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Diabetes mellitus and the risk of post-acute COVID-19 hospitalizations—a nationwide cohort study

Bente Mertz Nørgård[1,2] | **Floor Dijkstra Zegers**[1,2] | **Claus Bogh Juhl**[3,4] | **Jens Kjeldsen**[5,6] | **Jan Nielsen**[1,2]

[1]Center for Clinical Epidemiology, Odense University Hospital, Odense, Denmark

[2]Department of Clinical Research, Research Unit of Clinical Epidemiology, University of Southern Denmark, Odense, Denmark

[3]Steno Diabetes Center Odense, Odense University Hospital, Odense, Denmark

[4]Department of Endocrinology, University Hospital South West Jutland, Esbjerg, Denmark

[5]Department of Medical Gastroenterology S, Odense University Hospital, Odense, Denmark

[6]Research Unit of Medical Gastroenterology, Department of Clinical Research, University of Southern Denmark, Odense, Denmark

Correspondence
Bente Mertz Nørgård, Center for Clinical Epidemiology, Odense University Hospital, Kløvervænget 30, Entrance 216, DK-5000 Odense, Denmark.
Email: bente.noergaard@rsyd.dk

Abstract

Aims: This cohort study, based on Danish health registers, examined the post-acute consequences of hospitalization for COVID-19 in patients with diabetes.

Methods: The study population comprised all Danish citizens (≥18 years old) who had diabetes when the pandemic started. A patient was exposed if he/she had a hospitalization with COVID-19 after 1 March 2020. A patient was unexposed when he/she was not hospitalized with COVID-19 between 1 March 2020 and the end of follow-up (4 January 2022), or the first registered event of interest. The outcomes included post-COVID-19 hospitalizations and death. We used a Cox proportional hazards model with time varying exposure estimating the hazards ratio (HR) to analyze if the hazard for an outcome of interest was impacted by being hospitalized with COVID-19.

Results: In patients with type 1 diabetes, 101 were hospitalized with COVID-19, and 25,459 were not. We did not have sufficient statistical power to identify differences in risk for those with type 1 diabetes. In type 2 diabetes, 1515 were hospitalized with COVID-19, and 95,887 were not. The adjusted HRs of post-acute hospitalization for respiratory diseases and infections were 1.71 (95% CI 1.45–2.03) and 1.87 (95% CI 1.61–2.18), respectively. The HR of death was 2.05 (95% CI 1.73–2.43). Patients with uncertain type had results similar to those with type 2 diabetes.

Conclusions/Interpretation: In type 2 diabetes and diabetes of uncertain type, hospitalization with COVID-19 was associated with an increased risk of post-acute hospitalization for respiratory diseases, infections and death.

KEYWORDS

clinical epidemiology, COVID-19, diabetes mellitus, hospitalization, long-term COVID-19, post-COVID-19, post-acute COVID-19

1 | INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the pathogen responsible for the COVID-19 pandemic, which has caused morbidity and mortality at an unprecedented scale.[1,2] The pandemic has left a global burden for the long-term care of COVID-19 survivors. Evolving literature suggests that the disease affects multiple organ systems and it is imperative to study the long-term consequences of the disease.[1–6]

People with diabetes might experience worsening in control of diabetes due to COVID-19, and diabetes increases the severity and mortality related to acute COVID-19.[1,2,7–9] The long-term consequences for patients with diabetes are not known. To our knowledge, no studies based on nationwide data, have examined post-acute COVID-19 conditions in people with diabetes. The possible composition of a post-Covid-19 syndrome has been suggested in a review by Raveendran,[10] and a few papers have been published focusing on self-reported post-acute COVID-19 symptoms. Two case-control studies give data on self-reported post-acute COVID-19 symptoms[11,12] and a small descriptive study on 42 people with diabetes suggests that long-term persistent symptoms of COVID-19 were common 9 months after infection.[13]

We aimed to study post-acute COVID-19 hospitalizations in patients with type 1 and type 2 diabetes and in diabetes of uncertain type. Within a Danish nationwide cohort, we examined the risk of post-acute hospitalizations and death in those hospitalized with COVID-19, compared to patients with diabetes who had not been hospitalized with COVID-19. Hospitalizations were grouped according to major diagnostic groups in the International Classification of Diseases (ICD10 version) in the cardiovascular system, the respiratory system, diseases of the blood and blood-forming organs, the nervous system, and infections.

What is already known?

- The consequences of COVID-19 hospitalizations in diabetes mellitus are not known.
- We asked: Do patients with diabetes, hospitalized with COVID-19, have an increased risk of post-acute COVID hospitalizations, compared to patients with diabetes not hospitalized with COVID-19?

What this study has found?

- Patients with type 2 diabetes/diabetes of uncertain type had an increased risk of death and post-acute COVID hospitalizations (respiratory system, infections).
- Patients with type 1 diabetes may mirror those with type 2 diabetes but the confidence intervals were wide, and therefore there is considerable uncertainty around the true associations.

What are the implications of the study?

- Special attention should be given to patients with type 2 diabetes, and uncertain type, who have been hospitalized with COVID-19.

2 | METHODS

2.1 | Setting and data

In Denmark healthcare is available free of charge for all citizens. The total population is approximately 5.8 million and more than 90% are Caucasians. As all contacts in the health care system in Denmark are based on an individual's civil registration number, the possibility for a valid linkage between various national registries is provided. This allows us to conduct a nationwide population-based cohort study, where we combine data from the Danish National Patient Registry[14] and the Danish Civil Registration System.[15] The Danish National Patient Registry provides data on all discharges from Danish hospitals[14] and includes dates of admission and discharge and discharge diagnoses based on the ICD-10. The Danish Civil Registration System includes data on the civil registration number, date of birth and death, sex and emigration.

2.2 | Study population

The study population comprised all Danish citizens ≥18 years old as of 1 March 2020 who had one or more diabetes diagnoses (ICD-10: DE10 [type 1 diabetes mellitus] or DE11 [type 2 diabetes mellitus]) between 1 March 2015 and 1 March 2020 (pandemic start in Denmark). For the specified 5-year calendar period, the cohort was split into three groups according to the type of diabetes: only type 1 diagnosis, only type 2 diagnoses, and both type 1 and type 2 diagnostic codes (uncertain type of diabetes).

2.3 | Exposed and unexposed cohort

A patient was considered exposed if he/she had a registered hospitalization due to COVID-19 with primary diagnoses being coronavirus infection, unspecified site

(ICD-10: B342A) or coronavirus with the severe respiratory syndrome (ICD-10: B972A). In this case, to be hospitalized with COVID-19 required a ≥12-h hospitalization. Multiple hospitalizations were considered as belonging to the same sequence if there were 14 days or less between hospitalizations due to COVID-19, and the length of stay accounted for all the time between the first and last registration in such a sequence. If a patient had multiple non-connected hospitalizations for COVID-19, only the first hospitalization was considered. A patient was considered unexposed when he/she was not hospitalized with COVID-19 between 1 March 2020 and the end of the follow-up (January 4, 2022), or the first registered event of interest.

2.4 | Outcomes

We considered the following outcomes based on diagnoses registered in the National Patient Registry (ICD10 version). * indicates that all subgroups of the diagnoses are included.

(i) Hospitalization within the following categories (groups ii, iii, iv, v or vi below),
(ii) Hospitalization with diseases of the cardiovascular system (ICD-10: I*),
(iii) Hospitalization with diseases of the respiratory system (ICD-10: J*),
(iv) Hospitalization with diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism (ICD-10: D5*, D6*, D7*, D8*),
(v) Hospitalization with diseases of the nervous system (ICD-10: G*),
(vi) Overall hospitalizations with infections excluding coronavirus infection. See Table S1 for the included types of infections.

We furthermore examined death after discharge with COVID-19 as an outcome.

The outcome was disregarded if an exposed patient experienced an outcome of interest (hospitalization as mentioned above or death) within 14 days after discharge for their COVID-19 hospitalization. The rationale is that a re-admission occurring within 14 days is unlikely to be a post-acute COVID-19 problem, but is rather related to the acute COVID-19 hospitalization.

2.5 | Additional information

Data from the Danish civil registration system provided information on sex, date of birth and death. Age was categorized into four groups (18–40, 41–60, 61–80 and ≥80 years). Charlson Comorbidity Index (CCI) was calculated for all individuals, and CCI covers 19 diseases each of those scored according to their prognostic impact. CCI was calculated based on data from the National Patient Registry, using all relevant diagnoses within 5 years before 12 March 2020. Diabetes was excluded from the CCI (exclusion of ICD-10 DE10 and DE11 diagnoses). CCI was categorized according to no comorbidity (CCI = 0), intermediate comorbidity (CCI = 1, 2) and high comorbidity (CCI ≥ 3).[16] The National Patient Registry provided information on the usage of ventilation during COVID-19 hospitalization (Danish Classification System for surgical procedures: BGDA0). The length of diabetes was calculated as the time since the first registered diabetes diagnostic code (<5 years or ≥5 years).

2.6 | Statistical analysis

Contingency tables for main study variables according to exposed and unexposed cohorts, stratified according to the type of diabetes, were constructed. Data were analyzed using a time to event approach with COVID-19 hospitalization as a time varying exposure. Analysis time started on the date of birth,[17] and for all individuals, the study entry was specified to be 12 March 2020. The time of follow-up ended either on the date of the first diagnosis of the outcome of interest after March 12,020, or death, emigration, or end of follow-up (January 4, 2022) whichever came first. A patient with diabetes became exposed on the date of hospital discharge after hospitalization for acute COVID-19 (if such an event occurred). Thus, if a patient experienced an outcome of interest before hospitalization for COVID-19, he/she did not count as exposed in the analysis in question. To analyze if the hazard for an outcome was impacted by being hospitalized with COVID-19, we used time-to-event analyses, a Cox proportional hazards model with left-truncation at the study entry, estimating the hazards ratio (HR) along with 95% confidence intervals (95% CI). For all outcomes, a crude and adjusted analysis was performed, where adjustment was made for sex, CCI categories at study entry, and a binary indicator for the duration of diabetes. Naturally, we did not adjust for age as age was automatically counted in the model using time from birth as the time scale. The Cox proportional hazards assumption was assessed graphically using Schoenfeld residual plots. No estimates were presented if the number of outcomes in either the exposed or unexposed cohort was 5 or less.

In a sub-analysis, we included an alternative reference population. For the analyses of patients with type 2

diabetes hospitalized with COVID-19, we used a reference population of patients with type 2 diabetes hospitalized for non-COVID-19 infections. The intention was to explore whether COVID was worse than other infections in the prediction of future disease. These analyses were done only for type 2 diabetes where the dataset is most robust.

In a sensitivity analysis, instead of adjusting for the CCI score, we included each relevant co-morbid disease in the model. In the same sensitivity analysis, we also included the length of diabetes as a continuous variable.

All analyses were performed using STATA version 17 (StataCorp LP).

3 | RESULTS

3.1 | Descriptive data of the study populations of patients with diabetes

The data for the three study populations of the patient with diabetes are given in Table 1. Of 25,560 patients with type 1 diabetes, 101 were hospitalized with COVID-19 and 25,459 were not. Their median age was 62 years for those who were hospitalized, and 51 years for those who were not. Of patients with type 1 diabetes, who were hospitalized with COVID-19, 22.8% had a CCI ≥ 3, compared to 5.9% in those not hospitalized.

The type 2 diabetes cohort included 97,402 patients of which 1515 were hospitalized for COVID-19 and 95,887 were not. Their median age was 73 years for those who were hospitalized, and 69 years for those who were not. Of patients with type 2 diabetes, who were hospitalized with COVID-19, 33.1% had a CCI ≥ 3, compared to 17.8% in those not hospitalized.

Finally, of 12,253 patients with an uncertain type of diabetes 235 were hospitalized with COVID-19 and 12,018 were not. The median age was 71 years for those who were hospitalized, and 65 years for those who were not. Of the patients who were hospitalized with COVID-19, 44.7% had a CCI ≥ 3, compared to 24.5% of those not hospitalized.

3.2 | The risk of post-acute hospitalizations and death in patients with type 1 diabetes

Table 2 shows crude and adjusted HRs (aHRs) for the examined outcomes in patients with type 1 diabetes. The aHRs of hospitalizations due to respiratory diseases and infections were 1.82 (95% CI 0.81–4.07) and 1.61 (95% CI 0.77–3.39), respectively. In those with respiratory diseases, the three most frequent categories of post-acute hospitalizations were "chronic diseases in the lower part of airways" (38%), "influenza/pneumonia" (33%) and "other diseases in the airways" (13%). The three most frequent categories of post-acute hospitalizations due to infections were "respiratory infections" (25%), "skin infections" (22%), and "urological/gynaecological infections (22%). The overall risk of hospitalization, and the risk of hospitalization due to cardiovascular diseases, was not increased. Amongst those who were hospitalized with COVID-19, there were no subsequent hospitalizations in the group of diseases belonging to the blood and blood-forming organs and only three cases belonged to the nervous system. In total, 2 out of 101 patients hospitalized with COVID-19 died during follow-up (2,0%).

3.3 | The risk of post-acute hospitalizations and death in patients with type 2 diabetes

Table 3 shows crude and aHRs for the examined outcomes in patients with type 2 diabetes. The aHRs of hospitalizations due to respiratory diseases, infections and overall hospitalizations were 1.71 (95% CI 1.45–2.03), 1.87 (95% CI 1.61–2.18), and 1.35 (95% CI 1.16–1.56), respectively. In those who had been hospitalized for COVID-19, the three most frequent categories of respiratory diseases were "influenza/pneumonia" (38%), "chronic diseases in the lower part of airways" (31%), and "other diseases in the airways" (14%). The three most frequent categories of post-acute hospitalizations due to infections were "respiratory infections" (36%), "urological/gynaecological infections (23%), and "other infections" (15%). The risk of hospitalization due to cardiovascular diseases, diseases of the blood and blood-forming organs, and the nervous system was not increased. In total, 135 out of 1515 patients hospitalized with COVID-19 died during follow-up (8.9%), corresponding to an aHR of death of 2.05 (95% CI 1.73–2.43).

3.4 | The risk of post-acute hospitalizations and death in patients with diabetes of uncertain type

Table 4 shows crude and aHRs for the examined outcomes in patients with diabetes of uncertain type. In these patients, the aHR of hospitalization due to respiratory diseases and infections was 1.62 (95% CI 1.11–2.38) and 1.44 (95% CI 1.00–2.08), respectively. The most frequent categories within the respiratory and infectious diseases belonged to the same categories as mentioned above. In total, 28 out of 235 patients hospitalized with COVID-19 died during follow-up (11.9%), corresponding to an aHR of death of 1.81 (95% CI 1.24–2.64).

TABLE 1 Descriptive characteristics of the study cohorts of patients with diabetes, stratified by type of diabetes. For each cohort, descriptive data are given according to those who were hospitalized with COVID-19, and those who were not

	Type 1 diabetes (n = 25,560)		Type 2 diabetes (N = 97,402)		Mixed types (n = 12,253)	
	COVID-hospitalized	Not COVID-hospitalized	COVID-hospitalized	Not COVID-hospitalized	COVID-hospitalized	Not COVID-hospitalized
	N = 101	N = 25,459	N = 1515	N = 95,887	N = 235	N = 12,018
Age per 1 March 2020, median (25%–75% percentiles)	62 (45–74)	51 (35–64)	73 (64–80)	69 (59–76)	71 (60–78)	65 (54–74)
Patient's age per 1 March 2020 in categories (years)						
≥18–40, N (%)	18 (17.8)	8228 (32.3)	24 (1.6)	3134 (3.3)	8 (3.4)	1028 (8.6)
41–60, N (%)	31 (30.7)	9525 (37.4)	267 (17.6)	24,297 (25.3)	51 (21.7)	3735 (31.1)
61–80, N (%)	38 (37.6)	6758 (26.5)	887 (58.5)	54,493 (56.8)	137 (58.3)	6015 (50.0)
≥81, N (%)	14 (13.9)	948 (3.7)	337 (22.2)	13,963 (14.6)	39 (16.6)	1240 (10.3)
Gender						
Female, N (%)	42 (41.6)	11,298 (44.4)	610 (40.3)	41,129 (42.9)	96 (40.9)	4941 (41.1)
Male, N (%)	59 (58.4)	14,161 (55.6)	905 (59.7)	54,758 (57.1)	139 (59.1)	7077 (58.9)
Length of diabetes (time since first registered diabetes diagnosis)						
<5 years	22 (21.8)	4489 (17.6)	571 (37.7)	45,873 (47.8)	41 (17.4)	2975 (24.8)
≥5 years	79 (78.2)	20,970 (82.4)	944 (62.3)	50,014 (52.2)	194 (82.6)	9043 (75.2)
Length of diabetes (time since first registered diabetes diagnosis), years, median (25%–75% percentiles)	14 (6–17)	14 (7–17)	7 (3–12)	5 (2–10)	13 (7–15)	11 (5–15)
Charlson comorbidity index[a]						
No co-morbidity (CCI = 0)	44 (43.6)	18,822 (73.9)	424 (28.0)	41,377 (43.2)	31 (13.2)	4737 (39.4)
Intermediate co-morbidity (CCI = 1,2)	34 (33.7)	5145 (20.2)	620 (40.9)	37,433 (39.0)	99 (42.1)	4334 (36.1)
High co-morbidity (CCI ≥ 3)	23 (22.8)	1492 (5.9)	471 (31.1)	17,077 (17.8)	105 (44.7)	2947 (24.5)
Ventilation during COVID-hospitalization[b], N (%)	7 (6.9)	-	118 (7.8)	-	19 (8.1)	-
Length of hospitalization due to COVID-19, median (25%–75% percentiles)	4.9 (2.7–10.2)	-	6.7 (3.5–12.2)	-	7.9 (4.1–13.4)	-

[a]Charlson Comorbidity index = CCI.

[b]Procedure code BGDA0.

TABLE 2 Outcomes for patients with type 1 diabetes. Hazard ratios for hospitalizations and death after COVID-19 discharge in patients with type 1 diabetes, based on Cox proportional hazard models with crude and adjusted estimates with 95% confidence intervals (CI). Observation time starts at birth with left-truncation on 1 March 2020 for all subjects

	COVID-hospitalized *N* = 101		Not COVID-hospitalized *N* = 25,459		Hazard ratios (95% CI)	
Outcomes	***N* events**	**Time at risk in months**	***N* events**	**Time at risk in months**	**Crude**	**Adjusted[a]**
Hospitalization according to the first outcome of interest	9	794	8189	450,102	1.20 (0.62–2.31)	1.02 (0.53–1.97)
Hospitalization with diseases of the cardiovascular system (ICD-10: I[b])	7	1309	4969	495,370	1.00 (0.48–2.10)	0.83 (0.39–1.74)
Hospitalization with diseases of the respiratory system (ICD-10: J[b])	6	1769	1404	546,703	2.49 (1.11–5.58)	1.82 (0.81–4.07)
Hospitalization with diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism (ICD-10 D5[b], D6[b], D7[b], D8[b])	0	0	516	557,156	-	-
Hospitalization with diseases of the nervous system (ICD-10: G[b])	3	2040	2665	527,554	-	-
Hospitalization with infection	7	1576	2201	537,844	1.96 (0.93–4.13)	1.61 (0.77–3.39)
Death	2	1985	745	554,094	-	-

[a]Adjusted for gender, Charlson Comorbidity Index (3 groups) and diabetes length ≥5 years.

[b]All subtypes.

TABLE 3 Outcomes for patients with type 2 diabetes. Hazard ratios for hospitalizations and death after COVID-19 discharge in patients with type 2 diabetes, based on Cox proportional hazard models with crude and adjusted estimates with 95% confidence intervals (CI). Observation time starts at birth with left-truncation on 1 March 2020 for all subjects

	COVID-hospitalized *N* = 1515		Not COVID-hospitalized *N* = 95,887		Hazard ratios (95% CI)	
Outcomes	***N* events**	**Time at risk in months**	***N* events**	**Time at risk in months**	**Crude**	**Adjusted[a]**
Hospitalization according to the first outcome of interest	181	9256	47,169	1,453,253	1.40 (1.21–1.62)	1.35 (1.16–1.56)
Hospitalization with diseases of the cardiovascular system (ICD-10: I[b])	164	16,060	33,479	1,658,853	1.01 (0.86–1.17)	0.94 (0.80–1.09)
Hospitalization with diseases of the respiratory system (ICD-10: J[b])	137	23,167	12,324	1,967,800	1.86 (1.57–2.20)	1.71 (1.45–2.03)
Hospitalization with diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism (ICD-10 D5[b], D6[b], D7[b], D8[b])	44	30,487	4675	2,064,947	1.18 (0.87–1.58)	1.07 (0.80–1.44)
Hospitalization with diseases of the nervous system (ICD-10: G[b])	70	28,620	11,178	1,975,987	0.93 (0.74–1.18)	0.87 (0.69–1.10)
Hospitalization with infection	172	20,998	15,686	1,937,007	2.01 (1.73–2.34)	1.87 (1.61–2.18)
Death	135	28,451	9514	2,013,561	2.21 (1.87–2.62)	2.05 (1.73–2.43)

[a]Adjusted for gender, Charlson Comorbidity Index (3 groups) and diabetes length ≥5 years.

[b]All subtypes.

TABLE 4 Outcomes for patients with diabetes of uncertain type. Hazard ratios for hospitalizations and death after COVID-19 discharge in patients with diabetes of uncertain type, based on Cox proportional hazard models with crude and adjusted estimates with 95% confidence intervals (CI). Observation time starts at birth with left-truncation on 1 March 2020 for all subjects

	COVID-hospitalized $N = 235$		Not COVID-hospitalized $N = 12{,}018$		Hazard ratios (95% CI)	
Outcomes	***N* events**	**Time at risk in months**	***N* events**	**Time at risk in months**	**Crude**	**Adjusted[a]**
Hospitalization according to the first outcome of interest	28	1307	7442	155,996	1.03 (0.71–1.50)	0.87 (0.60–1.26)
Hospitalization with diseases of the cardiovascular system (ICD-10: I[b])	25	2067	5578	186,034	0.81 (0.55–1.20)	0.69 (0.46–1.02)
Hospitalization with diseases of the respiratory system (ICD-10: J[b])	27	3341	1872	242,751	2.05 (1.40–3.00)	1.62 (1.11–2.38)
Hospitalization with diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism (ICD-10 D5[b], D6[b], D7[b], D8[b])	5	4669	755	256,796	0.68 (0.28–1.65)	0.57 (0.24–1.37)
Hospitalization with diseases of the nervous system (ICD-10: G[b])	13	4150	2386	233,784	0.65 (0.37–1.12)	0.59 (0.34–1.02)
Hospitalization with infection	29	3045	2778	231,623	1.70 (1.18–2.45)	1.44 (1.00–2.08)
Death	28	4553	1436	249,584	2.16 (1.48–3.15)	1.81 (1.24–2.64)

[a]Adjusted for gender, Charlson Comorbidity Index (3 groups) and diabetes length ≥5 years.

[b]All subtypes.

3.5 | Sub- and sensitivity analyses

In the sub-analysis, using the alternative reference population, we found that patients with type 2 diabetes hospitalized with COVID-19 did not have worse long-term outcomes than patients with type 2 diabetes hospitalized with other infections (data not shown). An exception though was respiratory diseases with an aHR of 1.14 (95% 0.93–1.39). In the sensitivity analysis, we included each relevant co-morbid disease in the regression model instead of CCI, and we included the length of diabetes as a continuous variable. These analyses did not change any of the conclusions (data not shown).

4 | DISCUSSION

In patients with type 2 diabetes, hospitalization with COVID-19 was associated with an increased risk of post-acute hospitalizations, a 1.7-fold increased risk of respiratory diseases, a 1.9-fold increased risk of infections, and a 2.0-fold increased risk of death. The results for patients with diabetes of uncertain type were similar to the results in patients with type 2 diabetes. The results for people with type 1 diabetes appear to mirror those for people with type 2 diabetes, but there were wide confidence intervals and therefore there is considerable uncertainty around the true associations. It was reassuring that neither patients with type 1 nor type 2 diabetes had an increased risk of post-acute COVID-19 hospitalization due to cardiovascular diseases, nervous system diseases, or diseases related to the blood and blood-forming organs. This study specifically estimates the risk of severe outcomes after a COVID-19 hospitalization as our outcomes are captured as hospitalizations. It is well known that there is a conglomeration of post-COVID-19 symptoms including fatigue, breathlessness myalgia and headache,[10,11] but our study does not measure these outcomes. Whether patients with diabetes are at special risk of long-term consequences after hospitalization with COVID-19, or after just a positive test for COVID-19, still has to be settled. Diabetes and especially poorly controlled diabetes increases the severity of COVID-19 and is associated with increased morbidity and mortality,[10,18,19] and furthermore, complex underlying interactions involving hyperlipidemia, islet β-cell hyperinsulinemia, hypertension and hyperglycemia have been suggested.[18] It is, however, unknown whether such interacting mechanisms are significant with regard to the long-term consequences of COVID-19. Our study contributes to knowledge of post-acute consequences in terms of hospitalizations after hospitalization with COVID-19 in diabetic patients. When studying "long-term" consequences, the length of follow-up

time is critical. At present, we can study post-acute hospitalizations that have occurred within approximately 2 years (from the pandemic start until the last update of our dataset), and our results should be seen from this perspective. The choice of the reference population is also relevant to discuss. We chose a reference population of patients with diabetes because otherwise, it would be difficult fully to adjust for factors related to diabetes and diabetic-related outcomes. Furthermore, we wanted the reference population to be patients with type 1, type 2 or diabetes of uncertain type, who were not hospitalized for COVID to get an indication of whether severe COVID (measured by hospitalization for COVID) had an impact on post-acute COVID-19 disease and death. Therefore, we used non-hospitalized patients with diabetes as references. Another relevant question would be whether a COVID-19 infection is worse than other infections in the prediction of future disease, and our sub-analysis indicated that it was not the case, except for respiratory diseases.

To our knowledge, no nationwide studies have examined post-acute hospitalizations in patients with type 1 and type 2 diabetes. Former publications have concentrated on reporting post-acute COVID-19 symptoms and not on hospitalizations. One case-control study showed a high prevalence of post-COVID-19 fatigue in patients with type 2 diabetes (based on 52 cases who had proven COVID-19 by reverse transcriptase polymerase chain reaction, compared to 56 who had not).[11] The average time of presenting patients' symptoms was 92 days.[11] Another case-control study was based on patients with diabetes hospitalized for COVID-19 ($n = 145$ patients) and matched non-diabetic patients as controls ($n = 290$).[12] The study assessed a variety of post-COVID symptoms 7 months after discharge based on telephone interviews and showed that the most prevalent symptoms were fatigue, dyspnea on exertion, and musculoskeletal pain (66.2%, 53.8%, and 44.8%, respectively). This study, however, did not distinguish between type 1 and type 2 diabetes, did not use diabetic patients as controls, and did not report post-acute hospitalizations.[12] A small descriptive study on 42 patients with diabetes suggested that long-term persistent symptoms of COVID-19 were common 9 months after infection.[13] Several studies have discussed whether there is a link between patients with COVID-19 and post-acute cardiovascular complications,[20,21] but our study does not support that diabetic patients who have been hospitalized with COVID-19 have a subsequently increased risk of hospitalizations due to cardiovascular diseases.

Ayoubkhani et al. confirmed the severity of post-COVID-19 in general for patients who had been hospitalized for COVID-19.[22] The study showed that individuals discharged from the hospital after COVID-19 had increased rates of multiorgan dysfunction, with a risk of death after hospitalization with COVID-19 of 12.3%.[22] The study did not analyze data on patients specifically with diabetes, but the overall risk of death reported by Ayoubkhani et al. is similar to our findings in patients with type 2 diabetes and diabetes of uncertain type (9% and 12% died, respectively).

This study has important strengths. The nationwide design provides a study on unselected cohorts of patients with diabetes in Denmark, and therefore our results can be widely generalized. One of the most important strengths is that the Danish national registries comprise unique and valid data,[14,23,24] in which it is possible to study long-term health outcomes. In addition, we were able to assess post-acute hospitalizations from a variety of different organ systems. Due to valid record linkage between registries, and mandatory registration to the Danish health registries, our study virtually has no patients who were lost to follow-up, which prevents selection bias. Furthermore, information on the exposure and outcomes was collected independently of the hypothesis, thereby preventing information bias.

The study also has limitations. We cannot rule out that the higher post-acute risks may be associated with a priory risk factor that we could not adjust for. However, we do not see a general increased post-acute risk across all our outcomes which may speak for a specific relation to COVID, and not just a consequence of severe illness requiring hospitalization. Unknown confounders and residual confounding can never be ruled out in an observational study like ours. We did not have data on the type of COVID-19 variant, but in our study period, most patients with a COVID-19 hospitalization were infected with the first variants, i.e. Wuhan, alpha and delta. One study has found a linearly increasing trend in the likelihood of COVID-19 hospitalization with increasing body weight.[25] As we did not have information on body weight we cannot rule out body weight as a confounder. It is, however unlikely that body weight is a major confounder as we compare type 2 diabetes patients with a COVID-19 hospitalization to other type 2 diabetes patients. The same argument applies to the analyses of patients with type 1 diabetes and diabetes of uncertain type. Also, we did not have access to data on glycaemic control, and whilst data regarding the impact of COVID-19 on diabetes regulation are conflicting, poor glycaemic control seems to be associated with a longer stay of hospitalization and high mortality.[26] We did not have data on ethnicity or socio-economic status, and cannot rule out an impact of these factors.

COVID-19 causes post-acute COVID-19 symptoms,[1] but the critical questions are to what degree it affects long-term health and which patient categories are at special risk. In our study, patients with type 2 diabetes and diabetes of uncertain type, who were hospitalized with COVID-19, had a significantly increased risk of post-acute hospitalization for respiratory and infectious diseases, and a 2-fold increased risk of death. It was

reassuring that neither patients with type 1 diabetes, type 2 diabetes nor diabetes of uncertain type had an increased risk of post-acute COVID-19 hospitalization due to cardiovascular diseases, nervous system diseases, or diseases related to the blood and blood-forming organs. Clinicians should pay special attention to patients with diabetes who have been hospitalized with COVID-19, and in particular, be alert to symptoms from the respiratory system and infections.

AUTHOR CONTRIBUTIONS

Bente Mertz Nørgård: conception, design, assistance with data analysis, interpretation of results, manuscript writing and editing and approved the final version. Floor Dijkstra Zegers: design, data analysis, interpretation of results, manuscript editing and approved the final version. Jan Nielsen: design, data collection, data analysis, interpretation of results, manuscript editing and approved the final version. Jens Kjeldsen and Claus Bogh Juhl: interpretation of results, manuscript editing and approved the final version.

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None.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

According to Danish legislation, our own approvals to use these register data for the current study do not allow us to distribute or make patient data directly available to other parties. Any interested researchers may apply for access to data through an application to the Research Service at the Danish Health Data Authority (forskerservice@sundhedsdata.dk). Access to data from the Danish Health Data Authority requires approval from the Danish Data Protection Agency. The authors of this paper do not have special access privileges to the data used in the current study.

ETHICS STATEMENT

This study follows all currently applicable Danish laws regarding scientific research. According to Danish law, no ethical approvals of register-based studies are necessary. The study was approved by the Danish Data Protection Agency (j.nr. 20/16376). The study was non-interventional and did not require direct patient contact or influence on the patient's treatment.

PATIENT AND PUBLIC INVOLVEMENT

Patient representatives are part of the research committee at our department, and they have participated in the discussion about the study outcome measurements. The patient representatives were not involved in the design of the study or in the writing of the paper.

GUARANTOR/PRINCIPAL INVESTIGATOR STATEMENT

Bente Mertz Nørgård, Center for Clinical Epidemiology, Odense University Hospital, Odense C, Denmark, is the guarantor of the manuscript.

ORCID

Bente Mertz Nørgård https://orcid.org/0000-0002-9514-3033
Floor Dijkstra Zegers https://orcid.org/0000-0002-8318-5332
Claus Bogh Juhl https://orcid.org/0000-0002-4285-5459
Jens Kjeldsen https://orcid.org/0000-0001-8148-6572
Jan Nielsen https://orcid.org/0000-0002-7634-6812

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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