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The association between total energy intake and early mortality: data from the Malmö Diet and Cancer Study

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Abstract. Leosdottir M, Nilsson P, Nilsson J-Å, Månsson H, Berglund G (Lund University, University Hospital (UMAS), Malmö, Sweden). The association between total energy intake and early mortality: data from the Malmö Diet and Cancer Study. *J Intern Med* 2004; **256**: 499–509.

Objectives. In animal studies, low energy intake (EI) has been associated with a longer lifespan. We examine whether EI is an independent risk factor for prospective all-cause mortality, cardiovascular and cancer mortality in humans.

Design. Population-based, prospective cohort study.

Setting and subjects. The Malmö Diet and Cancer Study is a population-based prospective cohort study. A total of 28 098 individuals, mean age 58.2 years, completed questionnaires on diet and life-style and attended a physical examination during 1991–96.

Main outcome measures. Information on mortality was acquired from national registries during a mean follow-up time of 6.6 years. Subjects were categorized by quartiles of total EI. The first quartile was used as a reference point in

estimating multivariate relative risks (RR; 95% CI, Cox's regression model). Adjustments were made for confounding by age and various life-style factors.

Results. The lowest total mortality was observed for women in the third quartile (RR: 0.74; CI: 0.57–0.96) and for men in the second and third quartiles (RR: 0.85; CI: 0.69–1.04 and RR: 0.85; CI: 0.69–1.04 respectively). Similar U-shaped patterns were observed for cardiovascular mortality amongst women and cancer mortality amongst men. A statistically significant trend ($P = 0.029$) towards lower cardiovascular mortality from the first to the fourth quartile was observed for men.

Conclusions. Low caloric consumers did, on average, not have lower mortality than average or high caloric consumers. Generally, individuals approximately meeting national recommendations for total EI had the lowest mortality. For men, high caloric intake was associated with lower cardiovascular mortality.

Keywords: caloric intake, cancer, cardiovascular, mortality, population.

Introduction

The effect of total caloric intake on mortality and disease-specific morbidity has been the subject of extensive research for many years [1, 2]. Studies based on animal models have shown that dietary energy restriction of up to 30–50% seems to increase longevity and slow the process of ageing [3, 4]. This effect seems to exist independent of whether the animals remain sedentary or are exercised [3]. Multiple metabolic changes have been observed in calorie-restricted animals, such as lower

concentrations of plasma glucose, insulin, cholesterol and triglycerides, lower systolic and diastolic blood pressure, increased insulin sensitivity, increased levels of high-density lipoprotein (HDL) cholesterol, lower arterial stiffness, various neuroendocrine and autonomic nervous system activity alterations, lower body temperature and reduced metabolic rates [1, 2, 5]. Along with the fact that many of these observed changes affect cardiovascular risk factors, it is hypothesized that some of these metabolic alterations attenuate the degree of oxidative stress and formation of free radicals, together

underlying the observed decrease in cancer and cardiovascular disease incidence, and generally slowing the process of ageing [5].

Life-expectancy has been steadily increasing over the last century in industrialized countries [6]. Although most researchers agree on improved nutrition being one of the main factors contributing to this increase, the changing nutritional status has bred new problems. Daily energy intake (EI) amongst inhabitants of western countries has been increasing over the last decades and physical activity decreasing, with consequent rises in the incidence of obesity [7–9]. Reduction in caloric intake to keep the equilibrium between EI and energy expenditure (EE) in balance, is widely recommended as means to fight obesity [10, 11]. For obvious reasons, large prospective studies on caloric restriction and mortality in humans are difficult to conduct. Most studies examining the effect of a recommended diet on disease-specific mortality and morbidity of humans, focus more on the composition of the diet rather than the total number of calories, although such recommendations usually favour caloric-restricted diets [12–14]. All the same, these studies along with various observational studies have indicated that the positive effect of caloric restriction or low calorie diets on health and longevity could be applicable to humans [15–17].

The objective of this study was to examine whether total caloric intake is an independent risk factor for prospective all-cause mortality, cardiovascular mortality, and cancer mortality, within the Malmö Diet and Cancer cohort, hypothesizing that individuals who report low calorie diets also have lower mortality than average or high calorie consumers, even when adjustments for possible confounders have been made.

Material and methods

The Malmö Diet and Cancer Study

The Malmö Diet and Cancer Study (MDC) was launched in Malmö, south Sweden, in 1991. It is a population-based prospective cohort study designed to identify dietary risk factors in relation to cancer [18]. A cohort of 74 138 individuals, including all men born between 1923 and 1945 and all women born between 1923 and 1950 living at the time in the city of Malmö, were invited to participate.

Exclusion criteria included mental incapacity and inadequate Swedish language skills.

Baseline examinations took place between 1991 and 1996 and included two separate visits at the MDC Centre at the University Hospital in Malmö. A 141-item questionnaire was administered to record socio-economic status, various life-style aspects, physical activity, use of medication, family history of disease and more. A medical examination was performed to evaluate body composition and to measure blood pressure. Blood samples were drawn from the participants and stored in a bio-bank. A dietary questionnaire and a 7-day menu-diary were administered to evaluate dietary intake [19]. A total of 28 098 individuals (approximately 40% of those invited) completed both questionnaires and attended the physical examination. For a follow-up period of approximately 6.6 years, information on mortality has been gathered from local and national registries. The MDC study was approved by the Lund University Ethics Committee.

Study population

All 28 098 individuals, 17 035 women (60.6%, mean age at baseline 57.5 years) and 11 063 men (39.4%, mean age at baseline 59.3 years), were included in the analysis.

Dietary, life-style and anthropometric variables

The dietary questionnaire, composed of 168 questions, recorded consumption of regularly eaten foods other than cooked meals during the past year. The menu-diary recorded descriptions of cooked meals, nutrient supplements and cold beverages for 7 consecutive days. Studies on the reproducibility and validity of these methods have previously been published [20, 21].

Total daily EI, measured as kcal day⁻¹ coming from all major dietary energy sources (carbohydrates, protein, fat and alcohol) was used in this study, as this measurement of total EI is used in most nutrient recommendations around the world, including those followed in the Nordic countries [22]. Intake of the various energy sources was recorded in grams consumed per day. Relative energy coming from different energy sources was calculated exclusive of alcohol, in accordance with Nordic countries nutrient recommendations [22].

Information on smoking habits, socio-economic status, physical activity, marital status and prior history of diabetes was retrieved from the life-style questionnaire. Subjects were defined as current smokers, former smokers or never-smokers. Socio-economic status was recorded according to the Swedish population census, based on present or latest occupation [23]. In the current study, three categories were formed from the original classification: blue-collar workers, white-collar workers and employers/self-employed. Questions on leisure time physical activity were adapted from the Minnesota Leisure Time Physical Activity Questionnaire [24]. An overall physical activity score was calculated from these questions, which subsequently was categorized into low, moderate and high levels of leisure time physical activity. The degree of physical activity at work was self-rated as very light, light, medium heavy, or very heavy. In the current study marital status was categorized as (i) single, divorced or widowed versus (ii) married or co-habiting. Information on medical history was derived from the questionnaire (for diabetes) and from local or national registries (for diagnosis of cancer, myocardial infarction or stroke).

Trained nurses measured weight (kg), height (m) and blood pressure (mmHg) at one of the visits to the MDC centre. From the weight and height, body mass index (kg m^{-2}) was calculated.

Statistical analysis

All analyses were stratified by gender. Cox's proportional hazards regression was used to estimate multivariate relative risks (RR) and 95% confidence intervals (CI). Adjustments were made for confounding by age, smoking habits, alcohol consumption, socio-economic status, marital status, leisure time and work-related physical activity, body mass index, and for cardiovascular mortality blood pressure as well. Calculations were repeated after excluding subjects with <1 year of follow-up and subjects with prior history of myocardial infarction, stroke, diabetes or cancer ($n = 4611$). This was done to evaluate whether individuals likely to have poorer health, leading to both higher mortality rates and lower EI, would bias the result.

Univariate general linear model procedure was used to calculate age-adjusted mean values. One-way ANOVA and chi-square tests were used to

compare mean values between quartiles. The SPSS data configuration program was used for statistical procedures. A traditional two-sided significance level of $P < 0.05$ was used.

Results

A total of 1250 deaths were registered till the end of year 2000, for a mean follow-up period of 6.6 years (range: 0.1–9.8). Mean age at death was 66.2 (47.3–77.9) years for women and 66.7 (48.2–77.8) years for men. Most deaths were from cancer, or 59% amongst women (310 of 522) and 43% amongst men (313 of 728). Ninety-seven of the 522 women (19%) and 242 (33%) of the men died from cardiovascular disease. Of the 28 098 subjects participating in the study, 12.1% were born outside of Sweden, mostly in Eastern Europe and the other Nordic countries. A total of 139 individuals (81 women and 58 men) were lost to follow-up, main reason being emigration from the country. Baseline characteristics for subjects, categorized by survival status at the end of follow-up, are shown in Tables 1 and 2.

Total energy intake and sources of energy

Tables 3 and 4 show the average daily EI and relative percentage of energy coming from the major energy sources (excluding energy from alcohol), for the different quartiles of total EI. Women in the first quartile (reference group) consumed on average 1425 (504–1659) kcal day^{-1} . This is approximately 35% less than what is recommended by the Swedish National Food Administration, where an average intake of 2200 kcal day^{-1} is recommended for adult women [25]. Women in the fourth quartile consumed on average 2662 (2279–5556) kcal day^{-1} , or approximately 21% more than what is recommended. Men in the first quartile consumed on average 1842 (570–2144) kcal day^{-1} , or approximately 32% less than what national guidelines advise (2700 kcal day^{-1} for adult men). Daily energy consumption amongst men in the fourth quartile amounted to 3496 (2973–8304) kcal day^{-1} , which is approximately 29% more than what is recommended. For both sexes, percentage of energy coming from fat increased by approximately 4% from the first to the fourth quartile, with relative protein and carbohydrate intake decreasing respectively (Tables 3 and 4). Selected baseline

Table 1 Baseline characteristics for women categorized by survival status at the end of follow-up

	Alive (<i>n</i> = 16 432)	Dead (all causes) (<i>n</i> = 522)	Dead from CVD (<i>n</i> = 97)	Dead from cancer (<i>n</i> = 310)
Mean age in years (range)	57.3 (45–73)	61.8 (45–73)	63.8 (45–73)	60.9 (45–73)
Social status				
Blue-collar worker (%)	38.0	43.8	58.3	42.2
White-collar worker (%)	54.5	49.0	33.3	52.0
Employer/self-employed (%)	7.6	7.2	8.3	5.9
Current smoker (%)	27.6	40.8	47.4	41.0
Marital status				
Married/co-habiting (%)	60.8	50.3	54.6	48.9
Single/divorced/widowed (%)	39.2	49.7	45.4	51.1
Alcohol consumption (g pure ethanol day ⁻¹)	7.7 (0.0–109.5)	6.8 (0.0–73.7)	6.3 (0.0–45.3)	6.8 (0.0–73.7)
Physical activity score	7935 (0–316 120)	7490 (0–39 825)	7184 (0–33 600)	8011 (0–39 825)
Blood pressure (mmHg)				
Systolic	139.3 (61–230)	140.4 (90–210)	147.2 (110–210)	138.9 (98–200)
Diastolic	84.0 (40–136)	84.6 (56–126)	86.9 (65–126)	84.2 (60–110)
Body mass index (kg m ⁻²)	25.4 (14.0–50.9)	25.3 (15.1–44.8)	25.6 (15.1–39.7)	25.4 (16.7–44.8)
Total energy intake (kcal day ⁻¹)	1999 (504–5556)	2015 (742–4104)	1923 (776–4072)	2063 (742–4085)

Subjects lost to follow-up (*n* = 81) are not included. All mean values are age-adjusted, with range presented in parentheses.

Table 2 Baseline characteristics for men categorized by survival status at the end of follow-up

	Alive (<i>n</i> = 10 277)	Dead (all causes) (<i>n</i> = 728)	Dead from CVD (<i>n</i> = 242)	Dead from cancer (<i>n</i> = 313)
Mean age in years (range)	59.1 (46–73)	62.7 (46–73)	63.3 (48–73)	62.8 (46–73)
Social status				
Blue-collar worker (%)	35.3	42.3	46.7	36.7
White-collar worker (%)	47.1	43.6	37.6	47.9
Employer/self-employed (%)	17.6	14.1	15.7	15.4
Current smoker (%)	27.5	42.9	44.2	42.8
Marital status				
Married/co-habiting (%)	73.2	61.8	58.5	68.1
Single/divorced/widowed (%)	26.8	38.2	41.5	31.9
Alcohol consumption (g pure ethanol day ⁻¹)	15.5 (0.0–194.0)	14.3 (0.0–161.6)	12.9 (0.0–92.1)	14.8 (0.0–95.4)
Physical activity score	8386 (0–209 556)	7969 (0–95 200)	7606 (0–95 200)	8270 (0–58 790)
Blood pressure (mmHg)				
Systolic	143.9 (90–230)	147.3 (90–220)	149.2 (92–220)	146.3 (108–210)
Diastolic	87.9 (52–136)	89.8 (60–128)	91.1 (60–128)	88.9 (60–115)
Body mass index (kg m ⁻²)	26.3 (13.9–50.7)	26.2 (15.2–43.4)	26.7 (17.4–43.4)	25.9 (15.6–38.4)
Total energy intake (kcal day ⁻¹)	2603 (570–6789)	2598 (999–8304)	2484 (999–5229)	2675 (1296–8304)

Subjects lost to follow-up (*n* = 58) are not included. All mean values are age-adjusted, with range presented in parentheses.

characteristics of individuals in different quartiles can also be seen in Tables 3 and 4.

Total mortality

Relative risks for total mortality amongst men and women can be seen in Table 5. Women in the third

quartile (mean intake 2104 kcal day⁻¹) had the lowest RR for all-cause mortality (RR: 0.74; CI: 0.57–0.96, *P* = 0.024) with women in the fourth quartile (mean intake 2662 kcal day⁻¹) having similar RR as women in the first quartile. No statistically significant difference was observed between different quartiles of EI amongst men,

Table 3 Mean caloric intake, diet composition and selected baseline characteristics within different quartiles of average daily energy intake for women

	First	Second	Third	Fourth
N (<i>n</i>)	4258 (159)	4259 (120)	4259 (101)	4259 (142)
Energy intake (kcal day ⁻¹)	1425 (504–1659)	1806 (1659–1947)	2104 (1947–2279)	2662 (2279–5556)
From fat (%)	36.4	37.9	38.9	40.4
From carbohydrates (%)	46.2	45.7	45.2	44.6
From protein (%)	17.1	16.2	15.7	14.8
Intake of fruit and vegetables (g day ⁻¹)	393.6	396.2	393.3	396.5
Age (years)	58.6	57.6	57.2	56.6
Socio-economic status				
Blue-collar worker (%)	43.1	36.5	35.6	37.4
White-collar worker (%)	49.6	56.3	46.6	54.6
Self-employed (%)	7.3	7.2	7.8	8.0
Current smoker (%)	29.0	25.8	26.8	30.6
Married/co-habiting (%)	60.5	62.7	62.1	56.8
Prior history of cancer, DM, MI or stroke (%)	21.3	18.4	17.9	16.1
Use of antihypertensive medication (%)	20.8	17.8	16.4	14.6
BMI (kg m ⁻²)	26.0	25.6	25.2	24.8
SBP (mmHg)	140	140	139	138
Alcohol intake (g pure ethanol day ⁻¹)	5.6	7.5	8.4	8.8
Physical activity score	7462	7589	8048	8603

Numbers are presented as age-adjusted mean values or percentages. Range of energy intake is given in parentheses. Relative energy coming from different energy sources is calculated exclusive of alcohol, in accordance with Swedish National Food Administration guidelines [26]. For reference, approximately 2200 kcal day⁻¹ are recommended by the Swedish National Food Administration for adult women [26]. Mean intake of vegetables and fruit is age and energy adjusted.

N, number of individuals within each quartile; *n*, number of deaths from all causes; BMI, body mass index; SBP, systolic blood pressure.

Table 4 Mean caloric intake, diet composition and selected baseline characteristics within different quartiles of average daily energy intake for men

	First	Second	Third	Fourth
N (<i>n</i>)	2765 (223)	2766 (163)	2766 (157)	2766 (185)
Energy intake (kcal day ⁻¹)	1748 (570–2043)	2229 (2043–2414)	2621 (2415–2859)	3377 (2859–8304)
Percentage from fat	38.0	39.1	40.1	41.8
Percentage from carbohydrates	45.2	45.2	44.5	43.6
Percentage from protein	16.6	15.6	15.3	14.6
Intake of fruit and vegetables (g day ⁻¹)	343.2	346.7	350.4	341.7
Age (years)	60.6	59.8	59.0	57.8
Socio-economic status				
Blue-collar worker (%)	37.3	32.9	34.1	38.7
White-collar worker (%)	46.0	49.7	48.9	42.8
Self-employed (%)	16.6	17.4	17.0	18.4
Current smoker (%)	25.5	24.8	28.6	35.4
Married/co-habiting (%)	72.8	74.6	73.5	69.0
Prior history of cancer, DM, MI or stroke (%)	21.7	14.5	11.9	9.6
Use of antihypertensive medication (%)	30.3	20.5	18.6	15.7
BMI (kg m ⁻²)	26.8	26.3	26.1	26.0
SBP (mmHg)	145	144	144	143
Alcohol intake (g pure ethanol day ⁻¹)	12.0	15.1	16.5	18.3
Physical activity score	7580	8073	8568	9205

Numbers are presented as age-adjusted mean values or percentages. Range of energy intake is given in parentheses. Relative energy coming from different energy sources is calculated exclusive of alcohol, in accordance with Swedish National Food Administration guidelines [26]. For reference, approximately 2700 kcal day⁻¹ are recommended by the Swedish National Food Administration for adult men [26]. Mean intake of vegetables and fruit is age and energy adjusted.

N, number of individuals within each quartile; *n*, number of deaths from all causes; BMI, body mass index; SBP, systolic blood pressure.

Table 5 Relative risk (95% CI) for all-cause mortality by quartiles of total energy intake

	First	Second	Third	Fourth	Total [N (n)]
Women					
All subjects included					
RR	1.00	0.88	0.74*	1.06	17 035 (522)
CI	Ref	0.69–1.13	0.57–0.96	0.84–1.34	
After exclusion ^a					
RR	1.00	0.90	0.82	1.00	13 921 (312)
CI	Ref	0.66–1.24	0.59–1.14	0.73–1.36	
Men					
All subjects included					
RR	1.00	0.85	0.85	0.89	11 063 (728)
CI	Ref	0.69–1.04	0.69–1.04	0.72–1.09	
After exclusion ^a					
RR	1.00	0.88	0.78	0.93	9539 (470)
CI	Ref	0.68–1.13	0.60–1.02	0.72–1.20	

Adjusted for age, alcohol intake, smoking, leisure-time and work-related physical activity, socio-economic status, marital status and body mass index.

N, total number of individuals in all quartiles; n, number of cases; Ref, reference quartile.

^aPatients with <1 year follow-up time, prior history of diabetes, stroke, myocardial infarction or cancer excluded (3101 women and 1510 men).

* $P = 0.024$.

although a similar pattern was observed, with subjects in the second (mean intake 2229 kcal day⁻¹) and third quartiles (mean intake 2621 kcal day⁻¹) having somewhat lower RRs (0.85; CI: 0.69–1.04 and 0.85; CI: 0.69–1.04 respectively, $P = \text{NS}$) (Fig. 1) than the first and fourth quartiles.

After excluding individuals with <1 year follow-up or prior history of myocardial infarction, stroke, cancer and diabetes (3101 women and 1510 men), significance was lost for the third quartile for women (0.82; CI: 0.59–1.14, $P = \text{NS}$). However, the observed trend towards lower RRs in the middle quartiles for women and men did not change (Table 5).

Cancer mortality

Similar nonsignificant U-shaped patterns as for total mortality were observed for cancer mortality amongst men, where the first and fourth quartiles had compatible RRs and the second quartile the lowest RR of 0.75 (CI: 0.54–1.05, $P = \text{NS}$) (Fig. 2). Women in the fourth quartile had a slightly higher RR of cancer, although not statistically significant

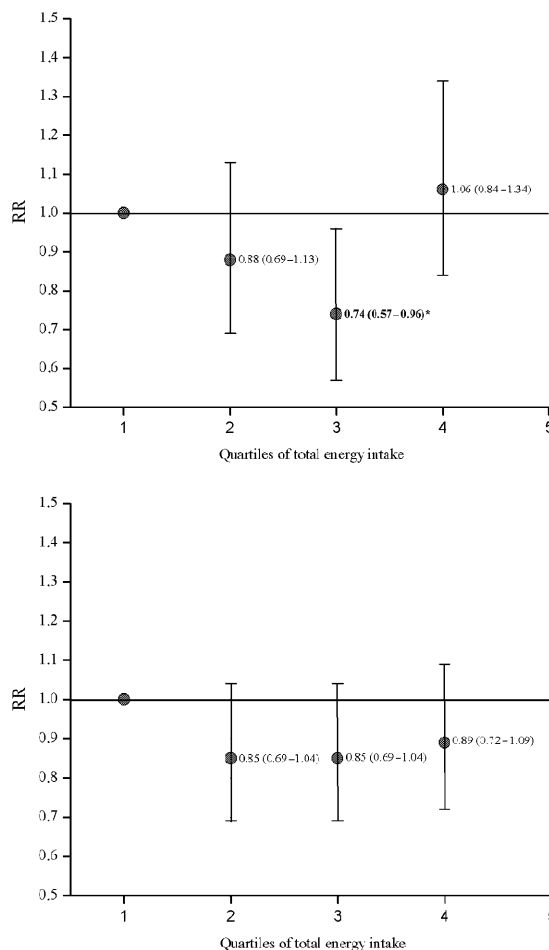


Fig. 1 Relative risk (RR; 95% CI) of total mortality by quartiles of total energy intake (kcal day⁻¹) for women (above) and men (below). Adjusted for age, smoking, alcohol intake, socio-economic status, marital status, leisure time and work-related physical activity and body mass index. * $P = 0.024$.

(RR: 1.31; CI: 0.95–1.80, $P = \text{NS}$), with the first three quartiles having compatible RRs (Fig. 2). Excluding patients with <1 year follow-up or prior history of myocardial infarction, stroke, cancer and diabetes did not change the observed pattern.

Cardiovascular mortality

For women, average calorie consumers in the third quartile had a significantly lower cardiovascular mortality (RR: 0.47; CI: 0.25–0.90, $P = 0.022$), again with the fourth quartile approaching the first quartile in RR (Fig. 3). When looking at cardiovascular mortality for men, a statistically

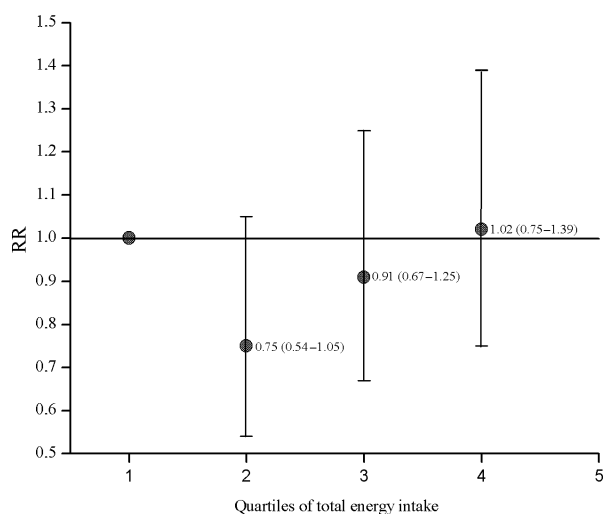
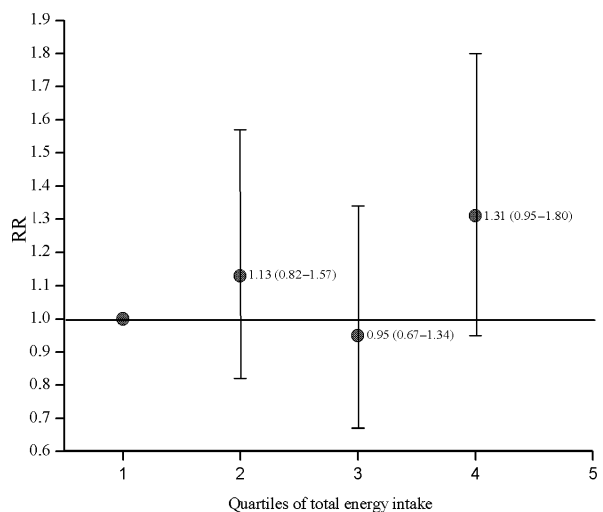


Fig. 2 Relative risk (RR; 95% CI) of cancer mortality by quartiles of total energy intake (kcal day^{-1}) for women (above) and men (below). Adjusted for age, smoking, alcohol intake, socio-economic status, marital status, leisure time and work-related physical activity and body mass index.

significant trend ($P = 0.029$) towards lower mortality from the first to the fourth quartile was observed, with the fourth quartile having the lowest RR (0.66; CI: 0.45–0.97, $P = 0.033$) (Fig. 3). Significance did not hold for women in the third quartile (RR: 0.70; CI: 0.33–1.47) or for men in the fourth quartile (RR: 0.82; CI: 0.50–1.34) after exclusion of subjects with <1 year follow-up or prior history of myocardial infarction, stroke, cancer and diabetes, although the pattern in RR distribution was similar.

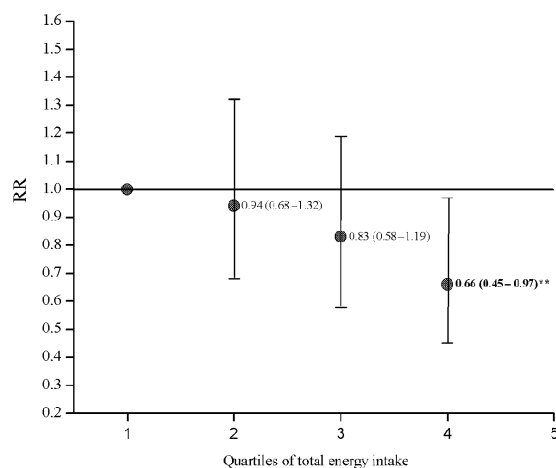
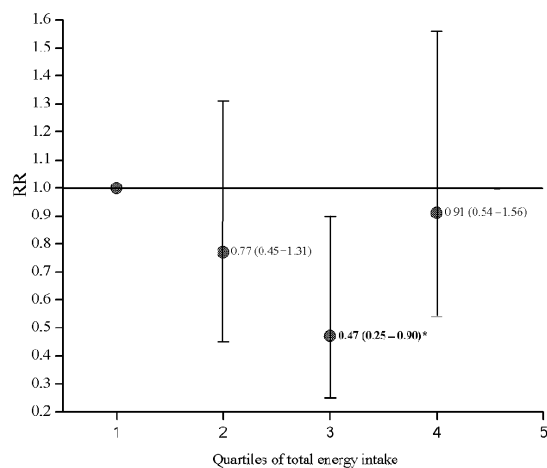


Fig. 3 Relative risk (RR; 95% CI) of cardiovascular mortality by quartiles of total energy intake (kcal day^{-1}) for women (above) and men (below). Adjusted for age, smoking, alcohol intake, socio-economic status, marital status, leisure time and work-related physical activity, body mass index and systolic blood pressure. * $P = 0.022$, ** $P = 0.033$. P -value for downwards trend from first to fourth quartile for men = 0.029.

Discussion

In contrast to our hypothesis, low calorie consumers did on average not have lower relative mortality than average or high calorie consumers. Generally, individuals approximately meeting national recommendations for total EI had the lowest mortality, although statistical significance was not always reached.

The equilibrium between EE and EI is influenced by many factors (Fig. 4). The EE is determined mainly by the basal metabolic rate (BMR), physical activity and involuntary or spontaneous body movements, e.g.

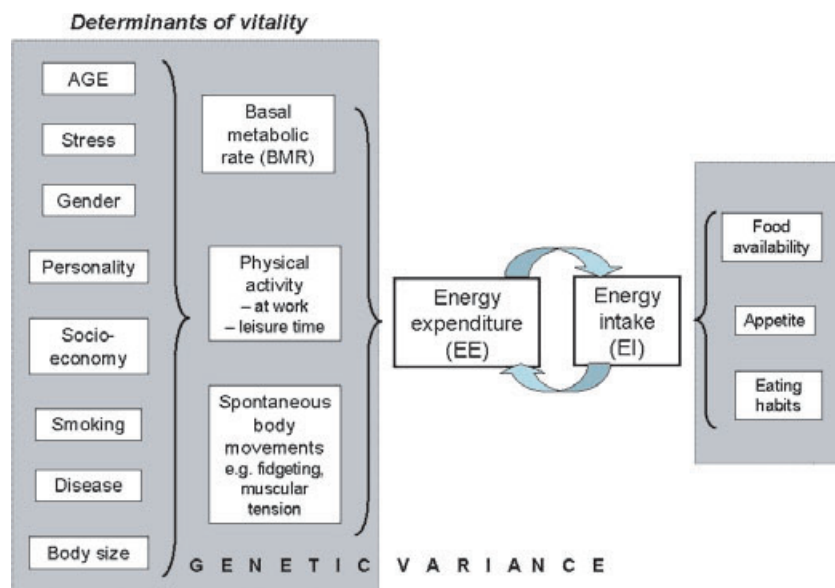


Fig. 4 The complex equilibrium between energy intake (EI) and expenditure (EE). Main determinants of energy expenditure are basal metabolic rate (BMR) and physical activity, both voluntary (at work and leisure time) and spontaneous. Factors influencing these variables are demonstrated to the far left. Genetic variance has influence on all levels.

fidgeting and muscular rigidity [26, 27]. These are in turn influenced by a variety of factors such as age, body size, socio-economic factors and personality. Behavioural and environmental factors can also influence EI directly, for example, by affecting eating habits and food availability. Most of the above-mentioned variables may in addition be affected by genetic variance. The complex interplay between all of these factors ultimately affect the rate of ageing and, hence, vitality.

Changes in these *determinants of vitality*, such as increased age or physical activity, consequently alter the EE and thus affect EI. Changes in EI can, on the other hand, also reversibly affect these determinants in a variety of ways. Increased EI in excess of energy need, for example, undisputedly increases body weight and as such in long-term affects disease incidence [26, 28]. Paradoxically, we have previously shown that spontaneous decrease in body weight in healthy men during adult life increased noncancer mortality after 16 years of follow-up [29]. Decreasing the energy load has been shown to affect ageing and disease incidence in animals [3–5]. Note that the beneficial effects of caloric restriction in animals have usually depended on the intervention being introduced relatively early in life and maintained throughout the lifespan of the animal, with concomitant weight stability [4, 5].

A possible explanation why low calorie consumers in our cohort had relatively higher mortality, might be that they have been and still are ageing faster

than average, with lower vitality and BMRs, diminished energy demand and decreased appetite, resulting in lower daily caloric intakes. If individuals in the first quartiles were ageing prematurely, they might also have had higher prevalence of latent chronic disease, limiting their appetite and thus both decreasing their EI and increasing mortality. As this is an observational study, we have to assume that the low calorie consumers were consuming energy in accordance with their metabolic needs and hence they should have been in energy balance. Intervention studies are needed to elucidate whether deliberate caloric restriction in otherwise healthy subjects can reverse the cause–effect relationship between EI, EE and its determinants, and by that affecting disease risk and longevity.

Subjects in the first quartiles more often had a history of diabetes, myocardial infarction, stroke or cancer and a higher use of antihypertensive medication ($P < 0.001$ for men and women; Tables 3 and 4). The difference was more evident for men, possibly in part explaining the observed downward trend from the first to the fourth quartile of EI on cardiovascular mortality. To our knowledge, no studies have examined the effect of caloric restriction on cardiovascular mortality in humans. However, a few prospective cohort studies evaluating the effect of diet on cardiovascular disease incidence have included EI in their analyses, and most have shown similar results [30–32]. After exclusion of individuals with <1 year follow-up,

prior history of myocardial infarction, stroke, cancer or diabetes, the trend pattern of higher mortality in the first quartiles remained, although the significance disappeared.

Animal studies have repeatedly shown that caloric restriction decreases the incidence and delays the onset of various tumours [33]. A recent retrospective cohort study on the incidence of breast cancer amongst women with a previous diagnosis of anorexia nervosa, showed that these previously calorie restricted women had a significantly lower incidence of breast cancer compared with the general population [34]. Several observational studies have proposed excessive caloric intake being a risk factor for various cancers, although results have not always been conclusive [16, 35]. Our results did not show any statistical difference between quartiles of EI for men or women concerning cancer mortality, although women in the fourth quartile had somewhat higher RR (1.32; CI: 0.96–1.81, $P = \text{NS}$). When interpreting these findings it must be taken into account that the follow-up time was relatively short, subjects were middle-aged at entry and confounding by latent disease cannot be ruled out. The theory that cancer is the result of cumulative oxidative damage throughout life, stresses the need for registration of dietary variables and/or dietary interventions in early life, before the mechanisms of disease progression and possibly, premature ageing, become evident.

In experiments with rodents and nonhuman primates, the calorie-restricted animals have been fed to achieve undernutrition without malnutrition, assuring good diet quality in spite of limited quantity [36]. Also, observational and intervention studies amongst humans on the effect of calorie-restricted diets on mortality, morbidity and longevity usually include relatively healthy diets. Amongst the best-known examples are studies on the inhabitants of the Japanese island of Okinawa, where the island inhabitants have the highest life-expectancy in the world [37, 38]. Apart from being low in calories, the Okinawa diets tend to be rich in vegetables, meat and various vitamins, but very low in sugars and salt [37]. The opposite might be the case in our study, where low calorie diets might instead be coupled to poor diet quality. Individuals in the first quartiles of EI were of lower socio-economic class than individuals in the middle quartiles (women $P < 0.001$, men $P = 0.010$)

and lower social class has been associated with poorer diet quality [39].

Limitations

There are several limitations to our study. First, the participation rate in the MDC Study was quite low (approximately 40%). Hence, the risk of selection bias must be considered when interpreting our results.

Secondly, confounding effects from factors not adjusted for in this study, for example, undetected chronic disease that might diminish appetite and at the same time increase mortality, cannot be ruled out. The diet in MDC was only evaluated at one point in time, and the number of people changing their diet during the follow-up period is unknown.

Thirdly, the follow-up time was relatively short, with mean age at death being 66.5 years and thus only early mortality being observed. Other factors might be of greater importance for death later in life.

Fourthly, dietary measurement errors must be considered. It is well known that underreporting of EI when using self-reported dietary assessment methods is substantial [40, 41]. As the OPEN study showed, such errors can vary considerably between different instruments and thus make it more difficult to adjust for such errors when multiple instruments are used in the same study, as in the MDC Study [42]. Mattisson *et al.* showed that in a subsample of the MDC cohort, 41.6% of the subjects would be classified as underreporters [43], when using a model designed by Black *et al.* including EI, BMR and physical activity [44]. Various adjustment models, which take biomarker measurements such as doubly labelled water and urinary nitrogen into account, have been created to try and elucidate further the effect of misreporting [40, 45]. Although such models were not directly applied in the MDC Study, the dietary assessment instruments used in MDC were validated against weighed food records and urinary nitrogen measurements, showing correlations with r -values in the range of 0.50–0.60 for total EI and energy-adjusted protein intake, which is comparable with the highest observations in similar validation studies [21]. Because of these dietary measurement errors, one might argue that measurements of EE would better evaluate EI than devices that rely on self-reporting. All the same, such methods also involve risk of measurement errors

and are difficult to conduct in large materials. Finally, it is generally agreed that dietary measurement errors have a diluting effect on statistical associations [45]. This fact might have decreased the possibility to find significant statistical relationships between EI and mortality in the present study.

Future implications

Although epidemiological studies such as the current study can give important clues on the relationship between EI and mortality, large-scale randomized-controlled trials are much needed to further evaluate the effect of quality assured low calorie diets on human health. One such study, the Comprehensive Assessment of Long-term Effects of Reducing Intake of Energy (CALERIE) trial is under way [1]. This trial was designed to determine the effects of caloric restriction on physiology, body composition and risk factors for age-related pathologies amongst humans and preliminary results are awaited.

Internationally used nutrition guidelines on total EI are based mainly on data from physiological research on energy metabolism, recommending intakes that approximately match the EE and not based on clinical or epidemiological research concerning the association between EI and disease [22, 46]. Our results might thus contribute to that much needed pool of evidence, although conclusions drawn from epidemiological observations are always limited to statistical associations [47]. To our knowledge, nothing in the current literature, complemented by our findings, does contribute any evidence to suggest that EI guidelines are not safe to follow and should thus in our opinion be used on the individual and clinical level, when providing dietary guidance and advice.

Conclusions

In contrast to our hypothesis, low calorie consumers in our cohort did on average not have lower RRs for mortality than average or high calorie consumers. Generally, individuals approximately meeting national recommendations for total EI had the lowest mortality, thus more or less strengthening the foundation of guidelines on EI used today in most western countries. A possible explanation to our observed result, might be that low calorie

consumers were already ageing prematurely, with lower vitality and BMRs, diminished energy demand and decreased appetite, resulting in lower daily caloric intakes and higher mortality. Whether the beneficial effects of caloric restriction seen in animal studies are indeed applicable to humans, calls for randomized-controlled intervention trials on the effect of calorie restricted quality assured diets on mortality and morbidity.

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Conflict of interest statement

No conflict of interest was declared.

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