

International Comparison of the Relationship of Chronic Kidney Disease Prevalence and ESRD Risk

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ESRD incidence is much lower in Europe compared with the United States. This study investigated whether this reflects a difference in the prevalence of earlier stages of chronic kidney disease (CKD) or other mechanisms. CKD prevalence in Norway was estimated from the population-based Health Survey of Nord-Trøndelag County (HUNT II), which included 65,181 adults in 1995 through 1997 (participation rate 70.4%). Data were analyzed using the same methods as two US National Health and Nutrition Examination Surveys in 1988 through 1994 ($n = 15,488$) and 1999 through 2000 ($n = 4101$). The primary analysis used gender-specific cutoffs in estimating persistent albuminuria for CKD stages 1 and 2. ESRD rates and other relevant data were extracted from national registries. Total CKD prevalence in Norway was 10.2% (SE 0.5): CKD stage 1 (GFR >90 ml/min per 1.73 m² and albuminuria), 2.7% (SE 0.3); stage 2 (GFR 60 to 89 ml/min per 1.73 m² and albuminuria), 3.2% (SE 0.4); stage 3 (GFR 30 to 59 ml/min per 1.73 m²), 4.2% (SE 0.1); and stage 4 (GFR 15 to 29 ml/min per 1.73 m²), 0.2% (SE 0.01). This closely approximates reported US CKD prevalence (11.0% in 1988 through 1994 and 11.7% in 1999 through 2000). The relative risk for progression from CKD stages 3 or 4 to ESRD in US white patients compared with Norwegian patients was 2.5. This was only modestly modified by adjustment for age, gender, and diabetes. Age and GFR at start of dialysis were similar, hypertension and cardiovascular mortality in the populations were comparable, but US white patients were referred later to a nephrologist and had higher prevalence of obesity and diabetes. In conclusion, CKD prevalence in Norway was similar to that in the United States, suggesting that lower progression to ESRD rather than a smaller pool of individuals at risk accounts for the lower incidence of ESRD in Norway.

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There has been a dramatic rise in the number of patients with ESRD in both Europe and North America during the past decades. There is significant disparity, however, in ESRD incidence rates between the two continents: Incidence rates are three times higher in the United States compared with Norway and Great Britain (1,2). Data on the prevalence of chronic kidney disease (CKD) in Europe are limited, making it unclear whether the higher ESRD incidence in the United States reflects a higher burden of all stages of CKD (3,4).

The relationship between the prevalence of earlier stages of CKD and the incidence of ESRD is complex (5–9): US CKD prevalence has been relatively stable in the past decade, whereas ESRD incidence has increased significantly, and US black patients have a three times higher incidence of ESRD

despite similar prevalences of CKD. This can be due to differences in other mechanisms, such as more rapid progression or greater initiation of dialysis. Early stages of CKD also result in a higher risk for complications, cardiovascular disease, and mortality, which pose a larger absolute risk than ESRD. Furthermore, identifying and treating individuals with early stages of CKD is increasingly proposed for prevention of ESRD and cardiovascular disease (9,10). This requires solid documentation of a high prevalence of preclinical disease. Thus far, European studies on CKD prevalence have been hampered by selection bias or incomplete data for defining CKD stages (11–13).

Therefore, there is a need for more information on the prevalence of CKD in European populations as well as a better understanding of the relationship of CKD prevalence to ESRD incidence. The second Health Survey of Nord-Trøndelag County (HUNT II) is a large, population-based, cross-sectional study that was conducted in central Norway with a high participation rate (14). We used HUNT II data to assess the prevalence of CKD using calibrated serum creatinine values and repeated measurements of albuminuria. Combining these prevalence estimates with available information on ESRD, health

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care, and population characteristics, we also examined the extent to which the low incidence of ESRD in Norway compared with the United States reflects a difference in the earlier stages of CKD between the two countries.

Materials and Methods

During August 1995 through July 1997, a large-scale general health survey was conducted in Nord-Trøndelag County, Norway (HUNT II). Every individual who was 20 years or older and residing in the county ($n = 92,939$) was invited, and 70.4% of this total adult population participated. The survey comprised an extensive questionnaire and a brief clinical examination, including analysis of serum creatinine in all participants and urine albumin in a subgroup. The population in Nord-Trøndelag is stable (net out migration of 0.3% per year) and ethnically homogeneous (97% white). Nord-Trøndelag County is located in central Norway, and it is representative regarding geography, economy, industry, morbidity, and total and cardiovascular mortality (15). The age and gender distribution of Nord-Trøndelag County is identical to Norway, but the participation rate in HUNT II was strongly age dependent. Participation rate was highest in the age group 60 to 69 yr (86%) and declined toward 50% in the youngest as well as the oldest age groups (14). A more detailed description on objectives, contents, and methods (including reasons for nonparticipation) in HUNT II has been given elsewhere (14). All participants signed an informed consent, and additional permissions were obtained from the Regional Ethics Review Committee and the National Data Inspectorate.

Data Collected

The participants self-reported health status, family history, socioeconomic status, and medication use. The clinical examination included measurement of height, weight, and BP. Three consecutive standardized BP measurements were recorded in the sitting position using an automatic oscillometric method (Dinamap 845XT; Criticon, Tampa, FL). Participants were classified as hypertensive when the mean of the two last measurements was ≥ 140 mmHg systolic or ≥ 90 mmHg diastolic or when they reported taking antihypertensive medication (16). Participants were classified as having diabetes when they reported having diabetes ("sugar disease") or when they were found to have venous plasma glucose ≥ 200 mg/dl (11.2 mmol/L) 2 h or more after the last meal (17).

Laboratory Investigations

Blood was drawn, often in the nonfasting state, from all participants, and fresh serum and urine samples were analyzed within 2 d at the Central Laboratory of Levanger Hospital on a Hitachi 911 Autoanalyzer (Mito, Japan). Glucose was measured by means of an enzymatic hexokinase method, cholesterol by an enzymatic calorimetric cholesterol esterase method, and serum creatinine by a kinetic Jaffe method with water blank using reagents from Roche (Roche Diagnostics, Mannheim, Germany). Day-to-day coefficients of variation were 1 to 2% for all analyses. There was no drift in mean serum creatinine over time when the entire population was examined (-0.001 mg/dl per month [-0.1 $\mu\text{mol/L}$]). Local serum creatinine cutoffs for abnormality (97.5th percentile) were 1.30 mg/dl (115 $\mu\text{mol/L}$) for women and 1.50 mg/dl (133 $\mu\text{mol/L}$) for men.

A 5% random sample of the total population was included for screening of albuminuria. Participants delivered urine samples for analysis on three consecutive mornings, and those who reported urine infection during the previous week or menstruation at time of collection were excluded. Urine albumin was measured by an immunoturbidimetric method (anti-human serum albumin; Dako AS, Glostrup,

Denmark), and urine creatinine was measured with the Jaffe method. The albumin-to-creatinine ratio (ACR) was used as an expression for urine albumin excretion. We used similar cutoffs as in previous analysis of the Third National Health and Nutrition Examination Survey (NHANES III) study (18): Participants with two or three ACR determinations that ranged from 17 to 250 mg/g (1.9 to 28.3 mg/mmol) for men and 25 to 355 mg/g (2.8 to 40.2 mg/mmol) for women were classified as having persistent microalbuminuria, and participants with one or more samples above the microalbuminuric range were classified as having macroalbuminuria.

GFR Estimation

GFR was estimated with the new re-expressed four-variable Modification of Diet in Renal Disease (MDRD) formula for isotope dilution mass spectrometry (IDMS) traceable serum creatinine values: $\text{GFR} = 175 \times (\text{serum creatinine})^{-1.154} \times \text{age}^{-0.203} (\times 0.742 \text{ if female}) (\times 1.21 \text{ if black})$ (19). The Jaffe method used for analyzing HUNT II samples in 1995 through 1997 was switched to an enzymatic creatinine test (CREA Plus; Roche Diagnostics) in 2003. Two hundred samples from the HUNT II study were thawed and reanalyzed to ensure stability of the Jaffe method over time (mean difference 0.018 mg/dl [1.6 $\mu\text{mol/L}$]; $r^2 = 0.994$), and a recalibration of the Jaffe assay in HUNT II to the enzymatic method was established: Serum creatinine (mg/dl, enzymatic) = $-0.31 + 1.11 \times \text{serum creatinine (mg/dl, Jaffe)}$. This enzymatic method was the same as used for recalibrating the original MDRD creatinine values to the IDMS level (19), and the method also was found to be comparable to the IDMS level in the Nordic Reference Interval Project (20). The resulting GFR estimates also were found to be unbiased at all ages in the general population (21).

To unmask analytical bias in our comparisons of the HUNT II and NHANES III studies, we also compared estimated GFR (eGFR) in a subgroup of healthy, low-risk participants in HUNT II with a corresponding group in NHANES III. Participants who were included fulfilled the criteria that would make them eligible for kidney donation: No hypertension, no diabetes, no macroalbuminuria, good or excellent general health, and a normal serum creatinine. For all age groups (10 yr), mean GFR differed by 0 to 3 ml/min per 1.73 m², indicating minimal calibration bias between the two studies. Additional analyses were performed with the original four-variable MDRD formula (22) with an indirect recalibration of our creatinine values to the same level as used when developing the MDRD formula (23). This indicated a 3- to 7-ml/min per 1.73 m² difference between the two studies; we therefore used the new MDRD formula for analysis unless otherwise stated.

Statistical Analyses

Stage 1 CKD was defined as an eGFR ≥ 90 ml/min per 1.73 m² and either macroalbuminuria or persistent microalbuminuria. Stage 2 CKD was eGFR 60 to 89 ml/min per 1.73 m² and either macroalbuminuria or persistent microalbuminuria. Stages 3 through 5 CKD were classified according to the level of kidney function (eGFR 30 to 59, 15 to 29, and < 15 ml/min per 1.73 m², respectively), regardless of the presence of other markers of kidney damage (9). Participants with stage 5 CKD were excluded because of the small number of participants, and nonparticipation rates caused by related illness would be expected to be particularly high, biasing downward these prevalence estimates. Microalbuminuria was defined using gender-specific cutoffs in the primary analysis with additional results presented for non-gender-specific cutoffs.

Statistical analyses were performed using SPSS version 12.0.1 (SPSS Inc., Chicago, IL). Descriptive statistics were used to characterize variables, to calculate prevalence estimates, and for stratification of the

HUNT II data. When odds ratios (OR) in various strata were homogeneous, the Mantel-Haenszel common OR estimate was used. A logistic regression model for prevalence of CKD stages 3 to 4 was fitted to the data to predict prevalence in various subgroups. Linearity in age was checked, and significant interactions were accounted for by using separate models.

HUNT prevalence estimates were age and gender standardized by the direct method to the Norway 1996 or US 1991 populations as appropriate (24). US prevalence estimates were obtained from the published literature (6,25), with the exception of some subgroup analyses that were obtained directly from the authors (J.C. and B.C.A., personal communication, February 2005). An ecologic estimate for risk for progression from CKD stages 3 or 4 to ESRD was calculated by dividing the annual ESRD incidence rate among individuals who were older than 20 yr by the number of patients who had CKD and were at risk.

Results

Participants in HUNT II had a mean age of 50.2 yr, and 10.0% were 75 yr or older. They were characterized by the following renal and cardiovascular risk factors: The prevalence of diabetes was 3.4%; BP was ≥ 140 systolic or ≥ 90 diastolic in 44.4%, and 11.0% were on antihypertensive medication; 33% reported daily smoking; the mean cholesterol level was 5.9 mmol/L; 8% reported having angina pectoris, previous myocardial infarction, or previous stroke; obesity, defined as body mass index (BMI) > 30 kg/m², was present in 15.9%, and morbid obesity (BMI > 40) was found in 0.7%. Serum creatinine was analyzed in 65,181 (99.4%) participants. Values above normal levels (1.30 mg/dl [115 μ mol/L] for women and 1.50 mg/dl [133 μ mol/L] for men) were found in 0.1% of participants at ages 20 to 39 yr,

0.5% at ages 40 to 59, 2.1% at ages 60 to 69, and 6.2% at ages ≥ 70 yr.

Table 1 presents the prevalence of normal and decreased kidney function in the HUNT II study by demographics and clinical characteristics. The prevalence of mildly decreased (eGFR 60 to 89 ml/min per 1.73 m²), moderately decreased (eGFR 30 to 59 ml/min per 1.73 m²), and severely decreased kidney function (eGFR 15 to 29 ml/min per 1.73 m²) were 38.6, 4.5, and 0.2%, respectively (45.1, 4.7, and 0.2% using the original four-variable equation). Older age was very strongly associated with decreased kidney function: The prevalence of eGFR < 60 ml/min per 1.73 m² was 50 to 100 times higher in the oldest compared with the youngest group. Hypertensive individuals had five-fold higher prevalence compared with nonhypertensive individuals, but adjustment for age reduced the OR to 1.5 (95% confidence interval [CI] 1.3 to 1.6). Similarly, individuals with diabetes had 1.5 (95% CI 1.3 to 1.7) higher odds for CKD than individuals without diabetes after adjustment for age. Gender-specific prevalence was only slightly confounded by age, with an adjusted OR in women compared with men of 1.5 (95% CI 1.4 to 1.6).

Table 2 gives the prevalence of CKD in the HUNT II study as based on the Kidney Disease Outcomes Quality Initiative classification system. CKD stages 1 and 2 require macroalbuminuria or persistent microalbuminuria as well as normal (≥ 90 ml/min per 1.73 m²) or only mildly decreased eGFR (60 to 89 ml/min per 1.73 m²), respectively. Albuminuria was measured at three visits in a randomly selected subgroup ($n = 3270$), with a 77.2% response rate, whose characteristics were similar to the

Table 1. Prevalence of normal and decreased kidney function in the HUNT II study by demographics and clinical characteristics (Norway, 1995 to 1997)^a

	Overall		Prevalence of eGFR Category (ml/min per 1.73 m ²)			
	No. of Participants	% of Study Population	≥ 90	60 to 89	30 to 59	15 to 29
Total	65,181	100	56.7 (0.2)	38.6 (0.2)	4.5 (0.1)	0.16 (0.01)
Gender						
male	30,480	46.8	62.4 (0.3)	34.0 (0.3)	3.4 (0.1)	0.17 (0.02)
female	34,701	53.2	51.6 (0.3)	42.7 (0.3)	5.5 (0.1)	0.16 (0.02)
Age (yr)						
20 to 39	20,190	31.0	82.5 (0.3)	17.3 (0.3)	0.2 (0.03)	0.02 (0.01)
40 to 59	24,666	37.8	58.2 (0.3)	40.4 (0.3)	1.4 (0.1)	0.02 (0.01)
60 to 69	9,040	13.9	36.7 (0.5)	56.9 (0.5)	6.1 (0.3)	0.22 (0.05)
> 70	11,285	17.3	23.2 (0.4)	58.1 (0.5)	17.9 (0.4)	0.71 (0.07)
Diabetes ^b						
no	62,554	96.6	57.6 (0.2)	38.2 (0.2)	4.0 (0.1)	0.12 (0.01)
yes	2,174	3.4	35.9 (1.0)	49.4 (1.1)	13.6 (0.8)	0.83 (0.2)
Hypertension ^c						
no	35,636	55.2	67.2 (0.3)	30.9 (0.3)	1.8 (0.1)	0.10 (0.01)
untreated	21,784	33.7	50.0 (0.3)	44.7 (0.4)	5.2 (0.2)	0.13 (0.02)
treated	7,191	11.1	28.2 (0.5)	55.6 (0.6)	15.5 (0.4)	0.61 (0.1)

^aData are % (SE), except where indicated. HUNT II, Health Survey of Nord-Trøndelag County.

^bSelf-reported diabetes or venous plasma glucose ≥ 200 mg/dl (11.2 mmol/L).

^cSystolic BP ≥ 140 mmHg or diastolic BP ≥ 90 mmHg or taking antihypertensive medication.

Table 2. Prevalence of CKD stages 1 through 4 in the HUNT II study as based on kidney function and albuminuria (Norway, 1995 to 1997)^a

Kidney Function		Albuminuria within Each Level of eGFR ^b		CKD	
eGFR (ml/min per 1.73 m ²)	Prevalence	Microalbuminuria	Macroalbuminuria	Stage	Prevalence in HUNT
≥90	56.7 (0.2)	4.9 (0.6)	0.5 (0.2)	1	3.1 (0.3)
60 to 89	38.6 (0.2)	8.2 (0.8)	0.6 (0.2)	2	3.4 (0.4)
30 to 59	4.5 (0.1)	21.0 (3.7)	5.6 (2.1)	3	4.5 (0.1)
15 to 29	0.16 (0.01)	^c	^c	4	0.16 (0.01)
Total	100.0				11.2 (0.5)

^aData are % (SE). CKD, chronic kidney disease; eGFR, estimated GFR.

^bAlbuminuria was measured in three urine samples from a random sample of 3270 individuals. Two or three albumin-to-creatinine ratio (ACR) determinations ranging from 17 to 250 mg/g (1.9 to 28.3 mg/mmol) for men and 25 to 355 mg/g (2.8 to 40.2 mg/mmol) for women were classified as persistent microalbuminuria. Patients with one or more samples above the microalbuminuric range were classified as having macroalbuminuria.

^cCells with fewer than 5 observations.

other individuals (gender, age, diabetes, hypertension, cardiovascular disease, cholesterol, smoking, BMI, eGFR; $P > 0.45$ for all comparisons). Persistence was defined as the presence of albuminuria in two or more urine samples, and its prevalence at each eGFR range was applied to the proportion of individuals with eGFR in that range. The overall prevalence of CKD stages 1 through 4 was 11.2% (11.5% using the old four-variable MDRD formula with indirect recalibration of creatinine values). The prevalence for CKD stages 3 and 4 by age, gender, hypertension, and diabetes was estimated using stratified logistic regression models. The prevalence was equal to $1/[1 + \exp(-\text{Logit})]$, where $\text{Logit} = -11.01 + 0.117 \times \text{age} (+0.71 \text{ if diabetes present})$ for nonhypertensive men; $\text{Logit} = -9.079 + 0.095 \times \text{age} (+0.302 \text{ if diabetes present})$ for hypertensive men; $\text{Logit} = -8.728 + 0.091 \times \text{age} (+0.678 \text{ if diabetes present})$ for nonhypertensive women; and $\text{Logit} = -8.048 + 0.087 \times \text{age} (+0.262 \text{ if diabetes present})$ for hypertensive women. For ex-

ample, the group of 75-yr-old nonhypertensive women with diabetes will have $\text{Logit} = -8.728 + 0.091 \times 75 + 0.678 = -1.23$ and an estimated prevalence for CKD stages 3 through 4 = $1/[1 + \exp(-(-1.23))] = 22.7\%$.

Table 3 compares prevalence of CKD in Norway with that in the United States. After age and gender standardization of the HUNT II data to the Norwegian 1996 population, national prevalence of CKD stages 1 through 4 was 10.2% in Norway (95% CI 9.2 to 11.2). After age standardization to the US 1991 population, the prevalence was a little lower at 9.3%, still close to US white prevalence of 11.0%. As reported previously, the US prevalence of CKD stages 1 through 4 remained relatively stable from 1988 to 1994 through 1999 to 2000 and was not very different in black and white individuals. Because of the smaller sample size, the 1999 to 2000 estimates are not race stratified, and detailed comparisons of ESRD to CKD incidence in white individuals are made using the 1988 to 1994 data.

Table 3. Prevalence of CKD stages 1 through 4 in Norway and the United States^a

CKD Stage	Norway	United States			Overall (<i>n</i> = 4104)
	1995 to 1997	1988 to 1994	1988 to 1994	1999 to 2000	
	White (<i>n</i> = 65,181) ^b	White (<i>n</i> = 6635)	Black (<i>n</i> = 4163)	Overall (<i>n</i> = 15,625)	
1	2.7 (0.3)	2.8 (0.3)	5.8 (0.3)	3.3 (0.3)	3.8 (0.5)
2	3.2 (0.4)	3.2 (0.3)	2.5 (0.3)	3.0 (0.3)	4.0 (0.5)
3	4.2 (0.1)	4.8 (0.3)	3.1 (0.2)	4.3 (0.3)	3.7 (0.4)
4	0.16 (0.01)	0.21 (0.03)	0.25 (0.08)	0.20 (0.03)	0.13 (0.06)
Total	10.2 (0.5)	11.0 (0.6)	11.6 (0.5)	11.0 (0.5)	11.7 (0.8)

^aData are % (SE). CKD stages 1 to 2 are estimated using gender-specific ACR cutoffs (17 to 250 mg/g [1.9 to 28.3 mg/mmol] for men and 25 to 355 mg/g [2.8 to 40.2 mg/mmol] for women). The prevalence using 30 to 300 mg/g (3.4 to 34.0 mg/mmol) for both men and women for stages 1 through 4 and total are as follows: 1.6, 2.2, 4.2, 0.16, and 8.0 for Norway and 1.8, 2.2, 4.8, 0.2, and 9.0 for US white patients in 1988 through 1994 and 2.8, 2.8, 3.7, 0.13, and 9.4 for US patients in 1999 through 2000.

^bData from the HUNT II study were age and gender standardized to the Norwegian 1996 population. When the data were age and gender standardized to the US 1991 population, CKD prevalence was 9.3% (2.6, 2.9, 3.7, and 0.14% for stages 1 through 4, respectively).

Figure 1 shows that the incidence of ESRD increased from 1984 to 2002 in both countries but was much lower in Norway at all times. The incidence rate ratio for US white individuals to Norwegians increased from 2.1 in 1988 to 2.9 in 2000. Table 4 gives the risk for progression from CKD stages 3 or 4 to ESRD for adult US white individuals and Norwegians stratified by age, gender, and diabetes status. The risk for progression in general was higher for US white individuals than for Norwegians. Every year, there are 61 new ESRD patients in the United States and 24 in Norway for each 10,000 patients with CKD stages 3 to 4. Adjusting for age, gender, and diabetes only modestly affected the increased risk in US white individuals. US white patients without diabetes had 2.0 times higher risk for reaching ESRD, and the relative risk was 2.8, even higher, among patients with diabetes.

Table 5 shows characteristics of incident patients who started ESRD treatment in Norway and the United States. Incidence rates of ESRD that was caused by diabetes and hypertension were much lower in Norway compared with US white patients, whereas the incidence of ESRD that was not related to these factors was similar. Mean eGFR at start of ESRD treatment was equal, and similar proportions of older patients and those with disabilities were included. Norwegians were referred earlier to a nephrologist, and more had an adequate number of predialysis visits. More Norwegian patients were treated with erythropoietin, and they started dialysis with higher hemoglobin and albumin levels. More Norwegian patients had a kidney transplant as their first treatment, and more patients had an arteriovenous fistula as their first access. Data regarding economy and general population characteristics of importance for the incidence of ESRD are given in Table 6. Income per capita were similar in the two countries, but significant differences in the proportion living in poverty and without health insurance or

lacking functional literacy skills were present. Diabetes and obesity were much more prevalent in the United States, whereas the proportion of people who were on antihypertensive treatment was similar. Mortality rates from ischemic heart disease, one of the leading causes of death in the general population and among patients with CKD and ESRD, were similar.

Discussion

This large, population-based study found the overall CKD prevalence to be 10.2% in Norway, close to the prevalence in the United States, with similar estimates even for severe CKD (eGFR 15 to 30 ml/min per 1.73 m²). This is at odds with a three times lower incidence of ESRD in Norway than in US white patients. Stratification by race, gender, age, hypertension, and diabetes indicates that within each of these factors, the prevalence of CKD is similar between the two countries, whereas the risk for ESRD among individuals with CKD is markedly higher in the United States than in Norway. The ESRD to CKD ratio was nearly two-fold higher in the United States than in Norway at age <60 yr and three-fold higher at older ages. These ecologic data, although subject to bias, indicate that the higher risk for ESRD in the United States compared with Norway is not due to a markedly higher prevalence of CKD but a higher rate of progression from CKD to treated ESRD.

The risk for starting ESRD treatment is a combination of surviving competing causes of death, reaching kidney failure, being offered renal replacement therapy, and accepting this therapy. This study cannot dissect the relative contributions of these factors, but national data are informative in considering these aspects. Overall cardiovascular mortality, the leading cause of death in both countries, is similar, and life expectancy in Norway is higher than that in the United States, suggesting that competing mortality may not be a large factor. Kidney disease progression itself and the role of comorbidity and access to treatment are more difficult to assess. The lower prevalence of diabetes in Norway can explain some of the lower progression to ESRD. However, even among patients with diabetes, US white patients had a much higher risk for progression to ESRD. Hypertension, the second established risk factor for progression, was equally prevalent in the two countries. Another difference that could affect progression was the striking difference in obesity; 4.0% of white participants in the NHANES 1999 Survey were morbidly obese (BMI > 40 kg/m²) compared with only 0.7% of HUNT II participants. Obesity is known to lead to ESRD through diabetes and hypertension, but emerging experimental evidence also indicates that obesity can contribute directly to kidney damage, through a cascade of additional hemodynamic, metabolic, and inflammatory mechanisms as well as by mechanical compression (26–29). Obesity thereby can be an important exacerbating factor, at least in patients with preexisting nephropathy or reduced renal mass. Ratios of ESRD to CKD in this article are based on ecologic rather than individual follow-up data, limiting inferences about risk factors for progression.

Pre-ESRD care is increasingly recognized as important for reducing ESRD mortality and, at least equally important, in

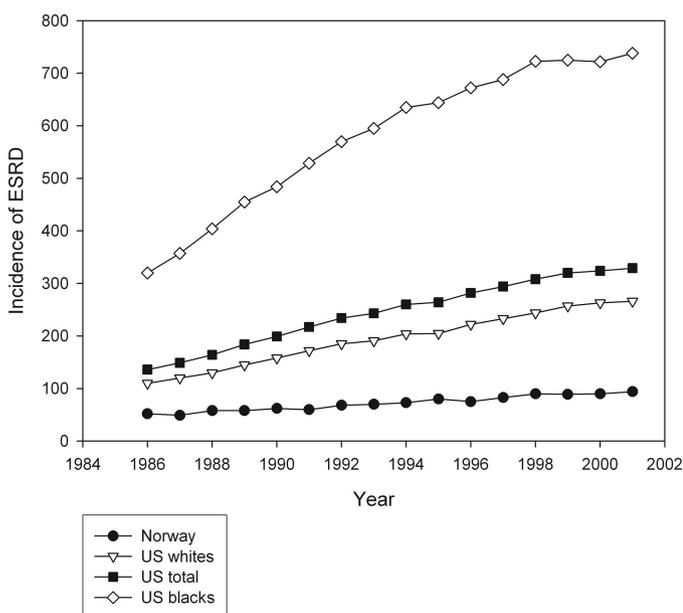


Figure 1. Annual incidence of ESRD (per million inhabitants) in Norway and the United States.

Table 4. US white *versus* Norwegian patients' relative risk for progression from CKD stages 3 or 4 to ESRD^a

	Per 100,000 Adults in General Population		Ratio, ESRD Incidence/CKD Prevalence	Increased Risk for US White Patients
	CKD Stages 3 to 4	New ESRD per Year		
Total				2.5
US white	5010	30.8	0.0061	
Norway	4360	10.6	0.0024	
Nondiabetes				2.0
US white	3772	16.7	0.0044	
Norway	3870	8.6	0.0022	
Diabetes				2.8
US white	1238	14.1	0.0114	
Norway	490	2.0	0.0041	
Age < 60 yr				1.7
US white	713	11.1	0.0156	
Norway	508	4.7	0.0093	
Age ≥ 60 yr				3.0
US white	4349	19.7	0.0045	
Norway	3835	5.9	0.0015	
Female				3.5
US white	3198	13.9	0.0043	
Norway	2993	3.6	0.0012	
Male				1.9
US white	1852	16.9	0.0091	
Norway	1407	7.0	0.0049	

^aPrevalence (per 100,000 adults) of CKD stages 3 to 4 is from the Third National Health and Nutrition Examination Survey (NHANES III; 1988 to 1994, which is not significantly different from NHANES 1999 to 2000) and from HUNT II (1995 to 1997). Incidence of ESRD (per 100,000 adults per year) is from the US Renal Data System (USRDS; 1995 to 1997) and from the Norwegian Renal Registry (1995 to 1997). Data on patients with diabetes represent CKD or ESRD in patients with diabetes as primary renal diagnosis or as a secondary complicating diagnosis (25,39,44–46).

slowing progression of CKD and development of ESRD (30,31). The quality of pre-ESRD care has been reported to be suboptimal in the United States (32,33), and several key markers of predialysis care in our study indicate differences between the two countries. Norwegian patients with CKD were referred earlier to a nephrologist and had more pre-ESRD visits. As a result, more patients received erythropoietin treatment, and they had a higher hemoglobin level when starting dialysis treatment compared with US white patients. Such treatment is increasingly recognized as potentially important for reducing the progressive loss of remaining nephrons (34–37). Norwegian patients also had higher serum albumin levels, indicating better nutritional status (38).

The lower incidence rate of ESRD in Norway could be due to different acceptance criteria and different indications for starting dialysis and transplantation. Acceptance criteria have become broad in Norway, as in most other Western countries. The mean age at start of renal replacement therapy was identical for Norwegians and US white patients and so was the proportion of patients with disabilities. The eGFR level at the start of treatment was similar in the two countries, suggesting similar timing of the start of dialysis. All health services, including predialysis treatment as well as ESRD treatment, are free in

Norway. An active transplantation program has managed to keep the pool of dialysis patients small; 73.1% of prevalent ESRD patients receive a transplant, median time on the waiting list is 10 mo, and only 15% have waited >2 yr (39). The available data do not suggest large differences in treatment availability, but quantification of treatment access is difficult. For example, we are not aware of data to allow for comparison of the proportion of patients who reach kidney failure but do not start long-term dialysis.

The situation for US white *versus* Norwegians patients are somewhat analogous to US black *versus* US white patients. Black Americans experience a three times higher incidence of ESRD compared with white Americans despite similar prevalence of CKD stages 3 to 4. Hsu *et al.* (8) concluded that this probably is due to different rates of progression. A higher prevalence of diabetes, hypertension, and other conventional risk factors as well as lower socioeconomic status explain part but not all of the difference (40). To eliminate the effect of true racial differences, we focused on comparing Norwegians with US white patients.

Our international comparison has a number of limitations. The MDRD formula is known to perform well in patients with CKD and low GFR, but its use in populations with higher GFR

Table 5. Characteristics of incident patients at start of ESRD treatment in Norway and the United States regarding incidence rates, causes, treatment indications, and predialysis care (1995 to 1997)^a

	Norway	United States		
		White	Black	Total
ESRD incidence (per million inhabitants/yr) ^{b,c}	79	222	672	285
diabetes	9	92	231	111
hypertension	20	49	222	61
glomerulonephritis	20	35	73	34
cystic kidney diseases	7	9	11	8
Age (yr; mean) ^{b,c}	62	62	57	60
Unable to ambulate or transfer (%) ^{c,d}	9	7	7	7
GFR (ml/min per 1.73 m ²) ^{b,c}	7.6	7.8	7.4	7.7
Predialysis care by a nephrologist ^{d,e}				
duration (mo; median)	23	13	8	12
duration (%; <4 mo)	19	28	37	30
≥5 visits (%)	73	NA	NA	41
Transplantation as first treatment (%) ^{b,c}	11	3	1	2
Arteriovenous fistula as first access (%) ^{c,d}	32	17	14	17
Predialysis treatment with erythropoietin (%) ^{c,d}	43	26	20	24
Hemoglobin (g/dl) ^{c,d}	10.6	9.7	9.1	9.5
Albumin (g/L) ^{c,d}	36	32	31	32

^aNA, data not available.

^bSource: Norwegian Renal Registry.

^cSource: USRDS Registry.

^dSource: Norwegian Renal Registry (data available only for patients who started renal replacement therapy in Nord-Trøndelag County and Sør-Trøndelag County, including St. Olavs Hospital, the regional tertiary care hospital).

^eSource: USRDS/DMMS Wave 2, 1996 to 1997 (31) and CHOICE study, 1995 to 1998 (47).

has shown varying results (41–43). Errors in eGFR are caused partly by calibration differences between the creatinine assay in the study and in the laboratory where the GFR equation was developed. This possible problem was addressed in both the HUNT and the NHANES analyses (23,25), and the new MDRD formula that was used in our analysis seems unbiased in the Norwegian population and at all ages (21). Imprecision in eGFR >60 ml/min per 1.73 m² is not critical, because classification into CKD stages 1 to 2 depends on the presence of proteinuria. Finally, methodologic limitations of the MDRD equation likely would apply similarly to the US and Norwegian populations. Although albuminuria was not measured in all participants in HUNT II, ACR was measured in multiple urine samples in a large random subsample. Both HUNT II and NHANES enrolled a large, representative sample of the general population, with high rates of participation and completion rates, suggesting that the similar prevalence rates of CKD represent true similarities.

Conclusion

We found a high prevalence of CKD (10.2%) in a European general population, close to the US prevalence (11.5%). Therefore, the much lower incidence of ESRD in Norway compared with US white patients is not explained by a lower prevalence of the earlier stages of the disease. National data from Norway

and the United States show no large differences in competing mortality, treatment availability, or timing of the start of dialysis. The difference in risk for ESRD remains large after accounting for the lower prevalence of diabetes in Norway compared with the United States. The effects of a lower prevalence of obesity as well as earlier referral to a nephrologist before the start of dialysis and national health care system could not be quantified. In conclusion, the large difference in ESRD rates between Norway and the United States lies in the management and fate of patients with existing CKD in these two populations rather than the prevalence of CKD.

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Table 6. Information regarding economy and general population characteristics of relevance for the incidence of ESRD (1995 to 1997)

	Norway	United States		
		White	Black	Total
Income per capita (US\$) ^{a,b}	22,193	19,579	10,982	17,227
African descent (%) ^{a,b}	0.4	—	—	12.6
Population below income poverty line (%) ^{a,c}	5.9	11.2	28.4	13.7
Without health insurance (%) ^{a,c}	0	14.2	21.0	15.4
Lack of functional literacy (%) ^{d,e}	8	14	38	20
Life expectancy (yr) ^{a,b}	78.1	76.5	69.6	75.8
Age (yr; % of total population) ^{a,b}				
20 to 54	48.5	50.6	49.1	50.6
55 to 74	18.1	16.7	10.8	14.8
≥75	7.1	5.9	3.0	5.0
Ischemic heart disease (deaths per 100,000/yr) ^{a,f}				
1980	262	348	334	345
1990	265	250	267	250
1995	221	219	245	220
BMI > 30 kg/m ² (%) ^g	16	28.7	38.9	30.5
BMI > 40 kg/m ² (%) ^g	0.7	4.0	9.3	4.7
On antihypertensive treatment (%) ^g	11.0	12.1	16.7	12.6
Diabetes (%) ^g	3.4	4.8	7.0	5.0
Persistent microalbuminuria (%) ^g	7.1	6.5	8.1	6.8
Macroalbuminuria (%) ^g	0.8	0.9	2.4	1.1

^aSource: Statistics Norway.

^bSource: US Census Bureau.

^cSource: Center of Budget and Policy Priorities.

^dSource: Organization for Economic Cooperation and Development.

^eSource: US Department of Education.

^fSource: Centers for Disease Control and Prevention.

^gSource: HUNT and NHANES studies.

revising. S.I.H. has had access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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References

- van Dijk PC, Jager KJ, de Charro F, Collart F, Cornet R, Dekker FW, Gronhagen-Riska C, Kramar R, Leivestad T, Simpson K, Briggs JD; ERA-EDTA registry: Renal replacement therapy in Europe: The results of a collaborative effort by the ERA-EDTA registry and six national or regional registries. *Nephrol Dial Transplant* 16: 1120–1129, 2001
- US Renal Data System: *USRDS 2003 Annual Data Report: Atlas of End-Stage Renal Disease in the United States*, Bethesda, National Institutes of Health; 2003. Available: <http://www.usrds.org/adr.htm>. Accessed May 2004
- Bello AK, Nwankwo E, El Nahas AM: Prevention of chronic kidney disease: A global challenge. *Kidney Int* 68: S11–S17, 2005
- Gambaro G, D'Angelo A, Conte M, Bonfante L, De Biase V, Lupo A: Silent chronic kidney disease epidemic seen from Europe: Designing strategies for clinical management of the early stages. *J Nephrol* 18: 123–135, 2005
- Muntner P, Coresh J, Smith JC, Eckfeldt J, Klag MJ: Plasma lipids and risk of developing renal dysfunction: The atherosclerosis risk in communities study. *Kidney Int* 58: 293–301, 2000
- Coresh J, Byrd-Holt D, Astor BC, Briggs JP, Eggers PW, Lacher DA, Hostetter TH: Chronic kidney disease awareness, prevalence, and trends among US adults, 1999 to 2000. *J Am Soc Nephrol* 16: 180–188, 2005
- Hsu CY, Vittinghoff E, Lin F, Shlipak MG: The incidence of end-stage renal disease is increasing faster than the prevalence of chronic renal insufficiency. *Ann Intern Med* 141: 95–101, 2004
- Hsu CY, Lin F, Vittinghoff E, Shlipak MG: Racial differences in the progression from chronic renal insufficiency to end-stage renal disease in the United States. *J Am Soc Nephrol* 14: 2902–2907, 2003
- K/DOQI clinical practice guidelines for chronic kidney

- disease: Evaluation, classification, and stratification. Kidney Disease Outcome Quality Initiative. *Am J Kidney Dis* 39: S1–S246, 2002
10. Remuzzi G, Weening JJ: Albuminuria as early test for vascular disease. *Lancet* 365: 556–557, 2005
 11. de Lusignan S, Chan T, Stevens P, O'Donoghue D, Hague N, Dzregah B, Van Vlymen J, Walker M, Hilton S: Identifying patients with chronic kidney disease from general practice computer records. *Fam Pract* 22: 234–241, 2005
 12. Verhave JC, Gansevoort RT, Hillege HL, Bakker SJ, De Zeeuw D, de Jong PE; PREVENTD Study Group: An elevated urinary albumin excretion predicts de novo development of renal function impairment in the general population. *Kidney Int Suppl* 92: S18–S21, 2004
 13. Magnason RL, Indridason OS, Sigvaldason H, Sigfusson N, Palsson R: Prevalence and progression of CRF in Iceland: A population-based study. *Am J Kidney Dis* 91: 955–963, 2002
 14. Holmen J, Midthjell K, Kruger O, Langhammer A, Lingaas Holmen T, Bratberg G, Vatten L, Lund-Lassen P: The Nord-Trøndelag Health Study 1995–97 (HUNT 2): Objectives, contents, methods and participation. *Norsk Epidemiol* 13: 19–32, 2003
 15. Statistics Norway; 2003. Available: <http://www.ssb.no/english/subjects/>. Accessed May 2004
 16. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, Jones DW, Materson BJ, Oparil S, Wright JT Jr, Roccella EJ; National Heart, Lung, and Blood Institute Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; National High Blood Pressure Education Program Coordinating Committee: The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: The JNC 7 report. *JAMA* 289: 2560–2572, 2003
 17. World Health Organization: *Diabetes Mellitus: Report of a WHO Study Group*, Geneva, World Health Organization, 1985. Technical Report Series 727
 18. Warram JH, Gearin G, Laffel L, Krolewski AS: Effect of duration of type I diabetes on the prevalence of stages of diabetic nephropathy defined by urinary albumin/creatinine ratio. *J Am Soc Nephrol* 7: 930–937, 1996
 19. Levey AS, Coresh J, Greene T, Marsh J, Stevens LA, Kusek J, Van Lente F: Expressing the MDRD study equation for estimating GFR with IDMS traceable (gold standard) serum creatinine values [Abstract]. *J Am Soc Nephrol* 16: 69A, 2005
 20. Rustad P: Reference intervals for 25 of the most frequently used properties in clinical chemistry; proposal by Nordic Reference Interval Project (NORIP). *Klin Biokem Norden* 15: 10–17, 2003
 21. Hallan S, Astor BC, Lydersen S: Estimating glomerular filtration rate in the general population: The second Health Survey of Nord Trøndelag (HUNT II). *Nephrol Dial Transplant* 21: 1525–1533, 2006
 22. Levey AS, Greene T, Kusek J, Beck GJ, Group MS: A simplified equation to predict glomerular filtration rate from serum creatinine [Abstract]. *J Am Soc Nephrol* 11: A0828, 2000
 23. Hallan S, Aasberg A, Lindberg M, Johnsen H: Validation of the Modification of Diet in Renal Disease formula for estimating GFR with special emphasis on calibration of the serum creatinine assay. *Am J Kidney Dis* 44: 85–93, 2004
 24. Rothman KJ, Greenland S: *Modern Epidemiology*, 2nd Ed.; Lippincott Williams and Wilkins, Philadelphia, 2002
 25. Coresh J, Astor BC, Greene T, Eknoyan G, Levey AS: Prevalence of chronic kidney disease and decreased kidney function in the adult US population: Third National Health and Nutrition Examination Survey. *Am J Kidney Dis* 41: 1–12, 2003
 26. Adelman RD: Obesity and renal disease. *Curr Opin Nephrol Hypertens* 11: 331–335, 2002
 27. Beddhu S: The body mass index paradox and an obesity, inflammation, and atherosclerosis syndrome in chronic kidney disease. *Semin Dial* 17: 229–232, 2004
 28. Hall JE: The kidney, hypertension, and obesity. *Hypertension* 41: 625–633, 2003
 29. Kincaid-Smith P: Hypothesis: Obesity and the insulin resistance syndrome play a major role in end-stage renal failure attributed to hypertension and labelled 'hypertensive nephrosclerosis.' *J Hypertens* 22: 1051–1055, 2004
 30. Powe NR: Early referral in chronic kidney disease: An enormous opportunity for prevention. *Am J Kidney Dis* 41: 505–507, 2003
 31. Stack AG: Impact of timing of nephrology referral and pre-ESRD care on mortality risk among new ESRD patients in the United States. *Am J Kidney Dis* 41: 310–318, 2003
 32. Obrador GT, Ruthazer R, Arora P, Kausz AT, Pereira BJ: Prevalence of and factors associated with suboptimal care before initiation of dialysis in the United States. *J Am Soc Nephrol* 10: 1793–1800, 1999
 33. Owen WF Jr: Patterns of care for patients with chronic kidney disease in the United States: Dying for improvement. *J Am Soc Nephrol* 14: S76–S80, 2003
 34. Deicher R, Horl WH: Anaemia as a risk factor for the progression of chronic kidney disease. *Curr Opin Nephrol Hypertens* 12: 139–143, 2003
 35. Gouva C, Nikolopoulos P, Ioannidis JP, Siamopoulos KC: Treating anemia early in renal failure patients slows the decline of renal function: A randomized controlled trial. *Kidney Int* 66: 753–760, 2004
 36. Rossert J, Fouqueray B, Boffa JJ: Anemia management and the delay of chronic renal failure progression. *J Am Soc Nephrol* 14[Suppl]: S173–S177, 2003
 37. Rossert JA, McClellan WM, Roger SD, Verbeelen DL, Horl WH: Contribution of anaemia to progression of renal disease: A debate. *Nephrol Dial Transplant* 17[Suppl 1]: 60–66, 2002
 38. Morris D, Samore MH, Pappas LM, Ramkumar N, Beddhu S: Nutrition and racial differences in cardiovascular events and survival in elderly dialysis patients. *Am J Med* 118: 671–675, 2005
 39. Annual Report 2003: The Norwegian Renal Registry. Available: <http://www.nephro.no/registry/AARSM2003.html>. Accessed May 2004
 40. Tarver-Carr ME, Powe NR, Eberhardt MS, LaVeist TA, Kington RS, Coresh J, Brancati FL: Excess risk of chronic kidney disease among African-American versus white subjects in the United States: A population-based study of potential explanatory factors. *J Am Soc Nephrol* 13: 2363–2370, 2002
 41. Lin J, Knight EL, Hogan ML, Singh AK: A Comparison of prediction equations for estimating glomerular filtration rate in adults without kidney disease. *J Am Soc Nephrol* 14: 2573–2580, 2003
 42. Poggio ED, Wang X, Greene T, Van Lente F, Hall PM: Perfor-

- mance of the Modification of Diet in Renal Disease and Cockcroft-Gault equations in the estimation of GFR in health and in chronic kidney disease. *J Am Soc Nephrol* 16: 459–466, 2005
43. Rule AD, Larson TS, Bergstralh EJ, Slezak JM, Jacobsen SJ, Cosio FG: Using serum creatinine to estimate glomerular filtration rate: Accuracy in good health and in chronic kidney disease. *Ann Intern Med* 141: 929–937, 2004
44. Prevalence of diabetes and impaired fasting glucose in adults—United States, 1999–2000. *MMWR Morb Mortal Wkly Rep* 52: 833–837, 2003
45. Coresh J, Byrd-Holt D, Astor BC, Briggs JP, Eggers PW, Lacher DA, Hostetter TH: Chronic kidney disease awareness, prevalence and trends among US adults, 1999–2000. *J Am Soc Nephrol* 16: 180–188, 2004
46. Hajjar I, Kotchen TA: Trends in prevalence, awareness, treatment, and control of hypertension in the United States, 1988–2000. *JAMA* 290: 199–206, 2003
47. Kinchen KS, Sadler J, Fink N, Brookmeyer R, Klag MJ, Levey AS, Powe NR: The timing of specialist evaluation in chronic kidney disease and mortality. *Ann Intern Med* 137:

See the related editorials, “Risk for Progression to ESRD: Further Evidence from Population-Based Studies,” on pages 2092–2093, and “Chronic Kidney Disease Prevalence and Treated End-Stage Renal Disease Incident: A Complex Relationship,” on pages 2094–2096.