**Name of Journal:** *World Journal of Methodology*

**Manuscript NO:** 73515

**Manuscript Type:** ORIGINAL ARTICLE

***Clinical and Translational Research***

**COVID-19 and thyroid disease: An infodemiological pilot study**

Ilias I *et al*. COVID-19 and thyroid disease

Ioannis Ilias, Charalampos Milionis, Eftychia Koukkou

**Ioannis Ilias, Charalampos Milionis, Eftychia Koukkou,** Department of Endocrinology, Diabetes & Metabolism, Elena Venizelou Hospital, Athens GR-11521, Greece

**Author contributions:** All authors conceived this work, searched the literature, analyzed the data, performed the analyses, and wrote this manuscript.

**Corresponding author: Ioannis Ilias, MD, PhD, Consultant Physician-Scientist,** Department of Endocrinology, Diabetes & Metabolism, Elena Venizelou Hospital, 2, Elena Venizelou Sq., Athens GR-11521, Greece. iiliasmd@yahoo.com

**Received:** November 23, 2021

**Revised:** February 11, 2022

**Accepted:** March 26, 2022

**Published online:**

**Abstract**

BACKGROUND

Google Trends searches for symptoms and/or diseases may reflect actual disease epidemiology. Recently, Google Trends searches for coronavirus disease 2019 (COVID-19)-associated terms have been linked to the epidemiology of COVID-19. Some studies have linked COVID-19 with thyroid disease.

AIM

To assess COVID-19 cases *per se vs* COVID-19-associated Google Trends searches and thyroid-associated Google Trends searches.

METHODS

We collected data on worldwide weekly Google Trends searches regarding “COVID-19”, “severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)”, “coronavirus”, “smell”, “taste”, “cough”, “thyroid”, “thyroiditis”, and “subacute thyroiditis” for 92 wk and worldwide weekly COVID-19 cases' statistics in the same time period. The study period was split in half (approximately corresponding to the preponderance of different SARS-COV-2 virus variants) and in each time period we performed cross-correlation analysis and mediation analysis.

RESULTS

Significant positive cross-correlation function values were noted in both time periods. More in detail, COVID-19 cases *per se* were found to be associated with no lag with Google Trends searches for COVID-19 symptoms in the first time period and in the second time period to lead searches for symptoms, COVID-19 terms, and thyroid terms. COVID-19 cases *per se* were associated with thyroid-related searches in both time periods. In the second time period, the effect of “COVID-19” searches on “thyroid’ searches was significantly mediated by COVID-19 cases (*P* = 0.048).

CONCLUSION

Searches for a non-specific symptom or COVID-19 search terms mostly lead Google Trends thyroid-related searches, in the second time period. This time frame/sequence particularly in the second time period (noted by the preponderance of the SARS-COV-2 delta variant) lends some credence to associations of COVID-19 cases *per se* with (apparent) thyroid disease (*via* searches for them).

**Key Words:** Data collection; Epidemiology; Thyroid; Medical informatics; Methods; Trends

Ilias I, Milionis C, Koukkou E. COVID-19 and thyroid disease: An infodemiological pilot study. *World J Methodol* 2022; In press

**Core Tip:** Google Trends searches for coronavirus disease 2019 (COVID-19)-associated terms have been linked to the epidemiology of COVID-19. In this study we aimed to assess worldwide COVID-19 cases *per se* *vs* COVID-19-associated Google Trends searches and thyroid-associated Google Trends searches for 92 wk. The study period was split in half and in each time period we performed cross-correlation analysis and mediation analysis. Significant cross correlation function factors for “COVID-19” and “severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)” were mostly found in the second time period, whereas COVID-19 cases *per se* were associated with “thyroid” searches in both time periods. In the second time period, which was characterized by the spread of SARS-CoV-2 delta variant, the effect of “COVID-19” searches on “thyroid” searches was significantly mediated by COVID-19 cases (*P* = 0.048). The observed time frame/sequence lends some credence to associations of COVID-19 cases *per se* with (apparent) thyroid disease.

**INTRODUCTION**

Digital epidemiology uses digital data which was not generated with the primary goal of serving epidemiological research[1]; such data are within the domain of “infodemiology”[2]. Google Trends (available at https://trends.google.com) searches may - according to some researchers - accurately reflect the epidemiology of infectious, acute, or chronic diseases, including, among others, coronary or thyroid disease[2-10]. Recently, Google Trends searches for COVID-19-associated terms have been tentatively linked to the epidemiology of COVID-19[11-17]. Some - but not all – clinical studies have linked COVID-19 with thyroid function abnormalities and more particularly with a form of subacute-like thyroiditis[18-22]. Since the use of Google Trends to study a wide range of medical topics is becoming more widespread and the available research on COVID-19-related thyroid disease is conflicting, with this work we aimed to look at the issue of COVID-19-related thyroid disease from a different angle, namely, that of digital epidemiology, since the latter may be a useful adjunct to classical epidemiology.

**MATERIALS AND METHODS**

***Data and data collection***

We collected data on worldwide weekly Google Trends searches, by means of their “relative search volumes” (RSVs). The latter is normalized internet search volume values over a given time period, with a minimum of 0 and a maximum of 100 (see also <https://support.google.com/trends/).> More in detail, we used the worldwide RSVs of the search terms in the English language for “COVID-19”, “SARS-CoV-2”, “coronavirus”, “smell”, “taste”, “cough”, “thyroid”, “thyroiditis”, and “subacute thyroiditis” for 92 wk, from January 26, 2020 to October 24, 2021. The search terms were chosen because of their ubiquity and uniformity in lay and medical terms. For the same time period, worldwide weekly COVID-19 cases' statistics, as provided by the Johns Hopkins University Coronavirus Resource Center (available at <https://coronavirus.jhu.edu/map.html)>, were collected[23]. The study period was split in half: The first half corresponded to the time period with preponderance of the SARS-CoV-2 alpha variant and the second to the time period with preponderance of the delta variant (Figure 1).

***Statistical analysis***

In each of the aforementioned time periods, we performed cross-correlation analysis. The threshold for statistical significance of each cross-correlation factor value at the *P* = 0.05 level was set according to lag, thus the cross-correlation factor had to be higher than 0.290 at lag = 0 and 0.324 at lag = 8. A lag = 0 indicates contemporaneous correlation, a negative lag indicates that the first variable leads within a set time frame the second variable, and a positive lag indicates that the first variable follows (lags) within a set time frame the second variable. After the calculation of cross-correlation factor values, further evaluation among the variables was done with mediation analysis, implementing Sobel’s test. Statistical analyses were done with Minitab v.17.1 (Minitab Inc, State College, PA, United States, 2010) and JASP v0.15 (JASP Team, University of Amsterdam, NL, 2021).

**RESULTS**

Worldwide, COVID-19 weekly cases *per se* gradually increased over time and showed wide fluctuations during the second half of the study period (Figure 1). The RSVs of the studied search terms also showed fluctuations (Figure 1 and Supplemental Figures 1 and 2). Significant positive cross-correlation factor values were noted in both time periods. More in detail, significant cross-correlation factors for “COVID-19” and “SARS-COV-s” were mostly found in the second time period (Table 1), whereas COVID-19 cases *per se* were associated with “thyroid” searches in both time periods. In the second time period, the effect of “COVID-19” searches on “thyroid” searches was significantly mediated by COVID-19 cases (Sobel test statistic *P* = 0.048).

**DISCUSSION**

COVID-19 cases *per se* were found to be associated with no lag with Google Trends searches for COVID-19 symptoms in the first time period and in the second time period to lead searches for symptoms, COVID-19 terms, and thyroid terms. Searches for a non-specific symptom or COVID-19 search terms mostly led Google Trends “thyroid” searches, in the second time period. This time frame/sequence particularly in the second time period, which was noted by the preponderance of the SARS-CoV-2 delta variant, lends some credence to associations of COVID-19 cases *per se* with (apparent) thyroid disease (*via* searches for them). Moreover, this finding, points to a possible higher probability of thyroid disease with SARS-CoV-2 delta variant compared to the alpha variant (and may also explain discrepancies regarding COVID-19 *vs* thyroid disease among previous relevant studies).

Digital health is in the spotlight as the COVID-19 crisis progresses[24,25]. At the same time, digital epidemiology is emerging at a very fast pace[25]. More and more of what we do and say - including epidemiologically relevant behaviors - is stored electronically, often in an accessible form. Internet data mining has a revolutionary impact on the way we monitor global health and health behaviors. Infectious and chronic disease data can be collected and disseminated in almost real time through a number of online sources. Google Trends provides a powerful measure of public interest in a topic, being a proxy of internet searches for it. The frequency of internet searches for disease terms may not reflect directly the epidemiological characteristics of a given disease, which is related and/or described by such search terms. Media coverage may skew subsequent internet searches. Nevertheless, the frequency of internet queries for various diseases’ symptoms are correlated to a degree with physician visits for these diseases[26,27]. Google Trends has been used – despite its shortcomings – to monitor the yearly influenza epidemics[24,28]. Another source that has provided health data is Twitter. A smartphone application can be used to assess COVID-19 symptoms and may indicate future disease hotspots within 5-7 d[29]. The collection and classification of data ranging from the detection of suspected cases to the monitoring and assessment of pandemic risk is crucial. However, as this is a very evolving field, validation of digital health measures vis-à-vis input data, tentative associations, or predictive models is still needed. Regarding COVID-19, the influence of media on Google Trends RSVs has been studied and was found to be maximal after a week[30], whereas the effect of COVID-19 cases on “COVID-19” searches has been studied[31], and has been found to be most notable after 11.5 d[32]. Thus, with the lags in the observed cross-correlation factors, we believe that the Google Trends searches for COVID-19 and/or thyroid-related items may reflect personal interest fuelled by probable real disease (COVID-19 or thyroid disease).

Receptors for the SARS-CoV-2 virus are found in tissues beyond the respiratory system, such as the thyroid, thus an effect of COVID-19 on the thyroid is plausible[33]. Indeed, there is some evidence of thyroid dysfunction in patients with COVID-19, characterized by changes in hormone levels (low triiodothyronine or low thyrotropin levels) or laboratory results compatible with the presence of subacute thyroiditis[20,34]. Italian researchers observed that in the spring of 2020, 15% of COVID-19 patients (*n* = 93) admitted to the intensive care unit (ICU) at a hospital in Milan had changes in thyroid hormones. By comparison, only 1% of patients in the same period of 2019 (*n* = 101) had changes in thyroid hormones[19]. Considering the fact that viral infections can cause thyroiditis, the researchers began a monitoring program to look at thyroid function 3 mo after COVID-19 treatment. The researchers found that thyroiditis, in patients with moderate to severe COVID-19, was different from common subacute thyroiditis: Many patients had mild dysfunction and the rate of thyroid disease was higher in men. Thyroid dysfunction appeared to be associated with more severe COVID-19 disease. After 3 mo, thyroid function was normal in all followed patients (*n* = 53), with persistence of ultrasound findings of thyroiditis in one third of them[35]. Another study from Greece was based on the premise that the interpretation of thyroid tests in ill patients is hampered by changes that ensue in the context of non-thyroidal illness syndrome and studied thyroid function in cohorts of COVID-19 positive (*n* = 102, 46 in the ICU) and COVID-19 negative patients (*n* = 94, 41 in the ICU)[18]. The researchers noted a non-thyroidal illness syndrome pattern in 60% of ICU and 36% of ward patients (with no significant differences between COVID-19 positive and negative patients)[18]. The thyroid laboratory work-up was compatible with thyrotoxicosis in 14.6% of SARS-CoV-2 positive ICU patients *vs* 7.7% in SARS-CoV-2 negative ICU patients (P = NS) and, overall in 8.8% of SARS-CoV-2 positive *vs* 7.4% of negative patients. Thus, the authors concluded that a non-thyroidal illness syndrome pattern is common in COVID-19 but it relates to the severity of disease rather than SARS-CoV-2 infection, whereas a thyrotoxicosis pattern was less frequently observed and was not different between patients with and without COVID-19[18].

Our study has several limitations and its caveats have to be considered. We collected only Google Trends data for English-language searches; however, we have shown in an older study that searches in this language dwarf searches in all other languages[4]. Additionally, Northern hemisphere internet searches dwarf Southern hemisphere searches[4]. Analyses were done on a weekly worldwide basis since Google Trends searches for extended time periods are provided as such. From the literature, worldwide and weekly or monthly Google Trends data are considered to be more reliable than country-wide and daily data[36,37]. No periodicity in the data was assessed since the total time duration of data collection was rather short. As stated above, the datasets were split in half given the vast differences in COVID-19 epidemiology in 2020-2021 due to the preponderance of different SARS-CoV-2 variants. Finally, we have to bear in mind the fact that Google Trends searches are limited to internet-literate persons, who are easily influenced by media items, although few (medical) research articles are reported by news outlets (targeting diverse audiences) and generate public interest[38].

**CONCLUSION**

Given the relatively recent onset of SARS-CoV-2 virus infection, the available monitoring data are limited in time and therefore long-term studies are needed to evaluate even longer-term effects on the endocrine glands. Research into the virus continues to grow, shedding more light on the real health risks posed by COVID-19. Ideally, it would be interesting to assess time and localization-delimited Google Trends searches with the corresponding thyroid disease incidence, as reported by physicians or as recorded in healthcare databases, to verify the associations observed. Understanding the nature of a pandemic of this magnitude means saving human lives and proper knowledge of ways to prevent further infection.

**ARTICLE HIGHLIGHTS**

***Research background***

Google Trends searches for symptoms and/or diseases may reflect actual disease epidemiology. Recently, Google Trends searches for coronavirus disease 2019 (COVID-19)-associated terms have been linked to the epidemiology of COVID-19. Some studies have linked COVID-19 with thyroid disease.

***Research motivation***

Since the use of Google Trends to study a wide range of medical topics is becoming more widespread and the available research on COVID-19-related thyroid disease is conflicting, with this work we aimed to look at the issue of COVID-19-related thyroid disease from a different angle, namely, that of digital epidemiology, since the latter may be a useful adjunct to classical epidemiology.

***Research objectives***

We assessed worldwide COVID-19 cases *per se* *vs* COVID-19-associated Google Trends searches and thyroid-associated Google Trends searches for 92 wk.

***Research methods***

We collected data on worldwide weekly GT searches regarding “COVID-19”, “severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)”, “coronavirus”, “smell”, “taste”, “cough”, “thyroid”, “thyroiditis”, and “subacute thyroiditis” for 92 wk and worldwide weekly COVID-19 cases' statistics in the same time period. The study period was split in half (approximately corresponding to the preponderance of different SARS-COV-2 virus variants) and in each time period we performed cross-correlation analysis and mediation analysis.

***Research results***

Significant positive cross-correlation function values were noted in both time periods. More in detail, COVID-19 cases *per se* were found to be associated with no lag with Google Trends searches for COVID-19 symptoms in the first time period and in the second time period to lead searches for symptoms, COVID-19 terms, and thyroid terms.

***Research conclusions***

Searches for a non-specific symptom or COVID-19 search terms mostly led Google Trends thyroid-related searches, in the second time period. This time frame/sequence particularly in the second time period (noted by the preponderance of the SARS-COV-2 delta variant), lends some credence to associations of COVID-19 cases *per se* with (apparent) thyroid disease (*via* searches for them).

***Research perspectives***

Given the relatively recent onset of SARS-CoV-2 virus infection, the available monitoring data are limited in time and therefore long-term studies are needed to evaluate even longer-term effects on the endocrine glands. Research into the virus continues to grow, shedding more light on the real health risks posed by COVID-19. Ideally, it would be interesting to assess time and localization-delimited Google Trends searches with the corresponding thyroid disease incidence, as reported by “sentinel” physicians or as recorded in healthcare databases, to verify the associations observed. Understanding the nature of a pandemic of this magnitude means saving human lives and proper knowledge of ways to prevent further infection.

**REFERENCES**

1 **Salathé M**. Digital epidemiology: what is it, and where is it going? *Life SciSoc Policy* 2018; **14**: 1 [PMID: 29302758 DOI: 10.1186/s40504-017-0065-7]

2 **Eysenbach G**. Infodemiology and infoveillance: framework for an emerging set of public health informatics methods to analyze search, communication and publication behavior on the Internet. *J Med Internet Res* 2009; **11**: e11 [PMID: 19329408 DOI: 10.2196/jmir.1157]

3 **Mavragani A**, Ochoa G. Google Trends in Infodemiology and Infoveillance: Methodology Framework. *JMIR Public Health Surveill* 2019; **5**: e13439 [PMID: 31144671 DOI: 10.2196/13439]

4 **Ilias I**, Alexiou M, Meristoudis G. Is There Seasonality in Hypothyroidism? A Google Trends Pilot Study. *Cureus* 2019; **11**: e3965 [PMID: 30956917 DOI: 10.7759/cureus.3965]

5 **Lippi G**, Cervellin G. Is digital epidemiology reliable?-insight from updated cancer statistics. *Ann Transl Med* 2019; **7**: 15 [PMID: 30788362 DOI: 10.21037/atm.2018.11.55]

6 **Monnaka VU**, Oliveira CAC. Google Trends correlation and sensitivity for outbreaks of dengue and yellow fever in the state of São Paulo. *Einstein (Sao Paulo)* 2021; **19**: eAO5969 [PMID: 34346987 DOI: 10.31744/einstein\_journal/2021AO5969]

7 **Senecal C**, Widmer RJ, Lerman LO, Lerman A. Association of Search Engine Queries for Chest Pain With Coronary Heart Disease Epidemiology. *JAMA Cardiol* 2018; **3**: 1218-1221 [PMID: 30422176 DOI: 10.1001/jamacardio.2018.3459]

8 **Santangelo OE**, Provenzano S, Gianfredi V. Infodemiology of flu: Google trends-based analysis of Italians' digital behavior and a focus on SARS-CoV-2, Italy. *J Prev Med Hyg* 2021; **62**: E586-E591 [PMID: 34909483 DOI: 10.15167/2421-4248/jpmh2021.62.3.1704]

9 **Satpathy P**, Kumar S, Prasad P. Suitability of Google Trends™ for Digital Surveillance During Ongoing COVID-19 Epidemic: A Case Study from India. *Disaster Med Public Health Prep* 2021: 1-10 [PMID: 34343467 DOI: 10.1017/dmp.2021.249]

10 **Borchering RK**, Viboud C, Howerton E, Smith CP, Truelove S, Runge MC, Reich NG, Contamin L, Levander J, Salerno J, van Panhuis W, Kinsey M, Tallaksen K, Obrecht RF, Asher L, Costello C, Kelbaugh M, Wilson S, Shin L, Gallagher ME, Mullany LC, Rainwater-Lovett K, Lemaitre JC, Dent J, Grantz KH, Kaminsky J, Lauer SA, Lee EC, Meredith HR, Perez-Saez J, Keegan LT, Karlen D, Chinazzi M, Davis JT, Mu K, Xiong X, Pastore Y Piontti A, Vespignani A, Srivastava A, Porebski P, Venkatramanan S, Adiga A, Lewis B, Klahn B, Outten J, Schlitt J, Corbett P, Telionis PA, Wang L, Peddireddy AS, Hurt B, Chen J, Vullikanti A, Marathe M, Healy JM, Slayton RB, Biggerstaff M, Johansson MA, Shea K, Lessler J. Modeling of Future COVID-19 Cases, Hospitalizations, and Deaths, by Vaccination Rates and Nonpharmaceutical Intervention Scenarios - United States, April-September 2021. *MMWR Morb Mortal Wkly Rep* 2021; **70**: 719-724 [PMID: 33988185 DOI: 10.15585/mmwr.mm7019e3]

11 **Lippi G**, Mattiuzzi C, Cervellin G. Google search volume predicts the emergence of COVID-19 outbreaks. *Acta Biomed* 2020; **91**: e2020006 [PMID: 32921704 DOI: 10.23750/abm.v91i3.10030]

12 **Nindrea RD**, Sari NP, Lazuardi L, Aryandono T. Validation: The Use of Google Trends as an Alternative Data Source for COVID-19 Surveillance in Indonesia. *Asia Pac J Public Health* 2020; **32**: 368-369 [PMID: 32643957 DOI: 10.1177/1010539520940896]

13 **Lampos V**, Majumder MS, Yom-Tov E, Edelstein M, Moura S, Hamada Y, Rangaka MX, McKendry RA, Cox IJ. Tracking COVID-19 using online search. *NPJ Digit Med* 2021; **4**: 17 [PMID: 33558607 DOI: 10.1038/s41746-021-00384-w]

14 **Kurian SJ**, Bhatti AUR, Alvi MA, Ting HH, Storlie C, Wilson PM, Shah ND, Liu H, Bydon M. Correlations Between COVID-19 Cases and Google Trends Data in the United States: A State-by-State Analysis. *Mayo Clin Proc* 2020; **95**: 2370-2381 [PMID: 33164756 DOI: 10.1016/j.mayocp.2020.08.022]

15 **Sulyok M**, Ferenci T, Walker M. Google Trends Data and COVID-19 in Europe: Correlations and model enhancement are European wide. *TransboundEmerg Dis* 2021; **68**: 2610-2615 [PMID: 33085851 DOI: 10.1111/tbed.13887]

16 **Ahmed S**, Abid MA, Santos de Oliveira MH, Ahmed ZA, Siddiqui A, Siddiqui I, Jafri L, Lippi G. Ups and Downs of COVID-19: Can We Predict the Future? Local Analysis with Google Trends for Forecasting the Burden of COVID-19 in Pakistan. *EJIFCC* 2021; **32**: 421-431 [PMID: 35046760]

17 **Aragón-Ayala CJ**, Copa-Uscamayta J, Herrera L, Zela-Coila F, Quispe-Juli CU. Interest in COVID-19 in Latin America and the Caribbean: an infodemiological study using Google Trends. *Cad SaudePublica* 2021; **37**: e00270720 [PMID: 34730692 DOI: 10.1590/0102-311X00270720]

18 **Vassiliadi DA**, Ilias I, Pratikaki M, Jahaj E, Vassiliou AG, Detsika M, Ampelakiotou K, Koulenti M, Manolopoulos KN, Tsipilis S, Gavrielatou E, Diamantopoulos A, Zacharis A, Athanasiou N, Orfanos S, Kotanidou A, Tsagarakis S, Dimopoulou I. Thyroid hormone alterations in critically and non-critically ill patients with SARS-CoV-2 infection. *Endocr Connect* 2021; **10**: 646-655 [PMID: 34010152 DOI: 10.1530/EC-21-0029]

19 **Muller I**, Cannavaro D, Dazzi D, Covelli D, Mantovani G, Muscatello A, Ferrante E, Orsi E, Resi V, Longari V, Cuzzocrea M, Bandera A, Lazzaroni E, Dolci A, Ceriotti F, Re TE, Gori A, Arosio M, Salvi M. SARS-CoV-2-related atypical thyroiditis. *Lancet Diabetes Endocrinol* 2020; **8**: 739-741 [PMID: 32738929 DOI: 10.1016/S2213-8587(20)30266-7]

20 **Șandru F**, Carsote M, Petca RC, Gheorghisan-Galateanu AA, Petca A, Valea A, Dumitrașcu MC. COVID-19-related thyroid conditions (Review). *ExpTher Med* 2021; **22**: 756 [PMID: 34035853 DOI: 10.3892/etm.2021.10188]

21 **Lisco G**, De Tullio A, Jirillo E, Giagulli VA, De Pergola G, Guastamacchia E, Triggiani V. Thyroid and COVID-19: a review on pathophysiological, clinical and organizational aspects. *J Endocrinol Invest* 2021; **44**: 1801-1814 [PMID: 33765288 DOI: 10.1007/s40618-021-01554-z]

22 **Speer G**, Somogyi P. Thyroid complications of SARS and coronavirus disease 2019 (COVID-19). *Endocr J* 2021; **68**: 129-136 [PMID: 33473054 DOI: 10.1507/endocrj.EJ20-0443]

23 **Dong E**, Du H, Gardner L. An interactive web-based dashboard to track COVID-19 in real time. *Lancet Infect Dis* 2020; **20**: 533-534 [PMID: 32087114 DOI: 10.1016/s1473-3099(20)30120-1]

24 **Tarkoma S**, Alghnam S, Howell MD. Fighting pandemics with digital epidemiology. *EClinicalMedicine* 2020; **26**: 100512 [PMID: 32864592 DOI: 10.1016/j.eclinm.2020.100512]

25 **McDonald DJ**, Bien J, Green A, Hu AJ, DeFries N, Hyun S, Oliveira NL, Sharpnack J, Tang J, Tibshirani R, Ventura V, Wasserman L, Tibshirani RJ. Can auxiliary indicators improve COVID-19 forecasting and hotspot prediction? *Proc Natl AcadSci U S A* 2021; **118** [PMID: 34903655 DOI: 10.1073/pnas.2111453118]

26 **Ginsberg J**, Mohebbi MH, Patel RS, Brammer L, Smolinski MS, Brilliant L. Detecting influenza epidemics using search engine query data. *Nature* 2009; **457**: 1012-1014 [PMID: 19020500 DOI: 10.1038/nature07634]

27 **Hochberg I**, Allon R, Yom-Tov E. Assessment of the Frequency of Online Searches for Symptoms Before Diagnosis: Analysis of Archival Data. *J Med Internet Res* 2020; **22**: e15065 [PMID: 32141835 DOI: 10.2196/15065]

28 **Yang S**, Ning S, Kou SC. Use Internet search data to accurately track state level influenza epidemics. *Sci Rep* 2021; **11**: 4023 [PMID: 33597556 DOI: 10.1038/s41598-021-83084-5]

29 **Drew DA**, Nguyen LH, Steves CJ, Menni C, Freydin M, Varsavsky T, Sudre CH, Cardoso MJ, Ourselin S, Wolf J, Spector TD, Chan AT; COPE Consortium. Rapid implementation of mobile technology for real-time epidemiology of COVID-19. *Science* 2020; **368**: 1362-1367 [PMID: 32371477 DOI: 10.1126/science.abc0473]

30 **Sousa-Pinto B**, Anto A, Czarlewski W, Anto JM, Fonseca JA, Bousquet J. Assessment of the Impact of Media Coverage on COVID-19-Related Google Trends Data: Infodemiology Study. *J Med Internet Res* 2020; **22**: e19611 [PMID: 32530816 DOI: 10.2196/19611]

31 **Mavragani A**, Gkillas K. COVID-19 predictability in the United States using Google Trends time series. *Sci Rep* 2020; **10**: 20693 [PMID: 33244028 DOI: 10.1038/s41598-020-77275-9]

32 **Effenberger M**, Kronbichler A, Shin JI, Mayer G, Tilg H, Perco P. Association of the COVID-19 pandemic with Internet Search Volumes: A Google TrendsTM Analysis. *Int J Infect Dis* 2020; **95**: 192-197 [PMID: 32305520 DOI: 10.1016/j.ijid.2020.04.033]

33 **Deshmukh V**, Motwani R, Kumar A, Kumari C, Raza K. Histopathological observations in COVID-19: a systematic review. *J ClinPathol* 2021; **74**: 76-83 [PMID: 32817204 DOI: 10.1136/jclinpath-2020-206995]

34 **Trimboli P**, Cappelli C, Croce L, Scappaticcio L, Chiovato L, Rotondi M. COVID-19-Associated Subacute Thyroiditis: Evidence-Based Data From a Systematic Review. *Front Endocrinol (Lausanne)* 2021; **12**: 707726 [PMID: 34659109 DOI: 10.3389/fendo.2021.707726]

35 **Muller I,**Cannavaro D, Dazzi D, Mantovani G, Longari V, Cuzzocrea M, Re TE, Gori A, Arosio M, Salvi MG. Early Follow-up of Atypical Thyroiditis Induced by SARS-CoV-2. *J EndocrSoc* 2021; **5:** A61-A61 [DOI: 10.1210/jendso/bvab048.124]

36 **Rovetta A**. Reliability of Google Trends: Analysis of the Limits and Potential of Web InfoveillanceDuring COVID-19 Pandemic and for Future Research. *Front Res Metr Anal* 2021; **6**: 670226 [PMID: 34113751 DOI: 10.3389/frma.2021.670226]

37 **Jensen PM**, Danielsen F, Skarphedinsson S. Monitoring Temporal Trends in Internet Searches for "Ticks" across Europe by Google Trends: Tick-Human Interaction or General Interest? *Insects* 2022; **13** [PMID: 35206749 DOI: 10.3390/insects13020176]

38 **Szmuda T**, Ali S, Hetzger TV, Rosvall P, Słoniewski P. Are online searches for the novel coronavirus (COVID-19) related to media or epidemiology? A cross-sectional study. *Int J Infect Dis* 2020; **97**: 386-390 [PMID: 32535297 DOI: 10.1016/j.ijid.2020.06.028]

**Footnotes**

**Institutional review board statement:** The statement isnot applicable since this is a web-based data study.

**Clinical trial registration statement:** The statement isnot applicable since this is a web-based data study.

**Informed consent statement:** The statement isnot applicable since this is a web-based data study.

**Conflict-of-interest statement:** The authors declare that they have no conflict of interest to disclose.

**Data sharing statement:** All the data for this study can be obtained from the publicly available sources <https://coronavirus.jhu.edu/map.html>&<https://trends.google.com>.

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: https://creativecommons.org/Licenses/by-nc/4.0/

**Provenance and peer review:** Invited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review started:** November 23, 2021

**First decision:** February 8, 2022

**Article in press:**

**Specialty type:** Endocrinology and metabolism

**Country/Territory of origin:** Greece

**Peer-review report’s scientific quality classification**

Grade A (Excellent): 0

Grade B (Very good): B

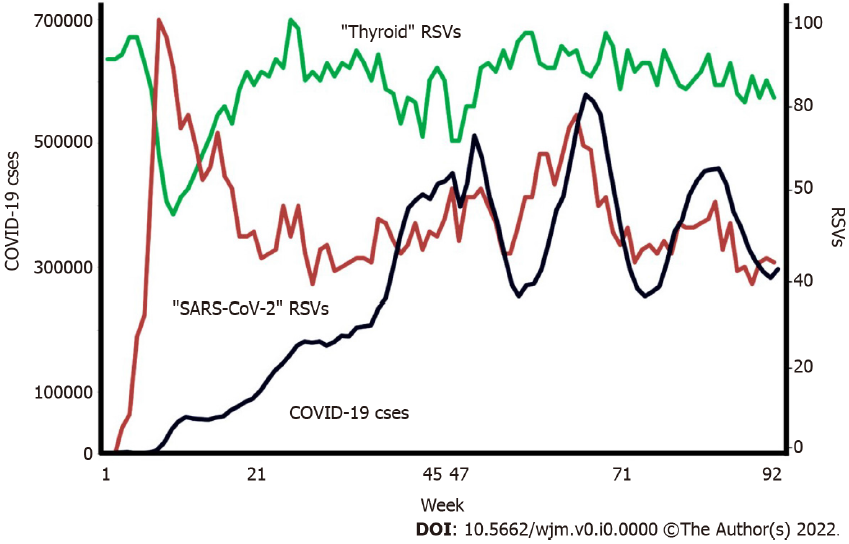
Grade C (Good): C

Grade D (Fair): D

Grade E (Poor): 0

**P-Reviewer:** Hu H, China; Ozair A, India **S-Editor:** Liu JH **L-Editor:** Wang TQ **P-Editor:** Liu JH

**Figure Legends**



**Figure 1 Time series plot of selected study data: Worldwide coronavirus disease 2019 weekly cases and Google Trends relative search volumes for “severe acute respiratory syndrome coronavirus 2” and “thyroid” during the study period.** Note the differences in magnitude, particularly during the second half of the study period. COVID-19: Coronavirus disease 2019; RSVs: Relative search volumes; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.

**Table 1 Positive cross correlation function values between variables; only significant values are presented (please see text for details)**

|  |  |  |  |
| --- | --- | --- | --- |
|  |  | **1st time period** | **2nd time period** |
| COVID-19 cases *vs* | “Smell” | CCF: +0.644; Lag: 0 | CCF: +0.540; Lag: 0 |
| “Taste” | CCF: +0.604; Lag: 0 | CCF: +0.433 to +0.368; Lag: -2 to 0 |
| “COVID-19” | -- | CCF: +0.412 to +0.315; Lag: -3 to 0 |
| “SARS-CoV-2” | -- | CCF: +0.677 to +0.589; Lag: -2 to 0 |
| “Thyroid” | CCF: +0.323 to +0.315; Lag: -8 to -7 | CCF: +0.412 to +0.343; Lag: -8 to -7 |
| “COVID-19” *vs* | “Thyroid” | -- | CCF: +0.374;Lag: -5 |
| “SARS-CoV-2” *vs* | -- | CCF: +0.323;Lag: -7 |

COVID-19: Coronavirus disease 2019; CCF: Cross correlation function; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.