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ORIGINAL ARTICLE

Prevalence and cardiovascular risk profile of chronic kidney disease in Italy: results of the 2008–12 National Health Examination Survey

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ABSTRACT

Background. National surveys in countries outside Europe have reported a high prevalence (11–13%) of chronic kidney disease (CKD). Studies in Europe have provided a variable prevalence likely due to differences in study design, including age and extent of geographic areas, equation used to evaluate estimated glomerular filtration rate (eGFR) and CKD stages examined.

Methods. The 2008–12 National Health Examination Survey in Italy randomly extracted samples from the general population aged 35–79 years, stratified by age and gender, from the resident list of each Italian region (440 persons/1.5 million of residents). We estimated the prevalence of CKD by means of urinary albumin : creatinine ratio and eGFR (CKD-EPI equation–enzymatic assay of serum creatinine). Cardiovascular (CV) risk profile was also evaluated.

Results. Three thousand eight hundred and forty-eight men and 3704 women were examined. In the whole population, mean age was 57 ± 12 and 56 ± 12 years in men and women, respectively; hypertension was prevalent in men and women, respectively (56 and 43%) and the same held true for

overweight (48 and 33%), obesity (26 and 27%), diabetes (14 and 9%) and smoking (21 and 18%), whereas CV disease was less frequent (9 and 6%). Overall, the prevalence of CKD (95% confidence interval) was 7.05% (6.48–7.65). Early stages constituted 59% of the CKD population [Stage G1–2 A2–3: 4.16% (3.71–4.61) and Stage G3–5: 2.89% (2.51–3.26)]. At multivariate regression analysis, age, obesity, hypertension, diabetes, CV disease and smoking were all independent correlates of CKD.

Conclusions. CKD has a relatively lower prevalence in Italy, in particular for advanced stages, when compared with similar national surveys outside Europe. This occurs despite older age and unfavourable CV risk profile of the whole population.

Keywords: albuminuria, chronic kidney disease, health survey, glomerular filtration rate, risk profile

INTRODUCTION

Chronic kidney disease (CKD) is a prevalent condition and public health priority worldwide [1]. Aging, nutrition status, prevalence of infectious diseases and environmental and genetic factors, as well as access to health care, can profoundly modify CKD epidemiology [2–4]. Prevalence of end-stage renal disease (ESRD), in fact, differs substantially across countries [1, 3]. More important, mortality related to CKD has almost doubled in the past two decades worldwide, with the overall increase in years of life lost due to premature mortality being the third largest behind HIV–AIDS and diabetes mellitus [5]. Even moderate reductions in estimated glomerular filtration rate (eGFR) and/or increases in albuminuria worldwide enhance the risk of ESRD as well as all-cause and cardiovascular (CV) death independently of age, hypertension and diabetes [6–8]. Therefore, CKD is a public health priority characterized by poor prognosis worldwide and variable prevalence across countries.

Studies estimating at the national level the prevalence of CKD are urgently needed to properly inform health-care planners and to increase awareness of this problem, which remains disturbingly low in the general population and in the medical community as well [1, 9, 10]. National, population-based surveys of CKD prevalence that incorporate both albuminuria and proper estimates of eGFR [i.e. based on the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [2, 11] have been conducted in North America, China and Australia [12–15]. These studies reported a high prevalence (11–13%) of CKD in the general adult population. In Europe, similar prevalence rates have been suggested [16–23]; however, these studies were mostly based on the MDRD equation [16–19, 21, 22], were geographically circumscribed to regions [18, 21–23] or towns [16, 17, 19, 20], or did not examine the early (albuminuric) stages [19, 21].

The first survey of the Cardiovascular Epidemiology Observatory/Health Examination Survey (OEC/HES) in Italy, founded by the Italian Ministry of Health, was performed between 1998 and 2002 by the National Institute of Health (ISS) and the National Association of Hospital Cardiologists (ANMCO) to provide a complete picture of the Italian population's health and to facilitate implementation of preventive programmes [24]. From 2008 to 2012, a second survey was conducted using the same methodologies and procedures used in the first survey. Here, we describe the results of CArdiovascular risk profile in Renal patients of the Italian Health Examination Survey (CARHES), a project embedded into the OEC/HES 2008–12. CARHES aimed at estimating the prevalence of a whole spectrum of CKDs and associated CV risk factors in a nationally representative sample from the general adult population in Italy.

MATERIALS AND METHODS

Cardiovascular Epidemiology Observatory/Health Examination Survey

The survey lasted from April 2008 to December 2012. Procedures were planned according to the recommendations of the European Health Risk Monitoring–Feasibility of European HES projects (available at www.ktl.fi/fehes/) and the WHO MONICA (Multinational MONItoring of trends and determinants in CArdiovascular disease) project [25]. Research was approved by the ethics committee of ISS and all recruited persons signed the informed consent.

According to the MONICA project methodology [25], sample size was planned to include 220 men and 220 women in the age range of 35–79 years per 1.5 million residents in each Italian region, randomly selected from the resident list. No additional restriction was applied to the list of residents; therefore, also subjects with any illness, even if severe, such as CKD treated with dialysis or kidney transplant, were eligible for screening. Subjects were stratified by age and gender (25 subjects for gender in each year of age in the range of 35–74 years, and 20 subjects for gender in each year of age in the range of 75–79 years). This allowed at least 500 men and women in each 10-year age group to be obtained, according to the European recommendations (European HES) for conducting a national HES [26]. The list of invited subjects in each of the 20 regions of Italy included the number of participants to be three times higher to ensure the achievement of the planned sample in the presence of potential refusals. All subjects were invited by letter and phone contacts. If the extracted subject refused the visit or he/she was not found after three attempts, he/she was substituted with the subsequent one on the list until the number of subjects, established for the specific age stratum and gender, was reached. The participation rate, defined as the percentage of acceptance of first candidates on the list, was 53%. The rate was higher in the north than in the Centre and south (59, 48 and 49%, respectively, $P < 0.0001$). Participants were invited to public hospitals, one in each of the 20 regions of Italy, to undergo interviews and medical examinations conducted by health personnel specifically trained for HES. All procedures were standardized and centres were kept under quality control by the ISS staff during the fieldwork. Research personnel administered a questionnaire (personal and medical history) and measured anthropometric features (height, weight, waist and hip circumferences), blood pressure (BP), and collected blood and

24-h urine samples. Complete haemochrome analysis was immediately obtained, while frozen aliquots of serum and urine were sent to the central laboratory (Genetic and Environmental Epidemiology Deptartment of the Catholic University of Campobasso) for biochemical testing.

CARHES

This analysis was aimed at estimating the prevalence of CKD and associated CV risk profile in the national population-based sample of the OEC/HES 2008–12. Persons identified as having CKD were classified in the current six CKD stages [2]. The first two stages were defined by the presence of albumin-to-creatinine ratio (ACR) ≥30 mg/g and either eGFR ≥90 mL/min/1.73 m^2 (Stage G1 A2–3) or eGFR 89–60 mL/min/1.73 m^2 (Stage G2 A2–3); more advanced stages were only defined on the basis of eGFR values: 59–45 mL/min/1.73 m^2 (Stage G3a), 44–30 mL/min/1.73 m^2 (Stage G3b), 29–15 mL/min/1.73 m^2 (Stage G4) and <15 mL/min/1.73 m^2 (Stage G5). A2 identified subjects with ACR 30-299 mg/g and A3 those with ACR ≥300 mg/g.

Questionnaires on personal and medical history, BP, body mass index (BMI), waist–hip ratio, lipids, glycaemia and haemoglobin (Hb) levels were used to assess CV risk profile. We recorded the following comorbidities: hypertension (BP ≥140/90 mmHg or any use of antihypertensive medication), diabetes (fasting glycaemia ≥126 mg/dL or diagnosis or treatment), anaemia (Hb <13 g/dL in male and <12 g/dL in female), obesity (BMI ≥30 kg/m^2), previous CV events (self-reported and/or documented by electrocardiography myocardial infarction and self-reported angina pectoris, cerebrovascular events and revascularization or coronary artery bypass) and high cholesterol (>200 mg/dL or treatment). Information on smoking (current smoker), alcohol habit (alcoholic drink ≥1per day) and high education level (≥high school graduation) were also collected.

Laboratory analyses

Isotope dilution mass spectrometry (IDMS)-traceable creatinine measurement (enzymatic assay) was used to allow proper estimates of GFR by means of the CKD-EPI equation [2, 11]. Twenty-four urine samples, stored at −80°C, were used to calculate ACR; albuminuria was measured by immunoturbidimetric tests and urine creatinine by the same method used for serum creatinine (enzymatic assay).

All tests were performed by using reagents and automatic analyser (MODULAR Analytic) by ROCHE Diagnostics (Monza, Italy). Interday coefficients of variation were 1.82 and 1.56% for serum creatinine, 1.31 and 1.17% for urinary creatinine and 1.92 and 2.31% for albuminuria, respectively, for normal and pathological controls.

Total and high-density lipoprotein (HDL) cholesterol, triglycerides and glucose were measured in serum samples using commercial enzyme colorimetric kits (Instrumentation Laboratory, Milan, Italy) and an automatic analyser (IL 350). Coefficients of variation for high-level external standards were 5.5% for cholesterol, 5.0% for triglycerides, 6.1% for HDL cholesterol and 5.0% for glucose. Corresponding coefficients of variation for low-level external standards were 5.8, 7.9, 7.0 and 7.6%; corresponding coefficients of variation for an in-house plasma pool were 2.6, 3.5, 5.3 and 3.8%. Low-density lipoprotein (LDL) cholesterol was calculated by Friedewald formula.

Statistical analysis

Prevalence and 95% confidence intervals (95% CIs) of CKD are reported in total, by gender, age class and stage of disease. Owing to the small number of persons identified as having advanced stages of CKD, adequate estimates of age–gender standardized prevalence could only be estimated for CKD overall and combined CKD Stages G1–2 and G3–5. We calculated both crude and age-standardized means and prevalence for continuous and categorical variables, respectively, stratified by gender. Since 2010 is the middle year of the screening, the Census 2010 Italian resident population 35–79 years old was used as the standard for the age standardization. Mean values were compared by Student's *t*-test or Mann–Whitney test, as appropriate; prevalence rates were compared by the χ^2test.

The association between indicators of kidney damage and relevant covariates was explored using multivariable logistic regression models and reported as odds ratios (ORs) with 95% CI. SAS software (version 9.2) was used for data management and statistical analyses. Two-sided P-values of <0.05 were statistically considered significant.

RESULTS

CKD prevalence

In the OEC/HES, 8693 persons out of the planned sample of 9020 underwent interviews and examinations (96.4%). Information on ACR or serum creatinine was lacking in 1141 individuals. Thus, CARHES included 7552 Caucasian subjects (84% of the planned sample). In the sample, 28 persons with eGFR <60 mL/min/1.73 m^2 did not have ACR measured; therefore, the evaluation of distribution of albuminuria by eGFR category was obtained in 7524. The general characteristics of the whole population are reported in Table 1.

Table 2 describes unadjusted prevalence estimates of CKD. Overall, prevalence of CKD increased remarkably across age strata, from 2.7% at age 35–49 years to 17.0% at 70–79 years. Early stages of disease accounted for most of the estimated CKD population, the prevalence of the first two CKD stages (4.16%) being higher than that of CKD Stage G3a–5 (2.89%). In particular, persons with eGFR <45 mL/min/1.73 m^2 (Stage G3b–5) represented only 0.78% of the whole population and the 11% of the CKD population. Prevalence of CKD was similar in North [7.0% (95% CI 6.1–7.9)], Centre [5.6% (95% CI 4.3–7.0)] and South [7.8% (95% CI 6.8–8.8)]. When considering the prevalence rates of single stages of disease by gender, we observed a higher prevalence of early—albuminuric—stages in males, with the difference being not maintained in the more advanced stages of disease, G3a–5. Questionnaire-reported awareness of CKD was poor with 10.0% of person with CKD being aware of their condition; awareness increased to 18.4% in those with eGFR <60 mL/min/1.73 m^2.

Table 1. Characteristics of survey participants overall and stratified by gender and presence of CKD

	All ($n = 7552$)	Males			Females		
		No CKD ($n = 3558$)	CKD ($n = 290$)	P-value	No CKD ($n = 3462$)	CKD ($n = 242$)	P-value
Age (years)	56.7 ± 12.4	56.3 ± 12.3	66.3 ± 10.7	<0.001	55.8 ± 12.0	64.8 ± 12.0	<0.001
ACR (mg/g)	15.0 [12.3–17.6]	3.8 [3.6–4.0]	213.5 [148.0–279.0]	<0.001	5.7 [5.5–5.9]	91.3 [67.8–114.7]	<0.001
eGFR (mL/min/1.73 m^2)	95.9 ± 16.3	97.1 ± 13.9	74.3 ± 25.7	<0.001	97.9 ± 14.1	75.1 ± 27.6	<0.001
Systolic BP (mmHg)	132 ± 19	134 ± 17	143 ± 21	<0.001	129 ± 20	139 ± 21	<0.001
Diastolic BP (mmHg)	82 ± 10	84 ± 10	83 ± 11	0.08	79 ± 10	80 ± 11	0.4
Total cholesterol (mg/dL)	213 ± 44	209 ± 43	198 ± 47	0.001	218 ± 43	213 ± 46	0.07
HDL cholesterol (mg/dL)	56 ± 15	51 ± 13	47 ± 12	<0.001	62 ± 15	57 ± 15	<0.001
LDL cholesterol (mg/dL)	132 ± 38	131 ± 37	120 ± 41	<0.001	135 ± 37	130 ± 40	0.06
Triglycerides (mg/dL)	122 [120–124]	133 [131–136]	156 [146–167]	<0.001	107 [105–109]	129 [122–136]	<0.001
Haemoglobin (g/dL)	14.2 ± 1.4	15.0 ± 1.1	14.7 ± 1.6	<0.001	13.4 ± 1.1	13.3 ± 1.4	0.4
Glycaemia (mg/dL)	99 ± 24	102 ± 24	116 ± 39	<0.001	94 ± 20	107 ± 40	<0.001
BMI (kg/m^2)	27.5 ± 4.9	27.6 ± 4.1	29.2 ± 4.9	<0.001	27.2 ± 5.5	29.1 ± 6.2	<0.001
Waist (cm)	92.3 ± 13.3	96.6 ± 11.3	101.4 ± 11.4	<0.001	87.2 ± 13.2	93.3 ± 15.6	<0.001
Waist–hip ratio	0.91 ± 0.10	0.96 ± 0.07	0.99 ± 0.07	<0.001	0.85 ± 0.09	0.87 ± 0.10	<0.001
Hypertension (%)	50.1 [48.9–51.2]	54.6 [53.0–56.2]	78.3 [73.5–83.0]	<0.001	41.5 [39.9–43.2]	71.5 [65.8–77.2]	<0.001
Diabetes (%)	11.8 [11.1–12.5]	12.9 [11.9–14.1]	33.1 [27.7–38.5]	<0.001	7.9 [7.0–8.8]	24.4 [19.0–29.8]	<0.001
Previous CV disease (%)	7.4 [6.8–8.0]	7.3 [6.4–8.1]	23.8 [18.9–28.7]	<0.001	5.9 [5.1–6.7]	11.8 [7.5–15.6]	<0.001
Anaemia (%)	6.9 [6.3–7.6]	4.1 [3.3–4.8]	13.1 [8.6–17.5]	<0.001	9.0 [7.9–10.1]	12.6 [7.9–17.3]	0.1
Obesity (%)	26.4 [25.4–27.4]	24.6 [23.2–26.0]	38.3 [32.7–43.9]	<0.001	26.2 [24.8–27.7]	40.5 [34.3–46.7]	<0.001
Smoking (%)	19.9 [19.0–20.8]	21.4 [20.0–22.7]	19.0 [14.5–23.5]	0.3	18.7 [17.4–20.0]	15.3 [10.8–19.8]	0.2
Alcohol habit (%)	49.6 [48.4–50.7]	64.7 [63.2–66.3]	66.2 [60.8–71.7]	0.6	33.5 [31.9–35.1]	36.8 [30.7–42.9]	0.3
High education (%)	48.7 [47.6–49.8]	50.6 [49.0–52.3]	37.3 [31.7–42.9]	<0.001	49.1 [47.4–50.7]	27.7 [21.9–33.5]	<0.001

Data are mean ± SD or mean [95% CI].
OEC/HES-CARHES 2008–12: 3848 men and 3704 women 35–79 years of age.
ACR, albumin-to-creatinine ratio; eGFR, estimated glomerular filtration rate; BMI, body mass index; CV, cardiovascular. See Materials and methods for definitions.

Table 2. Crude prevalence estimates of CKD in the adult Italian population overall and by disease stage and demographic characteristics

	Total CKD		G1 A2–3		G2 A2–3		G3a		G3b		G4		G5	
	%	95% CI	%	95% CI	%	95% CI	%	95% CI	%	95% CI	%	95% CI	%	95% CI
Total	7.05	6.48–7.65	2.64	2.29–3.02	1.52	1.26–1.83	2.11	1.79–2.45	0.50	0.36–0.69	0.16	0.08–0.28	0.12	0.05–0.23
Male	7.54	6.72–8.42	2.68	2.19–3.24	2.10	1.68–2.61	1.95	1.54–2.44	0.47	0.28–0.74	0.21	0.09–0.41	0.13	0.04–0.30
Female	6.54	5.76–7.38	2.59	2.10–3.16	0.92	0.64–1.28	2.27	1.81–2.80	0.54	0.33–0.83	0.11	0.03–0.28	0.11	0.03–0.28
35–49 years	2.65	2.05–3.34	2.01	1.50–2.64	0.20	0.06–0.46	0.20	0.02–0.37	0.04	0.00–0.22	0.08	0.01–0.28	0.12	0.02–0.35
50–59 years	3.41	2.61–4.37	2.79	2.07–3.67	0.17	0.04–0.50	0.28	0.09–0.66	0.11	0.01–0.41	0.06	0.00–0.21	0.06	0.00–0.32
60–69 years	8.71	7.44–10.11	4.02	3.16–5.03	1.95	1.36–2.71	2.06	1.46–2.83	0.45	0.19–0.88	0.17	0.03–0.49	0.06	0.00–0.31
70–79 years	16.97	15.09–18.99	1.84	1.22–2.67	4.91	3.86–6.14	7.63	6.33–9.11	1.84	1.22–2.67	0.48	0.19–0.98	0.27	0.07–0.70

OEC/HES-CARHES 2008–12: 7552 subjects (3848 men and 3704 women) 35–79 years old.
The first two stages, G1 A2–3 and G2 A2–3, were defined by the presence of ACR ≥30 mg/g (A2) and ≥300 mg/g (A3) and either eGFR ≥90 mL/min/1.73 m^2 (Stage G1 A2–3) or eGFR 89–60 mL/min/1.73 m^2 (Stage G2 A2–3). More advanced stages were only defined on the basis of eGFR values: 59–45 mL/min/1.73 m^2 (Stage G3a), 44–30 mL/min/1.73 m^2 (Stage G3b), 29–15 mL/min/1.73 m^2 (Stage G4) and <15 mL/min/1.73 m^2 (Stage G5).
CI, confidence intervals.

CKD prevalence slightly decreased after age standardization to the resident population (overall: 6.29%, 95% CI 5.74–6.84, CKD Stage G1–2 A2–3: 3.78%, 95% CI 3.36–4.22; CKD Stage G3a–5: 2.50%, 95% CI 2.15–2.85), with men showing higher rates of Stage G1–2 A2–3 (4.2 versus 3.4% in females) and slightly lower rates of Stage G3a–5 (2.1 versus 2.8% in females). We can therefore estimate that, in Italy, there is a total number of 2 180 542 adult persons (age 35–79 years) with CKD (1 075 354 men and 1 105 187 women), most with early disease (60.4%) and older age (69.8%; Supplementary data, Table SA).

An ACR of ≥30 mg/g was detected in 4.77% of subjects. In particular, ACR was moderate (ACR 30–299 mg/g, formerly defined as microalbuminuria) in 84.3% of albuminuric persons, with the remaining 15.7% having severe albuminuria (ACR ≥300 mg/g, formerly defined as macroalbuminuria).

Table 3 provides estimates of the prevalence of subjects at cardio-renal risk based on the combined measure of eGFR and albuminuria level. Very few persons can be considered at high or very high risk considering the concomitant presence of reduced eGFR and high albuminuria. Specifically, among subjects with eGFR <60 mL/min/1.73 m^2, albuminuria was present in 23.7%, that is 17.0% with moderate and 6.7% with severe albuminuria. The prevalence of moderate and severe albuminuria in individuals with eGFR <60 was, however, substantially higher than that found in the whole group (that is, with and without low eGFR) of hypertensive (5.7 and 1.3%,

Table 3. Estimated prevalence (%) of subjects at risk of cardio-renal events by estimated GFR and albuminuria

	Albuminuria category (mg/g)			Total
	A1 (<30)	A2 (30–299)	A3 (≥300)	
eGFR category (mL/min/1.73 m^2)				
G1 (>90)	68.63	2.35	0.29	71.28
G2 (60–90)	24.67	1.24	0.29	26.20
G3a (45–59)	1.57	0.29	0.01	1.87
G3b (30–44)	0.28	0.11	0.05	0.44
G4 (15–29)	0.04	0.03	0.08	0.15
G5 (<15)	0.04	0.00	0.03	0.07
Total	95.23	4.02	0.75	100.0

OEC/HES-CARHES 2008–12: 7524 subjects 35–79 years old.
Low risk (white), medium risk (light grey), high risk (medium grey) and very high risk (dark grey). Risk stratification made according to KDIGO (ref. [2]).

Table 4. Multivariate logistic regression analysis estimating clinical correlates of CKD, low eGFR and pathological albuminuria

	CKD		eGFR < 60		ACR ≥ 30	
	OR	95% CI	OR	95% CI	OR	95% CI
Age (year)	**1.06**	**1.05–1.07**	**1.13**	**1.11–1.15**	**1.03**	**1.02–1.04**
Males	1.07	0.87–1.31	0.75	0.55–1.03	**1.42**	**1.11–1.82**
High cholesterol	1.09	0.88–1.34	1.21	0.88–1.71	1.05	0.82–1.34
Obesity	**1.42**	**1.17–1.73**	**1.46**	**1.08–1.96**	1.24	0.98–1.58
Hypertension	**1.55**	**1.23–1.94**	**1.53**	**1.05–2.22**	**1.71**	**1.30–2.25**
Diabetes	**1.98**	**1.59–2.46**	1.23	0.88–1.73	**2.68**	**2.08–3.46**
High education	0.95	0.78–1.17	1.13	0.82–1.57	0.94	0.73–1.20
CV disease	**1.90**	**1.47–2.42**	**2.43**	**1.72–3.44**	**1.65**	**1.21–2.25**
Smoking	**1.34**	**1.05–1.72**	0.76	0.46–1.26	**1.69**	**1.29–2.21**
Alcohol habit	0.94	0.77–1.15	1.08	0.80–1.47	0.84	0.67–1.07

OEC/HES-CARHES 2008–12: 7552 subjects (3848 men and 3704 women) 35–79 years old. Bold values are statistically significant.
BMI, body mass index; CV, cardiovascular. See Materials and methods for definitions.

for moderate and severe albuminuria, respectively) and diabetic subjects (10.6 and 3.1%, respectively).

CV risk profile

In the whole sample, hypertension was prevalent in men and women (56.4 and 43.5%, respectively) and the same held true for overweight (48.4 and 33.2%), obesity (25.6 and 27.2%), diabetes (14.5 and 9.0%) and smoking (21.2 and 18.5%), whereas a positive history of CV disease was relatively less frequent (8.5 and 6.3%). Table 1 compares CV risk profile in survey participants with and without CKD. When compared with non-CKD subjects, men and women with CKD had higher fasting glucose, triglycerides, systolic BP, BMI, waist circumference and waist–hip ratio, while HDL cholesterol was lower. CKD was also associated with higher prevalence of hypertension, diabetes, obesity, anaemia, CV disease and low education level. As persons with CKD were on average 10 years older than non-CKD subjects, we repeated the same analysis after age standardization (Supplementary data, Table SB). This analysis showed that age attenuated but did not substantially modify the differences in the CV risk profile.

Multivariate regression analysis (Table 4) identified age, hypertension and presence of CV disease as main independent correlates of CKD. These results were in fact consistent when analysing separately low GFR and albuminuria. Diabetes and smoking also associated with CKD, but correlated more strictly with albuminuria than low GFR. Conversely, obesity was an independent correlate of CKD, being associated with low eGFR. Males exclusively correlated with albuminuria. Waist–hip ratio or overweight did not correlate with CKD when replacing obesity in the analysis (data not shown).

DISCUSSION

Early European studies have shown a variable CKD prevalence, with significant differences in men and women in most cases [27]. Observed variability may be explained at least in part by heterogeneity of study design, such as differences in population sampling, including age and extent of geographic area, equation used to estimate eGFR and examined stages. The peculiarities of the main CKD surveys are summarized in Table 5. CARHES is the first study estimating CKD prevalence in an European country at the national level and based on a large sample size (the number of screened subjects/resident population was greater when compared with the other four national surveys outside Europe) and adequate measures (CKD stages were defined by ACR and CKD-EPI eGFR).

Unadjusted prevalence of CKD averaged 7% in men and women, with predominance of early stages (Table 2). Similar figures were observed after age and gender adjustment; indeed, standardized rates were 6.3% for all stages of CKD, 3.8% for CKD Stage G1–2 and 2.5% for Stage G3–5. Accordingly, we can estimate 2.2 million adult persons with CKD in Italy, 60% with Stages I and II. Noteworthy, among those with CKD, only 1 of 10 was aware of the pathology, and the perception of disease was similarly scarce also in those with low eGFR (18%), thus confirming that low awareness of CKD is a global problem [1, 9, 10, 27].

CARHES findings differ from the results of the other four main surveys in nationally representative samples of the general population (Table 5). In the National Health and Nutrition Examination Survey (NHANES) 1999–2004 [12], CKD prevalence was 13.1% overall, and the dimension of overt phases (Stages G3–5) was remarkably higher versus Italy. In Canada, comparable estimates with those in the USA were reported; however, at variance with NHANES, there were higher rates for Stages G1–2 (9.4%) than for Stages G3–5 (3.1%) were found [13]. The survey in China yielded comparable results with US and Canadian surveys in terms of overall CKD prevalence; however, prevalence of Stage G1–2 was higher than that reported in NHANES 1999–2004 and the overt stages of disease were poorly represented [14]. In Australia, CKD prevalence has been recently recalculated according to the CKD-EPI equation in the original cohort representative of the adult population examined in 1999–2000 [15]; also in this country, the overall prevalence is high; however, at variance with the other national surveys, the prevalence rates of early and advanced stages are remarkably similar. An additional peculiarity of CKD in Italy is the lower prevalence of albuminuria with decreasing eGFR. Indeed, a reverse association has been

Table 5. Summary of main studies estimating CKD prevalence in the general adult population

Study [Ref.]	Period	Country (city or area)[a]	Sample	Mean age (years)[b]	eGFR equation	Examined stages	Overall prevalence (%)[b]	Prevalence by stage (%)	Main features
NHANES [12]	1999–2004	USA	13 233	46	MDRD	I–IV	13.1	Stage I–II: 5.0 Stage III–IV: 8.1	eGFR by MDRD
CHMS [13]	2007–09	Canada	3689	45	CKD-EPI	I–V	12.5	Stage I–II: 9.4 Stage III–V: 3.1	Small sample
CNS-CKD [14]	2007–10	China	47 204	50	MDRD modified	I–V	10.8	Stage I–II: 9.1 Stage III–V: 1.7	In-depth analysis of heterogeneity
AusDiab [15]	1999–2000	Australia	11 247	51	CKD-EPI	I–V	11.5	Stage I–II: 5.7 Stage III–V: 5.8	Outdated screening
PREVEND [16]	1997–98	Netherlands (Groningen)	2489	49	MDRD	I–V	10.4	Stage I–II: 5.1 Stage III–V: 5.3	eGFR by MDRD, analysis in a single town, outdated screening
ICELAND [17]	1967–96	Iceland (Reykjavik)	19 256	53 M, 54 F	MDRD	I–V	7.2 all, 3.7 M, 10.5 F	Not available	eGFR by MDRD, analysis in a single town, outdated screening
HUNT [18]	1995–97	Norway (Nord-Trondelag)	65 181	50	MDRD	I–IV	11.2	Stage I–II: 6.5 Stage III–IV: 4.7	eGFR by MDRD, analysis in a single region, outdated screening
GUBBIO [19]	1989–92	Italy (Gubbio)	4574	40 M 51 F	MDRD (modified)	III–V	6.4 all, 6.6 M, 6.2 F	Not available	eGFR by MDRD, analysis in a single town, lack of albuminuria, outdated screening
CoLaus[20]	2003–06	Switzerland (Lausanne)	5921	52 M 53 F	CKD-EPI	I–V	10.0	Stage I–II: 5.5 Stage III–V: 4.5	analysis in a single town
BIRNH [21]	1980–84	Belgium	8913	48 M 48 F	MDRD (calibration)	III–V	7.4	Not available	eGFR by MDRD, analysis in a single region, lack of albuminuria, outdated screening
EPIRCE [22]	2004–08	Spain	2746	50	MDRD	I–V	9.1	Stage I–II: 2.3 Stage III–V: 6.8	Small sample, eGFR by MDRD
INCIPE [23]	2006	Italy (Veneto)	3629	60	CKD-EPI	I–IV	12.7 all, 13.2 M, 12.2 F	Stage I–II: 6.0 Stage III–V: 6.7	Analysis in a single region, sampling in GP offices, age–gender standardization to the US population

M, male; F, female; GP, general practitioner.
[a]If not specified, screening covers the whole country.
[b]If not specified, data by gender are not available.

shown in the USA, Canada and China [12–14], whereas a similar prevalence by CKD stages was found in Australia [15]. The Gubbio study specifically addressed the relationship between albuminuria and GFR in a sample of Italian adult subjects of the general population of a town in central Italy [28]. The authors did not find any correlation, with high albuminuria and low eGFR that provided complementary information in defining kidney dysfunction and predicting CV risk. In this regard, it is interesting that a recent large population-based study found a strong association between hyperhomocysteinaemia and higher prevalence of albuminuria that was independent of eGFR level [29]. Therefore, the association between renal function and albuminuria may not be as simple as expected and deserves further *ad hoc* studies.

Conversely, in agreement with other surveys [30, 31], we found that males were characterized by higher prevalence of early, albuminuric CKD stages versus females, but the difference was not maintained for more advanced disease. It is possible to hypothesize that also in Italy men are more prone to develop proteinuric CKD due to the higher rates of hypertension, diabetes, smoking and overweight and, due in part to these differences, being exposed to faster progression to ESRD and premature death with respect to women [31].

The different findings reported by national surveys of the general population, including albuminuria distribution by eGFR, indicate that epidemiology of non-dialysis CKD is mainly influenced by features inherent to the population examined; this hypothesis is supported by the different rates of ESRD reported by national registries of dialysis and transplantation. [1]. Of note, the comparison of CKD prevalence between our study and the surveys in USA and China may be affected by the different methods of eGFR estimation to define CKD; indeed, NHANES 1999–2004 used the MDRD equation and the survey in China used a modified MDRD equation. In this regard, in NHANES 1999–2006, prevalence of CKD was slightly lower (11.5%) when based on the CKD-EPI versus MDRD equation (13.1%) [32]. This difference has been consistently found in other surveys that reported similar overestimation of prevalence rate when GFR was calculated by means of MDRD versus CKD-EPI [15, 20, 30]. Nonetheless, the high prevalence of CKD in USA (14.0%) has been confirmed by the most recent report of NHANES (2005–10) publically available (http://www.usrds.org/2013/pdf/v1_ch1_13.pdf), where the CKD-EPI equation was used.

Knowledge on the early, albuminuric, stages of disease is critical. Pathological albuminuria acts as an independent predictor of *de novo* development of renal function impairment, ESRD and mortality in the general population [1, 6–8, 33], and its remission heralds a better cardio-renal prognosis [1, 2, 33]. CARHES shows a lower prevalence of CKD Stages I–II in Italy when compared with the other main surveys in the rest of the world. Specifically, prevalence was 4.2%, and 3.8% after standardization to the resident population, that corresponds to a concomitance of albuminuria and eGFR ≥60 in ∼1.3 million of adult persons in Italy. In this regard, our data suggest that urine testing would be especially indicated in elderly, smokers, diabetics, hypertensives and those with a history of CV disease, being that these factors are significantly associated with the risk of pathological albuminuria (Table 4). Noteworthy, we found albuminuria to be more prevalent in overt CKD than among individuals with hypertension or diabetes, which are conditions where albuminuria testing is traditionally common. The knowledge that coexistence of albuminuria and low eGFR confers a substantial increase in the risk for ESRD and all-cause mortality should therefore stimulate physicians to routinely perform urine testing also in subjects with impaired eGFR [2, 6–8].

The reason why the prevalence of CKD is lower in Italy is puzzling, and this holds particularly true when taking into account age and CV risk profile. In the whole population, the mean age was ∼10 years higher with respect to surveys in North Europe (Table 5), USA [12], Canada [13], China [14] and Australia [15]. Older age is expected to be a factor that predisposes to CKD development because aging is itself associated with reduced GFR and because older age associates with increased prevalence of obesity, hypertension and diabetes that are all well-known determinants of CKD [1, 2]. Noteworthy, in the whole sample, >50% of subjects had hypertension, one of the four was obese, 20% were smokers and over 10% subjects were affected by diabetes. This picture is not dissimilar when compared with data from the other countries of the Western world. In particular, in the USA, which is the country with the highest prevalence of CKD, hypertension is less frequent (33%) but obesity is more prevalent (35%), while similarities are observed for diabetes, smoking and lipid profile as well [12, 34]. Interestingly, as observed for CKD, also the prevalence of persons with a positive history of CV, disease is significantly lower in Italy (Table 1) than in the USA [34]. Therefore, it is possible that features inherent to the population living in Italy may be protective not only for CV events, but also for CKD development, even in the presence of unfavourable risk profile. Whether this is a 'renal' aspect of the genetic low background risk [35–37], and/or dependent on the still high adherence to the Mediterranean diet [38–40], deserves further studies.

CARHES has three limitations that are shared with the other main surveys on CKD prevalence. First, it is limited by the single measurement of serum creatinine and ACR, while correct identification of CKD requires confirmation of abnormalities in eGFR and/or albuminuria over at least a 3-month period. Secondly, the 53% response rate of the first ones on the list may introduce a bias because these subjects may be healthier or sicker than the rest of population. Thirdly, the dimension of CV disease may not be accurately quantified being mostly based on questionnaires. Finally, as a further potential confounder, we observed a different rate of response to survey, higher in the north versus the rest of Italy, which is compatible with the higher educational and economic level of this region.

In conclusion, in Italy, when compared with other countries, CKD prevalence is relatively low, being ∼7.0% in men and women, with predominance of the early stages (59%). The prevalence of CKD appears to be unexpectedly lower when considering the older age and the unfavourable CV risk profile of the whole population. Low background risk (genetic factors) and/or dietary habits (Mediterranean diet) may play a protective role.

The consequences of CKD, in terms of life years lost and ESRD incidence, vary significantly worldwide and even within Europe [1, 3, 5, 41]. Comparison of CARHES data with those

obtained in the other national surveys outside Europe suggests that CKD may be considered as a 'geographic pathology' also in terms of disease prevalence. Country-level studies on epidemiology of CKD are therefore needed to attain proper estimates of the burden of this high-risk condition.

SUPPLEMENTARY DATA

Supplementary data are available online at http://ndt.oxfordjournals.org.

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CONFLICT OF INTEREST STATEMENT

None declared.

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ORIGINAL ARTICLE

Predictors of renal and patient outcomes in anti-GBM disease: clinicopathologic analysis of a two-centre cohort

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ABSTRACT

Background. Patients with anti-glomerular basement membrane (GBM) disease are at increased risk of morbidity and mortality from renal failure, pulmonary haemorrhage or complications of treatment. One-third also have circulating anti-neutrophil cytoplasmic antibodies (ANCA). The aim of this study was to determine the clinicopathologic predictors of patient and renal outcomes in anti-GBM disease with or without ANCA.

Methods. Retrospective review of 43 patients diagnosed with anti-GBM disease over 20 years in two centres, including nine with dual anti-GBM and ANCA positivity. Renal biopsies from 27 patients were scored for the presence of active and chronic lesions.

Results. Dual-positive patients were almost 20 years older than those with anti-GBM positivity alone (P = 0.003). The overall 1-year patient and renal survivals were 88 and 16%, respectively. Oligoanuria at diagnosis was the strongest predictor of mortality; none of the 16 patients without oligoanuria died. In a Cox regression model excluding oligoanuria, age was the only other independent predictor of survival. Pulmonary haemorrhage and dialysis dependence did not influence mortality. Thirty-five of the forty-three (81%) patients required dialysis at presentation, including all nine dual-positive patients. Of them, only two (5.7%) regained renal function at 1 year. By logistic regression, oligoanuria at diagnosis and percentage of crescents were independent predictors of dialysis independence at 3 months. However, in biopsied patients, the presence of crescents (>75%) added little to the presence of oligoanuria in predicting dialysis independence. Histological activity and chronicity indices did not predict renal outcome. Two of the nine (22%) dual-positive patients relapsed compared with none of the anti-GBM alone patients. Seven patients received kidney transplants without disease recurrence.

Conclusions. Oligoanuria is the strongest predictor of patient and renal survival while percentage of glomerular crescents