Prognosis, Proof and Priorities in dietetic practice

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Prognosis, Proof and Priorities in dietetic practice

Prognose, bewijs en prioriteiten in de diëtistenpraktijk

(met samenvatting in het Nederlands)

Proefschrift

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Our little systems have their day;
They have their day and cease to be:
They are but broken lights of thee,
And thou, O Lord, art more than they.

Alfred Lord Tennyson (1809-1892)

Manuscripts based on the studies described in this thesis

Chapter 2.1
Iestra JA, Fibbe WE, Zwinderman AH, Romijn JA, Kromhout D. *Parenteral nutrition following intensive cytotoxic therapy: an exploratory study on the need for parenteral nutrition after various treatment approaches for haematological malignancies.* Bone Marrow Transplant. 1999 May;23(9):933-9.

Chapter 2.2
Iestra JA, Fibbe WE, Zwinderman AH, van Staveren WA, Kromhout D. *Body weight recovery, eating difficulties and compliance with dietary advice in the first year after stem cell transplantation: a prospective study.* Bone Marrow Transplant. 2002 March;29(5):417-24.

Chapter 3.1
Iestra JA, Knoops KTB, Kromhout D, de Groot CPGM, Grobbee DE, van Staveren WA. Lifestyle, *Mediterranean Diet and Survival in European post-Myocardial Infarction Patients.* Eur J Cardiovasc Prev Rehabil 2006: in press

Chapter 3.2
Iestra JA, Kromhout D, van der Schouw YT, Grobbee DE, Boshuizen HC, van Staveren WA. *Effect size estimates of lifestyle and dietary changes on all-cause mortality in coronary artery disease patients: a systematic review.* Circulation. 2005 Aug;112(6):924-34.

Contents

Chapter 1 Introduction

Prognosis, proof and priorities in dietetic practice

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1 Introduction and outline of the thesis

The Dutch prevention policy document 2004-2007[1] expresses the need for more disease prevention interventions, not only at work, school or living area, but also in the curative domain of health care. In hospitals the dietitian is traditionally involved with preventive activities. In the field of dietetics it is even hard to make a clear distinction between curative and preventive interventions.

Because of the direct relationship between dietary determinants and health outcomes, changes in diet may be beneficial for many hospitalised patients, irrespectively of their actual treatment indication. In contrast to the - literally infinite- number of opportunities for nutrition related preventive actions in a hospital, the available budget for dietetic interventions is restricted. The new focus on prevention provides an opportunity to reflect upon, and evaluate, which facts and principles should guide the priorities in hospital-based dietetic practice.

Focus and problem analysis

Priorities can be set implicitly or explicitly. Implicit decisions are decisions taken in accordance with existing traditions without being questioned. Several patient selections are possible: referral by unspecified criteria, waiting lists, patients self selection, or selections based on reimbursement procedures. In many of these selection traditions prevention will probably not receive a high priority.

Potential barriers for a focus on prevention in clinical health care are:

- curative interventions are always more urgent in the clinical setting,
- where the need for cure is typically indicated by observable complaints, prevention decisions are to be made on an assessed but yet invisible risk,
- where curative interventions are often rewarded with a release from the complaint, the effect of preventive measures is often not immediately measurable,
- the structure of the Dutch health care system is very compartmentalised: preventive actions in hospitals are generally badly financed,
- in the vision of many hospital-based health professionals their responsibility is to repair bodily dysfunction but health promotion is deemed to be the task of professionals in the primary care and public health sector,
- grateful patients are few in prevention, where success is marked by a non-event[2].

Awareness of these barriers helps to understand that prevention requires a strategic approach. Defining priorities more explicitly may help to improve the quality of decisions and to anticipate continuing changes in the medical environment.

What information, knowledge and values are needed to guarantee the quality of priority decisions in a hospital-based dietetic department? In this thesis four examples of research projects aiming to provide a knowledge base for preventive priorities in dietetic practice are described. Also, ethical aspects of priority decisions are discussed. Before describing the outline of this thesis, several concepts related to preventive interventions in dietetic practice will be explained.

Prevention

Preventive measures in health care are commonly classified according to three levels of disease progression: primary (prevention of occurring), secondary (prevention of disease recurrence) and tertiary (prevention of complications and handicaps). In practice no clear distinction can be made as these categories are only an attempt to define discrete stages in a continuous natural history of disease[3]. The relevance of these categories can be questioned, because in many cases the relative impact of preventive measures (whether pharmacological or lifestyle interventions) does not differ between primary or secondary prevention groups[4-7]. A distinction in prevention categories probably more relevant to clinical practice can be made in terms of anticipated effects:

1. Short-term effects related to the primary diagnosis: e.g. actions targeted at nutritional intake as a determinant of infection risk, complication risk, treatment outcome or in-hospital mortality.
2. Long-term effects related to the primary diagnosis: e.g. actions targeted at specific dietary behaviours as a determinant of recurrence of disease or a disease-related high-risk for future disease or complications (e.g. the cardiovascular risk in patients with renal insufficiency).
3. Long-term effects on health not related to the primary diagnosis (health promotion): e.g. breast feeding patterns as a determinant of childhood health, nutritional adequacy in vulnerable population groups as a determinant of future health, quality of life or life expectancy.

Among hospital professionals no one will doubt whether the first category belongs to their responsibility, but responsibility for the second and third category is often discussed. Some argue that these tasks should be performed by primary care and public health professionals respectively. Others are challenged by a vision on hospital care that not only reduces disease symptoms and burden but also contributes to the pursuit of health in the community[8]. In the context of targeting and tailoring preventive interventions, three concepts are central: prognosis, proof and priority setting.

Prognosis

The word prognosis comes from the Greek word ‘prognostikos’. It combines pro (before) and gnosis (knowing). A medical prognosis comprises the prediction of the course and outcome of a disease process. In clinical decision making, prognosis is the answer to several questions: What is the natural course of this disease? What gain can be expected from treatment? And what are the expected benefits of treatment A compared to treatment B? Prognosis is preferably reported as the number of (healthy) life years gained, a survival rate (or its inverse: mortality rate), or the absolute risk for a specific event (e.g. a 30% risk for re-infarction during 10 years) or a specific complication (e.g. infection risk). These outcome measures are examples of hard endpoints. In contrast to hard endpoints also intermediate or surrogate endpoints can be reported, for example when a treatment effect is reported on blood pressure or serum cholesterol level. Blood pressure or serum cholesterol levels are not the primary goals for treatment, but they are established risk factors for disease and can be determined more easily than hard endpoints.

Prognostic questions are typically answered in cohort studies. Data are obtained by observing and describing baseline characteristics from a cohort of patients with a specific disease and by counting the number of events during a follow-up period. Analysis of subgroups with different baseline characteristics (e.g. older versus younger patients) can help to identify prognostic differences between patients and to better predict the risk of a patient. A comparison of the risk of two different groups is commonly expressed as a rate ratio (RR). For example, if the risk for an infection is two times higher in undernourished patients as compared to well-nourished patients the RR=2.

Prediction is surrounded with uncertainty. In general the larger the sample size of the studied group (statistical uncertainty) and the more comparable the studied individuals are (generalisability) to the new patient, the more reliable the prediction for the prognosis. Statistical uncertainty is commonly expressed by a 95% confidence interval (95%CI), which means that, if the study is repeated a 100 times, in 95 of these studies the value of the estimate lies between the two boundaries. For example a RR = 2 (95%CI 1.65 – 2.25). If there is an overlap between the confidence intervals of two estimates, there is no statistically significant difference between the two.

Proof

Proof is evidence that is sufficiently convincing to direct action. Evidence for effectiveness of a treatment requires convincing data showing significantly better health outcome in a treated patient group as compared with an untreated patient group. Non-experimental cohort studies are able to show a significant association between a specific treatment or behaviour at baseline and a health outcome after a follow-up period. However, this may not be sufficient proof of causality as the treatment or behaviour under study may not have been the only difference between the observed groups. Other, unobserved, factors may also have caused the effect (confounding by indication)[9]. Evidence for causality between treatment and health outcome is therefore preferably obtained from experimental studies, such as randomised controlled trials (RCTs). In RCTs an experimental and a control treatment regimen are randomly assigned to study participants, while preferably both study participants and investigators are blinded for treatment allocation.

In contrast to pharmacological research, studies on the effectiveness of dietary and lifestyle interventions are more often non-experimental or quasi-experimental. This is due to practical reasons (how to blind patients for an intervention consisting of an advice to eat more fruit?), ethical reasons (you cannot

prescribe patients to continue smoking to prove that quitters live longer), or financial reasons (dietary and lifestyle interventions often require an exposure time of at least several years, which makes studies expensive). In medical research evidence from experimental studies is generally better accepted than evidence from non-experimental studies. However, experimental studies have their own drawbacks. Because of their highly selected study populations, the study setting and the relatively short duration of the study, their ability to predict the true effect of dietary changes in the 'real life' situation of a mixed population is often limited. Cohort studies do not commonly have these generalisation problems. Usually, results of several studies with different study designs are needed to demonstrate effectiveness.

Outcome measures in studies on effectiveness can either be surrogate endpoints (e.g. blood pressure) or hard endpoints (e.g. complications or mortality risk). Effect sizes are often expressed as the mean difference between the groups (e.g. decrease in blood pressure, absolute risk reduction).

Priority decisions

In contrast to 'proof' and 'prognosis', 'priorities' cannot be solely based on scientific data. Facts have to be valued before they can guide our decisions. Many priorities in clinical practice, however, reflect routine habits, which means they are based on historical values. It has to be evaluated periodically – especially in a rapidly changing environment such as in health care – whether the assumptions and values that underlay these decisions may have changed over time.

How priorities are set in a complex organisation - as hospitals generally are - depends on how responsibilities and power are distributed within the organisation. For example: who defines and controls referral procedures to the dietitian and who can influence allocation decisions that define the departmental budget? Does the power structure within the organisation guarantee that decisions are based on the best information available?

Outline of the thesis

This thesis is a collection of studies concerning priority decisions on preventive interventions in dietetics. Chapter two presents studies on nutritional prognosis in oncohaematologic patients. The first study (paragraph 2.1) addresses the question whether withdrawal of total parenteral nutrition is safe in specific subgroups of patients undergoinf intensive cytotoxic therapy. The second (paragraph 2.2) aims to identify subgroups of this patient population that may benefit from more intensive nutritional counselling during the first year post-transplant.

Chapter three describes studies that aim to provide proof (evidence) to support priority decisions related to nutritional counselling of coronary artery disease patients. The first study (paragraph 3.1) is a cohort study on adherence to the Mediterranean diet and other lifestyle factors and their impact on prognosis in European post-Myocardial Infarction patients. The second study (paragraph 3.2) is a literature review that investigates the existing evidence for an effect of lifestyle and dietary changes on survival in coronary artery disease patients.

Chapter four switches from facts to values. A literature study is performed to describe relevant ethical values and to provide guiding principles for priority setting processes in dietetic practice, especially related to prevention.

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Chapter 2 Prognosis,

Proof and Priorities

2.1 Medical prognosis and nutritional policy in hospital

a study in patients with haematological malignancies

2.2 Prognostic factors for body weight recovery after discharge

a study in patients with haematological and other malignancies

Abstract

Background: Patients receiving intensive cytotoxic therapy are traditionally supported with parenteral nutrition, although it is unclear whether all patients benefit from Parenteral nutrition. This study aimed (1) to identify regimen-associated differences in parenteral nutrition requirements, (2) to reveal discrepancies between the number of parenteral nutrition indications and the frequency parenteral nutrition was actually given, and (3) to describe characteristics of patients who met nutritional goals without parenteral nutrition.

Methods: Parenteral nutrition indications were defined as: (1) severe malnutrition at admission, (2) a prolonged period (> 7 days) of minimal oral intake or (3) clinical weight loss >10%.

Results: Parenteral nutrition was needed in 80% of the remission induction courses, in 35% of the consolidation courses and in 55% of the admissions for bone marrow transplantation (BMT). Significant differences were also seen between BMT-protocols: Parenteral nutrition was required for only 37% of autologous BMT recipients conditioned without total body irradiation (for lymphoma) *vs* 92% of recipients of a mismatched graft. A high body mass index was the only significant characteristic of patients who could do without parenteral nutrition.

Conclusion: Parenteral nutrition is not required for all patients undergoing intensive cytotoxic therapy. Screening of nutritional status at the start of therapy and monitoring oral intake following cytotoxic treatment may allow more appropriate identification of patients requiring parenteral nutrition.

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2.1 Medical prognosis and nutritional policy in hospital

a study in patients with haematological malignancies

J.A. Iestra, W.E. Fibbe, A.H. Zwinderman, J.A. Romijn, and D. Kromhout,

Since parenteral nutrition was shown to be safe and feasible in patients undergoing bone marrow transplantation[1;2], it has been widely used during intensive cytotoxic therapy. Parenteral nutrition support was believed to be indispensible in bridging the period of severe gastrointestinal toxicity and pancytopenia[3-8]. Despite this, the efficacy of parenteral nutrition support on treatment tolerance or prognosis has never been demonstrated. Recent developments, such as the advent of improved antiemetics and haematopoietic growth factors, have shortened the period of reduced oral food intake. In addition, more awareness has grown of the disadvantages of parenteral nutrition in terms of complication risk and costs.

Recent clinical guidelines[9;10] advocate reserving parenteral nutrition support for those cancer patients not tolerating enteral nutrition support, who are either severely malnourished at admission or who are expected to undergo a prolonged period (more than 7 to 10 days) of inadequate oral intake. An additional indication may be: the occurrence of more than 10% weight loss during admission. To define the need for parenteral nutrition support in patients receiving different cytotoxic regimens we retrospectively studied the occurrence of these three indications.

In this study the frequency is described of ‘malnutrition at the start of therapy’, ‘a prolonged period of inadequate oral intake’ and ‘severe clinical weight loss’ occurring either during the clinical phases (remission induction, consolidation and transplantation) of the treatment protocol for AML or during admissions for one of four standard protocols for bone marrow transplantation (BMT). The number of parenteral nutrition indications is compared with the number of admissions where

parenteral nutrition support was actually given. Finally, personal and medical features are described of those who managed to keep their energy intake at an acceptable level without parenteral nutrition.

Methods

Patients

Data of all consecutive patients who received intensive cytotoxic therapy between 1993 and 1998 and participated in a nutritional monitoring program on the BMT unit were retrospectively analysed. Intensive cytotoxic therapy was defined as all treatment schemes comprising high-dose (combination) chemotherapy, with or without total body irradiation and eventually followed by BMT, resulting in a neutropenic period ($<0.1 \times 10^9$/l neutrophils) for at least 7 days.

Study designs

Three analyses were performed: (1) A longitudinal analysis comparing three clinical phases (remission induction, consolidation and transplantation) of treatment for AML. (2) A cross-sectional analysis comparing four standard conditioning protocols for BMT. (3) A cross-sectional analysis comparing personal and medical features of those supported *vs* those not supported with parenteral nutrition in a homogenous group undergoing BMT.

The first cohort consisted of patients treated for primary AML according to the EORTC LAM-10 protocol. The remission induction course consisted of cytarabine 100 mg/m2 by continuous i.v. infusion over 24 h from days 1 to 10 (total dose 1000 mg/m2), etoposide 100 mg/m2 once daily i.v. from days 1 to 5 (total dose 500 mg/m2) and on days 1, 3 and 5 either idarubicin 10 mg/m2 once daily i.v.(total dose 30 mg/m2) or daunorubicin 50 mg/m2 once daily i.v. (total dose 150 mg/m2) or mitoxantrone 12 mg/m2 once daily i.v. (total dose 36 mg/m2). The consolidation course consisted of cytarabine 500 mg/m2 twice daily i.v. from days 1 to 6 (total dose 6000 mg/m2) and on days 4, 5 and 6 either idarubicin 10 mg/m2 once daily i.v. (total dose 30 mg/m2) or daunorubicin 50 mg/m2 once daily i.v. (total dose 150 mg/m2) or mitoxantrone 12 mg/m2 once daily i.v. (total dose 36 mg/m2). Conditioning for BMT consisted of cyclophosphamide 60 mg/kg once daily i.v. on days 25 and 24 (total dose 120 mg/kg) and single dose total body irradiation 9 Gy (long shielding to 6 Gy) on day 0. Only those patients were included who underwent both induction, consolidation and transplantation in the BMT unit of our hospital. Patients with refractory AML needing a second remission induction course were excluded.

Patients in the second cohort underwent BMT because of haematological malignancies and were conditioned with one of four preparative regimens: (1) The BEAC regimen: 300 mg/m2 BCNU once daily i.v. on day -6, 200 mg/m2 etoposide and 200 mg/m2 cytarabine once daily i.v. on days -5, -4, -3, -2 and 140 mg/m2 once daily i.v. on day -1 followed by autologous BMT (for lymphoma). (2) Cyclophosphamide 60 mg/kg once daily i.v. on days -5 and -4 (total dose 120 mg/kg) and total body irradiation 9 Gy (lung shielding to 6 Gy) on day 0 followed by autologous BMT. (3) Cyclophosphamide 60 mg/kg once daily i.v. on days -5 and -4 (total dose 120 mg/kg) and total body irradiation 9 Gy (lung shielding to 6 Gy) on day 0 followed by allogeneic BMT (T cell-depleted using Campath-1G in the bag) from an HLA-matched donor. (4) Cyclophosphamide 60 mg/kg once daily i.v. on days -5 and -4 (total dose 120 mg/kg) and total body irradiation 9 Gy (lung shielding to 6 Gy) on day 0 and 5 consecutive days of 5 mg Campath-1G i.v. (days -8 to -3) followed by an allogeneic BMT from a HLA-mismatched donor. Only patients receiving their first BMT were included.

The third cohort consisted of BMT patients who underwent a conditioning regimen consisting of cyclophosphamide 60 mg/kg once daily i.v. on days -5 and -4 (total dose 120 mg/kg) and total body irradiation 9 Gy (lung shielding to 6 Gy) on day 0 followed by either autologous or allogeneic transplantation from an HLA-matched donor. Regimens without TBI and HLA-mismatched protocols were excluded in this analysis to compile a homogeneous group with comparable gastrointestinal toxicity and complication rate.

Nutritional policy and monitoring

Energy requirements were estimated as 140% of resting energy expenditure calculated by the Harris and Benedict Equation[11]. Protein requirements were estimated as 1.5 g protein per kg actual body weight. Nutritional goals during admission were to achieve an average intake of at least 70% of the patients' energy requirements and at least 1 g protein per kg. Daily oral food intake was recorded three times per week. Energy and protein content were calculated using a computerised Dutch Nutrient Table[12]. Nutritional counselling was focused on improving oral food intake. Depending on the individual needs special between-meal snacks and commercial supplements were advised. Parenteral nutrition support was started when two measurements of oral energy intake were below 50% of the estimated needs and oral intake was not expected to improve within 1 week.

Supportive care related to GI tract

Supportive care measures were the same for all patients. Stomatitis prevention consisted of local non-absorbable antibiotics three times daily and careful teeth brushing. To prevent nausea and vomiting a serotonin antagonist was administered prophylactically. Other anti-emetics were provided when indicated clinically. Infection prevention measures included protective isolation, a low microbial diet and selective decontamination of the gut with oral nonabsorbable antibiotics (neomycin, amphotericin B, polymyxin B and pipemidic acid).

Definition of review criteria for parenteral nutrition support indications

In clinical guidelines it is advocated that parenteral nutrition support in cancer treatment be reserved for two indications: 'Severe malnutrition at start of therapy' (indication 1) and 'A prolonged period of minimal oral intake of at least 7 to 10 days' (indication 2). To ensure identification of all patients who needed parenteral nutrition, we added 'severe weight loss during admission' as a third indication. We attributed these indications retrospectively to the admissions present on our data base.

'Severe malnutrition at start of therapy' (indication 1) was defined as the presence of at least one of the following criteria: baseline serum albumin <30 g/l; body mass index (weight/height2)[13] at start of therapy below 18.5 kg/m2. A 'prolonged period of minimal oral intake' (indication 2) was defined as at least one of the following criteria: Three or more measurements (a period of at least 7 days) with oral energy intake less than 10% of the individual's estimated energy requirement; five or more measurements (a period of at least 11 days) with oral energy intake less than half the individual's estimated energy requirement. The third indication 'severe weight loss during admission' was defined as weight loss between admission date and discharge of more than 10% of initial weight.

Statistical analysis

Results of parametric data were expressed as means and standard deviation, non-parametric as median and the interquartile range, and dichotomous variables as frequency and percentage. In the longitudinal analysis, non-parametric variables were tested by the Friedman-rank test and dichotomous variables by the Cochran Q test. In the second analysis differences between the four subgroups were tested by the Kruskal–Wallis test for the non-parametric data and the Fisher exact test for dichotomous variables. In the third analysis differences between the two groups were tested by the Student's *t*-test for parametric variables and the Mann–Whitney test for the non-parametric variables.

Table 2.1.1 Clinical characteristics of 20 patients treated for AML

	Remission induction	*Consolidation*	*BMT*	*P*
Basline characteristics				
time since diagnosis (days)[a]	0	48 (40-57)	139 (120-180)	—
initial body weight (kg)[a]	72.5 (61-85)	70.5 (57-82)	72.3 (59-85)	0.009
body mass index (kg/m2)[a,c]	23.5 (21.1-26.1)	22.5 (20.9-24.8)	23.1 (21.8-26.7)	0.002
serum albumin (g/l)[a,d]	40 (38-46)	41 (39-44)	42 (40-44)	NS
Clinical outcome				
duration of hospitalization (days)[a]	33 (29-39)	29 (26-31)	36 (30-43)	0.004
mean oral intake (%REEb)[a]	64 (46-81)	106 (82-139)	93 (71-113)	0.007
duration parenteral nutrition (days)[a]	18 (12-25)	0 (0-11)	9 (7-26)	0.002
clinical weight loss (% start)[a]	4.0 (1.7-7.4)	2.0 (0.8-4.2)	5.6 (3.8-9.6)	0.001

[a]Median (quartile interval); Friedman test.
[b]REE = resting energy expenditure. Daily energy requirement is
[c]Reference value BMI for normal weight (WHO): 18.5–25 kg/m2.
[d]Reference value serum albumin in our hospital: 40–50 g/l.

Table 2.1.2 Indications for parenteral nutrition per treatment phase in 20 patients treated for AML

	Remission induction n (%)	*Consolidation n (%)*	*BMT n (%)*	*P*
serum albumin < 30 g/l	2 (10)	0	0	NS
BMI <18.5 kg/m[a]	3 (15)	2 (10)	2 (10)	NS
≥7 days with no intake per os	11 (55)	1 (5)	6 (30)	0.002
≥11 days with less than half the required energy intake per os	13 (65)	4 (20)	8 (40)	0.01
clinical weight loss ≥10%	2 (10)	0	5 (25)	0.04
parenteral nutrition indicated	16 (80)	7 (35)	12 (60)	0.004
parenteral nutrition actually given	19 (95)	9 (45)	16 (80)	0.002

Frequency (percentage), Cochran Q test

Results

Parenteral nutrition requirements per treatment phase

Of 50 patients with AML admitted for remission induction, only 20 patients (13 males, 7 females, age 44±10 years) underwent consolidation treatment and BMT on the BMT-unit. Table 2.1.1 shows their clinical and nutritional characteristics. Weight and body mass index were lowest at the start of the consolidation phase. The consolidation phase was also associated with the shortest length of stay, the highest mean oral intake, the least number of days on parenteral nutrition and lowest weight loss.

Table 2.1.2 shows the number of admissions meeting one of the criteria for parenteral nutrition support. Hypoalbuminaemia and underweight were rare at the start of each treatment phase. Prolonged periods of reduced oral intake occurred in only 20% of the patients undergoing consolidation treatment against 65% during remission induction courses. Weight loss of more than 10% of initial weight was rare during both remission induction and consolidation courses, but occurred in 20% of BMT admissions. The need for parenteral nutrition was significantly different between the three phases; consolidation courses had the lowest requirement for parenteral nutrition ($P < 0.01$). In each phase parenteral nutrition support was given more frequently than actually needed.

Parenteral nutrition requirements per BMT protocol

This cohort consisted of 93 patients. Seven patients were excluded because their data set was incomplete (due to death within 1 week after transplantation or for other reasons). Clinical and nutritional characteristics of the remaining 86 admissions are shown in Table 2.1.3. Patients undergoing an autologous transplant were significantly older than those receiving an allogeneic graft ($P<0.01$). All patients conditioned without TBI were treated for lymphoma, whereas most patients whose preparative regimen consisted of cyclophosphamide and TBI suffered from AML. Duration of hospitalization was significantly longer for those patients undergoing a mismatched transplant (48 days) when compared with the other regimens (28, 36 and 37 days; $P < 0.01$). No significant differences were found in nutritional status at start of therapy, in oral intake capacity, in duration of parenteral nutrition support or in clinical weight loss, although a trend was seen towards a longer parenteral nutrition period in group 4 and less clinical weight loss in group 1.

Table 2.1.4 shows the number of admissions that met one of the criteria for parenteral nutrition support. Hypoalbuminaemia as well as underweight at the start of therapy were rare in all subgroups. A prolonged period of reduced oral intake

Table 2.1.3 Clinical characteristics of four BMT groups

	1 Auto-BMT -TBI n=16	*2 Auto-BMT +TBI n=28*	*3 Allo-BMT +TBI HLA-matched n=30*	*4 Allo-BMT +TBI mismatched n=12*	*P*
Patient characteristics					
gender ratio (%m)[b]	75%	61%	60%	50%	NS
age (years)[a]	47 (35-58)	46 (34-54)	39 (30-47)	31 (21-38)	0.001
diagnosis:[b]					
leukemia		24 (86%)	24 (80%)	10 (83%)	0.01
lymphoma	16 (100%)	3 (11%)	1 (3%)	0	
other		1 (3%)	5 (17%)	2 (17%)	
Baseline characteristics					
initial body weight (kg)[a]	78 (64-89)	77 (67-88)	77 (67-85)	74 (67-86)	NS
body mass index (kg/m2)[a,c]	23.8 (21.9-28.7)	24.7 (22.2-27.1)	24.7 (22.2-26.6)	25.4 (21.2-26.7)	NS
serum albumin (g/l)[a,d]	44 (41-47)	42 (40-44)	43 (40-46)	44 (43-47)	NS
Clinical outcome					
length of hospital stay (days)[a]	28 (25-34)	36 (29-41)	37 (33-43)	48 (42-82)	0.001
mean oral intake (%REE)[a]	84 (69-122)	105 (76-140)	94 (74-130)	76 (47-89)	NS
duration parenteral nutrition (days)[a]	8 (0-14)	7 (0-19)	9 (2-22)	20 (5-55)	NS
clinical weight loss (%)[a]	3.6 (2.1-6.4)	6.7 (4.5-8.6)	5.2 (3.0-8.2)	6.4 (0-8.2)	NS

[a]Median (quartile interval); Kruskal–Wallis test.
[b]Frequency (percentage); Fisher exact test.
[c]Reference value BMI for normal weight (WHO): 18.5–25 kg/m2.
[d]Reference value serum albumin in our hospital: 40–50 g/l.
REE = resting energy expenditure. Daily energy requirement is estimated as 140% of REE.
TBI = total body irradiation.

was common (92%) in group 4 (mismatched BMT) and less frequent (40%) in the other groups. Although not statistically significant, there appeared to be a trend toward a higher frequency of severe weight loss in the groups with a regimen-containing TBI (groups 2–4). The percentage of patients requiring parenteral nutrition according to the three criteria differed significantly between the four subgroups, group 4 (mismatched BMT) showing the highest percentage. In all

Table 2.1.4 Number of admissions meeting one of the criteria for PNS in four BMT groups

	1 Auto-BMT -TBI *n=16*	*2 Auto-BMT +TBI* *n=28*	*3 Allo-BMT +TBI HLA-matched* *n=30*	*4 Allo-BMT +TBI mismatched* *n=12*	*P*
serum albumin < 30 g/l	0	0	0	0	NS
BMI <18.5 kg/m^2	0	1 (4%)	4 (13%	0	NS
≥7 days with no intake per os	5 (30%)	7 (25%)	9 (30%)	6 (50%)	NS
≥11 days with less than half the required energy intake p.o.	6 (37%)	11 (39%)	12 (40%)	11 (92%)	0.01
clinical weight loss ≥10%	1 (6%)	5 (18%)	5 (17%)	2 (17%)	NS
parenteral nutrition indicated	6 (37%)	14 (50%)	17 (58%)	11 (92%)	0.03
parenteral nutrition actually given	12 (75%)	19 (70%)	23 (77%)	10 (83%)	NS

Frequency (percentage), chi-square test.
TBI = total body irradiation.
p.o.=per os

groups parenteral nutrition was given more frequently than actually needed. The discrepancy was greatest in group 1: Parenteral nutrition support indicated in 37% of the cases *versus* 75% given.

Characteristics of patients without parenteral nutrition

In Table 2.1.5 a group of 58 BMT patients was retrospectively divided into a subgroup who could manage without parenteral nutrition (28%) *versus* a subgroup who received parenteral nutrition support (72%). The first subgroup was able to keep their oral intake at the acceptable level of at least 70% of their estimated energy requirement and 1 g protein/kg/day. Between groups, no significant differences were seen in gender ratio, age, diagnosis or type of transplant. Body mass index at the start of therapy was significantly higher (27 kg/m2) in the non-supported group compared with the supported group (24 kg/m2; $P = 0.01$). No significant difference was seen in weight loss during admission (-5% of start weight in the non-supported group *vs* -6% in the supported group).

Discussion

The objectives of the present study were to identify regimen-associated differences in requirements for parenteral nutrition support during intensive cytotoxic therapy, to reveal discrepancies between the number of indications for parenteral nutrition and the frequency of parenteral nutrition support actually given and to describe characteristics of patients who met nutritional goals without parenteral nutrition. Comparing three treatment phases for AML, we found that during the consolidation phase only a minority of the patients required parenteral nutrition support. During remission induction and transplantation the number of indications was higher. Comparing four subgroups undergoing BMT, the group conditioned without TBI needed parenteral nutrition in less than 40% of cases. In other groups parenteral nutrition was indicated in more than 50% of cases. Except for the group of mismatched BMT recipients, all groups received more parenteral

Table 2.1.5 Characteristics of two subgroups of 58 BMT recipients conditioned with cyclophosphamide and TBI

		Not supported with parenteral nutrition n=16 (28%)	*Supported with parenteral nutrition n=42 (72%)*	*P*
Patient characteristics				
gender ratio (% males) [a]		50%	64%	NS
age (yrs) [b]		42 ± 10	40 ± 12	NS
diagnosis [a]	AML	56%	67%	NS
	other	44%	33%	
transplantation [a]	auto	56%	45%	NS
	allo	44%	55%	
Nutritional status at baseline				
serum albumin (g/l) [b]		41.8 ± 4.3	42.4 ± 3.0	NS
body mass index (kg/m^2) [b]		27.0 ± 4.5	23.9 ± 3.6	0.01

[a] Percentage; Chi-square-test
[b] mean ± s.d; Student's t-test

nutrition support than was actually needed. In the BMT recipients with lymphoma, parenteral nutrition was given twice as frequently (75 *vs* 37%) as needed. The only significant characteristic of those patients meeting nutritional goals without parenteral nutrition support was a higher body mass index.
Clinical measurements such as oral food intake and body weight are susceptible to error. In the case of oral intake records this error is random and the high frequency of measurement (three times per week) may solve the problem. The occurrence of vomiting and diarrhoea may have led to an overestimation of net energy intake. In case of body weight measurement changes in hydration status, especially in patients receiving parenteral nutrition[14;15] might cause a systematic underestimation of loss of body mass. To reduce the confounding influence of hydration status we have used body weight data of admission date and discharge (after termination of parenteral nutrition support) only. Because criteria for parenteral nutrition indications were rather stringent in this study, it is unlikely that we have underestimated the need for parenteral nutrition support at group level.

In the first analysis only a small number of the patients admitted was included (20 out of 50 patients admitted for remission induction). The reduction was partly due to dropouts who never reached remission, relapsing early or dying before transplantation and partly to factors (not patient-related) necessitating admission to another ward. To check the representativeness of the included patients, we performed an analysis comparing the number of parenteral nutrition indications and the frequency of given parenteral nutrition support between patients included and patients excluded. No significant differences were found. In the cross-sectional analysis, seven out of 93 patients were excluded because of an incomplete data-set, mainly due to death or relocation to the ICU within the first week after transplantation. It is unlikely that nutritional support would have influenced the cause of death at this stage. We conclude that our findings can be generalised to all patients treated with the defined treatment regimens.

The rationale for parenteral nutrition support in cancer patients is to prevent severe tissue wasting in patients with mucositis and whose nutritional status might already have been poor at the start of therapy. However, for most cancer patients the efficacy of parenteral nutrition support in improving tolerance to treatment, quality of life or prognosis is not proven. Meta-analyses, both in the field of cancer surgery[16] as well as chemotherapeutic treatment[17;18] show that for many patients parenteral nutrition support did not reduce complication rate, but did increase infection risk. Only patients who are severely malnourished at the start seem to benefit from parenteral nutrition support. These findings have led to clinical guidelines[10;19] that advocate reserving parenteral nutrition support for two groups

of cancer patients: those who are severely malnourished (while responding to therapy) and those in whom gastrointestinal or other toxicities preclude enteral intake for 7–10 days or longer.

Although these guidelines are recognised for cancer treatment in general, they are usually not applied to patients undergoing intensive cytotoxic therapy resulting in a prolonged period of granulocytopenia. Clinical trials on the efficacy of parenteral nutrition in BMT patients[5;20;21] are scarce and mainly performed in selected groups, not allowing extrapolation to other subgroups. In contrast to other groups of cancer patients, we found severe malnutrition at the start of therapy to be rare in patients with haematological malignancies admitted for intensive cytotoxic therapy. Although the variables used in this study are not very specific for identifying 'severe malnutrition', the observation that current BMT recipients are usually well-nourished at the time of hospital admission has also been found by others[3;22;23]. This fact might be partly due to the short disease history before diagnosis and subsequent remission induction therapy and partly to the length of the recovery period prior to BMT.

The most important parenteral nutrition indication in this patient group is the presence of 'a prolonged period of minimal oral intake'. The length of this period may differ significantly per regimen. This implies that further reductions of gastrointestinal toxicity or duration of the neutropenic period (for instance the replacement of BMT by peripheral blood stem cell transplantation) may further decrease the need for parenteral nutrition. In most groups more patients received parenteral nutrition support than was actually indicated by our criteria. This is due to the fact that length of inadequate oral intake is difficult to predict in clinical practice. Clinical guidelines based on regimen-related differences in oral intake patterns may help to improve clinical decision-making in the future.

We found a high body mass index being a consistent characteristic of those patients who could do without parenteral nutrition. This suggests that obese persons are less hampered in their eating behaviour than their normal weight counterparts. Two explanations are possible: firstly that difference in body composition causes a different distribution of toxic agents, resulting in less toxicity, and secondly that obese persons cope differently with feelings of nausea and lack of appetite. The absence of parenteral nutrition in the non-supported group was not likely to be harmful, as is shown by the comparable weight losses in both groups.

In summary, our data suggest that parenteral nutrition support is not necessary for all patients undergoing intensive cytotoxic therapy. Significant regimen-associated differences in the number of patients requiring parenteral nutrition

demand a differentiated policy. For example, during consolidation for AML and during a BMT protocol without TBI (for lymphoma), parenteral nutrition is needed in only a minority of patients. For almost all intensive cytotoxic therapy regimens the routine use of parenteral nutrition support is no longer required. Screening for severe malnutrition at start of therapy and monitoring of the oral intake capacity during admission are practical tools allowing more rational, individualised decisions regarding parenteral nutrition support during intensive cytotoxic therapy.

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2.2 Prognostic factors for body weight recovery after discharge

a study in patients with oncohaematological and other malignancies

Abstract

Background: Among healthcare professionals there is no consensus about the best policy to increase oral intake and promote recovery in the post-hospital phase after bone marrow or blood stem cell transplantation. In order to evaluate body weight recovery and compliance with dietary advice among these patients, we performed a prospective longitudinal study in the first year posttransplant.

Methods: At five time intervals (days 50, 75, 125, 200 and 350) patients received a nutritional questionnaire with items on nutrition-related symptoms, physical condition, body weight recovery and compliance with dietary advice.

Results: From the initial cohort of 135 patients 69 completed the study. Prevalence of eating difficulties was high (66% at day 50). Anorexia, dry mouth, altered taste, nausea and tiredness were the symptoms most strongly associated with eating difficulties. Compliance with dietary advice was poor. Conditioning regimen was found to be a prognostic factor for body weight status at day 350. In more than 50% of the TBI-treated patients body weight was not restored to 95% of the pre-treatment value within 1 year after transplant.

Conclusion: The severety of long term gastrointestinal toxicity symptoms and the recovery rate of nutritional status after bone marrow or stem cell transplantation varies widely between patient subgroups. The post discharge energy and protein intake of TBI-treated patients require special attention.

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2.2 Prognostic factors for body weight recovery after discharge

a study in patients with oncohaematological and other malignancies

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Current indications for bone marrow transplantation (BMT) and peripheral blood cell transplantation (BCT) include not only haematological malignancies but also solid tumours (breast carcinoma, childhood sarcomas) and non-malignant diseases such as scleroderma. The spectrum of conditioning and treatment regimen has expanded to include a great number of schedules varying in combinations and dosages of cytotoxic agents, inclusion of total body irradiation (TBI), donor type and recruitment procedure of stem cells (peripheral or bone marrow). Gastro-intestinal side-effects such as nausea, mouth complaints and anorexia are common with all treatment modalities, although severity and duration may differ per conditioning regimen. As the effects of toxicity may reduce oral intake for a prolonged period of time, monitoring of nutritional status and nutritional intake is an essential part of supportive care for patients receiving BMT or BCT.

Over the past decade there have been several publications[1-5] on nutritional support strategies during the clinical treatment phase of blood cell transplant recipients. Less attention has been paid to body weight recovery and eating problems in the post-hospital phase[6-9]. Lenssen et al[6] reported nutritional problems in 23% and weight loss in 28% of 192 patients in the first year after allogeneic bone marrow transplantation. Chao et al[7] found that at 90 days post transplant about one-third of patients reported poor appetite. In practice, there is no consensus among healthcare professionals about the best policy to increase oral intake and promote recovery in the post-hospital phase. Some consider

eating problems in this phase as transient and pay little attention to them, while others[9] choose invasive procedures such as home parenteral nutrition to guarantee nutrient provision.

The policy at the Department of Haematology of the Leiden University Medical Centre is to educate patients during their in-hospital period on how to enhance the nutritional value of their diet by choosing food constituents with either a high protein or energy density or by taking oral nutritional supplements. At discharge, patients are advised to monitor their body weight and enhance their energy and protein intake according to their individual needs. Dietary follow-up consults in the post-hospital phase are provided on request of the patient or his physician. In order to evaluate the nutritional aspects of the recovery process and compliance with dietary advice given at discharge, we performed a prospective longitudinal study on body weight recovery, prevalence of eating problems and compliance with dietary advice in the first year post-transplant. We were especially interested in prognostic factors which might help select patients needing more intensive counselling in the post-discharge phase.

Patients and methods

Patients

All consecutive patients who were discharged after receiving BMT or BCT at the Department of Haematology of the Leiden University Medical Centre (LUMC) between May 1996 and November 1998 were eligible. Treatment indications were: leukaemia (acute myeloid, acute lymphoblastic and chronic myeloid leukaemia), multiple myeloma, lymphoma (Burkitt's, Hodgkin's and non-Hodgkin's lymphoma), solid tumours (breast carcinoma, testis carcinoma and soft tissue sarcoma) and a few miscellaneous conditions (aplastic anaemia, thalassemia, scleroderma). Inclusion criteria were informed consent and ability to understand written Dutch. Due to the compromised physical condition of the patients and the high risk of relapse or other fatal complications in the first year after transplantation a high dropout rate (50%) was expected. In order to have at least 75 evaluable patients, we planned to include 150 patients.

Conditioning procedures

The pretransplant conditioning regimens for leukaemia, aplastic anaemia and multiple myeloma consisted of cyclophosphamide and total body irradiation followed by autologous or allogeneic (matched or mismatched) blood cell or bone marrow transplantation; for lymphoma of BCNU, etoposide and

cytarabine followed by autologous blood cell or bone marrow transplantation (BEAC regimen); for breast carcinoma of carboplatin, cyclophosphamide and thiopeta followed by autologous blood cell transplantation; for Ewing sarcoma of carboplatin, etoposide and melphalan followed by autologous blood cell or bone marrow transplantation and for scleroderma of cyclophosphamide followed by autologous blood cell transplantation.

Nutritional counselling

During hospital stay daily oral food intake was recorded three times a week and nutritional counselling focused on improving oral energy and protein intake. The goal for energy intake during the in-hospital period was: 130% of the outcome of the Harris–Benedict equation[10], for protein intake 1.3 g/kg and for micronutrients the Recommended Daily Intake[11]. In these calculations actual body weight was used for non-obese patients. For overweight patients (BMI > 25 kg/m2) the adjusted ideal body weight was used (calculated as body weight value for BMI = 25 kg/m^2 plus 0.25 the difference between this value and actual body weight)[8]. During their stay in hospital patients were educated on their individual nutritional requirements and on products with a high energy or protein density. Patients were advised to comply with general healthy diet advice[12] to guarantee their micronutrient intake. In cases of prolonged reduced intake, milkshakes and commercial supplements (protein-rich drinks or powder fortified with vitamins and minerals) were introduced and information was provided on how to prepare them or where to buy them at home. The use of micronutrient preparations was not routinely advocated, because a combined provision of energy, protein and other nutrients was preferred. At discharge from hospital patients received a written summary of the nutritional information given during their stay. Patients were advised to continue monitoring their daily intake and body weight and enrich their home diet according to their individual needs. They were encouraged to contact their dietitian when necessary.

Study procedure

The Medical Ethics Committee of the LUMC approved the research protocol. Written information about the study was given to the patients and informed consent was obtained some days prior to their discharge from hospital. Medical information such as diagnosis and type of transplant was collected from the case report forms completed by the physicians. A nutritional questionnaire was sent at five time points during the post-transplantation year and was accompanied by an explanatory letter and a stamped return envelope.

Measurement points

At five time points in the first year after transplantation (days 50, 75, 125, 200 and 350 post transplantation) patients were asked to measure their body weight and to complete a nutritional questionnaire. The time points were chosen to reflect stages in the recovery process: most patients are discharged before day 50, the highest prevalence of nutrition-related problems is expected at days 75 and 125, immunosuppressive therapy (allogeneic transplants only) is withdrawn in most cases before day 200 and nutritional status is assumed to be close to the pre-morbid state at day 350. Pre-treatment body weight was measured before the start of conditioning between days -10 and -2 before transplantation. (In the figures on body weight recovery the pre-treatment value is noted at day 0 for layout technical reasons.).

Instrument

The questionnaire was designed based upon known side effects that were expected to interfere with adequate nutrient intake. An expert panel tested face validity. Reference period was the last 14 days before the day the questionnaire was completed. The first item questioned the occurrence of 'eating difficulties'. The next item explored the frequency and duration of 17 nutrition-related side-effects and complications (decreased appetite, increased appetite, sore mouth, dry mouth, altered taste, painful chewing, painful swallowing, heart burn, nausea, retching, vomiting, gut complaints, more frequent defecation, less frequent defecation, more solid stool, more liquid stool, tiredness). Subsequently, patients were asked to report their actual body weight, the mean number of resting hours per 24 h and a subjective score for their physical well-being (range 1–10). Open-ended questions were added in order to acquire insight into adaptations patients made to cope with these problems and their compliance with dietary advice. These questions concerned changes in food volume, food consistency, food avoidances and actions taken to enrich the energy, protein or micro-nutrient content of the menu. Cronbachs alpha for the 12 items related to the severity of eating difficulties was 0.74 indicating a good internal consistency. Predictive validity was satisfying, since the number of episodes with eating difficulties and the number of episodes with inadequate intake correlated -0.38 ($P < 0.05$) and -0.49 ($P < 0.01$) with body weight status at day 350.

Definition of outcome parameters

Body weight status (expressed as % of pre-treatment) and the presence of eating difficulties at the various time points were chosen as primary outcome parameters. A period with a specific symptom was defined as the presence of the symptom for

more than 2 days during the last fortnight. A period of inadequate food intake was defined as a period of more than 2 days during the last fortnight with at least one of the following sentences being true: 'I had no intake at all', 'I used only liquids' or 'I used only half or less of my usual amount'. Dietary compliance was defined as being present when patients reported relevant actions in response to one of the following questions: 'what did you do to enrich your diet with energy/protein/micronutrients?'.

Statistics

Study participants consisted of study completers (those who remained in the study until the end), dropouts (those who left the study before day 350) and non-responders (no questionnaires returned). Not all data sets of the study completers were fully completed. In some longitudinal analyses only data of complete responders (those who completed and returned all five questionnaires) were included. Four analyses were performed: First, we described the characteristics of our study population and differences between study completers and dropouts. Secondly, we studied longitudinal data of all available patients by using mixed-model analyses of variance to describe the body weight recovery pattern. Also, prevalence and duration of symptoms and diet compliance was described. Differences in time and differences between study completers and dropouts were tested by chi-square tests. Thirdly, in order to identify what baseline characteristics were prognostic for a body weight status of less than 95% of pre-treatment value at day 350, we performed a logistic regression analysis. In this analysis *y* was body weight status at day 350 (yes or no $\geq$ 95% of baseline) and *x* were all baseline characteristics. Fourthly, we compared longitudinal data about body weight recovery, eating difficulties, symptoms and compliance with dietary advice between subgroups determined by the prognostic factors. For this analysis we used data of the complete responders. Parametric statistical measures were used for variables that were normally distributed. For non-normally distributed variables non-parametric statistical measures were used. The level of statistical significance was set at $p < 0.05$.

Results

Study population

Out of 161 consecutive patients who received BCT or BMT at the Leiden University Medical Centre between May 1996 and November 1998 a cohort of 135 (69 men and 66 women) entered the study. Twenty-six patients were excluded: due to early death ($n = 9$), illiteracy ($n = 1$), insufficient knowledge of the Dutch language

(*n* = 6), poor mental condition (*n* = 1), no informed consent obtained (*n* = 5), planned re-hospitalisation within the study period for second stem cell infusion (*n* = 1) or organisational reasons (*n* = 3). During the 1-year follow-up period of the initial cohort of 135 patients 17 patients did not return any questionnaire (non-responders), 49 patients left the study before day 350 (dropouts) and 69 patients completed the study (study completers). Complete data sets were available for 58 patients (complete responders). A total of 440 questionnaires was returned. Response rate at day 50 was 74% (*n* = 100), at day 75 76% (*n* = 103), at day 125 64% (*n* 87), at day 200 60% (*n* = 81) and at day 350 51% (*n* =69). Reasons for non-response in the groups of dropouts and non-responders were death, relapse, worsening physical condition, psychological distress or unknown.

Table 2.2.1 Patient characteristics of 135 study participants

	Completers n=69	*Dropouts* n=49	*Non-responders* n=17	*P*
alive at 1 year post transplant[1]	69 (100%)	19 (39%)	11 (65%)	<0.05
gender[1]				
female	39 (57%)	18 (37%)	9 (53%)	NS
male	30 (43%)	31 (63%)	8 (47%)	
age[2] (years)	44 ± 11	40 ± 11	36 ± 11	<0.05
diagnosis[1]				
leukemia or multiple myeloma	34 (49%)	37 (76%)	12 (71%)	NS
others	35 (51%)	12 (25%)	5 (29%)	
conditioning regimen[1]				
- TBI	32 (46%)	11 (22%)	7 (41%)	<0.05
+ TBI	37 (54%)	38 (78%)	10 (59%)	
donor[1]				
autologous	44 (64%)	16 (33%)	8 (47%)	<0.01
allogeneic	25 (36%)	33 (67%)	9 (53%)	
type of transplant[1]				
BCT	48 (70%)	35 (71%)	11 (65%)	NS
BMT	21 (30%)	14 (29%)	6 (35%)	
initial Body Mass Index[2] (kg/m2)	24.9 ± 4.8	24.4 ± 4.2	24.6 ± 4.0	NS
length of hospital stay[2] (days)	26 ± 8	29 ± 11	28 ± 9	NS
weight change in hospital[2] (%)	-4.1 ± 3.9	-4.6 ± 3.8	-3.9 ± 4.7	NS

1. Frequency (proportion); Chi-square test
2. Mean ± standard deviation; ANOVA

Fig 2.2.1 Body weight recovery after intensive cytotoxic therapy and stem cell transpantation in study completers and study dropouts (n = 118)

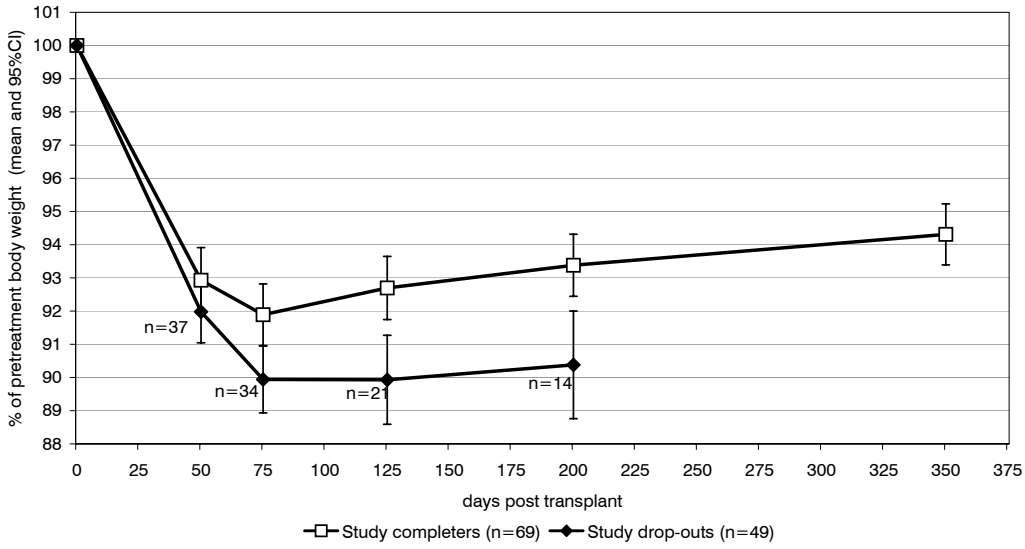

Table 2.2.1 shows population characteristics of study completers, dropouts and non-responders. Groups differed with respect to age (dropouts and non-responders were younger), conditioning regimen (more patients treated with TBI dropped out) and donor (more recipients of an allogeneic transplant dropped out). No significant differences were seen with respect to gender ratio, diagnosis, type of transplant, pre-treatment body mass index, length of hospital stay or weight loss during admission.

Longitudinal data

Body weight recovery was analysed in all available patients (n = 118) using mixed-model analysis of variance. Average body weight status was 93% at day 50, 91% at day 75, 92% at day 125, 93% at day 200 and 94% at day 350. There was, however, an important difference between patients who completed, and those who dropped out. Figure 2.2.1 shows the body weight recovery curve of both study completers (n = 69) and dropouts (n = 49). For the study completers body weight kept falling until day 75 to 92% of pre-treatment value. After day 75 mean body weight slowly recovered to 94% of pre-treatment value at day 350. At all measurement points body weight value of the dropouts was lower compared to that of the study completers. For days 125 and 200 this difference was statistically significant ($P < 0.05$).

Table 2.2.2. Eating difficulties, symptoms, diet adaptations and 'well being' at 5 time points post transplant in 2 subgroups of 118 responders

	n=	*day 50*	*day 75*	*day 125*	*day 200*	*day 350*	*P*
symptoms							
'eating difficulties'[a]							
completers	69	66%	57%	30%	21%	22%	<0.01
dropouts	49[c]	79%	66%	48%	43%		<0.05
poor appetite > 2 days[a]							
completers	69	65%	47%	* 22%	16%	9%	<0.01
dropouts	49[c]	68%	63%	* 43%	36%		NS
dry mouth > 2 days[a]							
completers	69	56%	* 54%	55%	* 36%	20%	<0.01
dropouts	49[c]	71%	* 77%	74%	* 64%		NS
altered taste > 2 days[a]							
completers	69	61%	47%	22%	19%	7%	<0.01
dropouts	49[c]	63%	49%	35%	36%		NS
nausea > 2 days[a]							
completers	69	37%	31%	13%	7%	3%	<0.01
dropouts	49[c]	42%	40%	26%	14%		NS
tiredness > 2 days[a]							
completers	69	85%	75%	61%	33%	43%	<0.01
dropouts	49[c]	87%	71%	61%	57%		NS
nutritional intake							
half or less of usual intake > 2 days[a]							
completers	69	* 42%	32%	17%	* 1%	9%	<0.01
dropouts	49[c]	* 63%	46%	26%	* 14%		<0.01
energy enrichements[a]							
completers	69	42%	25%	* 17%	15%	9%	<0.01
dropouts	49[c]	26%	31%	* 39%	29%		NS
protein enrichements[a]							
completers	69	29%	25%	16%	12%	4%	<0.01
dropouts	49[c]	26%	23%	13%	7%		NS
micronutrient enrichements[a]							
completers	69	36%	34%	34%	31%	26%	NS
dropouts	49[c]	39%	46%	30%	50%		NS
physical well being							
resting hours / 24 hours[b]							
completers	69	* 11 (11-12)	11 (11-12)	* 10 (9-11)	10 (9-10)	9 (9-10)	<0.01
dropouts	49[c]	* 13 (12-14)	12 (11-13)	* 11 (10-12)	10 (9-11)		<0.05
'well being' (score 1-10)[b]							
completers	69	5.5 (5.1-5.9)	5.7 (5.3-6.0)	* 6.5 (6.2-6.8)	6.8 (6.4-7.1)	6.8 (6.4-7.2)	<0.01
dropouts	49[c]	5.2 (4.7-5.7)	5.0 (5.1-5.8)	* 5.7 (4.9-6.4)	6.1 (5.2-7.0)		NS

a. reference period: preceding 14 days; count (proportion); chi-square test
b. mean (95%CI); ANOVA
c. Dropouts n=49; day 50 n=38; day 75 n=35; day 125 n=23; day 200 n=14; day 350 n=0
* significant difference between groups (P<0.01)

Table 2.2.2 shows the prevalence of eating difficulties and nutrition-related symptoms at the five time points. The question 'Have you had any eating difficulties in the last 2 weeks?' was answered with yes in 66% of the study completers at day 50. At day 350 eating difficulties were still present in 22% of the cases. Of 17 nutrition-related side effects, poor appetite, dry mouth, taste alterations, nausea and tiredness were the most frequent complaints and were also most strongly associated with the presence of eating difficulties. The correlation with eating difficulties was highest for poor appetite ($r = 0.76$, $p < 0.01$). Poor appetite was present in 65% of the study completers at day 50 and remained in 9% at day 350. Dry mouth complaints were also frequent (56%) at day 50 and disappeared slowly (still 20% at day 350). Taste alterations occurred in 61% of the patients at day 50 and remained in 7% at day 350. Nausea was seen most in the first months (37% at day 50) and almost disappeared after day 125 (3% at day 350). Tiredness had the highest frequency at the start (85%) and still occurred in 43% of the patients at day 350. Other symptoms such as sore mouth, chewing and swallowing problems, heartburn, gut complaints and altered defecation patterns occurred in less than 20% of the cases at all time points. The prevalence of all symptoms was higher in dropouts than in study completers. Complaints about poor appetite and dry mouth were more often ($P < 0.05$) reported by dropouts than by study completers.

In the second part of Table 2.2.2, data are shown on the presence of inadequate intake and actions taken to enrich the nutritional value of the diet. Especially in the first three measurement points, many patients (42% at day 50, 32% at day 75 and 17% at day 125) reported having had an inadequate food intake ('eaten half or less than usual') for more than 2 days in the preceding fortnight. At day 50, 42% of the study completers reported having taken special actions to enrich energy content of their diet, 29% to enrich protein content and 35% to enrich micronutrient content of their diet. Frequency of energy and protein enrichments decreased to 25% at day 75. For micronutrient enrichments the percentage remained about 30% throughout the study. Commercial energy and protein supplements (data not shown) were used by less than 10% of the study population at each time point. Commercial micronutrient preparations were used in about 15–30% of the patients throughout the year. The number of patients that actively enriched their diet was not significantly different in study completers and dropouts. The number of resting hours per 24 h and a self-report subjective score for 'well-being' improved significantly in time (from 11 resting h at day 50 to 9 h at day 350 and from a well-being score of 5.5 at day 50 to 6.8 at day 350). Study completers reported a lower number of resting hours and a higher score for well-being than dropouts.

Prognostic factors

In order to determine what baseline characteristics were prognostic for successful body weight recovery, we split the group into good and bad performers. Good performers were defined as those who kept or regained at least 95% of their pre-treatment weight at day 350. Body weight value of the bad performers was below 95% of baseline at day 350. We compared baseline characteristics of good ($n = 36$) and bad ($n = 33$) performers and found that of all baseline characteristics only initial Body Mass Index (BMI) and conditioning regimen were significantly different between groups. Initial BMI was 26.5 ± 4.1 kg/m^2 for the bad performers versus 23.5 ± 5.0 kg/m^2 for the good performers ($P < 0.01$; Student's *t*-test). Conditioning included TBI in 67% of the bad performers versus 42% in the good performers ($P < 0.05$, Chi Square test). Since the presence of overweight at baseline might interact with full restoration of pre-treatment body weight, we performed logistic regression analysis to correct for this effect. After adjustment for pre-treatment overweight (defined as BMI > 25 kg/m2), conditioning regimen (with or without TBI) was the only baseline characteristic that contributed significantly to predicting classification of body weight status at day 350 ($P < 0.05$; percent correct classification of the model 68%).

Fig 2.2.2 Body weight recovery after intensive cytotoxic therapy and stem cell transplantation in 4 subgroups of responders (n = 118) using mixed model analyses of variance

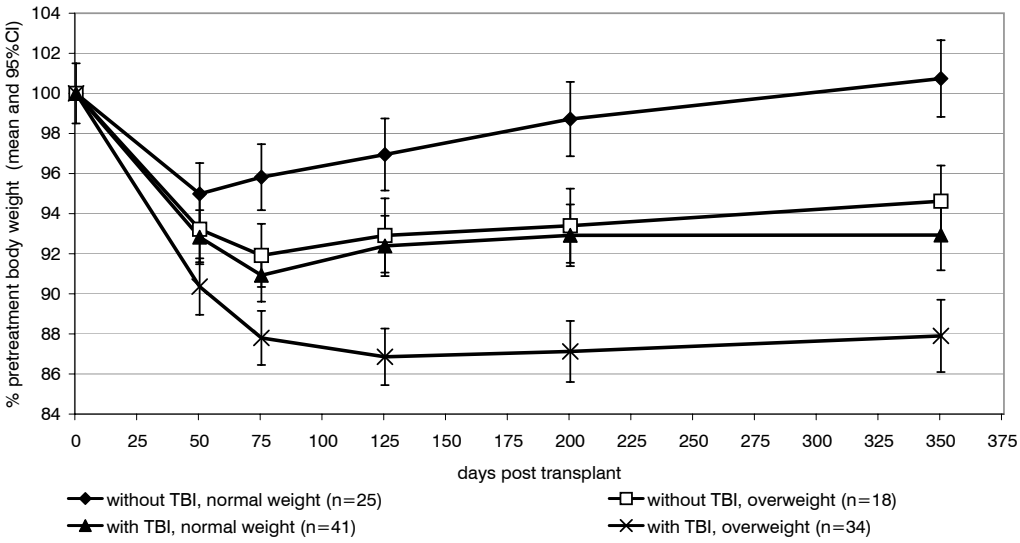

Table 2.2.3 Patient characteristics of 2 subgroups of complete responders (n=58)

	-TBI *n=27*	*+TBI* *n=31*	*P*
Demographical variables			
gender[1]			
female	18 (67%)	15 (48%)	NS
male	9 (33%)	16 (52%)	
age[2] (years)	45 ± 9	42 ± 12	NS
Clinical variables			
diagnosis[1]			
leukaemia or m.myeloma	1 (4%)	28 (90%)	<0.01
other	26 (96%)	4 (10%)	
donor type[1]			
autologous	26 (96%)	10 (32%)	<0.01
allogeneic	1 (4%)	21 (68%)	
type of transplant[1]			
BCT	21 (78%)	19 (61%)	NS
BMT	6 (22%)	12 (39%)	
Nutritional status			
initial Body Mass Index[2] (kg/m2)	25.9 ± 5.6	24.5 ± 4.5	NS
body weight class[1]			
BMI <= 25 kg/m2	14 (52%)	18 (58%)	NS
BMI > 25 kg/m2	13 (48%)	13 (42%)	
Outcome			
length of hospital stay[2] (days)	23 ± 6	28 ± 7	<0.01
weight change in hospital[2] (%)	-2.6 ± 3.4	-5.3 ± 3.9	<0.01

1. Frequency (proportion); Chi-square test
2. Mean (95%confidence interval); student-t test

Subgroups

Body weight recovery was analysed for four subgroups characterised by pre-treatment body weight status and conditioning regimen using data of all available patients (n =118) in a mixed-model analysis of variance. Figure 2.2.2 shows body weight recovery curves of the four subgroups. Differences between groups with the same pre-treatment body weight classification but different conditioning

regimen (with or without TBI) were statistically significant at all time points after day 50. The percentage of normal weight patients treated without TBI who had at least 95% of their pre-treatment body weight was 58% at day 50, 64% at day 75, 68% at day 125, 83% at day 200 and 88% at day 350. For normal weight patients treated with TBI this percentage was 36% at day 50, 20% at day 75, 28% at day 125, 41% at day 200 and 48% at day 350. We used data of 58 complete responders to compare longitudinal data on eating difficulties and symptoms between subgroups treated with and without TBI. Table 2.2.3 shows baseline data of subgroups treated with and without TBI. Groups differed significantly with respect to diagnosis (more leukaemia and multiple myeloma in the +TBI group), donor type (more allogeneic transplants in the +TBI group), length of hospital stay (longer stay in the +TBI group) and weight loss between baseline and discharge from hospital (more weight loss in the +TBI group). Patients with pre-treatment overweight were equally distributed among the two groups. Table 2.2.4 shows the median number of measurements (0–5) with eating difficulties, symptoms or inadequate food intake or dietary adaptations. Between groups, a significant difference is seen in the number of episodes with eating difficulties, poor appetite, dry mouth complaints and inadequate intake. No statistical difference was seen for the number of episodes of taste alterations, nausea, tiredness or actions to enrich the diet.

Discussion

This study was performed to evaluate nutritional aspects of the recovery process and compliance with dietary advice in a heterogeneous patient group in the first year after blood stem cell transplantation. We found that only half of the patients regained at least 95% of their pre-treatment body weight. After adjusting for pre-existing overweight we found that this percentage was 88% in patients treated without TBI and 48% in patients treated with TBI. Retarded weight recovery in the TBI-treated groups was accompanied by lengthier episodes of experiencing poor appetite, dry mouth and inadequate food intake compared to the non-TBI group. Compliance with dietary advice was poor. At day 50 about 42% of the patients reported having enriched the energy content of their diet, but this percentage diminished sharply with time. For protein enrichments the percentage was even lower. No significant differences in compliance were seen between the groups treated with and without TBI, although –looking at their weight recovery curve– TBI-treated patients should have had more reasons to enrich their diet. From all commercial oral supplements micronutrient preparations were more popular than energy, protein supplements or combined preparations.

Table 2.2.4 Number of positive scores for symptoms or dietary intake at 5 time points during the first year post-transplant in two subgroups by conditionings regimen

	-TBI *n=27*	*+TBI* *n=31*	*P*
symptoms			
eating difficulties	1 (0-2)	2 (2-4)	<0.01
poor appetite > 2 days	1 (0-1)	2 (1-3)	<0.01
dry mouth > 2 days	0 (0-2)	4 (2-4)	<0.01
altered taste > 2 days	1 (0-2)	2 (1-3)	NS
nausea > 2 days	0 (0-1)	1 (0-2)	NS
tiredness > 2 days	3 (2-4)	3 (2-5)	NS
nutritional intake			
'eaten half of usual or lessl' > 2 days[1]	0 (0-1)	1 (1-2)	<0.01
actions to enrich energy content[1]	1 (0-1)	1 (0-2)	NS
actions to enrich protein content	0 (0-1)	0 (0-2)	NS
actions to enrich micro-nutrient content	1 (0-3)	1 (0-2)	NS

median (25th - 75th percentile); Mann Whitney U test

As expected in this patient population, response rate in this study was low (43%). Explanatory factors are the poor physical condition of the patients and a mortality rate within 1 year after discharge of 25% of all responders (n = 118). Study completers were not comparable to dropouts and non-responders with respect to baseline characteristics (more low risk patients in the completers group) and outcome (higher values for body weight and a lower frequency of symptoms and inadequate food intake in the completers group). This limits generalizability of our results. We conclude that our rather negative findings, might still give an over positive view of the recovery process and frequency of nutritional problems after blood cell transplantation in a miscellaneous patient population. With respect to data quality, we assessed internal consistency and predictive validity. Internal consistency was satisfactory with a Cronbach's alpha of 0.74. Predictive validity was satisfactory with correlation coefficients for body weight status at day 350 and the number of episodes with eating difficulties or inadequate intake of -0.38 and -0.49, respectively. We conclude that our data give a reliable view of the body weight recovery process and its related problems.

Earlier reports note the prevalence of eating difficulties after discharge from hospital. Lenssen *et al*[6] reported nutritional problems in 23%, and weight loss in 28% of 192 patients in the first year after allogeneic bone marrow transplantation.

Chao *et al*[7] reported that at 90 days post transplant about one-third of patients reported poor appetite. The prevalence in our patient group was higher, probably due to the fact that our measurements were more frequent (five times) and our first measurement (day 50) was earlier in the recovery phase. The fact that only a minority of patients appears to regain their pre-morbid nutritional status at day 350 is also reported by Schulte *et al*[13]*.* They found in a group of 100 stem cell transplant recipients with haematological malignancies that the survivors after 1 year did not regain their pre-transplant physical condition, showed lower body weights, decreased muscle mass and grip strength as compared to baseline. We did not find any study that shed light on the dietary intake and compliance with dietary advice in the first year post transplant.

While the present study is one of the first studies that focuses on body weight recovery and compliance with dietary advice in the first year post transplant, several weaknesses in this study should be addressed in future research. First, numbers were small, especially in the subgroup analyses. This implies that we might have missed relevant differences that could have been picked up in a bigger sample size. We suggest that more prognostic research in larger groups, especially in patients treated with TBI might be helpful in understanding what factors can improve nutritional outcome in this group. Secondly, compliance with dietary advice has been measured by open-ended questions. This might have resulted in underreporting. Also information on individuals' need for enrichments was missed because we had no quantitative information on the individuals' intake. We suggest that addition of a food recording method might be a useful tool in future studies. Thirdly, weight loss and retarded recovery in the post-transplant phase are multi-factorial. Unfortunately, several factors which might underlie this problem were not assessed in this study. For example, complications, prevalence of graft-versus-host disease, supportive care measures (such as anti-emetic medication etc) and social factors deserve attention in future studies. Fourthly, all data were self reported. Addition of observational data as a crosscheck would strengthen future research.

In conclusion, our study revealed that eating difficulties and retarded weight recovery in the first year post transplant are relevant problems, especially in the TBI-treated group. TBI-treated patients need more attention after discharge with respect to their intake and nutritional status. We suggest that screening of intake and nutritional status should be routinely performed in this patient group around day 75. Compliance with dietary advice can possibly be improved by refreshing the information at that time. Clear information on the value of micronutrient supplementation and combined preparations with protein and energy is required. More insight into the reasons why the use of commercial oral energy and protein supplements is low in this patient population might challenge future research.

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Chapter 3 Prognosis, Proof and Priorities

3.1 Diet, lifestyle and survival after myocardial infarction

a prospective cohort study in European elderly

3.2 Diet, lifestyle and survival in coronary heart disease patients

a systematic literature review

Abstract

Background: The extent and benefits of adherence to lifestyle and dietary recommendations in secondary prevention are largely unknown. We examined the frequency of healthy dietary and lifestyle behaviours and their impact on survival in post-myocardial infarction (MI) patients in a prospective cohort study of elderly Europeans.

Methods: Adherence to a Mediterranean-type diet was measured with a modified Mediterranean Diet Score (MDS) on an eight-point scale.

Results: Participants were 426 men and women, aged 70 years or more, from 10 European countries, with a history of MI. During 10 years of follow-up mortality was 53%. Frequency of non-smoking behaviour (85%), moderate to vigorous physical activity (54%), moderate alcohol consumption (45%) and a Mediterranean-type diet (63%) in patients differed only marginally as compared with 'healthy' elderly. The median MDS in patients from northern Europe was two points lower than in southern Europe. Non-smoking (HR 0.62; 95% confidence interval (95% CI) 0.44–0.88), physical activity (HR 0.69; 95% CI 0.53–0.90), moderate alcohol consumption (HR 0.77; 95%CI 0.58–1.02) and a Mediterranean-type diet (HR 0.75; 95% CI 0.57–0.97) were associated with lower all-causes mortality. Presence of at least three healthy behaviours was associated with 40% lower mortality.

Conclusion: There is a strong relationship between lifestyle and dietary habits and mortality in post-MI patients. The findings implicate that also in secondary prevention groups substantial health gain can be obtained by better adherence to dietary and lifestyle recommendations.

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3.1 Diet, lifestyle and survival after myocardial infarction

a prospective cohort study in European elderly

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Diet and lifestyle factors (smoking habits, physical activity and alcohol consumption) have been shown to play an important role in prognosis of patients with symptomatic Coronary Artery Disease[1]. European Guidelines for Secondary Prevention of Cardiovascular Diseases[2] have translated research findings into practical recommendations for the individual patient. Research on the implementation of these guidelines has generally focused on prescription of drugs and prevalence of the classical risk factors[3]. While some have described the proportion of patients receiving dietary or lifestyle advice[4], adherence to these recommendations and its impact on survival in cardiac patients have only scarcely been addressed.

An alternative approach to evaluating an individual's diet by analysing the nutrient content has been proposed by Trichopoulou et al[5]. As many of the recommended dietary components are integral parts of the Mediterranean diet and substantial prognostic benefits are associated with a Mediterranean–type diet, they developed an instrument to measure the resemblance of an individual's diet with the traditional Greek Mediterranean diet. This Mediterranean Diet Score (MDS) has been shown to be associated with survival in several populations[6-9].

The prognostic value of the MDS and other lifestyle factors has been demonstrated in the 'healthy' population of the HALE (Healthy Ageing: a Longitudinal study in Europe) project[10]. In the present study the frequency of healthy dietary and lifestyle behaviours and the associations with mortality were evaluated in HALE participants with a history of myocardial infarction (MI). We

compared the frequency of healthy behaviours between post-MI patients and 'healthy' study participants, as well as between subgroups of patients by gender and region.

Methods

Study population

We selected patients with a history of MI from the HALE project. This project consists of participants from two European cohort studies: the Survey in Europe on Nutrition and the Elderly: a Concerted Action (SENECA) and the Finland, Italy and The Netherlands Elderly (FINE) study. The HALE project and both cohort studies have been described elsewhere[10-12]. Briefly, the SENECA study started in 1988 and consisted of a random age- and gender-stratified sample of inhabitants, born between 1913 and 1918. Of the 19 participating centres, 13 carried out a mortality follow-up in 1993 and 1999. Participation rates varied between the SENECA centres, from 37 to 81%[13]. The FINE cohort is an extension of the Seven Countries Study beyond the 25 years' follow-up. It started in 1984 including men aged 65–85 years. Participation rates were between 74 and 92%[14]. For the HALE project, participants were selected with a baseline age of 70 or older in the 1989–1991 surveys and a mortality follow-up until 2000. The diagnosis of MI in our study population was self-reported (SENECA) or medically confirmed (FINE). We excluded patients who reported a history of cancer, as this might have changed their diet, lifestyle and mortality risk. Included patients originated from 20 study centres.

Ten study centres in northern Europe were: Ilomantsi (FINE), East Finland; Pöytyä and Mellilä (FINE), West Finland; Roskilde (SENECA), Denmark; Zutphen (FINE) and Culemborg (SENECA), The Netherlands; Hamme (SENECA), Belgium; Strasbourg (SENECA), France; Burgdorf (SENECA), Switzerland. Ten centres located in southern Europe were: Vila Franca de Xira (SENECA), Portugal; Betanzos (SENECA), Spain; Valence (SENECA), France; Yverdon (SENECA) and Bellinzona (SENECA), Switzerland; Padua (SENECA), Crevalcore (FINE) and Montegiorgio (FINE), Italy; Iraklion (SENECA), Greece.

Demographic, lifestyle, anthropometric and medical variables

Baseline information was collected using a questionnaire on chronic disease (cancer, myocardial infarction, stroke or diabetes mellitus), educational achievement (number of years), marital status, smoking habits, physical activity level and alcohol consumption. For FINE participants, the presence of chronic disease was confirmed by information from general practitioners or hospital

registers. We classified smoking habits in current smokers and non-smokers (including ex-smokers). The questionnaires on habitual physical activity differed between the two studies: in SENECA the Voorrips questionnaire was used, in FINE the Morris questionnaire[15;16]. Both validated questionnaires were developed for retired elderly and focused on activities such as walking, cycling and gardening. We calculated gender- and study-specific tertiles of the distribution. Subjects with a score in the lowest tertile were defined as physically inactive; those in the second or third tertile as moderately to vigorously active.

In contrast to the studies of Trichopoulou et al[5;6;8;9]. we defined alcohol consumption as a lifestyle factor rather than considering this as part of the Mediterranean diet. Categories were abstainers (alcohol intake <1 g/day), moderate drinkers (1–20 g/day for women and 1–30 g/day for men) and excessive drinkers (>20 g/day for women and >30 g/day for men). In the Cox proportional hazards models we used only two groups for alcohol consumption (abstainers versus alcohol users), because the Kaplan–Meier survival curves of the moderate and more excessive drinkers showed no difference. Anthropometric measurements were obtained by trained study personnel using standard procedures[14;17]. Body Mass Index (BMI) was calculated as weight in kilograms divided by height in squared metres. Obesity was defined as a BMI > 30 kg/m^2. Non-fasting blood samples were collected and analysed for total- and high-density lipoprotein (HDL)-serum cholesterol and fasting blood samples for triglycerides, using standardized enzymatic methods[14;18].

Food consumption data

In both studies, food consumption data were collected by trained dietitians using a dietary history method[19]. This method provides information about the usual food intake. The main part of the interview was the same in both studies, but the reference period was 1 month in SENECA and 2–4 weeks in FINE. The interview data from both studies were coded using the EUROCODE-system[20]. Nutrient intakes were calculated using the food composition tables of each country. Validation of the methods used in both studies is described elsewhere[11;21]. Each dietary component was energy adjusted by dividing the daily intake (in grams) by the individual's total energy intake (in kcal) and multiplying it by the gender and study population specific median of energy intake: 2150 kcal for men and 1750 kcal for women.

Mediterranean diet score

The original MD score was constructed in 1995 by Trichopoulou et al[5] and revised several times[6-8;10] to include fish and to change the lipid ratio from

monounsaturated/saturated to unsaturated/saturated (as this makes it more applicable to the northern European countries as well). In the current study the score components were defined as follows:

- the ratio between unsaturated fats and saturated fats in the diet,
- vegetables, including potatoes (in EUROCODE potatoes were coded as vegetables),
- fruit and fruit products (including canned fruit, but not fruit juices),
- cereals (including bread, breakfast cereals, pasta, rice, etc.),
- legumes, nuts and seeds,
- fish,
- dairy (including milk, milk products and cheese),
- meat, poultry and derived products.

Values 0 or 1 were assigned to each of the eight components, using as cut-off the gender-specific median for the energy adjusted daily intake of the component in the chronic-disease-free HALE participants (excluded were those with a history of cancer, diabetes mellitus, myocardial infarction or stroke at baseline). Persons whose energy-adjusted consumption of the five beneficial components (vegetables, fruits, cereals, legumes or fish) was below the median consumption were assigned a value of 0, whereas for individuals with consumption above the median, a value of 1 was given. In contrast, persons with below-the-median consumption of presumed detrimental components (meat and dairy) were assigned a value 1, whereas individuals whose consumption of these two components was above the corresponding median were given a value 0. Finally, for lipid intake, the ratio of unsaturated to saturated fats was calculated. A ratio below the chronic-disease-free participant's median was rewarded with 0 and a ratio above the median with 1. The MD score was calculated by adding up the scores for the eight items. Beside this European-wide MD score, a regional MD score was calculated. For the regional MD score, a value 0 or 1 was assigned for each dietary component using the region- and gender-specific median of the chronic-disease-free HALE population as the cut-off point.

Follow-up

Information on vital status and causes of death was collected every 5 years in FINE. For SENECA this was done after 10 years of follow-up. Vital status was available for 99.7% of the HALE participants.

Data analysis

Data were analysed using SAS statistical software version 8.2 (SAS Institute, Cary, North Carolina, USA). Before pooling, mortality data from the SENECA and FINE studies were tested for heterogeneity ($p = 0.93$). Baseline data and

Table 3.1.1. Baseline characteristics of post-MI patients compared to other participants in the HALE-project not suffering from chronic diseases

	Males			*Females*			
	post-MI patients	*other participants*		*post-MI patients*	*other participants*		
	(n=284)	*(n=1671)*	*P[1]*	*(n=142)*	*(n=857)*	*P[2]*	*P[3]*
Demographic variables							
age (years)	75 ± 4	75 ± 4	NS	73 ± 2	73 ± 2	NS	<0.01
educational achievement[5] (yrs)	8 (5-10)	8 (5-10)	NS	7 (4-8)	8 (6-9)	<0.05	<0.05
marital status (% married)	79%	79%	NS	43%	43%	NS	<0.01
region (% North Europe)	62%	55%	<0.05	46%	43%	NS	<0.01
Clinical characteristics							
T-chol/HDL ratio[5]	5.5 (4.5-6.8)	4.8 (3.9-5.9)	<0.01	5.2 (4.2-6.6)	4.6 (3.7-5.7)	<0.01	NS
triglycerides[5] (mmol/l)	1.4 (1.0-2.0)	1.2 (0.9-1.7)	<0.01	1.4 (1.0-1.2)	1.2 (0.9-1.7)	<0.01	NS
obesity	15%	14%	NS	32%	25%	NS	<0.01
diabetes mellitus	10%	8%	NS	14%	8%	<0.05	NS
stroke	8%	3%	<0.01	5%	1%	<0.01	NS
Diet							
energy intake [5] (kcal/day)	2186 (1793-2529)	2272 (1915-2698)	<0.01	1758 (1356-2032)	1782 (1491-2081)	NS	<0.01
mediterranean diet[6] (score≥4)	60%	62%	NS	70%	61%	<0.05	<0.05
Other Lifestyle variables							
non-smokers	80%	75%	NS	95%	93%	NS	<0.01
physically active	53%	66%	<0.01	60%	66%	NS	NS
alcohol pattern							
abstainers	29%	21%	<0.01	66%	49%	<0.01	<0.01
moderate drinkers	54%	53%		28%	42%		
excessive drinkers	17%	26%		6%	9%		
Number of healthy behaviours							
0-1	15%	14%	NS	13%	11%	NS	NS
2	35%	32%		32%	31%		
3	36%	37%		47%	42%		
4	14%	17%		8%	16%		
Clinical outcome							
mortality rate	67%	50%	<0.01	40%	25%	<0.01	<0.01

1.testing males: patients vs other participants; 2.testing females: patients versus other participants; 3.testing patients: all males vs all females; 4.Average ± SD , t-test; 5.median (interquartile limits), Wilcoxon test; 6.score based on gender specific cut-of points of the healthy part of the HALE-population

healthy behaviours were compared and tested for differences between the post-MI patients and the reference group of healthy HALE participants and between patient subgroups. The chi-square test was used for the dichotomous variables, the Student's *t*-test for normally distributed continuous variables (presented as mean ± SD) and the Wilcoxon test for data that were not normally distributed (presented as median and 25 and 75 percentiles).

To address the mortality risk associated with diet and lifestyle in the total patient population and subgroups by gender and region, we used the Cox proportional hazards model. One model was used to assess the association between mortality and each of the single dietary components (0/1). This model was adjusted for study (FINE, SENECA), gender, age (continuously), years of education (continuously), BMI (continuously), history of diabetes (Y/N) or stroke (Y/N), smoking (Y/N), physical activity (Y/N) and alcohol consumption (Y/N). In a second Cox proportional hazards model we assessed the association between mortality and each of the four healthy habits [non-smoking (Y/N), physical activity (Y/N), alcohol consumption (Y/N) and Mediterranean diet (score ≥4 versus <4)], while adjusting for the same variables (except lifestyle and dietary factors). A third model assessed the association between mortality and the number of healthy behaviours (0–2 versus 3–4), while adjusting for the same variables (except lifestyle and dietary factors). The proportional hazards assumptions for each model were tested and met. The interaction of gender and region was tested for each model but was not significant at alpha equal to 0.1.

Results

Information about diet, lifestyle factors and vital status was available for 2954 HALE participants without cancer at baseline (1955 men and 999 women; 2002 from SENECA and 952 from FINE). Mean follow-up time was 10 years (range 8.9–10.5 years). Of these 2954 participants, 426 reported a history of MI, of whom 285 (67%) were males and 314 (74%) came from the SENECA study. The post-MI patients had fewer years of education (females only), a worse serum lipid profile and a higher prevalence of a history of stroke compared to the other study participants (Table 3.1.1). Dietary and lifestyle differences between post-MI patients and other participants were small. In the patients, the frequency of a Mediterranean-type diet was higher (in female patients only), while the frequency of moderate to vigorous physical activity was lower. Patients were more often alcohol abstainers. The distribution of the number of healthy behaviours was not significantly different between patients and other participants. Mortality rate was 1.5 times higher among patients. Between male and female patients differences were seen in age and educational level (both lower in females). Obesity, non-

Table 3.1.2 Characteristics of 426 European post-myocardial infarction patients by gender and region

	Males (n=284)			*Females (n=142)*		
	Northern Europe (n=175)	*Southern Europe (n=109)*	*P[1]*	*Northern Europe (n=66)*	*Southern Europe (n=76)*	*P[1]*
Demographic variables						
age ≥75 years	35%	30%	NS	15%	24%	NS
education ≥6 years	84%	51%	<0.01	98%	42%	<0.01
Clinical characteristics						
T-chol/HDL ratio > 5	67%	48%	<0.01	53%	43%	NS
triglycerides > 2 mmol/l	25%	21%	NS	29%	13%	<0.05
obesity (BMI>30 kg/m2)	11%	20%	<0.05	26%	38%	NS
diabetes mellitus	8%	13%	NS	14%	14%	NS
stroke	10%	4%	<0.05	5%	5%	NS
Diet						
median intakes[2] for						
fat ratio[3]	1.46	1.92	<0.01	1.63	2.24	<0.01
vegetables (g)	303	244	<0.01	235	242	NS
fruit (g)	172	236	<0.01	189	244	<0.01
cereals (g)	170	256	<0.01	150	201	NS
legumes, seeds, nuts(g)	4	5	NS	0	1	NS
fish (g)	19	33	<0.01	22	41	<0.01
dairy (g)	383	258	<0.01	267	242	NS
meat & poultry (g)	122	103	<0.01	118	78	<0.01
mediterranean diet score	3 (2-4)	5 (4-6)	<0.01	3 (2-4)	5 (4-6)	<0.01
mediterranean diet score ≥4	45%	83%	<0.01	45%	92%	<0.01
Other lifestyle factors						
non-smoker	79%	82%	NS	91%	99%	<0.05
physically active	53%	52%	NS	48%	66%	<0.05
alcohol habits						
abstainer	35%	18%	<0.01	52%	79%	<0.01
moderate drinker	55%	53%		41%	16%	
excessive drinker	9%	29%		7%	5%	
Number of healthy behaviours						
0-1	21%	5%	<0.01	24%	3%	<0.01
2	36%	35%		32%	32%	
3	30%	46%		36%	57%	
4	13%	15%		8%	9%	
Outcome						
Mortality rate	71%	59%	<0.05	47%	33%	NS

1. Proportions tested by chi-square test; Medians tested by Wilcoxon test; 2. Standardized for energy intake;
3. Unsaturated fats / saturated fats

smoking behaviour and a Mediterranean-type diet were more frequent in females, while moderate alcohol consumption was more frequent in men. No difference between the genders was found in the median number of healthy behaviours. Female patients had a lower mortality.

Male patients from northern Europe (Table 3.1.2) had a higher frequency of ≥6 years of education and a higher proportion of patients with dyslipidaemia, obesity or a history of stroke than those from the southern regions. The percentage of alcohol consumers and adherence to the Mediterranean diet was higher in southern European patients. A higher proportion of patients in the southern region adhered to three or more healthy behaviours. Mortality was lower in the southern European male patients. Female patients from both regions differed with respect to education (more frequently ≥ 6 years in the north), serum lipid profile (worse in the north), MD score (two points higher in the south), smoking behaviour (more non-smokers in the south), physical activity (more moderate to vigorously active in the south) and alcohol consumption (more abstainers in the south). The proportion of female patients adhering to three or more healthy behaviours was significantly higher in the south. Mortality in southern females was lower, although not statistically significant ($P = 0.09$).

Table 3.1.3 shows the Cox proportional hazard ratios (HRs) for all-causes mortality, comparing patients with a healthy behaviour to those with an unhealthy behaviour. Of the individual dietary components, only the high fruit consumption was significantly associated with a lower mortality in the total group. A Mediterranean diet (MD Score ≥4) was significantly associated with a lower mortality risk (HR 0.75; 95% CI 0.57–0.97), in the total group as well as in the subgroup from northern Europe. Protective effects were also shown for non-smoking (HR 0.62; 95% CI 0.44–0.88), a higher level of physical activity (HR 0.69; 95% CI 0.53–0.90) and moderate alcohol consumption, although the latter relationship was not statistically significant (HR 0.77; 95% CI 0.58–1.02) in the total patient population. A combination of at least three healthy habits was associated with a 42% lower mortality rate (95% CI 22–56%) in the total patient group. All subgroups showed a lower mortality associated with a higher level of adherence to the four lifestyle recommendations, although not always statistically significant.

Discussion

Our data show that post-MI patients do not live more healthily than elderly without a history of cardiac disease. Adherence to healthy behaviours differs between subgroups by gender and European region. Patients with a healthier lifestyle or

Table 3.1.3 Cox proportional Hazards Ratio (HR) for all-causes mortality for dietary components, diet score and lifestyle factors in 426 European post-Myocardial Infarction patients

	All[2]	*Men*[2]	*Women*[2]	*Northern Europe*[3]	*Southern Europe*[3]
	HR (95% CI)[1]	*HR (95% CI)*[1]	*HR (95% CI)*[1]	*HR (95% CI)*[1]	*HR (95% CI)*[1]
	n=426	*n=284*	*n=142*	*n=241*	*n=185*
Dietary components[4]					
unsaturated / saturated fat	0.92 (0.70-1.20)	0.85 (0.62-1.15)	1.21 (0.66-2.21)	0.84 (0.58-1.21)	0.88 (0.51-1.53)
vegetables (incl. potatoes)	1.06 (0.82-1.38)	1.15 (0.85-1.55)	0.75 (0.42-1.32)	0.91 (0.95-1.28)	1.36 (0.85-2.18)
fruits	0.74 (0.57-0.96)*	0.79 (0.59-1.06)	0.57 (0.32-1.02)	0.72 (0.52-1.00)	0.85 (0.54-1.36)
cereals	0.83 (0.63-1.08)	0.86 (0.63-1.16)	0.75 (0.43-1.30)	0.83 (0.57-1.20)	1.14 (0.69-1.89)
legumes, nuts, seeds	0.91 (0.70-1.18)	0.91 (0.67-1.23)	0.90 (0.52-1.55)	1.03 (0.74-1.43)	0.74 (0.48-1.14)
fish	0.80 (0.70-1.18)	0.79 (0.59-1.06)	1.04 (0.57-1.89)	0.81 (0.58-1.13)	1.20 (0.74-1.97)
dairy	0.83 (0.64-1.09)	0.73 (0.53-10.7)	1.29 (0.74-1.34)	0.68 (0.47-0.97)	1.07 (0.68-1.67)
meat & poultry	0.99 (0.76-1.29)	0.95 (0.70-1.29)	1.30 (0.72-2.33)	1.32 (0.92-1.88)	1.07 (0.68-1.68)
Mediterranean Diet[5]					
MD-score ≥4	0.75 (0.57-0.97)*	0.74 (0.55-1.00)	0.86 (0.46-1.61)	0.68 (0.49-0.95)*	1.33 (0.82-2.17)
Lifestyle[5]					
non-smoking	0.62 (0.44-0.88)*	0.67 (0.47-0.97)*	0.38 (0.12-1.24)	0.72 (0.47-1.10)	0.51 (0.28-0.96)*
physically active	0.69 (0.53-0.90)*	0.72 (0.53-0.97)*	0.62 (0.36-1.10)	0.70 (0.50-0.98)*	0.72 (0.46-1.13)
moderate alcohol consumption	0.77 (0.58-1.02)	0.77 (0.56-1.07)	0.77 (0.42-1.42)	0.62 (0.44-0.89)*	1.01 (0.58-1.76)
Number of healthy habits[6] (0 - 4)					
3 or more	0.58 (0.45-0.75)*	0.59 (0.44-0.78)*	0.71 (0.41-1.21)	0.54 (0.39-0.74)*	0.83 (0.53-1.28)

* $p<0.05$;

1. comparing the healthy to the unhealthy behaviour (reference group);
2. Cut-off points for dietary components were based on sex-specific medians of the healthy population.
3. Cut-off points for dietary components were based on sex- and region- specific medians of the healthy population.
4. Model 1, this model was adjusted for study (FINE, SENECA), gender, age (continuously), years of education
5. Model 2, this model was adjusted for the same variables as in model 1 except the lifestyle factors.
6. Model 3, this model was adjusted for the same variables as in model 1 except the lifestyle factors.

dietary habits had a better prognosis than those with more unhealthy behaviour. Mortality differences associated with the individual diet and lifestyle factors varied between 20 and 40%.

Advantages of this study include its prospective nature, its reliance on a European-wide sample, the population of free-living post-MI patients outside the hospital setting and its almost 100% mortality follow-up. A possible limitation of the study is that the data could have been affected by selective participation (more health-conscious people included) or self-reporting of diet and lifestyle (social expectation bias), resulting in an overestimation of the frequency of the healthy behaviours. The definition of the components of the MD score was influenced by the EUROCODE data-coding system used. In contrast to the original Greek study[5], in the present study potatoes were grouped with vegetables, poultry with meat, and nuts and seeds with legumes. These combinations of foods hamper the interpretation of the differences in vegetable consumption between the regions. They possibly also attenuated the observed relationship with mortality, as it is unlikely that potatoes have the same protective effect as vegetables. Also the original definitions[5] of some score-components (e.g. a negative value for all milk products, without distinction between low- or high-fat milk products; a positive value for all cereals, both refined and wholemeal cereals) might have attenuated the observed associations. Our definition of physical inactivity was based on a relative criterion: the tertile distribution of the healthy population. Prevalence of this behaviour is therefore difficult to compare with other studies. Due to the small sample size and the low mortality rate in some of the subgroups (females and southern European patients), the power of our study was limited and the association between the lifestyle determinants and mortality could not be determined for all subgroups. Finally, we cannot rule out the possibility of unmeasured and residual confounding.

With respect to the frequency of healthy behaviours in post-MI patients, other studies[9;22-24] show various outcomes. Panagiotakos *et* al[23] described a significantly lower frequency of healthy lifestyle factors and dietary characteristics in 800 Greek post-MI patients in the year preceding their first event, compared to healthy controls. Barzi *et* al.[22] found in a longitudinal study of 13,000 Italian post-MI patients a substantial improvement of dietary quality between time of event and 6 months' follow-up, which was maintained for 3 years. Spencer et al.[24] in an Australian cohort, found a better adherence to a 'healthy lifestyle' in post-MI patients than in healthy controls. The absence of a difference in healthy habits between patients and healthy participants in our study should be interpreted in the light of these studies. It might have been that the post-MI patients initially had

worse habits (which placed them at higher risk) than their healthy counterparts, and had already made a substantial change in the desired direction after their first myocardial infarction.

The strength of the associations between healthy habits and mortality in the present study (20–40% lower mortality) is comparable with those observed in the healthy participants in the HALE project[10]. Other studies in patients with cardiovascular diseases also showed prognostic benefits associated with healthy dietary behaviours (27%[9] and 50%[22] lower mortality) or a combination of healthy dietary and lifestyle habits (25% lower mortality[24]).

Promoting longstanding dietary and lifestyle changes in post-MI patients is evidence-based, relevant[1] and achievable[22], yet this knowledge is not fully implemented in many hospitals[4]. Many patients are not appropriately informed about the potential benefits of a healthy diet and lifestyle. The MD score may offer a useful tool to promote adherence to the dietary recommendations in patients. Compared with dietary recommendations about nutrients, the MD score has the advantage of comprehensibility as most of its components are formulated in terms of foods. The cut-off points used are medians of intake in a specific population and not an absolute minimum (or maximum) amount as defined in nutritional guidelines (e.g. 400 g of fruits and vegetables). Aiming at an intake of at least the median of the local population has the advantage of feasibility in the local situation. Research might further improve the applicability of the MD score for patient education. Definitions of some of the score components need further reflection for application in different countries. Another research topic is the development of effective organizational and educational strategies to enhance longstanding compliance with dietary and lifestyle recommendations. A tailored approach is required as the frequency of health behaviours differs substantially between subgroups by gender and region.

In conclusion, there is a strong relationship between lifestyle and dietary behaviours and survival in post-MI patients. Post-MI patients do not live more healthily than elderly people without a history of MI. There is wide variation in the frequency of healthy behaviours between subgroups of the European patient population. The findings suggest that considerable health gain can be expected from efforts to promote a healthy diet and lifestyle in patients after myocardial infarction.

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3.2 Diet, lifestyle and survival in coronary heart disease patients

a systematic review

Abstract

Background: Guidelines for lifestyle and dietary modification in coronary artery disease (CAD) patients are mainly supported by evidence from general population studies. CAD patients, however, differ from the general population in age (older) and treatment with preventive drugs. This review seeks to provide evidence for a prognostic benefit of lifestyle and dietary recommendations from studies in CAD patients.

Methods: A literature search was performed on the effect of lifestyle and dietary changes on mortality in CAD patients. Prospective cohort studies and randomised controlled trials of patients with established CAD were included if they reported all-causes mortality and had at least 6 months follow-up.

Results: The effect estimates of smoking cessation (relative risk (RR) 0.64; 95% CI, 0.58 to 0.71), increased physical activity (RR, 0.76; 95%CI, 0.59 to 0.98) and moderate alcohol use (RR, 0.80; 95%CI, 0.78 to 0.83) were studied most extensively. For the 6 dietary goals data were too limited to provide reliable effect size estimates. Combinations of dietary changes were associated with reduced mortality (RR, 0.56; 95%CI, 0.42 to 0.74).

Conclusion: Available studies show convincingly the health benefits of lifestyle changes in CAD patients. Effect estimates of combined dietary changes look promising. Future studies should confirm these findings and assess the contribution of the individual dietary factors.

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3.2 Diet, lifestyle and survival in coronary heart disease patients

a systematic literature review

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More than 40 years ago Ancel Keys was the first to explore the relationship between coronary artery disease (CAD) and environmental factors[1]. Since then several lifestyle and dietary factors have been found to be associated with the risk of cardiovascular morbidity and mortality[2]. This knowledge has been translated into recommendations for the general population (primary prevention) and clinical guidelines for those with manifest cardiovascular diseases (secondary prevention).

Patients with CAD, i.e., myocardial infarction (MI) or angina pectoris (AP), are the largest of the secondary prevention groups. This group is characterized by older age (80% is older than 50 years) and a minority of women (30%)[3;3]. Although the prognosis of CAD patients has improved considerably during the last decades[4], they still carry a high absolute risk for future CAD events (10-year absolute risk from 20 to 80%)[5]. International guidelines[6] defined this patient group as top priority for preventive strategies.

Guidelines for CAD prevention[6-9] agree more or less on the nine lifestyle and dietary recommendations shown in Table 3.2.1. These recommendations are supported largely by evidence from population-based cohort studies and trials with surrogate endpoints. The effects on life expectancy in patients with CAD are unclear. These patients differ from the general population not only by their older age and compromised vasculature, but also by the drugs they take to prevent secondary events. Patients contemplating behavioural changes, as well as professionals designing preventive strategies, want to be able to make choices

Table 3.2.1 Lifestyle and dietary recommendations for prevention of (recurrence of) coronary artery diesease

1.	Stop smoking
2.	Engage in moderate intensive physical activity (for 30 minutes or more on at least five, but preferably all, days of the week)
3.	If you use alcohol: do so in moderation (max. 2 alcoholic drinks/day for women and max. 3 drinks/d for men)
4.	Maintain or attain a healthy body weight (BMI < 25 kg/m2); obese patients (BMI ≥ 30 kg/m2) should try to loose 10-15% of their current body weight
5.	Limit your saturated fat intake (to a maximum of 10 energy%) and the intake of trans fatty acids (to maximal 1 energy%)
6.	Consume fish regularly (at least 1 and preferably 2 portions oily fish a week)
7.	Consume sufficient amounts of fruits and vegetables (at least 400 gram / day)
8.	Use sufficient fibre containing grains products, legumes and/or nuts (at least 3 units / day)
9.	Reduce your salt intake (to maximal 2400 mg / day)

and rationally prioritize one goal before another. Information on the magnitude of the effect that can be expected of each of the recommended lifestyle and dietary changes is therefore needed.

This study seeks to summarize the evidence that the individual lifestyle and dietary goals formulated in Table 3.2.1 can improve prognosis in CAD patients. Second, we want to provide estimates of the magnitude of the effects on survival for each individual lifestyle and dietary goal based on the available studies in CAD patients.

Methods

We conducted a systematic review of the literature on benefits of the recommended lifestyle and dietary changes in CAD patients applying the following selection criteria:

Study population
Studies had to investigate a population of at least 50% patients diagnosed with CAD. CAD patients were defined as patients with a history of Myocardial Infarction (MI) or Angina Pectoris (AP) or who underwent coronary bypass surgery (CABG) or percutaneous transluminal coronary angioplasty (PTCA)).

Determinants and Interventions
We excluded studies on nutrient supplements if the dosage of the nutrient they provide goes beyond the amount that can reasonably be achieved by changing food habits without the use of supplements. For each lifestyle and dietary recommendation (Table 3.2.1), we defined the following determinants or interventions to be accepted in our study:

- *Smoking Cessation*: Studies reporting smoking cessation after the diagnosis of CAD were accepted.
- *Physical Activity:* Time spent on moderate intensive activity is the best operationalisation of the current recommendations[10]. Moderately intensive activities are those with an absolute intensity of 4 to 6 METs or a relative intensity of 40-60% of VO_2max[11]. We also accepted studies on total energy expenditure, habitual daily activity scores, time spent in vigorous intensive physical activity, physical fitness or participation in structured exercise programs.
- *Alcohol Consumption*: Alcohol consumption had to be reported in the number of units or grams alcohol per day. Studies reporting only alcohol intake as a percentage of total energy intake were excluded.
- *Energy Balance:* The recommendation to maintain or attain a healthy body weight refers to both the actual as well as the previous history of the balance between energy intake and energy expenditure (physical activity). Accepted were studies on body weight maintenance after the first manifestation of CAD and studies on intentional body weight reduction in overweight or obese CAD patients in relation to survival. Studies on the association between body weight status (body mass index (BMI)) at time of event and survival were excluded, because BMI at time of diagnosis does not reflect lifestyle and dietary habits after the first manifestation of CAD.
- *Saturated Fat and Trans-Fatty Acids*: We accepted all studies investigating a reduced intake of saturated fat and/or trans fatty acids without a substantial restriction of total fat intake. Interventions on total fat intake restrictions beyond 25 energy% were excluded, because of supposed detrimental effects on HDL and triglycerides levels[12]. Given the mean intake of saturated fat in most

Western countries at about 15 energy %, we defined a reduction of 5 energy % as a relevant difference.

- *Regular Fish(Oil) Consumption*: The recommended two portions (400 gram) oily fish per week are equivalent to a daily dose of 500-1000 mg n-3 fatty acids (eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)) [13]. We accepted all studies on fish consumption and on fish oil supplements to a maximum increase of 1000 mg n-3 fatty acids /day. We excluded studies with higher doses, because it is unlikely that these levels can be achieved by increasing fish consumption alone.
- *Fruit and Vegetables*: We included studies that examined the effect of the daily intake of fruits and vegetables in all available forms (fresh, canned, frozen, dried or as juice).
- *Whole Grains, Legumes and Nuts:* We included studies on the effect of the daily intake of whole grains, legumes and nuts or that studied the effect of intake of fiber from these products.
- *Salt:* We included all studies examining the effect of sodium restriction. Because the recommended maximal salt intake is 6 grams[14] per day (2400 mg or 100 mmol sodium) and current intake in Western societies is about 9 grams, a restriction was defined as a reduction of at least 30% or 50 mmol sodium.
- *Combined Lifestyle and Dietary Interventions or Combined Determinant Scores:* We also included studies that examined a combination of two or more of the aforementioned individual factors.

Outcome Measures

We only included studies that reported an effect on all-causes mortality.

Study Design and Follow-Up Period

Studies had to have a prospective design, being either a cohort study or a randomized controlled trial, and the follow-up period had to be at least 6 months. If available, meta-analyses of prospective studies were preferred and replaced the individual studies that they described.

Search Strategy

Data for this review were identified by searches in PubMed (1966 to May 2004) with the MeSH terms ‘coronary artery disease’ and ‘patients’ in combination with the MeSH terms or text words ‘lifestyle, smoking, physical activity, physical fitness, exercise, alcohol drinking, body weight, weight control, diet, saturated fat, trans

fatty acids, cholesterol, fish, fruit, vegetables, whole grains, cereals, legumes, nuts, fiber, salt, sodium, mortality, survival and death'. There was a restriction on English language. Relevant articles not identified by this strategy, but referenced in the bibliographies of these selected articles, were also included.

Data Extraction and Standardisation

Details of the included studies were systematically described as shown in Table 3.2.2. The relative risk (RR) was used as a measure of strength of the relationship between exposure to the lifestyle or dietary factor and all-causes mortality or other endpoints. The RR should compare the risk in the group practicing the desired healthy behaviour (exposed group) with the group not showing the healthy behaviour (reference group). For studies that reported the RR from the unhealthy lifestyle or dietary factor (eg, BMI > 30 kg/m2) compared with the healthy lifestyle or dietary factor (eg, BMI <25 kg/m2), the RR from the exposed group was calculated as 1 divided by the RR in the non-exposed group. If the RR or the 95% confidence interval (95%CI) of the RR was not reported in the original studies they were calculated from the study data with the use of the number of subjects (N) and the number of cases (A) in both the exposed (1) and the unexposed (0) groups (RR = (A1/N1 divided by A0/N0) and 95%CI = EXP(lnRR ± 1.96√(1/A1+ 1/A0)) if incidence is sufficiently rare).

Summary Effect Estimates

We decided that an effect estimate per lifestyle or dietary goal could only be provided if a meta-analysis was available or if at least two randomized controlled trials or two cohort studies were available meeting the following quality criteria:

- in case of cohort studies the effect estimate should be based on findings that were adjusted for confounders, at least for age and gender,
- in case of randomized trials information should be given that compliance with the intervention under study was checked and considered satisfactory,
- the effect estimate of each study should be based on at least 20 mortality cases to guarantee that the power of the study allowed meaningful effect estimation.

Results for the lifestyle or dietary goals that fulfilled these criteria are shown in Table 3.2.3. Before we pooled the data heterogeneity between the studies was tested with the Chi Square statistic. We used the random effects model for calculating a pooled estimate for the RR if the probability value for heterogeneity was ≤ 0.5. In case the probability value for heterogeneity >0.5, a fixed effects model was used.

Table 3.2.2a Studies on lifestyle and dietary factors and all-causes mortality in CAD-patients

Study	*Study population*	*Enrolment / Follow-up*	*Determinant/ Intervention*	*Reference/ Controls*	*All-causes mortality RR (95%CI)*
Smoking cessation					
Critchley, 2003 Meta-analysis 20 cohort studies	CAD-patients, n=12.603; 2928 deaths Age: 20-95 y >70% men	Enrolment: 1960-1995 Mean follow-up: 5.5 yr	Smoking cessation after CAD-diagnosis	Continued smoking	0.64 (0.58-0.71)
Wilson, 2000 Meta-analysis 12 cohort studies	Post MI-patients, n=5878; 915 deaths Age: not reported	Enrolment: 1949-1988 follow-up: 2 - 10yr	Smoking cessation after MI-diagnosis	Continued smoking	0.54 (0.46-0.62)
Physical activity					
Brown, 2003 Meta-analysis 12 RCT's	CAD-patients, n= 2,585; 212 deaths age: 54 (50-70)y 95% men	Enrolment:1970-2000 Mean follow-up: 2 y (range 6 month-5 yrs)	Rehabilitation programme with exercise only	Usual care	0.76 (0.59-0.98)
Moderate alcohol consumption					
Cooper, 2000 Cohort study US	CAD-patients with Left ventricle dysfunction, n=5,331; 1,200 deaths mean age: 60 y 85% men	Enrolment: ca.1990 Follow-up: 33 month ±14 Adjusted for demographics, risk factors, medication	1-4 alcoholic drinks per week	no alcohol drinkers	0.85 (0.75-0.97)
Shaper, 2000 Cohort study UK	CAD-patients n=655; 294 deaths Age: 40-59 at baseline 100% men	Enrolment: 1983-1985 Follow-up: 12.8 y Adjustments: demographics, risk factors	1-15 units per week	occasional drinking	1.05 (0.78-1.42)
Muntwyler, 1998 Cohort study US	post MI patients n=5358; 920 deaths mean age: 63 (±9) y 100% men	Enrolment: 1982 Follow-up: 5 y Adjustments: demographics, risk factors	2-6 units per week	Rare and non-drinkers	0.72 (0.58-0.89)
Thun, 1997 Cohort study US	Patients with vascular disease n=71,232; 8,434 deaths mean age: 57 y 55% men	Enrolment: 1982; Follow-up: 9 y Adjustments: demographics, risk factors, fat intake	2 drinks per day	Non-drinkers (ex-drinkers excluded)	0.8 (0.8-0.9)
Doll, 1994 Cohort study UK	Patients with vascular disease n=5402; 2396 deaths Age: 48-78 y 100% men	Enrolment: 1978 Follow-up: 13 y Adjustments: age, smoking	1-14 units/week	Non-drinkers (incl. ex-drinkers)	0.79[1] (0.69-0.91)

Study	*Study population*	*Enrolment / Follow-up*	*Determinant/ Intervention*	*Reference/ Controls*	*All-causes mortality RR (95%CI)*
Body weight control					
Singh, 1992 Cohort study India	CAD-patients n=204; 21 deaths age: 51 ± 9 y 90% men	Enrolment: not reported Follow-up: 1 year Adjustments: none	Weight loss post MI > 0.5 kg	Weight loss post MI < 0.5 kg	0.46[1] (0,19-1,10)
Saturated fat					
Erkkila, 2003 Cohort study Finland	CAD-patients n=415; 34 deaths age: 61 (33-74) y 70% men	Enrolment: 1991-1994 Follow-up: 5 y Adjusted for: demographic and diagnostic factors, risk factors, energy intake	9 energy% saturated fat intake (average-SD)	13 energy% saturated fat intake (average)	0.64 (0.46-0.88)
Burr, 1989 RCT UK	Post MI patients n=2033; 224 deaths mean age: 57 y 100% men	Enrolment: 1985-1987 Follow-up: 2 y Compliance: moderate; as shown by 5% decrease in serum cholesterol	11 energy% saturated fat	15 energy% saturated fat	1.0 (0.77– 1.30)
Woodhill, 1978 RCT Australia	CAD-patients n=458; 67 deaths age: 30-59 y 100% men	Enrolment: 1966-1972 Follow-up: 5 y Compliance: moderate, as shown by 5% decrease in serum cholesterol	10 energy% saturated fat	13,5 energy% saturated fat	1,49[1] (0.92-2.43)
Morris, 1968 RCT UK	post MI-patients n=395; 59 deaths age: 60% 50-60 y 100% men	Enrolment: 1960-1965 Mean follow-up: 3.7 y Compliance: good, as shown by a 15% decrease in serum cholesterol	ca. 12 energy% saturated fat	ca.17 energy% saturated fat (ordinary UK-diet)	0.88[1] (0.53-1.47)
Leren, 1966 RCT Norway	post MI-patients n=412; 96 deaths age: 30-64 y 100% men	Enrolment: 1958-1959 Follow-up: 5 y Compliance: good, shown by a 15% decrease in serum cholesterol	9 energy% saturated fat	not described	0.75[1] (0.50-1.12)
Regular fish(oil) consumption					
Barzi, 2003 cohort study Italy	post MI-patients n=11,246; 1660 deaths age: 59 ± 11 85% men	Enrolment: 1993-1995 Follow-up: 6.5 y Adjustments: demographic, risk factors, food variables	2 portions fish per week	(almost) never fish	0.81 (0.69 – 0.94)

Table 3.2.2b Studies on lifestyle and dietary factors and all-causes mortality in CAD-patients

Study	*Study population*	*Enrolment / Follow-up*	*Determinant/ Intervention*	*Reference/ Controls*	*All-causes mortality RR (95%CI)*
Erkkila, 2003 cohort study Finland	CAD-patients n=400; 34 deaths age 61 (33-74) 70% men	Enrolment: 1991-1994 Follow-up: 5 y Adjusted for: demographic, diagnostic, risk factors, energy intake	1-57g fish per day >57 g fish per day	0 g fish per day 0 g fish per day	0.50 (0.20-1.28) 0.37 (0.14-1.00)
Burr, 2003 RCT UK	AP-patients n=3114; 525 deaths mean age: 61 y 100% men	Enrolment: 1990-1996 Follow-up: 3 to 9 y Compliance checked by food records in subset at 6 months; no significant difference en serum EPA level between groups	advice to eat at least two weekly portions oily fish (200-400 g) or fish oil capsules	'sensible eating' advice	1.15 (0.96-1.36)
GISSI, 1999/2002 RCT Italy	post MI patients n=11323; 1017 deaths mean age: 59± 11y; 85% men	Enrolment: 1993-1995 Follow-up: 3.5 y Compliance confirmed 3-monthly by biomarkers and refill check drug supplies	supplement 900 mg EPA/ DHA	placebo	0.79 (0.66-0.93)
Burr, 1989 RCT UK	Post MI-patients n=2033; 224 deaths mean age: 57 y 100% men	Enrolment: 1985-1987 Follow-up: 2 y Compliance confirmed at 6 months and at 2 y by food records en biomarkers (serum EPA)	advice to eat at least two weekly portions oily fish (200-400 g) or fish oil capsules	'sensible eating' advice	0.71 (0.54-0.93)
Fruit & vegetables					
Burr, 2003 RCT UK	AP-patients n=3114; 525 deaths mean age: 61 y 100% men	Enrolment: 1990-1996 Follow-up: 3 to 9 y Compliance: bad; no change in biomarkers (serum levels of folate and carotenoids)	advice 4-5 portions of fruit and vegetables plus 1 glass of orange juice	'sensible eating' advice	1.12 (0.94-1.34)
Barzi, 2003 cohort study Italy	Post MI-patients n=11246; 1660 deaths age: 59 ± 11 y 85% men	Enrolment: 1993-1995 Follow-up: 6.5 y 4 intake measurements in 3,5 yrs Adjustments: demographic. Risk factors, food variables	**fruit:** > 1 time per day **raw** vegetables: 1 time per day **cooked** vegetables: 1 time per day	(almost) never fruit (almost)never raw vegetables (almost) never cooked vegetables	fruit: 0.73 (0.54-0.98) raw: 0.67 (0.56-0.79) cooked: 0.84 (0.71-1.00)

Study	*Study population*	*Enrolment / Follow-up*	*Determinant/ Intervention*	*Reference/ Controls*	*All-causes mortality RR (95%CI)*
Whole grains, legumes and nuts					
Erkkila, 2003 cohort study Finland	CAD-patients n=400; 34 deaths mean age: 61y 70% men	Enrolment: 1991-1994 Follow-up: 5 y Adjusted for: demographic and diagnostic factors, risk factors, energy intake	30 grams fibre /day	22 gram fibre/day	0.81 (0.55-1.19)
Burr, 1989 RCT UK	Post MI-patients n=2033; 224 deaths mean age: 57 year 100% men	Enrolment: 1985-1987 Follow-up: 2 y Compliance confirmed by food records at 6 months and 2 y, no biomarkers	30 grams total fibre, of which 20 gram cereal fibre	20 grams total fibre, of which 10 grams cereal fibre	1.27 (0.99-1.65)
Combined lifestyle factor studies					
Barzi, 2003 Cohort study Italy	Post MI-patients n=11246; 1660 deaths age: 59 ± 11y 85% men	Enrolment: 1993-1995 Follow-up: 6.5 y Adjustments: demographic, risk factors, food variables	4th quartile of dietary score for intake of fish, fruit, vegetables, olive oil	lowest quartile of the dietary score	0.51 (0.44-0.59)
Singh, 2002 RCT India	High risk patients (59% CAD) n=1000 , 65 deaths age: 49 ±10; 90% men;	Enrolment: not reported Follow-up:2 y Compliance was confirmed by three-monthly food records	Advice AHA step 1 diet plus extra fruits, vegetables, whole grains, legumes, nuts and alpha-linolenic acid rich oil	Advice AHA step 1 diet: ≤30 energy% fat, ≤10 energy% saturated fat, ≤300 mg cholesterol/ day	0.63[1] (0.38-1.06)
De Lorgeril, 1994/1999 RCT France	Post first MI-patients n=605; 38 deaths mean age: 53.5 y 90% men	Enrolment: 1988-1992 Follow-up: 3.8 y Compliance was checked at each visit by 24-hour recall and a food frequency questionnaire and confirmed by bio-markers (plasma fatty acids)	Mediterranean diet advice and alpha-linolenic acid enriched margarine	advice AHA step 1 diet: ≤30 energy% fat, ≤10 energy% saturated fat, ≤300 mg cholesterol/ day	0.44 (0.21- 0.94)
Singh, 1992 RCT India	Post MI-patients n=406; 59 deaths mean age: 51 ± 10y 90% men	Enrolment: < 24 hours post MI Follow-up: 1 y Compliance was confirmed by three-monthly food records	AHA step 1 diet + extra fruit vegetables (≥400g/ d), legumes, nuts and fish	advice AHA step 1 diet: ≤30 energy% fat, ≤10 energy% saturated fat, ≤300 mg cholesterol/ day	0.55 (0.34-0.75)

[1] = RR not reported, but calculated from the study data (see methods)

RCT= Randomised Controlled Trial; CAD= Coronary Artery Disease; MI= Myocardial Infarction, AP= Angina Pectoris; LVD= Left Ventricle Dysfunction; BMI= Body Mass index;

Results

A total of three meta-analyses, 10 randomised controlled trials (studying 13 interventions) and nine cohort studies fulfilled the inclusion criteria. Details of the available studies per lifestyle or dietary goal are shown in Table 3.2.2. For five goals - three on lifestyle and two on dietary changes- the available studies fulfilled our additional criteria for calculating pooled effect size estimates (Table 3.2.3). For the combined interventions only studies on combined dietary changes were available, their pooled effect estimate is shown in Table 3.2.3.

Goals With Sufficient Studies to Calculate a Pooled Effect Estimate

Smoking Cessation: Two meta-analyses of cohort studies were found on smoking cessation. Duration of follow-up ranged from 2 to 20 years. All included studies consistently showed a protective effect of smoking cessation. Wilson et al.[15] performed a meta-analyses of 12 studies in patients with MI and found a pooled RR for all-causes mortality of 0.54 (95% CI, 0.46 to 0.62) for those who had quit smoking. Critchley and Capewell[16] published a meta-analysis of 20 studies in patients with previous MI or AP and reported a pooled RR of 0.64 (95% CI, 0.58 to 0.71). Half of the studies were the same as in the first analysis. On the basis of these two meta-analyses we conservatively estimate the effect size of smoking cessation in CAD patients as a 35% mortality risk reduction.

Habitual Physical Activity: We found no studies on the effect of increased physical activity on mortality in CAD patients. The effect of participation in a structured exercise program after a cardiac event (MI, AP, CABG or PTCA) on morbidity and mortality has been evaluated in several meta-analyses[17-21]. Reported effect size estimates of mortality reduction varied between 20 and 25%. Here we review the analysis by Brown et al.[20], which is a 2003 update from earlier meta-analyses and which studied exercise-based rehabilitation programs separately from the comprehensive rehabilitation programs that also included educational and psychosocial interventions. In this study mortality data were available of 2585 patients in 12 randomized controlled trials. The interventions varied widely from gym based aerobic exercise twice a week for 4 weeks to interventions lasting for 30 months with inpatient stays. Mean follow-up time was 24 months (range 6 to 60 months). The study showed a significant beneficial effect of an exercise program. The effect on all-causes mortality was estimated as about 25% risk reduction (RR, 0.76; 95%CI, 0.59 to 0.98).

Table 3.2. 3 Relative risk estimates for mortality for lifestyle and dietary with sufficient studies

Goals	*Randomized controlled trials RR (95%CI)*			*Prospective cohort studies RR (95% CI)*		
Smoking cessation				Critchley[a], 2003 Wilson[a], 2000	0.64 0.54	(0.58-0.71) (0.46-0.62)
Physical activity	Brown[a], 2003	0.76	(0.59-0.98)			
Moderate alcohol consumption				Cooper, 2000 Shaper, 2000 Muntwyler, 1998 Thun, 1997 Doll, 1994 Pooled:	0.85 1.05 0.72 0.80 0.79 0.80	(0.75-0.97) (0.78-1.42) (0.58-0.89) (0.8-0.9) (0.69-0.91) (0.78-0.83)[b]
Saturated fat reduction	Burr, 1989 Woodhill, 1978 Morris, 1968 Leren, 1966 Pooled (4 studies): Pooled (2 studies)[c]:	1.0 1.49 0.88 0.75 0.98 0.79	(0.77-1.30) (0.92-2.43) 0.53-1.47) (0.50-1.12) (0.81-1.18)[d] (0.58-1.09)[b]	Erkkila, 2003	0.64	(0.46-0.88)
Regular fish (oil) consumption	Burr, 2003 GISSIP, 1999 Burr, 1989 Pooled (3 studies): Pooled (2 studies)[e]:	1.15 0.79 0.71 0.88 0.77	(0.96-1.36) (0.66-0.93) (0.54-0.93) (0.69-1.11)[d] (0.66-0.89)[b]	Barzi, 2003 Erkkila, 2003 Pooled:	0.81 0.50 0.80	(0.69-0.94) (020-1.28) (0.69-0.93)[b]
Combined dietary factors	Singh, 2002 Lorgeril, 1999 Singh, 1992 Pooled estimate:	0.63 0.44 0.55 0.55	(0.38-1.06) (0.21-0.94) (0.34-0.75) (0.41-0.74)[b]	Barzi, 2003	0.51	(0.44-0.59)

a. Meta-analysis
b. P for heterogeneity >0.5; fixed effects model
c. studies by Burr, 1989 and Woodhill, 1978 excluded
d. P for heterogeneity ≤ 0.5; random effects model
e. study by Burr, 2003 excluded

Moderate Alcohol Consumption: We found five cohort studies[22-26] examining the effect of moderate drinking versus rare drinkers or non-drinkers in CAD patients. All studies, except for one[23], found a statistically significant reduction of all-causes mortality between 15 and 25% for moderate drinking. Duration of follow-up varied between 3 and 13 years. Effect estimates are shown in Table 3.2.3. The pooled effect estimate for the RR for all-causes mortality in the 5 studies was 0.80 (P-value for heterogeneity 0.53; 95%CI, 0.78 to 0.83), summarized in an effect estimate of 20% reduction of all-causes mortality.

Saturated Fat Reduction: Four [27-30] randomised controlled trials and one cohort study[31] met our criteria for fat modification. They all concerned saturated fat intake reduction. No studies were detected on the relation between trans-fatty acid intake and mortality in CAD patients. The randomised controlled trials were performed between 1960 and 1988 and intended to study a reduction of about 5 energy% in saturated fat intake during 2 to 5 years of follow-up. The resulting reduction in serum cholesterol was about 15% in two studies[27;28] and only 5% in the other two[30], raising doubts on adherence to the regimen in the latter two studies.[29] Only in the two studies with the largest serum cholesterol reductions was total mortality reduced (12% and 25%), but the power of the studies was too limited to show statistically significant reductions. The probability value for heterogeneity was 0.18 for the four studies and 0.63 when the two studies with unsatisfying serum cholesterol reductions were excluded. The pooled effect estimates were not statistically significant, for either the four or the two studies (Table 3.2.3). The cohort study[31] in 400 Finnish CAD patients was supportive of a beneficial effect of a lower saturated fat intake. For every 4 energy% reduction in saturated fat intake RR for all-causes mortality was 0.64 (95%CI, 0.46 to 0.88). However, this study on its own is not sufficient to be conclusive. Because the pooled effects are not statistically significant, we provide no summary effect estimate for saturated fat restriction.

Regular Fish (Oil) Consumption: We found three randomised controlled trials[30;32-34] and two cohort studies[31;35] fulfilling our selection criteria. The trials tested either the effect of advice to increase fatty fish consumption up to 200-400 grams per week[30;32] or the effect of a fish oil supplement containing about 900 mg EPA and DHA per day[33;34].Two of them[30;33;34] showed a significant mortality reduction, but the trial in AP patients[32] found a non- significant mortality increase in the intervention group.

Both cohort studies were supportive of a protective effect of a higher fish intake. The study by Barzi et al[35] (n=11,246) was performed in the participants of the GISSI-Prevenzione-trial studying the effects of fish oil (900 mg EPA and DHA) and/or vitamin E (300 mg) supplements. Irrespective of their assignment to the study intervention most patients increased their fish consumption subsequent to the MI as was advised by the hospital. Fish intake was assessed 4 times during the intervention period of 3.5 years and duration of follow-up was 6.5 years. In the small cohort study by Erkkila et al[31] fish consumption was assessed at baseline only and patients were followed for 5 years. Both cohort studies fulfilled our quality criteria on adjustment for confounding and the number of cases. Table 3.2.3 shows the effect estimates of the presented studies. Before the data were pooled, the data heterogeneity tests were performed. Heterogeneity existed (P=0.002) for the three fish trials, but disappeared when the AP patients' trial was excluded (P=0.56). Pooled effect estimates for both the three and the two trials as well as for the two cohort studies are shown in Table 3.2.3. Because of the unexplained heterogeneity in the results no summary effect estimate is provided for regular fish (oil) consumption.

Remaining Goals

For the remaining dietary goals, the available studies (Table 3.2.2) were insufficient to provide a reliable effect estimate on life expectancy in CAD patients. For body weight control, we found only one study[36] on the effect of weight reduction after MI, but this study was considered of low quality because the results were not adjusted for confounding, not even for age and gender. For fruits and vegetables the available randomized controlled trial[32] was not a good test for the effect of increased fruit and vegetable consumption because compliance with the intervention was doubted as a result of a lack of any rise in serum concentrations of folate or carotenoids. The cohort study by Barzi et al[35] supported a beneficial effect of the recommendation on both fruit (RR, 0.73; 95%CI, 0.54 to 0.98)) and vegetables (raw vegetables RR, 0.67; 95%CI, 0.56 to 0.79; cooked vegetables RR, 0.84; 95%CI, 0.71 to1.00) but was insufficient on its own to be included in Table 3.2.3. For dietary fiber and whole grain products available studies were not consistent. The only trial[30] showed no effect (because compliance was not measured it is unclear whether this is due to a lack of effect or a lack of compliance) and the cohort study[31] on total fiber intake was too small (n=400; 34 mortality cases) to show a statistical significant difference (RR, 0.81; 95% CI, 0.55 to 1.19). No studies were found relating the intake of trans-fatty acids, legumes, nuts or salt to mortality in CAD patients.

Combined Interventions

We found no studies on the mortality effects of combinations of both lifestyle and dietary changes. On combined dietary changes alone three randomized controlled trials[36-39] and one cohort study[35] met our inclusion criteria for the summary effect estimate. The interventions consisted of an increased intake of fiber rich foods (fruits, vegetables, nuts, legumes) and fish and eventually an enhanced intake of unsaturated fatty acid intake through the use of oils or special margarines. Average duration of follow-up varied between one and four year. Mortality reduction was statistically significant in two of the three trials[36;38]. Both the individual as the pooled effect estimates on mortality are shown in Table 3.2.3. The pooled RR for all-causes mortality was 0.56 (P for heterogeneity = 0.73; 95%CI,: 0.42 to 0.74). The effect estimate in the cohort study[35] was based on a combined score on the consumption of fish, fruit, cooked vegetables, raw vegetables and olive oil. All-causes mortality was 49% lower in patients in the highest quartile of the dietary score compared with the lowest quartile. We estimate the mortality risk reduction potential for combinations of individual dietary goals (as formulated in Table 3.2.1) to be 45%.

Discussion

Although many of the commonly provided lifestyle and dietary recommendations (Table 3.2.1) are supported with evidence from surrogate endpoint studies and studies in the general population, there is only limited evidence from studies in CAD patients that these recommendations indeed improve their life expectancy. The available studies show significant effects for 3 lifestyle recommendations on prognosis of CAD patients. Effects for smoking cessation, increased physical activity and moderate alcohol consumption vary from a 20 to 35% reduction in all-causes mortality. For individual dietary goals evidence from studies in CAD patients was not available or too limited to provide reliable effect estimates. A few studies on combinations of dietary changes show promising results with mortality reductions of about 45%.

In this review we included both experimental and observational studies. Randomized controlled trials are generally rated as a higher level of evidence, than prospective cohort studies because they exclude self-selection and confounding by indication as a source of bias. Randomized clinical trials however, have their own drawbacks: their inclusion criteria often limit generalization to the average patient population in routine care, their costs often limit the duration of the study, in the case of lifestyle or dietary interventions double blinding is

often impossible or the intervention itself is unethical (eg, smoking or alcohol consumption). Prospective cohort studies on the other hand may be confounded by unknown prognostic factors associated with lifestyle or dietary habits, but they have the advantage of giving a better reflection of the 'real life' situation with long-term exposure and mostly a mixed patient population. The advantages and disadvantages of each design do not outweigh those of the other. In this review we reported effect sizes of both study designs (if available) separately and did not make an attempt to rank one above the other.

This review has several potential limitations. Most evidence was available for studies on lifestyle changes in CAD patients. Studies on dietary changes are scarce and several are of poor methodological quality. Confounding due to clustering of lifestyle and dietary factors as well as bias because of unblinding or poor compliance with the intervention or changes in habits of the control group is more common in lifestyle and dietary studies than in drugs trials. Many of the studies included in this review were underpowered to assess effects on total mortality. This problem may be solved by pooling the results of individual studies, but, even if tests for heterogeneity are not significant, this operation may be problematic because of the heterogeneity of studies with respect to background habits, intervention characteristics, exposure (time and dose) and length of follow-up. Sometimes the point estimates are impressive, but the wide confidence intervals indicate a high degree of uncertainty. Therefore, caution is needed in interpreting the results and particularly in translating the effect size estimates to the individual patient.

Nevertheless most of the presented effect estimates are in accord with results from studies in the general population. Table 3.2.4 compares the effect size estimates in CAD patients with results of cohort studies in the general population. *Smoking Cessation:* Our effect estimate of about 35% risk reduction is similar to findings from population-based cohort studies indicating that quitters before age 50 have a 50% lower risk of dying compared with continuing smokers[40;41]. *Physical Activity Level:* An effect estimate of 25% mortality risk reduction for an increased level of physical activity was obtained from a meta-analysis on the effect of exercise-based revalidation. Although the best available, this is not a very good estimate for adherence to the guideline[10] to increase habitual physical activity level to a daily amount of at least 30 minutes moderate intensive activity. Participation in a program is not necessarily related to a higher physical activity level in the long run[42;43]. However, the estimated 25% mortality risk reduction compares well with estimates from other populations. A review[44]of 44 population-based cohort studies reported that adherence to the guideline was associated with a 20% to 30% reduction in all-causes mortality. Further reductions were observed

Table 3.2.4 Estimated effect sizes on mortality of lifestyle and dietary changes from studies in coronary artery disease patients (secondary prevention) and cohort studies in the general population (primary prevention)

Recommendation	*Mortality risk reduction estimate in CAD-patients*	*Mortality risk reduction estimate in the general population*
smoking cessation	35%	50%
physical activity	25%	20-30%
moderate alcohol	20%	15%
combined dietary changes	45%	15-40%

at higher volumes of energy expenditure. Not only high baseline levels but also increments in physical activity level later in life are shown to be associated with lower mortality[45;46].

Alcohol: Although the protective effect of moderate alcohol consumption on cardiovascular risk has been sufficiently demonstrated in the general population cohorts[47], for CAD patients there was concern about the adverse effects on the cardiovascular system, such as hypertension, arrhythmias, hemorrhagic stroke and cardiomyopathy[48]. The presented studies are consistent in their finding that moderate alcohol consumption can improve the prognosis in CAD patients, even in patients with associated heart failure[22], as long as the alcohol intake is moderate (2 to 3 units per day). The estimate of 20% mortality risk reduction in CAD patients is in range with a pooled estimate of 15% mortality reduction in cohort studies in middle-aged populations[49]. Of course the benefits of moderate alcohol consumption should always be mentioned in relation to the potential risks of excessive alcohol consumption, because there are still more deaths caused by alcohol than prevented[50].

Saturated Fat: Reliable effect estimates could be provided for none of the individual dietary factors. The pooled effect estimates for saturated fat reduction were not statistically significant (for the 4 studies: RR, 0.98; 95%CI: 0.81 to1.18) but agreed with the findings of 2 meta-analyses on fat modification combining the results of both primary and secondary prevention trials: RR, 0.94 (95%CI, 0.89 to 0.99; 17 trials)[51] and RR, 0.98 (95%CI, 0.86-1.12; 11 trials)[52]. In contrast to our study these meta-analyses also included studies on total fat restriction, which might have attenuated the effect. They confirm our finding that a trend was seen toward a greater risk reduction in trials in which better adherence to the intervention is shown by a greater reduction in serum cholesterol.

Regular Fish (Oil) Consumption: There was heterogeneity between the studies, but the calculated pooled effect estimates for the trials (12-23% mortality risk reduction) are in agreement with an estimate of 20% all-causes mortality reduction in a meta-analysis by Bucher et al.[53] based on 9 trials in CAD patients on the effects of dietary fish or fish oil supplementation in doses up to 10 grams of n-3 fatty acids per day. The pooled effect estimate from the cohort studies in CAD patients was also 20%. Data on fish and all-causes mortality from population-based cohorts are inconsistent and vary from 0 to 30%[54-59]. Null findings in some of the studies can possibly be explained by the adverse effects of the high mercury content of fish in some geographical area's [55;60] or by the fact that the protective effect is specific for fatty fish and not for total fish consumption[61]. The association with CAD mortality is more frequently studied than all-causes mortality and significant risk reductions are reported[62-64].

For the remaining individual goals, studies on mortality were too few to provide effect estimates. This should not be interpreted as a lack of scientific support for these recommendations. The evidence from surrogate endpoint or clinical endpoint studies is reviewed elsewhere[65-76]. Studies on all-causes mortality, however, are scarce, not only in CAD patients but also in other populations. Given the alarming signals[77;78] on a high prevalence (80%) of overweight and obesity in CAD patients, it is surprising that no studies were found on the effect of intentional weight loss on mortality in CAD patients. Weight loss might be one of the mechanisms through which other lifestyle or dietary changes (e.g. regular exercise or increased intake of whole grains and vegetables) might exert their protective effect, but few authors report on body weight changes[39]. Cohort studies in the general population have shown that mortality is 30 to 50% lower in normal weight individuals as compared with their obese peers[79], although this difference decreases with age[80]. The effect that can be expected from weight reduction in patients already treated with preventive drugs is unclear. Some studies in CAD patients[81-85] (not meeting our inclusion criteria) suggest even a prognostic benefit of obesity. These studies however are inconclusive as they often lack appropriate adjustments for confounding (eg, confounding by age as obese persons are generally 7 years younger at time of their first MI as compared to normal weight individuals), but they stress the need for high quality additional research. Finally, population-based cohort studies that study all-causes mortality in relation to the intake of fruits and vegetables[86-89], whole grains[86;90;91], legumes[92], nuts[93;94] or salt[95-97] are scarce, but generally supportive for a protective effect of the recommendations.

The trials on combined dietary interventions showed impressive results, varying from 35 to 55% mortality reduction. Other intervention studies in CAD patients showed benefits of combined lifestyle and dietary changes on surrogate endpoints

Table 3.2.5 Estimates of effect sizes on all-causes mortality of routine prophylactic drug interventions in meta-analyses of studies in coronary artery disease patients

Intervention	*Mortality risk reduction Mean (95%CI)*
low dose Aspirin (ref 110)	18% (1 – 30%)
Statins (ref 111)	21% (14 - 28%)
Beta-blockers (ref 112)	23% (15 – 31%)
ACE-inhibitors (ref 113)	26% (16 – 35%)

and cardiac events[98;99]. The cohort study in 11,000 CAD patients by Barzi et al.[35] showed an almost 50% lower mortality risk for those with the highest dietary quality score. Mortality risk reductions associated with dietary quality reported from other populations were generally smaller (15 to 25%), but a significant benefit was demonstrated in many studies[100-109]. Two studies in elderly people[100;103] showed a 60 to 70% lower mortality associated with a higher quality score for a combination of both lifestyle and dietary habits. Although the studies on combined changes are promising, they shed no light on the dominant mechanism and on the contribution of the individual lifestyle and dietary factors. More knowledge on the benefits of the 6 individual dietary goals in particular is necessary for designing effective preventive strategies.

If the effect sizes of lifestyle and dietary changes in Table 3.2.4 reflect the true value, they compare favourably with effect size estimates for cardio preventive drugs as shown in Table 3.2.5[110-113]. In contrast to these pharmacological interventions, the prognostic effects of lifestyle and dietary changes are, however, less rigorously studied. For the future well-designed and powered studies are needed to test the effect of dietary changes on prognosis. Second, because compliance with the recommendations is crucial, research is needed on strategies to enhance adaptation and maintenance of healthy lifestyle and dietary habits in CAD patients.

In conclusion, there is evidence from mortality studies in CAD patients that smoking cessation, physical activity, moderate alcohol consumption, and combined dietary changes improve prognosis. Effect size estimates for the lifestyle goals vary between 20% and 35% mortality reductions. Data on the benefits of individual dietary goals are limited. For the future more and better quality studies are needed to reduce the uncertainty that surrounds these effect size estimates.

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Note to chapter 3.2

Simultaneously with the publication of our review (August 2005), reports of an international research fraud investigation[1-4] appeared raising suspicion on the work of Dr. RB Singh. As is shown in table 3.2.2, three studies by RB Singh are used in this chapter: one in the analysis of studies on 'Body weight control' and two under the heading 'Combined Interventions'. Withdrawal of the studies of Dr. RB Singh has consequences for the conclusions of this chapter.

Our conclusion of the evaluation of body weight control studies is not changed by the withdrawal of the suspected study. We concluded that studies on body weight management in CAD-patients are insufficient to provide a reliable estimate of the mortality effect. The study by Singh on this issue was already considered as a low quality study and not used in an effect estimate.

With respect on the combined dietary interventions, we conclude that after withdrawal of the two suspected studies, the available data are even more "meagre" than previously thought. The remaining randomised controlled trial and cohort study alone are insufficient to provide a reliable effect estimate.

The analyses on the lifestyle factors smoking cessation, physical activity and moderate alcohol consumption are unaffected by the research fraud problem. For dietary interventions we are left with the situation that no reliable effect estimate can be provided for any of the six investigated dietary goals, individually nor in combination. We conclude that there is an urgent need for more evidence from randomised controlled trials in this field and that these trials should be monitored to high quality standards.

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Chapter 4

Prognosis, Proof and Priorities

Priority decisions in hospital-based dietetic practice

weighing needs, evidence and ethics

Abstract

Background: The number of treatment options in dietetic practice has expanded during the last 25 years, notably in the field of prevention. Competing goals and scarce resources urge professionals to sort out priorities in serving different patient groups. This study aims to clarify concepts, define guiding principles and explore implications for priority setting in hospital-based dietetic departments.

Method: Literature was reviewed to answer four questions: What is the professional responsibility of dietitians? What role does scientific evidence play in priority setting? What core ethical values should guide priority decisions? How should priority decisions be made in the absence of consensus?

Results: Due to their specific expertise and relationship with patients, dietitians are responsible to set, defend and influence priority decisions at different levels of health care. Priority decisions should be based on a critical appraisal of the available evidence and be guided by a vision on beneficence, autonomous choice and distributive justice. In western societies at least three societal factors should be weighed in priority decisions of hospital-based dietitians: the substantial burden of cardiovascular diseases, the extending health disparities between socio-economic groups and the increasing frequency of unhealthy dietary behaviours. Transparency and accountability are important when priority decisions have to be made in the absence of consensus.

Conclusion: Priority policies require a clear vision on ethical values as well as the disposal of reliable data on the diet-related needs and risks of all patient groups. Hospital-based dietitians are in a unique position to promote health in society.

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Prognosis, Proof and Priorities in dietetic practice / J.A. Iestra
University of Utrecht, 2006

4 Priority decisions in hospital-based dietetic practice

weighing needs, evidence and ethics

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The environment of dietetics has changed considerably during the past 25 years. At least three factors have contributed to this change. First, the enormous growth of biomedical science data: the annual number of nutrition related research reports in medical literature (Medline database) has increased from 5,000 in 1980 to 122,000 in 2004. As a result many improvements can be mentioned in dietetic curative treatment options (e.g. in the field of inherited metabolic disorders and nutritional requirements during metabolic stress). However, most pronounced is the increase in evidence to support nutritional preventive treatment strategies, due to epidemiological research[1].

Secondly, relationships in dietetic practice have been changed as a result of the improved accessibility of medical and nutritional research reports through the World Wide Web. Patients became better informed on basic concepts of nutritional interventions and have taken a more active role in treatment decisions. Relationships between dietitians and physicians became more symmetric and new health care professionals, such as physician assistants and nutritional practitioners, took over some of the tasks formerly assigned to dietitians.

Thirdly, the economic aspect of treatments became more prominent due to the explosive growth of health care expenses and the many competing goals. Indication and allocation decisions are no longer solely professional decisions, but the influence of politicians, insurance companies and managers has increased. A substantial literature[2] has emerged on how to guarantee an efficient and fair distribution of health care resources. Proven effectiveness appeares to be

no longer sufficient, treatments also have to be shown cost-effective in comparison with other therapies.

In this context managers of dietetic departments seek to guarantee the quality of dietetic practice and the optimal use of limited resources. Confronted with many different patient groups with an infinite number of needs for dietary interventions they are forced to set priorities. Difficult questions arise. Should dietitians actively invite some patient groups, while limiting access to others? Is it justifiable to base the selection of patients on criteria such as patients' level of motivation to change or prospect of success? Should the available consulting time per treatment be determined by expected health gain or by patients' skills to understand and implement recommendations?

This paper aims to clarify several concepts for priority setting in hospital-based dietetic practice. Literature will be reviewed to seek answers to four questions: What is the professional responsibility of dietitians? What role does scientific evidence play in priority setting? What core ethical values should guide these priority decisions? How should priority decisions be made in the absence of consensus? Guiding principles will be defined and implications explored for dietetic departments in western societies.

Professional responsibility

The core business of dietetics is care. Care can be defined as a sensitive and competent response to someone's need. Dietetic care is the response to patient's health needs in the field of dietetics, in the context of a professional relationship. Health care professionals are usually characterised by their expertise and their professional responsibility towards both the individual patient and society. They have a certain degree of professional autonomy which allows them some freedom in decision making and priority setting. Hoogland et al.[3] describe how this professional autonomy is limited in three ways. First by the obligation of professional organisations to control the professional conduct of their members. As the quality of professional conduct is generally uncontrollable by lay people, professional organisations have a special responsibility to guarantee the competence and trustworthiness of their members. Professional standards of competence[4;5] and professional performance[6] and ethical codes[7] are instruments for this quality control. Secondly, professional autonomy is limited by societal laws and health care policies which define to some extent what health needs (treatment indications) are to be met and what budget is available. Finally, the professional autonomy

is also limited by respect for patients' autonomy: without his or her informed consent a treatment can not be applied.

In summary, health care professionals have – because of their expertise and special relationship with the patient - a special responsibility and are accountable for how they set priorities in their practices and influence priority decisions at higher levels of the health care system. Their decisions should be guided by the best interests of their patients while respecting laws and values broadly endorsed in society.

Dietetics can be defined as the branch of medicine aiming at " the integration and application of principles derived from the sciences of food, nutrition, management, communication, and biological, physiological, behavioural, and social services to achieve and maintain optimal human health"[4]. In dietetic practice the focus is on health needs and risks related to nutritional status or nutritional behaviour. Dietary interventions can vary from providing nutrients through an intravenous line to counselling patients with severe eating disorders.

An important development in dietetics in recent years is the introduction of evidence based medicine (EBM) as a basic skill in clinical decision making. It involves combining the best available research evidence with clinical expertise and patient values. Central are the abilities to ask answerable clinical questions, find the current best evidence, critically appraise the evidence and apply it to individual patients [8;9]. One of the products of the EBM-movement is the appearance of an impressive amount of practice guidelines for all kinds of diagnoses and circumstances. These guidelines are generally based on broadly accepted values related to health as well as the best available scientific knowledge. They guide and restrict clinical decisions, although responsible departure from these guidelines is always possible when justified by specific requirements of the situation or the condition of the patient. Acknowledging that the skilful use of evidence in clinical reasoning is essential for the quality of clinical decision making[10], evidence is also important for the quality of decisions at the level of prioritising care for specific patient groups.

Scientific evidence

Scientific data facilitate priority decisions: they are needed to evaluate the extent of the problem, the effectiveness of the available treatment options and the cost-benefit ratio of comparable treatment options. However, there are two reasons why facts alone are not enough to direct priority decisions. First because it is only possible to collect the right data if there is agreement about the relevant questions. In practice this agreement may be absent. Ideas may differ about what should

count as benefits and as costs in the particular situation and what weighing factor should be used[11]. Different ethical positions may lead to different interpretations of scientific data as is illustrated for example in the debate on health care resources allocation[2]. Three main stream ethical positions are described in appendix A. The other reason why priority decisions can not be based on evidence alone, is that in many situations the required evidence is not available. For rare diseases, patient populations are often too small to perform research. In other situations study results from highly selected study populations may not be generalisable to clinical practice, for example to patients with several co-morbidities and different age groups.

These practical limitations have moral implications as soon as a certain amount or a certain quality of evidence is made conditional for priority assignment. The problem is not only the limited availability of evidence, but also the systematic biases in the availability of evidence. Allocation of research funds is often guided by the commercial attractiveness of a treatment option and not by motives to serve all patient populations fairly according to their needs. Frequently it is considered that the more study results available, the better the priority position. Evidence-based medicine is defined by its founders[8] as 'the conscientious, explicit and judicious use of the best evidence available in making decisions'. However, many editors, guideline committees and funding organisations do not appraise the total body of available evidence, but only accept results from randomised controlled trials (RCT's) in their recommendations or funding decisions. The benefits of dietary and lifestyle changes are often impossible to study in a randomised controlled design, for example because randomisation is unethical, blinding is impossible or results are less attractive for commercial financiers. Consequently, policies that restrict their priorities to RCT-supported interventions may adversely affect the interests of certain patient groups and do not respect patients who prefer dietary and lifestyle interventions over pharmacological interventions.

We conclude that research data are essential but will never fully eliminate the uncertainty associated with priority decisions. There is a danger that professionals in their enthusiasm for the existing evidence may be withheld from deliberately discussing and weighing all relevant interests and preferences of different stakeholders. In that case the former paternalism ("the professional knows best") is replaced by a new brand of paternalism: "the evidence knows best"[12]. Therefore priority policies require an overview of the interests of all stakeholders, a critical appraisal of the available evidence and guidance by ethical values.

A set of core ethical values in decision making is described for clinical practice[13] and public health policy[14] respectively. In our opinion three core values from these sets are central in priority setting in dietetic practice: beneficence, autonomous choice and distributive justice.

Beneficence and the goals of health care

Beneficence (the moral duty to benefit others) is acknowledged as a central value in health care in almost all places of the world and episodes of history. In the Hippocratic oath physicians pledge that they will apply treatments "for the benefit of the sick according to their ability and judgement" and "will keep patients from harm and injustice". However, what is meant by beneficence may differ from time to time and place to place.

In contemporary western societies the impressive results of medical science and technology have attracted fascination and raised expectations of medicine to utopical heights. But awareness has grown that the benefits they brought were accompanied by several disadvantages. Illich[15] stated that the complex organisation in hospitals and the presence of so many medical technologies negatively affected the communication and relationships between patients and health care professionals. Callahan[16] argued that the dominant place of medical technology in society and the mechanistic-materialistic view on health diminished our ability to meaningfully respond to situations such as suffering and death, inducing alienation from our own subjective experiences. Others[17] pointed at the autonomic development of the medical technological revolution offering solutions for problems that did not previously exist and marketing treatments for not yet identified needs. Finally, the ever increasing costs urged many to reflect on the goals of health care and to attempt health care reform.

It was felt that new goals for medicine should be more temperate: "societies should learn to live within the boundaries of a finite body and finite resources"[16]. Health should no longer be defined as a state of "complete well-being" (WHO-definition, 1947) but as "the acceptable absence of significant malady, and consequently by a person's ability to pursue his or her vital goals and to function in ordinary social and work context"[18]. This definition acknowledges that some degree of malady is part of the life of every person at some time or other, and that some degree of health is part of life of every patient. The authors[18] argue that the maintenance of health in patients deserves priority and they plead for more attention for quality of care and palliation in contrast to a too obsessive drive for curation alone.

A comparable sound could be heard in public health circles, where in 1986 the Ottawa Charter for Health Promotion[19] was released. This document expresses a re-orientation on lifestyle determinants for health and their complex interaction with cultural, socio-economical and environmental factors. It focuses on individuals as the main resources of their own health and calls health care professionals to enable people to increase control over the determinants of their health. Hospitals

are challenged to redirect their disease-orientation into a health-gain-orientation and allocate a relevant part of their budgets to health promotion programs.

Consequently in 1990 an international network of Health Promoting Hospitals was founded[20;21], aiming to anchor a more holistic and socio-ecological health view in the hospital culture and organisation. The network[22] argues that hospitals have special opportunities and a societal obligation for health promotion. They have a high concentration of expertise, are a credible source for public advice, have close connections with research and education, command an extensive budget (in the Netherlands ca. 30% of the health budget[23]) and can reach a large sector of the population (in some countries annually up to 20% of the population contact hospitals as patients; the number of visitors is even far greater). Moreover, because of actual health problems people in a hospital environment commonly are more susceptible for health education.

How beneficence is defined and weighed in priority setting in dietetic practice, depends on the underlying view on health and the needs of all relevant patient groups. In a disease-orientated environment it is tempting to give high priority to short-term health gain through curative actions (e.g. artificial nutrition in the critically-ill), while neglecting the future health impact through preventive actions (e.g. dietary and lifestyle counselling of patients at high risk for cardiovascular diseases).

Autonomous choice

In contrast to curative interventions, preventive actions to promote future health are often not preceded by a request of the patient. Some professionals (physicians as well as dietitians) give low priority to preventive dietary and lifestyle interventions, because they fear to be paternalistic. On the other hand some professionals are tempted to exclude some patients from counselling (e.g. for weight reduction) as they assume a low prospect of success. What is paternalism and what implies respect for 'autonomous choice'?

Paternalism can be defined as the intentional overriding of a person's known preferences, justified by the goal of beneficence[13]. In case of dietary and lifestyle counselling it is paternalistic to subject a patient to some behavioural change program against his expressed wish. It is also paternalistic to withhold information that would have enabled the patient to make better autonomous choices. The obligation to respect "autonomous choices" of patients flows from the recognition of everyone's dignity and right to make choices based on personal values and beliefs. The ideal of autonomous choices assumes complete voluntariness and requires decisional competence, understanding of relevant information and

freedom from controlling influences[14]. In practice this ideal is seldom (if ever) met: choices are generally not completely independent and rationally controlled. Relationships and prejudices may play a role and can be supportive or hindering. Lack of self-confidence or lack of social support may withhold people from making the choices they desire. In this context professionals' obligation to respect the 'autonomous choice' may go further than mere disclosure of relevant information. Their obligation includes building up patient's capacities for autonomous choices and assisting to remove barriers[13].

Priority decisions should not be guided by a false view on paternalism, but facilitate open and respectful communication with patients. Prioritising based on prospect for success is discriminative and not justifiable if it excludes individuals with characteristics such as low self-confidence or lack of social support.

Distributive justice

As health care is collectively funded, priority setting should guarantee a fair distribution of services. In the words of Aristotle: 'equals should be treated equally and unequals should be treated unequally'. However, no good is so unequally distributed in society as health. To some extent these inequalities in health are random, but a systematic relationship with socio-economic determinants is established for many western societies[24]. People from lower socio-economic strata (defined by level of education, occupation or income) have higher rates of mortality and morbidity from chronic diseases than the socio-economically more advantaged groups. There is evidence that these health disparities are increasing[25]. In the Netherlands men in less educated groups have a 5 year lower life-expectancy and have 16 years less to spend in experienced good health[23].

A substantial part of socio-economic differences in health can be explained by unhealthy behaviours, such as smoking, inactivity, alcohol abuse, excess energy intake, high intake of saturated fat and low fruit and vegetable consumption[26]. The high prevalence of unhealthy behaviours is often associated with material factors (unemployment, bad housing conditions, low income) or psychosocial factors (low perceived control)[27].

Based on these observations, an extended literature has been developed during the last decades discussing the fair distribution of health. Some[28], mostly libertarians, argue that health disparities in society are just a matter of bad luck in 'the lottery of life'. Falling ill is unfortunate but not unfair and there is no societal obligation to reduce health disparities between socio-economic groups. Distributive justice means that the state should guarantee fair procedures, for example equal access for all citizens to a certain minimum of health care

functions. Opposing authors[29], egalitarians, stress the impact of disease and disability on the range of opportunities open to individuals. They state that there is a societal obligation for 'fair equality of opportunity' that should result in active policies to reduce socio-economic disparities in health and give priority to the worst off.

In an increasing number of countries the egalitarians point of view seems to win. In those countries politicians give high priority to the reduction of socio-economic health disparities[30]. Policies and interventions are being developed[23;31] targeting at determinants in many policy areas: e.g. income, housing, education, social security, public health and health care.

Accountability for reasonableness

Before exploring the implications of the three ethical core values for priority setting in dietetic practice, the question will be evaluated how priority decisions should be made in absence of consensus. As is shown in the former paragraph the interpretation of ethical values is influenced by ethical positions. In appendix A possible interpretations of beneficence, autonomous choice and distributive justice related to different ethical positions are presented. Understanding of alternative viewpoints may improve professionals contributions to policy discussions[32]. But even if we expect and respect diversity in views, consensus cannot always be achieved.

Daniels[29] argues that in absence of consensus, the fairness of priority decisions should be guaranteed by the quality of the democratic process. In an attempt to connect views on deliberative democracy to priority decisions in health care, a decision model has been developed, called 'accountability for reasonableness'. This model identifies four conditions of a fair priority setting process:

- a publicity condition stating that decisions and their rationales should be transparent and made publicly accessible,
- a relevance condition demanding that decisions should be made on the basis of reasons (i.e. evidence, principles, arguments) which "fair minded" people can agree are relevant under these circumstances,
- a revision condition stating that there should be opportunities to revisit and revise decisions in light of further evidence or arguments, and there should be a mechanism for challenge and dispute resolution,
- an enforcement condition requiring that there should be either voluntary or public regulation of the process to ensure that the other three conditions are met.

This model provides guidance for the way to perform professional accountability towards patients and society.

Implications for priority setting in dietetic practice

Distribution of the time budget of hospital-based dietetic departments is commonly based on what was done the year before, with adjustments in the margin depending on experienced time pressures. Occasionally reprioritisation takes place as a result of new evidence, changes in patient groups, initiatives for multidisciplinary co-operation, decisions of the hospital management or societal developments. Reprioritisation should preferably be based on a clear overview of the diet-related needs and risks of all (potential) patient groups in the local situation as well as on up to date knowledge of the effectiveness of dietary interventions. An explicit vision on beneficence, autonomous choice and distributive justice and the meaning of these values in the specific societal context should provide the framework in which these data can be weighed.

Based on their personal interpretation of the three ethical core values and their view on the health problems in western societies, the authors advocate to weigh three societal factors in future priority decisions:

1. the sizeable burden of cardiovascular diseases (and their related metabolic disorders), which is the main cause of premature death and disability in western society. A substantial part of this burden is preventable through healthier dietary and lifestyle behaviours[33].
2. the increasing health disparities between socio-economic groups. Diets affect the health of socially disadvantaged people from the cradle to the grave and provide significant opportunities for health gain[26].
3. the rapid increase in unhealthy dietary and lifestyle behaviours. This happens in all age-groups[34;35]. Many professionals underestimate the impact and the socio-ecological roots of this problem[36].

In the authors' opinion hospital-based dietitians are in a favoured position to contribute to the reduction of these problems. Nutritional interventions in hospitals should not be restricted to needs directly related to the medical diagnosis. Priority should also be given to preventive and health promoting nutritional interventions. These should be made recognized, rewarded and structurally integrated tasks of hospital dietitians.

In contrast to the individual approach in curative interventions, prevention and health promotion require a strategic approach. It demands defining specific target groups, developing tailored programs and maintaining a quality system collecting data for evaluation of accessibility, tailoredness and effectiveness. Departments should invest more in activities such as:

- Efforts to provide other health care professionals with up to date nutritional information and to motivate them to integrate nutritional messages in their practices, considering them as important intermediary target groups.
- Optimizing communication with patients' primary care professionals (general practitioners, nurse practitioners, practice assistants) to ensuring support for the maintenance of behavioural changes initiated in hospital.
- Building relationships with local health promotion initiatives and public health professionals in order to tune health promotion messages from different sources, especially in local priority 'settings', e.g. deprived areas in the city.

It should be anticipated that developing such a strategic prevention approach in a primarily cure-oriented hospital environment will meet many barriers. Developing an effective strategy is more than just 'doing a project', it requires substantial time investments and continuity should be guaranteed. Therefore a strong organizational commitment is needed, endorsed by key players both in and outside the organisation and facilitated by the allocation of necessary resources. A higher priority for prevention also requires further development of special competencies for dietitians. Many hospital-based dietitians have had only limited exposure to epidemiology, ethical and health psychological theories. Preventive and health promotion activities require other organisational and communicative skills than individual counselling. To guarantee the quality of priority decisions, also competences related to appraisal of scientific data, ethical deliberation, coping with social diversity and quality management are essential.

Conclusion

Scarcity (lack of resources), uncertainty (lack of knowledge) and diversity of views (plurality) will always surround dietitians' clinical as well as management decisions. It should not restrain them from striving for well-informed, justifiable and accountable decisions. An explicit vision on beneficence, respect for autonomous choice and distributive justice should provide the framework in which scientific data on patients needs and the effectiveness of dietary intervention can be weighed. Decisional procedures should be in accordance with the principle of accountability for reasonableness.

We make a plea for a broader view on health care with prevention and health promotion as integrated and appropriately facilitated tasks of the hospital. Hospital-based dietitians should perceive their professional responsibility not only as an obligation toward the short-term health needs of the individual patient but also toward his or her health from a life-time perspective. Hospital-based dietitians have unique opportunities to contribute to a reduction of premature deaths and

disabilities as well as a reduction in the growing socio-economic health disparities in society. A higher priority for preventive and health promotion tasks requires organizational commitment and adequate resource allocation. Close co-operation with the local primary care and public health sectors should be sought and additional education and training for hospital-based dietitians is required.

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Chapter 5 Summary

Prognosis, proof
and priorities
in dietetic practice

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5 Summary

Prognosis, proof and priorities in dietetic practice

There are several relationships between diet and health. Hospital patients may benefit from dietary interventions in many ways, not necessarily related to their primary diagnosis. In contrast to the – virtually infinite - number of opportunities for nutrition related preventive actions in hospitals, the available budget of hospital-based dietetic departments is restricted. Priorities in health care are generally based on the urgency and severity of health needs. Some needs are clear and visible, while others concern risks for events in the near or far future. In dietetics benefits are often related to future risks. Scientific data may help to quantify these needs and risks and predict the anticipated benefits of dietary interventions.

This thesis consists of a collection of studies addressing questions related to patient selection based on future risks (prognosis), selection of interventions based on evidence for effectiveness (proof) and principles for priority setting (priorities). The central question in this thesis is: What information, knowledge and values are needed to guarantee the quality of priority decisions in a hospital-based dietetic department?

Chapter two presents two studies on prognosis. Both were performed in oncohaematologic patients. Medical treatment of these patients (high-dose chemotherapy or bone marrow transplantation procedures) causes severe gastrointestinal toxicity, hampering oral intake. In the past, parenteral nutritional support (a method to bypass the gastro-intestinal tract) was proven to be indispensable for survival. However, because of increased skills to tailor

treatments for different patient groups, severity of toxic side effects was reduced. Doubts were raised for some patient subgroups whether the advantages of parenteral nutrition (maintenance of nutritional status) still outweighed the disadvantages (increased infection risk).

The first study (chapter 2.1) addresses this question. The study aimed to identify regimen-associated differences in requirements for parenteral nutrition and evaluate current practices. Included were patients receiving intensive cytotoxic therapy (high-dose chemotherapy courses or bone marrow transplantation protocols). Indications for parenteral nutrition were defined as: 1. malnutrition at admission; 2. a prolonged period (> 7 days) of minimal oral intake; or 3. body weight loss of more than 10% during admission.

Two analyses were performed. The first analysis included 20 patients (13 males; mean age 44 years) undergoing three consecutive treatment courses: remission induction (RI), consolidation (CO) and bone marrow transplantation (BMT). We found that parenteral nutrition was needed in 80% of the RI-courses, 35% of the CO-courses and 55% of the BMT-regimen. The second analysis involved 86 patients (53 males; mean age 42 years) undergoing one out of four different BMT-regimen. Parenteral nutrition was required in only 37% of autologous bone marrow transplantation recipients conditioned without total body irradiation versus 92% of recipients of a mismatched graft. We concluded that parenteral nutrition is not required for all patients undergoing intensive cytotoxic therapy. Screening of nutritional status at the start of therapy and monitoring oral intake following cytotoxic treatment may allow more appropriate identification of patients requiring parenteral nutrition.

The second study (chapter 2.2) deals with the recovery period after intensive cytotoxic therapy and stem cell transplantation. In this period many patients experience late toxicity effects of treatment, hampering their oral intake. The extent and severity of these problems were largely unknown. The study aimed to identify subgroups of patients that may benefit from more intensive nutritional counselling during the first year post-transplant. At five intervals (50, 75, 125, 200 and 350 days post-transplant) patients received a questionnaire with items on nutrition-related symptoms, physical condition, body weight recovery and adherence to a protein- and energy- dense diet.

Questionnaires of 118 responders (61 males; mean age 42 years) could be used. The prevalence of eating difficulties was high (66% at day 50) and compliance with dietary advice was poor (42% at day 50). The conditioning regimen preceding the transplantation was found to be a prognostic factor for body weight recovery at day 350. In more than 50% of the patients treated with total body irradiation, body weight was not fully restored to pre-treatment

value within one year. We concluded that the nutrition-related toxicity problems in this subgroup were extensive and severe and require more intensive dietary counselling during the first year post-transplant.

Chapter three describes two studies aiming to provide proof (evidence). Both were performed in coronary heart disease patients. These studies sought to answer the question whether there is sufficient evidence for a relevant effect of lifestyle and dietary changes on survival in these patients. The first study (chapter 3.1) describes adherence to a Mediterranean-type diet and three other lifestyle factors and their impact on all-cause mortality in a cohort of European post-myocardial infarction patients. Adherence to a Mediterranean-type diet was measured with a modified Mediterranean Diet Score on an eight point scale.

Participants were 426 men and women, aged 70 years or more, from 10 European countries, with a history of myocardial infarction. During 10 years of follow-up mortality was 53%. Frequency of non-smoking behaviour (85%), moderate to vigorous physical activity (54%), moderate alcohol consumption (45%) and a Mediterranean-type diet (63%) in patients differed only marginally from frequencies in European elderly without chronic diseases. The median Mediterranean Diet Score in patients from Northern Europe was two points lower than in Southern Europe. Non-smoking (RR 0.62 (95%CI 0.44-0.88), physical activity (RR 0.69 (95%CI 0.53-0.90), moderate alcohol consumption (RR 0.77 (95%CI 0.58-1.02) and a Mediterranean-type diet (RR 0.75 (95%CI 0.57-0.97) were associated with lower all-causes mortality. Presence of at least three of these healthy behaviours was associated with 40% lower mortality. We concluded that a strong relationship exists between lifestyle and dietary habits and mortality in post-myocardial infarction patients. The findings implicate that substantial health gain can be obtained in this patientgroup by better adherence to dietary and lifestyle recommendations.

The second study (chapter 3.2) addresses the same question on the impact of dietary and lifestyle changes on survival in coronary heart disease patients in a different way. In a systematic literature review all available studies on this subject were collected and assessed to appraise the existing evidence and –if possible- estimate common effect sizes. Prospective cohort studies and randomised controlled trials of patients with established coronary disease (a history of angina pectoris or myocardial infarction) were selected and included if they reported on all-cause mortality and had at least a six months follow-up. The effects ‘smoking cessation’ and ‘moderate alcohol consumption’ were estimated in non-experimental prospective studies. The effect estimates were RR 0.64 (95% CI 0.58 – 0.71) for smoking cessation and RR 0.80; (95%CI 0.78-0.83) for ‘moderate

alcohol consumption'. The effect of 'increased physical activity' was estimated in a meta-analysis of experimental studies and amounted to RR 0.76 (95%CI 0.59-0.98). For the six dietary goals data was too limited to provide reliable effect size estimates. Combinations of dietary changes were associated with significant mortality reduction in randomised clinical trials (RR 0.56; 95%CI 0.42-0.74).

We concluded that the results from available studies strongly suggest health benefits of lifestyle and dietary changes in coronary heart disease patients. The effect estimates were in the same order of magnitude as the effects of e.g. pharmacological prophylactics (statines, anti-hypertensive drugs or anti-trombolitics). The effect estimates of combined dietary changes are promising, but the number and quality of yet available studies is poor. In addition, simultaneuosly with the publication of our review reports of an international research fraud investigation raised suspicion on some of the included studies. Future studies should confirm our findings and also assess the contribution of the individual dietary factors.

Chapter four concerns principles that should guide priority setting in dietetic practice. The chapter aims to clarify concepts, to define guiding principles and to explore implications for priority setting in hospital-based dietetic departments. Literature was studied on four questions: What is the professional responsibility of dietitians? What role plays scientific evidence in prioritisation? What core ethical values should guide priority decisions? How should priority decisions be made in the absence of consensus?

We found that priority decisions of dietetic departments should not be fully determined by the patients that happen to be present in the waiting rooms or by the reimbursement rules of insurance companies. Because of their specific expertise and relationship with patients, dietitians are responsible to set their own priorities and influence priority decisions at different levels of the health care system. Priority decisions should be built on a critical appraisal of the available scientific evidence on the needs and risks of patient groups and the effectiveness of dietary interventions. An explicit vision on ethical values such as 'beneficence', 'autonomous choice' and 'distributive justice' and their interpretation in the particular societal context should provide the framework in which scientific data can be weighed. Being accountable for professional priority decisions means providing transparent policy documents and guaranteeing democratic procedures.

In the opinion of the authors at least three societal factors in western societies should be weighed in the priorities of hospital-based dietitians: the large burden of cardiovascular diseases, the substantial health disparities between socio-economic groups and the increasing frequency of unhealthy dietary behaviours.

Hospital-based dietitians are in a unique position to promote health in the society. They should not limit their scope to the short-term needs of their patients, but also aim for health gain from a lifetime perspective.

The central question in this thesis is: What information, knowledge and values are needed to guarantee the quality of priority decisions in a hospital-based dietetic department? The studies presented show that priority decisions should be based on reliable information on the needs of all relevant patient groups as well as on knowledge about evidence-based benefits of dietary interventions. Central ethical values in priority decisions are ‘beneficence’, ‘autonomous choice’ and ‘distributive justice’. The interpretation of these values in the particular societal context should provide the framework in which the scientific data can be weighed. To guarantee the quality of priority decisions by dietitians, competencies related to appraisal of scientific data, ethical deliberation, coping with social diversity and quality management are essential.

Chapter 6 Epilogue

Prognosis, proof and priorities in dietetic practice

This chapter is part of the PhD thesis:
Prognosis, Proof and Priorities in dietetic practice / J.A. Iestra
University of Utrecht, 2006

6 Epilogue

Prognosis, proof and priorities in dietetic practice

The words “Prognosis”, “Proof” and “Priorities” are primarily language of researchers and managers. They reflect thinking in patient groups instead of individual patients. How do the studies presented in this thesis apply to the lives of the individual patients who dietitians meet in everyday practice?

The first two studies add to the existing knowledge of treatment-defined prognosis in oncohaematological patients. This knowledge may help dieticians to improve selection of patients who benefit either from parenteral nutrition support during admission or from a more intensive counselling program during the recovery phase post-transplant. As a result individual patients may have a lower risk of complications, experience a better quality of life or have an improved life-expectancy. Moreover, the selective use of parenteral nutrition saves money that can be used for other purposes.

The two studies in chapter three add to our knowledge on the effectiveness and effect sizes of specific dietary and lifestyle changes to improve life-expectancy in patients with established coronary artery disease. The results show that effect sizes of dietary and lifestyle changes are relevant and comparable to the effects of routine prophylactic pharmacological treatments. This knowledge may motivate health professionals to give more attention to dietary and lifestyle education and stimulate resource allocation to facilitate better lifestyle and dietary counselling programmes. This will enable individual patients to make better informed choices and motivate them to attain and maintain healthy behaviours.

In the fifth study (chapter four) the patient selection policies of dietetic departments are the main concern. Priority decisions can not be based on the best available scientific evidence alone, but should be guided by reflection on ethical values and their meaning in the particular societal context. Professional responsibility assumes commitment to build up necessary competencies, to maintain adherence to ethical principles, develop sensitivity to a diverse patient population and be accountable through transparent policies.

I hope this thesis may encourage dietitians to reflect on, discuss and weigh both scientific evidence as well as the ethical implications of their priority decisions. That individual patients from all societal subgroups may benefit from a growing understanding and awareness of the impact of dietary behaviours on (future) health.

A person who works with his head or his hands is a labourer.
A person who works with his hands and his mind is a craftsman.
A person who works with his hands, mind and heart is an artist.

(adapted from J.D. Lubahn[1])

(1) Lubahn JD. Professionalism: the essence of competence. J Surg Orthop Adv 2005; 14(2):53-58.

Appendices

Prognosis, proof
and priorities
in dietetic practice

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Appendix A: Utilitarianism, Liberalism and Communitarianism

How ethical values are interpreted in a specific situation depends among other things on the stakeholders and decision makers ethical positions[1]. To support understanding of alternative viewpoints, a framework is provided by Roberts et al.[2]. In this framework three main stream ethical positions are distinguished: utilitarianism, liberalism and communitarianism. In table A we illustrate how these ethical positions may lead to different interpretations of the three core values presented in chapter 4 (beneficence, autonomous choice, distributive justice).

Utilitarianism (or consequentialism) states that decisions should be judged by their consequences, in particular their effects on the sum total of individual well-being in society. Within utilitarianism there are two camps: the subjective utilitarians hold that well-being is best defined by each individuals personal experience (subjective health gain), whereas the objective utilitarians want to centralise the assessment and let experts define well-being in 'rationally knowable components'(e.g. disability adjusted life years). Where subjective utilitarians prefer the market mechanism for resource allocation as it responds to autonomous choices, objective utilitarians favour central planning processes, based on data-driven methods.

Liberalism starts at the rights and opportunities people have. It holds that human beings ought to be treated with respect, as ends in themselves, not as means to another individual's ends. This principle of mutual respect can be interpreted in different ways: libertarians restrict the role of the state to protection of individual property rights and personal liberty. By contrast, egalitarian liberals argue that rights are meaningless without adequate resources. They state that people have a positive right for equality of opportunity related to their health status. Because of this right they justify prioritisation of health care needs of the worst off. Liberals also differ in their views on respect for autonomous choice as expressed by unhealthy behaviours. Some restrict the role of the state to informing and education, while others propose aggressive efforts to control behaviour, to improve societal health outcomes.

Communitarianism includes a diversity of visions that highly value an appropriate social order and the virtues that will maintain such an order in a particular community. Communitarians generally do not strive for equality, but stress the variations in individual talents and reward the complementary value of individuals while fulfilling the duties in society. Autonomous choice is subordinated to community goals and meaningful relationships. Communitarians may offer different answers to the question who decides what is virtuous. Relativist communitarians see morality as inherently contextual: every community defines its own norms and cultural diversity has to be respected. Universalist

communitarians believe in a single ideal of a good society and the associated virtues: certain behaviours (non-smoking, healthy eating) should be promoted in all societies, regardless of local cultural norms.

This description of the three main stream ethical positions is certainly not complete. Within each category many variations are possible. People seldom fully affiliate with one type of theory, but use them to sharpen their reflection. Roberts[2] argues that health care professionals should increase their ethical knowledge and vocabulary to better participate in the process of democratic deliberation preceding policy decisions.

Table A. Ethical theories and the interpretations of core values

		Beneficence How measured?	**Autonomous choice** Overruling allowed?	**Distributive justice** Role of health care professional?
Utilitarians	**Subjectivists**	Health index based on subjective experience	Sometimes, to maximise societal utility (preferably free market mechanism)	Facilitator of maximising health
	Objectivists	Expert defined health index (e.g. disability adjusted life years)	Yes, to maximise societal utility (by central planning)	Performer of central health policy
Liberals	**Libertarians**	In terms of realised life plans	No, only to protect individual property and freedom	Health care provider in a free market system
	Egalitarians	Health disparities is society	Yes, to guarantee fair equality of opportunity	Manager of fair equality of opportunity
Communitarians	**Relativists**	According to community norms, traditions	Yes, if it competes with interests of community or relationships	Caregiver, respecting community values and traditions
	Universalists	According to universal norms	Yes, if it competes with universal norms	Caregiver, respecting universal norms of the good society

Based on Roberts MJ and Reich MR. Lancet 2002; 359(9311):1055-1059

References appendix A

(1) Beauchamps T, Childress JF. Principles of Biomedical Ethics. 5 ed. New York: Oxford University Press; 1998.

(2) Roberts MJ, Reich MR. Ethical analysis in public health. Lancet 2002; 359(9311):1055-1059.

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Appendix C: Samenvatting in het Nederlands

Prioriteiten worden in de gezondheidszorg doorgaans gebaseerd op de urgentie en ernst van gezondheidsproblemen. Dit kunnen zichtbare klachten zijn, maar het kan ook gaan om een risico voor de toekomstige gezondheid. In de diëtetiek zijn behandelingen vaker gericht op het verminderen van risico's, dan op het genezen van bestaande klachten. Wetenschappelijke gegevens kunnen helpen om de omvang van deze risico's in kaart te brengen en een inschatting te maken van de mogelijke gezondheidswinst door een voedingsverandering.

Dit proefschrift omvat verschillende studies, die betrekking hebben op het stellen van prioriteiten in de diëtetiek. Enerzijds gaat het om het prioriteren van patiëntengroepen, gebaseerd op hun toekomstige gezondheidsverwachting ('prognose'). Anderzijds wordt gezocht naar wetenschappelijke onderbouwing ('proof') om het belang van een bepaalde behandeling ten opzichte van andere behandelingen goed te kunnen inschatten. Ook wordt ingegaan op ethische principes die –bewust of onbewust – onze prioriteiten bepalen. De centrale vraagstelling van dit proefschrift is: Welke informatie, kennis en waarden zijn nodig om de kwaliteit van prioriteitsbeslissingen te waarborgen in diëtetiek-afdelingen van ziekenhuizen.

In de studies in hoofdstuk 2 staat de 'Prognose' centraal. Beide studies werden uitgevoerd bij oncohaematologische patiënten. De medische behandeling van deze patiënten veroorzaakt onder meer ernstige maagdarmklachten. In het verleden was gebleken dat het toedienen van parenterale voeding (kunstvoeding via een infuus) voor deze patiënten onmisbaar was om te overleven. Door de jaren heen verbeterde de behandeling echter en verminderde de ernst van de bijwerkingen bij verschillende subgroepen. De vraag rees of het voordeel van het routinematig toedienen van parenterale voeding (behoud van de voedingstoestand) voor sommige subgroepen nog wel opwoog tegen de nadelen (verhoogd infectierisico).

De eerste studie (paragraaf 2.1) richt zich op deze vraag. Het doel van de studie was om de behoefte aan parenterale voeding per medisch behandelschema in kaart te brengen en om deze behoefte te vergelijken met de bestaande praktijk. Geïncludeerd werden patiënten die intensieve cytotoxische therapie ondergingen: hooggedoseerde chemotherapie al of niet gecombineerd met totale lichaamsbestraling en beenmergtransplantatie. Er werden drie indicaties voor parenterale voeding gedefinieerd: 1. ondervoeding bij opname in het ziekenhuis, 2. een lange periode (meer dan 7 dagen) van minimale voedselinname tijdens opname of 3. meer dan 10% gewichtsverlies tijdens opname.

De eerste analyse in deze studie betrof 20 patiënten (13 mannen, 7 vrouwen) die met tussenpozen drie kuren ondergingen: een remissie inductiekuur (RI), een consolidatie kuur (CO) en beenmergtransplantatie (BMT). Ondersteuning met parenterale voeding bleek volgens de criteria geïndiceerd te zijn bij 80% van de RI-kuren, 35% van de CO-kuren en 55% van de BMT-behandelingen. De tweede analyse betrof 86 patiënten (53 mannen en 33 vrouwen; gemiddelde leeftijd 42 jaar) die behandeld werden met een van vier verschillende BMT-protocollen. Parenterale voeding was geïndiceerd bij 37% van de autologe transplantaties zonder totale lichaamsbestraling (TBI), 50% van de autologe beenmergtransplantaties met TBI, 58% van de allogene transplantaties met donorcellen met vergelijkbare weefseltypering, en bij 92% van de allogene transplantaties met donorcellen met afwijkende weefseltypering. In beide analyses was het percentage patiënten dat in praktijk parenterale voeding had gekregen veel hoger dan geïndiceerd. We concludeerden dat het standaard geven van parenterale voeding niet nodig is voor alle patiënten die intensieve cytotoxische therapie ondergaan. Het screenen van de voedingstoestand aan het begin van de behandeling en het systematisch bijhouden van de voedselinname tijdens opname kunnen helpen om patiënten die parenterale voeding nodig hebben te identificeren.

De tweede studie (paragraaf 2.2) betreft de herstelperiode na de ziekenhuis-opname voor intensieve kankerbehandeling en stamceltransplantatie. In het eerste jaar na transplantatie ervaren veel patiënten voedingsproblemen als gevolg van de late bijwerkingen van de behandeling. Hoe ernstig en langdurig deze voedingsproblemen waren, was onbekend. Het doel van deze studie was om de veroorzakende symptomen (verminderde eetlust, maagdarmklachten) in kaart te brengen en subgroepen te identificeren, die baat zouden hebben bij intensievere begeleiding door de diëtist in het eerste jaar na transplantatie. Op vijf tijdstippen in het eerste jaar (dag 50, 75, 125, 200 en 350) ontvingen de patiënten een enquête met vragen over onder meer symptomen, voeding en lichaamsgewicht.

Van 118 respondenten (61 mannen, 57 vrouwen; gemiddelde leeftijd 42 jaar) konden de vragenlijsten worden gebruikt voor de analyse. Problemen om voldoende te eten kwamen veel voor (bij 66% op dag 50) en slechts weinig patiënten (42% op dag 50) waren in staat hun voeding energie of eiwitrijker te maken. Wel of geen totale lichaamsbestraling voorafgaand aan de transplantatie was een prognostische factor voor gewichtsherstel op dag 350. Bij meer dan 50% van de patiënten die totale lichaamsbestraling ondergingen, was op dag 350 het lichaamsgewicht van voor de behandeling nog niet hersteld. We concludeerden dat de voedinggerelateerde bijwerkingen van de behandeling in deze subgroep

frequent voorkomen en ernstig en langdurig zijn. Aan patiënten die totale lichaamsbestraling ondergaan moet daarom extra voedingsbegeleiding worden gegeven in het eerste jaar na transplantatie.

De studies in hoofdstuk 3 gaan in op het 'Bewijs' dat nodig is om aan te tonen dat een bepaalde voedingsinterventie relevant is in vergelijking tot andere interventies. Concreet onderzochten we welk bewijs er is dat het veranderen van voedingsgewoonten en leefstijl de levensverwachting verbetert bij patiënten, die al een coronaire (kransslagaderlijke) hartziekte hebben. De eerste studie (paragraaf 3.1) beschrijft het verband tussen gezonde leefgewoonten en de sterfte in een cohort van oudere hartpatiënten. De kwaliteit van ieders voedingsgewoonten werd gemeten met behulp van een Mediterraan Dieet Score op basis van acht kenmerken van dit dieet.

Deelnemers waren 426 mannen en vrouwen uit 10 Europese landen, in de leeftijd van 70 jaar of ouder, die eerder een hartinfarct hadden doorgemaakt. Tijdens de follow-up periode van 10 jaar overleed 53% van deze patiënten. In vergelijking tot Europese ouderen zonder een chronische ziekte hadden deze patiënten geen gezondere of ongezondere leefstijl of voedingsgewoonten: 85% rookte niet, 54% was regelmatig lichamelijk actief, 45% had een matig alcohol gebruik en 63% had een Mediterraan Dieet Score van 4 of hoger. Alle vier deze gewoonten bleken bij de patiënten samen te hangen met een lagere sterfte, hoewel de associatie voor matig alcoholgebruik niet statistisch significant was. Bij patiënten die niet (meer) rookten was de 10-jaars sterfte 38% lager dan bij rokers, bij lichamelijk actieven 31% lager dan bij inactieven, bij matige alcohol gebruikers 23% lager dan bij alcoholonthouders en bij degene met een Mediterraan Dieet Score van vier of meer 25% lager dan bij lagere scorers. Bij aanwezigheid van drie of meer van deze gezonde gewoonten was de sterfte 40% lager dan bij minder dan drie. We concludeerden dat er een sterk verband bestaat tussen leefstijl, voedingsgewoonten en sterfte bij patiënten, die een hartinfarct doormaakten. Door het intensiveren van de voedings- en leefstijlvoorlichting aan deze groep is er een aanzienlijke gezondheidswinst te behalen.

De tweede studie (paragraaf 3.2) gaat op een andere manier in op dezelfde vraag. In een systematische literatuurstudie werden alle beschikbare studies verzameld over negen voedings- en leefstijlfactoren in relatie tot sterfte bij patiënten met een coronaire hartziekte (patiënten die een hartinfarct doormaakten of leden aan angina pectoris). De studies werden beoordeeld volgens een aantal selectiecriteria. Indien voldoende goede studies beschikbaar waren, werd een schatting gemaakt van de grootte van het mogelijke effect van iedere factor

op de sterfte. Het effect van 'stoppen met roken' en ' matig alcohol gebruik' kon geschat worden op basis van niet-experimentele prospectieve studies. De geschatte effectgroottes waren een relatief risico (RR) van 0.64 (95%CI, 0.58-0.71) voor stoppen met roken en een RR van 0.80 (95%CI, 0.78-0.83) voor 'matig alcohol gebruik'. Het effect van 'extra lichaamsbeweging' werd geschat uit een meta-analyse van experimentele studies, het RR bedroeg 0.76 (95%CI, 0.59-0.98). De gegevens over de zes onderscheiden voedingsveranderingen waren te beperkt om een betrouwbare effectschatting op te leveren. Combinaties van de zes voedingsfactoren waren wel onderzocht in experimentele studies en de effectschatting kwam uit op een RR van 0.56 (95%CI, 0.42-0.74).

We concludeerden dat de beschikbare studies sterke aanwijzingen geven voor gezondheidswinst door leefstijl – en voedingsveranderingen in deze patiëntengroep. De effectgroottes zijn van dezelfde orde als de effecten van gebruikelijke medicatie in deze groep (statines, bloeddrukverlagende medicatie en anti-trombolitica). De effectschattingen uit de studies met de gecombineerde dieetinterventies zijn veelbelovend, maar het aantal studies en de kwaliteit van de studies is erg beperkt. Dit wringt des te meer, aangezien er gelijktijdig met de publicatie van dit literatuuroverzicht berichten verschenen dat de auteur van enkele van de gebruikte studies verdacht is van research fraude. Toekomstige studies zijn daarom nodig om de bevindingen uit onze studie te bevestigen en om de bijdrage van de zes onderscheiden voedingsfactoren apart te kunnen schatten.

Hoofdstuk 4 gaat over de principes die belangrijk zijn bij het stellen van 'Prioriteiten' in de diëtistenpraktijk. Dit hoofdstuk is bedoeld om begrippen te verduidelijken, principes te definiëren en de implicaties te onderzoeken. De literatuur werd bestudeerd aan de hand van vier vragen: Wat is de beroepsverantwoordelijkheid van diëtisten? Welke rol moet wetenschappelijke bewijsvoering spelen bij het stellen van prioriteiten? Welke ethische kernwaarden moeten centraal staan bij prioriteitsbeslissingen? En hoe moeten prioriteitsbeslissingen genomen worden als er geen consensus is over wie of wat in een concrete situatie prioriteit verdient?

We vonden dat diëtisten hun prioriteiten niet volledig kunnen laten afhangen van wie er in hun wachtkamer verschijnt of welke behandelingen door zorgverzekeraars worden vergoed. Vanwege hun rol als deskundige en belangenbehartiger van patiënten, moeten zij een actieve rol spelen bij het stellen en verdedigen van diëtetiek-prioriteiten binnen en buiten de eigen afdeling. Prioriteitsbeslissingen moeten rusten op een kritische beoordeling van de beschikbare wetenschappelijke gegevens en geleid worden door een

visie op kernwaarden als ‘beneficence’ (goed doen), ‘respect voor autonome keus’ en ‘verdelende rechtvaardigheid’. Beneficence als centrale waarde in de geneeskunde omvat behalve het behandelen van ziekte, ook het bevorderen van gezondheid in bredere zin. Respect voor autonome keuzes betekent onder meer voorwaarden scheppen voor goed geinformeerde keuzes. Bijvoorbeeld door extra consulttijd te reserveren en ondersteuning op maat te geven aan groepen met een minder dan gemiddeld begrips- of communicatievermogen. Verdelende rechtvaardigheid vraagt ook oog te hebben voor gezondheidsrisico’s die niet direct samenhangen met de diagnose, maar bijvoorbeeld met iemands sociaal-economische omstandigheden.

Naar de mening van de auteurs impliceren deze kernwaarden dat bij het prioriteitenbeleid van afdelingen diëtetiek in ziekenhuizen drie maatschappelijke factoren moeten worden meegewogen: de omvang van het probleem van hart- en vaatziekten in de samenleving, de aanzienlijke gezondheidsverschillen tussen socio-economische groepen en de snelle toename van ongezond voedingsgedrag. We concludeerden in dit hoofdstuk dat informatie over de ‘Prognose’ van lokale patiëntengroepen en ‘Bewijzen’ voor de relevantie van voedingsinterventies belangrijk zijn, maar niet voldoende om goede prioriteiten te kunnen stellen. Een interpretatie van ethische kernwaarden en de bredere maatschappelijke context vormen het kader waarin deze informatie gewogen moet worden.

De centrale vraag in deze dissertatie is: welke informatie, kennis en waarden zijn van belang om de kwaliteit te garanderen van prioriteitsbeslissingen in de diëtistenpraktijk in ziekenhuizen? De beschreven studies illustreren het antwoord. Een verantwoord prioriteitenbeleid in de diëtistenpraktijk steunt op:

- informatie over lokale patiëntengroepen, hun voedinggerelateerde gezondheidsproblemen, voedingsgedrag en voedingsprognose,
- actuele kennis over de effectiviteit van beschikbare voedingsinterventies in vergelijking tot andere behandelopties,
- reflectie op eigen en andermans interpretaties van ethische kernwaarden zoals ‘beneficence’, ‘autonome keuze’ en ‘verdelende rechtvaardigheid’.

Bij prioriteitsbeslissingen heb je altijd te maken met financiele beperkingen (schaarste), gebrek aan informatie (onzekerheid) en verschillende meningen (pluraliteit). Dit hoeft proefessionals er niet van te weerhouden om te streven naar verantwoorde beslissingen. Het vereist competenties op het gebied van het beoordelen van wetenschappelijke gegevens, het maken van ethisch afwegingen, het omgaan met sociale diversiteit en kwaliteitsmanagement. Door hun prioriteiten te formuleren in toegankelijke beleidsdocumenten, zijn diëtisten beter aanspreekbaar op hun keuzes.

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Appendix D: Dankwoord

Promoveren is … een lange adem hebben. Zelf kom ik daarvoor adem tekort. Dat dit boekje toch tot stand kwam, is mede te danken aan de inbreng en steun van een groot aantal mensen. Enkelen daarvan wil ik met name bedanken:

Allereerst mijn drie promotoren: Prof. Dr. Rick Grobbee, Prof. Dr. Wija van Staveren en Prof. Dr. Daan Kromhout. Daan leerde mij de eerste stapjes op de weg van de wetenschap. Het moet rond 1990 zijn geweest dat wij als AZL-diëtisten een cursus Epidemiologie bij jou volgden. Ik herinner me dat ik je schokte met mijn vraag wat ziekenhuisdiëtisten nou met die kennis moesten. Geduldig gaf je uitleg en geduldig ben je al die jaren gebleven. Ik hoop dat dit boekje je overtuigt dat ik er iets van heb opgestoken. Bedankt, voor je stimulerende begeleiding door de jaren heen, je enthousiasme voor de voedingswetenschap en de manier waarop je betrokken bent bij zo ongeveer alles wat de voeding en gezondheid van de Nederlandse burger betreft.

Wija, zonder jouw aanmoedigingen was dit boekje nooit tot stand gekomen. Jij hebt een belangrijke rol gespeeld bij mijn overstap van Leiden naar Utrecht en later van management naar wetenschap. Van die keuzes heb ik geen spijt. Vanaf het moment dat jij het plan had opgevat om mij te laten promoveren, heb je als een trouwe herdershond om me heen gelopen om me voor afdwalen te behoeden. Bij de keuze van mijn onderzoeksthema's heb je me veel vrijheid gegeven voor eigen plannen en interesses. Ook jij bent in je enthousiasme voor het 'evidence-based' handelen en je inzet voor voedingsvraagstukken uit de praktijk een belangrijke voorbeeld voor me geweest.

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van destijds en de Nederlandse Werkgroep Diëtisten Cardiologie van nu, wil ik bedanken voor de leuke en leerzame momenten. Met name de enthousiaste deelnemers van de Journal Club Cardiologie zorgden voor veel werkplezier.

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De artikelen in dit boekje zijn tot stand gekomen in samenwerking met een groot aantal co-auteurs. Aan de samenwerking met ieder van jullie koester ik leuke herinneringen. Prof. Dr. Koos Zwinderman, volgens mij was jij de eerste die vond dat ik op mijn tabellen zou kunnen promoveren. Dat sprak me toen niet aan, maar gaf me wel vrijmoedigheid om je vaker met statistische vragen lastig te vallen. Achteraf bedankt voor de bemoediging.

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Jolein Iestra

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Appendix E: Publications in Pubmed-indexed journals

1. Iestra, JA, Knoops KTB, Kromhout D, de Groot LCPGM, Grobbee DE, van Staveren WA. Lifestyle, Mediterranean Diet and Survival in European post-Myocardial Infarction Patients. Eur J Cardiovasc Prev Rehabil 2006: in press

2. Iestra JA, Kromhout D, van der Schouw YT, Grobbee DE, Boshuizen HC, van Staveren WA. Effect size estimates of lifestyle and dietary changes on all-cause mortality in coronary artery disease patients: a systematic review. Circulation. 2005 Aug 9;112(6):924-34.

3. Wamsteker EW, Geenen R, Iestra J, Larsen JK, Zelissen PM, van Staveren WA. Obesity-related beliefs predict weight loss after an 8-week low-calorie diet. J Am Diet Assoc. 2005 Mar;105(3):441-4.

4. Iestra JA, Fibbe WE, Zwinderman AH, van Staveren WA, Kromhout D. Body weight recovery, eating difficulties and compliance with dietary advice in the first year after stem cell transplantation: a prospective study. Bone Marrow Transplant. 2002 Mar;29(5):417-24.

5. Iestra JA, Fibbe WE, Zwinderman AH, Romijn JA, Kromhout D.Parenteral nutrition following intensive cytotoxic therapy: an exploratory study on the need for parenteral nutrition after various treatment approaches for haematological malignancies. Bone Marrow Transplant. 1999 May;23(9):933-9.

6. Lammers GJ, Pijl H, Iestra J, Langius JA, Buunk G, Meinders AE. Spontaneous food choice in narcolepsy. Sleep. 1996 Jan;19(1):75-6.

7. Pijl H, Cohen AF, Verkes RJ, Koppeschaar HP, Iestra JA, Schoemaker HC, Frolich M, Onkenhout W, Meinders AE. Plasma amino acid ratios related to brain serotonin synthesis in response to food intake in bulimia nervosa. Biol Psychiatry. 1995 Nov 15;38(10):659-68.

8. Pijl H, Koppeschaar HP, Cohen AF, Iestra JA, Schoemaker HC, Frolich M, Onkenhout W, Meinders AE. Evidence for brain serotonin-mediated control of carbohydrate consumption in normal weight and obese humans. Int J Obes Relat Metab Disord. 1993 Sep;17(9):513-20.

9. Iestra J. [Oral feeding in intensive cancer treatment. Creatively and flexibly anticipating diet preferences] TVZ. 1992 Jan 23;(2):62-4. Dutch.

10. Kok DJ, Iestra JA, Doorenbos CJ, Papapoulos SE. The effects of dietary excesses in animal protein and in sodium on the composition and the crystallization kinetics of calcium oxalate monohydrate in urines of healthy men. J Clin Endocrinol Metab. 1990 Oct;71(4):861-7.

11. Doorenbos CJ, Iestra JA, Papapoulos SE, Odink J, Van Brummelen P. Atrial natriuretic peptide and chronic renal effects of changes in dietary protein and sodium intake in man.Clin Sci (Lond). 1990 Jun;78(6):565-72.

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Appendix F: Curriculum vitae

The author was born on January 29th, 1960 in Voorschoten, the Netherlands. She graduated from high school ('Chr. Scholengemeenschap Visser 't Hooft') in Leiden in 1978. She received her professional education at the 'HBO-diëtetiek' in Groningen, where she graduated as a dietitian in 1982.
Between 1982 and 1986 she worked as a tutor at the Nursing School of the University Hospital Leiden and subsequently between 1986 and 1998 as a dietitian at several clinical departments of the the University Hospital Leiden (Head Department of Dietetetics: M. 'tHart-Eerdmans). She was head of the specialised kitchens of the Metabolic Ward and the Bone Marrow Transplant Unit. She participated in research projects on 'Chronic renal effects of changes in protein and sodium intake'(C.J. Doorenbos, finished 1990), 'Nutrition and urolithiasis'(D.J. Kok, finished 1991) and 'Serotonin and food selection'(H.Pijl, finished 1994). In the same period she completed an advanced course in Management and courses in Research Methodology, Epidemiology and Medical Statistics.
Between 1993 and 1998 she was responsible for research projects on clinical nutrition at the Bone Marrow Transplantation Unit of the Leiden University Medical Center and worked under supervision of Prof. dr. D. Kromhout on the studies presented in the second chapter of this thesis.
From 1998 to 2002 she worked as a manager in the Department of Dietetics and Nutritional Sciences (Head: Prof. dr. W.A. van Staveren) of the University Medical Centre Utrecht. In 2002, when the Department became part of the Julius Center for Health Sciences and Primary Care (Head: Prof. dr. D.E. Grobbee), she became an Assistant Professor involved in quality projects of the Department (evidence based guidelines and training), in research projects (presented in the third and fourth chapter of this thesis), and in teaching Clinical Nutrition to medical students.
The author is married to Leo Hoenderboom. They live in Amersfoort.