Title: Lithium-rich mineral water is a highly bioavailable lithium source for human consumption

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Abstract

Scope

Lithium is an important trace element in human nutrition and medicine. Mineral and medicinal waters may represent a significant source of dietary lithium intake.

Methods and results

We determined the lithium concentration of 360 German mineral and 21 medicinal waters. Based on our systematic screening, we chose three different mineral waters exhibiting low (1.7 µg/L), medium (171 µg/L) and high lithium (1724 µg/L) concentrations for an acute bioavailability study in male healthy volunteers. In Germany, a north-east to south-west gradient of analysed lithium concentrations was observed in the 381 tested waters. The lithium concentration in the water was significantly correlated with its sodium (r = 0. 810), potassium (r = 0.716) and magnesium (r = 0.361) but not with its calcium concentration. In a randomized cross-over trial, volunteers (n = 3 x 10 each) drank 1.5 litres of the respective mineral waters, and lithium concentrations in serum and urine were monitored over 24 hours. Consumption of the mineral waters with a medium and high lithium content resulted in a dose-dependent response in serum lithium concentrations and total urinary lithium excretion.

Conclusion

Lithium-rich mineral and medicinal waters may be an important and highly bioavailable lithium source for human consumption.

Graphical abstract

Lithium concentrations of 381 German mineral and medicinal waters were determined. Substantial geographical differences in lithium concentrations of the analysed waters were observed. Three different mineral waters exhibiting low, medium and high lithium concentrations were chosen for a bioavailability study in humans. There was a dose-dependent response in serum lithium concentrations and total urinary lithium excretion after the consumption of the respective mineral waters.

Graphical abstract
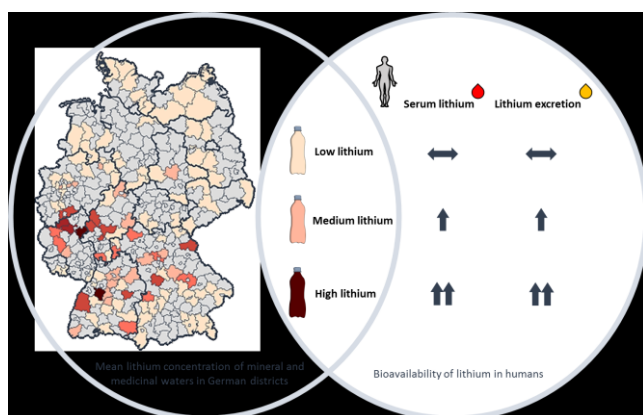
Introduction

Although an essential function of the naturally occurring trace element lithium in man and animals has not yet been fully established there is increasing epidemiological and experimental evidence indicating that lithium exhibits various health benefits [1]. Studies in model organisms including Drosophila melanogaster indicate that dietary lithium may

promote longevity and health span [2]. Furthermore, exposure to a low concentration of lithium chloride increased the life span of the nematode Caenorhabtitis elegans [3]. Accordingly, in the Japanese population, an inverse correlation between lithium levels in drinking water and all-cause mortality was evident [3]. Likewise, lithium exposure via tap water was associated with a lower risk of dementia [4] , Alzheimer disease mortality [5] and lower suicide rates [6]. However, in other studies, a proposed association between lithium in drinking water and suicide risk was not fully supported [7].

Pharmacological doses of lithium are commonly used for the treatment of psycho-neurological diseases, esp., bipolar disorders. However, there is a rather narrow therapeutic window (0.6 and 1.2 mmol/L blood serum) for lithium medication [8], which has to be continuously monitored [9]. Chronic lithium medication may be accompanied with side effects, such as nephrotoxicity [10, 11], thyroid abnormalities [12] or malformations of the newborn, if lithium was taken by the mother during pregnancy (For review see [13]). Nevertheless, in response to dietary lithium, serum lithium levels are multiple times lower than those obtained under medicinal conditions [14] and, as mentioned above, dietary lithium may rather mediate preventive health effects.

In many countries throughout the world tap water is the major source of water intake. However, in Germany mineral water is widely consumed (144 litre per capita and year, which equals 400 mL per day), whereas the consumption of tap water is rather low [15]. Currently, German consumers can choose among hundreds of different brands of mineral waters. Globally, the consumption of bottled mineral water is on the rise despite good tap water quality [16]. Thus, bottled water is one of the fastest-growing drinks markets, and it has been stated that bottled water will globally become the most important beverage category by volume [17]. In Germany, approximately 500 mineral and 35 medicinal waters

are available for consumption [18]. For all member states of the European Union (EU), bottled waters are categorized into "natural mineral water", "spring water" and "bottled drinking water". Natural mineral waters and spring waters originate from mineral springs and bottled directly at source but, unlike spring waters, natural mineral waters need to be officially registered. Bottled drinking water, also known as table water, does not have to be sourced from mineral springs (Directive 2009/54/EC and Directive 98/83/EC) [19, 20] . To the best of our knowledge, medicinal waters are not regulated by the EU law. In Germany, mineral water is regulated by the Mineral and Drinking Water Ordinance (Min/TafelWV). In general, modification of mineral water is restricted, and the composition of minerals, such as lithium, depend only on their source [21]. Medicinal waters are produced as mineral waters but are considered pharmaceuticals. They should possess a minimum of valuable elements and a scientifically proven therapeutic effect. Medicinal waters are admitted by the Federal Institute for Drugs and Medical Devices (BfArM) and regulated by the Drug Registration and Administration Act (AMG) [22].

It has been previously demonstrated that mineral water may significantly contribute to the supply of calcium and magnesium (for review see [23]) in humans, but bioavailability data for trace elements, such as lithium, are scarce. There may be substantial regional variations in the mineral and trace element concentration of mineral waters including lithium that mainly depend on geological factors. Therefore, within this study we systematically determined the lithium concentration of nearly all commericially available German mineral and medicinal waters. In addition to this systematic lithium screening approach we also determined if and to what extent lithium from mineral water affects serum lithium levels and urinary lithium excretion in human volunteers as biomarkers of lithium bioavailability.

Materials and Methods

Sampling of mineral waters

Sampling took place between November 2017 and February 2018 throughout Germany. Mineral and medicinal waters were purchased from supermarkets, drinks markets, petrol stations, and kiosks. In most cases sparkling waters declared as "medium" were used for lithium analysis, if not available sparkling waters declared as "classic" or "still" were used. The geographical distribution of the collected mineral water samples is given in figure 1. In total, 360 mineral and 21 medicinal waters were collected. Regarding bottling, 248 of the analysed waters were bottled in glass, 218 in polyethylene terephthalate (PET) bottles and one mineral water was filled in a Tetra Pak. Eighty-six waters were available both in glass as well as in PET bottles. 10 mL aliquots of the corresponding waters were filled into polyethylene falcon tubes with screw caps (Sarstedt, Nuembrecht, Germany). Tubes were stored in in carton boxes at 10 °C until lithium analysis.

Human bioavailability study

Study population

Ten healthy men aged between 20 and 40 years and with a BMI between 20 and 30 kg/m^2 were recruited in August 2018 by notice board postings at the Christian-Albrechts-University Kiel, Germany and on social networks. We excluded women partly because of changes in fluid retention over the course of the menstrual cycle. Further exclusion criteria were chronic diseases, regular use of medication or supplements, alternative eating habits (e.g., vegan diet), food allergies or intolerances and smoking. The study protocol was approved by the ethics committee of the medical faculty, Christian-Albrechts-University Kiel, Germany (D

484/18) and registered with the DRKS-ID: DRKS00016063. All subjects provided written informed consent before participation.

Study protocol

Bioavailability of lithium from three different mineral waters was investigated in a randomized cross-over study (3 x 24 hours). The sequence of intervention days was block-randomized and the primary outcome was bioavailability of lithium (incremental area under the serum lithium curve; iAUC). On intervention days, participants came to the institute at 0700 after an overnight fast and without beverage consumption. Intervention days were separated by ≥9 days of washout where participants were instructed to follow their normal eating habits.

Study beverages and diet composition

To ensure equal baseline conditions, subjects were provided a standard dinner (mozzarella pizza, Ristorante, Dr. Oetker) and low lithium mineral water (max. 3.0 L) the day before intervention days. The study beverages were three commonly available sparkling mineral waters differing in lithium content: "Trendic medium" (Hansa-Heemann AG, Rellingen, Germany) with 1.7 µg lithium / kg (low lithium); "Gerolsteiner medium" (Gerolsteiner Brunnen GmbH & Co. KG, Gerolstein, Germany) with 171 µg lithium / kg (medium lithium); and "Perling medium" (Rhenser Mineralbrunnen GmbH, Rhens, Germany) with 1724 µg lithium / kg (high lithium). After fasting blood sampling, subjects consumed 1.5 L of mineral water with low, medium or high lithium content within 45 minutes and further blood samples were taken at fixed intervals. No other beverages were allowed until lunch. Lunch was served at 1200 and dinner was consumed between 1900 and 2000 at home. From lunch until 2100, subjects consumed another 1.5 L of low lithium mineral water on all intervention days until final blood sampling after 24 hours. Participants received the same

meals with low lithium content on all intervention days, consisting of fried noodles with sunflower margarine and salt for lunch, rice pudding with vanillin sugar as dessert and noodles with chicken-cream sauce for dinner. Meals were consumed within 30 minutes, and samples of the meals were analysed for lithium content. Breakfast was skipped due to the expected peak of serum lithium in the first hours after consumption. Subjects were instructed to eat an *ad libitum* amount of the provided food on the first intervention day. All foods and leftovers were weighted to the nearest 1.0 g using an electronic scale, and individual food intake was calculated. On the following intervention days, participants consumed the exact amount of foods which they had eaten on the first day. All food and mineral waters were provided. Subjects were instructed to abstain from vigorous physical activity during the study periods to avoid lithium-losses due to increased sweating.

Blood sampling

Blood sampling by ante cubital vein cannula was performed before and 0.5, 1, 1.5, 2, 4, 8 and 24 hours after mineral water consumption to assess serum lithium. After clotting for ≥ 30 minutes at room temperature, serum samples were centrifuged at 2000 x g for 10 minutes at 18 °C. To assess total lithium excretion, 24 h-urine was collected. Aliquots of all samples were stored at -40 °C until analysis.

Lithium analysis

In general, lithium concentrations were determined via an Inductively coupled plasma - mass spectrometry (ICPMS) ICAP Q instrument (Thermo Fisher Scientific, Waltham, USA) and conducted by SYNLAB (Jena, Germany). Measurements were conducted in accordance to DIN EN ISO 17294-2: 2017-01. Water samples were degassed and diluted 1 to 10 to

reduce matrix effects. The solution was stabilized by addition of 2 % (v/v) concentrated nitric acid. Rhodium (2 µg/L) was added as the internal standard. Samples with a higher lithium concentration or samples with signal depression were further diluted. The limit of detection (LOD) of water samples was 0.02 µg/L. To increase the sensitivity, the use of the mass spectrometry collision chamber was neglected, and the LOD was lowered to 0.002 µg/L. Serum samples were diluted 1 to 50 and stabilized with 2-propanol and Triton X. Rhodium (2 µg/L) was added as the internal standard. The limit of detection (LOD) of serum samples was 0.1 µg/L.

Calculations and statistical analysis

The geographical distribution of the collected mineral water samples and the chloropleth map were created by datawrapper.de. For the chloropleth map, the mean lithium concentration of all mineral and medicinal waters that were collected within the same district was used. Bioavailability of lithium was assessed by the serum parameter such as iAUC, the maximum lithium concentration (C_{max}), time of maximum lithium concentration (T_{max}) as well as the half-life of lithium ($T_{1/2}$). Calculations were performed using GraphPad PRISM software (San Diego, United States) whereby iAUC was determined by the trapezoidal method. Total urinary lithium excretion was determined as the product of the lithium concentration [µg/L] in urine and the 24 h-urine volume. Statistical analyses were conducted with IBM SPSS Statistics 24 (Ehningen, Germany). For bivariate analysis, Pearson's correlation coefficient and linear regression were calculated. For statistical hypothesis tests, groups were analysed for normality of the distribution (Kolmogorov-Smirnov and Shapiro-Wilk tests). In the case of a normal distribution, Levene's-test was conducted to assess the homogeneity of variances. If the null hypothesis was rejected

(Levene's-test not significant), a one-way analysis of variance (ANOVA) with a one-sided Tukey-test as post hoc analysis was performed. In the absence of normally distributed data, the Games- Howell- test was conducted.

Results

Geographical distribution of mean lithium values in mineral and medicinal waters

In total, 381 water samples comprising 360 mineral waters (94% of the analysed samples) and 21 medicinal waters (6 % of the analysed samples) were examined. As shown in figure 1, springs and corresponding wells for mineral and medicinal water production are not equally distributed across Germany. There are fewer springs in the the north and north-east than in central and southern regions of Germany. The median lithium concentration of all analysed mineral and medicinal waters was 31.2 µg/L, and the medium lithium concentration was 107.6 µg/L. The majority (64.6 %) of the analysed waters contained lithium concentrations below 50 µg/L. In particular, mineral and medicinal waters from the eastern and northern parts of Germany exhibited low lithium concentrations whereas in some waters from the south-west of Germany, rather high lithium levels were evident. In figure 2, the mean lithium concentrations of mineral and medicinal waters are depicted. Interestingly, all mineral waters collected from the northern states, Schleswig Holstein (n=23) and Mecklenburg Western Pomerania (n=8) as well as from the eastern states, Brandenburg (n=18) and Saxony (n=10) contained lithium concentrations below 50 µg/L. In contrast, highest lithium concentrations (> 600 µg/L) were found in 17 (4.5 %) analysed waters that originated from the south-west region of Germany. These waters comprises 10 mineral and 7 medicinal waters, and the corresponding mineral springs were located in the following states: Rhineland Palatinate (n=6) , Hesse (n=5), Baden-Wuerttemberg (n= 5) and

Bavaria (n=1). Interestingly, considerable differences among mean lithium concentrations were found in adjacent districts. Calw, a district in Baden-Wuertemberg, exhibited the highest mean lithium value (865.1 µg/L). In Freudenstadt, which is next to Calw, the lowest mean lithium concentrations (0.6 µg/L) were measured. The water with the highest lithium concentration measured within our analyses comprised 1724 µg/L. This water was also used in the following bioavailability study in humans.

Analysed versus labelled lithium and the impact of the bottle material

In terms of 14 medicinal waters and 4 mineral waters, the lithium concentration was declared on the corresponding labels. Thus, the labelled lithium concentration could be compared with the corresponding analysed values (Figure 3). The declared lithium concentrations were mostly in accordance with their analysed values (r=0.897). In 8 of 18 cases, the analysed lithium was slightly above or below the labelled lithium concentration, respectively. However, in terms of two samples, the analysed lithium concentrations were substantially lower than the declared value on the label of the bottles (44 vs. 130 µg/L and 79 vs. 900 µg/L).

Regarding bottling, 47 % of the collected waters were bottled in PET and 53 % in glass. In total, 86 waters were available, which were filled into both glass as well as PET plastic bottles. Therefore, a regression and correlation analysis between lithium concentrations of mineral and medicinal waters in glass and PET plastic bottles was conducted. As summarized in Figure 3, there was a highly significant correlation between the lithium concentration in mineral waters filled in plastic and glass bottles ($r = 0.998$, $p < 0.001$).

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Statistical relationship of analysed lithium with labelled concentrations of sodium, potassium, magnesium and calcium

The lithium concentration was significantly correlated with the sodium concentrations declared in our mineral waters. Furthermore, a significant correlation between lithium and potassium was evident. There was also a correlation between lithium and magnesium in mineral waters, but lithium and magnesium were correlated to a lower extent than sodium and potassium (Figure 4).

Bioavailability study

Based on our systematic screening we choose three different mineral waters exhibiting a low (1.7 µg/L), medium (171 µg/L) and high lithium (1724 µg/L) concentration for an acute bioavailability study in male healthy volunteers. Volunteers (n = 3 x 10 each) drank 1.5 litres of the respective mineral waters, which equals a lithium intake of 2.55, 256 and 2586 µg per day. Lithium concentrations in serum were monitored over 24 hours and total urinary lithium excretion was calculated (Figure 5).

Serum lithium concentration peaked 30 minutes after intake. Consumption of the mineral waters with the medium and high lithium content resulted in a dose-dependent response in serum lithium concentration and urinary lithium excretion. There were relatively few interindividual variations in terms of serum lithium levels, and all volunteers responded in a similar manner to the medium and high lithium intake (see inset of Figure 5). Serum lithium concentrations in the group receiving the mineral water with the high lithium content were approximately 10-fold higher than those in the group receiving the mineral water with the medium lithium content. Interestingly, the serum lithium concentration in the group receiving the mineral water with the high and medium lithium content did not fully return

to baseline levels over 24 hours. However, in the group receiving the low lithium mineral water, no increase in serum lithium concentration was evident and a slightly negative iAUC rather occurred. Furthermore, the percentage excretion of lithium was calculated as proportion of excreted lithium from the total uptake of lithium via food and mineral water (not shown in figure 5). In response to the ingestion of medium and high lithium water, 51 % and 45 % of the total lithium were excreted via urine, respectively. In the group that received the low lithium water, the 24 hour urinary lithium excretion exceeded the total uptake (119 % excretion of total lithium uptake).

Discussion

Little is known how dietary lithium may affect the lithium status in humans. Under the conditions investigated, there was a clear dose-dependent relationship between lithium intake due to lithium-rich mineral water and lithium concentrations in serum and urinary lithium excretion. Collectively, our data indicate that lithium derived from lithium-rich mineral water is highly bioavailable in a dose-dependent manner and that the consumption of selected mineral waters could significantly improve the lithium status in humans. In our study, the consumption of the mineral water with a lithium concentration of 1724 µg/L resulted in a peak serum lithium concentration of up to 10-12 µmol/L. Interestingly, this lithium concentration was sufficient to increase life span in the nematode Caenorhabditis elegans [3]. However, it should be noted that in Drosophila melanogaster, a higher lithium concentration was applied to improve the life and health span [2].

The present study was designed as an acute cross over bioavailability study, and lithium levels in serum and urine were monitored. A dose-dependent effect of lithium from mineral water on serum concentrations of lithium was observed. In general, pharmacokinetic

parameters indicate that lithium originated from mineral water is highly bioavailable for humans. An efficient intestinal absorption of lithium was also reported in other studies showing that pharmocokinetic parameters of lithium such as iAUC, c_{max} and renal clearance did not differ between intravenous and oral administered lithium [24]. After the consumption of medium and high lithium water the serum lithium concentration did not fully returned to baseline levels within 24 hours. Furthermore, the total urinary excretion of lithium was positively associated with the lithium uptake via mineral water. However, within the given timeline, these groups excreted approximately 50 % of the ingested lithium. In contrast, the consumption of low lithium water did not result in a positive lithium balance. In this group, serum levels of lithium were lower than the initial baseline levels resulting in a slightly negative iAUC. Concomitantly, the 24 hour urinary lithium excretion exceeded the total lithium. Similar to sodium, lithium homeostasis is adaptively regulated by the kidney and lithium is mainly reabsorbed in the proximal tubule [24, 25]. However, even at very low dietary intake, filtered lithium is not fully reabsorbed [26] and there could be a minimum dietary need for lithium to ensure a positive lithium balance. Additionally, there are also lithium losses via sweat and faeces which were not considered within the current bioavailability study [27, 28]. According to studies in adult rats 80 – 90 % of the dietary lithium is excreted via urine and 10 – 15 % via faeces within 72 hours [29].

Apart from this, there is little data regarding the tissue distribution of lithium in humans and other mammals in response to dietary lithium intake. Therefore, it would be interesting to study to what extent a chronic dietary lithium intake via lithium-rich mineral water may affect the lithium status in humans and laboratory animals (including tissue levels). In addition to mineral water, there are also other beverages including coffee, tea, milk, beer

and wine that should be considered in terms of lithium intake via beverages in humans. Ultimately, there is a need for a comprehensive lithium food data base.

Within our systematic screening approach, we determined the lithium concentration of 381 German mineral and medicinal waters. The present data are in accordance (r = 0.94, p < 0.001) with a previously [22] published study eight years ago by Birke and coworkers who monitored minerals and trace elements including lithium in German bottled water and their regional distribution [22]. The median lithium concentration of our study was 31.2 µg/L, whereas in the study by Birke et al., a median lithium concentration of 29.0 µg/L was evident, suggesting only minor differences between our study and data in the literature regarding lithium in German mineral water. Comprehensive surveys of lithium in mineral water are scarce. However, there are some data regarding lithium in public drinking water. Low lithium levels were found in some Japanese municipipalities [30], areas of Macedonia [31], the East of England [32] and Lithuania [33], while higher lithium levels in public drinking water were found in several Texas counties [34]. Interestingly, lithium levels in public drinking water comprising more than 1000 µg lithium/L were observed in distinct areas of several countries with high lithium salt deposits, such as Australia [35], Northern Argentina [36], Chile [37, 38] and Bolivia [39].

From a consumer's perspective, it is important to note that there were no differences in the lithium content in mineral waters bottled in PET or glass. Thus, the packaging material does not affect the nutritional value of mineral water to the extent that the lithium content is concerned. The declared lithium concentrations were largely in accordance with their analysed values, which is crucial for consumer trust in food labelling.

Based on our data, lithium-rich mineral waters may contain relatively high amounts of sodium, potassium and magnesium. Thus, lithium-rich mineral water may also contribute to

the potassium and magnesium supply of the consumer. The lithium content of mineral and medicinal water was not correlated with its calcium content. Nevertheless, it has been shown that lithium may have a positive effect on bone mineral density in humans by improving calcium absorption [40].

Lithium is widely used as a drug for bipolar disorders [41–43]. In terms of pharmacological treatments lithium doses between 500 and 1200 mg per day are administred [44]. These concentrations are 100-250 - fold higher than the highest dietary lithium concentration used within our mineral water bioavailability study. Nevertheless, future work should investigate if low-dose lithium via lithium-rich foods and/or supplements may affect functional biomarkers in humans. Interestingly, microdose lithium (300 μg/d) has been reported to stabilize cognitive impairment in patients with Alzheimer disease although the underlying molecular mechanisms have not yet been fully defined [45].

A limitation of the present work may be that only German mineral and medicinal waters were analysed. Importantly, there are also imported bottled waters (e.g., from France) that are consumed by the German population which were not considered within the present study. Additionally, we did not address the question regarding the extent to which locally produced waters may be available across the country. Thus, it may be rather challenging to associate lithium intake via mineral water with chronic disease and suicide rate risk in the German population. Therefore human intervention studies should look into the relation between dietary lithium intake and chronic disease risk in more detail. Furthermore, robust functional biomarkers of dietary lithium intake need to be established in the future.

To date, lithium has not been officially considered as an essential trace element and the provisional dietary intakes set at 1000 μg/day that are recommended by some authors [1, 46, 47], are still controversially discussed. This intake of lithium could be established due to

the consumption of approximately 600 mL of our lithium-rich (containing 1724 µg lithium per litre) mineral water. Overall, the data of the present study suggest that lithium-rich mineral waters are an important and highly bioavailable lithium source for human consumption in the German population.

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Author contribution

GR and MB designed the study. GR, US and MB wrote the manuscript. EB collected the

water samples throughout Germany. ABW and FH conducted the human bioavailability

study.

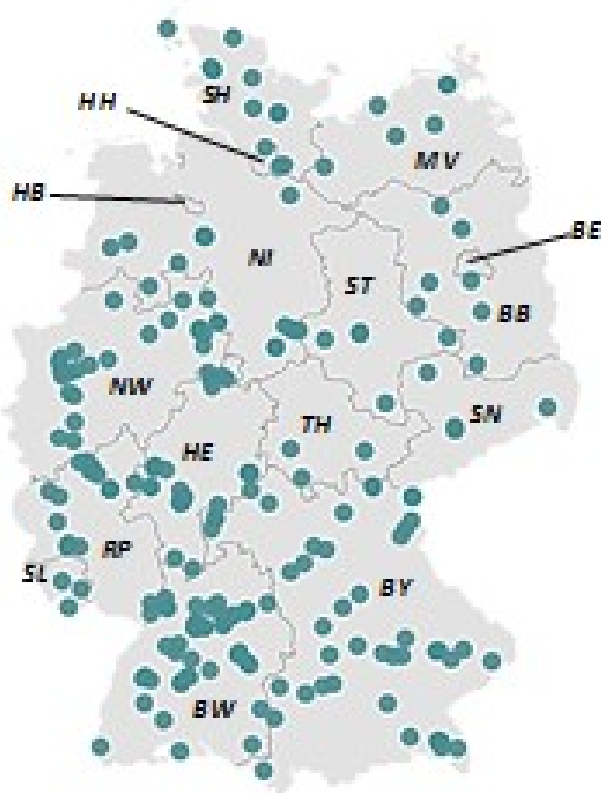**Conflict of interest**

The authors declare no conflict of interest.

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Figure 1

Geographical distribution of mineral springs included in the study. Overview of springs in Germany that are currently used for production of traded mineral and medicinal waters. For lithium analysis, 204 (blue dots) out of 264 official springs could be included. At present, several official springs aren`t in operation or are combined with other springs. In many cases, various mineral waters originated from the same source. Abbreviations of federal states in Germany: BB (Brandenburg), BE (Berlin), BW (Baden-Wuerttemberg), BY (Bavaria), HB (Bremen), HE (Hesse), HH (Hamburg), MV (Mecklenburg Western Pomerania), NI (Lower Saxony), NW (Northrhine-Westphalia), RP (Rhineland Palatinate) SH (Schleswig Holstein), SL (Saarland), SN (Saxony), ST (Saxony-Anhalt), TH (Thuringia).

Figure 2
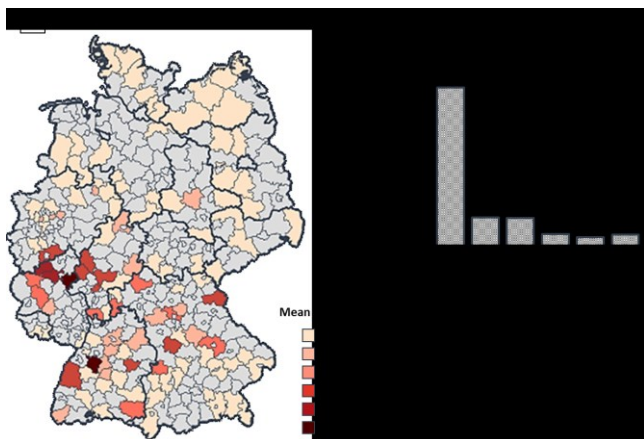
Figure 2

Mean lithium concentration of mineral and medicinal waters in German districts. A) According to the geographical distribution of mineral springs, the mean lithium concentrations could be calculated for 120 German districts. The values vary from 0.6 to 865.1 µg/L with the highest value in the south-west and the lowest in the northern part of Germany. B) Frequency distribution of lithium concentrations in the tested waters. Lithium concentrations analysed in individual mineral and medicinal waters were clustered into six groups. Low lithium containing waters (0.6 – 49 µg/L) account for 246 out of 281 waters whereas highest lithium concentrations (600 – 1724 µg/L) were found in 17 waters.
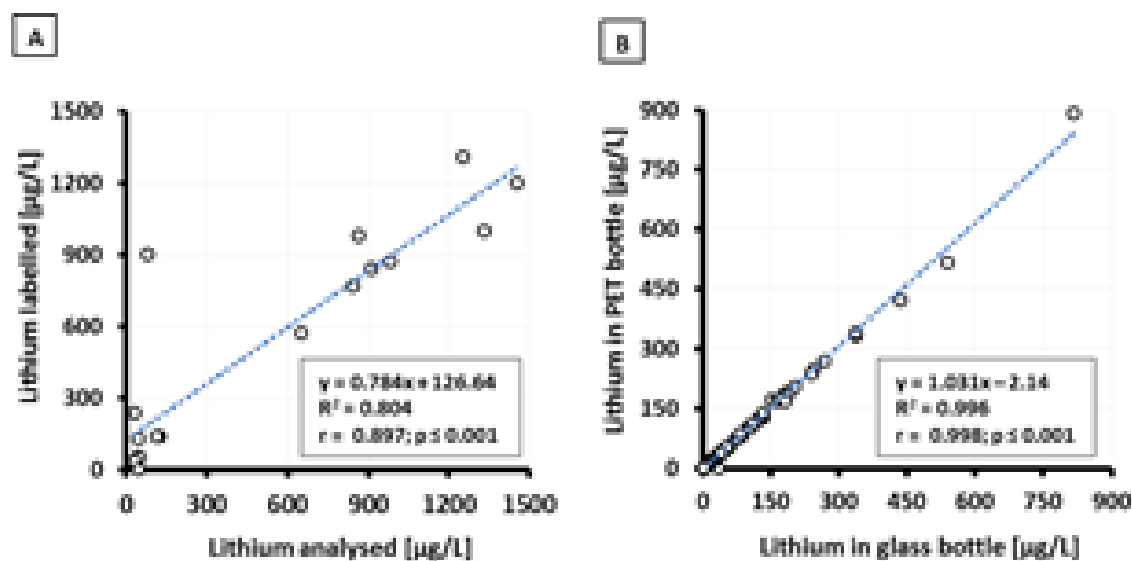
Figure 3

Analysed lithium [μg/L] is comparable to corresponding labelled lithium concentration without any impact of the bottle material. In 14 medicinal and 4 mineral waters, the lithium concentration was declared on the bottle and statistically compared to the analysed lithium values. There was a significant positive correlation ($r = 0.804$; $p \leq 0.001$) between labelled and analysed lithium concentrations in mineral and medicinal waters. In two samples, negative deviations that were more than threefold from the labelled lithium were observed. B) There was no effect of the bottle material on the lithium concentrations of mineral and medicinal waters. The lithium content of 86 mineral waters that were available in glass and plastic bottles were compared via bivariate analysis. There was a positive linear relationship between analysed lithium in water filled in glass compared to PET bottles with $r = 0.998$ and $p \leq 0.001$.
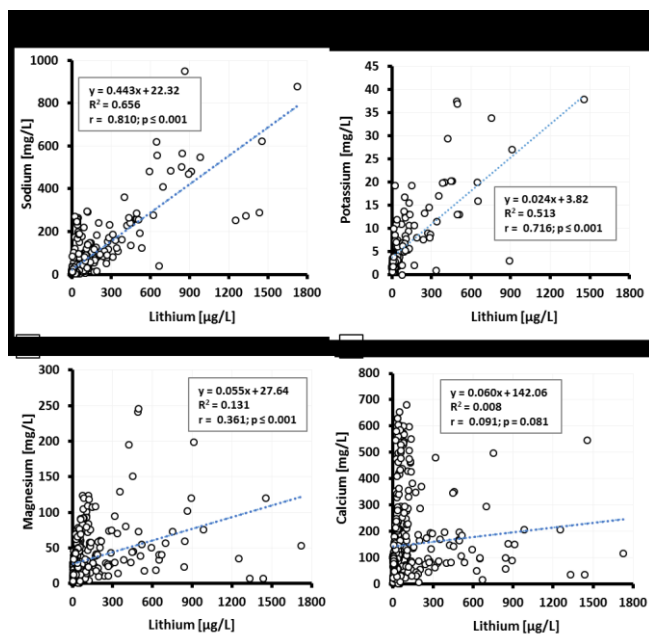
Figure 4

Figure 4

Positive correlation of lithium [µg/L] with sodium [mg/L], potassium [mg/L] and magnesium [mg/L] but not with calcium [mg/L] concentrations in tested waters. Analysed lithium concentrations were compared to labelled concentrations of sodium (365 samples), potassium (151), magnesium (363 samples) and calcium (368 samples). A) The analysed lithium concentration significantly correlates with the sodium concentration in mineral and medicinal water. B) The analysed lithium concentrationsignificantly correlates with the potassium concentration in mineral and medicinal water C) The analysed lithium concentration significantly correlates with the magnesium concentration in mineral and medicinal water. D) There is no significant relation between analysed lithium and labelled calcium concentrations. With increasing calcium concentrations, lithium increases merely in tendency (p = 0.081).
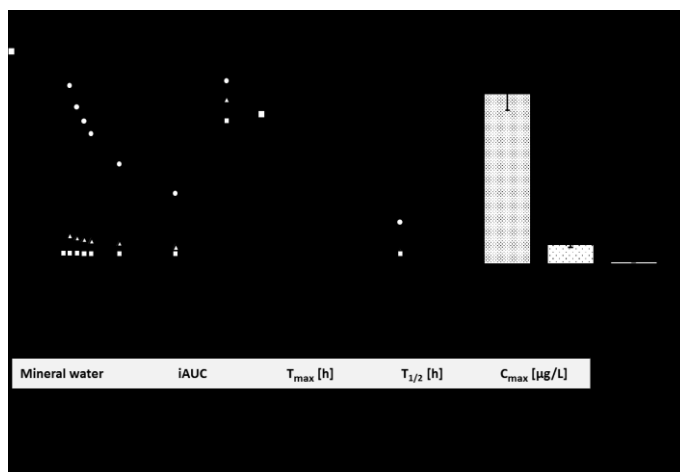
Figure 5

Figure 5

Dose-dependent response in serum lithium concentrations and total urinary lithium excretion. A) The mean serum concentration-time profiles of lithium 0, 0.5, 1, 1.5, 2, 4, 8 and 24 hours after oral ingestion of 1.5 L of the indicated mineral waters. After consumption of mineral water with medium or high lithium content, the serum lithium levels rapidly increased and reached their peak after 0.5 hours (=T_{max}). No effect on serum levels of lithium was observed after the consumption of low lithium containing water. Serum concentrations of lithium were significantly different for each time point between all tested mineral waters except for the basal concentration (p < 0.001). B) Pharmacokinetic

parameters of serum lithium in volunteers who received respective mineral waters. The iAUC as well as c_{max} were significantly different between groups and were highest after consumption of water with a high lithium concentration. Interestingly, 1.5, 2, 4, 8 and 24 hours after the consumption of the low lithium mineral water, serum lithium was lower than the baseline level (0 hours) and a negative iAUC occurred. Furthermore, there was no substantial lithium peak in response to the low lithium mineral water, thus $T_{1/2}$ could not be calculated. $T_{1/2}$ of lithium did not significantly differ between groups receiving the medium and high lithium water. C) The total lithium excretion 24 hours after water ingestion significantly differs between groups. The group that received the water with high lithium content excreted highest amount of lithium followed by the group that consumed the medium and low lithium waters. Abbreviations: incremental area under curve (iAUC), maximum lithium concentration (C_{max}), time of maximum lithium concentration (T_{max}), half-life of lithium ($T_{1/2}$). All values are the mean ± SD (n=10). Values with different superscripts are significantly different between groups (p ≤ 0.001).