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The effect of immunosuppressants on the prognosis of SARS-CoV-2 infection.

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ABSTRACT

Background: Immunosuppression may worsen SARS-CoV-2 infection. We conducted a nationwide cohort study of the effect of exposure to immunosuppressants on the prognosis of SARS-CoV-2 infection in Denmark.

Methods: We identified all SARS-CoV-2 test-positive patients from February to October 2020 and linked health care data from nationwide registers, including prescriptions for the exposure, immunosuppressant drugs. We estimated relative risks of hospital admission, intensive care unit (ICU) admission, and death (each studied independently up to 30 days from testing) with a log linear binomial regression adjusted for confounders using a propensity score-based matching weights model.

Results: A composite immunosuppressant exposure was associated with a significantly increased risk of death (adjusted relative risk 1·56 [95% confidence interval 1·10-2·22]). The increased risk of death was mainly driven by exposure to systemic glucocorticoids (aRR 2·38 [95% CI 1·72-3·30]), which were also associated with an increased risk of hospital admission (aRR 1·34 [95% CI 1·10-1·62]), but not ICU admission (aRR 1·76 [95% CI [0·93-3·35]); these risks were greater for high cumulative doses of glucocorticoids than for moderate doses. Exposure to selective immunosuppressants, tumour necrosis factor inhibitors, or interleukin inhibitors, was not associated with an increased risk of hospitalisation, ICU admission, or death, nor was exposure to calcineurin inhibitors, other immunosuppressants, hydroxychloroquine, or chloroquine.

Conclusions: Exposure to glucocorticoids was associated with increased risks of hospital admission and death. Further investigation is needed to determine the optimal management of COVID-19 in patients with pre-morbid glucocorticoid usage, specifically whether these patients require altered doses of glucocorticoids.

SHORT SUMMARY

In a nationwide cohort study of SARS-CoV-2 infections in Denmark, pre-morbid exposure to systemic glucocorticoids was associated with an increased risk of hospital admission and death, whereas other immunosuppressants were not.

INTRODUCTION

Coronavirus disease (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), manifests with varying clinical severity. [1,2] An inflammatory response with virus-specific T cells clears the virus and leads to recovery in most patients, however an aberrant inflammatory response can lead to severe disease. [3] Severe cases are predominantly characterised by viral pneumonia and may feature multi-organ inflammatory involvement, including elevated pro-inflammatory cytokines such as interleukins IL-6 and IL-8, and tumour necrosis factor (TNF). [3-5] Patients receiving immunosuppressant therapies for conditions including inflammatory diseases and solid organ transplantation are susceptible to intercurrent viral and bacterial infections, [6,7] and although evidence is lacking regarding their effect on COVID-19, expert groups concerned that immunosuppression may worsen the prognosis have advised withholding or reducing immunosuppressants during intercurrent COVID-19. [8–10]

Immunosuppressants differ in their mechanisms of action and may therefore have differing effects on the disease course of COVID-19, and effects may vary with the severity of disease, and timing in the disease course. Certain immunosuppressants may have beneficial effects in COVID-19 by regulating the elevated inflammatory response associated with severe disease. Randomised controlled trials (RCTs) have demonstrated improved survival of COVID-19 patients treated with corticosteroids. [11,12] A number of clinical trials of biological immunosuppressants including anti-IL-6 agents have been performed without conclusive evidence of improved outcomes, [13] but preliminary reports of a large RCT indicate improved survival in patients treated with tocilizumab. [14] The majority of RCTs and a meta-analysis of chloroquine or hydroxychloroquine to treat COVID-19 did not support efficacy. [15,]

In addition to efficacy studies of immunosuppressants as treatment for COVID-19, their safety also requires investigation to guide optimal management of comorbid diseases during the pandemic, as the presence of pre-existing immunosuppression may influence the prognosis of intercurrent COVID-19. Currently published studies of patients with COVID-19 receiving immunosuppressants for underlying conditions have been limited by small sample sizes or surveillance bias. [16-19]

We therefore aimed to conduct a nationwide cohort study of the effect of exposure to immunosuppressants on the risk of hospital admission, intensive care unit (ICU) admission, and death among all SARS-CoV-2 test-positive patients in Denmark from February to October 2020.

METHODS

DATA SOURCES

We conducted a nationwide cohort study using the Danish COVID-19 cohort, [20] based on data from the Danish Microbiology Register, a national register of all test results from all clinical microbiology departments in Denmark. [21] We defined the cohort as all individuals with a positive result for SARS-CoV-2 polymerase chain reaction (PCR) on an oro- or nasopharyngeal swab or lower respiratory tract specimen, from the first detected case on 26 February until 18 October 2020 (30 days before data extraction on 18 November 2020). We used individuals' first positive test date in the Danish Microbiology Register (the index date) and a pseudonymised unique identifier to link individual-level health care data from other Danish national registers. We obtained information on prescription drugs dispensed at retail pharmacies from the Danish National Prescription Register,[22] and information on diagnoses, and medical procedures (including the administration of intravenous drugs) from the Danish National Patient Register, a register of hospital activities. [23] We obtained the date of death from the Danish Register of Causes of Death, if present. [24]

EXPOSURES AND OUTCOMES

The exposure was immunosuppressants drugs including hydroxychloroquine and chloroquine (immunomodulators which are suspected to alter the immune response in COVID-19), and systemic glucocorticoids, which in moderate to high doses can cause immunosuppression (see Appendix Table 1 for drug level ATC codes and procedure codes). The validity of the registration of immunosuppressants in our data sources has not been analysed, but studies have demonstrated a high validity of other procedures codes, such as antineoplastic procedures. [25] The exposure assessment window was 120 days preceding the index date, as packs contained up to 120 tablets, and treatments given more than 120 days before infection are unlikely to cause ongoing immunosuppression. We used a minimum daily dose of systemic glucocorticoids equivalent to 7·5 mg prednisone per day, to exclude doses unlikely to cause significant immunosuppression (Appendix Table 2). [26] As the prescribed daily dose is not available in the Danish National Prescription Register, [22] we estimated the daily dose as the sum of the amount of glucocorticoids dispensed to an individual during the exposure assessment window divided by the number of days from the first prescription to the index date. Unexposed patients did not receive any immunosuppressant during the exposure assessment window.

We studied immunosuppressants as a composite exposure in our main analysis. In secondary analyses, seeking to investigate the effect of classes of immunosuppressants, while maintaining sufficient sample size to detect an effect, we broke down immunosuppressants into smaller categories. Biological and targeted immunosuppressants indicated in severe immune-mediated inflammatory diseases (IMID) or to prevent transplant rejection (TNF inhibitors, interleukin inhibitors, selective immunosuppressants, and rituximab) comprised one group. Conventional disease modifying anti-rheumatic drugs, as well as other immunosuppressants (calcineurin inhibitors, other immunosuppressants, hydroxychloroquine, and chloroquine) formed a second group. Systemic glucocorticoids formed a third group.

The study outcomes were hospital admission, ICU admission, and death, each event studied separately and independently. We included events occurring up to 30 days from patients' first positive test date, as well as hospital and ICU admission up to 7 days before that date to include relevant events occurring before testing, while reducing unrelated events occurring after recovery. Previous studies have indicated that a small percentage of patients were hospitalised before testing, [27] and approximately 80% of deaths occur within 14 days of hospital admission. [28]

COVARIATES

We controlled for confounding by including covariates for the exposure and outcomes in a propensity score (PS) model. These covariates were selected based on background knowledge, despite incomplete knowledge of the relation between all covariates, while excluding instrumental variables or mediators. We included demographic variables (age and sex), number of past hospital contacts, diagnoses, and co-medications

(including medications as proxies for disease, such as for diabetes) as covariates of immunosuppressive treatment and prognosis of SARS-CoV-2 infection (ATC and ICD-10 codes listed in Appendix Table 3). To control for confounding by indication, we included diagnoses such as inflammatory diseases (included with in skin diseases, and gastrointestinal diseases categories), organ transplantation, and certain malignancies that indicate treatment with immunosuppressants. Procedures and non-immunosuppressant medications used to treat IMID were included as proxies of underlying disease severity.

STATISTICAL METHODS

Clinical characteristics of the cohort were assessed, with standardised mean differences (SMD) less than 0.1 considered well balanced. We estimated the PS as the probability of treatment conditional on observed covariates. [29] We used a PS-weighting model where exposed subjects' weights were calculated as (minimum(PS,1-PS))/PS, and unexposed subjects' weights were calculated as (minimum(PS, 1-PS))/(1-PS), known as 'matching weights'. This gave a better covariate balance than inverse probability of treatment weighting (IPTW) as initially planned (Appendix Figure 1 and Appendix Tables 13-20). [30] Weights were truncated at the 1st and 99th centile. We removed antianaemic drugs from the final PS model due to imbalance; adjusting for it in the log binomial regression model gave similar results (Appendix Tables 4-12).

We estimated crude and adjusted (weighted) relative risks (and 95% confidence intervals with robust variance estimates) of the outcomes for exposed patients compared to unexposed patients using a log linear binomial regression model. We preferred this model to a survival analysis with competing risks model because a high number of events such as death often occurred very close to the date of testing, and hospital and ICU admission could occur before testing, resulting in negative time-to-event. For the analyses of subgroups of immunosuppressants, we fitted separate PS models for each of the subgroups, selecting variables from the list of covariates (Appendix Table 21). Exposure to combinations of the described groups of immunosuppressants was relatively rare and unlikely to alter results, so we did not study their effect. We performed a post-hoc analysis of the dose-effect of systemic glucocorticoids. To create two exposure groups of approximately equal size to maintain statistical power, we categorised the prednisolone-equivalent cumulative dose within 120 days preceding the index date as moderate dose (<2000 mg) or high dose (≥2000 mg), which were each compared to unexposed patients.

SENSITIVITY ANALYSES

To control for residual confounding, we performed an analysis comparing current users exposed 120 days preceding the index date to former users exposed to immunosuppressants 121-365 days preceding the index date. To study the effect of immunosuppressants in patients with more severe COVID-19, we restricted the cohort to hospital admissions coded with COVID-19 as the primary diagnosis, studying the outcomes ICU admission or death.

To reduce selection bias due to patients immunosuppressants, amongst other clinically vulnerable people, being prioritised for testing (mainly before a policy change in Denmark 21 April 2020), we made separate analyses of the cohort tested before or after 21 April 2020, and made calculations to estimate the effect of selection bias (see Appendix Methods). We used the statistical software Stata 16.1 (StataCorp LLC, College Station, TX).

RESULTS

CHARACTERISTICS OF SARS-COV-2 POSITIVE PATIENTS

From 26 February–18 October 2020, there were 36,727 individuals with positive SARS-CoV-2 PCR tests in Denmark, of which 527 were exposed to immunosuppressants and 36,200 were unexposed. There were 66 exposed to selective immunosuppressants, 105 to TNF inhibitors, 25 to interleukin inhibitors, 29 to calcineurin inhibitors, 218 to other immunosuppressants, 31 to hydroxychloroquine or chloroquine, 136 to systemic glucocorticoids, and zero to rituximab. The median age of exposed patients was 57 years (IQR 42 to 73), and the median age of unexposed patients was 39 years (IQR 23-55), with a greater prevalence of comorbid diagnoses in the exposed population (Table 1). In total, there were 715 deaths, and 492 (69%) of those were during hospital stays. There were 425 ICU admissions, and 105 (25%) of those patients died, all occurring within 28 days of ICU admission. Few patients were exposed to both glucocorticoids and selective immunosuppressants (<5), TNF inhibitors (<5), interleukin inhibitors (<5), calcineurin inhibitors (<5), or other immunosuppressants (14).

COMPOSITE IMMUNOSUPPRESSANT EXPOSURE: RELATIVE RISK OF SEVERE OUTCOMES OF SARS-COV-2 INFECTION.

Among patients exposed to the composite measure of immunosuppressants there were 165 hospital admissions, 25 ICU admissions, and 57 deaths, and among the unexposed there were 3373 hospital admissions, 400 ICU admissions and 658 deaths (Table 2 and Appendix Table 4). After weighting in our PS-based model, there were 346 exposed to immunosuppressants, and 339 unexposed, with a well-balanced distribution of covariates (Table 1 and Appendix Figure 1). The distribution of antianaemic drug usage was not balanced in the weighting model, but including it as a variable in our regression model had little effect (Appendix Table 4), so we removed it from the final model. The crude relative risk of hospital admission was 3·36 (95% CI 2·95 to 3·83), of ICU admission was 4·29 (95% CI 2·89 to 6·37), and of death was 5·95 (95% CI 4·60 to 7·69) (Table 2). The after weighting in our PS-based model, the adjusted relative risk (aRR) of hospital admission was 1·13 (95% CI 0·95 to 1·33), the aRR of ICU admission 1·16 (95% CI 0·66 to 2·03), and the aRR of death 1·56 (95% CI 1·10 to 2·22) (Table 2).

SUBGROUPS OF IMMUNOSUPPRESSANTS: RELATIVE RISK OF SEVERE OUTCOMES OF SARS-COV-2 INFECTION

For patients exposed to selective immunosuppressants, TNF inhibitors or interleukin inhibitors, compared to unexposed patients, the aRR of hospital admission was 0·83 (95% CI 0·51 to 1·34), the aRR of ICU admission was 0·92 (95% CI 0·23 to 3·71), and the aRR of death was 1·17 (95% CI 0·38 to 3·62) (Table 3 and Appendix Tables 5, 6, and 7). For patients exposed to calcineurin inhibitors, other immunosuppressants, hydroxychloroquine or chloroquine, compared to unexposed patients, the aRR of hospital admission was 0·82 (95% CI 0·60 to 1·12), the aRR for ICU admission was 1·03 (0·43 to 2·49), and the aRR for death was 0·93 (0·47 to 1·85). For patients exposed to systemic glucocorticoids, compared to unexposed patients, the aRR for hospital admission was 1·34 (95% CI 1·10 to 1·62), the aRR for ICU admission was 1·76 (95% CI 0·93 to 3·35), and the aRR for death was 2·38 (95% CI 1·72 to 3·30).

When cumulative glucocorticoid dose was categorised as moderate or high, compared to unexposed patients, the aRR of hospital admission was 1·20 (95% CI 0·89 to 1·62) and 1·47 (95 % CI 1·15 to 1·89); the aRR of ICU admission 1·92 (95% CI 0·82 to 4·46) and 1·58 (95% CI 0·62 to 4·04); and the aRR of death was 1·84 (95% CI 1·08 to 3·13) and 2·91 (95% CI 1·92 to 4·39), respectively (Table 4 and Appendix Table 8).

SENSITIVITY ANALYSES: RELATIVE RISK OF SEVERE OUTCOMES OF SARS-COV-2 INFECTION.

Comparing current users of immunosuppressants to former users, the aRR of hospital admission was 1·13 (95% CI 0·83 to 1·52), the aRR of ICU admission was 1·21 (95% CI 0·68 to 2·15), and the aRR of death was 1·21 (95% CI 0·68 to 2·15) (Table 5 and Appendix Table 9). When restricting to admitted patients with COVID-19 as their primary diagnosis, the risk of death was not significantly increased in patients exposed to

immunosuppressants (aRR 1·30, 95% CI 0·94 to 1·82) nor was the risk of ICU admission (aRR 0·89, 95% CI 0·50 to 1·56) (Appendix Table 10).

Prior to the change in testing strategy on 21 April 2020, there were 199 exposed to immunosuppressants and 7794 unexposed; from 21 April-18 October 2020, there were 328 exposed, and 28,406 unexposed (Appendix Table 11 and 12). For hospital admission the aRR was 0·99 (95% CI 0·82 to 1·20) in the first period, and 1·34 (95% CI 1·00 to 1·80) in the second period, the aRR of ICU admission was 0·65 (95% CI 0·29 to 1·46) and 3·23 (95% CI 1·50-6·98), and the aRR of death was 1·06 (95% CI 0·70 to 1·63) and 2·60 (95% CI 1·52 to 4·46) respectively.

DISCUSSION

Using a nationwide cohort of 36,727 individuals tested positive for SARS-CoV-2, of whom 527 were exposed to immunosuppressants, we assessed the effect of immunosuppressants on the prognosis of intercurrent SARS-CoV-2 infection. A composite immunosuppressant exposure was associated with a significantly increased risk of death, which was mainly driven by a doubling of risk associated with systemic glucocorticoids. Glucocorticoids were also associated with a 34% increased risk of hospital admission, while the risk of ICU admission was not significantly increased (Table 3). The risks of hospitalisation, ICU admission, or death associated with selective immunosuppressants, TNF inhibitors, or interleukin inhibitors were not significantly increased or decreased, nor were they in patients exposed to calcineurin inhibitors, other immunosuppressants, hydroxychloroquine, or chloroquine (Table 3). These findings are in agreement with two multinational studies of COVID-19 patients: glucocorticoids were associated increased risk of ICU admission or death in patients with comorbid inflammatory bowel diseases; glucocorticoids were associated with greater risk of hospital admission in patients with comorbid rheumatic diseases. [18,20]

The finding of an increased risk of death associated with glucocorticoids early in the course of COVID-19 contrasts with studies finding that high dose glucocorticoids reduces mortality in patients with severe disease [10, 11]. Nonetheless, patients not requiring supplemental oxygen in the RECOVERY trial did not benefit from dexamethasone and the effect could be compatible with harm (RR 1·19, 95% CI 0·91 to 1·55). [10] This deleterious effect of glucocorticoids early in the disease course could be due to a suppressed adrenal stress-response, as well as their suppressive effect on interferon production, resulting in impaired innate responses to viral infection. Chronic glucocorticoid exposure also has pleiotropic metabolic effects including impaired glucose handling and skeletal muscle catabolism among other effects that may contribute to adverse outcomes. By contrast, the initiation of glucocorticoids in severe disease appears to suppress the dysregulated inflammatory response which otherwise leads to multi-organ involvement and coagulation. The effect seen in our study appears to be dose related, but these subgroups were small, so interpretation of dose effects must be tentative. By contrast, treatment with high dose glucocorticoids reduces mortality in patients with severe COVID-19 disease. The majority of patients in our study were not admitted to hospital, and would have had milder COVID-19 not requiring oxygen therapy, similar to that subset of the RECOVERY trial. These findings prompt the important question of how to improve outcomes of COVID-19 in patients taking glucocorticoids. Whether patients on glucocorticoids require increased doses during COVID-19, as in other intercurrent illnesses, or reduced doses, requires further investigation.

Important strengths of this nationwide cohort study include the use of prescription and hospital activity data from national registers. Our study reduced surveillance bias, which is the limitation of studies based on spontaneously reported cases, by including all of SARS-CoV-2 test positive person in Denmark. We maximised power by using the full cohort, without restricting to specific patient populations. This facilitated extensive control of confounders, including the diverse diseases that indicate the use of immunosuppressants and glucocorticoids, further improving the reliability of our results. Controlling for covariates using a propensity score weighting model optimised the covariate distribution in a subset of the population with clinical equipoise for immunosuppressant exposure. Our analysis of bias suggested that the risk associated with immunosuppressants may be greater than estimated, as selection bias that attenuated the relative risk estimates (see Appendix Methods). Selection bias had a greater effect in the period before 21 April, when patients on immunosuppressants were prioritised for testing, which may have contributed to the lower relative risks estimated compared to after that date (Appendix Table 9 and 10).

We also recognise limitations to our study. Our conclusions on the effects of classes of immunosuppressants are cautious, as the selected groups (other than glucocorticoids) included a number of drug classes, which may have divergent effects, impairing our ability to detect associations with individual drugs. As the number of exposed subjects was small, the matching weights model targeted the population average treatment effect in the treated, and this hinders the generalisability of the risk estimates to people without an underlying condition that could require immunosuppressant therapy. The number of covariates in our model was statistically limited by the number of outcome events, so there may be residual confounding caused by unmeasured disease severity. Residual confounding is suggested by the attenuation in the risk estimate for death associated with immunosuppressants when current users were compared to former users, which remained numerically increased but no longer statistically significant. Diagnostic coding is affected by differences in practices among clinicians, an inherent limitation when nationwide register data is used. Further studies may benefit from more detailed measures of severity. However, this is unlikely to completely account for the association of glucocorticoid exposure and severe outcomes, as other immunosuppressants such as TNF inhibitors are also treatments for severe IMIDs, but by contrast, those exposures were not significantly associated with severe outcomes.

In our cohort the majority of people with COVID-19 who died were never admitted to ICU, and a substantial number were not receiving hospital-based care when they died. Frailty may account for the greater number of deaths, and greater relative risks associated with immunosuppressants, compared to ICU admissions. Admission to ICU depends not only on clinical assessment of the admitted patient, but also on factors such as frailty, short life expectancy, as well as patient and family preferences; for example, a care home resident with such conditions might not be moved to hospital, thus would not be assessed for ICU admission. Further health system factors may also be important in the context of the pandemic [31].

In conclusion, this nationwide cohort study found that pre-morbid exposure to glucocorticoids was associated with a worsened prognosis of SARS-CoV-2 infection. [18, 19] Studies are warranted to determine whether altered doses are beneficial, with attention to the severity of COVID-19 at treatment initiation. While other pharmacological interventions remain relevant research candidates, evidence from multiple sources indicate the importance of glucocorticoids on prognosis, the effect of which may depend on timing in the disease course. Our findings that other immunosuppressants were not significantly associated with severe outcomes are tentative, but in context, they support the continued use of steroid-sparing immunosuppressants for a broad patient population with ongoing health care needs during the pandemic.

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Table 1. Characteristics of SARS-CoV-2 PCR test positive patients in Denmark, 26 February–18 October 2020, by exposure to immunosuppressants.

	Full cohort			Propensity score weighted dataset		
Characteristics	**Exposed (n=527)**	**Unexposed (n=36,200)**	**SMD**	**Exposed (n=346)**	**Unexposed (n=339)**	**SMD**
Age in years, median (IQR)	57 (42-73)	39 (23-55)	0·80	57 (43-74)	56 (41-71)	0·11
Male, N (%)	256 (48·6)	17,544 (48·5)	0·00	149 (43·1)	154 (45·4)	0·05
Number of admissions and outpatient contacts	**N (%)**	**N (%)**	-	**N (%)**	**N (%)**	-
0	20 (3·8)	18,787 (51·9)	1·27	14 (4·0)	11 (3·4)	0·04
1-2	38 (7·2)	9,574 (26·4)	0·53	36 (10·4)	47 (13·8)	0·10
3-5	113 (21·4)	4,264 (11·8)	0·26	107 (30·9)	82 (24·2)	0·15
6+	356 (67·6)	3,575 (9·9)	1·47	189 (54·6)	199 (58·7)	0·08
Diagnoses	**N (%)**	**N (%)**	-	**N (%)**	**N (%)**	-
Cardiovascular disease	176 (33·4)	4,269 (11·8)	0·53	111 (32·1)	98 (29·0)	0·07
Neoplasms, blood and blood-forming organs	27 (5·1)	101 (0·3)	0·30	(n<5)	n<5	0·09
Solid organ transplantation	24 (4·6)	27 (0·1)	0·30	(n<5)	n<5	0·12
Pulmonary disease	131 (24·9)	2,742 (7·6)	0·48	73 (21·1)	66 (19·6)	0·04
Liver disease	15 (2·8)	302 (0·8)	0·15	11 (3·2)	7 (2·0)	0·07
Kidney disease	76 (14·4)	1,049 (2·9)	0·42	34 (9·8)	30 (8·8)	0·04
Diseases of the gastrointestinal tract	91 (17·3)	365 (1·0)	0·59	17 (4·9)	12 (3·4)	0·07
Other gastrointestinal pathologies	94 (17·8)	1,934 (5·3)	0·40	43 (12·4)	43 (12·5)	0·00
Neurological and musculoskeletal disease	353 (67·0)	8,101 (22·4)	1·00	231 (66·8)	209 (61·7)	0·11
Skin disease	112 (21·3)	1,399 (3·9)	0·54	51 (14·7)	35 (10·3)	0·13
Medications	**N (%)**	**N (%)**	-	**N (%)**	**N (%)**	-
Antianaemic drugs (ATC B03)	276 (52·4)	2,946 (8·1)	1·10	185 (53·5)	61 (18·0)	0·80
Cardiovascular drugs (ATC C01-10)	370 (70·2)	14,144 (39·1)	0·66	235 (67·9)	224 (66·2)	0·04
Antimicrobials (ATC J01-06)	515 (97·7)	32,201 (89·0)	0·36	335 (96·8)	329 (97·1)	0·02
Anticoagulants (ATC B01AA)	39 (7·4)	633 (1·7)	0·27	19 (5·5)	19 (5·5)	0·00
Diabetes drugs (ATC A10)	65 (12·3)	2,211 (6·1)	0·22	44 (12·7)	39 (11·4)	0·04

Obstructive airway disease drugs (ATC R03)	212 (40·2)	9,502 (26·2)	0·30	135 (39·0)	126 (37·1)	0·04
Proxies for IMID severity	**N (%)**	**N (%)**	**-**	**N (%)**	**N (%)**	**-**
Procedures for IMID	162 (30.7)	2,239 (6.2)	0.67	82 (23.7)	78 (23.1)	0.01
IMID drugs	252 (47.8)	7,651 (21.1)	0.58	156 (45.1)	144 (42.6)	0.05

Due to data protection laws exact counts of individuals between 1-4 are reported only as <5. Abbreviations: SMD: standardized mean difference; IMID: immune mediated inflammatory diseases; IQR: interquartile range**.** Due to imabalance of antianaemic drugs, this variable was removed from the final model. Numbers of exposed and unexposed in the propensity score weighted dataset are weighted subjects and do not refer to individual subjects.

Table 2. The relative risk of severe outcomes of SARS-CoV-2 infection in patients exposed to immunosuppressants compared to unexposed.

	Exposed (n=527)	**Unexposed (n=36,200)**	**Relative risk (95% CI)**	
Outcome	**Events**	**Events**	**Crude**	**Adjusted**
Hospital admission	165	3373	3·36 (2·95 to 3·83)	1·13 (0·95 to 1·35)
ICU admission	25	400	4·29 (2·89 to 6·37)	1·16 (0·66 to 2·03)
Death	57	658	5·95 (4·60 to 7·69)	1·56 (1·10 to 2·22)

Abbreviations: CI: confidence interval; ICU: intensive care unit.

Table 3. Relative risk of severe outcomes of SARS-CoV-2 infection in patients exposed to subgroups of immunosuppressants compared to unexposed.

Selective immunosuppressants, TNF inhibitors, or interleukin inhibitors				
	Exposed (n=192)	**Unexposed (n=36,200)**	**Relative risk (95% CI)**	
Outcome	**Events**	**Events**	**Crude**	**Adjusted**
Hospital admission	33	3373	1·84 (1·35 to 2·52)	0·83 (0·51 to 1·34)
ICU admission	6	400	2·83 (1·28 to 6·25)	0·92 (0·23 to 3·71)
Death	5	658	1·43 (0·60 to 3·41)	1·17 (0·38 to 3·62)
Calcineurin inhibitors, other immunosuppressants, hydroxychloroquine, or chloroquine				
	Exposed (n=268)	**Unexposed (n=36,200)**	**Relative risk (95% CI)**	
Outcome	**Events**	**Events**	**Crude**	**Adjusted**
Hospital admission	77	3373	3·08 (2·55 to 3·73)	0·82 (0·60 to 1·12)
ICU admission	16	400	5·40 (3·33 to 8·78)	1·03 (0·43 to 2·49)
Death	17	658	3·49 (2·19 to 5·56)	0·93 (0·47 to 1·85)
Systemic glucocorticoids				
	Exposed (n=136)	**Unexposed (n=36,200)**	**Relative risk (95% CI)**	
Outcome	**Events**	**Events**	**Crude**	**Adjusted**
Hospital admission	83	3373	6·55 (5·71 to 7·52)	1·34 (1·10 to 1·62)
ICU admission	10	400	6·65 (3·64 to 12·18)	1·76 (0·93 to 3·35)
Death	42	658	16·99 (13·07 to 22·09)	2·38 (1·72 to 3·30)

Abbreviations: CI: confidence interval; ICU: intensive care unit; TNF: tumour necrosis factor; NA: not applicable.

Table 4. Relative risk of severe outcomes of SARS-CoV-2 infection in patients exposed to glucocorticoids, by cumulative prednisolone-equivalent dose <2000 mg (moderate) or ≥2000 mg (high).

				Relative risk (95% CI)	
Outcome	**Dose**	**Events/ Exposed**	**Events/ Unexposed**	**Crude**	**Adjusted**
Hospital admission	Moderate	38/69	3373/36200	5·91 (4·76 to 7·33)	1·20 (0·89 to 1·62)
	High	45/67	3373/36200	7·21 (6·08 to 8·55)	1·47 (1·15 to 1·89)
ICU admission	Moderate	5/69	400/36200	6·56 (2·80 to 15·34)	1·92 (0·83 to 4·46)
	High	5/67	400/36200	6·75 (2·89 to 15·78)	1·60 (0·62 to 4·14)
Death	Moderate	18/69	658/36200	14·35 (9·58 to 21·50)	1·83 (1·08 to 3·11)
	High	24/67	658/36200	19·71 (14·18 to 27·39)	2·96 (2·00 to 4·37)

Abbreviations: CI: confidence interval; ICU: intensive care unit.

Table 5. Relative risk of severe outcomes of SARS-CoV-2 infection in current users compared to former users of immunosuppressants.

	Current users (n=527)	Former users (n=177)	Relative risk (95% CI)	
Outcome	**Events**	**Events**	**Crude**	**Adjusted**
Hospital admission	165	43	1·29 (0·96 to 1·72)	1·13 (0·83 to 1·52)
ICU admission	<5	<5	2·80 (0·85 to 9·17)	2·39 (0·71 to 8·11)
Death	57	14	1·37 (0·78 to 2·39)	1·21 (0·68 to 2·15)

Abbreviations: CI: confidence interval; ICU: intensive care unit.

Appendix

Appendix to 'The effect of immunosuppressants on the prognosis of SARS-CoV-2 infection: a nationwide Danish cohort study.'

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Appendix Table 1. Medications studied as exposures and corresponding ATC and procedure codes.

Medication	ATC code	Procedure code
Selective immunosuppressants		
Muromonab-CD3	L04AA02	
Antilymphocyte immunoglobulin (horse)	L04AA03	
Antithymocyte immunoglobulin (rabbit)	L04AA04	BOHJ12
Mycophenolic acid	L04AA06	BOHJ22
Sirolimus	L04AA10	BOHJ23
Leflunomide	L04AA13	
Everolimus	L04AA18	BOHJ24
Natalizumab	L04AA23	BOHJ26
Abatacept	L04AA24	BOHJ18C1
Eculizumab	L04AA25	BWHB84
Belimumab	L04AA26	BOHJ19H6
Fingolimod	L04AA27	BOHJ27
Belatacept	L04AA28	
Tofacitinib	L04AA29	BOHJ28D
Teriflunomide	L04AA31	BOHJ28A
Aprelimast	L04AA32	
Vedolizumab	L04AA33	BOHJ19H4
Alemtuzumab	L04AA34	BOHJ16A
Ocrelizumab	L04AA36	
Baricitinib	L04AA37	
Ozanimod	L04AA38	
Emapalumab	L04AA39	
Cladribine	L04AA40	BWHA178
Imlifidase	L04AA41	
Siponimod	L04AA42	BWHB87
Ravulizumab	L04AA43	
Upadacitinib	L04AA44	
Tumor necrosis factor inhibitors		
Etanercept	L04AB01	BOHJ18A2
Infliximab	L04AB02	BOHJ18A1
Adalimumab	L04AB04	BOHJ18A3
Certolizumab pegol	L04AB05	BOHJ18A5
Golimumab	L04AB06	BOHJ18A4
Interleukin inhibitors		
Basiliximab	L04AC02	
Anakinra	L04AC03	BOHJ18B1
Ustekinumab	L04AC05	BOHJ18B3
Tocilizumab	L04AC07	BOHJ18B2
Canakinumab	L04AC08	BOHJ18B4
Secukinumab	L04AC10	BOHJ18B5
Siltuximab	L04AC11	
Brodalumab	L04AC12	BOHJ18B6
Ixekizumab	L04AC13	
Sarilumab	L04AC14	BOHJ18B9
Guselkumab	L04AC16	
Tildrakizumab	L04AC17	BOHJ18B7
Risankizumab	L04AC18	BOHJ19N1
Calcineurin inhibitors		
Ciclosporin	L04AD01	BOHJ20

Tacrolimus	L04AD02	BOHJ21
Other immunosuppressants		
Azathioprine	L04AX01	BWHB83
Thalidomide	L04AX02	BWHB81
Methotrexate	L04AX03	BWHA115
Lenalidomide	L04AX04	BWHB82
Pirfenidone	L04AX05	BWHB85
Pomalidomide	L04AX06	BWHB86
Dimethyl fumarate	L04AX07	BOHJ28B
Darvadstrocel	L04AX08	
Systemic glucocorticoids	H02AB	
Aminoquinolines		
Chloroquine	P01BA01	
Hydroxychloroquine	P01BA02	
Rituximab	L01XC02	

Abbreviations: ATC; anatomical therapeutic chemicals.

Appendix Table 2. Minimum daily dose of glucocorticoids in exposed persons

Compound	**Equivalent dose**
Cortisone	38 mg
Hydrocortisone	30 mg
Prednisone	7·5 mg
Prednisolone	7·5 mg
Triamcinolone	6 mg
Methylprednisolone	6 mg
Betamethasone	1·2 mg
Dexamethasone	1·2 mg

Appendix Table 3. Covariates for propensity scores.

Variable	Categories/ ATC/ICD codes	Time window prior to prior to cohort entry
Demographics		
Date of birth	Restricted cubic spline with 3 knots	
Sex	Male/female	
Healthcare utilisation		
Hospital admissions and outpatient contacts	0, 1-2, 3-5, 6+	1 year before cohort entry date
Date of SARS-COV-2 testing	Restricted cubic spline with 3 knots	
Co-medications		
Antianaemic drugs	B03	Since 1994
Cardiovascular drugs	C01-10	Since 1994
Antimicrobials	J01-06	Since 1994
Anticoagulants	B01AA	Since 1994
Drugs used in diabetes	A10	Since 1994
Drugs for obstructive airway diseases	R03	Since 1994
Conditions indicating imunnosuppressive therapy		
Neoplasms, blood and blood-forming organs		All since 1994
Paroxysmal nocturnal haemoglobulinuria	DD595	
Sarcoidosis	DD86	
Osteomyelofibrosis (Castleman's disease)	DD474	
Multiple myeloma	DC900	
Neurological and musculoskeletal disease		All since 1994
Seronegative arthritis	DM05	
Seropositive arthritis	DM06	
Psoriatic arthropathy	DM07	
Juvenile idiopathic arthritis	DM08	
Generalized connective tissue diseases	DM30-36	
Spondylopathies	DM45-49	
Diseases of the muscles	DM60-63	
Soft-tissue rheumatism	DM70-79 DG70-73	
Neuromuscular and muscular disease		
Multiple sclerosis	DG35	
Solid organ transplantation		All since 1994
Kidney transplanted	DZ940	
Heart transplanted	DZ941	
Lung transplanted	DZ942	
Heart and lung transplanted	DZ943	
Liver transplanted	DZ944	
Pulmonary disease		All since 1994
Chronic disease of the lower airways	DJ4	
Other interstitial lung disease	DJ84	
Diseases with pus and necrosis in the lower airway	DJ85	
Interstitial lung emphysema	DJ982	
compensatory emphysema	DJ983	
Liver disease	DK7	All since 1994
Kidney disease		All since 1994
Glomerular disease	DN0	
Tubulointerstitial kidney disease and kidney insufficiency	DN1	
Diseases of the gastrointestinal tract		All since 1994
Crohn's disease	DK50	
Ulcerative colitis	DK51	
Cholangitis	DK830	
Skin disease		All since 1994
Hidradenitis suppurativa	DL73.2	
Psoriasis	DL40	
Bullous skin disease	DL10-14	
Dermatitis and eczema	DL20-30	
Alopecia areata	DL63	
Vitiligo	DL80	
Granulomatous disease in the skin and subcutaneous tissue	DL92	
Lupus	DL93	
Other localised connective tissue disease	DL94	
Vasculitis limited to the skin	DL95	
Other comorbidities		
Cardiovascular disease		All since 1994
Ischaemic heart disease	DI2	
Diseases of the endocardium, pericardium and valves	DI3	

Diseases of the endocardium, conductive tissue and cardiac arrest	DI4	
Vascular disease in the brain	DI5	
Heart failure	DI6	
Disease the arteries, arterioles and capillaries	DI7	
Oesophageal varices	DI85	
Abdominal varices	DI864	
Hypertensive liver disease	DI12	
Vascular disease in the bowel	DK550	
Indicators of severity of the underlying disease		
Medications for immune-mediated inflammatory diseases		1 year before cohort entry
Intestinal corticosteroids	A07EA	
Aminosalicylic acid and similar agents	A07EC	
Topical corticosteroids	D07	
Antipsoriatic medications	D05	
Anti-rheumatic therapies, non-steroidals, and combination medications	M01	
Gastrointestinal pathologies		All since 1994
Gingivitis and periodontal disease	DK05	
Inflammation of the oral mucosa and related	DK12	
Stomach and duodenal ulcers	DK25-27	
Fissure and rifts in and around the anus	DK60	
Abscess in and around the anus	DK61	
Other diseases of the rectum and anus	DK62	
Other bowel disease	DK63	
Procedures on the skin, GI tract, or joints		1 year before cohort entry
Ultraviolet therapy: UV-A with psoralen/broad-spectrum UVB / narrow-spectrum UVB	BNGA1-3	
Operations on the skin or subcutaneous tissue	KQ	
Drainage of pelvic abscess to the rectum	KJAJ	
Lysis of adhesions in the abdominal cavity	KJAP	
Operations of the small intestine and colon	KJF	
Operations on the rectum	KJG	
Operations on the anus and perianal tissue	KJH	
Closure of intestinovaginal fistula with graft or flap	KLEE30	
Closure of vesicointestinal fistula	KKCH30	
Endoscopy of the gastro-intestinal tract	KUJ	
Shoulder and upper arm		
Primary insertion of joint prosthesis	KNBB	
Secondary insertion of joint prosthesis	KNBC	
Operations on the joint capsule and ligaments	KNBE	
Operations of the synovia and joint surface	KNBF	
Joint resections, arthroplasties, and arthrodesis	KNBG	
Excision of bursa	KBM79	
Elbow and lower arm		
Primary insertion of joint prosthesis	KNCB	
Secondary insertion of joint prosthesis	KNCC	
Operations on the joint capsule and ligaments	KNCE	
Operations of the synovia and joint surface	KNCF	
Joint resections, arthroplasties, and arthrodesis	KNCG	
Excision of bursa	KNCM79	
Wrist and hand		
Primary insertion of joint prosthesis	KNDB	
Secondary insertion of joint prosthesis	KNDC	
Operations on the joint capsule and ligaments	KNDE	
Operations of the synovia and joint surface	KNDF	
Joint resections, arthroplasties, and arthrodesis	KNDG	
Operations on the fascia, tendon sheaths, ganglia and bursae	KNDM	
Hip and thigh		
Primary insertion of joint prosthesis	KNFB	
Secondary insertion of joint prosthesis	KNFC	
Operations on the joint capsule and ligaments	KNFE	
Operations of the synovia and joint surface	KNFF	
Joint resections, arthroplasties, and arthrodesis	KNFG	
Excision of bursa	KNFM79	
Knee and lower leg		
Primary insertion of joint prosthesis	KNGB	
Secondary insertion of joint prosthesis	KNGC	
Operations on the joint capsule and ligaments	KNGE	
Operations of the synovia and joint surface	KNGF	

Joint resections, arthroplasties, and arthrodesis	KNGG	
Excision of bursae	KNGM79	
Ankle and foot		
Primary insertion of joint prosthesis	KNHB	
Secondary insertion of joint prosthesis	KNHC	
Operations on the joint capsule and ligaments	KNHE	
Operations of the synovia and joint surface	KNHF	
Joint resections, arthroplasties, and arthrodesis	KNHG	
Operations on the fascia, tendon sheaths, ganglia and bursae	KNHM	
Therapeutic steroid injection in the joints and soft tissues	BLHN0	

Abbreviations: ATC; anatomical therapeutic chemicals, ICD: international classifications of diseases. Each cell with a heading in bold represents one variable, comprising the diseases or medications listed below, with corresponding ICD/ATC codes.

Appendix Table 4. Relative risk of severe outcomes of SARS-CoV-2 infection for patients exposed to immunosuppressants compared to unexposed patients, with crude, inverse probability of treatment weighting (IPTW) and matching weights models, with further adjustment for antianaemic drugs.

Outcome	Events/ Exposed	Risk % (95% CI)	Events/ Unexposed	Risk % (95% CI)	Risk difference % (95% CI)	Relative risk (95% CI)	Relative risk adjusted for antianaemics (95% CI)
Crude							
Death	57/527	10·8 (8·2 to 13·5)	658/36200	1·8 (1·7 to 2·0)	9·0 (6·3-11·7)	5·95 (4·60-7·69)	2·46 (1·83-3·30)
ICU admission	25/527	4·7 (2·9 to 6·6)	400/36200	1·1 (1·0 to 1·2)	3·6 (1·8-5·5)	4·29 (2·89-6·37)	3·00 (1·91-4·72)
Admission	165/527	31·3 (27·3 to 35·3)	3373/36200	9·3 (9·0 to 9·6)	22·0 (18·0-26·0)	3·36 (2·95-3·83)	1·93 (1·67-2·23)
IPTW							
Death	29/273	10·7 (4·2 to 17·2)	606/22570	2·7 (2·5 to 2·9)	8·0 (1·5-14·5)	3·99 (2·17-7·35)	1·98 (1·06-3·68)
ICU admission	4/273	1·5 (0·2 to 2·8)	362/22570	1·6 (1·4 to 1·8)	-0·1 (-1·4-1·2)	0·93 (0·40-2·18)	0·73 (0·30-1·74)
Admission	60/273	22·0 (11·5 to 32·5)	2981/22570	13·2 (12·8 to 13·7)	8·8 (-1·7-19·3)	1·67 (1·03-2·69)	1·11 (0·69-1·80)
Matching weights							
Death	32/346	9·2 (6·2 to 12·3)	20/339	5·9 (5·2 to 6·7)	3·3 (0·2-6·5)	1·56 (1·10-2·22)	1·71 (1·11-2·65)
ICU admission	13/346	3·8 (1·8 to 5·8)	11/339	3·2 (2·7 to 3·8)	0·5 (-1·6-2·6)	1·16 (0·66-2·03)	1·40 (0·74-2·66)
Admission	100/346	28·9 (24·1 to 33·7)	87/339	25·5 (24·2 to 26·8)	3·4 (-1·6-8·3)	1·13 (0·95-1·35)	1·25 (1·01-1·55)

Abbreviations: ICU; intensive care unit. Numbers of exposed and unexposed in the propensity score weighted dataset are weighted subjects and do not refer to individual subjects.

Appendix Table 5. Relative risk of severe outcomes of SARS-CoV-2 infection for patients exposed to selective immunosuppressants, TNF inhibitors, or interleukin inhibitors compared to unexposed patients, with crude, inverse probability of treatment weighting (IPTW) and matching weights models, with further adjustment for antianaemic drugs.

Outcome	Events/ Exposed	Risk % (95%CI)	Events/ Unexposed	Risk % (95% CI)	Risk difference % (95% CI)	Relative risk (95% CI)	Relative risk adjusted for antianaemics (95% CI)
Crude							
Death	5/192	2·6 (0·3 to 4·9)	658/36200	1·8 (1·7 to 2·0)	0·8 (-1·5 to 3·0)	1·43 (0·60 to 3·41)	0·58 (0·24 to 1·39)
ICU admission	6/192	3·1 (0·7 to 5·6)	400/36200	1·1 (1·0 to 1·2)	2·0 (-0·4 to 4·5)	2·83 (1·28 to 6·25)	1·88 (0·83 to 4·27)
Admission	33/192	17·2 (11·8 to 22·5)	3373/36200	9·3 (9·0 to 9·6)	7·9 (2·5 to 13·2)	1·84 (1·35 to 2·52)	1·07 (0·79 to 1·47)
IPTW							
Death	0/46	0·7 (to 0·2 to 1·6)	280/8468	3·3 (2·9 to 3·7)	-2·6 (-3·6 to -1·6)	0·22 (0·06 to 0·76)	0·15 (0·04 to 0·50)
ICU admission	0/46	0·4 (to 0·2 to 1·1)	183/8468	2·2 (1·9 to 2·5)	-1·7 (-2·4 to -1·0)	0·20 (0·05 to 0·88)	0·17 (0·04 to 0·74)
Hospital admission	13/46	27·6 (0·9 to 54·2)	1479/8468	17·5 (16·7 to 18·3)	10·1 (-16·4 to 36·6)	1·58 (0·60 to 4·14)	1·23 (0·49 to 3·08)
Matching weights							
Death	-	-	-	-	-	1·17 (0·38 to 3·62)	0·83 (0·22 to 3·10)
ICU admission	-	-	-	-	-	0·92 (0·23 to 3·71)	1·32 (0·25 to 6·93)
Hospital admission	14/87	16·1 (8·3 to 23·9)	18/91	19·5 (18·0 to 21·0)	-3·4 (-11·3 to 4·5)	0·83 (0·51 to 1·34)	0·76 (0·43 to 1·34)

Abbreviations: ICU; intensive care unit. Numbers of exposed and unexposed in the propensity score weighted dataset are weighted subjects and do not refer to individual subjects.

Appendix Table 6. Relative risk of severe outcomes of SARS-CoV-2 infection for patients exposed to calcineurin inhibitors, other immunosuppressants, hydroxychloroquine or chloroquine compared to unexposed patients, with crude, inverse probability of treatment weighting (IPTW) and matching weights models, with further adjustment for antianaemic drugs.

Outcome	Events/ Exposed	Risk % (95%CI)	Events/ Unexposed	Risk % (95% CI)	Risk difference % (95% CI)	Relative risk (95% CI)	Relative risk adjusted for antianaemics (95% CI)
Crude							
Death	17/268	6·3 (3·4 to 9·3)	658/36200	1·8 (1·7 to 2·0)	4·5 (1·6 to 7·4)	3·49 (2·19 to 5·56)	1·15 (0·71 to 1·86)
ICU admission	16/268	6·0 (3·1 to 8·8)	400/36200	1·1 (1·0 to 1·2)	4·9 (2·0 to 7·7)	5·40 (3·33 to 8·78)	3·32 (1·91 to 5·77)
Admission	77/268	28·7 (23·3 to 34·2)	3373/36200	9·3 (9·0 to 9·6)	19·4 (14·0-24·8)	3·08 (2·55 to 3·73)	1·57 (1·29 to 1·91)
IPTW							
Death	8/161	4·9 (to 2·0 to 11·9)	599/23922	2·5 (2·3 to 2·7)	2·4 (-4·5 to 9·3)	1·96 (0·48 to 8·06)	0·86 (0·22 to 3·45)
ICU admission	2/161	1·2 (to 0·2 to 2·6)	368/23922	1·5 (1·4 to 1·7)	-0·3 (-1·7 to 1·0)	0·78 (0·25 to 2·44)	0·57 (0·18 to 1·82)
Admission	16/161	10·1 (2·6 to 17·7)	3044/23922	12·7 (12·3 to 13·1)	-2·6 (-10·1 to 4·9)	0·79 (0·38 to 1·67)	0·52 (0·25 to 1·07)
Matching weights							
Death	8/171	4·7 (1·5 to 7·9)	9/170	5·0 (4·4 to 5·7)	-0·4 (-3·6 to 2·9)	0·93 (0·47 to 1·85)	0·75 (0·28 to 1·99)
ICU admission	5/171	2·9 (0·4 to 5·5)	5/170	2·8 (2·4 to 3·3)	0·1 (-2·5 to 2·7)	1·03 (0·43 to 2·49)	1·48 (0·46 to 4·75)
Admission	33/171	19·3 (13·4 to 25·2)	40/170	23·5 (22·3 to 24·7)	-4·2 (-10·2 to 1·8)	0·82 (0·60 to 1·12)	0·75 (0·49 to 1·14)

Abbreviations: ICU; intensive care unit. Numbers of exposed and unexposed in the propensity score weighted dataset are weighted subjects and do not refer to individual subjects.

Appendix Table 7. Relative risk of severe outcomes of SARS-CoV-2 infection for patients exposed to systemic glucocorticoids compared to unexposed patients, with crude, inverse probability of treatment weighting (IPTW) and matching weights models, with further adjustment for antianaemic drugs.

Outcome	Events/ Exposed	Risk % (95%CI)	Events/ Unexposed	Risk % (95% CI)	Risk difference % (95% CI)	Relative risk (95% CI)	Relative risk adjusted for antianaemics (95% CI)
Crude							
Death	42/136	30·9 (23·1 to 38·7)	658/36200	1·8 (1·7 to 2·0)	29·1 (21·3 to 36·8)	16·99 (13·07 to 22·09)	8·33 (6·44 to 10·78)
ICU admission	10/136	7·4 (3·0 to 11·8)	400/36200	1·1 (1·0 to 1·2)	6·2 (1·9 to 10·6)	6·65 (3·64 to 12·18)	5·34 (2·90 to 9·86)
Hospital admission	83/136	61·0 (52·8 to 69·3)	3373/36200	9·3 (9·0 to 9·6)	51·7 (43·5 to 59·9)	6·55 (5·71 to 7·52)	3·78 (3·32 to 4·30)
IPTW							
Death	5/70	7·6 (2·0 to 13·1)	565/18196	3·1 (2·8 to 3·4)	4·5 (-1·0 to 10·0)	2·45 (1·18 to 5·08)	2·07 (1·06 to 4·05)
ICU admission	2/70	2·2 (to 0·2 to 4·6)	362/18196	2·0 (1·8 to 2·2)	0·2 (-2·1 to 2·6)	1·12 (0·38 to 3·28)	1·08 (0·37 to 3·09)
Hospital admission	25/70	35·4 (7·9 to 62·9)	2911/18196	16·0 (15·5 to 16·5)	19·4 (-7·9 to 46·7)	2·21 (1·02 to 4·79)	1·96 (0·97 to 3·96)
Matching weights							
Death	28/94	29·8 (20·5 to 39·1)	11/85	12·5 (11·2 to 13·8)	17·3 (7·9 to 26·6)	2·38 (1·72 to 3·30)	2·36 (1·69 to 3·28)
ICU admission	9/94	9·6 (3·6 to 15·6)	5/85	5·4 (4·6 to 6·3)	4·1 (-1·9 to 10·2)	1·76 (0·93 to 3·35)	1·75 (0·92 to 3·32)
Hospital admission	50/94	53·2 (43·1 to 63·3)	34/85	39·8 (38·1 to 41·5)	13·4 (3·2 to 23·6)	1·34 (1·10 to 1·62)	1·34 (1·10 to 1·64)

Abbreviations: ICU; intensive care unit. Numbers of exposed and unexposed in the propensity score weighted dataset are weighted subjects and do not refer to individual subjects.

Appendix Table 8. Relative risk of severe outcomes of SARS-CoV-2 infection in patients exposed to cumulative dose <2000mg (moderate dose) or ≥2000mg (high dose) compared to unexposed patients, with crude, inverse probability of treatment weighting (IPTW) and matching weights models, with further adjustment for antianaemic drugs.

Outcome	Events/ Exposed	Risk % (95%CI)	Events/ Unexposed	Risk % (95% CI)	Risk difference % (95% CI)	Relative risk (95% CI)	Relative risk adjusted for antianaemics (95%CI)
Crude							
Death							
Moderate dose	18/69	26·1 (15·7 to 36·5)	658/36200	1·8 (1·7 to 2·0)	24·3 (13·9 to 34·6)	14·35 (9·58 to 21·50)	1·70 (1·16 to 2·49)
High dose	24/67	35·8 (24·3 to 47·4)	658/36200	1·8 (1·7 to 2·0)	34·0 (22·5 to 45·5)	19·71 (14·18 to 27·39)	4·79 (· to ·)
ICU admission							
Moderate dose	5/69	7·2 (1·1 to 13·4)	400/36200	1·1 (1·0 to 1·2)	6·1 (0·0 to 12·3)	6·56 (2·80 to 15·34)	5·41 (2·31 to 12·68)
High dose	5/67	7·5 (1·1 to 13·8)	400/36200	1·1 (1·0 to 1·2)	6·4 (0·1 to 12·7)	6·75 (2·89 to 15·78)	5·28 (2·26 to 12·36)
Hospital admission							
Moderate dose	38/69	55·1 (43·2 to 66·9)	3373/36200	9·3 (9·0 to 9·6)	45·8 (34·0 to 57·5)	5·91 (4·76 to 7·33)	3·77 (3·16 to 4·50)
High dose	45/67	67·2 (55·8 to 78·5)	3373/36200	9·3 (9·0 to 9·6)	57·8 (46·6 to 69·1)	7·21 (6·08 to 8·55)	3·79 (3·23 to 4·44)
IPTW							
Death							
Moderate dose	2/39	6·0 (to 0·5 to 12·5)	565/18196	3·1 (2·8 to 3·4)	2·9 (-3·5 to 9·3)	1·93 (0·66 to 5·64)	1·98 (0·73 to 5·39)
High dose	3/31	9·6 (to 0·5 to 19·7)	565/18196	3·1 (2·8 to 3·4)	6·5 (-3·5 to 16·4)	3·09 (1·09 to 8·76)	2·15 (0·87 to 5·28)
ICU admission							
Moderate dose	1/39	2·9 (to 1·2 to 7·1)	362/18196	2·0 (1·8 to 2·2)	1·0 (-3·1 to 5·0)	1·48 (0·37 to 5·91)	1·48 (0·38 to 5·81)
High dose	0/31	1·4 (to 0·5 to 3·2)	362/18196	2·0 (1·8 to 2·2)	-0·6 (-2·5 to 1·2)	0·68 (0·18 to 2·63)	0·62 (0·17 to 2·29)
Hospital admission							
Moderate dose	17/39	44·2 (5·7 to 82·6)	2911/18196	16·0 (15·5 to 16·5)	28·2 (-9·9 to 66·2)	2·76 (1·16 to 6·54)	1·87 (· to ·)
High dose	8/31	24·5 (0·1 to 48·9)	2911/18196	16·0 (15·5 to 16·5)	8·5 (-15·6 to 32·6)	1·53 (0·57 to 4·10)	0·53 (0·21 to 1·30)
Matching weights							
Death							
Moderate dose	11/48	22·9 (10·9 to 34·9)	11/85	12·5 (11·2 to 13·8)	10·4 (-1·5 to 22·4)	1·83 (1·08 to 3·11)	1·84 (1·08 to 3·13)
High dose	17/46	37·0 (22·9 to 51·1)	11/85	12·5 (11·2 to 13·8)	24·5 (10·4 to 38·5)	2·96 (2·00 to 4·37)	2·91 (1·92 to 4·39)
ICU admission							
Moderate dose	5/48	10·4 (1·7 to 19·1)	5/85	5·4 (4·6 to 6·3)	5·0 (-3·7 to 13·7)	1·92 (0·83 to 4·46)	1·92 (0·82 to 4·46)
High dose	4/46	8·7 (0·5 to 16·9)	5/85	5·4 (4·6 to 6·3)	3·3 (-4·9 to 11·5)	1·60 (0·62 to 4·14)	1·58 (0·62 to 4·04)
Hospital admission							
Moderate dose	23/48	47·9 (33·6 to 62·2)	34/85	39·8 (38·1 to 41·5)	8·1 (-6·1 to 22·3)	1·20 (0·89 to 1·62)	1·21 (0·90 to 1·63)
High dose	27/46	58·7 (44·3 to 73·1)	34/85	39·8 (38·1 to 41·5)	18·9 (4·6 to 33·2)	1·47 (1·15 to 1·89)	1·50 (1·16 to 1·94)

Abbreviations: ICU; intensive care unit. Numbers of exposed and unexposed in the propensity score weighted dataset are weighted subjects and do not refer to individual subjects.

Appendix Table 9. Relative risk of severe outcomes of SARS-CoV-2 infection in current users versus former users of immunosuppressants, with crude, inverse probability of treatment weighting (IPTW) and matching weights models, with further adjustment for antianaemic drugs.

Outcome	Events/ Exposed	Risk % (95%CI)	Events/ Unexposed	Risk % (95% CI)	Risk difference % (95% CI)	Relative risk (95% CI)	Relative risk adjusted for antianaemics (95%CI)
Crude							
Death	57/527	10·8 (8·2 to 13·5)	14/177	7·9 (3·9 to 11·9)	2·9 (-1·9 to 7·7)	1·37 (0·78 to 2·39)	1·37 (0·79 to 2·40)
ICU admission	-	-	-	-	-	2·80 (0·85 to 9·17)	2·81 (0·86 to 9·17)
Admission	165/527	31·3 (27·3 to 35·3)	43/177	24·3 (18·0 to 30·6)	7·0 (-0·4 to 14·5)	1·29 (0·96 to 1·72)	1·30 (0·97 to 1·74)
IPTW							
Death	55/509	10·8 (8·1 to 13·4)	16/171	9·6 (4·6 to 14·6)	1·2 (-4·5 to 6·9)	1·12 (0·63 to 2·00)	1·12 (0·63 to 2·00)
ICU admission	23/509	4·5 (2·7 to 6·3)	4/171	2·5 (-0·4 to 5·5)	1·9 (-1·5 to 5·4)	1·76 (0·52 to 5·96)	1·76 (0·52 to 5·94)
Hospital admission	155/509	30·4 (26·4 to 34·4)	52/171	30·4 (22·5 to 38·3)	-0·0 (-8·8 to 8·8)	1·00 (0·75 to 1·34)	1·01 (0·75 to 1·35)
Matching weights							
Death	17/168	10·2 (7·3 to 13·1)	14/166	8·4 (4·2 to 12·7)	1·8 (-3·3 to 6·9)	1·21 (0·68 to 2·15)	1·22 (0·69 to 2·16)
ICU admission	-	-	-	-	-	2·39 (0·71 to 8·11)	2·39 (0·71 to 8·08)
Hospital admission	48/168	28·5 (24·2 to 32·8)	42/166	25·3 (18·7 to 31·9)	3·2 (-4·7 to 11·1)	1·13 (0·83 to 1·52)	1·12 (0·83 to 1·53)

Abbreviations: ICU; intensive care unit. Numbers of exposed and unexposed in the propensity score weighted dataset are weighted subjects and do not refer to individual subjects.

Appendix Table 10. Relative risk of severe outcomes of SARS-CoV-2 infection in patients admitted to hospital with COVID-19 exposed to immunosuppressants, compared to unexposed patients, with crude, inverse probability of treatment weighting (IPTW) and matching weights models, with further adjustment for antianaemic drugs.

Outcome	Events/ Exposed	Risk % (95%CI)	Events/ Unexposed	Risk % (95% CI)	Risk difference % (95% CI)	Relative risk (95% CI)	Relative risk adjusted for antianaemics (95% CI)
Crude							
Death	42/165	25·5 (18·8 to 32·1)	467/3373	13·8 (12·7 to 15·0)	11·6 (4·9 to 18·4)	1·84 (1·40 to 2·42)	1·48 (1·11 to 1·97)
ICU admission	19/165	11·5 (6·6 to 16·4)	387/3373	11·5 (10·4 to 12·5)	0·0 (-4·9 to 5·0)	1·00 (0·65 to 1·55)	1·05 (0·68 to 1·62)
IPTW							
Death	43/116	37·3 (19·4 to 55·3)	372/2180	17·1 (15·5 to 18·6)	20·3 (2·3 to 38·3)	2·19 (1·34 to 3·57)	2·13 (1·33 to 3·38)
ICU admission	10/116	8·4 (1·0 to 15·8)	259/2180	11·9 (10·5 to 13·2)	-3·5 (-11·0 to 4·0)	0·71 (0·29 to 1·72)	0·71 (0·29 to 1·72)
Matching weights							
Death	32/120	26·7 (18·7 to 34·6)	25/122	20·4 (17·4 to 23·5)	6·2 (-2·2 to 14·7)	1·30 (0·94 to 1·82)	1·31 (0·94 to 1·82)
ICU admission	12/120	10·0 (4·6 to 15·4)	14/122	11·3 (9·2 to 13·4)	-1·3 (-7·0 to 4·5)	0·89 (0·50 to 1·56)	0·88 (0·50 to 1·55)

Abbreviations: ICU; intensive care unit. Numbers of exposed and unexposed in the propensity score weighted dataset are weighted subjects and do not refer to individual subjects.

Appendix Table 11. Relative risk of severe outcomes of SARS-CoV-2 infection in patients exposed to immunosuppressants, 26 February–20 April, with crude, inverse probability of treatment weighting (IPTW) and matching weights models, with further adjustment for antianaemic drugs.

Outcome	Events/ Exposed	Risk % (95%CI)	Events/ Unexposed	Risk % (95% CI)	Risk difference % (95% CI)	Relative risk (95% CI)	Relative risk adjusted for antianaemics (95% CI)
Crude							
Death	34/199	17·1 (11·8 to 22·3)	439/7794	5·6 (5·1 to 6·1)	11·5 (6·2 to 16·7)	3·03 (2·20 to 4·17)	1·61 (1·13 to 2·29)
ICU admission	13/199	6·5 (3·1 to 10·0)	288/7794	3·7 (3·3 to 4·1)	2·8 (-0·6 to 6·3)	1·77 (1·03 to 3·03)	1·48 (0·83 to 2·62)
Admission	94/199	47·2 (40·3 to 54·2)	1951/7794	25·0 (24·1 to 26·0)	22·2 (15·2 to 29·2)	1·89 (1·62 to 2·20)	1·37 (1·17 to 1·62)
IPTW							
Death	29/106	27·5 (9·1 to 45·9)	420/6258	6·7 (6·1 to 7·3)	20·8 (2·5 to 39·1)	4·10 (2·09 to 8·03)	2·90 (1·47 to 5·73)
ICU admission	2/106	1·7 (0·2 to 3·3)	263/6258	4·2 (3·7 to 4·7)	-2·5 (-4·1 to -0·9)	0·41 (0·16 to 1·02)	0·39 (0·16 to 0·96)
Admission	42/106	39·8 (24·2 to 55·5)	1793/6258	28·6 (27·5 to 29·8)	11·2 (-4·5 to 26·8)	1·39 (0·94 to 2·06)	1·21 (0·84 to 1·75)
Matching weights							
Death	21/136	15·4 (9·3 to 21·5)	19/134	14·5 (12·2 to 16·8)	0·9 (-5·6 to 7·4)	1·06 (0·70 to 1·63)	1·08 (0·69 to 1·68)
ICU admission	6/136	4·4 (0·9 to 7·9)	9/134	6·8 (5·3 to 8·3)	-2·4 (-6·1 to 1·4)	0·65 (0·29 to 1·46)	0·67 (0·29 to 1·52)
Admission	64/136	47·1 (38·6 to 55·5)	63/134	47·4 (44·5 to 50·4)	-0·4 (-9·3 to 8·5)	0·99 (0·82 to 1·20)	1·00 (0·82 to 1·22)

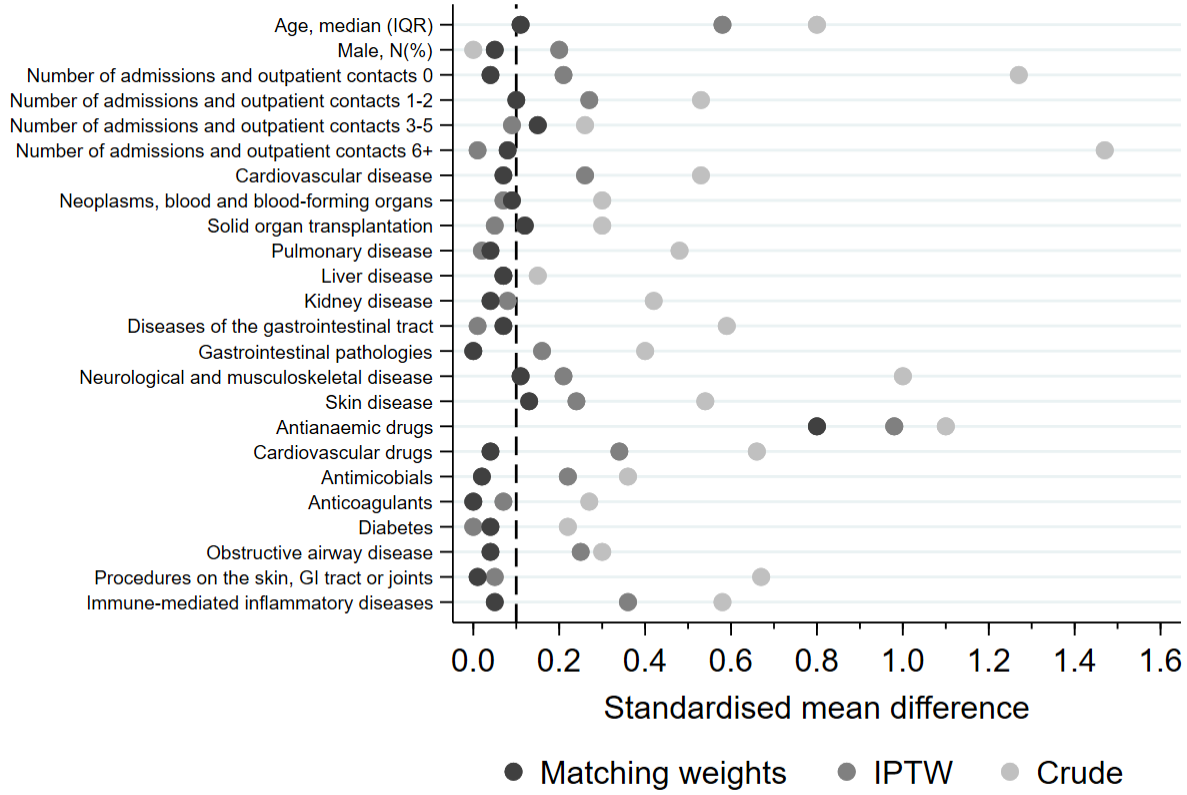
Abbreviations: ICU; intensive care unit. Numbers of exposed and unexposed in the propensity score weighted dataset are weighted subjects and do not refer to individual subjects.

Appendix Table 12. Relative risk of severe outcomes of SARS-CoV-2 infection in patients exposed to immunosuppressants, 21 April–18 October, with crude, inverse probability of treatment weighting (IPTW) and matching weights models, with further adjustment for antianaemic drugs.

Outcome	Events/ Exposed	Risk % (95%CI)	Events/ Unexposed	Risk % (95% CI)	Risk difference % (95% CI)	Relative risk (95% CI)	Relative risk adjusted for antianaemics (95% CI)
Crude							
Death	23/328	7·0 (4·2 to 9·8)	219/28406	0·8 (0·7 to 0·9)	6·2 (3·5 to 9·0)	9·10 (6·00 to 13·78)	3·32 (2·02 to 5·45)
ICU admission	12/328	3·7 (1·6 to 5·7)	112/28406	0·4 (0·3 to 0·5)	3·3 (1·2 to 5·3)	9·28 (5·17 to 16·66)	6·19 (2·91 to 13·17)
Hospital admission	71/328	21·6 (17·2 to 26·1)	1422/28406	5·0 (4·8 to 5·3)	16·6 (12·2 to 21·1)	4·32 (3·50 to 5·35)	2·26 (1·78 to 2·87)
IPTW							
Death	13/146	8·8 (1·3 to 16·3)	198/18300	1·1 (0·9 to 1·2)	7·7 (0·3 to 15·2)	8·13 (3·44 to 19·19)	6·32 (2·79 to 14·28)
ICU admission	5/146	3·1 (to 0·5 to 6·7)	98/18300	0·5 (0·4 to 0·6)	2·6 (-1·1 to 6·2)	5·76 (1·75 to 18·92)	5·43 (1·65 to 17·89)
Hospital admission	25/146	17·2 (6·9 to 27·5)	1226/18300	6·7 (6·3 to 7·1)	10·5 (0·2 to 20·8)	2·57 (1·41 to 4·68)	2·27 (1·30 to 3·96)
Matching weights							
Death	15/183	8·2 (4·2 to 12·2)	6/178	3·1 (2·4 to 3·9)	5·1 (1·0 to 9·1)	2·60 (1·52 to 4·46)	2·64 (1·51 to 4·64)
ICU admission	-	-	-	-	-	3·23 (1·50 to 6·98)	3·41 (1·56 to 7·43)
Hospital admission	39/183	21·3 (15·4 to 27·3)	28/178	15·9 (14·4 to 17·3)	5·5 (-0·6 to 11·6)	1·34 (1·00 to 1·80)	1·42 (1·05 to 1·92)

Abbreviations: ICU; intensive care unit. Numbers of exposed and unexposed in the propensity score weighted dataset are weighted subjects and do not refer to individual subjects.

Appendix Figure 1. Standardised mean differences of covariates with unadjusted (crude), inverse probability of treatment weighting and matching weights models, for patients exposed to immunosuppressants compared to unexposed.



Abbreviations: IPTW: inverse probability of treatment weighting.

Appendix Table 13. Characteristics of SARS-CoV-2 PCR test positive patients in Denmark 26 February–18 October 2020, by exposure to immunosuppressants, and with inverse probability of treatment weighting (IPTW) and matching weights propensity score models.

Characteristics	Unadjusted			Adjusted with IPTW			Adjusted with matching weights		
	Exposed (n=527)	Unexposed (n=36,200)	SMD	Exposed (n=273)	Unexposed (n=22,570)	SMD	Exposed (n=346)	Unexposed (n=339)	SMD
Age, median (IQR)	57 (42-73)	39 (23-55)	0·80	57 (41-77)	47 (29-60)	0·58	57 (43-74)	56 (41-71)	0·11
Male, N (%)	256 (48·6)	17,544 (48·5)	0·00	104 (38·1)	10,810 (47·9)	0·20	149 (43·1)	154 (45·4)	0·05
Number of admissions and outpatient contacts	**N (%)**	**N (%)**		**N (%)**	**N (%)**		**N (%)**	**N (%)**	
0	20 (3·8)	18,787 (51·9)	1·27	92 (33·7)	5,449 (24·1)	0·21	14 (4·0)	11 (3·4)	0·04
1-2	38 (7·2)	9,574 (26·4)	0·53	80 (29·4)	9,474 (42·0)	0·27	36 (10·4)	47 (13·8)	0·10
3-5	113 (21·4)	4,264 (11·8)	0·26	61 (22·4)	4,243 (18·8)	0·09	107 (30·9)	82 (24·2)	0·15
6+	356 (67·6)	3,575 (9·9)	1·47	40 (14·6)	3,404 (15·1)	0·01	189 (54·6)	199 (58·7)	0·08
Diagnoses	**N (%)**	**N (%)**		**N (%)**	**N (%)**		**N (%)**	**N (%)**	
Cardiovascular disease	176 (33·4)	4,269 (11·8)	0·53	73 (26·7)	3,601 (16·0)	0·26	111 (32·1)	98 (29·0)	0·07
Neoplasms, blood and blood-forming organs	27 (5·1)	101 (0·3)	0·30	0 (0·0)	71 (0·3)	0·07	1 (0·3)	(n<5)	0·09
Solid organ transplantation	24 (4·6)	27 (0·1)	0·30	0 (0·1)	(n<5)	0·05	(n<5)	0 (0·0)	0·12
Pulmonary disease	131 (24·9)	2,742 (7·6)	0·48	31 (11·3)	2,435 (10·8)	0·02	73 (21·1)	66 (19·6)	0·04
Liver disease	15 (2·8)	302 (0·8)	0·15	5 (1·9)	253 (1·1)	0·07	11 (3·2)	7 (2·0)	0·07
Kidney disease	76 (14·4)	1,049 (2·9)	0·42	15 (5·5)	856 (3·8)	0·08	34 (9·8)	30 (8·8)	0·04
Diseases of the gastrointestinal tract	91 (17·3)	365 (1·0)	0·59	(n<5)	257 (1·1)	0·01	17 (4·9)	12 (3·4)	0·07
Gastrointestinal pathologies	94 (17·8)	1,934 (5·3)	0·40	10 (3·6)	1,616 (7·2)	0·16	43 (12·4)	43 (12·5)	0·00
Neurological and musculoskeletal disease	353 (67·0)	8,101 (22·4)	1·00	123 (45·1)	7,896 (35·0)	0·21	231 (66·8)	209 (61·7)	0·11
Skin disease	112 (21·3)	1,399 (3·9)	0·54	33 (12·3)	1,244 (5·5)	0·24	51 (14·7)	35 (10·3)	0·13
Medications	**N (%)**	**N (%)**		**N (%)**	**N (%)**		**N (%)**	**N (%)**	
Antianaemic drugs	276 (52·4)	2,946 (8·1)	1·10	139 (51·0)	2,341 (10·4)	0·98	185 (53·5)	61 (18·0)	0·80
Cardiovascular drugs	370 (70·2)	14,144 (39·1)	0·66	178 (65·2)	10,921 (48·4)	0·34	235 (67·9)	224 (66·2)	0·04
Antimicrobials	515 (97·7)	32,201 (89·0)	0·36	267 (98·0)	21,136 (93·6)	0·22	335 (96·8)	329 (97·1)	0·02
Anticoagulants	39 (7·4)	633 (1·7)	0·27	(n<5)	551 (2·4)	0·07	19 (5·5)	19 (5·5)	0·00
Diabetes	65 (12·3)	2,211 (6·1)	0·22	22 (8·0)	1,779 (7·9)	0·00	44 (12·7)	39 (11·4)	0·04
Obstructive airway disease	212 (40·2)	9,502 (26·2)	0·30	111 (40·7)	6,483 (28·7)	0·25	135 (39·0)	126 (37·1)	0·04
Proxies for IMID severity	**N (%)**	**N (%)**		**N (%)**	**N (%)**		**N (%)**	**N (%)**	
Procedures on the skin, GI tract or joints	162 (30·7)	2,239 (6·2)	0·67	22 (7·9)	2,131 (9·4)	0·05	82 (23·7)	78 (23·1)	0·01
Immune-mediated inflammatory disease drugs	252 (47·8)	7,651 (21·1)	0·58	124 (45·4)	6,384 (28·3)	0·36	156 (45·1)	144 (42·6)	0·05

Abbreviations: IMID; immune mediated inflammatory diseases.

Appendix Table 14. Characteristics of SARS-CoV-2 PCR test positive patients in Denmark 26 February–18 October 2020, by exposure to selective immunosuppressants, TNF inhibitors, interleukin inhibitors, with inverse probability of treatment weighting (IPTW) and matching weights propensity score models.

Characteristics	Unadjusted			Adjusted with IPTW			Adjusted with matching weights		
	Exposed (n=192)	Unexposed (n=36,200)	SMD	Exposed (n=46)	Unexposed (n=8468)	SMD	Exposed (n=87)	Unexposed (n=91)	SMD
Age, median (IQR)	48 (33-58)	39 (23-55)	0·34	55 (29-61)	47 (30-61)	0·20	52 (40-62)	47 (32-59)	0·23
Male, N (%)	96 (50·0)	17,544 (48·5)	0·03	17 (37·5)	3,812 (45·0)	0·15	34 (39·1)	38 (42·0)	0·06
Number of admissions and outpatient contacts	**N (%)**	**N (%)**		**N (%)**	**N (%)**		**N (%)**	**N (%)**	
0	n<5	18,787 (51·9)	1·47	n<5	36 (0·4)	0·09	n<5	0 (0·1)	0·04
1-2	n<5	9,574 (26·4)	0·79	6 (12·0)	1,405 (16·6)	0·13	n<5	(n<5)	0·11
3-5	29 (15·1)	4,264 (11·8)	0·10	27 (59·1)	3,732 (44·1)	0·30	26 (29·9)	16 (17·8)	0·29
6+	161 (83·9)	3,575 (9·9)	2·21	13 (28·8)	3,295 (38·9)	0·21	60 (69·0)	72 (79·5)	0·24
Diagnoses	**N (%)**	**N (%)**		**N (%)**	**N (%)**		**N (%)**	**N (%)**	
Cardiovascular disease	42 (21·9)	4,269 (11·8)	0·27	20 (43·3)	1,750 (20·7)	0·50	25 (28·7)	18 (19·6)	0·21
Neoplasms, blood and blood-forming organs	5 (2·6)	101 (0·3)	0·20	1 (1·3)	50 (0·6)	0·07	n<5	n<5	0·13
Solid organ transplantation	13 (6·8)	27 (0·1)	0·37	0 (0·5)	5 (0·1)	0·09	n<5	0 (0·1)	0·20
Pulmonary disease	37 (19·3)	2,742 (7·6)	0·35	10 (22·4)	1,112 (13·1)	0·24	13 (14·9)	14 (15·8)	0·02
Liver disease	6 (3·1)	302 (0·8)	0·17	0 (0·8)	157 (1·8)	0·09	n<5	n<5	0·10
Kidney disease	23 (12·0)	1,049 (2·9)	0·35	9 (19·1)	534 (6·3)	0·39	8 (9·2)	7 (7·7)	0·06
Diseases of the gastrointestinal tract	59 (30·7)	365 (1·0)	0·89	0 (0·7)	206 (2·4)	0·14	n<5	n<5	0·01
Gastrointestinal pathologies	36 (18·8)	1,934 (5·3)	0·42	n<5	834 (9·8)	0·11	9 (10·3)	11 (12·1)	0·06
Neurological and musculoskeletal disease	135 (70·3)	8,101 (22·4)	1·10	26 (55·7)	3,931 (46·4)	0·19	65 (74·7)	55 (60·7)	0·30
Skin disease	48 (25·0)	1,399 (3·9)	0·63	n<5	619 (7·3)	0·10	16 (18·4)	10 (10·5)	0·23
Medications	**N (%)**	**N (%)**		**N (%)**	**N (%)**		**N (%)**	**N (%)**	
Antianaemic drugs	98 (51·0)	2,946 (8·1)	1·06	18 (39·6)	1,234 (14·6)	0·59	46 (52·9)	15 (16·5)	0·83
Cardiovascular drugs	123 (64·1)	14,144 (39·1)	0·52	30 (63·6)	4,820 (56·9)	0·14	55 (63·2)	55 (60·6)	0·05
Antimicrobials	192 (100·0)	32,201 (89·0)	0·50	46 (100·0)	8,056 (95·1)	0·32	87 (100·0)	88 (96·4)	0·28
Anticoagulants	11 (5·7)	633 (1·7)	0·21	n<5	295 (3·5)	0·05	5 (5·7)	n<5	0·12
Diabetes	16 (8·3)	2,211 (6·1)	0·09	0 (0·9)	990 (11·7)	0·46	(n<5)	12 (13·3)	0·31
Obstructive airway disease	61 (31·8)	9,502 (26·2)	0·12	19 (41·0)	2,779 (32·8)	0·17	24 (27·6)	32 (35·6)	0·17
Proxies for IMID severity	**N (%)**	**N (%)**		**N (%)**	**N (%)**		**N (%)**	**N (%)**	
Procedures on the skin, GI tract or joints	62 (32·3)	2,239 (6·2)	0·70	7 (14·2)	1,504 (17·8)	0·10	21 (24·1)	22 (23·7)	0·01
Immune-mediated inflammatory disease drugs	89 (46·4)	7,651 (21·1)	0·55	19 (41·8)	2,901 (34·3)	0·16	40 (46·0)	37 (40·8)	0·10

Abbreviations: IMID; immune mediated inflammatory diseases.

Appendix Table 15. Characteristics of SARS-CoV-2 PCR test positive patients in Denmark 26 February–18 October 2020, by exposure to calcineurin inhibitors, other immunosuppressants, hydroxychloroquine or chloroquine with inverse probability of treatment weighting (IPTW) and matching weights propensity score models.

Characteristics	Unadjusted			Adjusted with IPTW			Adjusted with matching weights		
	Exposed (n=268)	Unexposed (n=36,200)	SMD	Exposed (n=161)	Unexposed (n=23,922)	SMD	Exposed (n=171)	Unexposed (n=170)	SMD
Age, median (IQR)	56 (44-69)	39 (23-55)	0·78	51 (40-70)	47 (30-60)	0·35	54 (40-70)	54 (41-68)	0·01
Male, N (%)	118 (44·0)	17,544 (48·5)	0·09	69 (42·9)	11,052 (46·2)	0·07	72 (42·1)	72 (42·1)	0·00
Number of admissions and outpatient contacts	**N (%)**	**N (%)**		**N (%)**	**N (%)**		**N (%)**	**N (%)**	
0	16 (6·0)	18,787 (51·9)	1·17	78 (48·2)	6,997 (29·2)	0·40	14 (8·2)	10 (5·7)	0·10
1-2	21 (7·8)	9,574 (26·4)	0·51	39 (24·1)	9,364 (39·1)	0·33	21 (12·3)	29 (17·0)	0·13
3-5	65 (24·3)	4,264 (11·8)	0·33	24 (15·1)	4,229 (17·7)	0·07	56 (32·7)	43 (25·2)	0·17
6+	166 (61·9)	3,575 (9·9)	1·29	20 (12·7)	3,333 (13·9)	0·04	80 (46·8)	89 (52·1)	0·11
Diagnoses	**N (%)**	**N (%)**		**N (%)**	**N (%)**		**N (%)**	**N (%)**	
Cardiovascular disease	83 (31·0)	4,269 (11·8)	0·48	32 (19·8)	3,546 (14·8)	0·13	46 (26·9)	42 (24·6)	0·05
Neoplasms, blood and blood-forming organs	20 (7·5)	101 (0·3)	0·38	-	56 (0·2)	0·07	-	(n<5)	0·14
Solid organ transplantation	21 (7·8)	27 (0·1)	0·41	-	-	.	-	-	.
Pulmonary disease	58 (21·6)	2,742 (7·6)	0·41	9 (5·4)	2,272 (9·5)	0·16	26 (15·2)	30 (17·6)	0·06
Liver disease	11 (4·1)	302 (0·8)	0·21	(n<5)	266 (1·1)	0·04	(n<5)	(n<5)	0·01
Kidney disease	45 (16·8)	1,049 (2·9)	0·48	7 (4·2)	880 (3·7)	0·02	15 (8·8)	15 (8·7)	0·00
Diseases of the gastrointestinal tract	36 (13·4)	365 (1·0)	0·49	(n<5)	275 (1·1)	0·08	12 (7·0)	6 (3·5)	0·16
Gastrointestinal pathologies	42 (15·7)	1,934 (5·3)	0·34	(n<5)	1,586 (6·6)	0·18	15 (8·8)	19 (11·2)	0·08
Neurological and musculoskeletal disease	183 (68·3)	8,101 (22·4)	1·04	59 (36·5)	7,839 (32·8)	0·08	113 (66·1)	105 (62·0)	0·09
Skin disease	66 (24·6)	1,399 (3·9)	0·62	19 (11·8)	1,207 (5·0)	0·24	30 (17·5)	18 (10·4)	0·21
Medications	**N (%)**	**N (%)**		**N (%)**	**N (%)**		**N (%)**	**N (%)**	
Antianaemic drugs	182 (67·9)	2,946 (8·1)	1·56	98 (60·9)	2,446 (10·2)	1·25	119 (69·6)	30 (17·6)	1·23
Cardiovascular drugs	188 (70·1)	14,144 (39·1)	0·66	111 (69·1)	11,808 (49·4)	0·41	107 (62·6)	113 (66·7)	0·09
Antimicrobials	261 (97·4)	32,201 (89·0)	0·34	147 (91·3)	22,228 (92·9)	0·06	164 (95·9)	165 (96·9)	0·05
Anticoagulants	16 (6·0)	633 (1·7)	0·22	1 (0·4)	546 (2·3)	0·17	(n<5)	8 (4·5)	0·12
Diabetes	38 (14·2)	2,211 (6·1)	0·27	6 (3·6)	1,968 (8·2)	0·20	18 (10·5)	24 (14·0)	0·11
Obstructive airway disease	100 (37·3)	9,502 (26·2)	0·24	52 (32·6)	6,703 (28·0)	0·10	58 (33·9)	63 (36·8)	0·06
Proxies for IMID severity	**N (%)**	**N (%)**		**N (%)**	**N (%)**		**N (%)**	**N (%)**	
Procedures on the skin, GI tract or joints	82 (30·6)	2,239 (6·2)	0·66	11 (7·1)	2,113 (8·8)	0·06	37 (21·6)	40 (23·3)	0·04
Immune-mediated inflammatory diseases	132 (49·3)	7,651 (21·1)	0·62	75 (46·9)	6,861 (28·7)	0·38	84 (49·1)	77 (45·6)	0·07

Abbreviations: IMID; immune mediated inflammatory diseases.

Appendix Table 16. Characteristics of SARS-CoV-2 PCR test positive patients in Denmark 26 February–18 October 2020, by exposure to systemic glucocorticoids with inverse probability of treatment weighting (IPTW) and matching weights propensity score models.

Characteristics	Unadjusted			Adjusted with IPTW			Adjusted with matching weights		
	Exposed (n=136)	Unexposed (n=36,200)	SMD	Exposed (n=70)	Unexposed (n=18,196)	SMD	Exposed (n=94)	Unexposed (n=85)	SMD
Age, median (IQR)	75 (65-82)	39 (23-55)	1·75	42 (29-60)	53 (42-64)	0·30	73 (60-82)	71 (58-80)	0·09
Male, N (%)	73 (53·7)	17,544 (48·5)	0·10	29 (41·1)	8,701 (47·8)	0·14	47 (50·0)	43 (50·3)	0·01
Number of admissions and outpatient contacts	**N (%)**	**N (%)**		**N (%)**	**N (%)**		**N (%)**	**N (%)**	
0	5 (3·7)	18,787 (51·9)	1·28	14 (19·5)	4,579 (25·2)	0·14	n<5	n<5	0·03
1-2	16 (11·8)	9,574 (26·4)	0·38	29 (41·3)	6,433 (35·4)	0·12	15 (16·0)	14 (15·9)	0·00
3-5	25 (18·4)	4,264 (11·8)	0·19	19 (27·3)	3,912 (21·5)	0·13	25 (26·6)	23 (27·2)	0·01
6+	90 (66·2)	3,575 (9·9)	1·42	8 (11·9)	3,271 (18·0)	0·17	50 (53·2)	44 (52·0)	0·02
Diagnoses	**N (%)**	**N (%)**		**N (%)**	**N (%)**		**N (%)**	**N (%)**	
Cardiovascular disease	81 (59·6)	4,269 (11·8)	1·15	14 (19·7)	3,722 (20·5)	0·02	52 (55·3)	43 (50·3)	0·10
Neoplasms, blood and blood-forming organs	7 (5·1)	101 (0·3)	0·30	n<5	75 (0·4)	0·09	n<5	n<5	0·16
Solid organ transplantation	n<5	27 (0·1)	0·04	n<5	27 (0·1)	0·05	n<5	0 (0·3)	0·08
Pulmonary disease	57 (41·9)	2,742 (7·6)	0·87	6 (8·4)	1,989 (10·9)	0·09	29 (30·9)	20 (23·7)	0·16
Liver disease	n<5	302 (0·8)	0·06	n<5	237 (1·3)	0·03	n<5	n<5	0·00
Kidney disease	23 (16·9)	1,049 (2·9)	0·48	n<5	736 (4·0)	0·03	16 (17·0)	10 (11·9)	0·15
Diseases of the gastrointestinal tract	15 (11·0)	365 (1·0)	0·43	n<5	286 (1·6)	0·20	9 (9·6)	n<5	0·27
Gastrointestinal pathologies	27 (19·9)	1,934 (5·3)	0·45	n<5	1,544 (8·5)	0·11	17 (18·1)	14 (16·4)	0·04
Neurological and musculoskeletal disease	82 (60·3)	8,101 (22·4)	0·83	34 (47·9)	6,594 (36·2)	0·24	53 (56·4)	45 (53·2)	0·06
Skin disease	11 (8·1)	1,399 (3·9)	0·18	6 (8·0)	848 (4·7)	0·14	9 (9·6)	6 (6·8)	0·10
Medications	**N (%)**	**N (%)**		**N (%)**	**N (%)**		**N (%)**	**N (%)**	
Antianaemic drugs	38 (27·9)	2,946 (8·1)	0·53	14 (19·9)	2,191 (12·0)	0·22	25 (26·6)	20 (23·2)	0·08
Cardiovascular drugs	113 (83·1)	14,144 (39·1)	1·01	38 (54·3)	10,704 (58·8)	0·09	75 (79·8)	70 (82·7)	0·07
Antimicrobials	130 (95·6)	32,201 (89·0)	0·25	67 (96·1)	17,146 (94·2)	0·09	90 (95·7)	83 (97·7)	0·11
Anticoagulants	18 (13·2)	633 (1·7)	0·45	n<5	550 (3·0)	0·09	10 (10·6)	8 (9·4)	0·04
Diabetes	22 (16·2)	2,211 (6·1)	0·32	7 (10·0)	1,881 (10·3)	0·01	14 (14·9)	17 (20·2)	0·14
Obstructive airway disease	74 (54·4)	9,502 (26·2)	0·60	23 (32·5)	5,180 (28·5)	0·09	44 (46·8)	35 (41·3)	0·11
Proxies for IMID severity	**N (%)**	**N (%)**		**N (%)**	**N (%)**		**N (%)**	**N (%)**	
Procedures on the skin, GI tract or joints	42 (30·9)	2,239 (6·2)	0·67	6 (8·7)	1,937 (10·6)	0·07	22 (23·4)	22 (25·3)	0·04
Immune-mediated inflammatory diseases	60 (44·1)	7,651 (21·1)	0·51	51 (72·5)	5,640 (31·0)	0·91	41 (43·6)	35 (41·3)	0·05

Abbreviations: IMID; immune mediated inflammatory diseases.

Appendix Table 17. Characteristics of SARS-CoV-2 PCR test positive patients in Denmark 26 February–18 October 2020, by current or former use of immunosuppressants, and with inverse probability of treatment weighting (IPTW) and matching weights propensity score models.

Characteristics	Unadjusted			Adjusted with IPTW			Adjusted with matching weights		
	Current (n=527)	former (n=177)	SMD	Current (n=509)	former (n=171)	SMD	Current (n=168)	Former (n=166)	SMD
Age, median (IQR)	57 (42-73)	54 (40-71)	0·10	56 (42-73)	58 (43-74)	0·05	56 (42-72)	56 (42-72)	0·02
Male, N (%)	256 (48·6)	81 (45·8)	0·06	242 (47·6)	81 (47·3)	0·01	77 (45·7)	74 (44·6)	0·02
Number of admissions and outpatient contacts	**N (%)**	**N (%)**		**N (%)**	**N (%)**		**N (%)**	**N (%)**	
0	20 (3·8)	16 (9·0)	0·22	21 (4·1)	6 (3·4)	0·04	11 (6·4)	9 (5·4)	0·04
1-2	38 (7·2)	25 (14·1)	0·23	43 (8·4)	16 (9·4)	0·04	19 (11·2)	23 (13·9)	0·08
3-5	113 (21·4)	34 (19·2)	0·06	115 (22·6)	33 (19·4)	0·08	42 (24·8)	34 (20·5)	0·10
6+	356 (67·6)	102 (57·6)	0·21	331 (65·0)	116 (67·9)	0·06	97 (57·6)	100 (60·3)	0·05
Diagnoses	**N (%)**	**N (%)**		**N (%)**	**N (%)**		**N (%)**	**N (%)**	
Cardiovascular disease	176 (33·4)	65 (36·7)	0·07	175 (34·5)	62 (36·0)	0·03	63 (37·8)	63 (37·9)	0·00
Neoplasms, blood and blood-forming organs	27 (5·1)	7 (4·0)	0·06	25 (4·9)	(n<5)	0·10	6 (3·6)	5 (3·0)	0·03
Solid organ transplantation	24 (4·6)	9 (5·1)	0·02	23 (4·4)	8 (4·8)	0·02	8 (4·9)	9 (5·4)	0·03
Pulmonary disease	131 (24·9)	39 (22·0)	0·07	125 (24·5)	42 (24·5)	0·00	39 (23·0)	39 (23·5)	0·01
Liver disease	15 (2·8)	8 (4·5)	0·09	15 (2·9)	7 (3·9)	0·05	7 (3·9)	7 (4·2)	0·02
Kidney disease	76 (14·4)	28 (15·8)	0·04	74 (14·6)	26 (15·3)	0·02	26 (15·5)	27 (16·3)	0·02
Diseases of the gastrointestinal tract	91 (17·3)	23 (13·0)	0·12	82 (16·1)	28 (16·2)	0·00	23 (13·5)	22 (13·3)	0·01
Gastrointestinal pathologies	94 (17·8)	21 (11·9)	0·17	80 (15·8)	29 (17·1)	0·04	20 (12·0)	21 (12·7)	0·02
Neurological and musculoskeletal disease	353 (67·0)	105 (59·3)	0·16	333 (65·4)	115 (67·3)	0·04	102 (61·0)	103 (62·0)	0·02
Skin disease	112 (21·3)	34 (19·2)	0·05	107 (21·0)	35 (20·7)	0·01	34 (20·2)	33 (19·9)	0·01
Medications	**N (%)**	**N (%)**		**N (%)**	**N (%)**		**N (%)**	**N (%)**	
Antianaemic drugs	276 (52·4)	92 (52·0)	0·01	266 (52·3)	89 (52·2)	0·00	87 (51·6)	86 (51·8)	0·00
Cardiovascular drugs	370 (70·2)	125 (70·6)	0·01	359 (70·5)	126 (73·4)	0·07	120 (71·7)	121 (72·9)	0·03
Antimicrobials	515 (97·7)	167 (94·4)	0·17	497 (97·7)	169 (98·6)	0·06	162 (96·7)	162 (97·6)	0·06
Anticoagulants	39 (7·4)	12 (6·8)	0·02	33 (6·5)	11 (6·4)	0·00	10 (6·0)	12 (7·2)	0·05
Diabetes	65 (12·3)	26 (14·7)	0·07	65 (12·7)	21 (12·2)	0·02	23 (14·0)	25 (15·0)	0·03
Obstructive airway disease	212 (40·2)	65 (36·7)	0·07	204 (40·1)	70 (40·8)	0·01	65 (38·9)	64 (38·5)	0·01
Proxies for IMID severity	**N (%)**	**N (%)**		**N (%)**	**N (%)**		**N (%)**	**N (%)**	
Procedures on the skin, GI tract or joints	162 (30·7)	52 (29·4)	0·03	156 (30·6)	50 (29·4)	0·03	50 (29·9)	50 (30·1)	0·01
Immune-mediated inflammatory disease drugs	252 (47·8)	80 (45·2)	0·05	236 (46·4)	79 (46·2)	0·00	74 (44·3)	74 (44·6)	0·01

Abbreviations: IMID; immune mediated inflammatory diseases.

Appendix Table 18. Characteristics of SARS-CoV-2 PCR test positive patients in Denmark 26 February–18 October 2020 restricted to those admitted with COVID-19, by exposure to immunosuppressants with inverse probability of treatment weighting (IPTW) and matching weights propensity score models.

Characteristics	Unadjusted			Adjusted with IPTW			Adjusted with matching weights		
	Exposed (n=165)	Unexposed (n=3,373)	SMD	Exposed (n=116)	Unexposed (n=2180)	SMD	Exposed (n=120)	Unexposed (n=122)	SMD
Age, median (IQR)	73 (61-80)	66 (50-78)	0·43	81 (69-87)	71 (57-80)	0·45	74 (61-82)	74 (63-81)	0·03
Male, N (%)	87 (52·7)	1,823 (54·0)	0·03	57 (49·6)	1,162 (53·3)	0·07	63 (52·5)	63 (51·5)	0·02
Number of admissions and outpatient contacts	**N (%)**	**N (%)**		**N (%)**	**N (%)**		**N (%)**	**N (%)**	
0	(n<5)	814 (24·1)	0·70	17 (14·9)	84 (3·8)	0·39	(n<5)	1 (0·6)	0·10
1-2	5 (3·0)	935 (27·7)	0·73	21 (18·3)	508 (23·3)	0·12	5 (4·2)	8 (6·8)	0·12
3-5	30 (18·2)	646 (19·2)	0·02	31 (26·9)	605 (27·7)	0·02	29 (24·2)	20 (16·7)	0·19
6+	127 (77·0)	978 (29·0)	1·10	46 (39·9)	983 (45·1)	0·11	84 (70·0)	92 (75·9)	0·13
Diagnoses	**N (%)**	**N (%)**		**N (%)**	**N (%)**		**N (%)**	**N (%)**	
Cardiovascular disease	97 (58·8)	1,337 (39·6)	0·39	76 (65·4)	1,041 (47·8)	0·36	68 (56·7)	68 (56·0)	0·01
Neoplasms, blood and blood-forming organs	11 (6·7)	23 (0·7)	0·32	1 (0·6)	18 (0·8)	0·03	(n<5)	(n<5)	0·06
Solid organ transplantation	16 (9·7)	9 (0·3)	0·44	0 (0·3)	(n<5)	0·03	(n<5)	1 (0·7)	0·09
Pulmonary disease	69 (41·8)	537 (15·9)	0·60	22 (19·2)	514 (23·6)	0·11	47 (39·2)	52 (43·0)	0·08
Liver disease	9 (5·5)	83 (2·5)	0·15	(n<5)	68 (3·1)	0·06	5 (4·2)	(n<5)	0·04
Kidney disease	43 (26·1)	336 (10·0)	0·43	14 (11·8)	297 (13·6)	0·05	26 (21·7)	24 (19·9)	0·04
Diseases of the gastrointestinal tract	22 (13·3)	64 (1·9)	0·44	(n<5)	57 (2·6)	0·07	8 (6·7)	8 (6·4)	0·01
Gastrointestinal pathologies	37 (22·4)	430 (12·7)	0·26	16 (13·7)	353 (16·2)	0·07	23 (19·2)	27 (22·4)	0·08
Neurological and musculoskeletal disease	106 (64·2)	1,305 (38·7)	0·53	61 (52·5)	1,074 (49·3)	0·06	73 (60·8)	77 (63·0)	0·05
Skin disease	27 (16·4)	202 (6·0)	0·33	13 (10·9)	179 (8·2)	0·09	18 (15·0)	16 (13·4)	0·05
Medications	**N (%)**	**N (%)**		**N (%)**	**N (%)**		**N (%)**	**N (%)**	
Antianaemic drugs	74 (44·8)	657 (19·5)	0·56	31 (26·7)	590 (27·1)	0·01	45 (37·5)	49 (40·0)	0·05
Cardiovascular drugs	141 (85·5)	2,463 (73·0)	0·31	88 (76·2)	1,729 (79·3)	0·08	100 (83·3)	103 (84·2)	0·02
Antimicrobials	160 (97·0)	3,201 (94·9)	0·10	114 (98·3)	2,087 (95·7)	0·15	115 (95·8)	118 (96·6)	0·04
Anticoagulants	26 (15·8)	274 (8·1)	0·24	8 (6·6)	224 (10·3)	0·13	16 (13·3)	16 (13·5)	0·00
Diabetes	26 (15·8)	636 (18·9)	0·08	17 (14·9)	428 (19·6)	0·13	19 (15·8)	21 (16·9)	0·03
Obstructive airway disease	95 (57·6)	1,162 (34·5)	0·48	44 (37·7)	940 (43·1)	0·11	67 (55·8)	72 (59·1)	0·07
Proxies for IMID severity	**N (%)**	**N (%)**		**N (%)**	**N (%)**		**N (%)**	**N (%)**	
Procedures on the skin, GI tract or joints	64 (38·8)	508 (15·1)	0·56	19 (16·8)	478 (21·9)	0·13	38 (31·7)	40 (32·5)	0·02
Immune-mediated inflammatory disease drugs	64 (38·8)	1,057 (31·3)	0·16	38 (32·5)	788 (36·1)	0·08	47 (39·2)	50 (41·1)	0·04

Abbreviations: IMID; immune mediated inflammatory diseases.

Appendix Table 19. Characteristics of SARS-CoV-2 PCR test positive patients in Denmark 26 February–20 April 2020, by exposure to immunosuppressants with inverse probability of treatment weighting (IPTW) and matching weights propensity score models.

Characteristics	Unadjusted			Adjusted with IPTW			Adjusted with matching weights		
	Exposed (n=199)	Unexposed (n=7794)	SMD	Exposed (n=106)	Unexposed (n=6258)	SMD	Exposed (n=136)	Unexposed (n=134)	SMD
Age, median (IQR)	63 (50-79)	50 (35-63)	0·61	65 (53-84)	53 (39-66)	0·67	67 (51-79)	63 (50-77)	0·04
Male, N (%)	95 (47·7)	3,321 (42·6)	0·10	39 (36·9)	2,931 (46·8)	0·20	61 (44·9)	61 (45·8)	0·02
Number of admissions and outpatient contacts	**N (%)**	**N (%)**		**N (%)**	**N (%)**		**N (%)**	**N (%)**	
0	9 (4·5)	3,122 (40·1)	0·94	17 (15·9)	1,671 (26·7)	0·27	7 (5·1)	(n<5)	0·09
1-2	11 (5·5)	2,317 (29·7)	0·67	24 (23·0)	2,257 (36·1)	0·29	10 (7·4)	17 (13·0)	0·19
3-5	37 (18·6)	1,202 (15·4)	0·08	35 (32·6)	1,198 (19·1)	0·31	33 (24·3)	31 (23·0)	0·03
6+	142 (71·4)	1,153 (14·8)	1·39	30 (28·5)	1,132 (18·1)	0·25	86 (63·2)	81 (60·7)	0·05
Diagnoses	**N (%)**	**N (%)**		**N (%)**	**N (%)**		**N (%)**	**N (%)**	
Cardiovascular disease	77 (38·7)	1,534 (19·7)	0·43	51 (48·5)	1,367 (21·8)	0·58	52 (38·2)	51 (38·1)	0·00
Neoplasms, blood and blood-forming organs	14 (7·0)	34 (0·4)	0·35	0 (0·3)	31 (0·5)	0·03	(n<5)	(n<5)	0·09
Solid organ transplantation	10 (5·0)	8 (0·1)	0·32	0 (0·1)	(n<5)	0·01	1 (0·7)	1 (0·6)	0·01
Pulmonary disease	61 (30·7)	723 (9·3)	0·55	28 (26·1)	702 (11·2)	0·39	36 (26·5)	36 (27·0)	0·01
Liver disease	5 (2·5)	108 (1·4)	0·08	1 (0·5)	95 (1·5)	0·10	(n<5)	(n<5)	0·04
Kidney disease	31 (15·6)	363 (4·7)	0·37	13 (12·3)	320 (5·1)	0·26	16 (11·8)	16 (12·3)	0·02
Diseases of the gastrointestinal tract	28 (14·1)	112 (1·4)	0·49	(n<5)	100 (1·6)	0·12	10 (7·4)	8 (6·3)	0·04
Gastrointestinal pathologies	42 (21·1)	566 (7·3)	0·40	10 (9·0)	523 (8·4)	0·02	23 (16·9)	22 (16·3)	0·02
Neurological and musculoskeletal disease	143 (71·9)	2,380 (30·5)	0·91	45 (42·9)	2,335 (37·3)	0·11	92 (67·6)	87 (65·3)	0·05
Skin disease	33 (16.6)	378 (4.8)	0.39	5 (4.9)	352 (5.6)	0.03	17 (12.5)	17 (12.6)	0.00
Medications	**N (%)**	**N (%)**		**N (%)**	**N (%)**		**N (%)**	**N (%)**	
Antianaemic drugs	109 (54.8)	871 (11.2)	1.05	30 (28.0)	843 (13.5)	0.37	62 (45.6)	56 (41.9)	0.07
Cardiovascular drugs	150 (75.4)	4,317 (55.4)	0.43	79 (74.7)	3,585 (57.3)	0.37	102 (75.0)	100 (74.8)	0.01
Antimicrobials	196 (98.5)	7,339 (94.2)	0.23	104 (98.1)	5,975 (95.5)	0.15	133 (97.8)	131 (97.8)	0.00
Anticoagulants	17 (8.5)	265 (3.4)	0.22	(n<5)	245 (3.9)	0.00	12 (8.8)	12 (8.6)	0.01
Diabetes	27 (13.6)	720 (9.2)	0.14	23 (21.5)	616 (9.8)	0.32	16 (11.8)	22 (16.2)	0.13
Obstructive airway disease	90 (45.2)	2,189 (28.1)	0.36	50 (47.2)	1,839 (29.4)	0.37	57 (41.9)	58 (43.4)	0.03
Proxies for IMID severity	**N (%)**	**N (%)**		**N (%)**	**N (%)**		**N (%)**	**N (%)**	
Procedures on the skin, GI tract or joints	61 (30·7)	724 (9·3)	0·55	16 (15·4)	712 (11·4)	0·12	35 (25·7)	35 (26·0)	0·01
Immune-mediated inflammatory disease drugs	84 (42·2)	2,110 (27·1)	0·32	39 (36·6)	1,875 (30·0)	0·14	55 (40·4)	58 (43·3)	0·06

Abbreviations: IMID; immune mediated inflammatory diseases.

Appendix Table 20. Characteristics of SARS-CoV-2 PCR test positive patients in Denmark 20 April-18 October 2020, by exposure to immunosuppressants, with inverse probability of treatment weighting (IPTW) and matching weights propensity score models.

Characteristics	Unadjusted			Adjusted with IPTW			Adjusted with matching weights		
	Exposed (n=328)	Unexposed (n=28,406)	SMD	Exposed (n=146)	Unexposed (n=18,300)	SMD	Exposed (n=183)	Unexposed (n=178)	SMD
Age, median (IQR)	54 (36-69)	34 (21-52)	0·78	70 (42-79)	43 (26-56)	0·92	54 (37-73)	52 (35-66)	0·14
Male, N (%)	161 (49·1)	14,223 (50·1)	0·02	54 (36·7)	9,624 (52·6)	0·32	82 (44·8)	80 (44·8)	0·00
Number of admissions and outpatient contacts	**N (%)**	**N (%)**		**N (%)**	**N (%)**		**N (%)**	**N (%)**	
0	11 (3·4)	15,665 (55·1)	1·38	51 (35·0)	5,838 (31·9)	0·07	8 (4·4)	9 (5·1)	0·03
1-2	27 (8·2)	7,257 (25·5)	0·48	39 (26·6)	7,178 (39·2)	0·27	26 (14·2)	29 (16·2)	0·05
3-5	76 (23·2)	3,062 (10·8)	0·33	31 (21·0)	3,040 (16·6)	0·11	65 (35·5)	48 (26·9)	0·19
6+	214 (65·2)	2,422 (8·5)	1·45	26 (17·5)	2,245 (12·3)	0·15	84 (45·9)	93 (51·8)	0·12
Diagnoses	**N (%)**	**N (%)**		**N (%)**	**N (%)**		**N (%)**	**N (%)**	
Cardiovascular disease	99 (30·2)	2,735 (9·6)	0·53	37 (25·1)	2,239 (12·2)	0·33	59 (32·2)	43 (24·2)	0·18
Neoplasms, blood and blood-forming organs	13 (4·0)	67 (0·2)	0·26	0 (0·2)	55 (0·3)	0·01	(n<5)	(n<5)	0·04
Solid organ transplantation	14 (4·3)	19 (0·1)	0·29	1 (0·4)	(n<5)	0·08	(n<5)	0 (0·1)	0·20
Pulmonary disease	70 (21·3)	2,019 (7·1)	0·42	11 (7·5)	1,634 (8·9)	0·05	33 (18·0)	29 (16·4)	0·04
Liver disease	10 (3·0)	194 (0·7)	0·18	(n<5)	161 (0·9)	0·15	7 (3·8)	(n<5)	0·12
Kidney disease	45 (13·7)	686 (2·4)	0·42	9 (6·2)	553 (3·0)	0·15	22 (12·0)	14 (7·9)	0·14
Diseases of the gastrointestinal tract	63 (19·2)	253 (0·9)	0·64	(n<5)	188 (1·0)	0·02	10 (5·5)	8 (4·7)	0·04
Gastrointestinal pathologies	52 (15·9)	1,368 (4·8)	0·37	6 (4·2)	1,076 (5·9)	0·08	21 (11·5)	20 (10·9)	0·02
Neurological and musculoskeletal disease	210 (64·0)	5,721 (20·1)	0·99	50 (34·5)	5,492 (30·0)	0·10	109 (59·6)	97 (54·2)	0·11
Skin disease	79 (24·1)	1,021 (3·6)	0·62	12 (8·1)	927 (5·1)	0·12	31 (16·9)	21 (11·5)	0·16
Medications	**N (%)**	**N (%)**		**N (%)**	**N (%)**		**N (%)**	**N (%)**	
Antianaemic drugs	167 (50·9)	2,075 (7·3)	1·09	27 (18·1)	1,896 (10·4)	0·22	69 (37·7)	56 (31·5)	0·13
Cardiovascular drugs	220 (67·1)	9,827 (34·6)	0·69	115 (78·7)	7,567 (41·4)	0·83	121 (66·1)	111 (62·1)	0·08
Antimicrobials	319 (97·3)	24,862 (87·5)	0·37	140 (95·9)	16,353 (89·4)	0·25	175 (95·6)	171 (96·1)	0·02
Anticoagulants	22 (6·7)	368 (1·3)	0·28	(n<5)	303 (1·7)	0·05	9 (4·9)	8 (4·5)	0·02
Diabetes	38 (11·6)	1,491 (5·2)	0·23	13 (8·7)	1,183 (6·5)	0·08	21 (11·5)	19 (10·9)	0·02
Obstructive airway disease	122 (37·2)	7,313 (25·7)	0·25	69 (47·0)	4,710 (25·7)	0·45	71 (38·8)	60 (33·4)	0·11
Proxies for IMID severity	**N (%)**	**N (%)**		**N (%)**	**N (%)**		**N (%)**	**N (%)**	
Procedures on the skin, GI tract or joints	101 (30·8)	1,515 (5·3)	0·70	10 (6·6)	1,421 (7·8)	0·05	33 (18·0)	37 (21·0)	0·07
Immune-mediated inflammatory disease drugs	168 (51·2)	5,541 (19·5)	0·70	61 (41·4)	4,914 (26·9)	0·31	80 (43·7)	79 (44·1)	0·01

Abbreviations: IMID; immune mediated inflammatory diseases.

Appendix Table 21. Variables for subgroups' propensity scores models.

Subgroup	Propensity score variables
Selective immunosuppressants (ATC group L04AA), TNF inhibitors (L04AB), and interleukin inhibitors (L04AC), and rituximab (L01XC02).	Date of birth Sex Date of SARS-COV-2 testing Hospital admission and outpatient contacts Neoplasms, blood and blood forming organs Neurological and musculoskeletal disease Solid organ transplant Pulmonary disease Diseases of the gastrointestinal tract Skin disease Cardiovascular disease Medications for IMID
Calcineurin inhibitors (L04AD), other immunosuppressants (L04AX), hydroxychloroquine and chloroquine (P01BA01 and P01BA02).	Date of birth Sex Date of SARS-COV-2 testing Hospital admission and outpatient contacts Neoplasms, blood and blood forming organs Neurological and musculoskeletal disease Solid organ transplant Pulmonary disease Diseases of the gastrointestinal tract Skin disease Cardiovascular disease Medications for IMID Procedures on the skin, GI tract, or joints Gastrointestinal pathologies Liver disease Kidney disease
Systemic glucocorticoids (H02AB).	Date of birth Sex Date of SARS-COV-2 testing Hospital admission and outpatient contacts Neoplasms, blood and blood forming organs Neurological and musculoskeletal disease Solid organ transplant Pulmonary disease Diseases of the gastrointestinal tract Skin disease Cardiovascular disease Medications for IMID Procedures on the skin, GI tract, or joints Gastrointestinal pathologies Liver disease Kidney disease Cardiovascular drugs Antimicrobials Anticoagulants Drugs used in diabetes Drugs for obstructive airway diseases

Abbreviations: ATC; anatomical therapeutic chemicals, GI: gastrointestinal, IMID: immune-mediated inflammatory diseases.

Appendix Methods

INTRODUCTION

During the first months of the pandemic people in defined risk groups, such as patients receiving immunosuppressants, as well as elderly people and people with chronic diseases, who were expected to be more susceptible to a severe course of COVID-19 disease than the general population, were prioritised for testing. From 21 April 2020, testing was open to a wider population, however, it cannot be ruled out that persons in risk groups could be more inclined towards being tested. Therefore, we expected that patients exposed to immunosuppressants were overrepresented in our cohort. However, as virtually all individuals infected with SARS-CoV-2 who required hospital admission and a large part of those who died were tested, this overrepresentation only occurs to a small degree among individuals with the outcomes. This oversampling decreases the proportion of the exposed who have the outcome, compared to a random sample of

individuals infected with SARS-CoV-2. This selection bias lowers risk estimates, but the influence will be attenuated as other persons in the risk groups, as well as health care workers, were also tested more than the general population.

RESULTS

We show below that the bias depends on known numbers from our dataset as well as the risk ratio of being tested, for the composite exposure of persons in the risk groups and health care workers compared to others, among those infected with SARS-CoV-2 and not requiring immediate hospital admission. Appendix Figure 2 shows bias corrected estimates for the main results comparing immunosuppressant exposed patients to unexposed patients, with this risk ratio ranging from 1 to 3.

PROOF

The argument uses the assumption that all persons with the outcomes among those with SARS-CoV-2 are tested. We will consider hospital admission first, and use the notation in Table S1 for the data in the sampled population (SARS-CoV-2 infected with a positive test) and the population of interest (SARS-CoV-2 infected).

Appendix Table S1. Notation for the numbers of individuals with or without the outcome hospital admission, by risk group and exposure status, for individuals tested and individuals infected with SARS-CoV-2.

		SARS-CoV-2 infected			
		Tested		**All**	
I	**R**	**Y=0**	**Y=1**	**Y=0**	**Y=1**
0	0	A	C	a.A	C
0	1	B		b.B	
1	0 or 1	D	E	b.D	E

I: immunosuppressant medications; R: risk groups and health care workers; Y: hospital admission. A-E: cell numbers; a and b: one over the probability of being tested in the respective cell.

As hospital admission is relatively rare for the total group of SARS-CoV-2 infected, we can approximate the risk ratio of *Y* (hospital admission) given I (exposure to immunosuppressants) with the odds ratio:

$$RR_{Y|I} \approx OR_{Y|I} = \frac{E}{C} \times \frac{aA + bB}{bD}$$

Among those that have been tested (*T*):

$$RR_{Y|I,T=1} = \frac{E}{C} \times \frac{A + B + C}{D + E}$$

which gives

$$RR_{Y|I} = RR_{Y|I,T=1} \times \frac{D + E}{A + B + C} \times \frac{aA + bB}{bD}$$

$$= RR_{Y|I,T=1} \frac{D + E}{A + B + C} \times \frac{\frac{a}{b}A + B}{D}$$

Note that

$$\frac{a}{b} = \frac{\frac{1}{b}}{\frac{1}{a}} = RR_{T|R,Y=0}$$

which is the risk ratio of being tested for risk groups and health care workers compared to others, restricted to those without hospital admission. The risk of testing given no hospital admission possibly later in time is hard to interpret, so

we will make an approximation. As around 80% of the hospital admissions happen on the same day as testing, we will make an approximation by changing the restriction from those without hospital admission to those without hospital admission on the day of the test (*S*):

$$RR_{T|R,Y=0} \approx RR_{T|R,S=0}$$

Thus, we have the following equation for the risk ratio (RR) of hospital admission (Y) given exposure (I) among those who have been tested (T=1):

$$RR_{Y|I} \approx RR_{Y|I,T=1} \times \frac{D+E}{A+B+C} \times \frac{A \times RR_{T\cdot(S=0)|R} + B}{D}$$

Where A is unexposed people, not in risk groups, without the outcome; *B* is unexposed people, in risk groups, without the outcome; C is unexposed people with the outcome; *D* exposed people without the outcome; and *E* is exposed people with the outcome.

To apply the equation to our data we split the matching weights dataset for hospital admission, with 89 events among 208 exposed, and 77 events among 201 exposed (as per Appendix Table 15) into risk and non-risk groups based on rough definitions and to produce the values in Table S2 (corresponding to Appendix Table S1).

Appendix Table S2. The numbers of individuals with or without the outcome hospital admission, by risk group and exposure status, for individuals tested and individuals infected with SARS-CoV-2.

		SARS-CoV-2 infected			
		Tested		**All**	
I	**R**	**Y=0**	**Y=1**	**Y=0**	**Y=1**
0	0	115	87	a x 115	87
0	1	137		b x 137	
1	0 or 1	246	100	b x 246	100

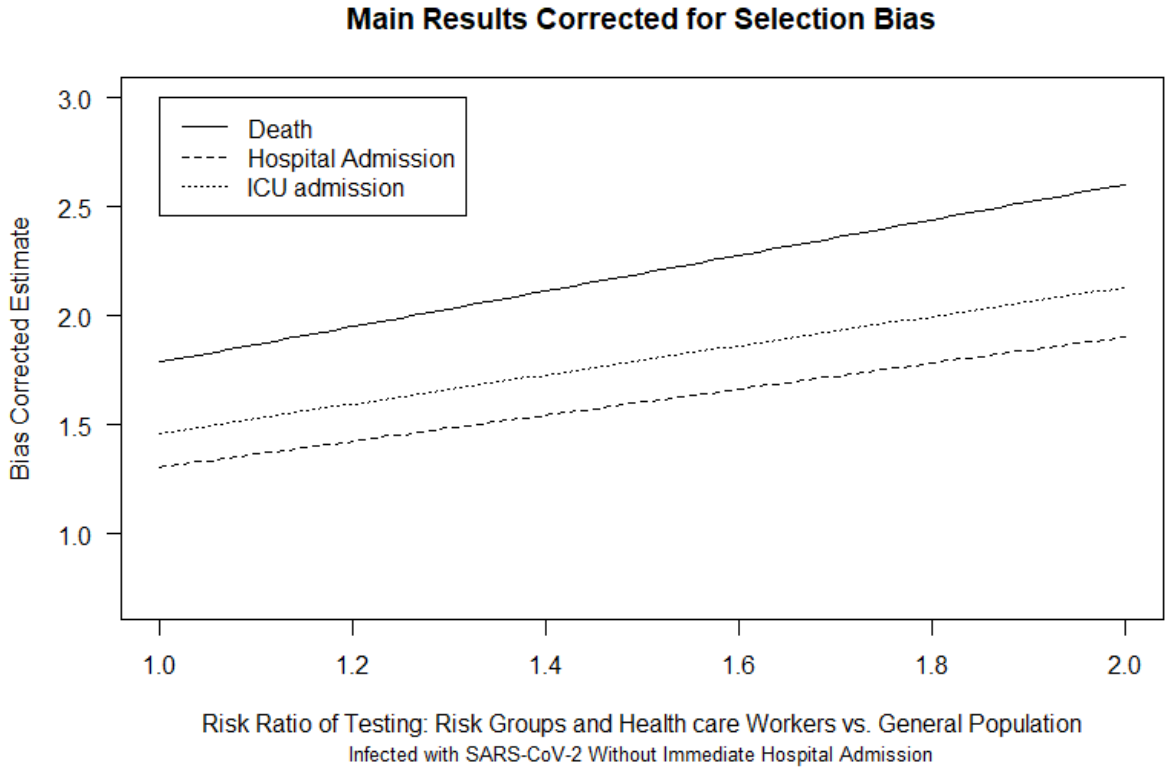
I: immunosuppressant medications; R: risk groups and health care workers; Y: hospital admission; a and b: one over the probability of being tested in the respective cell.

The values in Appendix Table S2 therefore give the following equation:

$$RR_{Y|I} \approx RR_{Y|I,T=1} \times \frac{346}{339} \times \frac{115 \times RR_{T|R,S=0} + 137}{246}$$

For intensive care unit (ICU) admission and death, we can again use the premise that hospital admission is relatively rare so $\frac{aA+bB}{aD}$ will not change much by adding any number of unexposed to the numerator, or exposed with admission to hospital to the denominator. Thus, as $\frac{D+E}{A+B+C}$ only depends on the total number of exposed and unexposed, the bias for ICU admission and death can be approximated by that for hospital admission. N.B, this bias analysis applies the main relative risk estimate with the composite exposure.

Appendix Figure 2. Relative risk of severe outcomes of SARS-CoV-2 in patients exposed to immunosuppressants compared to unexposed patients, corrected for selection bias (the risk ratio of being tested, for risk groups and health care workers compared to the general population, ranging from 1 to 3).



Abbreviations: ICU; Intensive care unit.