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Nutritional status in chronic dialysis patients : associations with development of disease and survival

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The association between body mass index and mortality is similar in the hemodialysis population and the general population at high age and equal duration of follow-up

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ABSTRACT

Background The association of body mass index (BMI) with mortality in hemodialysis patients has been found reversed in comparison to the general population. This study examined the association of BMI with mortality in the hemodialysis population and the general population when age and time of follow-up were made strictly comparable.

Methods Hemodialysis patients who were aged 50 to 75 yr at the start of follow-up were selected from The Netherlands Cooperative Study on the Adequacy of Dialysis-2 (NECOSAD), a prospective cohort study in incident dialysis patients in The Netherlands (n=722, age: 66 ± 7 years, BMI: 25.3 ± 4.5 kg/m²), and compared to adults who were aged 50 to 75 years included in the Hoorn Study, a population-based prospective cohort study in the same country (n=2436, age: 62 ± 7 years, BMI: 26.5 ± 3.6 kg/m²). In both populations, 2- and 7-years standardized mortality rates were calculated for categories of BMI. Adjusted hazard ratios (HR) of BMI categories were calculated with a BMI of 22.5-25 kg/m² as the reference category within each population.

Results In 7 yr of follow-up, standardized mortality rates were approximately 10 times higher in the hemodialysis population than those in the general population. Compared with the reference category, the HR of BMI < 18.5 kg/m² was 2.0 (95% confidence interval [CI]: 1.2 to 3.4) in the hemodialysis population and 2.3 (95% CI 0.7 to 7.5) in the general population. Obesity (BMI ≥ 30 kg/m²) was associated with a HR of 1.2 (95% CI 0.8 to 1.7) in the hemodialysis population and 1.3 (95% CI 0.9 to 2.0) in the general population.

Conclusion A hemodialysis population and a general population with comparable age and equal duration of follow-up showed similar mortality risk patterns associated with BMI. This suggests that there is no reverse epidemiology of BMI and mortality in hemodialysis patients. The clinical implication of the present study is that to improve survival in the hemodialysis population, more attention should be paid to patients who are underweight instead of overweight.

INTRODUCTION

Obesity is one of the established risk factors of cardiovascular disease (CVD) and is associated with increased mortality in the general population.¹⁻⁴ Many survival studies in hemodialysis patients, however, have indicated reverse associations of obesity with all-cause and cardiovascular mortality.⁵⁻¹³ More specific, low values for body mass index (BMI) are associated with increased mortality, whereas higher values for BMI were found to be protective and associated with improved survival in dialysis patients. This paradox has been referred to as 'reverse epidemiology'.^{14,15}

The observation of 'reverse epidemiology' is based on mortality data that were observed in the general population when followed for at least 10 yr.^{1-4,16} However, approximately 4 yr after starting dialysis, only 30% of the hemodialysis patients are still on treatment because of death or drop-out as a result of transplantation.¹⁷ Therefore, short-term mortality in dialysis patients is compared with long-term mortality in the general population. It is widely known that in the general population, overweight increases mortality only after a long-term exposure, whereas underweight is associated with short-term mortality.¹⁸ Studies in the general population with a short time of follow-up (<5 yr) did not detect a significant increase in the mortality risk associated with obesity.¹⁹ Moreover, lower values for BMI were found to be associated with poor survival in the short term in the general population as well. This early mortality is likely to be due to underlying illness at baseline.^{18,19}

In addition, long-term survival data have most frequently been obtained in middle-aged general populations, whereas hemodialysis populations are on average past middle-age.⁽¹⁷⁾ Studies in the general population have documented that the relationship between overweight and all-cause mortality becomes less pronounced with aging, whereas thinness and weight loss are risk factors of mortality in elderly people.^{1,16,20,21} Hence, mortality patterns may differ among different age groups as a result of age-related changes.^{22,23}

The observed 'reverse epidemiology' of baseline BMI and the risk for mortality in the hemodialysis population may be due to differences in duration of follow-up and age at baseline. Therefore, we studied whether the association between BMI and mortality in hemodialysis patients is reversed in comparison with the general population when duration of follow-up and baseline age were made strictly comparable. To that end, a population-based cohort study of Dutch adults in the age range of 50 to 75 was selected to compare with Dutch hemodialysis patients from a prospective cohort study when restricted to the same age and racial group.

METHODS

Study design

The Netherlands Cooperative Study on the Adequacy of Dialysis-2 (NECOSAD) is an observational, prospective follow-up study in which consecutive patients who had end-stage renal disease (ESRD) and started dialysis were enrolled in 38 participating dialysis centers between 1997 and 2004 in The Netherlands. Patients were followed from the start of dialysis at intervals of 6 months until the end of follow-up. For a comparison of the hemodialysis population with the general population, we used the data from the Hoorn Study. Hoorn is a town with 60,000 inhabitants in the northwest part of The Netherlands. The Hoorn Study is a Dutch population-based prospective cohort study of glucose metabolism among 2484 healthy white adults, aged 50 to 75 yr, which started in 1989 and has been described in detail elsewhere.²⁴

Population selection

Patients who had ESRD and were eligible for NECOSAD had to be at least 18 yr of age and had to start with their first renal replacement therapy. The medical ethical committees of all participating dialysis centers approved the NECOSAD study, and all participants gave their written informed consent before inclusion. In this study, patients who started hemodialysis treatment with a recorded weight and height at the initiation of the treatment were included.

A random sample of all inhabitants aged 50 to 75 yr from the population register of the municipality of Hoorn were invited to participate in the Hoorn study. Of the eligible individuals, 71.5% agreed to participate.

For an optimal comparison with the general population, all hemodialysis patients in the age range of 50 to 75 yr were selected for the analyses. Furthermore, the analyses were restricted to white individuals because the BMI mortality relationship may differ between ethnicities.⁶

Data collection

In NECOSAD, baseline demographic data and clinical data such as age, sex, ethnicity, smoking habits, BMI, primary kidney disease, renal function, and comorbidity were collected between 4 weeks before and 2 weeks after the start of chronic hemodialysis treatment. For assessment of renal function, both urea and creatinine were measured in plasma and urine samples from the same day. The glomerular filtration rate (GFR) was calculated as the mean of renal creatinine and urea clearance, adjusted for body surface area (mL/min/1.73 m²). Primary kidney diseases were classified according to the coding system of the European Renal Association – European Dialysis and Transplantation Association (ERA-EDTA).²⁵ Comorbid conditions that were present at baseline were reported by the patients' nephrologists.

In the Hoorn Study, baseline demographic data and information on smoking habits and the presence of diabetes was obtained. Information on prevalent CVD was obtained using a translated version of the Rose questionnaire.²⁶ Serum creatinine level was determined to calculate GFR by the Cockcroft-Gault formula in ml/min per 1.73 m² body surface area. In both cohorts, height and weight were measured at baseline while participants were barefoot and wearing light clothes only, and BMI was calculated as weight (kg) divided by height (m) squared.

Mortality data

In NECOSAD, causes of death were classified according to the coding system of the ERA-EDTA.²⁵ The following codes were classified as death as a result of CVD: 11 myocardial ischaemia and infarction; 12 hyperkalaemia; 14 other causes of cardiac failure; 15 cardiac arrest, cause unknown; 16 hypertensive cardiac failure; 17 hypokalaemia; 18 fluid overload; 22 cerebro-vascular accident; 26 haemorrhage from ruptured vascular aneurysm; 29 mesenteric infarction; and 0 cause of death uncertain / not determined. Survival time was defined as the number of days between the start of the dialysis treatment and the date of death, the date of loss to follow-up, or the end of the follow-up at November 1, 2005, at a maximum of 7 yr (2556.75 days) of follow-up. For calculation of short-term mortality, survival times were censored at a maximum of 2 yr or at the date of leaving the study when this occurred earlier.

In 1995, the follow-up of mortality among participants of the Hoorn Study was started by checking the vital status of all participants in the population registry. Since then, a prospective registration was continued. Causes of death were extracted from the medical records of the general practitioner and the local hospital. Mortality was coded according to the *International Classification of Diseases, Ninth Revision (ICD-9)*.²⁷ Cardiovascular mortality was defined as diseases of the circulatory system (ICD-9 codes 390 to 459) or sudden death (ICD-9 798), because sudden death is in general of cardiovascular origin.²⁸ Of those who had moved out of Hoorn, vital status was checked in the population registers of the cities where the individuals had moved. Survival time was defined as the number of days between the date of inclusion and the date of death or the date of loss to follow-up at a maximum of 7 yr, or at a maximum of 2 yr to represent short-term mortality.

Statistical analysis

For investigation of the shape of the curve of the BMI and mortality relationship, participants were divided into six categories based on their baseline BMI: <18.5, 18.5 to 22.5, 22.5 to 25, 25 to 27.5, 27.5 to 30, and ≥ 30 kg/m². This categorization is in accordance with the World Health Organization classification for

obesity²⁹ with two additional cutoff points at 22.5 and 27.5 kg/m² to allow a more detailed estimation of the association between BMI and mortality. Obesity class I (30 to 34.9 kg/m²), class II (35 to 39.9 kg/m²), and class III (40 kg/m² or higher) were combined into one category.

Absolute mortality rates

The observed survival of both cohorts was computed by the Kaplan-Meier method. Absolute mortality rates were calculated for both populations within each BMI category per 100 person-years of follow-up. Mortality rates were calculated for 2 yr and 7 yr of follow-up and standardized with the direct method. Per BMI category, mortality rates were calculated for 10 categories of 5 yr of age and sex. These mortality rates were standardized to a uniform distribution for both populations (with equal weight for all strata).

Relative mortality risks

Cox regression analysis was used to calculate hazard ratios (HR; equivalent to relative risks of mortality) with 95% confidence intervals (CI) using the BMI category of 22.5 to 25 kg/m² as the reference category within each population. HRs were calculated for a short-term (2 yr) and a long-term (7 yr) follow-up. The crude associations were adjusted for age, sex and smoking. Additional survival analyses were performed excluding mortality in the first 2 yr to study the mortality in the period of 2 to 7 yr after baseline. SPSS 12.0.1 for windows (SPSS, Chicago, IL) was used for all analyses.

RESULTS

Patient characteristics

A total of 799 chronic renal patients in the age range of 50 to 75 yr started hemodialysis treatment between 1997 and 2004; 731 were white. In 9 white patients, data on weight and/or height were missing at the start of dialysis. In this analysis, 722 hemodialysis patients (421 men and 301 women) were included. The mean age (\pm SD) of the patients was 66 yr (\pm 7), and the mean BMI was 25.3 kg/m² (\pm 4.5). When the survival time of this cohort was censored at a maximum follow-up

of 7 yr, the mean follow-up was 2.6 yr (± 1.9). A total of 338 patients died during follow-up, 165 due to CVD (49%), and 121 patients left the study because of a kidney transplantation. Other reasons for censoring during follow-up included recovery of renal function (n=19), moving to a nonparticipating dialysis center (n=30), refusal of further participation (n=73), or other (n=13).

From the 2484 participants of the Hoorn Study, 2436 were 50 to 75 years of age at baseline and had their BMI determined. During 7 yr of follow-up, 226 participants died, 103 (46%) as a result of CVD, and nine participants were lost to follow-up because they moved to an unknown address.

Table 1. Baseline characteristics of all Caucasian subjects of 50 to 75 years selected from NECOSAD (hemodialysis patients) and the Hoorn Study (general population)

	Hemodialysis patients	General population
N	722	2436
Males (%)	58	46
Age (years)	66 \pm 7	62 \pm 7
GFR (ml/min/1.73 m ²) ^a	4.9 \pm 3.2	70.4 \pm 12.7
BMI (kg/m ²)	25.3 \pm 4.5	26.5 \pm 3.6
Diabetes mellitus (%) ^b	24	10
Cardiovascular disease (%) ^c	45	16
Current smoker (%)	26	32
Primary kidney disease (%)		
Diabetes mellitus	16	-
Glomerulonephritis	9	-
Renal vascular disease	22	-
Other	54	-

Values expressed as n, (%) or mean \pm SD

GFR=Glomerular filtration rate corrected for body surface area, BMI=Body mass index

^aUrea and creatinine clearance in NECOSAD and Cockcroft-Gault in Hoorn Study

^bReported by patients' nephrologists in NECOSAD and oral glucose test in Hoorn Study

^cReported by patients' nephrologists in NECOSAD and self-reported in Hoorn Study

Baseline characteristics of the two populations are shown in Table 1. The distribution of individuals per BMI category showed a shift towards the lower BMI categories in the hemodialysis population as compared with the general population (Figure 1). The 7-yr all-cause mortality was 76.0% in the hemodialysis population and 9.3% in the general population (Figure 2).

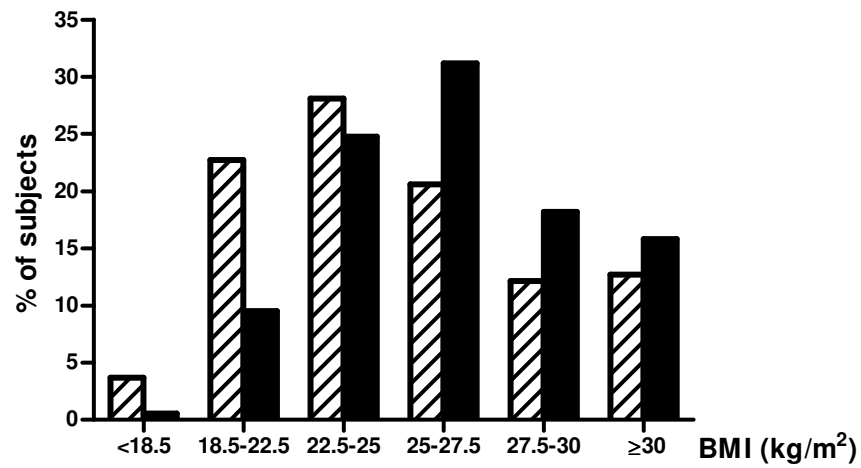


Figure 1. Distribution of subjects (in percentages) in the hemodialysis population (shading) and the general population (black) per category of BMI at baseline.

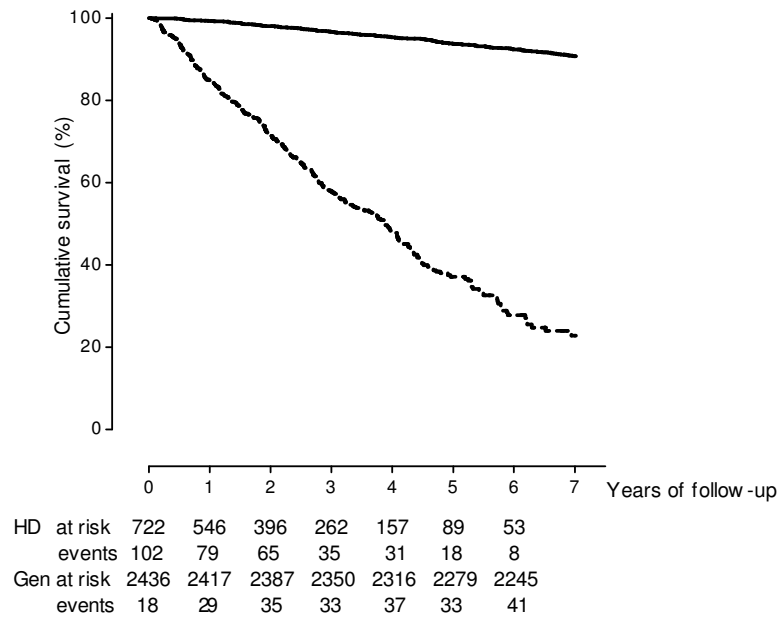


Figure 2. Cumulative survival in the hemodialysis (HD, - -) and the general (Gen, —) population. Numbers at risk and numbers of events are shown per year of follow-up.

Absolute mortality rates

Overall, the crude mortality rate was 18.0 per 100 person-years in the hemodialysis population and 1.4 per 100 person-years in the general population. Within each BMI category, the crude mortality rates were a factor of 10 higher in the hemodialysis population than in the general population (Table 2).

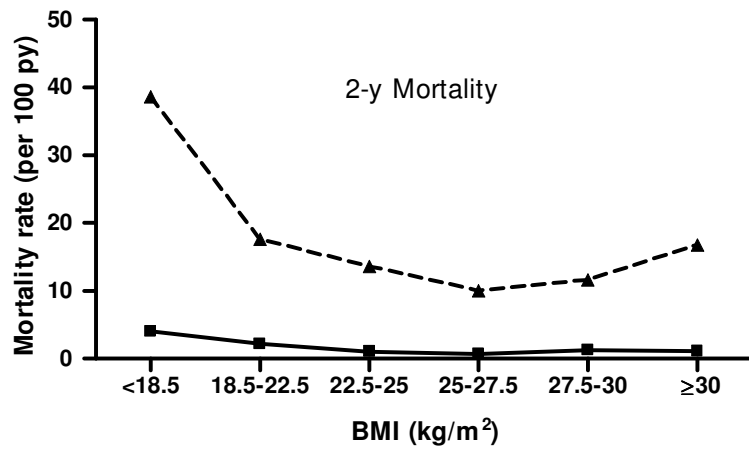
Table 2. Crude mortality rates per BMI category in seven years of follow-up

Variable	BMI (kg/m ²)					
	<18.5	18.5-22.5	22.5-25	25-27.5	27.5-30	≥ 30
Hemodialysis population (NECOSAD)						
Person-years (py)	49	403	550	403	237	233
Deaths from all causes	18	85	90	66	34	45
Deaths from CVD ^a	7	41	44	38	18	17
Deaths from all causes /100 py	36.7	21.1	16.4	16.4	14.3	19.3
Deaths from CVD/100 py	14.3	10.2	8.0	9.4	7.6	7.3
General population (Hoorn Study)						
Person-years (py)	75	1524	4050	5145	2967	2560
Deaths from all causes	3	29	56	51	43	44
Deaths from CVD ^b	1	8	29	23	20	22
Deaths from all causes /100 py	4.0	1.9	1.4	1.0	1.4	1.7
Deaths from CVD/100 py	1.3	0.5	0.7	0.4	0.7	0.8

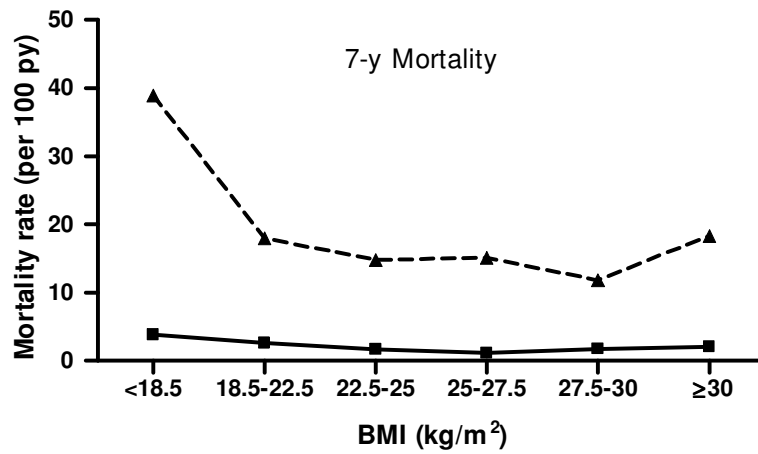
^aCardiovascular mortality according to the ERA-EDTA coding system

^bCardiovascular mortality according to the ICD-codes 390-459 or 798

The crude cardiovascular mortality rate in the highest BMI category in the hemodialysis population (7.3 per 100 person-years) was slightly lower than in the BMI category of 22.5 to 25 kg/m² (8.0 per 100 person-years), which was not the case in the general population (0.8 per 100 person-years and 0.7 per 100 person-years, respectively). Overall, mortality rates in the highest BMI categories were increased in both populations compared with the BMI category of 22.5 to 25 kg/m². Furthermore, within each population, the short-term (2 yr) and long-term (7 yr) mortality rates were similar, and subsequent results are given for 7-yr all-cause mortality.



A.



B.

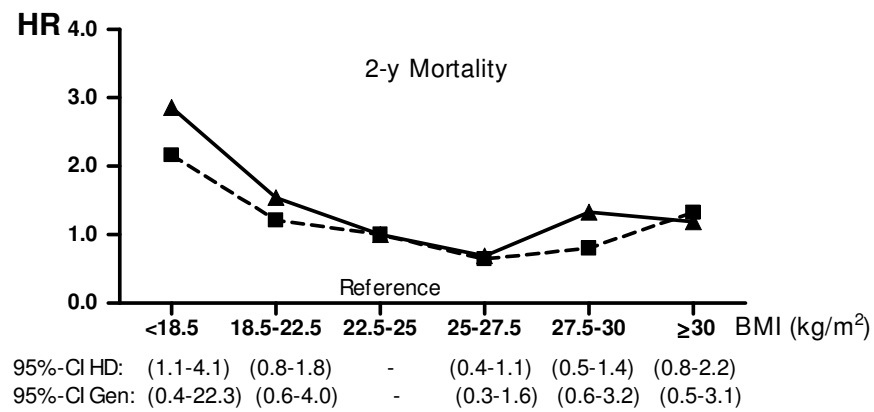
Figure 3. Age and sex standardized mortality rates (per 100 person years, py) in categories of baseline BMI in Caucasian subjects from the hemodialysis population (---) and the general population (—), aged 50 to 75 years, in two years (A) and seven years (B) of follow-up.

After standardization for age and sex, the 7-yr mortality rates in the hemodialysis population were increased from 6.8 times (category of 27.5 to 30 kg/m²) to 13.5 times (category of 25 to 27.5 kg/m²) as compared with the general population (Figure 3). Within the category of BMI<18.5 kg/m², the standardized mortality rate in the hemodialysis population of 38.9 per 100 person-years was 10.1 times higher than the standardized mortality rate in the general population (3.8 per 100 person-years). However, not all age and sex combinations had patients at risk within this category. Joining the BMI categories of BMI<18.5 kg/m² and 18.5 to 22.5 kg/m² in one analysis showed that the 7-yr age and sex standardized mortality rate was 7.3 times increased in the hemodialysis population (19.5 per 100 person-years) as compared with the general population (2.7 per 100 person-years), which is consistent with the other BMI categories.

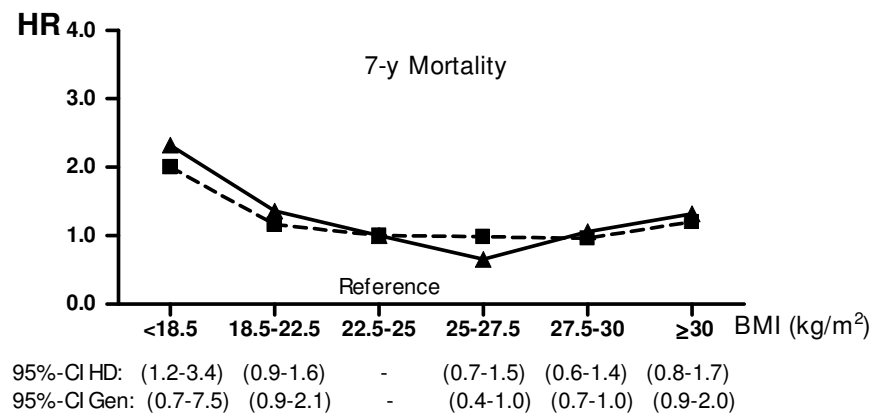
Relative mortality risks

The HRs for all-cause mortality per BMI category were calculated relative to the reference category within each population and adjusted for age, sex and smoking (Figure 4). In 7 yr of follow-up, the adjusted mortality risk in hemodialysis patients with BMI<18.5 kg/m² was increased (HR 2.00; 95% CI 1.18 to 3.39) as compared with patients with a BMI of 22.5 to 25 kg/m². The mortality risk in patients with a BMI≥30 kg/m² was similar to that of the reference category (HR 1.20; 95% CI 0.83 to 1.74).

In the general population, the 7-yr adjusted HR that was associated with a BMI<18.5 kg/m² was 2.32 (95% CI 0.72 to 7.45), and with a BMI≥30 kg/m², it was 1.32 (95% CI 0.87 to 1.98), compared with the reference category. In the patients who survived the first 2 yr of dialysis, the adjusted HR for a BMI<18.5 kg/m² in the hemodialysis population was 1.68 (95% CI 0.65 to 4.29), and it was 2.10 (95% CI 0.51 to 8.70) in the general population.



A.



B.

Figure 4. Relative mortality risks (HR) of baseline BMI, adjusted for age, sex and smoking, in Caucasian subjects from the hemodialysis population (-) and the general population (—), aged 50 to 75 years, in two years (A) en seven years (B) of follow-up. A BMI of 22.5-25 kg/m² was chosen as the reference category. 95%-CI=95% confidence intervals.

DISCUSSION

The term ‘reverse epidemiology’ has been widely used to describe the association between BMI and mortality in hemodialysis patients, defined as opposite directions of associations of traditional risk factors in the hemodialysis population and the general population.^{14,15,30,31} Our study examined the association between BMI and mortality in Dutch white hemodialysis patients of 50 to 75 yr of age and in the Dutch general population of the same age range when both populations were followed for an equal duration. The relative mortality patterns that were associated with BMI categories were similar and not reversed, showing that a low BMI but not a high BMI was associated with an increased mortality risk as compared with a normal BMI.

In addition, our analyses showed that the absolute all-cause and cardiovascular mortality rates in the hemodialysis population were approximately 10 times those of the general population, which is in accordance with earlier reports.³² The overall crude mortality rate in our hemodialysis population of 18 per 100 person-years was in line with mortality rates reported in the Dialysis Outcomes and Practice Patterns Study (23 per 100 person-years in the US sample and 13 per 100 person-years in the European sample).⁸

One strength of the present study is that the two populations were compared for equal durations of follow-up. In a hypothesis-generating review, relative risks that were found in the prevalent US hemodialysis population were compared with relative risks from the US general population. The authors concluded a reverse epidemiology of obesity in dialysis patients compared with the general population.¹⁴ However, the association in the US general population was calculated over 14 yr of follow-up, whereas the hemodialysis population had been followed for a maximum of 4 yr. The comparison of short-term survival data from a prevalent hemodialysis cohort with a long-term J-shaped relation from the US general population may not be valid because the long-term effect of BMI differs from the short-term effect.^{22,23} Indeed, in the general population early mortality can be observed among lean

individuals in a short period of follow-up¹⁸, whereas obesity is particularly associated with an increased mortality risk after a long period of follow-up.^{1,20}

Another strength of our study is that we were able to compare a cohort of hemodialysis patients to the general population within the same age range. The relationship between BMI and mortality has been found to vary by age at baseline²² and seems to be less pronounced in older than in younger populations.³⁴ One of the explanations is a different body composition as body height diminishes, fat mass redistributes, and fat-free mass decreases with ageing.³⁴⁻³⁶ Within the age range of 50 to 75 yr, there were relatively more hemodialysis patients in the lower BMI categories compared with the general population. Similar to other studies, when stratified for age and sex, hemodialysis patients had a lower mean BMI in all age and sex groups than did individuals from the general population.^{7,12} However, it is unlikely that this affected the mortality rates within each BMI category.

Smoking is known to modify the effect of BMI on mortality in the general population.^{37,38} Failure to control for smoking produces an artifactually high mortality in lean individuals.^{1,3} The obesity-related mortality therefore is underestimated when the mortality of obese and lean subjects is compared.¹⁹ In this study, it was not possible to stratify according to smoking habits, but the proportion of current smokers was similar in both populations. Adjustment for smoking slightly reduced the mortality risk in lean individuals in both populations but did not substantially alter the overall associations.

In this study, we were unable to confirm a survival advantage of obesity in the hemodialysis patients, which has been reported in overweight and obese hemodialysis patients.⁵⁻¹² Even when restricting to 2-yr mortality, or extending to hemodialysis patients in the age range of 18 to 100 yr (n=1225, data not shown), we could not establish a survival advantage in the obese. We realize that most studies on BMI and mortality have been performed in US patient populations with a different prevalence and distribution of BMI, which might explain the discrepancy with the findings in the Dutch population. In this study, it was not possible to explore mortality risks for BMI \geq 40 kg/m², because less than 1% of both the Dutch

hemodialysis population and the general population was in this category. Also, differences in race might explain discrepant findings between the US and Dutch population.^{6,39,40}

This study has potential limitations that are inherent in a comparison of two different cohorts. Information on comorbidity at baseline had been collected differently in both cohorts. We did not adjust for comorbidity at baseline because this would affect the comparability of the two populations. After exclusion of mortality in the first 2 yr from the analyses, as a proxy for adjustment for important comorbidity at baseline, the relative mortality risks that were associated with lean individuals were reduced in both populations, but the overall associations stayed in the same directions. Furthermore, we realize that BMI might not be an optimal predictor of outcome. Several studies in the dialysis population suggest that lean body mass is a better predictor of outcome than BMI, but results are inconsistent.^{6,11,41,42} The different components of body composition should be explored further in relation to mortality in hemodialysis patients.

A recent analysis of representative samples of the US general population suggested that the impact of obesity on mortality may have decreased over time.⁴³ However, relative risks for death in each sample were calculated during different periods of follow-up. A secondary analysis of the prospective cohort of the Cancer Prevention Study II found that overweight and obesity are significant predictors of death from any cause during 20 yr of follow-up until calendar year 2002 and concluded that there was no evidence that the magnitude of the association between obesity and mortality is decreasing over time.⁴⁴

One of the hypotheses to explain why low rather than high BMI is associated with an increased mortality risk is that there are time discrepancies between competing risk factors.¹⁴ This study supports the idea that there may be discrepancies between short-term and long-term mortality effects of a single risk factor, BMI. The association of overweight with long-term mortality in the general population is considered causal. In our populations, we could not detect an increased mortality risk of obesity during 7 yr of follow-up. A possible explanation is that a follow-up of

7 yr is still too short for obesity to result in increased mortality. A recent analysis in more than 300,000 middle-aged adults who had been followed for 15 to 35 yr showed that high BMI was associated with increased risks for the development of ESRD as well as of mortality.⁴⁵ This suggests that in the very long term, BMI might also be a risk factor of mortality in patients with ESRD. Increased short-term mortality that is associated with thinness is, however, is most likely due to illness at baseline.^{18;22} Underweight may be a consequence of disease and thus an indicator of early mortality. This is known as reverse causation. It is interesting that in our analyses, individuals with a low BMI in both populations had a mortality risk that was twice as high as that in individuals with a BMI within the normal range, suggesting reverse causation in both populations. However, no reverse epidemiology was observed as the BMI-mortality patterns were similar in both populations.

The clinical implication of this study is that to improve survival in the hemodialysis population, more attention should be paid to patients who are underweight instead of overweight. Weight loss as a consequence of disease may induce the early mortality that is associated with a low BMI.^{18;20;46} Recently, it was shown that weight loss in the hemodialysis population was associated with increased cardiovascular and all-cause death.¹³ Furthermore, the 'malnutrition-inflammation-cachexia syndrome' has been proposed to explain the increased mortality risk of low BMI in the hemodialysis population.^{14;15;30;47} Indeed, this syndrome might represent the cachectic status of the patients and be an indicator of early mortality in the hemodialysis population. However, in a large database analysis, low BMI remained associated with an increased mortality risk even after extensive adjustment for surrogates of malnutrition and inflammation¹³, suggesting that malnutrition and inflammation may not completely explain the increased risk that is associated with a low BMI. Factors that are associated with a low BMI and weight loss should be explored further in the hemodialysis population.

In conclusion, the absolute mortality rates within each BMI category were strongly increased in the white hemodialysis population as compared with the general population. However, the association between BMI and mortality was not reversed

compared with the general population of equal baseline age and duration of follow-up. On the basis of our results, effects of duration of follow-up and age should be taken into account for a valid interpretation of the association between BMI and mortality in the hemodialysis population.

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