Frequency of adding salt is a stronger predictor of chronic kidney disease in individuals with genetic risk

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The incidence of chronic kidney disease (CKD) is increasing worldwide, but there is no specific treatment available. Therefore, understanding and controlling the risk factors for CKD are essential for preventing disease occurrence. Salt intake raises blood pressure by increasing fluid volume and contributes to the deterioration of kidney function by enhancing the renin-angiotensin system and sympathetic tone. Thus, a low-salt diet is important to reduce blood pressure and prevent kidney diseases. With recent advancements in genetic research, our understanding of the etiology and genetic background of CKD has deepened, enabling the identification of populations with a high genetic predisposition to CKD. It is thought that the impact of lifestyle or environmental factors on disease occurrence or prevention may vary based on genetic factors. This study aims to investigate whether frequency of adding salt has different effects depending on genetic risk for CKD. CKD polygenic risk scores (PRS) were generated using CKDGen Consortium GWAS (N= 765,348) summary statics. Then we applied the CKD PRS to UK Biobank subjects. A total of 331,318 European individuals aged 40-69 without CKD were enrolled in the study between 2006-2010. The average age at enrollment of the participants in this study was 56.69, and 46% were male. Over an average follow-up period of 8 years, 12,279 CKD cases were identified. The group that developed CKD had a higher percentage of individuals who added salt (46.37% vs. 43.04%) and higher CKD high-risk PRS values compared to the group that did not develop CKD (23.53% vs. 19.86%). We classified the individuals into four groups based on PRS: low (0-19%), intermediate (20-79%), high (80-94%), very high (≥ 95%). Incidence of CKD increased incrementally according to CKD PRS even after adjusting for age, sex, race, Townsend deprivation index, body mass index, estimated glomerular filtration rate, smoking, alcohol, physical activity, diabetes mellitus, dyslipidemia, hypertension, coronary artery diseases, cerebrovascular diseases at baseline. Compared to the "never/rarely" frequency of adding salt group, "always" frequency of adding salt group had an increasing incidence of CKD proportionate to the degree of frequency of adding salt. However, the significant association of "always" group on incident CKD disappeared in the low PRS group. This study validated the signal from PRSs for CKD across a large cohort and confirmed that frequency of adding salt contributes to the occurrence of CKD. Additionally, it confirmed that the effect of frequency of "always" adding salt on CKD incidence is greater in those with more than intermediate CKD-PRS. This study suggests that increased salt intake is particularly concerning for individuals with genetic risk factors for CKD, underscoring the clinical importance of reducing salt intake for these individuals.

Keywords: chronic kidney disease; polygenic risk score; salt; lifestyle factors; UK Biobank

1. Introduction

With an aging population and changes in dietary habits, 10-16% of adults are experiencing chronic kidney disease (CKD)[1, 2]. CKD increases the incidence of cardiovascular disease and raises mortality rates, posing a threat to human health. However, aside from controlling the underlying causes, there is no definitive treatment for CKD, making it difficult for patients to be free from the disease once diagnosed. The causes of CKD are highly variable, and the heterogenous genetic backgrounds make it challenging to pinpoint the genetic predisposition for CKD[3]. While Genome-Wide Association Studies (GWAS) provide with information on thousands of candidate genetic variants associated with diseases, the individual contribution of each genetic variant to the disease is very small, making clinical application difficult. However, polygenic risk score (PRS) analysis allows us to effectively utilize GWAS results by analyzing the cumulative effect of all common variants and their correlation with disease occurrence. Several studies have used PRS to predict disease occurrence and stratify the genetic risk to enhance traditional factors in diabetes, heart disease, and obesity using PRS[4-7]. Despite high heritability, genetic factors offer relatively low predictive ability for CKD[8]. Nevertheless, Khan et al. developed a strong CKD PRS based on meta-analyzed GWAS studies using good quality medical data on large-sized populations across ancestries[9]. They demonstrated a reproducible and high-performing PRS to predict the incidence of CKD, which was consistent across various ancestries.

Lifestyle factors have also been known to play a crucial role in the development and progression of CKD. High physical activity reduces the risk of obesity, metabolic diseases, and cardiovascular diseases, and contribute to alleviating CKD[10, 11]. Excessive salt intake increases fluid volume in the body and stimulates the renin-angiotensin system (RAS) and the neurohormonal system, leading to hypertension, which increases the risk of CKD[12]. Therefore, reducing salt intake is critical not only for preventing and managing hypertension and heart disease, but also for preventing and controlling CKD. However, there are conflicting results on the relationship between salt intake and CKD[13, 14]. Accurately assessing the amount of salt consumed is challenging, so most studies indirectly estimate salt intake based on the amount of salt excreted in urine. Urine salt excretion is influenced by expression and activation of numerous renal tubular transporters and is intertwined with neurohormonal factors that control them[15]. This regulatory system can change based on age, sex, underlying diseases, and medications. Therefore, it is difficult to assert that measuring the amount of salt in urine accurately reflects the amount of salt consumed. Consequently, there have not been many studies clearly elucidating the relationship between CKD and salt intake. In the UK Biobank, participants were surveyed about adding salt to their meals, and it was found that adding salt increases the risk of cardiovascular disease, diabetes, premature mortality, and induces CKD[16-19]. However, it has not yet been clear how the salt affects the incidence of CKD in groups with high versus low genetic risk for the CKD. For CKD, which has such diverse and complex genotypes and phenotypes, personalized and customized precision medicine is crucial. This study focuses on precision medicine to examine how various dietary habits influence disease manifestation within different genetic environments. Therefore, this study aimed to develop a CKD PRS model and apply it to the UK Biobank population to identify individuals at high risk of developing CKD[20] (**Figure**

1). Additionally, we conducted a stratified analysis based on genetic risk factors to determine the extent to which adding salt contributes to CKD development in association with CKD genetic risks.

2. Methods

2.1. *Study population*

The UK Biobank is a large, prospective observational cohort study designed to improve the prevention, diagnosis, and treatment of various illnesses and to promote health[21]. Between 2006 and 2010, the study recruited over 500,000 adults aged 40 to 69 years from 22 assessment centers across England, Scotland, and Wales. Participants provided written informed consent, allowing their data and samples to be used for medical research. Initial recruitment included taking baseline measurements such as social demography, lifestyle, health information, and physical assessments through touch-screen questionnaires and direct physical measurements. Further information on UK Biobank is available in a previous study[21]. In this study, we included only 409,384 participants who had their genetic ethnicity identified as 'Caucasian'. Furthermore, we filtered out participants for whom genetic data was unavailable or did not meet quality control criteria, resulting in 377,186 participants. We further removed 39 participants who had missing salt intake information and 33,550 participants who had prevalent CKD at baseline, leading to a final sample size of 343,597.

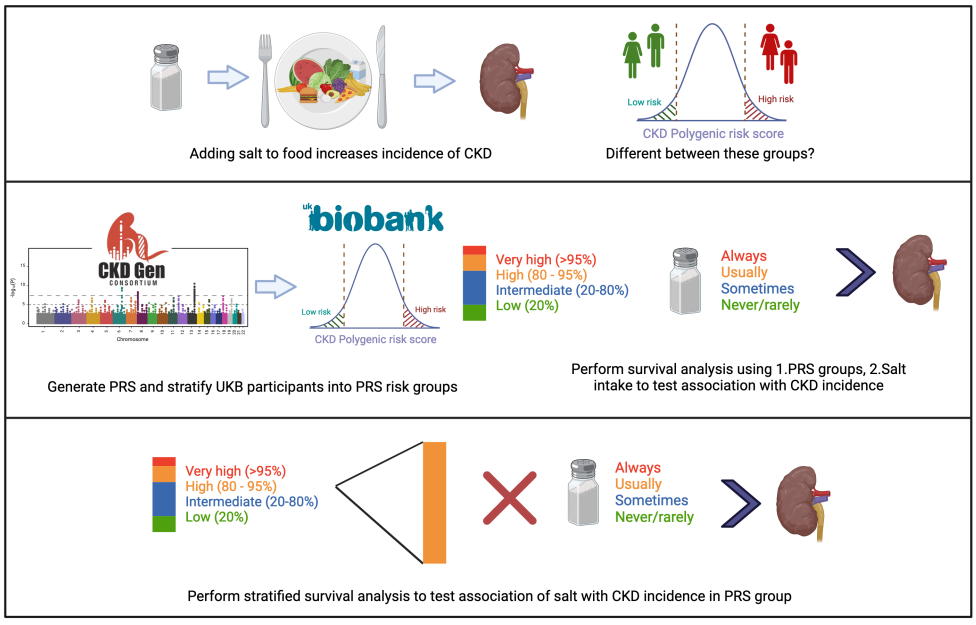

Figure 1. Study overview for assessment of the association between salt intake and CKD incidence across polygenic risk score (PRS) groups.

2.2. *Genotyping and quality control*

The genotyping process utilized by the UK Biobank has been comprehensively described in prior publications[21]. In summary, 487,409 samples were genotyped using the Affymetrix UK BiLEVE

Axiom Array and the Affymetrix UK Biobank Axiom Array (Thermo Fisher Scientific, Waltham, MA). Samples flagged for poor quality by the UK Biobank were excluded. To eliminate related samples, a greedy algorithm was employed to retain the minimal number of samples among second-degree or closer relationships. Given the predominantly European ancestry of the UK Biobank participants, we included only those with 'White British' ancestry. This classification was based on the UK Biobank showcase data field "Genetic ethnic grouping," which identifies participants who self-reported as 'White British' and exhibited very similar genetic ancestry according to principal component (PC) analysis. Samples with discrepancies between reported sex and genetically inferred sex were also excluded. For variant quality control (QC), variants were filtered out if they had an info score of <0.3 or a minor allele frequency (MAF) of <0.01. After applying these QC measures, 377,186 samples and 9,505,768 variants were included in the final dataset used in this study.

2.3. *Polygenic risk score for chronic kidney disease*

The PRS for CKD was generated using Chronic Kidney Disease Genetics (CKDGen) Consortium meta-analysis summary statistics available at https://ckdgen.imbi.uni-freiburg.de/datasets[20]. We generated PRS weights using PRS-CS[22]. PRS-CS leverages summary statistics from GWAS and linkage disequilibrium (LD) information from a reference panel, applying a Bayesian framework to estimate effect sizes. Using the weights generated by PRS-CS, we generated CKD PRS scores for 377,186 samples.

2.4. *Definitions of chronic kidney disease*

In this study, we defined both prevalent and incident CKD. Incident CKD was defined using the tenth Revision (ICD-10) codes and Office of Population Census and Surveys Classification of Interventions and Procedures, version 4 (OPCS-4) codes from primary care data, hospital inpatient data, and death register records[19]. Detailed information for CKD assessment is provided in the Supplementary Table 1. Prevalent CKD was defined as having CKD diagnosis based on the above criteria before first visit to the UK Biobank assessment center. The participants were also considered prevalent CKD if their estimated glomerular function (eGFR) was lower than 60 ml/min per 1.73m^2 or having albuminuria over 30 mg/gCr at baseline measurement. The eGFR was measured using the CKD-EPI Creatinine-Cystatin Equation 2021 with serum creatinine and cystatin C [23]. The follow-up time for the incident CKD cases was calculated from the baseline (first visit to the assessment center) to whichever date came first: diagnosis of CKD, death, date from when a person was lost to follow-up, or May 2017, last date when the “Date lost to follow-up” in UK Biobank was updated. All the events after May 2017 were ignored.

2.5. *Exposure assessment*

The frequency of adding salt phenotype in the UK Biobank was assessed through self-reported dietary questionnaires completed by participants at baseline. Specifically, participants were asked "Do you add salt to your food? (Do not include salt used in cooking)". They were asked to provide an average considering their intake over the last year. The response options included “never/rarely”, “sometimes”, “usually”, “always” and “prefer not to answer”. The “prefer not to answer” was coded as -3 and we removed all participants who selected this option.

2.6. *Covariates ascertainment*

We adjusted for a comprehensive range of covariates to ensure the robustness of our models. These covariates included age, sex, Townsend deprivation index, body mass index (BMI), eGFR, smoking status, alcohol consumption, physical activity, diabetes, dyslipidemia, hypertension, coronary heart disease, and ischemic stroke. Age was determined at the time of assessment, and sex was identified based on genetic information provided by the UK Biobank. The Townsend deprivation index and BMI data were sourced directly from the UK Biobank. Smoking and alcohol consumption statuses were reclassified to current smoker or drinker by combining the "Never" and "Previous" categories. Physical activity was quantified based on achieving either 150 minutes or more per week of moderate intensity, 75 minutes or more per week of vigorous activity, or an equivalent combination[19]. Conditions such as diabetes, dyslipidemia, hypertension, coronary heart disease, and ischemic stroke were defined based on self-reports, ICD-10, and OPCS-4 codes from primary care data, hospital inpatient data, and death register records, as detailed in Supplementary Table 1. For continuous variables, we employed mean imputation to address missing values, and a missing indicator was used for categorical covariates[19].

2.7. *Statistical analysis*

The demographic characteristics of cases and non-cases were evaluated for differences using chi-square tests for categorical variables and independent t-tests for continuous variables. All samples were divided into four groups based on the PRS scores: low (0–19th percentile), intermediate (20–79th percentile), high (80–94th percentile), and very high (>95th percentile).
We conducted three analyses:
1. The association of PRS groups with incident CKD.
2. The combined association of frequency of adding salt and PRS groups with incident CKD.
3. The association of frequency of adding salt with incident CKD, stratified by PRS groups.

For each analysis, we used three models to adjust for various confounding factors:
- Model 1: Adjusted for age and sex.
- Model 2: Adjusted for all variables in model 1, plus Townsend deprivation index, BMI, eGFR, smoking, alcohol consumption, and physical activity.
- Model 3: Adjusted for all variables in model 2, plus diabetes, dyslipidemia, hypertension, coronary artery disease, and ischemic stroke. All variables were measured at baseline.

We calculated hazard ratios (HRs), 95% confidence intervals (CIs), and p-values using univariate and multivariate Cox proportional hazards models, with follow-up time as the time scale to estimate the associations between frequency of adding salt, PRS, and CKD risk. Schoenfeld residuals were used to assess the proportional hazards assumption. Sex was found to violate the proportional hazards assumption ($P = 0.003$ in Model 3); therefore, we stratified all models by sex using the `strata` function, which allows the baseline hazard functions to differ across strata (levels of a categorical variable) while keeping the coefficients for other covariates constant across these strata. In Model 3, we also observed that age slightly violated the proportional hazards assumption ($P = 0.045$). Thus, we modeled age using a penalized smoothing spline with degree 2. After stratifying by sex and modeling age, there was no further violation of the proportional hazard assumption, as

confirmed by Schoenfeld residuals (Supplementary Table 2). The significance of trend was calculated using Jonckheere-Terpstra trend test.

3. Results

3.1. *The baseline characteristics of incident chronic kidney disease population*

The study sample included 331,318 non-CKD participants and 12,279 participants with incident CKD. **Table 1** presents the baseline characteristics of the incident CKD group compared to the non-CKD population. Individuals in the incident CKD group were more likely to fall into the higher PRS categories. Participants with incident CKD had higher prevalence rates of adding salt to their food. Among CKD cases, 53.64% reported "never/rarely" adding salt, 28.14% reported "sometimes," 12.79% reported "usually," and 5.44% reported "always." In contrast, non-CKD participants showed a distribution of 56.95%, 27.62%, 11.2%, and 4.22% for the same categories. Sex distribution showed a higher percentage of males in the incident CKD group (52.54%) compared to the non-CKD group (45.48%). The Townsend deprivation index also indicated higher levels of deprivation in the CKD group (mean = -1.36, SD = 3.07) compared to the non-CKD group (mean = -1.62, SD = 2.9). Additionally, higher prevalence rates of hypertension (74.99%), diabetes (12.54%), dyslipidemia (30.33%), and coronary heart disease (16.42%) were observed in the incident CKD group, compared to the non-CKD group with rates of 58.64%, 4.39%, 15.97%, and 6.32% respectively. The mean eGFR was significantly lower in the incident CKD group (86.11, SD = 13.92) compared to the non-CKD group (96.13, SD = 12.47). Additionally, smoking rates were slightly higher in the incident CKD group (10.51%) than in the non-CKD group (9.76%).

Table 1. Baseline Characteristics for incident CKD and Non-CKD population.

	Non-CKD	Incident CKD	P
N	331318	12279	
PRS risk			
Low	66564 (20.09)	2157 (17.57)	< 0.001
Intermediate	198928 (60.04)	7233 (58.91)	0.012
High	49444 (14.92)	2091 (17.03)	< 0.001
Very high	16382 (4.94)	798 (6.5)	< 0.001
Salt intake			
Never/rarely	188689 (56.95)	6586 (53.64)	< 0.001
Sometimes	91515 (27.62)	3455 (28.14)	0.213
Usually	37120 (11.2)	1570 (12.79)	< 0.001
Always	13994 (4.22)	668 (5.44)	< 0.001
Age (SD)	56.54 (7.94)	60.65 (6.81)	< 0.001
BMI (SD)	27.21 (4.61)	28.71 (4.98)	< 0.001
Sex			
Male	150678 (45.48)	6451 (52.54)	< 0.001

Female	180640 (54.52)	5828 (47.46)	< 0.001
Townsend deprivation index (SD)	-1.62 (2.9)	-1.36 (3.07)	< 0.001
Hypertension	194297 (58.64)	9208 (74.99)	< 0.001
eGFR (SD)	96.13 (12.47)	86.11 (13.92)	< 0.001
Smoking	32344 (9.76)	1290 (10.51)	0.007
Diabetes	14561 (4.39)	1540 (12.54)	< 0.001
Dyslipidemia	52926 (15.97)	3724 (30.33)	< 0.001
Coronary heart disease	20932 (6.32)	2016 (16.42)	< 0.001
Alcohol	311022 (93.87)	11135 (90.68)	< 0.001
Physical activity	211697 (63.9)	7097 (57.8)	< 0.001

3.2. *Chronic kidney disease occurred more in the very high-PRS group*

Categorizing PRS into risk groups revealed significant incremental trend of incident CKD across the PRS categories (P = 0.00023, **Figure 2a**). Incident CKD was significantly higher among subjects in the top 5% of PRS compared to those in other PRS groups. The hazard ratio (HR) of incident CKD for the top 5% PRS group was 1.50 (CI = 1.38 – 1.62, p-value < 2e-16) in the univariate analysis, and 1.52 (CI = 1.41 – 1.65, p-value < 2e-16) in the multivariate Cox proportional hazards model adjusting for age and sex (model 1). Even though the HR decreased when additional predictors were included in Models 2 and 3 of the Cox model, the very high PRS group still showed significantly high HR values for incident CKD (**Figure 2b,** Supplementary figure 1-3).

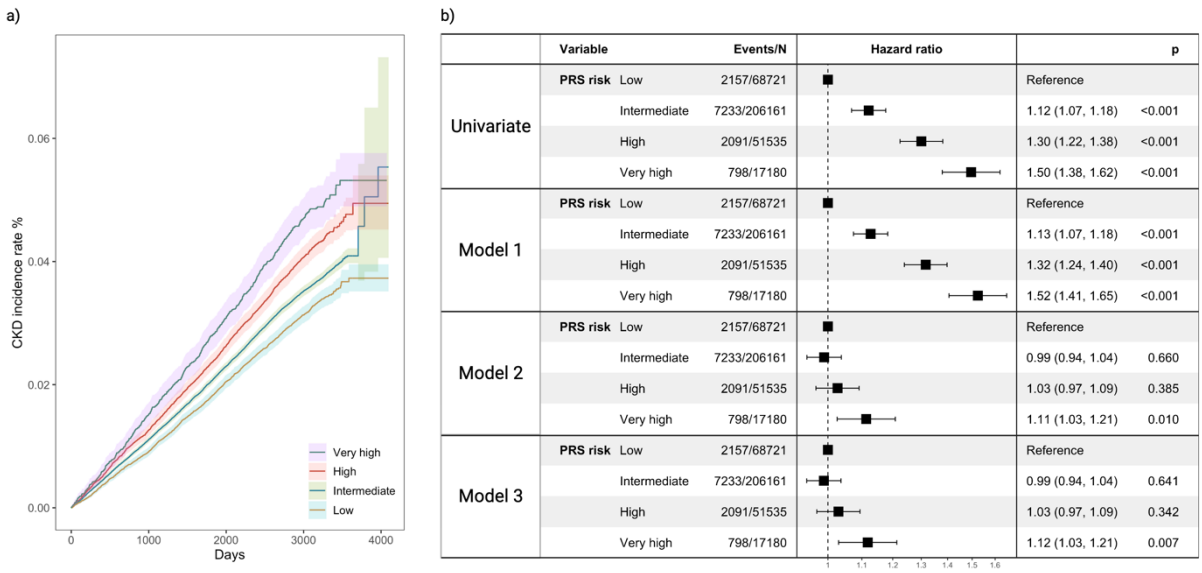

Figure 2. a) Cumulative incidence of CKD stratified by PRS groups b) Hazard ratios for PRS risk groups in different models. Model 1 includes sex and age; Model 2 adds TDI, BMI, eGFR, smoking, alcohol consumption, and physical activity; Model 3 further adds diabetes, dyslipidemia, hypertension, coronary artery disease, and ischemic stroke as covariates.

3.3. *The Frequency of adding salt contributed to incidence of chronic kidney disease*

To determine if frequency of adding salt is associated with CKD incidence, we evaluated all the 4 cox models, indicating a clear positive association between the frequency of adding salt and the incidence of CKD (Figure 3, Supplementary figure 4-6). In the univariate analysis, the HR for CKD incidence increased significantly with higher frequency of adding salt, with the "always" category showing the highest HR of 1.36. In Model 1, which adjusted for age and sex, the HRs remained

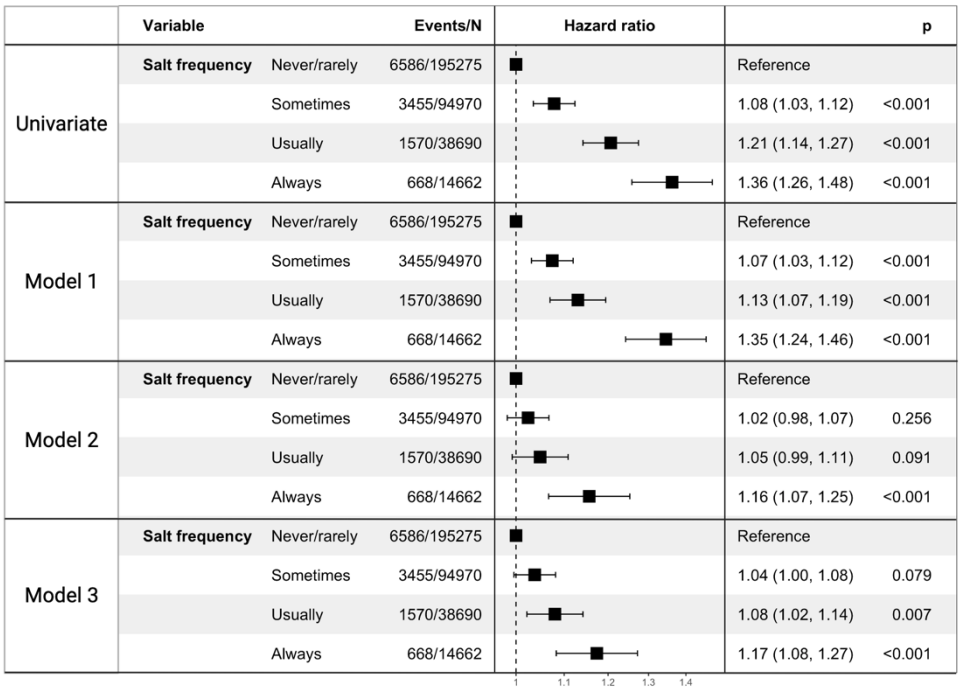

Figure 3. Hazard ratios for salt addition for all models. Model 1 includes sex and age; Model 2 adds TDI, BMI, eGFR, smoking, alcohol consumption, and physical activity; Model 3 further adds diabetes, dyslipidemia, hypertension, coronary artery disease, and ischemic stroke as covariates.

significant for all frequency of adding salt, though reduced, with the "always" category having an HR of 1.35. In Model 2, which included additional variables, the significance for the "sometimes" category diminished (P = 0.256), but the "always" categories remained significantly associated with higher CKD incidence, with HR of 1.16. Finally, in Model 3, which comprehensively adjusted for various predictors, the "sometimes" category was borderline significant (P = 0.079), while the "usually" and "always" categories continued to show significant associations with increased CKD incidence, with the highest HR of 1.17 for the "always" category. These results underscore that more frequency of adding salt is consistently linked to a higher risk of developing CKD (trend P = 0.0028). We also conducted an analysis using PRS as a continuous variable instead of categorical PRS groups as covariates and found similar results (Supplementary figure 7). No significant interaction was observed between PRS score and the frequency of adding salt.

3.4. *The effect of adding salt on incident chronic kidney disease was only significant in those with more than intermediate polygenic risk*

Finally, we stratified individuals by PRS risk groups and evaluated all the Cox models, to check how frequency of adding salt to food is associated with CKD incidence in each of the PRS groups (**Figure 5**, Supplementary figure 8-11). The stratified analysis of frequency of adding salt by PRS

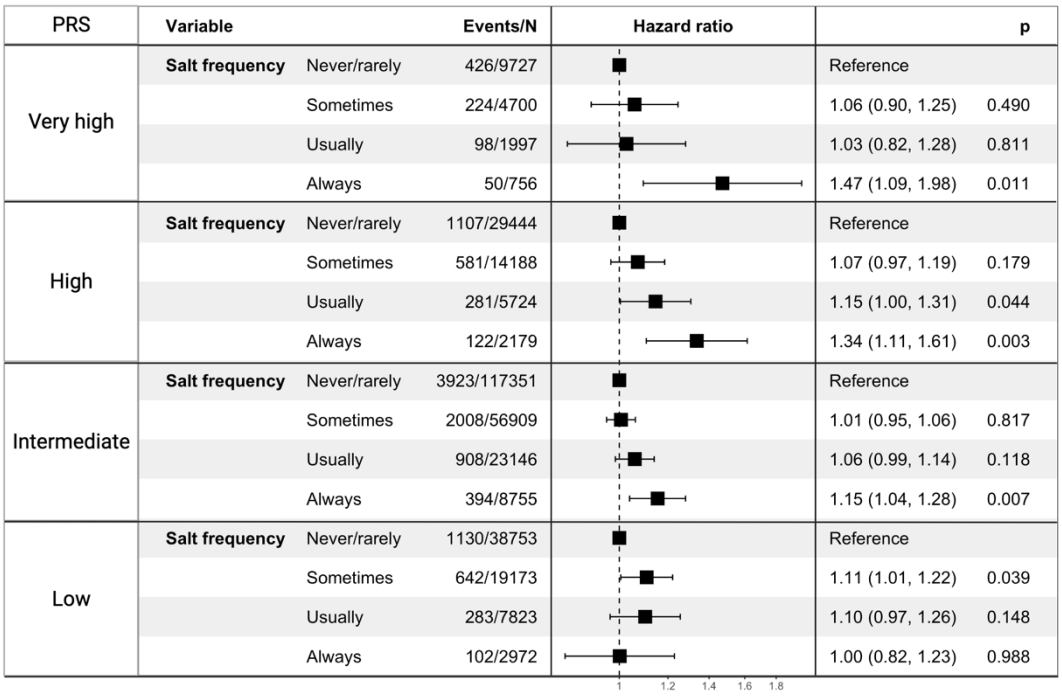

Figure 4. Hazard ratios from model 3 for Salt intake stratified by PRS risk. Model 3 includes age, sex, TDI, BMI, eGFR, smoking, alcohol consumption, physical activity, diabetes, dyslipidemia, hypertension, coronary artery disease, and ischemic stroke

categories revealed significant associations with CKD incidence in several groups. In the very high PRS category, the HR for "always" adding salt to food was significantly elevated (HR = 1.47, CI = 1.09 - 1.98, P = 0.01), indicating increased CKD risk. Similarly, in the high PRS group, both "usually" (HR = 1.15, CI = 1.00 - 1.31, P = 0.04) and "always" (HR = 1.34, CI = 1.11 - 1.61, P = 0.003) adding salt were significantly associated with higher CKD incidence. In the intermediate PRS group, "always" adding salt was also significantly associated with increased CKD risk (HR = 1.15, CI = 1.04 - 1.28, P = 0.007). The low PRS category showed a significant association for "sometimes" adding salt (HR = 1.11, CI = 1.01 - 1.22, P = 0.039), but not for "always" adding salt (HR = 1.00, CI = 0.82 - 1.23, P = 0.988). Overall, the data suggests that "always" frequency of adding salt group is associated with increased CKD risk, especially in individuals with higher genetic predisposition (intermediate, high, and very high PRS categories). There was increasing trend in high PRS (P = 0.049) and intermediate PRS group (P = 0.033), but the trend was not significant in very high PRS group (P = 0.21) and low PRS group (0.12).

4. Discussion

Individuals with a very high CKD PRS showed a significantly higher incidence of CKD, even after adjusting for other contributing factors. The addition of salt to their diet increased the incidence of CKD in proportion to the frequency of salt addition. However, in populations with a low genetic risk for CKD, the effect of adding salt on CKD generation was mitigated. In contrast, in populations with more than intermediate PRS, the incident CKD was exacerbated incrementally by the higher genetic risk.

Genetic studies have estimated the heritability of kidney diseases to between 30-75% through family studies and have identified several critical genetic loci associated with CKD, including *SHROOM3*, *UMOD,* and solute carriers[24-28]. However, most kidney diseases are etiologically complex and heterogenous, making it difficult to identify clear causal pathways and common susceptible genes. The most common causes of CKD are diabetes and hypertension, so CKD often arises as a secondary complication due to these other diseases rather than from primary kidney issues[29]. Both diabetes and hypertension have diverse genetic backgrounds, and the genetic background of kidney damage resulting from these conditions can vary depending on the underlying cause and the stage of the disease. For complex diseases that cannot be explained by candidate genes, PRS aggregates the associations of numerous single nucleotide polymorphisms (SNPs) associated with the disease or trait for a large population. Therefore, a well-validated PRS is a valuable tool for understanding the genetic background of CKD and stratifying risk factors. This study utilized meta-analysis GWAS data generated from SNPs associated with eGFR levels below 60 ml/min per $1.73m^2$ [20]. One of the challenges of optimizing PRS is its application to diverse ancestries with significantly different genetic backgrounds. African ancestry individuals have a higher risk for developing CKD than the other population because they tend to have high-risk alleles in the *APOL1* gene[30]. For this reason, we did not include the small portion of African ancestry in UK Biobank. Finally, when we applied the PRS to the enrolled UK Biobank population in this study, a significant association with actual CKD incidence was found. CKD occurrence proportionally increased with higher PRS, but the predictive power was markedly augmented in the population of top 5% PRS, even after adjusting for many critical CKD risk factors. In line with our study, the extreme tail with the top 1-5% CKD PRS showed about a threefold increase in incident CKD[9].

Dietary salt is known to elevate blood pressure, particularly in individuals with hypertension, those over the age of 55, and those consuming more than 4g of sodium daily[31]. Salt sensitivity refers to the physiological response to blood pressure with sodium intake. In salt sensitive individuals, kidneys retain more sodium by up-regulating the sodium transporters, increasing sympathetic nervous tone, and activating RAS, which leads to higher blood pressure and increased risk of cardiovascular diseases[32]. Elderly individuals, African Americans, and those with CKD are more likely to be salt-sensitive[33]. Our study found that individuals who developed CKD had a significantly higher frequency of adding salt to their food compared to those who did not develop CKD. The "always" frequency of adding salt was significantly associated with the occurrence of CKD. However, this association was observed in the high and intermediate CKD-PRS groups but not in

the low PRS group, where the "always" frequency of adding salt did not show a significant association with CKD incidence. The kidneys play a significant role in blood pressure regulation, and conversely, hypertension can worsen kidney disease. Additionally, both hypertension and CKD share common genetic factors to a considerable extent[34, 35]. Kidney aging also contributes to salt sensitivity by increasing the activation of sodium channels in renal tubules[36]. Therefore, it is hypothesized that populations with genetic variants related to salt sensitivity or renal aging may experience an increased incidence of CKD due to up-regulation of salt sensitivity. Experimental models revealed several candidate genes that increased salt-sensitivity and induce kidney damage, suggesting renal tubular sodium transporters could be involved in the pathogenesis[37, 38]. For those with CKD, reducing salt intake not only helps lower blood pressure but also reduces proteinuria and improves composite kidney outcomes[39, 40]. This study suggests that frequency of adding salt is particularly concerning for individuals with genetic risk factors for CKD, highlighting the clinical importance of reducing salt intake for these individuals. This study has some limitations. The precise amount of salt intake was not available, as we only had information on the frequency of adding salt to meals, which could introduce bias. However, the frequency of adding salt has been shown to be correlated with the 24-hour urinary sodium excretion[17, 41]. n Models 2 and 3, significant hazard ratios were only observed in the 'Very high' PRS-CKD group (Figure 3) and for the 'Usually' or 'Always' frequency of adding salt (Figure 4). This may be due to the inclusion of covariates that are strong predictors of the outcome, which absorb part of the risk previously attributed to PRS or salt frequency alone, reducing the significance of their associations. Additionally, some of these covariates may be masking the true effects of PRS or salt frequency, as they could act as mediators in the causal pathway. In addition, this study did not collect national health insurance data, so the incidence of CKD was only identified through self-report, ICD codes and follow-up eGFR values. This limitation may have led to the underestimation of the actual number of CKD cases. Although we adjusted for socioeconomic status and some lifestyle factors, unmeasured factors may still confound the association. We were also unable to replicate our findings in other datasets due to the lack of comparable definitions of salt intake.

This study developed and validated a PRS for predicting CKD and analyzed how the frequency of adding salt, a crucial trigger, impacts individuals based on their genetic risk factors. While salt restriction has long been considered a vital lifestyle factor in CKD management, this study demonstrated that the influence of frequency of adding salt is more pronounced in individuals with higher genetic risk. Looking ahead, it is anticipated that personalized salt intake recommendations based on genetic risk will become available, allowing for more tailored and effective lifestyle interventions for individuals.

Acknowledgement

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Supplementary Material https://biomedinfolab.s3.amazonaws.com/supp/CKD_salt_supp.pdf

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