

**Effectiveness and cost-effectiveness of  
nutritional intervention in elderly subjects  
after hip fracture**

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# Effectiveness and cost-effectiveness of nutritional intervention in elderly subjects after hip fracture

PROEFSCHRIFT

Ter verkrijging van de graad van doctor  
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Denk iets goeds  
En denk iets lekkers  
Denk iets gek  
Of nog iets gekkers

Denk iets aardigs  
Denk iets liefs  
Maar hoe dan ook...  
Iets positiefs

*Toon Hermans*



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# Chapter 1

## General introduction

## HIP FRACTURES

In The Netherlands, as well as in other countries, the incidence of hip fractures in the elderly, people aged 55 years and above, is high and it is expected to increase in the future. In 2007, the total number of hip fracture cases in the Netherlands was 17,900 of which 15,000 hip fractures occurred in the elderly (1). Hip fractures occur more often in women, they account for 75% of the hip fracture cases. Because of the increased life expectancy, it is estimated that the number of hip fractures worldwide will increase to 6,3 million by the year 2050 (2).

Hip fractures can have severe consequences for the patient. Only 37% of the hip fracture patients return to their pre-fracture functional status, and half of the patients experience disability (2, 3). Mortality rates after hip fracture are high, ranging from 8.4% to 36% in the first year after the fracture (3-6). In the Netherlands, the one year mortality rate is reported to be 25% (1). Mortality risk is highest immediately after fracture and decreases over time (7). Hip fracture patients often suffer from co-morbidities, e.g. cardiovascular diseases and respiratory diseases, which may require special attention both before and after surgical treatment of the fracture (8). The presence of co-morbidities can influence surgical treatment as well as recovery and the occurrence of postoperative complications. Furthermore, patients with prior fractures have an increased risk of future fractures (9-12).

Hip fractures are one of the most common reasons for hospital admissions (13). As a consequence, hip fractures are a major burden on the available budgets for health care (14). In Europe, the direct medical costs of hip fractures are estimated at € 24,4 billion (2). Direct medical costs of hospitalisation for hip fracture were € 14,000 per patient. In the Netherlands, the average costs during four months after hip fracture were approximately € 15,000 (15). Hip fracture costs do not only result from the hospital stay and the surgical treatment of the fracture, but also from the stay in the rehabilitation clinic, home care, informal care and medical consumption such as medication use and visits to the general practitioner and medical specialist. The costs after hospitalisation will influence the total costs at least as much as the hospitalisation costs (16, 17). Within the last years, there is a tendency to discharge the patients as soon as possible from the hospital, because recovery after hip fracture can also take place in a rehabilitation clinic or at home. It was expected that the early discharge policy would lead to a reduction of total costs, but instead of the cost reduction, a shift from hospital costs to rehabilitation costs or nursing home costs was seen (15).

Hip fractures are classified according to the location of the fracture line in the femur. Almost all hip fractures are treated surgically. Depending on the classification of the fracture and bone quality, the fracture is repaired by fixation with three screws, with an intramedullary nail, with a sliding hip screw fixation or with a (hemi)arthroplasty (18). The aim of surgical treatment of the fracture is to reduce pain and to get the patient mobilised as soon as possible. Therefore, hip fracture surgery should be performed as soon as possible, because a delay in hip fracture fixation causes stress to the patient and it increases mortality rate (19, 20). According to Statistics Netherlands (Centraal Bureau voor de Statistiek), the mean length of hospital stay in 2009 was 10.8 days for males, and 12.0 days for females (1, 21). Since 2000, the mean length of hospital stay has halved (1, 21). One of the causes of this reduction in length of stay is

the transfer of recovery from the fracture from the hospital to a rehabilitation clinic or to the patients' home with professional home care and informal care.

Falling in elderly is the most important cause of hip fractures; at least 90% of hip fractures occur after a fall inside or outside the house. Several risk factors for hip fractures can be identified (Box 1).

#### **Box 1 Risk factors for hip fracture**

Female gender  
 Increased age  
 Caucasian ethnicity  
 Low bone mineral density  
 Hip fracture in family (mother or father)  
 Sedentary lifestyle  
 Impaired nutritional status, low Body Mass Index, low body weight  
 Smoking  
 Alcohol abuse  
 Medical conditions such as osteoporosis, cardiovascular disease, parkinson's disease, bone diseases and endocrinal diseases  
 Medication use  
 Living in an institution

Hip fractures occur more often in women because women have a higher life expectancy than men, a lower bone mineral density and a higher bone loss (22). While ageing, the risk of sustaining a hip fracture increases for both men and women. People from Caucasian ethnicities have also a higher hip fracture risk. A low bone mineral density (1 SD lower as the peak bone mass) at the femoral neck or at the lumbar spine increases hip fracture risk (13, 23, 24). Previous fractures after the age of 50 years also increase the risk of hip fracture (9, 11, 12, 25), with the highest risk of a new fracture during the first year after the initial fracture. If one of the parents sustained a hip fracture at old age, the children have also an increase risk of hip fracture (25). People having a sedentary lifestyle or having less physical activity have an increased risk because muscle strength and balance can be impaired. Also, people using a walking device have an increased hip fracture risk (26-29). An impaired nutritional status, a low Body Mass Index (< 20 kg/m<sup>2</sup>) or body weight below 60 kg increases also hip fracture risk (27, 30, 31). Smoking, especially currently smoking, is also associated with an increased hip fracture risk and can be explained by the association of smoking with a low body weight, a sedentary lifestyle, co-morbidity and medication use for co-morbidity (27, 32). The daily consumption of at least three units of alcoholic beverages increases hip fracture risk (32). Several medical conditions also increase the risk of hip fractures, i.e. rheumatoid arthritis, cardiovascular disease, Parkinson's disease, bone diseases (Paget's disease, Khaler's disease) and endocrinal diseases (hyperthyroidism, hyperparathyroidism). These diseases increase hip fracture risk by decreasing bone mineral density. The use of benzodiazepines and the use of anticonvulsant drugs also increase hip fracture risk. Osteoporosis is also an important risk factor for hip

fractures. It is defined by the World Health Organisation (33) as “a disease characterised by low bone mass and microarchitectural deterioration of bone tissue, leading to enhanced bone fragility and a consequent increase in fracture risk”. As in hip fractures, the prevalence of osteoporosis is higher in postmenopausal women. Hip fractures, falling and osteoporosis have several risk factors in common. Malnutrition or a poor nutritional status is one of these risk factors. The next paragraph will focus on malnutrition in the elderly.

## **MALNUTRITION IN ELDERLY**

Over the past decade, malnutrition in elderly has become an important issue in health care. In a recently published report by the Health Council of the Netherlands (in Dutch Gezondheidsraad) entitled ‘Malnutrition in the elderly’ (34), prevalence rates of malnutrition in The Netherlands are reported from two sources. The first source is the “International Prevalence Survey of Care Problems”, in Dutch known as the “Landelijke Prevalentiemeting Zorgproblemen (LPZ)”, in which malnutrition was defined as recent unintentional weight loss (at least three kg in the past three month or six kg in the past six months) or a recent reduction in food intake (no or very low intake for three days or food intake lower than usual intake for one week) (34). According to this definition, the prevalence of malnutrition ranged from 16% in elderly living at home receiving home care, via 21% in institutionalised elderly, to 33% in hospitalised elderly (data from the surveys carried out in 2008, 2009 and 2010) (34). Second, malnutrition prevalence rates were reported by the “Longitudinal Aging Study Amsterdam (LASA)” (35), in which malnutrition was defined as a low body mass index (BMI < 20 kg/m<sup>2</sup>) or unintentional weight loss of at least 5% of body weight over the past six months. According to this definition, the prevalence of malnutrition ranged from 12% in elderly living at home receiving home care, and 18% in both institutionalised and hospitalised elderly (34). As reported by LASA, 7% of the independently living elderly were malnourished (data collection was carried out in 2005 and 2006) (34).

One of the reasons for difference in the prevalence rates of malnutrition is the lack of a nationally or internationally accepted definition of malnutrition. In 2006, The European Society for Clinical Nutrition and Metabolism (ESPEN) proposed the following general definition of malnutrition (36): “A state resulting from a lack of uptake or intake of nutrition leading to an altered body composition and diminished function.” So far, this definition is not generally accepted or operationalised to a golden standard to identify individuals at risk of malnutrition. In daily practice in the Netherlands, several screening instruments are used: the Mini Nutritional Assessment (MNA) (37-39), the Short Nutritional Assessment Questionnaire (SNAQ) (40), and the Malnutrition Universal Screening Tool (MUST) (41). The MNA was developed for identifying malnutrition in elderly people and it’s also used in other (European) countries. The SNAQ is a screening tool developed in the Netherlands for the early detection and treatment of malnutrition in elderly hospitalised subjects (40). In the past years, two additional screening instruments based on the SNAQ have been developed: the SNAQ<sup>RC</sup> to identify malnutrition in elderly subjects living in nursing homes or elderly homes, and the SNAQ<sup>65+</sup> to identify malnutrition in community-dwelling elderly (42).

The MUST was developed by the British Association of Parenteral and Enteral Nutrition (BAPEN) to identify malnutrition in all health care settings (43, 44).

Once malnutrition is identified and the subject is referred to a dietician, a nutritional intervention can start. As a first step of the treatment of malnutrition, the patient's usual and current nutritional intake has to be evaluated and food preferences and problems with eating, chewing or swallowing should be identified. Next, the dietician calculates the patient specific nutritional needs with regard to energy and protein intake. To meet the nutritional recommendations, the dietician can advise the patient to adjust the usual nutritional intake or to use in-between meals. If necessary, oral nutritional supplements can be advised to increase the nutritional intake. If oral nutritional supplements are not enough to improve the nutritional intake, parenteral nutrition or enteral tube feeding can be used as a nutritional intervention. Individual tailoring of the nutritional intervention is essential to receive good compliance with the nutritional intervention and to maximise the results of the dietary treatment.

In elderly, malnutrition has a major impact on physiological as well as biochemical systems. For several diseases and medical conditions, malnutrition has been associated with impaired immune response, impaired muscle function, impaired respiratory function, delayed wound healing, overall increased complications, longer duration of hospital stay, longer rehabilitation, apathy, depression, fatigue, and increased mortality (45, 46). In addition, if malnourished elderly are hospitalised, they have higher hospital costs as compared to well-nourished patients, independently of their medical condition for which they are admitted to the hospital (43, 47-51). These higher costs result from longer hospital stay, increased use of hospital resources, higher rate of hospital readmissions, increased infection or pressure ulcer and poor wound healing (47, 52, 53).

One of the most important causes of malnutrition is inadequate nutritional intake due to a loss of appetite, inadequate availability or quality of food (e.g. poverty, difficulties with shopping or preparing meals) or to underlying medical conditions (54). Loss of appetite can also be caused by diseases (cancer, Crohn's Disease) or medication use. Furthermore, being depressed, eating alone, disliking meals in institutions, difficulties with chewing and swallowing can also influence appetite and thereby increase the risk for malnutrition (43, 55).

According to a guideline on enteral nutrition published in 2006 by ESPEN, malnutrition in the elderly should be treated as soon as possible, and treatment of malnutrition should be incorporated in usual health care (56). This ESPEN guideline is not implemented in the Netherlands and screening and treatment of malnutrition is not incorporated in usual health care which leads to under-diagnosis and under-treatment of malnutrition. According to a recent report of the Health Council of the Netherlands, further research is needed to identify the magnitude of malnutrition in the Netherlands and to identify the most appropriate way to treat malnutrition (34).

## **MALNUTRITION IN HIP FRACTURE PATIENTS**

In hip fracture patients, malnutrition appears to be more severe than in the general aging population (57, 58), with a prevalence ranging from 42% (59) up to 63% (60). At hospital admission, hip fracture patients can have a poor nutritional status which can deteriorate further during hospitalisation because of a spontaneous reduction in food intake due to nausea or a lack of appetite (61-71).

A poor nutritional status in hip fracture patients has been reported to be associated with muscle wasting, impaired muscle function, disability, loss of independence, mental apathy, impaired cardiac function, delayed wound healing, a higher postoperative complication and infection rate, prolonged rehabilitation time, decreased quality of life and increased mortality rate (8, 49, 64, 65, 72-79).

In the 2006 ESPEN guideline on enteral nutrition in elderly it is recommended that hip fracture patients are advised to receive oral nutritional support after their fracture (56). As mentioned earlier, this guideline is not implemented in the Netherlands, nor other guidelines for the treatment of malnutrition in elderly hip fracture patients exist in the Netherlands are implemented.

## **EARLIER NUTRITIONAL INTERVENTION STUDIES IN HIP FRACTURE PATIENTS**

Since the early 1980s, a number of Randomised Controlled Trials (RCTs) have been conducted to determine the effect of various types of nutritional supplementation on the length of stay, postoperative complications, functional status, and mortality in elderly hip fracture patients. These RCTs have been conducted in Australia (80, 81), Spain (82, 83), Sweden (84, 85), Switzerland (63, 86, 87), The Netherlands (88), United Kingdom (66, 74, 89, 90) and the United States of America (91-93). The most commonly tested types of nutritional intervention are ONS and tube feeding. Below, results of these RCTs are briefly presented.

### **Oral nutritional supplementation as nutritional intervention**

ONS is a commonly used, easy, well-tolerated and relatively cheap method of nutritional support. Previous studies evaluating nutritional interventions have shown that ONS increases energy and protein intake, as well as micro-nutrient intake (66, 83, 91). Several previous studies indicated that patients receiving ONS had a significantly shorter length of hospital stay (63, 86, 87, 89), an improved clinical outcome presented as a significantly lower number of postoperative complications (63, 87) and deaths (63) as compared to patients receiving the standard hospital diet. Furthermore, ONS in hip fracture patients can help to maintain functional status defined as maintaining independence in activities of daily living (85). In contrast to these findings, several studies failed to show an improvement or maintenance of these outcomes: nutritional status (82, 85, 89), functional status, and quality of life (85) or a reduction in length of stay (80-82, 85), a reduction in postoperative complications (82) or a reduction in mortality rate. Espauella et al. (83) were not able to show any beneficial effects of high protein ONS compared to low protein ONS.

One of the reasons why the above studies show inconsistent results can be because of poor compliance with the nutritional supplements which is reported in several studies. Another reason can be that although nutritional intake was improved in supplemented patients, the nutritional requirements were still not met during hospital stay (63). The period the patients in the intervention groups received ONS varied also between these studies, ranging from one week supplementation or only during hospitalisation to only nutritional intervention during the stay in the rehabilitation clinic. Nutritional supplements were also provided to patients without dietetic advice or without individual tailoring, which may result in poor compliance and thereby limiting the effects of the nutritional intervention. Further, it has to be noticed that these nutritional intervention studies are carried out with a small number of participants which may result in an inadequately powered study. These RCTs are conducted in different countries, each with their specific organisation of health care, which may result in different types of usual care, different discharge policies (i.e. presence or absence of rehabilitation clinics) among other factors which may influence the generalisability of the studies separately and the comparisons of the results between studies.

### **Tube feeding as nutritional intervention**

Tube feeding has been used as nutritional intervention in few studies in hip fracture patients, because this is a quite invasive way of nutritional support. Bastow et al. (74) reported a beneficial effect of tube feeding on nutritional status in very thin hip fracture patients. In addition, very thin patients who were tube-fed had a shorter length of hospital stay as compared with controls who received the normal ward diet (74). In the study of Hartgrink et al. (88), no effect of tube feeding was shown on the development of pressure ulcers. Sullivan et al. (92) reported that nightly enteral feeding in hip fracture patients resulted in a higher total nutrient intake as compared to patients receiving standard postoperative care. These authors did not find any reduction in the rate of postoperative life-threatening complications or in mortality during hospitalisation (92). However, over the first six months postoperatively, mortality in tube fed patients was significantly lower than in the control group (92).

In two studies, combined nutritional intervention by tube feeding or parenteral feeding and ONS was evaluated. Sullivan et al. (93) found no reduction in length of stay, no improvement of activities of daily living, nor a reduction in postoperative complications and mortality in patients receiving tube feeding combined with ONS. Eneroth et al. (84) showed that intravenous feeding combined with ONS reduced the number of postoperative complications, but not in length of stay and mortality.

### **Support by a dietetic assistant as nutritional intervention**

Within the last decade, dietetic or nutritional assistants have been introduced in some hospitals as a part of the nutritional care. A dietetic or nutritional assistant is a person who ensures that hospitalised patients have a good and healthy nutritional intake, who assists the patient in choosing suitable meals from the hospital menu, and who orders nutritional supplements when necessary. Duncan et al. (90) have investigated the effect of additional support from dietetic assistants on postoperative clinical outcomes

in hip fracture patients. The dietetic assistants in this trial were also sitting with the frailest patients while they were eating to encourage them and feeding them if necessary, in addition to the previously mentioned tasks. Results showed an improved energy intake and an improved intake of nutritional supplements in hip fracture patients who received support from dietetic assistants, compared to patients receiving usual care. With respect to nutritional status, the patients receiving dietetic support showed a significant attenuation of the decrease in mid-arm circumference which was found in patients receiving usual care. Furthermore, the intervention group had a lower mortality rate. Non-significant favourable effects were reported for triceps skin fold thickness, weight, handgrip strength and biochemical parameters. No effect was found on length of stay or postoperative complication rates.

### **Overall effectiveness of nutritional supplementation in hip fracture patients**

In 2010, an update of a Cochrane Review entitled “Nutritional supplementation for hip fracture aftercare in older people” was published, summarising the results of RCTs on the effectiveness of nutritional supplementation (94).

In this Cochrane Review, the authors drew the following conclusions:

1. ONS has no proven effect on the reduction of length of stay or mortality.
2. However, it may reduce unfavourable outcomes such as postoperative complications and mortality.
3. Results from studies using tube feeding as nutritional intervention show that tube feeding, or the combination of tube feeding followed by ONS, may reduce length of stay and postoperative complications.
4. A higher intake of protein may reduce length of stay and the number of postoperative complications.

The authors of the Cochrane Review indicated the need to perform large, well-designed and adequately powered studies to evaluate the effectiveness of ONS with respect to functional status and quality of life in addition to nutritional status, postoperative complications, length of stay and mortality. Furthermore, they expressed the need to evaluate direct and indirect costs of nutritional supplementation in hip fracture patients.

## **ECONOMIC EVALUATION OF NUTRITIONAL INTERVENTION**

Within the past decades, economic evaluations of new treatments have gained more and more attention. The relevance and importance of economic evaluations has increased because of the continuous rising health care costs and the limited budgets available. As a consequence, new or additional treatments should not only be effective but also cost-effective, and policy makers and health insurance companies want to know how much a new intervention costs compared with current practice in addition to information on its effectiveness. However the importance of economic evaluations and the importance of malnutrition in elderly, previous research on costs and cost-effectiveness of nutritional support or intervention in elderly is scarce. The few studies

performed indicated that health care costs can be reduced by nutritional support in malnourished elderly (95-98). Kruiženga et al. (99) reported that nutritional screening and treatment of malnourished patients at an early stage of hospitalisation is cost-effective.

In the “Health Economic Report on Malnutrition in the UK” the British Association for Parenteral and Enteral Nutrition (BAPEN) has calculated based on the results of the RCTs by Delmi et al. (63) and Lawson et al. (98) that oral nutritional support in elderly orthopaedic patients resulted in a net saving in hospitalisation costs and complication costs as compared to usual care (97). The BAPEN society indicates that the cost saving can also be due to the transfer of patients to a rehabilitation setting. So far, no economic evaluation of nutritional intervention in elderly subjects after hip fracture has been performed next to an effectiveness evaluation (97).

## AIMS AND OUTLINE OF THIS THESIS

In this thesis, we present the first combined effectiveness and cost-effectiveness study of nutritional intervention in elderly subjects after hip fracture. The aim of this study was to assess the effect of an intensive dietary intervention, comprising a combination of dietetic counselling and ONS during hospitalisation and after discharge, on the nutritional status, total length of stay and health care costs in elderly subjects after hip fracture. We hypothesized that the combination of dietetic counselling and ONS in hip fracture patients would improve patients’ energy and protein intake, improve their nutritional status, reduce the number of complications and total length of stay in the hospital and rehabilitation clinics, and lower health care costs. The primary outcome measure was total length of stay in hospital and rehabilitation clinics including hospital readmissions. Secondary outcome measures, assessed at three and six months after hip fracture, were nutritional status, functional status, quality of life, complication rate and one-year mortality.

As described in **Chapter 2**, the study was designed as a RCT; this chapter provides details about patient recruitment, the nutritional intervention, usual care, and the methods used for the effect evaluation and economic evaluation. In **Chapter 3**, the effects of the nutritional intervention on length of stay, postoperative complications, functional status, quality of life and mortality are presented. **Chapter 4** describes the effects of the nutritional intervention on nutritional intake and nutritional status, and **Chapter 5** the cost-effectiveness of the nutritional intervention. Finally, in **Chapter 6**, we discuss the findings of this thesis as well as strengths and limitations, and give recommendations for future research.

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## Chapter 2

# **Efficacy and cost-effectiveness of nutritional intervention in elderly after hip fracture: design of a randomised controlled trial**

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## **ABSTRACT**

### **Purpose**

Hip fracture patients often have an impaired nutritional status at the time of fracture, which can result in a higher complication rate, prolonged rehabilitation time and increased mortality. A study was designed to evaluate the effect of nutritional intervention on nutritional status, functional status, total length of stay, postoperative complications and cost-effectiveness.

### **Methods**

Open-labelled, multi-centre, randomised controlled trial in hip fracture patients aged 55 years and above. The intervention group receives dietetic counselling (by regular home visits and telephone calls) and ONS for three months after surgery. The control group receives usual dietetic care as provided by the hospital. Outcome assessment is performed at three and six months after hip fracture.

### **Discussion**

Patient recruitment has started in July 2007 and has ended in December 2009. First results are expected in 2011.

## INTRODUCTION

In the elderly, the incidence of hip fractures is high and it will increase in the nearby future due to the changes in the age demographics, the increased life expectancy and the continuous improvement of health care (1, 2). Hip fractures are one of the most common reasons for hospital admission and transfers to nursing home (3). Only 37% of the hip fracture patients will return to their pre-fracture functional status, leading to high health care costs and a major burden on health care utilization. These costs are not only determined by acute hospital costs, but even more by the long term costs such as recovery in rehabilitation clinics, the need for home care and the increased burden on informal care givers (4, 5).

At the time of hospitalisation for hip fracture, the prevalence of malnutrition ranges from 42% (6) to 63% (7). Poor nutritional status in hip fracture patients is associated with impaired muscle function, disability (8), loss of independency, lower mental function, decreased quality of life (8), delayed wound healing, higher complication rate (9, 10), prolonged rehabilitation time (8, 9, 11) and increased mortality both during and after hospital admission (9, 12-16). During hospital admission, the nutritional status can deteriorate further due to increased energy expenditure caused by metabolic stress, combined with a low intake due to the lack of appetite, nausea and psychological factors.

In the past decades, several studies have been conducted to determine the effectiveness of various types of nutritional intervention in elderly hip fracture patients on the length of stay, mortality, complications, nutritional and functional status. Results of these studies are inconsistent and the evidence for nutritional supplementation remains limited (17). ONS is the simplest type of nutritional intervention for hip fracture patients to improve the energy and protein intake and nutritional status, although compliance is often poor (18). Personal attention from a dietetic assistant can improve compliance with and tolerance of nutritional supplements (19) and help to establish a prolonged effect of the nutritional intervention.

The aim of the present study is to investigate the effect of intensive dietary intervention, comprising a combination of dietetic counselling and ONS during hospitalisation and after discharge, on the nutritional status, total length of stay and health care costs after hip fracture. We hypothesize that the combination of dietetic counselling and ONS in hip fracture patients will improve patients' energy and protein intake, improve their nutritional status, reduce the number of complications and total length of stay in the hospital and rehabilitation clinics, and lower health care costs.

## **METHODS**

### **Study design, general outline and randomisation**

Figure 1 shows the design of the study, which is an open-label, randomised controlled, multi-centre trial. Patient allocation to intervention or control group is performed after stratification for hospital, gender, and age (55-74 years vs. 75 years and above). Patients allocated to the intervention group receive dietetic counselling and ONS for 3 months following surgery. The control group receives usual nutritional care. Patients are enrolled within 5 days after surgical treatment of hip fracture, and baseline measurements are performed immediately after enrolment. Outcome measurements are performed at the patient's home at three and six months following hip fracture. The study has been approved by the Medical Ethical Committee of Maastricht University Medical Centre and Maastricht University and is conducted according to the Declaration of Helsinki.

### **Study population and recruitment of the study population**

For patient recruitment, a daily inventory is made of hip fracture patients admitted to the surgical and orthopaedic wards of three hospitals in South-Limburg in The Netherlands: Maastricht University Medical Centre, Maastricht; Atrium Medical Centre, Heerlen; and Orbis Medical Centre, Sittard. Based on this inventory, eligible candidates are invited to participate and written informed consent is obtained within 5 days after surgery. Inclusion criteria are aged 55 years and above and hospital admission for surgical treatment of hip fracture. Patients are excluded if they have a pathological or periprosthetic fracture; disease of the bone metabolism (e.g. Paget's disease, Kahler's disease, hyperparathyroidism); life expectancy of less than 1 year due to underlying disease (e.g. cancer); use oral nutritional supplements before hospital admission; are unable to speak Dutch; live outside the region of South-Limburg, or are bedridden before the hip fracture. Patients who suffer from dementia or who are cognitively impaired according to the Abbreviated Mental Test (AMT) (a score of less than 7) are also excluded (20, 21).

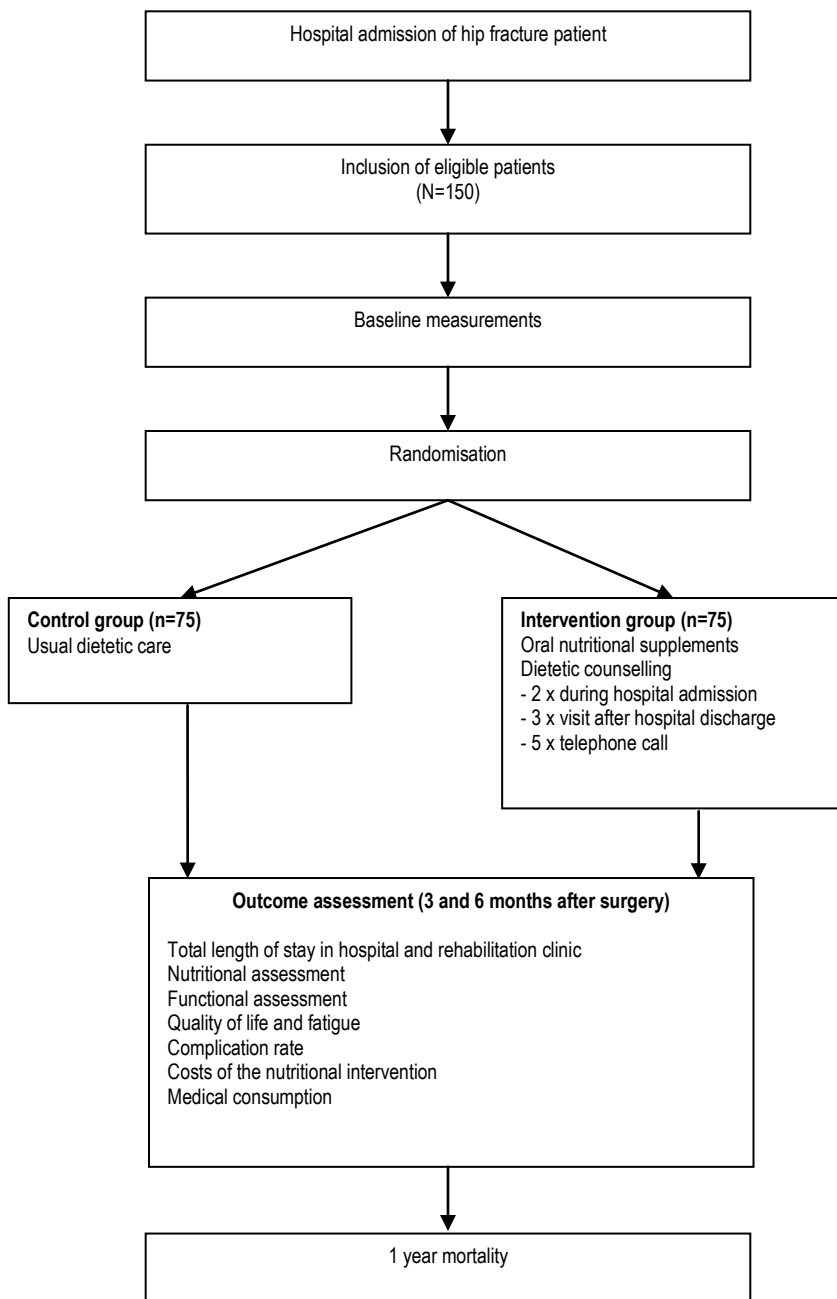


Figure 1 - Study design

**Nutritional intervention**

The nutritional intervention is a combination of dietetic counselling and oral nutritional supplements for three months. The intervention starts during hospital admission and continues after discharge during the stay at the rehabilitation clinic or at the patient's home. During hospitalisation, the study dietician visits the patient twice. At the first visit, two to five days after surgery and immediately after baseline measurements, the dietician interviews the patient regarding medical and social status, and pre-fracture mobility. The dietician also performs a 24-hour recall and takes a general dietary history of the patients' diet before hospitalisation. Next, the patient receives the nutritional supplement, a milk-based supplement providing 2.1 MJ (500 kcal) and 40 g of protein. The dietician advises the patient on the consumption of the supplement and arranges extra care or services to optimize the food intake if necessary. Before hospital discharge, the dietician visits the patient for the second time. During this visit, a 24-hour recall is performed and the consumption of the nutritional supplement is evaluated. Furthermore, arrangements are made to continue the dietetic advice and the consumption of the nutritional supplement at home or during the stay at the rehabilitation clinic. At home or during the stay in a rehabilitation clinic, the dietician visits the patient three times (one week, two weeks and six weeks after discharge) and makes five telephone calls with the patient (three, four, five, eight and ten weeks after discharge). During these visits, food intake and supplement use is assessed by a 24-hour dietary recall, and tailor-made dietetic advice is given to optimize the amount and composition of the diet. As soon as the patient meets nutritional requirements with a normal diet, the use of the nutritional supplement is stopped. Compliance with the nutritional supplement is evaluated by the 24-hour dietary recalls, patients' registration of the consumption in a diary and by collecting the capsules of the cans of the nutritional supplement during the home visits.

**Usual care**

Patients allocated to the control group receive usual care as provided in the hospital, rehabilitation clinic or at home, i.e. dietetic care or nutritional supplements are only provided on demand of the medical doctor in charge.

**Outcome assessment**

The primary outcome measure is total length of stay in hospital and rehabilitation clinic including hospital readmissions. Secondary outcome measures, assessed at three and six months after hip fracture, are nutritional status, functional status, quality of life, complication rate and one-year mortality.

Assessment of nutritional status includes total food and supplement intake, measurement of body composition, muscle strength and biochemical parameters in blood. Anthropometric measurements are body weight, height, thickness of biceps, triceps, sub scapula and supra-iliac skin fold, and circumference of mid-arm, waist and hip. Body composition is measured by bio-electrical impedance spectroscopy. Biochemical parameters include albumin, pre-albumin, CRP, haemoglobin and hematocrit in blood.

Functional status is measured by the Groningen Activity Restriction Scale (GARS) (22), which assesses disability with regard to (instrumental) activities of daily living, and by the Harris Hip Score to evaluate changes in hip function.

Quality of life is measured using the EuroQoL (23, 24) and the Medical Outcomes Study 36-item Short-Form Health Survey (25, 26). Mental state and depression are assessed by the Mini-Mental State Examination (MMSE) and the Hospital Anxiety and Depression Scale (HADS) (27, 28). To measure fatigue, the Checklist Individual Strength (CIS) (29) is used.

### **Confounders**

Pre-fracture information on co-morbidity, medication use and fracture history is obtained by interviewing the patient. Information on type of hip fracture, surgical treatment, admission and discharge dates, and post-operative complications are obtained from medical charts.

### **Economic evaluation**

The costs analysis will compare the costs of the nutritional intervention and the usual care over a 6-month period (30). Medical and non-medical costs are obtained from a 3-month retrospective standardized costing questionnaire. Health care costs will be estimated according to the Dutch guideline for cost-analysis in health care research (31). Incremental costs between the strategies will be related to a difference in outcome during 6 months follow up and being expressed in a incremental cost-effectiveness ratio. Statistical uncertainty will be assessed using bootstrap simulations (32).

### **Process evaluation**

A process evaluation is carried out to evaluate whether the nutritional intervention follows the protocol, with regard to the dietetic counselling and the consumption of the nutritional supplement. The feasibility of the nutritional intervention program is evaluated through summative evaluation with the identified stakeholders being patients and health care providers (medical doctors, dieticians, nurses). Experiences and opinions on feasibility, barriers and stimulating or facilitating factors for implementing the nutritional intervention in the transmural care are identified from the stakeholders' perspective. Data are collected by structured interviews with patients and in-depth interviews in a representation of patients and health care providers. A subsample of health care providers is asked to participate in a focus group meeting. The results of the process evaluation will be used as a basis for successful implementation of the nutritional intervention program in the transmural care for hip fracture patients.

### **Sample size / power calculation**

Nutritional intervention in hip fracture patients can result in an estimated reduction in total length of hospital and rehabilitation stay by 31.3% (SD: 59.0%). A sample of 75 patients per treatment arm is sufficient to detect this effect with a power of 90% and a

two tailed alpha of 0.05. To detect a between-group difference in weight of 2.13 kg (SD: 3.72 kg), a number of 61 patients per treatment arm is sufficient using the same power and alpha.

### **Statistical analysis**

The intervention effects of primary and secondary outcome measures will be analyzed according to the intention-to-treat principle. In addition, a secondary per protocol analysis will be performed in patients with adequate compliance. After initial univariate analyses of differences in the primary outcome between the intervention and control group, multivariate analyses will be used to adjust for potential confounders such as age, gender, baseline values of nutritional status, physical disability, co-morbidity, and mental state including depression.

## **DISCUSSION**

Patient recruitment has started in July 2007 and has ended in December 2009. Follow-up of the patients is to be completed in June 2010, except for data of one-year mortality. First results are expected in 2011. We expect that this study will answer the question whether nutritional intervention in hip fracture patients improves their nutritional and functional status, resulting in a shorter length of stay in hospital and rehabilitation clinics, fewer postoperative complications, lower mortality, and cost-effectiveness.

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## Chapter 3

# Effect of nutritional intervention on length of stay, postoperative complications, functional status and mortality in elderly subjects after hip fracture: a multi-centre randomised controlled trial

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## **ABSTRACT**

### **Objective**

To assess whether nutritional intervention in elderly hip fracture patients reduces length of stay, postoperative complications, and one-year mortality rate, and improves functional status and quality of life.

### **Design**

Open-label, multi-centre randomised controlled trial.

### **Setting**

Three hospitals in South-Limburg, the Netherlands.

### **Interventions**

Patients allocated to the intervention group received regular dietetic counselling (10 home visits and/or telephone calls) and ONS for three months postoperatively. Patients allocated to the control group received care as usual.

### **Main outcome measures**

Primary outcome measure was total length of stay in hospital and rehabilitation clinic. Secondary outcome measures were functional, mental and cognitive status, quality of life and complications over six months post-surgery, as well as one-year mortality.

### **Results**

Of 152 patients enrolled, 73 were randomised to the intervention group and 79 to the control group. Total length of stay was comparable in both groups (36 days intervention vs. 38 days control), as were length of stay in hospital (11 days intervention vs. 10 days control) and in rehabilitation clinic (44 days in both groups). At three and six months postoperatively, no significant effect of nutritional intervention on secondary outcomes was detected.

### **Conclusions**

Intensive nutritional intervention comprising dietetic counselling and ONS for three months after hip fracture surgery did not influence length of stay, postoperative complication rate, one-year mortality, functional, mental, and cognitive status, or quality of life.

## INTRODUCTION

In the Netherlands, as well as in other countries, the incidence of hip fractures in the elderly is high and it is expected to increase in the nearby future. Hip fractures are one of the most common reasons for hospital admission and transfer to nursing facilities in the elderly (1). After hip fracture, only 37% of the patients returns to their pre-fracture functional status leading to high health care costs and a major burden on health care utilization (2).

At hospital admission, hip fracture patients can have a poor nutritional status which can deteriorate further during hospitalisation because of a spontaneous reduction in food intake due to nausea or a lack of appetite (3-8). A poor nutritional status in hip fracture patients has been reported to be associated with an impaired muscle function, disability, loss of independency, impaired cognitive function, decreased quality of life, delayed wound healing, a higher complication rate after surgery, a prolonged rehabilitation time, and an increased mortality both during hospitalisation and afterwards (6, 7, 9-15).

In the past decades, several studies have been conducted to determine the effect of various types of nutritional supplementation on the length of stay, postoperative complications, functional status, and mortality. Some studies indicated that ONS in geriatric hip fracture patients can reduce length of stay in hospital or rehabilitation clinic (5, 13, 16). ONS has also been reported to improve activities of daily living at six months postoperatively (17), to reduce the number of postoperative complications (5, 16-20), and to reduce mortality after hip fracture (5, 20-22). In contrast to these positive results, several studies failed to show a significant effect of nutritional intervention on length of stay (18, 21, 22), functional status (21, 23), postoperative complications (16, 18), or mortality (21, 23). Suboptimal compliance with ONS may be an explanation for these disappointing results. Duncan et al. (22) suggested that personal attention from a dietetic assistant could improve compliance with ONS and nutritional recommendations. In a recently updated Cochrane Review (24) it was concluded that the overall evidence for the effectiveness of ONS in elderly hip fracture patients remains limited, and that adequately powered studies should be set up to investigate the role of ONS and dieticians or extra staff providing feeding assistance.

The aim of the present study was to assess the effect of intensive dietary intervention comprising combined dietetic counselling and ONS on the total length of stay in hospital and rehabilitation clinic in elderly subjects after hip fracture. Secondary aims were to investigate the effect on postoperative complications, one-year mortality, functional status, and quality of life. We hypothesized that the nutritional intervention would reduce total length of stay, postoperative complications and one-year mortality, and improve functional status and quality of life as compared to usual care.

## **MATERIALS AND METHODS**

### **Subjects**

Eligible patients were admitted to one of the participating hospitals for surgical treatment of hip fracture, and aged 55 years and above (25). Patients were excluded if they had a pathological or periprosthetic fracture; a disease of bone metabolism (e.g. Paget's disease, Kahler's disease, hyperparathyroidism); a life expectancy of less than 1 year due to underlying disease; used oral nutritional supplements before hospital admission; if they were unable to speak Dutch; lived outside the region; or were bedridden before the hip fracture. Patients were also excluded if they had dementia or were cognitively impaired, defined as a score of < 7 on the Abbreviated Mental Test (AMT) as assessed before inclusion (26).

### **Study design**

The study was designed as an open-label multi-centre, randomised controlled trial (25). For patient recruitment, a daily inventory of hip fracture patients admitted to the surgical and orthopaedic wards of three hospitals in South-Limburg in The Netherlands: Maastricht University Medical Centre (Maastricht), Atrium Medical Centre (Heerlen), and Orbis Medical Centre (Sittard) was made. Eligible patients were invited to participate and written informed consent was obtained within five days after surgery. After informed consent, baseline measurements were performed by a trained researcher. Following baseline measurements, the patient was randomised according to a computer-generated random-number sequence list after pre-stratification for hospital, gender and age (55-74 years vs. 75 years and above). The researcher made a telephone call to an independent research assistant who took a sequentially numbered and sealed envelope, and informed the researcher to which group the patient had been allocated. After randomisation, all patients were visited by a study dietician who evaluated nutritional intake. Then, patients allocated to the intervention group received dietetic counselling and ONS for three months after fracture, whereas patients in the control group received usual nutritional care. All patients were discharged from the hospital to either a rehabilitation clinic or to the patient's home with home care, or to the nursing home or home for the elderly if they had lived there before hospitalisation. Three and six months postoperatively, the trained researcher performed the outcome measurements, and one of the study dieticians took a 24h recall to evaluate nutritional intake at the patient's home.

The study was approved by the Medical Ethical Committee of Maastricht University Hospital and Maastricht University (06-3-098) and conducted according to the Declaration of Helsinki (verified in Seoul, 2008).

### **Sample size**

A sample size of 75 patients per treatment arm was calculated to be sufficient to detect a clinically relevant reduction in total length of stay in hospital and rehabilitation clinics of 30% (SD 59%) with a power of 90% and a two-tailed alpha of 0.05 (5, 13, 16, 27).

## Nutritional intervention

The nutritional intervention was a combination of dietetic counselling and consumption of a multi-nutrient ONS for a period of three months. The dietetic counselling included the following elements: checking the patients' food habits and preferences, identifying possible deficiencies in nutrient intake, and checking practical difficulties with eating during hospitalisation, as well as in the home situation. The nutritional intervention started during hospital admission and continued in the rehabilitation centre and/or at the home if applicable.

During hospitalisation, patients were visited twice by a dietician. At the first visit, the dietician took a 24h recall of the patient's diet during hospitalisation. To optimize food intake, all patients received an energy- and protein-enriched diet and recommendations were given with regard to choice, quantity and timing of food products, the ONS, and increasing the intake of energy-dense and protein-rich products both within and in-between meals. Nutritional requirements for energy were calculated according to Harris-Benedict equation (28), using a factor of 20% for surcharge for metabolic stress due to hip fracture, and surcharge for activity, desired increase of body weight and/or energy-losses if indicated, with a maximum surcharge of 40%. Daily protein requirement was calculated as body weight x 1.5 g protein (29). As a part of the energy- and protein enriched diet, all patients were advised to consume two bottles of an ONS daily in-between the main meals. The nutritional supplement was a milk-protein based ONS (Cubitan, N.V. Nutricia, Zoetermeer, The Netherlands) providing 2.1 MJ (500 kcal) and 40 g of protein per two bottles. If a patient did not tolerate the milk-based supplement, a yoghurt-style or juice-style supplement (Nutridrink Yoghurt Style or Nutridrink Juice Style, N.V. Nutricia, Zoetermeer, The Netherlands) was offered. Furthermore, the dietician made the necessary arrangements in order to solve any problems, e.g. feeding problems, in collaboration with the medical and nursing staff. The dietician also assisted the patient in choosing the preferred taste of the ONS.

At the second visit during hospitalisation, seven to eight days after surgery, the dietician evaluated nutritional intake, including the intake of ONS using a 24h recall, and gave individually tailored advice to optimize dietary intake. During this visit, the transfer of the patient to the rehabilitation centre or the patient's home was prepared by evaluating the patient's physical restrictions with regard to nutritional care, i.e. purchasing food products and the preparation of meals, and by making arrangements to enable adequate food intake, e.g. support of informal caregivers (family, friends or neighbours) and delivery of information on meal services. The dietician also informed the general practitioner and the informal care givers (if present), as well as the nursing staff and the dietician or nutritional assistant of the rehabilitation centre.

After hospital discharge, the dietician visited each patient three times (1, 2 and 6 weeks after discharge) at the patient's home or in the rehabilitation centre, to evaluate dietary intake, including the intake of the ONS, nutritional care, and to give dietary advice if necessary. If the patient was still unable to meet nutritional requirements by normal food intake, continuation of the ONS consumption was advised. In addition, in-between these face-to-face contacts, weekly telephone calls were made (3, 4, 5, 8, and 10 weeks after discharge) to evaluate both the dietary

intake and the intake of the ONS by a 24h recall. If necessary, a telephone call was replaced by a home visit. . As the patient's diet increased towards normal nutritional requirements (30), the consumption of the ONS was gradually decreased and the patient was advised to maintain a healthy diet (31).

### **Usual care**

Patients allocated to the control group received usual care as provided in the hospital, rehabilitation clinic or at home, i.e. dietetic care or ONS were only provided on demand of the medical doctor in charge.

### **Outcome measurements**

#### ***Primary outcome measurements***

Total length of stay in hospital and rehabilitation clinic was set as the primary outcome measure. Dates of admission and discharge from hospital and rehabilitation clinics were obtained from the medical charts. Length of stay was measured for a period of 6 months.

#### ***Secondary outcome measurements***

Postoperative complications were obtained retrospectively from the medical charts, and were divided in surgery-related complications (surgical bleeding, wound infection, dislocation of the prosthesis or loosening or breakout of the osteosynthesis material) and general medical complications, such as urinary tract infections, pulmonary infection, thrombo-embolism, surgical bleeding, sepsis, pressure ulcers, delirium, cardiovascular disease, neurological disease, and anaemia.

Survival status and date of decease was obtained from medical records of general practitioners.

All questionnaires were filled out by patients at baseline (i.e. shortly after hip fracture surgery), and three and six months postoperatively, except for the Checklist Individual Strength (CIS) which was only filled out at three and six months postoperatively. With regard to the questionnaires filled out at baseline, the patient was asked to refer to his/her status before hospitalisation, except for the Mini Mental State Examination (MMSE) which had to be filled out for the current situation at the time of measurement. At three and six months postoperatively, the current mental status, depression and anxiety state, functional status, fatigue state, and quality of life, were assessed with the questionnaires.

MMSE is a screening tool for cognitive impairment and was used to assess mental status (32, 33). MMSE scores range from 0 to 30, with a score of less than 24 indicating an impaired cognitive function (32, 33).

The Hospital Anxiety and Depression Scale (HADS) was used to assess symptoms of depressive and anxiety states (34). The HADS contains 14 items, scored on a 4-point Likert scale, divided in a subscale assessing anxiety and a subscale assessing depression, each with scores ranging from 0-21, a higher score indicating a higher degree of being in a state of anxiety or depression (34).

Functional status and physical restriction were assessed using the Groningen Activity Restriction Scale (GARS) (35). GARS contains 28 items to assess disability in the domain of basic activities of daily living (11 items), and in household activities of daily living (7 items). All items are scored on a 4-point Likert scale with a higher score representing a higher level of disability (35).

CIS was used to assess fatigue (36). By filling the CIS, patients are asked to indicate how they felt during the last two weeks. The CIS is a questionnaire containing 20 items, scored on a 7-point Likert scale, covering four dimensions of fatigue: subjective fatigue, reduced concentration, reduced activity, and reduced motivation; higher scores represent a higher degree of fatigue (36).

Quality of life was measured using the Dutch version of the EuroQoL (37-39). The first part (EQ-5D-3L) asks the patient to make a statement on the degree of problems (no problem, some problems or major problems) he/she experiences with regard to mobility, self-care, usual activities, pain or discomfort, and anxiety or depression (37-39). The second part (EQ-VAS) asks the patient to rate his/her current health state on a VAS scale ranging from 0 to 100, where 0 represents the worst possible health status and 100 the best possible health status (37-39).

### **Confounders**

The following potential confounders of the association between the nutritional intervention and length of stay were recorded from the medical charts: type of fracture, type of surgery (osteosynthesis vs. hemi-arthroplasty), type of anaesthesia, American Society of Anaesthesiologists (ASA) score assessing the patients' physical status before surgery, medical history, and medication use. All hip fracture patients received daily physical therapy during hospitalisation, as well as in the rehabilitation clinic or at the patient's home.

### **Data analysis**

Statistical analysis was performed using SPSS 15.0 for Windows (SPSS Inc., Chicago, IL, USA). Baseline characteristics of both groups were analyzed using descriptive statistics. Normality of data was tested using the Komolgorov-Smirnov test. Normally distributed data are summarized as means  $\pm$  standard errors (SEM); not normally distributed data as median and range of scores. Data analysis was performed according to the intention-to-treat principle. Kaplan-Meier Curves and Cox proportional hazards models were fitted to assess the effect of the intervention on total length of stay in hospital and rehabilitation clinic, as well as length of stay in the hospital and rehabilitation clinic separately. Analyses to detect differences between both groups for secondary outcome measures were performed using analysis of covariance for continuous outcomes and logistic regression analysis for dichotomous outcomes, adjusting for the stratification variables (centre, gender, and age) and for the baseline value of the concerned outcome parameter (partially adjusted models). Next, multivariable adjusted models were fitted with additional adjustment for fracture type, neurological disease, rheumatoid arthritis, ASA score and health status before fracture. Since the results of the partially adjusted models and the fully adjusted models – based on multivariable modelling – were not appreciably different, only the fully adjusted

models are presented. The intervention effect over 3 and 6 months postoperatively was defined as the difference between the intervention and control group of the change from baseline to three months and six months postoperatively, respectively. P-values of  $< 0.05$  were considered to reflect statistically significant differences.

## RESULTS

### Participants and baseline characteristics

Between July 2007 and December 2009, 1304 hip fracture patients admitted to the surgical and orthopaedic wards of the participating hospitals were assessed for eligibility (**Figure 1**). Of the eligible patients, 895 (69%) did not meet the inclusion criteria and 257 (20%) patients refused to participate. Of the resulting 152 patients who gave informed consent, 73 were randomly allocated to the intervention group and 79 to the control group. During the three-month intervention period, seven patients (4 intervention, 3 control) passed away, and seven patients (3 intervention, 4 control) withdrew their participation, resulting in 138 patients for analysis (68 intervention, 72 control) at 3 months. During the follow-up period (3-6 months after surgery), another four patients (2 intervention, 2 control) passed away, and three patients (1 intervention, 2 control) withdrew their participation, resulting in 63 patients in the intervention group and 68 patients in the control group who completed 6 months of follow-up.

At baseline, both groups were comparable with respect to sex and age (**Table 1**), and in both groups the majority of patients were admitted to the hospital from their home situation (86% vs. 83%). In the intervention group, 69% were classified as ASA class II and 20% as ASA class III, compared to 61% ASA class II and 27% ASA class III in the control group. Rheumatoid arthritis was more prevalent in the intervention group (30% vs. 20%), whereas neurological diseases were less prevalent (23% vs. 35%). At the time of hospital admission, both groups were comparable with respect to biochemical parameters, time elapsed between hospital admission and hip fracture surgery, and duration of surgery. In both groups, the majority of the patients had a fracture of the medial neck of the femur (49% vs. 57%). However, in the intervention group as compared to the control group, more patients had received a gamma nail (51% vs. 30%) and fewer patients had a hemi-arthroplasty (26% vs. 38%). Both groups were comparable with respect to functional status, mental status, and anxiety and depression state assessed at baseline, but patients in the intervention group reported a better health status before hip fracture compared to the control group. All variables which differed between intervention and control group were included as covariates in the statistical analyses.

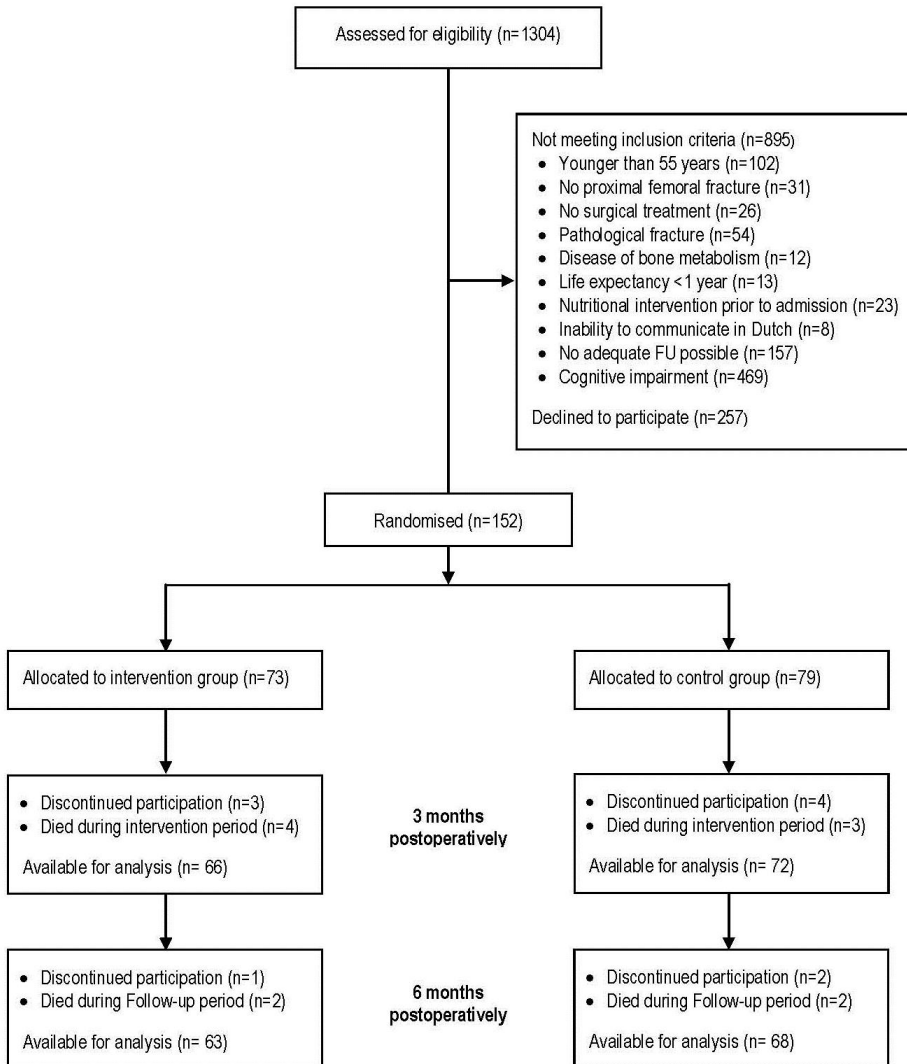


Figure 1: Study population flow chart

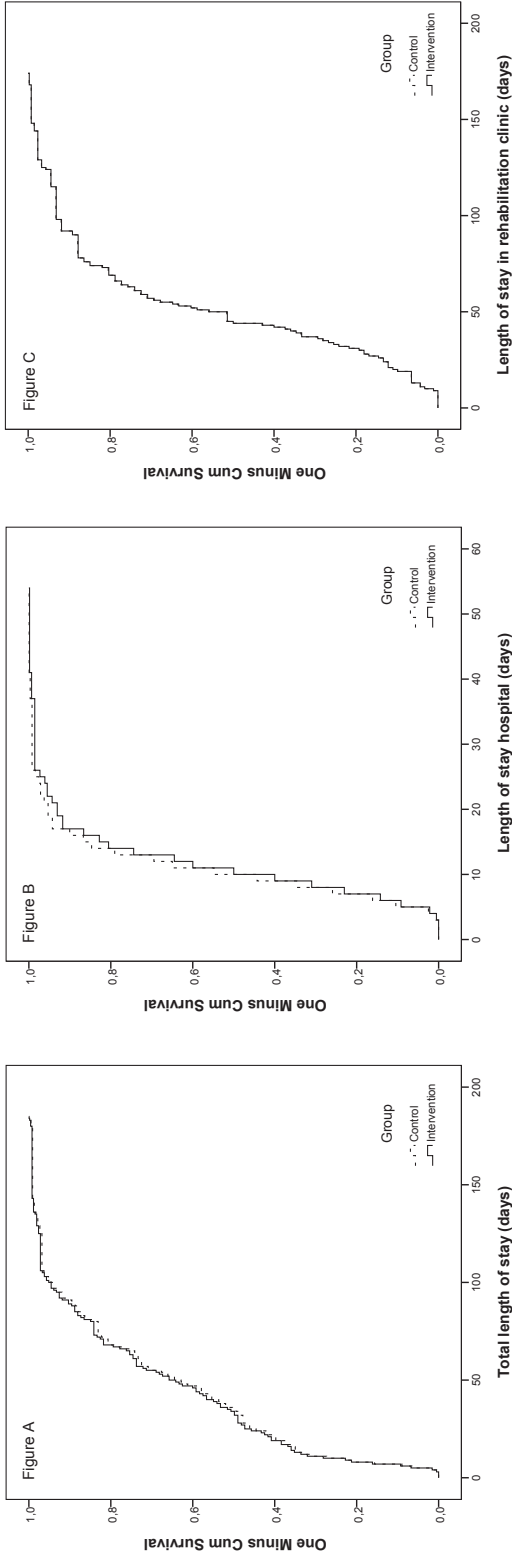
**Table 1: Baseline characteristics**

	Intervention group (N=73)		Control group (N=79)	
	N	(%)	N	(%)
<b>Sex</b>				
Female	54	(74)	54	(68)
Male	19	(26)	25	(32)
<b>Age</b>	<b>79</b>	<b>(55-93)</b>	<b>78</b>	<b>(57-94)</b>
<b>Type of residence before fracture</b>				
Home	63	(86)	66	(83)
Nursing home	2	(3)	4	(5)
Home for the elderly	8	(11)	7	(9)
Rehabilitation clinic / hospital	0	(0)	2	(3)
<b>Medical history</b>				
Diabetes mellitus	16	(22)	15	(19)
Neurological disease	17	(23)	28	(35)
COPD	4	(5)	6	(8)
Cardiovascular disease	40	(55)	40	(51)
Parkinson	2	(3)	2	(3)
Rheumatoid arthritis	22	(30)	16	(20)
Osteoporosis	9	(12)	9	(11)
Crohn's disease	5	(7)	9	(11)
<b>ASA classification</b>				
I	8	(11)	9	(11)
II	49	(69)	49	(61)
III	14	(20)	21	(27)
IV	0	(0)	1	(1)
<b>Biochemical parameters</b>	<b>Mean</b>	<b>± SEM</b>	<b>Mean</b>	<b>± SEM</b>
Haemoglobin (mmol/L)	8.2	± 0.1	8.0	± 0.1
Haematocrit (mmol/L)	0.39	± 0.01	0.38	± 0.01
Leucocytes (10E9/L)	9.7	± 0.4	11.8	± 1.4
Creatinine (µmol/L)	94.2	± 4.9	90.7	± 3.8
INR	1.1	± 0.05	1.1	± 0.04
<b>Fracture type</b>				
Medial neck	36	(49)	45	(57)
Pertrochanteric	32	(44)	33	(42)
Subtrochanteric	5	(7)	1	(1)
<b>Type of surgery</b>				
Gamma nail	37	(51)	24	(30)
Dynamic hip screw	6	(8)	11	(14)
Hemiarthroplasty	19	(26)	30	(38)
Total hip replacement	4	(5)	7	(9)
3 cannulated screws	7	(10)	6	(8)
Femoral nail	0	(0)	1	(1)
	<b>Median</b>	<b>Range</b>	<b>Median</b>	<b>Range</b>
Time between admission and surgery (hours)	18	0-60	19	1-173
Duration of surgery (minutes)	65	20-135	65	26-147
Functional status	25	18-58	28	18-65
Activities of daily living	14	11-32	14	11-42
Household activities of daily living	10	7-28	12	7-28
Cognitive status*	26	19-30	26	15-30
Anxiety state	3	0-15	3	0-18
Depression state	3	0-13	4	0-16
Health status before fracture	70	20-100	65	0-100

\*Data available for 52 patients in the intervention group and 60 patients in the control group

**Primary outcome measure**

Median total length of stay in hospital (including readmissions until 6 months postoperatively) and rehabilitation clinic was 36 days (range: 4-185 days) in the intervention group compared to 38 days (range: 3-183 days) in the control group. The median length of hospital stay was 11 days (range: 4-46 days) in the intervention group compared with 10 days (range: 3-54 days) in the control group. The median length of stay of the intervention group in the rehabilitation clinic was 44 days (range: 9-174 days) compared to 44 days (range: 10-168 days) in the control group. No significant differences in total length of stay ( $p=0.85$ ), in length of hospital stay ( $p=0.45$ ), or in length of stay in the rehabilitation clinic ( $p=0.99$ ) were detected. In the intervention group, 42 patients (57%) were discharged to a rehabilitation clinic and 31 (43%) to their home situation with home care if necessary, compared to 42 (53%) of the control group patients discharged to the rehabilitation clinic and 35 patients (44%) discharged to their home situation. As shown in **Figure 2**, no significant difference in length of hospital stay between both groups was detected.



**Figure 2:** Cox proportional hazard plots of total length of stay in hospital and rehabilitation clinic (A), length of stay in hospital (B) and length of stay in rehabilitation clinic (C) in intervention and control group. The x-axis represents length of stay (in days), the y-axis represents the cumulative percentage of patients discharged from hospital and/or rehabilitation clinic.

## Secondary outcome measures

### *Postoperative complications and hospital re-admissions*

Within the intervention group, 30 patients (40%) had at least one postoperative complication compared to 35 patients (44%) in the control group. As shown in **Table 2**, fracture-related complications (i.e. independent from the nutritional intervention) such as wound infection, dislocation of the implant and surgical revision were more prevalent in the intervention group compared to the control group; however, the difference was only statistically significant for dislocation of the implant ( $p=0.01$ ). These patients underwent surgical revision of the implant. Other postoperative complications such as urinary tract infections, respiratory infections, pulmonary embolism, pressure ulcers, delirium and postoperative anaemia were not significantly different between both groups.

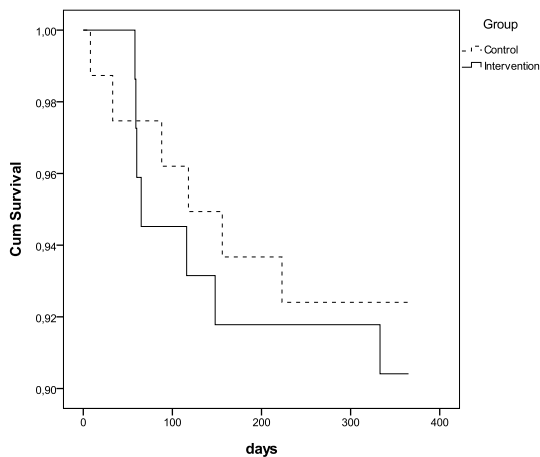
Fourteen patients in the intervention group and ten patients of the control group were re-admitted to the hospital one or more times (Table 2). In each group, eight patients were re-admitted to the hospital once; in all cases because of fracture related reasons (pain, dislocation or surgical revision). Five patients were re-admitted twice; four in the intervention group and one patient in the control group, with pain, dislocation and surgical revision of the osteosynthesis material as reasons for hospitalisation; one patient in the intervention group was re-admitted twice because of cholecystectomy. Three patients were re-admitted three times: two patients in the intervention group and one patient in the control group, in all cases because of general deterioration in health status of the patient. These frequencies of hospital readmissions were not significantly different between both groups.

**Table 2: Hospital readmissions and postoperative complications in intervention and control group**

	Intervention group			Control group		
	N	Median	Range	N	Median	Range
<b>Hospital readmissions</b>						
One hospital readmission	8	9	1-29	8	7	1-16
Two hospital readmissions	4	12.5	2-27	1	25	
Three hospital readmission	2	35.5	26-45	1	105	
<b>Postoperative complications</b>						
	<b>N</b>	<b>(%)</b>		<b>N</b>	<b>(%)</b>	<b>p-value</b>
Wound infection	5	(6.8)		3	(3.8)	0.40
Dislocation of the hip implant	8	(11.0)		1	(1.3)	<b>0.01</b>
Surgical revision of osteosynthesis material	13	(17.8)		6	(7.6)	0.05
Urinary tract infection	5	(6.8)		7	(8.9)	0.47
Other infections	5	(6.8)		2	(2.5)	0.20
Respiratory infection	2	(2.7)		2	(2.5)	0.94
Pulmonary Embolism	0	(0.0)		2	(2.5)	0.17
Sepsis	1	(1.4)		0	(0.0)	0.30
Surgical bleeding	3	(4.1)		2	(2.9)	0.59
Pressure ulcers	4	(5.5)		2	(2.5)	0.35
Myocardial infarction	0	(0.0)		1	(1.3)	0.34
Congestive heart failure	1	(1.4)		0	(0.0)	0.30
Cerebrovascular accident	0	(0.0)		1	(1.3)	0.34
Delirium	5	(6.8)		5	(6.3)	0.90
Anaemia	8	(11.0)		13	(16.5)	0.64

### **Mortality**

One patient of the control group died during hospital admission. In the period between hospital discharge and the end of the follow-up period (6 months postoperatively), nine patients (6 intervention, 3 control) died. Between six months and one year after hip fracture, two patients passed away (1 intervention, 1 control), resulting in a total one-year mortality of 7 patients (10%) in the intervention group and 6 patients (8%) in the control group. As shown in **Figure 3**, mortality over the first year after hip fracture was not significantly different between both groups ( $p=0.80$ ).



**Figure 3:** Survival plot of one-year mortality in intervention and control group. In the intervention group 7 patients passed away, in the control group 6 patients.

### **Functional, mental and cognitive status, and quality of life**

At three and six months postoperatively, we found no significant intervention effect on activities of daily living, household activities of daily living, total functional status, and mental, and cognitive status (**Table 3**). At six months postoperatively, a beneficial intervention effect on the domain reduced motivation was found ( $p=0.009$ ). Furthermore, no statistically significant effect of the intervention on quality of life assessed by means of the EuroQoL could be identified at three and six months postoperatively.

Table 3: Intervention effect on mental and functional status and fatigue at three months and six months postoperatively<sup>a</sup>

	3 months postoperatively				6 months postoperatively					
	N	Estimate	SEE	95% CI	p-value	N	Estimate	SEE	95% CI	p-value
<b>Groningen Activity Restriction Scale</b>										
Functional status	126	1.39	1.76	-2.11 - 4.89	0.37	123	2.27	1.71	-1.11 - 5.66	0.19
Activities of daily living	127	0.85	0.94	-1.01 - 2.70	0.37	123	1.32	0.93	-0.53 - 3.16	0.17
Household activities of daily living	126	0.52	1.04	-1.54 - 2.58	0.62	123	0.95	0.87	-0.98 - 2.88	0.34
Cognitive status	100	0.82	0.46	-0.09 - 1.73	0.08	98	0.53	0.39	-0.24 - 1.30	0.18
<b>Hospital Anxiety and Depression Scale</b>										
Anxiety	121	-0.18	0.67	-1.51 - 1.15	0.79	112	0.01	0.71	-1.40 - 1.41	0.99
Depression	121	-0.76	0.72	-2.18 - 0.66	0.29	112	-1.37	0.79	-2.93 - 0.19	0.08
<b>Checklist Individual Strength</b>										
Subjective fatigue	106	-0.84	1.54	-3.89 - 2.22	0.59	102	0.47	1.47	-2.87 - 2.97	0.97
Concentration	107	-1.15	1.81	-4.45 - 2.45	0.53	102	-1.13	1.81	-4.72 - 2.46	0.53
Activity	105	0.06	1.25	-2.42 - 2.54	0.96	101	-0.99	1.30	-3.57 - 1.59	0.45
Motivation	106	-0.94	1.46	-3.85 - 1.96	0.36	102	-4.03	4.52	-7.05 - -1.01	0.01
Total score	105	-2.62	4.66	-11.89 - 6.65	0.58	101	-5.58	4.59	-14.70 - 3.54	0.23
<b>Quality of Life</b>										
Mobility	115	1.59	3.08	0.59 - 4.30	0.36	113	0.64	2.77	0.22 - 5.33	0.41
Self care	115	0.96	3.08	0.40 - 2.32	0.92	113	0.99	2.77	0.39 - 5.66	0.99
Usual activities	115	1.68	3.08	0.70 - 3.99	0.24	113	1.02	2.77	0.42 - 5.66	0.96
Pain / Discomfort	115	1.44	3.08	0.53 - 3.92	0.48	113	0.55	2.77	0.22 - 5.33	0.19
Anxiety / Depression	115	2.76	3.08	0.58 - 8.96	0.09	113	0.92	2.77	0.37 - 5.33	0.92
Current health status	115	1.47	3.08	-4.65 - 7.58	0.48	113	0.17	2.77	-5.33 - 5.66	0.95

<sup>a</sup> Values represent the difference in change from baseline to three months or six months postoperatively between the intervention and control group, adjusted for hospital, gender, age, fracture type, neurological disease, rheumatoid arthritis, ASA score, and baseline value of the concerned variable

## DISCUSSION

Nutritional intervention has been proposed as an approach to improve clinical outcome in elderly hip fracture patients. However, despite several decades of research, the overall evidence for the effectiveness of ONS in elderly hip fracture patients with respect to length of stay and functional outcome is still limited (24).

In the present study, we assessed the effect of an intensive nutritional intervention, combining frequent dietetic counselling and ONS over three months after hip fracture, on total length of stay in hospital and rehabilitation clinic, postoperative complication rate, one-year mortality rate, functional, mental, and cognitive status, and quality of life in elderly subjects. Results showed that the nutritional intervention had no significant effect on total length of stay in hospital and rehabilitation clinic, nor on length of stay in hospital or rehabilitation clinic separately. Also, we failed to detect a significant effect of the nutritional intervention on the overall complication rate and the type of complications. Finally, at three and six months postoperatively, no significant intervention effect was detected on functional status, mental status, cognitive status, anxiety and depression, or quality of life; only reduced motivation, as a sub-domain of the Checklist Individual Strength, showed a favourable intervention effect at six months postoperatively. Furthermore, mortality over the first year after hip fracture was similar in both groups.

Our study is the first multicentre randomised controlled trial combining intensive dietetic counselling with ONS. The high frequency of contacts (10 times over 3 months) between the dietician and the patient allowed us to quickly anticipate in case of nutritional problems, postoperative complications or hospital re-admissions. As a result, the compliance with dietetic advice and ONS in our study was very high (40). Our study is also the first study in which nutritional intervention was continued for a period of three months after hip fracture. In earlier studies, nutritional intervention was limited to the hospital or to the rehabilitation setting. This long intervention period gave us the opportunity to follow the patient during the complete trajectory from hospitalisation throughout rehabilitation, regardless of the location of rehabilitation (rehabilitation clinic or at home). Validity of data was safeguarded by the prospective collection of information on postoperative complications and hospital readmissions.

Our unexpected findings raise the question why, despite the intensive and long-term approach towards nutritional intervention and high compliance by the patients, we did not find any reduction in length of stay in hospital and rehabilitation clinic (5, 13), postoperative complications (5, 20) nor an improvement in functional status (17) or quality of life (17) as opposed to previous studies, which were performed during another decade (5, 13), which were limited to malnourished patients (13), or which were performed within another country with different organisation of health care.

Several potential explanations can be put forward. First, over the past decades, the organization of health care has changed dramatically. Medical treatments, such as hip fracture surgery and recovery from hip fracture surgery, have become more and more standardized into formal guidelines and health care standards. For example, in the Netherlands, patients are discharged from hospital to a rehabilitation clinic or to the patient's home much faster than they used to be. Also, the actual time point of

discharge of an individual patient to a rehabilitation clinic is to a large extent determined by space limitations, resulting in a waiting list. The point of time at which a patient is discharged from hospital or rehabilitation clinic to his/her home depends on several factors. For instance, discharge of a patient to his/her home depends on housing conditions, such as the presence of stairs, the absence of medical aids or assistant devices such as a toilet raiser, and on necessary adaptations to get e.g. into the bathroom. The time point of discharge can also be determined by social factors, such as the presence of an informal care giver (e.g. spouse or children) who can assist in activities of daily living, in household activities, or in nutritional care such as purchasing food products and preparation of meals: if such basic conditions are fulfilled, the patient can be discharged faster compared to patients for whom formal home care must be organized. In fact, the time both in hospital and rehabilitation clinics tends to be standardized beforehand, with exceptions being avoided, which further limits the potential effect of nutritional intervention on length of stay in hospitals and rehabilitation clinics nowadays.

The above view is consistent with the recent report "Malnutrition in the elderly" published by the Health Council of the Netherlands (41). In this report, it is concluded that while various studies have demonstrated the existence of a link between malnutrition and mortality rate, it is not known whether a causal connection is involved. The Health Council questions the current approach to malnutrition in the elderly which is based on the view that the treatment of this condition is always worthwhile: part of elderly people who have experienced weight loss may also recover by receiving proper medical treatment without any contribution of supplementary nutrition. A better understanding of this issue is needed if malnutrition is to be dealt with effectively (41)

Several limitations of the present study should be mentioned. First, our negative result may be related to the rigorous design of a randomised controlled trial, which was performed according to strict GCP and ethical guidelines, with inherent informed consent and extensive outcome assessment, including quality of life questionnaires. The requirement of informed consent and questionnaire data led to strict in- and exclusion criteria. As a result, 68% of the patients who were screened for eligibility did not meet the inclusion criteria, mainly due to cognitive impairment; another 20% refused to participate. Additionally, the need for informed consent in a RCT may have led to the selection of patients with the best prognosis, attenuating the possible beneficial effect of nutritional intervention. The one-year mortality rate in our study population (8-10%) was quite low when compared with the average mortality rate of 25% in Dutch hip fracture patients, according to figures published by the Dutch Institute for Health Care Improvement (42), which supports the notion that our study population was apparently a relatively healthy subset of hip fracture patients. Second, because of the informed consent procedure, the nutritional intervention could only be started several days after hip fracture surgery, when the patients were fully conscious and had had sufficient time to discuss their participation in the study with relatives. By this delay, we may have missed valuable time in which the patient could have had rapid benefit from the ONS and/or dietetic advice: We found a favourable effect of the intervention on the sub domain "reduced motivation" of the Checklist Individual Strength. While this could be simply explained either as a false positive result or as a

placebo effect, this option may be too simplistic as this effect was only present at six months after fracture (i.e. three months after the end of the intervention), and was highly statistically significant ( $p=0.009$ ). We previously reported that the participants generally perceived the intervention as useful and valuable (40); especially, participants highly valued the individual tailoring of the nutritional intervention. It is therefore possible that the consistent attention of dieticians to factors which are not only relevant for improving the patients' diet, but also for their general well-being and comfort (e.g. organizing shopping, cooking etc.) may explain the increased motivation of this elderly patient group. If this is true, it would underscore the importance of individual attention in the rehabilitation trajectory of this patient group.

In conclusion, intensive nutritional intervention combining dietetic counselling and oral nutritional supplementation in a population of elderly subjects after hip fracture did not affect the total length of stay in hospital and rehabilitation clinic, postoperative complication rate, functional status, cognitive status, or quality of life. Whereas the concept of long-lasting and intensive dietetic counselling and nutritional support is both appealing and feasible (40), our results suggest that future research on nutritional intervention after hip fracture should focus more on the frail elderly.

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## Chapter 4

# Effects of nutritional intervention on nutritional intake and status in elderly subjects after hip fracture: a randomised controlled trial

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## **ABSTRACT**

### **Background & aims**

Hip fracture patients are often malnourished at hospitalisation and nutritional status can deteriorate further during admission. We investigated whether nutritional intervention combining dietetic counselling and oral nutritional supplementation improves nutritional intake and nutritional status in elderly subjects after hip fracture.

### **Methods**

Open-label multi-centre randomised controlled trial with patients in the intervention group receiving nutritional intervention comprising regular dietetic counselling and oral nutritional supplementation for three months. The control group received usual dietetic care. Nutritional intake and nutritional status were assessed at baseline during hospitalisation and at three and six months postoperatively.

### **Results**

One-hundred fifty-two patients were included; 73 were randomised to the intervention group and 79 to the control group. Three months postoperatively, dietary intake of fat, fatty acids, calcium and vitamins, as well as weight, BMI, supra-iliac skin fold thickness, and blood levels of vitamin C and 5-methyl-tetrahydrofolate had increased to a significantly larger extent in the intervention group compared to the control group. At six months postoperatively, only the increase of the supra-iliac skin fold thickness remained significantly different.

### **Conclusions**

Intensive dietetic counselling and oral nutritional supplementation for three months improved nutritional intake of both macro-and micro-nutrients, and induced weight gain in elderly hip fracture patients.

## INTRODUCTION

The incidence of hip fractures in the elderly is high, with a total number of 17941 reported cases in the Netherlands in 2007, and it is expected that the incidence will increase in the future (1, 2). Hip fractures are one of the most common reasons for hospital admission and transfers to nursing homes in the elderly (3).

An impaired nutritional status is not only a risk factor for hip fracture, but also a predictor of recovery after hip fracture (4). At the time of hospitalisation, the prevalence of malnutrition ranges from 42% (5) up to 63% (6) within hip fracture patients. During hospitalisation, dietary intake is often insufficient (7-13), due to a spontaneous reduction of food intake, lack of appetite, nausea or disliking hospital meals, resulting in further deterioration of nutritional status. A poor nutritional status among hip fracture patients has been reported to be associated with impaired muscle function, disability, loss of independence, lower mental function, decreased quality of life, delayed wound healing, a higher complication rate after surgery, prolonged rehabilitation time, and increased mortality both during and after hospital admission (7, 8, 10, 14-19).

Previous studies on the effect of nutritional intervention have shown that nutritional intervention with oral nutritional supplements (ONS) starting soon after hospital admission improved dietary intake (12, 13, 20, 21) and nutritional status (12), while others failed to show this effect (22-26). Compliance with nutritional supplements is often reported to be suboptimal (22, 23, 27-29). In one study, the authors concluded that personal attention by a dietetic assistant was effective in stimulating both dietary intake and intake of a nutritional supplement, and helped to establish a prolonged effect of the nutritional intervention (30). In a recently updated Cochrane review (31) it was concluded that the overall evidence for the efficacy of ONS in elderly hip fracture patients remains limited, and future research should investigate both the role of ONS and the role of dieticians or extra staff providing feeding assistance. Furthermore, such future trials should be adequately powered and nutritional status should be taken into account as an outcome parameter (31).

The aim of the present study was to investigate the effect of intensive dietary intervention comprising combined dietetic counselling and ONS during hospitalisation and after discharge on nutritional intake and status in elderly subjects after hip fracture. We hypothesized that the combination of dietetic counselling and ONS would improve patients' energy and protein intake and nutritional status.

## SUBJECTS AND METHODS

### Subjects

Eligible patients were admitted for surgical treatment of hip fracture, and aged 55 years and above (32). Patients were excluded if they had a pathological or periprosthetic fracture; a disease of bone metabolism (e.g. Paget's disease, Kahler's disease, hyperparathyroidism); a life expectancy of less than 1 year due to underlying disease; used ONS before hospital admission; if they were unable to speak Dutch; lived

outside the region; or were bedridden before the hip fracture. Patients were also excluded if they had dementia or were cognitively impaired, defined as a score of < 7 on the Abbreviated Mental Test (AMT) (33).

### **Study design**

The study was designed as an open-label parallel multi-centre, randomised controlled trial (32). For patient recruitment, a daily inventory of hip fracture patients admitted to the surgical and orthopaedic wards of three hospitals in South-Limburg in The Netherlands was made. Eligible patients were invited to participate and written informed consent was obtained within five days after surgery. After informed consent, baseline measurements were performed by a trained researcher and randomisation was performed according to a computer-generated random-number sequence list after pre-stratification for hospital, gender and age (55-74 years vs. 75 years and above) with allocation ratio 1:1. The researcher made a telephone call to an independent research assistant who took a sequentially numbered and sealed envelope, and informed the researcher to which group the patient had been allocated. Patients allocated to the intervention group received dietetic counselling and ONS for three months after fracture, whereas patients in the control group received usual nutritional care. All patients were discharged from the hospital to either a rehabilitation clinic or to the patient's home with home care or to the nursing home if they had lived there before hospitalisation. Three and six months postoperatively, the trained researcher performed the outcome measurements, and one of the study dietitians took a general dietary history and 24h recall at the patient's home. The study was approved by the Medical Ethical Committee of Maastricht University Hospital and Maastricht University and conducted according to the Declaration of Helsinki.

### **Sample size calculation**

We calculated that 61 patients per treatment arm would be sufficient to detect a between group difference in weight change of 2.1 kg (SD: 3.7 kg) with a power of 90% and a two-tailed alpha of 0.05 (25, 32).

### **Nutritional intervention**

The nutritional intervention was a combination of regular dietetic counselling and consumption of a multi-nutrient ONS for a period of three months, starting during hospital admission and continuing in the rehabilitation centre or at home. Dietetic counselling included the following elements: checking the patients' food habits and preferences, identifying possible deficiencies in nutrient intake, and checking practical difficulties with eating during hospitalisation and rehabilitation, as well as in the home situation.

A dietician visited each patient twice during their hospital stay. At the first visit, the dietician took a 24h recall of the patient's diet. To optimise normal food intake, all patients received an energy- and protein-enriched diet and recommendations were given with regard to choice, quantity and timing of food products and the ONS.

Nutritional requirements for energy were calculated according to Harris-Benedict equation (34), including an individual surplus stress and activity factor ranging from 20% to 40%. Protein requirement was calculated as body weight x 1.5 g protein (35) In addition to the energy- and protein enriched diet, all patients were advised to consume two bottles of an ONS daily in-between the main meals. The nutritional supplement was a milk-protein based ONS (Cubitan, N.V. Nutricia, Zoetermeer, The Netherlands) providing 2.1 MJ (500 kcal) and 40 g of protein per two bottles. If a patient did not tolerate the milk-based supplement, a yoghurt-style or juice-style supplement (Nutridrink Yoghurt Style or Nutridrink Juice Style, N.V. Nutricia, Zoetermeer, The Netherlands) was offered. Furthermore, the dietician made necessary arrangements in order to solve any problems, e.g. feeding problems, in collaboration with the hospital medical and nursing staff.

At the second visit during hospitalisation, seven to eight days after surgery, the dietician evaluated nutritional intake, including the intake of ONS using a 24h recall, and gave individual tailored advice to optimize dietary intake. During this visit, the transfer of the patient to the rehabilitation centre or the patient's home was prepared by evaluating the patient's physical restrictions with regard to nutritional care, i.e. purchasing food products and the preparation of meals, and by making arrangements to enable adequate food intake, e.g. support of informal caregivers and delivery of information on meal services.

After hospital discharge, the dietician visited each patient three times (1, 2 and 6 weeks after discharge) at the patient's home or in the rehabilitation centre to evaluate dietary intake including the intake of the ONS, to evaluate the constraints in the nutritional care, and to give dietary advice if necessary. If the patient was still unable to meet nutritional requirements by normal food intake, continuation of the ONS consumption was advised. In addition, in-between these face-to-face contacts, weekly telephone calls were made (3, 4, 5, 8, and 10 weeks after discharge) to evaluate both the dietary intake and the intake of the ONS by a 24h recall. If necessary, a telephone call was replaced by a home visit. As the patient's diet increased towards the nutritional requirements according to the guidelines for a healthy diet, the consumption of the ONS was gradually decreased and the patient was advised to maintain a healthy diet. If necessary, a vitamin D supplement was advised.

### **Usual care**

Patients allocated to the control group received usual care as provided in the hospital, rehabilitation clinic or at home, i.e. dietetic care or nutritional supplements were only provided on demand of the medical doctor in charge.

### **Outcome assessment**

To evaluate dietary intake, the dietician took a 24h recall at baseline, one week, three months and six months postoperatively. Intake of energy, protein and other nutrients were calculated by Komeet (BaS Nutrition Software, Arnhem, The Netherlands) using the Dutch Food Composition Table 2006 (NEVO, The Hague, The Netherlands). The intake of energy was sufficient if the patient consumed at least 80% of the energy requirements as proposed by the Netherlands Nutrition Centre Foundation (women

55-70 years 1900 kcal/day; women >71 years 1600 kcal/day; men 55-70 years 2300 kcal/day; men >71 years 1900 kcal/day).

Patients' adherence to recommendations regarding the ONS and on improving dietary intake were evaluated over two periods; an early post-operative period (between 0 -10 days after surgery), and a late postoperative period (between 11 days after surgery until 3 months after surgery). Patients were considered to be adherent with ONS advice if the intake of the supplement was at least 75% of the recommended amount. With regard to the nutritional recommendations, patients were considered to be adherent if they had followed the recommendations in at least 75% of the visits and telephone calls. Patients not needing nutritional advice were considered to be adherent.

Anthropometric measurements were performed at baseline, three months and six months postoperatively. At baseline, body weight and height were reported by the patient and used for calculation of energy and protein requirement, and Body Mass Index (BMI). Three and six months postoperatively, weight and height were measured using an electronic weighing scale (Seca 862, Seca Ltd, Birmingham, UK), and a portable stature meter (Instrument Development Engineering & Evaluation – IDEE Maastricht University Medical Centre, Maastricht, The Netherlands). Upper arm circumference was measured with a flexible measuring tape (Seca 201, Seca Ltd, Birmingham, UK). A Holtain Skin fold Calliper (CMS weighing equipment LTD, London, UK) was used to measure the thickness of biceps, triceps, and supra-iliac skin folds. Handgrip strength was measured using a Jamar hydraulic handgrip dynamometer (Saehan Corp., Masan, Korea). Mid arm muscle area was calculated according to the formula of Frisancho (36).

Biochemical parameters, albumin, pre-albumin, C-reactive protein (CRP), vitamin A, vitamin E, vitamin C, uric acid, homocysteine, and 5-methyl-tetrahydrofolate were measured in blood samples at baseline, three weeks, and three and six months postoperatively.

### **Confounders and stratification variables**

The following potential confounders were recorded from the medical charts; fracture type (medial neck, pertrochanteric fracture, subtrochanteric fracture), type of surgery (gamma nail, dynamic hip screw, 3 cannulated screws, hemi-arthroplasty, total hip replacement), type of anaesthesia, American Society of Anaesthesiologists (ASA) score assessing the patients' physical status before surgery, medical history, and medication use. All patients received daily physical therapy during hospitalisation, and after discharge in the rehabilitation clinic or at the patient's home.

At baseline, the Mini Nutritional Assessment (MNA) was used to classify the patients according to their risk of malnutrition at baseline (37, 38). The MNA distinguishes three categories; malnutrition, at risk of malnutrition and no malnutrition. For our study, the categories malnutrition and at risk of malnutrition were combined, further called "malnourished", and compared with patients without malnutrition, called "well nourished".

## Data analysis

Statistical analysis was performed using SPSS 15.0 for Windows (SPSS Inc., Chicago, IL, USA). Baseline characteristics were analyzed using descriptive statistics. Normality was tested using the Komolgorov-Smirnov test. Normally distributed data are presented as means  $\pm$  standard errors (SEM); not normally distributed data as median and range. Data analysis was performed according to the intention-to-treat principle, and missing values for outcome parameters six months postoperatively for patients who otherwise had a complete data set were imputed by last observation (three months) carried forward. Data substitution for all patients, including deceased patients, did not yield different results and were therefore not reported. First, analyses to detect differences between both groups were performed using, analysis of covariance, adjusting for the stratification variables (centre, gender, and age), and baseline values of the concerned outcome parameter. Next, multivariate analyses of covariance were performed with additional adjustment for fracture type, neurological disease, Crohn's disease, rheumatoid arthritis, and risk of malnutrition according to the MNA. The results of both models were not different, and only fully adjusted models are presented. The intervention effect was defined as the difference in change between the intervention and control group from baseline to one week, three weeks, three months and six months postoperatively. P-values of  $< 0.05$  were considered to be statistically significant.

## RESULTS

### Participants and baseline measurements

From July 2007 until December 2009, a total of 1304 hip fracture patients were screened for eligibility, resulting in 895 (69%) patients who did not meet the inclusion criteria, mainly due to cognitive impairment (52%) (**Figure 1**). Two-hundred fifty-seven (20%) patients refused to participate. Of the resulting 152 patients who gave informed consent, 73 were allocated to the intervention group and 79 to the control group. During the three-month intervention period, seven patients passed away, and seven patients withdrew their participation, resulting in 138 assessable patients (68 intervention, 72 control) at 3 months. During the follow-up (3-6 months after surgery), four patients passed away, and three patients withdrew their participation, resulting in 63 patients in the intervention group and 68 patients in the control group who completed follow-up.

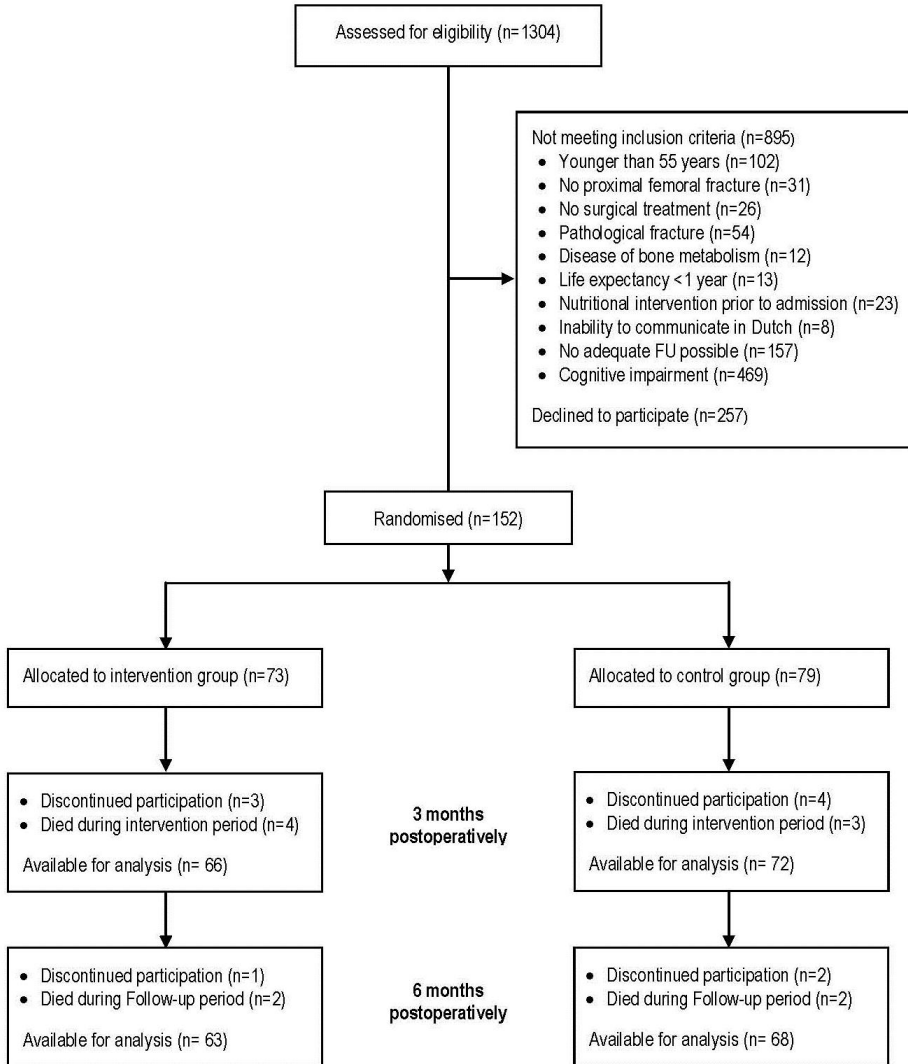


Figure 1: Study population flow chart

At baseline, both groups were comparable with respect to sex and age (**Table 1**). In both groups, the majority of the patients had sustained a fracture of the medial neck of the femur (49% vs. 57%), but in the intervention group as compared to the control group more patients had received gamma nail (51% vs. 30%) and fewer patients had received hemi-arthroplasty (26% vs. 38%). With respect to medical history, rheumatoid arthritis was more prevalent in the intervention group (30% vs. 20%), whereas neurological diseases were less prevalent than in the control group (23% vs. 35%). Furthermore, in the intervention group, 35% of the patients were malnourished (including patients at risk of malnutrition as defined by the MNA) as compared to 47% of the patients in the control group. Baseline nutritional intake of macro- and micro-nutrients were comparable (**Table 2**). With respect to baseline nutritional status (**Table 3**), all mean values of the parameters were higher in the intervention group, except handgrip strength which was higher in the control group. Biochemical parameters (**Table 4**) were comparable in both groups.

### **Oral nutritional supplementation and dietetic counselling**

In the intervention group, three out of 73 patients already had started with the consumption of an ONS on medical indication. After randomisation, all patients in the intervention group, except one, had started the consumption of ONS, with a median delay of 4 days (range: 1-6 days) postoperatively. The median period of supplementation use was 76 days (range: 3-91 days). At the end of the intervention period (3 months postoperatively), 11 (15%) patients randomised to the intervention group still did not meet the nutritional requirements and were therefore transferred to the home care dietician for continued dietetic counselling.

During hospitalisation, 67% of the patients were adherent with the nutritional recommendations as given by the dietician and 79% were adherent with ONS. After discharge, the adherence with the nutritional recommendations increased up to 73%, and the adherence with ONS remained at 80%. One patient in the intervention group developed bleeding due to a stomach ulcer. The ONS was temporarily stopped and restarted after recovery. No adverse events related to the nutritional intervention were noted.

In the control group, five out of 79 patients had started with the consumption of ONS on medical indication before randomisation; over the 6 months study period, seven additional patients randomised to the control group received ONS provided by the usual care dietician on demand of the medical doctor in charge (2 patients during hospitalisation, 3 patients in the rehabilitation clinic, and 2 patients at home). Seven patients received dietetic counselling by a dietician and were advised to change their diet (3 patients during hospitalisation, and 4 patients in the rehabilitation clinic).

**Table 1: Baseline characteristics of the study population**

	Randomised patients		Assessable patients	
	Intervention (N=73) N (%)	Control (N=79) N (%)	Intervention (N=66) N (%)	Control (N=72) N (%)
<b>Sex</b>				
Female	54 (74)	54 (68)	49 (74)	49 (68)
Male	19 (26)	25 (32)	17 (26)	23 (32)
<b>Age</b>	79 (55-93)	78 (57-94)	79 (55-92)	78 (57-90)
<b>Fracture type</b>				
Medial neck	36 (49)	45 (57)	34 (51)	41 (57)
Pertrochanteric	32 (44)	33 (42)	27 (41)	30 (42)
Subtrochanteric	5 (7)	1 (1)	5 (8)	1 (1)
<b>Type of surgery</b>				
Gamma nail	37 (51)	24 (30)	31 (47)	21 (29)
Dynamic hip screw	6 (8)	11 (14)	6 (9)	11 (15)
Hemi-arthroplasty	19 (26)	30 (38)	18 (27)	26 (36)
Total hip replacement	4 (5)	7 (9)	4 (6)	7 (10)
3 cannulated screws	7 (10)	6 (8)	7 (11)	6 (8)
Femoral nail	0 (0)	1 (1)	0 (0)	1 (1)
<b>Medical history</b>				
Diabetes Mellitus	16 (22)	15 (19)	15 (23)	13 (18)
Neurological disease	17 (23)	28 (35)	16 (24)	25 (35)
COPD	4 (5)	6 (8)	4 (6)	5 (7)
Cardiovascular disease	40 (55)	40 (51)	34 (52)	36 (50)
Parkinson	2 (3)	2 (3)	2 (3)	2 (3)
Rheumatoid Arthritis	22 (30)	16 (20)	20 (30)	14 (19)
Osteoporosis	9 (12)	9 (11)	8 (12)	9 (13)
Crohn's disease	5 (7)	9 (11)	5 (8)	9 (13)
<b>MNA<sup>a</sup></b>				
No malnutrition	46 (63)	41 (52)	43 (65)	38 (53)
Malnutrition	27 (37)	38 (42)	23 (35)	34 (47)

<sup>a</sup> Mini Nutritional Assessment. In our study, malnourished patients and patients at risk of malnutrition were combined

## Dietary intake

At baseline, the median required energy intake according to Harris-Benedict (34) including 20% stress factor was similar in both groups. In both groups, energy and protein intake increased during the intervention period, and the increase was higher in the intervention group, mainly due to ONS consumption (**Figure 2, Figure 3**). One week postoperatively, the intake of all nutrients except total fat, saturated fatty acids and cholesterol had increased to a significantly larger extent in the intervention group compared to the control group (**Table 2**). In the intervention group, 75% of the patients met their energy requirements as compared to only 55% in the control group. Mean protein intake in the intervention group was 1.2 g/kg as compared to 0.9 g/kg in the control group.

Three months postoperatively, this intervention effect remained significant for total fat, saturated fatty acids, mono-unsaturated fatty acids, calcium, vitamin B2, vitamin C, vitamin E and folic acid (Table 2). Seventy percent in the intervention group vs. 68% in the control group met the nutritional requirements for energy. Mean protein intake was similar in both groups (0.9 g/kg).

Six months postoperatively, the intervention effect on nutritional intake was no longer statistically significant (Table 2). The energy intake met the nutritional requirements in 75% of the intervention group and in 69% of the control group. Mean protein intake was similar in both groups (1.0 g/kg).

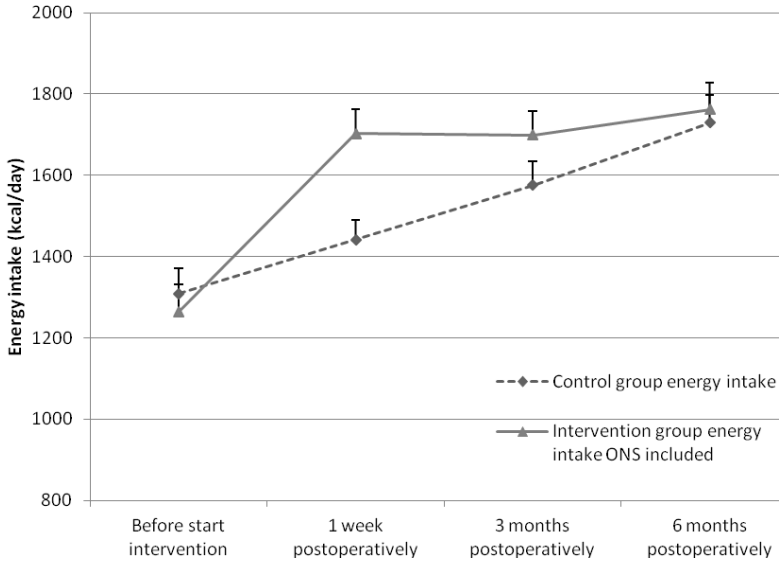


Figure 2: Energy intake over time in the intervention and control group

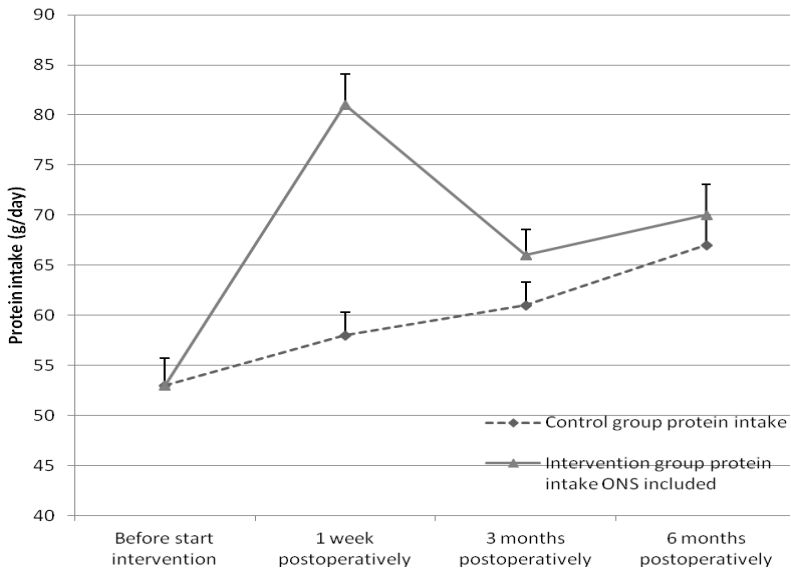


Figure 3: Protein intake over time in the intervention and control group

Table 2: Energy and nutrient intake at baseline, 1 week, 3 months and 6 months postoperatively <sup>a</sup>

	Baseline				1 week postoperatively		3 months postoperatively		6 months postoperatively	
	Intervention Mean (SEM)	Control Mean (SEM)	Intervention Mean (SEM)	Control Mean (SEM)	Intervention Mean (SEM)	Control Mean (SEM)	Intervention Mean (SEM)	Control Mean (SEM)	Intervention Mean (SEM)	Control Mean (SEM)
Energy (kcal)	1268 (67)	1304 (65)	1703 (60) <sup>***</sup>	1488 (50)	1699 (58.0)	1602 (61)	1763 (66)	1762 (72)		
Protein total (g)	54.2 (2.8)	53.1 (2.9)	81.2 (3.1)	60.2 (2.2)	66.0 (2.5)	62.4 (2.3)	70.1 (3.0)	68.9 (3.2)		
Protein vegetable (g)	17.8 (0.9)	18.3 (0.9)	25.9 (1.1) <sup>***</sup>	20.2 (1.0)	23.6 (0.9)	24.2 (1.0)	25.1 (1.4)	25.1 (1.2)		
Protein animal (g)	36.2 (2.1)	34.8 (2.2)	54.5 (2.4) <sup>***</sup>	39.3 (1.7)	40.6 (2.2)	37.2 (1.9)	43.4 (2.4)	43.1 (2.8)		
Fat total (g)	45.6 (2.9)	48.4 (3.0)	60.7 (2.5)	55.8 (2.4)	70.1 (3.3) <sup>**</sup>	60.3 (2.9)	70.9 (3.4)	69.1 (3.5)		
Saturated fatty acids (g)	19.2 (1.2)	22.0 (1.6)	22.5 (1.9)	23.9 (1.2)	26.8 (1.4) <sup>*</sup>	23.6 (1.2)	28.1 (1.5)	27.0 (1.4)		
Monounsaturated fatty acids (g)	13.2 (1.0)	13.7 (0.9)	20.5 (0.9) <sup>***</sup>	16.5 (0.8)	21.6 (1.2) <sup>**</sup>	17.8 (1.0)	21.4 (1.3)	21.8 (1.4)		
Polysaturated fatty acids (g)	7.8 (0.6)	7.6 (0.5)	11.7 (0.6) <sup>***</sup>	9.3 (0.5)	12.6 (0.7)	11.7 (0.7)	13.4 (0.8)	13.4 (0.9)		
Cholesterol (g)	137 (13)	131 (12)	150 (12)	152 (11)	177 (15)	174 (13)	191 (16)	152 (11)		
Carbohydrates (g)	160 (9)	164 (9)	207 (9) <sup>**</sup>	194 (7)	195 (7)	194 (8)	200 (8)	209 (9)		
Polysaccharides (g)	78.0 (4.2)	80.8 (4.0)	106 (57) <sup>***</sup>	91.4 (4.1)	96.6 (4.4)	100 (5)	99.2 (5.3)	105 (6)		
Calcium (mg)	633 (45)	647 (47)	1243 (63) <sup>***</sup>	709 (34)	853 (48) <sup>**</sup>	690 (37)	8214 (5)	825 (59)		
Vitamin D (µg)	2.3 (0.2)	2.5 (0.3)	637 (1) <sup>***</sup>	3.0 (0.20)	4.1 (0.4)	3.8 (0.4)	3.7 (0.3)	4.0 (0.4)		
Beta-Carotene (µg)	1767 (251)	1556 (225)	3105 (432) <sup>**</sup>	1593 (226)	1682 (218)	1184 (174)	1921 (444)	2141 (269)		
Vitamin B1 (mg)	0.63 (0.04)	0.65 (0.05)	1.5 (0.1)	0.79 (0.04)	1.1 (0.1)	1.0 (0.1)	1.2 (0.1)	1.3 (0.1)		
Vitamin B2 (mg)	0.85 (0.06)	0.89 (0.06)	2.6 (0.1) <sup>***</sup>	1.0 (0.1)	1.5 (0.1) <sup>**</sup>	1.1 (0.1)	1.3 (0.1)	1.3 (0.1)		
Vitamin B6 (mg)	1.0 (0.1)	1.0 (0.1)	2.8 (0.1) <sup>***</sup>	1.2 (0.1)	1.6 (0.1)	1.4 (0.1)	1.5 (0.1)	1.6 (0.1)		
Vitamin B12 (µg)	2.7 (0.2)	2.6 (0.2)	4.9 (0.2) <sup>***</sup>	2.9 (0.2)	3.7 (0.5)	2.7 (0.3)	3.9 (0.6)	3.1 (0.2)		
Folic acid (µg)	123 (8)	121 (9)	618 (43) <sup>***</sup>	143 (9)	234 (22) <sup>***</sup>	149 (11)	164 (14)	171 (16)		
Vitamin C (mg)	76.4 (9.4)	68.3 (9.2)	404 (26) <sup>***</sup>	64.5 (5.3)	136 (15) <sup>**</sup>	79.5 (9.0)	94.2 (12.5)	97.0 (9.0)		
Vitamin E (mg)	6.8 (0.8)	5.1 (0.3)	58 (4) <sup>***</sup>	6.8 (0.4)	18.6 (2.3) <sup>***</sup>	9.2 (0.70)	12.2 (1.6)	10.7 (0.7)		

<sup>a</sup> P-values represent the difference in change from baseline to one week, three months or six months postoperatively between the intervention and control group adjusted for centre, gender, age, fracture type, neurological disease, Crohn's disease, rheumatoid arthritis, and baseline value of the concerned variable.

\* p<0.05

\*\* p<0.01

\*\*\* p<0.001

### Nutritional status

As shown in **Table 3**, three months postoperatively, weight and BMI had significantly increased to a larger extent in the intervention group compared to the control group ( $p=0.005$  for weight;  $p=0.005$  for BMI); a positive intervention effect was also found for supra-iliac skin fold thickness ( $p=0.022$ ). No differences were found for other parameters. Six months postoperatively, the significant intervention effect only remained for supra-iliac skin fold thickness ( $p=0.021$ ). With respect to handgrip strength, no significant intervention effect was found at three and six months postoperatively.

At three weeks postoperatively, a positive intervention effect was found for the blood levels of vitamin C, vitamin E and 5-methyl-tetrahydrofolate (**Table 4**). At three months postoperatively, a positive intervention effect remained for the levels of vitamin C and 5-methyl-tetrahydrofolate. At six months postoperatively, a negative intervention effect was found for the blood level of vitamin E, it decreased to a significantly larger extent in the intervention group compared with the control group. The other levels of biochemical parameters did not show an intervention effect.

Table 3: Nutritional status at baseline, 3 months and 6 months postoperatively<sup>a</sup>

	Baseline		3 months postoperatively		6 months postoperatively	
	Intervention	Control	Intervention	Control	Intervention	Control
	Mean (SEM)	Mean (SEM)	Mean (SEM)	Mean (SEM)	Mean (SEM)	Mean (SEM)
Weight (kg)	69.1 (1.4)	67.6 (1.5)	70.4 (1.4)**	67.3 (1.5)	70.6 (1.5)	67.9 (1.5)
BMI (kg/m <sup>2</sup> )	26.0 (0.5)	25.2 (0.5)	26.5 (0.5)**	25.1 (0.5)	26.7 (0.6)	25.3 (0.5)
Upper arm circumference (cm)	30.0 (0.5)	28.6 (0.5)	29.3 (0.5)	28.0 (0.5)	30.0 (0.5)	28.3 (0.4)
Upper arm muscle area (mm <sup>2</sup> )	4704 (160) <sup>b</sup>	4331 (147) <sup>b</sup>	4437 (150)	4188 (157)	4552 (138)	4215 (132)
Biceps skin fold (mm)	14.7 (1.0) <sup>b</sup>	12.3 (0.9) <sup>b</sup>	14.5 (1.0)	12.1 (0.8)	15.4 (1.1)	12.9 (0.9)
Triceps skin fold (mm)	18.9 (1.0) <sup>b</sup>	16.7 (0.9) <sup>b</sup>	19.3 (1.1)	16.2 (0.8)	20.0 (1.0)	17.6 (0.9)
Supra-iliac skin fold (mm)	16.4 (1.1) <sup>c</sup>	15.3 (0.9) <sup>d</sup>	16.3 (0.9)*	13.6 (0.8)	16.5 (1.0)*	13.5 (0.8)
Handgrip strength (kg)	22.0 (1.2)	25.1 (1.3) <sup>b</sup>	23.0 (1.3)	26.6 (1.3)	23.6 (1.3)	26.8 (1.4)

<sup>a</sup> P-values represent the difference in change from baseline to three months or six months postoperatively between the intervention and control group adjusted for centre, gender, age, fracture type, neurological disease, Crohn's disease, rheumatoid arthritis, risk of malnutrition according to the MNA, and baseline value of the concerned variable

<sup>b</sup> Missing data of 1 patients

<sup>c</sup> Missing data of 7 patients

<sup>d</sup> Missing data of 10 patients

\* p<0.05

\*\* p<0.01

Table 4: Biochemical parameters at baseline, 3 weeks, 3 months and 6 months postoperatively<sup>a</sup>

	Baseline		3 weeks postoperatively		3 months postoperatively		6 months postoperatively	
	Intervention Mean (SEM)	Control Mean (SEM)	Intervention Mean (SEM)	Control Mean (SEM)	Intervention Mean (SEM)	Control Mean (SEM)	Intervention Mean (SEM)	Control Mean (SEM)
Albumin (g/l)	34.1 (0.9)	34.7 (0.6)	39.7 (0.7)	40.7 (0.6)	43.2 (0.6)	44.0 (0.6)	44.6 (0.5)	44.0 (0.5)
Pre-albumin (g/l)	0.17 (0.01)	0.16 (0.01)	0.26 (0.01)	0.27 (0.01)	0.25 (0.01)	0.26 (0.01)	0.26 (0.01)	0.26 (0.01)
CRP (mg/l)	108 (11)	109 (10)	20.5 (4.3)	23.6 (5.6)	11.1 (2.9)	11.2 (3.0)	8.9 (2.7)	17.0 (7.3)
Vitamin A (µmol/l)	1.9 (0.2)	1.8 (0.1)	3.3 (0.2)	3.3 (0.1)	2.9 (0.1)	3.0 (0.12)	3.0 (0.1)	3.0 (0.1)
Vitamin C (µmol/l)	35.9 (3.4)	27.0 (2.1)	66.4 (3.6) <sup>***</sup>	38.4 (2.9)	70.0 (3.9) <sup>***</sup>	50.9 (3.2)	56.6 (3.7)	52.9 (3.4)
Vitamin E (µmol/l)	32.3 (1.7)	28.3 (1.1)	43.8 (1.5) <sup>*</sup>	35.8 (1.3)	37.3 (1.3)	35.7 (1.5)	34.9 (1.2) <sup>*</sup>	34.6 (1.4)
Uric acid (µmol/l)	264 (11)	290 (15)	0.28 (0.01)	0.31 (0.01)	0.30 (0.01)	0.32 (0.02)	0.30 (0.01)	0.30 (0.01)
Homocysteine (µmol/l)	17.7 (1.1)	14.7 (0.9)	16.4 (0.8)	15.0 (0.8)	15.2 (1.0)	16.4 (1.1)	15.6 (0.7)	15.1 (0.71)
5-methyl-tetrahydrofolate (nmol/l)	21.9 (1.8)	22.8 (2.7)	29.8 (1.9) <sup>***</sup>	22.5 (2.5)	32.0 (3.1) <sup>***</sup>	20.1 (2.2)	23.0 (2.0)	20.8 (2.3)

<sup>a</sup> P-values represent the difference in change from baseline to one week, three months or six months postoperatively between the intervention and control group adjusted for centre, gender, age, fracture type, neurological disease, Crohn's disease, rheumatoid arthritis, and baseline value of the concerned variable.

\* p<0.05

\*\* p<0.01

\*\*\* p<0.001

## DISCUSSION

In this study we aimed to assess whether nutritional intervention comprising dietetic counselling and ONS would improve dietary intake and nutritional status of elderly subjects after hip fracture. Results showed that the intake of energy, protein, fat, carbohydrates, vitamins and micro-nutrients increased to a significantly larger extent in the intervention group at one week postoperatively. Blood levels of vitamin C, vitamin E, homocysteine and 5-methyl-tetrahydrofolate measured at three weeks postoperatively, also showed a positive intervention effect. At three months postoperatively, the positive intervention effect for the intake of total fat, fatty acids, calcium and several vitamins was still statistically significant. A positive intervention effect was also found for weight, BMI, supra-iliac skin fold thickness, and blood levels of vitamin C and 5-methyl-tetrahydrofolate at three months postoperatively. At six months postoperatively, the effect of the nutritional intervention on dietary intake was no longer significantly different; only supra-iliac skin fold thickness and the level of vitamin C in blood showed a positive intervention effect at this time point.

To our knowledge, this is the first study in hip fracture patients combining dietetic counselling and ONS over a three month period. Because of the regular home visits and telephone calls, as a part of the dietetic counselling, study dietitians could anticipate quickly if the patient experienced problems with their normal diet or with the consumption of ONS. Usual dietary intake was not decreased by the ONS (data not shown), possibly because it was offered as an in-between meal. We chose for a long intervention period of three months with continuation of the intervention after hospital discharge, because full recovery after hip fracture takes several months, and in addition, requires adaptations in the home environment due to increased nutritional requirements for energy and protein, combined with patient's physical restriction with regard to nutritional care, i.e. purchasing food products and the preparation of meals. We have included both well-nourished and malnourished patients as both are at risk to become malnourished or more severely malnourished during hospitalisation, due to a decline in nutritional intake caused by fasting before surgery and/or lack of appetite or nausea after surgery. By providing the nutritional intervention to all hip fracture patients regardless their baseline nutritional status, we aimed to minimise the effects of metabolic trauma after hip fracture.

Our data confirm the results of previous studies, which used only ONS or dietetic assistants as a nutritional intervention, with regard to the positive intervention effect on intake of energy, protein, micro-nutrients and vitamins (12, 13, 21, 30). Moreover, with regard to nutritional status, our data show an additional consistent positive intervention effect on weight, BMI, and supra-iliac skin fold thickness, while previous studies showed no or non-significant improvements only (12, 24, 27). Compliance with the ONS and the nutritional recommendations was high in our study, as also confirmed by blood levels of vitamin C and vitamin E three weeks postoperatively, as compared to studies in hip fracture patients in which compliance with the nutritional supplements was often suboptimal (22, 27-29). Our results corroborate the findings of Duncan et al. (30) who showed that patients receiving dietetic assistance had an improved supplement intake compared with patients not receiving assistance. Very recently, Hoekstra et al (39) reported an improvement of nutritional intake after

nutritional intervention in non-randomised in hip fracture patients; however, body composition was not improved.

Some limitations of our study should be noted. First, during the inclusion period, 68% of the patients who were screened for eligibility did not meet the inclusion criteria, mainly due to cognitive impairment, and 20% of patients refused to participate. To explore whether this might have influenced the external validity, we measured body weight, height, upper arm circumference and triceps skin fold thickness within a random selection of patients not meeting the inclusion criteria or refusing participation. Results indicated that these patients did not significantly differ in these nutritional status parameters from the patients included in the trial (data not shown). Second, our study was not blinded, meaning that patients, dieticians and researcher were not blinded for group allocation, which could have introduced bias. We tried to minimize this bias by having the outcome measurements performed by a trained researcher who was not involved in the nutritional intervention. Finally, several patients randomised to the control group have received nutritional support by ONS or dietetic counselling. It is possible that our study increased the awareness of nursing staff or dieticians with regard to malnutrition or identifying hip fracture patients at risk of malnutrition, resulting in a higher request for dietetic care, and thereby attenuating the effect of our nutritional intervention.

In conclusion, the combination of intensive dietetic counselling and ONS over three months after hip fracture had a favourable effect on energy, protein and micro-nutrient intake at one week postoperatively. Furthermore, we found a positive effect of the nutritional intervention on weight, BMI, and supra-iliac skin fold thickness at three months after hip fracture. At six months postoperatively, dietary intake and nutritional status were no longer significantly different between both groups. Our results indicate that future intervention studies should focus on long-lasting intervention, comprising both frequent dietetic counselling and ONS.

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## Chapter 5

# Cost-effectiveness of nutritional intervention in elderly subjects after hip fracture. A randomised controlled trial

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## **ABSTRACT**

### **Purpose**

Previous research on the effect of nutritional intervention on clinical outcome in hip fracture patients yielded contradictory results. Cost-effectiveness of nutritional intervention in these patients remains unknown. The aim of this study was to evaluate cost-effectiveness of nutritional intervention in elderly subjects after hip fracture from a societal perspective.

### **Methods**

Open-label, multi-centre randomised controlled trial investigating cost-effectiveness of intensive nutritional intervention comprising regular dietetic counselling and oral nutritional supplementation for three months postoperatively. Patients allocated to the control group received care as usual. Costs, weight and quality of life were measured at baseline and at 3 and 6 months postoperatively. Incremental cost-effectiveness ratios (ICERs) were calculated for weight at 3 months and quality adjusted life years (QALYs) at 6 months postoperatively.

### **Results**

Of 152 patients enrolled, 73 were randomised to the intervention group and 79 to the control group. Mean costs of the nutritional intervention was 613 Euro. Total costs and subcategories of costs were not significantly different between both groups. Based on bootstrapping of ICERs, the nutritional intervention was likely to be cost-effective for weight as outcome over the 3-month intervention period, regardless of nutritional status at baseline. With QALYs as outcome, the probability for the nutritional intervention being cost-effective was relatively low, except in subjects aged below 75 years.

### **Conclusion**

Intensive nutritional intervention in elderly hip fracture patients is likely to be cost-effective for weight but not for QALYs. Future cost-effectiveness studies should incorporate outcome measures appropriate for elderly patients, such as functional limitations and other relevant outcome parameters for elderly.

### **Summary**

Hip fracture patients can benefit from nutritional supplementation during their recovery. Up to now, cost-effectiveness evaluation of nutritional intervention in these patients has not been performed. Costs of nutritional intervention are relatively low as compared with medical costs. Cost-effectiveness evaluation shows that nutritional intervention is likely to be cost-effective.

## INTRODUCTION

In The Netherlands, as well as in other countries, the incidence of hip fractures in the elderly is high, and it is expected to increase in the nearby future. Hip fractures are one of the most common reasons for hospital admission and transfers to nursing facilities in the elderly (1). After hip fracture, only 37% of the patients will return to their pre-fracture functional status leading to high health care costs and a major burden on health care utilization (2). Not only costs resulting from a hip fracture during hospital stay are relevant, but also long-term costs such as recovery in a rehabilitation clinic, the need for home care, and the increased burden on informal care givers which may play an even more important role (2, 3).

At the time of hospital admission for surgical treatment of their hip fracture, hip fracture patients are reported to be malnourished, and the nutritional status can deteriorate further during hospital admission because of a spontaneous reduction in food intake due to lack of appetite or nausea (4-9). Malnutrition in hip fracture patients is reported to be associated with impaired muscle function, disability, loss of independency, decreased quality of life, delayed wound healing, higher complication rate, prolonged rehabilitation time, and increased mortality rate (7, 8, 10-17). Both hip fracture patients and malnourished patients in general have an increased use of health care as compared to well-nourished and non-fracture patients, and it is expected that it would result in higher health care costs (18-21). Early treatment of malnutrition is of vital importance to minimize losses and to achieve rapid weight recovery after hip fracture.

In the past decades, several studies have been conducted to determine the effectiveness of nutritional supplementation on length of stay, postoperative complications, mortality, nutritional status and functional status. Furthermore, within the past decades, economic evaluations have gained more and more attention, and their importance has increased because of the continuous rising health care expenses and the limited budgets available. As a consequence, new or additional treatments should not only have to be effective but also cost-effective. Previous research on costs and cost-effectiveness of nutritional support or intervention is scarce. A few studies have shown that health care costs can be reduced by nutritional support in malnourished elderly (20, 22, 23). Kruizenga et al. (24) reported that nutritional screening and treatment of malnourished patients at an early stage of hospitalisation is cost-effective.

Although several studies have shown the effectiveness of nutritional support in elderly hip fracture patients, none of these studies have incorporated an economic or cost-effectiveness evaluation. Therefore, the aim of the present study was to investigate the cost-effectiveness of an intensive dietary intervention comprising combined dietetic counselling and oral nutritional supplementation, as compared with usual nutritional care in elderly subjects after hip fracture from a societal perspective with a time horizon of 6 months.

## METHODS

### Subjects

Eligible were patients admitted for surgical treatment of hip fracture, aged  $\geq 55$  years (25). Patients were excluded if they had a pathological or periprosthetic fracture; a disease of bone metabolism (e.g. Paget's disease, Kahler's disease, hyperparathyroidism); an estimated life expectancy  $< 1$  year due to underlying disease; if they used an oral nutritional supplement before hospital admission; if they were unable to speak Dutch, lived outside the region or had been bedridden before their hip fracture. Patients were also excluded if they had dementia or were cognitively impaired, defined as a score of  $< 7$  on the Abbreviated Mental Test, as assessed before inclusion (26).

### Design

The present economic evaluation was embedded in an open-label parallel multi-centre, randomised controlled trial on the effectiveness of nutritional intervention in elderly subjects after a hip fracture (25). The economic evaluation was performed from a societal perspective using a time horizon of six months.

For patient recruitment, we made a daily inventory of all hip fracture patients admitted to the surgical and orthopaedic wards of Maastricht University Medical Centre (Maastricht), Atrium Medical Centre (Heerlen) and Orbis Medical Centre (Sittard). Eligible patients who met the inclusion criteria were invited to participate, and written informed consent was obtained within 5 days after surgery. After informed consent and baseline measurements, patients were randomised according to a concealed computer-generated random-number sequence list after pre-stratification for hospital, gender and age (55-74 vs.  $\geq 75$  years) with an allocation ratio of 1:1. After randomisation, all patients were visited by a study dietician who evaluated patients' nutritional intake by a 24-h recall. Then, patients allocated to the intervention group received dietetic counselling and an oral nutritional supplement as needed, for 3 months after fracture, whereas patients in the control group received usual nutritional care. Costs and outcome measurements were assessed at 3 and 6 months postoperatively (25). Patients were discharged from the hospital according to standard care, either to a rehabilitation clinic or to the patient's home with home care, or to the nursing home or elderly home where they had lived there before hospitalisation. The study was approved by the Medical Ethical Committee of Maastricht University Hospital and Maastricht University and conducted according to the Declaration of Helsinki.

### Nutritional intervention

Patients in the intervention group received a combination of frequent dietetic counselling and consumption of a multi-nutrient oral nutritional supplement (ONS), starting during hospital admission and continued in the rehabilitation centre and/or at home, until 3 months after hip fracture surgery.

A dietician visited each patient twice during their hospital stay. At the first visit, the dietician took a 24-h recall of the patient's diet during hospitalisation. To optimize normal food intake, all patients received an energy- and protein-enriched diet, and recommendations were given with regard to choice, quantity and timing of food products. In addition, patients were advised to consume two bottles of ONS daily in-between the main meals. The ONS was a milk-protein based, or a yoghurt- or juice-style supplement (Cubitan, Nutridrink Yoghurt style, or Nutridrink Juice style, N.V. Nutricia, Zoetermeer, The Netherlands) providing 2.1 MJ (500 kcal) and 40 g of protein per 500 ml. Furthermore, the dietician made arrangements to solve any problems, e.g. feeding difficulties, in collaboration with the hospital medical and nursing staff.

At the second visit during hospitalisation, 7-8 days after surgery, the dietician evaluated food intake and the consumption of the ONS using a 24-h recall, and gave individually tailored advice to optimize dietary intake. Furthermore, the transfer of the patient to the rehabilitation centre or the patient's home was prepared by evaluating the patient's physical restrictions with regard to nutritional care, i.e. purchasing food products and the preparation of meals, and by making arrangements to enable adequate food intake, e.g. support of informal caregivers and delivery of information on meal services.

After hospital discharge, the dietician visited each patient three times (1, 2 and 6 weeks after discharge) at the patient's home or in the rehabilitation centre (whatever was applicable) in order to evaluate dietary intake including the intake of the ONS, to evaluate possible bottlenecks in nutritional care at home (e.g. shopping, cooking) and to give dietary advice as needed. In addition, in-between these home visits, weekly telephone calls were made (3, 4, 5, 8 and 10 weeks after discharge) to evaluate dietary intake (including the ONS) by 24-h recall. If necessary, a telephone call was replaced by a home visit.

### **Usual care**

Patients allocated to the control group received usual care as provided in the hospital, rehabilitation clinic or at home, i.e. dietetic care or nutritional supplements were only provided on demand of the medical doctor in charge. In the control group, ten patients (13%) received ONS and 18 patients (23%) received dietetic counselling.

### **Economic evaluation**

#### ***Effect measures***

##### **Weight**

At baseline, self-reported weight was used, because patients were not able to stand on a weighing scale because of hip fracture. At 3 months postoperatively, weight was measured using an electronic weighing scale (Seca 862, Seca Ltd, Birmingham, UK). The difference in weight in kilograms between baseline and 3 months postoperatively was calculated and used to evaluate the effectiveness of the nutritional intervention.

### **Quality Adjusted Life Years**

Quality of Life was estimated at baseline and at 3 and 6 months postoperatively using the Dutch version of EuroQoL (EQ-5D-3L) (27-29). In the EuroQoL, the patient was asked to make a statement on the degree of problems (no problem, some problems or major problems) he/she experienced on the dimensions of mobility, self-care, usual activities, pain or discomfort and anxiety or depression. The degree of problems on each dimension were combined to a health state. Based on these health states, utilities were calculated based on the social tariff by Dolan because this is the internationally accepted standard (30). Utilities are the preferences that individuals or the society may have for a particular set of health outcomes. These utilities were used to calculate Quality Adjusted Life Years (QALYs), which are defined as 'a measure of a person's length of life weighted by a valuation of their health related quality of life' (31). QALYs are used to make a comparison between the effects of different treatments and to evaluate cost-effectiveness of interventions. The value of the QALY can range from below zero, representing the worst possible health state, up to 1, representing the best possible health state.

### **Cost measures**

Medical and non-medical costs were measured at baseline and at 3 and 6 months postoperatively using a standardized 3-month retrospective patient costing questionnaire. Patients were asked to report the frequency and location of consultation with the general practitioner, physiotherapist and other paramedical care givers, as well as professional homecare for assistance with activities of daily living and household activities of daily living, and assistant devices and medical aids. Medication was registered from the patient's medical chart, the medication list as provided by the general practitioner or pharmacy, supplemented by registration of medication packages. Length of stay in hospital, rehabilitation clinic, nursing home and home for the elderly were calculated using admission and discharge dates. The number and duration of face-to-face visits and telephone calls were calculated using the dietician's time registries and used to calculate the costs of a face-to-face visit and telephone call. The quantity of the oral nutritional supplements was calculated based on the number of ONS as advised by the dietician.

We assessed nutritional intervention costs, health-care-related costs and patient and family costs. Nutritional intervention costs were defined as the costs of the dietetic counselling by the dietician (face-to-face visits and telephone calls) and nutritional supplementation (ONS and tube feeding). Health-care-related costs were hospital-related costs (hospital admissions and outpatient specialist care), other in-patient-related costs (admissions to rehabilitation clinic, nursing home or home for the elderly, and day centre activities), general practitioners, paramedical care (physiotherapy, occupational therapy, other alternative therapies), professional home care, assistant devices and medical aids and prescribed and over-the-counter medication. Patient and family costs included the costs of home adjustments, paid domestic help and meal services. Productivity costs were considered irrelevant for this population because 89% of the patients in the control group and 96% of the patients in the intervention group were retired; therefore, these costs were not included in the calculation.

To calculate the costs, the volumes of each cost category were multiplied by the cost price of each cost category. Cost prices, presented in Euros, were based on the “Dutch manual for costing: methods and standard costs for economic evaluations in healthcare” for the year 2010 (32). Standardized cost prices were used where available, or else real costs or tariffs were used to estimate the costs. Medication costs were calculated using prices based on the Defined Daily Dose which is defined by the Health Care Insurance Board as the assumed average maintenance dose per day for a drug used for its main indication in adults (33, 34). Prices of paid domestic help were based on tariffs for unpaid work. With respect to costs of hospital admissions, the cost price of a non-teaching hospital was used because hip fracture surgery does not require the expertise of a teaching hospital, and the Maastricht University Medical Centre has both the function of a non-teaching and teaching hospital. Costs of surgery were not included in the cost calculation because previous research by Haentjens et al (35) showed that the costs of the different types of surgery are comparable.

### **Incremental cost-effectiveness ratios, cost-effectiveness planes and cost-effectiveness acceptability curves**

To evaluate cost-effectiveness, incremental cost-effectiveness ratios (ICERs) were calculated. ICERs were calculated by dividing the difference in the mean costs (between two treatments or interventions) by the differences in the mean outcomes. In this study, ICERs were calculated for weight change and for QALYs. The ICERs were interpreted as the incremental cost per unit of additional outcome (29, 36).

These ICERs were plotted in a cost-effectiveness plane (CEP), in which the x-axis showed the difference in effect between the interventions and the y-axis the differences in costs between the interventions (29, 36, 37). In the CEP, four quadrants were shown; ICERs located in the North East (NE) indicated that the intervention was more effective and more costly as compared with usual care. ICERs in the South East (SE), the dominant quadrant, indicated that the intervention is more effective and less costly. ICERs in the South West (SW) indicated that the intervention was less effective and less costly, and ICERs located in the North West (NW) indicated that the nutritional intervention was less effective but more costly.

Based on the CEPs, cost-effectiveness acceptability curves (CEAC) were plotted (29, 36-38). In the CEAC, the probability that the nutritional intervention is more cost-effective as compared with the usual care (y-axis) was presented for several ceiling ratios (x-axis), which were defined as the amount of money the society is willing to pay to gain one unit of effect (29, 36-38). Within The Netherlands, the value the society is willing to pay to gain one QALY ranges from 20,000 Euro to 80,000 Euro, depending on the severity of the disease (39).

### **Sensitivity analyses**

Sensitivity analyses were performed for age categories (patients aged between 55 and 74 years versus  $\geq 75$  years) because elderly patients can have more co-morbidities and postoperative complications as compared with younger patients.

Sensitivity analyses were also performed for patients classified according to their risk of malnutrition at baseline, as measured by the Mini Nutritional Assessment (MNA).

The MNA was developed for elderly people and includes 18 items grouped in four categories: anthropometric assessment (including BMI, weight loss, arm circumference and calf circumference); general assessment of lifestyle, medication use, mobility, presence of signs of depression or dementia); short dietary assessment (number of meals, food and fluid intake, autonomy of feeding) and subjective assessment (self perception of health and nutrition) (40, 41). A score of  $\geq 24$  indicates no malnutrition; a score between 17 and 23.5 indicates being at risk of malnutrition, and a score less than 17 indicates malnutrition. For this purpose, the group malnutrition and the group at risk of malnutrition are combined and compared with the group no malnutrition.

### Statistical analysis

Data were analysed using SPSS version 15 and Excel 2003 and based on the intention-to-treat principle. Missing values for the EuroQoL at 6 months postoperatively were imputed by last observation carried forward. If volume data were missing to calculate the costs, these missing data were replaced by individual means of valid volume data before multiplying the volumes by the cost prices. Costs were presented as means and standard deviations, and Mann-Whitney *U* tests were used to test for significant differences in costs between the intervention and control group. The robustness of the cost analyses was also tested by bootstrapping (1,000x). Furthermore, bootstrapping (5,000x) was used to calculate the uncertainty around the cost-effectiveness ratios, and CEPs and CEACs were plotted (29, 36-38). Sensitivity analyses were performed for age categories (aged 55-74 years vs.  $\geq 75$  years) and for the risk of malnutrition at baseline (at risk of malnutrition and malnutrition vs. no malnutrition). Bootstrapping was also used to calculate the uncertainty around the ICERs resulting from the sensitivity analyses, and CEPs and CEACs were also plotted.

## RESULTS

From July 2007 until December 2009, a total of 1,304 hip fracture patients were admitted to the surgical and orthopaedic wards of the participating hospitals and screened for eligibility. Of the screened patients, 895 (69%) did not meet the inclusion criteria, mainly due to cognitive impairment (52%). Two-hundred fifty-seven (20%) patients refused to participate. Of the resulting 152 patients who gave informed consent, 73 were randomly allocated to the intervention group and 79 to the control group. During the 3-month intervention period, seven patients (four, intervention; three, control) passed away, and seven patients (three, intervention; four, control) withdrew their participation, resulting in 138 assessable patients (68 intervention, 72 control) at 3 months. During the follow-up (3-6 months after surgery), four patients (two intervention, two control) passed away, and three patients (one, intervention; two, control) withdrew their participation, resulting in 63 patients in the intervention group and 68 patients in the control group who completed follow-up.

At baseline, the intervention and control group were comparable with respect to gender and age. In both groups, the majority of the patients sustained a fracture of the

medial neck of the femur. In the intervention group, more patients had received gamma nail, and fewer patients had received hemi-arthroplasty as compared with the control group (**Table 1**). After hospitalisation, in the intervention group as well as in the control group, 42 patients were discharged to a rehabilitation clinic. At baseline, 37% of the patients in the intervention group were malnourished or at risk of malnutrition as compared with 48% of the patients in the control group. Medical costs measured at baseline over a 3-month period before hip fracture were comparable between both groups (data not shown).

**Table 1: Baseline characteristics**

	Intervention group (N=73) N (%)	Control group (N=79) N (%)
<b>Sex</b>		
Female	54 (74)	54 (68)
Male	19 (26)	25 (32)
<b>Age</b>	79 (55-93)	78 (57-94)
<b>Type of residence before fracture</b>		
Home	63 (86)	66 (83)
Nursing home	2 (3)	4 (5)
Home for the elderly	8 (11)	7 (9)
Rehabilitation clinic / hospital	0 (0)	2 (3)
<b>Fracture type</b>		
Medial neck	36 (49)	45 (57)
Pertrochanteric	32 (44)	33 (42)
Subtrochanteric	5 (7)	1 (1)
<b>Type of surgery</b>		
Gamma nail	37 (51)	24 (30)
Dynamic hip screw	6 (8)	11 (14)
Hemiarthroplasty	19 (26)	30 (38)
Total hip replacement	4 (5)	7 (9)
3 cannulated screws	7 (10)	6 (8)
Femoral nail	0 (0)	1 (1)
<b>MNA<sup>1</sup></b>		
No malnutrition	46 (63)	41 (52)
At risk of malnutrition or malnourished	27 (37)	38 (48)

<sup>1</sup>Mini Nutritional Assessment

## Costs

As shown in **Table 2**, the mean cost of the nutritional intervention per patient in the intervention group was 613 Euro. Several patients in the control group also received dietetic counselling and ONS, with mean cost of 88 Euro ( $p=0.000$ ). The additional costs of the nutritional intervention were only 3% of the total costs, and were thus relatively low as compared with other health care-related costs and patient- and family-related costs. Total healthcare costs, patient and family costs, as well as the subcategories of these costs, were not significantly different between both groups.

## Cost-effectiveness

### *Weight as outcome*

The intervention effect for weight, defined as the difference in change between the intervention and control group from baseline to 3 months postoperatively has a statistically significant positive value, meaning that the patients in the intervention group gained more weight as compared with patients in the control group. The estimated intervention effect from baseline to three months postoperatively was 1.91 kg (95% C<sub>i</sub>: 0.60-3.22;  $p=0.005$ ). The ICER for total societal costs per kilogram weight increase was 241 Euro. As presented in **Table 3**, the overwhelming majority of the dots in the CEP were located in the NE and SE quadrant. The ICERs located in the NE quadrant represent ratios indicating that the nutritional intervention was more costly and more effective as compared with usual care. The ICERs located in the SE represent ratios indicating that the nutritional intervention was less costly and more effective as compared with usual care. The CEAC (**Figure 1**) indicates that, with a willingness to pay of 5,000 Euro, the probability that the nutritional intervention was cost-effective based on its total societal costs per kilogram weight was as high as 98%. Even at a willingness to pay € 2,500, the intervention was still ~70% likely to be cost-effective.

### *QALYs as outcome*

At 6 months postoperatively, the intervention effect for QALYs was not statistically significant. The estimate of the intervention effect for change in QALYs was -0.02 (95% CI, -0.12–0.08;  $p>0.05$ ). The ICER for total societal costs per QALY was 36,943 Euro. As presented in **Table 3**, the majority of the dots in the CEP based on total societal costs per QALY were located in the NE and SE quadrants. The ICERs located in the NE quadrant represented ratios indicating that the nutritional intervention was more costly and more effective as compared to usual care. The ICERs located in the SE represented ratios indicating that the nutritional intervention was less costly and more effective as compared with usual care. The CEAC (**Figure 2**) showed that, with a willingness to pay of 20,000 Euro per QALY, the probability that the nutritional intervention was cost-effective based on its total societal costs per QALY was 45%. If the willingness to pay is 80,000 Euro per QALY, the probability that the intervention is cost-effective increased to 60%.

Table 2: Mean costs in Euro

Cost category	Intervention group (n = 73)				Control group (n = 79)				T-test		Bootstrap 95% Uncertainty interval		
	Mean	sd	Median	Min <sup>a</sup>	Max <sup>b</sup>	Mean	sd	Median	Min <sup>a</sup>	Max <sup>b</sup>	p-value	2.5th percentile	97.5th percentile
<b>Nutritional intervention</b>	<b>613</b>	<b>258</b>	<b>586</b>	<b>30</b>	<b>1 352</b>	<b>88</b>	<b>311</b>	<b>0</b>	<b>0</b>	<b>2 187</b>	<b>0,000</b>	<b>433</b>	<b>608</b>
Dietetic counselling	244	55	243	30	374	22	50	0	0	269	0,000	206	237
Oral nutritional supplement	370	225	346	0	1 095	67	269	0	0	1 918	0,000	219	381
<b>Health care related</b>	<b>22 449</b>	<b>16 003</b>	<b>20 577</b>	<b>2 911</b>	<b>73 719</b>	<b>22 491</b>	<b>16 741</b>	<b>21 470</b>	<b>2 332</b>	<b>73 362</b>	<b>0,849</b>	<b>- 5 203</b>	<b>5 119</b>
Hospital related	7 072	5 112	5 482	1 892	25 001	6 492	6 255	4 977	1 516	51 129	0,342	-1 282	2 185
Other inpatient related	10 967	12 783	10 677	0	59 929	11 481	14 032	8 266	0	57 863	0,959	-4 677	3 468
General practitioner	131	190	71	0	1 045	118	164	85	0	1 089	0,900	-43	71
Paramedical care	1 692	1 240	1 741	0	6 219	1 761	1 379	1 700	0	7 421	0,962	-493	362
Professional home care	1 743	2 465	156	0	10 187	1 660	2 519	0	0	9 919	0,718	-600	865
Assistive devices	531	1 393	103	0	8 466	662	1 395	193	0	5 383	0,843	-719	823
and medical aids	314	391	182	0	1 923	316	384	175	0	1 897	0,943	-120	125
<b>Patient and family related</b>	<b>291</b>	<b>568</b>	<b>0</b>	<b>0</b>	<b>3 216</b>	<b>317</b>	<b>585</b>	<b>0</b>	<b>0</b>	<b>3 267</b>	<b>0,959</b>	<b>-208</b>	<b>158</b>
Home adjustments	54	264	0	0	1 545	53	262	0	0	2 162	0,450	-87	89
Paid domestic help	161	393	0	0	1 823	185	491	0	0	3 267	0,782	165	115
Meal services	76	207	0	0	927	79	218	0	0	930	0,868	-201	175
<b>TOTAL</b>	<b>23 353</b>	<b>16 124</b>	<b>21 446</b>	<b>3 497</b>	<b>74 054</b>	<b>22 896</b>	<b>16 834</b>	<b>21 470</b>	<b>2 332</b>	<b>73 362</b>	<b>0,665</b>	<b>-4 604</b>	<b>5 827</b>

<sup>a</sup> Minimum<sup>b</sup> Maximum

**Table 3: Cost-effectiveness analyses and sensitivity analyses for QALY and weight difference**

	Participants		ICER <sup>a</sup>	Distribution on cost-effectiveness plane			
	Intervention	Control		NE <sup>b</sup> %	SE <sup>c</sup> %	SW <sup>d</sup> %	NW <sup>e</sup> %
<b>Weight</b>							
Weight base case	65	72	241	56	43	0	0
55-74 years	22	27	- 2 788	27	17	27	29
75 years and above	43	45	149	56	44	0	0
No malnutrition <sup>f</sup>	42	38	2 349	93	7	0	0
(At risk of) malnourished <sup>f</sup>	23	34	- 1 404	18	82	0	0
<b>QALY<sup>g</sup></b>							
QALY base case	62	69	36 943	42	31	5	22
55-74 years	20	28	- 4 880	40	60	0	0
75 years and above	42	41	- 104 521	22	13	12	52
No malnutrition <sup>f</sup>	40	39	60 300	74	14	0	12
(At risk of) malnourished <sup>f</sup>	22	30	- 67 577	14	10	12	64

<sup>a</sup> Incremental Cost-effectiveness Ratio

<sup>b</sup> North East Quadrant: the intervention was more effective and more costly as compared to usual care

<sup>c</sup> South East Quadrant: the intervention was more effective and less costly as compared to usual care

<sup>d</sup> South West Quadrant: the intervention was less effective and less costly as compared to usual care

<sup>e</sup> North West Quadrant: the intervention was less effective and more costly as compared to usual care

<sup>f</sup> According to Mini Nutritional Assessment (MNA)

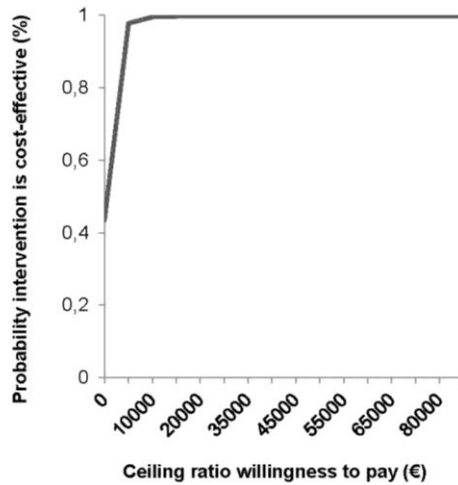
<sup>g</sup> Quality Adjusted life year

### Sensitivity analyses

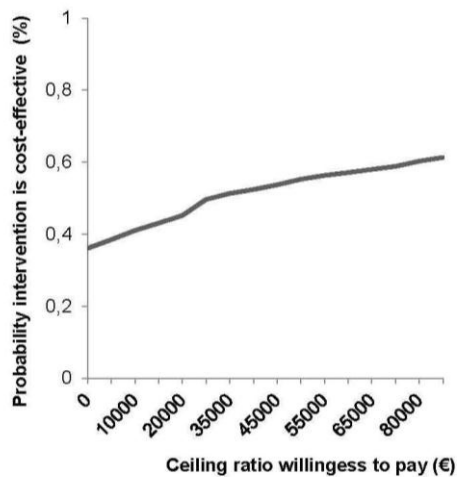
As cost-effectiveness of nutritional intervention may depend on nutritional status and age (co-morbidities and postoperative complications tend to increase with age), sensitivity analyses were performed by stratifying our population for age (55-74 vs. ≥75 years) and nutritional status (malnutrition + risk of malnutrition vs. no malnutrition, according to the MNA). In Table 3, ICERs and the distribution of the ICERs on the CEP are presented for these sensitivity analyses, both for weight and QALYs as outcomes.

In **Figure 3**, the probability that the nutritional intervention was cost-effective with respect to weight is shown for patients aged 55- 74 years and patients aged ≥75 years. In older patients, the probability that the nutritional intervention was cost-effective was 100% if the society would be willing to pay 5,000 Euro or more for 1 kg weight gained. In younger patients, the probability that the intervention was cost-effective was considerably lower (40-44%). As also shown in Figure 3, in malnourished patients and well-nourished patients, the probability that the nutritional intervention was cost-effective were 100% and 90%, respectively, if the society is willing to pay 5,000 Euro or more for 1 kg weight gain. With a willingness to pay of 2,500 Euro, these percentages would be 90% and ~50%, respectively, for malnourished and well-nourished patients. With respect to QALYs, if the nutritional intervention was targeted to patients aged between 55 and 74 years, with a willingness to pay of 20,000 Euro, the probability that the intervention was cost-effective was 85%, compared with only 26% in patients aged 75 years and above (**Figure 4**). If the willingness to pay is 80,000 Euro for one QALY, the probability for the nutritional intervention to be cost-effective in the younger group increases to 98% while, in the older group, the probability remains the same. As also shown in Figure 4, at a willingness to pay 20,000 Euro for one QALY, the probability that the nutritional intervention was cost-effective were 20% in malnourished patients

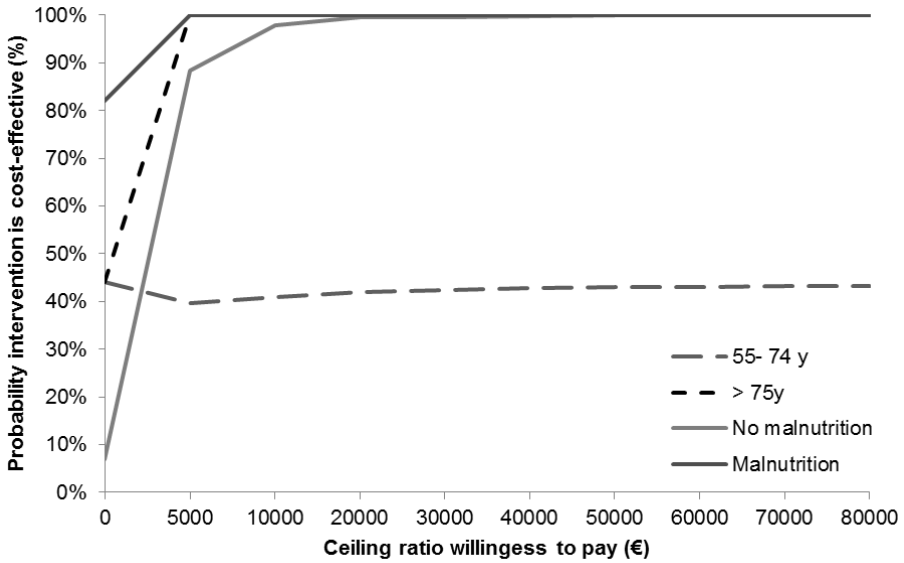
and ~25% in well-nourished patients. With increasing willingness to pay, the probability that the intervention was cost-effective remained similar in malnourished patients whereas, in well-nourished patients, the probability that intervention was cost-effective increased up to ~60% at a willingness to pay 80,000 Euro.



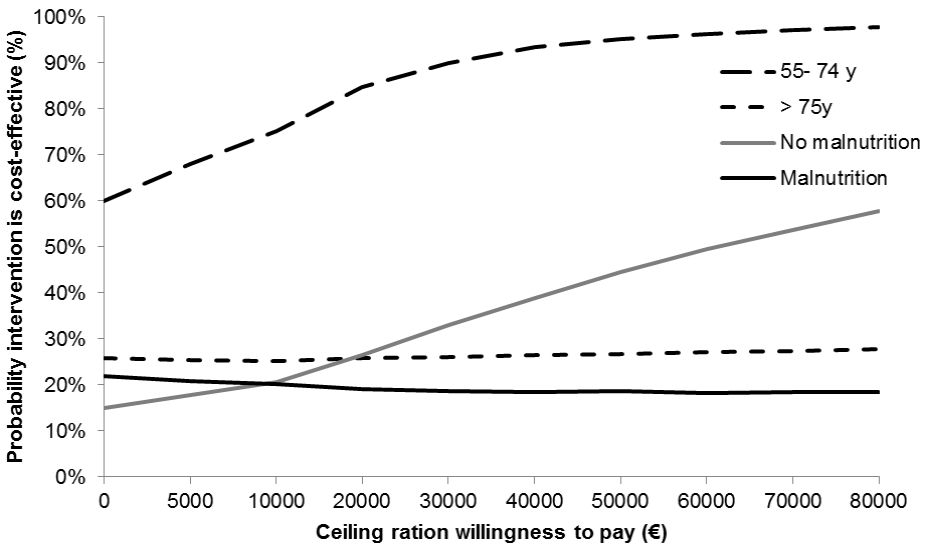
**Figure 1:** Cost-effectiveness acceptability curve presenting the probability that the nutritional intervention is cost-effective (y-axis) for weight increase, given various ceiling ratios for willingness to pay (x-axis)



**Figure 2:** Cost-effectiveness acceptability curve presenting the probability that the nutritional intervention is cost-effective (y-axis) for QALY, given various ceiling ratios for willingness to pay (x-axis)



**Figure 3:** Cost-effectiveness acceptability curve presenting the probability that the nutritional intervention is cost-effective (y-axis), given various ceiling ratios for willingness to pay (x-axis) with respect to weight increase. Sensitivity analyses performed for age groups and nutritional status at baseline, according to the Mini Nutritional Assessment (MNA).



**Figure 4:** Cost-effectiveness acceptability curve presenting the probability that the nutritional intervention is cost-effective (y-axis), given various ceiling ratios for willingness to pay (x-axis) with respect to QALY. Sensitivity analyses performed for age groups and nutritional status at baseline, according to the Mini Nutritional Assessment (MNA).

## DISCUSSION

Nutritional intervention in elderly hip fracture patients has been proposed as an approach to improve clinical outcome. Despite several decades of research, the overall evidence for the effectiveness of ONS in elderly hip fracture patients with respect to length of stay and functional outcome is limited (42), and no thorough economic evaluation of nutritional intervention in elderly subjects after hip fracture has been performed so far.

In the present study, we assessed the cost-effectiveness of an intensive nutritional intervention combining frequent dietetic counselling and ONS for 3 months postoperatively in elderly hip fracture patients. Results showed that the direct costs of the nutritional intervention were low-613 Euro per treated patient. Total health care costs, patient and family costs, as well as subcategories of these costs were similar in the intervention and control group. Results showed that the nutritional intervention was likely to be cost-effective for weight increase during the intervention period (3 months) in the total study population. Sensitivity analyses with stratification for nutritional status showed that the cost-effectiveness for weight as outcome was especially high in malnourished patients but also (though slightly less high) in well-nourished patients. If the nutritional intervention would be targeted to elderly patients ( $\geq 75$  years), the probability that the intervention was cost-effective was also high. This was in marked contrast with younger patients (55-74 years), where cost effectiveness was  $< 50\%$ , possibly due to the fact that younger patients generally have a better general condition than elderly patients, so that nutritional intervention will have less effect on their weight.

With respect to QALY, the probability for the intervention to be cost-effective was relatively low for the total population and subgroups; however, the probability that the nutritional intervention was cost-effective with respect to QALY was highest (60-90% depending on willingness to pay) in younger patients (55-74 years).

Our results confirm previous studies indicating that the costs of nutritional intervention are extremely low (in our case, less than 3%) compared with regular health care costs such as hospital costs (20, 22-24, 43, 44). Previous research in malnourished patients living in the community and in a heterogeneous group of malnourished patients admitted to a mixed medical and surgical ward indicated that nutritional intervention with oral nutritional supplementation alone or combined with dietetic counselling was cost-effective with regard to length of stay (24).

We found that, in hip fracture patients, the probability of the nutritional intervention to be cost-effective with regard to QALY as outcome was relatively low in the older age group of  $\geq 75$  years. Of note, older patients more often live in nursing homes even before the fracture and they tend to have more co-morbidities for which medical treatment is needed; both these factors may overrule the potential cost-reduction induced by the nutritional intervention. Also, after hip fracture, older and malnourished patients may have more postoperative complications and hospital re-admissions as compared with younger and well-nourished patients. As also noted in the literature, medical costs do not seem to be associated with the type of surgical procedure but are mainly determined by increasing age, living in an institution and the presence of co morbidity (21, 38, 41). Finally, home-dwelling older patients often live

alone, which may also result in a higher requirement of professional care as compared with patients living with their partner.

We used a time horizon of 6 months because weight gain or weight maintenance is especially relevant in the vulnerable period after hip fracture, since patients with a poor nutritional status are prone to develop postoperative complications which mostly occur in the first few weeks after hip fracture surgery. In addition, the period of 6 months was chosen because the overwhelming majority of medical costs are made in the first 3 months after hip fracture due to hospitalisation, hip fracture surgery, patients' stay in rehabilitation clinic, their visits to the general practitioner and medical specialist and the treatment of postoperative complications.

It is important to note here that, even though QALYs are often used in cost-effectiveness analyses, this may not be an ideal outcome measure for evaluating effectiveness and cost-effectiveness in elderly patients and in nutritional intervention studies (20, 45). In the elderly, improvement in nutritional intake and weight may be more clinically relevant, as weight recovery is of vital importance as a basis for overall recovery during the vulnerable period after hip fracture. Also, it may be noted that weight gain is easier to achieve by nutritional intervention than improvement in quality of life, which depends on many other factors than just nutritional status. Moreover, an improvement in weight is necessary to maintain physical activity and cognitive status of the hip fracture patient. In addition, quality of life and resulting QALYs are not only determined by nutrition, but other factors such as loneliness, social support, pain and mobility. Although pain and functional status are included in the EuroQoL 3 level, this questionnaire may not be sufficiently sensitive to detect small differences in quality of life in elderly individuals. Very recently, a new version of the EuroQoL was developed with five response categories. Future research should be performed to detect if the EuroQoL 5 level is sensitive enough to detect small changes in quality of life in the elderly.

Several limitations should be noted. First, although we excluded cognitive impaired patients, volumes of health care consumption might have been influenced by cognitive status of the patients, and therefore these volumes might be over- or underestimated by the patients. Second, the economic analyses were not adjusted for baseline differences between the intervention and control group. Although costs at baseline were similar in both groups, there was a lower proportion of malnourished patients in the intervention group compared with the control group (37% vs. 48%), which might have influenced the overall analyses. However, as cost-effectiveness ratios remained similar in our analyses stratified by malnutrition (yes vs. no), we think this has not influenced our results. Finally, weight at baseline was self-reported because the majority of the hip fracture patients were bedridden at baseline.

We conclude that the additional costs of our nutritional intervention were very low as compared with the total costs. With respect to weight as outcome, the nutritional intervention was likely to be cost-effective. The probability that the nutritional intervention was cost-effective for QALYs was relatively low. Future research should incorporate other outcome measures which are more appropriate for cost-effectiveness evaluations in elderly patients, such as functional limitations, and other outcome parameters relevant for the elderly. Furthermore, effectiveness evaluations should be accompanied with economic and cost-effectiveness evaluations.

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# Chapter 6

## General discussion

In the Netherlands, as well as in other countries, the incidence of hip fractures in the elderly is high and expected to increase further in the future. Because it is thought that a poor nutritional status can delay recovery from hip fracture, leading to prolonged hospital stay, increased rate of postoperative complications and increased mortality rate, we performed a RCT to investigate the effect of intensive dietary intervention on the nutritional and functional status, total length of stay and health care costs in elderly subjects after hip fracture. The nutritional intervention was a combination of regular dietetic counselling and oral nutritional supplementation for a period of three months. Patients allocated to the control group received usual care as provided in the hospital, rehabilitation clinic or at home, i.e. dietetic counselling and/or oral nutritional supplementation were only provided on demand of the medical doctor in charge. The primary outcome measure was total length of stay in hospital and rehabilitation clinics including hospital readmissions. Secondary outcome measures, assessed at three and six months after hip fracture, were nutritional status, functional status, quality of life, complication rate and one-year mortality. Since no previous studies on the cost-effectiveness of nutritional intervention in hip fracture patients had been performed, we included a cost-effectiveness evaluation.

In this chapter, we summarise the main findings of the studies described in the previous chapters. This is followed by a comparison with previous nutritional intervention studies and a reflection on the strengths and limitations of our study. Finally, implications for future research and overall conclusions are given.

## **MAIN FINDINGS OF THIS THESIS**

### **Study population**

Between July 2007 and December 2009, we enrolled 152 hip fracture patients of which 73 were randomised to the intervention group and 79 to the control group. The majority of the hip fracture patients were female and their median age was approximately 80 years. Only 15% of the hip fracture patients lived in a nursing home or home for the elderly before hospital admission. The majority of patients had at least one chronic disease such as diabetes mellitus, cardiovascular disease or rheumatoid arthritis, and as a consequence the majority of the patients used at least one type of medication.

After hospitalisation 84 out of 152 patients (42 in both groups) were discharged to a rehabilitation clinic, and 66 (31 intervention and 35 control) were discharged to their home with home care if necessary. Two patients (both control) passed away during hospitalisation. During the three-month intervention period, seven patients (4 intervention, 3 control) passed away, and seven patients (3 intervention, 4 control) withdrew their participation.

During the three-month follow-up period (3-6 months after surgery), four patients (2 intervention, 2 control) passed away, and three patients (1 intervention, 2 control) withdrew their participation.

### **Nutritional intervention and usual care**

All 73 patients randomised to the intervention group started with the dietetic counselling and the consumption of the multi-nutrient oral nutritional supplement containing energy, protein and several vitamins, within four days postoperatively (range: 1-6 days). The median period patients were advised by the dietician to use oral nutritional supplements was 76 days (range: 3-91 days). At the end of the intervention period, 11 patients did not meet the nutritional requirements. These patients were transferred to the home care dietician for continuation of the dietetic counselling.

During the early postoperative period (0-10 days after surgery), 67% of the patients were adherent with the nutritional recommendations as given by the dietician, defined as following the recommendations of the dietician in at least 75% of the visits and telephone calls, and 79% of the patients were adherent with the oral nutritional supplement, defined as intake of the oral nutritional supplement at least 75% of the recommended amount. During the late postoperative period, between 11 days and 3 months after surgery, 73% of the patients were adherent with regard to the recommendations as given by the dietician and 80% of the patients were adherent with the oral nutritional supplements.

In the control group, 19 out of 79 patients (24%) received dietetic counselling and/or nutritional supplementation on medical indication. Eleven out of those 19 patients were identified as malnourished or at risk of malnutrition using the Mini Nutritional Assessment (MNA) at baseline.

### **Effectiveness**

Our results did not show a reduction in total length of stay in hospital and rehabilitation clinic nor in length of stay in hospital or rehabilitation clinic separately. Also, we failed to detect a reduction in overall postoperative complication rate and one-year mortality rate.

Both in the intervention and control group, nutritional intake increased during the intervention period and the increase of the intake was higher in the intervention group, mainly due to the use of the oral nutritional supplements. One week postoperatively, the nutritional intake of energy, protein (total, vegetable and animal), saturated, monounsaturated and polyunsaturated fatty acids, carbohydrates, polysaccharides, calcium, vitamin D, beta-carotene, vitamin B1, vitamin B2, vitamin B6, vitamin B12 and folic acid had increased to a significantly larger extent in the intervention group compared to the control group; further called the 'intervention effect' (defined as the difference in change between the intervention and control group from baseline). At one week postoperatively, in the intervention group 75% of the patients met their energy requirements as compared to only 55% of the patients in the control group. Mean protein intake in the intervention group was 1.2 g/kg as compared to 0.9 g/kg in the control group.

Three months postoperatively, the intervention effect for nutritional intake remained statistically significant for fat, saturated and monounsaturated fatty acids, calcium, vitamin B2, vitamin C, vitamin E and folic acid. Energy intake met the requirements in 70% of the intervention group and 68% of the control group and median protein intake was comparable in both groups (0.9 g/kg).

At six months postoperatively, the intervention effect with respect to nutritional intake did not remain statistically significant. Energy intake met the nutritional requirements in 75% of the intervention group and 69% in the control group and mean protein intake was comparable in both groups (1.0 g/kg).

With regard to nutritional status, our data showed a positive intervention effect for weight, BMI and supra-iliac skin fold at three months postoperatively. These intervention effects disappeared at six months postoperatively for weight and BMI. With respect to functional status, no intervention effect on functional status as measured by activities of daily living (ADL), household activities of daily living (HDL), handgrip strength were found at three and six months postoperatively. Cognitive status, mental status and quality of life were also not improved by the nutritional intervention. Only for reduced motivation, as a sub-domain of the Checklist Individual Strength, a significant favourable intervention effect was found at six months postoperatively.

### **Cost-effectiveness**

The economic evaluation was performed from a societal perspective, and costs data were collected at baseline and at three and six months postoperatively by means of a costing questionnaire. Costs of the nutritional intervention were calculated based on the visit registration from the dietician and the number of advised oral nutritional supplements. The mean cost of the nutritional intervention per patient in the intervention group was € 613 (range: € 30-1352), with a mean cost of € 244 for the dietetic counselling and € 370 for the oral nutritional supplements. The additional costs of the nutritional intervention were only 3% of the total treatment costs. Total costs (including costs of nutritional intervention), healthcare related costs and patient and family costs, as well as subcategories of these costs (see Chapter 5), were not significantly different between both groups.

Cost-effectiveness analyses were performed for Quality Adjusted Life Years (QALYs) and weight as outcome measures. With respect to QALYs, the probability that the nutritional intervention was cost-effective was only 45% to 60%, based on the cost-effectiveness acceptability curves. The nutritional intervention was likely to be cost-effective for weight increase during the intervention period.

## COMPARISON WITH PREVIOUS RESEARCH

In this paragraph, our study population and the results regarding the effectiveness and cost-effectiveness of our study are compared with previous research.

### Study population

In our study, hip fracture patients could participate if they were 55 years or above. In previous studies, this age boundary was higher, ranging from 60 years to 70 years (1-14). Median age of the participants in our study was comparable with the median age of participants in previous studies. Although hip fractures occur more often in women, only a few studies included only women (8, 14, 15) and only in the studies of Sullivan et al. (11, 12) the majority were men. As in our study, cognitively impaired patients were excluded in most of other studies (2, 4-6, 8, 9, 13). Like in the studies of Delmi et al. (4), Eneroth et al. (13) and Espauella et al. (2), we included both well-nourished and malnourished hip fracture patients, whereas other researchers only included only well-nourished patients (7, 15), or only patients at risk of malnutrition or malnourished patients (8, 9, 16).

### Nutritional intervention

To our knowledge, our study is the first combining intensive dietetic counselling and oral nutritional supplementation in hip fracture. Previous studies only provided either oral nutritional supplements as a nutritional intervention or nasogastric tube without support by a dietician/dietetic assistant, or only support by a dietician or dietetic assistant but no nutritional supplement.

With respect to the nutritional intervention, our dieticians concluded that our hip fracture patients were advised to use the oral nutritional supplements for 10 weeks, while our intervention period lasted for three months. The nutritional intervention developed by Brown et al. (16) and Delmi et al. (4) lasted during hospital stay and the stay in the rehabilitation clinic, while other nutritional intervention periods were shorter for i.e. one month (3, 15); or lasted for two months (2); some nutritional interventions restricted to the period of hospital stay (7, 9, 13) or the period of stay in the rehabilitation clinic. Only the nutritional interventions developed by Schurch et al. (6) and Tkatch et al. (5) had a longer intervention period of 6 months, but it has to be mentioned that patients could be enrolled up to two weeks after hip fracture. The support by the dietetic assistants in the study by Duncan et al. (14) was only provided during hospital admission, which however included the stay in the rehabilitation department of the hospital.

In previous studies, compliance with the oral nutritional supplements varied from 15 up to 100%. In our study compliance with the oral nutritional supplements was 75% based on the 24h recalls (defined as a reported intake of 75% or more of the recommended amount of oral nutritional supplements was considered to be compliant). In our study, variable amounts of oral nutritional supplementation were advised, based on the individual nutritional requirements. In previous studies, like the nutritional intervention period, the prescribed amounts of oral nutritional

supplementation varied, i.e. a small amount of oral nutritional supplements, a large amount of oral nutritional supplements or a fixed amount of nutritional supplements.

### **Effectiveness**

With respect to our primary outcome measure length of stay, we were not able to show a reduction in total length of stay as well as a reduction in length of hospital stay or length of stay in rehabilitation clinic separately. Thereby, our results did not confirm the significantly shorter length of hospital stay observed in previous studies (4-6, 16).

Our results did show a significant positive intervention effect on weight and BMI, and thereby confirm the results of previous studies which detected a favourable effect (9, 14), while other studies were not able to show a significant improvement in weight. In a quasi-experimental study in elderly hip fracture patients at risk of malnutrition, a multidisciplinary nutritional intervention during hospitalisation and after hospital discharge improved the nutritional intake of energy and protein during hospitalisation (17). In the same study, a reduction in the number of malnourished patients at three months postoperatively is reported (17).

With respect to functional status as outcome, only in the study of Tidermark et al. (8) and in the quasi-experimental study of Hoekstra et al. (17) a significant improvement of functional status was reported, while we were not able to show a significant intervention effect on functional status. In line with previous studies, we were not able to detect an improvement in quality of life (8).

While previous studies showed a reduction in postoperative complications (4, 5, 13) and a lower mortality (4, 11, 14), we were not able to show a reduction in postoperative complications, an improvement in clinical outcome or a lower mortality. It has to be noted that the nutritional intervention studies were executed over a long time period, i.e. the past 30 years. Over this period, the care for hip fractures has changed substantially; for instance, it is now advised to provide surgical repair of hip fractures within 24h after hospital admission; the length of hospital stay has been dramatically reduced, with transfer of the recovery stage to the rehabilitation setting.

### **Cost-effectiveness**

Our economic evaluation is the first to evaluate the cost-effectiveness of nutritional intervention in hip fracture patients. Only a few studies are performed to evaluate cost-effectiveness of nutritional support in malnourished elderly (18-21). In these studies, it was concluded that health care costs can be reduced by nutritional support (18-20). In one study, it was concluded that nutritional screening and treatment of malnourished patients at an early stage was cost-effective (22). In the study of Norman et al. (21) it was concluded that a 3-month nutritional intervention with oral nutritional supplements was cost-effective in malnourished patients. The results of our study showed that health care costs are comparable between the intervention and control group, and that the additional costs of the nutritional intervention are low as compared to i.e. hospital related costs.

## METHODOLOGICAL CONSIDERATIONS

In this paragraph, methodological considerations regarding study design, study population, nutritional intervention, and outcome measures are discussed.

### Design

RCTs are considered to be the golden standard with respect to study designs, and thereby the results of RCTs have the highest degree of evidence. We have chosen the RCT design as the most suitable approach, because in this design confounding by prognostic factors such as type of hip fracture, type of surgery, type of anaesthesia, medical history and medication use, is prevented. In addition, because of the randomisation procedure, it is expected that the possible confounders such as medical history are equally distributed between both groups. If significant differences between both groups are detected after performing the outcome measurements, the significant effects can be attributed to the intervention. Therefore, based on RCTs a judgement can be made which treatment option yields the best results for several outcomes.

Our effectiveness and cost-effectiveness study was performed within the framework of The Health Care Efficiency Research programme (Doelmatigheidsonderzoek) of the Netherlands Organisation for Health Research and Development (ZonMw). This implies that our study was designed as a RCT, usual care was the control treatment, and length of stay was the primary outcome measure.

The first and perhaps the most important limitation of the RCT design was that the nutritional intervention could not start immediately after hospital admission. Before participating in a RCT, patients have to be informed by a researcher and they should have sufficient time to consider participation. Therefore, for ethical reasons, it was impossible to ask hip fracture patients immediately after fracture to participate in our trial. First, hip fracture patients had to receive surgical repair of the fracture. After surgery, patients experienced considerable pain and postoperative delirium could occur, whereas the patients had to be fully conscious before they could be informed about the study and informed consent could be obtained. Because of the essential and compulsory informed consent procedure, we could enrol patients only at 1-5 days after surgery, and thereby we might have missed an important vulnerable period in which nutritional supplementation could have been crucial to improve nutritional intake and minimizing deterioration of the nutritional status.

Second, blinding was not possible in our study due to the type of the intervention (combination of dietetic counselling and oral nutritional supplementation) and because of the requirement of The Health Care Efficiency Research programme that the control group received care as usual. In an unblinded design, patients as well as researchers and dietitians knew to which group the patient was allocated. In an unblinded design several types of bias can occur, i.e. observer bias, measurement bias, and drop-out bias. We tried to minimise observer bias by having the outcome measures performed by a trained researcher who was not involved in the nutritional intervention. In addition, the study dietitians, who carried out the nutritional intervention, followed a standardised protocol with respect to the evaluation of nutritional intake. Objective outcome measurements were also performed according

to standardised procedures and postoperative complications were collected from the medical charts in which no information about group allocation was present. Measurement bias could also occur if patients in the intervention group report less pain, unpleasant feelings or symptoms and respond more in favour of the intervention, i.e. reporting less problems with functional status or reporting a higher quality of life.

Third, by performing a nutritional intervention study and comparing it with usual care, it is possible that the awareness of nursing staff, dieticians and medical doctors with regard to malnutrition was increased, leading to “contamination”, meaning that the intervention was (partly) transferred to the usual care in the control group. In addition, malnutrition has become a major political issue in the Netherlands during the study period, which may have further increase the awareness of care givers on the potential importance of malnutrition. It is possible that this resulted in a higher request of dietetic care in the control group, and that as a consequence, the results of our nutritional intervention relative to the control group were attenuated. In the control group, 19 out of 79 patients received nutritional care during hospitalisation for the hip fracture and afterwards during the recovery in the rehabilitation clinic and at home.

Fourth, the effectiveness of the nutritional intervention had to be investigated in comparison with usual care, which was in our study dietetic care on demand of the medical doctor in charge. Because of the continuously developing health care, usual care can also change within the study period. In our study, we have tried to minimise the changes in usual care.

Final consequence of performing our study within the framework of The Health Care Efficiency Research programme was that length of stay was chosen as the primary outcome measure in both the effectiveness and cost-effectiveness evaluation. In the effectiveness evaluation length of stay has the limitation that it is influenced by a number of factors which will be discussed in the section of outcome measures. In the cost-effectiveness evaluation, length of stay is not only included in the costs, but also in the effects, which implies that interpretation of these results is difficult.

### **Study population**

As in many RCTs, patient inclusion in our study was not easy. During the inclusion period, from July 2007 to December 2009, 68% of the patients who were screened for eligibility did not meet the inclusion criteria, mainly due to cognitive impairment (52%). In addition to the high exclusion rate, 60% of the patients who met the inclusion criteria refused to participate in our study. The most important reasons why patients refused to participate were that participation would take too much of their time and patients could not oversee what the outcome of the hip fracture and the hospitalisation would be. Also, some patients refused to participate because their children or informal care givers did not support their participation in the trial.

To explore whether the high exclusion rate might have influenced the results, we measured body weight, upper arm circumference and triceps skin fold thickness within a random selection of patients not meeting the exclusion criteria or refusing to participate. The results of these measures indicated that the nutritional status of these patients was not significantly different from the participating patients in our trial. Nevertheless, we think that the findings of our study have to be extrapolated carefully

because one-year mortality in our study was low (9.6% in the intervention group and 7.6% in the control group) as compared to the average one-year mortality rate of 25% in hip fracture patients of the same age group in The Netherlands (23). In addition, cognitively impaired patients were excluded because an active participation was necessary to consume the nutritional supplements, to fill out the nutritional supplements diary and the questionnaires regarding the outcome measurements. The exclusion of cognitively impaired patients has also consequences for the interpretation of our results. If these patients would have been included, they might have benefited more from the nutritional intervention due to their higher risk of malnutrition, leading to underestimation of the benefits of our nutritional intervention. On the other hand compliance with the nutritional recommendations and the nutritional supplement might be high due to the exclusion of cognitively impaired patients, increasing the observed intervention effect.

The drop-out rate in our study was very low. In the intervention group only four (5.5%) patients discontinued their participation, and in the control group six patients (7.5%). In the intervention group, the low drop-out rate can be explained by the regular contacts between the dietician and the patient. In elderly, the number of social contacts is often decreased due to living alone, decease of his/her spouse, friends and peers, loss of independency and mobility because of a decline in functional and cognitive status (24-26). Loneliness has been reported in 30% of the elderly living in the Netherlands and the prevalence was higher in the older elderly (85 years and above) as compared to younger elderly (27). Loneliness has a negative impact on the general health status and increases the risk of becoming depressed. Therefore, the visits and telephone calls of the dietician might have been of social importance and support for these hip fracture patients. Of note, in the control group, which received fewer contacts, the drop-out rate was slightly higher, but still very low as compared to the drop-out rate in previous studies.

In our study population, we included both well-nourished and malnourished patients to improve generalisability. We performed a subgroup analysis to evaluate the effectiveness of the nutritional intervention in well-nourished patients and malnourished patients according to the Mini Nutritional Assessment (MNA). At baseline, in the intervention group, 27 (37%) patients were at risk of malnutrition or malnourished, while in the control group 38 (48%) patients were at risk of malnutrition or malnourished. In well-nourished patients, at one week postoperatively, the intake of energy (**Figure 1**) and protein (**Figure 2**) increased to a significantly larger extent in the intervention group compared to the control group. From baseline to three and six months postoperatively, the intervention effect for energy and protein intake did not remain significant in well-nourished patients. In malnourished patients, the nutritional intake of protein had increased to a significantly larger extent in the intervention group compared to the control group but no effects were found for total energy intake (**Figure 2**). Again, the change in protein intake was only statistically significant from baseline to one week postoperatively. With respect to weight, the intervention effect at three months was of similar size in the malnourished and non-malnourished group, but only reached statistical significance at in well-nourished patients; at six months postoperatively, no significant intervention effect was seen in either well-nourished or malnourished patients (**Figure3**). In malnourished patients, 55% of the patients

sustained a postoperative complication, while 34% of the well-nourished patients sustained a postoperative complication. In malnourished patients at six months postoperatively, the intervention effect was only statistically significant for functional status based on the Groningen Activity Restriction Scale (GARS) because in malnourished patients in the intervention group the functional status declined. This finding may be explained by the fact that malnourished hip fracture patients in the intervention group had more postoperative complications with regard to dislocation of the hip implant and needed surgical revision of the implant and as a consequence were admitted to the hospital and rehabilitation centre relative to the control group. In addition, their dependency on home care or informal care in malnourished patients may also be higher resulting in a higher score and a higher level of disability. For other outcome parameters such as cognitive status and quality of life, no statistically significant intervention effects were found. In well-nourished patients, at three months postoperatively, the intervention effect was only statistically significant for cognitive status as measured by the Mini Mental State Examination (MMSE).

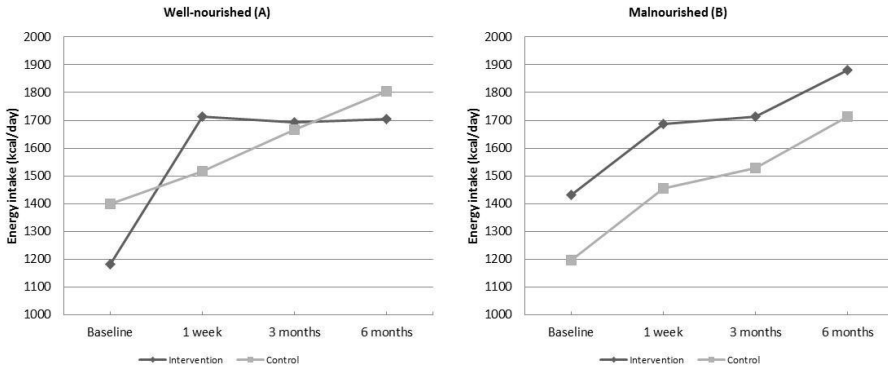


Figure 1: Energy intake over time in well-nourished patients (A) and in malnourished patients (B)

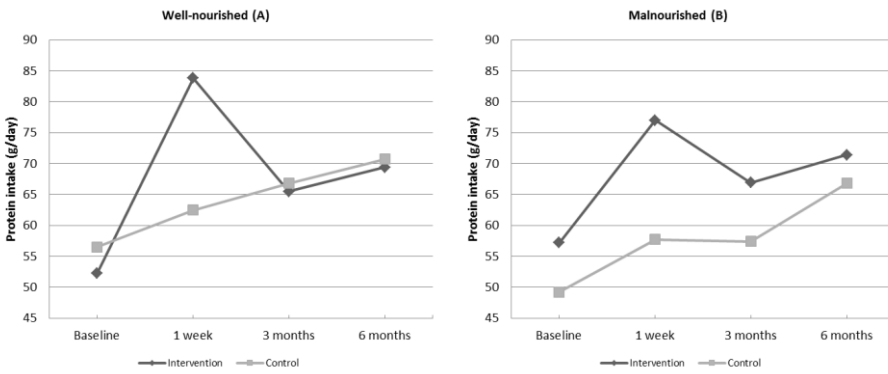


Figure 2: Energy intake over time in well-nourished patients (A) and in malnourished patients (B)

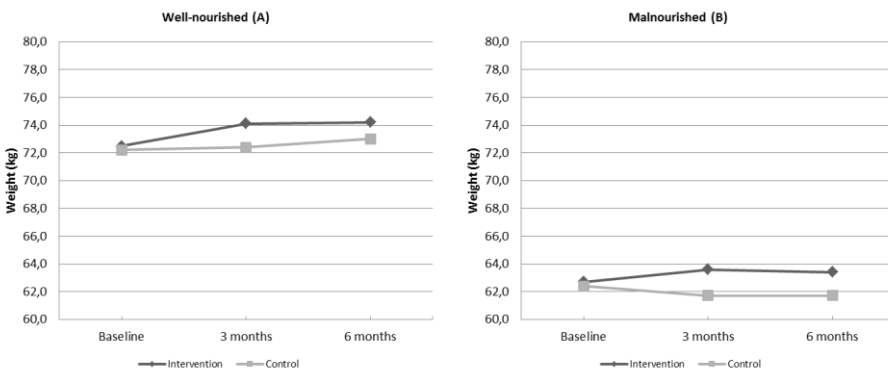


Figure 3: Weight over time in well-nourished patients (A) and in malnourished patients (B)

### **Nutritional intervention and usual care**

In most nutritional intervention studies in elderly hip fracture patients, only oral nutritional supplements were provided. Only in one study, the additional value of dietetic assistants as nutritional intervention was investigated (14). A dietetic or nutritional assistant is a person who ensures that hospitalised patients have a good and healthy nutritional intake, who assists the patient in choosing suitable meals from the hospital menu, and who orders nutritional supplements when necessary. Therefore, to our knowledge, our study was the first multicentre RCT combining dietetic counselling and oral nutritional supplementation in elderly subjects after hip fracture. During a three month intervention period, patients in the intervention group received regular dietetic counselling by face to face contacts and telephone calls with a dietician. Because of these regular visits, the dietician could anticipate quickly if the patient experienced problems with the normal dietary intake and with the supplement use. In addition, based on the individual requirements of the patients individually tailored nutritional advice was given to improve the usual dietary intake as well as the supplement use. This individually tailored nutritional intervention may be one of the reasons for the high compliance with both the nutritional recommendations and the oral nutritional supplement consumption. In elderly, individually tailoring of recommendations is also important because changing behaviour is difficult and it may take more time to change behaviour and usual patterns. Also, because of cognitive impairments they might forget the recommendations more often than younger people.

The nutritional intervention period encompassed a period of three months instead of the shorter periods in previous studies (i.e. intervention only during hospitalisation, or for a period of 1 month). Based on dieticians' judgement, patients in the intervention group needed the nutritional supplementation for a median period of 76 days, and 11 patients were still considered by the dietician to be in need of dietetic care after the three month intervention period. This prolonged intervention period gave us the opportunity to follow the patient during the complete trajectory from hospitalisation throughout rehabilitation and in the home situation.

The transfers from hospital to the rehabilitation clinic or to the home situation are stressful events for the hip fracture patients. In each setting, there are specific problems with respect to nutritional care. In the hospital and rehabilitation clinic, the patient can choose his/her meal from alternating options of the menu (a selection of starters and main dishes), but taking into account individual preferences with regard to food choice is difficult. In the home situation, hip fracture patients have to take care of their own meal, i.e. buying food and preparing meals have to be done by themselves or by the informal care giver. Because the dietician visited the patient in each setting, specific problems experienced by individual patients in each setting could be handled. The dietician took care of the optimisation of the nutritional care for the patient. In our study, the patients in the intervention group were visited by one and the same dietician throughout the entire nutritional intervention period of three months, which allowed the establishment of a confidential atmosphere and the trust that the dietician would provide the best possible care.

## Outcome measures

In our study, the outcome measurements were a combination of both objective endpoints such as length of stay, postoperative complications and anthropometric measurements, and subjective endpoints such as the nutritional intake measured by the 24h recalls and questionnaires measuring functional status, cognitive status and quality of life.

Length of stay in hospital and rehabilitation clinics was chosen as the primary outcome measure because we expected that a reduction in length of stay would lead to a reduction in costs. The hypothesis was that an improvement of nutritional status would lead to a reduction in length of stay. However length of stay is influenced by a variety of factors such as the patient's medical condition, domestic factors, social factors and, important health care related factors. As soon as the patient's medical condition permits the patient to be discharged from the hospital, the hospital staff has to evaluate whether the patient can be discharged to his/her home, e.g. does the patient has to climb stairs at home? Also social factors must be evaluated, such as the presence of a spouse or informal care givers: who can do the shopping and preparing meals, and who can assist in activities of daily living and household activities of daily living? If patients are discharged to a rehabilitation clinic, length of stay may be delayed if there is no bed available in the rehabilitation clinic. In that case, the patient has to stay longer in the hospital. Similarly, length of stay in the rehabilitation clinic is strongly determined by the period that the patient receives an indication to stay in the rehabilitation clinic and by the standardised weekly discharge dates.

As a consequence, to have a measurable impact on length of stay, the effect of the nutritional intervention has to be very substantial. We attempted to receive information with respect to the date the patients were ready to be discharge, by asking the medical doctors in charge to fill out an extra discharge form which was attached to the general discharge forms which have to be filled out at discharge. Unfortunately, as filling out this extra form was not part of their daily routine, very few forms were returned to the researchers. We tried to increase the number of responses by making phone calls to the medical doctors in charge to fill out the form and by asking the medical doctors while the researchers visited the wards. Since a few years, more attention is paid to the inappropriate bed problem (in Dutch "Verkeerde bed problematiek"), indicating that patients who are medically ready to be discharged from the hospital are still admitted. In hospitals, transfer offices or discharge offices are created, which are responsible for patient discharge by optimising the transfers between hospital and rehabilitation setting and by identifying "inappropriate bed patients". In the Netherlands, each hospital is required to report the number of inappropriate bed patients and the length of stay of inappropriate bed patients to The Health Care Inspectorate (in Dutch: Inspectie voor de Gezondheidszorg (IGZ)). Because of the discharge offices, medically induced length of stay and inappropriate bed length of stay are available for hospitalised patients. In conclusion, although length of stay is a very important outcome measure, it is less suitable as the primary outcome measure in an effectiveness study.

At baseline, weight was self-reported, because patients were not able to get in and out of bed independently due to pain after hip fracture surgery. It is known that patients

often underestimate their weight and overestimate their height (28). Furthermore, measuring waist and hip circumferences and skin folds in bedridden patients is also difficult to perform, which resulted in missing and less reliable values within these measurements. In all, it was difficult to make a comprehensive assessment of the nutritional status at baseline.

In addition to anthropometric measurements of nutritional status and body composition, we attempted to perform bioelectrical impedance analysis (BIA) measurement to assess the change in fat free mass in addition to weight change. Unfortunately, BIA measurements could only be completed in half of the patients. First, patients with a pacemaker had to be excluded. Second, performing the BIA in the home situation proved to be difficult since many patients wore elastic stockings, used body lotion or were unable to climb the stairs independently. Third, we noted that patients were not as comfortable as in the hospital with respect to partly undressing. In all cases, patients had been carefully instructed not to dress with elastic stockings or to use body lotion, but apparently, this was not sufficient in this elderly population, even despite the exclusion of cognitively impaired subjects. Our findings would suggest that the BIA technique is less suitable for application in elderly subjects in the home setting.

Another issue is the timing of the outcome assessment. In our study, nutritional and functional status had been measured only at baseline and three and six months postoperatively. If nutritional and functional status were measured more frequently, e.g. monthly, improvements in functional status might have been better visible since shortly after discharge, hip fracture patients are usually unable to perform household activities, while after three months, the majority of the patients were able to perform these household activities. In addition, healthy elderly individuals often receive assistance from an informal care giver or from a home care organisation for performing household activities of daily living. If they already receive this help prior to the hip fracture, an improvement in this activity is not possible. Further, if a major event such as a hip fracture occurs, a thorough evaluation of the patient's ability to live independent is often performed and home care or transfer to a nursing home or home for the elderly is organised. Patients might have the tendency to report that they are not able to perform e.g. activities of daily living themselves, while they still perhaps could do the activity if no help was available. This might have led to an underestimation of the actual functional status and thereby attenuated the effects of the nutritional intervention. In addition, in patients in the intervention group, regular evaluation of care by nursing staff and informal care givers (if present) was also a part of the dietetic counselling as given by the study dietitians.

Many outcome measures in questionnaires specifically designed for elderly are in practice not the most appropriate method to gain information on mental status, functional status and quality of life. Elderly patients may have the tendency to give socially acceptable answers which may introduce measurement bias in the results. In addition, filling out several questionnaires independently was found to be too exhausting for a majority of the patients. Therefore, we offered the patients some help e.g. by asking the questionnaires in an oral interview. The procedures for helping the patients filling out the questionnaires were standardised to avoid that patients would

give socially accepted answers or answers which did not fit in the answer categories of the questionnaires.

Quality of Life in our study was measured by means of the EuroQoL and the Short Form Health Survey (SF-36). In our study population, response rate to the EuroQoL was better than the SF-36 because the EuroQoL is a short questionnaire with questions that patients can easily answer. There is some evidence that in elderly the SF-36 has a higher sensitivity in patients with a lower level of morbidity, but the EuroQoL questionnaire has been reported to be sufficiently sensitive in elderly patients to evaluate changes in quality of life. Quality of life is a subjective outcome which may be influenced by a change in the patient's perception of the current health status or quality of life. After hip fracture, elderly may have the tendency to accept that e.g. their functional status is not as good as it was before fracture and that they need assistance to perform their activities of daily living. During the study period, several patients mentioned that they were happy they already had lived for such a long time without any help, and that after the fracture; they just adapted themselves to the current situation. This shift in pattern of thought and the perception of quality of life, which is called response shift, could have attenuated the effects of the nutritional intervention on this outcome measure. In addition, this might also be an explanation why the likelihood that the nutritional intervention is cost-effective with respect to quality of life is limited.

### **Economic evaluation**

Like for the effectiveness evaluation, use of length of stay as primary outcome measure in the cost-effectiveness evaluation has clear limitations. First, limitations of length of stay as outcome measure for the effectiveness evaluation, as described in the previous paragraph, do also hold for the economic evaluation. Second, length of stay is not only an outcome measure, but also an important determinant of health care costs, since the costs of the stay in hospital and rehabilitation clinic are taken into account when calculating total health care costs. In cost-effectiveness analysis, length of stay can be taken into account either on the effectiveness calculation or in the cost calculation but not in both the effect and cost calculation. Although the hypotheses that a reduction in length of stay results in a reduction in costs holds, it is difficult to make the cost reduction because of the reduction clear.

Another limitation of our economic evaluation is that it was only based on the costing questionnaires filled out by the patients at baseline, at three months postoperatively and at six-months postoperatively. Ideally, we would have based our analyses on the administrative data on all the activities carried out during hospital admission and control visits to the medical specialists.

Moreover, since January 2005, In the Netherlands, the hospital financing is based on the financing by "diagnosis treatment combinations" (diagnosebehandelcombinaties, DBC) instead of the previous financing based on the payment of costs based on tariffs for each separate activity conducted in the hospital. A DBC is a medical process description and encompasses all activities that result from the care question (e.g. hip fracture) of the patient. For each DBC (through adding up all activities in that DBC), a price ticket is determined. A DBC has a combination of product and price. The price of

the DBC is negotiated between insurance companies and individual hospitals, therefore prices between hospitals may vary. Even though hospitals still have the activity registrations, the DBC registration has become more important in practice. For simplifying the hospital financing, the use of DBCs may be of use, however to evaluate costs and cost-effectiveness the DBC registration has its limitations. Even though DBC codes are registered on a patient level, the actual activities performed within the DBC code are only visible for financial staff in the hospital. In addition, because prices for a DBC code vary between hospitals, the financial staff of hospitals is not willing to share these prices, even not for research purposes. Another item that made the cost-effectiveness evaluation difficult to perform was the fact that our study was a multi-centre trial resulting in difficulties in gathering the data on patient level. The introduction of the DBC system has introduced a major problem for cost-effectiveness research, and in the present study to the use of questionnaires turned out to be the only reliable alternative to perform the cost-effectiveness analysis. From January 2012 onwards, DBCs are replaced by DBCs route to transparency in Dutch “DBC’s Op weg naar Transparantie” (DBC’s on route to transparency, or DOTs). The major difference between DBC registration and DOT registration is that within the DBC registration, the caregiver determines, at the time of hospital admission, which care related to a specific DBC the patient will receive. In the DOT registration, both the diagnosis and the treatment are registered on admission of the patient; then, after the treatment has been completed, an independent national system determines which care trajectory will be financed. As a consequence, it will become more transparent which care is delivered and which care is financed. With respect to performing economic evaluations, the DOT registration might make it easier to gain insight in all activities performed at the patient level, and also the extraction of the data wanted for research purposes from multiple settings might become easier. If tariffs or standard costs prices are available for each activity, performing an economic evaluation or cost-effectiveness analysis may become easier and better standardised.

## IMPLICATIONS

The results of our study have several implications for health-care practice and future research on nutritional interventions.

### Implications for health-care practice

Health care is in continuous development and continuously improving. Within the past years, nutritional care in hospitals has become an important issue and the usual nutritional care has undergone changes. One of the developments in usual nutritional care is that The Health Care Inspectorate (in Dutch: Inspectie voor de Gezondheidszorg (IGZ)) has included malnutrition as a performance indicator which must be continuously monitored by every hospital (in Dutch: prestatie indicator). These performance indicators are used by the IGZ to determine which hospital care processes need extra attention or which hospital care processes should be improved. The performance indicator “Malnutrition” is a measure for the extent to which

patients are systematically screened for malnutrition and the extent to which malnourished patients receive adequate dietary treatment in time. Each hospital in The Netherlands has to report the number of patients screened for malnutrition (including which screening tool was used; i.e. Short Nutritional Assessment Questionnaire (SNAQ) or Malnutrition Universal Screening Tool (MUST)); the number of patients classified as malnourished or at risk of malnutrition, and the number of patients treated for malnutrition. Because of the introduction of malnutrition as a performance indicator, malnutrition has received more attention lately and patients are being screened and treated in a more systematic way. Even though (as already noted above) the frequency of nutritional support in the control group in our study would suggest that some contamination of nutritional intervention occurred in our control group, it is important to note that the hip fracture patients included in our study were not systematically screened for malnutrition by this “improved” usual care. As a consequence, it would be important to evaluate the “improved” usual care and the additional value of nutritional intervention combining intensive dietetic counselling and oral nutritional supplementation for specific groups such as hip fracture patients. The current policy in clinical practice is that, if the presence of malnutrition or risk for malnutrition in a patient is diagnosed, dietary treatment is always indicated. However, in a recently published report by the Health Council of the Netherlands (in Dutch Gezondheidsraad) entitled “Malnutrition in the elderly” (29) it is concluded that:

1. There are no appropriate measurements to identify the patient who are in need of dietary treatment and for which patients this dietary treatment would result in health gain such as a reduced length of stay and a reduced mortality risk.
2. By the current policy, too many patients might be classified as being malnourished or at risk of malnutrition and receive dietary treatment.

Unfortunately, the Health Council of the Netherlands does not indicate how these difficult issues of determining the nutritional status of patients and starting nutritional treatment should be dealt with in clinical practice. As a reaction to the report of the Health Council of the Netherlands a commentary was published in which the authors pointed out that malnutrition is as a huge problem associated with negative health outcomes especially in frail elderly (30). According to these authors, a clear and useful definition of malnutrition is lacking and therefore more research is needed to define malnutrition, with a special need for RCTs in homogeneous groups of elderly to give evidence on the most effective treatment strategies in the different populations in old age. These authors describe malnutrition in the elderly as a geriatric syndrome because of the multifactorial aetiology. Weight loss (amongst other risk factors) is considered by the authors as a reason for a full geriatric examination of the patient with respect to frailty, geriatric syndromes and disease burden, to be followed by a multifaceted intervention targeted at all identified risk factors in order to improve overall health, functional performance, and overall well-being. By this preventive geriatric examination, patients in need of dietary treatment (nutritional supplementation) will be identified. This geriatric examination could be performed during hospital admission, which ideally would result in an optimal treatment plan or passport for optimal care both in the hospital, the rehabilitation clinic and at home (30).

### Implications for future research

First, it should be investigated if nutritional intervention starting immediately after hospital admission improves the effectiveness of nutritional intervention. To answer this question, a RCT may not be the optimal design; instead a quasi-experiment over time may be a more appropriate design. The study could be executed as follows: during the first period, all consecutive patients are included as control group. Then, medical, nursing and dietetic staffs are trained regarding the intervention and during a second period, all consecutive patients are included as intervention group. Outcome measurements should be performed by trained researchers who are not involved in the care for hip fracture patients. Another possible design is randomisation of medical wards to which the patients are admitted, so in each hospital there is one ward in which admitted patients receive usual care and on the other ward were patients receive the nutritional intervention. The application of a non-randomised design would also allow the inclusion all hip fracture patients, and not only a (relatively healthy) subset of patients. The high risk of bias should be taken into account.

The participation rate of hip fracture patients to scientific research may be increased by informing relatives and informal caregivers as early as possible by the trained researcher or by the medical doctor in charge instead of informing by the patient themselves, especially in the old elderly this may help. These relatives or informal caregivers may also serve as a proxy to obtain informed consent in cognitively impaired patients, they can help filling out questionnaires, and they can be interviewed regarding the tasks they perform as informal care givers and the duration of the informal care.

Although the Cochrane Review (31) underlying the present study suggested that malnourished hip fracture patients might benefit more from the nutritional intervention, we were not able to draw this conclusion based on the subgroup analysis. The role of malnutrition in hip fracture patients is still unclear; it can be a cause and/or a consequence of hip fracture. Furthermore, all hip fracture patients are at risk of developing malnutrition and therefore future research should focus upon all hip fracture patients.

With respect to outcome measures, nutritional and functional status should be measured more frequently in order enhance the detection of changes in the speed of recovery, e.g. monthly instead of three-monthly measurements. In addition, the measurement of outcome parameters should be simplified and targeted to the population in and setting in which these measurements are performed i.e. a BIA can only be accurately performed in a health care setting such as a hospital or rehabilitation clinic, where nursing staff can help the patients to undress. Ideally, for this purpose, outcome measurements could be combined with the control visits to the hospital. This could be achieved by installing facilities where the BIA and other functional tests such as the timed chair-stand test and the timed Up&Go test can be executed.

For a detailed cost-effectiveness analysis, it might be helpful if the financial staff of the participating centres is a part of the project team, so that bottlenecks in data collection can be managed in the beginning of the data collection phase. In addition, future trials

investigating the effectiveness of a nutritional intervention should also incorporate a cost-effectiveness evaluation to investigate whether nutritional intervention reduces health care costs in all hip fracture patients.

## **CONCLUSIONS**

Despite all the efforts done to maximise the outcomes of the nutritional intervention, i.e. individually tailored nutritional intervention, high compliance with supplements and nutritional recommendations, nutritional intervention for a long period, the results of our study are limited. The findings in this thesis indicate that nutritional intake and weight status at three months postoperatively can be improved by intensive nutritional intervention combining regular dietetic counselling and oral nutritional supplementation for a period of three months postoperatively. This nutritional intervention did not result in a measurable improvement of functional status and quality of life, nor in a reduction of total length of stay in hospital and rehabilitation clinics, or in one-year mortality rate. Costs of the nutritional intervention are very low when compared with total costs following hip fracture.

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# Summary



## SUMMARY

In this thesis, the results of a nutritional intervention study in elderly hip fracture patients are presented.

**Chapter 1** is the general introduction of this thesis. This chapter presents an overview of the incidence and consequences of hip fractures, of malnutrition and of malnutrition in hip fracture patients. A concise review of the literature regarding nutritional intervention studies in hip fracture patients is presented. This thesis encompasses the results of the first combined effectiveness and cost-effectiveness study of nutritional intervention in elderly subjects after hip fracture. The aim of this study was to assess the effect of an intensive dietary intervention, comprising a combination of dietetic counselling and oral nutritional supplementation during hospitalisation and after discharge, on the nutritional status, total length of stay and health care costs in elderly subjects after hip fracture. We hypothesized that the combination of dietetic counselling and oral nutritional supplementation in hip fracture patients would improve patients' energy and protein intake, improve their nutritional status, reduce the number of complications and total length of stay in the hospital and rehabilitation clinics, and lower health care costs.

**Chapter 2** describes the design of an intervention study designed to evaluate the effect of nutritional intervention on nutritional status, functional status, total length of stay, postoperative complications and cost-effectiveness in elderly subjects after hip fracture. The study was an open-labelled, multi-centre, randomised controlled trial. The study population consisted of fracture patients aged 55 years and above admitted for surgical treatment of their hip fracture. Patients allocated to the intervention group received intensive dietetic counselling (by regular home visits and telephone calls) and oral nutritional supplementation for three months postoperatively. Patients allocated to the control group received usual dietetic care as provided by the hospital. The primary outcome measure was total length of stay in hospital and rehabilitation clinics including hospital readmissions. Secondary outcome measures, assessed at three and six months after hip fracture, were nutritional status, functional status, quality of life, complication rate and one-year mortality. Cost-effectiveness analyses were performed from a societal perspective, which means that all relevant costs and outcomes were taken into account.

**Chapter 3** describes the effects of the intensive nutritional intervention on the outcome parameters length of stay, postoperative complications, functional status, quality of life and one-year mortality rate. Of 152 patients enrolled, 73 patients were allocated to the intervention group and 79 patients were allocated to the control group. Results showed that total length of stay, as well as length of stay in the hospital and length of stay in the rehabilitation clinic separately, was comparable in both groups. At three and six months postoperatively, no difference in functional status, quality of life and one-year mortality rate was detected.

In **Chapter 4**, the results of the intensive nutritional intervention on nutritional intake and nutritional status are presented. Nutritional intake and nutritional status were assessed at baseline during hospitalisation and at three and six months postoperatively at the patients home. At three months postoperatively, dietary intake of fat, fatty acids, calcium and vitamins, as well as weight, BMI, supra-iliac skin fold thickness, and blood levels of vitamin C and 5-methyl-tetrahydrofolate had increased to a significantly larger extent in the intervention group compared to the control group. At six months postoperatively, only the increase of the supra-iliac skin fold thickness remained significantly different. From this chapter it can be concluded that intensive dietetic counselling and oral nutritional supplementation for three months improved nutritional intake of both macro-and micro-nutrients, and induced weight gain in elderly hip fracture patients.

**Chapter 5** reports the economic evaluation of this study, which aimed to assess the cost-effectiveness of the nutritional intervention compared to usual care in The Netherlands. The cost-effectiveness analysis was performed from a societal perspective. Incremental cost-effectiveness ratios (ICERs) were calculated for weight at 3 months and quality adjusted life years (QALYs) at 6 months postoperatively. Mean costs of the nutritional intervention amounted 613 Euro per patient. Total costs and subcategories of costs were not significantly different between the intervention and control group. Based on bootstrapping of ICERs, the nutritional intervention was likely to be cost-effective for weight as outcome over the 3-month intervention period, regardless of nutritional status at baseline. With QALYs as outcome, the probability for the nutritional intervention being cost-effective was relatively low, except in subjects aged below 75 years. From the cost-effectiveness analyses, it can be concluded that intensive nutritional intervention in elderly hip fracture patients is likely to be cost-effective for weight but not for QALYs.

The general discussion in **Chapter 6** provides an overview and discussion of the main findings presented in the previous chapters of this thesis. Methodological considerations and implications for future practice and future research are presented. The main conclusion of the study presented in this thesis is that despite all the efforts done to maximise the outcomes of the nutritional intervention, the results of our study are limited. The findings in this thesis indicate that nutritional intake and weight status at three months postoperatively can be improved by intensive nutritional intervention combining regular dietetic counselling and oral nutritional supplementation for a period of three months postoperatively. This nutritional intervention did not result in a measurable improvement of functional status and quality of life, nor in a reduction of total length of stay in hospital and rehabilitation clinics, or in one-year mortality rate. Costs of the nutritional intervention are very low when compared with total costs following hip fracture.

# Samenvatting



## SAMENVATTING

Dit proefschrift beschrijft de effectiviteit en de kosteneffectiviteit van een voedingsinterventie bij oudere heupfractuurpatiënten.

In **Hoofdstuk 1** wordt een overzicht gegeven van de incidentie, de risicofactoren en de gevolgen van een heupfractuur, van ondervoeding en van ondervoeding bij heupfractuurpatiënten. Verder wordt in dit hoofdstuk een beknopt overzicht gepresenteerd van eerdere wetenschappelijke studies waarbij een voedingsinterventie werd aangeboden bij heupfractuurpatiënten. Het doel van onze studie was: het bepalen van de effectiviteit en kosteneffectiviteit van een voedingsinterventie bij oudere heupfractuurpatiënten in vergelijking met de reguliere voedingszorg zoals deze aangeboden werd in het ziekenhuis en de herstelkliniek. De primaire uitkomstmaat was de totale opnameduur van het verblijf in het ziekenhuis en in de herstelkliniek. Secundaire uitkomstmaten waren: voedingstoestand, functionele status, kwaliteit van leven, postoperatieve complicaties en 1-jaars mortaliteit (sterftecijfer). De derde uitkomstmaat was de economische evaluatie van de voedingsinterventie.

In **Hoofdstuk 2** wordt het van de interventiestudie toegelicht. De studie is opgezet als een open-label, multicenter, gerandomiseerd onderzoek. De onderzoekspopulatie bestond uit heupfractuurpatiënten vanaf 55 jaar opgenomen in het ziekenhuis voor chirurgische behandeling van heupfractuur. De deelnemers werden door loting toegewezen aan twee groepen; de interventiegroep en de controlegroep. Patiënten toegewezen aan de interventiegroep kregen, voor een periode van 3 maanden, een intensieve voedingsinterventie bestaande uit voedingsadvies door een diëtiste (door regelmatige huisbezoeken en telefonische gesprekken), aangevuld met energie- en eiwitverrijkte drinkvoeding. Patiënten toegewezen aan de controlegroep kregen de gebruikelijke voedingszorg zoals deze in het ziekenhuis of de herstelkliniek aangeboden werd; dit betekent dat de patiënten alleen voedingsadvies kregen wanneer de behandelende arts dit nodig vond. Verder staat in dit hoofdstuk beschreven welke metingen bij de deelnemers werden uitgevoerd en op welk tijdstip.

**Hoofdstuk 3** beschrijft de effecten van de intensieve voedingsinterventie op de uitkomstmaten: opnameduur, postoperatieve complicaties, functionele status, kwaliteit van leven en 1-jaars mortaliteit. In totaal hebben 152 patiënten deelgenomen aan het onderzoek waarvan 73 patiënten toegewezen werden aan de interventiegroep en 79 patiënten aan de controlegroep. De resultaten lieten zien dat de totale opnameduur in het ziekenhuis en de herstelkliniek, evenals de opnameduur in het ziekenhuis en de herstelkliniek afzonderlijk, vergelijkbaar waren in beide groepen. Na 3 en 6 maanden na de heupfractuur, werd geen verschil gevonden in functionele status, kwaliteit van leven en 1-jaars mortaliteit.

In **Hoofdstuk 4** worden de resultaten van de intensieve voedingsinterventie beschreven betreffende de uitkomstmaten: voedingsinname en voedingstoestand. Voedingsinname en voedingstoestand werden beoordeeld tijdens het verblijf in het ziekenhuis en na 3 en 6 maanden na de heupfractuur bij de patiënt thuis. Drie

maanden na de heupfractuur was de inname van vetten, vetzuren, calcium en vitamines in een grotere mate toegenomen in de interventiegroep in vergelijking met de inname van deze voedingsstoffen in de controlegroep. Ook was drie maanden na de heupfractuur, het gewicht, de Body Mass Index (BMI), de dikte van de supra-iliacale huidplooi en de waarden van de bloedspiegels van vitamine C en 5-methyl-tetrahydrofolaat verhoogd in een grotere mate in de interventiegroep in vergelijking met de controlegroep. Zes maanden na de heupfractuur, was alleen de toename van de dikte van de supra-iliacale huidplooi verschillend tussen de beide groepen. Uit dit hoofdstuk kan geconcludeerd worden dat een intensieve voedingsbegeleiding aangevuld met energie- en eiwitverrijkte drinkvoeding voor een periode van 3 maanden zorgt voor een verbetering van de inname van zowel macro- als micronutriënten en voor gewichtstoename bij oudere heupfractuurpatiënten.

In **Hoofdstuk 5** wordt de economische evaluatie van deze studie gerapporteerd, met als doel het bepalen van de kosteneffectiviteit van de voedingsinterventie in vergelijking met de gebruikelijke voedingszorg. De kosteneffectiviteitanalyse werd uitgevoerd vanuit een maatschappelijk perspectief, dit wil zeggen dat alle relevante kosten voor de samenleving meegenomen worden in deze berekening. Er werden incrementele kosteneffectiviteit ratio (ICERS) berekend voor het gewichtsverschil op 3 maanden na de heupfractuur en voor kwaliteitgecorrigeerde levensjaren (quality adjusted life years) (QALY's) 6 maanden na de heupfractuur. De gemiddelde kosten van de voedingsinterventie waren € 613 per patiënt. De totale kosten en subcategorieën van de kosten waren niet verschillend tussen beide groepen. Uit de economische evaluatie blijkt dat de intensieve voedingsinterventie waarschijnlijk kosteneffectief is voor gewicht als uitkomstmaat over de 3-maands interventieperiode, ongeacht de voedingstoestand bij de ziekenhuisopname. Met QALY als uitkomstmaat is de kans dat de voedingsinterventie kosteneffectief is relatief laag, behalve bij personen jonger dan 75 jaar. Uit de kosteneffectiviteitanalyses kan geconcludeerd worden dat een intensieve voedingsinterventie bij oudere heupfractuurpatiënten waarschijnlijk kosteneffectief is voor gewicht, maar niet voor QALY's.

In **Hoofdstuk 6** worden de belangrijkste bevindingen zoals beschreven in de voorgaande hoofdstukken van dit proefschrift besproken. Er worden methodologische overwegingen en gevolgen voor de toekomstige praktijk en voor toekomstig wetenschappelijk onderzoek gepresenteerd. De belangrijkste conclusie van het onderzoek beschreven in dit proefschrift is dat ondanks alle inspanningen die gedaan zijn om de uitkomsten van de voedingsinterventie te maximaliseren, de resultaten van ons onderzoek beperkt zijn. De bevindingen in dit proefschrift geven aan dat voedingsinname en gewicht drie maanden na de heupfractuur verbeterd kunnen worden door intensieve voedingsinterventie bestaande uit de combinatie van voedingsadvies door een diëtiste en energie- en eiwitverrijkte drinkvoeding. Deze voedingsinterventie heeft niet geleid tot een meetbare verbetering van de functionele status en kwaliteit van leven, noch tot een vermindering van de totale opnameduur in het ziekenhuis en de herstelkliniek, of in een vermindering van de 1-jaars mortaliteit. Verder kan besloten worden dat de kosten van de intensieve voedingsinterventie zijn zeer laag in vergelijking met de totale kosten na een heupfractuur.

# Dankwoord

DANKWOORD

## DANKWOORD

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# List of publications

LIST OF PUBLICATIONS

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**Wyers CE**, Reijven PLM, van Helden SH, Willems PC, Evers S, Heyligers I, Verburg A, Dagnelie PC. Cost-effectiveness of nutritional intervention in elderly patients after hip fracture. *Osteoporos Int* (<http://dx.doi.org/10.1007/s00198-012-2009-7>)

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# Curriculum vitae



**CURRICULUM VITAE**

Caroline Wyers was born on August 10th 1983 in Hasselt (Belgium). She completed secondary school at Biotechnicum in Bocholt. In 2001, Caroline started studying Biomedical Sciences at the Transnational University Limburg (TUL) campus Limburgs Universitair Centrum (Nowadays known as Hasselt University). She continued her education at Maastricht University in 2003, which resulted in a Master's degree in Health Sciences with a specialisation in Health Education and Health Promotion and in Health Care Studies. In 2006, she also obtained the Master's degree in Health Sciences with specialisation Epidemiology at the same university. From January 2007 to March 2012, she was employed as a PhD-student at the Department of Epidemiology, Maastricht University on the research project entitled 'Effectiveness and cost-effectiveness of nutritional intervention in elderly subjects after hip fracture: A Multicentre Randomised Controlled Trial', resulting in the present thesis. Since April 2012, Caroline is employed as a post-doctoral researcher at the Department of Health Services Research, Maastricht University.

## LIST OF ABBREVIATIONS

ADL	Activities of Daily Living
AMT	Abbreviated Mental Test
ASA	American Society of Anesthesiologists
BAPEN	British Association for Parenteral and Enteral Nutrition
BMI	Body Mass Index
CEAC	Cost-effectiveness Acceptability Curve
CEP	Cost-effectiveness Plane
CIS	Checklist Individual Strength
CRP	C-reactive Protein
ESPEN	European Society for Clinical Nutrition and Metabolism
GARS	Groningen Activity Restriction Scale
GCP	Good Clinical Practice
HADS	Hospital Anxiety and Depression Scale
ICER	Incremental Cost-effectiveness Ratio
MMSE	Mini Mental State Examination
MNA	Mini Nutritional Assessment
MUST	Malnutrition Universal Screening Tool
NE	North East
NW	North West
ONS	Oral Nutritional Supplement
QALY	Quality Adjusted Life Year
SE	South East
SNAQ	Short Nutritional Assessment Questionnaire
SW	South West