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## **Nutritional status in chronic dialysis patients : associations with development of disease and survival**

Mutsert, R. de

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# 2

## **Obesity, smoking and physical inactivity as risk factors for chronic kidney disease; are men more vulnerable?**

S. Hallan  
R. de Mutsert  
S. Carlsen  
F.W. Dekker  
K. Aasarod  
J. Holmen

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**ABSTRACT**

**Background** The incidence of end-stage renal disease is especially high in men, and some studies indicated that smoking is a risk factor for men only. We investigated the association between obesity, smoking and physical inactivity and chronic kidney disease (CKD) in the general population and whether risk for CKD was restricted to men.

**Methods** This was a cross-sectional health survey of the entire adult population of Nord-Trøndelag County, Norway, 1995 to 1997, with a 70.6% participation rate. Glomerular filtration rate (GFR) was estimated in all subjects 20 years and older from calibrated serum creatinine levels by using the simplified Modification of Diet in Renal Disease study formula, and CKD cases are defined as GFR <45 mL/min/1.73 m<sup>2</sup> (<0.75 mL/s/1.73 m<sup>2</sup>).

**Results** A total of 30,485 men and 34,708 women were included, and prevalences of GFR <45 mL/min/1.73 m<sup>2</sup> (<0.75 mL/s/1.73 m<sup>2</sup>) were 0.8% and 1.1%, respectively. Age- and sex-adjusted logistic regression analyses showed dose-response relations for body mass index, smoking history and physical activity. Relative risks were 1.77 (95% confidence interval [CI], 1.47 to 2.14) for obesity (body mass index  $\geq$  30 kg/m<sup>2</sup>), 1.52 (95% CI, 1.13 to 2.06) for smoking (>25 pack-years), and 2.14 (95% CI, 1.39 to 3.30) for physical inactivity (no or some physical activity in leisure time). For subjects with all of these risk factors, relative risk was 5.10 (95% CI, 2.36 to 11.01). These results remained significant after adjusting for other known risk factors. No biological interactions between sex and obesity, smoking, or physical activity were found.

**Conclusion** Obesity, smoking, and physical inactivity were associated significantly with CKD. Men were not more susceptible to these risk factors than women.

## INTRODUCTION

The incidence of end-stage renal disease (ESRD) has doubled in the industrialized world during the last 2 decades, and the major part of this increase is caused by such lifestyle-related factors as hypertension and diabetic nephropathy.<sup>1,2</sup> The association between obesity,<sup>3-5</sup> smoking,<sup>4,6,7</sup> and physical activity<sup>4</sup> and chronic kidney disease (CKD) therefore could be important. However, findings are incongruous regarding the magnitude of the associated risks and dose-response, and there are also problems of insufficient adjustment of potential confounders and unequal risk-factor exposure in men and women. It is known that obesity leads to ESRD through diabetes mellitus and hypertension, but emerging evidence indicates that obesity also can contribute directly to kidney damage through obesity-related glomerulopathy, mechanical compression, and a cascade of other hemodynamic and metabolic mechanisms.<sup>8-12</sup> However, the leading epidemiological study found that the relation was mediated largely by diabetes and hypertension, and only the morbidly obese had an increased risk for CKD.<sup>4</sup>

Furthermore, men are overrepresented among patients with ESRD,<sup>13,14</sup> and both experimental animal studies and human clinical trials found that males have a faster progression rate toward ESRD than females.<sup>15,16</sup> The underlying mechanisms for this sex disparity are unclear, but it may be related to differences in hemodynamics, local cytokine production, or direct effects of sex hormones on kidney cells.<sup>17</sup> Several studies also indicated that harmful effects of smoking on kidney function were restricted to men,<sup>6,18,19</sup> and some studies reported that obesity was associated with impaired kidney function in men only.<sup>3,19</sup> However, other studies found that the risk for CKD was associated with smoking and obesity in both sexes.<sup>4,7</sup>

Better in-depth understanding of the influence of these risk factors therefore is needed to be able to take proper action to prevent CKD and ESRD. The second Health Survey of Nord-Trøndelag County (HUNT II) is a large population-based cross-sectional study conducted in Norway with a high participation rate (70%). We tested the hypothesis that obesity, smoking and physical inactivity are associated with the risk for CKD in the general population and whether this risk is greater in men than women.

## MATERIAL AND METHODS

### *Study sample and design*

Between 1995 and 1997, a large-scale general health survey was conducted in Nord-Trøndelag County, Norway. Inhabitants of the county (n=92,939) aged 20 years and older were invited to participate in the study, 70.6 % responded. The survey consisted of an extensive questionnaire and brief clinical examination, in addition to several clinical chemistry analyses. The population in Nord-Trøndelag is stable, with a net outmigration of 0.3% per year, and it is ethnically homogenous, with more than 97% whites. A detailed description on objectives, contents, methods, and participation in the HUNT study has been given elsewhere.<sup>20</sup> All participants in the HUNT II study gave informed consent, and the current study was approved by the Regional Ethics Review Committee, the Data Inspectorate, and the Ministry of Health.

### *Data collection and definitions*

Participants reported on several aspects of their current and former health, illness in the family, socioeconomic status, physical activity, and smoking. Clinical examination included measurements of height, weight, waist and hip circumference, and blood pressure. Three consecutive standardized blood pressure measurements were recorded in the sitting position at 1-minute intervals by using an automatic oscillometric method (Dinamap 845XT; Criticon, Tampa, FL).

CKD is classified as stages 1 to 5<sup>21,22</sup>: stages 1 and 2 are a glomerular filtration rate (GFR) of 60 mL/min/1.73 m<sup>2</sup> or greater ( $\geq 1.00$  mL/s/1.73 m<sup>2</sup>) plus albuminuria, stage 3 is a GFR OF 30 to 59 mL/min/1.73 m<sup>2</sup>, (0.50 to 0.98 mL/s/1.73 m<sup>2</sup>), stage 4 is a GFR of 15 to 29 mL/min/1.73 m<sup>2</sup> (0.25 to 0.48 mL/s/1.73 m<sup>2</sup>) and stage 5 is a GFR less than 15 ml/min/1.73 m<sup>2</sup> (<0.25 mL/s/1.73 m<sup>2</sup>). Stage 3 is sometimes divided further into 2 stages: GFRs of 30 to 44 and 45 to 59 mL/min/1.73 m<sup>2</sup> (0.50 to 0.73 and 0.75 to 0.98 mL/s/1.73 m<sup>2</sup>).<sup>23,24</sup> The diagnosis of CKD requires a GFR less than 60 mL/min/1.73m<sup>2</sup> (<1.00 mL/s/1.73 m<sup>2</sup>) during a period of 3 months. In this study, only 1 assessment of GFR was available for each subject. To prevent overestimation of CKD cases, we chose a more conservative definition of a single GFR less than 45 mL/min/1.73m<sup>2</sup> (<0.75 mL/s/1.73 m<sup>2</sup>) to define CKD. Further details on GFR estimation are given later.



Participants were classified as hypertensive if the mean of the 2 last blood pressure measurements was 140 mm Hg or greater systolic or 90 mm Hg or greater diastolic or if they reported use of antihypertensive medication. Participants were classified as diabetic if they reported having diabetes mellitus ("sugar disease"). Participants were classified as unknown diabetics, which includes impaired glucose tolerance and impaired fasting glucose, if they had glucose greater than the following levels: 140 mg/dL (7.8 mmol/L) at 2 hours after the last meal linearly decreasing to 110 mg/dL (6.1 mmol/L) at 6 hours or more after the last meal. Subjects reporting a history of myocardial infarction, angina, or stroke were classified as prior cardiovascular disease (CVD). Higher education is defined as an obtained college degree or higher.

Body mass index (BMI) is categorized as follows: underweight (<18.5 kg/m<sup>2</sup>), normal weight (18.5 to 24.9 kg/m<sup>2</sup>), overweight (25.0 to 29.9 kg/m<sup>2</sup>), obesity class I (30.0 to 34.9 kg/m<sup>2</sup>), obesity class II (35.0 to 39.9 kg/m<sup>2</sup>) and obesity class III (≥40.0 kg/m<sup>2</sup>). However, several reports indicated that abdominal fat, measured as waist circumference or waist-hip ratio, are better risk factors, at least for CVD. We used a waist circumference greater than 0.90 m and greater than 0.80 m<sup>25;26</sup> and waist-hip ratio greater than 0.95 and greater than 0.85<sup>27;28</sup> as cutoff values for increased risk in men and women, respectively. For smoking, there are no established risk levels, but several reports indicated that a long and heavy smoking history was needed to increase the risk for CKD.<sup>6;7</sup> In addition to smoking status (never smokers versus current or former smokers), we studied categories of pack-years (0, 1 to 24, 25 to 49, and ≥50 pack-years). Pack-years are calculated as number of cigarettes per day multiplied by number of years of smoking and divided by 20. Physical activity is reported as time per week with light and/or intensive activity (sweating and really breathless) in their leisure time (0, <1, 1 to 3, or ≥3 hours). We constructed categories by using the US Surgeon General's minimum recommendations as an approximate middle point, with 2 categories less than this level and 2 categories greater than this level:<sup>29</sup> high is defined as 3 or more hours of intensive activity; moderate, 1 to 3 hours of intensive activity; some, less than 1 hour of intensive activity or 1 or more hours of light activity; and none, up to 1 hour of light activity and no intensive activity.

*Laboratory methods and GFR estimation*

Blood was drawn, often in the non-fasting state, from all participants, and fresh serum samples were analyzed at the Central Laboratory of Levanger Hospital on a Hitachi 911 Autoanalyzer (Hitachi, Mito, Japan) within 2 days. Serum creatinine was analyzed by means of a kinetic Jaffé method with water blank by using reagents from Roche (Roche Diagnostics, Mannheim, Germany). Glucose was measured by means of an enzymatic hexokinase method, and total and high-density lipoprotein cholesterol were measured by means of an enzymatic calorimetric cholesterolesterase method. Day-to-day coefficients of variation were 1% to 2% for all analysis. GFR was estimated using the Modification of Diet in Renal Disease (MDRD) Study formula<sup>30</sup>:

$$\text{GFR}=186.3\times\text{serum creatinine (mg/dL)}^{-1.154}\times\text{age}^{-0.203}[\times 0.742 \text{ for women}][\times 1.21 \text{ for blacks}]$$

Studies have shown that the MDRD formula is based on an unusually low calibrated serum creatinine method, leading to underestimation of GFR in patients with mild renal insufficiency in most other laboratories.<sup>31,32</sup> We therefore used a recalibration equation we developed to ensure that local serum creatinine values were calibrated equally with the MDRD study:

$$\text{Serum creatinine (mg/dL)}=-0.21+1.08\times\text{serum creatinine}$$

Further details on recalibration and GFR estimation have been given previously.<sup>31</sup>

*Statistical analyses*

We evaluated the association between CKD (GFR < 45 mL/min/1.73 m<sup>2</sup> [ $<0.75$  mL/s/1.73 m<sup>2</sup>]) and possible risk factors. Odds ratios were estimated by using logistic regression analysis, and calculated odds ratios and 95% confidence intervals (CIs) are expressed as an approximation of relative risk (RR) because the disease frequency was low.<sup>33</sup> Crude analyses were adjusted for the confounding effects of age and sex. Furthermore, the variables obesity, smoking and physical activity were categorized into 4 to 6 groups, as described, to explore dose-response effects in subsequent regression analyses adjusted for age and sex.

Sex differences in susceptibility to the 3 lifestyle-related risk factors studied were explored by examining for biological interaction according to Rothman<sup>34</sup>: a new composite variable with 4 categories ( $\bar{a}\bar{b}$ ,  $\bar{a}b$ ,  $a\bar{b}$ ,  $ab$ ) was redefined for sex and a dichotomous exposure of interest where  $\bar{a}$  and  $\bar{b}$  denote unexposure. RR was calculated for each category after adjustment for age. An interaction effect is defined as departure from additivity of absolute effects, and the relative excess risk due to interaction (RERI) was calculated:

$$\text{RERI} = \text{RR}(ab) - \text{RR}(\bar{a}b) - \text{RR}(a\bar{b}) + 1$$

Where  $\text{RR}(ab)$  denotes the RR among those exposed to both factors where  $\text{RR}(\bar{a}\bar{b})$  is used as reference category ( $\text{RR}=1$ ). Ninety-five percent CIs were calculated as proposed by Hosmer and Lemeshow.<sup>35</sup> RERI of 0 means no interaction. RERI of 0.5 means that because of interaction between the 2 risk factors, RR is 0.5 greater than expected based on the addition of the 2 risk factors. The presence of biological interactions among obesity, smoking, and physical inactivity were assessed by using the same methods, and we also calculated the age- and sex-adjusted RRs for combinations of these 3 risk factors.

Because hypertension, diabetes mellitus, and lipids are possible intermediate variables in the causal pathway of the association between obesity and CKD, and not confounders for obesity, we did not adjust for these in previous analyses. However, we also wanted to explore how much of the unadjusted RR was explained by a set of other risk factors. To that end, we constructed a series of 5 logistic regression models for each of the 3 lifestyle-related risk factors studied: (1) unadjusted, (2) adjusted for age and sex, (3) additionally adjusted for hypertension, (4) additionally adjusted for diabetes mellitus, and (5) additionally adjusted for prior CVD and dyslipidemia. All statistical analyses were generated using SPSS version 12.0.1 (SPSS Inc., Chicago, IL).

## RESULTS

A total of 30,485 men and 34,708 women, ie 99.4% of all participants, had their GFR estimated. GFR less than 45 mL/min/1.73 m<sup>2</sup> (<0.75 mL/s/1.73 m<sup>2</sup>) was found in 246 men (0.8%) and 375 women (1.1%). Age ranged from 20 to 103 years (mean 50.2 ± 17.4 [SD] years). Hypertension was found in 44.9% of the general population, and 3.0 % had known diabetes mellitus. Patient characteristics and medical history by GFR level, as well as crude and adjusted RRs for all risk factors, are listed in Table 1.

Table 1. Association of GFR less than 45 mL/min/1.73m<sup>2</sup> with obesity, smoking, physical inactivity, demographics and medical history

	GFR ≥45 mL/ min/1.73 m <sup>2</sup>	GFR <45 mL/ min/1.73 m <sup>2</sup>	Crude RR (95% CI)	Age- and sex-adjusted RR (95% CI)
Female gender (%)	53.2	60.4	1.34 (1.14-1.57)	1.16 (0.98-1.37)*
Age (mean (SD))	49.9 ± 17.2	75.7 ± 10.7	3.04 (2.83-3.27)	3.02 (2.81-3.24)*
Higher education (%)	29.5	10.2	0.27 (0.20-0.36)	0.97 (0.71-1.32)
Diabetes Mellitus (%)	2.9	15.0	6.65 (5.30-8.34)	2.47 (1.95-3.12)
Prior CVD (%)	7.6	38.3	8.86 (7.48-10.50)	2.51 (2.10-3.01)
Hypertension (%)	42.5	75.4	6.45 (5.18-8.03)	1.56 (1.24-1.96)
Systolic BP (mean (SD))	137.8 ± 21.7	154.4 ± 27.6	1.31 (1.28-1.35)	0.98 (0.94-1.01)
Diastolic BP (mean (SD))	80.3 ± 12.2	84.1 ± 15.8	1.26 (1.18-1.34)	0.96 (0.90-1.02)
Cholesterol >230 mg/dl (%)	45.0	64.9	2.26 (1.91-2.66)	1.12 (0.98-1.39)
HDL cholesterol <40 mg/dl (%)	11.5	28.8	3.10 (2.60-3.70)	2.53 (2.10-3.05)
BMI > 25 kg/m <sup>2</sup> (%)	59.7	71.9	1.73 (1.43-2.09)	1.25 (1.03-1.52)
Waist-hip ratio > 0,95(M) or 0,85(F) (%)	17.5	40.7	3.23 (2.72-3.84)	1.52 (1.28-1.82)
Waist circumference > 0,90m(M) or 0,80m(F) (%)	54.2	70.4	2.00 (1.68-2.38)	1.19 (1.00-1.42)
Current or former smoking (%)	55.3	49.3	0.78 (0.66-0.93)	1.17 (0.96-1.43)
Pack-years (mean (SD))	6.9 ± 10.8	8.5 ± 16.1	1.11 (1.04-1.19)	1.10 (1.04-1.18)
Physical inactive (%)	19.9	49.6	2.18 (1.84-2.59)	1.67 (1.40-1.99)

Continuous variables are mean ± SD. RRs for continuous variables (age, blood pressure, and packyears) are per 10 units. To convert GFR in mL/min to mL/s, multiply by 0.01667; cholesterol in mg/dl to mmol/l, multiply by 0.02586. \* Sex is adjusted only for age, and age is adjusted for only sex.

Figure 1 shows age- and sex-adjusted RRs for CKD with categories of obesity (Figure 1A), smoking history (Figure 1B), and physical activity (Figure 1C) to explore the level of unhealthy lifestyle at which risk for CKD starts to increase. Overweight (BMI, 25 to 29 kg/m<sup>2</sup>) did not increase risk, but all classes of obesity (BMI ≥ 30 kg/m<sup>2</sup>) increased risk. Smokers with 25 to 49 pack-years had an increased risk of 42% (95% CI, 1 to 200) compared with never smokers. Those with 50 pack-years or greater, eg, more than 20 cigarettes/d for 50 years, had an increased risk of 105% (95% CI, 8 to 289). Subjects with a less intense smoking history did not seem to have an increased risk for CKD. There was no difference between high physical activity and moderate activity. However, subjects with only some activity had a 93% (95% CI, 0 to 290) increased risk compared with the high-activity group, and those with no activity had an increased risk of 275% (95% CI, 82 to 670).

A

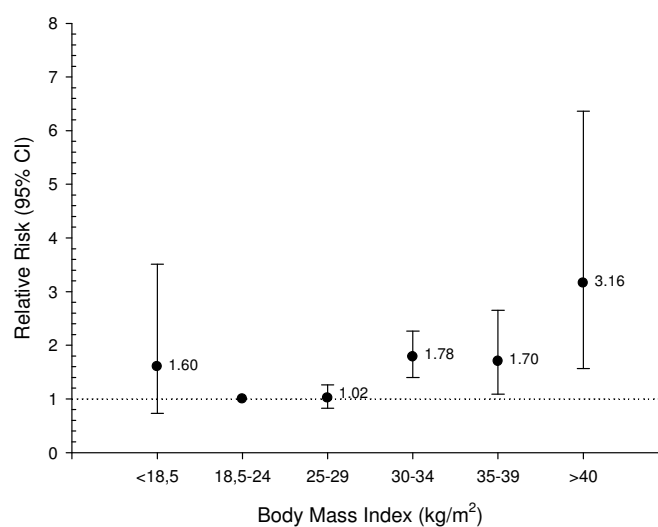
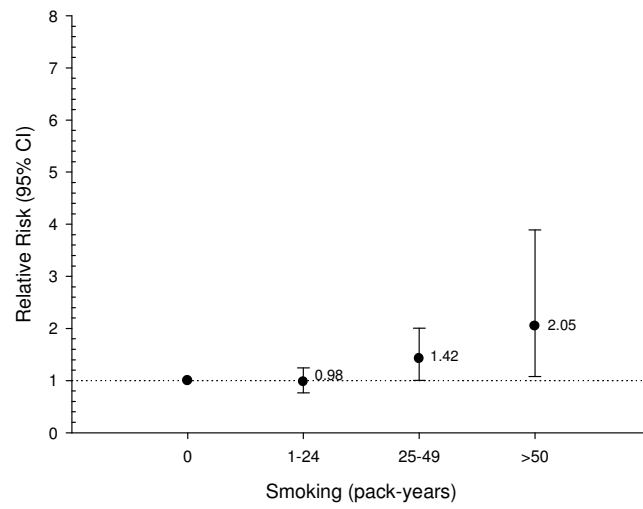


Figure 1. Relative risks and 95% CIs for CKD (GFR < 45 mL/min/1.73 m<sup>2</sup> [ $<0.75$  mL/s1.73 m<sup>2</sup>]) associated with categories of (A) obesity, (B) smoking and (C) physical activity adjusted for age and sex

B



C

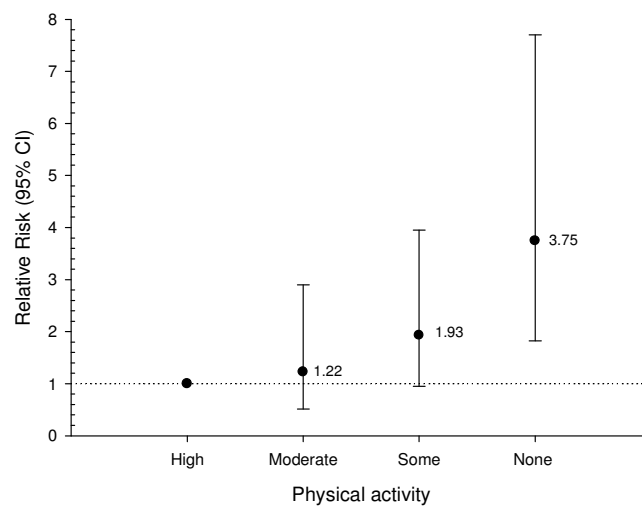


Table 2. Relative excess risks due to biological interaction (RERI) between sex and lifestyle-related risk factors

		RR (95% CI)				RERI (95% CI)
Sex and obesity	Female; BMI < 30 kg/m <sup>2</sup>	Male; BMI < 30 kg/m <sup>2</sup>	Female; BMI ≥ 30 kg/m <sup>2</sup>	Male; BMI ≥ 30 kg/m <sup>2</sup>		
	1	0.95 (0.77, 1.17)	1.68 (1.32, 2.13)	1.86 (1.37, 2.52)	0.23 (-0.40, 0.85)	
Sex and smoking	Female; pack-years < 25	Male; pack-years < 25	Female; pack-years ≥ 25	Male; pack-years ≥ 25		
	1	0.80 (0.64, 1.00)	1.45 (0.78, 2.68)	1.24 (0.90, 1.71)	-0.01 (-0.97, 0.94)	
Sex and activity	Female; moderate or high	Male; moderate or high	Female; none or some	Male; none or some		
	1	1.22 (0.48, 3.11)	2.64 (1.16, 6.00)	2.38 (1.05, 5.43)	-0.48 (-1.90, 0.95)	

Age-adjusted RRs for CKD (GFR < 45 mL/min/1.73 m<sup>2</sup> [ $<0.75$  mL/s/1.73 m<sup>2</sup>]). RERI = 0 means no interaction. RERI = 0.5 means that because of interaction between the 2 risk factors, the RR is 0.5 greater than expected based on the addition of the 2 risk factors.

Table 3. Relative excess risks due to biological interaction (RERI) between obesity, smoking, and physical activity

		RR (95% CI)				RERI (95% CI)
Obesity and smoking	BMI < 30 kg/m <sup>2</sup> ; pack-years < 25	BMI < 30 kg/m <sup>2</sup> ; pack-years ≥ 25	BMI ≥ 30 kg/m <sup>2</sup> ; pack-years < 25	BMI ≥ 30 kg/m <sup>2</sup> ; pack-years ≥ 25		
	1	1.38 (0.96, 1.98)	1.65 (1.31, 2.08)	3.04 (1.82, 5.07)	1.01 (-0.59, 2.60)	
Obesity and activity	BMI < 30 kg/m <sup>2</sup> ; moderate or high	BMI < 30 kg/m <sup>2</sup> ; none or some	BMI ≥ 30 kg/m <sup>2</sup> ; moderate or high	BMI ≥ 30 kg/m <sup>2</sup> ; none or some		
	1	1.93 (1.20, 3.11)	1.34 (0.45, 3.97)	3.24 (1.96, 5.36)	0.97 (-0.53, 2.46)	
Smoking and activity	Pack-years < 25; moderate or high	Pack-years < 25; none or some	Pack-years ≥ 25; moderate or high	Pack-years ≥ 25; none or some		
	1	1.92 (1.16, 3.18)	0.94 (0.22, 4.12)	3.17 (1.80, 5.59)	1.31 (-0.33, 2.95)	

Age-adjusted RR for CKD (GFR < 45 mL/min/1.73 m<sup>2</sup> [ $<0.75$  mL/s/1.73 m<sup>2</sup>]). RERI = 0 means no interaction. RERI = 0.5 means that because of interaction between the 2 risk factors, the RR is 0.5 greater than expected based on the addition of the two risk factors.



Table 4. Relative risks and 95% CIs for CKD (GFR < 45 mL/min/1.73 m<sup>2</sup> [ $<0.75$  mL/s1.73 m<sup>2</sup>]) associated with BMI, smoking, or physical inactivity when an increasing number of covariates is added

	Crude	Adjusted for			
		Age and sex	+ Diabetes	+ Hypertension	+ CVD and lipid levels
BMI > 30 kg/m <sup>2</sup>	2.29 (1.91, 2.75)	1.77 (1.47, 2.14)	1.68 (1.39, 2.04)	1.63 (1.35, 1.98)	1.44 (1.18, 1.75)
Pack-years > 25	1.98 (1.49, 2.62)	1.52 (1.13, 2.06)	1.51 (1.11, 2.04)	1.50 (1.11, 2.04)	1.47 (1.08, 2.00)
None or some physical activity	6.09 (3.99, 9.28)	2.14 (1.39, 3.30)	2.11 (1.37, 3.26)	2.09 (1.35, 3.22)	1.82 (1.18, 2.81)

For all variables, age was a major confounder, whereas the effect of sex was not significant. The influence of diabetes mellitus and hypertension on RR associated with obesity was only minor because RR was decreased by 8%. Likewise, RR associated with low physical activity was only decreased by 2%. Prior CVD and dyslipidemia decreased these RRs by 12%. A smoking history of more than 25 pack-years was not influenced by these other covariates at all. However, diabetes, hypertension and prior CVD were major independent risk factors for CKD: In a full multivariate logistic regression analysis, RR for diabetes was 1.91 (95% CI, 1.47 to 2.49); for hypertension, 1.63 (95% CI, 1.25 to 2.12); and for prior CVD, 2.75 (95% CI, 2.25 to 3.36) after adjusting for age, sex, obesity, smoking, and physical activity. Correspondingly, RR for obese inactive smokers was 4.01 (RR adjusted for only age and sex was 5.1; Figure 2).

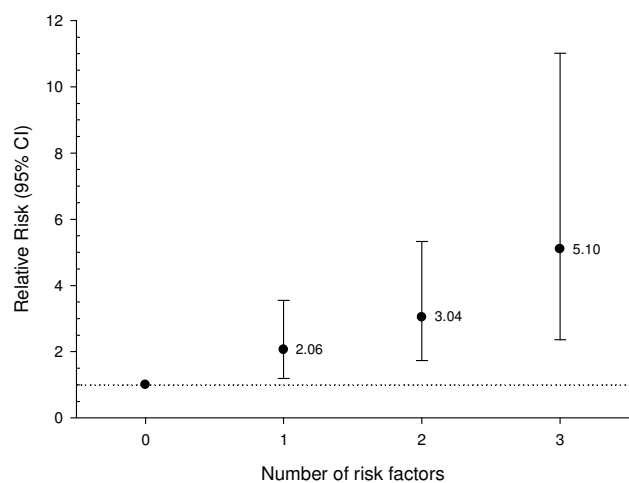


Figure 2. Relative risks and 95% CIs for CKD (GFR < 45 mL/min/1.73 m<sup>2</sup> [ $<0.75$  mL/s/1.73 m<sup>2</sup>]) associated with increasing number of risk factors (obesity, smoking, and physical activity) adjusted for age and sex. Subjects in the reference group (0) have neither BMI of 30 kg/m<sup>2</sup> or greater, smoking history of 25 pack-years or greater, nor no or some physical activity. Number of risk factors relates to any 1, 2 or 3 of these risk factors.

To assess the robustness of our main results, we conducted several subsidiary analyses. If we defined CKD as GFR less than 60 mL/min/1.73 m<sup>2</sup> ( $<1.00$  mL/s/1.73 m<sup>2</sup>) instead of GFR less than 45 mL/min/1.73 m<sup>2</sup> ( $<0.75$  mL/s/1.73 m<sup>2</sup>), we detected 1,021 male and 2,156 female cases. Main results were similar, but the associations in general were weaker. Age- and sex-adjusted RR associated with a BMI of 30 kg/m<sup>2</sup> or greater decreased from 1.77 to 1.57 (95% CI, 1.44 to 1.72); pack-years of 25 or greater, from 1.52 to 1.17 (95% CI, 1.01 to 1.37); and no or some physical activity, from 2.14 to 1.34 (95% CI, 1.15 to 1.57). In the full multivariate analysis, RRs associated with diabetes, hypertension, and prior CVD were attenuated to 1.31 (95% CI, 1.13 to 1.53), 1.49 (95% CI, 1.34 to 1.67), and 1.94 (95% CI, 1.74 to 2.15), respectively. If subjects with unknown diabetes mellitus were included, the prevalence of diabetes increased from 3.0% to 4.8%. However, results of all analyses remained unchanged. We also used waist-hip ratio and waist circumference to better assess the effect of abdominal obesity. Age- and sex-adjusted RRs with waist-hip ratio gave results similar to BMI: using the 25th, 50th, 75th and 95th

percentiles, we found RRs of 0.92 (95% CI, 0.63 to 1.33), 1.38 (95% CI, 0.96 to 2.02), 1.50 (95% CI, 0.98 to 2.09) and 2.13, (95% CI, 1.46 to 3.10), respectively.

## DISCUSSION

This study shows that obesity, smoking, and physical inactivity are associated with CKD, and there is no biological interaction between sex and the 3 risk factors studied. Dose-response relations were found for all 3 risk factors. The increased risk was seen for BMI greater than 30 kg/m<sup>2</sup>, smoking greater than 25 pack-years, and less than 1 hour of intensive physical activity per week. Diabetes mellitus and hypertension explained only a minor part of the risk associated with obesity, smoking and physical inactivity. Risk associated with the combined exposure of obesity, smoking and physical inactivity was 5 times greater compared with subjects without these risk factors, showing that these are among the major CKD risk factors.

Generally, our results are in accordance with previous reports providing documentation that obesity, smoking, and physical inactivity are injurious to the kidney, but some aspects need further discussion. Stengel et al found obesity to be a risk factor only at a BMI greater than 35 kg/m<sup>2</sup>,<sup>4</sup> whereas others found increased risk even at slightly elevated BMIs.<sup>3,5</sup> These incongruent dose-response results can be caused by differences in methods and race in these articles. We found a clear dose-response effect starting at a BMI of 30 kg/m<sup>2</sup>, well in accordance with the fact that most mechanisms proposed for obesity are of a kind that do not follow a threshold model for dose-response effect.<sup>36</sup> Adiposity therefore emerges as an independent and important risk factor for CKD.

Current smoking is not associated significantly with CKD in our study. This is surprising given the strong evidence between smoking and atherosclerosis in general and several earlier reports on the association between smoking and CKD.<sup>37</sup> It seems clear that smoking carries a risk for patients with diabetic nephropathy, patients with a renal transplant, and patients with preexisting primary renal disease,<sup>37</sup> but results from studies in the general population have been more

diverging. Two studies found that current smoking was an important risk factor for CKD.<sup>4,38</sup> However, 2 studies found no effect of smoking on renal function,<sup>5,39</sup> and 2 other studies found that only a high cumulative smoking dose increased the risk of CKD.<sup>6,7</sup> It therefore is highly probable that smoking increases the risk for CKD, but the risk might be restricted to subjects with a high cumulative smoking dose, and current smoking status might be of less importance. For myocardial infarction, the situation is opposite.<sup>40</sup> The reason for this might be that although acute cardiovascular events are heavily driven by the prothrombotic effect of smoking, which is a short-time effect, CKD is driven mainly by the atherosclerotic effect of smoking, which is more a long-term effect caused by increased oxidative stress and decreased nitric oxide bioavailability.<sup>41</sup>

Physical activity decreased the risk for CKD in our study, and this also was shown in a few other studies. Stengel et al. found that low physical activity doubled the risk compared with subjects with high physical activity in a population-based study.<sup>4</sup> A prospective study of patients with diabetes found physical activity to be protective against early renal function decline,<sup>42</sup> and experimental studies showed a renal protective action of exercise in rats.<sup>43-46</sup> However, the only randomized clinical study of humans showed no effect of increased physical activity on the slope of GFR versus time.<sup>47</sup> This might be caused by the small sample size of the study (30 patients) and the rather advanced CKD (median GFR, 25 mL/min/1.73 m<sup>2</sup> [0.42 mL/s/1.73 m<sup>2</sup>]).<sup>48,49</sup> Physical inactivity therefore seems to be an important risk factor for CKD.

Many subjects are exposed to the combined effects of obesity, smoking and physical inactivity. Our study shows that such exposure is associated with a very high risk for CKD, which is important for preventive medicine because these risk factors, contrary to diabetes, hypertension and CVD, are fully reversible. There also seemed to be biological interaction among obesity, smoking, and physical inactivity, ie, they increase the effect of each other. The 95% CI of RERI included 0, but statistical evaluation of biological interaction is not well established. Some consider every departure from a RERI of 0 as interaction, and the method we used is rather conservative.<sup>50</sup> Thus, our results can be considered compatible with

biological interaction. The pathophysiological mechanism for this could be their joint acceleration of atherosclerosis. There is increasing evidence that the processes of atherosclerosis and progressive kidney disease are tightly connected.<sup>51</sup>

Sex differences were reported in several studies of lifestyle-related risk factors and CKD. However, there were problems with low statistical power caused by fewer participants and lower doses of exposure, especially for women, and none have analyzed their data looking for biological interaction between risk factor and sex, which is the recommended statistical analysis.<sup>34</sup> The risk for renal impairment associated with smoking was found in several studies to be restricted to men, whereas no increased risk could be found for women.<sup>6,18,19</sup> Results of our study are not consistent with the hypothesis that women are insensitive to the effects of smoking. Two recent studies supported our results; risks associated with smoking in men and women was 2.4 and 2.9 in a large cohort study,<sup>52</sup> and a nationwide population-based case-control study also found an increased risk for CKD classified as nephrosclerosis and glomerulonephritis for both men and women.<sup>7</sup> Current factual evidence therefore does not support sex-specific effects of smoking. The large Okinawa study found that obesity increased the risk for ESRD in men only,<sup>3</sup> whereas a US study found a significant and positive relationship between BMI and nephrosclerosis in women only.<sup>5</sup> In our study, we found no indications of interaction between sex and obesity nor physical inactivity. We are not aware of any other reports of physical inactivity.

Strengths of this study include the high participation rate in a general population, generating a high number of participants and cases, as well as our ability to study several lifestyle-related risk factors in the same study. The validity of the classification of cases, a problem assigned little attention in other studies, is also important. Several studies used the MDRD formula without proper calibration of serum creatinine values, which leads to systematic overestimation of cases with CKD. The avoidance of such bias in our study contributes to the credibility of our results despite the limitations of a cross-sectional study design regarding interpretation of cause and effect.

The diagnosis of CKD requires a GFR less than 60 mL/min/1.73 m<sup>2</sup> (1.00 mL/s/1.73 m<sup>2</sup>) during a period of 3 months, and in our study, as in all other studies on the current topic, only 1 measurement for each subject was available. The lower limit for normal GFR for subjects older than 70 years also is close to 60 mL/min/1.73 m<sup>2</sup>. To prevent overestimation of CKD cases, we chose a more conservative definition of a single GFR less than 45 mL/min/1.73 m<sup>2</sup> (<0.75 mL/s/1.73 m<sup>2</sup>) to define CKD, and additional analysis with GFR less than 60 mL/min/1.73 m<sup>2</sup> as the cutoff value showed that our main results were robust.

In conclusion, obesity, smoking, and physical inactivity are associated significantly with CKD, and men are not more susceptible than women to these risk factors. Our data show significant dose-response effects. Subjects with combinations of obesity, smoking, and physical inactivity are at very high risk, possibly because of biological interaction between these variables. Hence, our study provides further documentation that lifestyle-related risk factors are of importance for CKD, and increased efforts should be taken to reduce these risk factors in the general population.

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