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In utero, childhood, and adolescence tobacco smoke exposure, physical activity, and chronic kidney disease incidence in adulthood: evidence from a large prospective cohort study

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Abstract

Background The adverse effects of early-life tobacco smoke exposure on chronic kidney disease (CKD) risk remain unclear. This study aimed to investigate the associations of early-life tobacco smoke exposure with CKD incidence in adulthood, and further explore the modification effects of physical activity (PA).

Methods A total of 352,883 participants were included from the UK Biobank. The information on early-life tobacco smoke exposure was assessed by employing in utero tobacco smoke exposure and age of smoking initiation. Weekly moderate-to-vigorous physical activity (MVPA) was calculated for each individual. Cox proportional hazard regression was fitted to estimate the hazard ratio (HR) and 95% confidence interval (CI) of CKD risk, and to investigate the modification effects of MVPA.

Results CKD incidence significantly increased in participants with in utero tobacco smoke exposure (HR: 1.08, 95% CI: 1.04, 1.12). Compared with never-smokers, we found a monotonic increase in the risk of CKD with smoking initiation across adulthood (HR: 1.21, 95% CI: 1.16, 1.27), adolescence (HR: 1.29, 95% CI: 1.24, 1.35), and childhood (HR: 1.34, 95% CI: 1.25, 1.43) (P trend < 0.001). Additionally, we identified joint cumulative effects of MVPA and early-life tobacco smoke exposure on incident CKD. Compared with never-smokers with recommended MVPA, prenatal or childhood tobacco smokers without recommended MVPA had the highest CKD risk, and the HRs (95% CIs) were 1.17 (1.10, 1.24) and 1.51 (1.36, 1.68), respectively.

Conclusions Early-life tobacco smoke exposure may contribute to CKD incidence in adulthood, and the observed associations could be modified by MVPA. These findings provide important information on CKD prevention in the participant's early life while urging a more rapid and powerful need for tobacco control among pregnant couples, children, and adolescents.

Keywords Early-life tobacco smoke exposure, Physical activity, Chronic kidney disease

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Background

Chronic kidney disease (CKD), also known as chronic kidney failure, is a progressive disease characterized by irreversible deterioration of renal structure and function [1, 2]. It affects over 10% of the world's population and has become a leading cause of death and suffering globally [3, 4]. The clinical practice guideline has underscored the importance of intervening in risk factors for primary and secondary prevention of CKD [5]. Although several risk factors such as age, obesity, diabetes, and cardiovascular conditions have been documented associated with the occurrence of CKD [6], considering the increasing prevalence of CKD, it is still imperative to investigate novel risk factors and explore interventions to mitigate the increased risk of CKD.

Tobacco smoking, the leading risk factor for many diseases [7, 8], accounted for over 8 million global deaths per year [9]. Compared with exposure to tobacco smoke in adulthood, early-life tobacco smoke exposure (including in utero tobacco smoke exposure and smoking initiation in childhood and adolescence) exerted profound effects on health [10, 11]. According to Lucas's programming theory, stimulation by adverse environmental factors during these early-life periods (e.g., fetal stage, childhood, and adolescence) can lead to adaptive and procedural changes during development, which could induce adverse consequences in adulthood [12]. Supported by this theory, previous studies have indicated that exposure to tobacco smoking in early life can increase the risk of cardiovascular disease [13], diabetes [14], obesity [15], and cancer [16, 17]. However, little is known about the adverse effects of in utero tobacco smoke exposure on CKD incidence in later life. Only a limited number of experiments studies have found that in utero smoking exposure impacted kidney development and function. For example, Al-Odat et al. found that cigarette smoke exposure of female mice before pregnancy, during pregnancy, and during lactation could result in significant renal underdevelopment and functional abnormalities of the offspring in adulthood [18]. Chen et al. also observed that maternal exposure to subcutaneous nicotine injection during pregnancy in rats could induce neonatal renal fibrosis [19]. Although these studies failed to observe a direct link between maternal tobacco smoke exposure during pregnancy and CKD incidence, these findings collectively offered evidence of the detrimental impact of early-life tobacco smoke exposure on kidney growth and function. Therefore, we hypothesized that in utero tobacco smoke exposure and smoking initiation at an earlier age could promote the occurrence of CKD in the later life.

World Health Organization (WHO) recently have recommended that regular physical activity (PA) is one of the most effective measures for people with chronic illnesses or disabilities to improve health [20]. Previous compelling evidence also provided evidence on the benefits of regular PA in improving the health status of chronic illnesses including CKD [21, 22]. Besides, a meta-analysis involving 1.2 million participants demonstrated that individuals with active PA had a decreased risk of CKD incidence compared to those with inactive PA [23]. However, as a modifiable lifestyle, whether PA offers risk reduction against early-life tobacco smoke exposure on CKD risk in adulthood has not been addressed.

The UK Biobank was a large-scale population-based prospective study, which included individuals aged 40–69 years. This age range captured individuals at higher risk for CKD [4], making it ideal for assessing the relationships between early-life tobacco smoke exposure and CKD risk. Therefore, in this prospective cohort study, we aimed to investigate the relationships between early-life tobacco smoke exposure (including in utero tobacco smoke exposure and age of smoking initiation) and CKD risk. Besides, we assessed the combined effects of in utero tobacco smoke exposure and smoking initiation age on CKD risk, and further explored the role of PA in modifying these associations.

Methods

Study population

Our study included participants drawn from the UK Biobank, which recruited 502,401 participants between the ages of 40 and 69 years at baseline across the UK from 2006 to 2010. At the time of enrollment, each participant provided biological specimens, took anthropometric measurements, and answered questionnaire information. Detailed information was described previously [24]. All participants were well-informed and signed informed consent. North West Multicenter Research Ethics Committee had granted the ethical approval.

Among 408,763 individuals who had complete information on kidney function and without prevalent CKD, we excluded participants with missing information on in utero tobacco smoke exposure ($n=55,880$) or smoking initiation age ($n=56,885$), leaving 352,883 participants in the primary analysis of in utero tobacco smoke exposure and 351,878 participants in the primary analysis of age of smoking initiation. To test the modification effects of PA, a total of 289,509 participants with complete information on PA were included in the analysis for in utero tobacco smoke exposure and 285,946 participants were included in the analysis for the age of smoking initiation (Additional file 1: Fig. S1).

Early-life tobacco smoke exposure assessment

The assessment of early-life tobacco smoke exposure (including in utero tobacco smoke exposure and age of smoking initiation) referred to previous studies and is currently used widely [14, 17]. The information on in utero tobacco smoke exposure was obtained by asking whether their mother smoked during pregnancy through a touchscreen questionnaire at baseline. For former and current smokers, we collected the information on smoking initiation age by asking participants about the age when started smoking regularly and then categorized them into adulthood initiators, adolescence initiators, and childhood initiators.

PA assessment

PA was assessed using a short version of the International Physical Activity Questionnaire (IPAQ), which has been shown to have validity and reliability in the UK population [25, 26]. Participants were asked about the number of days per week they participated in each category of PA and the minutes spent on each category of PA in a typical day. The average time for each type of PA per week was calculated by multiplying duration and frequency. According to WHO standard guidelines for PA and its health benefits, participants were categorized into two groups based on whether their moderate-to-vigorous physical activity (MVPA) levels met the WHO standard recommendations ($\geq$ 150 min MVPA per week): recommended MVPA or not recommended MVPA [20].

Incident CKD ascertainment

CKD was identified using International Classification of Diseases with the 10th edition (ICD-10) codes N18, N18.0–N18.9, I12.0–I12.9, I13.1, and I13.2 and ICD-9 codes 585 and 5859 referred to previous studies [27]. Besides, urinary albumin to creatinine ratio (UACR) > 30 mg/g or an estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2 at baseline was used to identify prevalent CKD at baseline. In this study, we used the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation to calculate eGFR [28].

Covariates ascertainment

The data on the demographic characteristics and health-related information include age, sex, ethnicity, education level, drinking status, healthy diet score, Townsend deprivation index (TDI), body mass index (BMI), eGFR, UACR, antihypertensive drug use, insulin use, cholesterol-lowering drug use, prevalent hypertension, diabetes, and hyperlipidemia were considered as potential confounders. The detailed description of covariates can be found in Supplementary Methods (Additional file 1: Methods S1) [29].

Statistical analysis

The baseline characteristics were appropriately compared by early-life tobacco smoke exposure status using *t*-tests, analysis of variance test, Kruskal–Wallis test, or Wilcoxon rank test for continuous variables, and using chi-square test for categorical variables. Missing values in categorical variables were set as a missing indicator category and missing values in continuous variables were replaced with sex-specific means. Follow-up time in this study was computed as the duration from attending the assessment center date through the time of incident CKD, death, loss to follow-up, or end of follow-up, whichever occurred first. Dates of end of follow-up were 31 October 2022 for centers in England, 31 May 2022 for centers in Wales, and 31 August 2022 for centers in Scotland.

We used multivariable Cox proportion hazard models to assess the association of early-life tobacco smoke exposure with CKD incidence. The proportional hazards assumption was verified using Schoenfeld residuals. In primary analysis, age, sex, and ethnicity were adjusted in model 1. In model 2, TDI, BMI, drinking status, MVPA, education level, and healthy diet score were additionally adjusted. In model 3, UACR, eGFR, antihypertensive medication use, insulin use, cholesterol-lowering medication use, prevalent hypertension, diabetes, and hyperlipidemia were further adjusted. To estimate the *P* trend, we assigned the ordinal value of each group of smoking initiation age and then entered this continuous variable into the models. In addition, we classified the participants into eight groups based on in utero tobacco smoking exposure (yes or no) and smoking initiation age categories (never-smokers, smoking initiation in adulthood, smoking initiation in adolescence, and smoking initiation in childhood) with the never-smokers without in utero tobacco smoke exposure as the reference to assess their joint effects on CKD risk.

To investigate whether MVPA modified the associations of early-life tobacco smoke exposure with CKD risk, a cross-product term between them was included in our fully adjusted model to test for the presence of the interaction effect. Additionally, to analyze the joint effects of early-life tobacco smoke exposure and MVPA on CKD risk, we categorized participants into four groups based on in utero tobacco smoke exposure (yes or no) and adherence to recommended levels of MVPA (recommended or not recommended), and participants with recommended MVPA and without in utero tobacco smoke exposure were used as the reference group. Besides, we divided participants into eight groups based on smoking initiation age categories (never-smokers, smoking initiation in adulthood, smoking initiation in adolescence, and smoking initiation in childhood) and

MVPA (recommended or not recommended), and the reference group consisted of never-smokers who adhered to the recommended MVPA levels.

To test the robustness of our results, we did two sensitivity analyses. First, we restricted the analysis to individuals who had complete covariate information. In addition, we excluded cases of CKD with an incident time of less than 2 years from the baseline to mitigate the reverse causal effects of the observed correlation.

We used R software version 4.3.2 for all statistical analyses and set statistical significance at two-sided *P* values < 0.05.

Results

Baseline characteristics

The baseline characteristics of study participants are presented in Table 1. A total of 103,711 (29.39%) participants were exposed to tobacco smoking in utero among

Table 1 Baseline characteristics of study participants according to in utero tobacco smoke exposure and age of smoking initiation

	In utero tobacco smoke exposure		Age of smoking initiation			
	No	Yes	Never-smokers	Adulthood ≥ 18 years	Adolescence 15–18 years	Childhood < 15 years
No. participants	249,172	103,711	224,002	52,142	55,195	20,539
Age, years	56.26 ± 8.26	55.76 ± 7.73	55.60 ± 8.12	57.81 ± 7.94	57.49 ± 7.67	55.43 ± 7.93
Male, *n* (%)	114,877 (46.10)	49,825 (48.04)	95,112 (42.46)	25,484 (48.87)	31,363 (56.82)	13,484 (65.65)
White, *n* (%)	230,670 (92.57)	101,963 (98.31)	209,175 (93.38)	49,600 (95.12)	53,847 (97.56)	19,926 (97.02)
BMI, kg/m^2	27.11 ± 4.56	27.86 ± 4.84	27.14 ± 4.67	27.52 ± 4.67	27.90 ± 4.58	28.49 ± 4.95
Townsend deprivation index	− 2.27 [− 3.72, 0.27]	− 2.04 [− 3.57, 0.67]	− 2.41 [− 3.79, − 0.07]	− 1.77 [− 3.45, 1.15]	− 1.80 [− 3.43, 1.06]	− 0.90 [− 3.02, 2.32]
College or university degree, *n* (%)	90,124 (36.17)	29,337 (28.29)	81,638 (36.45)	19,042 (36.52)	10,736 (19.45)	3342 (16.27)
Physical activity, *n* (%)						
Not recommended MVPA	92,553 (37.14)	38,662 (37.28)	82,976 (37.04)	20,076 (38.50)	20,354 (36.88)	7668 (37.33)
Recommended MVPA	111,469 (44.74)	46,825 (45.15)	99,246 (44.31)	22,868 (43.86)	24,013 (43.50)	8745 (42.58)
Missing	45,150 (18.12)	18,224 (17.57)	41,780 (18.65)	9198 (17.64)	10,828 (19.62)	4126 (20.09)
Alcohol drinker status, *n* (%)						
Never	12,600 (5.06)	2768 (2.67)	13,877 (6.20)	987 (1.89)	856 (1.55)	339 (1.65)
Previous	7880 (3.16)	3896 (3.76)	6175 (2.76)	2203 (4.23)	2504 (4.54)	1314 (6.40)
Current	228,420 (91.67)	96,958 (93.49)	203,739 (90.95)	48,898 (93.78)	51,782 (93.82)	18,845 (91.75)
Missing	272 (0.11)	89 (0.08)	211 (0.09)	54 (0.10)	53 (0.09)	41 (0.20)
Healthy diet score, *n* (%)						
0–1	26,283 (10.55)	13,318 (12.84)	23,066 (10.30)	6000 (11.51)	7987 (14.47)	4025 (19.60)
2–3	121,539 (48.78)	52,335 (50.46)	109,210 (48.75)	25,999 (49.86)	28,623 (51.86)	10,666 (51.93)
4–5	96,815 (38.85)	36,505 (35.20)	87,751 (39.17)	19,264 (36.94)	17,516 (31.73)	5291 (25.76)
Missing	4535 (1.82)	1553 (1.50)	3975 (1.78)	879 (1.69)	1069 (1.94)	557 (2.71)
UACR, mg/g	9.16 [5.94, 14.53]	8.86 [5.76, 14.18]	9.24 [5.96, 14.65]	9.06 [5.92, 14.47]	8.79 [5.79, 13.99]	8.29 [5.46, 13.23]
eGFR, mL/min/1.73 m^2	91.67 ± 11.94	91.99 ± 11.75	91.71 ± 11.88	91.48 ± 11.80	91.45 ± 11.84	93.07 ± 12.13
Antihypertensive drug use, *n* (%)	46,012 (18.47)	19,849 (19.14)	38,156 (17.03)	11,196 (21.47)	12,772 (23.14)	4763 (23.19)
Insulin use, *n* (%)	2051 (0.82)	896 (0.86)	1674 (0.75)	476 (0.91)	565 (1.02)	276 (1.34)
Cholesterol-lowering drug use, *n* (%)	38,731 (15.54)	16,912 (16.31)	29,286 (13.07)	10,488 (20.11)	12,201 (22.11)	4813 (23.43)
Personal medical condition, *n* (%)						
Hypertension	136,721 (54.87)	58,243 (56.16)	120,508 (53.80)	30,502 (58.50)	33,574 (60.83)	12,242 (59.60)
Diabetes	16,028 (6.43)	7264 (7.01)	11,790 (5.26)	4466 (8.57)	5371 (9.73)	2554 (12.43)
Hyperlipidemia	44,536 (17.87)	19,507 (18.81)	34,442 (15.38)	11,765 (22.56)	13,656 (24.74)	5422 (26.40)

Abbreviation: *BMI* Body mass index, *MVPA* Moderate-to-vigorous physical activity, *UACR* Urinary albumin to creatinine ratio, *eGFR* Estimated glomerular filtration rate

The values are given as numbers (percentage) for categorical variables and mean ± standard deviation or median [interquartile range] for continuous variables

352,883 participants in the analysis of in utero tobacco smoke exposure. Among participants with in utero tobacco smoke exposure, the mean eGFR was 91.99 mL/min/1.73 m^2. Compared with participants without in utero tobacco smoke exposure, participants exposed to tobacco smoking in utero had a higher TDI, a higher proportion of recommended MVPA, a higher proportion of unhealthy diet, and were more likely to have hypertension, diabetes, and hyperlipidemia.

Likewise, among 351,878 participants in the analysis of smoking initiation age, 224,002 (63.66%) were never-smokers, 52,142 (14.82%) smoked initiation in adulthood, 55,195 (15.68%) smoked initiation in adolescence, and 20,539 (5.84%) smoked initiation in childhood. The mean eGFR of participants smoking initiation in childhood, adolescence, or adulthood was 93.07, 91.45, and 91.48 mL/min/1.73 m^2, respectively. Compared to never-smokers, participants who initiated smoking in childhood, adolescence, or adulthood had a higher TDI, a lower proportion of recommended MVPA, a higher proportion of unhealthy diet, and were more likely to have hypertension, diabetes, and hyperlipidemia.

The association of early-life tobacco smoke exposure with CKD risk

During a median follow-up of 13.41 years, a total of 13,902 and 14,192 new-onset CKD cases were identified in the analysis of in utero tobacco smoke exposure and age of smoking initiation, respectively. As shown in Table 2, we observed positive associations of early-life tobacco smoke exposure with CKD risk. Compared with participants without exposure to tobacco smoking in utero, the hazard ratio (HR) and 95% confidence interval (CI) for participants exposed to tobacco smoking in utero were 1.08 (1.04, 1.12) for CKD incidence. Similarly, compared with never-smokers, we observed a monotonically increased CKD risk across smoking initiation in adulthood (HR: 1.21, 95% CI: 1.16, 1.27), adolescence (HR: 1.29, 95% CI: 1.24, 1.35), and childhood (HR: 1.34, 95% CI: 1.25, 1.43) in the fully adjusted model (*P* trend < 0.001). In our sensitivity analyses, the associations did not change appreciably (Additional file 1: Table S1).

Additionally, joint effects were observed between in utero tobacco smoke exposure and age of smoking initiation on CKD risk (Fig. 1). Taking never-smokers without in utero tobacco smoke exposure as the reference group, the highest CKD risk in adulthood was observed in participants without in utero tobacco smoking exposure and smoking initiation in childhood (HR: 1.40, 95% CI: 1.27, 1.53). The sensitivity analyses did not yield substantially different results (Additional file 1: Table S2).

The association of recommended MVPA with CKD risk

We demonstrated that performing the recommended MVPA had a protective effect on CKD risk (Additional file 1: Tables S3–S4). Compared with participants without recommended MVPA, the HRs (95% CIs) for those with recommended MVPA were 0.91 (0.88, 0.95) for CKD risk in the analysis of in utero tobacco smoke exposure and 0.92 (0.88, 0.95) for CKD risk in the analysis of age of smoking initiation.

Joint analyses of early-life tobacco smoking exposure and PA with CKD risk

The joint effects between MVPA and early-life tobacco smoke exposure on CKD risk are shown in Fig. 2. In the

Table 2 Association of in utero tobacco smoke exposure and age of smoke initiation with incident CKD

	In utero tobacco smoke exposure		Age of smoking initiation				*P* trend
	No	Yes	Never-smokers	Adulthood ≥ 18 years	Adolescence 15–18 years	Childhood < 15 years	
No. participants	249,172	103,711	224,002	52,142	55,195	20,539	
No. cases (%)	9689 (3.89)	4213 (4.06)	7671 (3.42)	2484 (4.76)	2980 (5.40)	1057 (5.15)	
Person-years	3,231,880	1,341,682	2,929,091	665,217	701,912	259,453	
HR (95% CI)							
Model 1	1.00 (ref.)	1.17 (1.13, 1.22)	1.00 (ref.)	1.20 (1.14, 1.25)	1.45 (1.39, 1.51)	1.70 (1.59, 1.81)	< 0.001
Model 2	1.00 (ref.)	1.08 (1.04, 1.12)	1.00 (ref.)	1.14 (1.09, 1.20)	1.27 (1.22, 1.33)	1.35 (1.26, 1.44)	< 0.001
Model 3	1.00 (ref.)	1.08 (1.04, 1.12)	1.00 (ref.)	1.21 (1.16, 1.27)	1.29 (1.24, 1.35)	1.34 (1.25, 1.43)	< 0.001

Abbreviations: *CKD* Chronic kidney disease, *HR* Hazard ratio, *CI* Confidence interval

Mode1 1 was adjusted for age, sex, and ethnic

Mode1 2 was additionally adjusted for body mass index, Townsend deprivation index, education level, physical activity, drinking status, and healthy diet score based on model 1

Mode1 3 was additionally adjusted for antihypertensive drug use, insulin use, cholesterol-lowering drug use, urinary albumin to creatinine ratio, estimated glomerular filtration rate, prevalent hypertension, diabetes, and hyperlipidemia based on model 2

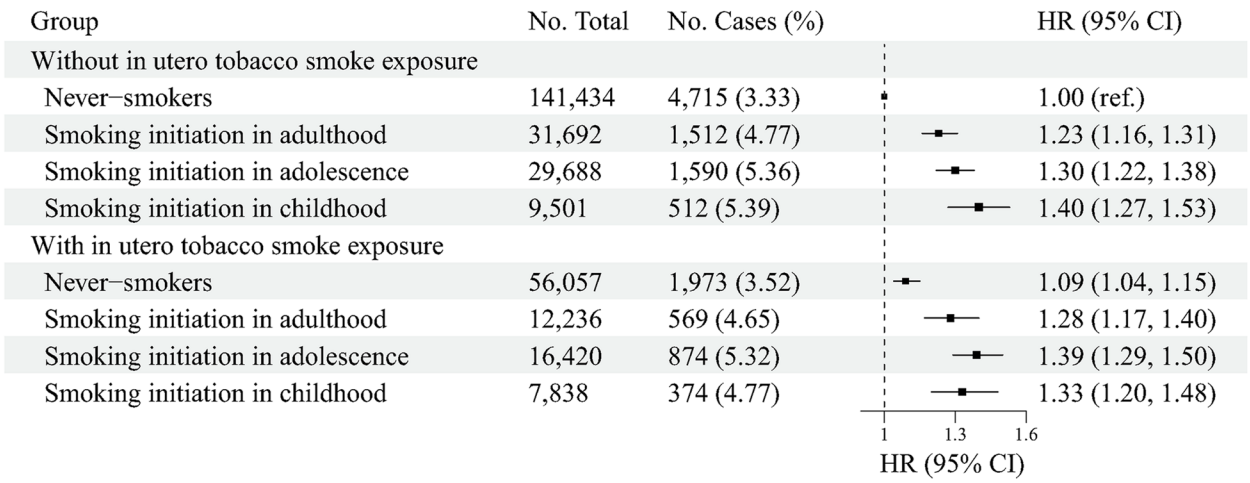

Fig. 1 Risk of incident chronic kidney disease according to in utero tobacco smoke exposure and age of smoking initiation. Models were adjusted for age, sex, ethnic, body mass index, Townsend deprivation index, education level, physical activity, drinking status, healthy diet score, antihypertensive drug use, insulin use, cholesterol-lowering drug use, urinary albumin to creatinine ratio, estimated glomerular filtration rate, prevalent hypertension, diabetes, and hyperlipidemia. Abbreviations: CI, confidence interval; HR, hazard ratio

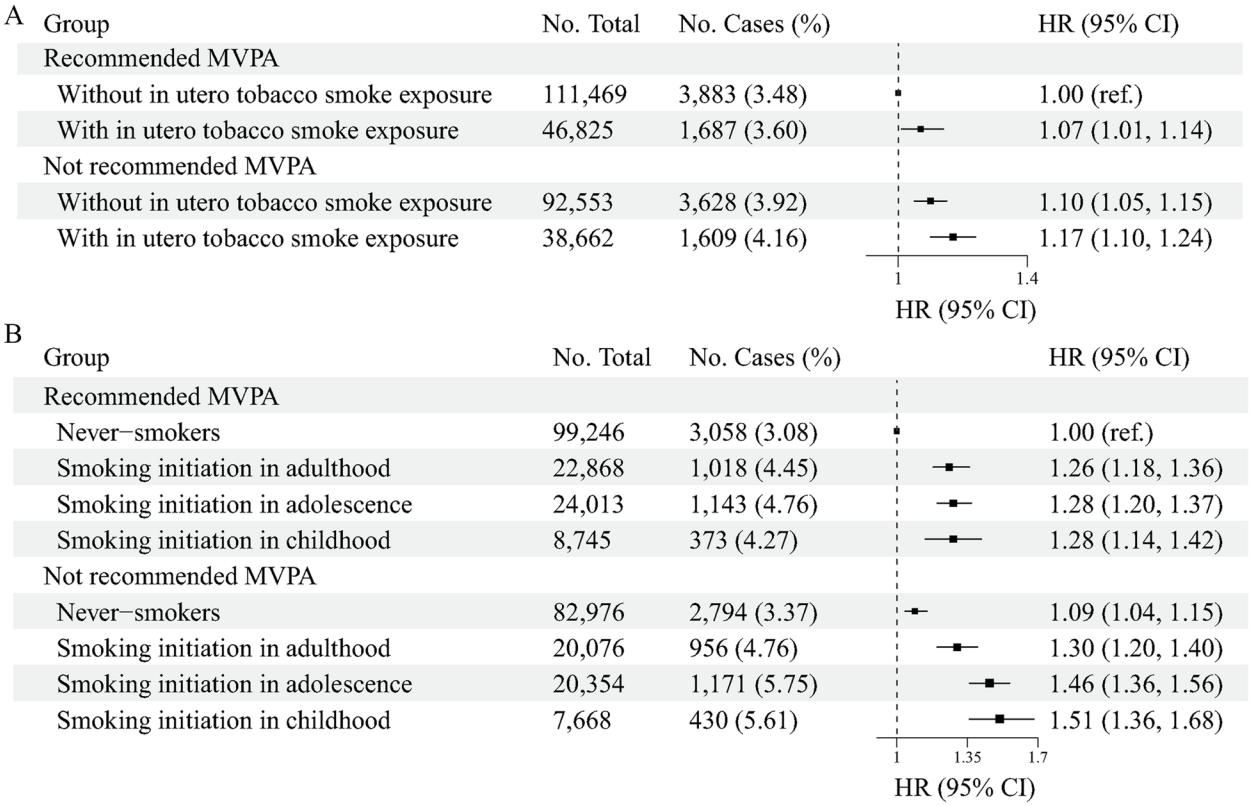

Fig. 2 Risk of incident chronic kidney disease according to in utero tobacco smoke exposure, age of smoking initiation, and physical activity. **A** Joint effects of in utero tobacco smoke exposure and physical activity on incident chronic kidney disease; **B** Joint effects of age of smoking initiation and physical activity on incident chronic kidney disease. Models were adjusted for age, sex, ethnic, body mass index, Townsend deprivation index, education level, drinking status, healthy diet score, antihypertensive drug use, insulin use, cholesterol-lowering drug use, urinary albumin to creatinine ratio, estimated glomerular filtration rate, prevalent hypertension, diabetes, and hyperlipidemia. Abbreviations: CI, confidence interval; HR, hazard ratio; MVPA, moderate-to-vigorous physical activity

analysis of in utero tobacco smoke exposure, compared to those with recommended MVPA and non-tobacco exposure, the highest risk of CKD was found in participants with tobacco smoking exposure in utero and without recommended MVPA (HR: 1.17, 95% CI: 1.10, 1.24) (Fig. 2A). In the analysis of age of smoking initiation, the highest risk of CKD was also found in participants without recommended MVPA and smoking initiation in childhood (HR: 1.51, 95% CI: 1.36, 1.68) compared with never-smokers with recommended MVPA (Fig. 2B). Results remained robustness across all sensitivity analyses (Additional file 1: Tables S5–S6).

Discussion

In this study, we demonstrated that tobacco smoking during pregnancy, childhood, adolescence, and adulthood period was significantly associated with a higher risk of CKD incidence in adulthood. In particular, the earlier participants began smoking, the greater risk of developing CKD in later life. The risk of CKD incidence increased under the combined effects of in utero tobacco smoking exposure and decreased smoking initiation age. In addition, we found that performing recommended MVPA was linked to a lower risk of CKD incidence and there were joint effects between recommended MVPA and early-life tobacco smoke exposure on CKD incidence. The highest risk of incident CKD was observed among participants without recommended MVPA and exposed to tobacco smoking during early life.

To our knowledge, this is the first study to demonstrate a significant positive association of early-life tobacco smoke exposure with an increased risk of CKD incidence in adulthood. Most of the current studies focused on the adverse effects of in utero tobacco smoke exposure on the development and function of kidneys. For example, Anblagan et al. using magnetic resonance imaging in fetuses observed that compared to non-smoking mothers, those who smoked during pregnancy had reduced fetal kidney growth [30]. Kooijman et al. reported that among school-aged children, prenatal tobacco smoking could lead to a significant decline in eGFR [31]. Due to the study population being infants or children and the shorter follow-up period, these studies failed to observe a direct association between maternal tobacco smoking during pregnancy and CKD incidence in adulthood. Our study filled this gap and confirmed the adverse effects of early-life tobacco smoke exposure on CKD incidence later in life. In addition, although previous studies have evaluated the joint effects between several behavioral factors and environmental factors on CKD [32, 33], the joint effects between early-life tobacco smoke exposure and MVPA on CKD incidence were still unclear. Our findings further emphasized the important benefits of early-life smoking cessation and adherence to guideline-recommended MVPA in the prevention of CKD occurrence.

The mechanisms underlying the relationship between early-life tobacco smoke exposure and CKD incidence in later life remain complex and unclear. Previous evidence indicated that the adverse effects of cigarette tobacco in utero might be attributed to nicotine, which penetrated the placenta and entered the fetal circulation [34, 35]. This exposure could lead to uteroplacental vasculature vasoconstriction, uteroplacental hypoperfusion, intrauterine growth restriction, and a decrease in fetal nephron numbers [36, 37], potentially increasing the risk of CKD later in life [38]. In addition, other possible mechanisms explaining the association between in utero tobacco smoke exposure and CKD incidence included reactive oxygen species production and caused mitochondrial dysfunction [36]. Previous studies suggested that reactive oxygen species production and mitochondrial dysfunction contribute to promote to epithelial-to-mesenchymal transition (EMT) in the kidneys [39, 40], a process that contributes to renal tubulointerstitial fibrosis, which was the histological hallmark of advanced CKD [41, 42]. In addition to intrauterine tobacco exposure, younger smoking initiation age may result in greater cumulative tobacco exposure dose [40]. Children and adolescents are more likely than adults to develop nicotine addiction because their brains are more sensitive to the pharmacological properties of nicotine [43]. This may further increase the cumulative dose of tobacco smoke in adulthood and lead to a higher risk of CKD. Since this is an epidemiological study, further experimental studies are warranted to validate our conclusions.

Joint effects between early-life tobacco smoke exposure and MVPA were observed in the current study, indicating that participants without recommended MVPA and exposure to tobacco smoking at an early age had a higher risk of CKD in later life. Additionally, the present study also observed that the negative effects of earlier smoking initiation age can be offset by recommended MVPA, which supports public health efforts that emphasize a healthy lifestyle of recommended MVPA for everyone, especially for individuals with early exposure to tobacco smoking. This suggests that both avoiding early exposure to tobacco smoking and strengthening MVPA may be more effective in the prevention or delay of CKD in middle-aged populations than solely targeting only one behavior. Therefore, it is necessary to encourage adherence to guideline-recommended MVPA levels to improve longevity, particularly in those exposed to tobacco smoking at an earlier age.

Our findings have important public health implications. Firstly, early-life tobacco smoke exposure has drawn much concern due to its adverse health effects.

Our study provided evidence that early-life tobacco smoke exposure could significantly increase the risk of CKD incidence in later life, highlighting the strong potential benefits of prevention and cessation of tobacco smoking early in life in reducing the risk of CKD incidence in later life. Secondly, our results suggested that the earlier individuals began smoking, the greater risk of developing CKD in later life. This emphasized the importance of protecting children/adolescents from exposure to tobacco smoke and called for smoke-free environment policies to be enforced in public places, especially in locations where these vulnerable groups frequently present. Finally, the joint effects between early-life tobacco smoke exposure and MVPA further highlighted the importance of adherence to guideline-recommended PA levels, which may help guide the improvement of personalized primary prevention strategies for CKD.

The present study has several advantages. First, the present study is conducted in well-established nationwide cohorts characterized by an extensive period of follow-up and a substantial sample size of participants from the UK, which enabled us to conduct the longitudinal and joint analyses of tobacco exposure during uterus and childhood/adolescence period on the incidence of CKD with sufficient statistical capabilities. All these findings provide public health evidence for the toxicity and pathogenicity of early exposure to tobacco smoking. Most importantly, our findings provide insight into the role of recommended MVPA in modifying the relationship of early-life tobacco smoke exposure with CKD risk. This investigation provides valuable clues to the complex relationship between environmental factors and healthy lifestyle in the progression of CKD, further enhancing our understanding of the etiology of CKD and providing important insights into personalized approaches to prevention and treatment. Besides, rigorous controls for confounding factors such as fundamental information, lifestyle, and disease history were implemented and extensive sensitivity analyses were conducted to ensure robustness and repeatability of results.

However, several limitations to this study should be mentioned. First, other information on early-life tobacco smoking, such as passive smoking and environmental tobacco smoking, was not included. This left us unable to quantify total exposure to tobacco smoking, which may have underestimated the exposure level of tobacco smoking. Second, the information on early-life tobacco smoke exposure was collected retrospectively through a questionnaire survey, which might result in recall bias and exposure misclassification. Third, although we had carefully adjusted for potential confounding factors in our analyses, we could not exclude the possibility that the results were confounded by unmeasured factors (i.e., parental socioeconomic status, maternal nutrition status, behavioral lifestyle during pregnancy, family history of CKD, maternal body size). Fourth, due to the majority of participants being Europeans, there may be limits to the generalizability of the research findings, which requires evaluating our study findings in other ethnic populations. Fifth, due to the UK Biobank could not collect information of early-life tobacco smoke exposure for all participants, we have to exclude individuals with missing data of in utero tobacco smoke exposure and age of smoking initiation, which may cause a selection bias to the findings. Sixth, it is difficult to obtain information on the mortality of the population before establishing the cohort. Finally, as the development of CKD is gradual and usually asymptomatic in the early stages of disease progression, calculating follow-up time based on CKD diagnosis date rather than CKD event date might introduce some measurement errors.

Conclusions

The current study provides new epidemiological evidence that early-life tobacco smoke exposure may increase the risk of CKD incidence in later life, and the observed associations could be modified by MVPA. The present study highlighted the adverse effects of exposure to tobacco smoking in early life on physical health, suggesting that smoking control measures should be vigorously promoted from prenatal to childhood and adolescence, especially among those without recommended MVPA, to alleviate the incidence of CKD.

Abbreviations

CKD	Chronic kidney disease
PA	Physical activity
WHO	World Health Organization
IPAQ	International Physical Activity Questionnaire
MVPA	Moderate-to-vigorous physical activity
ICD	International Classification of Diseases
UACR	Urinary albumin to creatinine ratio
eGFR	Estimated glomerular filtration rate
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
TDI	Townsend deprivation index
BMI	Body mass index
HR	Hazard ratio
CI	Confidence interval

Supplementary Information

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Supplementary Material 1.

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Authors' contributions
B.S. analyzed the data and drafted the manuscript; Y.Y. analyzed the data; H.Y. conceived and designed the study; Y.X., S.Y., X.Y., and H.L. coordinated and supervised the data analysis, M.W. reviewed and revised the manuscript; J.M. acquired the data, helped to interpret the results, contributed to the critical revision of the manuscript for important intellectual content, and is the study guarantor. All authors read and approved the final manuscript.

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Data availability
The UK Biobank resources are available from the authors upon reasonable request and can be accessed through applications on their website (https://www.ukbiobank.ac.uk/).

Declarations

Ethics approval and consent to participate
Ethical approval was obtained from the North West Multi-Center Research Ethics Committee (reference: 11/NW/0382). All participants were well-informed and signed informed consent.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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