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Smoking is a risk factor in the progression to kidney failure

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To study the role of smoking in renal damage, we measured gender-specific effects, dose-response relationships, and whether cessation reduced the risk of smoking on future kidney failure. During a median follow-up of 10.3 years, 124 of 65,589 participants of the HUNT II study, a Norwegian population, progressed to stage 5 chronic kidney disease. Former- and current-smokers less than 70 years of age at inclusion had significant multi-adjusted hazard ratios of 3.32 and 4.01 for kidney failure compared to those who never smoked. In men, the risk increased with a significantly higher trend for cumulative smoking (pack-years); however, the risk significantly decreased with increased elapsed years since smoking cessation. Although the prevalence of current smoking did not differ between genders, females had smoked less (10.2 compared to 15.8 pack-years) and the number of kidney failure cases was lower in females than in men (46 compared to 78). The effect of smoking on the risk of kidney failure was similar (hazard ratios of 2.94 and 4.30 in current-smoking women and men, respectively), but did not reach statistical significance in women. Thus, in this large population-based sample, we found that smoking is a significant risk factor for future kidney failure. Smoking cessation decreased this risk, at least in men.

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The worldwide high prevalence of chronic kidney disease (CKD) and the strong increase in the incidence of patients reaching end-stage renal disease have urged nephrologists to identify renal risk factors. In recent years it has become apparent that cigarette smoking, besides its traditionally accepted carcinogenic effects and its detrimental role as a promoter of cardiovascular disease (CVD), is an important independent renal risk factor. Despite a substantial number of studies documenting a deleterious effect of smoking on renal function (see Orth and Hallan[1] for review), several important aspects of smoking-induced renal damage remain unclear. Although there are enough nonrenal reasons to not smoke, establishing smoking as an independent risk factor for kidney failure is important for improving focus and motivation for smoking cessation among CKD patients and to further increase awareness about this renal risk factor among nephrologists.

First, it is controversial whether the renal effects of smoking equally affect both genders. A large population-based study from Australia including 11,247 randomly selected subjects found lifetime smoking exposure to be significantly associated with CKD stage 3 or higher in men, but not in women.[2] However, other studies have reported similar effects of smoking on the risk of kidney failure in both genders.[3,4] Second, it is unclear whether the smoking-related risk of kidney failure depends on the amount of cigarettes smoked. Dose-response relationships have only been demonstrated for surrogate end points like renal function decline and urine albumin excretion rate.[5,6] Third, it is unknown to what extent smoking cessation reduces the risk of kidney failure. Very few studies have investigated this topic, and data are based on a limited number of patients with diabetes mellitus, again using only surrogate markers of renal damage, that is, no hard end points.[7–9] Data from general population-based subjects are not available at all.

Therefore, the aim of the present study was to investigate how the above-mentioned aspects of smoking influence the risk of kidney failure in a large population-based sample. Smoking susceptibility could be different in men and women, and it is also increasingly clear that the excess risk caused by smoking may be apparently weakened in the elderly because

of differential survivorship and competing risks in ever-smokers, that is, a survival bias.[10–12] This phenomenon extends to several cardiovascular risk factors,[13] and several studies show that the genetic background plays an important role for the susceptibility of individual subjects to smoking-related damage.[14,15] Thus, to avoid the presence of a survival bias in elderly smokers, we separately investigated men and women <70 years and $\geqslant 70$ years of age at study start.

RESULTS

Among the 65,589 participants, 45.0% were never-smokers, 26.1% were former-smokers, 27.7% were current-smokers, and information about the smoking status was missing in 1.2%. Baseline characteristics of these four groups are given in Table 1. Mean (s.d.) length of smoking among current-smokers was 25.6 (13.3) years, whereas mean time since quitting smoking in former-smokers was 14.8 (11.3) years. The smoking pattern was slightly different in women compared with men: 20.3% vs 33.4% were former-smokers and 27.4% vs 28.6% were current-smokers, respectively. The number of cigarettes consumed per day by current-smokers was 10.0 (4.8) in women vs 12.3 (6.3) in men. The cumulative smoking dose among former-smokers was 7.4 (7.9) pack-years in the female population vs 14.2 (13.7) pack-years in the male population, and corresponding numbers among current-smokers were 12.1 (8.8) and 17.3 (12.4), respectively.

The cohort had a median observation time of 10.3 years (range 0.1–11.3), and 124 patients (78 men and 46 women) progressed to kidney failure (CKD stage 5): 58 started renal replacement therapy (RRT) and in 66 others the cause of death reported was CKD with an estimated glomerular filtration rate (eGFR) of <15 ml/min per 1.73 m^2 documented in their medical records. Table 2 shows the multiadjusted risk of future kidney failure conferred by smoking using Cox proportional hazard regression analysis. In subjects below age 70 at study start, former-smokers had a 3.3 times higher risk ($P=0.02$) and current-smokers had a 4.0 times higher risk ($P=0.01$) compared with never-smokers, respectively. In subjects above age 70, the associations were attenuated and neither former-smokers nor current-smokers had a significantly increased risk of kidney failure. Independent of age, the two major baseline predictors of future kidney failure were albuminuria and eGFR, but gender and systolic blood pressure were also significant, although less powerful risk factors.

In subjects below age 70, the renal risk associated with ever-smoking was 4.3 ($P=0.02$) among men and 2.9 ($P=0.10$) among women. In subjects $\geqslant 70$ years old, there was no significant association of kidney failure risk with smoking, neither in men nor women. Table 3 also shows the risk of kidney failure associated with former- and current-smoking. Multiadjusted hazard ratios (HRs) are displayed for a combined smoking–gender variable using never-smoking men and women, respectively, as the reference category. Figure 1 shows the distribution of subjects and kidney failure cases in men and women by total smoking dose and time since smoking cessation, respectively. In women, there were very few subjects with a moderate to high smoking dose and nearly no kidney failure cases. Likewise, there were less than five kidney failure cases in each group of former-smoking females. Therefore, further analyses of dose-response relationships and the effect of smoking cessation were limited to men.

Tables 4 and 5 illustrate the influence of smoking dose and of smoking cessation on the risk of kidney failure in men below age 70. Table 4 shows that total smoking dose had a strong independent effect on the risk of kidney failure. The risk increased nearly linearly with increasing number of pack-years (P for trend <0.001). For example, a man who had smoked 20 cigarettes (that is, one 'pack') for 15 years (that is, 15 pack-years) had a ninefold higher kidney failure risk compared with never-smokers. Table 5 shows that time since quitting was related to kidney failure risk. Former-smoking males who had quitted many years ago had only a moderate increased risk whereas those having quitted more recently had a much higher kidney failure risk (P for trend $=0.005$).

A total of 6% of current-smokers reported smoking cigars or pipe, and their risk could be different from cigarette smokers. We therefore performed a sensitivity analysis where cigar and pipe smokers were excluded. All results remained unchanged. For example, the adjusted HR associated with former and current smoking in subjects below age 70 years was 3.3 and 3.6 compared with 3.3 and 4.0 in the original analyses. Furthermore, to reduce the effect of survival bias, we performed a competing risk analysis using the 'stcrreg' procedure in STATA (Stata, College Station, TX), which is able to handle multiple imputed data sets. However, neither this analysis allowed us to use the total cohort in a common analysis: when using the total material, no significant effect of smoking was found, restricting to age <70 gave a significant effect, that is, similar to our previous analyses.

DISCUSSION

Using this large population-based sample with a median follow-up of 10.3 years and a hard clinical end point, we were able to investigate the deleterious effect of smoking on renal function in detail. In subjects below age 70, current-smokers had a 4.0 times and former-smokers had a 3.3 times higher risk of kidney failure when compared with never-smokers, respectively. The risk seemed to be similar in men and women and was independent of all known major renal risk factors. A significant influence of the cumulative smoking dose and the time since quitting was found in men. This could not be documented in women because of the low number of females with a high cumulative smoking dose and the low number of kidney failure cases observed in this subgroup.

Many studies have assessed the effect of smoking on renal function, but study design and samples have varied considerably.[1] Significant associations have been found between smoking and surrogate end points like kidney

Table 1 | Baseline data by smoking category

Variable (*n*)	Smoking categories			
	Never (*n*=29,515)	Former (*n*=17,119)	Current (*n*=18,168)	Unknown (*n*=787)
Smoking				
Length (years)	NA	19.1 (13.5)	25.6 (13.3)	NA
Time since quitting (years)	NA	14.8 (11.3)	NA	NA
Pack-years	NA	11.4 (12.8)	14.5 (11.1)	NA
Cigarette smoker	NA	NA	94	NA
Age (years)	49.2 (18.8)	54.4 (15.7)	46.9 (14.6)	71.6 (18.9)
Male gender	40.4	59.2	45.8	37.9
High education	37.0	25.0	21.2	21.9
Physical inactivity	18.4	19.6	23.3	27.4
Diabetes mellitus	3.5	4.3	2.0	10.9
Cardiovascular disease	6.3	13.0	5.6	15.3
Treated hypertension	11.8	14.4	6.7	20.6
Systolic blood pressure	139.0 (22.6)	140.1 (21.7)	133.7 (19.7)	149.3 (26.1)
BMI (kg/m^2)	26.5 (4.2)	27.0 (16.2)	25.6 (4.0)	27.0 (4.6)
Total cholesterol (mg/dl)	224 (50)	232 (46)	228 (46)	228 (54)
HDL cholesterol (mg/dl)	54 (15)	54 (15)	50 (15)	46 (15)
ACR (mg/g)	22.6 (85.6)	34.2 (118.4)	31.7 (105.1)	33 (66.6)
eGFR (ml/min per 1.73 m^2)	97.9 (20.5)	93.8 (18.7)	102.5 (16.8)	78.2 (23.3)

Abbreviations: ACR, urine albumin-to-creatinine ratio; BMI, body mass index; eGFR, estimated glomerular filtration rate; HDL cholesterol, high-density lipoprotein cholesterol; NA, not applicable.
Categorical data are presented as percent, and continuous data are presented as mean (s.d.).

Table 2 | Multiadjusted risk for future kidney failure according to age at study start

	Age <70 years			Age ⩾70 years		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Smoking						
Never-smoker	1.00			1.00		
Former-smoker	3.32	1.23–8.85	0.02	0.84	0.47–1.50	0.56
Current-smoker	4.01	1.43–11.25	0.008	1.09	0.51–2.33	0.82
Age (per 10 years)	0.64	0.46–0.88	0.006	1.21	0.82–1.89	0.41
Female gender	0.65	0.32–1.34	0.25	0.28	0.15–0.50	<0.001
High education	2.35	1.03–5.31	0.04	1.02	0.39–2.64	0.97
Physical inactivity	2.44	1.11–5.37	0.03	1.65	0.92–2.97	0.09
Diabetes mellitus	2.55	1.00–6.48	0.05	1.25	0.62–2.51	0.54
Prevalent CVD	0.26	0.09–0.78	0.02	0.88	0.53–1.44	0.61
Antihypertensive medication	1.19	0.55–2.58	0.65	0.92	0.56–1.52	0.75
Systolic blood pressure (per 10 mm Hg)	1.27	1.11–1.46	0.001	1.10	1.01–1.20	0.04
Waist circumference (per 10 cm)	1.16	0.98–1.55	0.30	0.96	0.76–1.22	0.75
Total/HDL cholesterol	1.09	0.94–1.28	0.26	1.15	1.02–1.28	0.02
eGFR (per 10 ml/min per 1.73 m^2)	0.33	0.28–0.39	<0.001	0.45	0.40–0.52	<0.001
ACR (per 88 mg/g)	1.20	1.11–1.30	<0.001	1.17	1.11–1.23	<0.001

Abbreviations: ACR, urine albumin-to-creatinine ratio; CI, confidence interval; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HDL, high density lipoprotein; HR, hazard ratio.
HRs were adjusted for all the variables displayed in the table.

Table 3 | Multiadjusted risk for kidney failure in men and women below age 70

	Never-smoking men as reference category		Never-smoking women as reference category	
	Men	Women	Women	Men
Never-smoker	1.00	0.87 (0.20–3.70) *P*=0.9	1.00	1.13 (0.27–4.90) *P*=0.9
Former-smoker	3.74 (1.05–13.20) *P*=0.04	2.77 (0.65–11.95) *P*=0.2	3.19 (0.76–13.52) 0.10	4.30 (1.31–14.05) 0.02
Current-smoker	5.75 (1.46–22.61) *P*=0.01	2.40 (0.52–11.15) *P*=0.3	2.77 (0.64–11.93) *P*=0.2	6.62 (1.73–25.36) *P*=0.01

The association of kidney failure with smoking in men and women was calculated using a six-category combined smoking-gender variable. To show the association in men, we used never-smoking men as the reference category (i.e., the interesting results showing the effects of smoking in men are in the gray-shaded column to the left). A similar analysis was done with never-smoking women as the reference category (i.e., the two columns to the right). Data are given as hazard ratio (95% confidence interval) and all Cox analyses are adjusted for age, education, physical activity, diabetes mellitus, prevalent cardiovascular disease, antihypertensive medication, systolic blood pressure, lipids, waist circumference, estimated glomerular filtration rate, and albumin-creatinine ratio.

function and albuminuria in cross-sectional, population-based studies.[2,6,16,17] Although low eGFR and increased albuminuria are very strong risk factors for progression to kidney failure, cross-sectional studies are hampered by substantial limitations. In contrast, prospective population-based studies allow to draw much more significant conclusions, and in studies with this latter design smoking has been associated with significant changes in kidney function.[4,5]

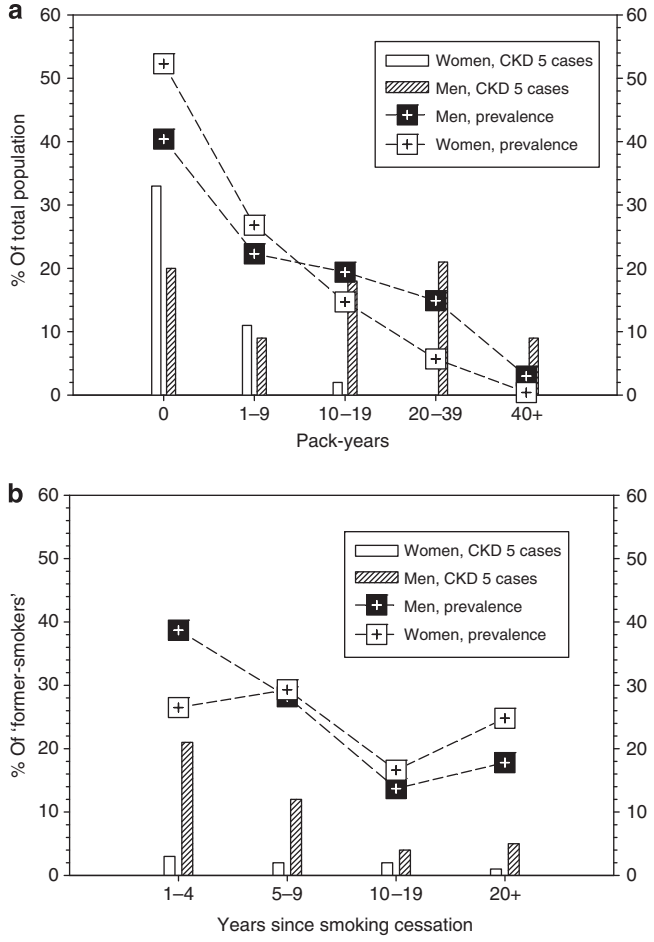

Figure 1 | Distribution of study participants and outcomes. Panel **a** displays data by total (cumulative) smoking dose. Panel **b** displays data by time since smoking cessation.

However, only few studies have previously reported on the effect of smoking using hard clinical end points (see Orth and Hallan[1] for review), and smoking-related kidney failure was often not the primary focus of these studies. As one of the most relevant studies, Haroun *et al.*[3] followed 23,534 US subjects for 20 years and found that current smoking was associated with the HR of 2.6 for future RRT or having kidney disease listed on the death certificate compared with former- and never-smokers. Of note, this analysis could only be adjusted for age, gender, blood pressure, and diabetes status, as there was no information on baseline serum creatinine, lipids, urinary albumin, and other relevant renal risk factors. Bash *et al.*[18] followed 15,324 participants of the Atherosclerosis Risk in Communities study for 16 years and found an adjusted HR for serious kidney-related events (transplantation, acute or chronic dialysis, or death) of 1.6 in former-smokers and 1.9 in current-smokers, respectively. On the contrary, Hsu *et al.*[19] followed 177,570 subjects of the Kaiser Permanente cohort in California for 25 years and did not find that smoking was a significant risk factor for end-stage renal disease after adjusting for other relevant renal risk factors. The reason for this difference is unclear, but substantial changes in lifestyle risk factors could have taken place during the long observation period of the latter cohort, and no correction for time-related changes in risk exposure was done. Current smoking was reduced from 38% at study baseline to 13% according to a survey of Californian adults in 2000,[20] that is, the end of the observation period of the study by Hsu *et al.*[19] In summary, there is substantial evidence that smoking leads to an increased risk of serious kidney damage leading to kidney failure in the end. Our current study strongly supports this general finding, but several important aspects need further consideration and have been addressed in the present study.

Gender-specific kidney effects of smoking have been suggested in several studies, with men being more susceptible than women.[2,21,22] In the cross-sectional Aus-Diab study an association between smoking and eGFR <60 ml/min per 1.73 m^2 was found in men only,[2] and women had no increased risk of proteinuria in a Japanese cohort.[22] This is contrasting sharply with the fact that for major health outcomes like cancer and CVD, studies have repeatedly found women to be more susceptible to smoking than men.[23,24]

Table 4 | Influence of total smoking dose on the risk of kidney failure in men below age 70 years

	Unadjusted			Adjusted for age, eGFR, and ACR			Multiadjusted		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Never-smokers	1.00			1.00			1.00		
1–9 pack-years	1.18	0.22–6.29	0.8	4.10	0.62–26.6	0.1	4.21	0.50–35.16	0.18
10–19 pack-years	3.35	0.90–12.5	0.07	6.62	1.38–31.5	0.02	8.84	1.58–49.89	0.01
20–39 pack-years	5.93	1.73–20.1	0.004	11.1	2.50–49.9	0.002	13.5	2.20–81.5	0.005
$\geqslant$40 pack-years	17.6	4.43–70.1	$<$0.001	14.0	2.75–70.8	0.001	37.7	4.17–336	0.001
Test for trend			$<$0.001			$<$0.001			$<$0.001

Abbreviations: ACR, urine albumin-to-creatinine ratio; CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio.
Data are HRs, 95% CIs, and *P*-values from Cox proportional hazard regression analyses. The multiadjusted analysis was adjusted for age, education, physical activity, diabetes mellitus, prevalent cardiovascular disease, antihypertensive medication, systolic blood pressure, lipids, waist circumference, and kidney status (eGFR and ACR).

Table 5 | Influence of time since smoking cessation on the risk of kidney failure in men below age 70 years

	Unadjusted			Adjusted for age, eGFR, and ACR			Multiadjusted		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value	HR	95% CI	*P*-value
1–4 years	3.45	0.64–18.7	0.2	10.5	1.32–82.3	0.03	21.5	2.04–225	0.01
5–9 years	4.90	0.90–26.8	0.07	19.9	2.48–154	0.005	40.4	3.71–441	0.002
10–19 years	3.78	0.85–16.9	0.08	9.49	1.43–62.8	0.02	7.10	0.59–85.6	0.12
⩾20 years	8.16	2.34–27.9	0.001	8.84	1.70–45.6	0.009	10.5	1.45–75.9	0.02
Never-smokers	1.00			1.00			1.00		
Test for trend			0.06			0.01			0.006

Abbreviations: ACR, urine albumin-to-creatinine ratio; CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio.
Data are HRs, 95% CIs, and *P*-values from Cox proportional hazard regression analyses. The multiadjusted analysis was adjusted for age, education, physical activity, diabetes mellitus, prevalent cardiovascular disease, antihypertensive medication, systolic blood pressure, lipids, waist circumference, and kidney status (eGFR and ACR).

However, other studies have demonstrated that smoking increases the risk of low eGFR in both men and women in population-based case–control and cross-sectional studies,[17,25] and even more importantly, equal risk of serious CKD was found in a longitudinal study.[3] Our study seems to confirm the detrimental effect of smoking in both men and women, even after adjusting for current kidney function and other important renal risk factors. Although we included 35,000 women with equal current-smoking prevalence as in men, total smoking dose was lower and progression to kidney failure occurred in very few females. The relative risk in ever-smoking women was very similar to the male results, but it did not reach full statistical significance ($P = 0.10$).

A dose-response relationship is usually considered as evidence supporting causality. For smoking and kidney damage such evidence has not been documented in a satisfactory way so far. A significant association has been found between the number of cigarettes and surrogate end points like low eGFR and albuminuria in cross-sectional and case–control studies from the general population.[2,5,25,26] Stengel *et al.*[27] followed 9082 NHANES (National Health and Nutrition Examination Survey) II participants for 13.2 years in one of the very few population-based cohort studies available investigating this topic. The adjusted risk of RRT or CKD death was 1.4 (95% confidence interval 0.7–2.7) times increased in the group smoking 1–20 cigarettes per day, and the risk was 2.3 (1.2–4.3) for those smoking >20 cigarettes per day. This could indicate a threshold effect, but the results could be biased as the rather imprecise 'CKD as a contributing cause of death' was the most frequent study outcome and baseline serum creatinine was missing in 31% of study participants. We found that in men there was a clear trend of increasing risk for RRT or CKD death with a documented eGFR <15 ml/min per 1.73 m^2 with increasing number of 'pack-years' with no apparent threshold. Thus, the current scarce evidence for a dose-response relationship of smoking and kidney failure is substantially strengthened by the data that we obtained analyzing the HUNT II study population, at least as far as men are concerned.

An investigation about the role of age in the context of smoking-associated renal risk has not been done so far, but studies including only elderly people have found that smoking is an important risk factor even in this subgroup. Baggio *et al.*[28] studied 2981 elderly subjects from Italy and found that smoking >20 cigarettes per day was a very strong risk factor for a pathological loss of kidney function. Other studies have found similar results.[5,29] In contrast, we did not find an increased risk of kidney failure in elderly smoking participants in the HUNT II study. A hypothesis that smoking is not harmful in elderly is biologically not very plausible, and hence study-related explanations for our findings should rather be sought. A 'smoker's paradox', that is, improved outcomes in the smoking group, has been reported in heart failure,[30] and a smoking-related survival bias has been shown to be of statistical relevance in both cohort and case–control studies.[31] Other examples on 'reverse epidemiology' have been documented for well-established risk factors like blood pressure, cholesterol, and body mass index in patients with chronic obstructive pulmonary disease, rheumatoid arthritis, end-stage renal disease, and the elderly.[32] Survival bias, which is a form of selection bias that might heavily influence the epidemiologic associations in subgroups of cardiovascular survivors, is probably one of the major mechanisms leading to these inverse associations. Those who manage to survive long enough to reach kidney failure despite smoking may have other protective factors that otherwise negate the adverse effects of smoking. As no modern competing risk analysis was able to handle the survival bias effect of age in our cohort, we separately analyzed subjects <70 and ⩾70 years of age, being aware that this is not a perfect solution of this problem.

Our study has some limitations that must be discussed. The validity of our smoking-related variables has not been tested in the HUNT II study specifically. Smoking underreporting and change in smoking habits as well as other risk factors during the observation period can lead to misclassification and contribute to an attenuation of our results, whereas residual confounding can always lead to erroneous associations in cohort studies. However, the well-known associations between various smoking variables and cardiovascular mortality in both men and women have been found in previous HUNT publications, which strengthen the validity of our kidney failure results.[33,34] Other studies have

found that misclassification of smoking status is low (10%) in both general populations and more 'vulnerable' groups like pregnant women and patients with acute coronary syndromes.[35–37] Furthermore, we were not able to adjust for the use of therapeutic drugs, which also may have changed during follow-up. Although HUNT II is a large study, kidney failure is a rare outcome that could lead to analytical problems. For example, high education turned out to be a borderline significant risk factor in Table 2. This is probably just a kind of coincidence, dependent on the many other variables in the model, as the crude education effect (as well as after adjusting for age, sex, smoking, eGFR, and urine albumin-to-creatinine ratio) was close to HR 1 and not significant. The generalizability of our results to other ethnic groups and countries can also be debated, as strikingly different consequences of smoking have been reported depending on the populations investigated.[38]

However, our study also has several strengths. We included a large number of participants from a prospective cohort study with a very high participation rate, which substantially reduces the risk of selection and information bias. Information on many potential confounders was available and could be adjusted for, and missing data were handled by multiple imputations to avoid loss of power and biased estimates. The major focus of our analysis was on smoking-related kidney failure, and dose-response relationship and the effect of quitting smoking could be tested. We used a hard clinical end point also including kidney failure patients not treated with dialysis, which is a large and important group and an increasingly discussed treatment option.[39,40]

The clinical implications of ours as well as previous results are obvious, although randomized controlled trials with hard clinical end points like kidney failure risk after quitting smoking are not available (it might even be unethical to carry out such studies nowadays). All CKD patients should now be very strongly encouraged to quit smoking. This has probably not been highlighted sufficiently in clinical practice even if clearly stated in the 2002 KDOQI (Kidney Disease Outcomes Quality Initiative) guidelines. At that time, the deteriorating effect of smoking on kidney function was not very well documented. A further rational is the very high risk of cardiovascular death among CKD patients.[34,41] For CKD stage 1–3 patients, serious cardiovascular events are much more probable than progression to kidney failure.[42] Smoking has been documented to be a significant cardiovascular risk factor even in CKD stage 5 patients.[43]

Regarding smoking and kidney pathophysiology, direct vascular effects are probably a major mechanism. Smoking is particularly associated with atherosclerosis in the aorta and lower extremity arteries,[44,45] and increased stiffness of central vessels causes increased energy transmission to low-resistance arterioles in the kidneys, which is a key factor in the pathogenesis of glomerular and tubular damage.[46] This could potentiate the effect of media calcification caused by disturbances in vitamin D and calcium–phosphate metabolism.[47] More direct mechanisms of smoking-induced kidney damage are also possible; for example, it has been suggested, based on experimental studies, that nicotine could promote mesangial cell proliferation and spur on critical molecules that are involved in the extracellular matrix production.[48,49]

In summary, associations between smoking and CKD have been found in various studies with more or less optimal design. The current study investigated the deleterious effect of smoking on renal function in detail using a large population-based sample with long follow-up, adjusting for all relevant confounders, and using a hard clinical end point. We found that the risk of kidney failure was three to four times higher in smokers. Furthermore, a significant influence of the cumulative smoking dose and a decreasing risk after smoking cessation was documented. Thus, all CKD patients should now be very strongly encouraged to quit smoking, and if necessary given psychological and/or pharmacological support to achieve this very important goal. In this context, our finding of a progressive decrease in renal risk with increasing time since smoking cessation is very encouraging. Efforts to investigate smoking cessation strategies for the specific group of CKD patients are warranted.

MATERIALS AND METHODS

The HUNT II study is a Norwegian large-scale general health survey. From 1995 to 1997, all individuals residing in Nord-Trøndelag county (97% Caucasians) aged $\geqslant 20$ years were invited. Participants answered a comprehensive questionnaire, underwent clinical examination, and donated a blood sample. A more detailed description of the objectives, methods, and participation in the HUNT II study has been given elsewhere.[50] The participants gave informed consent, including linkage to central national registries. The current study was approved by the Regional Committee for Medical Research Ethics, the Norwegian Data Inspectorate and the Ministry of Health.

Of 92,939 subjects invited, 65,604 responded, representing 70.6% of the entire adult population. All participants reported on current and former health, illness in the family, education, and risk factors such as physical inactivity. Smoking was assessed by a set of questions: (1) Have you ever smoked? (2) Do you currently smoke cigarettes/cigars/pipes? (3) When did you start smoking? (4) When did you stop smoking? (5) How many cigarettes did/do you usually smoke per day? Three consecutive standardized blood pressure measurements were recorded in the sitting position (Dinamap 845XT; Criticon, Tampa, FL). Subjects were classified according to diabetes mellitus (self-report or non-fasting blood glucose $\geqslant 11.2$ mmol/l), treated hypertension (self-report of high blood pressure needing drug treatment), high education (>12 years at school), physical inactivity (<60 min of light exercise and no hard exercise per week), and prevalent CVD (self-reported angina pectoris, myocardial infarction, or stroke).

Blood was obtained from all participants, immediately centrifuged and refrigerated, and analyzed within 2 days using a Hitachi 911 autoanalyzer (Hitachi, Mito, Japan). The original Jaffé-based creatinine values were recalibrated, providing isotope dilution mass spectrometry traceable values. GFR was estimated with the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, which has a minimal negative bias even at near-normal GFR levels.[51] Subjects with an eGFR <15 ml/min per 1.73 m^2 ($n=15$) were excluded, and subjects with eGFR values $\geqslant 160$ ml/min per 1.73 m^2,

which is unlikely to be physiological, were given a value of 160 ml/min per 1.73 m^2 ($n = 541$).

By design, subjects with treated hypertension, diabetes mellitus, and a random 5% sample of nondiabetic nonhypertensive subjects were asked to deliver spot urine samples on three consecutive mornings. In all, 85.3% returned all requested urine samples. The nonresponders were not statistically different from those delivering all urine samples regarding important variables like age, gender, CVD, weight, blood pressure, lipids, and serum creatinine. Albumin concentration in the urine was measured within 5 days using an immunoturbidimetric method (Dako A/S, Glostrup, Denmark).

The study outcome was future kidney failure (CKD stage 5), defined as starting RRT or decrease of eGFR to <15 ml/min per 1.73 m^2 (ref. 52). The national identification number given to all live births enabled record linkage to the Norwegian Renal Registry and the Cause of Death Registry in all participants. We used CKD death, defined as ICD-10 (International Statistical Classification of Diseases and Related Health Problems 10th Revision) diagnosis N00–N19 excluding N17, to find subjects with kidney failure not starting RRT. Two experienced nephrologists manually searched hospital and general practice records to ensure that all cases had a documented CKD diagnosis before death and a documented eGFR <15 ml/min per 1.73 m^2 or other indications for chronic dialysis.

Statistical analyses were performed using Stata 10.0. We decided beforehand to do separate analyses for subjects <70 and $\geqslant 70$ years of age at study start because of possible survival bias. Multivariable analyses were performed using Cox regression adjusted for potential confounders available: age, gender, diabetes mellitus, hypertension, physical activity, prevalent CVD, total/high-density lipoprotein cholesterol, waist circumference, urine albumin-to-creatinine ratio, and eGFR. To study the effect of smoking in men and women, we analyzed the interaction between smoking and gender using a new composite six-category variable (three categories of smoking and two categories of gender).[53] Gender-specific analyses were also performed.

In general, there were $<5\%$ missing data for most variables, including smoking. However, a complete case Cox survival analysis would include only 85% of all subjects and 60% of all cases experiencing future kidney failure. Furthermore, repeated measurements of urine albumin-to-creatinine ratio were, by study design, available only in a subgroup.[54] Multiple imputation is now considered the standard method for optimal use of available data,[55–58] whereas complete case analysis would yield too imprecise as well as biased results. The multiple imputation technique estimates the mean and uncertainty of the missing data in individual subjects using all information from the actually observed data. The assumptions for the method of 'missing at random' were met. Using the Stata command 'ice' we created 20 complete data sets to achieve maximum accuracy.[59,60] Subsequently, the Stata command 'micombine' was used to combine these data sets for subsequent use together with standard statistical methods.

DISCLOSURE

The authors declared no competing interests.

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