COVID-19 and thyroid disease: an infodemiological pilot study

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Abstract

Introduction:

Some studies have linked COVID-19 with thyroid disease. Google Trends (GT) searches may reflect disease epidemiology. Recently, GT searches for COVID-19-associated terms have been linked to the epidemiology of COVID-19. In this study we aimed to assess COVID-19 cases per se vs COVID-19-associated GT searches and thyroid-associated GT searches.

Materials-Methods:

We collected data on worldwide weekly GT searches regarding “COVID-19”, “SARS-COV-2”, “coronavirus”, “smell”, “taste”, “fatigue”, “cough”, “thyroid”, “thyroiditis” and “subacute thyroiditis” for 92 weeks and worldwide weekly COVID-19 cases' statistics in the same time period. The study period was split in half and in each time period we performed cross-correlation analysis and mediation analysis.

Results

Significant positive CCF values were noted in both time periods; while COVID-19 cases per se were associated with “thyroid” searches in both time periods, significant CCFs for “fatigue”, “COVID-19” and “SARS-COV-s” were mostly found in the second time period. In the latter period, the effect of “COVID-19” searches on “thyroid” searches was significantly mediated by COVID-19 cases ($p=0.048$).

Discussion

COVID-19 cases per se were found to be associated with no lag with GT searches for COVID-19 symptoms in the first time period and in the second time period to lead searches for symptoms, COVID-19 terms as well as thyroid terms. Searches for a non-specific symptom or COVID-19 search terms mostly lead GT “thyroid” 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).

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 (GT, 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) [2–7]. Recently, GT searches for COVID-19-associated terms have been tentatively linked to the epidemiology of COVID-19 [8–12]. Some - but not all - studies have linked COVID-19 with thyroid function

abnormalities and more particularly with a form of subacute-like thyroiditis [13–17]. In this study we aimed to assess COVID-19 cases *per se* vs COVID-19-associated GT searches and thyroid-associated GT searches.

Materials-methods

We collected data on worldwide weekly GT searches (via “relative search volumes” [RSVs]; these are normalized values over a given time period, with a minimum of 0 and a maximum of 100; see also <https://support.google.com/trends/>) regarding “COVID-19”, “SARS-CoV-2”, “coronavirus”, “smell”, “taste”, “fatigue”, “cough”, “thyroid”, “thyroiditis” and “subacute thyroiditis” for 92 weeks (January 26, 2020 to October 24, 2021) and worldwide weekly COVID-19 cases' statistics in the same time period (as provided by the Johns Hopkins University Coronavirus Resource Center at <https://coronavirus.jhu.edu/map.html>) [18]. The study period was split in half (the first half corresponding to the preponderance of the SARS-CoV-2 alpha variant and the second to the preponderance of the delta variant) (Figure 1a) and in each time period we performed cross-correlation analysis; the threshold for statistical significance of each cross-correlation factor (CCF) value at the $p=0.05$ level was set according to lag, thus CCF 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 CCF 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, USA, 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 (Figures 2-4 and Supplemental Figures 1 and 2). Significant positive CCF values were noted in both time periods; while COVID-19 cases *per se* were associated with “thyroid” searches in both time periods, significant CCFs for “fatigue”, “COVID-19” and “SARS-COV-s” were mostly found in the second time period (Table 1). In the latter 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 GT searches for COVID-19 symptoms in the first time period and in the second time period to lead searches for symptoms, COVID-19 terms as well as thyroid terms. Searches for a non-specific symptom or COVID-19 search terms mostly lead GT “thyroid” 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).

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).

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 [15, 19]. 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 [14]. Considering the fact that viral infections can cause thyroiditis, the researchers began a monitoring program to look at thyroid function 3 months 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 months thyroid function was normal in all followed-up patients (n=53), with persistence of ultrasound findings of thyroiditis in one third of them [20]. 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 (NTIS) and studied thyroid function in cohorts of COVID-19 positive (n=102, 46 in the ICU) and negative patients (n=94, 41 in the ICU) [13]. The researchers noted a NTIS pattern in 60% of ICU and 36% of ward patients (with no significant differences between COVID-19 positive or negative patients)[13]. The thyroid laboratory work-up was compatible with thyrotoxicosis in 14.6% of SARS-CoV-2 ICU patients vs 7.7% in ICU negative (P = NS) and, overall in 8.8% of SARS-CoV-2 positive vs 7.4% of negative patients. Thus, the authors concluded that an NTIS 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 no different between patients with and without COVID-19 [13].

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 [21]. However, our study has several limitations and caveats: we collected only GT data for English-language searches; however these searches dwarf searches in all other languages (additionally Northern hemisphere searches dwarf Southern hemisphere searches) [4]. Analyses were done on a weekly worldwide basis since GT searches for extended time periods are provided as such (worldwide and weekly monthly GT data are considered to be more reliable than country-wide and daily data [22]). 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 GT 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 [23]. Regarding COVID-19 the influence of media on GT RSVs has been studied and was found to be maximal after a week [24], whereas the effect of COVID-19 cases on "COVID-19" searches has been studied [25], and has been found to be most notable after 11.5 days [26]. Thus with the lags in the observed CCFs we believe

that the GT searches for COVID-19 and/or thyroid-related items may reflect personal interest fuelled by probable real disease (COVID-19 or thyroid disease).

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 GT 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.

Declarations

Data availability:

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

Funding:

None.

Conflict of Interest:

All the Authors declare that they have no conflict of interest.

Tables

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

		1 st time period	2 nd 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
"Fatigue" vs	"Thyroid"	CCF: +0.389 to +0.611 Lag: -5 to -3	CCF: +0.594 Lag: 0
"COVID-19" vs		--	CCF: +0.374 Lag: -5
"SARS-CoV-2" vs		--	CCF: +0.323 Lag: -7

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Figures

Figure 1

COVID-19 weekly cases worldwide during the study period. Note the differences in magnitude, particularly during the second half of the study period.

Figure 2

Characteristic weekly Google Trends RSVs for "SARS-CoV-2" during the study period.

Figure 3

Characteristic weekly Google Trends RSVs for "Fatigue" during the study period.

Figure 4

Characteristic weekly Google Trends RSVs for "Thyroid" during the study period.

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