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ORIGINAL ARTICLE

Dietary Sodium Intake and Risk of Incident Type 2 Diabetes

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Abstract

Objective: To fill the knowledge gap of the relation between long-term dietary sodium intake and type 2 diabetes (T2D), we evaluate the association between the frequency of adding salt to foods, a surrogate marker for evaluating the long-term sodium intake, and incident T2D risk.

Methods: A total of 402,982 participants from UK Biobank (March 13, 2006 − October 10, 2010) who were free of diabetes, chronic kidney disease, cancer, or cardiovascular disease at baseline, and had completed information on adding salt were analyzed in this study.

Results: During a median of 11.9 years of follow-up, 13,120 incident cases of T2D were documented. Compared with participants who "never/rarely" added salt to foods, the adjusted HRs were 1.11 (95% CI, 1.06 to 1.15), 1.18 (95% CI, 1.12 to 1.24), and 1.28 (95% CI, 1.20 to 1.37) across the groups of "sometimes," "usually," and "always," respectively (P-trend<.001). We did not find significant interactions between the frequency of adding salt to foods and baseline hypertension status and other covariates on the risk of incident T2D. The observed positive association was partly mediated by body mass index, waist to hip ratio, and C-reactive protein, with a significant mediation effect of 33.8%, 39.9%, and 8.6%, respectively. The significant mediation effect of body mass index was largely driven by the body fat mass rather than the body fat-free mass.

Conclusion: Our findings for the first time indicate that higher frequency of adding salt to foods, a surrogate marker for a person's long-term salt taste preference and intake, is associated with a higher T2D risk.

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Sodium intake is essential to human health by serving several physiological functions including maintaining fluid balance, maintaining cellular homeostasis, and nutrient absorption.[1] Substantial evidence from observational studies, animal studies, and clinical trials has well shown that high sodium consumption is a major dietary risk factor for hypertension.[2-4] Type 2 diabetes (T2D) and hypertension often coexist and share many common risk factors, such as obesity, insufficient physical activity, and unhealthy diet.[5,6] However, very few studies have investigated the association of sodium intake with T2D risk, largely due to the lack of reliable measurements of dietary sodium.[7,8] To our knowledge, only two previous studies from a Finnish cohort have prospectively evaluated such association and found a J-shaped association between a single day's 24-hour urinary sodium excretion and T2D risk (ie, both high and low sodium intakes were associated with higher T2D risk compared with moderate sodium intake).[9,10]

Notably, sodium intakes vary widely from day to day. However, a single day's urine collection, which is the most common method for evaluating sodium intake, is inadequate to evaluate an individual's usual consumption levels.[7,8] The lack of assessment methods that can assess long-term dietary sodium intake is an important reason for the inconsistent results of sodium intake

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and disease outcomes in previous studies.[7,8] Intriguingly, our recent studies and several previous studies have found that the frequency of adding salt to foods (usually at the table) not only is a useful measure of discretionary sodium intake, but also reflects a person's long-term salt taste preference and sodium intake in Western diet.[11-14] We found a graded association between frequency of adding salt to foods and concentration of estimated 24-hour sodium excretion. Moreover, we also found the frequency of adding salt to foods was significantly related to risks of premature mortality and cardiovascular diseases.[13,14] Taken together, these results indicate that the frequency of adding salt to foods may be an effective surrogate marker for evaluating the long-term sodium intake. No study has examined whether the frequency of adding salt to food is related to T2D risk in the prospective settings.

In this study, we evaluated the associations between the frequency of adding salt to foods and the risk of T2D in 402,982 adults from the UK Biobank study. Moreover, previous evidence has shown that high sodium intake may induce obesity and high levels of inflammation, and both are closely related to T2D risk.[15-17] Thus, we also investigated whether the association between adding salt and T2D risk was mediated by adiposity or inflammation using mediation analyses.

METHOD

Study Design and Population

The UK Biobank is a prospective population-based study. Individuals volunteered to participate at the 22 assessment centers and were registered with the UK National Health Service. More than 500,000 participants from 37 to 73 years of age were recruited at baseline from 2006 to 2010. A total of 402,982 participants were included in this study by excluding participants who had incomplete data on the frequency of adding salt to foods at baseline (n=1126) and those who had prevalent diabetes, cardiovascular disease, chronic kidney disease, or cancer at baseline (n=98,379). All participants provided written informed consent, and the study was approved by the North West Multi-centre Research Ethics Committee and the Tulane University Biomedical Committee Institutional Review Board.

Exposure Assessment

The baseline information on the frequency of adding salt to foods was collected by using a touch-screen questionnaire. Participants were asked "Do you add salt to your foods? (Do not include salt used in cooking)." One of five options was selected by each participant, including (1) never/rarely; (2) sometimes; (3) usually; (4) always; or (5) prefer not to answer. Participants who choose "prefer not to answer" were assigned to missing value and then excluded from the analysis. In addition, participants were also asked "Have you made any major changes to your diet in the last 5 years?" One option was selected from the following: (1) no; (2) yes, because of illness; (3) yes, because of other reasons; or (4) prefer not to answer.

Urine samples (a random urinary spot) were collected at baseline. The urinary sodium and potassium were measured by the ion selective electrode method (potentiometric method) using Beckman Coulter AU5400, UK Ltd. Details of assays and quality control information for the urinary sodium and potassium are available elsewhere.[18] The 24-hour sodium excretion was estimated from the casual (spot) urinary concentration values based on the INTERSALT (International Cooperative Study on Salt and Blood Pressure) equations according to age, sex, sodium, creatinine, and body mass index (BMI).[19,20]

Covariates Assessment

A touch-screen questionnaire was used to assess the potential confounders at baseline, including age, sex, Townsend deprivation index, education level, income, smoking status (never, past, and current), physical activity, and drinking status (never, past, and current). Townsend deprivation index is a composite measure of deprivation based on unemployment, non-car ownership, non-

home ownership, and household overcrowding; a negative value represents high socioeconomic status.[21] Levels of educational attainment was classified into six levels, no qualifications, Certificate of Secondary Education or Ordinary Levels/General Certificate of Secondary Education or equivalent, Advanced Levels/Advanced Subsidiary Levels or equivalent, other professional qualification, National Vocational Qualification or Higher National Certificate or equivalent, or college or university degree. Total household income before tax was collected based on five groups: less than £18,000, £18,000—£29,999, £30,000—£51,999, £52,000—£100,000, and greater than £100,000. Regular physical activity was defined as 150 minutes or more of moderate intensity activity per week or greater than or equal to 75 minutes of vigorous activity per week or an equivalent combination per week. Standing height was measured using a Seca 202 height measure. Waist and hip circumference were measured at the levels of umbilicus and at the widest point by trained technicians. Weight and body composition were measured by the Tanita BC-418MA body composition analyzer which implemented bioelectrical impedance method. Body mass index was calculated as weight in kilogram divided by height in meters squared (kg/m^2), and the ratio of waist and hip circumference was calculated as waist circumference divided by hip circumference. C-reaction protein (CRP) was measured by immunoturbidimetric method using Beckman Coulter AU5800. High cholesterol was defined as a self-reported history of high cholesterol or taking medications. Hypertension was defined as a self-reported history of hypertension or a systolic blood pressure greater than or equal to 140 mm Hg or a diastolic blood pressure greater than or equal to 90 mm Hg or taking antihypertensive medications. The Dietary Approaches to Stop Hypertension (DASH) diet was evaluated in 155,328 participants who had complete data on dietary information and had realistic total energy intake (eg, 500—3500 kcal/d in women and 800—4000 kcal/d in men). Other details of the DASH diet and information on the 24-hour dietary recalls are described in the Supplementary Materials (available online at http://www.mayoclinicproceedings.org).

Outcome Assessment

Information on the diagnosis of T2D events were collected through medical history and linkage to data on hospital admissions, questionnaire, and the death register. The outcome is T2D which was defined according to the International Classification of Diseases 10th Revision code E11. Follow-up time was calculated from the date of baseline to diagnosis of outcome, death, or the censoring date (May 23, 2021), whichever occurred first. Detailed information on the ascertainment of outcomes is available online.[22]

Statistical Analysis

Linear regression model was used to evaluate the association between the frequency of adding salt to foods and concentrations of estimated 24-hour sodium excretion. Hazard ratios and 95% CIs were estimated in Cox proportional hazards models to evaluate the associations of the frequency of adding salt to foods and urinary biomarkers with the risk of T2D, with person-years (ie, calendar time) of follow-up as the underlying time metric. The proportional hazards assumption was tested by Kaplan-Meier method and Schoenfeld residuals, and all analyses were satisfied. Concentrations of spot urinary sodium and potassium were log-transformed before subsequent analyses to normalize the data distribution. Several covariates were adjusted in the models including age, sex, race/ethnicity, Townsend deprivation index, education level, income, smoking status, alcohol drinking, physical activity, and high cholesterol. We also conducted several sensitive analyses: (1) further adjustment for potential mediators including BMI and CRP; (2) further adjustment for hypertension; (3) we repeated the main analysis by excluding participants who had changed their diet in last 5 years due to illness or other reasons to control the impact of diet change; (4) further

TABLE 1. Baseline Characteristics According to the Frequency of Adding Salt to Foods[a]

Characteristics	Frequency of adding salt to food			
	Never/rarely	Sometimes	Usually	Always
n	223,762	113,319	46,636	19,265
Age, y (SD)	55.7 (8.1)	55.6 (8.1)	56.2 (8.1)	55.1 (8.3)
Female, %	57.2	54.9	49.9	52.3
White, %	96.7	93.6	93.6	87.3
BMI, kg/m^2 (SD)	26.9 (4.5)	27.3 (4.6)	27.5 (4.6)	27.7 (4.9)
Townsend deprivation index	−1.6 (3.0)	−1.3 (3.1)	−1.2 (3.1)	−0.3 (3.5)
Education, %				
No qualifications	13.4	16.1	17.4	28.1
CSEs or O levels/GCSEs or equivalent	16.7	17.4	17.7	18.9
A levels/AS levels or equivalent	5.9	5.5	5.5	4.7
Other professional qualification	12.3	11.8	11.5	9.6
NVQ or HNC or equivalent	15.2	16.2	16.2	17.0
College or university degree	36.4	33.1	31.7	21.7
Income, %				
<18,000£	16.2	17.5	18.9	25.4
18,000-30,999£	21.0	21.4	21.8	21.5
31,000-51,999£	23.7	23.3	22.4	19.0
52,000-100,000£	19.7	18.3	17.6	12.8
>100,000£	5.3	4.9	4.8	3.0
Current smoking, %	7.9	11.2	15.2	23.4
Current drinking, %	92.6	93.3	93.0	88.2
Regular physical activity, %	62.1	61.5	59.8	56.7
C-reactive protein, mg/L (SD)	2.3 (4.0)	2.5 (4.1)	2.7 (4.4)	3.0 (4.6)
High cholesterol, %	11.4	10.9	11.3	10.4
Hypertension, %	52.3	50.7	51.5	50.9
Total energy intake, kcal/d (SD)[b]	2039.1 (542.0)	2079.0 (559.1)	2104.2 (579.5)	2087.7 (620.0)
DASH diet score[b]	21.9 (4.8)	21.1 (4.7)	20.5 (4.8)	19.5 (4.8)

[a]AS, ; BMI, body mass index; CSE, ; DASH, Dietary Approaches to Stop Hypertension; GCSE, ; HNC, ; NVQ, ; O, .
[b]A total of 155,328 participants were available. Data are presented as mean (SD) or %.
[ea]A levels, Advanced Levels; AS, Advanced Subsidiary Levels; BMI, body mass index; CSE, Certificate of Secondary Education; DASH, Dietary Approaches to Stop Hypertension; GCSE, General Certificate of Secondary Education; HNC, Higher National Certificate or equivalent; NVQ, National Vocational Qualification; O levels, Ordinary Levels.

adjustment for DASH diet and total energy intake in participants who had available dietary data; (5) further adjustment for baseline glycated hemoglobin levels; and (6) further adjustment for dietary supplements including vitamin D, fish oil, and glucosamine.

We conducted several stratified analyses by the following factors: sex (women, men), age (<60, ≥60 years), race/ethnicity (Whites, non-Whites), Townsend deprivation index (quintiles 1, quintiles 2-4, quintiles 5), education level (≤Certificate of Secondary Education or Ordinary Levels/General Certificate of Secondary Education or equivalent, ≤National Vocational Qualification or Higher National Certificate or equivalent, ≥College or university degree), income (<31,000£, 31,000-51,999£, ≥52,000£), smoking (never, ever, current), alcohol drinking (never, ever, current), physical activity (<150 minutes/wk, ≥150 minutes/wk), high cholesterol (yes, no), hypertension (yes, no), BMI (18.5-24.9, 25-29.9, ≥30 kg/m^2), CRP (quintiles 1, quintiles 2-4, quintiles 5), and DASH diet

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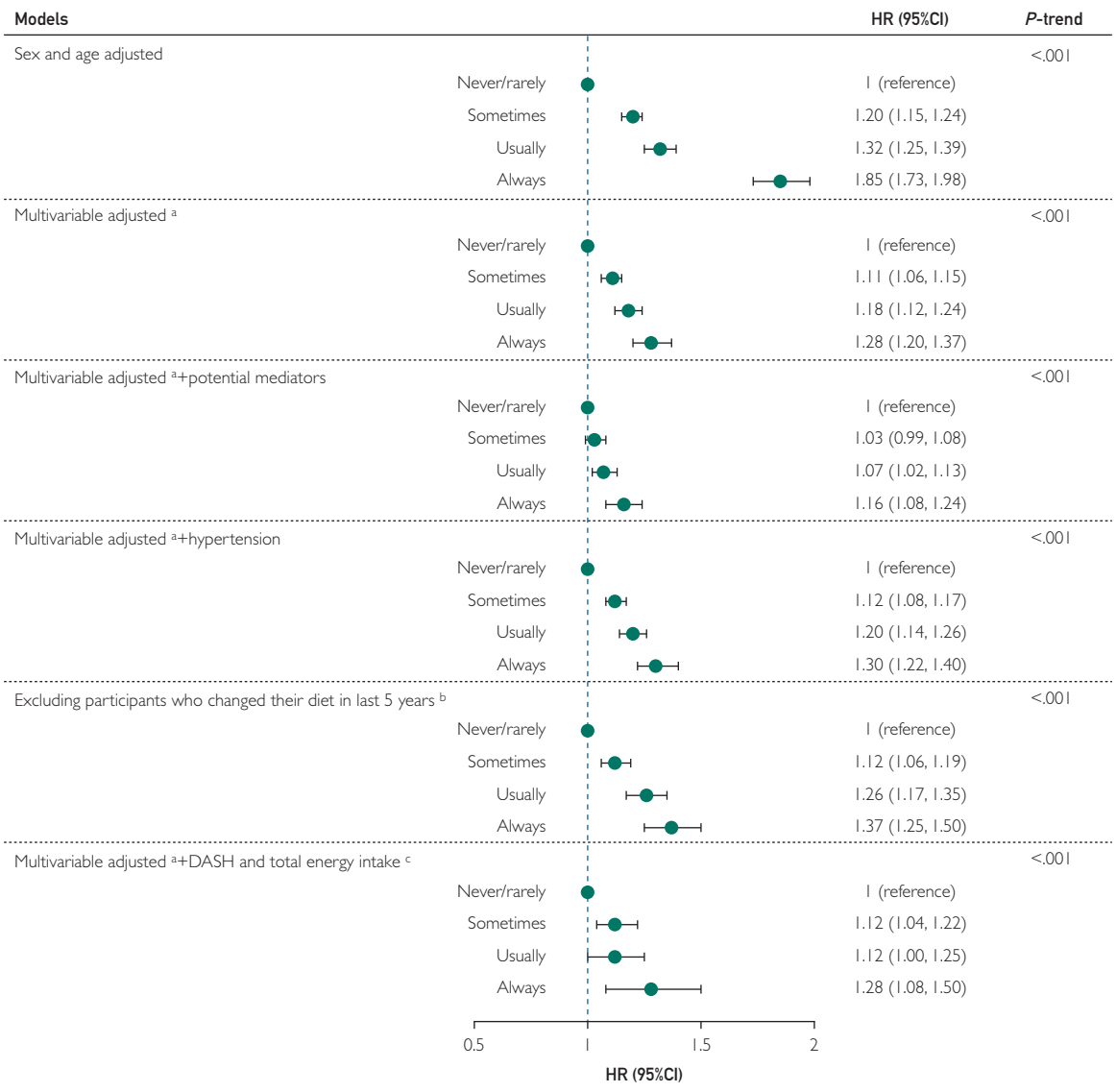

FIGURE. Hazard ratios and 95% CIs for the frequency of adding salt to foods with the hazard of type 2 diabetes. [a]Adjusted for sex, age, race, Townsend deprivation index, education level, income, smoking, drinking, physical activity, and high cholesterol. [b]A total of 257,389 participants were available. [c]A total of 155,328 participants were available. DASH, Dietary Approaches to Stop Hypertension.

(tertiles). Multiplicative interactions between the frequency of adding salt to foods and these factors were assessed by adding interaction terms into the original Cox models.

We further performed formal mediation analyses to examine whether the association between adding salt and T2D risk was mediated by adiposity measurements (BMI, ratio of waist and hip circumference, body fat percentage, body fat mass, and body fat-free mass) or CRP. Formal mediation analysis model was constructed and presented in Supplementary Figure 1 (available online at http://www.mayoclinicproceedings.org).[23,24] Adding salt was the predictor variable (X), adiposity measurements or CRP the mediator (M), and T2D the outcome variable

TABLE 2. Stratified Analyses for Association Between Frequency of Adding Salt to Food and Hazard of Type 2 Diabetes[a]

Subgroups[b]	Frequency of adding salt to food					*P* for interaction
	Never/rarely	Sometimes	Usually	Always	*P*-trend	
Age, y						.60
<60	1 (ref)	1.01 (0.95-1.07)	1.08 (1.00-1.16)	1.13 (1.03-1.23)	.006	
≥60	1 (ref)	1.06 (1.00-1.12)	1.07 (1.00-1.15)	1.17 (1.05-1.29)	.001	
Sex						.43
Female	1 (ref)	0.99 (0.94-1.05)	1.06 (0.98-1.15)	1.13 (1.02-1.26)	.02	
Male	1 (ref)	1.07 (1.01-1.13)	1.08 (1.01-1.16)	1.19 (1.09-1.30)	<.001	
Race						.47
Non-White	1 (ref)	0.98 (0.87-1.11)	1.07 (0.91-1.22)	1.14 (0.97-1.34)	.11	
White	1 (ref)	1.04 (0.99-1.08)	1.06 (1.01-1.12)	1.17 (1.08-1.26)	<.001	
Townsend deprivation index						.22
Low (Q1)	1 (ref)	1.06 (0.96-1.17)	1.08 (0.94-1.24)	1.16 (0.94-1.44)	.08	
Intermediate (Q2-Q4)	1 (ref)	1.02 (0.97-1.08)	1.05 (0.98-1.13)	1.24 (1.13-1.37)	<.001	
High (Q5)	1 (ref)	1.04 (0.97-1.12)	1.09 (0.99-1.20)	1.08 (0.96-1.20)	.06	
Education						.08
≤CSEs or O levels/GCSEs or equivalent	1 (ref)	1.02 (0.95-1.08)	1.11 (1.03-1.20)	1.12 (1.02-1.23)	.002	
≤NVQ or HNC or equivalent	1 (ref)	1.01 (0.95-1.09)	0.98 (0.90-1.08)	1.28 (1.13-1.44)	.02	
≥College or university degree	1 (ref)	1.08 (0.99-1.18)	1.08 (0.96-1.21)	1.03 (0.85-1.25)	.17	
Income						.85
<31,000£	1 (ref)	1.02 (0.96-1.08)	1.07 (0.99-1.15)	1.13 (1.03-1.24)	.006	
31,000-51,999£	1 (ref)	1.08 (0.99-1.19)	1.07 (0.95-1.21)	1.25 (1.05-1.49)	.01	
≥52,000£	1 (ref)	1.04 (0.93-1.17)	1.04 (0.89-1.21)	1.18 (0.93-1.50)	.23	
Smoking status						.19
Never	1 (ref)	1.05 (0.99-1.11)	1.09 (1.01-1.19)	1.16 (1.04-1.29)	.002	
Ever	1 (ref)	1.02 (0.96-1.09)	1.08 (0.99-1.17)	1.24 (1.11-1.39)	<.001	
Current	1 (ref)	1.02 (0.92-1.13)	0.98 (0.86-1.11)	1.01 (0.88-1.17)	.98	
Drinking status						.23
Never	1 (ref)	1.07 (0.92-1.24)	1.19 (0.98-1.42)	1.13 (0.91-1.40)	.09	
Ever	1 (ref)	0.96 (0.81-1.11)	1.18 (0.94-1.47)	0.89 (0.67-1.18)	.94	
Current	1 (ref)	1.04 (0.99-1.08)	1.06 (1.00-1.12)	1.19 (1.11-1.29)	<.001	
Regular physical activity, min/wk						.48
<150	1 (ref)	1.07 (1.01-1.14)	1.09 (1.01-1.18)	1.14 (1.03-1.27)	.001	
≥150	1 (ref)	1.01 (0.96-1. 07)	1.07 (0.99-1.15)	1.19 (1.08-1.31)	<.001	
High cholesterol						.08
No	1 (ref)	1.04 (0.99-1.09)	1.05 (0.99-1.11)	1.19 (1.10-1.29)	<.001	
Yes	1 (ref)	1.02 (0.94-1.10)	1.13 (1.02-1.26)	1.05 (0.90-1.22)	.07	
Hypertension						.25
No	1 (ref)	1.01 (0.93-1.10)	1.06 (0.96-1.18)	1.24 (1.09-1.41)	.004	
Yes	1 (ref)	1.05 (1.01-1.10)	1.09 (1.03-1.16)	1.15 (1.06-1.25)	<.001	
BMI, kg/m^2						.41
18.5-24.9	1 (ref)	0.95 (0.83-1.08)	0.98 (0.82-1.18)	1.09 (0.86-1.38)	.84	
25-29.9	1 (ref)	1.08 (0.98-1.12)	1.10 (1.01-1.20)	1.19 (1.06, 1.33)	<.001	
≥30	1 (ref)	1.04 (0.98-1.09)	1.06 (0.98-1.13)	1.14 (1.04-1.25)	.004	
C-reactive protein						.43
Low (Q1)	1 (ref)	0.93 (0.78, 1.11)	0.91 (0.71-1.16)	1.22 (0.88, 1.70)	.96	
Intermediate (Q2-Q4)	1 (ref)	1.05 (0.99, 1.11)	1.12 (1.04-1.20)	1.18 (1.06, 1.30)	<.001	
High (Q5)	1 (ref)	1.04 (0.98, 1.12)	1.06 (0.97-1.15)	1.17 (1.05, 1.30)	.005	

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TABLE 2. Continued

Subgroups[b]	Frequency of adding salt to food					*P* for interaction
	Never/rarely	Sometimes	Usually	Always	*P*-trend	
DASH diet[c]						.42
Low (T1)	1 (ref)	1.16 (1.03-1.31)	1.08 (0.93-1.27)	1.20 (0.97-1.50)	.045	
Intermediate (T2)	1 (ref)	1.05 (0.91-1.21)	0.96 (0.78-1.17)	1.10 (0.80-1.54)	.81	
High (T3)	1 (ref)	0.92 (0.78-1.08)	1.04 (0.83-1.30)	1.14 (0.78-1.68)	.83	

[a]BMI, body mass index; CSE, Certificate of Secondary Education; DASH, Dietary Approaches to Stop Hypertension; GCSE, General Certificate of Secondary Education; HNC, Higher National Certificate; NVQ, National Vocational Qualification; O levels, Ordinary Levels; Q, quintile; T, tertile; ref, reference.

[b]Adjusted for sex, age, race, Townsend deprivation index, smoking, drinking, physical activity, high cholesterol, BMI, and C-reactive protein in the corresponding model. Values shown are HR (95% CI).

[c]Results were restricted to 155,328 participants who completed at least one dietary recall (1-5 times) during the follow-up period (2009–2012). Models were further adjusted for total energy intake.

(Y). In general, there are 4 steps for mediation analyses: (1) showing that the predictor variable determines the outcome (model Y=c X) where c is total effect; (2) showing that the predictor variable affects the mediator (model M=β_1 X) where β_1 is indirect effect 1; (3) showing that the mediator determines the outcome controlling for the predictor (model Y=β_2 M+c' X) where β_2 is indirect effect 2, and c' is direct effect; and (4) calculating the proportion of mediation: mediation effect (%)=($\beta_1 \times \beta_2$/c)× 100%. A separate mediation model was constructed for each potential mediator. Mediation analyses were performed in R package *Lavaan*.[25]

Statistical analyses were conducted with SAS version 9.4 (SAS Institute Inc, Cary, NC, USA) and R version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria). All *P* values were two-sided and $P<.05$ was considered statistically significant.

RESULTS

Baseline Characteristics of Participants

The baseline characteristics of participants according to the frequency of adding salt to foods are presented in Table 1. Compared with participants with a lower frequency of adding salt to foods, participants with higher frequency were less likely to be women; Whites; had higher levels of Townsend deprivation index, BMI, and CRP; had lower levels of education and income; were more likely to be a current smoker and less likely to have regular physical activity; and had a lower prevalence of high cholesterol and hypertension. In addition, participants with a higher frequency of adding salt to foods were less likely to adhere to a DASH-style diet. The nutrient levels at baseline according to the frequency of adding salt to foods are presented in Supplementary Table 1 (available online at http://www.mayoclinicproceedings.org).

Frequency of Adding Salt to Foods and T2D

A graded relationship between lower frequency of self-reported adding salt to foods and lower concentrations of estimated 24-hour sodium excretion was observed at baseline. The concentrations of estimated 24-hour sodium excretion were 3.19 (95% CI, 3.18 to 3.21), 3.23 (95% CI, 3.22 to 3.25), 3.27 (95% CI, 3.26 to 3.28) and 3.30 (95% CI, 3.29 to 3.31) g, in "never/rarely," "sometimes," "usually," and "always" groups, respectively (P-trend$<.001$) (Supplementary Figure 2, available online at http://www.mayoclinicproceedings.org).

The association between the frequency of adding salt to foods and the risk of T2D is presented in the Figure. During a mean follow-up of 11.9 years, 13,120 incident events of T2D were documented. In a sex- and age-adjusted model, higher frequency of adding salt to foods was significantly related to a higher risk of T2D, with the HRs of 1 (reference) being 1.20 (95% CI, 1.15 to 1.24), 1.32 (95% CI, 1.25 to 1.39), and 1.86 (95% CI, 1.73 to 1.98) across

TABLE 3. HRs and 95% CIs for the Measurements With the Hazard of Type 2 Diabetes[a]

Measurements[b]	Quintile					*P*-trend
	1	2	3	4	5	
Sodium						
Sex and age adjusted	1 (ref)	1.28 (1.20-1.37)	1.56 (1.46-1.67)	1.95 (1.82-2.08)	2.47 (2.31-2.64)	<.001
Multivariable adjusted[c]	1 (ref)	1.12 (1.04-1.20)	1.17 (1.10-1.26)	1.28 (1.20-1.37)	1.34 (1.25-1.43)	<.001
Ratio of sodium and potassium						
Sex and age adjusted	1 (ref)	1.05 (0.99-1.12)	1.14 (1.07-1.21)	1.36 (1.28-1.44)	1.74 (1.64-1.84)	<.001
Multivariable adjusted[c]	1 (ref)	1.02 (0.96-1.09)	1.03 (0.97-1.09)	1.12 (1.06-1.19)	1.17 (1.11-1.24)	<.001
Estimated 24-h urinary sodium excretion						
Multivariable adjusted[c]	1 (ref)	0.95 (0.88-1.02)	1.04 (0.97-1.12)	1.27 (1.18-1.38)	1.51 (1.38-1.65)	<.001

[a]ref, reference.
[b]A total of 387,684 participants were available.
[c]Models were adjusted for sex, age, race, Townsend deprivation index, education level, income, smoking, drinking, physical activity, high cholesterol, body mass index, and C-reactive protein. For the analyses of sodium and estimated 24-h urinary sodium excretion, potassium was also adjusted.

groups of "never/rarely," "sometimes," "usually," and "always," respectively (*P*-trend<.001). After further adjusting for Townsend deprivation index, education level, income, smoking, drinking, physical activity, and high cholesterol, the association was attenuated but remained significant: compared with the "never/rarely" group, the HRs of the "sometimes," "usually," and "always" groups were 1.11 (95% CI, 1.06 to 1.15), 1.18 (95% CI, 1.12 to 1.24), and 1.28 (95% CI, 1.20 to 1.37), respectively (*P*-trend<.001). We also performed the analysis by further adjusting for potential mediators including BMI and CRP and found that the association was attenuated but still significant. The results were not appreciably changed after including hypertension as a covariate in the multivariable-adjusted model or excluding participants who changed their diet in last 5 years. Moreover, we found that higher frequency of adding salt to foods was significantly associated with a higher risk of T2D independent of DASH diet score and total energy intake in 155,328 participants with dietary data. In addition, similar results were observed if we further adjusted for glycated hemoglobin or dietary supplements (Supplementary Table 2, available online at http://www.mayoclinicproceedings.org).

To evaluate whether the covariates modified the relation between the frequency of adding salt to foods and the risk of T2D, we also performed stratified analyses according to age, sex, race, Townsend deprivation index, education levels, income, smoking, drinking, physical activity, high cholesterol, hypertension, BMI, CRP, and DASH diet. We did not find significant interactions between the frequency of adding salt to foods and covariates on the risk of incident T2D (Table 2).

Concentrations of Urinary Sodium With T2D

Table 3 shows the associations of biomarker measurements including urinary sodium, the ratio of sodium and potassium, and the estimated 24-hour urinary sodium excretion, with the risk of T2D. We observed a dose-response relationship between higher levels of urinary sodium and a higher risk of T2D. In a sex- and age-adjusted model, compared with the lowest quintile group, the HRs for the quintile 2 to the quintile 5 groups of urinary sodium were 1.28 (95% CI, 1.20 to 1.37), 1.56 (95% CI, 1.46 to 1.67), 1.95 (95% CI, 1.82 to 2.08), and 2.47 (95% CI, 2.31 to 2.64), respectively (*P*-trend<.001). After further adjusting for Townsend deprivation index, education level, income, smoking, drinking, physical activity, high cholesterol, BMI, CRP, and urinary potassium, the association was attenuated but still significant, with HRs of 1 (reference), 1.12 (95% CI, 1.04 to 1.20), 1.17 (95% CI, 1.10 to 1.26), 1.28 (95% CI, 1.20 to 1.37), and 1.34 (95% CI, 1.25 to

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TABLE 4. Mediation Effect of Potential Mediators on the Association Between Frequency of Adding Salt to Food and Type 2 Diabetes[a,b]

	Frequency of adding salt to food →Mediators		Mediators →Type 2 Diabetes		Mediation Effect % (95% CI)
	β1	*P*	β2	*P*	
Adiposity measurements					
Body mass index	0.036	<.001	0.246	<.001	33.8 (24.6-43.0)
Waist and Hip Ratio	0.032	<.001	0.320	<.001	39.9 (29.1-50.8)
Body fat percentage	0.031	<.001	0.319	<.001	37.9 (27.5-48.4)
Body fat mass	0.040	<.001	0.262	<.001	39.9 (29.0-50.8)
Body fat-free mass	0.002	.04	0.294	<.001	2.0 (0.1-4.0)
C-reactive protein	0.025	<.001	0.077	<.001	8.6 (5.6-11.5)

[a]β, standardized regression coefficients; β_1, indirect effect 1; β_2, indirect effect 2.
[b]Models were adjusted for sex, age, race, Townsend deprivation index, education level, income, smoking, drinking, physical activity, high cholesterol, hypertension, and C-reactive protein or body mass index.

1.43) across quintile groups, respectively (*P*-trend<.001). A similar dose-response relationship was observed for the ratio of sodium and potassium. For the estimated 24-hour urinary sodium excretion, higher quintile groups were also associated with the higher risks of T2D in multivariable-adjusted model: the HRs were 0.95 (95% CI, 0.88 to 1.02), 1.04 (95% CI, 0.97 to 1.12), 1.27 (95% CI, 1.18 to 1.38), and 1.51 (95% CI, 1.38 to 1.65) in quintile 2 to the quintile 5 group, as compared with quintile 1, respectively (*P*-trend<.001).

Potential Mediators in the Association Between Frequency of Adding Salt to Foods and T2D

To further explore whether adiposity or inflammation play a mediator role on the association between the frequency of adding salt to foods and T2D, we performed formal mediation analyses for several adiposity measurements and CRP (Table 4). The mediation analysis model of BMI is presented in Supplementary Figure 1 and Table 4. The total effect of the model (the standardized coefficient of the association between the frequency of adding salt to foods and T2D) was significant (c=0.026, *P*<.001). We observed significant positive associations between the frequency of adding salt to foods and BMI (indirect effect β_1=0.036; *P*<.001), and between BMI and T2D (indirect effect β_2=0.246; *P*<.001). The direct effect of the model was still significant (c'=0.017; *P*<.001), suggesting that other intermediate factors might also play a role. The mediation effect of BMI was estimated to be 33.8% (95% CI, 24.6% to 43.0%; *P*<.001). Similar results were observed for the ratio of waist and hip circumference (mediation effect 39.9%; 95% CI, 29.1% to 50.8%; *P*<.001). We also examined the mediation effect of body composition, including body fat percentage, body fat mass, and body fat-free mass. We observed that body fat percentage and body fat mass significantly mediated the association of adding salt with T2D, with an estimated mediation effect of 37.9% (95% CI, 27.5% to 48.4%; *P*<.001) and 39.9% (95% CI, 29.0% to 50.8%; *P*<.001), respectively. However, body fat-free mass did not appear to mediate the association of adding salt with T2D. Moreover, we found that CRP also played a mediator role in the association between adding salt and T2D, with a mediation effect of 8.6% (95% CI, 5.6% to 11.5%; *P*<.001).

DISCUSSION

In this prospective cohort study, we observed that a higher frequency of adding salt to foods, a surrogate marker for a person's long-term salt taste preference and sodium intake, was associated with a higher risk of incident T2D. This association was independent of lifestyle factors, socioeconomic factors, and other traditional risk factors for T2D. In addition, we found that the association between adding salt to foods and

T2D was partly mediated by adiposity measurements and CRP.

To our knowledge, this is the first prospective study to investigate the association of adding salt to foods with T2D risk. Very few studies have investigated the association of dietary salt or sodium intake with T2D risk. Our results were supported by a cross-sectional study which showed that diabetes patients have a higher prevalence of adding salt to foods than the non-diabetes population.[26] A previous prospective study from Finland observed a J-shaped association between single 24-hour sodium excretion and T2D risk: compared with the second quartile of the 24-hour sodium excretion, both the highest quartile and the lowest quartile of the 24-hour sodium excretion were associated with a higher risk of T2D.[9] The above results did not change appreciably after enrolling more participants and extending follow-up period.[10]

Notably, dietary sodium intake varies widely from day to day. Although a single 24-hour urine collection is useful in evaluating sodium intake in the population level, it is inadequate to evaluate an individual's usual consumption levels. Relying on data of single 24-hour urine collection may lead to systematic errors in sodium assessment and severely confounding effect in the direction of the associations between sodium intake and health outcomes.[8,12] Although the frequency of adding salt to foods cannot provide quantitative information on sodium intake, the graded relationship between the frequency of adding salt to foods and levels of objectively measured urinary sodium indicate that it could reflect individual's long-term salt taste preference.[13] The validity of adding salt to foods as a good marker for long-term sodium intake has been shown in our recent study and other studies.[13,14,27] In this study, we provided a unique perspective to evaluate the association between salt usage behaviors and T2D risk. Another strength of analysis on adding salt over the traditional methods is that it is less likely to be confounded by other dietary factors because the salt usage behaviors are independent of any food ingredients and the commonly used table salt contains 97% to 99% sodium chloride. The traditional methods (dietary recall or urine collection) for evaluating sodium intake cannot address the impact on the results due to the collinearity problem (eg, sodium and potassium).[7,28]

We also found that higher levels of sodium-related urinary biomarkers, including spot urinary sodium, the ratio of sodium and potassium, and the estimated 24-hour sodium excretion (estimated based on spot urinary sodium) were significantly associated with a higher risk of T2D. These observations at least partly support our findings of adding salt to foods and T2D because adding salt to foods showed a positive correlation with these urinary biomarkers. Notably, such results should be interpreted carefully. The sodium concentration in spot urine only reflects the sodium intake in a short period preceding the collection.[29] Moreover, it is also regulated by the renin-angiotensin-aldosterone system, estrogens, vitamin D, and cortisol that are associated with T2D risk.[30] Therefore, the observed association between concentrations of spot urinary sodium and T2D risk may be largely driven by the nondietary sodium factors. However, given the graded association of spot urinary sodium with T2D risk, the spot urinary sodium may be used as a potential biomarker for T2D risk in the future.

Although the biological mechanisms underlying the positive association of habitual high sodium intake with the risk of T2D remain to be explored, several lines of evidence support the potentially adverse effects of high sodium intake on T2D. First, increasing evidence has linked high sodium intake to obesity, which is a major risk factor for T2D.[15,16,31] An observational study from the United Kingdom showed that high sodium intake was significantly associated with obesity independent of total energy or sugar-sweetened beverage intake.[31] Animal studies indicate that high sodium intake may induce increased accumulation of white fat in rats.[15] A recent Mendelian

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randomization study also found a potential causal link between high sodium intake and obesity.[16] In our study, we did observe that measures of adiposity (eg, BMI, waist and hip ratio) significantly mediated 33.8% to 39.9% of the association between adding salt and T2D. Our further analyses on body composition indicate that the significant mediation effect of BMI was largely driven by the body fat mass rather than the body fat-free mass. In addition, other studies showed that high sodium intake was related to high levels of inflammation, which is closely related to T2D risk.[17] We found that CRP was estimated to mediate 8.6% of the association between adding salt and T2D. Our results suggest that, except for BMI and CRP, other intermediate factors may also be involved, and future studies must investigate the mechanisms underlying the association between the frequency of adding salt to foods and the risk of T2D.

The major strengths of this study include the unique methods for evaluating long-term sodium intake, the large sample size, the wealthy information of covariates and the consistent results in sensitivity analyses.

Study Limitations

Our study has several limitations. First, we could not exclude the possibility that high frequency of adding salt to foods is a marker for an unhealthy lifestyle. However, we have carefully controlled for lifestyle factors, and we found the association of adding salt with T2D was independent of unhealthy lifestyle factors, indicating that the observed positive association of adding salt to foods with risk of T2D was less likely due to its correlation with the unhealthier lifestyle. Second, the self-reported frequency of adding salt to foods might be subject to information bias and was unable to provide quantitative information on total sodium intake. However, the validity of this variable has been shown by our previous study and several other previous studies.[11-14] Third, the participants of UK Biobank were mainly of European descent; thus, it was unclear whether our findings could be applied to other ethnic groups. Fourth, given the observational study design, we cannot rule out residual confounding. Fifth, information on the frequency of adding salt to foods were available only at baseline; thus, we did not consider potential changes of salty preference during the follow-up period. Further studies may focus on the impact of salty-taste changes on subsequent T2D risk.

CONCLUSION

Our study indicates that a higher frequency of adding salt to foods is significantly associated with a higher risk of T2D. These findings provide support that reduction of adding salt to foods may act as a potential behavioral intervention approach for preventing T2D. Future clinical trials are needed to further validate our findings.

POTENTIAL COMPETING INTERESTS

The authors report no potential competing interests.

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SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at http://www.mayoclinicproceedings.org. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

Abbreviations and Acronyms: **BMI**, body mass index; **CRP**, C-reaction protein; **DASH**, diet to stop hypertension; **T2D**, type 2 diabetes

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