Article

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Worldwide Interest in Vitamin D, Negative Effects on Kidneys, and Bone Density: Analysis of Google Trends Data

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Background: Besides its role in calcium homeostasis and bone mineralization, vitamin D may also reduce the risk of cancer, cardiovascular and autoimmune diseases. Excessive vitamin D intake can lead to life-threatening hypercalcemia and toxicity, however. Here, we wanted to determine the relative search volume (RSV) of interest in vitamin D and its adverse biological effects (hypercalcemia, renal failure, kidney stones, bone density).
Methods: We used data from Google Trends to assess changes in RSV trends across the world's regions. Data were extracted via the search terms "cholecalciferol", "ergocalciferol, "hypercalcemia", "acute renal failure", "kidney stones", and "bone density" from queries in English from 1 January 2004 to 1 October 2018 in the tool's related query database. Statistical analysis was performed using SPSS® 22.0 for Windows (IBM Inc., Armonk, NY, USA, 10504-1722).
Results: There was a correlation between the RSV of cholecalciferol and ergocalciferol (Spearman's correlation) and the RSV of hypercalcemia, renal failure, kidney stones, and bone density. As measured by the change in RSV score, the trend for interest in kidney stones increased more rapidly than that for the other search terms. There was a positive correlation between the RSV score for cholecalciferol (or ergocalciferol) and renal failure and between the RSV score for cholecalciferol (or ergocalciferol) and kidney stones, whereas there was a negative correlation between cholecalciferol and hypercalcemia. The interest of ergocalciferol increased in parallel with the interest in bone density. The highest concentration of interest in cholecalciferol occurred in North America, Europe, India and Australia, whereas interest in ergocalciferol was greater in Central and South America, Spain, and Thailand. Interest in kidney stones was greater than cholecalciferol in North America, Brazil, India, and Australia, while interest in bone density was greater than cholecalciferol in North America, Brazil, Italy, Spain, South Africa, and Australia.
Conclusions: In the pre-pandemic COVID-19 (COronaVIrus Disease 19) era, our preliminary results showed a positive correlation between global interest in cholecalciferol and kidney stones and renal failure, respectively. However, we found an unexpected negative correlation between global interest in cholecalciferol and hypercalcemia. Additionally, we found a positive correlation between global interest in ergocalciferol and bone density. These correlations can inform health interventions and education.

Keywords: kidney stones; cholecalciferol; bone density; ergocalciferol; kidney failure; hypercalcemia; vitamin D; relative search volume

Introduction

Vitamin D plays numerous roles in body function. It is found in two primary forms: Ergocalciferol (D2) of plant origin and cholecalciferol (D3) derived from cholesterol and synthesised by the body. Vitamin D acquired from sunlight exposure or through diet is biologically inactive (1). The production of vitamin D by the skin is strongly influenced by seasonal variables and latitude (2,3). Cholecalciferol and ergocalciferol become active metabolites via successive hydroxylation in the liver and the kidney.

Vitamin D level is now one of the most frequently ordered laboratory tests due to growing awareness of vitamin D deficiency and scientific data suggesting the beneficial health effects of vitamin D. The primary function of vitamin D is to promote bone mineralisation, whereas vitamin D deficiency causes rickets, osteoporosis, and hypocalcemia (4). Vitamin D also aids the immune system in fighting off infection (2). However, there have also been reports of vitamin D toxicity due to manufacturing errors and overdose (1,5). Additionally, excessive vitamin D intake can increase the risk of hypercalcemia (6) and kidney disease (7).

Google Trends is a public search volume database and web tool that generates geographic and temporal information on specific terms of interest (8,9). Although many studies lack complete documentation of methodologies and reproducibility of results, surveillance studies have validated Google Trends output (10). Furthermore, recent evidence has suggested that Google Trends can be used to understand changes in health-related contexts (health, disease, treatment) (11). A recent study using Google Trends analysis to assess the relative search volume (RSV) of vitamins during the COVID-19 (COronaVIrus Disease 19) pandemic (12) reported an increase in search queries for vitamins D and C, zinc, and selenium (13), although considerable debate surrounds the efficacy of vitamin D in preventing and treating COVID-19 (14-18). Google Trends may provide a valuable tool for gauging general interest in diet (19) or for comparing the pre-COVID-19 interest in vitamin D (20). During the COVID-19 pandemic, search volume data on vitamins increased (21,22), as did vitamin D consumption (23).

With the present study we used pre-COVID-19 pandemic data from Google Trends to gauge interest in vitamin D and its adverse effects secondary to overuse (hypercalcemia, renal failure, kidney stones, bone density) based on RSV score. Our findings may inform measures of interest for health prevention and intervention.

Materials and Methods

Data Acquisition

The study data were obtained with Google Trends (https://trends.google.it/trends/?geo=IT). Searches were analyzed for a given search term for a specific geographic area and time period. The data were extrapolated as the query share of a search term related to the total number of queries during the study period scaled from 0 to 100, where a higher score indicates greater query share. The terms of interest were: "Cholecalciferol", "ergocalciferol", "hypercalcemia", "acute renal failure", "kidney stones", and "bone density". The RSV score was a numerical value extracted from monthly intervals between 1 January 2004 and 1 October 2018. All searches were conducted in English with the criterion "health". The RSV scores were downloaded from Google Trends as csv files and then tabulated in Microsoft® Excel software (Microsoft Office Professional Plus 2016, Microsoft Corporation, Impressa Systems, Santa Rosa, CA, USA) (12).

Statistical Analysis

Statistical analysis was performed using IBM® SPSS® 22.0 for Windows (IBM Inc., Armonk, NY, USA, 10504-1722). The Kolmogorov-Smirnov test was used to explore normality of the distribution of RSV scores by world region. Descriptive statistics of RSVs are the mean ± standard deviation (SD). We used Spearman's correlation analysis to explore the correlation between RSV scores. A statistically significant correlation was determined when $p < 0.05$. We also used the R^2 determination coefficient to evaluate the dependence of the RSV of the variable of interest on the considered time range, and the correlation coefficient r to determine if there is a relationship between the two variables of interest. RSV scores by world region were compared for cholecalciferol and ergocalciferol and hypercalcemia, renal failure, kidney stones, and bone density. The RSV scores are presented graphically with a temporal trend. Temporal trends were rendered in Google Trends graphs to show concentration of interest in each area for a given term and to compare cholecalciferol and ergocalciferol, cholecalciferol and kidney stones, and cholecalciferol and bone density.

Results

The RSV score for cholecalciferol and ergocalciferol correlated (Spearman's correlation) with the RSV score for hypercalcemia, renal failure, kidney stones, and bone density.

Table 1 shows the descriptive statistics (mean ± SD) of RSV scores by region for cholecalciferol and ergocalciferol (step 1) and for kidney stones, renal failure, bone density, and hypercalcemia (step 2). The monthly RSV score of each term of interest was analysed (total 177 months, see **Supplementary Materials**). The mean RSV score worldwide was higher for cholecalciferol (42.9 ± 21.8) than for ergosterol (24.1 ± 7.2). Worldwide, the RSV score was highest for kidney stones (61.1 ± 14.7) followed in decreasing order by hypercalcemia, bone density, and renal failure (lowest, 2.8 ± 1.0). The Kolmogorov-Smirnov test for one sample showed not normal distribution of RSV scores worldwide for each term of interest ($p \leq 0.001$).

Table 2 presents the results of the correlation analysis between the RSV of cholecalciferol (or ergocalciferol) and the RSV of variables of interest (kidney stones, hypercalcemia, bone density, and renal failure). According to the results of the Spearman's correlation analysis, there is a positive correlation between the RSV of cholecalciferol (or ergocalciferol) and the RSV of renal failure ($p < 0.001$) or kidney stones ($p < 0.002$) and a negative correlation between the RSV of cholecalciferol and the RSV of hypercalcemia ($p = 0.006$). Additionally, there is a positive correlation between the RSV of ergocalciferol and bone density ($p = 0.002$). The table also shows the correlation coefficients (r) between the variables of interest. Figs. 1, 2 provide graphical representation of the correlation between the RSV of cholecalciferol (or ergocalciferol) and the RSV of other variables of interest (kidney stones, hypercalcemia, bone density, and renal failure).

Fig. 3 shows the monthly changes in RSV scores for cholecalciferol (blue) and ergocalciferol (green). The change over time in RSV score for cholecalciferol expressed as coefficient of determination ($R^2 = 0.903$; Not shown in the table) was greater than that for ergocalciferol ($R^2 = 0.468$). Fig. 4 shows the RSV score for hypercalcemia (green), renal failure (purple), kidney stones (red),

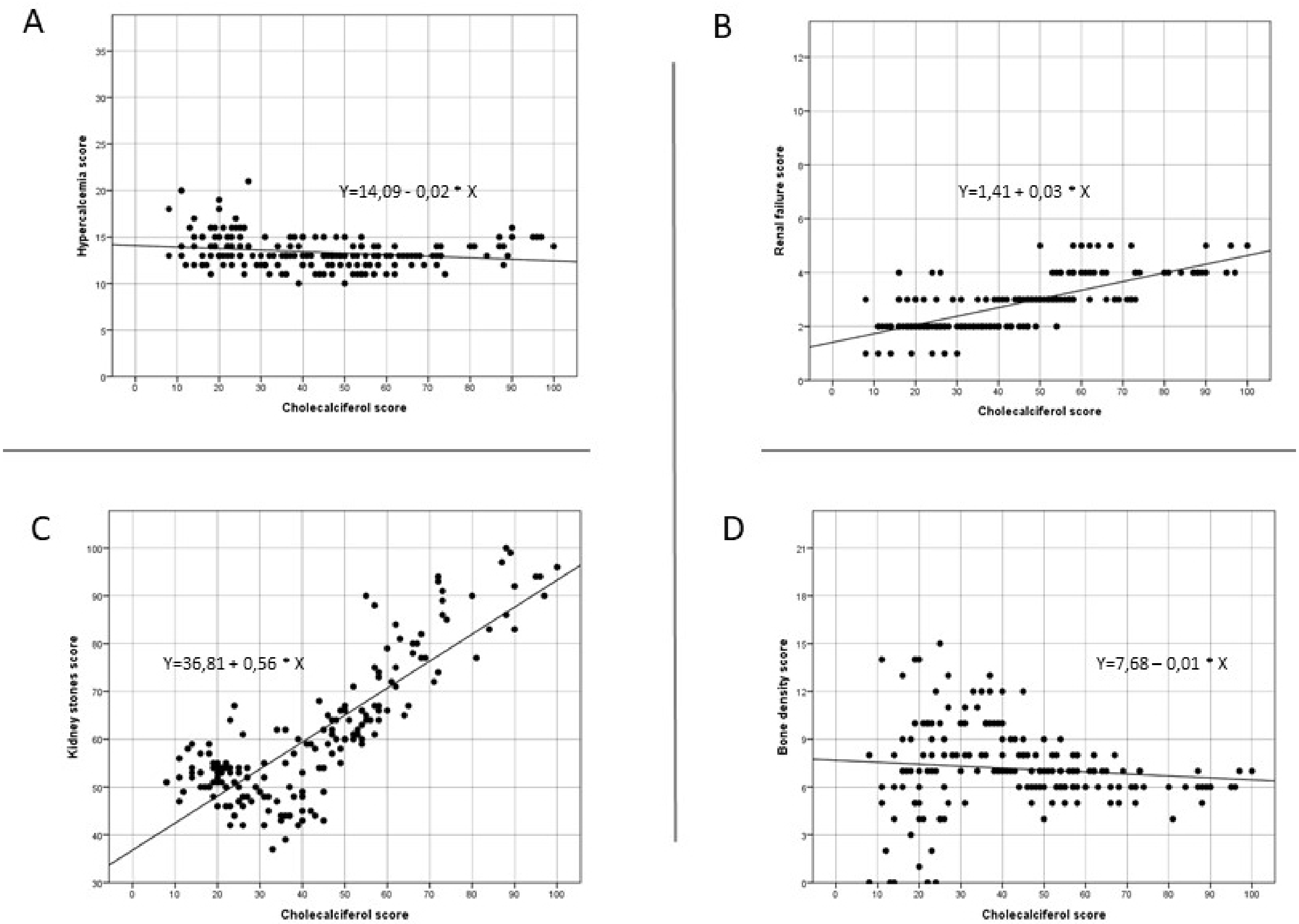

Fig. 1. The correlation between the RSV score for cholecalciferol (vitamin D3) and for hypercalcemia (shown in panel A), renal failure (shown in panel B), kidney stones (shown in panel C), and bone density (shown in panel D) is displayed. The equation of the respective regression lines is also shown in the figure.

Table 1. The descriptive statistics of the RSV score of world interest extracted with Google Trends is presented as follows: Step 1—the RSV score of cholecalciferol and ergocalciferol; Step 2—the RSV score of kidney stones, renal failure, bone density, and hypercalcemia.

Variables of world interest	Mean (SD)	Range (min-max)	Kolmogorov-Smirnov test for one sample (*p*, two tails)
n.177			
Step 1			
Cholecalciferol	42.9 (21.8)	8–100	0.001
Ergocalciferol	24.1 (7.2)	3–39	<0.001
Step 2			
Kidney stones	61.1 (14.7)	37–100	<0.001
Hypercalcemia	13.4 (1.8)	10–21	<0.001
Bone density	7.2 (2.7)	0–15	<0.001
Renal failure	2.8 (1.0)	1–5	<0.001

and bone density (blue). The highest and the lowest RSV score was observed for kidney stones and hypercalcemia, respectively. Variation in RSV over time was greatest for kidney stones (R^2 = 0.625) and least for bone density (R^2 = 0.006). The variation in RSV for renal failure and hypercalcemia expressed as coefficient of determination was R^2 = 0.491 and R^2 = 0.141, respectively. In brief, there was an increase in interest for kidney stones, while the interest in bone density remained practically unchanged.

Fig. 5 (Panel A) shows the distribution of world regional concentration of interest in cholecalciferol and ergocalciferol. A high concentration of interest in cholecalcif-

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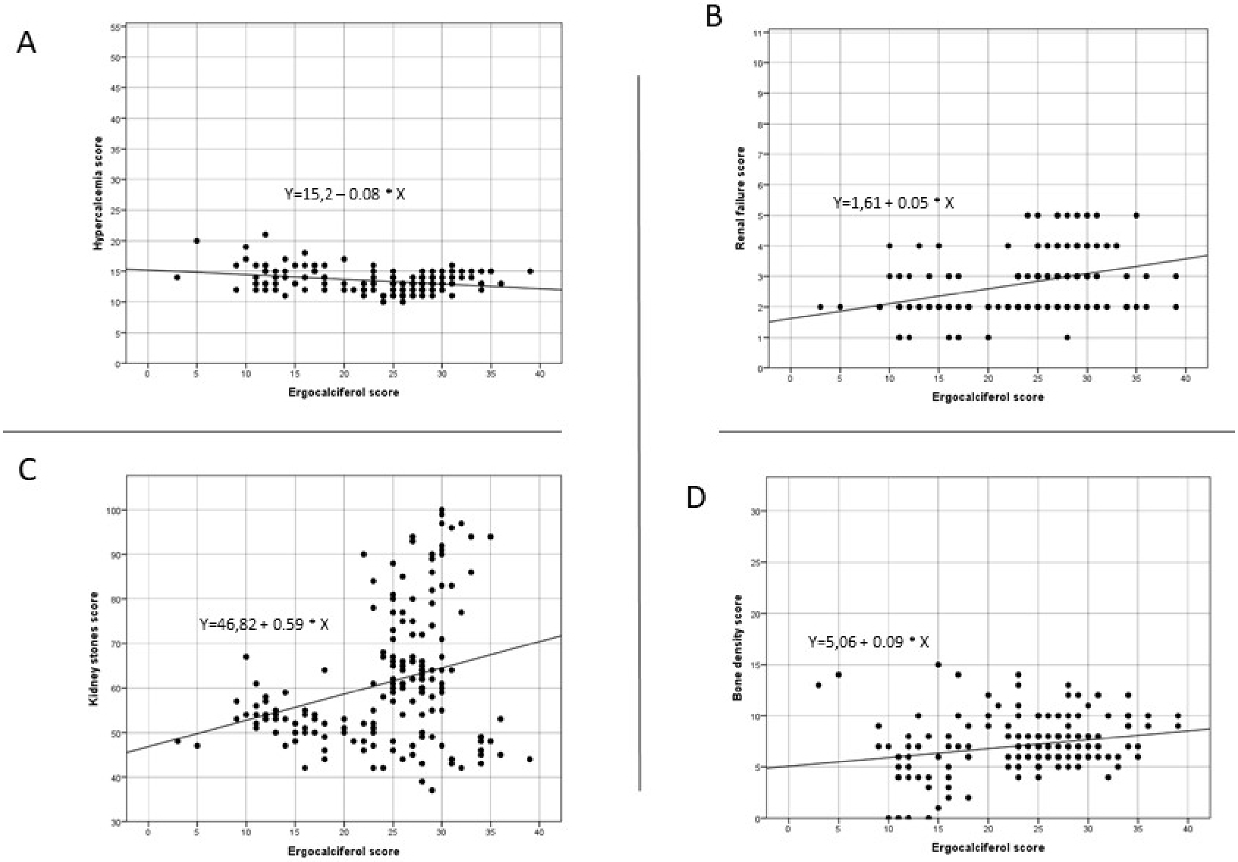

Fig. 2. The correlation between the RSV score for ergocalciferol (vitamin D2) and for hypercalcemia (shown in panel A), renal failure (shown in panel B), kidney stones (shown in panel C), and bone density (shown in panel D) is displayed. The equation of the respective regression lines is also shown in the figure.

Table 2. Spearman's correlation analysis of the worldwide monthly RSV score for cholecalciferol or ergocalciferol and its correlation with hypercalcemia, kidney stones, renal insufficiency, and bone density is shown (see also Figs. 1, 2).

Google Trend score	Renal failure r (*p*, two tails)	Kidney stones r (*p*, two tails)	Hypercalcemia r (*p*, two tails)	Bone density r (*p*, two tails)
n.177				
Cholecalciferol	0.731 ($p < 0.001$)	0.753 ($p < 0.001$)	–0.206 ($p = 0.006$)	–0.137 ($p = 0.069$)
Ergocalciferol	0.369 ($p < 0.001$)	0.228 ($p = 0.002$)	–0.110 ($p = 0.144$)	0.236 ($p = 0.002$)

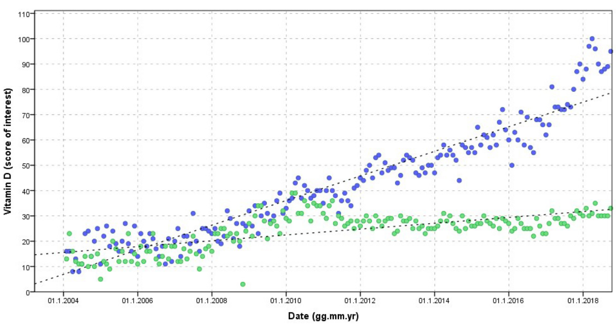

Fig. 3. The RSV scores for cholecalciferol (vitamin D3, represented in blue) and ergocalciferol (vitamin D2, represented in green) over time and their respective regression lines.

erol (blue) was noted for North America, Europe, India, and Australia, while a high concentration of interest in ergocalciferol (red) was observed for Central and South America, Spain, and Thailand. No difference in search volume data between the two terms was found for Greenland, Africa, and Asia. Panel B (upper-right) shows a greater concentration of interest in kidney stones than in cholecalciferol for North America, Brazil, India, and Australia (red). Panel B (lower-right) shows a greater concentration of interest in bone density than in cholecalciferol for North America, Brazil, Italy, Spain, South Africa, and Australia (red). In summary, interest in cholecalciferol was more frequent in areas of high economic status, where interest in bone density and kidney stones was more frequent than in cholecalciferol.

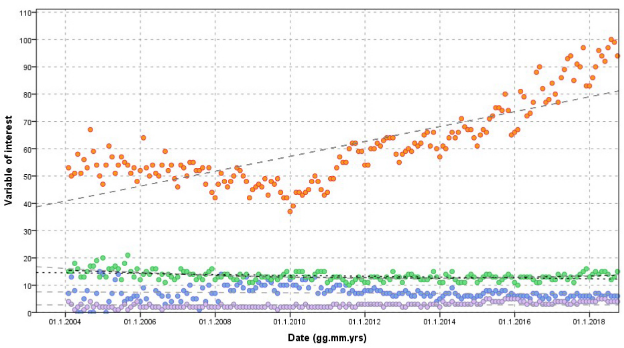

Fig. 4. The RSV scores for kidney stones (represented in red), renal failure (represented in purple), bone density (represented in blue), and hypercalcemia (represented in green) over time and their respective regression lines.

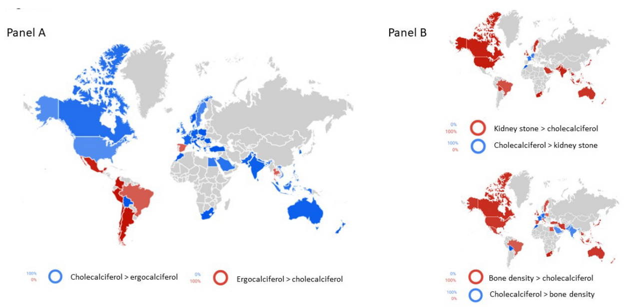

Fig. 5. The gauge of interest (high volume search mode) for cholecalciferol versus ergocalciferol (%) is shown in panel A. The RSV score for cholecalciferol and its correlation with kidney stones (shown in panel B, top) and bone density (shown in panel B, bottom) are displayed.

Discussion

We found significant differences in time and space of RSVs for the search terms selected via the Google Trends related query database. There was a positive correlation between the high RSV score for cholecalciferol and for kidney stones, whereas there was a negative correlation between the RSV score for cholecalciferol and for bone density. The RSV score for kidney stones and bone density was higher than the RSV score for cholecalciferol. These findings suggest that concentration of interest depends also on other search terms.

Hypercalciuria is a common cause of kidney stone formation, for which the estimated risk is increasing (24). In individuals predisposed to hypercalciuria, urinary calcium excretion is augmented in response to vitamin D, as is the risk of developing kidney stones (24). Excess vitamin D intake can raise the risk of urolithiasis, also in children with hypercalcemia (25). Finally, a systematic review and meta-analysis found an association between long-term vitamin D supplementation and heightened risk of hypercalcemia and hypercalciuria but not of developing kidney stones (26). The controversial relationship between excess vitamin D intake and the development of kidney stones continues to fuel debate on vitamin D supplementation.

Excessive vitamin D intake has been reported to cause hypercalcemia, renal calcification, and renal failure (27). The association between vitamin D and acute renal failure has rarely been described (28-30). However, we found a positive and statistically significant correlation between the global search volume data for vitamin D and kidney failure. Vitamin D supplementation is a part of therapy for patients with chronic renal failure (31).

Our analysis revealed a negative association between vitamin D and bone density. In their review, Chakhtoura *et al.* (32) showed that the prevalence of hypovitaminosis D (25 (OH) D <20 ng/mL) ranged between 12% and 96% in children and adolescents in the Middle East and North Africa, respectively, albeit no clinically significant fractures were reported. Previous studies found no benefit of high-dose vitamin D supplementation on bone health and concluded that more studies are needed to determine whether supplementation is harmful (33,34) and that vitamin D supplements should be considered only for at-risk individuals (35). Our findings may inform such studies on interest searches for vitamin D.

Our analysis also disclosed a differentiated distribution of the frequency of vitamin D queries in other countries. Moderate vitamin D deficiency was found for Europe, where there was greater interest in cholecalciferol, particularly in Italy and Switzerland, but less so in Spain. Search frequency for cholecalciferol was greater in North America (Canada and USA), where vitamin D deficiency has been reported (36). Vitamin D deficiency has been reported also for South America (36), along with a high interest in ergocalciferol (Mexico, Peru, Argentina, Chile, Brazil). An increased interest in cholecalciferol was noted for South Africa. Moderate vitamin D deficiency was reported for Africa and Asia and Oceania (36). Our results indicate a rising interest in vitamin D in world regions where bone health is low.

Interest in cholecalciferol was greater in North America, Europe, India, and Australia than in certain South American countries (Argentina and Chile), while general interest in ergocalciferol was frequent in Central and most South America, where interest in kidney stones and bone density was greater than in vitamin D. This difference may be explained by the inclusion of other variables of interest not investigated here and separated from that of vitamin D.

The limitations of the study are the reduced access to IT tools in world regions of low socioeconomic status. Another limitation is that the study was based on search volume data published in English. This limitation notwithstanding, use of the same language and normalisation of the data extracted with Google Trends validates the results of our analysis.

Conclusions

In the pre-pandemic COVID-19 era, our preliminary results showed a positive correlation between global interest in cholecalciferol and kidney stones and renal failure, respectively. However, we found an unexpected negative correlation between global interest in cholecalciferol and hypercalcemia. Additionally, we found a positive correlation between global interest in ergocalciferol and bone density. These correlations can inform health interventions and education.

Abbreviations

RSV, relative search volume; SD, standard deviation.

Availability of Data and Materials

Not applicable.

Author Contributions

MZ, AP, FA—Conception or design of the work; LN—Critical revision of the article and drafting the article; MZ, MP, GF, AG—Data collection; MZ, AP, FA, GP—Data analysis and interpretation; MZ, AP—Drafting the article; GP, FA—Critical revision of the article. All authors published final approval of the version.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.23812/j.biol.regul.homeost.agents.20223606.183.

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