Prevalence of CKD in Northeastern Italy: Results of the INCIPE Study and Comparison with NHANES

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Background and objectives: Sufficiently powered studies to investigate the CKD prevalence are few and do not cover southern Europe.

Design, setting, participants, & measurements: For the INCIPE study, 6200 Caucasian patients ≥40 years old were randomly selected in northeastern Italy in 2006. Laboratory determinations were centralized. The albumin to creatinine ratio in urine and estimated GFR from calibrated creatinine (SCr) were determined. A comparison with 2001 through 2006 NHANES surveys was performed.

Results: Prevalence of CKD was 13.2% in northeastern (NE) Italy (age and gender standardized to the U.S. 2007 Caucasian population). Prevalence of CKD in U.S. Caucasians is higher (20.3%), the major difference being in CKD 3. Risk factors for CKD are more prevalent in the United States than in Italy. With use of CKD 3a and 3b stages, CKD prevalence decreased in NE Italy (8.5%) and in the United States (12.8%).

Conclusions: The prevalence of CKD is high in NE Italy, but lower than that in the United States. A large part of the difference in CKD prevalence in NE Italy *versus* that in the United States is due to the different prevalence of CKD 3. The higher prevalence of a number of renal risk factors in persons from the United States explains in part the different dimensions of the CKD problem in the two populations.

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According to a number of reports from different parts of the world, the burden of chronic kidney disease (CKD) is dramatically increasing (1). However, many of such studies are not comparable because of different criteria for defining CKD. In fact, screening has often been limited to measuring only estimated GFR (eGFR), not including the determination of albuminuria, which would offer identification of CKD stages 1 and 2. Furthermore, the issue of the serum creatinine assay and calibration has not been adequately addressed by some, thus biasing comparison between different populations. Consequently, there are a few large, sufficiently powered epidemiologic studies using similar methodologies and these do not cover significant geographical areas. The NHANES surveys (2) have constituted the template for CKD prevalence studies. Thus, all of the most significant CKD epidemiology surveys compare with them. In northern Europe, the Prevend (3) and the HUNT II study (4) investigated CKD prevalence. No other sufficiently powered study has been performed in Europe and in particular in the southern Mediterranean area which is known to differ consistently from northern Europe regarding nutritional habits and prevalence of pathologic conditions that increase the risk of developing CKD.

Because of the perception of a large and increasing burden of CKD in different parts of the world, the term "CKD epidemics" has been coined. However, much of the contribution to such a burden is due to CKD stage 3. The definition of CKD 3 is based only on an eGFR <60 ml/min per 1.73 m^2, which has been questioned as being a reliable marker of

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renal dysfunction, particularly in persons over 65 years and women (5). Different CKD 3 definitions have thus been proposed to better estimate the epidemiologic relevance of the CKD (5).

To assess the prevalence of CKD in Italy, in 2006, in NE Italy, we launched the "INCIPE" study (Initiative on Nephropathy, of relevance to public health, which is Chronic, possibly in its Initial stages, and carries a Potential risk of major clinical Endpoints).

Materials and Methods

Recruitment of INCIPE Patients

The ethics committees of the involved institutions approved the study protocol. For the INCIPE study 6200 patients, all Caucasians, ≥40-years old by January 1, 2006, were randomly chosen from the lists of patients of 62 randomly selected general practitioners (GPs) based in four geographical areas in the Veneto region, NE Italy. In Italy all citizens receive free health insurance from the National Health System. To this aim all are included in the list of patients of GPs of their own choice. Thus, drawing participants from the GPs' lists is likely to draw them directly from the community. Enrollment and clinical examination were performed locally in four units, by trained medical doctors. Pregnant women were not enrolled. After written informed consent was obtained, each participant completed a self-administered questionnaire (e.g., family and personal medical history, pharmacologic treatments, and smoking habits). Patients were asked to refrain from smoking beginning from the night before. BP, waist circumference, body weight, and height were measured as in the NHANES study.

Freshly voided morning urine was collected. In menstruating women the sample was btained a few days later. Standard urine examination by a plastic strip (Aution Sticks 10 EA; Arkray, Menarini Diagnostics, Firenze, Italy) was immediately performed.

Laboratory

Blood and urine samples were frozen at −80°C by 5 hours after collection. All determinations were centralized (Verona General Hospital, Central Laboratory).

With reference to the urine albumin assay we chose to prescreen the samples with a strip test (Clinitek Microalbumin; Siemens Medical Solutions Diagnostics, Mishawaka, IN) and to confirm the positive results (≥3.4 mg/mmol creatinine) measuring albumin immunochemically by a specific antibody and a nephelometer (Immage 800; Beckman Coulter, Inc., Fullerton, CA), and creatinine on RxL Dimension (Dade-Behring, Inc., Newark, DE) using an alkaline picrate method as described (6).

Serum creatinine (SCr) was measured using a kinetic rate Jaffe method. For GFR estimation, SCr measurements were recalibrated to standardized creatinine measurements obtained at The Cleveland Clinic Research Laboratory as described (7).

NHANES Data

Only data from Caucasians (non-Hispanic whites) aged 40 years or over in the NHANES 2001 through 2002, 2003 through 2004, and 2005 through 2006 surveys were considered (8).

CKD Classification

The GFR was estimated with the CKD Epidemiology Collaboration (EPI) equation using calibrated creatinine (9). Albuminuria was defined as an albumin to creatinine ratio (ACR) ≥3.4 mg/mmol creatinine (6), with microalbuminuria as an ACR of 3.4 mg/mmol (30 mg/g) to 33.9 mg/mmol (299 mg/g), and macroalbuminuria as an ACR ≥34 mg/mmol (300 mg/g).

Definition of the five CKD stages was according to the KDOQI classification (10). Stage 3 was also substratified into two classes: 3a, GFR of 45 to 59 ml/min per 1.73 m^2 with ACR ≥3.4 mg/mmol creatinine; and 3b, GFR of 30 to 44 ml/min per 1.73 m^2.

We have measured SCr and ACR at one time point only. Correct classification of CKD requires confirmation of abnormalities over at least a 3-month period. For the analysis of the NHANES data we used the same criteria.

Definition of Clinical Phenotypes

Participants were classified as hypertensive when they reported having received a diagnosis of hypertension and as diabetics when they reported having received a diagnosis of diabetes or when found to have fasting plasma glucose ≥126 mg/dl. Hypercolesterolemic individuals were those with blood cholesterol levels ≥240 mg/dl. For metabolic syndrome definition we used the American Heart Association/National Heart, Lung, and Blood Institute Scientific Statements (11). People who smoke (current and past) were those who had smoked >100 cigarettes in their entire life. Previous cardiovascular (CV) events included self-reported diagnosis performed by a physician of coronary heart disease, angina, heart attack, transitory ischemic attack, or stroke.

Statistical Analyses

The sample size was calculated by considering the estimated prevalence of asymptomatic renal dysfunction. Because there were no available data from the Italian population, we considered the prevalence of patients with a creatinine clearance ≤50 ml/min, which was 13% in a sample representative of the U.S. general population (12). A sample of 4345 patients is necessary to obtain an estimate precision of 1% with a confidence level of $1 - \alpha = 95\%$ (nQuery Advisor 6.01). Assuming that 30% of patients were not willing to participate in the study, we singled out 6200 patients from a total general population of 56,841 people. Analyses of NHANES databases were performed by pooling data from three survey periods as previously outlined and incorporating the sampling weights to obtain unbiased estimates from the complex NHANES sampling design.

The standard error of the mean (SEM) for all estimates was obtained using the Taylor series (linearization) method following NHANES-recommended procedures and weights.

A multivariate logistic regression analysis was performed to evaluate the simultaneous effects of population (NHANES *versus* INCIPE), gender, age, smoking, body mass index, diabetes, cardiovascular diseases, hypertension, and kidney disease history on CKD 3 to 5 and albuminuria. To investigate the effect of diabetes, hypertension, and gender on CKD (all stages) in each study, we used separate logistic regression models, considering diabetes and hypertension adjusted for age and/or gender. The results were expressed as odds ratios (OR) with their 95% confidence interval (95% CI).

The appropriate statistical methodology was used for complex survey analysis as recommended by the CDC in the continuous NHANES tutorial (13).

In hypothesis testing, the level of significance was $P < 0.05$. All the analyses were performed with SAS 9.1.3 for Windows (SAS Institute Inc., Cary, NC).

Results

In the INCIPE study, 3870 (62% of the randomized sample) subjects were enrolled. Because we limited our analysis to people with a complete data set, this report is based on 3629

subjects, a number lower than the calculated sample size. However, as the observed prevalence of CKD was much lower in the INCIPE population than in the U.S. population (see below), the chance of incorrect inference is marginal, even given the slightly reduced sample size.

Participants in INCIPE had a mean age of 59.8 years, and 21.4% were ≥70 years; 47.8% were men (Supplemental Table 1; the table also shows corresponding data in the NHANES survey). The clinical characterization of INCIPE and NHANES populations is shown in Supplemental Table 2. The prevalence of high SCr in the INCIPE population was about one third compared with that in the NHANES population (1.2 *versus* 3.9%).

Table 1 shows the prevalence of CKD in the INCIPE study as based on the KDOQI classification. Statistics for the CKD 5 class is not shown in the INCIPE tables because only two patients were recognized in this class. The overall prevalence of CKD was 12.7%. After age and gender standardization of the INCIPE data to the U.S. 2007 population (14), prevalence in NE Italy is 13.2%. Prevalence of CKD in the United States is much higher (20.3%) (Table 2), the largest difference being in CKD 3 (Figure 1).

In both studies the eGFR was negatively associated with older age: in the older than 70 years group compared with the 40- to 49-year old group the prevalence of GFR 30 to 59 ml/min per 1.73 m^2 (CKD 3) was 59 and 37 times higher, in NE Italy and in the United States, respectively. Between these age classes, in the oldest (≥70 years) the condition of GFR ≥90 was prominently less prevalent (12 and 23 times lower in NE Italy and in the United States, respectively). Actually, the GFR was gradually decreasing with age, by an average of 8.5 and 8.8 ml/min per decade in the Caucasians from Italy and the United States, respectively.

Prevalence of a number of CKD risk conditions is consistently higher in the United States than in NE Italy in each age class (Figure 2, Supplemental Table 2).

After adjustment for age and gender, in the INCIPE population hypertensive individuals had 2.09-fold (95% CI 1.68, 2.61) higher odds of CKD (all stages) compared with normotensive patients. Similarly, individuals with diabetes had 2.66 (95% CI 2.03, 3.49) higher odds for CKD than individuals without diabetes. Very similar data were obtained in the NHANES Caucasians (OR 1.85, 95% CI 1.61, 2.13; OR 2.51, 95% CI 2.05, 3.08, respectively). Women (adjusted for age) were not revealed to have an increased risk (OR 0.89, 95% CI 0.72, 1.09 and OR 1.11, 95% CI 0.97, 1.28, in INCIPE and NHANES, respectively).

In both populations only a minority of CKD 3 patients had micro-/macroalbumin excretion rate (AER); in particular, in patients with GFR 45 to 59 ml/min per 1.73 m^2, 4 of 5 had no micro-/macro-AER (Table 3a and Table 3b, Supplemental Table 3). The prevalence of albuminuria was noticeably different between genders in the CKD 3 stage in both populations (Supplemental Table 3). Consequently, the prevalence of those CKD 3 patients with micro-/macro-AER was higher in men than in women (29.9 and 15.1%, respectively, in NE Italy and 25.2 and 18.1%, respectively, in the United States).

When CKD 3a and 3b stages are used instead of a CKD stage 3, the total prevalence of patients with CKD (all stages) changes considerably, from 12.7 to 8.5% in NE Italy and from 20.3 to 12.8% in the NHANES (Table 3) population, the differences being homogeneously distributed among different age classes.

The risk of having CKD 3 to 5 is 2.7 times higher in the NHANES population than in the INCIPE population after adjustment for differences in age, gender, diabetes, CV history, hypertension, renal history, smoking, and obesity (Table 4).

The difference between the two populations remains substantially of the same extension if we analyze the risk of having CKD 3b to 5. A major role in the two models is due to renal history (Table 4).

Regarding the risk of having albuminuria, it also is higher in the NHANES population, 45%, with diabetes having a major

Table 1. INCIPE: Prevalence of CKD by demographic and clinical characteristics

	CKD 1		CKD 2		CKD 3		CKD 4		CKD 1 + 2 + 3 + 4	
	%	95% CI	%	95% CI	%	95% CI	%	95% CI	%	95% CI
Total	1.7	1.2,2.1	4.3	3.6,5.00	6.4	5.6,7.2	0.3	0.1,0.4	12.7	11.6,13.7
Men	1.7	1.1,2.3	5.0	3.9,6.0	6.2	5.0,7.3	0.3	0.1,0.6	13.2	11.6,14.8
Women	1.6	1.0,2.2	3.7	2.9,4.6	6.7	5.5,7.8	0.2	0.0,0.4	12.2	10.7,13.6
40 to 49 years	1.8	0.9,2.8	0.7	0.2,1.3	0.4	0.0,0.8	0.0		2.9	1.8,4.1
50 to 59 years	2.0	1.2,2.9	1.7	0.9,2.5	1.6	0.9,2.4	0.0		5.3	4.0,6.7
60 to 69 years	2.0	1.2,2.9	5.7	4.2,7.1	4.3	3.0,5.5	0.3	0.0,0.7	12.3	10.2,14.3
70 to 79 years	0.7	0.0,1.3	9.2	7.0,11.5	17.7	14.7,20.7	0.7	0.0,1.3	28.2	24.7,31.8
≥80 years	0.0		11.8	6.8,16.8	38.5	31.0,46.0	1.9	0.0,4.0	52.2	44.5,59.9
Diabetes	4.4	2.3,6.5	12.3	9.0,15.7	14.0	10.4,17.5	0.3	0.0,0.8	31.0	26.2,35.7
Hypertension	2.1	1.3,2.9	7.6	6.2,9.1	11.6	9.8,13.3	0.6	0.2,1.0	21.9	19.6,24.1
BMI >30	2.8	1.7,4.0	6.4	4.7,8.1	7.7	5.8,9.5	0.0		16.8	14.2,19.5
Previous kidney disease	2.4	0.5,4.2	5.9	3.0,8.8	14.6	10.2,18.9	1.6	0.0,3.1	24.4	19.1,29.7
None of the previous	1.1	0.6,1.6	1.5	1.0,2.1	3.0	2.2,3.8	0.1	0.0,0.3	5.8	4.7,6.9
Metabolic syndrome	2.6	1.7,3.5	7.6	6.1,9.1	11.4	9.6,13.2	0.5	0.1,0.9	22.1	19.8,24.5

Table 2. NHANES: Prevalence of CKD by demographics and clinical characteristics

	CKD 1		CKD 2		CKD 3		CKD 4		CKD 5		CKD 1+2+3+4+5	
	%	95% CI	%	95% CI	%	95% CI	%	95% CI	%	95% CI	%	95% CI
Total	2.8	2.2,3.3	4.7	4.0,5.4	12.0	10.9,13.1	0.7	0.5,1.0	0.1	0.0,0.2	20.3	18.7,21.8
Men	2.7	2.1,3.4	4.8	4.0,5.6	10.1	9.0,11.3	0.5	0.3,0.8	0.1	0.0,0.1	18.3	16.6,19.9
Women	2.8	2.1,3.5	4.6	3.6,5.6	13.7	12.2,15.1	0.9	0.5,1.3	0.1	0.0,0.3	22.1	20.1,24.1
40 to 49 years	3.3	1.9,4.4	2.3	1.4,3.2	1.0	0.5,1.6	0.0		0.2	0.0,0.1	6.5	4.8,8.2
50 to 59 years	3.7	2.1,5.2	2.8	1.7,3.8	4.1	2.8,5.5	0.0		0.0		10.5	8.6,12.5
60 to 69 years	3.0	1.6,4.5	5.4	4.0,6.8	15.3	13.2,17.1	0.5	0.0,1.0	0.1	0.0,0.4	24.2	21.9,26.5
70 to 79 years	0.8	0.2,1.5	10.7	8.6,12.7	29.8	26.9,32.6	1.8	0.8,2.9	0.3	0.0,0.6	43.4	39.7,47.1
≥80 years	0.0		11.4	9.3,13.6	55.0	51.1,59.0	5.9	3.6,8.3	0.2	0.0,0.5	72.6	69.2,75.9
Diabetes	10.2	6.8,13.6	10.6	7.6,13.6	19.2	14.4,24.1	1.2	0.2,2.1	0.0		41.2	35.1,47.3
Hypertension	3.5	2.5,4.4	6.4	5.4,7.4	19.2	17.2,21.2	1.4	0.8,2.0	0.2	0.0,0.4	30.6	28.4,32.9
BMI >30	3.6	2.6,4.6	5.8	4.5,7.1	11.3	9.4,13.21	0.6	0.3,1.0	0.1	0.0,0.1	21.4	18.8,23.9
Previous kidney disease	3.6	0.2,7.0	11.8	5.6,18.0	42.8	34.7,50.9	7.8	3.0,12.6	4.0	0.0,7.9	70.0	61.9,78.2
None of the previous	1.8	1.0,2.6	3.0	1.7,4.3	7.3	5.5,9.1	0.5	0.1,0.9	0.0		12.6	9.9,15.3
Metabolic syndrome	3.9	2.5,5.3	5.6	4.1,7.1	15.0	12.8,17.3	0.8	0.4,1.3	0.1	0.0,0.2	25.5	22.0,28.9

effect (Table 4). Although women have a higher risk than men of having CKD 3 to 5, they are at reduced risk of albuminuria.

Discussion

The INCIPE study is the first sufficiently large study exploring the prevalence of CKD in Italy and in southern Europe. Only in a tiny minority of European countries do data exist on the epidemiology of CKD. It is perhaps because of this lack of information that just a few European countries have started surveillance programs on the CKD epidemic and even less put in place specific plans to halt it. We feel our survey, by providing relevant information on CKD in one of the most populous European countries, is an important addition to the knowledge base on this still overlooked problem and could fuel the interest of health agencies in implementing preventive programs.

Major findings of the study are as follow: (*1*) abnormal serum creatinine values are less frequent in persons from Italy than in persons from the United States; (*2*) the prevalence of CKD is higher in the United States than in NE Italy; (*3*) persons from NE Italy have lower prevalence of certain renal risk factors than persons from the United States; (*4*) in both populations CKD stage 3 represents most of the CKD.

Prevalence of CKD in the INCIPE and NHANES Populations

The prevalence of CKD in Caucasians ≥40 years old is much higher in the United States (20.3%) than in NE Italy (13.2%) and this is confirmed also by the 3 times higher prevalence of abnormal SCr values in the U.S. population. The two populations differ regarding a number of renal risk factors. Actually, the prevalence of diabetes, obesity, and metabolic syndrome (Figure 2) is higher in persons from the United States. This may

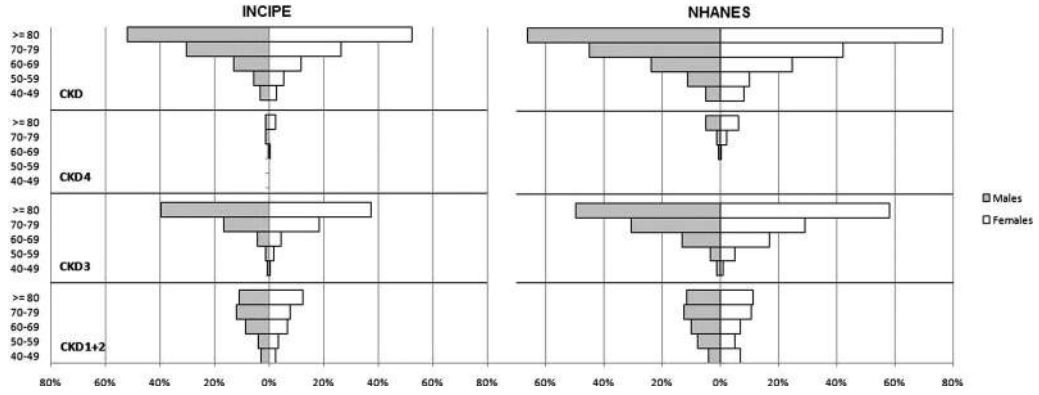

Figure 1. Prevalence of CKD according to age classes, in men and women, in INCIPE and NHANES populations.

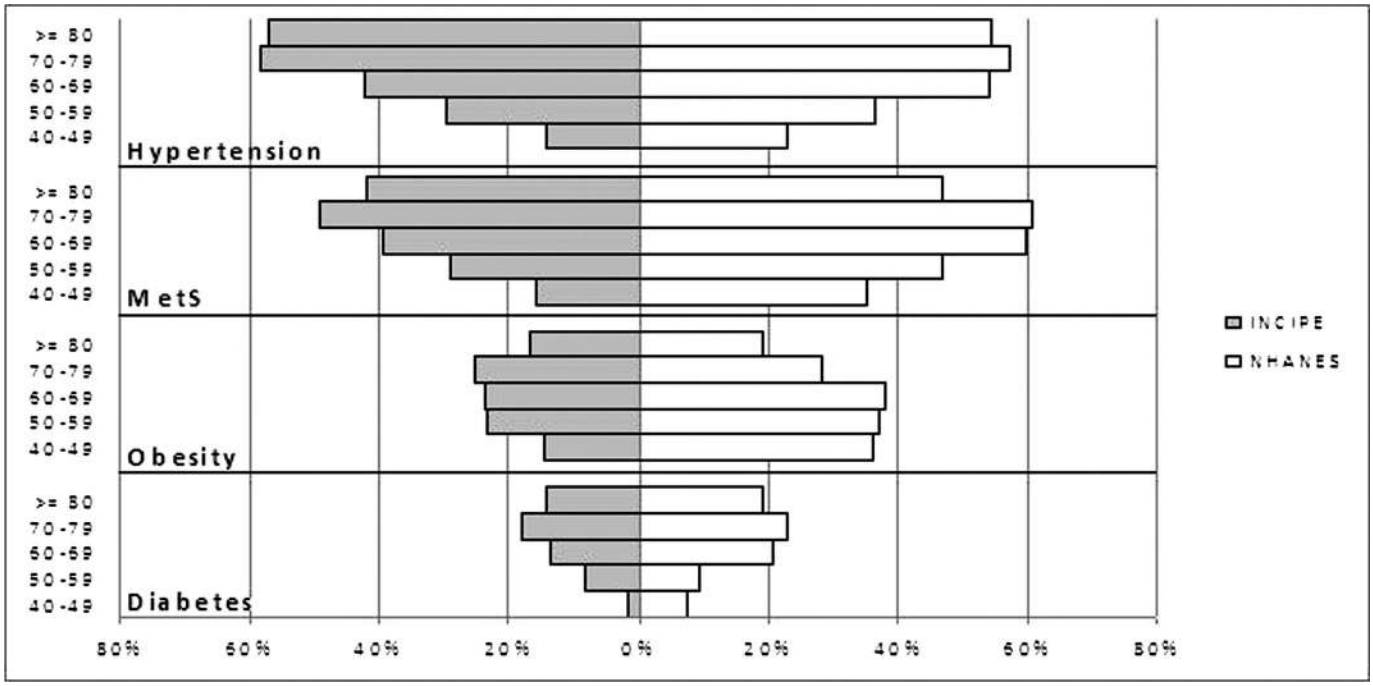

Figure 2. Prevalence of hypertension, metabolic syndrome, obesity, and diabetes according to age classes in INCIPE and NHANES populations.

explain why CKD appears to be more prevalent in the United States than in NE Italy.

Another explanation could be that the CKD EPI equation for the determination of the eGFR performs differently in persons from Italy. This has been shown in other nationalities in reference to the Modification of Diet in Renal Disease (MDRD) equation (15). However, in a study carried out by us, the MDRD formula performed quite well in persons from Italy in whom GFR was measured with the iohexol clearance method (unpublished). Furthermore, the higher prevalence of micro- and macroalbuminuria in the NHANES population (Supplementary Table 3) supports the idea that CKD is really more prevalent in persons from the United States.

Because our prevalence data are based on a single measurement, we may have overestimated the true prevalence of CKD. If we consider that 50% of microalbuminuric patients with GFR >90 ml/min per 1.73 m^2 and 70% of those with GFR 60 to 89, and 100% of the macroalbuminuric individuals have persistent albuminuria

Table 3a. INCIPE: Proportion of people with CKD stage 3 split into substages

	GFR 45 to 59 and Normoalbuminuria		GFR 45 to 59 and Albuminuria (CKD 3a)		GFR 30 to 44 (CKD 3b)	
	%	95% CI	%	95% CI	%	95% CI
Total	4.1	3.5,4.8	1.0	0.6,1.3	1.3	1.0,1.7
Men	3.6	2.7,4.5	1.2	0.6,1.7	1.4	0.8,1.9
Women	4.6	3.6,5.5	0.8	0.4,1.2	1.3	0.8,1.8
40 to 49 years	0.2	0.0,0.6	0.0		0.1	0.0,0.4
50 to 59 years	1.2	0.6,1.9	0.3	0.0,0.6	0.1	0.0,0.3
60 to 69 years	3.0	2.0,4.1	0.7	0.2,1.2	0.5	0.1,1.0
70 to 79 years	10.4	8.0,12.8	3.1	1.7,4.4	4.2	2.6,5.8
≥80 years	25.5	18.7,32.2	3.7	0.8,6.7	9.3	4.8,13.8
Diabetes	5.8	3.4,8.1	4.4	2.3,6.5	3.8	1.9,5.8
Hypertension	6.7	5.3,8.1	2.0	1.2,2.8	2.9	1.9,3.8
BMI >30	4.2	2.8,5.6	1.1	0.4,1.9	2.3	1.2,3.3
Previous kidney disease	7.1	3.9,10.2	2.4	0.5,4.2	5.1	2.4,7.8
None of the previous	2.6	1.8,3.3	0.2	0.0,0.4	0.2	0.0,0.4
Metabolic syndrome	6.0	4.7,7.4	2.3	1.5,3.2	3.0	2.1,4.0

Table 3b. NHANES: Proportion of people with CKD stage 3 split into substages

	GFR 45 to 59 and Normoalbuminuria		GFR 45 to 59 and Albuminuria (CKD 3a)		GFR 30 to 44 (CKD 3b)	
	%	95% CI	%	95% CI	%	95% CI
Total	7.5	6.7,8.3	1.6	1.3,2.0	2.8	2.3,3.4
Men	6.3	5.4,7.1	1.7	1.2,2.2	2.2	1.6,2.7
Women	8.6	7.5,9.7	1.6	1.2,1.9	3.5	2.7,4.3
40 to 49 years	0.9	0.3,1.5	0.0	to	0.1	0.0,0.3
50 to 59 years	3.0	1.9,4.2	0.7	0.0,1.3	0.4	0.0,0.9
60 to 69 years	11.6	9.9,13.3	1.3	0.6,2.1	2.2	1.2,3.3
70 to 79 years	17.9	15.1,20.7	3.6	2.4,4.9	8.2	6.2,10.2
≥80 years	27.4	24.0,30.7	10.4	8.5,12.2	17.3	14.5,20.0
Diabetes	11.3	7.6,14.9	2.8	1.2,4.4	5.1	2.8,7.5
Hypertension	11.0	9.6,12.4	3.0	2.1,3.8	5.2	4.1,6.2
BMI >30	6.6	5.2,8.0	1.7	1.0,2.5	3.0	2.0,3.9
Previous kidney disease	16.0	9.9,22.0	9.8	3.5,16.1	17.0	10.7,23.3
None of the previous	5.2	3.6,6.8	0.9	0.4,1.4	1.2	0.5,1.8
Metabolic syndrome	9.4	7.7,11.1	2.1	1.4,2.8	3.5	2.6,4.3

(16), the total prevalence of CKD changes only modestly, from 12.7 to 10.8% in NE Italy and from 20.3 to 17.7% in the United States.

Prevalence of CKD 3 According to Different Definitions

The possibility exists that we are overestimating the prevalence of CKD because of the criteria used for CKD categorization (17). Definition of CKD 3 is particularly questioned (17). This stage is the most prevalent among all stages in both populations with a dramatic increase in the more advanced age classes (Figure 1).

It is not known which renal diseases explain the condition, although part of these patients could simply have an aging kidney. Actually, among patients with CKD 3, most are ≥60 years old (91.4% in NE Italy and 87.3% in the United States) and the majority have normoalbuminuria (77.9 and 78.1%), whereas only a few (6.1 and 5.1%) have macroalbuminuria.

CKD 3 is also more prevalent in women. However, the proportion of them not disclosing abnormal AER is larger than that in men (Supplemental Table 3). Thus, very few have evidence of kidney damage. Actually, there is an opposite effect of the female gender on the risk of having albuminuria (decreased) than of having CKD 3 to 5 (Table 4), which may suggest an over-representation of CKD stage 3 because of the underestimation of GFR in women by the CKD EPI formula.

With subclassification of CKD 3 into CKD 3a and CKD 3b, the prevalence of CKD (all stages) changes from 12.7 to 8.5% in NE Italy and from 20.3 to 12.8% in the United States. The rationale for such subclassification of the CKD stage 3 is that in these patients it is the presence of abnormal albuminuria that plays a crucial role in the determination of the CV and renal risk. In prospective studies in the general population, Foster *et al.* (18) have shown that risk of a CV event in CKD 3 without albuminuria is not increased

Table 4. Multivariate logistic regression of albuminuria and CKD 3-4-5 (by different definitions of CKD 3), comparing NHANES and INCIPE

	CKD 3 (GFR<60 ml/min per 1.73 m^2)			CKD 3b (GFR<45 ml/min per 1.73 m^2)			AER		
	OR	95% CI	*P*	OR	95% CI	*P*	OR	95% CI	*P*
NHANES *versus* INCIPE	2.70	2.25,3.26	<0.0001	2.50	1.79,3.49	<0.0001	1.45	1.21,1.73	<0.0001
Gender (women *versus* men)	1.20	1.03,1.39	0.0195	1.28	1.01,1.64	0.0441	0.85	0.73,0.98	0.0302
Age (per year)	1.13	1.12,1.14	<0.0001	1.14	1.12,1.15	<0.0001	1.05	1.04,1.06	<0.0001
Diabetes	1.20	0.99,1.45	0.0672	1.32	1.00,1.76	0.0525	2.69	2.27,3.20	<0.0001
CV history	1.70	1.43,2.01	<0.00001	1.91	1.49,2.44	<0.0001	1.41	1.18,1.68	0.0001
Hypertension	1.70	1.50,2.00	<0.0001	1.92	1.49,2.47	<0.0001	1.43	1.23,1.67	<0.0001
Renal history	3.62	2.72,4.83	<0.0001	5.56	3.88,7.96	<0.0001	2.25	1.72,2.95	<0.0001
Smoke	0.91	0.77,1.07	0.2345	1.03	0.80,1.34	0.8050	1.10	0.94,1.30	0.2483
BMI >30	1.30	1.09,1.52	0.0025	1.52	1.17,1.97	0.0016	1.27	1.08,1.49	0.0034

with respect to patients without CKD, whereas Hallan *et al.* (19) have observed that both conditions increase the risk, but in the presence of abnormal albuminuria the CV risk increases dramatically. Furthermore, it has also been shown that most of the patients with CKD 3 have fairly stable renal function and that it is the concurrence of abnormal albuminuria that imparts the risk of progressive renal disease (20).

Risk Factors for CKD and Albuminuria in Both Populations

In the two populations the effect of hypertension (OR 2.09 *versus* 1.85 in INCIPE and NHANES, respectively) and diabetes (2.66 *versus* 2.51) on the risk of having CKD (any stage) is almost the same. However, as observed, the different prevalence of diabetes and hypertension, more frequent in the United States, concurs in explaining the higher CKD prevalence in the NHANES population. The finding that even after adjustment for a number of variables the risk of having CKD 3 to 5 and albuminuria is definitely higher in the NHANES population (Table 4) than in the INCIPE population suggests a significant role by other indeterminate factors.

Limitations of the Study

The study has a number of limitations. Some have been discussed before. The participation of >60% was lower than expected; however, for an epidemiologic, voluntary study it is certainly good. In fact, whereas in the NHANES (2) and the HUNT II (4) surveys the participation rate among those approached was 70%, in the Nijmegen Biomedical Study it was only 29% (21). The reduced participation is probably the cause of the distortion of the sample in terms of age and gender from the randomized population, that is, a reduced representation of the 4th decade of age, particularly in men, and of the >80 years in women. However, differences are <6% of the crude frequencies in each age and gender class, thus suggesting that such a response bias is probably very modest.

The study enrolled only patients older than 40 years and thus its data cannot be generalized to the whole population. However, the causal relationship of CKD with disorders such as hypertension, type 2 diabetes mellitus, and obesity—which typically occur after the 4th decade of age—makes this section of the population the most affected by CKD.

We have used the same cutoff for the definition of microalbuminuria in both genders, although most likely a higher one should be used in women (22). Because of the two-steps strategy used for the determination of albuminuria (a prescreening of samples with a strip test and confirmation of positive results measuring albumin immunochemically), because the cutoff for strip-positive results—≥3.4 mg/mmol creatinine—is independent of gender, we cannot analyze our data by considering gender-specific ranges for albuminuria. However, others used the same cutoff for both genders (4,16). Furthermore, the comparison between the two populations was not affected because we used the same criteria in both. The opposite effect of gender on the risk of CKD 3 to 5 and on abnormal albuminuria cannot be influenced by such a definition because the use of a higher cutoff for albuminuria in women would have magnified such a divergence.

Conclusions

The prevalence of CKD is higher in the United States than in NE Italy probably because of the higher prevalence of a number of renal risk factors in persons from the United States. In both populations the implementation of the definition of the CKD 3 stage with albuminuria impressively decreases the prevalence of CKD because a large number of patients with GFR <60 ml/min do not have abnormal albuminuria.

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Disclosures

None.

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