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Sodium content of dietary supplements and over-the-counter medication effervescent tablets

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Question: Do dietary supplement and over-the-counter effervescent tablets have a high, clinically relevant sodium content?

Findings: Dietary supplement and over-the-counter effervescent tablets can contain a high amount of sodium, which is often unknown or neglected. Some products contain more sodium than others, although comparable in (active) ingredients.

Meaning: The variability between preparations is high and these amounts of additional sodium intake may contribute to poor blood pressure control, cardiovascular events, including hospitalization for acute heart failure and death. Patients at risk should be advised to abstain from effervescent tablets.

Abstract

Importance

Dietary sodium intake represents a risk factor for cardiovascular disease and premature death.

Objective

The present study systematically examined the sodium content of dietary supplement effervescent tablets and drugs provided as effervescent tablets from pharmacies.

Design

The sodium content of 39 dietary supplement effervescent tablets available in Germany was measured by optical emission spectrometry with inductively coupled argon plasma. The sodium content of 33 common pharmacy-only effervescent tablets, referred to as "over-the-counter (OTC) drugs", was obtained from the summary of product characteristics or package inserts. We compared the sodium content of the tablets available in Germany to that of 51 dietary supplement effervescent tablets available in the US.

Results

The dietary supplements available in Germany contained 283.9±122.6 mg sodium/tablet, equivalent to 14±6% of the maximum recommended daily sodium intake (MRDSI). Vitamin products had the highest (378.3±112.8 mg, 19±6% of MRDSI) and calcium products the lowest mean sodium content (170.4±113.2 mg, 9±6% of MRDSI). Vitamin products contained significantly more sodium than magnesium ($p=0.004$), calcium ($p=0.006$), and mineral products ($p=0.048$). The sodium content in products available in Germany was higher when compared to those in the US ($p<0.001$). The median sodium content of a single dosage of the OTC drugs was 157.0 mg (interquartile range (IQR): 98.9-417.3 mg); pain/common cold drugs contained the most sodium (median sodium content: 452.1 mg; IQR: 351.3-474.0 mg). Pain/common cold tablets contained significantly more sodium than calcium/vitamin D tablets ($p<0.0001$). The recommended daily dose of the pain/common cold drugs contained 2,776.5 mg sodium (IQR: 1,299.8-3,333.0 mg; 139% of the MRDSI).

Conclusion and Relevance

Nutritional supplements and OTC drugs in effervescent tablets contain a high amount of sodium. Information on sodium content is frequently missing or neglected. Patients with sodium-sensitive conditions such as hypertension and heart failure should avoid effervescent tablets.

Key words:

sodium, dietary supplement, effervescent tablets, over-the-counter drugs, salt, cardiovascular risk, hypertension, heart failure

Introduction

Dietary sodium intake is associated with elevated blood pressure (BP), increased cardiovascular events including stroke and death from any cause.[1–5] In patients with arterial hypertension, the long-term reduction of 1,800 mg less sodium/day (this corresponds to 4,600 mg table salt/day) was associated with a reduction in systolic/diastolic BP of 5.1/2.7 mmHg.[4] The extent of the sodium restriction was proportional to the reduction in BP, with a more pronounced effect in patients with hypertension.[6] Even modest reductions in dietary sodium have been shown to reduce cardiovascular events, including myocardial infarction and stroke.[1,2,7] Dietary sodium consumption is an important risk factor for premature death and disability-adjusted life-years globally.[8] The World Health Organization (WHO) recommends reducing sodium intake to <2,000 mg/day in adults, which is equivalent to 5,000 mg of table salt (sodium chloride).[9] However, only a small proportion of the population achieves this goal.[10] The daily amount of table salt consumed is often much higher (9,000-12,000 mg/day; 3,500-7,700 mg sodium/day), which may, in part, relate to hidden sodium consumption.[10,11]

Effervescent tablets often contain a relatively high amount of sodium in form of sodium bicarbonate, sodium carbonate, or sodium citrate and are frequently consumed without awareness of their sodium content.[12,13] This may be particularly relevant for dietary supplements and over-the-counter (OTC) effervescent tablets (e.g., vitamin C, magnesium, or analgesics) from groceries, drugstores, discounter, and pharmacies because many manufacturers do not provide information on sodium content on the label. The present study systematically examined the sodium content of dietary supplement effervescent tablets from large groceries- and drugstores and sodium-containing effervescent tablets used as drugs from pharmacies.

Methods

The sodium content of 39 different dietary supplement effervescent tablets available in Germany (divided into the categories vitamins, magnesium, calcium, minerals, and other products) from 11 manufacturers and five distributors was analyzed in May and June 2022. The effervescent tablets were divided into categories based on the main active ingredient (e.g., if a product mainly contains magnesium and only a little calcium related to the recommended daily dose, then it is assigned to the category magnesium). Products with main active ingredients other than those of the above categories have been grouped under "other products". The products were purchased from two discounters (ALDI SÜD GmbH & Co. and Netto Marken-Discount Stiftung & Co. KG), one grocery store (Edeka Stiftung & Co. KG), and two drugstores (DM drogerie markt GmbH & Co. KG and Müller Handels GmbH & Co. KG) in Germany and then delivered to the laboratory unopened.

The analyses were performed by an accredited chemical laboratory in Germany (CBA GmbH, Kirkel-Limbach, Germany, Deutsche Akkreditierungsstelle D-PL-14360-01-00). After appropriate standardized sample preparation, optical emission spectrometry with inductively coupled argon plasma (ICP-OES) was used for analysis. The sample preparation (pressure digestion in Teflon-pressure-vessels with microwave-assisted heating) proceeded as follows. The effervescent tablets were ground up and a sample amount corresponding to the expected sodium content was weighed out exactly. This amount of powder was displaced firstly with 1 mL water and then with 3 mL 65% nitric acid and transferred to the Teflon-pressure-vessel. The digestion took place at 180° Celsius in the digestion apparatus (microwave digestion system, CEM) for at least 20 minutes, followed by a cooling period. The vessels were filled up with water again to the nominal volume. Reference solutions and blank values were treated in the same way. After sample preparation, the solutions were transferred directly into the ICP-OES equipment (ICP-OES iCAP 6300 Duo, Thermo-Fisher Scientific). All digestion and

reference solutions were sprayed into an argon plasma, followed by selective detection of sodium emission radiation at 589.59 nm. Regarding blank and reference solutions signals and the resulting linear calibration curve, sodium content in all different effervescent tablets was determined. Details to measurement accuracy of the method can be found elsewhere.[14]

The sodium content of 33 commonly sold pharmacy-only effervescent tablets (30 OTC and tree prescription drugs, all referred to as "OTC drugs" for convenience) from German pharmacies was derived from the respective package inserts or summary of product characteristics.[15] The drugs were divided into the categories pain/common cold, cough, calcium/vitamin D, and other drugs based on the main active ingredient. Drugs with an active ingredient other than those of the above categories have been grouped under "other products". The analysis was based on data from the German Institute for Drug Use Evaluation (Deutsches Arzneiprüfungsinstitut e.V. (DAPI))[16]. This database contains anonymized dispensing data from more than 95% of the community pharmacies in all 16 German federal states, claimed at the expense of the statutory health insurance (SHI) funds, and a DataWare House to identify every product by a specific code ("Pharmazentralnummer", PZN). The SHI system, consisting of nearly 100 funds, covers 88% of the population i.e., approximately 73.3 million people. As the unit for prescribed drugs, we used defined daily doses (DDD) – that is, the assumed average maintenance dose per day for a drug used for its main indication in adults. Further, we analyzed the aggregate amount of dispensed packages of drugs and diet supplements as effervescent tablets in community pharmacies and via mail-order using dispensing data reimbursed by SHI funds as well as private health insurance companies and over-the-counter sales from the INSIGHT Health[17] and DatamedIQ[18] databases, respectively. The INSIGHT Health database includes extrapolated data from a representative sample of over 5,800 community pharmacies.[17] The DatamedIQ database provides aggregated mail-order sales' data.[18] Usual package sizes of pain/common cold and cough effervescent tablets are 10 or 20, of calcium/vitamin D 20, 40, or 100 tablets.

The sodium content of the maximum recommended daily dose was also specified and confirmed by the data in the package insert and/or summary of products characteristics.

The sodium content of 51 dietary supplement effervescent tablets available in the United States (US) was derived from the Dietary Supplement Label Database. The National Institutes of Health's Dietary Supplement Label Database includes 156,957 current and historical label information from products marketed in the US.[19] Effervescent tablets with specified sodium content in the product information were included. The products were divided into the following categories based on the main active ingredient: vitamin, mineral, energy, and other products. Products with an active ingredient other than those of the above categories have been grouped under "other products".

The data are presented as means ± standard deviation (SD), medians and interquartile ranges (IQR), or numbers (%). Normal distribution was tested using Kolmogorov-Smirnov/ Shapiro-Wilk test and using a histogram. Analysis of variance (ANOVA) was used for comparisons of normally distributed parameters, and for comparisons between non-normally distributed parameters, the Kruskal-Wallis test was used. If these tests were significant, we used a post hoc method (Dunn-Bonferroni) for pairwise comparisons. For comparisons between two non-normally distributed parameters, the Mann-Whitney-U-test was used. A two-sided p-value <0.05 was considered statistically significant. Statistical analyses were performed with SPSS (version 27.0.1.0).

Patients and the public were not involved in any way so a patient and public involvement statement is not applicable.

Results

Dietary supplement effervescent tablets in Germany

Supplemental table 1 provides an overview of the included dietary supplement effervescent tablets available in Germany. The median weight of one tablet was 5.5 g, and the price ranged from 2.3 to 39.9 EUR cents/tablet (median price/tablet: 3.2 EUR cents). The sodium content of the various effervescent tablets is listed in table 1. On average, one effervescent tablet contained 283.9±122.6 mg sodium (table 2 A). Vitamin products had the highest (378.3±112.8 mg) and calcium products (170.4±113.2 mg) the lowest mean sodium content. Vitamin products contained significantly more sodium than magnesium (p=0.004), calcium (p=0.006), and mineral (p=0.048) products (figure 1). Based on the recommendations of the WHO,[9] a single effervescent tablet contained 4-28% of the maximum recommended daily sodium intake. The lowest sodium content/effervescent tablet was 76 mg (Magnesium400®, Fit + Vital), and the highest was 564.7 mg (VitaminC1000®, Fit + Vital). The median sodium content was 5.1 g/100 g effervescent tablets, with the highest being 9.63 g sodium/100 g (Eisen + Vitamin C®, Fit + Vital). Supplement figure 1 depicts the number of effervescent tablets according to sodium content (in 100 mg increments) grouped per category. One of ten (10.3%) products contained more than 500 mg sodium/tablet. Only 5 (12.8%) products declared the sodium content on the packaging (Mivolis).

Dietary supplement effervescent tablets in the US

The sodium content of the various effervescent tablets is listed in Supplemental table 2. Among all screened products (n=981), only few declared the sodium content on the label (5.2%), allowing 51 products to be included. The median sodium content of a single effervescent tablet was 190.0 mg (IQR: 100-250 mg; table 2 B) and no difference in sodium content between the various categories was found (p=0.061). A single effervescent tablet contained 2-18% of the maximum recommended daily sodium content. The sodium content of products available in Germany was higher when compared with products available in the US (p<0.001).

Pharmacy-only effervescent tablets

The sodium content of the OTC drugs is listed in table 3. The median sodium content of a single effervescent tablet was 157.0 mg (IQR: 98.9-417.3 mg; table 2 C). The percentage of sodium consumed per effervescent tablet in relation to the maximum recommended daily sodium intake ranged from 3-29%. Pain/common cold drugs had the highest median sodium content (452.1 mg; IQR: 351.3-474.0 mg) and calcium/vitamin D drugs the lowest (87.0 mg; IQR: 52.0-103.0 mg). A single pain/common cold effervescent tablet contained significantly more sodium than one calcium/vitamin D effervescent tablet ($p<0.0001$). Supplement figure 2 depicts the number of effervescent tablets according to sodium content (in 100 mg increments) grouped per category. The median sodium content of the recommended daily dose of all included drugs was 384.0 mg (IQR: 139.0-1295.5 mg; table 2 D) and for pain/common cold drugs 2,776.5 mg (IQR: 1,299.8-3,333.0 mg), representing 19%/139% of maximum recommended daily sodium intake, respectively. The intake of eight tablets (maximum recommended daily dose) of Alka-Seltzer classic® (aspirin, Bayer) would lead to the ingestion of 3,560 mg sodium (figure 2), which encompasses 178% of the maximum recommended daily sodium intake. The sodium content of the maximum daily dose of pain/common cold drugs was significantly higher than the sodium content of the maximum daily dose of calcium/vitamin D drugs ($p<0.0001$) and cough drugs ($p=0.007$). No significant difference in sodium content between the dietary supplement calcium effervescent tablets and the pharmacy-only calcium/vitamin D effervescent tablets was seen ($p=0.109$). A total of 3.96 million packs of the included pain/common cold drugs and 5.30 million packs of the included cough drugs were sold in German pharmacies and via mail-order in 2021 (table 3).[17,18] In 2021, a total of 52.32 million defined daily doses of prescribed calcium/vitamin D drugs, mainly as effervescent tablets, have been dispensed to the expense of the SHI funds in German community pharmacies.[20]

Discussion

This study assessed the sodium content of nutritional supplement effervescent tablets available in Germany and found the sodium amount to range from 76.0 mg to 564.7 mg (average 283.9 mg) sodium/one tablet representing up to 28% of the maximum recommended daily sodium intake. Vitamin products contained more sodium than magnesium, calcium, and mineral products. The sodium amount/tablet of OTC drugs ranged from 52 mg to 575 mg (median 157.0 mg) representing up to 29% of the maximum recommended daily sodium intake. The sodium content was particularly high for pain/common cold tablets. The intake of the recommended daily dose of one OTC drug would lead to a median consumption of 384.0 mg sodium, but as high as 2,776.5 mg for pain/common cold drugs. The major differences in the product classes´ sodium contents are probably due to the variable CO_2-dependent solubilities. More sodium bicarbonate and/or sodium citrate is required for poorly soluble active ingredients in effervescent tablets for them to dissolve quickly and completely in water. The large variations within individual product classes remain unexplained. Products available in the US also contain a relevant amount of sodium with contents ranging from 40 to 360 mg. Of note, dietary supplement effervescent tablets available in Germany contained more sodium than those available in the US. This may, in part, be related to selection bias since only a few US manufactures voluntarily provide information about the sodium content.

Dietary sodium intake has been linked with serious harmful effects, including BP elevation and all-cause death.[1–5] The 2017 report of the Global Burden of Disease study listed excess sodium intake among the major dietary risks, estimated to cause 3 million deaths every year worldwide.[8] A recently published, randomized trial in 20,995 subjects showed that using a table salt substitute containing 75% sodium chloride and 25% potassium chloride (as opposed to regular table salt containing 100% sodium chloride) reduced stroke, cardiovascular events, and death.[1] Against this background, the WHO recommends that daily sodium intake should not exceed 2,000 mg.[9] Many national and international societies have advocated for actions to lower dietary sodium intake through public education, labelling of foods, and improved

formulations of convenience food. Nonetheless, the daily sodium intake around the world is often much higher (9,000-12,000 mg table salt/day; 3,500-7,700 mg sodium/day), which may, in part, aggravated by hidden sodium consumption.[10,11]

For improved and quick solubility, effervescent tablets contain often high amounts of sodium[12] as sodium bicarbonate, sodium carbonate, and/or sodium citrate. The impact of sodium-containing effervescent, mainly paracetamol (acetaminophen) tablets on BP, acute heart failure events, and cardiovascular risk was investigated in several studies.[21–24] The intake of effervescent paracetamol tablets (with 545 mg sodium/dose) was shown to increase 24-hour systolic BP by 5.0 mmHg.[21] Other trials showed an association between the intake of sodium-containing effervescent paracetamol tablets (390-440 mg of sodium/tablet) and an increased risk of hospitalization for heart failure[22], cardiovascular risk, and all-cause mortality among patients with and without hypertension.[12,23,24] The mechanism by which the active substance paracetamol increases blood pressure has not been conclusively clarified; inter alia an influence on the cyclooxygenase pathway is discussed.[25,26] Nevertheless, sodium containing paracetamol effervescent tablets deteriorate blood pressure control mainly caused by the sodium in the effervescent tablets, as evident by the fact that after switching from paracetamol effervescent tablets to paracetamol tablets (without sodium), a decrease in blood pressure was observed.[27]

This provides evidence that effervescent tablets increase sodium intake which might be associated with an increased risk for cardiovascular diseases.[1–5] A large case-control study comprising 1,292,337 patients with a mean follow-up of 7.2 years investigated the association between cardiovascular events and sodium-containing effervescent, dispersible, and soluble drugs.[24] Participants were prescribed sodium-containing formulations or matched standard formulations of the same drug. A total of 61,072 patients with a cardiovascular event were matched with controls. The sodium-containing substances were largely painkillers or calcium

drugs with a wide range of sodium content (4.6-427.8 mg/tablet).[24] The adjusted odds ratio for exposure to sodium-containing drugs were 1.16 for the composite of myocardial infarction, stroke, or vascular death, 1.28 for all-cause mortality, and 7.18 for hypertension.[24] Of note, the sodium content of some of the included effervescent tablets in this study is comparably high.

The ancillary sodium intake through effervescent tablets is often neglected or unknown. Herein, the average sodium content of effervescent food supplements tablets in Germany was 283.9 mg, and the median sodium content of the pharmacy-only effervescent tablets was 157.0 mg. Consuming one of the included effervescent vitamin tablets or pain/common cold tablets corresponds to about one fifth (19%/23%) of the maximum recommended daily sodium intake. Six products (8.3%) contained more than 500 mg sodium/tablet (e.g., VitaminC1000®, Fit + Vital, with 564.7 mg sodium/tablet). Vitamin products contained significantly more sodium than magnesium (p=0.004), calcium (p=0.006) and mineral (p=0.048) products; this might be due to different solubility properties. Of the OTC drugs, doxylamine 25 mg (Gittalun®, Hermes Arzneimittel) and aspirin 500 mg (Aspirin Migräne®, Bayer) had the highest amount of sodium/tablet (575 mg and 544 mg). With a maximum recommended daily dose of eight tablets/day, Alka-Seltzer classic® (324 mg aspirin, Bayer) would add a total of 3,560 mg sodium. The sodium content of the maximum daily dose of pain/common cold drugs was significantly higher than the sodium content of the maximum daily dose of calcium/vitamin D drugs (p<0.0001) and cough drugs (p=0.007). The majority of the general population and healthcare professionals alike are unaware of the high sodium content of effervescent tablets.[12]

A relevant proportion of the population regularly consumes effervescent tablets as a dietary supplement and/or drugs.[13] In a cross-sectional study from France including 1,043 healthy individuals, 26.9% of the participants reported regular intake of effervescent tablets (once in

the last 30 days) and 7.3% reported intake of two or more effervescent tablets/week during the last 30 days.[13] A vast majority of 93.8% of these effervescent tablets were OTC drugs and nutritional supplements, such as vitamins.[13] The presence of hypertension, which should require table salt/sodium restriction, did not result in a reduced intake of effervescent tablets.[13] The exposure to effervescent tablets was estimated using a questionnaire that possibly underestimated the actual consumption.[13] The study was performed in spring/summer, and the intake of effervescent tablets could vary seasonally with an increase during the season of common colds in fall and winter.

According to the Federal Statistical Office of Germany (Statistisches Bundesamt, Destatis), the production of dietary supplements in 2020, which include effervescent tablets, increased by 11% compared with the previous year, most likely as a consequence of the COVID-19 pandemic.[28] In 2020, 180,200 tons of dietary supplements were produced with a value of 1.1 billion Euros in Germany, which corresponds to an increase of 23.4%.[28] In Germany, the sodium content must be indicated on the medicinal products sold in pharmacies but is not mandatory on dietary supplements sold in drugstores or supermarkets.[29,30] Only five (13%) of the included dietary supplements available in Germany and only 5.2% of the investigated dietary supplements available in the US declared sodium content on the packaging, hence, consumers are frequently not informed.

Various sodium-containing drugs applied as effervescent tablets are available. In German pharmacies alone, 3.96 million packages of the included pain/common cold and 5.30 million packs of the included cough effervescent tablets were sold in 2021.[17,18] A total of 52.32 million DDD of calcium/vitamin D drugs, mainly as effervescent tablets, were claimed by community pharmacies at the expense of the SHI funds alone in Germany in 2021.[20] Based on these high sales, we assume that a relevant proportion of the population, occasionally or regularly, consumes effervescent tablets.

A dietary reduction of 1,200 mg sodium/day could translate into an annual reduction of 60,000-120,000 new coronary heart disease patients, 32,000-66,000 fewer strokes, and 54,000-99,000 fewer myocardial infarctions.[2] This amount of sodium is already contained in approximately 3 of the included effervescent vitamin tablets. A modelling study from China showed that a reduction of 1,000 mg table salt/day could prevent approximately 9 million cardiovascular events by 2030, of which approximately 4 million are fatal.[31] Of note, a total of 1,000 mg table salt contains approximately 394 mg sodium. This amount of sodium approximately corresponds to the sodium content of one of the examined vitamin or pain/common cold effervescent tablets.

Limitations

Some limitations of our study should be considered. This study provides relevant insights into the sodium content in dietary supplemental and pharmacy-only effervescent tablets but does not assess the association between the ingestion of the drugs and cardiovascular outcomes. Therefore, only assumptions can be made. Nevertheless, the included effervescent tablets contained a relevant amount of sodium comparable to prior studies investigating the association between sodium-containing effervescent tablets and cardiovascular risk. Randomized clinical trials are needed to investigate the impact of effervescent tablets from grocery stores, discounters, drug stores, and pharmacies on cardiovascular risk. We provide sales figures for effervescent tablets sold in pharmacies. The quantity of dietary supplement effervescent tablets from discounters, grocery- and drugstores is not publicly available.

Conclusion

Dietary supplement and OTC effervescent tablets investigated herein contained a high amount of sodium, which is often unknown or neglected. Some products contain more sodium than others, although comparable in (active) ingredients.

Perspectives

As the variability between preparations is high and these amounts of additional sodium intake may contribute to poor BP control, cardiovascular events, including hospitalization for acute heart failure and death, a front-package labelling of sodium content and associated risk should be demanded by regulators before market access. Patients at risk should be advised to abstain from effervescent tablets, and manufacturers are requested to reduce sodium in effervescent formulations.

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Authors' Contributions

Concept and design: Kunz, Götzinger, Schulz, Mahfoud.

Acquisition, analysis, or interpretation of data: Kunz, Götzinger, Jacobs, Schulz, Mahfoud.

Drafting of the manuscript: Kunz, Schulz, Mahfoud.

Critical revision of the manuscript for important intellectual content: Jacobs, Lauder, Ukena, Meyer, Laufs, Schulz, Böhm, Mahfoud.

Statistical analysis: Kunz, Lauder.

Supervision: Böhm, Mahfoud.

The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Tables

Table 1. Sodium content of German dietary supplement effervescent tablets

Category	Brand name®	Sodium content/tablet (mg)	% of maximum recommended daily sodium intake*	Sodium (g)/ 100g product	Weight/ tablet (g)
Vitamins	fit+Vital Vitamin C1000	564.70	28	9.01	6.27
	elkos Vivede Vitamin C +Zink, Selen, und Vitamin D3	541.10	27	8.95	6.05
	Doppelherz aktiv Vitamin C +Zink	512.80	26	8.11	6.32
	ProLife Vitamin C +Zink, Selen, Vitamin D3	507.90	25	8.48	5.99
	Doppelherz aktiv Vitamin D3 2000 I.E.	485.10	24	7.44	6.52
	SilaVit Vitamin B12	367.30	18	9.05	4.06
	Vitalis Vitamin C 120 mg	341.50	17	8.54	4.00
	Mivolis Vitamin B12	333.00	17	8.08	4.12
	Mivolis Vitamin C	330.30	17	8.02	4.12
	Doppelherz aktiv A-Z Multivitamin+ Mineralien	321.40	16	5.10	6.30
	SilaVit Vitamin C	318.00	16	7.92	4.02
	fit+Vital Multivitamin	304.60	15	7.57	4.02
	elkos Vivede Multivitamin+ Mineralstoffe	273.50	14	4.56	6.00
	ProLife Multivitamin+ Mineralstoffe	263.20	13	4.38	6.01
	fit+Vital Multivitamin+ Mineral	210.70	11	5.26	4.01
Magnesium	Doppelherz aktiv Magnesium 400	332.50	17	5.11	6.51
	Vitalis Magnesium 240 mg	306.10	15	5.58	5.49
	Abtei Magnesium 400 Plus Vitamin C+E	298.70	15	5.56	5.38
	Doppelherz aktiv Magnesium+ Calcium+ D3	271.20	14	4.12	6.59
	Doppelherz aktiv Magnesium 500+ B12	268.90	13	4.12	6.53

	Mivolis Magnesium	262.70	13	6.39	4.11
	elkos Vivede Magnesium+ B-Komplex, Vitamin C und E	248.40	12	4.13	6.01
	Doppelherz aktiv Magnesium+ Kalium Sport	245.50	12	3.72	6.60
	ProLife Magnesium+ B-Komplex, Vitamin C&E	238.00	12	3.95	6.03
	Kneipp Magnesium+ Calcium+ D3	221.30	11	4.91	4.51
	Abtei Magnesium+ Kalium Aktiv Plus	138.10	7	2.52	5.48
	fit+Vital Magnesium	117.80	6	2.95	3.99
	fit+Vital Magnesium 400	76.00	4	1.40	5.41
Calcium	ProLife Calcium+ Vitamin K1, D3, Folsäure	335.90	17	5.60	6.00
	Mivolis Calcium	145.90	7	3.53	4.14
	fit+Vital Calcium+ D3	116.20	6	2.89	4.02
	fit+Vital Calcium 1000	83.70	4	1.36	6.17
Minerals	Kneipp Männer Mineralstoffe	217.00	11	3.87	5.61
	Kneipp Frauen Mineralstoffe	209.40	10	3.33	6.29
	Mivolis Multi-Mineral	148.40	7	3.62	4.10
Other products	fit+Vital Eisen+ Vitamin C	382.90	19	9.63	3.98
	SilaVit Immun Aktiv	363.80	18	8.55	4.25
	sanotact Recovery+ Aminosäuren	187.60	9	3.54	5.29
	isostar Hydrate & Perform	181.00	9	1.51	11.99
*Maximum recommended daily sodium intake according to World Health Organization recommendations[9]					

Table 2. Sodium content per: (A) Dietary supplement effervescent tablet available in Germany, (B) Dietary supplement effervescent tablet in the US, (C) OTC effervescent tablet, (D) recommended daily dose of the included OTC effervescent tablets

A		
Category	**Sodium content (mg)/tablet mean±SD**	**% of the maximum recommended daily sodium intake* mean±SD**
…all included products	283.9±122.6	14±6
…vitamin products	378.3±112.8	19±6
…magnesium products	232.7±76.7	12±4
…calcium products	170.4±113.2	9±6
…mineral products	191.6±37.6	10±2
…other products	278.8±109.5	14±6
B		
Category	**Sodium content (mg)/tablet Median (IQR)**	**% of the maximum recommended daily sodium intake* Median (IQR)**
…all included products	190.0 (100.0-250.0)	10 (5-13)
…vitamin products	100.0 (72.5-230.0)	5 (4-12)
…mineral products	250.0 (140.0-360.0)	13 (7-18)
…energy products	190.0 (150.0-260.0)	10 (8-13)
…other products	210.0 (158.8-256.3)	11 (8-13)
C		
Category	**Sodium content (mg)/tablet Median (IQR)**	**% of the maximum recommended daily sodium intake* Median (IQR)**
…all included drugs	157.0 (98.9-417.3)	8 (5-21)
…pain/common cold	452.1 (351.3-474.0)	23 (18-24)
…cough	138.8 (112.8-157.9)	7 (6-8)
…calcium/vitamin D	87.0 (52.0-103.0)	4 (3-5)
…other drugs	267.0 (119.8-387.5)	13 (6-19)
D		
Category	**Sodium content (mg) of the maximum daily dose Median (IQR)**	**% of the maximum recommended daily sodium intake* Median (IQR)**
…all included drugs	384.0 (139.0-1295.5)	19 (7-65)
…pain/common cold	2,776.5 (1,299.8-3,333.0)	139 (65-167)
…cough	297.0 (144.5-427.0)	15 (7-21)
…calcium/vitamin D	104.0 (96.3-104.8)	5 (5-5)
…other drugs	801.0 (312.8-1,155.5)	40 (16-58)

*Maximum recommended daily sodium intake according to World Health Organization recommendations[9]
IQR= interquartile range; OTC= over-the-counter, SD= standard deviation

Table 3. Sodium content of OTC effervescent tablets

Category	Brand name® (manufacturer)	sodium content/tablet (mg)	% of the maximum recommended daily sodium intake* of one tablet	sodium content of maximum recommended daily dose (mg)	% of maximum recommended daily sodium intake* of the maximum recommended daily dose	Maximum recommended tablets per day	OTC	Active ingredients	Sales figures
Pain/common cold (frequently dispensed products)	Aspirin Migräne (Bayer)	544	27	3,264	163	6	yes	aspirin	3.96 million packs of this class sold in 2021 in Germany[17,18]
	ASS + C-ratiopharm gegen Schmerzen (Ratiopharm)	477	24	2,385	119	5	yes	aspirin, ascorbic acid	
	ASPIRIN plus C forte (Bayer)	473	24	1,419	71	3	yes	aspirin, ascorbic acid	
	ASPIRIN plus C (Bayer)	466	23	2,796	140	6	yes	Aspirin, ascorbic acid	
	Togal Kopfschmerz-Brause + Vitamin C (Kyberg Pharma)	459	23	2,754	138	6	yes	Aspirin, ascorbic acid, caffeine	
	Alka-Seltzer classic (Bayer)	445	22	3,560	178	8	yes	aspirin	
	FIZAMOL 500 mg (Accord Healthcare)	419	21	3,352	168	8	yes	acetaminophen	
	PARACETAMOL-ratiopharm 500 mg (Ratiopharm)	416	21	3,328	166	8	yes	acetaminophen	
	WICK DayMed Erkältungsgetränk (WICK Pharma)	157	8	942	47	6	yes	acetaminophen, guaifenesin, phenylephrine	
	Grippostad C Stickpack (STADA Consumer Health)	128	6	384	19	3	yes	acetaminophen, chlorpheniramine, ascorbic acid, caffeine	
Cough (frequently dispensed products)	NAC-ratiopharm 200 mg, (Ratiopharm)	190	10	570	29	3	yes	acetylcysteine	5.30 million packs of this class sold in 2021 in Germany[17,18]
	Fluimucil 200 mg (Zambon)	158	8	474	24	3	no	acetylcysteine	
	Fluimucil long 600 mg (Zambon)	158	8	158	8	1	no	acetylcysteine	
	NAC-ratiopharm 600 mg (Ratiopharm)	150	8	150	8	1	yes	acetylcysteine	
	ACC akut 600mg (Hexal)	139	7	139	7	1	yes	acetylcysteine	
	NAC 600 akut (1A Pharma)	139	7	139	7	1	yes	acetylcysteine	
	Ambrobeta 30 (betapharm Arzneimittel)	127	6	381	19	3	yes	ambroxol	
	ACC akut 200mg (Hexal)	99	5	297	15	3	yes	acetylcysteine	
	NAC 200 akut (1A Pharma)	99	5	297	15	3	yes	acetylcysteine	

Calcium/ vitamin D3 (colecalciferol; examples of frequently prescribed effervescent tablets)	Calcium Sandoz forte (Hexal)	288	14	864	43	3	yes	Calcium + vitamin D	52.32 million DDD of the entire class claimed to the expense of the SHI funds in 2021 in Germany[20]
	Calcium D3 acis 1.200/ 800 (acis Arzneimittel)	105	5	105	5	1	yes	Calcium + vitamin D	
	CalciCare-D3 forte 1.000 mg/ 880 I.E. (ORION Pharma)	97	5	97	5	1	yes	Calcium + vitamin D	
	Calcilac 1000 mg/ 880 I.E. (MIBE Arzneimittel)	96	5	96	5	1	yes	Calcium + vitamin D	
	Osteoplus 1.000 mg/ 1.000 I.E. (Recordati Pharma)	78	4	78	4	1	yes	Calcium + vitamin D	
	Calcigen D 600/ 400 (MEDA Pharma)	52	3	104	5	2	yes	Calcium + vitamin D	
	Calcium D3-ratiopharm 600/ 400 (Ratiopharm)	52	3	104	5	2	yes	Calcium + vitamin D	
	Calcium Sandoz D Osteo 600 mg/ 400 I.E. (Hexal)	52	3	104	5	2	yes	Calcium + vitamin D	
Other drugs (examples)	Gittalun (Hermes Arzneimittel)	575	29	1,150	58	2	yes	doxylamine	-
	Zink-ratiopharm 25mg (Ratiopharm)	325	16	325	16	1	yes	zinc	
	Magnesium Verla (Verla-Pharm Arzneimittel)	314	16	942	47	3	yes	magnesium	
	Lösferron (MIBE Arzneimittel)	220	11	660	33	3	yes	Fe-(II)-D-gluconat	
	Magnesiocard 7,5 mmol (Verla-Pharm Arzneimittel)	138	7	276	14	2	yes	magnesium	
	Morphin Painbreak akut 20 mg (PB Pharma)	65	3	1,170	59	18	no	morphine	

*Maximum recommended daily sodium intake according to World Health Organization recommendations[9]
DDD= defined daily doses; OTC= over-the-counter; SHI= statutory health insurance

Figure Legends

Central Illustration.

Figure 1. Mean sodium content of the respective category of the dietary supplement effervescent tablets available in Germany.

Figure 2. Sodium content of the maximum recommended daily dose of some included effervescent OTC tablets.

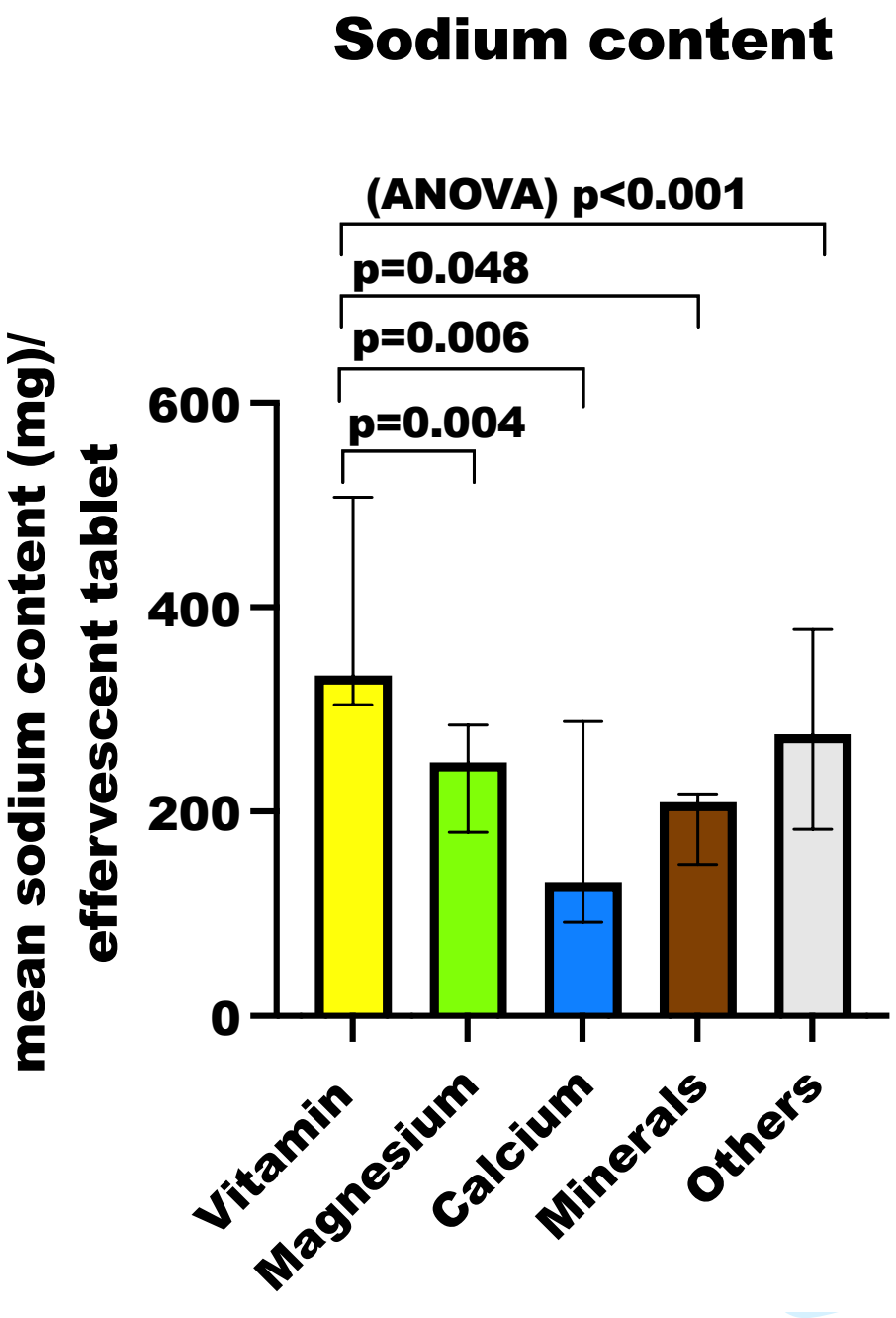


Figure 1. Mean sodium content of the respective category of the German dietary supplement effervescent tablets. P values are given for between-group comparisons (adjusted for post hoc method). ANOVA = analysis of variance.

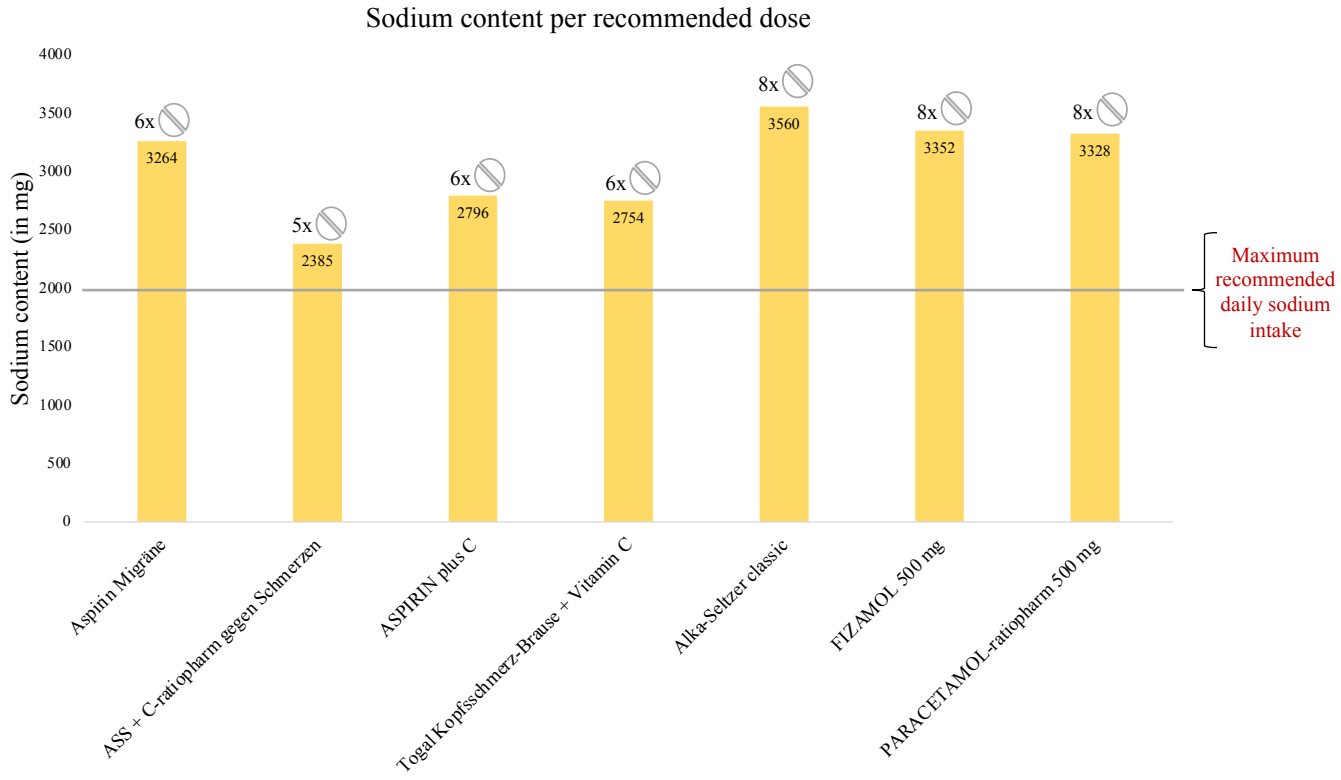


Figure 2. Sodium content of the maximum recommended daily dose of some included effervescent OTC tablets. The number above the bars corresponds to the maximum daily number of tablets. (Aspirin Migräne®: Bayer; ASS + C-ratiopharm gegen Schmerzen®: Ratiopharm; ASPIRIN plus C®: Bayer; Togal Kopfschmerz-Brause + Vitamin C®: Kyberg Pharma; Alka-Seltzer classic®: Bayer; FIZAMOL 500 mg®: Accord Healthcare, Paracetamol-ratiopharm 500mg®: Ratiopharm

What is known ?

- Dietary sodium intake → BP ↑ and CV events ↑
- Recommended daily sodium intake: < 2000 mg
- ETs contain high amounts of sodium (often not labeled)
- approx. 30% of the population regularly consume ETs as dietary supplements and/or drugs

Dietary supplement ETs

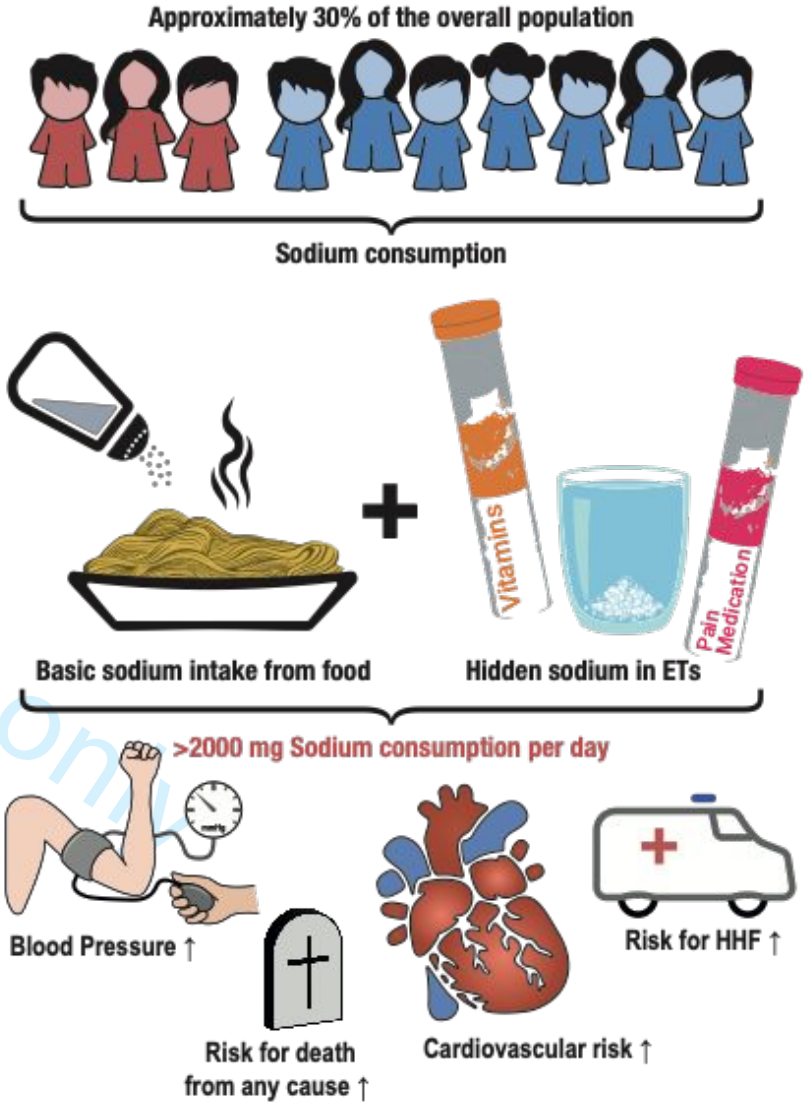
- 39 included
- Average sodium content: 283.9±122.6 mg → 4-28% of the RDSI
- Highest average sodium content: vitamin products (378.3±112.8 mg)
- Lowest average sodium content: calcium products (170.4±113.2 mg)
- Vitamin products: more sodium than magnesium (p=0.004), calcium (p=0.006) and mineral (p=0.048) products

Pharmacy-only ETs

- Median sodium content: 157.0 mg (IQR: 98.9-417.3 mg) → 3-29% of the RDSI
- Highest median sodium content: pain/ common cold drugs (452.1 mg; IQR: 351.3-474.0 mg)
- Lowest median sodium content: calcium/ vitamin D drugs (87.0 mg; IQR: 52.0-103.0 mg)
- Median sodium content of the MDD of pain/ common cold drugs: 2,776.5 mg (IQR: 1,299.8-3,333.0 mg)

Conclusion

- ETs contain a relevant amount of sodium (often unknown or neglected)
- Additional sodium intake → poor BP control and CV events ↑
- Sodium loaded ETs should be avoided in patients at risk



Central Illustration. BP= blood pressure; CV= cardiovascular; ET= effervescent tablets; HHF= hospitalization for acute heart failure; IQR= interquartile range; MDD= maximum daily dose; RDSI= recommended daily sodium intake.

Supplement:

Supplement table 1. Overview of the included German products.

Supplement table 2. Sodium content of the included American products.

Supplement figure 1. Number of different German dietary supplement effervescent tablets that contain a certain amount of sodium (classified in 100 mg increments).

Supplement figure 2. Number of different pharmacy-only effervescent tablets that contain a certain amount of sodium (classified in 100 mg increments).

Supplement table 1. Overview of the included German products.

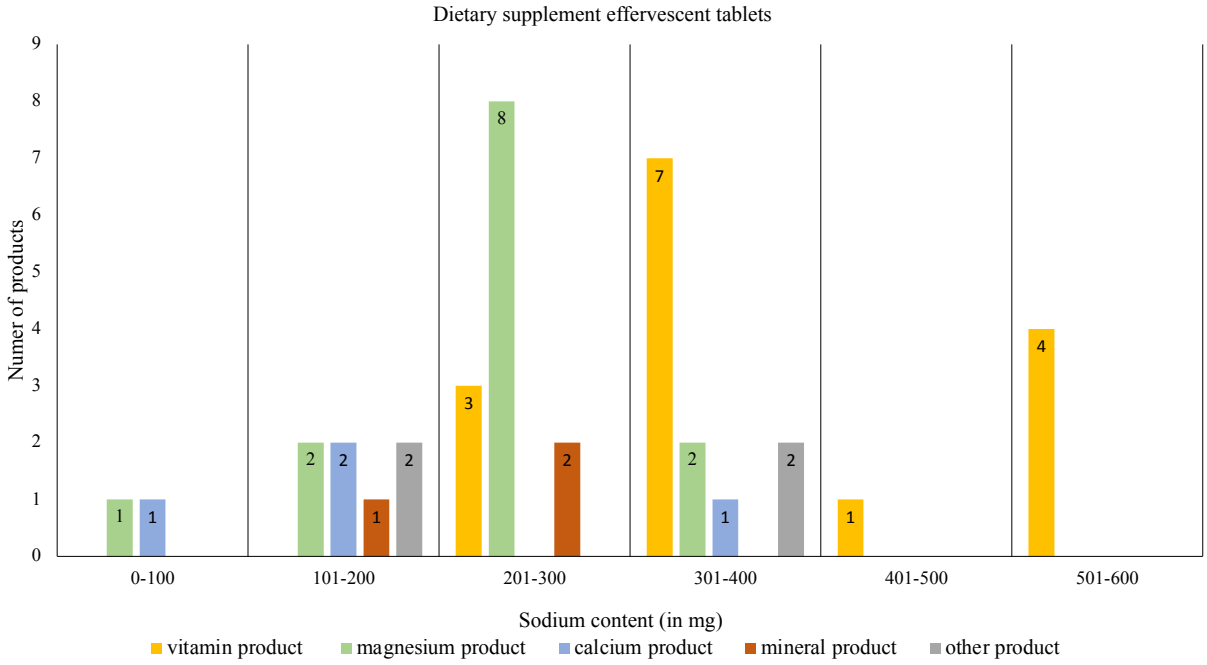
Offeror	Manufacturer	Brand name®	Number of tablets	Total weight (g)	Weight/ tablet (g)	Total price (cent)	Price/ tablet (cent)
ALDI SÜD GmbH & Co.	Vitalis	Magnesium 240 mg	14	78	5.6	45	3.2
		VitaminC 120 mg	20	80	4.0	45	2.3
Edeka Stiftung & Co. KG	ELKOS Vivede	VitaminC+ Zink, Selen, Vitamin D3	17	102	6.0	55	3.2
		Magnesium+ B-Komplex, Vitamin C und E	17	102	6.0	55	3.2
		Multivitamin+ Mineralstoffe	17	102	6.0	55	3.2
Netto Marken-Discount Stiftung & Co. KG	ProLife	VitaminC+ Zink, Selen, Vitamin D3	17	102	6.0	55	3.2
		Magnesium+ B-Komplex, Vitamin C&E	17	102	6.0	55	3.2
		Multivitamin+ Mineralstoffe	17	102	6.0	55	3.2
		Calcium+ Vitamin K1, D3, Folsäure	17	102	6.0	55	3.2
DM drogerie markt GmbH & Co. KG	Mivolis	Magnesium	20	82	4.1	45	2.3
		VitaminB12	20	82	4.1	45	2.3
		Calcium	20	82	4.1	45	2.3
		Multi-Mineral	20	82	4.1	45	2.3
		VitaminC	20	82	4.1	45	2.3
	Kneipp	Magnesium+ Calcium+ D3	20	90	4.5	245	12.3
Müller Handels GmbH & Co. KG	Kneipp	Frauen Mineralstoffe	15	94	6.3	345	23.0
		Männer Mineralstoffe	15	84	5.6	399	26.6
	Abtei	Magnesium400 Plus Vitamin C+E	15	81	5.4	295	19.7
		Magnesium+ Kalium Aktiv Plus	15	82.5	5.5	275	18.3
	Sanotact	Recovery+ Aminosäuren	15	79.5	5.3	295	19.7
	Doppelherz	VitaminC+ Zink	15	94.5	6.3	295	19.7
		VitaminD3 2000 IE	15	97.5	6.5	275	18.3
		A-Z Multivitamin+ Mineralien	15	93	6.2	279	18.6
		Magnesium 400	15	97.5	6.5	275	18.3

		Magnesium+ Calcium+ D3	15	97.5	6.5	279	18.6
		Magnesium 500+ B12	15	97.5	6.5	249	16.6
		Magnesium+ Kalium Sport	15	99	6.6	299	19.9
	Fit + Vital	Caclium+ D3	20	80	4.0	139	7.0
		Multivitamin	20	80	4.0	45	2.3
		Vitamin C1000	15	93	6.2	139	9.3
		Multivitamin+ Mineral	20	80	4.0	45	2.3
		Magnesium	20	80	4.0	45	2.3
		Eisen+ VitaminC	20	80	4.0	139	7.0
		Cacium 1000	15	93	6.2	45	3.0
		Magnesium 400	15	81	5.4	45	3.0
	SilaVit	Immun Aktiv	20	84	4.2	139	7.0
		Vitamin B12	20	80	4.0	125	6.3
		Vitamin C	20	80	4.0	45	2.3
	Isostar	Hydrate & Perform	10	120	12.0	399	39.9

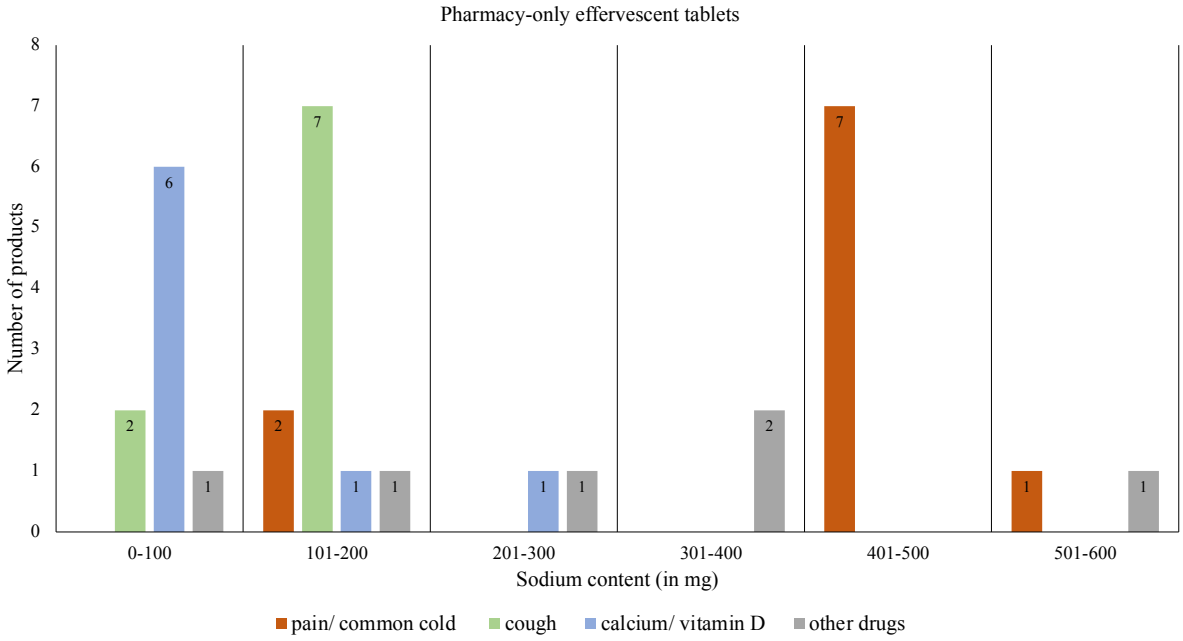
Supplement table 2. Sodium content of the included American products.

Brand name®	Manufacturer	Category	Sodium content/tablet (mg)
ActivJoint Tangerine	Trace Minerals Research	Other	155
Advanced Anti-Aging Formula Effervescent Drink Mix Orange	TimeFighters	Other	55
Airborne Dual Action Citrus	Airborne	Vitamin	230
Airborne Elderberry Effervescent Tablets	Airborne	Mineral	230
Airborne Immune Support Effervescent Tablets	Airborne	Vitamin	230
Airborne Vitamin C Original Lemon Lime	Airborne	Vitamin	230
Airborne Zesty Orange	Airborne	Mineral	150
Alka-Seltzer Plus Immunity Complex	Bayer	Vitamin	313
Amino X Fruit Punch	BSN	Other	160
AngiNOX Natural Orange Flavor	XYMOGEN	Other	220
Berocca Orange Flavor	Bayer	Energy	260
Best Defense Orange Boost	Herbalife Nutrition	Vitamin	115
BetaBoost + Vitamin C Citrus	Airborne Advanced	Vitamin	240
Carni-Fizz Natural Lemon Lime Flavor	Body Fizzics	Other	245
CuraMed Natural Tangerine Flavor	Terry Naturally	Other	130
CuraPro 350 mg Tangerine Effervescent	EuroMedica	Mineral	130

Effer-C Lemon-Lime Effervescent Drink Mix	NOW	Vitamin	50
Effervescent Effer-Energy Tropical Punch	NOW Sports	Mineral	360
Effervescent Effer-Hydrate	NOW Sports	Mineral	360
Effervescent Energy Lava Lime	Eruption	Energy	240
Effervescent Vitamin C 1000 mg Natural Orange Flavor	Sundown Naturals	Vitamin	60
Effervescent Vitamin C Orange Flavored	365 Everyday Value	Vitamin	60
Energize Isotropin Lemon Flavor Effervescent	Newton-Everett	Energy	150
Energy Berry Blast	Nuun	Energy	100
Ester-C Effervescent 100 mg Plus Electrolytes Natural Orange Flavor	American Health	Vitamin	100
Ester-C Effervescent 1000 mg Natural Orange Flavor	NatureSmart	Vitamin	100
Ester-C Effervescent 1000 mg Natural Raspberry	American Health	Vitamin	55
Ester-C Effervescent 1000 mg Natural Raspberry Flavor	Solgar	Vitamin	40
Evotest Black Cherry	BSN	Other	300
Garcinia Cambogia Lineatabs Passion Fruit Flavor	Apax	Other	190
Green Superfood Detox Orange Turmeric Flavor	Amazing Grass	Other	260
Immune Oxylent Effervescent Supplement Drink	Immune Oxylent	Vitamin	90
Immune Support Orange Flavor	Equate	Vitamin	230
Immuni-V Orange Effervescent	MRI Performance	Vitamin	85
Immunity Blueberry Tangerine	Nuun	Vitamin	100
Isotropin Rejuvenation Tangerine Flavor	NewtonEverett	Other	255
Liftoff Tropical Fruit Force	Herbalife Nutrition	Vitamin	230
Lineatabs	Apax	Other	270
Nuun Active Fruit Punch	Nuun	Vitamin	360
Nuun Hydration Tri-Berry	Nuun	Mineral	360
POW Berry-Melon Fizz	EBOOST	Energy	190
POW Berry-Melon Fizz	EBOOST	Energy	155
Power Pak Cranberry	Trace Minerals Research	Vitamin	175
Pumped Edge Fruit Punch	BSN	Other	200
Sambucus Fizzy Berry Flavored	Nature's Way	Other	160
Sport +Caffeine Fresh Lime	Nuun	Energy	300
Sport Fruit Punch	Nuun	Mineral	300
Sport Oxylent 3-In-1 Performance Supplement Drink Blueberry Burst	Sport Oxylent	Mineral	90
Vitamins Blueberry Pomegranate	Nuun	Vitamin	100
Wal-Born Orange Flavor	Well At Walgreens	Other	230
ZYM Electrolyte Drink Tablets	ZYM	Mineral	250



Supplement figure 1. Number of different German dietary supplement effervescent tablets that contain a certain amount of sodium (classified in 100 mg increments).



Supplement figure 2. Number of different pharmacy-only effervescent tablets that contain a certain amount of sodium (classified in 100 mg increments).

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The hidden sodium in effervescent tablets of dietary supplements and over-the-counter drugs – A comparative cross-sectional study

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The hidden sodium in effervescent tablets of dietary supplements and over-the-counter drugs – A comparative cross-sectional study

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Abstract

Objective: Dietary sodium intake represents a risk factor for cardiovascular disease and mortality. The study sought to analyze the sodium content of effervescent dietary supplements and drugs in Germany and the United States of America.

Design: Comparative cross-sectional study.

Setting and Methods: The sodium content of 39 dietary supplement effervescent tablets available in Germany was measured using optical emission spectrometry with inductively coupled argon plasma. The sodium content of 33 common pharmacy-only effervescent tablets ("over-the-counter (OTC) drugs") in Germany was obtained from the summary of product characteristics. We compared the sodium content of the measured German dietary supplement effervescent tablets to that of 51 dietary supplement effervescent tablets available in the United States of America (data: National Institutes of Health's Dietary Supplement Label Database).

Results: The measured sodium content in the German dietary supplements was 283.9±122.6 mg sodium/tablet, equivalent to 14±6% of the maximum recommended daily sodium intake (MRDSI). Vitamin products had the highest (378.3±112.8 mg, 19±6% of MRDSI), and calcium products had the lowest mean sodium content (170.4±113.2 mg, 9±6% of MRDSI). Vitamin products contained significantly more sodium than magnesium (p=0.004), calcium (p=0.006), and mineral products (p=0.048). The sodium content measured in products available in Germany was higher when compared to the declared sodium content on the label of the products sold in the United States of America (p<0.001). The median summary of product characteristics-declared sodium content of a single dose of the German OTC drugs was 157.0 mg (interquartile range (IQR): 98.9-417.3 mg); pain/common cold drugs contained the most sodium (median: 452.1 mg; IQR: 351.3-474.0 mg). The median sodium content of recommended daily doses of the pain/common cold drugs was 2,776.5 mg (IQR: 1,299.8-3,333.0 mg; 139% of the MRDSI).

Conclusion: Effervescent tablets of nutritional supplements and OTC drugs contain high amounts of sodium, which often is not disclosed.

Data Availability Statement

All data relevant to the study are included in the article or uploaded as supplementary information. No additional data available.

Key words:

sodium, dietary supplement, effervescent tablets, over-the-counter drugs, salt, cardiovascular risk, hypertension, heart failure

Strengths and limitations of this study:

- The measurement of sodium content in dietary supplement and pharmacy-only effervescent tablets gives detailed insights into the hidden sodium amounts in these dosage forms.
- We provide sales figures for effervescent tablets sold in German pharmacies.
- The quantity of dietary supplement effervescent tablets from discounters, grocery- and drugstores is not publicly available.
- The association between the ingestion of effervescent tablets and cardiovascular outcomes was not investigated.

Introduction

Dietary sodium intake is associated with elevated blood pressure (BP), increased cardiovascular events including stroke and death from any cause.[1–5] In patients with arterial hypertension, the long-term reduction of 1,800 mg less sodium/day (this corresponds to 4,600 mg table salt/day) was associated with a reduction in systolic/diastolic BP of 5.1/2.7 mmHg.[4] The extent of the sodium restriction was proportional to the reduction in BP, with a more pronounced effect in patients with hypertension.[6] Even modest reductions in dietary sodium have been shown to reduce cardiovascular events, including myocardial infarction and stroke.[1,7] Dietary sodium consumption is an important risk factor for premature death and disability-adjusted life-years globally.[7] The World Health Organization (WHO) recommends reducing sodium intake to <2,000 mg/day in adults, which is equivalent to 5,000 mg of table salt (sodium chloride).[8] However, only a small proportion of the population achieves this goal.[9] The daily amount of table salt consumed is often much higher (9,000-12,000 mg/day; 3,500-7,700 mg sodium/day), which may, in part, relate to hidden sodium consumption.[9,10]

Effervescent tablets often contain a relatively high amount of sodium in form of sodium bicarbonate, sodium carbonate, or sodium citrate and are frequently consumed without awareness of their sodium content.[11,12] This may be particularly relevant for dietary supplements and over-the-counter (OTC) effervescent tablets (e.g., vitamin C, magnesium, or analgesics) from groceries, drugstores, discounter, and pharmacies because many manufacturers do not provide information on sodium content on the label. The present study sought to provide information about the often not labeled sodium content of dietary supplement effervescent tablets from large groceries- and drugstores and sodium-containing effervescent tablets used as drugs from pharmacies. Country-specific differences in sodium content (products from Germany vs. products from the United States of America) were set forth.

Methods

Study design

A comparative cross-sectional study was conducted in 2022 and 2023 to examine and compare the sodium content of different categories of effervescent tablets.

Classification, place of purchase and analyses of the dietary supplements available in Germany

The sodium content of 39 different dietary supplement effervescent tablets available in Germany (divided into the categories vitamins, magnesium, calcium, minerals, and other products) from 11 manufacturers and five distributors was analyzed in May and June 2022. The effervescent tablets were divided into categories based on the main active ingredient (e.g., if a product mainly contains magnesium and only a little calcium related to the recommended daily dose, then it is assigned to the category magnesium). The products were purchased from two discounters (ALDI SÜD GmbH & Co. and Netto Marken-Discount Stiftung & Co. KG), one grocery store (Edeka Stiftung & Co. KG), and two drugstores (DM drogerie markt GmbH & Co. KG and Müller Handels GmbH & Co. KG) in Germany and then delivered to the laboratory unopened.

The analyses were performed by an accredited chemical laboratory in Germany (CBA GmbH, Kirkel-Limbach, Germany, Deutsche Akkreditierungsstelle D-PL-14360-01-00). After appropriate standardized sample preparation, optical emission spectrometry with inductively coupled argon plasma (ICP-OES) was used for analysis. The sample preparation (pressure digestion in Teflon-pressure-vessels with microwave-assisted heating) proceeded as follows. The effervescent tablets were ground up and a sample amount corresponding to the expected sodium content was weighed out exactly. This amount of powder was displaced firstly with 1 mL water and then with 3 mL 65% nitric acid and transferred to the Teflon-pressure-vessel. The digestion took place at 180° Celsius in the digestion apparatus (microwave digestion

system, CEM) for at least 20 minutes, followed by a cooling period. The vessels were filled up with water again to the nominal volume. Reference solutions and blank values were treated in the same way. After sample preparation, the solutions were transferred directly into the ICP-OES equipment (ICP-OES iCAP 6300 Duo, Thermo-Fisher Scientific). All digestion and reference solutions were sprayed into an argon plasma, followed by selective detection of sodium emission radiation at 589.59 nm.

Classification and data source of the over-the-counter drugs

The sodium content of 33 commonly sold pharmacy-only effervescent tablets (30 OTC and tree prescription drugs, all referred to as "OTC drugs" for convenience) from German pharmacies was derived from the respective package inserts or summary of product characteristics. The drugs were divided into the categories pain/common cold, cough, calcium/vitamin D, and other drugs based on the main active ingredient. The analysis was based on data from the German Institute for Drug Use Evaluation (Deutsches Arzneiprüfungsinstitut e.V. (DAPI)). This database contains anonymized dispensing data from more than 95% of the community pharmacies in all 16 German federal states, claimed at the expense of the statutory health insurance (SHI) funds, and a DataWare House to identify every product by a specific code ("Pharmazentralnummer", PZN). The SHI system, consisting of nearly 100 funds, covers 88% of the population i.e., approximately 73.3 million people. As the unit for prescribed drugs, we used defined daily doses (DDD) – that is, the assumed average maintenance dose per day for a drug used for its main indication in adults. Further, we analyzed the aggregate amount of dispensed packages of drugs and diet supplements as effervescent tablets in community pharmacies and via mail-order using dispensing data reimbursed by SHI funds as well as private health insurance companies and over-the-counter sales from the INSIGHT Health (https://www.insight-health.de/) and DatamedIQ (https://www.datamediq.com/) databases, respectively. Usual package sizes of pain/common cold and cough effervescent tablets are 10

or 20, of calcium/vitamin D 20, 40, or 100 tablets. The sodium content of the maximum recommended daily dose was also specified and confirmed by the data in the package insert and/or summary of products characteristics.

Classification and data source of the dietary supplements available in the United States of America

The sodium content of 51 dietary supplement effervescent tablets available in the United States of America was derived in May 2023 from the Dietary Supplement Label Database. The National Institutes of Health's Dietary Supplement Label Database includes 156,957 current and historical label information from products marketed in the US. Effervescent tablets with specified sodium content in the product information were included. The products were divided into the following categories based on the main active ingredient: vitamin, mineral, energy, and other products.

Statistical methods

The data are presented as means ± standard deviation (SD), medians and interquartile ranges (IQR), or numbers (%). Normal distribution was tested using Kolmogorov-Smirnov/ Shapiro-Wilk test and using a histogram. Analysis of variance (ANOVA) was used (after tested for all assumptions for ANOVA: normally distribution, independence of cases, homogeneity of variance) for comparisons of normally distributed parameters, and for comparisons between non-normally distributed parameters, the Kruskal-Wallis test was used. If these tests were significant, we used a post hoc method (Dunn-Bonferroni) for pairwise comparisons. For comparisons between two non-normally distributed parameters, the Mann-Whitney-U-test was used. A two-sided p-value <0.05 was considered statistically significant. Statistical analyses were performed with SPSS (version 27.0.1.0).

Patient and public involvement

None.

Results

Dietary supplement effervescent tablets in Germany

Supplemental table 1 provides an overview of the included dietary supplement effervescent tablets available in Germany. The median weight of one tablet was 5.5 g, and the price ranged from 2.3 to 39.9 EUR cents/tablet (median price/tablet: 3.2 EUR cents). The sodium content of the effervescent tablets measured by ICP-OES is listed in table 1. On average, one effervescent tablet contained 283.9±122.6 mg sodium (table 2 A). Vitamin products had the highest (378.3±112.8 mg) and calcium products (170.4±113.2 mg) the lowest mean sodium content. Vitamin products contained significantly more sodium than magnesium (p=0.004), calcium (p=0.006), and mineral (p=0.048) products (figure 1). Based on the recommended maximum intake of 2,000 mg sodium/day, a single effervescent tablet contained as much as 4-28% of the maximum recommended daily sodium intake. The lowest sodium content/effervescent tablet was 76 mg (Magnesium400®, Fit + Vital), and the highest was 564.7 mg (VitaminC1000®, Fit + Vital). The median sodium content was 5.1 g/100 g effervescent tablets, with the highest being 9.63 g sodium/100 g (Eisen + Vitamin C®, Fit + Vital). Supplement figure 1 depicts the number of effervescent tablets according to sodium content (in 100 mg increments) grouped per category. One of ten (10.3%) products contained more than 500 mg sodium/tablet. Only 5 (12.8%) products (all of the Mivolis brand) declared the sodium content on the packaging which was nearly identical to the measured sodium content.

Dietary supplement effervescent tablets in the United States of America

The sodium content of the various effervescent tablets is listed in Supplemental table 2. Among all screened products (n=981), only few declared the sodium content on the label (5.2%),

allowing 51 products to be included. The median sodium content of a single effervescent tablet was 190.0 mg (IQR: 100-250 mg; table 2 B) and no difference in sodium content between the various categories was found (p=0.061). A single effervescent tablet contained 2-18% of the maximum recommended daily sodium content. The measured sodium content of dietary supplements available in Germany was higher when compared with the declared sodium content of products available in the United States of America (p<0.001).

Pharmacy-only effervescent tablets

The sodium content declared on the summary of product characteristics of the OTC drugs sold in Germany is listed in table 3. The median sodium content of a single effervescent tablet was 157.0 mg (IQR: 98.9-417.3 mg; table 2 C). The percentage of sodium consumed per effervescent tablet in relation to the maximum recommended daily sodium intake ranged from 3-29%. Pain/common cold drugs had the highest median sodium content (452.1 mg; IQR: 351.3-474.0 mg) and calcium/vitamin D drugs the lowest (87.0 mg; IQR: 52.0-103.0 mg). A single pain/common cold effervescent tablet contained significantly more sodium than one calcium/vitamin D effervescent tablet (p<0.0001). Supplement figure 2 depicts the number of effervescent tablets according to sodium content (in 100 mg increments) grouped per category. The median sodium content of the recommended daily dose of all included drugs was 384.0 mg (IQR: 139.0-1295.5 mg; table 2 D) and for pain/common cold drugs 2,776.5 mg (IQR: 1,299.8-3,333.0 mg), representing 19%/139% of maximum recommended daily sodium intake, respectively. The intake of eight tablets (maximum recommended daily dose) of Alka-Seltzer classic® (aspirin, Bayer) would lead to the ingestion of 3,560 mg sodium (figure 2), which encompasses 178% of the maximum recommended daily sodium intake. The sodium content of the maximum daily dose of pain/common cold drugs was significantly higher than the sodium content of the maximum daily dose of calcium/vitamin D drugs (p<0.0001) and cough drugs (p=0.007). No significant difference in sodium content between the dietary supplement

calcium effervescent tablets and the pharmacy-only calcium/vitamin D effervescent tablets was seen (p=0.109).

Supplement figure 3 summarizes the main results.

Discussion

This study assessed the sodium content of nutritional supplement effervescent tablets available in Germany and found the sodium amount to range from 76.0 mg/tablet to 564.7 mg/tablet (average 283.9 mg/tablet) representing up to 28% of the maximum recommended daily sodium intake. Vitamin products contained more sodium than magnesium, calcium, and mineral products. The sodium amount/tablet of OTC drugs ranged from 52 mg to 575 mg (median 157.0 mg) representing up to 29% of the maximum recommended daily sodium intake. The sodium content was particularly high for pain/common cold tablets. The intake of the recommended daily dose of one OTC drug would lead to a median consumption of 384.0 mg sodium, but as high as 2,776.5 mg for pain/common cold drugs. The major differences in the product classes´ sodium contents are probably due to the variable CO_2-dependent solubilities. More sodium bicarbonate and/or sodium citrate is required for poorly soluble active ingredients in effervescent tablets for them to dissolve quickly and completely in water. The large variations within individual product classes remain unexplained. Products available in the United States of America also contain a relevant amount of sodium (ranging from 40 to 360 mg/tablet). Of note, dietary supplement effervescent tablets available in Germany contained more sodium than declared in those available in the United States of America. This may, in part, be related to selection bias since only a few manufactures from the United States of America voluntarily provide information about the sodium content.

Dietary sodium intake has been linked with serious harmful effects, including BP elevation and all-cause death.[1,3,4,13,14] The 2017 report of the Global Burden of Disease study listed excess sodium intake among the major dietary risks, estimated to cause 3 million deaths every year worldwide.[7] A recently published, randomized trial in 20,995 subjects showed that using a table salt substitute containing 75% sodium chloride and 25% potassium chloride (as opposed to regular table salt containing 100% sodium chloride) reduced stroke, cardiovascular events, and death.[1] Consequently, the WHO recommends that daily sodium intake should not exceed 2,000 mg.[8] Many national and international societies have advocated for actions to lower dietary sodium intake through public education, labelling of foods, and improved formulations of convenience food. Nonetheless, the daily sodium intake around the world is often much higher (9,000-12,000 mg table salt/day; 3,500-7,700 mg sodium/day), which may, in part, be aggravated by hidden sodium consumption.[10,15]

For improved and quick solubility, effervescent tablets contain often high amounts of sodium[11] as sodium bicarbonate, sodium carbonate, and/or sodium citrate. The impact of sodium-containing effervescent, mainly paracetamol (acetaminophen) tablets on BP, acute heart failure events, and cardiovascular risk was investigated in several studies.[16–19] The intake of effervescent paracetamol tablets (with 545 mg sodium/dose) was shown to increase 24-hour systolic BP by 5.0 mmHg.[17] Other trials showed an association between the intake of sodium-containing effervescent paracetamol tablets (390-440 mg of sodium/tablet) and an increased risk of hospitalization for heart failure[18], cardiovascular risk, and all-cause mortality among patients with and without hypertension.[11,16,19] The mechanism by which the active substance paracetamol increases blood pressure has not been conclusively clarified; inter alia an influence on the cyclooxygenase pathway is discussed.[20,21] Nevertheless, sodium containing paracetamol effervescent tablets deteriorate blood pressure control mainly caused by the sodium in the effervescent tablets, as evident by the fact that after switching from

paracetamol effervescent tablets to paracetamol tablets (without sodium), a decrease in blood pressure was observed.[22]

This provides evidence that effervescent tablets increase sodium intake which might be associated with an increased risk for cardiovascular diseases.[1,3,4,13,14] A large case-control study comprising 1,292,337 patients with a mean follow-up of 7.2 years investigated the association between cardiovascular events and sodium-containing effervescent, dispersible, and soluble drugs.[19] Participants were prescribed sodium-containing formulations or matched standard formulations of the same drug. A total of 61,072 patients with a cardiovascular event were matched with controls. The sodium-containing substances were largely painkillers or calcium drugs with a wide range of sodium content (4.6-427.8 mg/tablet).[19] The adjusted odds ratio for exposure to sodium-containing drugs were 1.16 (95%-confidence interval (95%-CI): 1.12-1.21) for the composite of myocardial infarction, stroke, or vascular death, 1.28 (95%-CI: 1.23-1.33) for all-cause mortality, and 7.18 (95%-CI: 6.74-7.65) for hypertension.[19] Of note, the sodium content of some of the included effervescent tablets in this study is comparable with the sodium content of the drugs included in the mentioned study.[19] Consequently, the consumption of effervescent tablets investigated herein may contribute to an increased cardiovascular risk.

The ancillary sodium intake through effervescent tablets is often neglected or unknown. Herein, the average sodium content of effervescent food supplements tablets in Germany was 283.9 mg/tablet, and the median sodium content of the pharmacy-only effervescent tablets was 157.0 mg/tablet. Consuming one of the included effervescent vitamin tablets or pain/common cold tablets corresponds to about one fifth (19%/23%) of the maximum recommended daily sodium intake. Six products (8.3%) contained more than 500 mg sodium/tablet, Vitamin C 1000® (fit+Vital) and Vitamin C+Zink+Selen+Vitamin D3® (elkos Vivede) had the highest amount of sodium/tablet (564.7 mg and 541.1 mg) of the dietary supplements available in Germany.

Vitamin products contained significantly more sodium than magnesium (p=0.004), calcium (p=0.006) and mineral (p=0.048) products; this might be due to different solubility properties. Of the OTC drugs, doxylamine 25 mg (Gittalun®, Hermes Arzneimittel) and aspirin 500 mg (Aspirin Migräne®, Bayer) had the highest amount of sodium/tablet (575 mg and 544 mg). With a maximum recommended daily dose of eight tablets/day, Alka-Seltzer classic® (324 mg aspirin, Bayer) would add a total of 3,560 mg sodium. The sodium content of the maximum daily dose of pain/common cold drugs was significantly higher than the sodium content of the maximum daily dose of calcium/vitamin D drugs (p<0.0001) and cough drugs (p=0.007). The majority of the general population and healthcare professionals alike are unaware of the high sodium content of effervescent tablets.[11]

A relevant proportion of the population regularly consumes effervescent tablets as a dietary supplement and/or drugs.[12] In a cross-sectional study from France including 1,043 healthy individuals, 26.9% of the participants reported regular intake of effervescent tablets (once in the last 30 days) and 7.3% reported intake of two or more effervescent tablets/week during the last 30 days.[12] A vast majority of 93.8% of these effervescent tablets were OTC drugs and nutritional supplements, such as vitamins.[12] The presence of hypertension, which should require table salt/sodium restriction, did not result in a reduced intake of effervescent tablets.[12]

According to the Federal Statistical Office of Germany (Statistisches Bundesamt, Destatis), the production of dietary supplements in 2020, which include effervescent tablets, increased by 11% compared with the previous year, most likely as a consequence of the COVID-19 pandemic. In 2020, 180,200 tons of dietary supplements were produced with a value of 1.1 billion Euros in Germany, which corresponds to an increase of 23.4%. In Germany, the sodium content must be indicated on the medicinal products sold in pharmacies but is not mandatory on dietary supplements sold in drugstores or supermarkets.[23,24] Only five (13%) of the

included dietary supplements available in Germany and only 5.2% of the investigated dietary supplements available in the US declared sodium content on the packaging, hence, consumers are frequently not informed.

Various sodium-containing drugs administered as effervescent tablets are available. In German pharmacies alone, 3.96 million packages of the included pain/common cold and 5.30 million packs of the included cough effervescent tablets were sold in 2021. (https://www.insight-health.de/ and https://www.datamediq.com/) A total of 52.32 million DDD of calcium/vitamin D drugs, mainly as effervescent tablets, were claimed by community pharmacies at the expense of the SHI funds alone in Germany in 2021.[25] Based on these high sales, we assume that a relevant proportion of the population, occasionally or regularly, consumes effervescent tablets.

A dietary reduction of 1,200 mg sodium/day could translate into an annual reduction of 60,000-120,000 new coronary heart disease patients, 32,000-66,000 fewer strokes, and 54,000-99,000 fewer myocardial infarctions in the United States of America.[13] This amount of sodium is already contained in approximately 3 of the included effervescent vitamin tablets available in Germany (378.3 mg sodium/tablet on average). A modelling study from China showed that a reduction of 1,000 mg table salt/day could prevent approximately 9 million cardiovascular events in China by 2030, of which approximately 4 million are fatal.[26] Of note, a total of 1,000 mg table salt contains approximately 394 mg sodium. This amount of sodium approximately corresponds to the sodium content of one of the examined vitamin or pain/common cold effervescent tablets.

The intake of one sodium containing dietary supplement effervescent tablet per day for the whole year increases cardiovascular risk more likely than several pain/common cold effervescent tablets/day taken for 5-7 days only. A typical common cold lasts approximately 5-7 days, so the duration of the medical therapy is limited and the intake of OTC-effervescent tablets is rarely permanent. However, studies investigating the (temporary) intake of sodium-

containing acetaminophen (paracetamol) effervescent tablets showed an increased risk for hospitalization for acute heart failure, cardiovascular disease and all-cause mortality.[16,18]. The effect of permanent intake of sodium containing dietary supplement effervescent tablet could therefore be higher.

The benefits of pharmacotherapy should always outweigh the risks/side effects. Most likely, the majority of the general population is unaware of the sodium content of effervescent tablets and dietary supplements are often regarded as "sweets". Dietary supplements are considered "foods" by regulators and health benefits of many dietary supplements for healthy, asymptomatic and well-nourished adults have not yet been demonstrated in randomized clinical trials.[27,28]. Consequently, the harm might outweigh the benefit when people ingest several vitamin and electrolyte effervescent tablets daily, assuming they are doing something good for their health.

Limitations

Some limitations of our study should be considered. This study provides relevant insights into the sodium content in dietary supplemental and pharmacy-only effervescent tablets but does not assess the association between the ingestion of these products and cardiovascular outcomes. Therefore, only assumptions can be made. Nevertheless, the included effervescent tablets contained a relevant amount of sodium comparable to prior studies investigating the association between sodium-containing effervescent tablets and cardiovascular risk. Randomized clinical trials are needed to examine the impact of effervescent tablets from grocery stores, discounters, drug stores, and pharmacies on cardiovascular risk. We provide sales figures for effervescent tablets sold in pharmacies. The quantity of dietary supplement effervescent tablets from discounters, grocery- and drugstores is not publicly available. Measured (Germany) sodium contents of dietary supplements were compared with declared (United States of America). Assuming the manufacture declares the correct sodium content on the packing, the detection of

national differences is possible. Nevertheless, the assumption that the declared sodium content of dietary supplements available in the United States of America are valide, is a limitation. It is not guaranteed that the ingredients declared on the packing are "correct".[29–31]

Conclusion

Dietary supplements and OTC effervescent tablets investigated herein contained high sodium, often unknown or neglected. Some products contain more sodium than others, although comparable in (active) ingredients. As the variability between preparations is high and these amounts of additional sodium intake may contribute to poor BP control and cardiovascular events, including hospitalization for acute heart failure and death, we think regulators should demand a front-package labelling of sodium content and associated risk before market access. Based on the study findings, patients at risk should be advised to limit effervescent tablets to prevent the ingestion of hidden sodium. Finally, we suggest that manufacturers should be requested to reduce sodium in their effervescent formulations.

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Authors' Contributions

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Drafting of the manuscript: Kunz, Schulz, Mahfoud.

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The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Statement

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Ethical Approval

Not applicable.

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Tables

Table 1. Sodium content of German dietary supplement effervescent tablets

Category	Brand name®	Sodium content/tablet (mg)	% of maximum recommended daily sodium intake*	Sodium (g)/ 100g product	Weight/ tablet (g)
Vitamins	fit+Vital Vitamin C1000	564.70	28	9.01	6.27
	elkos Vivede Vitamin C +Zink, Selen, und Vitamin D3	541.10	27	8.95	6.05
	Doppelherz aktiv Vitamin C +Zink	512.80	26	8.11	6.32
	ProLife Vitamin C +Zink, Selen, Vitamin D3	507.90	25	8.48	5.99
	Doppelherz aktiv Vitamin D3 2000 I.E.	485.10	24	7.44	6.52
	SilaVit Vitamin B12	367.30	18	9.05	4.06
	Vitalis Vitamin C 120 mg	341.50	17	8.54	4.00
	Mivolis Vitamin B12	333.00	17	8.08	4.12
	Mivolis Vitamin C	330.30	17	8.02	4.12
	Doppelherz aktiv A-Z Multivitamin+ Mineralien	321.40	16	5.10	6.30
	SilaVit Vitamin C	318.00	16	7.92	4.02
	fit+Vital Multivitamin	304.60	15	7.57	4.02
	elkos Vivede Multivitamin+ Mineralstoffe	273.50	14	4.56	6.00
	ProLife Multivitamin+ Mineralstoffe	263.20	13	4.38	6.01
	fit+Vital Multivitamin+ Mineral	210.70	11	5.26	4.01
Magnesium	Doppelherz aktiv Magnesium 400	332.50	17	5.11	6.51
	Vitalis Magnesium 240 mg	306.10	15	5.58	5.49
	Abtei Magnesium 400 Plus Vitamin C+E	298.70	15	5.56	5.38
	Doppelherz aktiv Magnesium+ Calcium+ D3	271.20	14	4.12	6.59
	Doppelherz aktiv Magnesium 500+ B12	268.90	13	4.12	6.53

	Mivolis Magnesium	262.70	13	6.39	4.11
	elkos Vivede Magnesium+ B-Komplex, Vitamin C und E	248.40	12	4.13	6.01
	Doppelherz aktiv Magnesium+ Kalium Sport	245.50	12	3.72	6.60
	ProLife Magnesium+ B-Komplex, Vitamin C&E	238.00	12	3.95	6.03
	Kneipp Magnesium+ Calcium+ D3	221.30	11	4.91	4.51
	Abtei Magnesium+ Kalium Aktiv Plus	138.10	7	2.52	5.48
	fit+Vital Magnesium	117.80	6	2.95	3.99
	fit+Vital Magnesium 400	76.00	4	1.40	5.41
Calcium	ProLife Calcium+ Vitamin K1, D3, Folsäure	335.90	17	5.60	6.00
	Mivolis Calcium	145.90	7	3.53	4.14
	fit+Vital Calcium+ D3	116.20	6	2.89	4.02
	fit+Vital Calcium 1000	83.70	4	1.36	6.17
Minerals	Kneipp Männer Mineralstoffe	217.00	11	3.87	5.61
	Kneipp Frauen Mineralstoffe	209.40	10	3.33	6.29
	Mivolis Multi-Mineral	148.40	7	3.62	4.10
Other products	fit+Vital Eisen+ Vitamin C	382.90	19	9.63	3.98
	SilaVit Immun Aktiv	363.80	18	8.55	4.25
	sanotact Recovery+ Aminosäuren	187.60	9	3.54	5.29
	isostar Hydrate & Perform	181.00	9	1.51	11.99
*Maximum recommended daily sodium intake according to World Health Organization recommendations[8]					

Table 2. Sodium content per: (A) Dietary supplement effervescent tablet available in Germany, (B) Dietary supplement effervescent tablet in the United States of America, (C) OTC effervescent tablet, (D) recommended daily dose of the included OTC effervescent tablets

A		
Category	**Sodium content (mg)/tablet mean±SD**	**% of the maximum recommended daily sodium intake* mean±SD**
…all included products	283.9±122.6	14±6
…vitamin products	378.3±112.8	19±6
…magnesium products	232.7±76.7	12±4
…calcium products	170.4±113.2	9±6
…mineral products	191.6±37.6	10±2
…other products	278.8±109.5	14±6
B		
Category	**Sodium content (mg)/tablet Median (IQR)**	**% of the maximum recommended daily sodium intake* Median (IQR)**
…all included products	190.0 (100.0-250.0)	10 (5-13)
…vitamin products	100.0 (72.5-230.0)	5 (4-12)
…mineral products	250.0 (140.0-360.0)	13 (7-18)
…energy products	190.0 (150.0-260.0)	10 (8-13)
…other products	210.0 (158.8-256.3)	11 (8-13)
C		
Category	**Sodium content (mg)/tablet Median (IQR)**	**% of the maximum recommended daily sodium intake* Median (IQR)**
…all included drugs	157.0 (98.9-417.3)	8 (5-21)
…pain/common cold	452.1 (351.3-474.0)	23 (18-24)
…cough	138.8 (112.8-157.9)	7 (6-8)
…calcium/vitamin D	87.0 (52.0-103.0)	4 (3-5)
…other drugs	267.0 (119.8-387.5)	13 (6-19)
D		
Category	**Sodium content (mg) of the maximum daily dose Median (IQR)**	**% of the maximum recommended daily sodium intake* Median (IQR)**
…all included drugs	384.0 (139.0-1295.5)	19 (7-65)
…pain/common cold	2,776.5 (1,299.8-3,333.0)	139 (65-167)
…cough	297.0 (144.5-427.0)	15 (7-21)
…calcium/vitamin D	104.0 (96.3-104.8)	5 (5-5)

…other drugs	801.0 (312.8-1,155.5)	40 (16-58)
*Maximum recommended daily sodium intake according to World Health Organization recommendations[8] IQR= interquartile range; OTC= over-the-counter, SD= standard deviation		

Table 3. Sodium content of OTC effervescent tablets

Category	Brand name® (manufacturer)	sodium content/tablet (mg)	% of the maximum recommended daily sodium intake* of one tablet	sodium content of maximum recommended daily dose (mg)	% of maximum recommended daily sodium intake* of the maximum recommended daily dose	Maximum recommended tablets per day	OTC	Active ingredients	Sales figures
Pain/common cold (frequently dispensed products)	Aspirin Migräne (Bayer)	544	27	3,264	163	6	yes	aspirin	3.96 million packs of this class sold in 2021 in Germany
	ASS + C-ratiopharm gegen Schmerzen (Ratiopharm)	477	24	2,385	119	5	yes	aspirin, ascorbic acid	
	ASPIRIN plus C forte (Bayer)	473	24	1,419	71	3	yes	aspirin, ascorbic acid	
	ASPIRIN plus C (Bayer)	466	23	2,796	140	6	yes	Aspirin, ascorbic acid	
	Togal Kopfschmerz-Brause + Vitamin C (Kyberg Pharma)	459	23	2,754	138	6	yes	Aspirin, ascorbic acid, caffeine	
	Alka-Seltzer classic (Bayer)	445	22	3,560	178	8	yes	aspirin	
	FIZAMOL 500 mg (Accord Healthcare)	419	21	3,352	168	8	yes	acetaminophen	
	PARACETAMOL-ratiopharm 500 mg (Ratiopharm)	416	21	3,328	166	8	yes	acetaminophen	
	WICK DayMed Erkältungsgetränk (WICK Pharma)	157	8	942	47	6	yes	acetaminophen, guaifenesin, phenylephrine	
	Grippostad C Stickpack (STADA Consumer Health)	128	6	384	19	3	yes	acetaminophen, chlorpheniramine, ascorbic acid, caffeine	
Cough (frequently dispensed products)	NAC-ratiopharm 200 mg, (Ratiopharm)	190	10	570	29	3	yes	acetylcysteine	5.30 million packs of this class sold in 2021 in Germany
	Fluimucil 200 mg (Zambon)	158	8	474	24	3	no	acetylcysteine	
	Fluimucil long 600 mg (Zambon)	158	8	158	8	1	no	acetylcysteine	
	NAC-ratiopharm 600 mg (Ratiopharm)	150	8	150	8	1	yes	acetylcysteine	
	ACC akut 600mg (Hexal)	139	7	139	7	1	yes	acetylcysteine	
	NAC 600 akut (1A Pharma)	139	7	139	7	1	yes	acetylcysteine	
	Ambrobeta 30 (betapharm Arzneimittel)	127	6	381	19	3	yes	ambroxol	
	ACC akut 200mg (Hexal)	99	5	297	15	3	yes	acetylcysteine	
	NAC 200 akut (1A Pharma)	99	5	297	15	3	yes	acetylcysteine	

Calcium/ vitamin D3 (colecalciferol; examples of frequently prescribed effervescent tablets)	Calcium Sandoz forte (Hexal)	288	14	864	43	3	yes	Calcium + vitamin D	52.32 million DDD of the entire class claimed to the expense of the SHI funds in 2021 in Germany[25]
	Calcium D3 acis 1.200/ 800 (acis Arzneimittel)	105	5	105	5	1	yes	Calcium + vitamin D	
	CalciCare-D3 forte 1.000 mg/ 880 I.E. (ORION Pharma)	97	5	97	5	1	yes	Calcium + vitamin D	
	Calcilac 1000 mg/ 880 I.E. (MIBE Arzneimittel)	96	5	96	5	1	yes	Calcium + vitamin D	
	Osteoplus 1.000 mg/ 1.000 I.E. (Recordati Pharma)	78	4	78	4	1	yes	Calcium + vitamin D	
	Calcigen D 600/ 400 (MEDA Pharma)	52	3	104	5	2	yes	Calcium + vitamin D	
	Calcium D3-ratiopharm 600/ 400 (Ratiopharm)	52	3	104	5	2	yes	Calcium + vitamin D	
	Calcium Sandoz D Osteo 600 mg/ 400 I.E. (Hexal)	52	3	104	5	2	yes	Calcium + vitamin D	
Other drugs (examples)	Gittalun (Hermes Arzneimittel)	575	29	1,150	58	2	yes	doxylamine	-
	Zink-ratiopharm 25mg (Ratiopharm)	325	16	325	16	1	yes	zinc	
	Magnesium Verla (Verla-Pharm Arzneimittel)	314	16	942	47	3	yes	magnesium	
	Lösferron (MIBE Arzneimittel)	220	11	660	33	3	yes	Fe-(II)-D-gluconat	
	Magnesiocard 7,5 mmol (Verla-Pharm Arzneimittel)	138	7	276	14	2	yes	magnesium	
	Morphin Painbreak akut 20 mg (PB Pharma)	65	3	1,170	59	18	no	morphine	

*Maximum recommended daily sodium intake according to World Health Organization recommendations[8]
DDD= defined daily doses; OTC= over-the-counter; SHI= statutory health insurance

Figure Legends

Figure 1. Mean sodium content of the respective category of the dietary supplement effervescent tablets available in Germany.

Figure 2. Sodium content of the maximum recommended daily dose of some included effervescent OTC tablets.

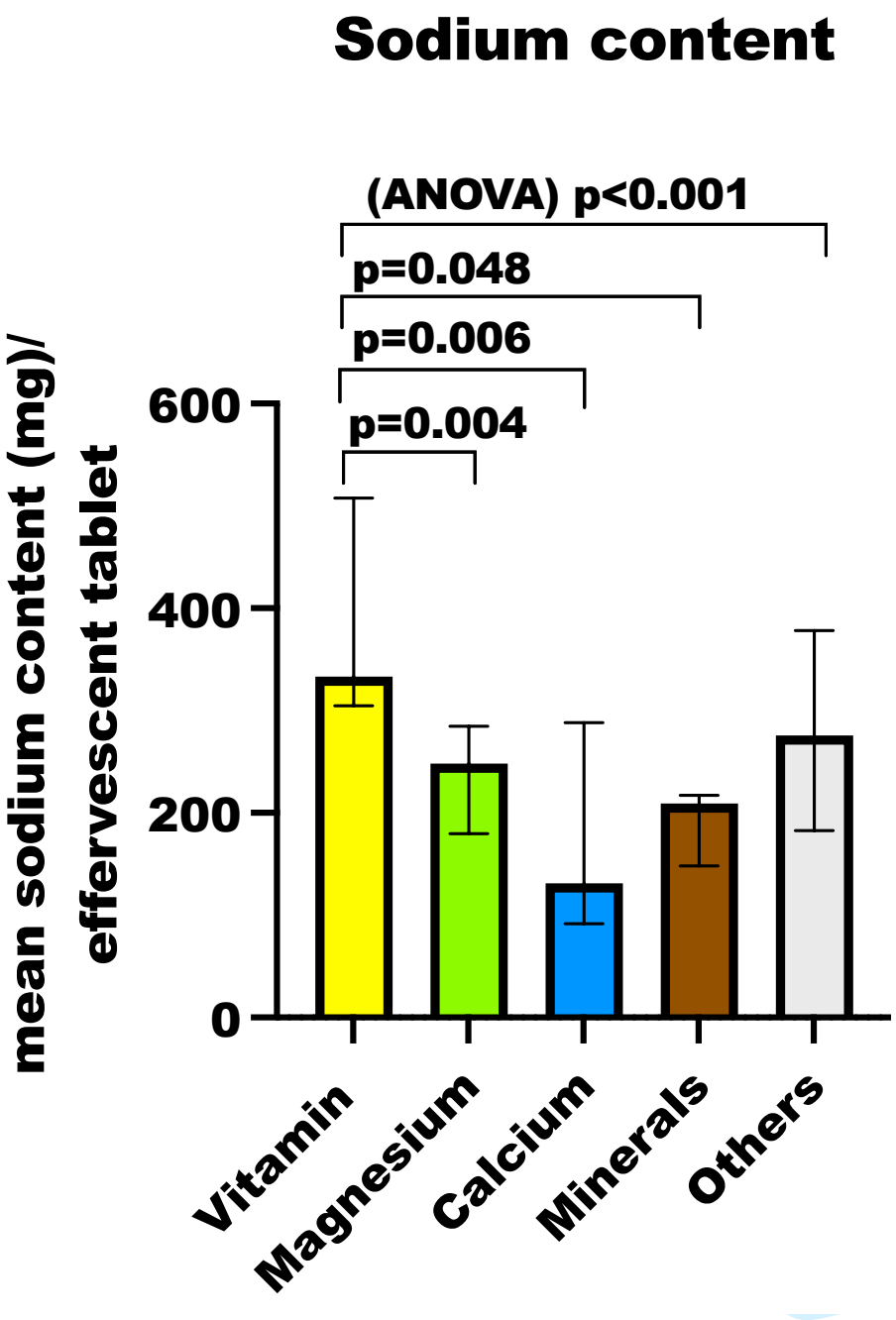


Figure 1. Mean sodium content of the respective category of the German dietary supplement effervescent tablets. P values are given for between-group comparisons (adjusted for post hoc method). ANOVA = analysis of variance.

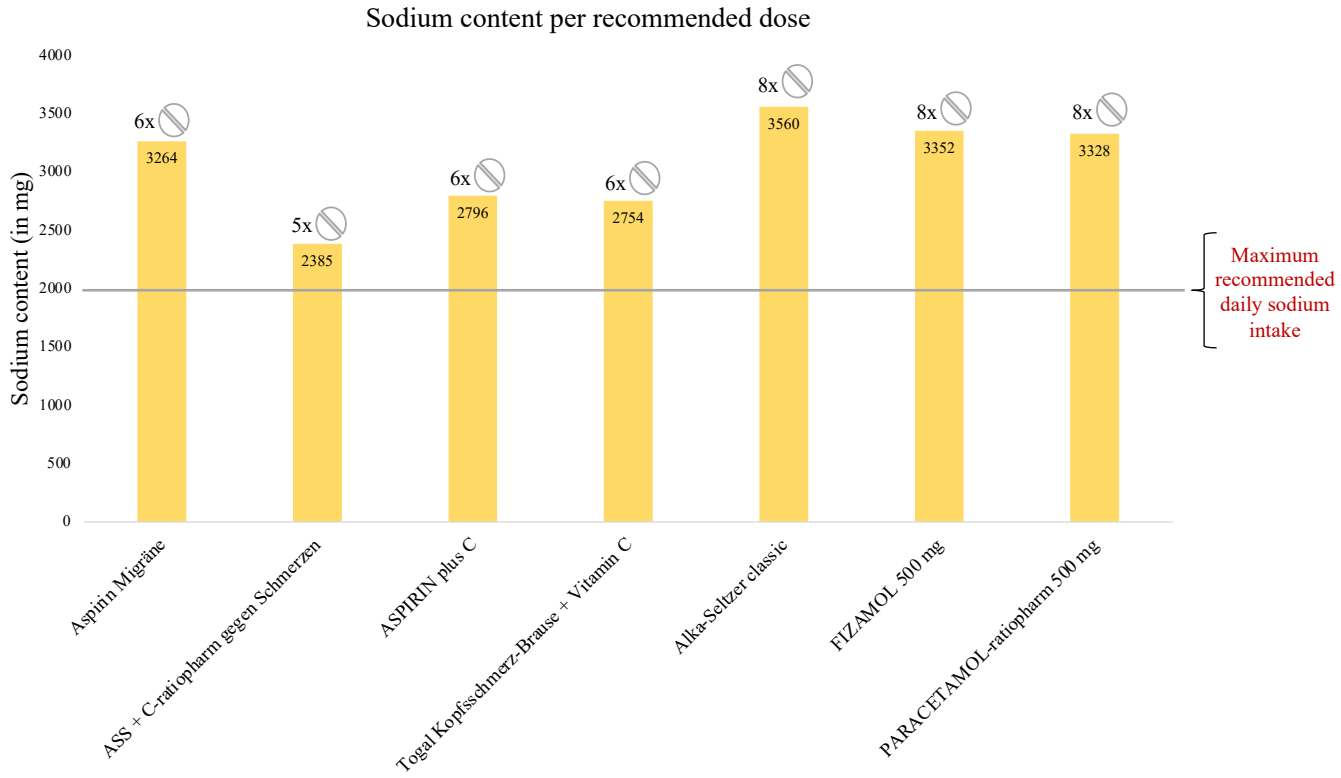


Figure 2. Sodium content of the maximum recommended daily dose of some included effervescent OTC tablets. The number above the bars corresponds to the maximum daily number of tablets. (Aspirin Migräne®: Bayer; ASS + C-ratiopharm gegen Schmerzen®: Ratiopharm; ASPIRIN plus C®: Bayer; Togal Kopfschmerz-Brause + Vitamin C®: Kyberg Pharma; Alka-Seltzer classic®: Bayer; FIZAMOL 500 mg®: Accord Healthcare, Paracetamol-ratiopharm 500mg®: Ratiopharm

Supplemental table 1. Overview of the included German products.

Supplemental table 2. Sodium content of the included products from the United States of America.

Supplement figure 1. Number of different German dietary supplement effervescent tablets that contain a certain amount of sodium (classified in 100 mg increments).

Supplement figure 2. Number of different pharmacy-only effervescent tablets that contain a certain amount of sodium (classified in 100 mg increments).

Supplement figure 3. Central illustration.

Supplement table 1. Overview of the included German products.

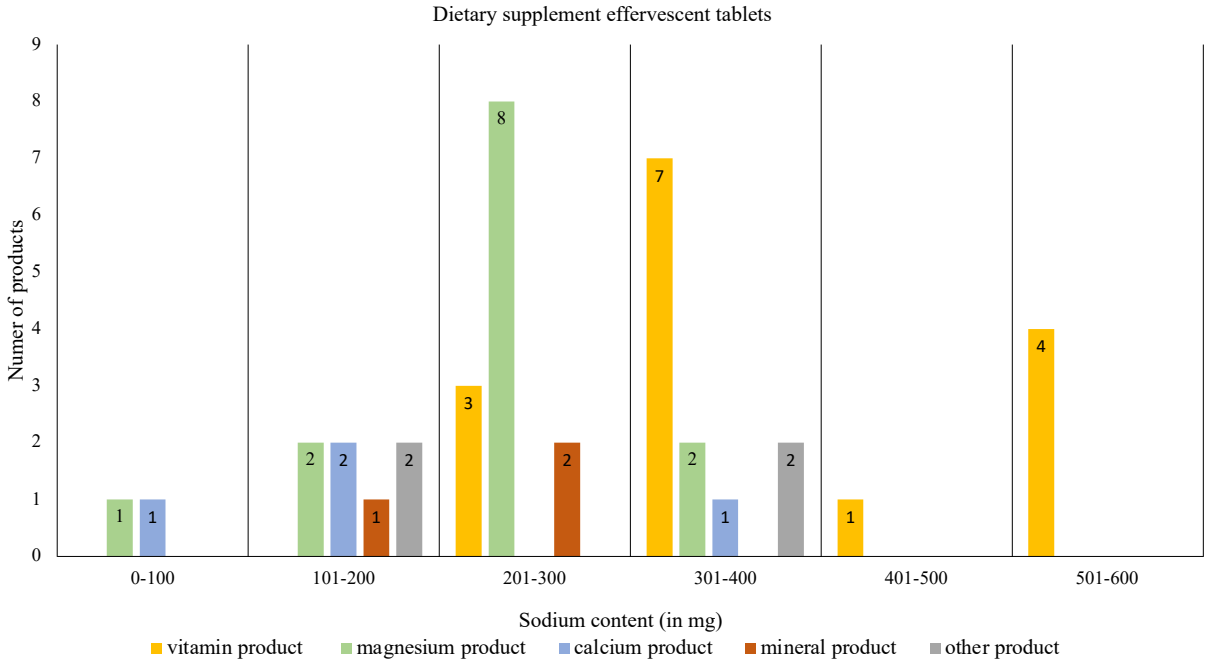
Offeror	Manufacturer	Brand name®	Number of tablets	Total weight (g)	Weight/ tablet (g)	Total price (cent)	Price/ tablet (cent)
ALDI SÜD GmbH & Co.	Vitalis	Magnesium 240 mg	14	78	5.6	45	3.2
		VitaminC 120 mg	20	80	4.0	45	2.3
Edeka Stiftung & Co. KG	ELKOS Vivede	VitaminC+ Zink, Selen, Vitamin D3	17	102	6.0	55	3.2
		Magnesium+ B-Komplex, Vitamin C und E	17	102	6.0	55	3.2
		Multivitamin+ Mineralstoffe	17	102	6.0	55	3.2
Netto Marken-Discount Stiftung & Co. KG	ProLife	VitaminC+ Zink, Selen, Vitamin D3	17	102	6.0	55	3.2
		Magnesium+ B-Komplex, Vitamin C&E	17	102	6.0	55	3.2
		Multivitamin+ Mineralstoffe	17	102	6.0	55	3.2
		Calcium+ Vitamin K1, D3, Folsäure	17	102	6.0	55	3.2
DM drogerie markt GmbH & Co. KG	Mivolis	Magnesium	20	82	4.1	45	2.3
		VitaminB12	20	82	4.1	45	2.3
		Calcium	20	82	4.1	45	2.3
		Multi-Mineral	20	82	4.1	45	2.3
		VitaminC	20	82	4.1	45	2.3
	Kneipp	Magnesium+ Calcium+ D3	20	90	4.5	245	12.3
Müller Handels GmbH & Co. KG	Kneipp	Frauen Mineralstoffe	15	94	6.3	345	23.0
		Männer Mineralstoffe	15	84	5.6	399	26.6
	Abtei	Magnesium400 Plus Vitamin C+E	15	81	5.4	295	19.7
		Magnesium+ Kalium Aktiv Plus	15	82.5	5.5	275	18.3
	Sanotact	Recovery+ Aminosäuren	15	79.5	5.3	295	19.7
	Doppelherz	VitaminC+ Zink	15	94.5	6.3	295	19.7
		VitaminD3 2000 IE	15	97.5	6.5	275	18.3
		A-Z Multivitamin+ Mineralien	15	93	6.2	279	18.6
		Magnesium 400	15	97.5	6.5	275	18.3

		Magnesium+ Calcium+ D3	15	97.5	6.5	279	18.6
		Magnesium 500+ B12	15	97.5	6.5	249	16.6
		Magnesium+ Kalium Sport	15	99	6.6	299	19.9
	Fit + Vital	Caclium+ D3	20	80	4.0	139	7.0
		Multivitamin	20	80	4.0	45	2.3
		Vitamin C1000	15	93	6.2	139	9.3
		Multivitamin+ Mineral	20	80	4.0	45	2.3
		Magnesium	20	80	4.0	45	2.3
		Eisen+ VitaminC	20	80	4.0	139	7.0
		Cacium 1000	15	93	6.2	45	3.0
		Magnesium 400	15	81	5.4	45	3.0
	SilaVit	Immun Aktiv	20	84	4.2	139	7.0
		Vitamin B12	20	80	4.0	125	6.3
		Vitamin C	20	80	4.0	45	2.3
	Isostar	Hydrate & Perform	10	120	12.0	399	39.9

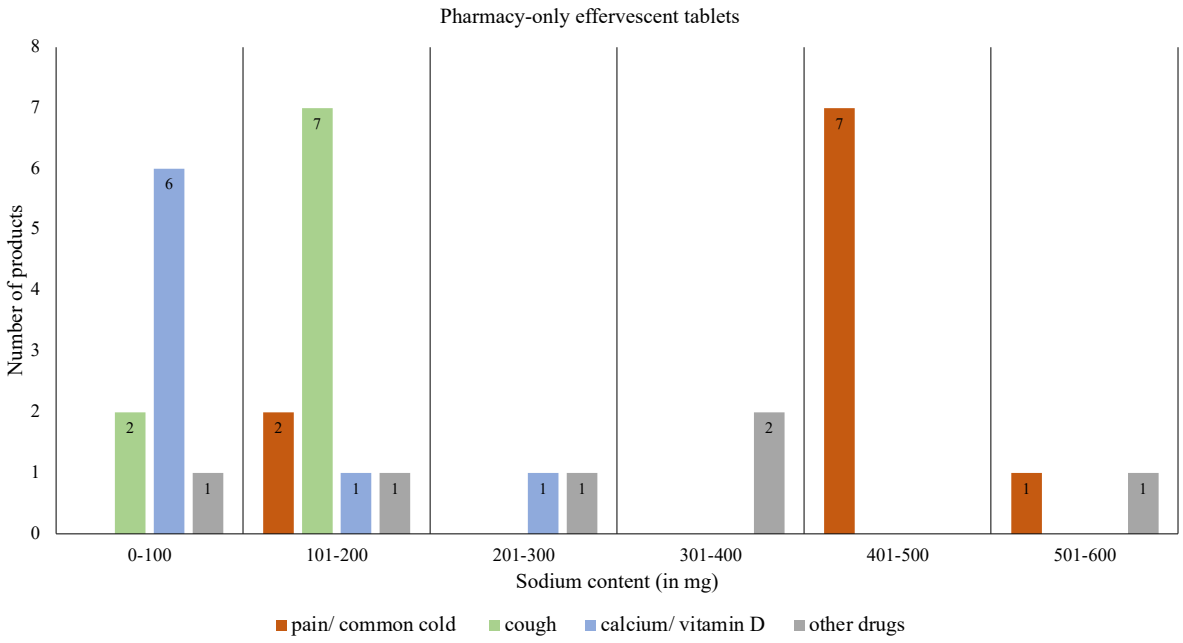
Supplement table 2. Sodium content of the included products from the United States of America.

Brand name®	Manufacturer	Category	Sodium content/tablet (mg)
ActivJoint Tangerine	Trace Minerals Research	Other	155
Advanced Anti-Aging Formula Effervescent Drink Mix Orange	TimeFighters	Other	55
Airborne Dual Action Citrus	Airborne	Vitamin	230
Airborne Elderberry Effervescent Tablets	Airborne	Mineral	230
Airborne Immune Support Effervescent Tablets	Airborne	Vitamin	230
Airborne Vitamin C Original Lemon Lime	Airborne	Vitamin	230
Airborne Zesty Orange	Airborne	Mineral	150
Alka-Seltzer Plus Immunity Complex	Bayer	Vitamin	313
Amino X Fruit Punch	BSN	Other	160
AngiNOX Natural Orange Flavor	XYMOGEN	Other	220
Berocca Orange Flavor	Bayer	Energy	260
Best Defense Orange Boost	Herbalife Nutrition	Vitamin	115
BetaBoost + Vitamin C Citrus	Airborne Advanced	Vitamin	240
Carni-Fizz Natural Lemon Lime Flavor	Body Fizzics	Other	245
CuraMed Natural Tangerine Flavor	Terry Naturally	Other	130

CuraPro 350 mg Tangerine Effervescent	EuroMedica	Mineral	130
Effer-C Lemon-Lime Effervescent Drink Mix	NOW	Vitamin	50
Effervescent Effer-Energy Tropical Punch	NOW Sports	Mineral	360
Effervescent Effer-Hydrate	NOW Sports	Mineral	360
Effervescent Energy Lava Lime	Eruption	Energy	240
Effervescent Vitamin C 1000 mg Natural Orange Flavor	Sundown Naturals	Vitamin	60
Effervescent Vitamin C Orange Flavored	365 Everyday Value	Vitamin	60
Energize Isotropin Lemon Flavor Effervescent	Newton-Everett	Energy	150
Energy Berry Blast	Nuun	Energy	100
Ester-C Effervescent 100 mg Plus Electrolytes Natural Orange Flavor	American Health	Vitamin	100
Ester-C Effervescent 1000 mg Natural Orange Flavor	NatureSmart	Vitamin	100
Ester-C Effervescent 1000 mg Natural Raspberry	American Health	Vitamin	55
Ester-C Effervescent 1000 mg Natural Raspberry Flavor	Solgar	Vitamin	40
Evotest Black Cherry	BSN	Other	300
Garcinia Cambogia Lineatabs Passion Fruit Flavor	Apax	Other	190
Green Superfood Detox Orange Turmeric Flavor	Amazing Grass	Other	260
Immune Oxylent Effervescent Supplement Drink	Immune Oxylent	Vitamin	90
Immune Support Orange Flavor	Equate	Vitamin	230
Immuni-V Orange Effervescent	MRI Performance	Vitamin	85
Immunity Blueberry Tangerine	Nuun	Vitamin	100
Isotropin Rejuvenation Tangerine Flavor	NewtonEverett	Other	255
Liftoff Tropical Fruit Force	Herbalife Nutrition	Vitamin	230
Lineatabs	Apax	Other	270
Nuun Active Fruit Punch	Nuun	Vitamin	360
Nuun Hydration Tri-Berry	Nuun	Mineral	360
POW Berry-Melon Fizz	EBOOST	Energy	190
POW Berry-Melon Fizz	EBOOST	Energy	155
Power Pak Cranberry	Trace Minerals Research	Vitamin	175
Pumped Edge Fruit Punch	BSN	Other	200
Sambucus Fizzy Berry Flavored	Nature's Way	Other	160
Sport +Caffeine Fresh Lime	Nuun	Energy	300
Sport Fruit Punch	Nuun	Mineral	300
Sport Oxylent 3-In-1 Performance Supplement Drink Blueberry Burst	Sport Oxylent	Mineral	90
Vitamins Blueberry Pomegranate	Nuun	Vitamin	100
Wal-Born Orange Flavor	Well At Walgreens	Other	230
ZYM Electrolyte Drink Tablets	ZYM	Mineral	250



Supplement figure 1. Number of different German dietary supplement effervescent tablets that contain a certain amount of sodium (classified in 100 mg increments).



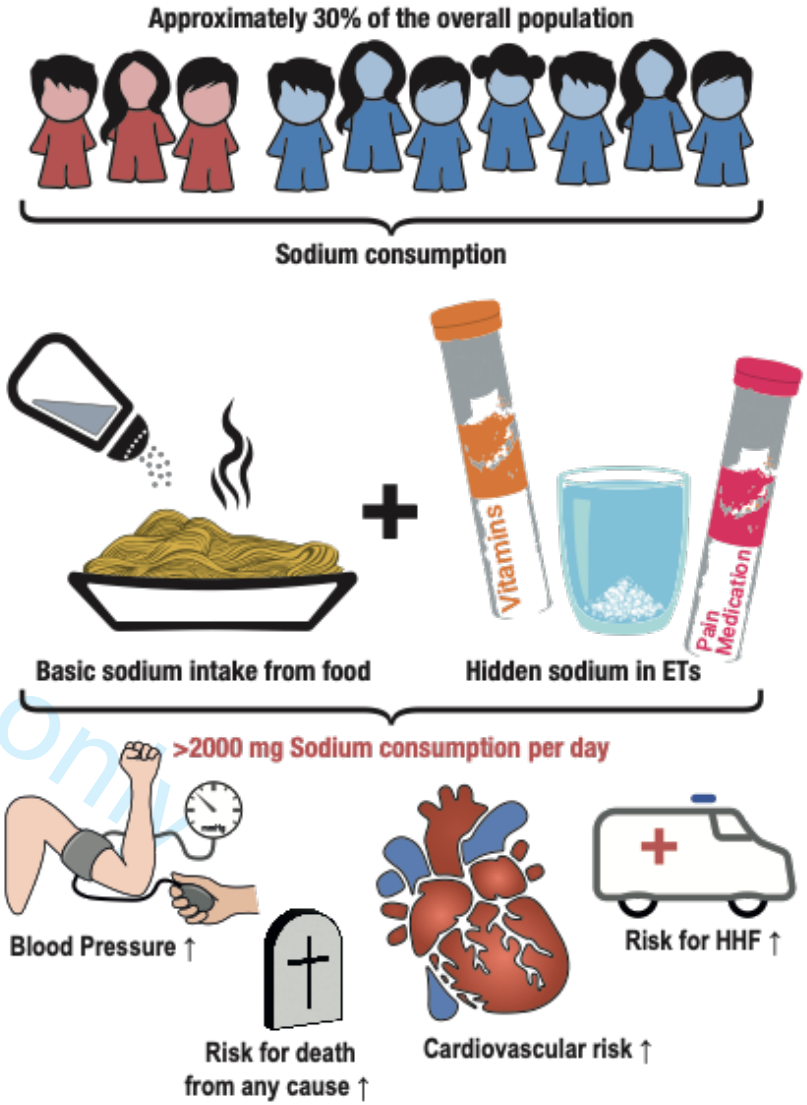
Supplement figure 2. Number of different pharmacy-only effervescent tablets that contain a certain amount of sodium (classified in 100 mg increments)

What is known ?
- Dietary sodium intake → BP ↑ and CV events ↑
- Recommended daily sodium intake: < 2000 mg
- ETs contain high amounts of sodium (often not labeled)
- approx. 30% of the population regularly consume ETs as dietary supplements and/or drugs

Dietary supplement ETs
- 39 included
- Average sodium content: 283.9±122.6 mg → 4-28% of the RDSI
- Highest average sodium content: vitamin products (378.3±112.8 mg)
- Lowest average sodium content: calcium products (170.4±113.2 mg)
- Vitamin products: more sodium than magnesium (p=0.004), calcium (p=0.006) and mineral (p=0.048) products

Pharmacy-only ETs
- Median sodium content: 157.0 mg (IQR: 98.9-417.3 mg) → 3-29% of the RDSI
- Highest median sodium content: pain/ common cold drugs (452.1 mg; IQR: 351.3-474.0 mg)
- Lowest median sodium content: calcium/ vitamin D drugs (87.0 mg; IQR: 52.0-103.0 mg)
- Median sodium content of the MDD of pain/ common cold drugs: 2,776.5 mg (IQR: 1,299.8-3,333.0 mg)

Conclusion
- ETs contain a relevant amount of sodium (often unknown or neglected)
- Additional sodium intake → poor BP control and CV events ↑
- Sodium loaded ETs should be avoided in patients at risk



Supplement figure 3. Central illustration. BP= blood pressure; CV= cardiovascular; ET= effervescent tablets; HHF= hospitalization for acute heart failure; IQR= interquartile range; MDD= maximum daily dose; RDSI= recommended daily sodium intake.

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The hidden sodium in effervescent-tablet dietary supplements and over-the-counter drugs: a comparative cross-sectional study

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The hidden sodium in effervescent-tablet dietary supplements and over-the-counter drugs: a comparative cross-sectional study

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Abstract

Objective: Dietary sodium intake represents a risk factor for cardiovascular disease and mortality. The study sought to analyse the sodium content of effervescent dietary supplements and drugs in Germany and the USA.

Design: Comparative cross-sectional study.

Setting and methods: The sodium content of 39 dietary supplement effervescent tablets available in Germany was measured in May and June 2022 using optical emission spectrometry with inductively coupled argon plasma. The sodium content of 33 common pharmacy-only effervescent tablets (over-the-counter [OTC] drugs) in Germany was obtained from the summary of product characteristics. We compared the sodium content of the measured German dietary supplement effervescent tablets to that of 51 dietary supplement effervescent tablets available in the USA (data: National Institutes of Health's Dietary Supplement Label Database).

Results: The measured sodium content in the German dietary supplements was 283.9±122.6 mg sodium/tablet, equivalent to 14±6% of the maximum recommended daily sodium intake (MRDSI). Vitamin products had the highest (378.3±112.8 mg, 19±6% of MRDSI), and calcium products had the lowest mean sodium content (170.4±113.2 mg, 9±6% of MRDSI). Vitamin products contained significantly more sodium than magnesium (378.3 mg vs. 232.7 mg; p=0.004), calcium (378.3 mg vs. 170.4 mg; p=0.006), and mineral products (378.3 mg vs. 191.6 mg; p=0.048). The sodium content measured in products available in Germany was higher when compared to the declared sodium content on the label of the products sold in the USA (283.9 mg vs. 190.0 mg; p<0.001). The median summary of product characteristics-declared sodium content of a single dose of the German OTC drugs was 157.0 mg (interquartile range (IQR): 98.9-417.3 mg); pain/common cold drugs contained the most sodium (median: 452.1 mg; IQR: 351.3-474.0 mg).

Conclusion: Effervescent tablets of nutritional supplements and OTC drugs contain high amounts of sodium, which often is not disclosed.

Keywords:

sodium, dietary supplement, effervescent tablets, over-the-counter drugs, salt, cardiovascular risk, hypertension, heart failure

Strengths and limitations of this study

- The measurement of sodium content in dietary supplement and pharmacy-only effervescent tablets gives detailed insights into the quantities of hidden sodium in these dosage forms.
- We provide sales figures for effervescent tablets sold in German pharmacies.
- However, data for the quantities sold of dietary supplement effervescent tablets from discounters, grocery stores and drugstores are not publicly available.
- The association between the ingestion of effervescent tablets and cardiovascular outcomes was not investigated.

Introduction

Dietary sodium intake is associated with elevated blood pressure (BP), increased cardiovascular events including stroke and death from any cause.[1–5] In patients with arterial hypertension, the long-term reduction of 1,800 mg less sodium/day (this corresponds to 4,600 mg table salt/day) was associated with a reduction in systolic/diastolic BP of 5.1/2.7 mmHg.[4] The extent of the sodium restriction was proportional to the reduction in BP, with a more pronounced effect in patients with hypertension.[6] Even modest reductions in dietary sodium have been shown to reduce cardiovascular events, including myocardial infarction and stroke.[1,7] Dietary sodium consumption is an important risk factor for premature death and disability-adjusted life-years globally.[7] The World Health Organization (WHO) recommends reducing sodium intake to <2,000 mg/day in adults, which is equivalent to 5,000 mg of table salt (sodium chloride).[8] However, only a small proportion of the population achieves this goal.[9] The daily amount of table salt consumed is often much higher (9,000-12,000 mg/day; 3,500-7,700 mg sodium/day), which may, in part, relate to hidden sodium consumption.[9,10]

Effervescent tablets often contain a relatively high amount of sodium in form of sodium bicarbonate, sodium carbonate, or sodium citrate and are frequently consumed without awareness of their sodium content.[11,12] This may be particularly relevant for dietary supplements and over-the-counter (OTC) effervescent tablets (e.g., vitamin C, magnesium, or analgesics) from groceries, drugstores, discounter, and pharmacies because many manufacturers do not provide information on sodium content on the label. The present study sought to provide information about the often not labelled sodium content of dietary supplement effervescent tablets from large groceries- and drugstores and sodium-containing effervescent tablets used as drugs from pharmacies. Country-specific differences in sodium content (products from Germany vs. products from the USA) were set forth.

Methods

Study design

A comparative cross-sectional study was conducted in 2022 and 2023 to examine and compare the sodium content of different categories of effervescent tablets.

Classification, place of purchase and analyses of dietary supplements available in Germany

The sodium content of 39 different dietary supplement effervescent tablets available in Germany (divided into the categories vitamins, magnesium, calcium, minerals, and other products) from 11 manufacturers and five distributors was analysed in May and June 2022. The effervescent tablets were divided into categories based on the main active ingredient (e.g., if a product mainly contains magnesium and only a little calcium related to the recommended daily dose, then it is assigned to the category magnesium). The products were purchased from two discounters (ALDI SÜD GmbH & Co. and Netto Marken-Discount Stiftung & Co. KG), one grocery store (Edeka Stiftung & Co. KG), and two drugstores (DM drogerie markt GmbH & Co. KG and Müller Handels GmbH & Co. KG) in Germany and then delivered to the laboratory unopened.

The analyses were performed by an accredited chemical laboratory in Germany (CBA GmbH, Kirkel-Limbach, Germany, Deutsche Akkreditierungsstelle D-PL-14360-01-00). After appropriate standardized sample preparation, optical emission spectrometry with inductively coupled argon plasma (ICP-OES) was used for analysis. The sample preparation (pressure digestion in Teflon-pressure-vessels with microwave-assisted heating) proceeded as follows. The effervescent tablets were ground up and a sample amount corresponding to the expected sodium content was weighed out exactly. This amount of powder was displaced firstly with 1 mL water and then with 3 mL 65% nitric acid and transferred to the Teflon-pressure-vessel. The digestion took place at 180° Celsius in the digestion apparatus (microwave digestion

system, CEM) for at least 20 minutes, followed by a cooling period. The vessels were filled up with water again to the nominal volume. Reference solutions and blank values were treated in the same way. After sample preparation, the solutions were transferred directly into the ICP-OES equipment (ICP-OES iCAP 6300 Duo, Thermo-Fisher Scientific). All digestion and reference solutions were sprayed into an argon plasma, followed by selective detection of sodium emission radiation at 589.59 nm.

Classification and data source for over-the-counter drugs

The sodium content of 33 commonly sold pharmacy-only effervescent tablets (30 OTC and tree prescription drugs, all referred to as "OTC drugs" for convenience) from German pharmacies was derived from the respective package inserts or summary of product characteristics. The drugs were divided into the categories pain/common cold, cough, calcium/vitamin D, and other drugs based on the main active ingredient. The analysis was based on data from the German Institute for Drug Use Evaluation (Deutsches Arzneiprüfungsinstitut e.V. (DAPI)). This database contains anonymized dispensing data from more than 95% of the community pharmacies in all 16 German federal states, claimed at the expense of the statutory health insurance (SHI) funds, and a DataWare House to identify every product by a specific code ("Pharmazentralnummer", PZN). The SHI system, consisting of nearly 100 funds, covers 88% of the population i.e., approximately 73.3 million people. As the unit for prescribed drugs, we used defined daily doses (DDD) – that is, the assumed average maintenance dose per day for a drug used for its main indication in adults. Further, we analysed the aggregate amount of dispensed packages of drugs and diet supplements as effervescent tablets in community pharmacies and via mail-order using dispensing data reimbursed by SHI funds as well as private health insurance companies and over-the-counter sales from the INSIGHT Health (https://www.insight-health.de/) and DatamedIQ (https://www.datamediq.com/) databases, respectively. Usual package sizes of pain/common cold and cough effervescent tablets are 10

or 20, of calcium/vitamin D 20, 40, or 100 tablets. The sodium content of the maximum recommended daily dose was also specified and confirmed by the data in the package insert and/or summary of products characteristics.

Classification and data source of dietary supplements available in the USA

The sodium content of 51 dietary supplement effervescent tablets available in the USA was derived in May 2023 from the Dietary Supplement Label Database. The National Institutes of Health's Dietary Supplement Label Database includes 156,957 current and historical label information from products marketed in the US. Effervescent tablets with specified sodium content in the product information were included. The products were divided into the following categories based on the main active ingredient: vitamin, mineral, energy, and other products.

Statistical methods

The data are presented as means ± standard deviation (SD), medians and interquartile ranges (IQR), or numbers (%). Normal distribution was tested using Kolmogorov-Smirnov/ Shapiro-Wilk test and using a histogram. Analysis of variance (ANOVA) was used (after tested for all assumptions for ANOVA: normally distribution, independence of cases, homogeneity of variance) for comparisons of normally distributed parameters, and for comparisons between non-normally distributed parameters, the Kruskal-Wallis test was used. If these tests were significant, we used a post hoc method (Dunn-Bonferroni) for pairwise comparisons. For comparisons between two non-normally distributed parameters, the Mann-Whitney-U-test was used. A two-sided p-value <0.05 was considered statistically significant. Statistical analyses were performed with SPSS (version 27.0.1.0).

Patient and public involvement

None.

Results

Dietary supplement effervescent tablets in Germany

Supplemental table 1 provides an overview of the included dietary supplement effervescent tablets available in Germany. The median weight of one tablet was 5.5 g, and the price ranged from 2.3 to 39.9 EUR cents/tablet (median price/tablet: 3.2 EUR cents). The sodium content of the effervescent tablets measured by ICP-OES is listed in table 1. On average, one effervescent tablet contained 283.9±122.6 mg sodium (table 2 A). Vitamin products had the highest (378.3±112.8 mg) and calcium products (170.4±113.2 mg) the lowest mean sodium content. Vitamin products contained significantly more sodium than magnesium (p=0.004), calcium (p=0.006), and mineral (p=0.048) products (figure 1). Based on the recommended maximum intake of 2,000 mg sodium/day, a single effervescent tablet contained as much as 4-28% of the maximum recommended daily sodium intake. The lowest sodium content/effervescent tablet was 76 mg (Magnesium400®, Fit + Vital), and the highest was 564.7 mg (VitaminC1000®, Fit + Vital). The median sodium content was 5.1 g/100 g effervescent tablets, with the highest being 9.63 g sodium/100 g (Eisen + Vitamin C®, Fit + Vital). Supplement figure 1 depicts the number of effervescent tablets according to sodium content (in 100 mg increments) grouped per category. One of ten (10.3%) products contained more than 500 mg sodium/tablet. Only 5 (12.8%) products (all of the Mivolis brand) declared the sodium content on the packaging which was nearly identical to the measured sodium content.

Dietary supplement effervescent tablets in the USA

The sodium content of the various effervescent tablets is listed in Supplemental table 2. Among all screened products (n=981), only few declared the sodium content on the label (5.2%), allowing 51 products to be included. The median sodium content of a single effervescent tablet

was 190.0 mg (IQR: 100-250 mg; table 2 B) and no difference in sodium content between the various categories was found (p=0.061). A single effervescent tablet contained 2-18% of the maximum recommended daily sodium content. The measured sodium content of dietary supplements available in Germany was higher when compared with the declared sodium content of products available in the USA (p<0.001).

Pharmacy-only effervescent tablets

The sodium content declared on the summary of product characteristics of the OTC drugs sold in Germany is listed in table 3. The median reported sodium content of a single effervescent tablet was 157.0 mg (IQR: 98.9-417.3 mg; table 2 C). The percentage of sodium consumed per effervescent tablet in relation to the maximum recommended daily sodium intake ranged from 3-29%. Pain/common cold drugs had the highest median sodium content (452.1 mg; IQR: 351.3-474.0 mg) and calcium/vitamin D drugs the lowest (87.0 mg; IQR: 52.0-103.0 mg). A single pain/common cold effervescent tablet contained significantly more sodium than one calcium/vitamin D effervescent tablet (p<0.0001). Supplement figure 2 depicts the number of effervescent tablets according to sodium content (in 100 mg increments) grouped per category. The median sodium content of the recommended daily dose of all included drugs was 384.0 mg (IQR: 139.0-1295.5 mg; table 2 D) and for pain/common cold drugs 2,776.5 mg (IQR: 1,299.8-3,333.0 mg), representing 19%/139% of maximum recommended daily sodium intake, respectively. The intake of eight tablets (maximum recommended daily dose) of Alka-Seltzer classic® (aspirin, Bayer) would lead to the ingestion of 3,560 mg sodium (figure 2), which encompasses 178% of the maximum recommended daily sodium intake. The sodium content of the maximum daily dose of pain/common cold drugs was significantly higher than the sodium content of the maximum daily dose of calcium/vitamin D drugs (p<0.0001) and cough drugs (p=0.007). No significant difference in sodium content between the dietary supplement

calcium effervescent tablets and the pharmacy-only calcium/vitamin D effervescent tablets was seen (p=0.109).

Supplement figure 3 summarizes the main results.

Discussion

This study assessed the sodium content of nutritional supplement effervescent tablets available in Germany and found the sodium amount to range from 76.0 mg/tablet to 564.7 mg/tablet (average 283.9 mg/tablet) representing up to 28% of the maximum recommended daily sodium intake. Vitamin products contained more sodium than magnesium, calcium, and mineral products. The sodium amount/tablet of OTC drugs ranged from 52 mg to 575 mg (median 157.0 mg) representing up to 29% of the maximum recommended daily sodium intake. The intake of the recommended daily dose of one OTC drug would lead to a median consumption of 384.0 mg sodium, and as high as 2,776.5 mg for pain/common cold drugs. The major differences in the product classes´ sodium contents are probably due to the variable CO_2-dependent solubilities. More sodium bicarbonate and/or sodium citrate is required for poorly soluble active ingredients in effervescent tablets for them to dissolve quickly and completely in water. The large variations within individual product classes remain unexplained. Products available in the USA also contain a relevant amount of sodium (ranging from 40 to 360 mg/tablet). Of note, dietary supplement effervescent tablets available in Germany contained more measured sodium than that declared in those available in the USA. This may, in part, be related to selection bias since only a few manufactures from the USA voluntarily provide information about the sodium content.

Dietary sodium intake has been linked to serious harmful effects, including BP elevation and all-cause death.[1,3,4,13,14] The 2017 report of the Global Burden of Disease study listed

excess sodium intake among the major dietary risks, estimated to cause 3 million deaths every year worldwide.[7] A recently published, randomized trial in 20,995 subjects showed that using a table salt substitute containing 75% sodium chloride and 25% potassium chloride (as opposed to regular table salt containing 100% sodium chloride) reduced stroke, cardiovascular events, and death.[1] Consequently, the WHO recommends that daily sodium intake should not exceed 2,000 mg.[8] Many national and international societies have advocated for actions to lower dietary sodium intake through public education, labelling of foods, and improved formulations of convenience food. Nonetheless, the daily sodium intake around the world is often much higher (9,000-12,000 mg table salt/day; 3,500-7,700 mg sodium/day), which may, in part, be aggravated by hidden sodium consumption.[10,15]

For improved and quick solubility, effervescent tablets contain often high amounts of sodium[11] as sodium bicarbonate, sodium carbonate, and/or sodium citrate. The impact of sodium-containing effervescent, mainly paracetamol (acetaminophen) tablets on BP, acute heart failure events, and cardiovascular risk was investigated in several studies.[16–19] The intake of effervescent paracetamol tablets (with 545 mg sodium/dose) was shown to increase 24-hour systolic BP by 5.0 mmHg.[17] Other trials showed an association between the intake of sodium-containing effervescent paracetamol tablets (390-440 mg of sodium/tablet) and an increased risk of hospitalization for heart failure[18], cardiovascular risk, and all-cause mortality among patients with and without hypertension.[11,16,19] The mechanism by which the active substance paracetamol increases blood pressure has not been conclusively clarified; inter alia an influence on the cyclooxygenase pathway is discussed.[20,21] Nevertheless, sodium containing paracetamol effervescent tablets deteriorate blood pressure control mainly caused by the sodium in the effervescent tablets, as evident by the fact that after switching from paracetamol effervescent tablets to paracetamol tablets (without sodium), a decrease in blood pressure was observed.[22]

This provides evidence that effervescent tablets increase sodium intake which might be associated with an increased risk for cardiovascular diseases.[1,3,4,13,14] A large case-control study comprising 1,292,337 patients with a mean follow-up of 7.2 years investigated the association between cardiovascular events and sodium-containing effervescent, dispersible, and soluble drugs.[19] Participants were prescribed sodium-containing formulations or matched standard formulations of the same drug. A total of 61,072 patients with a cardiovascular event were matched with controls. The sodium-containing substances were largely painkillers or calcium drugs with a wide range of sodium content (4.6-427.8 mg/tablet).[19] The adjusted odds ratio for exposure to sodium-containing drugs were 1.16 (95%-confidence interval (95%-CI): 1.12-1.21) for the composite of myocardial infarction, stroke, or vascular death, 1.28 (95%-CI: 1.23-1.33) for all-cause mortality, and 7.18 (95%-CI: 6.74-7.65) for hypertension.[19] Of note, the sodium content of some of the included effervescent tablets in this study is comparable with the sodium content of the drugs included in the mentioned study.[19]

The ancillary sodium intake through effervescent tablets is often neglected or unknown. Herein, the average sodium content of effervescent food supplements tablets in Germany was 283.9 mg/tablet, and the median sodium content of the pharmacy-only effervescent tablets was 157.0 mg/tablet. Consuming one of the included effervescent vitamin tablets or pain/common cold tablets corresponds to about one fifth (19%/23%) of the maximum recommended daily sodium intake. Six products (8.3%) contained more than 500 mg sodium/tablet. Vitamin products contained significantly more sodium than magnesium ($p=0.004$), calcium ($p=0.006$) and mineral ($p=0.048$) products; this might be due to different solubility properties. The sodium content of the maximum daily dose of pain/common cold drugs was significantly higher than the sodium content of the maximum daily dose of calcium/vitamin D drugs ($p<0.0001$) and cough drugs ($p=0.007$). Yet, the majority of the general population and healthcare professionals alike are unaware of the high sodium content of effervescent tablets.[11]

A relevant proportion of the population regularly consumes effervescent tablets as a dietary supplement and/or drugs.[12] In a cross-sectional study from France including 1,043 healthy individuals, 26.9% of the participants reported regular intake of effervescent tablets (once in the last 30 days) and 7.3% reported intake of two or more effervescent tablets/week during the last 30 days.[12] A vast majority of 93.8% of these effervescent tablets were OTC drugs and nutritional supplements, such as vitamins.[12] The presence of hypertension, which should require table salt/sodium restriction, did not result in a reduced intake of effervescent tablets.[12]

According to the Federal Statistical Office of Germany (Statistisches Bundesamt, Destatis), the production of dietary supplements in 2020, which include effervescent tablets, increased by 11% compared with the previous year, most likely as a consequence of the COVID-19 pandemic. In 2020, 180,200 tons of dietary supplements were produced with a value of 1.1 billion Euros in Germany, which corresponds to an increase of 23.4%. In Germany, the sodium content must be indicated on the medicinal products sold in pharmacies but is not mandatory on dietary supplements sold in drugstores or supermarkets.[23,24] Only five (13%) of the included dietary supplements available in Germany and only 5.2% of the investigated dietary supplements available in the US declared sodium content on the packaging, hence, consumers are frequently not informed.

Various sodium-containing drugs administered as effervescent tablets are available. In German pharmacies alone, 3.96 million packages of the included pain/common cold and 5.30 million packs of the included cough effervescent tablets were sold in 2021. (https://www.insight-health.de/ and https://www.datamediq.com/) A total of 52.32 million DDD of calcium/vitamin D drugs, mainly as effervescent tablets, were claimed by community pharmacies at the expense of the SHI funds alone in Germany in 2021.[25] Based on these high sales, we assume that a relevant proportion of the population, occasionally or regularly, consumes effervescent tablets.

A dietary reduction of 1,200 mg sodium/day could translate into an annual reduction of 60,000-120,000 new coronary heart disease patients, 32,000-66,000 fewer strokes, and 54,000-99,000 fewer myocardial infarctions in the USA.[13] This amount of sodium is already contained in approximately 3 of the included effervescent vitamin tablets available in Germany (378.3 mg sodium/tablet on average). A modelling study from China showed that a reduction of 1,000 mg table salt/day could prevent approximately 9 million cardiovascular events in China by 2030, of which approximately 4 million are fatal.[26] Of note, a total of 1,000 mg table salt contains approximately 394 mg sodium. This amount of sodium approximately corresponds to the sodium content of one of the examined vitamin or pain/common cold effervescent tablets.

The intake of one sodium containing dietary supplement effervescent tablet per day for the whole year increases cardiovascular risk more likely than several pain/common cold effervescent tablets/day taken for 5-7 days only. A typical common cold lasts approximately 5-7 days, so the duration of the medical therapy is limited and the intake of OTC-effervescent tablets is rarely permanent. However, studies investigating the (temporary) intake of sodium-containing acetaminophen (paracetamol) effervescent tablets showed an increased risk for hospitalization for acute heart failure, cardiovascular disease and all-cause mortality.[16,18]. The effect of permanent intake of sodium containing dietary supplement effervescent tablet could therefore be higher.

The benefits of pharmacotherapy should always outweigh the risks/side effects. Most likely, the majority of the general population is unaware of the sodium content of effervescent tablets and dietary supplements are often regarded as “sweets”. Dietary supplements are considered “foods” by regulators and health benefits of many dietary supplements for healthy, asymptomatic and well-nourished adults have not yet been demonstrated in randomized clinical trials.[27,28]. Consequently, the harm might outweigh the benefit when people ingest several vitamin and electrolyte effervescent tablets daily, assuming they are doing something good for

their health. In addition, there is little reason to prescribe effervescent tablets because most active ingredients are also available as tablets not containing sodium.

Limitations

Some limitations of our study should be considered. This study provides relevant insights into the sodium content in dietary supplemental and pharmacy-only effervescent tablets but does not assess the association between the ingestion of these products and cardiovascular outcomes. Therefore, only assumptions can be made. Nevertheless, the included effervescent tablets contained a relevant amount of sodium comparable to prior studies investigating the association between sodium-containing effervescent tablets and cardiovascular risk. We provide sales figures for effervescent tablets sold in pharmacies. The quantity of dietary supplement effervescent tablets from discounters, grocery- and drugstores is not publicly available. Measured (Germany) sodium contents of dietary supplements were compared with declared (USA). Assuming the manufacture declares the correct sodium content on the packing, the detection of national differences is possible. Nevertheless, the assumption that the declared sodium content of dietary supplements available in the USA are valid, is a limitation. It is not guaranteed that the ingredients declared on the packing are "correct".[29–31]

Conclusion

Dietary supplements and OTC effervescent tablets investigated herein contained high sodium. Some products contain more sodium than others, although comparable in (active) ingredients. As the variability between preparations is high and these amounts of additional sodium intake may contribute to poor BP control and cardiovascular events, including hospitalization for acute heart failure and death, we think regulators should demand a front-package labelling of sodium content and associated risk before market access. Based on the study findings, patients at risk should be advised to limit effervescent tablets to prevent the ingestion of hidden sodium, and

to select non-effervescent alternatives containing the same active ingredients. Finally, we suggest that manufacturers should be prompted to reduce sodium in their effervescent formulations.

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Competing interests

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Contributors

Concept and design: Kunz, Götzinger, Schulz, Mahfoud. Acquisition, analysis, or interpretation of data: Kunz, Götzinger, Jacobs, Schulz, Mahfoud. Drafting of the manuscript: Kunz, Schulz, Mahfoud. Critical revision of the manuscript for important intellectual content: Jacobs, Lauder, Ukena, Meyer, Laufs, Schulz, Böhm, Mahfoud. Statistical analysis: Kunz, Lauder.
Supervision: Böhm, Mahfoud. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Statement

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Ethical approval

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Data availability statement

All data relevant to the study are included in the article or uploaded as supplementary information. No additional data available.

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Tables

Table 1. Sodium content of German dietary supplement effervescent tablets

Category	Brand name®	Sodium content/tablet (mg)	% of maximum recommended daily sodium intake*	Sodium (g)/ 100g product	Weight/ tablet (g)
Vitamins	fit+Vital Vitamin C1000	564.70	28	9.01	6.27
	elkos Vivede Vitamin C +Zink, Selen, und Vitamin D3	541.10	27	8.95	6.05
	Doppelherz aktiv Vitamin C +Zink	512.80	26	8.11	6.32
	ProLife Vitamin C +Zink, Selen, Vitamin D3	507.90	25	8.48	5.99
	Doppelherz aktiv Vitamin D3 2000 I.E.	485.10	24	7.44	6.52
	SilaVit Vitamin B12	367.30	18	9.05	4.06
	Vitalis Vitamin C 120 mg	341.50	17	8.54	4.00
	Mivolis Vitamin B12	333.00	17	8.08	4.12
	Mivolis Vitamin C	330.30	17	8.02	4.12
	Doppelherz aktiv A-Z Multivitamin+ Mineralien	321.40	16	5.10	6.30
	SilaVit Vitamin C	318.00	16	7.92	4.02
	fit+Vital Multivitamin	304.60	15	7.57	4.02
	elkos Vivede Multivitamin+ Mineralstoffe	273.50	14	4.56	6.00
	ProLife Multivitamin+ Mineralstoffe	263.20	13	4.38	6.01
	fit+Vital Multivitamin+ Mineral	210.70	11	5.26	4.01
Magnesium	Doppelherz aktiv Magnesium 400	332.50	17	5.11	6.51
	Vitalis Magnesium 240 mg	306.10	15	5.58	5.49
	Abtei Magnesium 400 Plus Vitamin C+E	298.70	15	5.56	5.38
	Doppelherz aktiv Magnesium+ Calcium+ D3	271.20	14	4.12	6.59
	Doppelherz aktiv Magnesium 500+ B12	268.90	13	4.12	6.53

	Mivolis Magnesium	262.70	13	6.39	4.11
	elkos Vivede Magnesium+ B-Komplex, Vitamin C und E	248.40	12	4.13	6.01
	Doppelherz aktiv Magnesium+ Kalium Sport	245.50	12	3.72	6.60
	ProLife Magnesium+ B-Komplex, Vitamin C&E	238.00	12	3.95	6.03
	Kneipp Magnesium+ Calcium+ D3	221.30	11	4.91	4.51
	Abtei Magnesium+ Kalium Aktiv Plus	138.10	7	2.52	5.48
	fit+Vital Magnesium	117.80	6	2.95	3.99
	fit+Vital Magnesium 400	76.00	4	1.40	5.41
Calcium	ProLife Calcium+ Vitamin K1, D3, Folsäure	335.90	17	5.60	6.00
	Mivolis Calcium	145.90	7	3.53	4.14
	fit+Vital Calcium+ D3	116.20	6	2.89	4.02
	fit+Vital Calcium 1000	83.70	4	1.36	6.17
Minerals	Kneipp Männer Mineralstoffe	217.00	11	3.87	5.61
	Kneipp Frauen Mineralstoffe	209.40	10	3.33	6.29
	Mivolis Multi-Mineral	148.40	7	3.62	4.10
Other products	fit+Vital Eisen+ Vitamin C	382.90	19	9.63	3.98
	SilaVit Immun Aktiv	363.80	18	8.55	4.25
	sanotact Recovery+ Aminosäuren	187.60	9	3.54	5.29
	isostar Hydrate & Perform	181.00	9	1.51	11.99
*Maximum recommended daily sodium intake according to World Health Organization recommendations[8]					

Table 2. Sodium content per: (A) Dietary supplement effervescent tablet available in Germany, (B) Dietary supplement effervescent tablet in the USA, (C) OTC effervescent tablet, (D) recommended daily dose of the included OTC effervescent tablets

A		
Category	**Sodium content (mg)/tablet mean±SD**	**% of the maximum recommended daily sodium intake* mean±SD**
…all included products	283.9±122.6	14±6
…vitamin products	378.3±112.8	19±6
…magnesium products	232.7±76.7	12±4
…calcium products	170.4±113.2	9±6
…mineral products	191.6±37.6	10±2
…other products	278.8±109.5	14±6
B		
Category	**Sodium content (mg)/tablet Median (IQR)**	**% of the maximum recommended daily sodium intake* Median (IQR)**
…all included products	190.0 (100.0-250.0)	10 (5-13)
…vitamin products	100.0 (72.5-230.0)	5 (4-12)
…mineral products	250.0 (140.0-360.0)	13 (7-18)
…energy products	190.0 (150.0-260.0)	10 (8-13)
…other products	210.0 (158.8-256.3)	11 (8-13)
C		
Category	**Sodium content (mg)/tablet Median (IQR)**	**% of the maximum recommended daily sodium intake* Median (IQR)**
…all included drugs	157.0 (98.9-417.3)	8 (5-21)
…pain/common cold	452.1 (351.3-474.0)	23 (18-24)
…cough	138.8 (112.8-157.9)	7 (6-8)
…calcium/vitamin D	87.0 (52.0-103.0)	4 (3-5)
…other drugs	267.0 (119.8-387.5)	13 (6-19)
D		
Category	**Sodium content (mg) of the maximum daily dose Median (IQR)**	**% of the maximum recommended daily sodium intake* Median (IQR)**
…all included drugs	384.0 (139.0-1295.5)	19 (7-65)
…pain/common cold	2,776.5 (1,299.8-3,333.0)	139 (65-167)
…cough	297.0 (144.5-427.0)	15 (7-21)
…calcium/vitamin D	104.0 (96.3-104.8)	5 (5-5)
…other drugs	801.0 (312.8-1,155.5)	40 (16-58)

*Maximum recommended daily sodium intake according to World Health Organization recommendations[8]
IQR= interquartile range; OTC= over-the-counter, SD= standard deviation

Table 3. Sodium content of OTC effervescent tablets

Category	Brand name® (manufacturer)	sodium content/tablet (mg)	% of the maximum recommended daily sodium intake* of one tablet	sodium content of maximum recommended daily dose (mg)	% of maximum recommended daily sodium intake* of the maximum recommended daily dose	Maximum recommended tablets per day	OTC	Active ingredients	Sales figures
Pain/common cold (frequently dispensed products)	Aspirin Migräne (Bayer)	544	27	3,264	163	6	yes	aspirin	3.96 million packs of this class sold in 2021 in Germany
	ASS + C-ratiopharm gegen Schmerzen (Ratiopharm)	477	24	2,385	119	5	yes	aspirin, ascorbic acid	
	ASPIRIN plus C forte (Bayer)	473	24	1,419	71	3	yes	aspirin, ascorbic acid	
	ASPIRIN plus C (Bayer)	466	23	2,796	140	6	yes	Aspirin, ascorbic acid	
	Togal Kopfschmerz-Brause + Vitamin C (Kyberg Pharma)	459	23	2,754	138	6	yes	Aspirin, ascorbic acid, caffeine	
	Alka-Seltzer classic (Bayer)	445	22	3,560	178	8	yes	aspirin	
	FIZAMOL 500 mg (Accord Healthcare)	419	21	3,352	168	8	yes	acetaminophen	
	PARACETAMOL-ratiopharm 500 mg (Ratiopharm)	416	21	3,328	166	8	yes	acetaminophen	
	WICK DayMed Erkältungsgetränk (WICK Pharma)	157	8	942	47	6	yes	acetaminophen, guaifenesin, phenylephrine	
	Grippostad C Stickpack (STADA Consumer Health)	128	6	384	19	3	yes	acetaminophen, chlorpheniramine, ascorbic acid, caffeine	
Cough (frequently dispensed products)	NAC-ratiopharm 200 mg, (Ratiopharm)	190	10	570	29	3	yes	acetylcysteine	5.30 million packs of this class sold in 2021 in Germany
	Fluimucil 200 mg (Zambon)	158	8	474	24	3	no	acetylcysteine	
	Fluimucil long 600 mg (Zambon)	158	8	158	8	1	no	acetylcysteine	
	NAC-ratiopharm 600 mg (Ratiopharm)	150	8	150	8	1	yes	acetylcysteine	
	ACC akut 600mg (Hexal)	139	7	139	7	1	yes	acetylcysteine	
	NAC 600 akut (1A Pharma)	139	7	139	7	1	yes	acetylcysteine	
	Ambrobeta 30 (betapharm Arzneimittel)	127	6	381	19	3	yes	ambroxol	
	ACC akut 200mg (Hexal)	99	5	297	15	3	yes	acetylcysteine	
	NAC 200 akut (1A Pharma)	99	5	297	15	3	yes	acetylcysteine	

Calcium/ vitamin D3 (colecalciferol; examples of frequently prescribed effervescent tablets)	Calcium Sandoz forte (Hexal)	288	14	864	43	3	yes	Calcium + vitamin D	52.32 million DDD of the entire class claimed to the expense of the SHI funds in 2021 in Germany[25]
	Calcium D3 acis 1.200/ 800 (acis Arzneimittel)	105	5	105	5	1	yes	Calcium + vitamin D	
	CalciCare-D3 forte 1.000 mg/ 880 I.E. (ORION Pharma)	97	5	97	5	1	yes	Calcium + vitamin D	
	Calcilac 1000 mg/ 880 I.E. (MIBE Arzneimittel)	96	5	96	5	1	yes	Calcium + vitamin D	
	Osteoplus 1.000 mg/ 1.000 I.E. (Recordati Pharma)	78	4	78	4	1	yes	Calcium + vitamin D	
	Calcigen D 600/ 400 (MEDA Pharma)	52	3	104	5	2	yes	Calcium + vitamin D	
	Calcium D3-ratiopharm 600/ 400 (Ratiopharm)	52	3	104	5	2	yes	Calcium + vitamin D	
	Calcium Sandoz D Osteo 600 mg/ 400 I.E. (Hexal)	52	3	104	5	2	yes	Calcium + vitamin D	
Other drugs (examples)	Gittalun (Hermes Arzneimittel)	575	29	1,150	58	2	yes	doxylamine	-
	Zink-ratiopharm 25mg (Ratiopharm)	325	16	325	16	1	yes	zinc	
	Magnesium Verla (Verla-Pharm Arzneimittel)	314	16	942	47	3	yes	magnesium	
	Lösferron (MIBE Arzneimittel)	220	11	660	33	3	yes	Fe-(II)-D-gluconat	
	Magnesiocard 7,5 mmol (Verla-Pharm Arzneimittel)	138	7	276	14	2	yes	magnesium	
	Morphin Painbreak akut 20 mg (PB Pharma)	65	3	1,170	59	18	no	morphine	

*Maximum recommended daily sodium intake according to World Health Organization recommendations[8]
DDD= defined daily doses; OTC= over-the-counter; SHI= statutory health insurance.

Figure titles

Figure 1. Mean sodium content of dietary supplement effervescent tablets available in Germany, by category

Figure 2. Sodium content of the maximum recommended daily dose of some included effervescent over-the-counter tablets

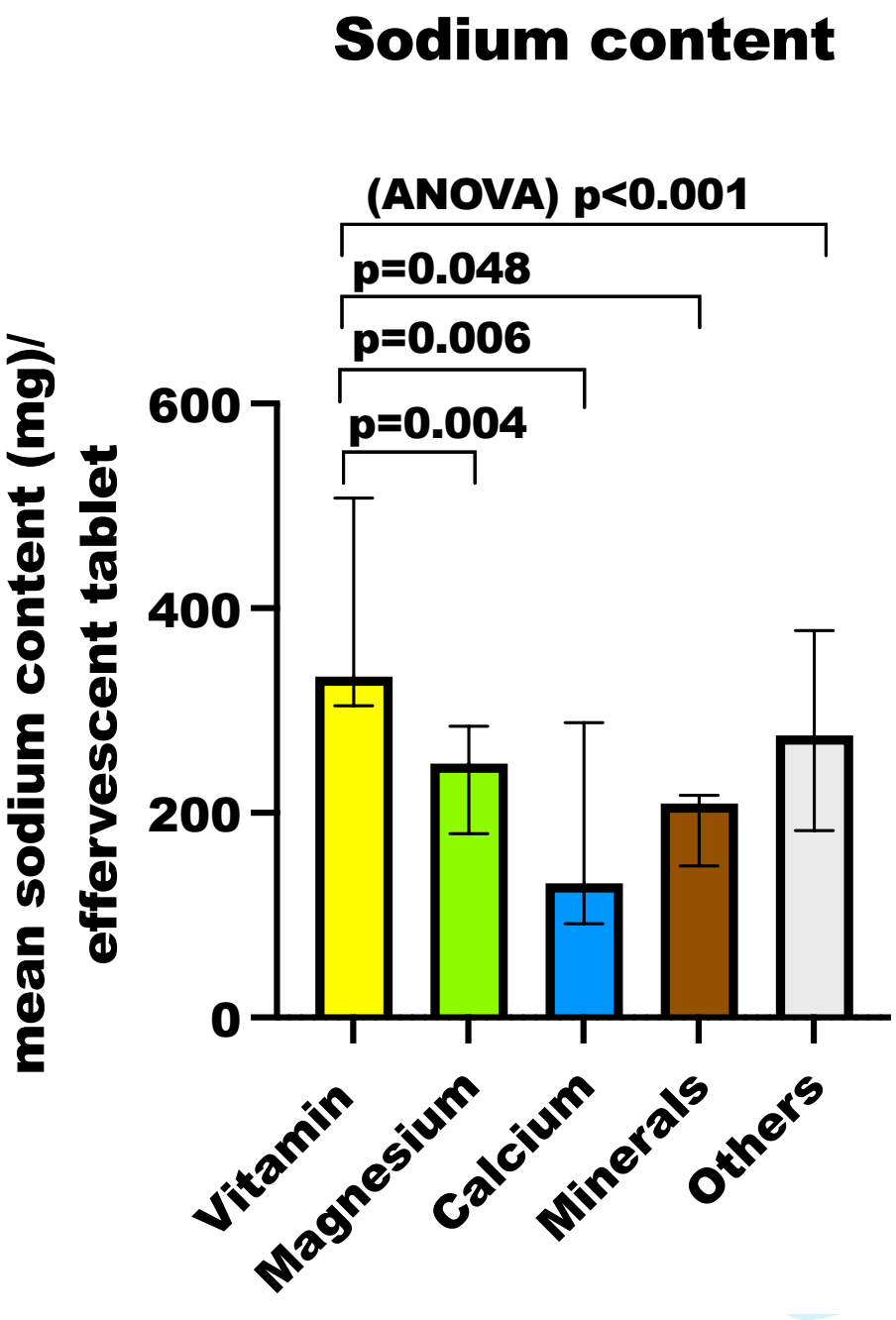


Figure 1. Mean sodium content of the respective category of the German dietary supplement effervescent tablets. P values are given for between-group comparisons (adjusted for post hoc method). ANOVA = analysis of variance.

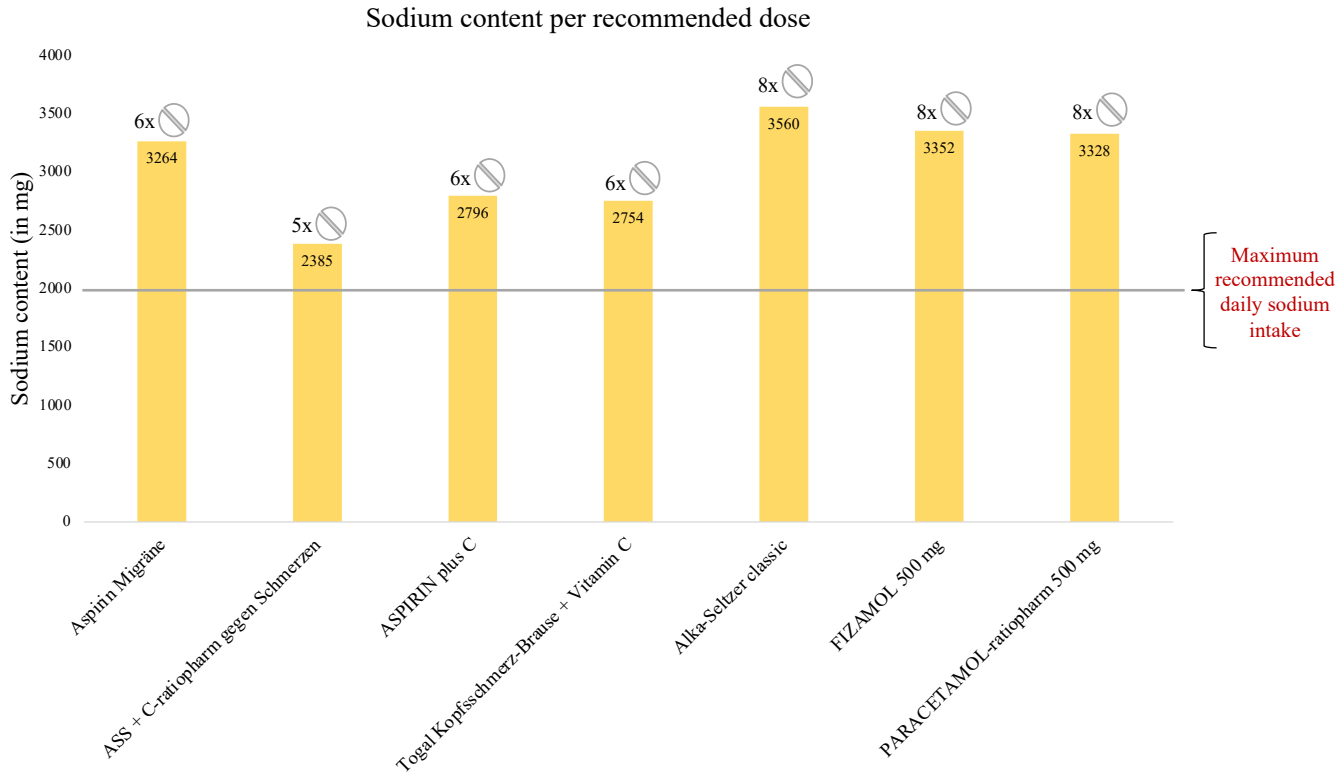


Figure 2. Sodium content of the maximum recommended daily dose of some included effervescent OTC tablets. The number above the bars corresponds to the maximum daily number of tablets. (Aspirin Migräne®: Bayer; ASS + C-ratiopharm gegen Schmerzen®: Ratiopharm; ASPIRIN plus C®: Bayer; Togal Kopfschmerz-Brause + Vitamin C®: Kyberg Pharma; Alka-Seltzer classic®: Bayer; FIZAMOL 500 mg®: Accord Healthcare, Paracetamol-ratiopharm 500mg®: Ratiopharm

Supplemental table 1. Overview of the included German products.

Supplemental table 2. Sodium content of the included products from the United States of America.

Supplement figure 1. Number of different German dietary supplement effervescent tablets that contain a certain amount of sodium (classified in 100 mg increments).

Supplement figure 2. Number of different pharmacy-only effervescent tablets that contain a certain amount of sodium (classified in 100 mg increments).

Supplement figure 3. Central illustration.

Supplement table 1. Overview of the included German products.

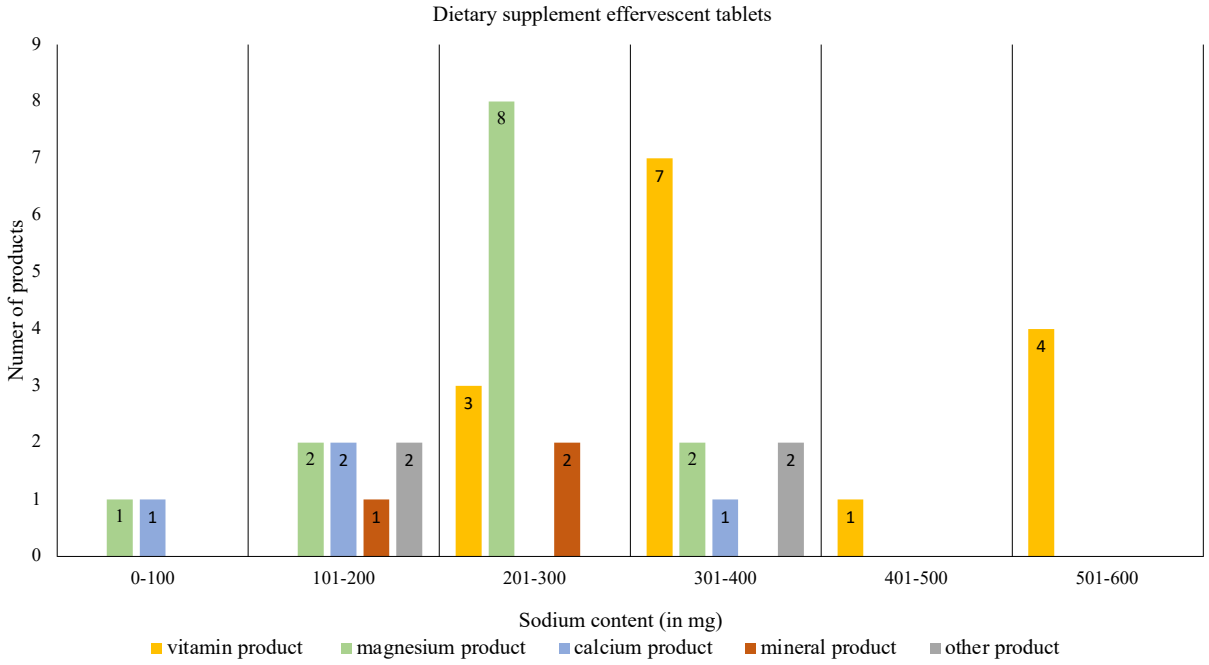
Offeror	Manufacturer	Brand name®	Number of tablets	Total weight (g)	Weight/ tablet (g)	Total price (cent)	Price/ tablet (cent)
ALDI SÜD GmbH & Co.	Vitalis	Magnesium 240 mg	14	78	5.6	45	3.2
		VitaminC 120 mg	20	80	4.0	45	2.3
Edeka Stiftung & Co. KG	ELKOS Vivede	VitaminC+ Zink, Selen, Vitamin D3	17	102	6.0	55	3.2
		Magnesium+ B-Komplex, Vitamin C und E	17	102	6.0	55	3.2
		Multivitamin+ Mineralstoffe	17	102	6.0	55	3.2
Netto Marken-Discount Stiftung & Co. KG	ProLife	VitaminC+ Zink, Selen, Vitamin D3	17	102	6.0	55	3.2
		Magnesium+ B-Komplex, Vitamin C&E	17	102	6.0	55	3.2
		Multivitamin+ Mineralstoffe	17	102	6.0	55	3.2
		Calcium+ Vitamin K1, D3, Folsäure	17	102	6.0	55	3.2
DM drogerie markt GmbH & Co. KG	Mivolis	Magnesium	20	82	4.1	45	2.3
		VitaminB12	20	82	4.1	45	2.3
		Calcium	20	82	4.1	45	2.3
		Multi-Mineral	20	82	4.1	45	2.3
		VitaminC	20	82	4.1	45	2.3
	Kneipp	Magnesium+ Calcium+ D3	20	90	4.5	245	12.3
Müller Handels GmbH & Co. KG	Kneipp	Frauen Mineralstoffe	15	94	6.3	345	23.0
		Männer Mineralstoffe	15	84	5.6	399	26.6
	Abtei	Magnesium400 Plus Vitamin C+E	15	81	5.4	295	19.7
		Magnesium+ Kalium Aktiv Plus	15	82.5	5.5	275	18.3
	Sanotact	Recovery+ Aminosäuren	15	79.5	5.3	295	19.7
	Doppelherz	VitaminC+ Zink	15	94.5	6.3	295	19.7
		VitaminD3 2000 IE	15	97.5	6.5	275	18.3
		A-Z Multivitamin+ Mineralien	15	93	6.2	279	18.6
		Magnesium 400	15	97.5	6.5	275	18.3

		Magnesium+ Calcium+ D3	15	97.5	6.5	279	18.6
		Magnesium 500+ B12	15	97.5	6.5	249	16.6
		Magnesium+ Kalium Sport	15	99	6.6	299	19.9
	Fit + Vital	Caclium+ D3	20	80	4.0	139	7.0
		Multivitamin	20	80	4.0	45	2.3
		Vitamin C1000	15	93	6.2	139	9.3
		Multivitamin+ Mineral	20	80	4.0	45	2.3
		Magnesium	20	80	4.0	45	2.3
		Eisen+ VitaminC	20	80	4.0	139	7.0
		Cacium 1000	15	93	6.2	45	3.0
		Magnesium 400	15	81	5.4	45	3.0
	SilaVit	Immun Aktiv	20	84	4.2	139	7.0
		Vitamin B12	20	80	4.0	125	6.3
		Vitamin C	20	80	4.0	45	2.3
	Isostar	Hydrate & Perform	10	120	12.0	399	39.9

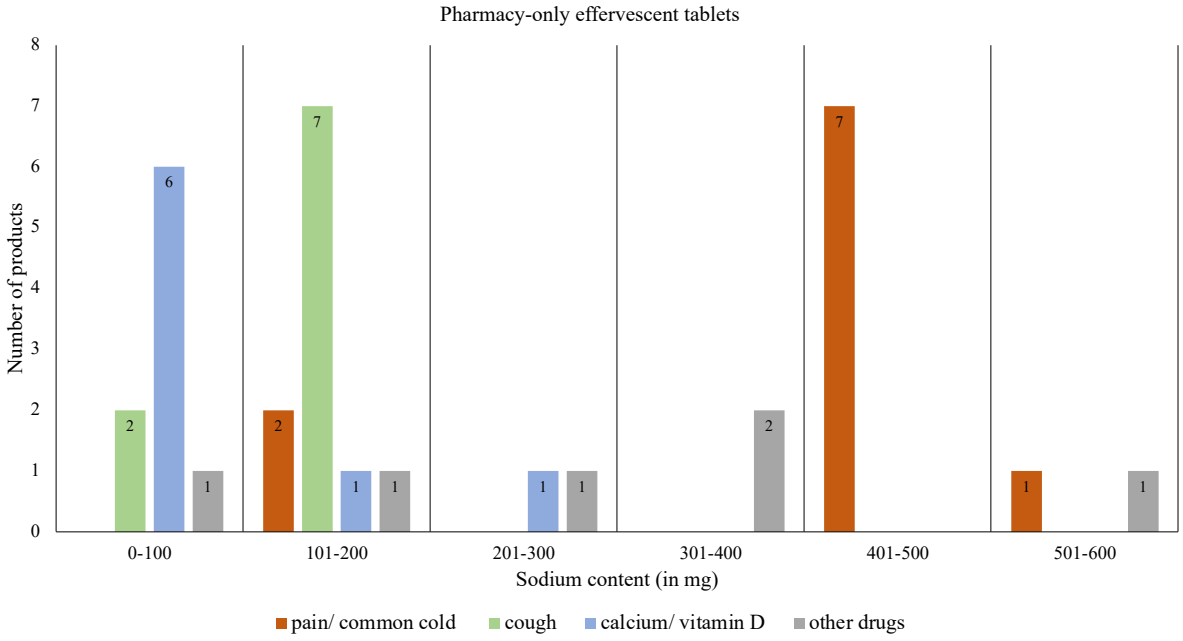
Supplement table 2. Sodium content of the included products from the United States of America.

Brand name®	Manufacturer	Category	Sodium content/tablet (mg)
ActivJoint Tangerine	Trace Minerals Research	Other	155
Advanced Anti-Aging Formula Effervescent Drink Mix Orange	TimeFighters	Other	55
Airborne Dual Action Citrus	Airborne	Vitamin	230
Airborne Elderberry Effervescent Tablets	Airborne	Mineral	230
Airborne Immune Support Effervescent Tablets	Airborne	Vitamin	230
Airborne Vitamin C Original Lemon Lime	Airborne	Vitamin	230
Airborne Zesty Orange	Airborne	Mineral	150
Alka-Seltzer Plus Immunity Complex	Bayer	Vitamin	313
Amino X Fruit Punch	BSN	Other	160
AngiNOX Natural Orange Flavor	XYMOGEN	Other	220
Berocca Orange Flavor	Bayer	Energy	260
Best Defense Orange Boost	Herbalife Nutrition	Vitamin	115
BetaBoost + Vitamin C Citrus	Airborne Advanced	Vitamin	240
Carni-Fizz Natural Lemon Lime Flavor	Body Fizzics	Other	245
CuraMed Natural Tangerine Flavor	Terry Naturally	Other	130

CuraPro 350 mg Tangerine Effervescent	EuroMedica	Mineral	130
Effer-C Lemon-Lime Effervescent Drink Mix	NOW	Vitamin	50
Effervescent Effer-Energy Tropical Punch	NOW Sports	Mineral	360
Effervescent Effer-Hydrate	NOW Sports	Mineral	360
Effervescent Energy Lava Lime	Eruption	Energy	240
Effervescent Vitamin C 1000 mg Natural Orange Flavor	Sundown Naturals	Vitamin	60
Effervescent Vitamin C Orange Flavored	365 Everyday Value	Vitamin	60
Energize Isotropin Lemon Flavor Effervescent	Newton-Everett	Energy	150
Energy Berry Blast	Nuun	Energy	100
Ester-C Effervescent 100 mg Plus Electrolytes Natural Orange Flavor	American Health	Vitamin	100
Ester-C Effervescent 1000 mg Natural Orange Flavor	NatureSmart	Vitamin	100
Ester-C Effervescent 1000 mg Natural Raspberry	American Health	Vitamin	55
Ester-C Effervescent 1000 mg Natural Raspberry Flavor	Solgar	Vitamin	40
Evotest Black Cherry	BSN	Other	300
Garcinia Cambogia Lineatabs Passion Fruit Flavor	Apax	Other	190
Green Superfood Detox Orange Turmeric Flavor	Amazing Grass	Other	260
Immune Oxylent Effervescent Supplement Drink	Immune Oxylent	Vitamin	90
Immune Support Orange Flavor	Equate	Vitamin	230
Immuni-V Orange Effervescent	MRI Performance	Vitamin	85
Immunity Blueberry Tangerine	Nuun	Vitamin	100
Isotropin Rejuvenation Tangerine Flavor	NewtonEverett	Other	255
Liftoff Tropical Fruit Force	Herbalife Nutrition	Vitamin	230
Lineatabs	Apax	Other	270
Nuun Active Fruit Punch	Nuun	Vitamin	360
Nuun Hydration Tri-Berry	Nuun	Mineral	360
POW Berry-Melon Fizz	EBOOST	Energy	190
POW Berry-Melon Fizz	EBOOST	Energy	155
Power Pak Cranberry	Trace Minerals Research	Vitamin	175
Pumped Edge Fruit Punch	BSN	Other	200
Sambucus Fizzy Berry Flavored	Nature's Way	Other	160
Sport +Caffeine Fresh Lime	Nuun	Energy	300
Sport Fruit Punch	Nuun	Mineral	300
Sport Oxylent 3-In-1 Performance Supplement Drink Blueberry Burst	Sport Oxylent	Mineral	90
Vitamins Blueberry Pomegranate	Nuun	Vitamin	100
Wal-Born Orange Flavor	Well At Walgreens	Other	230
ZYM Electrolyte Drink Tablets	ZYM	Mineral	250



Supplement figure 1. Number of different German dietary supplement effervescent tablets that contain a certain amount of sodium (classified in 100 mg increments).



Supplement figure 2. Number of different pharmacy-only effervescent tablets that contain a certain amount of sodium (classified in 100 mg increments)

What is known ?

- Dietary sodium intake → BP ↑ and CV events ↑
- Recommended daily sodium intake: < 2000 mg
- ETs contain high amounts of sodium (often not labeled)
- approx. 30% of the population regularly consume ETs as dietary supplements and/or drugs

Dietary supplement ETs

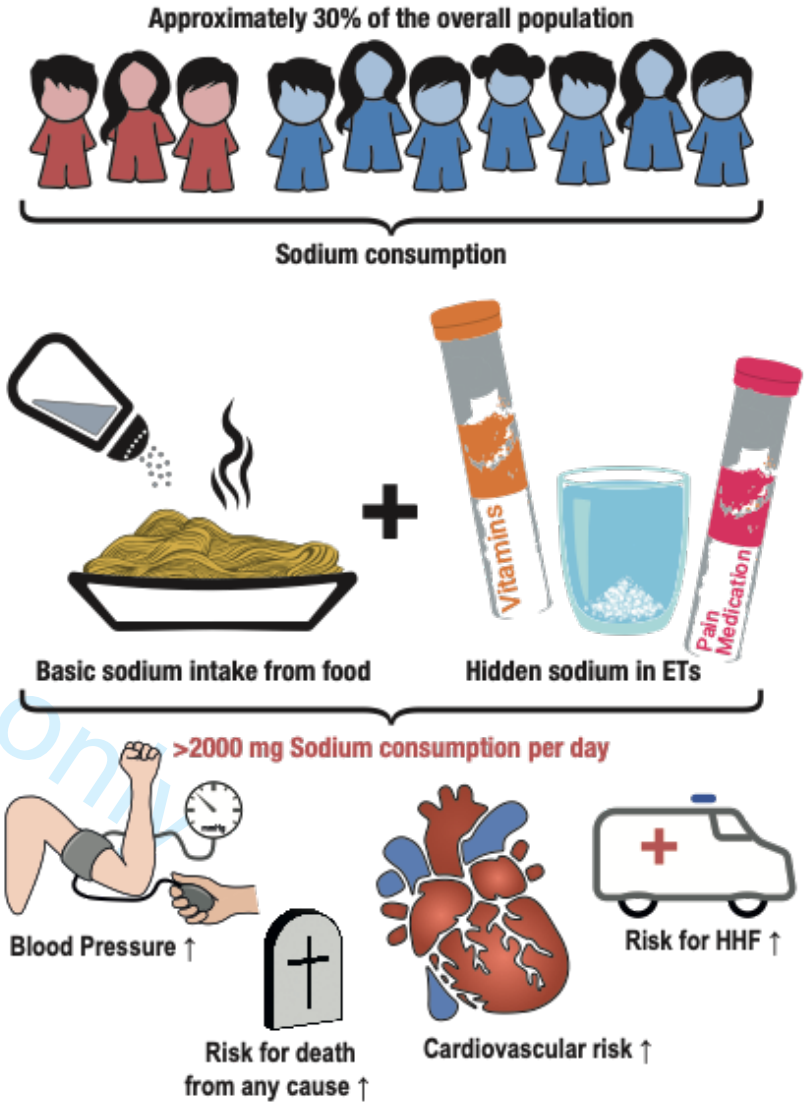
- 39 included
- Average sodium content: 283.9±122.6 mg → 4-28% of the RDSI
- Highest average sodium content: vitamin products (378.3±112.8 mg)
- Lowest average sodium content: calcium products (170.4±113.2 mg)
- Vitamin products: more sodium than magnesium (p=0.004), calcium (p=0.006) and mineral (p=0.048) products

Pharmacy-only ETs

- Median sodium content: 157.0 mg (IQR: 98.9-417.3 mg) → 3-29% of the RDSI
- Highest median sodium content: pain/ common cold drugs (452.1 mg; IQR: 351.3-474.0 mg)
- Lowest median sodium content: calcium/ vitamin D drugs (87.0 mg; IQR: 52.0-103.0 mg)
- Median sodium content of the MDD of pain/ common cold drugs: 2,776.5 mg (IQR: 1,299.8-3,333.0 mg)

Conclusion

- ETs contain a relevant amount of sodium (often unknown or neglected)
- Additional sodium intake → poor BP control and CV events ↑
- Sodium loaded ETs should be avoided in patients at risk



Supplement figure 3. Central illustration. BP= blood pressure; CV= cardiovascular; ET= effervescent tablets; HHF= hospitalization for acute heart failure; IQR= interquartile range; MDD= maximum daily dose; RDSI= recommended daily sodium intake.