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Dietary Salt, Nitrate and Stomach Cancer Mortality in 24 Countries

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Background. High salt and nitrate intake are considered as risk factors for stomach cancer, but little is known about possible interactions. This ecological study examines the respective importance of both factors for stomach cancer mortality at the population level using data obtained under standardized conditions and with biochemical analyses performed in the same laboratories.

Method. Randomly selected 24-hour urine samples from 39 populations, sampled from 24 countries (N = 5756 people for sodium, 3303 for nitrate) were obtained from the INTERSALT study. Median sodium and nitrate levels were age- and sex-standardized between ages 20–49 years and averaged per country. Ecological correlation–regression analyses were done in relation to national stomach cancer mortality rates.

Results. The Pearson correlation of stomach cancer mortality with sodium for the 24 countries was 0.70 in men and 0.74 in women (both $P < 0.001$), and with nitrate: 0.63 ($P = 0.001$) in men and 0 56 ($P < 0.005$) in women. In multiple regression of stomach cancer mortality, using sodium and nitrate as independent variables, the adjusted R^2 was 0 61 in men and 0.54 in women (both $P < 0.001$). Addition of the interaction term (sodium × nitrate) to the previous model increased the adjusted R^2 to 0.77 in men, and to 0.63 in women. The analysis of this model showed that the importance of nitrate as risk factor for stomach cancer mortality increased markedly with higher sodium levels. However, the relationship of stomach cancer mortality with sodium was always stronger than with nitrate.

Conclusions. Salt intake, measured as 24-hour urine sodium excretion, is likely the rate-limiting factor of stomach cancer mortality at the population level.

Keywords: stomach cancer mortality, atrophic gastritis, 24-hour urine sodium, 24-hour urine nitrate, *Helicobacter pylori*, fruits and vegetables

Based upon an observation in 1965—that stomach cancer mortality (SCM) and stroke mortality were strongly correlated and that the regression lines were similar in different countries and over time[1]—the hypothesis was presented that salt could be involved in the aetiology of both diseases, though by different mechanisms. For SCM it was postulated that the continuous use of high doses of salt (caustic when hypertonic) would result in early atrophic gastritis, thereby increasing the risk of stomach cancer later on. This hypothesis was expanded in 1975 by Correa, namely that anacidity from atrophic gastritis and the resulting bacterial invasion would favour the conversion of nitrate (NO_3) to nitrite and to powerful nitro–mutagens and nitrocarcinogens.[2]

This salt hypothesis has recently been gaining ground.[3–7] There is conflicting evidence about the role of NO_3. In some countries positive relationships of NO_3 with SCM were found,[8] whereas they were inverse in others.[9] Nitrate in drinking water was found to be inversely related to SCM in UK[10] and France.[11] There is consensus on the protective influence of fresh fruits and vegetables[3–6] on SCM, although, at least in western countries, vegetables are the major source of NO_3 in food. Gastric infection with *Helicobacter pylori* (HP) as a risk factor for SCM is generating much interest, although its role is still not clear.[4,7,12,13]

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POPULATIONS AND METHODS

The INTERSALT study collected data in 1986–1987 on 10 079 people, age- and sex-stratified (20–59 years) by random or whole population sampling, from 52 population centres in 32 countries worldwide. Selection of 200 participants per centre, standardized methods and their quality control have been described.[14] Urine samples preserved with boric acid were kept deep-frozen in the INTERSALT laboratory in Leuven, Belgium. From each centre an approximate 50% subsample was randomly selected, stratified by sex and age (20–29, 30–39 and 40–49 years) and sent frozen to Porton Down Laboratories (Wiltshire, UK) for analysis with a modified Griess technique, including quality control.[15] Results of the NO_3 study are given in the accompanying paper.[16] For the present study, data on SCM were available for 24 of the countries that participated in INTERSALT, i.e. for 39 of the 52 centres. Nitrate data are available for 1654 men and 1649 women; data on all the other variables are based on 2877 men and 2879 women, i.e. all men and women from the 39 centres ages 20–49. First, for each of the INTERSALT variables, the median value was obtained within each 10-year age band. The mean of these values was then obtained within each centre and where necessary the resulting values were averaged over two or more centres to obtain the value for the country, thereby reducing the number of observations to 24 countries.

The SCM data from either 1986, or 1987, or 1988 (except Colombia 1984) were obtained from WHO, Geneva and age-adjusted (45–74 years) per 100 000 to the standard European population. The weights (5-year groups) of this standard population from age 45–49 years to 70–74 years are respectively 7, 7, 6, 5, 4, 3.

Statistical Methods

The selection of the means of median values was done to maintain the age–sex standardization and for reasons of comparability with other ecological analyses in the INTERSALT study.[14] The present study was also repeated using mean values of sodium (Na) and NO_3 instead of medians, yielding similar results.

The selection of the age groups 20–49 years instead of 20–59 years as used in the INTERSALT study was done for comparability with the NO_3 analyses which were done only for ages 20–49 years for reasons explained elsewhere.[16] Again, in the present study, the use of 20–59 years age group for variables other than NO_3 produced similar results for all calculations.

Stomach cancer mortality (SCM) was always the dependent variable in the Pearson, product moment, correlations with various independent variables.

Similarly, using the 'REG' procedure of SAS for linear multiple regression, SCM was the dependent variable versus Na, NO_3, potassium and creatinine, weight and height. Since there was evidence that NO_3 behaved differently at a lower salt intake, e.g. UK,[3] than at a higher one (Columbia[4]) an interaction term, multiplying Na and NO_3, was added to the most important variables from the previous multiple regression. An R^2 adjusted for the number of independent variables was used for all the results of multiple regression.

All *P*-values are without correction for multiple testing and are guidelines for the evaluation of thefindings.

RESULTS

Descriptive Statistics

Mean, range and sex ratios of the key variables of 24 countries are listed in Table 1. Variability between countries is large, especially for SCM and NO_3. The sex ratio (men/women) of the mean values is largest for SCM followed by urinary creatinine, sodium, potassium and weight (Table 1).

South Korea and the Peoples' Republic of China have the highest values in both men and women for SCM and for NO_3 and among the four highest values for sodium (Appendix). In both men and women the US has the lowest SCM.

Pearson correlation coefficients between values for both sexes—0.95 for SCM, 0.83 for Na and 0.98 for NO_3—are high, suggesting similarity of life styles between sexes.

All the values for men and women used in this paper are given in the Appendix, by country and by centre.

Relation of 24-hour Urinary Na and NO_3 to Stomach Cancer Mortality

Regression lines of SCM with urinary Na/24-hour in 24 countries are shown for men and women in Figures 1 and 2; for NO_3/24-hour, in Figures 3 and 4. Pearson r values between SCM and other variables are summarized in Table 2, together with their level of significance. Sodium and NO_3 are significantly positively related to SCM, whereas weight, creatinine, BMI, height and potassium are negatively, though not always significantly, related (Table 2).

Interrelations could play a role in some results since sodium in women is significantly positively related to NO_3 ($r = 0.57$) and negatively to creatinine ($r = -0.60$), weight ($r = -0.75$), height ($r = -0.63$) and BMI ($r = -0.43$). Nitrate is also negatively related to weight ($r = -0.43$ in men and -0.53 in women) and to height ($r = -0.43$ in men and -0.40 in women).

TABLE 1 *Summary descriptive statistics*

	Men		Women		Sex ratio of mean (men/women)
	Mean value[a]	Range	Mean value[a]	Range	
Stomach cancer[b]	54	15–180	24	7–70	2.25
Nitrate (mmol/24-hours)	1.23	0.47–2.94	1.10	0.44–2.37	1.12
Sodium (Na) (mmol/24-hours)	179	115–232	140	91–187	1.28
Potassium (K) (mmol/24-hours)	62.4	31.7–83.1	50.5	31.0–66.8	1.24
Creatinine (mmol/24-hours)	13.8	9.1–15.6	9.1	6.4–10.6	1.52
Body mass index (kg/m^2)	24.5	21.8–26.7	23 7	21.4–28.2	1.03
Weight (kg)	73.0	57 8–82.3	60.8	52.0–76.5	1.20
Height (cm)	173	160–180	160	150–167	1.08

Data for individual centres and countries are in the Appendix.

[a] For stomach cancer mortality the mean and the range of the 24 rates is given. For all other variables the average (mean) of the median values in the 24 countries is given.

[b] Stomach cancer mortality (rates/100 000/year), age-adjusted 45–74 years, N = 24 countries.

Conversion factors: mmol Na to g NaCl: 0.0585; mmol K to g: 0.0391; mmol nitrate to mg: 62; mmol creatinine to g: 0.113.

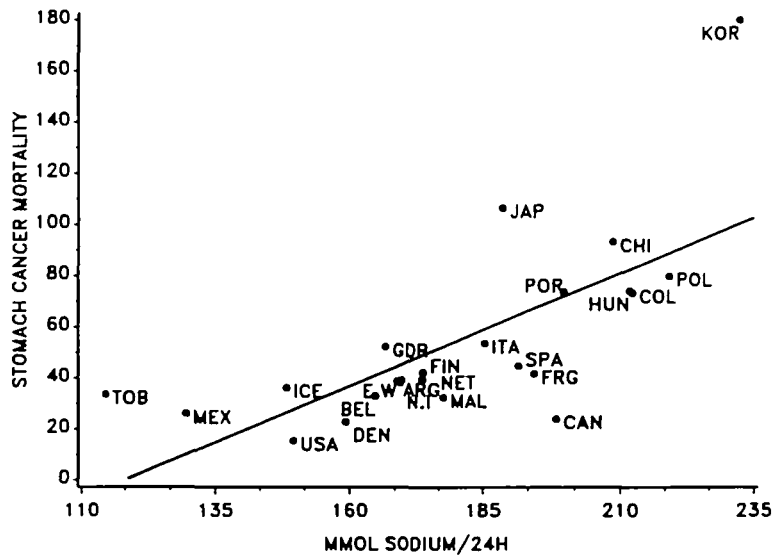

FIGURE 1 *Linear regression between stomach cancer mortality per 100 000/year, age-adjusted between 45–74 years and mmol Na/24-hours, r = 0.70, P < 0.001 in men, n = 24*

ARG = Argentina; BEL = Belgium; CAN = Canada; CHI = P.R. of China; COL = Colombia; DEN = Denmark; E.W = England and Wales; FIN = Finland; FRG = Fed. Rep. of Germany; GDR = German Dem. Rep.; HUN = Hungary; ICE = Iceland; ITA = Italy; JAP = Japan; KOR = South Korea; MAL = Malta; MEX = Mexico; NET = the Netherlands; N.I = Northern Ireland; POL = Poland; POR = Portugal; SPA = Spain; TOB = Trinidad and Tobago; USA = United States.

Creatinine and weight are strongly related (r = 0.90 in men and 0.72 in women).

Because of these interrelations a preliminary multiple stepdown ($P < 0.05$) linear regression was performed with SCM as the dependent variable and urinary Na, NO_3, potassium, creatinine, weight and height as independent variables. The latter four variables made no significant contribution and therefore only Na and NO_3, the major factors of this study, were retained yielding an adjusted R^2 of 0.61 in men and 0.53 in women (model 1, Table 3). Nitrate did not significantly relate to SCM in women when both Na and NO_3 were

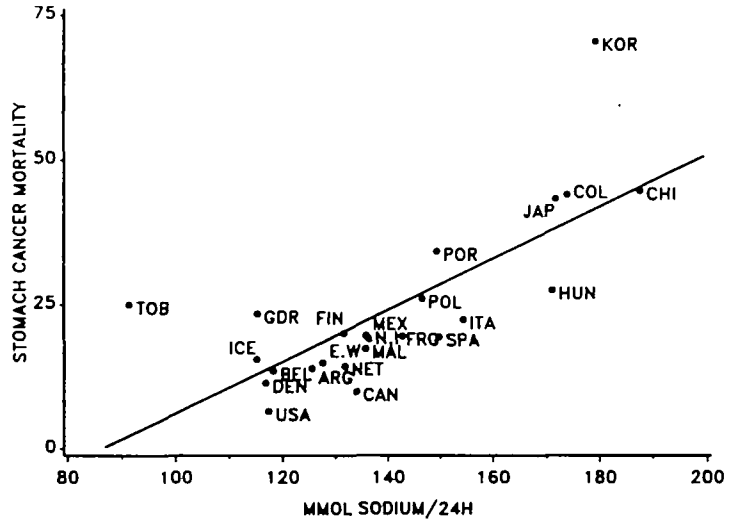

FIGURE 2 *Linear regression between stomach cancer mortality per 100 000/year, age-adjusted between 45–74 years and mmol Na/24-hours, r = 0.74, P < 0.001 in women, n = 24*

ARG = Argentina; BEL = Belgium; CAN = Canada; CHI = P.R. of China; COL = Colombia; DEN = Denmark; E.W = England and Wales; FIN = Finland; FRG = Fed. Rep. of Germany; GDR = German Dem. Rep.; HUN = Hungary; ICE = Iceland; ITA = Italy; JAP = Japan; KOR = South Korea; MAL = Malta; MEX = Mexico; NET = the Netherlands; N.I = Northern Ireland; POL = Poland; POR = Portugal; SPA = Spain; TOB = Trinidad and Tobago; USA = United States.

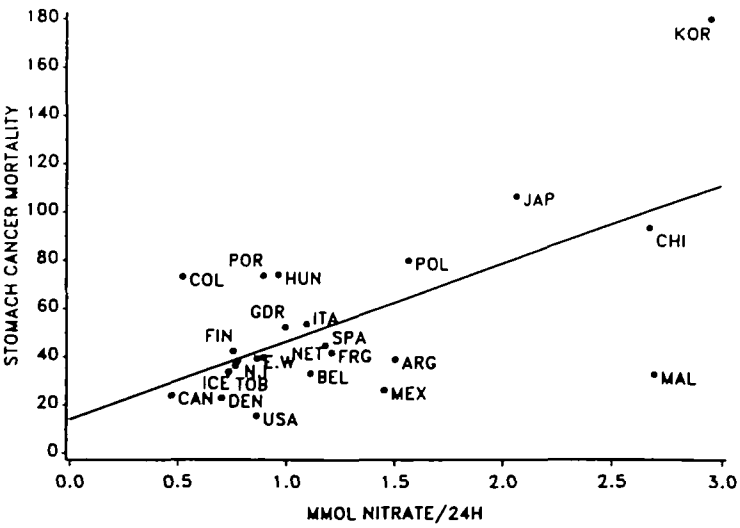

FIGURE 3 *Linear regression between stomach cancer mortality per 100 000/year, age-adjusted between 45–74 years and mmol NO_3/24-hours, r = 0.63, P = 0.001 in men, n =24*

ARG = Argentina; BEL = Belgium; CAN = Canada; CHI = P.R. of China; COL = Colombia; DEN = Denmark; E.W = England and Wales; FIN = Finland; FRG = Fed. Rep. of Germany; GDR = German Dem. Rep.; HUN = Hungary; ICE = Iceland; ITA = Italy; JAP = Japan; KOR = South Korea; MAL = Malta; MEX = Mexico; NET = the Netherlands; N.I = Northern Ireland; POL = Poland; POR = Portugal; SPA = Spain; TOB = Trinidad and Tobago; USA = United States.

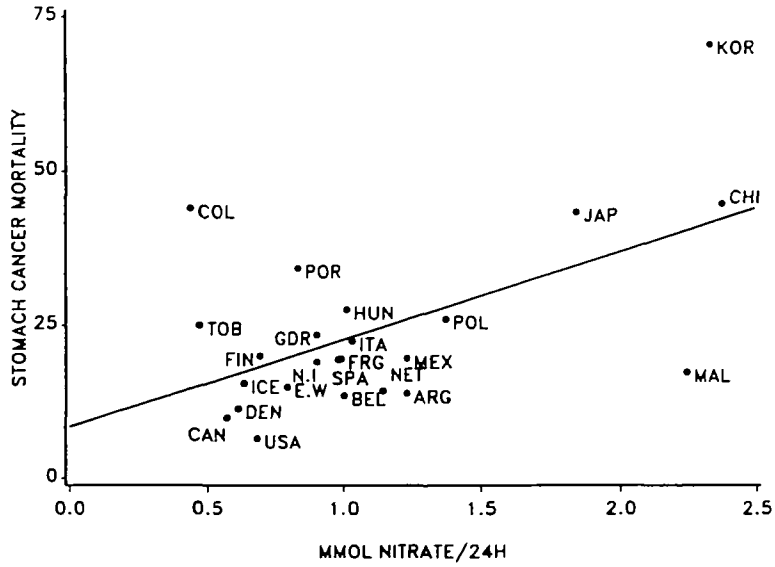

FIGURE 4 *Linear regression between stomach cancer mortality per 100 000/year, age-adjusted between 45–74 years and mmol NO_3/24-hours, r = 0.56, P < 0.05 in women, n = 24*

ARG = Argentina; BEL = Belgium; CAN = Canada; CHI = P.R. of China; COL = Colombia; DEN = Denmark; E.W = England and Wales; FIN = Finland; FRG = Fed. Rep. of Germany; GDR = German Dem. Rep.; HUN = Hungary; ICE = Iceland; ITA = Italy; JAP = Japan, KOR = South Korea; MAL = Malta; MEX = Mexico; NET = the Netherlands; N.I = Northern Ireland; POL = Poland; POR = Portugal; SPA = Spain; TOB = Trinidad and Tobago; USA = United States.

in the model (model 1, Table 3). As explained under Methods an interaction term (Na × NO_3) was added to the previous model (model 2, Table 3). The adjusted R^2 was 0.77 in men and 0.63 in women. The interaction term has a *P*-value of 0.001 for men and 0.02 for women.

DISCUSSION

Dietary Salt and Stomach Cancer Mortality

Stomach cancer data rely on mortality statistics. Although no validation of these data from autopsy exists worldwide, there is reasonable correlation with incidence data (e.g. very high in Japan and very low in the US)[17] probably related to the specificity of stomach cancer symptoms and the increased facility to obtain stomach mucosal biopsies. The present results on salt and SCM are consistent with the majority of the findings from the literature. Sodium—from foods preserved with salt,[3] and from salted high carbohydrate foods[5] (mainly bread, and rice with fermented salty sauces)—is associated with a higher risk of SCM in case-control studies,[3–5,18] in salt preference studies,[3] in a large cohort study,[19] and in ecological studies in Japan,[7,20] Switzerland[21] and Belgium.[22] Worldwide decreasing trends in SCM are consistent with

TABLE 2 *Product moment (Pearson) correlation coefficient (r) between stomach cancer mortality and sodium (Na), potassium (K), nitrate, creatinine, weight, height and body mass index (BMI)*

	Na	K	Nitrate	Creatinine	Weight	Height	BMI
Men	0.70***	–0.36	0.63+++	–0.37	–0.52**	–0.36	–0.55**
Women	0.74***	–0.26	0.56**	–0.59**	–0.53**	–0.42*	–0.31

*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$; +++$P = 0.001$.

TABLE 3 *Linear multiple regression of stomach cancer mortality, age-adjusted 45–74 years, rate/100 000/year, against average daily sodium (Na) and nitrate excretion (mmol/24-hours) 20–49 years, N = 24 countries*

	Men		Women	
	Coeff (SE)	Adjusted R^2	Coeff (SE)	Adjusted R^2
Model 1				
Stomach cancer mortality related to median 24-hour urinary sodium and nitrate				
Na	0.679 (0.176)***	0.61***	0.380 (0.105)**	0.53***
Nitrate	21.97 (7.17)**		4.97 (4.44)	
Model 2				
Stomach cancer mortality related to median 24-hour urinary sodium and nitrate and their interaction				
Na	−0.219	0.77***	0.058	0.63***
Nitrate	−130		−46.1	
Na × Nitrate	0.763 (0.199)$^{+++}$		0.321 (0.124)*	

For the interaction model significance levels are given only for the interaction term and the adjusted R^2.
*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$; $^{+++}P = 0.001$.

decreasing salt consumption resulting from increased availability of refrigerators, making preservation by salt no longer necessary. Health education may also play a role (Belgium, US, Finland, Australia). Urinary 24-hour salt excretion, measured in Belgium from 1966 to 1986, decreased by about 25%.[23] At the same time refrigerators in Belgian households increased in the lowest income group from 37.5% to 91.3% between 1975 and 1985, but not in the highest income group (98.8 to 99.5%).[24] Only 9% of households in Japan had a refrigerator in 1960 versus 91% in 1970.[18] Mean urinary Na/24-hour in Japan was 360 mmol around 1955[25] and 187 mmol in 1987.[14] Concordantly both SCM and stroke mortality in Japan started to decline in the 1960s, whereas both types of mortality declined simultaneously from the 1930s in the US and after World War II in Western Europe,[26] except in Portugal where this occurred only after 1970. The 'salt hypothesis' also explains why SCM and stroke mortality are quantitatively similarly linked between and within populations,[1,26] why lower socioeconomic groups with their higher salt intake[27] have higher rates of SCM and stroke mortality, and why high carbohydrate foods, which are heavily salted in industrialized countries, are a risk factor.[5]

Salt is not carcinogenic by itself, but in experimental animals hypertonic sodium chloride solutions which produce increased DNA synthesis,[28] i.e. more cellular growth in the gastric mucosa, resulting ultimately in atrophic gastritis,[29] become co-carcinogenic when given with nitrosamides, and promoting when administered after the carcinogen.[30] These experimental results are consistent with the salt hypothesis (see Introduction).

Dietary Nitrate, Salt and Stomach Cancer Mortality

Nitrate *per se* is not carcinogenic either. It is produced in the body in amounts ranging from 0 to 0.5 mmol/day.[31] One known source of endogenous NO_3 is synthesis of nitrite from arginine.[32]

Nitrite, metabolized from NO_3, is found in saliva but not in normal gastric juice.[31] With increasing pH in the stomach due to atrophic gastritis, bacterial overgrowth is the rule and nitrites, nitrosamides, and nitrosamines are formed.[2] As noted above, there is good evidence linking salt intake to the prevalence of atrophic gastritis, a well known precursor of SCM.[7,33]

Data on NO_3 availability and metabolism and on the relation with SCM are extensively discussed by Hartman.[31,34]

The statistically significant interaction term for Na × NO_3 in the present analyses (model 2, Table 3) suggests that the combined relationships of ingested Na and NO_3 are complex. For example, they suggest that at lower Na intake SCM rates are lower with higher NO_3 intake. It is unlikely that this is indicative of a direct influence of NO_3 itself. It is more likely explained by a higher intake of fresh fruits and vegetables. Under those circumstances NO_3 is acting as a marker for these protective foods.[3–6] Findings in the literature are consistent with this concept. Thus, in England and Wales higher SCM in the north is associated with lower NO_3/nitrite level in the saliva and higher intake of salted bacon, whereas lower mortality levels in the south go together with higher NO_3/nitrite levels in the saliva and a higher intake of vegetables.[9] In a Spanish case-control study NO_3, mostly from vegetables, was inversely related to SCM.[35] In contrast, for countries (especially

East Asian) with high Na intake the origin of NO_3 is mainly from pickled, cured products (e.g. kimchi in Korea, salted fish and vegetables in Japan) and from fermented sauces. Those salted foods and sauces are also high in NO_3, either added to the foods or from synthesis from amino acids during fermentation. Potent nitromutagens and carcinogens, e.g. N-methyl-N'-nitro-N-nitro guanidine (NMNG) can develop under those circumstances.[2] Salt enhances the mutagenicity of nitrosated black beans.[36] Salted black beans are the staple food of most Costa Ricans. Costa Rica has one of the highest stomach cancer levels on record in international comparisons.[36]

Helicobacter pylori, Dietary Salt and Stomach Cancer Mortality

An important question is the role of *Helicobacter pylori*.[4,7,12,13] *H.pylori* prevalence worldwide is significantly related to SCM.[12] INTERSALT salt excretion level for 10 European countries[14] is also significantly related to the *H.pylori* prevalence in population samples of the same countries that were included in the Eurogast study.[12] It is unlikely that a higher prevalence of *H.pylori* led to a higher intake of salt at the population level. The opposite is more likely and is consistent with observations from five regions in Japan where *H.pylori* prevalence was not significantly related to SCM or to atrophic gastritis prevalence, whereas both latter factors were strongly related to salt excretion ($r = 0.98$, $P < 0.003$).[7] In the same areas prevalence of *H.pylori* was strongly related to intake of salty foods.[37]

A recent case-control study from Japan is consistent with the previous findings.[38] The strongest risk factor for SCM was atrophic gastritis, as detected by pepsinogen analysis.[38] No significant relation was found between *H.pylori* infection and SCM in either sex and the per cent prevalence of *H.pylori* was similar in the control and case groups (74% and 76% respectively).[38] However, they found some indications that *H.pylori* infection could be reduced by extended gastric atrophy, thereby obscuring the relation between *H.pylori* and stomach cancer. Those results were only significant in males.[38]

Another discrepancy is the low SCM in Africa combined with a high prevalence of *H.pylori*.[13] The salt concept could explain this paradox, since measured salt excretions are generally below observed usual values of both sexes (Appendix), e.g. 57 mmol/24-hour in Kenya,[14] 100 in Nigeria (unpublished data from Joossens J V and Oviasu O V; n = 174), and 141 in Zimbabwe.[14] The *H.pylori* hypothesis cannot either explain the strong correlation between SCM and stroke mortality,[9,26] nor the worldwide decrease in SCM, starting already in the 1930s in the US.[26]

CONCLUDING REMARKS

A drawback of this study was the relatively small number of samples from each country. One could therefore question the representativeness of the data. However, the relationship of SCM with sodium[39] and with NO_3[34] was previously investigated. Both studies were unstandardized and used data from different laboratories. The data from the SCM-Na study were from the literature from 14 countries during 1961–1983 (n = 26). Those of the SCM-NO_3 study came from 12 countries before 1982. The regression lines between SCM and Na or NO_3 were not significantly different from those obtained in this study under strictly controlled circumstances. These concordant results lend weight to the inference of a significant relationship between these variables and SCM at the population level.

It is reasonable to suggest that the role of NO_3 and of *H.pylori* infection in the incidence of atrophic gastritis at low Na intake could be investigated, e.g. among the Xingu Indians, surveyed in 1986–1987 in the INTERSALT study.[14,16] They have a very low Na excretion (12.3 mmol/24-hour) combined with an excretion of creatinine expected for their average weight (9.3 mmol/24-hour and 57 kg, respectively).[14] On the other hand, due to their high intake of vegetables, their NO_3 excretion is high (median 1.4, mean 2.2 mmol/24-hour).[16] The prevalence of atrophic gastritis at ages 40–60 years could be checked by blood analysis for pepsinogens.[7] The determination of IG antibodies against HP[7,12] could also be done on the same blood sample.

A controlled prospective preventive trial to reduce SCM by salt intake lowering could be done in e.g. Korea, but it is doubtful that it will ever be done due to the long duration of such a study and the lack of economic incentives. However, a 'natural' (observational) experiment is already underway as salt intake is being decreased in a number of countries worldwide, and it will be important to continue monitoring trends in SCM and stroke mortality, preferably with 24-hour Na excretion at the population level.[1]

The present study, combined with the congruent data obtained over many decades all over the world,[1–39] offers further evidence for the thesis that salt intake is the rate-limiting factor for SCM, whereas NO_3 appears only to be important with higher salt intake levels. The latter could also be true for *H.pylori* infections. Preventive strategies—lower salt intake combined with higher intake of fruits and vegetables—follow from those observations.

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REFERENCES

[1] Joossens J V La relation entre l'épidémiologie des accidents cérébro-vasculaires et du cancer de l'estomac In. *L'évolution Médicale*. Paris, 1968; **12:** 381–85.

[2] Correa P, Haenszel W, Cuello C *et al.* A model for gastric cancer epidemiology. *Lancet* 1975; **ii:** 58–60.

[3] Forman D. The etiology of gastric cancer. In· O'Neill I K, Chen J, Bartsch H (eds) *Relevance to Human Cancer of N-Nitroso Compounds, Tobacco Smoke and Mycotoxins.* Lyon: International Agency for Research on Cancer, 1991, pp. 22–31.

[4] Correa P. Diet modification and gastric cancer prevention. *J Natl Cancer Inst Monogr* 1992; **12:** 75–78.

[5] Graham S, Haughey B, Marshall J *et al.* Diet in the epidemiology of gastric cancer. *Nutr Cancer* 1990; **13:** 19–34.

[6] Weisburger J H. Causes of gastric and esophageal cancer. Possible approach to prevention by vitamin C. *Int J Vit Nutr Res* 1985; **27:** 381–402.

[7] Tsugane S, Kabuto M, Imai H *et al. Helicobacter pylori*, dietary factors, and atrophic gastritis in five Japanese populations with different gastric cancer mortality. *Cancer Causes Control* 1993; **4:** 297–305.

[8] Cuello C, Correa P, Haenszel W *et al.* Gastric cancer in Colombia. I. Cancer risk and suspect environmental agents. *J Natl Cancer Inst* 1976; **57:** 1015–20.

[9] Forman D, Al-Dabbagh S, Doll R. *Geographic and social class variation within the UK in levels of salivary nitrates and nitrites. A preliminary report.* IARC Sci Publ 1984; **57:** 901–09.

[10] Beresford S A A. Is nitrate in the drinking water associated with the risk of cancer in the urban UK? *Int J Epidemiol* 1985; **14:** 57–63.

[11] Leclerc H, Vincent P, Vandevenne P. Nitrates de l'eau de boisson et cancer. *Bull Acad Natl Med* 1991; **175:** 651–71.

[12] The Eurogast Study Group. An international association between *Helicobacter pylori* infection and gastric cancer. *Lancet* 1993; **341:** 1359–62.

[13] Holcombe C. *Helicobacter pylori*: the African enigma. *Gut* 1992; **33:** 429–31.

[14] INTERSALT Cooperative Research Group. Intersalt: an international study of electrolyte excretion and blood pressure. Results for 24 h urinary sodium and potassium excretion. *Br Med J* 1988; **297:** 319–28.

[15] Packer P. The pharmacology and metabolism of nitrate in relation to human cancer. (Thesis) CNAA.

[16] Hill M, Elliott P, Joossens J V *et al.* Twenty-four hour urinary nitrate excretion in 48 populations from 30 countries: An ECP–INTERSALT collaborative study. *Int J Epidemiol* 1996: **25**; 503–510.

[17] Doll R, Muir C, Waterhouse J. *Cancer Incidence in Five Continents.* Berlin: Springer–Verlag, 1970; II.

[18] Hirayama T. Epidemiology of stomach cancer in Japan. With special reference to the strategy for the primary prevention. *Jpn J Clin Oncol* 1984; **14:** 159–68.

[19] Hirayama T. Life-style and cancer: from epidemiological evidence to public behavior change to mortality reduction to target cancers. *J Natl Cancer Inst Monograph* 1992; **12:** 65–74.

[20] Yamori Y. The salt balance in Asia. In: Rettig R, Ganten D, Luft F C (eds). *Salt and Hypertension. Dietary Minerals, Volume Homeostasis and Cardiovascular Regulation.* Berlin: Springer-Verlag, 1989, pp. 323–27.

[21] Joossens J V, Geboers J. Dietary salt and risks to health. *Am J Clin Nutr* 1987; **45:** 1277–88.

[22] Joossens J V. Digestive cancers and nutrition in Belgium. *Acta Gastroenterol Belg* 1988; **51:** 313–21.

[23] Joossens J V, Kesteloot H. Trends in systolic blood pressure, 24-hour sodium excretion, and stroke mortality in the elderly in Belgium. *Am J Med* 1991; **90(Suppl. 3A):** 5S–11S.

[24] Joossens J V, Kesteloot H. Community control of hypertension in Belgium: the role of nutrition. In: Cuervo C A, Robinson B E, Sheppard H L (eds). *Geriatric Hypertension.* Tampa (Florida): University of South Florida, 1989, pp. 157–89.

[25] Sasaki N. The relationship of salt intake to hypertension in the Japanese. *Geriatrics* 1964; **19:** 735–44.

[26] Joossens J V, Geboers J. Epidemiology of gastric cancer: a clue to etiology. In: Sherlock P, Morson B C, Barbari L *et al.* (eds). *Precancerous Lesions of the Gastrointestinal Tract.* New York: Raven Press, 1983, pp. 97–113.

[27] Joossens J V, Claessens J, Geboers J, Claes J H. Electrolytes and creatinine in multiple 24-h urine collections (1970–1974). In: Kesteloot H, Joossens J V (eds). *Epidemiology of Arterial Blood Pressure.* The Hague, Boston, London: Martinus Nijhoff Publishers, 1980, pp. 45–63.

[28] Furihata C, Sato Y, Hosaka M *et al.* NaCl induced ornithine decarboxylase and DNA synthesis in rat stomach mucosa. *Biochem Biophys Res Comm* 1984; **121:** 1027–32.

[29] Kodama M, Kodama T, Suzuki H, Kondo K. Effect of rice and salty rice diets on the structure of mouse stomach. *Nutr Cancer* 1984; **6:** 135–47.

[30] Takahashi M, Hasegawa R. Enhancing effects of dietary salt on both initiation and promotion stages of rat gastric carcinogenesis. In: Hayashi Y, Nagao M, Sugimura T *et al.* (eds). *Diet, Nutrition and Cancer.* Utrecht: Japan Sci Soc Press, 1986, pp. 169–82.

[31] Hartman P E. Nitrates and nitrites: ingestion, pharmacodynamics, and toxicology. *Chem Mutagens* 1982; **7:** 211–94.

[32] Moncada S, Palmer M J, Higgs E A. Nitric oxide: physiology, pathophysiology, and pharmacology. *Pharmacol Rev* 1991; **43:** 109–42.

[33] Yamakawa H. The relationship between stomach cancer and intestinal metaplasia of the gastric mucosa and food intake. (In Japanese.) *Gan No Rinsho* 1986; **32:** 681–91.

[34] Hartman P E. Review: Putative mutagens and carcinogens in foods. I. Nitrate/nitrite ingestion and gastric cancer mortality. *Environ Mutagen* 1983; **5:** 111–21.

[35] Gonzáles C A, Riboli E, Badosa J *et al.* Nutritional factors and gastric cancer in Spain. *Am J Epidemiol* 1994, **139:** 466–73.

[36] Correa P, Rojas-Campos N, Sigaran M F *et al.* Salt enhances the mutagenecity of nitrosated black beans. *Nutr Cancer* 1990; **14:** 1–3.

[37] Tsugane S, Tei Y, Takahashi T, Watanabe S, Sugano K. Salty food intake and risk of *Helicobacter pylori* infection. *Jpn J Cancer Res* 1994; **85:** 474–78.

[38] Fukuda H, Saito D, Hayashi S *et al. Helicobacter pylori* infection, serum pepsinogen level and gastric cancer: a case-control study in Japan. *Jpn J Cancer Res* 1995; **86:** 64–71.

[39] Joossens J V, Kesteloot H. Salt and stomach cancer. In: Reed P I, Hill M J (eds). *Gastric Carcinogenesis.* Amsterdam, New York, Oxford: Excerpta Medica, 1988, pp. 105–26.

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APPENDIX

Stomach Cancer Mortality, Median Urinary Nitrate and Sodium (Na) Excretion, and Other Variables in 24 Countries. Men

	Stomach cancer mortality[a]	Nitrate[b] (n[f])	Na[b]	Cr[b,c]	K[b,d]	Weight kg	Height cm	BMI kg/m^2	n[e]
Argentina	38.8	1.50 (44)	169	13.9	58.2	74.3	174	24.6	75
Belgium	33.0	1.11 (44)	165	15.1	78.3	77.0	176	25.0	75
Canada	23.9	0.47 (78)	198	15.5	57.6	73.3	171	24.8	139
Labrador		0 42 (44)	184	14.6	46.8	71.3	168	25.0	64
St John's		0.52 (34)	213	16 3	68.4	75.4	175	24.6	75
China (PR)	93.1	2 67 (132)	209	11.6	31.8	62.7	169	21.9	225
Beijing		3.52 (45)	216	11 4	34.7	63.6	170	22.1	75
Nanning		3.36 (45)	154	11.3	24.2	57.7	166	20.7	75
Tianjin		1.12 (42)	256	12.1	36.4	66.8	169	22.9	75
Colombia	73.1	0.52 (45)	212	9.51	73.9	58.6	165	21.8	72
Denmark	22.8	0.70 (40)	159	15.2	74.8	80.8	178	25.2	74
England + Wales	39.1	0.86 (81)	170	14.0	72.8	74.3	174	24.7	150
Birmingham		0.79 (43)	157	13.5	68.7	71.6	172	24.5	75
South Wales		0.93 (38)	183	14.6	76 8	77.1	176	24.8	75
Finland	42.2	0.75 (86)	174	14.8	83.1	76.1	177	24.4	150
Joensuu		0.64 (42)	192	15.0	85.4	76 2	176	24.5	75
Turku		0.86 (44)	156	14.6	80.8	76.0	178	24.4	75
Fed. Rep. Germany	41.5	1.21 (87)	194	14 5	79.7	78.2	178	24.6	146
Bernreid		1.31 (45)	191	14.9	80.0	77.8	177	24.5	74
Heidelberg		1.11 (42)	198	14.2	79.5	78.6	179	24.7	72
German Dem. Rep.	52.2	0.99 (45)	167	14.6	62.7	76 8	176	24.8	75
Hungary	73.9	0.96 (43)	212	13.8	55.0	75.8	170	26.0	75
Iceland	36.2	0.76 (43)	148	15.0	66.9	81.2	180	24.3	75
Italy	53.5	1.09 (172)	185	14 1	61.7	74.1	171	25.5	295
Bassiano		0.84 (45)	191	13.3	64.8	73 0	168	26.9	74
Gubbio		1.00 (43)	183	14.7	57 2	74.3	172	25.4	74
Mirano		1.24 (41)	185	14.8	60.9	75.3	173	25.0	75
Naples		1.29 (43)	183	13.7	63.9	73.8	171	24.9	75
Japan	106.4	2.06 (114)	189	12.5	45.0	62.2	168	22.5	220
Osaka		1.60 (32)	183	12.2	42.8	62.7	170	22.1	75
Tochigi		2.44 (44)	166	12.1	43.8	60.0	167	22.3	70
Toyama		2.14 (38)	216	13.1	48.3	64.0	167	23.1	75
Korea (South)	179.6	2.94 (42)	232	12.2	51.3	64.1	169	22.4	75
Malta	32.4	2.69 (44)	177	13.5	68.8	74.8	168	26.7	75
Mexico	26.1	1.45 (41)	130	9.14	43.7	57.8	160	23.3	69
Netherlands	39.6	0.89 (44)	174	15.1	82.0	75.6	178	23.7	75
Northern Ireland	38.1	0.77 (45)	169	13.2	61.4	72.8	173	24.5	74
Poland	79.7	1.56 (82)	219	15.1	54.4	76.8	174	25.7	150
Krakow		1.42 (41)	235	14.8	57.7	74.2	172	25.4	75
Warsaw		1.69 (41)	204	15.4	51.0	79.3	175	26.0	75
Portugal	73 5	0.89 (44)	200	13.3	66.9	72.7	171	24.9	74
Spain	44.6	1.18 (87)	192	14.3	71.6	71.3	169	25.0	150
Manresa		1.40 (42)	184	14.9	71.8	71.2	170	24.5	75
Torrejon		0.95 (45)	199	13.7	71.5	71.3	169	25.5	75
Trinidad and Tobago	33.6	0.73 (40)	115	15.6	41.5	78.5	175	25.9	65
USA	15.4	0.86 (131)	150	14.4	55.6	82.3	177	26.2	221
Chicago		0.78 (43)	155	15.4	57.8	82.6	177	26.2	72
Goodman (White)		0.98 (45)	143	13.6	51.8	84.9	175	27.1	74
Jackson (White)		0.83 (43)	150	14.2	57.2	79.4	178	25.2	75

NB Medians are age and where necessary centre standardized.

[a] Mortality per 100 000/year, adjusted 45–74 years, N = 24. Data obtained from WHO.

[b] mmol/24-hours in urine.

[c] Creatinine.

[d] Potassium.

n[e] number per centre for INTERSALT analyses of Na, Cr, K, Weight, Height and BMI, age 20–49.

n[f] number per centre for INTERSALT Nitrate only, age 20–49.

Stomach Cancer Mortality, Median Urinary Nitrate and Sodium (Na) Excretion, and Other Variables in 24 Countries. Women

	Stomach cancer mortality[a]	Nitrate[b] (n[f])	Na[b]	Cr[b,c]	K[b,d]	Weight kg	Height cm	BMI kg/m^2	n[e]
Argentina	13.9	1.23 (43)	125	8.68	51.1	60.3	161	22.3	75
Belgium	13.5	1.00 (42)	118	9.57	57.8	62.3	162	23.9	75
Canada	9.9	0.57 (82)	134	10.3	43.2	57.7	157	23.3	140
Labrador		0.51 (42)	115	9.72	40.9	53.9	155	23.0	65
St John's		0.64 (40)	153	10.9	45.6	61.4	160	23.7	75
China (PR)	44.6	2.37 (131)	187	8.05	31.0	55.5	158	22.2	225
Beijing		3.44 (45)	167	7.88	33.0	57.2	159	22.4	75
Nanning		2.76 (44)	155	7.99	27.6	50.3	155	21.0	75
Tianjin		0.91 (42)	240	8.30	32.4	59.1	159	23.3	75
Colombia	44.0	0.44 (44)	174	6.41	64.5	54.7	152	23.1	71
Denmark	11.4	0.61 (41)	117	10.3	57.9	62.2	165	23.1	75
England + Wales	14 9	0.79 (78)	127	9.06	53.7	61.2	160	23.6	149
Birmingham		0.72 (39)	135	8.90	56.3	60.1	159	23.6	75
South Wales		0.86 (39)	119	9.22	51.0	62.3	162	23.6	74
Finland	20.0	0.69 (84)	132	9.66	66.8	62.1	163	22.9	150
Joensuu		0.76 (41)	139	9.48	63.4	60.3	163	22.6	75
Turku		0.62 (43)	124	9.83	70.2	63.8	164	23.3	75
Fed. Rep. Germany	19.5	0.99 (87)	143	9.61	62.1	60.6	164	22.4	147
Bernreid		0.90 (44)	137	9.75	61.6	60.7	164	22.1	73
Heidelberg		1.09 (43)	149	9.48	62.6	60.6	164	22.7	74
German Dem. Rep.	23.4	0.90 (45)	115	9.94	46.6	61.3	163	22.9	74
Hungary	27.5	1.01 (43)	171	9.31	39.6	61 5	157	25.1	75
Iceland	15.5	0.63 (42)	115	9.92	56.4	64.6	167	23.3	75
Italy	22.4	1.03 (166)	154	9.77	52.0	62.2	158	24.6	300
Bassiano		0.99 (44)	162	9.68	50.8	65.0	155	26.6	75
Gubbio		0.98 (44)	152	9.73	51.7	59.8	159	23.2	75
Mirano		1.06 (36)	159	10.6	51.9	62.2	161	23.7	75
Naples		1.10 (42)	145	9.09	53.7	61.7	157	24.6	75
Japan	43.3	1.84 (126)	172	7.85	39.5	52.2	155	21.8	222
Osaka		1.29 (43)	137	7.80	35.7	49.7	155	20.6	73
Tochigi		2.22 (44)	182	7.82	39.7	53.0	154	22.4	74
Toyama		2.01 (39)	196	7.93	43.0	54.0	155	22.5	75
Korea (South)	70.3	2.32 (45)	179	7.48	45.0	52.0	157	21.4	73
Malta	17.3	2.24 (43)	136	9.20	57.5	60.6	156	24.4	75
Mexico	19.6	1.23 (40)	136	6.80	39.0	56.0	150	24.7	61
Netherlands	14.3	1.14 (44)	132	10.6	61.8	63.5	164	23.1	75
Northern Ireland	19.0	0.90 (45)	136	9.31	50.3	61.3	162	23.2	75
Poland	26.0	1.37 (81)	146	9.89	41.6	63.2	159	24.8	150
Krakow		1.11 (41)	155	10.0	43.7	64.0	158	25.1	75
Warsaw		1.63 (40)	138	9.77	39.4	62.4	160	24.5	75
Portugal	34.2	0.83 (44)	149	9.34	56.8	62.7	161	24.5	75
Spain	19.4	0.98 (86)	150	9.18	60.9	60.8	156	24.5	150
Manresa		1.12 (41)	149	9.22	59.1	58.5	157	23.6	75
Torrejon		0.84 (45)	150	9.14	62.7	63.2	156	25.4	75
Trinidad and Tobago	25.0	0.47 (39)	91	10.4	35.6	76.5	164	28.2	70
USA	6.5	0.68 (128)	117	8 91	41.8	63.8	162	24.3	222
Chicago		0.70 (42)	122	9.46	42.9	67.1	163	24.9	74
Goodman (White)		0.79 (41)	110	8.79	37.9	62.7	158	25.6	74
Jackson (White)		0.57 (45)	120	8.46	44.7	61.7	165	22.6	74

Medians are age and where necessary centre standardized.

[a] Mortality per 100 000/year, adjusted 45–74 years, N = 24. Data obtained from WHO.

[b] mmol/24-hours in urine.

[c] Creatinine.

[d] Potassium.

n[e] number per centre for INTERSALT analyses of Na, Cr, K, Weight, Height and BMI, age 20–49.

n[f] number per centre for INTERSALT Nitrate only, age 20–49.