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EDUCATIONAL LEVEL AND RISK OF CHRONIC KIDNEY DISEASE: LONGITUDINAL DATA FROM THE PREVEND STUDY

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ABBREVIATIONS

BMI	body-mass index
CKD	chronic kidney disease
eGFR	estimated glomerular filtration rate
PREVEND Study	Prevention of renal and vascular end-stage disease study
SES	socioeconomic status
UAE	urinary albumin excretion
WHR	waist-to-hip ratio

ABSTRACT

Introduction. The longitudinal association between low education and chronic kidney disease (CKD) and its underlying mechanisms are poorly characterized. We therefore examined the association of low education with incident CKD and change in kidney function, and explored potential mediators of this association.

Methods. We analyzed data on 6078 participants from the community-based PREVEND Study. Educational level was categorized into low, medium, and high (<secondary, secondary/equivalent, >secondary schooling). Kidney function was assessed by estimating glomerular filtration rate (eGFR) by serum creatinine and cystatin C at five examinations during ~11 years of follow-up. Incident CKD was defined as new-onset eGFR<60mL/min/1.73m^2 and/or urinary albumin≥30mg/24h in those free of CKD at baseline. We estimated main effects with Cox regression and linear mixed models. In exploratory causal mediation analyses, we examined mediation by several potential risk factors.

Results. Incident CKD was observed in 861 (17%) participants. Lower education was associated with higher rates of incident CKD (low vs high education; HR[95%CI]=1.25 [1.05 to 1.48], p_{trend}=0.009) and accelerated eGFR decline (B[95%CI]=-0.15 [-0.21 to -0.09] mL/min/1.73m^2 per year, p_{trend}<0.001). The association between education and incident CKD was mediated by smoking, potassium excretion, BMI, WHR, and hypertension. Analysis on annual eGFR change in addition suggested mediation by magnesium excretion, protein intake, and diabetes.

Conclusions. In the general population, we observed an inverse association of educational level with CKD. Diabetes, and the modifiable risk factors smoking, poor diet, BMI, WHR, and

hypertension are suggested to underlie this association. These findings provide support for targeted preventive policies to reduce socioeconomic disparities in kidney disease.

Keywords: chronic kidney disease, educational level, socioeconomic status, health disparities

BACKGROUND

Chronic kidney disease (CKD) is a heterogeneous group of disorders characterized by sustained diminished kidney function and/or kidney damage. CKD affects ~10-15% of the global population, and its incidence is increasing[1-4]. CKD can progress to end-stage renal disease (ESRD), and is associated with an increased incidence of cardiovascular disease and all-cause mortality[5, 6]. As such, CKD poses a major burden on patients and global health resources.

CKD is unequally distributed across socioeconomic groups: higher prevalence and incidence rates of CKD and ESRD have consistently been observed among those with lower socioeconomic status (SES). Socioeconomic gradients have also been observed for eGFR and urinary albumin. However, large heterogeneity exists between studies of the SES-CKD association[7, 8]. One possible explanation for this heterogeneity is that factors underlying the SES-CKD association vary between populations due to differences in e.g. ethnicity, lifestyle, prevalence of comorbid conditions, or healthcare[9, 10]. Currently, the available literature is limited: 1) most observations were made in US-based cross-sectional data[7, 8] and 2) European studies established cross-sectional associations of SES measures with CKD[11-13]; however no European study explicitly examined the association of SES with CKD, or mediators of this association, in a longitudinal setting. Hence, it is uncertain to what extent SES conveys risk of CKD in the European general population, and which factors underlie this association. Characterization of underlying mechanisms may help identify targets for disease prevention and management, thus help alleviate the burden of CKD and its consequences among disadvantaged populations.

Our aim was therefore to examine the strength of the association of SES with the longitudinal outcomes, CKD incidence and annual change in eGFR, in a sample of the Dutch general population. Furthermore, we explored health-related behaviors and comorbid conditions that potentially mediate this association.

MATERIALS AND METHODS

Study design and population

We used data from the Prevention of REnal and Vascular ENdstage Disease (PREVEND) cohort study. PREVEND was initiated to investigate the natural course of increased urinary albumin levels and its association to renal and vascular outcomes. Details of this study have been described elsewhere[14]. Briefly, 8592 individuals, sampled from the general population of Groningen, the Netherlands, underwent extensive examination between 1997-1998. Four follow-up examinations were completed in 2003, 2006, 2008, and 2012. All subjects gave written informed consent. PREVEND was approved by the medical ethics committee of the University Medical Center Groningen and conducted in accordance with the Helsinki Declaration guidelines. In the present study, we excluded participants with incomplete data on educational level, kidney outcomes, or important covariates.

Measures

We defined CKD according to Kidney Disease: Improving Global Outcomes guidelines (eGFR<60mL/min/1.73m^2 or UAE≥30mg/24h)[15]. Incident cases were those participants free of CKD at baseline who developed CKD during follow-up. We calculated eGFR from serum creatinine and serum cystatin C, using the corresponding CKD-EPI equation[16].

Collection procedures of blood and two consecutive 24h-urine specimens at each examination has been described previously[17]. Measurement of serum creatinine was performed by an enzymatic method on a Roche Modular analyzer using reagents and calibrators from Roche (Roche Diagnostics, Mannheim, Germany), with intra- and interassay coefficients of variation of 0.9% and 2.9%, respectively. Serum cystatin C concentration was measured by a Gentian cystatin C Immunoassay (Gentian AS Moss, Norway) on a Modular analyzer (Roche Diagnostics). Cystatin C was calibrated directly using the standard supplied by the manufacturer (traceable to the International Federation of Clinical Chemistry Working Group for Standardization of Serum Cystatin C)[18]. Intra- and interassay coefficients of variation were <4.1% and <3.3%, respectively. Urinary albumin concentration (UAC) was measured by nephelometry with a lower threshold of detection of 2.3mg/L, and intra- and interassay coefficient of variation of 2.2% and 2.6%, respectively (Dade Behring Diagnostic, Marburg, Germany). UAC was multiplied by urine volume to obtain a value of UAE in mg/24h. The two 24h-urinary albumin values of each subject per examination were averaged.

SES was measured by educational level, categorized into low (no, primary, basic vocational, and secondary education), medium (senior secondary vocational and general senior secondary education), and high (higher professional and higher academic education) according to the International Standard Classification of Education[19]. Furthermore, we examined associations of income as alternative measure of SES. For this, we categorized income into low, medium, and high according to tertiles of the ratio between reported income and the 1998 poverty line (1658 guilders per month).

Age, sex, and baseline eGFR were included as potential confounders. Included as potential mediators were: current smoking (self-reported yes/no), alcohol consumption (labelled as none, occasional {<10g/wk), light (10-69.9g/wk), moderate (70-210g/wk), heavier (>210g/wk)}, 24h urinary excretions of sodium (Na^+), potassium (K^+), and magnesium (Mg^{2+}) (as surrogates for dietary intake of sodium, potassium, and magnesium), 24h protein intake (estimated from 24h urea excretion by the Maroni formula[20, 21]), body-mass index (BMI, weight/height^2), waist-to-hip ratio (WHR, waist/hip circumference), diabetes (fasting glucose>7.0mmol/L, non-fasting glucose>11.0mmol/L, anti-diabetic treatment, or self-reported), hypertension (systolic blood pressure>140mmHg, diastolic blood pressure>90mmHg, blood pressure lowering treatment, or self-reported), hypercholesterolemia (total cholesterol≥6.21mmol/L, lipid lowering treatment, or self-reported). Covariates were collected at baseline by questionnaires, anthropometry, urine collections, or pharmacy records. Urinary concentrations of Na^+, K^+, and Mg^{2+} were determined as previously described[17, 22].

Statistical analyses

Statistical analyses were performed using R v3.4.1[23] and SPSS v23 software (IBM corp, Amonk, NY, USA) during years 2017 and 2018. Two-sided significance level was set at α=0.05 unless otherwise stated. Baseline characteristics were examined for the total population and compared across categories of education using one-way ANOVA, Jonckheere-Terpstra, or χ^2-tests for linear trend. We used the *survival* R-package[24] for Cox proportional hazards modelling of time to CKD. Time of CKD was estimated using a midpoint imputation method. Crude effects were examined in an unadjusted model. Next, we adjusted for age, sex, and

baseline eGFR. In a final model, we introduced potential mediators. We calculated p for linear trend by analyzing education as a continuous rather than an ordinal variable. Using the *lme4* R-package[25], we estimated eGFR change by modelling eGFR as a function of time in a random intercept, random coefficient linear mixed model. To examine the crude effect of SES on annual eGFR change, an interaction term between time and SES was introduced. Next, we adjusted for age and sex, as well as their interaction with time. Finally, we introduced all potential mediators, and the interaction of each with time.

Next, we performed exploratory mediation analyses. Figure 1 shows a graph of hypothesized pathways tested in the present study. Main effects of potential mediators on kidney outcomes were examined with Cox proportional hazards and linear mixed models adjusting for age, sex, and baseline eGFR. Next, we used the *mediation* R-package[26] to estimate mediation within the counterfactual framework described by Imai et al[27]. Here, we simplified our statistical models by using one contrast for education (low vs high education). Furthermore, we used individual eGFR slopes (extracted from a linear mixed-effects model) as outcome variable in mediation analysis of eGFR change. Finally, we used parametric survival models implemented in the *survival* R-package. Due to these alternative methods, effects may deviate slightly from those of our main effects analyses. Each potential mediator was analyzed separately, adjusting for age, sex, and baseline eGFR. Any significant SES x mediator interaction was controlled for in the mediation model. Non-parametric bootstrap CIs and p-values were estimated from 1000 simulations. One-sided hypotheses were tested to assess potential mediators (i.e. current smoking[28], higher alcohol consumption, higher Na^+ excretion[29], lower K^+ excretion[17], lower Mg^{2+} excretion[30], higher estimated protein intake[31], higher BMI[32], higher WHR[33], diabetes, hypertension, and hypercholesterolemia).

In secondary analyses, we examined associations of education with incident CKD_{eGFR} (eGFR<60 mL/min/1.73m^2), incident CKD_{UAE} (UAE≥30mg/24h) and annual change in UAE (natural-log transformed to approximate normality, *ln*UAE).

RESULTS

Baseline characteristics by educational level for 6078 participants with complete baseline data are presented in Table 1. Traditional risk factors (i.e. diabetes, hypertension, high cholesterol, smoking, higher BMI) were more prevalent in participants with low education. At baseline, low education participants were more likely to have CKD, lower eGFR, and higher UAE compared to high education participants. A higher attrition rate was observed for participants with low education: follow-up time was shorter for these participants. Low education was univariably associated with lower dietary quality as indicated by higher Na^+ excretion, lower K^+ excretion, lower Mg^{2+} excretion, and higher protein intake. Low education participants reported less alcohol consumption.

After excluding N=883 participants with baseline CKD, N=5195 remained for time-to-CKD analysis. Among these, 861 (17%) experienced new-onset CKD, with a significant socioeconomic gradient (low; med; high education: 22%; 14%; 12%, χ^2[df] =62.8[1], p_{trend}<0.001). In the crude model, we observed an inverse association of education with CKD, again with a significant gradient (low vs high education: HR [95%CI] =1.97 [1.67 to 2.32], p_{trend}<0.001; Table 2). After adjusting for age, sex, and baseline eGFR, the association was attenuated, but significance remained (low vs high education: HR [95%CI] =1.25 [1.05 to 1.48], p_{trend}=0.009). After introducing all potential mediators to the model, the education-

CKD association was no longer significant, suggesting mediation within our hypothesized framework (Figure 1).

Average estimated annual eGFR change for the total N=6078 population was -0.93 (95%CI: -0.95 to -0.91) mL/min/1.73m^2 per year. Low education was associated with accelerated eGFR change, with a significant gradient (low vs high education: B [95%CI] =-0.15 [-0.21 to -0.09], p_{trend}<0.001, adjusted for age and sex; Table 2). Addition of potential mediators to the model attenuated the association, although significance remained (low vs high education: B [95%CI] =-0.11 [-0.16 to -0.04], p_{trend}<0.001).

All potential mediators were associated with either CKD or annual eGFR change (Supplementary Table S4). We tested interactions of education with each potential mediator separately (age, sex, and baseline eGFR adjusted); none were significant (p>0.05). The association of low education and CKD was mediated by higher likelihood of smoking (proportion mediated [95%CI] =0.14 [0.02 to 0.51), p=0.009; Table 3), lower 24h K^+-excretion (0.12 [0.02 to 0.45], p=0.008), higher BMI (0.29 [0.13 to 0.96], p=0.004), higher WHR (0.31 [0.14 to 1.16], p=0.002), and higher prevalence of hypertension (0.14 [0.05 to 0.47], p=0.006) in this subpopulation. We observed no significant mediation by 24h Na^+ excretion, Mg^{2+} excretion, protein intake, diabetes, or hypercholesterolemia.

There were no education x mediator interactions with eGFR change as outcome except for smoking (low education [vs high education] x smoking: B [95%CI] =-0.07 [-0.10 to -0.05], p=0.01). The association of low education and accelerated eGFR decline was mediated by lower 24h K^+ excretion (Table 3, proportion mediated [95%CI] =0.08 [0.03 to 0.16], one-sided p<0.001), higher BMI (0.22 [0.12 to 0.42], p<0.001), higher WHR (0.09 [0.01 to 0.18], p=0.008), and higher prevalence of hypertension (0.13 [0.08 to 0.24], p<0.001). Additionally,

lower Mg^{2+} excretion (0.03 [-0.003 to 0.07], p=0.030), higher protein intake (0.01 [-0.001 to 0.04], p=0.032) and higher prevalence of diabetes (0.04 [0.01 to 0.10], p=0.009) mediated the association of low education with accelerated eGFR decline. A protective effect of smoking on eGFR change was observed; higher prevalence of smoking in those with low education appeared to offset risk of accelerated eGFR decline (proportion mediated [95%CI] =-0.12 [-0.22 to -0.06], p=1.000). Higher alcohol consumption was not a mediating risk factor, rather, alcohol seemed protective of CKD and accelerated eGFR decline (Supplementary Table S4). Estimates of average causal mediation effects and direct effects are listed in Supplementary Tables S5-6.

No significant associations between education with CKD_{eGFR} or CKD_{UAE} were found, although directions of effect for these outcomes were consistent with our main analysis (Supplementary Table S1-S2). Average estimated increase in UAE for the total population was 1.1% (95%CI: 0.9% to 1.3%) per year. Low education was associated with accelerated increase in UAE (low vs high education: 0.7% [0.2% to 0.11%] accelerated increase in UAE per year, p_{trend}=0.003), but no longer significantly after adjusting for age and sex (Supplementary Table S3). There were no significant associations of household income, as alternative measure of socioeconomic status, with kidney outcomes after confounder adjustment (data not shown).

DISCUSSION

In a middle-aged community-based cohort, we examined the associations of SES, as indicated by educational level, with the longitudinal kidney outcomes, incident CKD and

eGFR decline. Low education was associated with higher incidence rates of CKD, independent of age, sex, and baseline eGFR, but not of potential mediators. Furthermore, low education was associated with accelerated eGFR decline, independent of age, sex, and potential mediators. Exploratory longitudinal mediation analysis suggested that the association between education and CKD can partly be explained by diabetes and the modifiable risk factors, BMI, WHR, smoking, potassium, and hypertension. No significant associations of household income with kidney outcomes were observed.

With this longitudinal study, we corroborate previous cross-sectional observations that in the Netherlands, education, not income, is associated with kidney outcomes[12]. Recent longitudinal data from the US-based Atherosclerosis Risk in Communities study show effects of education on CKD incidence and eGFR decline comparable to the present data[34]. However, in contrast to the Netherlands, income is associated to CKD in the US[12, 34]. Possible explanations for this discrepancy are: 1) in the US, healthcare access is income-dependent[35], and 2) there is larger income inequality compared to the Netherlands [36].

Our results are generally consistent with a previous mediation analysis on the SES-CKD association. This study assessed SES by household income, and was performed in a cross-sectional sample of the general US population[37]. Similar to that study, we observed mediation by smoking, (abdominal) obesity, diabetes, and hypertension. However, we could not corroborate a mediation effect of hypercholesterolemia. Vart et al[37] used questionnaires on availability of fruits and vegetables at home to assess dietary quality but did not observe mediation. In contrast, we used urinary measures to objectively assess dietary intake of various nutrients. We found strong mediation effects of lower potassium

intake on both incident CKD and accelerated eGFR decline, as well as suggestions for effects of lower magnesium intake and higher protein intake.

Of all nutrients examined in the present study, lower potassium intake was the strongest mediator. A large body of epidemiological data shows that low SES is associated with poor diet, especially with a lower consumption of micronutrients such as potassium[38]. Low potassium intake was previously observed to associate with an increased risk of incident hypertension[39], but also with incident CKD independent of hypertension[17]. A proposed mechanism involves induction of tubulointerstitial injury by ammoniagenesis caused by potassium deficiency[40, 41]. Furthermore, potassium itself might be renoprotective by upregulating renal kinins[42]. On the other hand, potassium intake might reflect dietary quality more generally. The main dietary sources of potassium are fruits/vegetables, legumes, whole grains, and dairy products[43]. These potassium-rich foods contain fibers, polyphenols, antioxidants, and vitamins, which have health benefits[44] that may be renoprotective.

Interestingly, no mediation through sodium intake was observed. High sodium intake reflects poor diet due to its high content in processed foods[45, 46], and is associated with the major renal risk factor, hypertension[47]; we therefore expected sodium to mediate the relation between education and CKD. However, we did not observe a strong educational gradient in sodium at baseline (Table 1). Furthermore, sodium intake was not found to be associated with CKD in PREVEND[17], which likely explains the observed lack of mediation in the present study.

Three counterintuitive findings need to be addressed. Firstly, despite its association with an elevated risk of CKD (concordant with literature[28]), smoking was associated with decelerated eGFR decline. We therefore further examined the main effect of smoking on eGFR decline in fully adjusted models: compared to non-smokers, smokers had lower baseline eGFR, and despite decelerated decline, eGFR on average remained lower in these participants (data not shown). Therefore, this finding is likely the result of a floor effect. Secondly, alcohol consumption was inversely associated with risk of CKD and eGFR decline. Moreover, lower alcohol consumption among low education participants partly explained the elevated risk of CKD. This may be due to residual confounding, a sick quitter/sick non-starter effect[48], or a cohort-specific effect; for a detailed discussion we refer to a study by Koning et al. that previously observed this association in PREVEND[49]. Thirdly, mediation effects of diabetes were significant on eGFR decline, but only borderline significant (p=0.064) on incident CKD. This is likely the result of reduced statistical power of a dichotomous outcome compared to a continuous outcome, and low prevalence of diabetes (3% at baseline) in the PREVEND sample.

The mechanisms underlying the education-CKD association are incompletely understood. We therefore tested several biologically plausible mediating pathways. However, some are overlapping (e.g. BMI, WHR), or on the same causal pathway (e.g. low potassium intake leading to CKD possibly through hypertension). Hence, we examined each mediator separately, correcting only for age, sex, and baseline eGFR to prevent overadjustment. Due to sparse adjustment and the observational nature of PREVEND, we cannot exclude residual confounding. However, results were broadly concordant with the literature, i.e. effects were generally in the hypothesized direction. Therefore, any confounding has likely only biased magnitude, not direction, of mediation effects. Future

work may involve further characterization of the education-CKD association by estimating effects of multiple mediators relative to one another using multivariable techniques (e.g. structural equation modelling or the counterfactual approach described by Lange et al[50, 51]).

To the best of our knowledge, the present study is the first in Europe examining the longitudinal association between education and CKD in the general population, and the first exploring its underlying mechanisms in a longitudinal setting. Strengths of this study are its considerable size (N=6078) and follow-up time (~11 years). GFR was estimated from serial measurements of serum creatinine and cystatin C, currently considered the best proxy of kidney function in population-based studies. Furthermore, data on urinary albumin was available for all included participants. Finally, dietary variables were objectively measured from 24h urinary collections. Several limitations should be addressed. Firstly, PREVEND consists of >95% whites; we therefore could not address the influence of ethnicity in the education-CKD association. Secondly, we observed a higher attrition rate of participants with low education, which may have resulted in a bias towards the null. Thirdly, we lacked baseline information on several potential mediators (e.g. physical activity/sedentary time, healthcare access, health literacy, psychological factors). Finally, only individual-level socioeconomic data were available; we therefore could not examine effects of area-level SES.

In an effort to characterize socioeconomic disparities in CKD, we explored a number of plausible mediating pathways (i.e. health behaviors and clinical risk factors) that link education to CKD. Future research may focus on e.g. 1) confirming the pathways suggested in the present study; 2) exploring other potential mediating factors such as health care

access, health literacy, and psychological factors; 3) establishing the interrelationship between these factors. Understanding how and why socioeconomically disadvantaged groups (e.g. those with a lower educational level) show higher vulnerability to CKD may prove helpful in designing interventions to reduce socioeconomic disparities in CKD. Given the challenges of intervening on education itself, managing and/or modifying downstream effects of low education may be a more promising approach.

To conclude: in the Dutch general population, low SES, as indicated by educational level, is associated with elevated risk of CKD. This association is suggested to be driven by higher rates of diabetes and the modifiable risk factors, (abdominal) obesity, smoking, low potassium intake, and hypertension, in those with lower education. The data presented are a first step towards potential targeted public health interventions to reduce socioeconomic health disparities.

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CONFLICT OF INTEREST STATEMENT

None declared.

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EDUCATIONAL LEVEL AND RISK OF CHRONIC KIDNEY DISEASE: LONGITUDINAL DATA FROM THE PREVEND STUDY

Table 1. Baseline characteristics by categories of educational level.

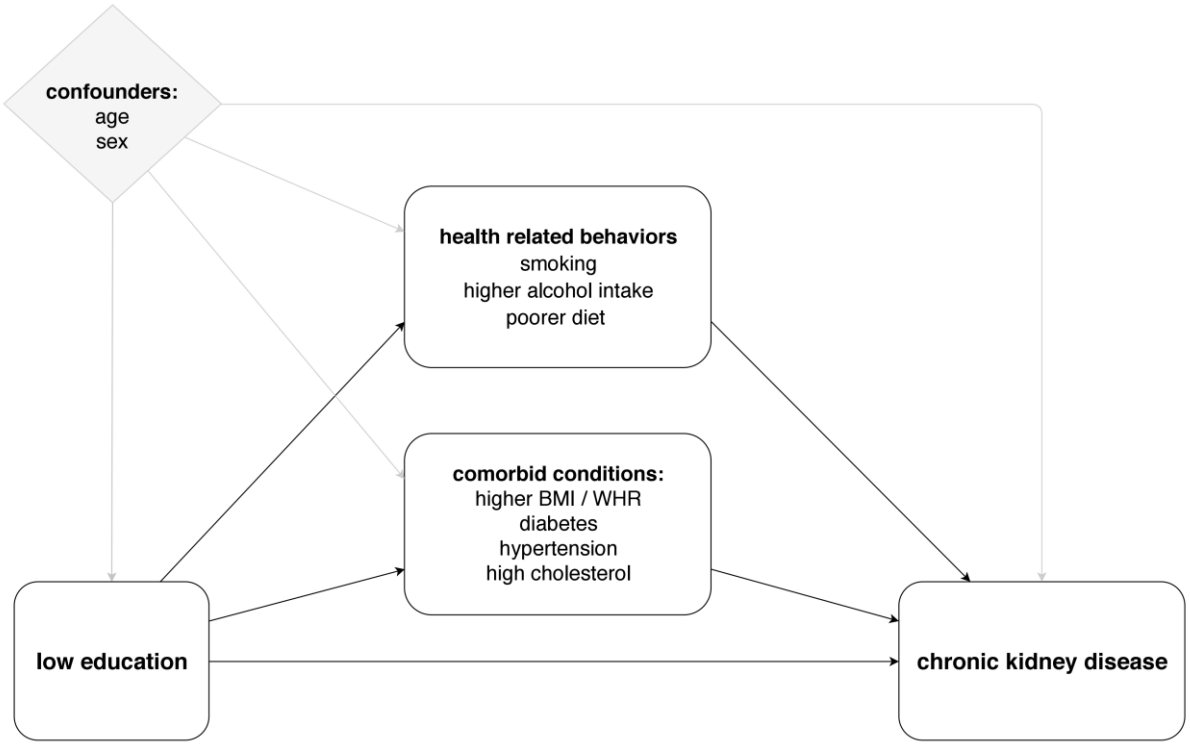
	Total	Educational level			p_{trend}
		Low (< secondary)	Medium (secondary or equivalent)	High (> secondary)	
N	6078	2637	1565	1876	
Males	3071 (51%)	1223 (46%)	855 (55%)	993 (53%)	**0.005**
Age, years	48 [39-59]	54 [45-63]	44 [36-54]	43 [37-51]	**<0.001**
BMI, kg/m^2	26 (4.1)	27 (4.3)	26 (4.0)	25 (3.3)	**<0.001**
WHR	0.88 (0.09)	0.90 (0.09)	0.87 (0.09)	0.86 (0.09)	**<0.001**
Current smoking	1956 (32%)	951 (36%)	529 (34%)	476 (25%)	**<0.001**
Alcohol					
None	1438 (24%)	881 (33%)	346 (22%)	211 (11%)	
Occasional (<10 g/wk)	956 (16%)	436 (17%)	263 (17%)	257 (14%)	
Light (10-69.9 g/wk)	2120 (35%)	782 (30%)	573 (37%)	765 (41%)	**<0.001**
Moderate (70-210 g/wk)	1252 (21%)	404 (15%)	303 (19%)	545 (29%)	
Heavier (>210 g/wk)	312 (5%)	134 (5%)	80 (5%)	98 (5%)	
Na^+ excretion (mmol/24h)	143 (51)	143 (52)	145 (51)	140 (48)	**0.021**
K^+ excretion (mmol/24h)	72 (21)	69 (20)	73 (22)	76 (21)	**<0.001**
Mg^{2+} excretion (mmol/24h)	3.9 (1.5)	3.8 (1.5)	4.0 (1.6)	4.1 (1.5)	**<0.001**
Estimated protein intake (g/kg/24h)	1.16 (0.26)	1.18 (0.28)	1.15 (0.26)	1.16 (0.24)	**0.005**
Diabetes	202 (3%)	130 (5%)	43 (3%)	29 (2%)	**<0.001**
Hypertension	1912 (31%)	1112 (42%)	418 (27%)	382 (20%)	**<0.001**
High cholesterol	1879 (31%)	1062 (40%)	423 (27%)	4394 (21%)	**<0.001**
Creatinine (µmol/L)	72 (16)	72 (17)	72 (15)	73 (14)	**0.015**
Cystatin C (mg/L)	0.89 (0.17)	0.91 (0.19)	0.88 (0.16)	0.86 (0.14)	**<0.001**
eGFR, ml/min/1.73m^2	95 (17)	91 (17)	98 (16)	99 (15)	**<0.001**
UAE, mg/24h	9.1 [6.3-16]	10 [6.3-20]	8.9 [6.2-15]	8.4 [6.2-13]	**<0.001**
CKD at baseline	883 (15%)	510 (19%)	199 (13%)	174 (9%)	**<0.001**
CKD_{eGFR} at baseline	167 (3%)	109 (4%)	37 (2%)	21 (1%)	**<0.001**
CKD_{UAE} at baseline	805 (13%)	457 (17%)	181 (12%)	167 (9%)	**<0.001**
Follow-up time, yrs	11.2 [8.5-12.1]	11.1 [7.0-11.8]	11.3 [9.3-12.2]	11.4 [10.6-12.4]	**<0.001**

Baseline characteristics by categories of educational level. Data is presented as mean (standard deviation), median (interquartile range),

and number (%) where appropriate. P-values reflect significance of a linear trend across categories of educational level, using one-way ANOVA, χ^2, or Jonckheere-Terpstra tests where appropriate.

Abbreviations: BMI, body-mass index; WHR, waist-to-hip ratio; eGFR, estimated glomerular filtration rate; UAE, urinary albumin excretion; CKD, chronic kidney disease

Figure 1. Graph of potential mediating pathways between low education and chronic kidney disease.



Graph of tested pathways through which low education could potentially lead to chronic kidney disease. BMI, body-mass index; WHR, waist-to-hip ratio. Poorer diet: high in sodium, low in potassium, low in magnesium, high in protein. Black arrows indicate a posited causal pathway; grey arrows indicate potential confounding pathways.

Table 2. Association of education with incident CKD (Panel A) and annual change in eGFR (Panel B).

A) Incident CKD

	Educational level			
	Low (<secondary)	**Medium (secondary/equivalent)**	**High (>secondary)**	
N=5195	**N=2127**	**N=1366**	**N=1702**	**p_{trend}**
Events N=861	460 (22%)	193 (14%)	208 (12%)	**<0.001**
		HR (95%CI)		
Model 1	1.97 (1.67 to 2.32)	1.17 (0.96 to 1.42)	(ref.)	**<0.001**
Model 2[a]	1.25 (1.05 to 1.48)	1.07 (0.88 to 1.30)	(ref.)	**0.009**
Model 3	1.02 (0.85 to 1.22)	0.97 (0.80 to 1.19)	(ref.)	0.789

B) Annual eGFR change

	Educational level			
	Low (<secondary)	**Medium (secondary/equivalent)**	**High (>secondary)**	
N=6078	**N=2637**	**N=1565**	**N=1876**	**p_{trend}**
		B (95%CI)		
Model 1[b]	-0.30 (-0.36 to -0.24)	-0.10 (-0.17 to -0.04)	(ref.)	**<0.001**
Model 2[b]	-0.15 (-0.21 to -0.09)	-0.08 (-0.14 to -0.02)	(ref.)	**<0.001**
Model 3[b]	-0.11 (-0.16 to -0.04)	-0.06 (-0.12 to 0.00)	(ref.)	**<0.001**

Data are presented as hazard ratio (95%CI) or unstandardized regression coefficient (95%CI, in mL/min/1.73m^2 per year).

Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate.

Model 1: Crude Educational level (high educational level is reference category)

Model 2: Model 1 + age, sex, [a](and in addition baseline eGFR), [b](and in addition their interaction with time)

Model 3: Model 2 + potential mediators (body-mass index, waist-to-hip ratio, smoking, alcohol use, Na^+ excretion, K^+ excretion, Mg^{2+} excretion, estimated protein intake, diabetes, hypertension, high cholesterol) [b](and in addition their interaction with time)

Table 3. Mediators of the association between Educational level and kidney outcomes

Mediators	Incident CKD		Annual change in eGFR	
	Proportion mediated (95%CI)	p	Proportion mediated (95%CI)	p
Health-related behaviors				
Smoking	**0.14 (0.02 to 0.51)**	**0.009**	-0.12 (-0.23 to -0.05) [a]	1.000
Alcohol	0.24 (0.05 to 0.99)	0.989	0.26 (0.16 to 0.49)	1.000
24h Na^+ excretion	-0.01 (-0.09 to 0.09)	0.431	0.01 (-0.02 to 0.06)	0.216
24h K^+ excretion	**0.12 (0.02 to 0.45)**	**0.008**	**0.08 (0.03 to 0.16)**	**<0.001**
24h Mg^{2+} excretion	0.04 (-0.03 to 0.18)	0.098	**0.03 (-0.003 to 0.07)**	**0.030**
Estimated 24h protein intake	0.001 (-0.002 to 0.04)	0.447	**0.01 (-0.001 to 0.04)**	**0.032**
Comorbid conditions				
BMI	**0.29 (0.13 to 0.96)**	**0.004**	**0.22 (0.12 to 0.42)**	**<0.001**
WHR	**0.31 (0.14 to 1.16)**	**0.002**	**0.09 (0.01 to 0.18)**	**0.008**
Diabetes	0.08 (-0.005 to 0.06)	0.064	**0.04 (0.01 to 0.10)**	**0.009**
Hypertension	**0.14 (0.05 to 0.47)**	**0.006**	**0.13 (0.08 to 0.24)**	**<0.001**
Hypercholesterolemia	0.02 (-0.05 to 0.13)	0.223	-0.04 (-0.10 to 0.01)	0.962

Results from causal mediation analysis. N=6078. Effects are reported as proportion mediated of the association between education (low vs high) and kidney outcomes. Non-parametric bootstrap confidence intervals and one-sided p-values are estimated from 1000 simulations. Estimates are conditioned on age, sex, and baseline eGFR.

One-sided hypotheses were that low education leads to steeper eGFR decline through: current smoking, higher alcohol consumption, higher Na^+ excretion, lower K^+ excretion, lower Mg^{2+} excretion, higher protein intake, higher BMI, higher WHR, diabetes, hypertension, and hypercholesterolemia.

[a] In addition adjusted for the interaction term educational level x smoking.

EDUCATIONAL LEVEL AND RISK OF CHRONIC KIDNEY DISEASE IN THE NETHERLANDS: LONGITUDINAL DATA FROM THE PREVEND STUDY

SUPPLEMENTARY MATERIAL

Table S1. Association of education with incident CKD_{eGFR}

	Educational level			
N=5911	Low (<secondary) N=2528	Medium (secondary/equivalent) N=1528	High (>secondary) N=1855	P_{trend}
Events	264 (10%)	75 (5%)	69 (4%)	**<0.001**
		HR (95%CI)		
Model 1	3.11 (2.39 to 4.06)	1.35 (0.97 to 1.87)	(ref.)	**<0.001**
Model 2	1.21 (0.92 to 1.58)	1.01 (0.73 to 1.40)	(ref.)	0.117
Model 3	0.97 (0.74 to 1.29)	0.91 (0.65 to 1.26)	(ref.)	0.996

Data are presented as hazard ratio (95%CI)
Model 1: Crude Educational level
Model 2: Model 1 + age, sex, and baseline eGFR
Model 3: Model 2 + potential mediators (BMI, WHR, smoking, alcohol consumption, Na^+ excretion, K^+ excretion, Mg^{2+} excretion, estimated protein intake, diabetes, hypertension, high cholesterol)

Table S2. Association of education with incident CKD_{UAE}

	Educational level			
	Low (<secondary)	Medium (secondary/equivalent)	High (>secondary)	P_{trend}
N=5273	**N=2180**	**N=1384**	**N=1709**	
Events	348 (16%)	163 (12%)	180 (11%)	**<0.001**
		HR (95%CI)		
Model 1	1.68 (1.41 to 2.01)	1.14 (0.92 to 1.40)	(ref.)	**<0.001**
Model 2	1.15 (0.95 to 1.39)	1.00 (0.80 to 1.23)	(ref.)	0.132
Model 3	0.97 (0.79 to 1.19)	0.90 (0.72 to 1.12)	(ref.)	0.913

Data are presented as hazard ratio (95%CI)
Model 1: Crude Educational level
Model 2: Model 1 + age, sex, and baseline *ln*UAE
Model 3: Model 2 + potential mediators (BMI, smoking, alcohol consumption, Na^+ excretion, K^+ excretion, Mg^{2+} excretion, estimated protein intake, diabetes, hypertension, high cholesterol)

Table S3. Association of education with annual change in *ln*UAE

	Educational level			
	Low (<secondary)	Medium (secondary/equivalent)	High (>secondary)	P_{trend}
N=6078	N=2637	N=1565	N=1876	
	B (95%CI)			
Model 1	0.007 (0.002 to 0.011)	0.005 (0.000 to 0.010)	(ref.)	**0.003**
Model 2	0.001 (-0.003 to 0.006)	0.004 (-0.001 to 0.009)	(ref.)	0.625
Model 3	-0.003 (-0.008 to 0.002)	0.002 (-0.003 to 0.007)	(ref.)	0.199

Data are presented as annual change in natural log-transformed UAE in *ln*(mg/24h) per year(95%CI). Positive B x 100% corresponds to % annual increase in UAE.

Model 1: Crude Educational level and its interaction with time

Model 2: Model 1 + baseline age, sex, and interaction of each with time

Model 3: Model 2 + potential mediators (BMI, WHR, smoking, alcohol consumption, Na^+ excretion, K^+ excretion, Mg^{2+} excretion, estimated protein intake, diabetes, hypertension, high cholesterol, and interaction of each with time)

Table S4. Estimates of main effects of potential mediators on incident CKD and annual eGFR change

	Incident CKD_{KDIGO}	**Annual eGFR change**
	N=5195	N = 6078
	HR (95%CI)[a]	B (95%CI)[b]
Health –related behaviors		
Smoking (yes vs no)	**1.23 (1.07 to 1.43)****	**0.14 (0.09 to 0.19)*****
Alcohol		
None (Ref.)	Ref.	Ref.
Occasional (<10 g/wk)	0.85 (0.69 to 1.06)	0.06 (-0.02 to 0.13)
Light (10-69.9 g/wk)	**0.81 (0.68 to 0.97)***	**0.15 (0.08 to 0.21)*****
Moderate (70-210 g/wk)	**0.74 (0.61 to 0.91)****	**0.19 (0.11 to 0.26)*****
Heavier (>210 g/wk)	**0.68 (0.48 to 0.96)***	**0.16 (0.10 to 0.22)****
24h Na^{+} excretion (mmol/L)	1.00 (1.00 to 1.00)	**-5.5 x10^{-4} (-1.0 x10^{-3} to -5.8 x10^{-5})***
24h K^{+} excretion (mmol/L)	**0.995 (0.99 to 1.00)****	**1.8 x10^{-3} (6.4 x10^{-4} to 2.9 x10^{-3})****
24h Mg^{2+} excretion (mmol/L)	0.96 (0.92 to 1.01)	**0.02 (0.00 to 0.03)***
Estimated 24h protein intake (g/kg/24h)	1.04 (0.69 to 1.17)	**-0.21 (-0.30 to -0.12)*****
Comorbid conditions		
BMI (kg/m^2)	**1.04 (1.03 to 1.06)*****	**-0.02 (-0.02 to -0.01)*****
WHR	**16.54 (6.15 to 44.48)*****	**-0.52 (-0.87 to -0.17)****
Diabetes (yes vs no)	**2.12 (1.54 to 2.91)*****	**-0.56 (-0.70 to -0.42)*****
Hypertension (yes vs no)	**1.77 (1.53 to 2.05)*****	**-0.23 (-0.29 to 0.17)*****
Hypercholesterolemia (yes vs no)	1.08 (0.93 to 1.24)	**0.06 (0.01 to 0.11)***

Estimates of main effects of potential mediators on incident CKD from Cox proportional hazards analysis and annual change in eGFR (per unit increase in continuous variables or compared to reference of categorical variables).

[a] Hazard ratio estimated from Cox proportional hazards regression models, adjusted for age, sex, and baseline eGFR.

[b] Unstandardized regression coefficient from linear mixed-effects models for mediator x time interaction, adjusted for age, sex, and their interaction with time. A negative sign corresponds to steeper decline in eGFR.

*two-sided p<0.05 **p<0.01 ***p<0.001.

Table S5. Mediators of the association between education and CKD

Mediators	**ACME** (95%CI)	**p**	**ADE** (95%CI)	**p**	**Proportion mediated** (95%CI)	**p**
Health-related behaviors						
Smoking	**-1.16 (-2.08 to -0.21)**	**0.003**	**-7.02 (-14 to -0.63)**	**0.017**	**0.14 (0.02 to 0.51)**	**0.009**
Alcohol	-1.96 (-3.66 to -0.59)	0.998	**-6.13 (-13 to 0.56)**	**0.032**	0.24 (0.05 to 0.99)	0.989
24h Na^+ excretion	0.05 (-0.49 to 0.59)	0.436	**-8.06 (-15 to -1.80)**	**0.006**	-0.01 (-0.09 to 0.09)	0.431
24h K^+ excretion	**-0.96 (-1.90 to -0.18)**	**0.006**	**-7.07 (-14 to -1.31)**	**0.008**	**0.12 (0.02 to 0.45)**	**0.008**
24h Mg^{2+} excretion	-0.34 (-0.93 to 0.15)	0.093	**-7.76 (-14 to -1.35)**	**0.012**	0.04 (-0.03 to 0.18)	0.098
Estimated 24h protein intake	-0.001 (-0.14 to 0.09)	0.449	**-8.02 (-15 to -1.71)**	**0.007**	0.001 (-0.002 to 0.04)	0.447
Comorbid conditions						
BMI	**-2.52 (-3.76 to -1.40)**	**<0.001**	**-6.07 (-13 to -0.05)**	**0.023**	**0.29 (0.13 to 0.96)**	**0.004**
WHR	**-2.61 (-3.90 to -1.51)**	**<0.001**	**-5.69 (-13 to 0.44)**	**0.038**	**0.31 (0.14 to 1.16)**	**0.002**
Diabetes	-0.06 (-0.28 to 0.03)	0.064	**-7.63 (-15 to -2.01)**	**0.005**	0.08 (-0.005 to 0.06)	0.064
Hypertension	**-1.06 (-1.57 to -0.52)**	**<0.001**	**-6.53 (-13 to -0.84)**	**0.015**	**0.14 (0.05 to 0.47)**	**0.006**
Hypercholesterolemia	-0.19 (-0.73 to 0.29)	0.217	**-7.79 (-14 to -1.69)**	**0.007**	0.02 (-0.05 to 0.13)	0.223

Results from causal mediation analysis. N=5195. Low education vs. high education (reference). Non-parametric bootstrap confidence intervals and one-sided p-values are estimated from 1000 simulations. One-sided hypotheses were that low education leads to higher CKD incidence through: current smoking, higher alcohol consumption, higher Na^+ excretion, lower K^+ excretion, lower Mg^{2+} excretion, higher protein intake, higher BMI, higher WHR, diabetes, hypertension, and hypercholesterolemia.

Estimates are conditioned on age, sex, and baseline eGFR. Estimates of ACME and ADE are from parametric accelerated failure time models; negative sign corresponds to higher risk of CKD.

ACME, average causal mediation effect of potential mediator; ADE, average direct effect

Table S6. Mediators of the association between education and annual change in eGFR

Mediators	**ACME** (95%CI)	**p**	**ADE** (95%CI)	**p**	**Proportion mediated** (95%CI)	**p**
Health-related behaviors						
Smoking [a]	0.007 (0.003 to 0.013)	1.000	**-0.07 (-0.10 to -0.05)**	**<0.001**	-0.12 (-0.23 to -0.05)	1.000
Alcohol	-0.018 (-0.025 to -0.012)	1.000	**-0.05 (-0.07 to -0.02)**	**<0.001**	0.26 (0.16 to 0.49)	1.000
24h Na^+ excretion	-0.001 (-0.003 to 0.002)	0.216	**-0.07 (-0.09 to -0.04)**	**<0.001**	0.01 (-0.02 to 0.06)	0.216
24h K^+ excretion	**-0.005 (-0.008 to -0.002)**	**<0.001**	**-0.06 (-0.09 to -0.03)**	**<0.001**	**0.08 (0.03 to 0.16)**	**<0.001**
24h Mg^{2+} excretion	**-0.002 (-0.004 to 0.000)**	**0.030**	**-0.06 (-0.09 to -0.04)**	**<0.001**	**0.03 (-0.003 to 0.07)**	**0.030**
Estimated 24h protein intake	**-0.001 (-0.002 to 0.001)**	**0.032**	**-0.07 (-0.09 to -0.04)**	**<0.001**	**0.01 (-0.001 to 0.04)**	**0.032**
Comorbid conditions						
BMI	**-0.015 (-0.020 to -0.009)**	**<0.001**	**-0.02 (-0.08 to -0.02)**	**<0.001**	**0.22 (0.12 to 0.42)**	**<0.001**
WHR	**-0.006 (-0.010 to -0.001)**	**0.008**	**-0.06 (-0.09 to -0.04)**	**<0.001**	**0.09 (0.01 to 0.18)**	**0.008**
Diabetes	**-0.002 (-0.006 to -0.001)**	**0.009**	**-0.06 (-0.09 to -0.04)**	**<0.001**	**0.04 (0.01 to 0.10)**	**0.009**
Hypertension	**-0.009 (-0.014 to -0.005)**	**<0.001**	**-0.06 (-0.08 to -0.03)**	**<0.001**	**0.13 (0.08 to 0.24)**	**<0.001**
Hypercholesterolemia	0.003 (-0.000 to 0.006)	0.962	**-0.07 (-0.09 to -0.05)**	**<0.001**	-0.04 (-0.10 to 0.01)	0.962

Results from causal mediation analysis. N=6078. Low education vs. high education (reference). Non-parametric bootstrap confidence intervals and one-sided p-values are estimated from 1000 simulations. One-sided hypotheses were that low education leads to steeper eGFR decline through: current smoking, higher alcohol consumption, higher Na^+ excretion, lower K^+ excretion, lower Mg^{2+} excretion, higher protein intake, higher BMI, higher WHR, diabetes, hypertension, and hypercholesterolemia. Estimates are conditioned on age, sex, and baseline eGFR.

[a] In addition adjusted for the interaction term smoking x education.

ACME, average causal mediation effect of potential mediator; ADE, average direct effect of low education

Table S7. Author contributions

Conception and design	CT, PV
Data acquisition	RG
Analysis and interpretation of data	CT, PV, LK, HS, RG, UB
Drafting of article	CT, LK
Revision of article	PV, LK, HS, RG, UB
Supervision	HS, RG, UB