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Sodium intake and bronchial hyperresponsiveness in adults[☆]

Stefanie Sausenthaler^a, Iris Kompauer^a, Sabine Brasche^b,
Jakob Linseisen^{c,d}, Joachim Heinrich^{a,*}

^aGSF-National Research Centre for Environment and Health, Institute of Epidemiology, Neuherberg, Germany

^bFriedrich-Schiller-University Jena, Institute of Occupational, Social and Environmental Medicine, Department of Indoor Climatology, Erfurt, Germany

^cUnit of Human Nutrition and Cancer Prevention, TU Munich, Germany

^dDivision of Clinical Epidemiology, German Cancer Research Center, Heidelberg, Germany

KEYWORDS

Sodium;
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Summary *Background:* Several investigations suggested a relationship between sodium intake and asthma and bronchial hyperresponsiveness (BHR), respectively. However, clinical and epidemiological studies did not show consistent finding.

Objective: We analysed the association between dietary sodium intake and BHR to methacholine among 613 adults aged 20–65 years as one of the two German centres of the European Community Respiratory Health Survey (ECRHS).

Methods: Dietary sodium intake was estimated from a 3-day weighed record of food intake. We applied multiple logistic regression models contrasting the three higher quartiles of sodium intake versus the lowest to assess the risk of BHR and mild BHR estimated by PD₂₀ and PD₁₀, respectively, controlling for potential confounders and stratified for sex. In addition, we analysed PD₂₀ (dose of methacholine causing a fall of 20% in forced expiratory volume in 1 s) as continuous variable expressed as transformed dose–response slope (tDRS) in the linear model.

Results: Women were as expected more likely to be bronchial hyperresponsive (PD₂₀: 26.1%; PD₁₀: 52.2%) than men (PD₂₀: 15.8%; PD₁₀: 34.8%) and had a lower mean daily sodium intake (2.36 g) compared with men (3.15 g). Logistic regression did not show any significant relationship between sodium intake and BHR in terms of PD₂₀ after adjustment for age group, education, smoking status, body mass index and height in men or women. However, mild BHR assessed as PD₁₀ was statistically significant positively related to the third (OR: 2.35; CI: 1.11–5.00) and highest quartile of sodium intake (OR: 2.28; CI: 1.06–4.88) in women, but not in men for

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*Corresponding author. Tel.: +49 89 3187 4150; fax: +49 89 3187 3380.

E-mail address: joachim.heinrich@gsf.de (J. Heinrich).

third quartile (OR: 1.29; CI: 0.68–2.44) and for fourth quartile (OR: 1.07; CI: 0.56–2.07), respectively.

Conclusion: Sodium intake by several food items does not alter BHR assessed as PD₂₀ to methacholine but may increase mild BHR assessed as PD₁₀.

We conclude that, in addition, PD₁₀ has to be considered when the effect of sodium intake on BHR is studied.

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Introduction

The increase in the prevalence of asthma and other atopic diseases is often discussed as a consequence of a western lifestyle in affluent societies.^{1,2} Diet is one of these lifestyle factors, which is inevitably associated with the shift from traditional to modern way of life.³ After Burney⁴ had observed a strong correlation between regional mortality from asthma and purchases of table salt in England and Wales, the hypothesis that sodium might be important in the aetiology of asthma attracted a great deal of attention. Plausible biological mechanism is due to the constricting effect of the sodium ion on smooth muscle cells, whereby bronchial responsiveness and hence, asthma could be increased.

Animal experiments have shown that the hyper-reactivity of sensitised bronchial smooth muscle is associated with an increased influx of sodium with consequent stimulation of the electrogenic Na⁺–K⁺-pump. Subsequent alterations of membrane potential could lead to the increase in calcium influx via Na⁺/Ca²⁺ exchange resulting in higher contractility.⁵ Sodium loading may enhance this abnormality. Other studies suggest the production of a circulating inhibitor of the Na⁺–K⁺-pump probably resulting from extracellular expansion, which could be attributed to a high sodium intake. The following increased levels of intracellular sodium and, in turn, increased intracellular calcium could also strengthen the contractile response.^{6,7}

Even though there exist physiological plausible explanations, the results of both epidemiological and clinical studies are conflicting. While epidemiological studies in adults excepting the survey of Burney et al.⁸ predominantly found no or simply weak associations between sodium intake and bronchial hyperresponsiveness (BHR),^{9–13} clinical studies achieve consistently positive results.^{14–17} All of these former studies analysed BHR in terms of PD₂₀. Thus, the aim of the present study was to assess the relationship between dietary sodium, estimated by means of a 3-day weighed record, with BHR in a large sample of the general population taking into account BHR assessed as PD₂₀ and PD₁₀.

Methods

Study population

Present study is based on data from the German study centre in Erfurt, East Germany, as part of the European Community Respiratory Health Survey (ECRHS), which was conducted in adults aged 20–64 years from 1990 to 1992. Study design and population sampling are described in detail elsewhere.^{18,19} A total of 1282 subjects attended the medical examination, and lung function measurement by spirometry and bronchial challenge test was carried out in 932 participants. Additionally, a subset of 802 men and women participated in a dietary survey with 3-day weighed records. The final study population consisted of 368 men and 245 women with complete data for diet and bronchial challenge test.

The study protocol was approved by the local ethics committee.

Methacholine challenge test

This has been described in detail elsewhere.²⁰ In brief, baseline forced expiratory volume in 1 s (FEV₁) and forced vital capacity (FVC) were measured in all subjects who fulfilled the acceptance criteria.²⁰ All those, whose FEV₁ was at least 70% of the expected value calculated by an age- and height-related equation,²⁰ and more than 1.5 l, were invited to take part in methacholine challenge.

Bronchial challenge started with inhalation of saline diluent, and the maximum post-diluent FEV₁ recorded was used as the control value. Subsequently, all eligible subjects received standard methacholine using the Mefar dosimeter (Mefar, Bovezzo, Italy) at quadrupling doses starting with 0.0078 mg. After a fall in FEV₁ of 10% from the control value, doubling doses were used. The test was stopped if FEV₁ had dropped by 20% as compared to the control value or the maximum cumulative dose of 2 mg had been reached. PD₂₀ was calculated as the cumulative dose of

methacholine necessary to decrease FEV₁ by 20% while PD₁₀ was calculated according to a decrease in FEV₁ by 10%. BHR was defined as a greater fall than 20% of FEV₁ in methacholine challenge or more than a rise of 11% in bronchodilator challenge. Mild BHR was up to a greater than 10% fall in FEV₁.

Dietary assessment

Data on dietary intake were obtained using 3-day weighed records in the framework of MONICA (monitoring trends and determinants in cardiovascular disease) project. Participants were advised to keep a diary about all consumed foods on two working days and one Sunday or holiday with information about time, place and portion. While solid foods were weighed with letter scales, liquids were estimated with household measures and meals eaten out-of-home via a booklet of portion size pictures.²¹ Food records were rejected when containing leave days, diet days or celebrations due to variations from usual alimentation.

The collected dietary data were finally analysed using a programme developed in the GSF National Research Centre for Environment and Health based on the BLS-German national nutrient data file (Bundeslebensmittelschlüssel Version 2.2). The mean daily sodium intake was calculated as average from food intake, which also considered the table salt content of different dishes and recipes, whereas discretionary salt was not assessed.

Statistical methods

We applied multiple logistic regression analysis to estimate the strength of association between sodium intake and BHR for each gender. Odds ratios (OR) and 95% confidence intervals were computed for the second, third and highest quartile compared to the first quartile of sodium intake, controlling for age group, education, smoking status, body mass index and height. Beneath BHR (PD₂₀) and mild BHR (PD₁₀), we carried out a sensitivity analysis of the subgroup with a decrease in FEV₁ by 10% but not more than 20% and deal with them as exclusive mild BHR (PD_{10–20}).

In addition to the binary response variables, dose–response slope (DRS) was calculated in order to analyse the methacholine responsiveness as continuous variable in linear regression model. This allows interpretation of data from all subjects regardless of whether FEV₁ declined by 20% during the test or not.

Therefore, missing PD₂₀ values were estimated by linear interpolation between the last two points on the dose–response plot. Because the DRS was right-skewed, we used reciprocal transformation to create normal distribution and added a constant to get positive values. The transformed dose–response slope (tDRS) was calculated as $tDRS = 1/(DRS+0.1)$.²² Using the tDRS as dependent variable, the variance estimates are shown to be more stable (homoscedasticity) which is an important condition of the multiple linear regression model.²³

Results

Complete data for methacholine challenge test were available in 368 males and 245 females. Mean (SD) baseline FEV₁ in men and women was 4.10 (0.89) and 3.14 (0.50) l, respectively, and mean (SD) baseline FVC was 5.05 (0.94) and 3.81 (0.57) l, respectively. Table 1 describes the percentage of subjects with BHR, mild BHR and exclusive mild BHR by selected characteristics of the study population. The prevalence rate of BHR in terms of PD₂₀ was 15.8% in men and 26.1% in women. As expected, the prevalence was higher among current smokers than ex-smokers and never-smokers in both genders, while adiposity (body mass index $\geq 30.0 \text{ kg/m}^2$) and age seemed to be a risk factor only in men. High education was afflicted with a lower prevalence of BHR in men and women compared to low and middle education. Moreover, BHR showed a trend to increase with decreasing body height.

Mild BHR was prevalent in 52.2% women and 34.8% men. The distribution for age, educational level, smoking status and anthropometric measures were similar between PD₂₀ and PD₁₀, but not identical. Regarding exclusive mild BHR (PD_{10–20}) showed that 19.0% of men and 26.1% of women had a 10% but less than 20% decrease in FEV₁ during methacholine challenge.

The mean daily sodium intake in the total study population was 3.15 g/d (SD = 1.08) and 2.36 g/d (SD = 0.81) for men and women, respectively, and showed a normal distribution. After stratifying for age group, no differences in total sodium intake could be observed. The quartiles for sodium intake were 2.38 g/d (Q1), 2.93 g/d (Q2), 3.75 g/d (Q3), and 8.91 g/d (Q4) for men and 1.79 g/d (Q1), 2.17 g/d (Q2), 2.77 g/d (Q3), and 5.73 g/d (Q4) for women, respectively.

Table 1 Prevalence rates of BHR (PD₂₀), mild BHR (PD₁₀) and exclusive mild BHR (PD₁₀₋₂₀) in a random population sample of 613 subjects aged 20–64 years living in the City of Erfurt, Germany, and examined in 1991/1992.

	BHR (PD ₂₀)				Mild BHR (PD ₁₀)				Exclusive mild BHR (PD _{10–20})			
	Male (N = 368)		Female (N = 245)		Male (N = 368)		Female (N = 245)		Male (N = 368)		Female (N = 245)	
	n/N	%	n/N	%	n/N	%	n/N	%	n/N	%	n/N	%
Total	58/368	15.8	64/245	26.1	128/368	34.8	128/245	52.2	70/368	19.0	64/245	26.1
Age (years)												
20–29	10/73	13.7	18/64	28.1	22/73	30.1	32/64	50.0	12/73	16.4	14/64	21.9
30–39	8/93	8.6	19/79	24.1	25/93	26.9	41/79	51.9	17/93	18.3	22/79	27.9
40–49	13/79	16.5	16/61	26.2	23/79	29.1	33/61	54.1	10/79	12.7	17/61	27.9
50–65	27/123	22.0	11/41	26.8	58/123	47.2	22/41	53.7	31/123	25.2	11/41	26.8
Education												
< 10 classes	18/79	22.8	10/37	27.0	32/79	40.5	21/37	56.8	14/79	17.7	11/37	29.7
= 10 classes	20/115	17.4	31/92	33.7	43/115	37.4	53/92	57.6	23/115	20.0	22/92	23.9
> 10 classes	20/173	11.6	23/116	19.8	53/173	30.6	54/116	46.6	33/173	19.1	31/116	26.7
Smoking status												
Never smoker	9/111	8.1	23/116	19.8	25/111	22.5	59/116	50.9	16/111	14.4	36/116	31.0
Ex-smoker	20/123	16.3	14/51	27.5	44/123	35.8	25/51	49.0	24/123	19.5	11/51	21.6
Current smoker	29/134	21.6	27/78	34.6	59/134	44.0	44/78	56.4	30/134	22.4	17/78	21.8
BMI (kg/m ²)												
≤24.9	24/169	14.2	44/165	26.7	56/169	33.1	85/165	51.5	32/169	19.9	41/165	24.9
25.0–29.9	24/159	15.1	17/61	27.9	52/159	32.7	35/61	57.4	28/159	17.6	18/61	29.5
≥30.0	10/40	25.0	3/19	15.8	20/40	50.0	8/19	42.1	10/40	25.0	5/19	26.3
Height (cm)												
≤172* (≤160) [†]	25/119	21.0	19/71	26.8	9/119	41.2	43/71	60.6	24/119	20.2	24/71	33.8
≤177* (≤165) [†]	17/101	16.8	27/86	31.4	36/101	35.6	44/86	51.2	19/101	18.8	17/86	19.8
≥194* (≤181) [†]	16/148	10.8	18/88	20.5	43/148	29.1	41/88	46.6	27/148	18.2	23/88	26.1
*Male. †Female.												

*Male.
[†]Female.

Sodium intake and bronchial hyperresponsiveness

In multiple logistic regression analysis, no association between sodium intake and BHR in terms of PD₂₀ was observed. Table 2 presents the adjusted OR and 95% confidence intervals for men and women separately. The third quartile of total sodium intake in women was the only one which showed a statistically significant higher risk of BHR (OR: 2.59; CI: 1.11–6.01) compared to the lowest intake. Age (in men) and smoking appeared to increase BHR prevalence rates whereas height possibly is inversely associated (data not shown).

Sodium intake and mild bronchial hyperresponsiveness

According to mild BHR, which is defined as 10% fall in FEV₁, the results argue for a positive association between sodium intake and PD₁₀ in women as shown in Table 2. The fourth quartile of sodium intake was significantly related to mild BHR in women (OR: 2.28; CI: 1.06–4.88), whereas in men no statistically significant association could be shown again. By regarding a sub-sample of mild BHR, namely those subjects who had less than 20% fall in FEV₁ (exclusive mild BHR), it turned out that the strongest effects are due to this group. While women showed a highly significant risk in the highest quartile of sodium intake (OR: 3.26; CI: 1.29–8.36), men also showed a trend for increased exclusive mild BHR with increasing sodium intake, although not statistically significant.

Sodium intake and dose–response slope after methacholine challenge test (DRS)

A multiple linear regression confirmed the absence of a consistent relationship between sodium intake and tDRS. The estimates of regression coefficients were 0.01547 ($P = 0.7246$) and -0.10284 ($P = 0.1963$) for men and women, respectively.

Discussion

This study suggests that sodium intake is not associated with BHR to methacholine in adults, neither before nor after adjustment for potential confounders. This is in agreement with other observational studies in adults,^{9–13} except for the ecological study by Burney et al.⁸ Only two of these investigations analysed sodium intake by dietary assessment methods instead of excretory sodium as we did: One cross-sectional survey in a sample of 205 subjects (18–69 years) employed a 7-day dietary recall including discretionary salt and food-derived sodium. They found no significant difference between the three lower quartiles and the highest quartile of sodium intake and the risk of BHR.¹² Moreover, Woods et al.¹³ conducted a cross-sectional study in order to identify foods and nutrients increasing the risk of asthma in young adults by means of a food frequency questionnaire. Dietary sodium intake tended to be associated with bronchial reactivity to methacholine but did not reach statistical significance.

In contrast, the results of clinical trials argue for a correlation between sodium-excretion levels and BHR prevalence rates.^{14–17} The discrepancies may

Table 2 Adjusted odds ratios and 95% confidence intervals for the quartiles of sodium intake in logistic regression model predicting BHR (PD₂₀), mild BHR (PD₁₀) and exclusive mild BHR (PD_{10–20}).

Sodium intake (g/d)	BHR (PD ₂₀)	Mild BHR (PD ₁₀)	Exclusive mild BHR (PD _{10–20})
<i>Men (N = 368)</i>			
2.38 (Q1)	1	1	1
2.93 (Q2)	0.61 (0.26–1.40)	0.98 (0.51–1.88)	1.43 (0.62–3.30)
3.75 (Q3)	0.80 (0.36–1.74)	1.29 (0.68–2.44)	1.81 (0.80–4.11)
8.91 (Q4)	0.68 (0.30–1.56)	1.07 (0.56–2.07)	1.54 (0.66–3.57)
<i>Women (N = 245)</i>			
1.79 (Q1)	1	1	1
2.17 (Q2)	1.06 (0.44–2.60)	1.49 (0.70–3.15)	1.79 (0.69–4.64)
2.77 (Q3)	2.59 (1.11–6.01)	2.35 (1.11–5.00)	1.76 (0.67–4.68)
5.73 (Q4)	1.00 (0.40–2.48)	2.28 (1.06–4.88)	3.26 (1.29–8.36)

be partly explained due to the focus on asthmatic patients in clinical studies, whereas epidemiological investigations have focused on general population samples. Since BHR was found to be higher in asthmatic subjects,²⁴ results from clinical trials cannot give information about the conditions in the ordinary population.

While sodium intake and BHR assessed as PD₂₀ were not associated, the mild form of BHR defined as 10% fall in FEV₁ and exclusive mild BHR defined as more than 10% but not exceeding 20% fall in FEV₁ both showed a positive relationship with sodium intake. We might only speculate why increased intake of sodium was associated only with mild BHR. Other determinants of BHR might have hidden the additional minor effects of increased sodium intake. So residual confounding—although effect estimates were adjusted for known determinants and available data—could not be excluded. This is a highly speculative interpretation and not justified by own data. We also could not rule out that the positive association between sodium intake and increased mild BHR is an artefact. However, this speculation is also not justified by data.

There are several outcome definitions of bronchial hyperresponsiveness. We analysed the dichotomous variables BHR in terms of PD₂₀ and PD₁₀ as well as the reciprocally transformed slope of the individual dose–response curve. This transformation allows complying with the important condition of the multiple linear model to have stable variance (homoscedasticity).²³ To control the validity of our slope, we also calculated the logarithmically transformed slope suggested by Chinn²⁵ and the one recommended by O'Connor et al.²⁶ The results obtained by the various types of outcome definition did not differ when regarding 20% fall in FEV₁.

We chose 3-day weighed records to estimate daily sodium intake.²¹ This allows accurate recording of consumed foods that is substantial for quantification of micronutrients. Validation of dietary assessment methods showed weighed records yielding the highest correlation with biomarkers in urine in comparison with food frequency questionnaire (FFQ), 24-h recall and food diary.²⁷ To avoid random errors in the protocol due to day-to-day variability we chose two weekdays and one Sunday or holiday. Besides, systematic errors could occur during the assessment of food intakes. As subjects were not informed about the intention to analyse protocols regarding sodium intake, it is unlikely that under-recording have been occurred.

The present study is probably limited through the lacking assessment of sodium intake by discretionary salt. Sodium was simply estimated from the

weighed records including no information about salt use at the table. Estimates about mean discretionary salt intake range from 15%²⁸ to 20–30%²⁹ of total salt intake. Among the lack of information about this percentage in the study population, the actual problem lies in the unknown range of variation concerning discretionary salt. Since no linear relationship between sodium intake from food and discretionary salt use was found,³⁰ we assume that discretionary salt intake is pretty different between individuals.

As the assessment of the exposition is considerably afflicted with uncertainties, random misclassification of the exposition might have occurred. This would tend to bias the risk estimates towards the null and could not give reason to positive results. Thus, statements about the association between exposition and outcome can be made only under reserve. A more precise measurement of sodium including discretionary salt would therefore be necessary.

Another limitation is due to the cross-sectional design of the study. Both BHR and diet were measured only one time. Therefore, the results just describe point prevalence rates whereas time-cause relationships cannot be assessed. The time-slice between salt intake and measurement of BHR amounts 1 to 9 days in 75% of the participants, whereas in most of the cases, food intake was recorded after bronchial challenge test. Unfortunately, there was no adequate sub-sample available, which had both measurements at the same time. However, we believe that the 3-day weighed record method provide valid data for a large period of time. Therefore, sodium intake after the bronchial challenge test might be also used as surrogate for sodium intake previous to the challenge test.

In conclusion, even taking into account all the potential bias, dietary sodium is unlikely to be related to BHR to methacholine. In consideration of the findings of former epidemiological studies, these results argue for the absence of an association between sodium and BHR, but mild BHR needs consideration in future studies on determinants of BHR including dietary factors.

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