Prevalence of CKD and Its Relationship to eGFR-Related Genetic Loci and Clinical Risk Factors in the SardiNIA Study Cohort

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ABSTRACT

The prevalence of CKD and of renal failure vary worldwide, yet parallel increases in leading risk factors explain only part of the differential prevalence. We measured CKD prevalence and eGFR, and their relationship with traditional and additional risk factors, in a Sardinian founder population cohort. The eGFR was calculated using equations from the CKD Epidemiology Collaboration and Modification of Diet in Renal Disease studies. With use of the Kidney Disease Improving Global Outcomes guidelines, a cross-sectional analysis of 4842 individuals showed that CKD prevalence was 15.1%, including 3.6% of patients in the high-risk and 0.46% in the very-high-risk categories. Longitudinal analyses performed on 4074 of these individuals who completed three visits with an average follow-up of 7 years revealed that, consistent with other populations, average eGFR slope was −0.79 ml/min per 1.73 m^2 per year, but 11.4% of the participants had an eGFR decline >2.3 ml/min per 1.73 m^2 per year (fast decline). A genetic score was generated from 13 reported eGFR- and CKD-related loci, and univariable and multivariable analyses were applied to assess the relationship between clinical, ultrasonographic, and genetic variables with three outcomes: CKD, change in eGFR, and fast eGFR decline. Genetic risk score, older age, and female sex independently correlated with each outcome. Diabetes was associated with CKD prevalence, whereas hypertension and hyperuricemia correlated more strongly with fast eGFR decline. Diabetes, hypertension, hyperuricemia, and high baseline eGFR were associated with a decline of eGFR. Along with differential health practices, population variations in this spectrum of risk factors probably contributes to the variable CKD prevalence worldwide.

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Universal concern about CKD and renal failure has led to increasing questions about the basis of geographic differences in CKD prevalence.[1–5] However, only a small number of large, adequately powered studies have estimated prevalence in general populations. The "template" for such studies is the National Health and Nutrition Examination Surveys (NHANES), which showed an alarming increase in CKD prevalence during the last two decades in the United States. Other surveys in Europe and developing countries showed lower but variable prevalence.[6–14] These discrepancies can be partially explained by differences in the prevalence of risk factors, such as diabetes, hypertension, obesity, and atherosclerosis. Furthermore,

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the relative impact of a dissimilar distribution of genetic risk variants associated with eGFR and with ESRD and also of predisposing environmental risk factors in different populations[15–17] remains unclear.

General decline in eGFR is in fact a long-established feature of aging, as shown in the pioneering study of Lindeman *et al.*[18] However, some individuals show more rapid loss of renal function. The contribution of clinical and genetic conditions to the decline in eGFR has been largely conjectural.[19] Therefore, we investigated the clinical and genetic factors that may influence CKD prevalence and longitudinal renal function in a well powered Sardinian founder population cohort (SardiNIA study). Given the recent success in finding and replicating genetic loci affecting eGFR, we developed a genetic risk score for CKD in this population. Because the SardiNIA cohort is relatively less genetically and residentially heterogeneous than the NHANES cohort, it could be less prone to confounders.

RESULTS

General Demographic Characteristics of the SardiNIA Study Cohort

This cohort was representative of the regional population in Ogliastra with regard to mean age ± SD (43.7±17.6 years), sex (58% female), and distribution of age groups, as per the National Census data (Supplemental Figure 1).[20] As shown in Table 1, from the first to the third visit, the prevalence of all traditional risk factors increased.

Longitudinal Renal Function Evaluation

The average age of the cohort increased during the study, both because of normal aging and also because of selective dropout of some younger individuals (see below). As expected, the mean eGFR was thus lower for the population as a whole at the third visit than the first: 98±19.3 ml/min per 1.73 m^2 versus 104.6±20.7 ml/min per 1.73 m^2 (P=0.001) (Table 1). Consequently, individuals with normal renal function decreased from 79.8% to 67.5% (Figure 1A). The average change in renal function evaluated by eGFR during the follow-up period was approximately −0.79 ml/min per 1.73 m^2 per year among 4074 individuals who completed all three visits (Figure 1B). Other categories of patients showed mean changes in renal function (adjusted for starting eGFR) of −1.41 ml/min per 1.73 m^2 per year for patients with diabetes (versus −0.78 for patients without diabetes; P<0.001); −1.09 ml/min per 1.73 m^2 per year for hypertensive patients (versus −0.66 for those without hypertension; P<0.001); −1.06 ml/min per 1.73 m^2 per year among the obese (versus −0.75 among the nonobese; P<0.001); and −1.87 ml/min per 1.73 m^2 per year for individuals with a starting eGFR of <60 ml/min per 1.73 m^2 (versus −0.80 for individuals with starting eGFR of >60 ml/min per 1.73 m^2; P=0.01). A selected group of 915 individuals who were considered "normal" (showing none of the previously listed clinical conditions, and normal LDL and uric acid levels) showed the slowest change: −0.52 ml/min m^2 per year (versus −0.86 for all other individuals; P<0.001) (see Figure 1B). A decline in eGFR faster than 1 SD from the mean (>2.3 per year, "fast decline") was observed in 11.4% of the patients (Supplemental Figure 2). The mean slope of eGFR improved slightly but significantly with age in the whole cohort (β=0.002 ml/min per 1.73 m^2 per year; r^2=0.001; P=0.02) and in "normal" individuals (β=0.01 ml/min per 1.73 m^2per year; r^2=0.01; P=0.01). In these subgroups, the rates of decline seemed to vary little with aging. The rate of eGFR decline increased among patients with diabetes, but not significantly (β=−0.01 ml/min per 1.73 m^2 per year; r^2=0.003; P=0.5). A small but significant increase in the decline of eGFR with age was observed in obese patients (β=−0.01 ml/min per 1.73 m^2 per year; r^2=0.02; P<0.001) and in hypertensive individuals (β=−0.01 ml/min per 1.73 m^2 per year; r^2=0.01; P=0.001). A more pronounced decline in eGFR with aging was seen among individuals with baseline eGFR<60 ml/min per 1.73 m^2 (β=−0.06 ml/min per 1.73 m^2 per year; r^2= 0.26; P<0.001) (Supplemental Figure 3).

Prevalence of Albuminuria and CKD

At the third visit, 9.5% of patients had microalbuminuria and 3.4% had macroalbuminuria. The overall estimate of CKD stages 1–5 was 14.5% (12.9% among men and 15.4% among women according to Kidney Disease Outcomes Quality Initiative [KDOQI] guidelines). On the basis of the new 3D Kidney Disease Improving Global Outcomes (KDIGO) CKD guidelines, 15.5% of individuals had CKD:[21] Approximately 12% had normal or mildly decreased eGFR with microalbuminuria or mildly to moderately decreased eGFR without proteinuria (G1-A2; G2-A2 and G3a-A1: "moderately low risk"); 3.6% had normal or mildly decreased eGFR with macroalbuminuria, mildly to moderately decreased eGFR with microalbuminuria, or moderately to severely decreased eGFR (G1-A3; G2-A3, G3a-A2, G3b-A1: "high risk"); and 0.46% had mildly to moderately decreased eGFR with macroalbuminuria or moderately to severely decreased eGFR with microalbuminuria and/or macroalbuminuria or severely decreased eGFR (G3a-A3, G3b-A2, G3b-A3, G4/G5-A1/A3: "very high risk") (Supplemental Table 1). The overall prevalence of CKD was higher in women (16.6% versus 13.9%), but more men were at high to very high risk (5.3% versus 3.0%) (Figure 2). CKD prevalence in our study population was clearly associated with increasing age, rising from 13.4% in the 40- to 60-year-old group to 16.9% in the 60- to 70-year-old group, to 27.6% in the 70- to 80-year-old group, and to 33.9% in the >80-year-old group. This trend was confirmed in each KDIGO risk category (Supplemental Figure 4). The highest prevalence of CKD was in individuals with diabetes (24.9%), hypertension (20.7%), obesity (19.8%), hyperuricemia (19.2%), or metabolic syndrome (20.7%). The lowest CKD prevalence (*i.e.,* 12.7%) was observed in individuals who had none of the confounders listed above. The difference in CKD prevalence among individuals with the cited risk factors compared with

Table 1. Population characteristics of SardiNIA study cohort individuals by visit

Variable	Total Sample			
	Visit 1	Visit 2	Visit 3	Trend Test or Chi-Square ^{2} *P* Value
Total sample				
Patients (*n*)	6165	5256	4842	
Age range, *n* (%)				
<20 yr	542 (8.8)	187 (3.6)	34 (0.7)	<0.001
20–39 yr	2280 (37)	1785 (34.3)	1482 (30.6)	<0.001
40–59 yr	2058 (33.4)	1941 (37.3)	1942 (40.1)	<0.001
60–69 yr	764 (12.4)	718 (13.8)	746 (15.4)	<0.001
≥70 yr	518 (8.4)	572 (11)	639 (13.2)	<0.001
Men, *n* (%)	2625 (42.6)	2175 (41.8)	2048 (42.3)	0.64
Smoking, *n* (%)	1048 (17)	1114 (21.4)	1148 (23.7)	<0.001
Metabolic syndrome, *n* (%)	388 (6.3)	354 (6.8)	634 (13.1)	<0.001
Obesity, *n* (%)	967 (15.7)	869 (16.7)	876 (18.1)	<0.001
Large waist, *n* (%)	2440 (39.6)	2264 (43.5)	2382 (49.2)	<0.001
Diabetes, *n* (%)	320 (5.2)	385 (7.4)	441 (9.1)	<0.001
High glucose, *n* (%)	234 (3.8)	229 (4.4)	300 (6.2)	<0.001
Hypertension, *n* (%)	1842 (29.9)	1655 (31.8)	1549 (32)	<0.001
High BP, *n* (%)	1571 (25.5)	1296 (24.9)	1070 (22.1)	0.22
Previous cardiac disease, *n* (%)	259 (4.2)	245 (4.7)	271 (5.6)	<0.001
High uric acid, *n* (%)	813 (13.2)	781 (15)	818 (16.9)	<0.001
High total cholesterol, *n* (%)	3463 (56.2)	2899 (55.7)	3084 (63.7)	<0.001
High LDL, *n* (%)	4079 (66.2)	3497 (67.2)	3694 (76.3)	<0.001
Low HDL, *n* (%)	431 (7)	317 (6.1)	935 (19.3)	<0.001
Kidney measures, *n* (%)				
Reduced length (<10 cm)	—	—	876 (18.1)	—
Reduced cortical thickness (<10 mm)	—	—	121 (2.5)	—
Microalbuminuria, *n* (%)	—	—	460 (9.5)	—
Macroalbuminuria, *n* (%)	—	—	165 (3.4)	—
Age (yr)	43.7±17.6	46.9±16.8	49.7±16.3	<0.001
eGFR (ml/min per 1.73 m^2)	104.6±20.7	103.7±18.3	98.6±19.3	<0.001
BMI (kg/m^2)	25.3±4.7	25.6±4.6	25.9±4.7	<0.001
Waist circumference (cm)	84.8±13.2	85.6±12.5	87.2±12.3	<0.001
Glucose (mg/dl)	90.1±23.7	90.8±23.3	98.3±25.0	<0.001
Systolic BP (mm Hg)	125.6±18.6	124.5±17.9	119.4±26.0	0.23
Uric acid (mg/dl)	4.3±1.5	4.5±1.5	4.6±1.4	<0.001
Total cholesterol (mg/dl)	208.5±42.2	206.9±38.9	215.3±40.3	<0.001
LDL cholesterol (mg/dl)	126.8±35.4	125.7±32.7	135.5±34.6	<0.001
HDL cholesterol (mg/dl)	64.1±14.9	63.0±13.7	56.8±14.1	<0.001
Triglycerides (mg/dl)	88.1±68.2	91.4±70.7	115.3±69.3	<0.001
Individuals with all 3 visits				
Patients (*n*)	4074	4074	4074	
Age range, *n* (%)				
<20 yr	287 (7.04)	124 (3.04)	0 (0)	<0.001
20–39 yr	1539 (37.78)	1385 (34)	1166 (28.62)	<0.001
40–59 yr	1521 (37.33)	1619 (39.74)	1681 (41.26)	<0.001
60–69 yr	524 (12.86)	594 (14.58)	671 (16.47)	<0.001
≥70 yr	203 (4.98)	352 (8.64)	556 (13.65)	<0.001
Men, *n* (%)	1691 (41.5)	1691 (41.5)	1691 (41.5)	—
Smoking, *n* (%)	721 (17.7)	892 (21.9)	990 (24.3)	<0.001
Metabolic syndrome, *n* (%)	310 (7.6)	391 (9.6)	786 (19.3)	<0.001
Obesity, *n* (%)	603 (14.8)	664 (16.3)	758 (18.6)	<0.001
Large waist, *n* (%)	1601 (39.3)	1760 (43.2)	2041 (50.1)	<0.001
High glucose, *n* (%)	110 (2.7)	143 (3.5)	257 (6.3)	<0.001
Hypertension, *n* (%)	1145 (28.1)	1267 (31.1)	1401 (34.4)	<0.001

Table 1. Continued

Variable	Total Sample			
	Visit 1	Visit 2	Visit 3	Trend Test or Chi-Square ^{2} *P* Value
High BP, *n* (%)	986 (24.2)	1014 (24.9)	998 (24.5)	0.73
Previous cardiac disease, *n* (%)	145 (3.56)	172 (4.22)	242 (5.94)	<0.001
High uric acid, *n* (%)	489 (12)	591 (14.5)	697 (17.1)	<0.001
High total cholesterol, *n* (%)	2367 (58.1)	2334 (57.3)	2648 (65)	<0.001
High LDL, *n* (%)	2754 (67.6)	2791 (68.5)	3178 (78)	<0.001
Low HDL, *n* (%)	244 (6)	232 (5.7)	819 (20.1)	<0.001
Age (yr)	43.3±15.8	46.7±15.8	50.7±15.8	<0.001
eGFR (ml/min per 1.73 m^2)	105.0±19.2	104.1±17.4	97.7±19.1	<0.001
BMI (kg/m^2)	25.4±4.5	25.6±4.5	26.1±4.7	<0.001
Waist circumference (cm)	84.5±12.8	85.4±12.4	87.3±12.2	<0.001
Glucose (mg/dl)	88.7±20.7	89.9±21.7	98.8±24.6	<0.001
Systolic BP (mmHg)	124.9±17.6	124.6±17.4	125.4±18.9	0.26
Uric acid (mg/dl)	4.2±1.4	4.4±1.5	4.6±1.4	<0.001
Total cholesterol (mg/dl)	210.0±41.0	208.0±38.7	216.6±40.0	<0.001
LDL cholesterol (mg/dl)	127.8±34.7	126.8±32.5	136.9±34.3	<0.001
HDL cholesterol (mg/dl)	64.7±14.8	63.3±13.5	56.8±14.2	<0.001
Triglycerides (mg/dl)	87.7±69.7	89.9±66.8	114.9±69.8	<0.001

Values expressed with a plus/minus are the mean±SD. BMI, body mass index.

the "normal" individuals was largely attributable to the high prevalence of patients in high and very high CKD-KDIGO risk categories (Supplemental Figure 5).

Comparison of SardiNIA Study Results with NHANES 1988–1994 and 1999–2004, HUNT II, and Beijing Study Results

We compared our population to other populations using the KDOQI guidelines and the Modification of Diet in Renal Disease (MDRD) 175 formula, and prevalence was stratified by age. Prevalence in the SardiNIA study was approximately the same as in NHANES 1988–1994 (16.1% versus 16.5%) and in Beijing (12.4% versus 11.2%), although higher than in the Health Survey of Nord-Trondelag County II (HUNT II) (16.1% versus 11.2%), and lower than in NHANES 1999–2004 (16.8% versus 20.3%) (Table 2).

Similar results were seen by taking into account kidney function in normal, mildly reduced, moderately reduced, and severely reduced groups, stratified by age. The Sardinian cohort included significantly more individuals with normal renal function than did the United States cohorts (54.4% versus 51.9% in NHANES 1988–1994 and 52.7% versus 40.7% in NHANES 1999–2004), though fewer than in the HUNT II (52.6% versus 56.7%) and Beijing (56.3% versus 64.7%) studies. The opposite trend was evident for mildly reduced and moderately reduced eGFR, and no significant differences were observed for severely reduced eGFR (Table 2).

Risk Factors Associated with CKD

Univariate analysis revealed that 13 of 16 variables (*i.e.*, age, sex, metabolic syndrome, obesity, abdominal obesity, diabetes, high glycemia, hypertension (BP≥140 mmHg systolic or ≥90 mmHg diastolic, or when volunteers reported taking antihypertensive medication), high BP (high BP found during the visit), previous cardiac disease, high uric acid, genetic score, and abnormal kidney length) were significantly associated with the presence of CKD, while smoking, major lipid profile, and cortical thickness were not. In the final reduced multivariable model, older age (per 10 years; odds ratio [OR], 1.31), female sex (OR, 1.28), diabetes (OR, 1.48), and genetic risk score (per one risk allele; OR, 1.07) were independently associated with CKD. High uric acid (OR, 1.28; *P*=0.06) and abnormal kidney length (OR, 1.26; *P*=0.06) showed a trend toward association (Table 3).

Risk Factors Associated with Changing eGFR

In univariate analysis, the same 13 predictors listed above were significantly associated with the dichotomous outcome of fast decline of eGFR (>−2.3 ml/min per 1.73 m^2 per year), although previous cardiac disease showed a less significant positive trend (*P*=0.06). In the final reduced multivariable model, older age (per 10 years; OR, 1.67), female sex (OR, 1.39), hypertension (OR, 1.58), high uric acid (OR, 1.97), and genetic risk score (per one risk allele; OR, 1.05) were significantly independently associated with faster eGFR decline, whereas diabetes (*P*=0.11) was not (Table 3).

In a similar univariate analysis of linear decline in continuous eGFR with the same 16 variables and taking into account baseline eGFR, only smoking, low HDL cholesterol, and cortical thickness fell below significant association with eGFR decline. In the final reduced multivariable model, baseline eGFR (per 10 ml/min per 1.73 m^2; −0.52 ml/min per 1.73 m^2), older age (−3.5 ml/min per 1.73 m^2 per 10 years), female sex (−1.23 ml/min per 1.73 m^2), diabetes (−3.13 ml/min per 1.73 m^2), hypertension (−1.69 ml/

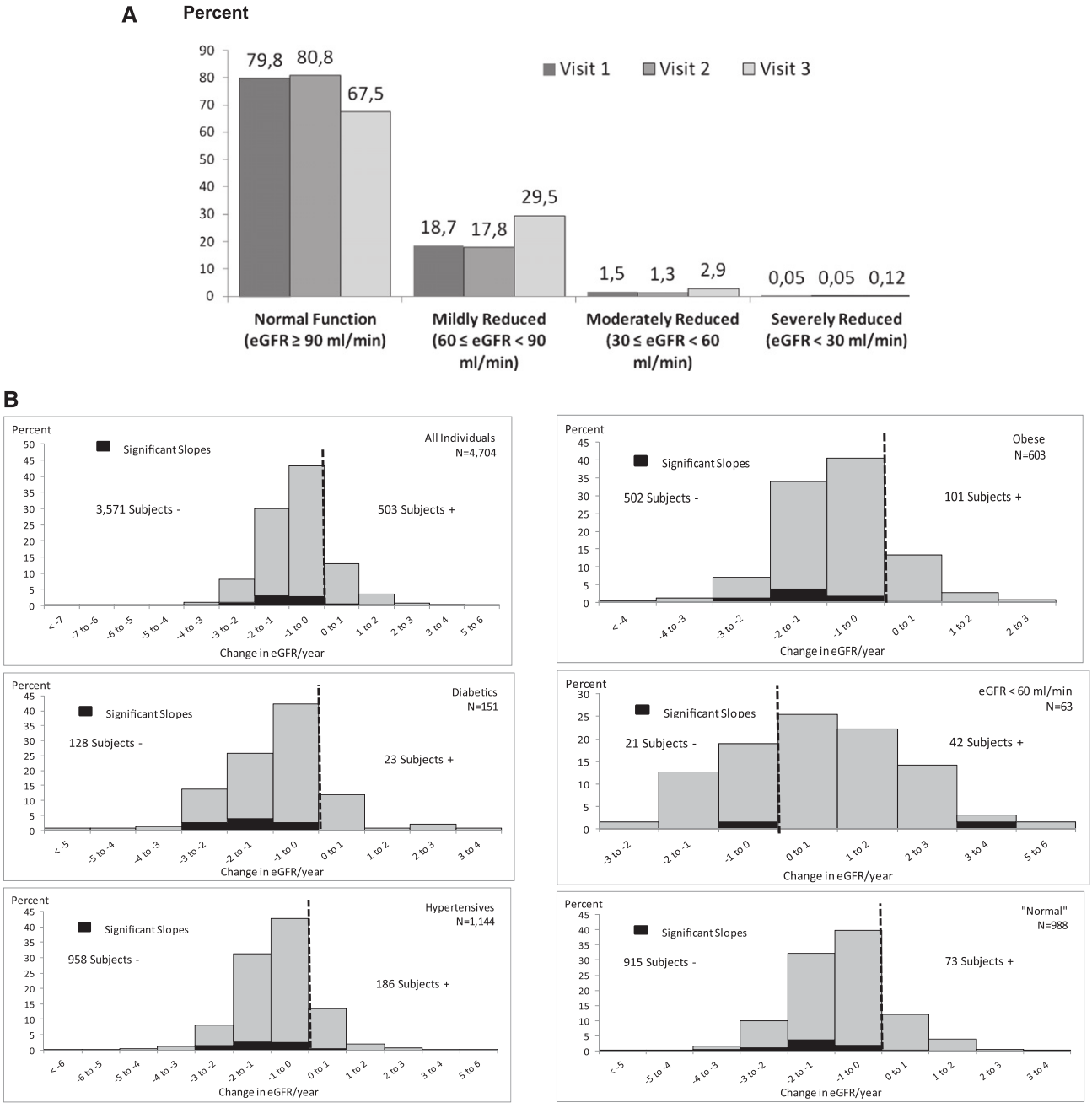

Figure 1. Progressive decline in kidney function in all individuals and in different subgroups of patients of SardiNIA Study Cohort over a 7-year period. (A) Prevalence of renal function categories in the three visits. The eGFR was evaluated with the CKD-Epidemiology Collaboration formula. (B) Histograms for slope of eGFR. Significant slopes are in black. The numbers of individuals with positive or negative slopes are on the right and left, respectively. The rate of decline of eGFR, assessed in the same 4074 SardiNIA study cohort individuals who participated in all three visits, was −0.79 ml/min per 1.73 m^2 per year. The rates of decline of eGFR (ml/min per 1/73 m^2 per year) in subgroups were −1.41 in patients with diabetes, −1.09 in hypertensive patients, −1.06 in obese individuals, −1.87 in patients with baseline eGFR<60 ml/min per 1.73 m^2, and −0.52 in individuals without comorbid conditions. The rate of decline of eGFR of each subgroup is reported in the text. All data were adjusted for starting eGFR and included interaction terms between the risk factor and starting eGFR. "Normal" individuals are those without the comorbid conditions listed in Table 1.

min per 1.73 m^2), high uric acid (−1.36 ml/min per 1.73 m^2), and genetic risk score (per one risk allele, −0.23 per 1.73 m^2) were associated with a change in eGFR (data are expressed in ml/min per 1.73 m^2 per 10 years) (Table 3).

DISCUSSION

Cross-sectional CKD prevalence was high (15.5%) in this relatively young cohort, and early stages of CKD were the most

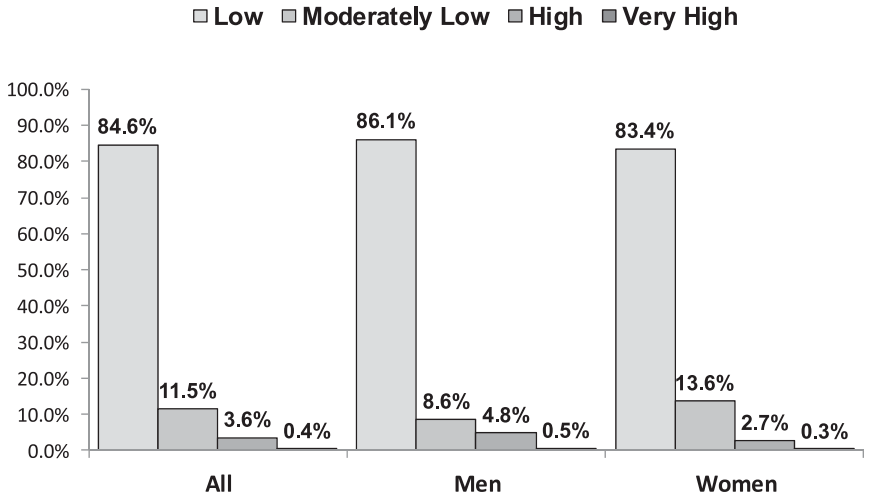

Figure 2. Prevalence of CKD risk categories in SardiNIA Study Cohort, adjusted by sex, according to KDIGO guidelines. CKD prevalences were 15.5% overall, 13.9% in men, and 16.6% in women. The eGFR was calculated using the CKD-Epidemiology Collaboration formula; CKD was staged as proposed by KDIGO.

frequent (moderately low KDIGO risk group, 11.4%), consistent with the high prevalence of microalbuminuria (9.5% in the whole cohort). We have shown that the genetic renal risk score is an independent risk factor for CKD and fast eGFR decline. We note that Sardinians have a common European origin[22] but also show numerous founder effects and a unique distribution of genetic variation at multiple loci, differentiating them from other populations, including those from the Italian mainland. Furthermore, other areas of the mainland Italian differ in many environmental factors (*e.g.*, city-dwelling rather than town-dwelling) from the cohort population examined here, so that any extension to the entire Italian population would require further comparative studies.

The prevalence estimate might have been lower if we had used urinary albumin-to-creatinine ratio to detect proteinuria and performed urinalysis more than once, but it seems more likely that the high number of patients with early CKD stages reflects an increasing level of risk factors (*i.e.,* diabetes and obesity) as lifestyle/diet changed over time, and especially in the last 10 years (Table 1).[23] Furthermore, on the basis of the level of early CKD, the current low percentage of individuals with eGFR$<$60 ml/min per 1.73 m^2 is expected to rise in the future. This rate may also be underestimated because patients with chronic disease tend to participate less in repeated visits: This is a common bias of surveys based on a volunteer participation.

Approximately 4% of patients fulfilled the criteria for "high" or "very high" risk as defined by KDIGO guidelines. The use of this new classification should make categorizing CKD patients at risk more reliable and consequently lead to an increase in the appropriateness of nephrologic referrals. In addition to using the KDIGO guidelines and the CKD-Epidemiology Collaboration formula, we also applied the KDOQI classification and MDRD 175 formula to compare SardiNIA to other large cross-sectional CKD studies.[24] As in other populations, CKD prevalence was greater in women than in men. According to the Registry of Dialysis and Transplantation, ESRD is more frequent in men than in women, but this does not conflict with our findings because the prevalence of patients at "high" or "very high" risk was greater in men. The high prevalence of "moderately at risk" women could be partly due to an underestimation of eGFR in the near-normal range for women by the formulas that were used.[25,26] Moreover, because women start with a somewhat lower GFR (even after correction for size and muscle mass), the final value of GFR in advanced age is usually lower in women than in men.[27]

Data stratified by age showed similar CKD prevalence in SardiNIA to the comparably rural population in Beijing in 2008 (12.4% versus 11.2%) and to NHANES in 1988–1994 (16.1% versus 16.5%), but lower than NHANES in 1999–2004 (16.8% versus 20.3%) and higher than HUNT II (16.1% versus 11.2%) (Table 2). These differences probably result from a combination of factors. Concerning general known risk factors, the results are consistent with the higher and increasing prevalence of diabetes and metabolic syndrome in the NHANES United States population. On the other hand, Norwegians have by far the highest prevalence of hypertension, often a major cause of ESRD, but the lowest prevalence of CKD. Differences around the world probably also depend on additional measures that have not yet been fully assessed, including environmental and genetic variations (see below).[28]

Longitudinal analysis in the 4074 individuals who underwent all three visits showed an overall reduction in mean eGFR. Over a mean 7-year follow-up, the number of individuals with normal renal function decreased, whereas the prevalence of mildly and moderately reduced eGFR consistently increased. This could be expected as a result of cohort aging.

Few groups have attempted to look at prevalence and course of CKD in detail, although aging itself appears to have the sharpest effect on eGFR decline. One of the rare studies, by Lindeman *et al.* in 1985, followed a normal volunteer cohort of 446 highly motivated educated men in the Baltimore Longitudinal Study of Aging (BLSA) between 1958 and 1981.[18] They found that in 254 "normal" participants—*i.e.,* without any indication of renal or urinary tract disease, hypertension, or diuretic therapy, but including diabetic patients—the mean decrease in creatinine clearance was 0.75 ml/min per 1.73 m^2 per year. Notably, our 988 "normal" participants, who had none of the comorbid conditions considered in Table 1, showed a lower rate of aging decline of eGFR (change, -0.52 ml/min per 1.73 m^2 per year, adjusted with standard interaction analysis). This is particularly notable given the differences between the studies. The BLSA had many more

Table 2. Prevalence of CKD stages and of kidney function categories stratified by age at the third visit in the SardiNIA study cohort compared with other worldwide populations

Cohort	CKD Stage (95% CI) (%)				Cohort	Kidney Function by MDRD eGFR (95% CI) (%)		
	CKD 1	CKD 2	CKD 3	Total (CKD 1–5)		Normal	Mildly Reduced	Moderately Reduced
Cohort per CKD stage					Cohort per kidney function			
Not stratified					Not stratified			
SardiNIA 3[a]	5.5 (4.9 to 6.2)	5.5 (4.9 to 6.2)	4.0 (3.5 to 4.7)	15.2 (14.2 to 16.3)	SardiNIA 3[f]	53.4 (51.3 to 55.5)	42.6 (40.7 to 44.5)	4.0 (3.4 to 4.6)
Stratified					Stratified			
NHANES 1988–1994[b]	4.2 (3.9 to 4.5)	4.8 (4.4 to 5.2)	7.1 (6.7 to 7.5)	16.5 (15.8 to 17.1)	SardiNIA 3[f]	54.4 (52.2 to 56.7)	41.0 (39.1 to 42.9)	4.5 (3.8 to 5.2)
SardiNIA 3[a]	5.6 (4.9 to 6.4)	6.0 (5.3 to 6.9)	5.0 (4.3 to 5.8)	16.8 (15.5 to 18.1)	NHANES 1988–1994[g]	51.9 (50.7 to 53.1)	42.4 (41.3 to 43.5)	5.4 (5.0 to 5.8)
NHANES 1999–2004[c]	4.0 (3.6 to 4.3)	5.5 (5.1 to 5.9)	10.2 (9.6 to 10.8)	20.3 (19.5 to 21.1)	SardiNIA 3[f]	52.7 (50.6 to 54.9)	42.3 (40.4 to 44.2)	4.9 (4.2 to 5.7)
SardiNIA 3[a]	5.5 (4.8 to 6.3)	5.9 (5.1 to 6.6)	4.6 (4.0 to 5.4)	16.1 (14.9 to 17.4)	NHANES 1999–2004[h]	40.7 (39.6 to 41.8)	51.2 (50.0 to 52.5)	7.7 (7.2 to 8.2)
HUNT II[d]	3.1 (3.0 to 3.2)	3.4 (3.3 to 3.5)	4.5 (4.3 to 4.7)	11.2 (10.9 to 11.5)	SardiNIA 3[f]	52.6 (50.6 to 54.7)	42.8 (40.9 to 44.7)	4.5 (3.8 to 5.2)
SardiNIA 3[a]	5.5 (4.8 to 6.3)	4.5 (3.9 to 5.2)	2.4 (2.0 to 2.8)	12.4 (11.4 to 13.4)	HUNT II[d]	56.7 (56.1 to 57.3)	38.6 (38.1 to 39.1)	4.5 (4.3 to 4.7)
Beijing[e]	5.5 (5.2 to 6.0)	3.8 (3.5 to 4.2)	1.7 (1.5 to 2.0)	11.2 (10.7 to 11.8)	SardiNIA 3[f]	56.3 (54.6 to 59.1)	40.9 (39.0 to 42.8)	2.3 (1.9 to 2.7)
					Beijing[e]	64.7 (63.4 to 66.1)	33.4 (32.4 to 34.4)	1.8 (1.5 to 2.0)

GFR was estimated by the MDRD 175 equation. Normal kidney function was an eGFR>90 ml/min per 1.73 m^2. Mildly reduced kidney function was an eGFR of 60–90 ml/min per 1.73 m^2. Moderately reduced kidney function was an eGFR of 30–60 ml/min per 1.73 m^2. The NHANES and HUNT II studies did not include patients with CKD stage 5. 95% CI, 95% confidence interval.

[a]4477 individuals.
[b]14,319 individuals.
[c]12,216 individuals.
[d]65,181 individuals.
[e]13,925 individuals.
[f]4731 individuals.
[g]15,488 individuals.
[h]13,233 individuals.

Table 3. Final multivariate models performed on SardiNIA study cohort individuals

Measure (yes/no)	Odds of CKD[a]		Additional Change in eGFR (ml/min per 1.73 m^2)[b]		Odds of Fast Decline[b]	
	OR (95% CI)	*P* Value	Estimate[c]	*P* Value	OR (95% CI)	*P* Value
Baseline eGFR (per 10 ml/min per 1.73 m^2)	–	–	−0.52	<0.001	–	–
Age (per 10 yr)	1.31 (1.22 to 1.40)	<0.001	−3.5	<0.001	1.67 (1.44 to 1.95)	<0.001
Male (yes/no)	0.72 (0.56 to 0.91)	0.01	1.23	<0.001	0.61 (0.47 to 0.76)	<0.001
Diabetes (yes/no)	1.48 (1.10 to 2.00)	0.01	−3.13	0.01	1.64 (0.90 to 2.96)	0.11
Hypertension (yes/no)	–	–	−1.69	<0.001	1.58 (1.17 to 2.12)	0.003
High uric acid (yes/no)	1.28 (1.00 to 1.67)	0.06	−1.36	0.03	1.97 (1.39 to 2.80)	0.001
Abnormal kidney length (yes/no)	1.26 (1.00 to 1.59)	0.06	–	–	–	–
Genetic risk score (per 1 risk allele)	1.07 (1.03 to 1.12)	0.001	−0.23	0.004	1.05 (1.00 to 1.10)	0.04

Fast decline was defined as a decline greater than 1 SD below the mean (*i.e.*, −2.3 ml/min per 1.73 m^2 per year). Odds ratios calculated using multivariate logistic regression analysis for CKD disease and for fast eGFR decline. Additional change in eGFR calculated using linear mixed models (accounts for family clustering). 95% CI, 95% confidence interval.

[a]4477 individuals who performed the third visit.

[b]4174 individuals who performed all three visits.

[c]Estimate per 10 years.

time points than ours (5–14), which could have provided more stable measurements, but it also had fewer participants, all of whom were men. Moreover, patients with diabetes were included in the "normal" group: because the BLSA study did not measure proteinuria, "hyperfiltration" may confound its data. By contrast, our study had five times the number of participants, with an almost equal number of men and women, no comorbidity in the "normal" group, but only three time points over 7 years. Thus, despite the methodologic differences, our data on "normal" individuals support the unrelenting loss of renal function with aging, regardless of superimposed diseases that can intensify it. This has important implications for the diagnosis of CKD because many individuals over age 65 years with slightly reduced eGFR and without proteinuria should not be considered diseased.[27] Rather, they fall within the "normal" range for their age. The decline in eGFR was approximately steady, both in individuals without comorbid conditions and in those with diabetes and hypertension. However, in individuals with a baseline eGFR<60 ml/min per 1.73 m^2, the loss of eGFR accelerates with aging, and age-related changes may aggravate the deterioration of renal function in elderly individuals who have renal disease.[29]

We observed an increased prevalence of clinical risk factors over 7 years. Diabetes, a major cause of ESRD in developed countries, increased by almost 100%. It was an independent risk factor for CKD, associated with significant additional changes in eGFR (−3.13 ml/min per 1.73 m^2 per year); however, it did not predict fast eGFR decline, most likely because of the high prevalence of CKD stage 1. In the early stages of diabetic nephropathy, glomerular hyperfiltration results in a misleading apparent "improvement" of renal function.

Hypertension, the other main cause of ESRD in developed countries but also a consequence of CKD, was associated with fast eGFR decline. In our cohort, however, hypertension was not an independent significant risk factor for CKD. This is consistent with the results of the HUNT II study.[8]

Obesity showed an increasingly high prevalence (18.2%), especially compared with the Italian mainland population (8%–10%),[30] although its correlation with CKD did not remain significant in multivariable analysis.

Hyperuricemia has not been extensively assessed in published surveys, but its prevalence was high in SardiNIA. The correlation of uric acid levels with fast eGFR decline was significant, suggesting it may be a risk factor.

Our study also used a genetic risk score. A multivariable model including traditional risk factors and other CKD-associated measures showed that the genetic renal risk score based on 13 published CKD-associated loci was independently associated with outcomes. An individual with one additional risk allele had a 7% higher probability of having CKD, a greater decline in eGFR (−0.23; *P*=0.004), and a 5% increased odds of fast eGFR decline. Although these estimates are relatively modest for one additional risk allele, when the range of data in the cohort is considered (6–24), risk increases are quite substantial: a 337% higher odds of CKD, a −4.14-ml/min per 1.73 m^2 per year greater decline in eGFR over 10 years, and a 240% higher odds of "fast decline" in comparing the risk for individuals with 24 versus those with 6 risk alleles. We also tested genes known to be associated with CKD[16,17] and found that they too are associated with progression. This is a step toward the final goal of integrating genetic and epidemiologic factors, including the effect of aging, to assess risk and possibly prognosis of CKD.

In conclusion, the genetic risk score can be added to the traditional CKD risk factors, although further work is required to cross-compare the results of our population with those of other ethnicities and to refine predictive models. Along with differences in health practice, differential prevalence of these risk factors may explain the variable CKD prevalence worldwide.[28]

CONCISE METHODS

Study Design

Clinical and genetic data were part of the longitudinal SardiNIA Project (https://sardinia.irp.nia.nih.gov/) supported by the National Institute on Aging. The study, which began in 2001, has measured >300

traits (endophenotypes, quantitative risk–related genetic factors, and environmental factors) that can be scored on a continuous scale for epidemiologic and genetic analyses. The sample was drawn from the 10,982 residents in a cluster of four towns in Ogliastra in eastern Sardinia.[20] About 56% (n=6162) underwent initial visits. The cohort ranged from 14 to 102 years of age. A total of 4074 individuals underwent three visits, with an average follow-up of 7 years. A total of 4842 had a visit in the third interval, 4471 of whom underwent proteinuria measurements (6–7 years after the start of the Project) (Supplemental Material).

Definitions

CKD was defined and staged according to the KDOQI classification[1] so that we could compare our results with those of the previous surveys published before 2013. We also staged CKD according to the KDIGO CKD classification.[21] Kidney damage was quantified by albuminuria (micro or macro), and decreased kidney function was quantified by eGFR assessed by serum creatinine concentrations.[2] The CKD-Epidemiology Collaboration formula was used in all association models because it is considered the best way to estimate GFR in general population-cohort studies.[31] We also estimated GFR with the MDRD 175 study equation to facilitate comparisons with other surveys.

Participants whose albuminuria ranged from 3 to 30 mg/dl and whose proteinuria on a urinary spot test was <30 mg/dl were classified as microalbuminuric, whereas individuals with proteinuria >30 mg/dl on a urinary spot test were classified as having macroalbuminuria. Individuals were defined as having a "fast decline" in eGFR if their slope was steeper than −2.3 ml/min per 1.73 m^2 per year, meaning that their decline was >1 SD below the mean (Supplemental Material).

Genotype Data

Genome-wide markers, assayed on a combination of Affymetrix platforms (500K and 1.0) and imputed using HapMap2 samples as a reference, were used to calculate a genetic risk score from a list of 18 published loci associated with CKD and renal function.[16,17,32,33] Sixteen of the loci were available for analysis, and the 13 found to have a moderate to significant association with CKD in this sample were ultimately included (Table 4). For each of the 13 loci, a score of 0, 1, or 2 was possible and indicated the number of risk alleles (the allele showing an increased risk for CKD) that were present. For example, if A2 is the allele that confers higher risk, the genotype A1:A1 corresponds to zero risk alleles, A1:A2–1 risk allele, and A2:A2 corresponds to the presence of two risk alleles. The score for each individual could then range from zero (meaning that he or she carries no risk allele at any of the 13 loci) to 26 (meaning that he or she carries two copies of the risk allele at each of the 13 loci). The average number of risk alleles that each individual carried was 16, and we observed a range of 6–24. The distribution of the scores was normal (Supplemental Figure 6). More complicated genetic risk scores were explored through use of weights based on their strength of association with each outcome. These scores yielded slightly smaller P values in the association models, but only the simple score is presented here for ease of interpretation.

Statistical Analyses

Quantitative data are presented as the mean±SD; categorical data are presented as percentages. Differences between groups were examined using chi-squared statistics for categorical variables.

Unadjusted ORs between risk factors and CKD were calculated using univariate logistic regression analysis, whereas adjusted ORs were calculated by multivariable logistic regression analysis, accounting for family membership by using generalized estimation equation methods.

Highly correlated variables were not included in the final multivariable model. Results from the univariate models were used in deciding which form of each measurement to keep in the final multivariable model. Therefore, final models do not include multiple measurements of the same trait (*e.g.*, obesity and body mass index) (Supplemental Material). Changes in eGFR during the study were assessed in individuals whose measurements were available at all three visits. Linear regression was used to determine the slope for each individual, using the three time points in the study. Differences in slopes by individual risk factors were determined using linear mixed models adjusted for starting eGFR and included an interaction terms between the risk factor and starting eGFR.

Linear mixed models, accounting for family membership as a repeated variable with compound symmetry covariance, were used to examine the association between known risk factors (including a genetic risk score) and change in eGFR (slope) across all individuals. Clinical and genetic risk factors were examined by logistic regression to determine their association with classification as "fast decline." P values <0.05 were considered to represent statistically significant differences. All analyses were performed using SAS software, version 9.3 (SAS Institute, Inc., Cary, NC).

Methodologic Considerations for Cross-Study Comparisons

Serum creatinine was calibrated to correctly estimate the prevalence of kidney disease in the study cohort, to assess rates of change in kidney function, and to compare the data to other surveys (Supplemental Material).[34] Our calibration included a correction factor similar to that used in the NHANES and HUNT II analyses.[34,35] With this correction, the MDRD 175 formula and the CKD-Epidemiology Collaboration formula can be considered unbiased in the cohort. The precision of the CKD-Epidemiology Collaboration equation is limited compared with that of measured GFR, but the formula corrects the bias of previous formulas in the classification of normal and mildly decreased eGFR groups.[24] Using the MDRD study equation, we avoided biases by comparing our eGFR results to the results of the other surveys we considered.

The SardiNIA project was not designed as an epidemiologic study of CKD, and in addition to the lack of determinations of microalbuminuria-macroalbuminuria and urinary albumin-to-creatinine ratio in all visits (see above), both quantitative determination of microalbuminuria and semiquantitative estimation of macroalbuminuria by a single dipstick (Albustix) test were performed only at the third visit. Consequently, the prevalence of microalbuminuria-macroalbuminuria and stages 1 and 2 CKD may be overestimated. Moreover, because microalbuminuria was not assessed by the urinary albumin-to-creatinine ratio, its borderline values (which can vary for different reasons) might slightly change the CKD risk category groups. Also to better classify CKD, we used the more detailed new KDIGO classification. To reduce any overestimation of albuminuria, participants

Table 4. Thirteen genetic loci included in the genetic risk score, selected from a list of 18 published loci found to be associated with CKD and renal function

Marker	Chromosome	Position	Risk Allele	Gene	SardiNIA β	CKD-Gen β	Comments
Identified in Köttgen, 2009							
rs12917707	16	20,275,191	G	*UMOD*	−0.3701	−1.02	Familial juvenile hyperuricemic nephropathy type 1 and medullary cystic kidney disease type 2
rs17319721	4	77,587,871	A	*SHROOM3*	−0.4081	−1.01	Susceptibility gene for kidney disease in an obese mouse model of type 2 diabetes
rs2467853	15	43,486,085	G	*SPATA5L1-GATM*	−1.0190	−1.01	SNPs in region association with renal tumors
rs13038305	20	23,558,262	C	*CST3-CST9*	−0.0084	1.07	SNPs in region associated with kidney function and endocrine-related traits
rs1731274	8	23,822,264	A	*STC1*	−0.2326	−1.02	May play a role in regulation of renal and intestinal calcium
Identified in Böger, 2011							
rs11959928	5	39,375,121	A	*DAB2*	−0.5816	NA	May modulate growth factor/Ras pathways
rs626277	13	72,347,446	A	*DACH1*	−0.4470	NA	Regulates gene expression and cell fate determination during development; expression of this gene is lost in some forms of metastatic cancer and is correlated with poor prognosis
rs10109414	8	23,750,901	C	*STC1*	−0.3411	NA	May play a role in the regulation of renal and intestinal calcium
rs13538	2	73,868,078	A	*NAT8*	−1.7967	NA	Specifically expressed in kidney and liver; may affect cell adhesion and gastrulation movements.
rs1260326	2	27,730,690	C	*GCKR*	−0.1417	NA	Considered a susceptibility gene candidate for a form of maturity-onset diabetes of the young
rs4744712	9	71,434,457	A	*PIP5K1B*	−0.4639	NA	May be involved in stable platelet adhesion
rs881858	6	43,806,359	A	*VEGFA*	−0.2690	NA	Mutations in this gene have been associated with proliferative and nonproliferative diabetic retinopathy
rs347685	3	141,806,887	A	*TFDP2*	−0.6510	NA	Transcriptional activation of cell cycle regulated genes

SNP, single-nucleotide polymorphism; NA, not applicable.

were defined as being affected by microalbuminuria when values were >3 mg/dl in both men and women.

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DISCLOSURES

None.

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