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Comorbidities and COVID-19 hospitalization, ICU admission and hospital mortality in Austria

A retrospective cohort study

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Summary
Background The protection of vulnerable populations is a central task in managing the Coronavirus disease 2019 (COVID-19) pandemic to avoid severe courses of COVID-19 and the risk of healthcare system capacity being exceeded. To identify factors of vulnerability in Austria, we assessed the impact of comorbidities on COVID-19 hospitalization, intensive care unit (ICU) admission, and hospital mortality.
Methods A retrospective cohort study was performed including all patients with COVID-19 in the period February 2020 to December 2021 who had a previous inpatient stay in the period 2015–2019 in Austria. All patients with COVID-19 were matched to population controls on age, sex, and healthcare region. Multiple logistic regression was used to estimate adjusted odds ratios (OR) of included factors with 95% confidence intervals (CI).
Results Hemiplegia or paraplegia constitutes the highest risk factor for hospitalization (OR 1.61, 95% CI 1.44–1.79), followed by COPD (OR 1.48, 95% CI 1.43–1.53) and diabetes without complications (OR 1.41, 95% CI 1.37–1.46). The highest risk factors for ICU admission are renal diseases (OR 1.76, 95% CI 1.61–1.92), diabetes without complications (OR 1.57, 95% CI 1.46–1.69) and COPD (OR 1.53, 95% CI 1.41–1.66). Hemiplegia or paraplegia, renal disease and COPD constitute the highest risk factors for hospital mortality, with ORs of 1.5. Diabetes without complications constitutes a significantly higher risk factor for women with respect to all three endpoints.
Conclusion We contribute to the literature by identifying sex-specific risk factors. In general, our results are consistent with the literature, particularly regarding diabetes as a risk factor for severe courses of COVID-19. Due to the observational nature of our data, caution is warranted regarding causal interpretation. Our results contribute to the protection of vulnerable populations and may be used for targeting further pharmaceutical interventions.

Keywords Epidemiology · Risk factors · Underlying conditions · Sex differences · Charlson comorbidity index

Availability of data and materials Data are available upon request for researchers who meet the criteria for access to confidential data.

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Background

At the end of February 2020 the first cases of the ongoing severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic were reported in Austria associated with one of the first European superspreading events. After a first peak in case numbers and hospitalizations in March and April 2020, the highest case numbers and hospitalizations have been ob-

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served during a second peak in November with 706 intensive care unit (ICU) beds occupied by patients with Coronavirus disease 2019 (COVID-19) accounting for 34% of the total number of ICU beds for adults in Austria. In a third peak in April 2021 and a fourth peak in December 2021, ICU occupancy exceeded 600 patients with COVID-19. Due to regional variation in COVID-19 incidence and ICU capacities, COVID-19 associated occupancy rates reached almost 70% in some regions leading to substantial pressure on the Austrian healthcare system, characterized by high ICU bed density compared to other countries [1].

To protect vulnerable populations, numerous protective measures were implemented including special working conditions or duty leave. The Austrian COVID-19 risk group regulation defines the high-risk group based on medical conditions, such as chronic lung diseases, chronic heart diseases or cancer drawing from available evidence by May 2020.

Recent literature identifies similar conditions as risk factors for severe courses of COVID-19, although ranking and magnitude differs across available studies. Based on a national surveillance study in Ireland, Bennett et al. identified body mass index (BMI) $\geq 40\,kg/m^2$ (OR 2.89, 95% CI 1.80–4.64), cancer (OR 2.77, 95% CI 2.21–3.47), chronic renal disease (OR 1.74, 95% CI 1.35–2.24) and chronic neurological condition (OR 1.41, 95% CI 1.17–1.69) as highest risk factors for COVID-19 mortality [2]. In a cohort study capturing the first wave of the pandemic in Scotland, McGurnaghan et al. identified diabetes as a risk factor for fatal or critical care unit-treated COVID-19 with an OR of 1.40 (95% CI 1.30–1.49) [3]. A surveillance study in Spain showed significant associations between chronic renal disease (OR 1.47, 95% CI 1.29–1.68) and diabetes (OR 1.23, 95% CI 1.14–1.33) and mortality among chronic conditions in hospital cases [4]. Ahlström et al. identified asthma (OR 3.61, 95% CI 2.76–4.71), type 2 diabetes (OR 2.42, 95% CI 2.10–2.79), obesity (OR 2.33, 95% CI 1.78–3.05) and chronic renal failure (OR 2.28, 95% CI 1.62–3.23) as the strongest risk factors for ICU admission among comorbidities diagnosed in the preceding 5-year period in Sweden. In this Swedish study, cancer (OR 0.93, 95% CI 0.72–1.20) was not identified as a risk factor for ICU admission [5]. Focusing on patients with diabetes in Sweden Rawshani et al. identified type 2 diabetes as a significant risk factor for hospitalization (hazard ratio, HR 1.40, 95% CI 1.34–1.47), ICU admission (HR 1.42, 95% CI 1.25-1.62), and death due to COVID-19 (HR 1.50, 95% CI 1.39–1.63) (HR adjusted for sociodemographic factors, pharmacological treatment and comorbidities) based on a cohort study [6]. Using the comorbidity classification of the Charlson comorbidity index (CCI), Cho et al. identified renal disease (OR 4.95, 95% CI 2.37–10.31), diabetes (OR 2.22, 95% CI 1.63–2.95), congestive heart failure (OR 2.14, 95% CI 1.42–3.23) and cancer (OR 1.88, 95% CI 1.17–3.02) as risk factors for mortality in patients with COVID-19 based on a cohort study in South Korea [7].

However, only few surveillance studies representative of the general population have been reported and observational studies on COVID-19 disease risk and severity may suffer from selection bias (collider bias) when samples rely on hospitalization with COVID-19 or voluntary participation [8, 9]. In addition, study results on the impact of major chronic conditions such as cancer on COVID-19 outcomes remain heterogeneous and inconclusive.

Furthermore, hardly any cohort studies on sex differences of comorbidities as risk factors for COVID-19 outcomes exists. In a literature review Kautzky-Willer analyzed sex differences with respect to risk factors for severe courses of COVID-19 [10]. Kautzky-Willer hypothesized that diabetes mellitus constitutes a higher risk factor for women compared to men due to biological factors; however, systematic empirical literature is missing for evaluating this hypothesis. In order to fill these gaps, we estimate the effect of comorbidities on COVID-19 hospitalization, ICU admission, and mortality, based on a matched cohort study using nationwide hospital billing data from Austria.

Methods

We performed a retrospective cohort study including all patients with COVID-19 in the period February 2020 to December 2021 who had an inpatient stay during the period 2015–2019 in Austria ($N = 46{,}740$). For each COVID-19 patient and outcome, we randomly drew five controls of the same age group, sex and healthcare region from the general inpatient population 2015–2019 without COVID-19 hospitalization ($N = 3{,}558{,}072$). We employed exact matching as an enrichment design in order to have a control group balanced at baseline. This is particularly important for young age-groups, which would be underrepresented in the control group without matching. Including healthcare region as a matching variable allows to control for the spatial variation in COVID-19 incidence and associated pressure on health system capacities across Austria. The choice of an appropriate baseline and follow-up period involves a trade-off between comprehensiveness and attrition. Choosing the 5-year period before the spread of COVID-19 in Austria (2015–2019) allows for measuring major baseline comorbidities, which is in line with the Swedish cohort study of Ahlström et al. [5]. In order to reduce attrition bias, we only included patients with a contact in the inpatient, outpatient or ambulatory care setting in 2019. Additionally, we excluded all patients discharged dead during 2019. However, we are not able to control for attrition with respect to other places of death due to lack of linked data, which is a caveat for analyzing severe comorbidities such as metastatic solid tumors. Due to the limited availability of data on comorbidities for other healthcare settings in Aus-

tria, we focused on the hospital inpatient sector as our study population. This approach limits generalizability, as the Austrian inpatient population accounts for only 40% of the general population. Aiming at identifying vulnerable population groups, we consider this limitation as acceptable as we can assume that most of the vulnerable population has an inpatient stay within a 5-year period.

Aiming at estimating causal effects using observational data, we used the target trial framework to organize our study design around our causal question for the example of the effect of the "exposure" diabetes on the risk of COVID-19 ICU admission [11, 12]. Ideally, we would like to measure the causal effect of diabetes on COVID-19 associated ICU admission based on a randomized control trial, where patients in the treatment group are randomly assigned to the exposure of diabetes and the per protocol effect is calculated as the relative cumulative risk of an ICU admission with COVID-19 as principal or additional diagnosis among individuals assigned to each treatment strategy (see Table 7).

The main data source for this cohort study are hospital billing data related to the Austrian Diagnosis Related Groups(DRG)-like system (*Leistungsorientierte Krankenhausfinanzierung*) administrated by the Federal Ministry of Social Affairs, Health, Care and Consumer Protection. Besides demographic information on sex and age group, these data include patient level information on principal and additional diagnoses (based on the International Statistical Classification of Diseases and Related Health Problems 10th Revision, ICD10). Data for the year 2021 are preliminary and may be subject to revision. COVID-19 is considered both as main and additional diagnosis because patients with COVID-19 as additional diagnosis often have main diagnoses associated with COVID-19 from a clinical perspective. Patients without valid patient IDs (i.e., 9% of all acute care admissions in 2019) had to be excluded as they cannot be matched over time. Moreover, patients who were not discharged by 31 December 2021 are not included.

For measuring comorbidities at baseline we consider all principal and additional diagnosis in the 5-year pre-COVID-19 period (2015–2019) and use categories of medical conditions according to the Charlson comorbidity index (CCI) [13] following the strategy of the comorbidity analysis of Cho et al. [7]. The advantage of clustering diagnosis to patient collectives according to the CCI is to obtain an easily comparable number of 19 comorbidities. We used the R package comorbidity [14] for mapping principal and secondary ICD-10 diagnosis codes with categories of medical conditions and computing CCI. For instance, type 1 diabetes mellitus without complications (ICD-10 E10.9) is categorized as diabetes without complication in the CCI. We additionally stratify for sex to account for potential sex differences in the impact of comorbidities on COVID-19 outcomes. While including sex as an interaction effect would increase statistical power due to larger sample size, we decided for stratification because of simpler interpretation of the adjusted odds ratios in the logistic regression model.

As robustness check, we use more granulated diagnoses categories based on the following aggregation strategy. As a starting point we aggregated the ICD-10 diagnoses at category level (e.g., E66: obesity). In order to avoid very low numbers of diagnoses we further aggregated diagnosis below a cut-off value of 0.5% to groups (e.g., E70–E90 metabolic disorders). In case of low frequencies of groups (below a cut-off of 1%) we further aggregated them to chapters (e.g., E00–E90: endocrine, nutritional and metabolic diseases) in order to analyze frequent categories (with a frequency above 0.5% of all documented diagnoses) individually while controlling for less frequent diagnosis as potential confounders. We considered chapter VII (diseases of the eye and adnexa) and VIII (diseases of the ear and mastoid process) as irrelevant conditions from a medical perspective and excluded them from the analysis. The aggregation strategy led to a list of 67 comorbidities.

For the primary analysis, we employ multivariable logistic regression to estimate adjusted odds ratios (OR) with 95 confidence intervals (95% CI) of comorbidities on the outcomes COVID-19 hospitalization, ICU admission, and hospital mortality using the 'glm' function of the 'stats' package and the 'summ' function of the 'jtools' package in R [15].

Additionally, we calculate unadjusted risk ratios for each comorbidity without controlling for other comorbidities based on age and sex-standardized incidence rates of patients with a COVID-19 ICU admission compared to the control group without a COVID-19 hospitalization. We compute p-values based on χ^2-tests, where the family-wise error rate is controlled for with the Holm method to reduce the likelihood of type 1 errors (false positives). Unless otherwise stated, we choose an alpha-level of 0.05 for statistical significance.

Results

Descriptive analysis

In the period February 2020 to December 2021, 1.26 million COVID-19 cases were identified in Austria. This represents a prevalence of identified cases of 14.2% of the total population. Thereof 13,360 died (case fatality rate, CFR: 1.06%), 68,183 were hospitalized (5.41%), and 11,793 were admitted to ICUs (0.94%) (see Table 1). Men show higher risks with respect to all three endpoints. This is particularly the case for ICU admissions, where rates for men (1.21%) are 83% higher compared to women (0.66%). Out of the 13,360 COVID-19 associated deaths 11,683 (87%) were registered in hospitals.

Table 1 COVID-19 incidence and outcomes (hospitalizations, ICU admissions, mortality) in Austria (26 Feb. 2020–31 Dec. 2021)

Sex	Age (years)	Detected cases		Mortality			Hospitalization			ICU admission			Hospital mortality		
		N	Incidence (Per 100k pop)	*N*	Incidence (Per 100k pop)	Proportion (% Cases)	*N*	Incidence (Per 100k pop)	Proportion (% Cases)	*N*	Incidence (Per 100k pop)	Proportion (% Cases)	*N*	Incidence (Per 100k pop)	Proportion (% Cases)
M	0–19	139,351	15,741.5	8	0.9	0.01	873	98.6	0.63	86	9.7	0.06	9	1.0	0.01
M	20–39	198,801	16,693.6	41	3.4	0.02	2,269	190.5	1.14	345	29.0	0.17	35	2.9	0.02
M	40–49	92,225	15,587.1	78	13.2	0.08	2,941	497.1	3.19	583	98.5	0.63	74	12.5	0.08
M	50–59	95,719	13,691.8	347	49.6	0.36	6,047	865.0	6.32	1,469	210.1	1.53	354	50.6	0.37
M	60–69	49,919	10,205.1	897	183.4	1.80	6,854	1,401.2	13.73	1,933	395.2	3.87	938	191.8	1.88
M	70–79	28,697	8,301.9	2,008	580.9	7.00	8,305	2,402.6	28.94	2,078	601.2	7.24	1,996	577.4	6.96
M	80+	18,920	10,686.4	3,803	2,148.0	20.10	8,579	4,845.6	45.34	1,067	602.7	5.64	3,291	1,858.8	17.39
M	Tot	623,632	14,242.2	7,182	164.0	1.15	35,868	819.1	5.75	7,561	172.7	1.21	6,697	152.9	1.07
F	0–19	129,119	15,450.9	3	0.4	0.00	901	107.8	0.70	69	8.3	0.05	2	0.2	0.00
F	20–39	199,856	17,436.1	17	1.5	0.01	3,091	269.7	1.55	228	19.9	0.11	21	1.8	0.01
F	40–49	102,465	17,214.6	47	7.9	0.05	2,075	348.6	2.03	242	40.7	0.24	45	7.6	0.04
F	50–59	96,180	13,783.5	149	21.4	0.15	3,672	526.2	3.82	595	85.3	0.62	147	21.1	0.15
F	60–69	46,243	8,777.1	434	82.4	0.94	4,490	852.2	9.71	927	175.9	2.00	425	80.7	0.92
F	70–79	30,798	7,271.7	1,148	271.1	3.73	6,810	1,607.9	22.11	1,265	298.7	4.11	1,106	261.1	3.59
F	80+	32,624	10,984.5	4,380	1,474.8	13.43	11,276	3,796.6	34.56	906	305.1	2.78	3,240	1,090.9	9.93
F	Tot	637,285	14,092.1	6,178	136.6	0.97	32,315	714.6	5.07	4,232	93.6	0.66	4,986	110.3	0.78
M + F	Tot	1,260,917	14,165.9	13,360	150.1	1.06	68,183	766.0	5.41	11,793	132.5	0.94	11,683	131.3	0.93

Authors' calculation based on [16, 17]
Pop refers to total population, *k* refers to 1000, and proportions refer to detected cases. Patients without valid patient IDs and patients who were not discharged by 31 December 2021 are not included
ICU intensive care unit

Table 2 COVID-19 hospitalizations, ICU admissions and hospital mortality of the study population (26 Feb. 2020–31 Dec. 2021)

Sex	Age (years)	Study population	Hospitalization		ICU admission		Hospital mortality	
		N	*N*	Per 100k pop	*N*	Per 100k pop	*N*	Per 100k pop
M	0–19	278,199	340	122.2	41	14.7	10	3.6
M	20–39	285,333	1,115	390.8	186	65.2	28	9.8
M	40–49	196,526	1,809	920.5	368	187.3	65	33.1
M	50–59	289,204	3,822	1,321.6	984	340.2	345	119.3
M	60–69	252,839	5,081	2,009.6	1,425	563.6	924	365.4
M	70–79	230,143	7,240	3,145.9	1,495	649.6	2,049	890.3
M	80+	109,093	4,654	4,266.1	404	370.3	1,954	1,791.1
M	Tot	1,641,337	24,061	1,465.9	4,903	298.7	5,375	327.5
F	0–19	229,341	451	196.7	29	12.6	–	–
F	20–39	516,913	2,019	390.6	179	34.6	25	4.8
F	40–49	230,508	1,431	620.8	207	89.8	52	22.6
F	50–59	289,878	2,412	832.1	415	143.2	161	55.5
F	60–69	248,482	3,373	1,357.4	724	291.4	417	167.8
F	70–79	268,097	6,541	2,439.8	977	364.4	1,276	475.9
F	80+	180,256	6,452	3,579.4	404	224.1	2,074	1,150.6
F	Tot	1,963,475	22,679	1,155.0	2,935	149.5	4,005	204.0
M + F	Tot	3,604,812	46,740	1,296.6	7,838	217.4	9,380	260.2

Authors' calculation based on [16, 17]
Pop refers to total population, *k* refers to 1000, and proportions refer to detected cases. Patients without valid patient-IDs and patients who were not discharged by 31 Dec 2021 are not included
ICU intensive care unit

Table 2 shows summary statistics for the study population ($N = 3{,}604{,}812$) representing 40.4% of the Austrian population, 68.6% of COVID-19 hospitalizations, 66.5% of ICU admissions and 80.3% of COVID-19 patients discharged dead. A proportion of 1.30% of the study population had a COVID-19 associated hospitalization in the study period, which is 69% higher compared to the total population (0.766%).

Multivariable analysis

The following results refer to the effects of comorbidities on COVID-19 hospitalization, ICU admission and hospital mortality, based on logistic regression analysis, expressed as adjusted ORs and 95% CIs. For our primary analysis we use CCI categories for clustering comorbidities. Our results are robust with respect to other diagnosis clustering strategies (see Table 8 for results at category, group and chapter levels).

For the endpoint of COVID-19 hospitalization, hemiplegia or paraplegia (OR 1.61, 95% CI 1.44–1.79), COPD (OR 1.48, 95% CI 1.43–1.53) and diabetes without complications (OR 1.41, 95% CI 1.37–1.46) constitute the comorbidities with the highest risk (see Table 3 and Fig. 1a). We observe significant sex differences for diabetes without complications, which is a higher risk factor for women. In general, the results are robust with respect to different clustering of diagnosis. Considering diagnoses at category level obesity (OR 1.35, 95% CI 1.29–1.40) and type 2 diabetes mellitus (OR 1.34, 1.30–1.38) constitute similar risk factors as summarized under the CCI category of diabetes with and without complications (see Table 8).

Table 4 shows the results of the logistic regression for the endpoint COVID-19 ICU admissions. Renal disease (OR 1.76, 95% CI 1.61–1.92), diabetes without complications (OR 1.57, 95% CI 1.46–1.69) and COPD (OR 1.53, 95% CI 1.41–1.66) constitute the highest risk factors. As for the endpoint of COVID-19 hospitalization, diabetes without complications is a higher risk factor for women (OR 2.00, 95% CI 1.77–2.26) compared to men (OR 1.39, 95% CI 1.27–1.52) (see also Fig. 1b). The results are robust with respect to different clustering of diagnoses. Considering diagnoses at category level obesity (OR 1.63, 95% CI 1.49–1.78) and type 2 diabetes mellitus (OR 1.46, 95% CI 1.36–1.58) constitute similar risk factors as summarized under the CCI category of diabetes with and without complications (see Table 8).

For the endpoint of COVID-19, hospital mortality Hemiplegia or paraplegia (OR 1.51, 95% CI 1.21–1.89), renal disease (OR 1.51, 95% CI 1.42–1.61) and COPD (OR 1.51, 95% CI 1.41–1.61) constitutes the highest risk factors. As for the other endpoints we observe significant sex differences for diabetes mellitus, which is a higher risk factor for women (see Table 5 and Fig. 1c).

Table 6 shows age-standardized and sex-standardized frequencies of comorbidities for the control group and the COVID-19 group admitted to ICU ordered by relative risk (RR) not adjusted for other comorbidities. Hemiplegia or paraplegia represents

Table 3 Adjusted effect sizes (OR) with 95% CIs of risk factors for COVID-19 hospitalization

Diagnosis (Group)	Adjusted OR (95% CI) (all)	Adjusted OR (95% CI) (male)	Adjusted OR (95% CI) (female)
Hemiplegia or paraplegia	1.61 (1.44–1.79)***	1.73 (1.50–1.99)***	1.44 (1.21–1.71)***
Chronic obstructive pulmonary disease	1.48 (1.43–1.53)***	1.46 (1.40–1.53)***	1.51 (1.43–1.59)***
Diabetes without complications	1.41 (1.37–1.46)***	1.33 (1.28–1.39)***	1.52 (1.45–1.60)***
Renal disease	1.39 (1.34–1.44)***	1.36 (1.29–1.43)***	1.42 (1.35–1.49)***
Diabetes with complications	1.35 (1.29–1.42)***	1.39 (1.30–1.48)***	1.32 (1.22–1.42)***
Rheumatoid disease	1.32 (1.23–1.43)***	1.19 (1.04–1.36)**	1.39 (1.26–1.52)***
Mild liver disease	1.26 (1.21–1.32)***	1.22 (1.15–1.29)***	1.33 (1.24–1.42)***
Dementia	1.25 (1.20–1.31)***	1.30 (1.21–1.39)***	1.22 (1.15–1.29)***
AIDS/HIV	1.18 (0.79–1.78)	0.98 (0.58–1.67)	1.62 (0.85–3.11)
Congestive heart failure	1.16 (1.12–1.20)***	1.18 (1.12–1.24)***	1.14 (1.08–1.21)***
Moderate or severe liver disease	1.12 (0.98–1.28)	1.11 (0.94–1.31)	1.18 (0.93–1.49)
Cerebrovascular disease	1.12 (1.08–1.15)***	1.10 (1.06–1.15)***	1.13 (1.08–1.19)***
Peptic ulcer disease	1.10 (1.02–1.20)**	1.08 (0.96–1.21)	1.14 (1.00–1.29)**
Peripheral vascular disease	1.09 (1.05–1.14)***	1.12 (1.07–1.18)***	1.06 (1.00–1.12)*
Cancer (any malignancy)	1.03 (0.99–1.07)	1.01 (0.96–1.06)	1.06 (1.00–1.12)**
Acute myocardial infarction	0.97 (0.92–1.03)	0.95 (0.88–1.01)	1.03 (0.94–1.13)
Metastatic solid tumour	0.84 (0.77–0.91)***	0.78 (0.69–0.87)***	0.93 (0.82–1.06)
Total number of observations	280,440	144,366	136,074

Authors' calculation based on [16, 17]
*, **, *** refer to significance at the $p < 0.10$, $p < 0.05$, and $p < 0.01$ level, respectively. Results refer to odds ratios (OR) and 95% confidence intervals (95% CI) obtained from logistic regression; analyses were adjusted for age group, sex and health care region

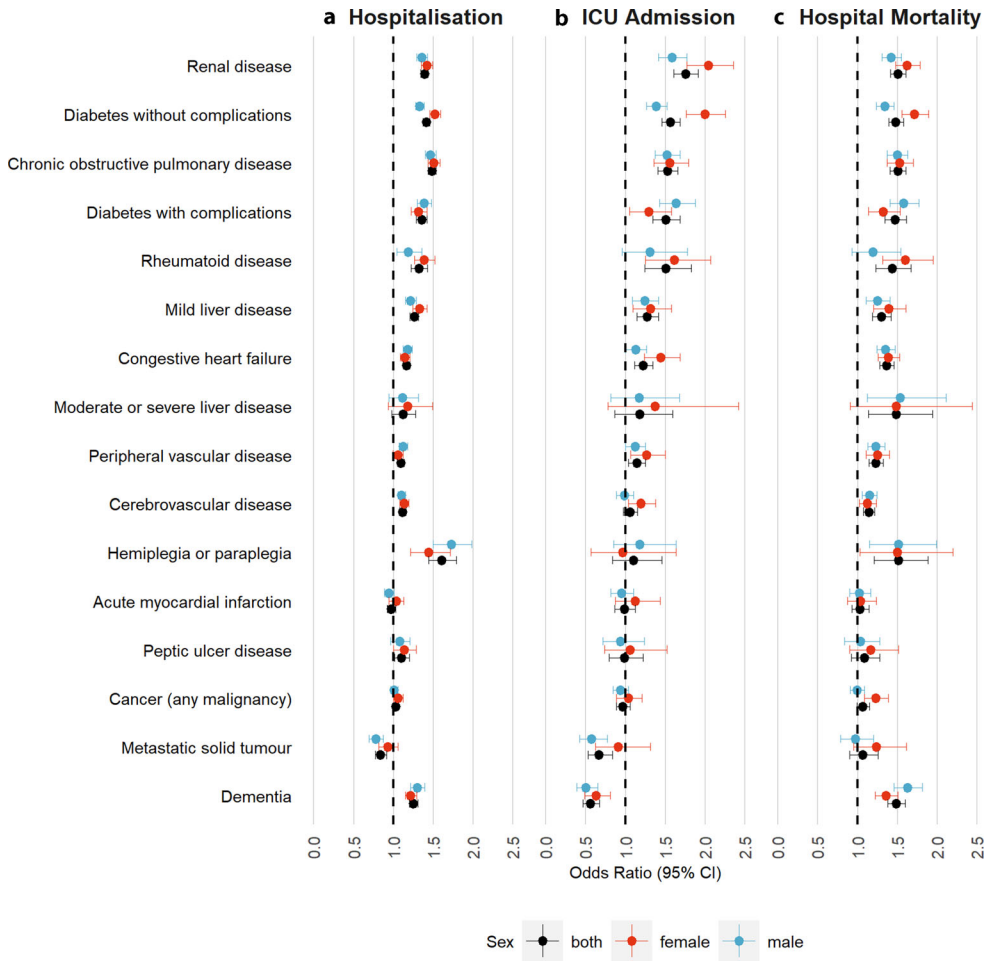

Fig. 1 Adjusted effect sizes (OR) with 95% CIs of risk factors for COVID-19 hospitalisation, ICU admission and hospital mortality (authors' calculation based on [16, 17]). *ICU* intensive care unit

Table 4 Adjusted effect sizes (OR) with 95% CIs of risk factors for COVID-19 ICU admission

Diagnosis (group)	Adjusted OR (95% CI) (all)	Adjusted OR (95% CI) (male)	Adjusted OR (95% CI) (female)
Renal disease	1.76 (1.61–1.92)***	1.58 (1.41–1.77)***	2.04 (1.77–2.36)***
Diabetes without complications	1.57 (1.46–1.69)***	1.39 (1.27–1.52)***	2.00 (1.77–2.26)***
Chronic obstructive pulmonary disease	1.53 (1.41–1.66)***	1.52 (1.37–1.68)***	1.56 (1.36–1.79)***
Diabetes with complications	1.51 (1.35–1.69)***	1.64 (1.43–1.88)***	1.29 (1.06–1.58)**
Rheumatoid disease	1.51 (1.24–1.83)***	1.31 (0.96–1.78)*	1.61 (1.25–2.07)***
Mild liver disease	1.27 (1.15–1.41)***	1.24 (1.09–1.41)***	1.32 (1.10–1.58)***
Congestive heart failure	1.23 (1.12–1.34)***	1.13 (1.00–1.27)**	1.44 (1.24–1.68)***
Moderate or severe liver disease	1.18 (0.87–1.60)	1.17 (0.82–1.68)	1.37 (0.78–2.42)
Peripheral vascular disease	1.14 (1.04–1.25)***	1.12 (1.00–1.25)**	1.27 (1.07–1.50)***
Hemiplegia or paraplegia	1.10 (0.84–1.46)	1.18 (0.85–1.64)	0.97 (0.57–1.64)
Cerebrovascular disease	1.06 (0.97–1.15)	0.99 (0.89–1.10)	1.20 (1.04–1.38)**
Peptic ulcer disease	0.99 (0.80–1.23)	0.94 (0.72–1.23)	1.06 (0.74–1.52)
Acute myocardial infarction	0.99 (0.87–1.12)	0.95 (0.82–1.11)	1.12 (0.88–1.44)
Cancer (any malignancy)	0.97 (0.89–1.06)	0.94 (0.84–1.04)	1.04 (0.89–1.21)
AIDS/HIV	0.81 (0.30–2.16)	0.59 (0.17–2.00)	2.18 (0.35–13.42)
Metastatic solid tumour	0.67 (0.53–0.84)***	0.57 (0.43–0.77)***	0.91 (0.62–1.32)
Dementia	0.56 (0.47–0.67)***	0.50 (0.39–0.65)***	0.63 (0.49–0.81)***
Total number of observations	47,028	29,418	17,610

Authors' calculation based on [16, 17]
*, **, *** refer to significance at the $p<0.10$, $p<0.05$, and $p<0.01$ level, respectively. Results refer to odds ratios (OR) and 95% confidence intervals (95% CI) obtained from logistic regression; analyses were adjusted for age group, sex and health care region

Table 5 Adjusted effect sizes (OR) with 95% CIs of risk factors for COVID-19 hospital mortality

Diagnosis (group)	Adjusted OR (95% CI) (all)	Adjusted OR (95% CI) (male)	Adjusted OR (95% CI) (female)
Hemiplegia or paraplegia	1.51 (1.21–1.89)***	1.51 (1.15–1.99)***	1.51 (1.03–2.20)**
Renal disease	1.51 (1.42–1.61)***	1.42 (1.31–1.55)***	1.62 (1.48–1.79)***
Chronic obstructive pulmonary disease	1.51 (1.41–1.61)***	1.50 (1.38–1.63)***	1.53 (1.38–1.70)***
Moderate or severe liver disease	1.49 (1.14–1.94)***	1.54 (1.12–2.12)***	1.49 (0.91–2.44)
Dementia	1.49 (1.38–1.60)***	1.63 (1.46–1.81)***	1.36 (1.22–1.51)***
Diabetes without complications	1.48 (1.39–1.58)***	1.35 (1.24–1.46)***	1.72 (1.56–1.89)***
Diabetes with complications	1.47 (1.35–1.61)***	1.58 (1.41–1.77)***	1.32 (1.14–1.53)***
Rheumatoid disease	1.44 (1.23–1.68)***	1.20 (0.93–1.54)	1.60 (1.31–1.95)***
Congestive heart failure	1.37 (1.28–1.46)***	1.35 (1.24–1.48)***	1.39 (1.26–1.53)***
Mild liver disease	1.30 (1.19–1.43)***	1.25 (1.11–1.41)***	1.39 (1.20–1.61)***
Peripheral vascular disease	1.23 (1.15–1.32)***	1.23 (1.13–1.34)***	1.25 (1.11–1.40)***
AIDS/HIV	1.17 (0.30–4.50)	1.03 (0.20–5.20)	1.73 (0.15–19.30)
Cerebrovascular disease	1.14 (1.07–1.22)***	1.15 (1.06–1.25)***	1.13 (1.02–1.24)**
Peptic ulcer disease	1.09 (0.92–1.28)	1.04 (0.84–1.28)	1.17 (0.90–1.51)
Cancer (any malignancy)	1.07 (1.00–1.15)*	1.00 (0.91–1.09)	1.23 (1.09–1.39)***
Metastatic solid tumour	1.07 (0.91–1.26)	0.97 (0.79–1.20)	1.24 (0.95–1.62)
Acute myocardial infarction	1.03 (0.93–1.14)	1.03 (0.90–1.17)	1.04 (0.87–1.24)
Total number of observations	56,280	32,250	24,030

Authors' calculation based on [16, 17]
*, **, *** refer to significance at the $p<0.10$, $p<0.05$, and $p<0.01$ level, respectively. Results refer to odds ratios (OR) and 95% confidence intervals (95% CI) obtained from logistic regression; analyses were adjusted for age group, sex and health care region

the comorbidity with the highest RR (5.23) as 2.6% of COVID ICU patients had an inpatient stay with this condition compared to 0.5% of the control group. Diabetes with complications (RR 3.22) and renal disease (RR 3.00) constitute the further most relevant risk factors. The most frequent comorbidity of COVID ICU patients was diabetes without complications (13.2%). The higher burden of comorbidities is also visible referring to the CCI. While 5.3% of COVID ICU patients had a CCI larger or equal to 5, this was only the case for 2.4% of the control group. 60% of COVID ICU

Table 6 Comorbidities of the study population 2015–2019 without and with COVID-19 ICU admission (Feb 2020–Dec 2021)

Diagnosis (group)	Control group without COVID-ICU admission (*N* = 39,190)		Treatment group with COVID-ICU admission (*N* = 7,838)		COVID/non-COVID		
	N	Share (%)	*N*	Share (%)	RR	*p*-value	
Hemiplegia or paraplegia	251	0.5	68	2.6	5.23	0.09	*
Diabetes with complications	1,331	1.4	655	4.5	3.22	0.00	***
Renal disease	2,505	2.6	1,091	7.8	3.00	0.00	***
Moderate or severe liver disease	180	0.2	64	0.6	2.84	0.00	***
AIDS/HIV	25	0.1	5	0.2	2.69	1.00	–
Diabetes without complications	4,154	5.0	1,534	13.2	2.66	0.00	***
Mild liver disease	1,759	2.5	574	6.7	2.65	0.00	***
Chronic obstructive pulmonary disease	2,789	4.1	998	9.7	2.40	0.00	***
Congestive heart failure	2,503	2.6	886	6.0	2.33	0.00	***
Rheumatoid disease	428	0.7	151	1.4	2.17	0.00	***
Peripheral vascular disease	2,579	2.5	820	4.7	1.83	0.00	***
Acute myocardial infarction	1,283	1.5	353	2.3	1.55	0.00	***
Cerebrovascular disease	3,465	3.8	892	5.5	1.43	0.00	***
Peptic ulcer disease	437	0.6	113	0.9	1.41	0.07	*
Cancer (any malignancy)	4,014	4.9	786	6.2	1.25	1.00	–
Metastatic solid tumour	648	0.8	93	0.8	1.00	0.01	**
Dementia	1,039	1.1	155	0.9	0.83	0.00	***
CCI >=5	2,281	2.4	827	5.3	2.22	0.00	***
CCI 3–4	3,245	3.4	1,044	9.0	2.62	0.00	***
CCI 1–2	10,013	14.8	2,357	25.5	1.72	0.00	***
CCI 0	23,651	79.4	3,610	60.2	0.76	0.00	***

Authors' calculation based on [16, 17]
*, **, *** refer to significance at the $p < 0.10$, $p < 0.05$, and $p < 0.01$ level, respectively. Age-standardized and sex-standardized shares and risk ratios based on the Austrian population 2020; *p*-values refer to $\chi 2$-tests, where the family-wise error rate is controlled for with the Holm method
CCI Charlson comorbidity index, *RR* relative risk, *ICU* intensive care unit

patients had a CCI of zero, compared to 79% of the control group.

Discussion

We performed a retrospective cohort study aiming at estimating the effect of comorbidities on COVID-19 hospitalization, ICU admission, and mortality, using nationwide hospital billing data from Austria. Our analysis revealed several comorbidities associated with an elevated risk of severe courses of COVID-19. Hemiplegia or paraplegia, COPD and diabetes without complications constitute the highest risk factor for COVID-19 hospitalization. The highest risk factors for ICU admission are renal disease, diabetes without complications and COPD. For the endpoint of COVID-19, hospital mortality hemiplegia or paraplegia, renal disease and COPD constitute the highest risk factors. The point estimates of the adjusted ORs range from 1.4 to 1.8. Diabetes without complications is a significantly higher risk factor for women, particularly with respect to ICU admission.

We contribute to the literature on risk factors for severe courses of COVID-19 by analyzing sex differences. This is, to the best of our knowledge, one of the first large-scale cohort studies providing sex-stratified results. Our results on diabetes as a higher risk factor for women supports the hypothesis of Kautzky-Willer, that women with type 2 diabetes seem to lose their biological female advantage with respect to severe courses of COVID-19 [10]. Our results are partly in line with other published cohort studies. Our results for diabetes as a risk factor for hospitalization and ICU admission are very similar to the adjusted results from Rawshani et al. for Sweden (1.40, 1.34–1.47, and 1.42, 1.25–1.62, respectively) [6]. Regarding hospital mortality our results are similar to the results from McGurnaghan et al. for Scotland (OR for fatal or critical care unit-treated of 1.40, 1.30–1.49) [3], and lower compared to the results from Cho et al. for South Korea (2.22; 1.63–2.95) [7]. In contrast to [2, 7] we hardly find any association of cancer and COVID-19 endpoints. We only find an association of cancer and COVID-19 hospitalization and mortality for women with a low effect size. We do not find an association of cancer and COVID-19 ICU admission, which is in line with the results of the Swedish cohort study conducted by Ahlström et al. [5]. Differences in the results might be partly explained by different periods where comorbidities are considered. By focusing on the 5-year period before COVID (2015–2019), we aim at capturing the most relevant period in terms of predicting severe courses of COVID-19.

As other observational studies our cohort study has several limitations. Firstly, causal inference is limited due to the observational nature of our data. Analyzing the effect of underlying risk factors such as diabetes rather than interventions exceeds the concept of treatment strategies and assignment procedures because such risk factors cannot be assigned in practice. Thus, our feasible strategy is to observe comorbidities from hospital billing data at baseline Since the causal effect of observed comorbidities may be confounded by unobserved factors such as socioeconomic status, our results should be interpreted with caution, particularly with respect to a causal interpretation of our comorbidity factors. For instance, the results for obesity or diabetes mellitus may be confounded by socioeconomic status. The results for dementia, and hemiplegia or paraplegia may be associated with living in long-term care institutions, which have been particularly exposed to COVID-19 clusters in Austria during the second wave in autumn 2020. By the end of December 2021, 30% of all COVID-19 associated deaths were reported for residents of long-term care facilities [18]; however, this effect does not distort the causal link of the conditions and COVID-19 outcomes as the conditions typically cause the admission to long-term care institutions.

Secondly, the comorbidity analysis relies on the coding quality in Austrian publicly funded hospitals. Since the data are primarily collected for accounting purposes within the Austrian DRG system, issues such as upcoding or incomplete diagnoses coding with respect to additional diagnoses exists. For instance, the distinction between diabetes with and without complications in diagnosis coding may get neglected in clinical practice due to time pressure. Due to the lack of linked data, we cannot control for the vaccination status of patients with COVID-19 which hinders the analysis of risk factors with respect to different vaccination status.

Thirdly, the analysis only contains patients with an inpatient stay in the period 2015–2019 due to limited data availability of comorbidities in other settings in Austria. Diagnoses coding in the ambulatory care sector is not yet fully implemented in Austria and information on medications is only available with substantial time lag. Thus, the cohort study is not representative for the general population as the inpatient population is characterized by higher burden of disease compared to the general population. The higher severity level of the inpatient population is, for instance, reflected by an 69% higher incidence rate of COVID-19 hospitalization compared to the general population. Aiming at identifying vulnerable population groups, we consider this limitation as acceptable as we can assume that most of the vulnerable population has an inpatient stay within a 5-year period.

Fourthly, individual behavior such as risk aversion may impact upon the results as patients are likely to choose their COVID risk behavior based on their medical record. Thus, patients with diagnoses listed on top of the Austrian COVID risk group regulation, such as chronic pulmonary disease, chronic heart diseases or cancer may have behaved more risk averse compared to patients with obesity or diabetes mellitus ranked number 7 and 8 on the list containing 9 groups of diagnosis in total, which may have partially led to a self-defeating prophecy. Of note, this would not be confounding but rather it means that the biological effect of such a comorbidity is superimposed by reactive protective behavior that is also by the comorbidity. Isolating the biological effect would require a mediation analysis, which was not the goal of this study [19].

Fifthly, we do not analyze how comorbidities affect each other over time, which may lead to time-varying confounding. Controlling for this phenomenon would require more sophisticated statistical models such as Robins' generalized methods (g methods) [20].

Sixthly, analyzing hospital mortality, we consider endpoints at time of discharge rather than 30-day mortality due to significant time lag in data availability of linked data.

Seventhly, some comorbidities such as metastatic solid tumurs may be so severe that they fall under palliative care, reducing the likelihood of hospitalization and mortality in a hospital. Therefore, the estimated effect size of such comorbidities may be true but does not reflect the overall mortality risk of such patients.

Conclusion

Our results may be used for sharpening the risk group definition, which is essential for the protection of vulnerable populations by pharmaceutical and non-pharmaceutical interventions. In particular our study may contribute to raise awareness of large population groups such as diabetics by communicating the risk of severe courses of Coronavirus disease 2019 (COVID-19) and thus communicating the benefits of vaccination or new antiviral therapies.

Further research should include the joint influence of socioeconomic status and comorbidities because major risk factors such as diabetes are likely confounded by socioeconomic status. Furthermore, the effect of the immunization status should be included in order to analyze the risk of comorbidities with respect to different immunization status. This could support policy makers in the implementation of more target group-oriented pharmaceutical interventions such as the further vaccination program or the use of antiviral therapies.

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Author Contribution The study was designed by all authors. LR wrote the first draft of the manuscript. LR and MZ performed all statistical analyses. All of the authors participated in analysis and interpretation. All authors vouch for the accuracy and completeness of the data and analyses and made the decision to submit the manuscript for publication. All authors meet the International Committee of Medical Journal Editors criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Declarations

Conflict of interest L. Rainer, F. Bachner, K. Eglau, H. Ostermann, U. Siebert and M. Zuba declare that they have no competing interests.

Appendix

Table 7 Summary of the protocol of a target trial to estimate the effect of diabetes without complications on COVID-19 ICU admission

Protocol component	Description
Eligibility criteria	At least one inpatient stay in the baseline period 2015–2019 in a public hospital in Austria and no presence or history of diabetes
Treatment strategies	Refrain from assigning diabetes without complications. Assigning diabetes without complications in the baseline and during the follow-up
Assignment procedures	Random assignment of participants to either strategy at baseline. Participants will be aware of the strategy to which they have been assigned
Follow-up period	Starts in January 2020 before the onset of COVID-19 in Austria and ends at COVID-19 associated ICU admission, death, loss to follow-up, or 24 months after baseline
Outcome	ICU admission with polymerase chain reaction (PCR) confirmed COVID-19 as principal or additional diagnosis
Causal contrasts of interest	Per-protocol effect
Analysis plan	Per-protocol effect estimated via comparison of 16-month risk of COVID-19 associated ICU admission among individuals assigned to each treatment strategy
Authors' illustration based on [12]	

Table 8 Robustness check: adjusted effect sizes (OR) with 95% CIs of risk factors for COVID-19 hospitalization, ICU admission and hospital mortality obtained from logistic regression (diagnoses at category, group or chapter level. Diagnoses ordered by decreasing OR with respect to ICU admission)

Diagnosis (category, group, or chapter)	Hospitalization	ICU admission	Hospital mortality
(P00-P96) Certain conditions originating in the perinatal period	1.43 (1.03–1.97)**	2.31 (0.92–5.79)*	No observations
(E66) Obesity	1.35 (1.29–1.40)***	1.63 (1.49–1.78)***	1.49 (1.36–1.63)***
(N18) Chronic kidney disease	1.20 (1.15–1.24)***	1.52 (1.38–1.67)***	1.37 (1.28–1.47)***
(E11) Type 2 diabetes mellitus	1.34 (1.30–1.38)***	1.46 (1.36–1.58)***	1.52 (1.43–1.62)***
(D50-D89) Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism	1.13 (1.08–1.17)***	1.27 (1.15–1.39)***	1.22 (1.14–1.31)***
(J44) Other chronic obstructive pulmonary disease	1.23 (1.18–1.29)***	1.26 (1.14–1.39)***	1.29 (1.19–1.40)***
(G40-G47) Episodic and paroxysmal disorders	1.15 (1.11–1.19)***	1.25 (1.15–1.36)***	1.09 (1.01–1.18)**
(J18) Pneumonia, unspecified organism	1.19 (1.14–1.25)***	1.25 (1.11–1.40)***	1.31 (1.21–1.42)***
(J00-J99) Diseases of the respiratory system	1.19 (1.15–1.22)***	1.24 (1.15–1.33)***	1.19 (1.12–1.26)***
(A00-B99) Certain infectious and parasitic diseases	1.18 (1.14–1.22)***	1.23 (1.13–1.34)***	1.17 (1.09–1.25)***
(I10) Essential (primary) hypertension	1.16 (1.13–1.19)***	1.23 (1.15–1.31)***	1.10 (1.04–1.16)***
(Z80-Z99) Persons with potential health hazards related to family and personal history and certain conditions influencing health status	1.05 (1.01–1.08)***	1.23 (1.13–1.33)***	1.10 (1.03–1.18)***
(F32) Depressive episode	1.16 (1.10–1.21)***	1.20 (1.06–1.35)***	1.08 (0.98–1.19)
(M54) Dorsalgia	1.15 (1.11–1.20)***	1.19 (1.08–1.32)***	1.12 (1.03–1.22)**
(L00-L99) Diseases of the skin and subcutaneous tissue	1.09 (1.04–1.13)***	1.15 (1.04–1.27)***	1.14 (1.05–1.23)***
(S00) Superficial injury of head	1.09 (1.03–1.16)***	1.15 (0.98–1.35)*	1.15 (1.03–1.28)**
(S00-T98) Injury, poisoning and certain other consequences of external causes	1.04 (1.00–1.07)*	1.12 (1.02–1.23)**	1.11 (1.03–1.19)***
(K29) Gastritis and duodenitis	1.07 (1.03–1.12)***	1.12 (1.01–1.24)**	0.97 (0.88–1.06)
(M51) Thoracic, thoracolumbar, and lumbosacral intervertebral disc disorders	0.97 (0.92–1.02)	1.09 (0.96–1.24)	0.91 (0.81–1.03)
(R00-R99) Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified	1.12 (1.09–1.15)***	1.09 (1.02–1.17)**	1.13 (1.07–1.20)***
(S00-S09) Injuries to the head	1.08 (1.03–1.14)***	1.08 (0.94–1.24)	1.10 (1.00–1.22)*
(N39) Other disorders of urinary system	1.12 (1.07–1.16)***	1.08 (0.97–1.19)	1.08 (1.00–1.16)**
(NA) Other diagnoses	1.04 (1.01–1.06)***	1.07 (1.00–1.13)**	1.00 (0.95–1.05)

Table 8 (Continued)

Diagnosis (category, group, or chapter)	Hospitalization	ICU admission	Hospital mortality
(Q00-Q99) Congenital malformations, deformations and chromosomal abnormalities	1.05 (0.98–1.12)	1.06 (0.90–1.26)	1.01 (0.87–1.18)
(F00-F99) Mental and behavioral disorders	1.13 (1.09–1.17)***	1.06 (0.97–1.15)	1.23 (1.13–1.32)***
(999) Other causes of exogenous noxious	1.00 (0.96–1.04)	1.06 (0.95–1.18)	0.94 (0.86–1.03)
(N00-N99) Diseases of the genitourinary system	1.06 (1.03–1.09)***	1.05 (0.98–1.13)	1.00 (0.94–1.07)
(I25) Chronic ischemic heart disease	1.03 (1.00–1.06)*	1.04 (0.96–1.13)	1.01 (0.95–1.08)
(I30-I52) Other forms of heart disease	0.99 (0.96–1.03)	1.03 (0.94–1.13)	1.03 (0.96–1.10)
(I00-I99) Diseases of the circulatory system	1.05 (1.02–1.08)***	1.03 (0.96–1.10)	1.07 (1.01–1.13)**
(I63) Cerebral infarction	1.03 (0.98–1.09)	1.03 (0.89–1.19)	1.10 (0.99–1.22)*
(E00-E90) Endocrine, nutritional and metabolic diseases	1.05 (1.02–1.09)***	1.02 (0.94–1.11)	1.04 (0.97–1.11)
(K76) Other diseases of liver	1.07 (1.02–1.12)***	1.02 (0.91–1.15)	1.11 (1.00–1.23)*
(I70) Atherosclerosis	0.99 (0.95–1.04)	1.02 (0.91–1.15)	1.18 (1.08–1.29)***
(E87) Other disorders of fluid, electrolyte and acid-base balance	0.95 (0.90–1.00)**	1.02 (0.88–1.17)	1.04 (0.95–1.14)
(E78) Disorders of lipoprotein metabolism and other lipidemias	0.95 (0.92–0.98)***	1.01 (0.94–1.09)	0.88 (0.83–0.94)***
(I50) Heart failure	1.00 (0.96–1.04)	1.00 (0.90–1.12)	1.20 (1.12–1.30)***
(K40-K46) Hernia	0.97 (0.94–1.01)	1.00 (0.92–1.09)	0.92 (0.84–0.99)**
(101-199) Reasons for revision in arthroplasty	1.06 (0.96–1.18)	1.00 (0.76–1.30)	0.90 (0.72–1.13)
(E70-E90) Metabolic disorders	0.99 (0.95–1.03)	0.99 (0.90–1.10)	0.97 (0.90–1.04)
(M45-M49) Spondylopathies	1.07 (1.02–1.11)***	0.99 (0.88–1.11)	1.01 (0.92–1.10)
(K80) Cholelithiasis	1.05 (1.00–1.10)**	0.99 (0.88–1.11)	1.09 (0.99–1.20)*
(M81) Osteoporosis without current pathological fracture	0.95 (0.91–0.99)**	0.99 (0.87–1.13)	1.04 (0.95–1.14)
(K00-K93) Diseases of the digestive system	1.04 (1.01–1.08)**	0.99 (0.90–1.08)	1.05 (0.97–1.13)
(E03) Other hypothyroidism	1.02 (0.98–1.07)	0.99 (0.87–1.11)	0.98 (0.89–1.08)
(K57) Diverticular disease of intestine	0.94 (0.90–0.98)***	0.98 (0.88–1.09)	0.88 (0.81–0.96)***
(K55-K64) Other diseases of intestines	1.00 (0.97–1.04)	0.97 (0.88–1.08)	0.96 (0.88–1.04)
(R50-R69) General symptoms and signs	1.13 (1.09–1.17)***	0.97 (0.89–1.07)	1.05 (0.98–1.12)
(M17) Osteoarthritis of knee	1.02 (0.98–1.07)	0.96 (0.86–1.07)	0.88 (0.80–0.97)***
(K20-K31) Diseases of esophagus, stomach and duodenum	1.02 (0.97–1.06)	0.96 (0.86–1.07)	1.01 (0.92–1.11)
(G00-G99) Diseases of the nervous system	1.10 (1.07–1.14)***	0.94 (0.87–1.03)	1.09 (1.02–1.16)***
(M00-M99) Diseases of the musculoskeletal system and connective tissue	0.97 (0.95–1.00)**	0.93 (0.87–0.99)**	0.89 (0.84–0.94)***
(M16) Osteoarthritis of hip	0.92 (0.88–0.96)***	0.92 (0.81–1.03)	0.95 (0.86–1.05)
(I48) Atrial fibrillation and flutter	0.99 (0.96–1.03)	0.91 (0.84–1.00)**	0.95 (0.89–1.01)
(929) Other accident in the private sphere	0.99 (0.95–1.04)	0.90 (0.81–1.01)*	0.97 (0.88–1.06)
(201-299) Documentation of strokes without treatment on stroke units	1.06 (0.93–1.20)	0.88 (0.61–1.27)	0.98 (0.77–1.25)
(Z00-Z99) Factors influencing health status and contact with health services	1.03 (0.99–1.07)	0.88 (0.78–0.98)**	0.96 (0.87–1.05)
(C00-D48) Neoplasms	0.95 (0.92–0.97)***	0.87 (0.82–0.93)***	1.02 (0.97–1.08)
(K63) Other diseases of intestine	0.94 (0.90–0.99)**	0.87 (0.77–0.98)**	0.90 (0.81–1.00)**
(I60-I69) Cerebrovascular diseases	0.98 (0.94–1.02)	0.85 (0.76–0.94)***	1.04 (0.97–1.12)
(O00-O99) Pregnancy, childbirth and the puerperium	1.16 (1.08–1.25)***	0.82 (0.64–1.05)	0.31 (0.13–0.73)***
(N40) Benign prostatic hyperplasia	0.93 (0.89–0.98)***	0.79 (0.70–0.90)***	0.81 (0.74–0.89)***
(901-999) Exogenous noxious—etiology	0.94 (0.88–1.00)*	0.79 (0.67–0.93)***	0.75 (0.62–0.90)***
(S72) Fracture of femur	0.97 (0.92–1.04)	0.78 (0.64–0.95)**	1.13 (1.01–1.26)**
(I35) Nonrheumatic aortic valve disorders	0.85 (0.80–0.90)***	0.76 (0.64–0.89)***	0.81 (0.73–0.90)***
(U00-U89) Codes for special purposes	1.23 (0.85–1.78)	0.70 (0.27–1.81)	1.25 (0.65–2.41)
(F00-F09) Organic, including symptomatic, mental disorders	1.06 (1.02–1.11)***	0.67 (0.57–0.78)***	1.22 (1.13–1.32)***

Authors' calculation based on [16, 17]
*, **, *** refer to significance at the $p < 0.10$, $p < 0.05$, and $p < 0.01$ level, respectively. Results refer to odds ratios obtained from logistic regression (95% confidence interval in brackets); Control variables include age group, sex and health care region

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