

Body Mass Index and Risk for End-Stage Renal Disease

Chi-yuan Hsu, MD, MSc; Charles E. McCulloch, PhD; Carlos Iribarren, MD, MPH, PhD; Jeanne Darbinian, MPH; and Alan S. Go, MD

Background: Although interest in the relationship between obesity and kidney disease is increasing, few epidemiologic studies have examined whether excess weight is an independent risk factor for end-stage renal disease (ESRD).

Objective: To determine the association between increased body mass index (BMI) and risk for ESRD.

Design: Historical (nonconcurrent) cohort study.

Setting: A large integrated health care delivery system in northern California.

Participants: 320 252 adult members of Kaiser Permanente who volunteered for screening health checkups between 1964 and 1985 and who had height and weight measured.

Measurements: The authors ascertained ESRD cases by matching data with the U.S. Renal Data System registry through 2000.

Results: A total of 1471 cases of ESRD occurred during 8 347 955 person-years of follow-up. Higher BMI was a risk factor for ESRD in multivariable models that adjusted for age, sex, race, education

level, smoking status, history of myocardial infarction, serum cholesterol level, urinalysis proteinuria, urinalysis hematuria, and serum creatinine level. Compared with persons who had normal weight (BMI, 18.5 to 24.9 kg/m²), the adjusted relative risk for ESRD was 1.87 (95% CI, 1.64 to 2.14) for those who were overweight (BMI, 25.0 to 29.9 kg/m²), 3.57 (CI, 3.05 to 4.18) for those with class I obesity (BMI, 30.0 to 34.9 kg/m²), 6.12 (CI, 4.97 to 7.54) for those with class II obesity (BMI, 35.0 to 39.9 kg/m²), and 7.07 (CI, 5.37 to 9.31) for those with extreme obesity (BMI ≥ 40 kg/m²). Higher baseline BMI remained an independent predictor for ESRD after additional adjustments for baseline blood pressure level and presence or absence of diabetes mellitus.

Limitations: Primary analyses were based on single measurements of exposures.

Conclusions: High BMI is a common, strong, and potentially modifiable risk factor for ESRD.

Ann Intern Med. 2006;144:21-28.

For author affiliations, see end of text.

www.annals.org

The increasing prevalence of end-stage renal disease (ESRD), with its associated high annual rates of mortality and cardiovascular complications, is a worldwide problem. In the United States alone, the prevalence of ESRD has more than doubled in the past decade (1), and the population living with ESRD is projected to increase to 650 000 persons by the year 2010, with associated Medicare expenditures of \$28 billion (2). Identifying new and potentially modifiable risk factors for ESRD is critical in order to devise effective, population-based preventive strategies.

Obesity is also a major worldwide public health problem (3). However, few studies have examined the relationship between excess weight and risk for ESRD (4–8). Previous studies have shown that obese patients are at higher risk for glomerulomegaly and focal segmental glomerulosclerosis (9–11). Studies have also reported that obesity was associated with more rapid loss of renal function among patients who underwent uninephrectomy (12) or who have IgA nephropathy (13).

We examined the hypothesis that overweight and obesity are risk factors for developing ESRD among a large, community-based sample of men and women.

METHODS

Study Sample

Our study is based on a large, well-characterized cohort of members of Kaiser Permanente of Northern California who participated in a Multiphasic Health Testing Services Program in Oakland and San Francisco medical

centers between 1964 and 1985 (14). Kaiser Permanente of Northern California is a large, integrated health care delivery system that currently cares for more than 35% of the insured adult population in the greater San Francisco Bay area (15). The Multiphasic Health Checkup was a voluntary health assessment offered at initial and yearly open enrollment periods (14). Analyzable data were available for 3 Multiphasic Health Checkup periods: June 1964 to August 1973, September 1973 to December 1977, and January 1978 to March 1985.

We studied all individuals who participated in the Multiphasic Health Checkups from 1964 to 1985; who were 18 years of age or older; and who had at least 1 concurrent measurement (that is, done at the same visit) of height, weight, blood pressure, serum creatinine level, and dipstick urinalysis. We excluded persons who had a baseline serum creatinine level greater than 884 μmol/L (>10 mg/dL) because they might already have ESRD. The final study sample included 320 252 eligible persons.

Institutional review boards at the collaborating institutions approved the study. Because of the low-risk nature of

See also:

Print

Editors' Notes 22
Summary for Patients I-28

Web-Only

Conversion of figure and tables into slides

Context

Few studies have asked whether obesity affects the risk for end-stage renal disease (ESRD).

Contribution

In this retrospective cohort study of 320 252 adults who were followed for 15 to 35 years, the rate of ESRD increased in a stepwise manner as body mass index (BMI) increased. Age-, sex-, and race-adjusted rates of ESRD increased from 10 per 100 000 person-years among those with normal weight (BMI, 18.5 to 24.9 kg/m²) to 108 per 100 000 among those with extreme obesity (BMI ≥ 40 kg/m²). This relationship was not affected by blood pressure levels or diabetes.

Cautions

Body mass index and potential confounders were measured only at baseline.

Implications

High BMI is a potentially modifiable risk factor for ESRD.

—The Editors

our study and the use of existing data, the need for obtaining informed consent was waived.

Assessment of Obesity

We calculated body mass index (BMI) as weight in kilograms divided by height in meters squared. Following National Heart, Lung, and Blood Institute guidelines (7), we defined overweight as a BMI of 25.0 to 29.9 kg/m², class I obesity as a BMI of 30.0 to 34.9 kg/m², class II obesity as a BMI of 35.0 to 39.9 kg/m², and class III obesity (extreme) as a BMI of 40 kg/m² or greater. Underweight was defined as a BMI less than 18.5 kg/m². We conducted all analyses relative to a normal BMI (18.5 to 24.9 kg/m²).

Assessment of Covariates

We obtained information about relevant covariates (such as history of myocardial infarction) from self-completed questionnaires administered within 45 days of laboratory tests. Medical history data were not available in an electronic format for participants from the second period (September 1973 to December 1977), and we classified these persons as missing those data elements.

We classified self-reported race as white, black, Asian, or other. We categorized education level as high school or less, some college, or college graduate or higher. We classified cigarette smoking status as never, former, or current (14). Dipstick urinalysis quantified urine protein as negative, trace, 1+ to 2+, or 3+ to 4+ and urine hemoglobin as negative, small, moderate, or large.

We measured sitting blood pressure once on the basis of the acoustic detection of the onset (systolic point) and disappearance (diastolic point) of Korotkoff sounds. We

classified participants' blood pressure by using the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) criteria for normal (systolic blood pressure < 120 mm Hg and diastolic blood pressure < 80 mm Hg), prehypertension (systolic blood pressure of 120 to 139 mm Hg or diastolic blood pressure of 80 to 89 mm Hg), stage 1 hypertension (systolic blood pressure of 140 to 159 mm Hg or diastolic blood pressure of 90 to 99 mm Hg), and stage 2 hypertension (systolic blood pressure ≥ 160 mm Hg or diastolic blood pressure ≥ 100 mm Hg) (16).

Information available for defining the presence or absence of diabetes mellitus varied across the 3 periods. Participant self-report of diagnosis or treatment of diabetes was available in the first and third periods. Blood glucose measurements were available for all periods but were done in the context of oral glucose challenge tests during the first period. We defined diabetes mellitus initially by either self-report or blood glucose measurement of 11.1 mmol/L or greater (≥200 mg/dL). We then considered several alternative definitions of diabetes in sensitivity analyses, including relying on only self-report (using data from the first and third periods), relying on only blood glucose measurements that were done outside the context of oral glucose challenge tests (from the first and third periods), and using 11.1 mmol/L (200 mg/dL) or 7.0 mmol/L (126 mg/dL) as the cutoff value to define the presence of diabetes mellitus.

Identification of Outcomes of ESRD and Death

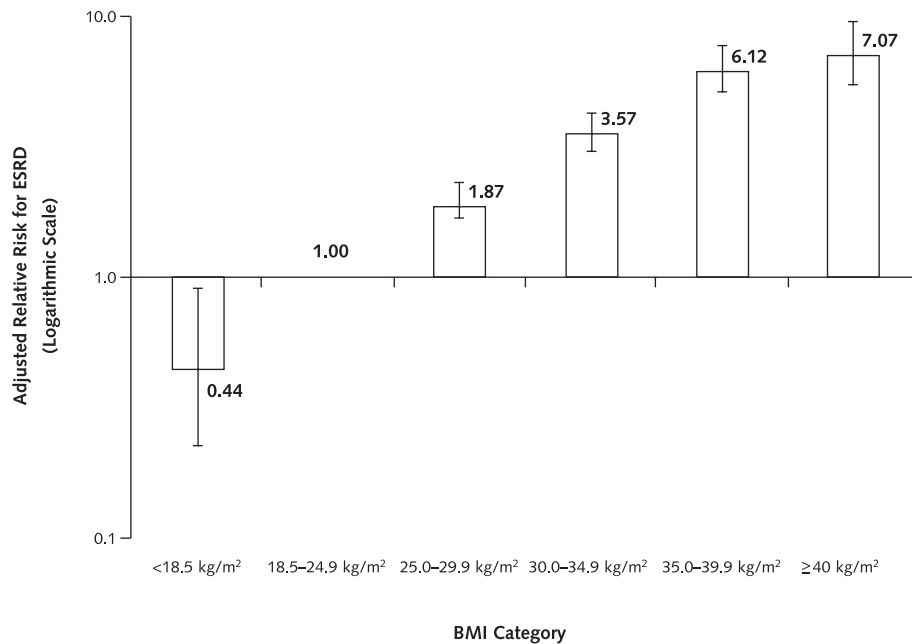
We defined ESRD as the receipt of renal transplantation or maintenance hemodialysis or peritoneal dialysis. We identified cases of ESRD by matching our cohort against the nationally comprehensive U.S. Renal Data System registry data (1). We performed matching, blinded to exposure status, by using Social Security number, first and last name, sex, and date of birth. We ascertained deaths by using the California Automated Mortality Linkage System, which has a sensitivity of 97% and a specificity of 93% compared with the U.S. National Death Index (17). We assessed both ESRD and death through 31 December 2000, the most recent date that data were available for both outcomes when this project was initiated.

We calculated person-years as years from baseline (date of Multiphasic Health Checkup) until death, development of ESRD, or the end of follow-up on 31 December 2000, whichever occurred first.

Statistical Analysis

We based main analyses on data collected at the first eligible Multiphasic Health Checkup examination for each person. We calculated age-, sex-, and race-adjusted rates of ESRD by using the direct method. We analyzed the relationship between category of BMI and subsequent risk for ESRD by using time-to-event methods (18). We conducted multivariable analyses by using Cox proportional hazards models. We confirmed that the proportional hazards assumption was not violated for BMI categories and

Figure. Adjusted relative risk for end-stage renal disease (ESRD) by body mass index (BMI).



Model adjusted for Multiphasic Health Checkup period, age, sex, race, education level, smoking status, history of myocardial infarction, serum cholesterol level, proteinuria, hematuria, and serum creatinine level. Error bars represent 95% CIs.

risk for ESRD by using a graph of estimated $\ln(-\ln)$ survival, stratified by BMI category (19). In all multivariable analyses, we adjusted for the Multiphasic Health Checkup period when baseline assessment occurred. All variables included a missing value category when needed.

Since hypertension and diabetes are likely to be intermediate variables in the pathway between increased BMI and ESRD, our main multivariable analysis did not include baseline blood pressure level or presence or absence of diabetes mellitus as exposures. We then compared this analysis with the results of multivariable analysis, which adjusted for baseline blood pressure level and presence or absence of diabetes.

We also performed stratified analyses by sex, race, age, diabetes mellitus, hypertension, and presence or absence of baseline kidney disease. Baseline kidney disease was defined as an estimated glomerular filtration rate less than $0.58 \text{ mL} \cdot \text{s}^{-2} \cdot \text{m}^{-2}$ ($<60 \text{ mL/min per } 1.73 \text{ m}^2$) calculated with the Modification of Diet in Renal Disease Study formula (20, 21) or as the presence of urinalysis proteinuria or hematuria (22). Hazard ratios are reported as relative risks.

Secondary Analysis among Persons with More than 1 Measurement of BMI

To assess the robustness of our findings, we conducted additional analyses among the subset of study cohort members who returned for at least 1 additional Multiphasic Health Checkup with repeated assessment of BMI, blood pressure, and diabetes status ($n = 134\,705$). In this subset, we first repeated our Cox regression analyses by using only

baseline exposures and then compared those findings with the results obtained by using time-dependent exposures, updating BMI and other covariates (excluding blood pressure and diabetes status) for each person.

Role of the Funding Source

The National Institutes of Health funded our study (grants HL71074 and DK61520). The funding source had no role in the collection, analysis, or interpretation of the data or in the decision to submit the manuscript for publication. The authors had full access to the data files for the study.

RESULTS

The mean BMI in the study sample was 24.5 kg/m^2 (SD, 4.3) (Table 1). Of the participants, 58% had normal weight (BMI, 18.5 to 24.9 kg/m^2) and 39% had a BMI of 25.0 kg/m^2 or greater. Higher BMI was associated with black race, presence of diabetes mellitus, and higher blood pressure level. The higher proportion of missing data on education level, smoking status, and history of myocardial infarction was due to the fact that medical history data were not available in an electronic format for participants from the second period (September 1973 to December 1977).

A total of 1471 cases of ESRD (and 56 336 deaths) occurred during 8 347 955 person-years of observation. We found a stepwise increase in the rate of ESRD with higher BMI (Table 2). The age-, sex-, and race-adjusted

Table 1. Baseline Characteristics of 320 252 Adults Stratified by Baseline Body Mass Index*

Characteristic	BMI Category					
	Underweight (n = 10 352)	Normal Weight (n = 186 730)	Overweight (n = 93 357)	Class I Obesity (n = 21 856)	Class II Obesity (n = 5540)	Class III Obesity (n = 2417)
BMI, kg/m²	<18.5	18.5–24.9	25.0–29.9	30.0–34.9	35.0–39.9	≥40.0
Mean (SD) height, cm	164.9 (8.7)	167.5 (9.6)	169.6 (9.8)	167.6 (10.0)	165.1 (10.4)	162.3 (11.8)
Mean (SD) weight, kg	48.1 (5.5)	62.4 (9.1)	77.9 (9.7)	89.9 (11.1)	101.3 (13.1)	116.4 (17.5)
Mean (SD) age, y	31 (12)	36 (13)	42 (14)	43 (14)	42 (13)	40 (13)
Women, n (%)	8644 (84)	112 784 (60)	35 002 (37)	11 005 (50)	3789 (68)	1915 (79)
Race, n (%)						
White	6285 (61)	132 647 (71)	65 021 (70)	13 414 (61)	3084 (56)	1235 (51)
Black	1766 (17)	28 982 (16)	19 193 (21)	6683 (31)	2032 (37)	1033 (43)
Asian	1499 (14)	13 048 (7)	2885 (3)	300 (1)	45 (1)	16 (1)
Other	800 (8)	11 981 (6)	6238 (7)	1446 (7)	378 (7)	133 (6)
Unknown	2 (0)	72 (0)	20 (0)	13 (0)	1 (0)	0 (0)
Education, n (%)						
≤High school	2895 (28)	57 820 (31)	37 473 (40)	9805 (45)	2447 (44)	1065 (44)
Some college	2629 (25)	44 860 (24)	19 722 (21)	4316 (20)	1100 (20)	538 (22)
≥College graduate	2069 (20)	38 326 (21)	15 044 (16)	2445 (11)	548 (10)	206 (9)
Unknown	2759 (27)	45 724 (24)	21 118 (23)	5290 (24)	1445 (26)	608 (25)
Cigarette smoking history, n (%)						
Never	3546 (34)	60 754 (33)	29 116 (31)	7320 (33)	1939 (35)	871 (36)
Former	795 (8)	22 754 (12)	15 223 (16)	3255 (15)	757 (14)	305 (12)
Current	3130 (30)	54 118 (29)	26 130 (28)	5792 (27)	1355 (24)	621 (26)
Unknown	2881 (28)	49 104 (26)	22 888 (25)	5489 (25)	1489 (27)	620 (26)
Diabetes mellitus, n (%)						
No	9407 (87)	156 309 (84)	74 686 (80)	17 423 (80)	4394 (79)	1916 (79)
Yes	1304 (13)	30 418 (16)	18 671 (20)	4433 (20)	1146 (21)	501 (21)
Unknown	1 (0.01)	3 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Previous MI, n (%)						
No	7685 (74)	143 412 (77)	73 027 (78)	16 587 (76)	4088 (74)	1801 (75)
Yes	145 (1)	3069 (2)	2585 (3)	702 (3)	187 (3)	78 (3)
Unknown	2522 (24)	40 249 (22)	17 745 (19)	4567 (21)	1265 (23)	538 (22)
Mean (SD) systolic BP, mm Hg	117 (17)	125 (18)	134 (20)	140 (22)	142 (23)	144 (24)
Mean (SD) diastolic BP, mm Hg	69 (12)	73 (12)	79 (13)	84 (13)	87 (15)	87 (16)
Mean (SD) serum cholesterol level						
mmol/L	5.02 (1.0)	5.34 (1.1)	5.78 (1.2)	5.88 (1.2)	5.78 (1.2)	5.67 (1.2)
mg/dL	194 (40)	206 (43)	223 (45)	227 (46)	223 (46)	219 (46)
Urine protein, n (%)						
Negative	9802 (95)	179 866 (96)	89 662 (96)	20 717 (95)	5141 (93)	2220 (92)
Trace	288 (3)	3805 (2)	2070 (2)	564 (3)	184 (3)	96 (4)
1–2+	223 (2)	2721 (1)	1471 (2)	497 (2)	192 (3)	89 (4)
3–4+	39 (0.4)	338 (0.2)	194 (0.2)	78 (0.4)	23 (0.4)	12 (0.5)
Urine hemoglobin, n (%)						
Negative	9634 (93)	177 203 (95)	89 639 (96)	20 762 (95)	5155 (93)	2232 (92)
Small	452 (4)	6456 (3)	2600 (3)	737 (3)	228 (4)	105 (4)
Moderate	155 (2)	1878 (1)	706 (1)	224 (1)	90 (2)	40 (2)
Large	111 (1)	1193 (1)	412 (0.4)	133 (1)	67 (1)	40 (2)
Mean (SD) serum creatinine level						
μmol/L	71 (18)	80 (18)	88 (18)	88 (18)	80 (27)	80 (27)
mg/dL	0.8 (0.2)	0.9 (0.2)	1.0 (0.2)	1.0 (0.2)	0.9 (0.3)	0.9 (0.3)

* BMI = body mass index; BP = blood pressure; MI = myocardial infarction.

rate of ESRD increased from 10 per 100 000 person-years among those with normal weight (BMI, 18.5 to 24.9 kg/m²) to 108 per 100 000 person-years among those with extreme obesity (BMI $\geq$ 40 kg/m²) (Table 2).

This relationship between BMI and risk for ESRD persisted in multivariable analyses after adjustment for Multiphasic Health Checkup period, age, sex, race, education level, smoking status, history of myocardial infarction, serum cholesterol level, urinalysis proteinuria, urinalysis hematuria, and serum creatinine level (Figure). Compared with persons with normal weight (BMI, 18.5 to 24.9 kg/m²), the adjusted relative risk for ESRD was 1.87 (95% CI, 1.64 to 2.14) for those who were overweight (BMI, 25.0 to 29.9 kg/m²), 3.57 (CI, 3.05 to 4.18) for those with class I obesity (BMI, 30.0 to 34.9 kg/m²), 6.12 (CI, 4.97 to 7.54) for those with class II obesity (BMI, 35.0 to 39.9 kg/m²), and 7.07 (CI, 5.37 to 9.31) for those with extreme obesity (BMI $\geq$ 40 kg/m²). Higher BMI was independently associated with higher ESRD risk in all subgroups analyzed (Table 3).

Analyses that Adjusted for Baseline Blood Pressure and Diabetes Status

Additional adjustment for baseline blood pressure and presence or absence of diabetes attenuated the association between higher BMI and risk for ESRD, but the relationship remained strong. Compared with persons with normal weight (BMI, 18.5 to 24.9 kg/m²), the adjusted relative risk for ESRD was 1.72 (CI, 1.50 to 1.96) for those who are overweight (BMI, 25.0 to 29.9 kg/m²), 2.98 (CI, 2.54 to 3.49) for those with class I obesity (BMI, 30.0 to 34.9 kg/m²), 4.68 (CI, 3.79 to 5.79) for those with class II obesity (BMI, 35.0 to 39.9 kg/m²), and 4.99 (CI, 3.77 to 6.60) for those with extreme obesity (BMI $\geq$ 40 kg/m²).

Elevated BMI remained a risk factor for ESRD if we alternatively defined diabetes mellitus status by relying on only self-report (that is, using data from only the first and third Multiphasic Health Checkup periods), with adjusted relative risks of 1.6 for those who were overweight, 2.9 for those with class I obesity, 4.2 for those with class II obesity, and 4.7 for those with extreme obesity ($P < 0.001$ for all). Elevated BMI remained a risk factor for ESRD if we alternatively defined diabetes mellitus status by using only blood glucose measurements performed outside the context

of oral glucose challenge tests (that is, using data from only the second and third Multiphasic Health Checkup periods) with adjusted corresponding relative risks of 1.7, 2.2, 4.3, and 2.9, respectively ($P < 0.001$ for all). Finally, elevated BMI remained a risk factor for ESRD if we alternatively defined diabetes mellitus status by using only blood glucose measurements performed outside the context of oral glucose challenge tests (that is, using data from only the second and third Multiphasic Health Checkup periods) but using 7.0 mmol/L (126 mg/dL) instead of 11.1 mmol/L (200 mg/dL) as the cutoff value, with adjusted corresponding relative risks of 1.7, 2.1, 4.1, and 2.8, respectively ($P < 0.001$ for all).

Higher BMI also predicted risk for ESRD in analyses that excluded persons with an estimated glomerular filtration rate less than 0.14 mL $\cdot$ s⁻² $\cdot$ m⁻² (<15 mL/min per 1.73 m²); in analyses that excluded participants with any missing data; in analyses that did not adjust for education level, smoking status, and history of myocardial infarction (which are the 3 covariates with the most missing data); and in analyses that were limited to each of the 3 individual Multiphasic Health Checkup periods (data not shown).

Secondary Analysis

Participants with 2 or more Multiphasic Health Checkup visits ($n = 134\,705$) were similar to participants with only 1 Multiphasic Health Checkup visit ($n = 185\,547$) in terms of sex distribution (55% vs. 53% women), mean BMI (24.7 kg/m² vs. 24.3 kg/m²), mean blood pressure (130/77 mm Hg vs. 128/75 mm Hg), mean serum creatinine level (84.8 μ mol/L [0.96 mg/dL] vs. 83.1 μ mol/L [0.94 mg/dL]), and prevalence of proteinuria (4% in both groups). However, persons with more than 1 visit were more likely than those with 1 visit to be older (mean, 41 years vs. 36 years) and to have diabetes (23% vs. 14%). In this subgroup, using baseline exposure information only, we found a similar relationship between each category of increased BMI and the risk for ESRD, with relative risks of 1.8, 3.8, 6.5, and 9.3, respectively ($P < 0.001$ for all). Our results were similar when we updated BMI and other covariates in our multivariable models with relative

Table 2. Age-, Sex-, and Race-Adjusted Rates of End-Stage Renal Disease for Each Category of Body Mass Index*

BMI Category	Persons, <i>n</i>	Mean (SD) BMI, kg/m ²	ESRD Events, <i>n</i>	Person-Years of Observation	Adjusted Rate per 100 000 Person-Years (95% CI)
Underweight (<18.5 kg/m ²)	10 352	17.6 (0.8)	8	264 280	7 (0.2–13)
Normal weight (18.5–24.9 kg/m ²)	186 730	22.1 (1.7)	414	4 921 700	10 (9–12)
Overweight (25.0–29.9 kg/m ²)	93 357	27.0 (1.4)	575	2 426 966	20 (18–22)
Class I obesity (30.0–34.9 kg/m ²)	21 856	31.9 (1.4)	291	543 835	46 (40–53)
Class II obesity (35.0–39.9 kg/m ²)	5540	37.0 (1.4)	122	134 006	76 (60–91)
Class III obesity ($\geq$ 40.0 kg/m ²)	2417	44.1 (4.6)	61	57 169	108 (72–143)
Total	320 252		1471	8 347 955	

* BMI = body mass index; ESRD = end-stage renal disease.

Table 3. Multivariable Associations between Categories of Body Mass Index and Risk for End-Stage Renal Disease in Subgroups of Participants*

Variable	Relative Risk (95% CI)					
	Underweight	Normal	Overweight	Class I Obesity	Class II Obesity	Class III Obesity
Sex						
Women	0.6 (0.3–1.2)	1.0	2.2 (1.7–2.7)	3.6 (2.8–4.6)	5.4 (4.1–7.3)	6.5 (4.6–9.3)
Men	0.2 (0.0–1.4)	1.0	1.8 (1.5–2.1)	3.6 (2.9–4.4)	7.3 (5.4–9.9)	9.4 (6.0–14.7)
Race						
Black	0.1 (0.0–1.0)	1.0	2.2 (1.8–2.7)	3.4 (2.7–4.3)	5.5 (4.1–7.5)	7.2 (5.0–10.4)
White	1.0 (0.4–2.2)	1.0	1.5 (1.2–1.8)	3.4 (2.7–4.4)	7.2 (5.2–10.0)	8.0 (5.0–12.8)
Age†						
<40 y	0.2 (0.1–0.8)	1.0	1.8 (1.4–2.2)	4.4 (3.5–5.7)	7.3 (5.3–10.1)	11.6 (8.0–16.9)
≥40 y	0.8 (0.3–2.0)	1.0	1.9 (1.6–2.2)	3.1 (2.5–3.8)	5.5 (4.2–7.2)	4.8 (3.2–7.2)
Diabetes						
Yes	1.3 (0.6–3.0)	1.0	1.9 (1.5–2.4)	3.3 (2.5–4.4)	5.0 (3.5–7.1)	3.6 (2.3–5.9)
No	0.1 (0.0–0.6)	1.0	1.9 (1.6–2.2)	3.4 (2.8–4.1)	5.7 (4.3–7.4)	7.6 (5.4–10.8)
Hypertension‡						
Yes	0.4 (0.1–1.5)	1.0	1.6 (1.3–1.9)	2.7 (2.2–3.4)	4.7 (3.7–6.1)	5.3 (3.9–7.3)
No	0.5 (0.2–1.1)	1.0	1.9 (1.6–2.3)	3.6 (2.8–4.7)	5.0 (3.3–7.5)	5.6 (3.1–10.2)
Baseline kidney disease§						
Yes	0.4 (0.1–1.3)	1.0	1.5 (1.2–2.0)	2.7 (2.0–3.6)	4.7 (3.3–6.8)	3.1 (1.8–5.3)
No	0.4 (0.2–1.0)	1.0	2.1 (1.8–2.4)	4.1 (3.4–5.0)	7.3 (5.6–9.4)	10.3 (7.5–14.1)

* Models adjusted for Multiphasic Health Checkup period, age, sex, race, education level, smoking status, history of myocardial infarction, serum cholesterol level, proteinuria, hematuria, and serum creatinine level. Body mass index (BMI) categories were as follows: underweight (BMI < 18.5 kg/m²), normal (BMI, 18.5–24.9 kg/m²), overweight (BMI, 25.0–29.9 kg/m²), class I obesity (BMI, 30.0–34.9 kg/m²), class II obesity (BMI, 35.0–39.9 kg/m²), and class III obesity (BMI ≥ 40 kg/m²).

† Stratified models also adjusted for age.

‡ Defined as systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg.

§ Defined as an estimated glomerular filtration rate < 0.58 mL · s⁻² · m⁻² (<60 mL/min per 1.73 m²) (by using the Modification of Diet in Renal Disease Study formula [20, 21]) or as the presence of urinalysis proteinuria or hematuria (22). These stratified models also adjusted for serum creatinine level and urinalysis proteinuria and hematuria.

risks of 1.7, 2.6, 4.2, and 6.5, respectively ($P < 0.001$ for all).

DISCUSSION

In our large cohort study, we observed a graded, strong relationship between the risk for ESRD and elevated BMI starting at a BMI of 25.0 kg/m². We consistently observed this association in men and women; younger and older persons; persons of different races; and persons with or without baseline kidney disease, diabetes, or hypertension.

Our findings are consistent with recently published data from the Framingham Offspring Study, which show that higher BMI is a risk factor for development of new-onset kidney disease (23). In that study, each SD increase in BMI was associated with an odds ratio of 1.23 (CI, 1.08 to 1.41) for “new-onset kidney disease,” defined as a decrease in glomerular filtration rate to 0.57 mL · s⁻² · m⁻² or less (≤59 mL/min per 1.73 m²) in women and 0.62 mL · s⁻² · m⁻² or less (≤64 mL/min per 1.73 m²) in men.

Few studies have examined the association between BMI and future risk for ESRD. Perry and colleagues (8) reported no association between baseline BMI and future risk for ESRD in their study of 11 912 male veterans with hypertension. Iseki and colleagues (5, 6) found that,

among 100 753 members of a screened Japanese cohort, baseline BMI predicted future risk for ESRD in men but not women. Compared with our study, these earlier studies had fewer persons with high BMI and fewer ESRD cases ($n = 245$ and 404). Stengel and colleagues (24) investigated the relationship between baseline BMI and risk for “chronic kidney disease” by using Second National Health and Nutrition Examination Survey (NHANES II) data. “Chronic kidney disease” was defined as the receipt of treatment for ESRD ($n = 44$) or “death related to chronic kidney disease” ($n = 145$) assessed by using death certificate codes of the International Classification of Diseases, Ninth Revision. They found an increased risk only for persons with a baseline BMI of 35 kg/m² or greater.

In contrast, we found a robust association between baseline BMI and risk for ESRD. Several possible pathophysiologic pathways may underlie this association. One possibility is that overweight patients are more likely to also have diabetes and hypertension, which are 2 well-established risk factors for ESRD. In our analysis, we found that baseline BMI remained a risk factor even after adjustment for baseline blood pressure and diabetes status. (However, as we later acknowledge, ascertainment of diabetes mellitus is not uniform in our cohort and a single

blood pressure measurement is associated with measurement error.) Another possibility is that patients with elevated BMI at baseline are more likely to develop new cases of diabetes and hypertension in the future, and these are the steps in the causal pathway linking elevated BMI to ESRD. A third possibility is that beyond high BMI being a risk factor for diabetes and hypertension, it also leads to renal failure through other mechanisms. Biopsy studies from humans have clearly established that obese patients have renal lesions that are distinct from diabetic nephropathy or hypertensive nephrosclerosis (9–11). Both animal and human studies have demonstrated that overweight leads to renal hyperperfusion and glomerular hyperfiltration, which, in turn, cause proteinuria and focal segmental glomerulosclerosis (25–31). More recently, some investigators have suggested that leptin produced from adipose tissue may directly lead to renal fibrosis (32). Although the exact mechanisms by which excessive weight leads to kidney disease are still being investigated (33, 34), our study provides epidemiologic support for their importance.

Our findings that underweight participants had the lowest risk for ESRD should be interpreted with caution, since the 95% CI for the multivariable risk estimate extended nearly to 1.0 (**Figure**). Few studies have examined the association between low body weight and future risk for renal disease (6). Ramirez and colleagues (35) noted that, among a sample of persons from Singapore, the relationship between proteinuria and BMI was J-shaped because those with a BMI of 18 kg/m² or less (and those with a BMI $\geq$ 25 kg/m²) were more likely to have proteinuria than those with a BMI of 18.01 to 22.99 kg/m². However, because that study was cross-sectional, preceding illness may have led to both proteinuria and malnutrition.

Our study is strengthened by the broad distribution of BMI among a large, diverse sample of screened ambulatory adults with comprehensive, longitudinal follow-up for ESRD. We could also control for important clinical and sociodemographic characteristics.

A limitation of our study is that many persons had only 1 measurement of BMI. However, within-person correlation of BMI over time is high (36). In addition, we confirmed our main conclusions in the secondary analysis of the subgroup of persons (42% of the cohort) who had at least 2 determinations of BMI. As detailed, availability of data to ascertain the presence or absence of diabetes was not uniform throughout the 3 Multiphasic Health Checkup periods. However, in sensitivity analysis, the strong association between elevated BMI and risk for ESRD seemed robust to alternate definitions of diabetes mellitus. We assessed blood pressure only once, and details about the standardization of this measurement were not available. We did not have complete information on use and type of antihypertensive and hypoglycemic medications and therefore could not evaluate the extent to which medical interventions confounded the reported associations. These limitations diminished our ability to deter-

mine the extent to which hypertension and diabetes mediated the association between excess weight and kidney failure. However, we believe that the overall association between increased BMI and risk for ESRD is the important finding in our study, more so than quantifying how much of this association is independent of hypertension or diabetes. We used a missing data category in our statistical analysis, and this approach is problematic in most instances. However, since data on education level, smoking status, and history of myocardial infarction are missing because medical history data were not available in an electronic format from the second Multiphasic Health Checkup period, this represents an uncommon instance when data are missing nearly at random. Since our study was conducted among insured members of a northern California integrated health care delivery system, our results may not be generalizable to other populations. Because this is an observational study, we could not assess whether intentional weight loss will reduce the risk for ESRD. Previous studies have shown that obese persons who lose weight have a reduction of absolute glomerular filtration rate, consistent with reversal of glomerular hyperfiltration (37, 38). Other studies have shown that weight loss is associated with a decrease in proteinuria, a major risk factor for future loss of glomerular filtration rate (39).

In summary, we have identified overweight or obesity as a strong and potentially modifiable risk factor for the development of ESRD. Conversely, kidney failure should be added to the list of adverse consequences of obesity. Given the rapidly increasing incidence of obesity and ESRD in the United States and internationally (1, 40), the confluence of these 2 public health problems is alarming. Vigorous efforts are needed to combat the epidemic of obesity and its complications.

From the University of California, San Francisco, San Francisco, California, and Kaiser Permanente of Northern California, Oakland, California.

Disclaimer: Some data were supplied by the U.S. Renal Data System. The interpretation and reporting of these data are the responsibility of the authors and in no way should be seen as an official policy or interpretation of the U.S. government.

Acknowledgment: The authors thank Mr. Shu-Cheng Chen of the U.S. Renal Data System for his assistance.

Grant Support: By the National Institutes of Health (grants HL71074 and DK61520).

Potential Financial Conflicts of Interest: None disclosed.

Requests for Single Reprints: Chi-yuan Hsu, MD, MSc, Division of Nephrology, University of California, San Francisco, 513 Parnassus Avenue, 672 HSE, Box 0532, San Francisco, CA 94143-0532; e-mail, hsuchi@medicine.ucsf.edu.

Current author addresses and author contributions are available at www.annals.org.

References

1. USRDS: the United States Renal Data System. *Am J Kidney Dis*. 2003;42:1-230. [PMID: 14655174]
2. Xue JL, Ma JZ, Louis TA, Collins AJ. Forecast of the number of patients with end-stage renal disease in the United States to the year 2010. *J Am Soc Nephrol*. 2001;12:2753-8. [PMID: 11729245]
3. Ogden CL, Carroll MD, Flegal KM. Epidemiologic trends in overweight and obesity. *Endocrinol Metab Clin North Am*. 2003;32:741-60, vii. [PMID: 14711060]
4. Manson JE, Skerrett PJ, Greenland P, VanItallie TB. The escalating pandemics of obesity and sedentary lifestyle. A call to action for clinicians. *Arch Intern Med*. 2004;164:249-58. [PMID: 14769621]
5. Iseki K, Ikemiya Y, Fukiyama K. Predictors of end-stage renal disease and body mass index in a screened cohort. *Kidney Int Suppl*. 1997;63:S169-70. [PMID: 9407450]
6. Iseki K, Ikemiya Y, Kinjo K, Inoue T, Iseki C, Takishita S. Body mass index and the risk of development of end-stage renal disease in a screened cohort. *Kidney Int*. 2004;65:1870-6. [PMID: 15086929]
7. Clinical Guidelines on the Identification, Evaluation and Treatment of Overweight and Obesity in Adults: The Evidence Report. NIH publication no. 98-4083. Bethesda, MD: National Institutes of Health; 1998.
8. Perry HM Jr, Miller JP, Fornoff JR, Baty JD, Sambhi MP, Rutan G, et al. Early predictors of 15-year end-stage renal disease in hypertensive patients. *Hypertension*. 1995;25:587-94. [PMID: 7721402]
9. Cohen AH. Massive obesity and the kidney. A morphologic and statistical study. *Am J Pathol*. 1975;81:117-30. [PMID: 1180328]
10. Kasiske BL, Crosson JT. Renal disease in patients with massive obesity. *Arch Intern Med*. 1986;146:1105-9. [PMID: 3718096]
11. Kambham N, Markowitz GS, Valeri AM, Lin J, D'Agati VD. Obesity-related glomerulopathy: an emerging epidemic. *Kidney Int*. 2001;59:1498-509. [PMID: 11260414]
12. Praga M, Hernández E, Herrero JC, Morales E, Revilla Y, Díaz-González R, et al. Influence of obesity on the appearance of proteinuria and renal insufficiency after unilateral nephrectomy. *Kidney Int*. 2000;58:2111-8. [PMID: 11044232]
13. Bonnet F, Deprele C, Sassolas A, Moulin P, Alamartine E, Berthezène F, et al. Excessive body weight as a new independent risk factor for clinical and pathological progression in primary IgA nephritis. *Am J Kidney Dis*. 2001;37:720-7. [PMID: 11273871]
14. Collen MF, ed. Multiphasic Health Testing Services. New York: J Wiley; 1978.
15. Krieger N. Overcoming the absence of socioeconomic data in medical records: validation and application of a census-based methodology. *Am J Public Health*. 1992;82:703-10. [PMID: 1566949]
16. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, et al. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension*. 2003;42:1206-52. [PMID: 14656957]
17. Arellano MG, Petersen GR, Petitti DB, Smith RE. The California Automated Mortality Linkage System (CAMLIS). *Am J Public Health*. 1984;74:1324-30. [PMID: 6507683]
18. Fisher LD, van Belle G. Biostatistics: A Methodology for the Health Sciences. New York: Wiley; 1996.
19. Kalbfleisch JD, Prentice RL. The Statistical Analysis of Failure Time Data. 2nd ed. Hoboken, NJ: Wiley-Interscience; 2002.
20. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med*. 1999;130:461-70. [PMID: 10075613]
21. Levey AS, Greene T, Kusek JW, Beck GJ. A simplified equation to predict glomerular filtration rate from serum creatinine [Abstract]. *J Am Soc Nephrol*. 2000;11:155A.
22. Levey AS, Coresh J, Balk E, Kausz AT, Levin A, Steffes MW, et al. National Kidney Foundation practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Ann Intern Med*. 2003;139:137-47. [PMID: 12859163]
23. Fox CS, Larson MG, Leip EP, Culleton B, Wilson PW, Levy D. Predictors of new-onset kidney disease in a community-based population. *JAMA*. 2004;291:844-50. [PMID: 14970063]
24. Stengel B, Tarver-Carr ME, Powe NR, Eberhardt MS, Brancati FL. Life-style factors, obesity and the risk of chronic kidney disease. *Epidemiology*. 2003;14:479-87. [PMID: 12843775]
25. Ribstein J, du Cailar G, Mimran A. Combined renal effects of overweight and hypertension. *Hypertension*. 1995;26:610-5. [PMID: 7558220]
26. Chagnac A, Weinstein T, Korzets A, Ramadan E, Hirsch J, Gafer U. Glomerular hemodynamics in severe obesity. *Am J Physiol Renal Physiol*. 2000;278:F817-22. [PMID: 10807594]
27. Henegar JR, Bigler SA, Henegar LK, Tyagi SC, Hall JE. Functional and structural changes in the kidney in the early stages of obesity. *J Am Soc Nephrol*. 2001;12:1211-7. [PMID: 11373344]
28. Adelman RD. Obesity and renal disease. *Curr Opin Nephrol Hypertens*. 2002;11:331-5. [PMID: 11981264]
29. de Jong PE, Verhave JC, Pinto-Sietsma SJ, Hillege HL. Obesity and target organ damage: the kidney. *Int J Obes Relat Metab Disord*. 2002;26 Suppl 4:S21-4. [PMID: 12457295]
30. Praga M. Obesity—a neglected culprit in renal disease [Editorial]. *Nephrol Dial Transplant*. 2002;17:1157-9. [PMID: 12105233]
31. Bosma RJ, van der Heide JJ, Oosterop EJ, de Jong PE, Navis G. Body mass index is associated with altered renal hemodynamics in non-obese healthy subjects. *Kidney Int*. 2004;65:259-65. [PMID: 14675058]
32. Wolf G, Chen S, Han DC, Ziyadeh FN. Leptin and renal disease. *Am J Kidney Dis*. 2002;39:1-11. [PMID: 11774095]
33. Hall JE, Henegar JR, Dwyer TM, Liu J, Da Silva AA, Kuo JJ, et al. Is obesity a major cause of chronic kidney disease? *Adv Ren Replace Ther*. 2004;11:41-54. [PMID: 14730537]
34. Abrass CK. Overview: obesity: what does it have to do with kidney disease? *J Am Soc Nephrol*. 2004;15:2768-72. [PMID: 15504929]
35. Ramirez SP, McClellan W, Port FK, Hsu SI. Risk factors for proteinuria in a large, multiracial, southeast Asian population. *J Am Soc Nephrol*. 2002;13:1907-17. [PMID: 12089388]
36. Brancati FL, Wang NY, Mead LA, Liang KY, Klag MJ. Body weight patterns from 20 to 49 years of age and subsequent risk for diabetes mellitus: the Johns Hopkins Precursors Study. *Arch Intern Med*. 1999;159:957-63. [PMID: 10326937]
37. Bröchner-Mortensen J, Rickers H, Balslev I. Renal function and body composition before and after intestinal bypass operation in obese patients. *Scand J Clin Lab Invest*. 1980;40:695-702. [PMID: 7280549]
38. Chagnac A, Weinstein T, Herman M, Hirsh J, Gafer U, Ori Y. The effects of weight loss on renal function in patients with severe obesity. *J Am Soc Nephrol*. 2003;14:1480-6. [PMID: 12761248]
39. Morales E, Valero MA, León M, Hernández E, Praga M. Beneficial effects of weight loss in overweight patients with chronic proteinuric nephropathies. *Am J Kidney Dis*. 2003;41:319-27. [PMID: 12552492]
40. Flegal KM, Carroll MD, Ogden CL, Johnson CL. Prevalence and trends in obesity among US adults, 1999-2000. *JAMA*. 2002;288:1723-7. [PMID: 12365955]

Current Author Addresses: Dr. Hsu: Division of Nephrology, University of California, San Francisco, 513 Parnassus Avenue, 672 HSE, Box 0532, San Francisco, CA 94143-0532.

Dr. McCulloch: Department of Epidemiology and Biostatistics, University of California, San Francisco, 500 Parnassus Avenue, San Francisco, CA 94143.

Drs. Iribarren and Go and Ms. Darbinian: Division of Research, Kaiser Permanente, 2000 Broadway, Oakland, CA 94612.

Author Contributions: Conception and design: C.-Y. Hsu, C. Iribarren, A.S. Go.

Analysis and interpretation of the data: C.-Y. Hsu, C.E. McCulloch, J. Darbinian, A.S. Go.

Drafting of the article: C.-Y. Hsu.

Critical revision of the article for important intellectual content: C.-Y. Hsu, C.E. McCulloch, C. Iribarren, J. Darbinian, A.S. Go.

Final approval of the article: C.-Y. Hsu, C.E. McCulloch, C. Iribarren, J. Darbinian, A.S. Go.

Statistical expertise: C.-Y. Hsu, C.E. McCulloch.

Obtaining of funding: C.-Y. Hsu, C. Iribarren, A.S. Go.

Administrative, technical, or logistic support: C.-Y. Hsu, A.S. Go.