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BAPEN Symposium on 'Artificial nutrition support: no longer an expensive luxury!!'

Outcomes of undernutrition in patients in the community with cancer or cardiovascular disease

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Public health concern has tended to focus on the dangers of obesity, but there is evidence that undernutrition may also pose a risk to physical and mental well-being, particularly in those who are already ill. Using the General Practice Research Database (see office for Population Censuses and Surveys, 1995), we followed up 10 128 men and women aged 18 years and over who had been diagnosed with cancer or cardiovascular disease to examine whether nutritional status, as indicated by BMI, affected rates of use of health care resources and mortality. In both diagnostic groups, patients with a BMI below 20 kg/m^2 had higher rates of consultation with GP, higher rates of prescription and higher death rates during the follow-up period compared with those with a BMI of 20 – < 25 kg/m^2. In men and women with cardiovascular disease, poor nutritional status was associated with a sharply increased risk of hospital admission. Patients whose BMI was 30 – < 40 kg/m^2 also tended to have increased rates of GP consultation and prescription, and if they were under the age of 65 years, they had an increased risk of death. The results of the present study suggest that in men and women with cancer or cardiovascular disease, even minor degrees of undernutrition are associated with a marked increase in morbidity and mortality.

Malnutrition: Cancer: Cardiovascular disease

In Britain, as in most other industrialized countries, growing evidence linking a raised BMI with an increased incidence of CHD and some forms of cancer has focused public health concern on the risks of being overweight (Staessen *et al*. 1989; Manson *et al*. 1990; Department of Health, 1992; World Cancer Research Fund, 1997; Shaper *et al*. 1998). With many affluent countries experiencing a rise in the prevalence of obesity in recent years, such anxiety seems well-founded (Seidell, 1997). However, although there is growing medical awareness of the physical and social costs of being overweight (Wolf & Colditz, 1996; Seidell, 1998), the problems of those individuals whose BMI lies at the other extreme of the distribution have been largely overlooked (Lennard-Jones, 1992).

According to WHO estimates, approximately 15 % of adults under the age of 65 years are too thin (World Health Organization, 1995). As BMI falls below 20 kg/m^2, the risk of adverse effects on health and general well-being increases. Physiological studies have demonstrated that individuals with a low BMI tend to have a smaller muscle mass than those who are better nourished, and their physical work capacity is reduced (Spurr, 1984; Satyanarayana *et al*. 1989; Kennedy & Garcia, 1994). This loss of muscle power has potentially serious implications during illness, since both myocardial and respiratory function are compromised (Heymsfield *et al*. 1978; Arora & Rochester, 1982). Psychological well-being may also be influenced by a poor nutritional status. When volunteers with an initially optimal BMI were put on a semi-starvation diet, those subjects

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whose BMI fell to $<18{\cdot}5\,kg/m^2$ became depressed, anxious and apathetic (Keys *et al*. 1950). Patients who are malnourished tend to take longer to recover after surgery and may be more susceptible to infection because of impaired immune function (Chandra, 1990; Hill, 1992). There is some evidence that individuals with a poor nutritional status are likely to have longer stays in hospital when they require in-patient care (Robinson *et al*. 1987), but little is known about the effects of malnutrition on patients who are being cared for by their GP.

Using the General Practice Research Database (see Office for Population Censuses and Surveys, 1995), we followed up a cohort of men and women who had been diagnosed with cancer or cardiovascular disease to examine the relationships between their nutritional status, their rates of use of health care resources and their mortality.

Subjects and methods

The General Practice Research Database was set up in 1987, and is currently owned by the Department of Health and maintained by the Office for National Statistics (Office for Population Censuses and Surveys, 1995; Whalley & Mantgani, 1997). It contains information on about 3·5 million patients registered with over 500 practices throughout the UK. The quality of collected data is continually monitored by the Office for National Statistics to ensure that research protocol standards are maintained. After obtaining approval from the General Practice Research Database Scientific and Ethical Advisory Group, we searched the database for all patients aged 18 years and over with a recorded diagnosis of cardiovascular disease, which included CHD, angina, myocardial infarction, stroke or transient ischaemic attack, and cancer of the prostate, breast, lung, bronchus or pleura, caecum, colon or rectum. Those patients for whom one of these diagnoses had been recorded since 1 January 1988 and whose height and weight had been measured at least once between 1 January 1993 and 31 December 1997 were included in the study. For each participant, we obtained information on sex, year of birth, date and details of diagnosis of the specific disease, smoking habit and the geographical location of the practice with which they were registered. After the date of measurement of height and weight, we obtained data on all recorded general practice consultations, hospital admissions, referrals to hospital outpatient departments, date and details of all prescriptions, and deaths for all study participants. No information was available about the participants' socio-economic status, their use of social services, or the severity of their disease.

We used a person-years approach (Hill, 1972) to calculate rates for each of the main outcome measures (consultations, prescriptions, hospital outpatient referrals, hospital admissions and mortality) according to four categories of BMI (kg/m^2): 15–<20, 20–<25, 25–<30 and 30–<40. Rates for each outcome were calculated within a Lexis diagram, in order to take account of any possible variation over time during the period of the study, and were directly standardized for age. Multivariate log-linear modelling (GLIM-4) was used to control for potentially confounding factors and to explore possible interactions between variables (Francis *et al*. 1993). Values given for statistical significance were calculated from the log-linear model using BMI as a continuous variable rather than a categorical variable.

Results

The characteristics of the 4584 men and 5733 women who were selected for the study are shown in Table 1, according to diagnosis. Of these 10 317 patients, 55 % suffered from cancer and 45 % from cardiovascular disease. The patients ranged in age from 19 to 102 years and had a mean age of 65·8 years. In both diagnostic groups, 57 % were aged 65 years or over. Fewer than 1·5 % of patients had a BMI of <15 or $\geq 40\,kg/m^2$. Since we had doubts about the reliability of the recordings of height and weight in some of these individuals, all patients with a BMI outside the range $15-<40\,kg/m^2$ were excluded from further analysis. The remaining 10 128 men and women were followed up for a total of 30 800 person-years.

Table 1. Characteristics of the study subjects according to diagnosis

	Cancer			Cardiovascular disease		
	Men	Women	All	Men	Women	All
n	1939	3689	5628	2645	2044	4689
Age (years): Mean	71·5	62·8	65·8	64·1	67·6	65·6
Range	24–95	23–102	23–102	19–94	21–95	19–95
Mean length of follow-up (years)	2·32	2·93	2·72	3·41	3·38	3·40
Percentage in each category of BMI kg/m^2)*:						
<15	0·8	0·8	0·8	0·3	0·7	0·4
15–<20	7·3	6·6	6·9	3·4	6·9	4·9
20–<25	38·6	40·1	39·6	30·9	31·9	31·3
25–<30	41·6	33·6	36·4	47·3	35·5	42·1
30–<40	11·4	17·3	15·3	17·7	22·5	19·8
≥40	0·2	1·6	1·1	0·5	2·5	1·3
Percentage by age (years)*:						
18–44	1·1	8·7	6·0	4·4	3·3	3·9
45–64	19·6	46·1	36·9	45·0	31·8	39·2
≥65	79·3	45·2	57·0	50·7	64·9	56·9

* Due to rounding errors, columns do not always add up to exactly 100.

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Consultation rates with general practitioners

Consultation rates tended to increase with age but differed little between the sexes. There was a 'U'-shaped relationship between BMI and age-standardized consultation rates (Table 2). In both diagnostic groups, patients whose BMI were at the extremes of the distribution (either < 20 or 30 – < 40 kg/m^2) had the highest consultation rates. Among the patients who had been diagnosed with cancer, the lowest consultation rates were seen in those patients whose BMI were 20 – < 25 kg/m^2. Among patients with cardiovascular disease, those whose BMI were 25 – < 30 kg/m^2 had the lowest rates. These trends, seen in both men and women, were highly statistically significant (for quadratic term; $P < 0·001$).

Prescription rates

On average, prescription rates were higher in older patients. In both diagnostic groups, age-standardized rates were lowest in patients whose BMI were 20 – < 25 kg/m^2 (Table 2). The highest prescription rates occurred in patients whose BMI were either < 20 or 30 – < 40. This 'U'-shaped relationship was seen in both men and women (for quadratic term; $P < 0·001$).

Hospital outpatient referral rates

There were no clear trends between BMI and hospital outpatient referral rates (Table 3). Among male patients with a diagnosis of cancer, referral rates tended to be slightly higher in those whose BMI were at the extremes of the distribution, but this trend was not apparent in women or in patients of either sex who had been diagnosed with cardiovascular disease.

Hospital admission rates

Among patients diagnosed with cancer, there were no associations between BMI and hospital admission rates (Table 3). However, among men and women with cardiovascular disease, there was a statistically significant 'U'-shaped relationship between admission rates and BMI (for quadratic term; $P < 0·001$). Hospital admission rates were highest in patients with BMI of < 20 kg/m^2. Rates were also increased in patients whose BMI were at the upper end of the distribution.

Use of health care resources by elderly people

On average, patients aged 65 years and over had lower BMI than the rest of the study population (25·7 kg/m^2 *v.* 26·7 kg/m^2). This age-group also contained a higher percentage of undernourished patients; 7·3 % had BMI < 20 kg/m^2, compared with 4·3 % in the remainder of the sample. However, there was no indication that the relationships described earlier between BMI and rates of use of health care resources were different in elderly patients. When the analyses were restricted to patients aged 65 years and over, the 'U'-shaped trends between BMI and rates of GP consultation, prescription and hospital admission were little changed.

Table 2. Age-standardized rates (per person-year) for consultation with GP and prescription, according to BMI and diagnostic group of study subjects†

	GP consultation rates						Prescription rates					
	Cancer			Cardiovascular disease			Cancer			Cardiovascular disease		
BMI (kg/m^2)	Men	Women	All	Men	Women	All	Men	Women	All	Men	Women	All
15 – < 20	9·62	7·35	8·05	7·40	7·93	7·74	33·4	31·4	32·0	34·6	37·8	36·7
20 – < 25	8·95	6·61	7·29	6·76	7·56	7·12	35·0	26·2	29·0	32·3	37·4	34·7
25 – < 30	8·20	7·21	7·58	6·65	7·81	7·08	32·1	30·5	31·1	35·3	40·0	37·0
30 – < 40	9·16***	8·14***	8·37***	7·20***	8·60***	7·92***	37·3***	37·0***	37·1***	39·3***	49·0***	44·2***

Trends were statistically significant (for quadratic term calculated from multivariate model): *** $P < 0·001$.
† For details of subjects, see p. 656 and Table 1.

Table 3. Age-standardized rates (per person-year) for hospital outpatient referral and hospital admission, according to BMI and diagnostic group of study subjects†

	Hospital outpatient referral rates						Hospital admission rates					
	Cancer			Cardiovascular disease			Cancer			Cardiovascular disease		
BMI (kg/m^2)	Men	Women	All	Men	Women	All	Men	Women	All	Men	Women	All
15 – < 20	0·74	0·66	0·68	0·76	0·84	0·81	0·17	0·15	0·16	0·25	0·22	0·23
20 – < 25	0·68	0·65	0·66	0·84	0·82	0·83	0·17	0·15	0·15	0·14	0·15	0·14
25 – < 30	0·64	0·75	0·71	0·83	0·96	0·88	0·19	0·13	0·16	0·14	0·16	0·14
30 – < 40	0·75	0·69	0·70	0·74	0·85	0·80	0·16	0·16	0·16	0·15***	0·21***	0·18***

Trends were statistically significant (for quadratic term calculated from multivariate model): *** $P < 0·001$.
† For details of subjects, see p. 656 and Table 1.

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Mortality

During the follow-up period, 2112 patients died. Although men and women whose BMI were at the extremes of the distribution (either < 20 kg/m^2 or 30 – < 40 kg/m^2) made the greatest use of health care resources, any increased risk of death in the study population as a whole was largely concentrated among those patients with the lowest BMI (Table 4). In both diagnostic groups, patients whose BMI were < 20 kg/m^2 had a greater than twofold risk of death compared with those whose BMI were 25 kg/m^2 or above (for linear trend; $P < 0.001$). Of the patients who died 78 % were elderly. In case the relationship between BMI and risk of death differed in younger patients, we compared the mortality experience of individuals aged 65 years and over with the rest of the study sample. Among elderly men and women, there was a linear association between BMI and risk of death in both diagnostic groups (Fig. 1). However, among younger men and women, the relationship between BMI and mortality was 'U'-shaped (Fig. 2).

Table 4. Age-standardized mortality rates (per person-year), according to BMI and diagnostic group of study subjects†

	Mortality rates					
	Cancer			Cardiovascular disease		
BMI (kg/m^2)	Men	Women	All	Men	Women	All
15 – < 20	0·21	0·13	0·17	0·10	0·09	0·09
20 – < 25	0·12	0·10	0·10	0·04	0·04	0·04
25 – < 30	0·09	0·08	0·08	0·04	0·04	0·04
30 – < 40	0·09***	0·08***	0·08***	0·04***	0·03***	0·04***

Trends were statistically significant (for linear trend calculated from multivariate model): *** $P < 0.001$.
† For details of subjects, see p. 656 and Table 1.

Regional variation

To investigate whether the relationships between BMI and rates of consultation, prescription, hospital admission and mortality varied across the country, we used a log-linear multiple regression model. Age, sex, time period, BMI and region of residence were included in the model as independent variables. Statistically significant regional differences were present ($P < 0.05$). However, the relationships between BMI and rates of consultation, prescription, hospital admission and mortality were little affected by adjustment for region of residence and remained highly statistically significant ($P < 0.001$).

Cigarette smoking

Information on smoking habits was available for 98 % of the study population. Patients who smoked tended to have lower BMI than non-smokers or ex-smokers. However, an analysis restricted to those patients for whom smoking data was available showed that the relationships between BMI and rates of consultation, prescription, hospital admission and mortality were similar in both smokers and non-smokers, and remained statistically significant after adjustment for smoking status ($P < 0.001$).

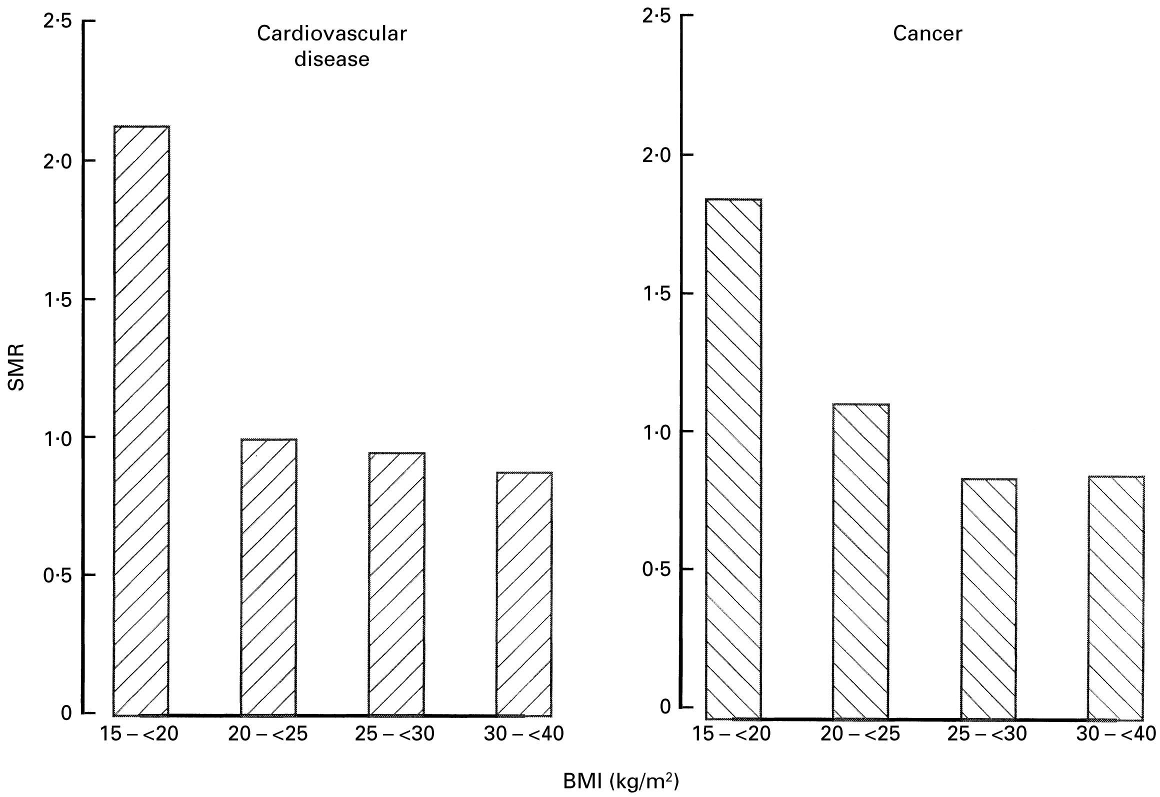

Fig. 1. Standardized mortality rates (SMR) in men and women aged 65 years and over, according to BMI and diagnostic group. For details of subjects, see p. 656 and Table 1.

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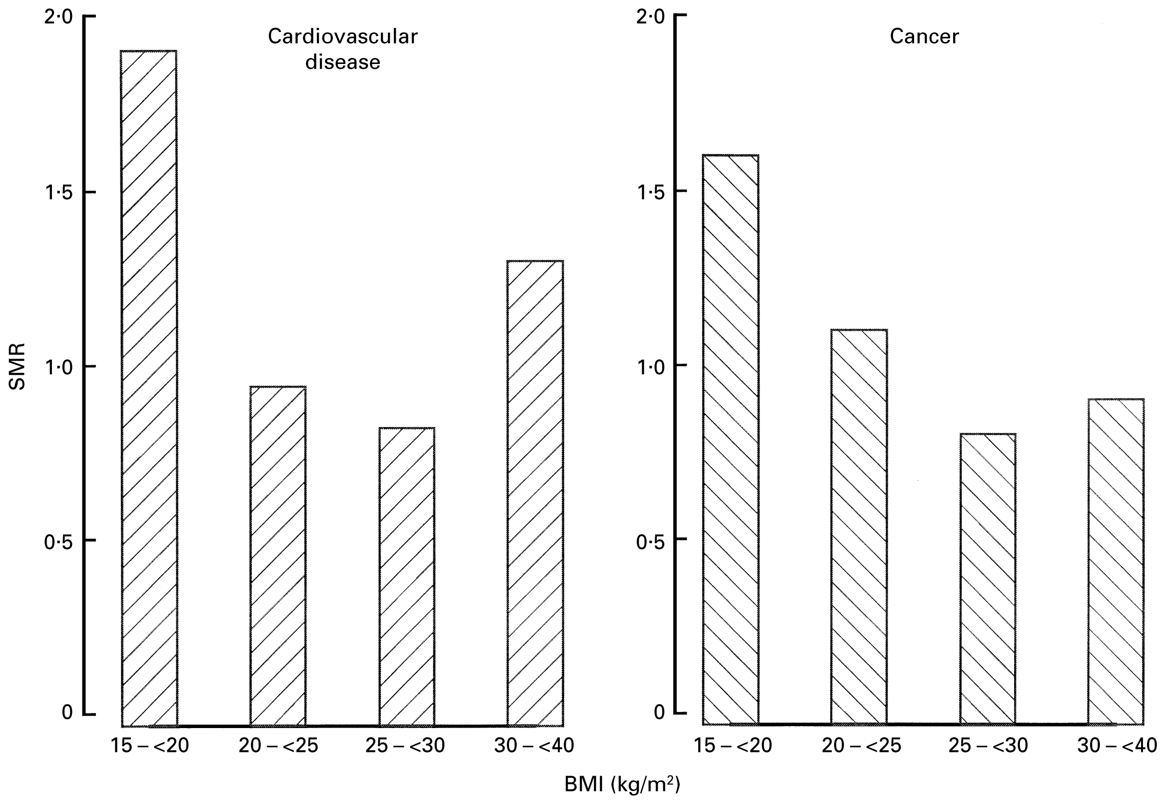

Fig. 2. Standardized mortality rates (SMR) in men and women aged 18–64 years, according to BMI and diagnostic group. For details of subjects, see p. 656 and Table 1.

Discussion

In this longitudinal study of 10 128 patients with cancer or cardiovascular disease, nutritional status, as indicated by BMI, was a strong predictor both of use of health care resources and of mortality. Men and women with BMI < 20 kg/m^2 had higher rates of consultation with their GP, higher rates of prescription and higher death rates during the follow-up period compared with patients with BMI of 20 – < 25 kg/m^2. In patients with cardiovascular disease, poor nutritional status was associated with a sharply increased risk of hospital admission. Men and women in both diagnostic groups whose BMI were 30 – < 40 kg/m^2 also tended to have increased rates of GP consultation and prescription, and if they were under the age of 65 years, they had an increased risk of death. In elderly patients, a higher BMI was associated with a reduced risk of death.

The participants in the present study were not a random sample of all individuals with cancer or cardiovascular disease in the General Practice Research Database, but were selected because their height and weight had been measured and recorded. However, the prevalence of patients with BMI of < 20 kg/m^2 in our sample is similar to that reported in an earlier study of the nutritional status of patients with cancer or chronic disease in general practice (Edington *et al.* 1996), and to that found in a national survey (Gregory *et al.* 1990). This finding suggests that the method of sampling is unlikely to have resulted in any serious bias. Further, all comparisons have been made within the cohort. Unless the relationships between nutritional status and measured outcomes are different in individuals who have not had their height and weight measured, it seems reasonable to infer that these findings apply generally to patients with cancer or cardiovascular disease.

Few studies have investigated the relationship between undernutrition and use of health care resources. In the USA, a study of over 17 000 men and women found positive associations between BMI and rates of hospital attendance and annual costs of treatment, but it was not possible to assess the effects of poor nutritional status because subjects with BMI of < 20 kg/m^2 were deliberately excluded (Quesenberry *et al.* 1998). In a study of 16 000 subjects who took part in the US National Medical Expenditure Survey (Heithoff *et al.* 1997), the likelihood of using any health care service rose as BMI increased, but there was evidence of a ‘U’-shaped relationship between BMI and expenditure on health care. Some of the highest annual expenditures were seen in men with BMI of < 20 kg/m^2. Although expenditure on health care provides only an indirect marker of morbidity, this finding is consistent with the results of the present study and with the results of an earlier investigation using the UK’s General Practice Research Database (Martyn *et al.* 1998). In this longitudinal study of over 11 000 patients with chronic disorders of the respiratory, gastrointestinal and neurological systems, patients with BMI of < 20 kg/m^2 had higher rates of consultation, prescription and hospital admission than those whose BMI were 20 – < 25 kg/m^2.

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Most prospective studies into the relationship between BMI and mortality have been carried out in the general population. They provide clear indications that being overweight increases the risk of death, although this risk seems to be less important in older patients (Lee *et al*. 1993; Manson *et al*. 1995; Stevens *et al*. 1998). The relationship between low BMI and mortality has been less easy to interpret. Although many studies have found evidence of a 'U'-shaped relationship, there has been much debate as to whether the higher death rates in underweight patients are due entirely to the ill-effects of undernutrition or to the impact of pre-existing disease (Lee & Manson, 1998). It is clear from the results presented here that in individuals who are already ill, a low BMI markedly increases the risk of earlier death. Similar findings have been reported from prospective studies of patients with diabetes and other chronic disorders (Chaturvedi *et al*. 1995; Martyn *et al*. 1998).

Whether improving the nutritional status of such patients would improve survival and lower morbidity is as yet unclear. In a recent systematic review of randomized controlled trials of protein–energy supplementation, adult patients who were treated with oral or enteral supplementation showed a consistent gain in body weight and mid-arm muscle circumference compared with controls (Potter *et al*. 1998). There was some evidence from these trials that case fatality was reduced in the supplemented groups, but there were insufficient mortality data from methodologically-sound studies to be certain of this trend. In the present study we had too few subjects with repeat measurements of body weight to be able to assess whether a gain in weight was associated with a reduction in morbidity, but in an earlier study of patients with chronic disease, those whose BMI increased from below 20 kg/m^2 to above 20 kg/m^2 showed a reduction in rates of general practice consultation and prescription (Martyn *et al*. 1998).

Cardiovascular disease and cancer are two of the leading causes of death in industrialized countries. Caring for patients with these conditions is inevitably a major drain on health service resources. The results of the present study provide evidence that even minor degrees of undernutrition in these patients result in increased morbidity and mortality. They also suggest that nutritional intervention might prove an effective strategy both in reducing the economic costs of such diseases and in improving patients' quality of life.

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