Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Risk and course of SARS-CoV-2 infection in patients treated for hypothyroidism and hyperthyroidism

COVID-19, caused by SARS-CoV-2, has spread dramatically, and by the end of January, 2021, had affected more than 100 million people, claiming more than 2·2 million lives. Older age, male sex, and the presence of comorbidities, such as hypertension, obesity, and diabetes have been identified as risk factors for severe disease and death.[1]

Patients with hypothyroidism or hyperthyroidism might have an increased risk of developing a severe course of COVID-19. First, because SARS-CoV-2 uses angiotensin-converting enzyme 2 (ACE2) as a receptor for host-cell entry,[2] thyroid dysfunction might influence the risk and course of COVID-19 because the tissue distribution of ACE2 is influenced by serum concentrations of thyroid hormones.[3] Second, patients with hypothyroidism and hyperthyroidism have an increased burden of cardiovascular[4,5] and psychiatric[6] comorbidities, which are also reported in patients with severe COVID-19. Third, the susceptibility to infection and course of infection might be negatively affected by thyroid dysfunction.[7] Whether these pathophysiological observations in patients with thyroid disease translate into increased risk of acquiring or a worse prognosis of SARS-CoV-2 infection is unknown. Because hypothyroidism and hyperthyroidism are common conditions, any such increased risk would have an important public health impact.

An absence of robust data prompted us to do a population-based case-control and cohort study using data from the Danish COVID-19 cohort[8] (appendix p 1) to evaluate the risk of contracting SARS-CoV-2 and the prognosis of SARS-CoV-2 infection in patients treated for hypothyroidism or hyperthyroidism. Patients using levothyroxine were defined as having hypothyroidism, patients using antithyroid drugs were defined as having hyperthyroidism, and patients who had never used levothyroxine or antithyroid drugs were classified as being euthyroid. The case-control study included all individuals who tested negative for SARS-CoV-2 (n=2 400 609) or positive for SARS-CoV-2 (n=28 078) in Denmark between Feb 27 and Sept 30, 2020. Odds ratios (ORs) and 95% CIs for testing positive for SARS-CoV-2 were estimated comparing users of levothyroxine or antithyroid drugs with non-users. Confounding was handled using matching (ratio of cases to controls 1:10; matched by age, sex, and week of test) and multivariable regression. The cohort study included only patients who tested positive for SARS-CoV-2 between Feb 27 and Aug 31, 2020 (n=16 502; baseline characteristics for the case-control study and the cohort study are shown in appendix pp 9–10). We estimated crude and confounder adjusted risk ratios (RR) and risk differences (RD) with 95% CIs for mortality, hospital stay beyond 12 h, intensive care unit admission, use of mechanical ventilation, and dialysis, all during the 30 days after a positive test for SARS-CoV-2 using generalised linear models (binomial distribution, log link, or identity link) with propensity score derived weights. Patients who had never used levothyroxine or antithyroid drugs were weighted according to the propensity score odds, whereas patients with hypothyroidism or hyperthyroidism were assigned a weight of 1 (see appendix pp 1–3 for exposures, outcomes, and statistical analyses).

In the case-control study, 809 (2·9%) of 28 078 SARS-CoV-2-positive patients and 7 994 (2·9%) of 280 007 matched SARS-CoV-2-negative patients were using levothyroxine; whereas 91 (0·3%) SARS-CoV-2-positive patients and 936 (0·3%) SARS-CoV-2-negative patients were using antithyroid drugs (appendix pp 9–10). Patients treated for hypothyroidism or hyperthyroidism did not have an increased risk of contracting SARS-CoV-2 infection (hypothyroidism: adjusted OR 1·03 [95% CI 0·95–1·11; hyperthyroidism: adjusted OR 1·03 [0·82–1·28]; covariates used for adjustment and handling of confounding are shown in appendix p 2).

Of the 16 502 individuals included in the cohort study, 572 (3·5%) were using levothyroxine and 75 (0·5%) were using antithyroid drugs. In the crude analyses, compared with patients who did not use levothyroxine, the use of levothyroxine was associated with an increased risk of death (RR 2·39 [95% CI 1·80–3·19]), hospitalisation (2·15 [1·84–2·50]), intensive care unit admission (1·88 [1·23–2·87]), mechanical ventilation (1·75 [1·06–2·87]), and dialysis (3·24 [1·63–6·44]; table). After propensity score weighting, these associations attenuated, and only the risk of hospitalisation (1·19 [1·02–1·40]) and dialysis (2·23 (1·06–4·69]) remained above the null value (table). We found no association between current use of antithyroid drugs and adverse outcomes of SARS-CoV-2 infection after propensity score weighting (table). Extending follow-up to 60 days (appendix p 11), taking different test strategies into account (appendix p 12), or including patients who had ever used levothyroxine or antithyroid drugs (appendix p 13) showed similar results for users of antithyroid drugs as in the main analysis, but for patients treated for hypothyroidism, the increased risk for hospitalisation and risk of dialysis shown in the main analysis was not found in the supplementary analyses.

Using population-based data we examined the risk of contracting SARS-CoV-2 and the prognosis of SARS-CoV-2 infection in patients treated for hypothyroidism or hyperthyroidism. The risk of testing positive for SARS-CoV-2 did not differ between patients treated for hypothyroidism or hyperthyroidism

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See Online for appendix

	Patients treated for hypothyroidism		Individuals presumed to be euthyroid*		Hypothyroidism *vs* euthyroidism		Patients treated for hyperthyroidism		Individuals presumed to be euthyroid†		Hyperthyroidism *vs* euthyroidism	
	Events	Risk (95% CI)	Events	Risk (95% CI)	Risk difference (95% CI)	Risk ratio (95% CI)	Events	Risk (95% CI)	Events	Risk (95% CI)	Risk difference (95% CI)	Risk ratio (95% CI)
Crude analysis												
Death	47/572	8·2% (6·0 to 10·5)	544/15 855	3·4% (3·1 to 3·7)	4·8% (2·5 to 7·1)	2·39 (1·80 to 3·19)	13/75	17·3% (8·8 to 25·9)	544/15 855	3·4% (3·1 to 3·7)	13·9% (5·3 to 22·5)	5·05 (3·06 to 8·34)
Hospital admission	133/529	25·1% (21·4 to 28·8)	1773/15 145	11·7% (11·2 to 12·2)	13·4% (9·7 to 17·2)	2·15 (1·84 to 2·50)	18/63	28·6% (17·4 to 39·7)	1773/15 145	11·7% (11·2 to 12·2)	16·9% (5·7 to 28·0)	2·44 (1·65 to 3·62)
Intensive care unit admission	NA	NA	NA	NA	1·8% (0·2 to 3·4)	1·88 (1·23 to 2·87)	NA	NA	NA	NA	0·6% (–3·1 to 4·3)	1·31 (0·33 to 5·17)
Mechanical ventilation	NA	NA	NA	NA	1·2% (–0·2 to 2·6)	1·75 (1·06 to 2·87)	NA	NA	NA	NA	1·1% (–2·6 to 4·8)	1·68 (0·43 to 6·65)
Dialysis	NA	NA	NA	NA	1·1% (0·1 to 2·1)	3·24 (1·63 to 6·44)	NA	NA	NA	NA	2·2% (–1·5 to 5·8)	5·49 (1·37 to 21·93)
Propensity score weighted analysis												
Death	47/572	8·2% (6·0 to 10·5)	54/574	9·4% (8·4 to 10·5)	–1·2% (–3·7 to 1·3)	0·87 (0·65 to 1·17)	13/75	17·3% (8·8 to 25·9)	12/75	16·7% (14·5 to 19·0)	0·6% (–8·3 to 9·5)	1·04 (0·62 to 1·73)
Hospital admission	133/529	25·1% (21·4 to 28·8)	108/513	21·1% (19·8 to 22·4)	4·1% (0·1 to 8·0)	1·19 (1·02 to 1·40)	18/63	28·6% (17·6 to 39·7)	16/62	24·9% (22·7 to 27·1)	3·6% (–7·7 to 15·0)	1·15 (0·77 to 1·71)
Intensive care unit admission	NA	NA	NA	NA	1·0% (–0·7 to 2·6)	1·34 (0·86 to 2·08)	NA	NA	NA	NA	–0·3% (–4·0 to 3·5)	0·90 (0·23 to 3·60)
Mechanical ventilation	NA	NA	NA	NA	0·7% (–0·7 to 2·1)	1·32 (0·79 to 2·22)	NA	NA	NA	NA	0·7% (–3·0 to 4·4)	1·35 0·34 to 5·39)
Dialysis	NA	NA	NA	NA	0·9% (–0·2 to 1·9)	2·23 (1·06 to 4·69)	NA	NA	NA	NA	1·9 (–1·7 to 5·6)	3·62 (0·86 to 15·14)

NA=not available because precise counts cannot be reported due to Danish data confidentiality laws. *Individuals in the propensity score weighted analysis matched to patients with hypothyroidism. †Individuals in the propensity score weighted analysis matched to patients with hyperthyroidism.

***Table*: Risk, risk differences, and risk ratios for different outcomes of SARS-CoV-2 infection in patients treated for hypothyroidism and hyperthyroidism compared with individuals presumed to be euthyroid**

and individuals in the control group. Likewise, patients treated for hypothyroidism or hyperthyroidism did not have an increased risk of adverse outcomes of SARS-CoV-2 infection, such as hospitalisation and death, after adjustment for confounders. Findings were robust in a range of supplementary analyses. Recently, evaluation of a small sample (n=3703) of SARS-CoV-2-positive patients, ascertained through the New York City health system, showed similar findings with respect to hypothyroidism and course of SARS-CoV-2 infection,[9] indicating that our findings obtained in a uniform, tax-financed health-care system can be generalised to other settings.

These results suggest that receiving treatment for thyroid dysfunction should not affect the clinical management of the patient's risk of acquiring SARS-CoV-2 infection, or the management of patients who already contracted the infection. The crude analysis shows an excess risk of adverse outcomes of SARS-CoV-2 infection in patients treated for hypothyroidism and hyperthyroidism, but these associations attenuate after adjustment for comorbidity and temporal changes in the Danish SARS-CoV-2 test strategy. One possible interpretation is that the excess risk observed in the crude analysis is mainly caused by comorbidity and not by the thyroid dysfunction per se. Other interpretations are possible but a formal causal analysis of the interplay between treatment of hypothyroidism and hyperthyroidism, comorbidity and co-prescribed medication is outside the scope of this paper.

The following factors should be considered when interpreting the absence of an association between hypothyroidism or hyperthyroidism and risk and course of SARS-CoV-2 infection. First, the effect of thyroid hormones per se on the innate and

adaptive immune response during infection,[7] as well as the distribution and activity of ACE2[3] in humans, might not be sufficient to influence the risk and course of SARS-CoV-2. Second, even if thyroid hormones influence the expression of ACE2 significantly,[3] this might not affect the risk and course of SARS-CoV-2 infection. Large-scale studies do not show an association between ACE inhibitors and angiotensin receptor blockers (both increase the level of ACE2 substantially) and a severe course of SARS-CoV-2 infection.[10] Third, and possibly most important, all the patients in our study received treatment with levothyroxine or antithyroid drugs. Thus, we cannot rule out that our patients were euthyroid or that the severity of thyroid dysfunction at the time of the SARS-CoV-2 infection was minor and therefore without influence on the immune response during the infection. Having no access to biochemical data of thyroid function, it is not possible to examine this further. Moreover, we have no information on the cause of hypothyroidism or hyperthyroidism in patients in our study, which would have allowed us to assess whether the risk and course of SARS-CoV-2 infection differs between autoimmune and non-autoimmune thyroid dysfunction.

One strength of the present study is the use of validated Danish nationwide registers, which allow identification of all individuals tested for SARS-CoV-2 during the study period, as well as individual information on prescription drug use, in-patient and out-patient hospital admissions, and death. By including patients managed in the primary health-care system (community settings) as well as patients treated in the secondary health-care system (hospital settings), our study sample, unlike many other studies, includes the entire clinical spectrum of patients infected with SARS-CoV-2.

In conclusion, our results suggest that patients treated for hypothyroidism or hyperthyroidism do not have an increased risk of contracting SARS-CoV-2 infection. The results also suggest that treatment for thyroid dysfunction, when controlling for relevant confounding, does not influence the prognosis of SARS-CoV-2 infection.

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National registries as a catalyst to development of diabetes care in low-income and middle-income countries

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In most low-income and middle-income countries (LMICs), diabetes data are sporadically recorded, dispersed among fragmented platforms, and often not shared within national health information exchanges or patient-level health information systems, such as electronic health records and national disease surveillance systems. The absence of patient data where and when it is needed impedes comprehensive care and continuity. For example, a patient receiving care for tuberculosis might not be recognised as living with diabetes—a common comorbidity—resulting in poorer tuberculosis treatment outcomes and potentially life-threatening interruption of diabetes care. Interruptions to diabetes treatment led to increased acute events and even excess deaths in 2020 during the COVID-19 pandemic.[1] Moreover, the scarcity of linked comorbidity data for patients with COVID-19 resulted in slow recognition of the additional vulnerability of people living with diabetes to the most severe COVID-19 outcomes.[2]

National-level diabetes registries are associated with better quality of care and long-term patient outcomes,[3] providing support for the systematic delivery of treatment and management interventions to diagnosed patients, and the identification of prevention priorities. WHO and diabetes organisations have encouraged the establishment of registries; however, progress remains weak in LMICs, where 80% of diabetes-related deaths occur.[4] National diabetes registries are clustered in high-income and upper-middle-income countries, and these often collect insufficient patient data: many focus exclusively on