled creative therapist. This program focused on creative activities, social activities and lectures about topics of interest for elderly. Transport to and from all sessions was arranged.

Measures

Questionnaires asked for information on age, sex, marital status, education, living conditions, illness, medicine and supplement use, and physical activity level. Anthropometric measurements were performed to determine body weight (to 0.01 kg on a digital scale: ED-6-T; Berkel) and height (to 0.001 m with a wall-mounted stadiometer). Body mass index was calculated as weight in kilograms divided by height in meters squared[26].

Neuropsychological parameters

Two validated tests were used for measuring the neuropsychological functioning. First, a block-transfer test was accomplished: the participant was instructed to replace 40 blocks with the preferred hand from a full board to an empty board as fast as possible in a prescribed sequence. Second, a reaction time test was conducted: the subject had to react to the onset of a light by pushing a button as fast as possible. Details about these two tests can be found elsewhere[27].

Biochemistry

Blood samples from fasting subjects were collected between 07.00 and 09.00 for all indicators except samples for complete blood count and homocysteine. For practical reasons these latter two samples were collected in our research center at noon and immediately put on ice, before further processing. For total homocysteine 0.5 ml non-fasting EDTA plasma was used for analysis (HPLC-fluorimetry). All samples were analyzed within one run, with a variation coefficient of 3.5%. A fresh 3 ml non-fasting EDTA sample was used for complete blood count (Coulter Counter type T-860).

With respect to the fasting blood samples 1.5 ml EDTA-plasma was preserved for analyses of vitamin B_{12} and folate, using ion capture IMx (Abott Labs, Abott Park, IL, USA)[28;29]. Between run coefficients of variation were <5% and <10% respectively. For red cell folate hemolysates were prepared out of 100µl fasting EDTA plasma and 2 ml 1% ascorbic acid in water. Lysis reagent, containing guanidine HCl was used to dilute the sample four times and added at the time of analysis. Determination, using ion capture IMx as well, was followed by calculation of corrected red blood cell folate concentration with % hematocrit and plasma folate concentration used in the formula. A regression formula was used to correct for the delayed dilution with lysis reagent. Coefficient of variation with respect to these red blood cell folate samples was found <13% between run. For vitamin B_6 pyridoxal-5'-phosphate (PLP) was determined (derivatives separated by reversed-phase HPLC and detected by fluorescence) in 1.0 ml of plasma[26]. Between assay CV was 5-10%.

Until analysis all samples were stored at -80°C. Pre- and postintervention samples were analyzed in the same batch. Analyses were performed by the TNO Nutrition and Food Research Institute, Zeist, The Netherlands (PLP), the Department of Clinical Chemistry, University Hospital Nijmegen, St. Radboud, Nijmegen (B_{12}, plasma and red cell folate) and the division of Human Nutrition and Epidemiology, Wageningen Agricultural University, The Netherlands (Hcy, hemocytometry).

Statistical analysis

Data were analyzed using the statistical program SAS (Statistical Analysis Program, version 6, NC: SAS Institute Inc., 1990). Means ± standard deviations (sd), medians (10^{th}- 90^{th} percentiles) or percentages of (baseline) values were calculated for all intervention groups. Means and mean changes (±sd) per intervention group were calculated and compared with mean changes in the control group (ANOVA followed by unpaired t-tests). The prevalence of subjects deviating from reference deficiency levels before and after intervention were calculated as frequencies: i.e. vitamin B_{12} < 221 pmol/l, PLP < 20 nmol/l, plasma folate < 6.3 nmol/l, red blood cell folate < 337 nmol/l and homocysteine > 16.2 μmol/l according to the manufacturer's stated lower limit of normal values and the literature[9;10;30-33] (with respect to Hcy, data and cut-off levels of fasting as well as non-fasting subjects were described). With respect to the two neuropsychological tests medians and median changes (10^{th}- 90^{th} percentiles) per intervention group were calculated and compared with the control group (rank-sum test). Spearman correlation coefficients were obtained between (baseline) blood vitamin values, homocysteine levels and the neuropsychologic tests. Multiple regression was used to determine the effect of both interventions and a possible interaction on the change in homocysteine level. Since no evidence of interaction was observed between both interventions a comparison was made between the supplemented group versus the non-supplemented group and the exercising group versus the non-exercising group respectively, by linear regression. Baseline homocysteine and vitamin values were added as covariates to the model to check for confounding.

RESULTS

In Table 5.1 baseline characteristics per intervention group are presented. Seventy-one percent of the population were women. Mean age was 78 years, mean BMI 24 kg/m^2, and mean subjective health was rated as 6.9 on a 10-point scale (1=very unhealthy and 10=very healthy).

Table 5.1: Baseline characteristics of the study population according to intervention group

Parameter	Nutrition (n=36) mean±sd	Exercise (n=31) mean±sd	Combination (n=33) mean±sd	Control (n=30) mean±sd
Women (%)	69	74	76	67
Age (years)	78.8 ± 4.8	76.9 ± 4.6	77.9 ± 5.2	79.0 ± 7.2
Weight (kg)	66.1 ± 8.9	65.2 ± 12.1	67.6 ± 8.0	66.9 ± 10.9
BMI (kg/m^2)	24.3 ± 2.4	24.1 ± 3.2	24.8 ± 2.7	24.5 ± 3.2
Living alone (%)	67	71	73	67
Activity score[a] (median; P_{10}-P_{90})	61 (34-103)	55 (27-89)	62 (30-115)	59 (34-110)
Subjective health[b]	6.9 ± 1.7	6.9 ± 1.3	6.9 ± 1.3	7.0 ± 1.5
No. of prescribed medicines (median; P_{10}-P_{90})	3 (0-6)	2 (0-6)	2 (0-5)	2 (0-5)
Subjects reporting ≥ 1 disease (%)	86	94	94	83
Energy intake (MJ/day)	7.8 ± 1.8	6.9 ±1.4	7.1 ± 1.5	7.8 ± 2.2

[a] range PASE: 0-400

[b] range: 1-10

In Table 5.2 mean vitamin levels, homocysteine levels and three hematological indicators and their 17-weeks changes (±sd) are shown. At baseline between 30% (combination group) and 55% (exercise group) of the subjects had vitamin B_{12} levels below the reference of 221 pmol/l. With respect to plasma folate none of the subjects had levels below the reference at baseline, whereas red blood cell folate revealed on average 21% (from 10% in control to 28% in the nutrition group) of deficient subjects at baseline. For homocysteine, we found that on average half of our population had baseline levels above the reference of 16.2 μmol/l.

Table 5.2: Mean blood vitamin levels (±sd) and 17-week change (±sd) in the frail elderly study population

Parameter	Nutrition (n=36) mean±sd	Exercise (n=31) mean±sd	Combination (n=33) mean±sd	Control (n=30) mean±sd
Vitamin B_{12} (pmol/l)				
baseline	281 ± 113[a]	233 ± 97	299 ± 142	229 ± 87.2
change	*78 ± 67**	*-5 ± 42*	*51 ± 72 **	*-2 ± 37*
% < 221 pmol pre/post intervention	42/11	55/52	30/18	50/47
Folate (nmol/l)				
baseline	19.0 ± 7.8	19.9 ± 8.1	18.0 ± 7.2[b]	16.4 ± 7.0
change	*18.0 ± 7.2**	*-2.1 ± 4.9*	*19.5 ± 6.8**	*-0.15 ± 3.2*
% < 6.3 nmol pre/post intervention	0/0	0/0	0/0	0/0
Red cell folate (nmol/l)				
baseline	502.1 ± 227.6	462.9 ± 146.9	491.6 ± 180.2[b]	540.5 ± 134.4
change	*488.0 ± 293.8**	*22.8 ± 121.2*	*376.8 ± 177.8**	*-10.8 ± 190.1*
% < 337 nmol pre/post intervention	28/0	23/13	22/0	10/17
PLP (nmol/l)				
baseline	38.3 ± 25.1	33.8 ± 22.7	35.8 ± 31.7	32.3 ± 22.4
change	*32.6 ± 29.4**	*-0.5 ± 28.8*	*17.7 ± 27.0**	*-3.9 ± 13.5*
% < 20 nmol pre/post intervention	14/0	26/19	30/3	23/23
Homocysteine (µmol/l)				
baseline	17.3 ± 5.7	16.8 ± 7.0[c]	16.3 ± 6.1	19.5 ± 7.8
change	*-4.0 ± 3.9**	*0.5 ± 2.4*	*-4.6 ± 4.8**	*0.3 ± 5.6*
% > 16.2 µmol pre/post intervention	53/22	45/45	48/9	57/63
Hemoglobin (mmol/l)				
baseline	8.6 ± 0.7	8.7 ± 0.7	8.9 ± 0.7	8.5 ± 0.7
change	*-0.2 ± 0.3*	*-0.3 ± 0.3*	*-0.3 ± 0.3*	*-0.2 ± 0.4*
Hematocrit (l/l)				
baseline	0.42 ± 0.03	0.42 ± 0.03	0.43 ± 0.03	0.41± 0.03
change	*-0.01 ± 0.02*	*-0.00 ± 0.01*	*-0.01 ± 0.01*	*-0.01 ± 0.02*
Mean corpuscular vol (fl)				
baseline	92 ± 4	91 ± 4	91 ± 4	92 ± 4
change	*0.5 ± 1.7*	*0.2 ± 1.1*	*1.0 ± 1.5*	*0.3 ± 1.6*

* $p < 0.001$ compared to the control group, [a] n=35, [b] n=32, [c] n=30

After intervention, this was slightly increased or still equal in the non-supplemented groups (63% in the control and 45% in the exercise group), whereas in the supplemented groups the proportion had dropped to 9% of subjects having levels above the reference in the combination and 22% in the nutrition group. These beneficial changes were also reflected in significant alterations in mean levels in both supplemented groups compared to the control group (p=0.001). No significant differences in change in vitamins or homocysteine were observed between the exercising group and controls. With respect to the hematological data at baseline, only a few subjects were classified outside the reference values. No significant change in any of the intervention groups after 17 weeks was encountered regarding these indicators. Yet, there was a trend towards a small increase in cell size and a decline in hemoglobin and hematocrit.

Baseline values were comparable among the four groups with two (statistically significant) exceptions: vitamin B_{12} was slightly higher in the combination and nutrition group, whereas Hcy level was little higher in the control group compared to the others. No interaction between the exercise program and nutritional supplementation had occurred, therefore effects could be analyzed separately. The difference in change in Hcy levels between the supplemented group versus the non-supplemented group rose to 5.0 μmol/l in the adjusted model (Table 5.3). Exercise showed no statistical significant benefit on Hcy compared to non-exercise.

Table 5.3: Difference in change (95% confidence intervals) of homocysteine levels in frail elderly, according to type of intervention (n=129)

	Nutrient dense foods vs regular foods difference (95% CI)	Exercise vs no exercise difference (95% CI)
Homocysteine (μmol/l)		
crude	-4.4 (-6.0 ; -2.8)	-0.04 (-1.7 ; 1.6)
adjusted[a]	-5.0 (-6.5 ; -3.5)	-0.7 (-2.2 ; 0.8)

[a] adjusted for baseline homocysteine level and baseline folate concentration

In Table 5.4 baseline median scores and changes in the two neuropsychological tests are presented. No differences at baseline between groups were found, nor were any statistically significant differences in change compared to the control group detected ($p \geq 0.34$). When exercisers were compared to non-exercisers in the multiple regression analysis the differences in changes remained insignificant (data not shown).

Table 5.4: Median (P_{10}-P_{90}) outcomes of neuropsychologic tests and 17-week median change (P_{10}-P_{90}) in the frail elderly studied

Parameter	Nutrition (n=36) median (P_{10}-P_{90})	Exercise (n=31) median (P_{10}-P_{90})	Combination (n=33) median (P_{10}-P_{90})	Control (n=30) median (P_{10}-P_{90})
Reaction time (ms)				
baseline	229 (177;403)	250 (201;309)	222 (183;361)	255 (206;338)
change[a]	*8 (-84;65)*	*-2 (-44;51)*	*-2 (-71;69)*	*-15 (-77;51)*
Block transfer test (s)				
baseline	57 (49;73)	55 (48;67)	54 (43;68)	56 (48;72)
change[a]	*0.1 (-8;9)*	*-2 (-8;3)*	*-2 (-8;7)*	*-0.8 (-11;8)*

[a] negative change indicates improvement

Baseline homocysteine level was (not surprisingly) correlated with vitamin B_{12} and (plasma) folate (Table 5.5). Furthermore Hcy and PLP, but not folate and vitamin B_{12} , were related to scores of the neuropsychological tests.

Table 5.5: Spearman correlation coefficients in baseline data[a], of the frail elderly studied (n=128)

	Reaction time (ms)		Block transfer test time (s)		Homocysteine (μmol/L)	
	r_s	p	r_s	p	r_s	p
Vitamin B_{12}	-0.12	0.17	-0.11	0.23	-0.42	0.0001
Folate, plasma	-0.16	0.07	-0.17	0.06	-0.55	0.0001
Folate, erythrocytes	0.03	0.75	0.06	0.48	-0.17	0.05
PLP	-0.26	0.003	-0.17	0.06	-0.13	0.12
Homocysteine	0.22	0.01	0.23	0.009	-	

[a] negative sign indicates improvement

The 17-weeks change in folate was inversely correlated with change in Hcy (plasma folate: r=-0.67, p<0.001; red blood cell folate: r=-0.52, p<0.001). Change in vitamin B_{12} and PLP also showed an inverse significant correlation with Hcy level, but to a lesser extent: r=-0.36, p<0.001 and r=-0.41, p<0.001 respectively. Changes in blood vitamins nor homocysteine level did correlate with the changes in the neuropsychologic tests (data not shown).

DISCUSSION

Seventeen weeks consumption of our physiologically dosed micronutrient enriched foods beneficially affected blood vitamin and homocysteine levels in a group of Dutch frail elderly. The considerable decrease (-25%) in the latter metabolite confirms a subclinical metabolic deficiency state in these elderly. There was no significant effect of the enriched foods on two indicative tests for neuropsychological functioning. In addition no significant effect of all-round moderate intense exercise was observed on any of the parameters, nor was an interaction between the enriched foods and exercise found.

Moderate increased concentrations of homocysteine may be an independent risk factor for cardiovascular disease[34-36]. Meta-analyses of observational studies predict that a 1 μmol/L decrease of homocysteine level, can result in a 10% reduction in risk of coronary heart disease. This prognosis has been based upon Hcy levels within the range of 10-15 μmol/L[35]. Our baseline Hcy values exceed this range, but the question arises whether the prediction of this 10% reduction still counts for a population at such an old age. More data are needed on the implication of this reduction in the younger-old moreover in elderly, already called 'survivors'. Another perhaps more important implication of high homocysteine and low B-vitamin levels in this population is the relation with mental health.

A comparison of our homocysteine data with other values of free-living and hospitalized elderly reveals that levels in our frail population were more elevated[10;30;37;38], thus confirming the assumption of a population being classified at risk of subclinical deficiency. Regarding the plasma concentrations we found lower baseline cobalamin and folate levels, compared to free-living elderly studied by several investigators[11;30;39]. Even similar cobalamin values were found in geriatric patients diagnosed for deficiencies[40]. However, compared to others, the opposite was revealed with our values being equal or even higher[2;10;11;39-41]. This demonstrates the striking variability in vitamin concentrations observed by many investigators. A partly explanation is the use of different methods and consequently different cut-off levels. For evaluation of folate deficiency it has been indicated to use method-specific reference ranges predominantly[42]. And only recently, it has been suggested to raise the screening level of cobalamin deficiency[4;30;31].

The focus on the functional parameters instead of sole plasma/serum vitamin concentrations is currently regarded as more appropriate[10;43]. A few studies have already mentioned the metabolic evidence of vitamin deficiency in elderly in the presence of normal plasma vitamin levels[7;10]. In our population, relatively high Hcy levels were accompanied with a considerable number of subjects found to be deficient in plasma cobalamin but not notably in plasma folate. On the other hand we detected a stronger association between (change in) folate status and (change in) Hcy level than between cobalamin and Hcy. The mean decline of approximately 5 μmol/L in total Hcy in the supplemented group compared to the non-supplemented group confirms once more the need for examining metabolic deficiency even in the absence of low plasma folate levels. Perhaps the current cut-off levels for folate deficiency might need a re-evaluation as well. We did not detect significant beneficial changes in the hematological parameters. It has been suggested that despite depletion of folate or cobalamin levels, anemia induced by this depletion is only occurring at the far end of vitamin deficiency spectrum. Consequently it is extremely difficult to prove beneficial effects on hematological parameters in only mildly deficient subjects[44].

The higher prevalence of cobalamin deficiency instead of folate deficiency is in agreement with findings of Hanger et al.[2] and results of the Framingham study[9], but not with Ortega et al.[11;45]. Review of present studies suggests that cobalamin deficient elderly develop a wide variety of neurologic abnormalities[43;46]. We have tested neuropsychologic functioning by two tests but found no relation between cobalamin status and neuropsychologic functioning at baseline, nor did we find an improvement in these tests despite significant increases in plasma vitamin levels. Up till now large scale well-controlled studies on elderly were not able to demonstrate overall improvements in neuropsychological function following therapy[1]. The reliability and validity of the two tests have been judged as sufficient on group level, according to several criteria on objectivity, stability, consistency and relative validity with respect to other tests. Test-retest and concurrent validity correlation coefficients were varying between 0.83 till 0.92 and between 0.46 till 0.75 respectively[27;47]. The question arising in the first place is whether the neurologic dysfunctioning was severe enough in our population. Despite a considerable proportion of cobalamin deficient subjects the deficiency might not have been rigid enough and/or the degenerating process may not have developed far enough to establish effect. On the other hand a degenerating process as such might not even be reversible. The 17-weeks consumption of oral physiologically dosed supplements may also not have been sufficient for improving performance on these tests. Comparison of baseline values with healthy elderly revealed a performance below moderate active and even sedentary Dutch healthy subjects[48]. Subtle neuropsychologic improvements, may on the other hand, perhaps only be detected with more sensitive, other types of tests or in more deficient, probably institutionalized patients. The favorable decline in Hcy levels and proportion of cobalamin deficient individuals is however noteworthy and confirms the prosperity of our nutritional intervention.

A few studies demonstrated a lowering of plasma Hcy by administration of pharmacological (intramuscular) doses of folic acid, vitamin B_{12} and/or B_6[10;23]. The effect of lower doses in the general population and more specifically in elderly has not been studied up till now, but has been recognized as highly relevant to the question of food fortification. Ward et al.[23] demonstrated an effective lowering of Hcy levels in apparently healthy volunteers with a daily dose of 200 μg of folic acid but not with 100 μg. The effectiveness of relatively low doses has been confirmed by a study of Brouwer et al.[49]. With respect to the (frail) elderly population with mildly elevated Hcy levels, we have now proven the effectiveness of physiologically (and thus low) dosed (at the highest 100% of the Dutch RDA) multiple micronutrients. Low doses are more likely to be reached by food enrichment, which is a more attractive way of increasing folate status in elderly than tablets or expanding total food intake. Simultaneous administration of folic acid and vitamin B_{12} is preferred above folic acid alone[9] since inappropriate mistreatment of clinical vitamin B_{12} deficiency signs should be precluded. However since we chose for a multiple nutrient approach we cannot determine the contribution of each particular nutrient to the lowering of Hcy, but the increase in folate was stronger correlated to the decrease in homocysteine than cobalamin and PLP.

The exercise program did not have an (additional) effect on blood vitamin concentrations or on Hcy. The effect of exercise was assumed to act through increased dietary intake. Change in total energy intake indeed differed slightly between exercisers and non-exercisers however this was mainly attributed to a decline in the latter group (manuscript submitted). Absolute increase in dietary intake in order to establish a biochemical change was probably too small. The limited mechanical load and endurance compartment of our all-round and moderate intense exercise program may be part of the explanation. The effect of exercise on the two neuropsychological tests could also have been established directly as well, through training of these modalities. The small improvement found in the exercisers on the neuropsychological tests was also found in the control group and therefore no effect of exercise can be referred to these two tests.

The beneficial effect on Hcy established by our oral physiologically dosed nutrient dense foods is considerable and seems relevant. Physiologically dosed nutrient dense foods have the potential of being a simple, easy-to-adopt, attractive and inexpensive intervention to improve the nutritional status in frail elderly. The beneficial decline in risk on among others cardiovascular diseases, comorbidity and the relation with mental health in a population at this age should be investigated in the long term.

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6

Dietary supplements and physical exercise affecting bone and body composition in frail elderly

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The objective was to determine the effect of enriched foods and all-round physical exercise on bone and body composition in frail elderly.
A 17-weeks randomized controlled intervention trial, following a 2x2 factorial design: a) enriched foods, b) exercise c) both, d) neither (control), was performed in 143 frail elderly (age: 78.6±5.6 years). Foods were enriched with multiple micronutrients (25-100% of the Dutch RDA); exercises focused on skill training: strength, endurance, coordination and flexibility. Main outcome parameters were bone and body composition, measured with DXA (dual energy X-ray absorptiometry).
Exercise preserved lean mass (mean difference between exercisers and non-exercisers: 0.5 kg±1.2 kg; $p<0.02$). Enriched food groups slightly increased their BMD (bone mineral density) (+0.4%), bone mass (+0.6%) and bone calcium (+0.6%) compared to small decreases of -0.1%, -0.2% and -0.4% resp. in the non-enriched groups. Differences between these two groups were for BMD: 0.006±0.020 g/cm^2 ($p=0.08$), total bone mass: 19±55 g ($p=0.04$) and bone calcium: 8±21 g ($p=0.03$).
Foods containing a physiological dose of micronutrients slightly increased bone mass, calcium and density in 17 weeks, whereas moderate intensive exercise preserved lean body mass in frail elderly.

INTRODUCTION

Physical frailty in elderly has been defined as a state of reduced physiologic reserve associated with increased susceptibility to disability[1]. Cornerstones of the process of frailty are a more sedentary lifestyle and consequently a lower energy expenditure. A declining appetite and dietary intake concurrently increases the risk of developing (micro)nutrient deficiencies. Further deterioration of health and nutritional status may in turn hamper the physical activity level.

Both inactivity and inadequate dietary intake are important contributors to sarcopenia. This loss of skeletal muscle mass, together with advancing age is associated with other changes in body composition, including a reduction in total lean body mass, total body water and bone density and an increase in body fat[2-5]. These alterations are known to affect health, physical functioning and the quality of life[6;7]. Moreover a decreased bone density may lead to fractures after minimal trauma[8].

The potential reversibility of especially sarcopenia but also bone loss and osteoporosis is therefore of great interest[2;7;9]. Up till now only one study examined the effects of dietary supplements combined with physical exercise on body composition in frail elderly[5]. It was shown that low muscle mass was strongly related to impaired mobility. Resistance training increased muscle size. The supplement on the other hand did not affect muscle mass. Other trials either investigated nutritional (energy+nutrients) supplementation[10;11] or only focused on strength training[9]. Supplementation increased body weight (both lean and fat mass). Strength training protected bone mineral density and muscle mass. Interactive effects or effectiveness of supplements on bone loss were not studied thoroughly.

For our intervention we specifically developed micronutrient dense foods with a physiological amount of only those vitamins (100% of the Dutch RDA) and minerals (25-100% of the RDA) frequently characterized as deficient in elderly. Furthermore, an unique progressive all-round exercise program aiming at long term feasibility was developed. The effect of micronutrient dense products, a physical exercise program and a combination of both on body composition and bone parameters in frail elderly were investigated.

MATERIAL AND METHODS

Subjects

The study population comprised of 217 frail elderly living in their private houses in the neighborhood of Wageningen, The Netherlands. Figure 1.2 *(Chapter 1)* gives an outline of the selection of the subjects. The main criterion was requirement of (health) care, which consisted of a) medical home care, or b) use of meals-on-wheels service, or c) household assistance through home care or d) through a social network. Other selection criteria were: age (70 years or older), no regular exercise, body mass index below average (BMI ≤ 25 kg/m^2, based on self reported weight and height) or recent weight loss, no use of multivitamin supplements and ability to understand the study procedures.

All subjects gave their written informed consent. The study protocol was approved by the external Medical Ethical Committee of the Division of Human Nutrition and Epidemiology.

Design, randomization and follow up

Enrollment took place between January and June 1997. After confirmation of eligibility, subjects were randomized to one of the four intervention groups, through selection of sealed envelopes:

a. nutrition: nutrient dense products + social program;

b. exercise: regular products + exercise program;

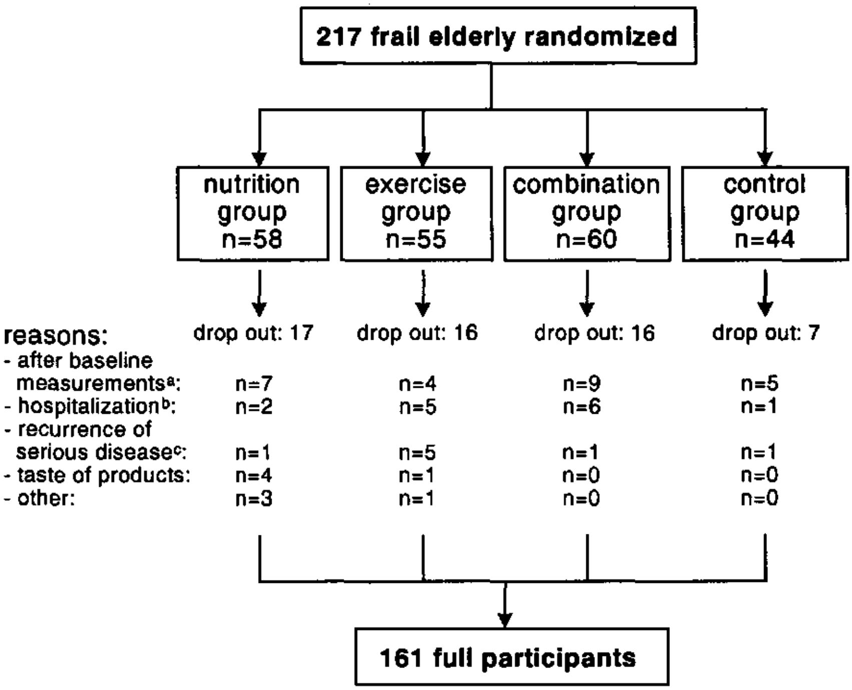
c. combination: nutrient dense products + exercise program;

d. control: regular products + social program.

Since a higher drop out rate was expected in the intervention groups more subjects were assigned to these groups. Couples were randomized together. After randomization, baseline measurements (week 0) were performed at our research center. The intervention period was 17 weeks, after which (week 18) data were collected again. Pre- and postintervention measurement(s) were available for 161 subjects. In total 56 (26%) subjects dropped out (Figure 6.1). In 25 cases this occurred immediately after baseline measurement, mainly because of too much distress. Other reasons for drop out (n=27) were mainly related to health problems, including (terminal) disease, hospital admittance, recent falling and/or fracturing. Of four subjects, who withdrew between week 8 and 17 of intervention, intermediate measurements were available, but they were not included in the data analysis. Valid DXA measurements were available for 143 subjects.

Nutrient dense foods

Subjects had to consume two products a day: one from a series of fruit products and one from a series of dairy products. Availability of a variety of products was intended to avoid monotony and to increase acceptability of the products. Every week fresh 100 g servings of fruit based products (two types of both fruit juice and compote) and dairy products (vanilla custard, two types of fruit yogurt and fruit quark (75 g)) were provided. Daily consumption of two enriched products delivered ~100% of the Dutch RDA[12;13] of the vitamins: D, E, B_1, B_2, B_6, folic acid, B_{12}, C and ~ 25-100% of the Dutch RDA of the minerals: calcium (25%), magnesium (25%), zinc (50%), iron (50%), iodine (100%). Subjects in the control and exercise group received the natural amount present in identical regular products (concentration vitamins/minerals at the highest 15% of the concentration in enriched products).



[a] too much distress,
[b] *cardiac infarct, hip fracture or hip replacement surgery, kidney stones, umbilical hernia*
[c] cancer, rheumatoid arthritis

Figure 6.1: Outline of the reasons of drop out

Total energy content of enriched products was equal to that of the regular products (0.48 MJ/day). Subjects were allowed to consume the intervention products either in addition to their habitual daily diet or as a replacement. Since change in spontaneous dietary intake was an additional outcome parameter, three day dietary records were obtained at baseline and follow-up (see *Chapter 3 and 4*). Compliance was checked by measurement of the following serum vitamin levels: D, B_1, B_2, B_6 and B_{12}.

Exercise program

The main objective of the exercise program was maintenance and/or improvement of mobility and performance of daily activities essential for independent functioning. Emphasis was placed on skill training: muscle strength, coordination, flexibility, speed and endurance were trained with usage of different materials as balls, ropes, weights and elastic bands. Group sessions were organized twice a week for 45 min and were of moderate, gradually increasing intensity. In order to guarantee uniformity, sessions were extensively rehearsed with all skilled teachers and the supervisor (MCAP). Moreover an instruction video and manual were developed. Participants and teachers were instructed to train at moderate to high intensity (value of 7) according to a 10 point RPE scale (rating of perceived exertion)[14]. A social program served as a control (for attention) for the exercise program. Sessions were organized biweekly by a skilled creative therapist. This program focused on creative activities, social activities and lectures about topics of interest for elderly people. Transport to and from the sessions was arranged. Compliance was checked by recording attendance to the sessions.

Questionnaires

The general questionnaire revealed information about age, sex, marital status, education, living conditions, use of care, illness, medicine use, recent falling and fracturing. Physical activity was assessed using the validated Physical Activity Scale for Elderly (PASE)[15;16].

Anthropometry and body composition

All anthropometric measurements were performed with subjects wearing underwear. Body weight was measured to the nearest 0.05 kg using a digital scale (ED-6-T; Berkel, Rotterdam, the Netherlands). Height was measured to the nearest 0.001 m using a wall-mounted stadiometer. Body mass index was calculated as weight in kg divided by height in m^2. Waist and hip circumferences were determined for calculation of the waist/hip ratio (WHR), as a measure of fat distribution[17].

Body composition of the subjects was determined by a DXA (dual energy X-ray) measurement (Lunar DPX-L, whole body scanner, Radiation, Madison, WI). The system uses a filtered X-ray source providing peak energies at 40 and 70 keV. The software divides pixels into bone mineral and soft tissue compartments. The soft tissue is then further separated into fat and fat-free soft tissue. For all subjects the fast scan mode was used.

Statistical analysis

Data were analyzed using the statistical program SAS (Statistical Analysis Program, version 6, NC: SAS Institute Inc., 1990). Means ± standard deviations (sd), medians (10^{th}- 90^{th} percentiles) or percentages of baseline values were calculated per intervention group for the primary outcome variables. Absolute changes±sd per intervention group were calculated and compared with changes in the control group (unpaired t-test). A multiple regression model was used to determine the effect of both interventions and a possible interaction on the change in body and bone composition variables. For all changes in these variables confounding by baseline age, weight, BMI, frequency of fracturing, change in energy intake, and interaction between sex and intervention program was checked. With respect to the models analyzing the change in bone parameters, change in body weight has also been taken into account. Since no evidence of interaction was observed between both interventions, a comparison was made between the supplemented group versus the non-supplemented group and the exercising group versus the non-exercising group respectively. Interaction between the exercise program and sex was evident with respect to change in lean body mass. Stratified analyses were performed additionally. No interaction between the nutrition program and sex was found concerning change in bone parameters. Adding all other covariates to the models did not markedly alter the results.

A rank procedure was carried out in which the population was divided in two: a relatively high compliant group of exercisers (attendance to the session high) and a low compliant group (attendance low) next to a relatively high compliant supplemented group (increase in serum vitamin levels high) vs a low compliant group (increase in serum vitamin levels low). A p-value ≤ 0.05 was considered statistically significant.

RESULTS

Baseline characteristics

Approximately, 70% of the participants were women (Table 6.1). Mean age of the study population was 79 years, with the exercise group being slightly younger. One or more diseases were present in at least 91% of the population. Subjective health on a 10-point scale (with 1=not healthy and 10=very healthy) was on average rated as 7. The majority lived alone and had a substantial fear for falling. In the control group the prevalence of fracturing was somewhat higher (24%) compared to the other groups (8-13%).

Table 6.1: Baseline characteristics of the study population

Parameter	Nutrition (n=35)	Exercise (n=36)	Combination (n=39)	Control (n=33)
Women, %	69	69	74	67
Age, y (mean±sd)	79.6 ± 5.0	76.5 ± 4.6	79.8 ± 5.8	78.8 ± 6.7
Activity score[a] (median; P_{10}-P_{90})	63 (34-103)	63 (30-100)	59 (30-111)	59 (34-100)
Subjective health[b] (mean±sd)	7.1 ± 1.3	7.1 ± 1.2	6.9 ± 1.3	7.0 ± 1.4
Chronic illness, %	86	92	95	88
Prescribed medicines, %	88	75	83	80
Living alone, %	69	64	67	67
Use of care for health reasons (%):				
- meals-on-wheels	31	31	44	39
- household assistance through home care	49	36	41	52
- assistance through social network	20	31	26	12
- medical home care	20	14	15	15
- physiotherapy	43	50	46	55
Recent falling, %	43	50	44	36
Recent fracturing, %	9	8	13	24
Fear of falling, %	71	64	49	70

[a] range PASE: 0-400

[b] range: 1-10

Changes in anthropometric variables

In none of the intervention groups, significant changes in anthropometric variables compared to the control group were observed (Table 6.2). A tendency however towards a decrease in body weight in the control and nutrition group was observed versus a preservation of body weight in the exercising and combination group.

Table 6.2: Mean anthropometric values (±sd) and mean 17-week changes (±sd) of the four intervention groups

Parameter	Nutrition (n=35)		Exercise (n=36)		Combination (n=39)		Control (n=33)	
	baseline mean ± sd	*change mean ± sd*	baseline mean ± sd	*change mean ± sd*	baseline mean ± sd	*change mean ± sd*	baseline mean ± sd	*change mean ± sd*
Height, m	1.65 ± 0.09	-	1.65 ± 0.10	-	1.65 ± 0.08	-	1.64 ± 0.08	-
Weight, kg	65.8 ± 9.1	*-0.2 ± 1.2*	67.0 ± 12.1	*0.1 ± 1.2*	67.3 ± 7.8	*0.2 ± 1.3*	64.7 ± 10.9	*-0.3 ± 1.7*
Body Mass Index, kg/m^2	24.1 ± 2.4	*-0.0 ± 0.0*	24.2 ± 3.0	*0.0 ± 0.0*	25.1 ± 2.5	*0.0 ± 0.0*	23.8 ± 3.1	*-0.0 ± 0.0*
Waist circumference, cm	87.9 ± 8.7	*4.3 ± 5.2*	88.7 ± 10.8	*3.2 ± 5.0*	90.5 ± 9.6	*1.9 ± 6.7*	87.8 ± 9.7	*2.4 ± 5.6*
Hip circumference, cm	97.9 ± 5.3	*1.0 ± 3.3*	97.6 ± 8.0	*1.8 ± 3.0*	98.6 ± 4.7	*1.8 ± 3.5*	97.0 ± 7.4	*1.8 ± 3.7*
Waist/hip ratio	0.90 ± 0.08	*0.03 ± 0.06*	0.91 ± 0.07	*0.01 ± 0.05*	0.92 ± 0.09	*0.00 ± 0.07*	0.91 ± 0.08	*0.01 ± 0.06*

Table 6.3: Mean baseline values (±sd) and mean changes (±sd) of the intervention groups with valid pre- and post DXA measures

Parameter	Nutrition (n=35)		Exercise (n=36)		Combination (n=39)		Control (n=33)	
	baseline mean ± sd	*change mean ± sd*	baseline mean ± sd	*change mean ± sd*	baseline mean ± sd	*change mean ± sd*	baseline mean ± sd	*change mean ± sd*
Lean tissue mass, kg	42.1 ± 8.2	*-0.4 ± 1.0*	2.8 ± 8.6	*0.2 ± 1.4**	42.6 ± 6.7	*-0.1 ± 1.0*	42.5 ± 7.5	*-0.5 ± 1.4*
Fat mass, kg	21.5 ± 6.6	*0.1 ± 1.2*	21.9 ± 7.4	*-0.1 ± 1.2*	22.6 ± 5.8	*0.2 ± 1.1*	20.1 ± 8.2	*0.1 ± 1.4*
Bone mass, kg	2.19 ± 0.47	*0.02 ± 0.06*	2.24 ± 0.71	*-0.01 ± 0.06*	2.31 ± 0.49	*0.01 ± 0.05*	2.20 ± 0.49	*0.00 ± 0.05*
Bone density, g/cm^2	1.028 ± 0.111	*0.006 ± 0.014**	1.031 ± 0.145	*0.000 ± 0.022*	1.065 ± 0.120	*0.003 ± 0.023*	1.031 ± 0.106	*-0.003 ± 0.018*
Bone calcium, kg	0.832 ± 0.179	*0.007 ± 0.020*	0.851 ± 0.270	*-0.006 ± 0.020*	0.866 ± 0.175	*0.004 ± 0.020*	0.835 ± 0.185	*0.002 ± 0.019*

* $p < 0.05$, change compared to change in control group

Changes in bone parameters and body composition

Table 6.3 presents mean baseline values and change (±sd) of the body composition and bone parameters of the DXA measurements. Significant differences ($p<0.05$) in change in lean body mass were found between the exercise group and the control group. With respect to change in bone mineral density a significant difference between the nutrition group and the control group was detected. Since no evidence of interaction was observed between the two interventions, the effect of each intervention was analyzed separately (Table 6.4).

Table 6.4: Estimates of the mean difference in change in body composition measured by DXA between groups receiving nutrient dense vs regular products and groups receiving exercise vs no exercise (n=143)

Parameter	Nutrient dense foods (n=74) vs regular foods (n=69)		Exercise (n=75) vs no exercise (n=68)	
	difference	p	difference	p
change in lean body mass, kg	-0.1	0.60	0.5[a]	0.02
change in fat mass, kg	0.1	0.48	0.0	0.95
change in calcium mass, kg	0.008	0.03	-0.005	0.15
change in bone mass, kg	0.019	0.04	-0.012	0.19
change in bone mineral density, g/cm^2	0.006	0.08	-0.000	0.99

[a] men (n=43): 1.0 kg; p=0.04, women (n=100): 0.3 kg; p=0.20

Supplementation showed a slightly positive, but not statistically significant, effect on bone mineral density (difference between supplemented and non-supplemented groups: 0.006 g/cm^2, p=0.08). Bone mass and bone calcium improved significantly in the supplemented group compared to the non-supplemented group (difference: 19 g, p=0.04 and 8 g, p=0.03 respectively). When bone parameters in a high compliant supplemented group (n=36) were compared with a less compliant supplemented group (n=36) it appeared that bone mineral density increased with +0.006 g/cm^2 in the first group vs +0.002 g/cm^2 in the latter group (ns). The improvement in bone mass (+25 g) and bone calcium (+9 g) was also higher in the more compliant group compared to the low compliant group (+3 g resp. +1 g) ($p=0.08$). Differences were of the same magnitude when high compliers ($n=36$) were compared to the controls ($n=33$): p-values between 0.03 to 0.1.

Exercise showed a positive effect on lean body mass compared to the non-exercising group (difference: 0.5 kg, $p=0.02$). For men this difference was 1.0 kg ($p=0.04$) and for women: 0.3 kg ($p=0.20$). No effect of exercise on bone parameters was found. The effect on lean body mass was mainly attributed to preservation in the exercise group towards a decrease among the non-exercising subjects. Comparison of the high compliant exercisers (relatively high attendance rate, $n=39$) vs low compliant exercisers ($n=36$) revealed that the lean body mass in the high compliant group increased +0.1 kg compared to +0.01 kg in the less compliant exercising group (ns). A significant difference was revealed ($p=0.04$) when high compliers ($n=39$) were compared to the controls ($n=33$).

DISCUSSION

As far as we know this is the first trial investigating effects of a progressive moderate intense all-round exercise program combined with special developed foods containing a physiological dose of micronutrients in frail elderly. This trial demonstrated a slight increase in bone mineral density, total bone mass and bone calcium as a result of a 17 weeks intervention with nutrient dense foods. Our exercise program showed a protective effect on the age-related decline in lean body mass. No evidence of interaction between both intervention programs was found.

Population

Since uniform criteria to select frail elderly are still lacking we defined our own and thereby put emphasis on the need for care, physical inactivity and BMI below average or involuntary weight loss. For practical reasons we had to rely on subjects' own reports. Since many elderly suffer from senile kyphosis, moreover often overestimate height and underestimate weight, the distribution of actual BMI shifted to the right compared to the initial calculated BMI. We however succeeded in recruiting a population with a worse health profile compared to Dutch healthy elderly. Their mean BMI was lower compared to Dutch elderly in the European Seneca study (24 kg/m^2 vs 26 kg/m^2 in men and 28 kg/m^2 in women)[18]. Furthermore, self rated health (7.0 vs 7.7) as well as activity level (PASE score 64 vs 85) were lower compared to healthy Dutch elderly[16]. Mean energy intake and scores on physical fitness tests were also below average[19] (Chin A Paw et al., submitted).

Concerning the drop outs, of 38 subjects additional information was available. Their mean age (78.9 years) and mean body weight (64.9 kg) was comparable with the ones who sustained. Their mean subjective health (6.6) was however slightly lower. Half of the drop outs (Figure 6.1) immediately withdrew before/during/after the baseline measurements, mainly because of too much distress. This seemed therefore not to be related to the type of intervention. Concerning the health related reasons (i.e. hospital admittance and recurrence of serious illnesses), slightly more subjects dropped out in both the exercise and combination group, which might point to a slight selective withdrawal. In case, a possibly worse health profile of drop outs would have caused little selectiveness of drop out, it would only have caused an underestimation of the effect of exercise.

Type of intervention

Studies with a combination of an all-round progressive exercise program and supplemented food products enriched with a physiological dose of micronutrients have not been performed yet in frail elderly. The specific aim of developing such an exercise program was to investigate effects of exercises which are feasible and acceptable for frail individuals at the long term, instead of investigating effects of monotonous resistance and endurance training programs using unfamiliar equipment.

We strictly added only vitamins and minerals of which intake is known to be frequently low in elderly. No extra energy or macronutrients were added since we expected that due to low levels of activity, energy requirements will also be relatively low. The need for sufficient micronutrients is often not altered in less active elderly[13;20;21], however debate about the latter is still going on[22;23]. Nutrient dense foods instead of vitamin/mineral pills are attractive and preferred since foods in general contain also other important nutrients. Additionally these elderly often use already a lot of medicines and vitamin/mineral pills may be regarded as another 'medicine' and as a consequence taken together and confused with the regular medicines.

Measurements

DXA is a non-invasive, relatively fast and therefore appealing method for the assessment of bone mass in elderly. Since the device is also capable of precisely assessing soft tissue mass it is clearly a promising method of choice[24]. There are however also indications of less valid measurements[25-27]. Moreover DXA, like other methods, still assumes constancy in constituents of fat free mass.

Our main objective was investigating changes, therefore the absolute validity of our data towards a reference was of less importance. With respect to repeatability DXA should allow accurate measurements of small changes in body composition[28-30]. Additional data obtained with the D_2O dilution technique demonstrated a small increase in lean body mass in the exercising group vs a small decrease in the non-exercising group although this reached no statistical significance. Calculation of the ratio between extracellular water and total body water with this method revealed that in none of the intervention groups changes in this ratio occurred. This means that effects determined, cannot be attributed to change in hydration state (data unpublished). These D_2O dilution data together with our data on (scale) body weight point in the same direction as our DXA data.

Effect on lean body mass

To date most studies only focused on the effects of high intensity resistance training in frail elderly. Progressive resistance training proved to be effective in the prevention of sarcopenia[31;32]. Several trials[5;9;33] clearly demonstrated beneficial effect of resistance training on muscle size, muscle mass and strength. Meredith et al.[11] concluded that strength training in elderly men combined with a nutritional supplement affected body composition, however their findings should be confirmed in a larger trial with sedentary controls.

We were able to detect a preserving effect of exercise on lean body mass. The response to exercise differed between men and women. Apparently men benefited more from exercise and also lost more lean mass with no exercise. Men simply have more lean mass to train or to lose and may also be more responsive to exercise. A higher 'trainability' might have been accompanied with more fanaticism.

The comparison of a high compliant with a relatively low compliant exercising group revealed that the preserving effect on lean body mass was indeed attributable to the exercise program; in the less compliant group lean body mass did not change whereas a small increase was found in the high compliant group. The decrease in the non-exercising groups may be attributed to the ongoing process of sarcopenia in frail elderly. The positive result of our exercise program is a valuable addition to all earlier findings, since we expect the long term feasibility of our program to be higher compared to high intensity strength training with monotonous exercises.

Our nutrient dense products did not have any effect on lean or fat mass in frail elderly. We hypothesized that extra micronutrients correct existent deficiencies and due to a better nutritional status subjects might develop a higher activity level, a better appetite and in turn a higher energy intake. Due to these changes sarcopenia might be reversed. The lack of effect on lean or fat mass with the nutrition intervention may be caused by several factors. First, the duration of intervention may not have been long enough to establish a considerable effect on the mechanism described. Second, at baseline the process of age-related sarcopenia may not have been severe enough to establish an improvement with nutrient dense products. In earlier reports[5;10] an increase in body weight due to (energy dense) supplements is described. No significant changes in muscle mass were found and therefore fat mass must have been increased. This effect may be attributed to the energy dense supplement used, which is not comparable to the nutrient dense foods we used in our study.

Effect on bone

The small but significant changes in bone parameters due to 17-weeks consumption of our nutrient dense products are of importance in the debate whether bone loss and osteoporosis are irreversible and whether changes found within one year can be ascribed to transient effects[34]. Several public health approaches to the problem of osteoporosis are currently recommended: a) maximization of the peak bone mass in the younger age groups, b) estrogen replacement therapy in post-menopausal women and c) recommendation of sufficient or extra calcium and vitamin D intake at older age. Optimal supplies of both nutrients are essential in the process of restoring bone and should be effective even at old age[35;36]. Additionally, exercise is often recommended. Since we found a larger increase in bone mass, bone calcium and bone density in the group with the largest increase in their serum vitamin levels it seems that indeed the enriched products contribute to the observed changes in bone parameters in these elderly. The response to the nutrient dense foods with respect to bone density, bone mass and bone calcium appeared not to be markedly different between men and women. Our results certainly should be interpreted with caution. Effects could be attributed to the variability of the DXA machine, although the magnitude of our effects is in agreement with effects from a 1-year walking program[9]. Additionally, several studies reporting effects on bone mass and density after one or two years of supplementation found already an effect within the first (half) year[37-39], after which effects were leveling off. Chapuy et al.,[40] showed effects on fracture rates even after two months, accompanied with a modest increase in bone density. Studies about the precision and stability of DXA measurements report coefficients of variation of total body parameters between 0.6-1.0%[30;41], so possibly only because of sufficient power we were able to detect statistical significant changes. Nevertheless, the change in control and experimental group is in the direction expected. A longer intervention period as well as biochemical markers of bone turnover might have given more convincing and more relevant results. This should be confirmed in future studies.

The exercise program did not have an (additional) effect on bone parameters. A possible explanation may be again the duration of the program. Controlled trials of longer duration showed that exercise can positively influence bone density by a few percent[42]. Nelson et al.[9;43] detected effects on bone density and bone mass after one year of resistance or endurance training. Because they did not report an earlier measurement, the time span requested before effects on bone parameters occur due to exercise is still unclear. Furthermore, the mechanical load of our exercise program may not have been large enough to establish an effect on bone. On the other hand, even a more important effect of exercise may be the decline in risk on falling solely due to improving balance and co-ordination. This effect may have a greater impact on prevention of fracturing than modest effects of exercise on bone density.

In summary, loss of bone, a decline in bone mineral density and the process of sarcopenia is a serious threat to independently functioning, community dwelling frail elderly. Investigating potential reversibility of sarcopenia but also bone loss and osteoporosis is important since a slight improvement in these factors, may improve physical functioning and quality of life and may subsequently lessen the need for support services. This trial confirms that supplementing and training frail elderly is beneficial even beyond the age of 70, since positive effects on both lean body mass and bone parameters appeared. However, since our interventions are unique and changes after 17 weeks of intervention only small, results should be confirmed in future studies.

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7

Appraisal of 4-months consumption of nutrient dense foods within the daily feeding pattern of frail elderly

Submitted

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Feasibility and long-term preference for nutrient dense foods in frail elders have only been addressed laterally in literature, while it is of major importance for a successful implementation. The appraisal and acceptance of 4 dairy and 4 fruit products either enriched with multiple micronutrients (25-100% of the Dutch RDA) or identical regular foods were assessed in 150 frail elders over a 4 months intervention period. Differences between both groups (enriched vs regular) emerged from the overall evaluation score (10-point scale): 6.4±1.6 and 7.7±1.7 respectively ($p<0.001$). Optimization of the hedonic parameters of nutrient dense foods and major long-term attention for application in the daily elderly feeding pattern is of essential importance.

INTRODUCTION

The public health interest in assisting elderly to remain autonomous, improving their quality of life and lowering health care costs is growing. Community support services in affluent societies are becoming more and more available, although governmental reduction of expenses of those services is inducing problems. Older populations requiring community support or meals-on-wheels services, have been studied by several investigators in order to describe the nutritional and health problems moreover to outline the effectiveness of several intervention programs[1-5].

In developing effective nutritional interventions aiming at reversion of a suboptimal nutritional state, sustainment of independence and limitation of health care costs, the question whether the program is feasible is often addressed laterally. Gray-Donald et al.[1] were attempting to assess the feasibility of their supplementation program, however their report is only based on 14 subjects and is lacking evaluative data other than feelings of general well-being. Little is known about long-term preference of the foods (in most cases milkshakes) provided. In fact, in-home judgement of fortified or novel foods by elderly has been scantily investigated in general[6].

Some demands for senior foods have been agreed upon already for years: easy-to-open and store containers, large readable labels, available at reasonable cost and sufficient variety[7;8]. Since appetite may be decreased in the frail due to lower activity levels[9], products should be served in small portions. In order to meet the declining sensory perception of elderly flavor, texture and color may need adaptation[7]. The foods should be palatable throughout the day, should fit in all main meals but also as snack between meals.

Debate about what nutrients or which energy density these foods should contain and in which (safe) concentration is still going on. Up till now some industries have marketed special 'formulas' with increased energy density and high concentrations of macro- as well as micronutrients. Target populations for these relatively expensive and mainly medicin-like products are hospitalized and institutionalized elderly.

Our goal was developing safe customary nutrient dense foods in several varieties containing a physiological dose of micronutrients, for the community dwelling (high-risk) frail elders in order to increase the micronutrient density of their diet. Due to a decreased activity level and a presumed lower basal metabolic rate, extension of energy density was not a major topic. The effectiveness of these foods on the nutritional and health status are described in *Chapters 3 - 6* of this thesis. The present paper focuses on the in-home long-term judgement and acceptance of the foods, the food choice behavior and the appropriateness of these foods for widespread implementation in the community.

METHODS

Subjects and Design

In total 217 free-living Dutch frail elderly were recruited through home-care services, meals-on-wheels organizations, elderly homes, elderly social services and general practitioners. The subjects were selected based on the following criteria: age ≥70 years, requirement of health care (home care, meals-on-wheels), inactive, body mass index ≤25 kg/m^2 (based on self reported weight and height) or involuntary weight loss, no usage of multivitamins and ability to understand the study procedures. A written informed consent was obtained. The study protocol was approved by the Medical Ethical Committee of the Division of Human Nutrition and Epidemiology.

Subjects were randomly assigned to the nutrient dense or the regular food group both combined with either an exercise program or a social program (total of 4 groups, details described in *Chapters 3 - 6*). The intervention period was 17 weeks. At baseline (week 0) and in the last week of intervention (week 17) a 3-day dietary food record was obtained. In week 1 and 2 of the intervention, subjects were asked to complete a product-diary with specific questions about the products provided. The same was asked at the end (week 16 and 17). In week 18 a general evaluation form was filled out.

Pre- and postintervention measurements were available from 165 subjects. Reasons for drop out (n=52) were mainly health problems. Additionally, 4 subjects were excluded because time between pre- and postintervention was less than 13 weeks due to hospitalization. Another 2 subjects were hospitalized in week 18. Seventy-one subjects in the nutrient dense group successfully completed product-diaries at both the start and the end, whereas 58 subjects in the regular food group filled out these diaries. Evaluation forms and baseline food records were available for 78 and 72 subjects and respectively. The remainder of the participants ended up with incomplete or invalid diaries due to forgetfulness or inaccurateness.

Nutrient dense foods

During the intervention subjects had to consume 2 products a day: one from a series of fruit based and one from a series of dairy products. The fruit products consisted of 100 grams servings of orange-peach juice, apple-berry-grape juice, apple compote and apple-peach compote. Dairy products consisted of 100 grams portions of vanilla custard, strawberry yoghurt, vanilla-apple yoghurt and a 75 grams portion of vanilla-mixed-fruit quark (quark was regarded as more 'satiating' compared to others). Of all products 4 fresh servings (with both compotes as exception: 2 servings) were provided weekly in a cooled container. This means that subjects received 28 products in total. Consumption of 7 dairy and 7 fruit products per week, resulted in 14 products as leftovers, which was checked. Availability of a variety of products (even at the end of the week) was intended to avoid boredom, to increase acceptability and to imitate daily life in which multiple types of products are available.

Daily consumption of two enriched products delivered ~100% of the Dutch RDA[10;11] of several vitamins and ~25-100% of the RDA of several minerals (see appendix). Only those vitamins and minerals were chosen of which intake or blood levels are known to be frequently low in frail elderly. Subjects in the regular group received identical products in the same portion sizes. The natural amount of vitamins and minerals of the regular products was at the highest 15% of the concentration in enriched products. Both the enriched and the regular products contained ~0.48 MJ energy per two products.

Diary and questionnaires

The specific product-diary consisted of 7 pages for each of the fruit and dairy products in order to cover a week. Information was gathered about type of product consumed, time of consumption (morning, afternoon, evening) and 'eating/drinking period' (breakfast, lunch, dinner or in between). On a 10-point scale, with 1=low and 10=high, the desire to eat the product just before consumption, pleasantness and attitude to product in general were rated. In addition, stomach or bowel problems (10-point scale) and the experience with opening the package (1=very easy, 2=in between, 3=very difficult) were reported.

The general evaluation form included questions about overall judgement of the supplementation program (10-point scale), argumentation for this judgement, the obligatory consumption of a total of two supplements (10-point scale), intention to buy the nutrient dense foods, if available, and in case which ones and for what reasons.

Energy intake at baseline and at the end of intervention was calculated from a 3-day (2 weekdays and one weekend day) dietary record. Three trained dietitians assisted the subjects with the recording. Portion sizes were documented in household measures, whereby frequently used household measures were weighed afterwards. Food consumption data were coded after which energy was calculated with a computerized Dutch Food Composition Table[12]. The energy content of the intervention products were included in the data.

Information about age, sex, marital status, living conditions, meal preparation, illness and medicine use was provided by a general questionnaire.

Statistical analysis

Data were analysed using the statistical program SAS (Statistical Analysis Program, version 6, NC: SAS Institute Inc., 1990). Means±sd, medians (10^{th}- 90^{th} percentiles) or percentages were calculated for both groups separately. Within each group all 8 types of products were evaluated. In case subjects consumed the same type of product several times per period; i.e. two weeks at the start (first period) and two weeks at the end of intervention (last period), a subject mean for that product was calculated first, before calculating the group mean (weighted means). Differences between both groups were tested with an unpaired t-test. Changes over time within the nutrient dense food group were compared with changes in the regular food group with a t-test. In case two or more dichotomous variables were compared, a chi-square test was provided. Pearson correlation coefficients were used for calculation of baseline relationships. A p-value of <0.05 was considered as statistically significant.

RESULTS

In Table 7.1 baseline characteristics of the population according to intervention group are presented. No relevant differences between both groups were observed. With respect to energy intake no significant difference in change over the intervention period was found: in the regular group (n=69) the mean change was 0.0±1.7 MJ/day, in the nutrient dense group (n=77): -0.09±1.4 MJ/day (p=0.69).

Table 7.1: Baseline characteristics of the study population (n=150)

Parameter	Nutrient dense food (n=78)	Regular food (n=72)
Women (%)	71	71
Age (years) (mean±sd)	79.0±5.4	77.3±5.7
Subjective health (range 1-10) (mean±sd)	6.9±1.5	6.9±1.3
Body Mass Index (kg/m^2)(mean±sd)	24.7±2.4	24.4±3.1
Living alone (%)	67	68
No. of prescribed medicines (median;P_{10}-P_{90})	3 (0-6)	2 (0-7)
No. of chronic diseases (median;P_{10}-P_{90})	2 (1-3)	1 (0-3)
Currently smoking (%)	10	11
Preparation of hot meal by (%):		
- self	58	58
- meals-on-wheels	27	28
- partner	12	13
Energy intake (MJ/day) (means±sd)	7.6 ± 1.7	7.6 ± 2.0

Of 53 subjects who were not included in the analyses (drop-outs or time between pre- and postintervention measurements too short) additional information was available: 34 were randomized to the nutrient dense and 19 to the regular group. Mean age of these subjects was 79 years and subjective health was rated as 6.6.

At baseline, no significant differences with respect to mean (±sd) hedonic ratings of the products between both groups were observed, although on average regular foods were rated slightly higher than nutrient dense foods (Table 7.2). Exceptions were both fruit compote products. Ratings at the end of intervention had slightly declined (in some cases significantly) or stayed equal. The decline did not differ between the nutrient dense and the regular food group. The fruit compotes were the least favourite foods reflected by frequency of consumption and significant declines in hedonic ratings. All three questions (pleasantness, attitude and desire-to-eat) were highly correlated: coefficients varied from 0.77 till 0.91 ($p<0.0001$) at the start and from 0.85 till 0.95 ($p<0.0001$) at the end of intervention (based on 723 observations). When baseline ratings of the subjects under study were compared with those of the drop outs it turned out that these were equal, in the regular as well as in the nutrient dense group.

The 'eating/drinking period' was for both categories (dairy and fruit) mainly as snack in the afternoon and in the evening (63% for fruit and 32% for dairy). Besides, dairy foods were consumed as dessert after a hot lunch (21%) or dinner (21%). The amount of the foods was on average rated as 'exactly enough'. No problems with opening of the cans were reported in either group. All mean scores were between 1 and 2 on a 3-point scale with 1=very easy and 3=very difficult to open. Slight but significant changes in both groups ($p<0.05$) over time were detected with subjects having more difficulties with opening of the cans at the end of the study.

Hardly any gastro-intestinal complaints were noted. On a 10-point scale (with 1 regarded as many problems and 10 as no problems at all) average ratings varied between 8.7±1.8 (apple compote) and 9.4±1.2 (vanilla custard). Overall slightly more bowel problems were reported by subjects who consumed the nutrient dense foods, but this was not significant, nor was a significant change over the intervention period detected (largest change -0.6±0.4 in enriched strawberry yoghurt).

Table 7.2: Mean (±sd) hedonic ratings for each product separately, at the beginning of the intervention and mean (±sd) change over time, according to intervention group

Parameter	Nutrient dense foods			Regular foods		
	mean	change	n	mean	change	n
desire to eat, just before consumption (1-10)						
- vanilla custard	6.8 ± 1.1	0.1 ± 0.1	56	7.0 ± 2.0	0.2 ± 0.2	40
- mixed fruit quark	6.3 ± 1.3	-0.2 ± 0.2	59	7.0 ± 1.7	-0.1 ± 0.2	53
- strawberry yoghurt	6.3 ± 1.2	-0.2 ± 0.2	49	6.6 ± 1.9	-0.1 ± 0.2	45
- vanilla apple yoghurt	6.1 ± 1.2	0.1 ± 0.2	50	6.3 ± 2.1	0.0 ± 0.2	49
- orange peach juice	6.7 ± 1.3	0.0 ± 0.2	60	6.9 ± 1.8	-0.1 ± 0.2	58
- apple berry grape juice	6.9 ± 1.3	-0.2 ± 0.2	62	6.8 ± 1.9	-0.1 ± 0.2	56
- apple compote	6.5 ± 1.3	-0.6 ± 0.2**	32	5.5 ± 2.1	0.2 ± 0.4	29
- apple peach compote	6.7 ± 1.0	-1.0 ± 0.3**	22	6.1 ± 2.4	0.2 ± 0.5	16
pleasantness, while consuming (1-10)						
- vanilla custard	7.5 ± 1.3	-0.1 ± 0.1	55	7.6 ± 1.8	-0.1 ± 0.2	40
- mixed fruit quark	6.7 ± 1.5	-0.3 ± 0.2	58	7.7 ± 1.8	-0.3 ± 0.2*	53
- strawberry yoghurt	6.5 ± 1.6	-0.3 ± 0.2	49	7.1 ± 2.1	-0.3 ± 0.2	45
- vanilla apple yoghurt	6.2 ± 1.5	0.0 ± 0.2	50	6.8 ± 1.9	-0.4 ± 0.2	47
- orange peach juice	7.1 ± 1.4	-0.1 ± 0.1	60	7.2 ± 1.8	-0.2 ± 0.2	58
- apple berry grape juice	7.4 ± 1.3	-0.3 ± 0.1*	61	7.3 ± 1.8	-0.3 ± 0.2	56
- apple compote	6.5 ± 1.9	-0.8 ± 0.3*	31	5.5 ± 2.1	-0.2 ± 0.5	29
- apple peach compote	6.3 ± 1.3	-1.0 ± 0.4*	21	6.3 ± 2.5	0.0 ± 0.5	16
attitude to product in general (1-10)						
- vanilla custard	7.4 ± 1.5	-0.1 ± 0.1	56	7.6 ± 1.9	0.1 ± 0.2	40
- mixed fruit quark	6.5 ± 1.8	-0.1 ± 0.2	58	7.5 ± 2.1	-0.2 ± 0.2	53
- strawberry yoghurt	6.4 ± 1.6	-0.3 ± 0.2	48	7.0 ± 2.3	-0.3 ± 0.3	42
- vanilla apple yoghurt	6.2 ± 1.8	-0.1 ± 0.2	50	6.4 ± 2.3	0.0 ± 0.3	47
- orange peach juice	6.9 ± 1.6	-0.1 ± 0.1	60	7.0 ± 1.9	0.0 ± 0.2	58
- apple berry grape juice	7.3 ± 1.3	-0.3 ± 0.2	62	7.1 ± 2.0	-0.0 ± 0.2	56
- apple compote	6.8 ± 1.9	-1.1 ± 0.3***	32	5.6 ± 2.4	-0.3 ± 0.5	29
- apple peach compote	6.5 ± 1.6	-1.0 ± 0.4*	22	6.2 ± 2.7	-0.1 ± 0.6	16

*$p<0.05$, ** $p<0.01$, ***$p<0.001$ compared to baseline. No significant differences when compared to regular food group

Table 7.3 presents results from the evaluation form. After intervention the nutrient dense group was on average less positive about the whole supplementation program. Reasons noted for this were not liking (several of the) products and monotonous experience. The evaluation score about the number of products which had to be consumed was also significantly different between both groups (6.6±1.8 vs 7.8±1.7, p<0.001). Arguments for a low rating were in the nutrient dense group mainly 'just too much' and 'not tasty'. Positive ratings were explained by arguments like 'healthy' and 'easy to include in daily eating pattern'. In the regular food group 'tasty' and 'easy to include in daily meals' were the most frequently mentioned arguments. The intention to buy the foods if available was different between both groups (χ^2=10.5, p=0.03). A definite 'no' was given more often in the nutrient dense group. In this latter group especially vanilla custard, vanilla-mixed-fruit quark and apple-berry-grape juice would be bought if available. In the regular group all dairy products were mentioned. Arguments for no consumption were 'preference for other types of food' and 'not tasty'. Main arguments for continuing consumption were health aspects.

Table 7.3: Results from the evaluation form, according to both intervention groups

Parameter	Nutrient dense food (n=78)	Regular food (n=72)
Overall evaluation score on supplements (range: 1-10) (mean±sd)	6.4 ± 1.6	7.7 ± 1.7***
Overall evaluation score on number of supplements provided (1-10) (mean±sd)	6.6 ± 1.8	7.8 ± 1.7***
Planning to continue consumption if foods are available (%):		
- no	36	21*
- yes, daily	13	24
- yes, weekly	31	46
- yes, monthly	17	8
- do not know	4	1

*p<0.05, ***p<0.001

DISCUSSION

This placebo controlled in-home appraisal study revealed that several products do have a 'market potential' as 'healthy' snacks or desserts. Since, already at baseline, small but consistent differences existed between the nutrient dense and regular foods, with the latter group scoring more positive on the preference ratings, it seems of essential importance that nutrient dense foods are developed without the slightest off-flavours or discolours. Hedonic ratings obtained at the end of intervention were only slightly lower or stayed equal compared to baseline. Because of the provision of a variety of foods, boredom was minimized in both groups.

Foods enriched with multiple micronutrients having the potential of being healthy and fitting in an elderly feeding pattern, aiming at optimizing the quality of life should meet the demands of this target population. Governmental health councils often advice consumption of nutrient dense foods by those at risk, but up till now not many special senior products have been marketed with respect to this issue. Perhaps this is an illustrative consequence of the difficulties, manufacturers experience in the development and long-term evaluation of these special types of 'senior' foods. The foods will have to be marketed next to the already existing highly dosed pharmaceutical products like multivitamin and -mineral pills.

The ratings observed in our study are not widely distributed. On the one hand this can be explained by the fact that we used just 'customary' foods which were all familiar to the elderly so no extremes may be expected. On the other hand it is evident from earlier studies[13;14] that elderly are hesitating to rate very positively or very negatively about food. In addition, they will not complain about food very soon (which is in experimental settings provided for free!). Therefore, emphasizing the importance of giving honest answers is essential in this study population.

The nutrient dense foods were at baseline consistently rated less positive than the regular foods, and this finally resulted in a large difference in the overall evaluation score. This latter finding indicates that development of optimal hedonic characteristics of the products is needed. Four subjects in the nutrient dense food group and one in the regular group specifically dropped out because of the type, taste and appearance of these foods. On average baseline ratings from drop outs did not differ from subjects under study.

It appears from our data that boredom was only slightly present after 17 weeks intervention. The small decline observed in some nutrient dense foods cannot be explained by the presence of very subtle off-flavours, triggering resistance after long-term consumption since the decline was equal in both groups. The stronger decline in ratings of the nutrient dense fruit compotes may be explained by the fact that instead of a weekly fresh stock, by exception they were produced only once, just before the start of intervention. Off-flavours could have had more chance to develop across the time of the study in these compotes. Last but not least, the obligatory consumption of the foods itself, may induce resistance but on average the ratings of the elderly were quite stable.

The intervention products were mainly consumed as snack in between meals or as dessert. No significant difference in change in energy intake appeared when the nutrient dense food group was compared with the regular group. This is confirming the fact that subjects replaced their normal desserts or snacks for our foods and did not alter their habitual dietary patterns considerably. Portion sizes of 100 grams appeared to be satisfying. The amount of vanilla-mixed-fruit quark was rated the lowest, so the smaller portion size was not essentially needed. No significant bowel problems occurred, meaning that the products were physiologically well tolerated, even at the long-term. Variety needed for prevention of boredom within a person has already been mentioned. This is, however, also essential with respect to the physiological heterogeneity in elderly. Due to a relative high prevalence of diabetes type II in these groups and the mythological fear of elderly diabetic patients of eating too much sucrose, artificial sweetened products should be available. Dairy products may sometimes induce problems due to intolerance. We furthermore observed subjects not liking 'sour' dairy products (opined stomach problems) or too sweet juices once more confirming the indispensability of diversity in nutrient dense foods.

Nutritionists should stress that 'medicalization' of elderly with vitamin pills is not a favourable direction. Next to the possibility of confusing real medicines with vitamin pills, simultaneous intake may also induce a negative drug-nutrient interaction. A physiological dose of micronutrients in foods aiming at reversion of a suboptimal state in community-dwelling elderly may be as effective as pharmaceutical concentrations at the long-term[15]. Pleasant and satisfying foods may be key factors for optimizing the quality of elderly life. External stimuli, like foods, are elements which will remain important till the very last end in human life[16] and thus should not be replaced by pharmaceutical products. Additionally, micronutrient enriched foods contain other ingredients of high nutritional value as well. Therefore we emphasized the development and evaluation of customary natural-like foods in contrast to the milkshake (medicine) type often used as intervention supplement.

This is the first extended trial which directly investigated hedonic aspects of enriched foods in a 4-months in-home setting. Long-term sensory studies are needed to be able to trustworthy evaluate newly developed foods. While part of the target population may not do their own shopping anymore, caretakers and relatives should also be made aware of the existence of such new foods. Pleasant, healthy snacks or desserts, available in a large variety to stimulate long-term eating and avoid boredom, moreover to guarantee physiological tolerance in a frail group with multiple widespread complaints and diseases are vital initial conditions.

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8

General Discussion

The core of this thesis describes the results of an intervention trial in frail elderly people in which the effects of nutrient dense foods and physical exercise on several indicators of nutritional and health status have been investigated (*Chapters 3 to 6*). Focus on the potential benefits, including quality of life, of relatively simple applicable and realistic interventions in frail elderly people is important. It may help to overcome the growing burden and societal costs associated with the provision of care and services for the elderly. In addition, understanding of dietary, biochemical and other clinical nutrition data to support our current marginal knowledge with regard to frail elderly people is essential for the development of adequate recommendations and public health policy.

The feasibility of both interventions is a prerequisite for future implementation. An important additional aspect of this thesis, therefore, is the focus on the acceptance of the newly developed foods and their appraisal within the daily eating pattern of elderly people (*Chapter 7*). The feasibility of the exercise program is described in the thesis of Marijke Chin A Paw[1]. Additionally, in a preliminary study (*Chapter 2*) the relationship between sensory functioning and a) its potential determinants and b) food intake has been investigated. Since sensory properties remain important till the very last end of life, it is of great value to investigate the decline in taste and smell perception and its impact on food enjoyment and total food intake. Firstly, the main findings with respect to the research questions formulated in *Chapter 1* are briefly summarized and put into perspective below. Secondly, the feasibility of the nutritional intervention is discussed as well as the methods used to investigate the outcome measures. Recommendations for future research are suggested all throughout. Finally, public health implications are considered. The chapter concludes with general remarks.

Main findings

Preliminary study

In the cross-sectional study described in *Chapter 2,* two groups of elderly people (i.e. independently living and institutionalized) have been investigated. The institutionalized group scored significantly lower on the sensory tests as well as on the questionnaire on appetite, hunger feelings and their own impressions about taste and smell functioning. This could be mainly ascribed to chronological age as well as to biological age factors. The differences between men and women in our data were highly attributable to differences in smoking behavior. Poor sensory perception was in our population, however, not indicative of adverse dietary quality, low food or energy intake nor indicative of low body mass index.

Although it is assumed that taste and smell dysfunction adversely influence dietary intake and nutritional status, fundamental relationships are lacking. The literature remains indecisive about this topic[2-8]. Our results point out that an impaired taste and smell perception probably influences the quality of life due to loss of appetite, less hunger feelings and a bland perception of the taste of foods. This is, however, not automatically conclusive regarding a decline in nutrient intake or nutritional status.

Comparison of the 'frail' with apparently 'healthy' elders

Frail elderly people finding themselves 'at risk' with reduced physiologic reserves, were considered to have suboptimal levels of several indicators of nutritional and health state. However, diagnosing low or abnormal levels, which are not yet signs of clinical malnutrition, is difficult[9-11]. On commencement of our study we assumed that the frail elderly had a worse health profile than apparently healthy elderly people. Before analyzing the effectiveness of our trial, a comparison was made between our frail elderly and other Dutch apparently healthy, independently living elderly populations for several outcome parameters[12-19]. Only those parameters have been outlined where comparability of the data could be assumed, based on the utilization of corresponding methods. Dutch Recommended Dietary Allowances[20;21] and established (clinically relevant) biochemical cut-off levels have also been used to evaluate the nutritional and health status of our frail elders.

On average, lower mean scores on the smell test and questions on appetite, and feelings of hunger emerged for frail elderly people as compared to apparently healthy, independently living elders, but not to (healthy) institutionalized elders (*Chapters 2 and 3*). Both mean daily energy intake (*Chapters 3 and 4*) and mean body mass index (*Chapter 6*) were lower in the frail as were their subjective health ratings and levels of activity compared to healthy independently living elderly people (*Chapter 3 to 6*). On average 30% had energy intakes below 6.3 MJ/day (mostly women), which is considered as the lower cut-off level for risk of micronutrient supply[22]. Approximately, 26% of the population had a low vitamin intake, based on a comparison of eight different vitamins with 2/3 of the Dutch RDA

(*Chapter 4*). With respect to blood vitamin levels (*Chapter 4*) we learned that up to 43% of the participants could be classified as deficient, depending on the type of vitamin studied. Generally, the blood vitamin levels in our population were less favorable compared to other Dutch healthy elderly populations (Table 8.1).

Table 8.1: Overview of mean blood vitamin levels measured in our frail population, compared to healthy Dutch elderly people[a]

Parameter	Frail elderly mean	Healthy elderly[a] mean
25 hydroxy vitamin D (nmol/l)	38	42
Erythrocyte transketolase-α[b]	1.13	1.10
Erythrocyte glutathione-α[b]	1.07	1.13
Pyridoxal-5-phosphate (nmol/l)	36	50
Cobalamin (pmol/l)	267	279
Homocysteine (μmol/l)[b]	17	15
Ascorbic acid (μmol/l)	61	75

[a] based on references: 12;15-19;23

[b] lower levels are favorable

Regarding biochemical indicators of overall nutritional and health status (*Chapters 4 and 5*), for example albumin, pre-albumin, hemoglobin, lymphocytes, ferritin, transferrin and C-reactive protein, no clinically relevant low levels were detected. In contrast to this we found the homocysteine concentration in 50% of the population above the reference, which may indicate, though, a subclinical metabolic deficiency state[24;25]. In summary, we conclude that on average the recruited frail elderly subjects had a less favorable health profile than other Dutch elderly people. The fact, that no clinically relevant low levels on most of the selected biochemical indices were found, is in agreement with other studies that focus on comparable 'at risk' populations[26-28]. This demonstrates the difficulty of showing milder deficiencies in populations other than hospitalized or nursing home elderly[13;29]. Nowadays, it is recognized that perhaps established cut-off levels of clinical deficiency need to be reconsidered with regard to other functional health parameters being more sensitive and indicating a subclinical deficiency state[10;11;19]. The adverse relatively high homocysteine levels indicative of a marginal vitamin state in our frail elderly population should be interpreted in this light.

Effectiveness of the interventions

Improvement of the nutritional and health state in frail elderly was expected by either consumption of nutrient dense foods, performance of regular physical exercise or a combination of both. The term effectiveness is used instead of efficacy, since we refer to a trial performed under field conditions. Although the degree of control was the maximum feasible, compliance may not have been maximal (as is the case in efficacy studies). The nutritional and health status parameters the present thesis focuses on, are depicted in Figure 8.1. Disuse and dysfunctioning are described in the complementary thesis of Marijke Chin A Paw[1].

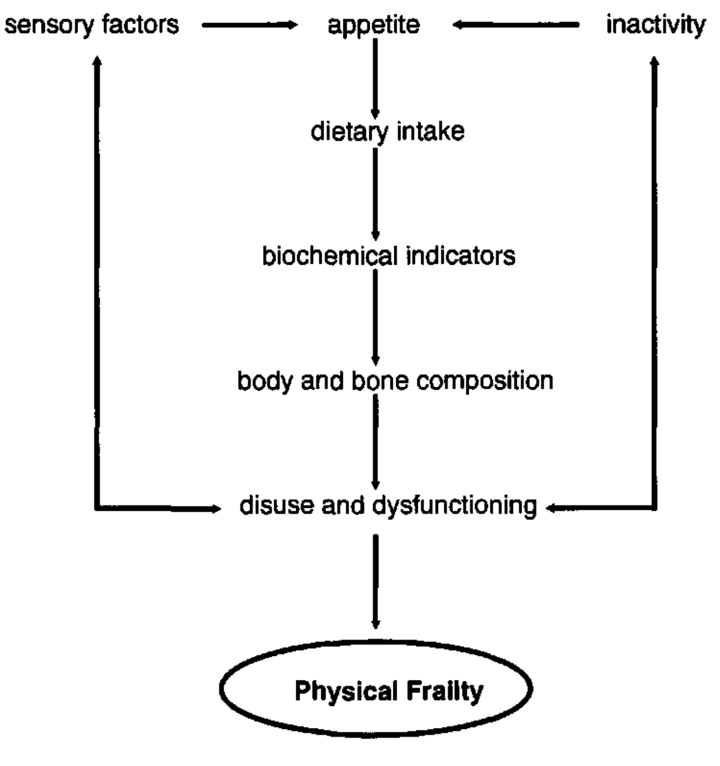

Figure 8.1: Underlying simplified mechanism of frailty hypothesized for this thesis

In Table 8.2 an overview of the measured direction of effects is given. Since we observed no interaction between the nutrition and exercise program, we compared the nutrient dense food group with the regular food group and the exercise group with the non-exercise group respectively. A possible interaction cannot be ruled out completely. As power calculations were based on desired main effects, larger numbers may have been necessary to find synergy between both programs.

Table 8.2: Overview of the main findings of the intervention study, as described in this thesis

Parameter	Enriched foods vs regular foods[a]	Exercise vs non-exercise[a]
blood vitamin levels	+	0
appetite	0	0
energy intake	0	+
functional biochemical indicators		
- homocysteine	+	0
- hematological parameters	0	0
- health related parameters (e.g. (pre-)albumin, CRP, ferritine, transferrin)	0	0
body composition		
- lean body mass	0	+
- fat mass	0	0
- bone parameters	+	0

[a] 0 = no effect, + = positive effect

Nutrient dense foods vs regular foods

After four months of intervention, a significant rise in blood vitamin levels was found in the group receiving extra nutrients (*Chapters 4 and 5*). This confirms earlier findings[30], and additionally verifies the assumption that subjects indeed consumed the supplied foods and that, accordingly, the nutrients had been absorbed and circulated in their blood. The significant improvements in vitamin levels were implicative for a beneficial lowering effect of approximately 25% of homocysteine

(*Chapter 5*), a potential risk factor for cardiovascular disease and impaired mental health[31-33].

Also for people who survive into old age, increased life expectancy makes it important to reduce such risk factors for disablement[14;34]. The younger old may especially benefit from a decline in homocysteine concentration with only physiologically dosed supplements. Our findings add substantial support to the current proposed health programs (for the elderly) in which low dose supplementation of those vitamins involved in the homocysteine metabolism is recommended instead of unnecessary and unethical high doses[35].

Another beneficial effect found in the nutrient dense food group compared to the non-supplemented subjects was related to bone mass, bone calcium and bone density (*Chapter 6*). The balance between bone formation and deformation can apparently be influenced positively, although we could not completely rule out transient effects[36]. In Figure 8.2 differences in percentage change over the study period of 17-weeks are presented for lean body mass and bone composition parameters comparing the nutrient dense food group with the regular food group and the exercising group with the non-exercising group.

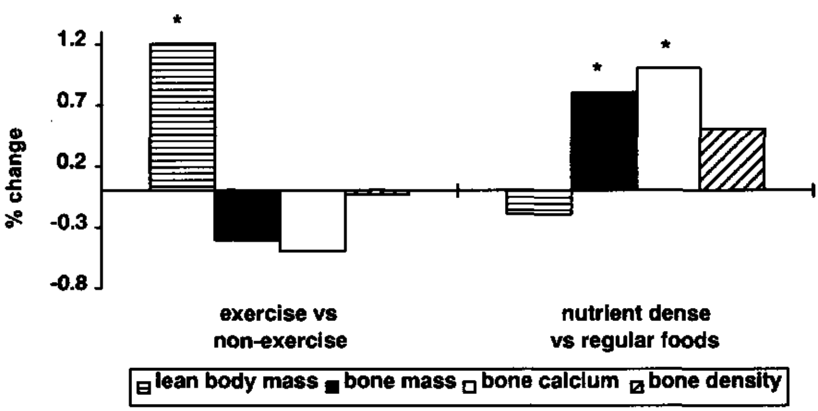

*Figure 8.2: Differences in 17-weeks change (%) in lean body mass and three bone parameters between the exercising group vs the non-exercising group and the nutrient dense food group vs the regular food group respectively (*p<0.05)*

The results with regard to bone parameters are in line with other trials which showed a divergence in bone density between controls and supplemented subjects within the first half-year of intervention[37-39]. Chapuy et al.[40] recorded within 2 months a reduction in fracture rate. However, this was accompanied by only modest bone density benefits. In contrast to our supplementation program, these trials intervened with larger doses of calcium and/or vitamin D (i.e. between 400 and 800 IU vitamin D/day, and between 0.5 and 1.2 g calcium/day). Whether the same effect can be established with physiological doses, may be confirmed in future studies. Longer term interventions in the frail should approve the steadiness of this interference in bone metabolism and should investigate the potential declining risk of falling and fracturing. Biochemical measures of bone turnover, for example serum parathyroid hormone or osteocalcin, might also confirm the results, although less convincing results have been noted with respect to these measurements compared to bone mineral density measurements[37;38].

Improvement in vitamin levels did not have any effect on appetite, spontaneous dietary intake, lean and fat mass or functional biochemical indicators of nutritional and health status, other than the decrease of homocysteine. Subjective scores on a questionnaire on appetite, feelings of hunger and sensory perception (*Chapter 3*) may not be decisive for the final nutritional state, but they reflect food enjoyment and quality of life[41]. A good appetite is generally regarded as a sign of good health. A decreasing acceptance of food can be an early warning of worsening health[42;43]. An improvement in appetite and spontaneous dietary intake through supplements only, may be extremely difficult to achieve. Perhaps only the very sick patients may benefit from such an intervention. Another explanation may be the fact that in older individuals the ability of ingested nutrients to affect the subjective state of hunger and satiety decreases[44].

For most healthy elderly, overt vitamin and mineral deficiencies are uncommon[16] though, it is possible that milder subclinical vitamin deficiencies play a role in the declining health of the frail elderly. The difficulty of demonstrating low levels and furthermore improving functional biochemical indicators (*Chapter 4*) has led to the assumption that abnormalities may be age or disease related, rather, than nutrition related[26;27]. Longer term protective effects of nutrient supplementation, due to maintenance of optimal levels, may be an important future topic.

In the supplemented group, no effect on fat and lean body mass was achieved compared to the regular food group. The stability of these body composition parameters may be partly explained by the subject's regulation of intake on food product level, i.e. subjects replaced their normal dessert or soft drink with our intervention products, which did not contain extra energy or macronutrients. Others, who intervened with both nutrients and energy, demonstrated an effect on total body weight in frail elderly[45;46], but not on lean body mass[45]. Favorable effects on body composition achieved by micronutrient dense supplements, measurable within four months, is again perhaps only achievable in frail bedridden elderly people, suffering from multiple diseases. Again, long term beneficial results through protection of these body tissues, by consumption of sufficient macro- or micronutrients should be investigated.

Exercise vs no-exercise

Adopting moderate intense regular exercise seems to stimulate a preserving effect on lean body mass in our frail elders (*Chapter 6*). This preservation of lean body mass correlates slightly to the effects on energy intake. The findings of Fiatarone et al.[45] indicate an improvement in thigh-muscle area in the exercisers compared to a decline in the non-exercisers. Our results are supportive to their observations. They furthermore showed, that only those who perform physical exercise were able to augment their nutritional intake. Reversal of inactivity, and the protection of lean body mass, may thus influence energy intake, though up till now effects of moderate intense amounts of exercise have yielded inconsistent results[47-49]. Maintenance of metabolic active cell mass may additionally be predictive for muscle strength, muscle functioning and mobility[50;51]. Preservation of muscle mass and strength, together with exercise, induced improved balance and coordination. This may also be meaningful for a decline in falling and fracture rates[45;52]. In Marijke Chin A Paw's thesis[1] beneficial effects of our exercise program, with respect to physical fitness and functioning (among others balance) have been described.

Improvement in appetite or hunger feelings by exercise was not observed, nor were any changes in biochemical parameters noted in the exercise group. With respect to the first issue, we might not have been able to pick up small changes with our questionnaire, which may only be suitable in classifying elderly in poor and healthy eaters. Up till now the effect on appetite of physical exercise has not been adequately examined. Our questionnaire was the first attempt to investigate this more thoroughly. Since changes in parameters like dietary intake and lean body mass may be ascribed to preservation in the exercising group versus a small decline in the non-exercisers, biochemical parameters were not expected to have changed much.

Appraisal of micronutrient dense foods

People, in both nutrient dense and regular food groups, were asked to rate the taste and pleasantness of the foods, their desire to eat and their attitude towards the products in general at the start and finish of the intervention (*Chapter 7*). They started off rating the food equally. Most of the foods were consumed as desserts or snacks between meals, usually as a replacement (*Chapter 3*). At the end of the intervention, a small decline in the hedonic ratings; presumably a kind of weariness, had occurred. This was not significantly different from baseline, nor between groups. Perhaps the obligatory consumption of two products a day was inducing the decline. The evaluation score, measured at the far end of the study, revealed, nevertheless, a substantial difference between groups, indicating that the nutrient dense foods were less accepted than the regular items. The intention to buy the foods, if commercially available, differed also between both groups. Immediate assessment of hedonic aspects of foods might not result in absolutely 'honest' answers since elderly people might experience difficulties in complaining about foods, which were provided for free. Therefore, for a successful future implementation, we conclude that the newly developed micronutrient dense foods need considerable adaptation with respect to their hedonic qualities.

Since we observed that the foods were predominantly taken as a replacement, we think that we succeeded in choosing the right types of nutrient dense foods. They fitted into the elderly feeding pattern, and the portion sizes seemed appropriate. We preferred a physiologically dosed multinutrient approach instead of single nutrients in mega doses since moderate multiple deficiencies due to low food intake are more likely to occur than a single severe nutrient deficiency[28]. The latter is more often the cause of a serious metabolic disease. In addition, possible effects of only micronutrients can be distinguished from effects of extra energy or other macronutrients. In line with this, the thesis focuses on spontaneous increases in energy intake due to, for example, exercise. Intakes in excess of adequate supply, might not be desirable or might even be counter-productive[9;53]. However, the interdependence between nutrients is not yet fully understood. Arguments for choosing multiple foods familiar to elders, instead of frequently used milkshake type supplements are related to compliance and imitation of daily life.

As far as we know, this is the first time that specific foods, developed for an intervention trial, have been evaluated as extensively as such. Perception of very subtle off-flavors do sometimes occur after repeated and long-term exposure. Therefore, it is of importance to focus on these adverse effects not only in laboratory trials, but also in longer lasting experiments in in-home settings, with varying examinations before marketing these types of products.

Indicators used to describe nutritional and health status

Sensory factors and appetite

In *Chapters 2 and 3* we outlined the use of a newly developed questionnaire on appetite, feelings of hunger and subject's own impression about taste and smell perception. A kind of reference was constructed by first investigating the scores of healthy independently living elderly as well as institutionalized elderly. The internal validity explored by Cronbach's alpha seemed to be sufficient, whereas the external validity is still a point of concern since a suitable 'forward biological measure' is lacking. Dietary intake may act as an absolute measure of appetite, though not always in the case of elderly. They just may eat because they simply have to, without necessarily feeling like eating. This might also be an explanation for our findings that appetite is related to energy intake in frail elderly (*Chapter 3*), whereas in healthy independently living and institutionalized elderly (*Chapter 2*) this was not observed. Meals are being served in institutions which may induce eating in the latter group and reduce the variability within this group. At the moment, several tests with hormone levels as biological markers of hunger and appetite are being explored. The questionnaire seems to be at least valuable in classification; it may, however, lack power to measure a small change.

We used a slightly adapted CCCRC smell test (*Chapters 2 and 3*), which has been validated against the Pennsylvania UPSIT test[54-56]. This latter test has been counted as the 'golden standard' and since both tests are highly correlated we assume no hampering of our data in this respect. The advantage of the (cheap) CCCRC smell test is that the smells offered are derived from natural products. The

UPSIT test, on the contrary, offers 'new' smells to elderly subjects as pizza and are constructed artificially to meet the requirements of a 'scratch and sniff' system.

Energy and nutrient intake

Having stated that dietary intake may not always act as a good measure of appetite in elderly, obtaining data about dietary intake is still important. Dietary intake is one of the determinants of nutritional status. We deliberately chose for a three day dietary record (*Chapters 3 and 4*). This method has shown to be a sufficiently reliable tool to get information on the regular food consumption pattern[57]. The method places some burden on the elderly subject, though three days seem feasible to handle (which may not be the case for seven days). With a proper explanation beforehand and a personal interview afterwards reliable data can be obtained. Some underestimation might have occurred, because of the effort of writing up. Along with debates on the value of dietary intake data, another controversial issue is choosing a 2/3 of the RDA as a cut-off level for insufficient intake. This point has arbitrarily been selected and is not based upon scientific evidence[58;59]. Minimum requirements are based on many other determinants and, to date, no absolute figures indicating pronounced undernutrition have been agreed upon[10]. Recently, under the supervision of the National Academy of Sciences in the United States, four different dietary reference intakes instead of one recommendation (RDA) have been postulated[60]. Next to the 'established' RDA, values of adequate intake, estimated average requirement and tolerable upper intake level have been calculated as well. Prevention of chronic diseases has been used as an additional criterion. Usage depends on the ultimate purpose of the study and the type of nutrient. For evaluation of intake on group level, the estimated average requirement is developed. This defines the intake level at which the need of 50% of healthy individuals of the population is met. This reference value is not yet available for all nutrients.

Other methods of investigating nutritional intake include a dietary history, food frequency questionnaires or 24-hour recalls. A serious disadvantage of the dietary history is that it is time consuming. The 24-hour recall deals with the short-term memory of the elderly and often does not give accurate information on an individual level. Food frequency questionnaires of moderate length may provide useful data on macronutrient level, but on a micronutrient level results do vary[57;61;62].

Biochemical parameters

Biochemical parameters used to judge the nutritional and health status are multiple and widespread (*Chapters 4 and 5*). Several parameters are chosen often to define the nutritional status, since up till now no sole measure has been found to indicate nutritional and health status adequately. In our study, we have separated the biochemical parameters into two categories: a) parameters describing the vitamin status and b) functional biochemical parameters which are likely to be more indicative of the overall health status. The first category describes the available body pool of vitamins. This pool is dependent on nutrient intake, but also on disease state, drug-nutrient interactions and other interfering internal factors like functioning of the gastro-intestinal tract and the ability of elderly skin to efficiently synthesize vitamin D[13;29;63-65]. With respect to water soluble vitamins the body pool is limited and an insufficient intake will be reflected shortly in those vitamin levels. Replenishment can occur rapidly. Vitamins obtained by excessive intake will be excreted through urine. With respect to fat soluble vitamins body pools are much higher (e.g. in fat tissue and liver) and take longer to exhaust[30].

The second category, the functional biochemical indicators, are assumed to reflect health state and endangered homeostasis more specifically than nutrient levels as they may depend more strongly on non-nutritive factors such as age, illness, drug use and internal metabolic processes, next to dietary intake[13;66]. Due to this interdependence, it is often not clear whether diseases cause unfavorable biochemical indicator levels or whether low biochemical levels cause the disease[58]. Another problem is the lack of uniform and clear cut-off levels, induced by different analyzing techniques. More sensitive parameters, defining suboptimal levels instead of parameters for clinical deficiency, should be established in the future, along with more insight into the whole interdependent complex of age-, nutrition-, disease- and metabolic-related factors.

Body and bone composition

With respect to measurement of body composition, various techniques are available. Up till now only one 'golden standard' has been appointed: densitometry (or underwater weighing). Since this method was not feasible for frail elderly, the dual-energy X-ray absorptiometer represented a promising alternative. Today it is the most commonly used measurement to determine bone parameters. An important feature of this method is that the procedure is fast, straightforward, non-invasive and convenient for the elderly population especially. Apart from the bone parameters, measurements of lean and fat mass obtained by DXA are also rather precise. Accuracy, is influenced by, for example, the thickness of the soft tissue[67]. Assumptions, with respect to constancy in fat and fat free mass constitute another drawback but we think that we have chosen the optimal feasible method for measuring body composition in frail elderly. We checked the DXA data with deuterium dilution technique results. Changes derived using this latter method did not reach statistical significance, as found with DXA, but pointed in the same direction.

Success of selection of a frail study population

In all epidemiological surveys focusing on the elderly, the problem of refusing participation especially by those less healthy, more socially isolated and less educated is noted[68]. Since nutritional problems are most likely to occur in these people, the problems in elderly registered so far are prone to underestimation. Research in frail elderly, therefore, is a challenging and important topic. Selecting frail elderly for participation in an intervention trial, is an even more difficult and time consuming process. Next to the 'natural' reluctance of many elderly to co-operate in research, especially the frail elderly deal with limited physical fitness and health. Besides, they often live on their own, do not have a 'sheltering support from nurses' as is the case in nursing homes and do not have the opportunity of discussing their inner thoughts with a close partner. All these factors finally influence their decisions on unascertained events.

Initially, we had planned to recruit frail elderly through co-workers at home care institutions in Wageningen and surrounding municipalities, after which the principal investigators would have invited the elderly for an introductory meeting. Several selection criteria, outlined in Figure 1.2 in *Chapter 1*, were defined. One early criterion, i.e. involuntary weight loss, was left out of our final criteria list. The outlining of this criterion was based on analyses in pre-existing data-bases (see Marijke Chin A Paw's thesis[1]) and indicated frailty or being 'at risk' the most specific. However, after a pilot test we noticed that weight loss was either unknown to the potential elderly volunteers or home care co-workers or it indicated and selected elderly who were too ill to participate. The downward process of frailty might already have been proceeded too far in this latter group of elderly. Therefore we chose for the standard of a body mass index below or equal to 25 kg/m^2, assumed to indicate limited body reserves as well.

Agreed co-operation of home care institutions was based on delicate grounds. Unexpected events prevented them from recruiting. With respect to this, we were forced to expand our recruitment activities to meals-on-wheels organizations, elderly social services, local newspapers and elderly homes as has been described in *Chapter 1*. With this adaptation of the selection procedure we had to rely solely on subject's own reports about fulfillment of the criteria, which was prone to bias. The fulfillment of criteria was investigated telephonically by the principal investigators. Unfortunately, in several cases the selection criteria were not completely met. Reported BMI was underestimated quite frequently compared to observed BMI. Care requirement was sometimes only based on convenience instead of need and occasionally activity pattern and supplement use turned out also to be different compared to the first telephonic report.

These issues result in a population being less frail than originally intended. On the other hand, taking the time and effort put into the whole recruitment procedure into account, it was the maximum feasible. Comparison of our elderly population with apparently healthy elders reveals that our elderly had, on average, a worse health profile. With respect to the feasibility of our programs, we believe now that interventions as such in a group of not too frail subjects have the most appealing strength and therefore success. Voluntary participation of the very old and frail is probably not a realistic aim. The effect of preserving 'health' in populations, as we dealt with, is perhaps even more relevant than trying to improve nutritional and health status in 'unwilling' elderly. In addition, we assume that the results found thus far with our types of interventions have only led to an underestimation rather than an overestimation of the effects, which at least upholds our conclusions.

Drop-out

In the intervention groups, drop-out rate was higher (27%) compared to the control group (14%). This is inevitable in intervention trials in the elderly. Reasons for drop out were mostly related to health problems, including (terminal) disease, hospital stay, recent falling and/or fracturing. A few subjects (n=4) withdrew because of holiday or too much distress. Most of the health related problems were not ascribed to the intervention programs themselves because a) drop out (n=25) occurred before the start of the actual intervention and b) the occurrence of diseases seemed not likely to be related, i.e. recurrence of cancer, umbilical hernia, kidney stones or eye-cataract (n=7). Other ailments might have been related to participation especially in the exercise part of the intervention including: hip fracture/surgery, cardiac infarction and rheumatoid arthritis (16 persons). In most of these cases, however, the medical problems were pre-existing. Only five subjects, of whom one was receiving the regular foods, did not like the foods supplied. In general, drop-outs were of the same age, but rated their subjective health slightly lower than those who sustained the intervention. Because of this, a little underestimation of the results might have taken place. Since only a small number withdrew because of reasons which may have been related to the type of intervention, we assume that the outcomes on group level are not altered dramatically.

Public health implications

It is recognized that people most likely to take action for elderly, classified as 'frail' or 'in need', are those responsible for the day-to-day care: i.e. partners, family, friends, neighbors, home-care assistants and social and health workers[9]. Interventions, therefore, should be designed firstly towards easy accessibility for the frail and secondly towards realistic application possibilities for non-medical personnel. We attempted to meet both conditions and focused on a population for whom relevant benefits may still be expected.

Given the diminished energy requirements in old age, it is often difficult to maintain a balanced diet, adequate in micronutrients. Hence, in 'at risk' populations nutrient dense foods should be considered. Those should have the same properties as familiar food, be served in small portions and should be easy to include in all daily meals. One promising way of administration is the replacement of a normal dessert with a nutrient dense item in the meals-on-wheels provision. Daily consumption of a physiological dose of nutrients significantly increases blood levels and, furthermore, lowers the homocysteine concentration, a risk factor for cardiovascular disease and impaired mental health. Although elderly people are survivors, they still may benefit from such interventions in order to extend the healthy or disability free life expectancy. The potential long term protective effects on health through supplementation, due to maintenance of optimal blood nutrient levels, have to be emphasized, but also need to be further investigated. Consumption of nutrient dense foods might have a beneficial effect on bone tissue, although we would like to stress the fact that our findings are preliminary. To what extent such an effect on bone tissue influences fracture rates (or in other words what is the final clinical relevance of the effects on bone tissue?) needs to be further established.

The physical exercise program, in addition, is feasible (see Marijke Chin A Paw's thesis[1]) but only if applied less frequently. Furthermore, it is logistically more difficult to apply than nutrient dense foods. Re-activation or keeping substantial activity levels by mobilizing the less healthy elderly and regain or hold an acceptable performance level is a time-consuming and difficult task. It is easier to adapt to daily consumption of a dessert than to take-up exercise. However, with respect to physical fitness and functioning more substantial results can be achieved (thesis of Marijke Chin A Paw[1]). In this thesis the preserving effect of our exercise program on muscle mass and energy intake has been determined. Long term protective effects of exercise due to maintenance of bodily tissues and functions are worth considering. A longer and perhaps more intense exercise program (a higher physical loading) could have had additional effects on bone tissue. Together with an improved balance, effects on bone tissue and skeleton stability should lower the rate of falling and fracturing.

In summary, perhaps the most important health implication is the consideration of preventive interventions. Preservation of optimal biochemical levels, muscle and bone tissue, as well as other organ systems, would imply establishment of physiologic reserves at longer term, associated with the maintenance of functional ability, autonomy and hence quality of life.

General conclusions

The core study described in this thesis contributes to the knowledge on the nutritional and health status of a group of elderly people 'classified' at risk, which adds to our current understanding of this status in apparently healthy elderly and institutionalized seniors. The intervention study shows that the main effects of nutrient dense foods and physical exercise may be complementary. Nutritional intervention increases nutrient blood levels effectively, thereby beneficially lowering homocysteine, a potential risk factor for cardiovascular disease or impaired mental health. Another potential beneficial effect of the nutritional supplementation might be the slight improvement in several bone parameters (bone density, bone mass and bone calcium). The physical exercise program complements this result with a preserving effect on lean body mass and total dietary intake. With these favorable effects on blood nutrient levels, body and bone composition, a potential preservation of physical functioning, mobility and independence might be achieved.

Inactivity, and consequently reduced appetite, energy expenditure and dietary intake and also disuse and dysfunctioning of muscles, is a major contributor to the downward process of frailty. As energy expenditure and dietary intake decline, difficulties in maintaining a balanced diet will increase. Improvement of the density of the diet may in that case be recommended. Sensory factors influence appetite and hence quality of life, though they do not always affect dietary intake or body composition to a measurable extent. Therefore, application of nutrient dense foods could be part of a feasible public health program, with the restriction that the nutrient dense foods should taste as good as regular, familiar foods even at the long-term.

Maintenance of enjoyment of life by either appetizing, tasty and 'healthy' nutrient dense foods or provision of physical exercise on different intensity levels is most important. Personal attention and guidance, low-threshold, easy accessible and cheap opportunities should lead to successful implementation of these types of interventions and should open promising pathways to reduce health care costs and a better quality of life.

EPILOGUE

(summarizing the findings described in this thesis and the complementary thesis of Marijke Chin A Paw[1])

Both adequate nutrition and physical exercise are recognized as essential and mutually interacting factors for optimal health. We have tried to develop an exercise and nutritional intervention program, feasible for widespread implementation among frail older people. Because of the interacting effects of nutrition and physical activity we hypothesized that simultaneous intervention with both nutrient dense foods and training would provide synergy, but in our trial no evidence of interaction was detected. However, the results do propose the combination of micronutrient enriched foods and physical exercise for optimal health promotion as both interventions exert different effects. We conclude that consumption of nutrient dense foods improves blood vitamin levels, homocysteine concentration, and bone mass and density. Exercise improves physical functioning and fitness and preserves muscle mass, energy intake and delayed-type hypersensitivity. Whether the observed effects on bone parameters, blood vitamins and delayed-type hypersensitivity are relevant for the prevention of fractures, maintenance of bodily functions and morbidity respectively, remains to be confirmed in longer-term interventions. Neither intervention was effective in improving subjective well-being, appetite and self-rated disabilities. A plausible explanation is that the questionnaires chosen were not sensitive enough to measure changes in time. As subjective feelings may reflect explicitly life satisfaction, they are extremely relevant for future research in this field.

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Summary

The elderly population is very heterogeneous, with individuals differing in responsiveness to factors involved in the complex process of aging. One of the more vulnerable groups among the aging elderly are the so-called 'frail elderly' people. Definitions of frailty vary, but denoting frailty as 'a state of reduced physiologic reserve, associated with an increased susceptibility to disability' seems an appropriate approach. As a consequence of present western health policy, an increasing number of (frail) elderly people are sustaining a living in the community. As many of these experience minor or major functional disabilities, the burden on, for example, home-care services and meal-on-wheels organizations is increasing. Research on the community-dwelling frail elderly is needed, in order to keep them healthy and strong in their own surroundings, improve their quality of life, and simultaneously reduce the societal health care costs.

The frail elderly have often been marked as non-responders. Therefore, information on their nutritional and health status is scarce. The first objective of this thesis was to address several descriptors of the nutritional and health status of the frail compared to a healthy elderly population. The second objective was to investigate whether two types of 'feasible' interventions (nutrition and exercise) could improve or maintain the nutritional and health status of frail elders. The third objective was to analyze the appraisal of newly developed foods.

The outcome of a 17-week randomized placebo-controlled intervention trial are described in *Chapters 3 to 6*. We operationalized frailty using several criteria, such as a) requirement of care, b) age above or equal to 70 years, c) no regular exercise and d) body mass index below average (BMI $\leq$ 25 kg/m^2) or recent weight loss. We developed a 2x2 factorial design to investigate possible interaction between the two types of intervention. In case of no evidence of interaction we could focus on the main effects. Subjects were randomized into one of four groups:

- *nutrient dense food group*: nutrient dense foods + social program (n=41);
- *exercise group*: regular foods + exercise program (n=39);
- *combination group*: nutrient dense foods + exercise program (n=44);
- *control (or placebo) group*: regular foods + social program (n=37).

The nutrient dense foods consisted of 100 gram portions of customary dairy and fruit products enriched with ~25-100% of the Dutch recommended daily allowances of the vitamins B_1, B_2, B_6, folic acid, B_{12}, C, D and E and the minerals calcium, magnesium, zinc, iron and iodine (see appendix). The exercise program focused on skill training: muscle strength, co-ordination, flexibility, speed, and endurance were worked on twice weekly in group sessions of 45 minutes. At baseline and after intervention, data were collected. In this thesis, the following outcome measures are described: sensory performance (by questionnaire and objective test), appetite, dietary intake, blood nutrient and functional biochemical health indices, and body composition. The foods were evaluated on hedonic parameters in the first two and last two weeks of intervention and by a general evaluation form. Preceding the intervention study, we performed a descriptive study in independently living healthy (n=89) vs institutionalized elders (n=67) regarding sensory performance, appetite, dietary intake and potential determinants of sensory performance (*Chapter 2*).

This latter cross-sectional study revealed that healthy elders performed better on sensory tests than institutionalized seniors. Both groups also differed in appetite, daily feelings of hunger and subjective feelings of taste and smell perception ($p<0.05$). Correlation coefficients between subjective outcomes of the questionnaire and objective tests ranged from 0.19 to 0.50 ($p<0.05$). However, sensory outcome was not correlated with energy and food intake or with BMI. Age and functional category (i.e. institutionalized or free-living) were important determinants of sensory performance. Influence of gender may be explained by differences in smoking habits.

In the subsequent intervention trial (*Chapters 3 to 6*), a significant correlation was found at baseline between the smell test and subjective feelings of smell perception ($p<0.0001$). Energy intake was significantly correlated with appetite ($r=0.30$, $p<0.0001$). After 17 weeks, no change in smell test scores or in appetite was revealed. Since no evidence of interaction occurred, the exercising group was compared with the non-exercising group and the enriched food group with the regular food group. A difference of 0.5 MJ in energy intake was noted between the exercisers and non-exercisers, along with a preserving effect of exercise on (lean) body mass (correlation: $r=0.18$, $p<0.05$).

Approximately 30% of the population (mainly women) had energy intakes below 6.3 MJ, the level below which several micronutrient deficiencies can be expected (*Chapter 4*). When micronutrient intake was compared with 2/3 of the Dutch RDA, between 3% (vitamin B_6) and 93% of the women (vitamin D) had inadequate intakes. The individual blood nutrient deficiency percentages ranged from 3% for erythrocyte glutathione reductase-α (functional measure for vitamin B_2) to 39% for 25(hydroxy) vitamin D and to 42% for vitamin B_{12}. Blood levels in the groups receiving nutrient dense foods increased after intervention (all $p<0.001$, with exception of the functional measures of vitamin B_1 and B_2), whereas no significant changes were observed in the exercise or control group. Chapter 4 also presents functional biochemical health indices including (pre-)albumin, ferritin, transferrin, C-reactive protein, thyroxin and hematological parameters. At baseline, no clinically relevant low levels of these parameters were detected, and in none of the intervention groups did a relevant change occur after intervention.

The mean baseline homocysteine level was 17.4 μmol/l (*Chapter 5*). Elevated levels are regarded as a potential risk factor for cardiovascular disease and impaired cognitive functioning. A significant decline of about 25% was detected in the groups receiving nutrient dense foods, which may indicate the existence of subclinical nutrient deficiency. Homocysteine concentrations changed -5.0 μmol/l ($p<0.001$) in the enriched compared to the non-enriched group.

Another measure of nutritional status is body and bone composition (*Chapter 6*). A feasible method of measuring body composition in frail elderly is dual energy X-ray absorptiometry (DXA). Like other methods measuring body composition, this technique makes use of estimates of the distribution of body water, the main component of the body. This implies that the potential to measure small changes in body composition is reduced. Therefore, our results should be cautiously interpreted. Exercise, compared to no-exercise, preserved lean body mass (mean difference both groups was 0.5 kg; $p<0.02$). Consumption of enriched foods, compared to regular foods, resulted in beneficial effects on bone density, mass and calcium content (differences between both groups were: 0.5% (mean: 0.006 g/cm^2, $p=0.08$), 0.8% (mean: 19 g, $p=0.04$) and 1.0% (mean: 8 g, $p=0.03$) respectively). Results obtained using other techniques measuring body composition (deuterium dilution technique and body weight measured on scale) pointed in the same direction.

In *Chapter 7* results of the acceptance of nutrient dense foods compared to identical regular foods are described. At the beginning, small (not significant) but consistent differences emerged in ratings of 'pleasantness' and 'desire-to-eat' between the nutrient dense and regular foods. At the end, ratings dropped slightly or remained equal. It emerged from the evaluation questionnaire, that regular foods scored significantly higher (7.7) than nutrient dense foods (6.4, $p<0.001$) on a 10-point scale.

In conclusion, blood nutrient levels in our population of frail elders significantly improved after 17 weeks consumption of nutrient dense foods, while homocysteine concentration significantly decreased. However, the prevalence of clinically relevant deficiency levels of blood vitamins varied. Results from our body composition data cautiously suggest that nutrient dense foods may have a beneficial effect on several bone parameters. Exercise may complement the effects of nutrient dense foods, as a preserving effect was observed on lean body mass. Long-term effects of exercise and supplementation with nutrient dense foods on biochemical health indicators, by maintenance of all bodily functions, as well as appetite should be investigated in the future. The supply of physiologically dosed micronutrient enriched foods, improving the density of the diet, may be part of a feasible, beneficial, and ethical public health program. However, the hedonic qualities of nutrient dense foods should be optimized in order to be suitable for such long-term application. The most important goal in implementing elderly health programs should be maintenance or improvement of enjoyment of life. Healthy and appetizing foods, as well as pleasant and feasible exercise programs, may help achieve that goal.

Samenvatting

In deze samenvatting wil ik graag aan mijn familie en vrienden in het kort uitleggen wat ik de afgelopen jaren heb gedaan en vooral wat de uitkomsten zijn van die grote interventiestudie waar ik toch zo druk mee was.

Verouderen

In de westerse wereld worden steeds meer mensen steeds ouder: een zogenaamde dubbele vergrijzing. De snelheid van verouderen verschilt per individu. Er zijn mensen die op hoge leeftijd nog de Nijmeegse vierdaagse lopen, er zijn er ook die al op relatief jonge leeftijd verpleegd worden. Dit proces van verouderen is afhankelijk van veel verschillende factoren die ook elkaar kunnen beïnvloeden. Naast erfelijkheid is bijvoorbeeld de omgeving waarin iemand leeft, van belang. Ziekten en medicijnen hebben invloed, alsook factoren die te maken hebben met de zogenaamde *'leefstijl'* (bijv. voedingsgewoonten, hoeveelheid stress en de mate waarin iemand nog actief is). De wisselwerking van al deze elementen zorgt ervoor dat iemand *'succesvol'* *'normaal'* of *'versneld'* veroudert. Met name deze laatste categorie ouderen is kwetsbaar en heeft maatschappelijke aandacht nodig.

De Nederlandse overheid richt haar beleid erop dat steeds meer ouderen zo lang mogelijk thuis, in hun eigen omgeving, blijven wonen. Het is daarbij belangrijk dat de gezondheid en vooral de kwaliteit van het leven van de thuis-wonende oudere gewaarborgd blijven. Verschillende instanties zijn (gedeeltelijk) verantwoordelijk voor deze zorg, waaronder thuiszorgorganisaties, maaltijdvoorzieningen (tafeltje-dek-je), dienstencentra voor ouderen, en ook de huisarts en familie.

Kans op negatieve spiraal

Wanneer mensen ouder worden, dan wordt er vaak als vanzelf een meer zittende leefstijl aangenomen. Door een minder actief leven kan de eetlust dalen en lijkt een verminderde voedselinname een logisch gevolg. Op zichzelf hoeft dat niet erg te zijn, want er wordt tenslotte ook minder energie verbruikt. Wanneer men echter onder een bepaalde minimumgrens komt bestaat het gevaar voor tekorten aan verscheidene vitaminen en mineralen. Hierdoor kan het lichamelijk functioneren op allerlei niveau's achteruitgaan. Voorbeelden zijn: organen die slechter werken, maar ook het uitvoeren van dagelijkse dingen zoals wassen en aankleden. Er kan gewichtsverlies optreden, men zal zich minder fit gaan voelen en tenslotte zal de activiteit nog verder afnemen. Er is een negatieve spiraal ontstaan.

Strategieën die de gezondheid kunnen beïnvloeden

Regelmatige lichaamsbeweging en voedingsmiddelen die rijk zijn aan vitaminen en mineralen zijn twee veelbelovende methoden die de kans op een gezonde oude dag kunnen verhogen. Ik heb het effect van deze methoden samen met mijn collega Marijke Chin A Paw onderzocht. De belangrijkse vragen van mijn onderzoek waren:

1. Verschillen de ouderen, die zich in een negatieve spiraal bevinden, ook daadwerkelijk van de 'op het oog gezonde' ouderen?
2. Wat is nu eigenlijk het effect van een speciaal ontwikkeld bewegings- en voedingsprogramma op de gezondheid van ouderen?
3. Wat vindt men van het voedingsprogramma? (Marijke evalueerde de mening over het bewegingsprogramma).

Vraag 1: *Verschillen tussen gezonde ouderen en ouderen 'in negatieve spiraal'?*
Voor veel aspecten gold dat beide groepen ouderen inderdaad van elkaar verschillen. De mensen 'in een negatieve spiraal' kregen minder energie met de voeding binnen en hadden een lager gewicht (rekening houdend met de lengte). De vitaminegehaltes in hun bloed waren ook minder gunstig. Het rapportcijfer dat mensen zichzelf voor hun gezondheid gaven was in die groep eveneens lager.

Vraag 2: *Wat is het effect van een speciaal voedings- en bewegingsprogramma?*

Het effect van een voedings- en bewegingsprogramma op de gezondheid werd onderzocht in de studie 'Fit op Leeftijd'. Ook werd bekeken of een combinatie van beide programma's wellicht een groter effect had. Om deelnemers te vinden werden ruim 7000 brieven verstuurd via: thuiszorgorganisaties, maaltijd-leveranciers (tafeltje-dek-je), dienstencentra voor ouderen, service-flats en aanleunwoningen.

In totaal waren 854 mensen geïnteresseerd. Zij werden via een telefonische enquête door ons geselecteerd. De belangrijkste kenmerken waarop wij selecteerden waren:
- gebruik maken van hulp (bijvoorbeeld thuiszorg of maaltijdvoorziening);
- weinig lichaamsbeweging;
- ongewenst gewichtsverlies of gewicht lager dan gemiddeld.

Uiteindelijk konden én wilden 217 personen meedoen. Van de deelnemers, die een gemiddelde leeftijd van 79 jaar hadden, was één kwart man en driekwart vrouw. Zij werden door loting ingedeeld in één van de volgende vier groepen:

1) voeding: verrijkte voedingsmiddelen + educatief programma (58 personen)
2) beweging: normale voedingsmiddelen + bewegingsprogramma (55 personen)
3) combinatie: verrijkte voedingsmiddelen + bewegingsprogramma (60 personen)
4) controle: normale voedingsmiddelen + educatief programma (44 personen)

Om te waken voor een zogenaamd 'placebo'-effect, dus b.v. het effect op de ervaren gezondheid door dénken dat men gezonde voedingsmiddelen eet en door méédoen aan een programma of onderzoek op zich, werden ter vergelijk ook normale voedingsmiddelen en een educatief programma aangeboden.

Het voedingsprogramma: Hiervoor werden speciaal produkten door diverse Nederlandse bedrijven ontwikkeld. We wilden graag kleine porties die gemakkelijk over de gehele dag te eten waren. De deelnemers kregen 17 weken lang verse zuivelprodukten (vanillevla, kwark, twee soorten vruchtenyoghurt) en fruitprodukten (sinaasappel-perziksap, appel-bes-druivensap en twee soorten vruchtenmoes). Aan de verrijkte produkten werden diverse vitaminen en mineralen toegevoegd: D, E, B_1, B_2, B_6, foliumzuur, B_{12}, C en calcium, magnesium, ijzer, zink en jodium. Per dag moest één zuivel- en één fruitprodukt gegeten worden. Dat leverde in totaal 25-100% van de dagelijks aanbevolen hoeveelheden van deze voedingsstoffen voor ouderen op. Ook van de normale produkten moesten er twee gegeten worden. Deze waren qua uiterlijk identiek aan de verrijkte produkten.

Het bewegingsprogramma: Er werd gedurende 17 weken, in 2 lessen per week van elk 45 minuten geoefend met verschillende materialen (b.v. pittenzakken, ballen, gewichten). Groepen van 10 à 15 personen werden getraind door ervaren sportdocenten. Het programma richtte zich op het verbeteren van het lichamelijk functioneren door het trainen van spierkracht, lenigheid, coördinatie, snelheid en uithoudingsvermogen.

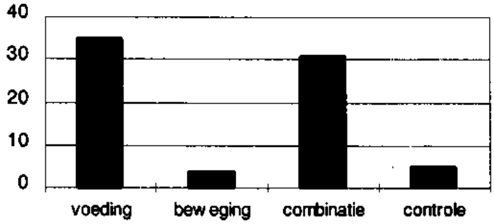
Het educatieve programma: Voor dit programma (gecoördineerd door een ervaren activiteitenleider) werden eenmaal per 14 dagen diverse activiteiten georganiseerd zoals lezingen, creatieve activiteiten of een voedingsquiz.

Metingen ter bepaling van gezondheid en voedingstoestand: In de week voor en na de 17 weken durende programma's werden metingen verricht om de voedingstoestand en de gezondheid te bepalen, bijvoorbeeld:

- eetlust en geurwaarneming
- dagelijkse voedingsinname (berekend uit de 3 dagen dat de voeding genoteerd werd)
- diverse factoren in het bloed (o.a. vitaminegehaltes)
- spier-, vet- en botmassa
- lichamelijke fitheid en functioneren (bijv. spierkracht, lenigheid en opstaan uit een stoel)

De resultaten

Het bewegingsprogramma had een gunstig effect op het behoud van spieren en de dagelijkse voedselinname. Ook werd het lichamelijk functioneren (bijv. het opstaan uit een stoel en de snelheid waarmee iemand loopt) en de fitheid (bijv. het in balans blijven en spierkracht) verbeterd. De verrijkte produkten verhoogden de vitaminegehaltes in het bloed. Dit betekende dat de deelnemers ook daadwerkelijk de produkten gegeten hadden. Hieronder is een voorbeeld te zien van de verandering van het vitamine D gehalte in het bloed.



De verandering in vitamine D gehalte (in nanomol per liter) in het bloed, weergegeven per groep: de verandering was in de voedings- en combinatiegroep ongeveer 6 x zo hoog vergeleken met de bewegings- en controlegroep

Verder leken de verrijkte produkten een gunstig effect te hebben op de botdichtheid en de hoeveelheid bot. Dit moet wel nog nader onderzocht worden, want een periode van 4 maanden is eigenlijk net iets te kort om effecten op het bot met zekerheid vast te stellen. Ook daalde bij de mensen met verrijkte produkten het *homocysteine* gehalte in het bloed met 25% ten opzichte van de mensen met normale produkten. Dit is gunstig want een verhoogde concentratie van homocysteine is een risicofactor voor hart- en vaatziekten.

Geen van beide programma's hadden een effect op de eetlust, geurwaarneming en het welbevinden. De combinatie, dus zowel verrijkte voedingsmiddelen als een bewegingsprogramma leverde geen waarneembaar extra effect op in vergelijking met de programma's afzonderlijk. Wel had de combinatie invloed op méér verschillende aspecten van de gezondheid, dan ieder van de programma's apart.

Vraag 3: *De beoordeling van de produkten?*

De beoordeling van de programma's was belangrijk om iets over de praktische haalbaarheid in de toekomst te kunnen zeggen. De evaluatiescore van de voedingsmiddelen leverde voor de normale produkten een rapportcijfer op van 8'. Echter voor de verrijkte varianten was dit een 6,5. Ook het percentage mensen wat na de studie de produkten zelf ook wel wilden kopen was lager binnen de verrijkte groepen. De vanillevla en beide vruchtensappen waren over het algemeen het meest populair. Men stond in het algemeen positief ten opzichte van verrijking van voedingsmiddelen, maar aan de nieuwe produkten moet nog wel gesleuteld worden voordat ze echt in de winkel verkocht kunnen worden.

Conclusie

Ik concludeer dat speciale voedingsmiddelen en ook bewegingsprogramma's de gezondheid van ouderen gunstig kunnen beïnvloeden. Het verbeteren van de gezondheid is belangrijk, evenals het hebben én houden van plezier in het leven. Smakelijke voedingsmiddelen en prettige maar efficiënte bewegingsprogramma's passen daarbij. Omdat beide programma's verschillende effecten laten zien, wil ik een combinatie van beiden aanbevelen.

Vanuit het standpunt van de jeugd bezien is het leven een oneindig lange toekomst; vanuit het standpunt van de ouderdom een zeer kort verleden. (A. Schopenhauer)

APPENDIX

Presentation of the Dutch Recommended Daily Amounts (RDA) for elderly, concerning the micronutrients added to the nutrient dense foods, and the target amounts which were aimed at, presented as percentage of the Dutch RDA[a]

Micronutrient	Unit	RDA men	RDA women	Dairy product (% RDA/100 g)	Fruit product (% RDA/100 g)
Vitamin D	μg (IU)	7.5 (300)	7.5 (300)	100	-
Vitamin E	mg	9.4	8.3	100	-
Vitamin B_1	mg	1.0	1.0	50	50
Vitamin B_2	mg	1.5	1.3	50	50
Vitamin B_6	mg	1.1	1.0	50	50
Folic acid	mg	0.25	0.25	50	50
Vitamin B_{12}	μg	2.5	2.5	50	50
Vitamin C	mg	70	70	50	50
Calcium	g	0.9	0.9	25	-
Iron	mg	9.0	8.0	25	25
Magnesium	g	0.33	0.28	12.5	12.5
Zinc	mg	10.0	9.0	25	25
Iodine	mg	0.23	0.28	50	50

[a] based on references: Commissie Voedingsnormen Voedingsraad: *Nederlandse voedingsnormen 1989*, Den Haag, Voedingsraad; Commissie Voeding van de Oudere mens: *Voeding van de oudere mens 1995*, Den Haag, Voedingsraad

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Geen echte voedingsproef, zonder voedingsmiddelen. Al die micronutriënten moesten in 100 gram produkt en dat moest ook nog prima smaken. Bijna onmogelijk.... Allita van Daatselaar (Roche Nederland B.V.), bedankt dat je de 'mixen-op-maat' zo snel geleverd kon krijgen. Ook wil ik dhr. van de Wiel (Chefaro International B.V.) hier bedanken. Sommige vitaminen en mineralen waren inderdaad beter geschikt voor tabletjes: we hebben een wijze les geleerd. Een andere schier onmogelijke taak was om wekelijks honderden porties vers af te leveren. Toch is het gelukt, ook al hebben we spannende momenten beleefd. Fantastisch, die logistieke inspanning van jullie, Rudi Fransen, Henk van der Hoek (Friesland Coberco Dairy Foods) en Frank Elbers (Mona, Campina Melkunie)! Frau Anneliese Mahrow (Bekina Lebensmittel GmbH), weit über 35.000 Gläser Apfel-(Pfirsich) mus, dass war von einer anderen Ordnung! Ich werde niemals den blauen Apfelmus vergessen, den wir zuerst entwickelt hatten. Vielen Dank für Ihre Gastfreundschaft in Beelitz. Wendy van Koningsbruggen, weet je nog?

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Nynke

About the author

Nynke de Jong was born in Amsterdam, The Netherlands, on 2 August 1970. In 1988 she completed secondary school at the Rijksscholengemeenschap in Purmerend. In the same year she started with her studies on Human Nutrition at the Wageningen Agricultural University. As a part of her studies she spent 6 months of research at the Netherlands Institute for Dairy Research (NIZO), Ede. She conducted a practical training period of 7 months in the rural area of Mpika, Zambia. Subsequently, at the department of Human Nutrition in Wageningen she studied the growth and nutritional status of previously macrobiotic fed children and finalized her studies at the Nutrition Research Department of Nutricia, Zoetermeer. In August 1994, she obtained her MSc degree with majors in human nutrition, physiology, and food chemistry. From October 1994 to April 1995, she was appointed as a research associate on sensory perception in elders at the department of Human Nutrition, Wageningen Agricultural University (now: division of Human Nutrition and Epidemiology, Wageningen University). At the same department, from April 1995 to October 1999, as PhD-fellow she performed the research in elderly people described in this thesis. This study was part of a multi-disciplinary project in which human nutrition and human movement sciences were combined. During this period she was board member of the Wageningen PhD Organization (WAIOO), editorial board member of the PhD-newsletter 'Newtrition' and member of the departmental 'postgraduate education' committee. She attended the annual international 'Erasmus Epidemiology Summer Program' in Rotterdam, and participated in international courses like 'Regulation of Food Intake', 'Nutritional and Lifestyle Epidemiology' and 'Use of Body Composition Techniques in Laboratory and Field Studies'. In February 2000, she will start a 1-year postdoctoral position at the Department of Human Nutrition at Otago University in New Zealand.

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