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Long-term temporal trends in incidence rate and case fatality of sepsis and COVID-19-related sepsis: A nationwide registry study

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Long-term temporal trends in incidence rate and case fatality of sepsis and COVID-19-related sepsis: A nationwide registry study

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Key Points

Question: Has there been a change in incidence rate and case fatality of sepsis over the past decade , and how did the COVID-19 pandemic influence sepsis incidence rates and in-hospital mortality?

Findings: In this nationwide longitudinal registry study the incidence rate of all sepsis episodes increased and the incidence rate of a first sepsis episode was stable during the period 2009-2019, whereas in 2020 and 2021, the incidence rate of a first and all sepsis episodes was lower than in the preceding 11-year period. Case fatality risk declined from 2009 to 2019, but increased somewhat in 2020 and 2021, when 9.7% of first sepsis cases were identified as COVID-19 related sepsis.

Meaning: Despite a stable incidence rate of first-time sepsis admissions over time, the burden of sepsis is rising due to an increased rate of patients admitted multiple times with sepsis. The COVID-19 pandemic have had an impact on sepsis incidence rate and hospital mortality and needs further evaluation.

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Abstract

Objectives: To estimate temporal trends in incidence rate (IR) and case fatality during a 14-year period from 2008 through 2021, and to assess possible shifts in these trends during the COVID-19 pandemic.

Setting: All Norwegian hospitals from 2008 through 2021.

Participants: 317.705 patients ≥ 18 year with an sepsis ICD-10 code retrieved from the Norwegian Patient Registry.

Primary and secondary measures: Annual age-standardized incidence rates with 95% confidence intervals (CI). Poisson regression was used to estimate changes in IRs across time, and logistic regression was used to estimate odds ratios for in-hospital death.

Results: Among 12.619.803 adult hospitalizations, 317.705 (2.5%) patients met the sepsis criteria and 222.832 (70.0%) had a first sepsis episode. The overall age-standardized IR of a first sepsis admission was 246/100.000 (95% CI, 245-247), whereas the age-standardized IR of all sepsis admissions was 352/100.000 (95% CI, 351-354). In the period 2009-2019, the annual IR for a first sepsis episode was stable (Incidence Rate Ratio (IRR) per year, 0.999; 95% CI, 0.994-1.004), whereas for all sepsis the IR increased by 15.5% (annual IRR, 1.013; 95% CI 1.007-1.019). During the COVID-19 pandemic, the IRR for a first sepsis was 0.877 (95% CI, 0.829-0.927) in 2020 and 0.929 (95% CI, 0.870-0.992) in 2021, and for all sepsis it was 0.870 (95% CI, 0.810-0.935) in 2020 and 0.908 (95% CI, 0.840-0.980) in 2021, compared to the previous 11-year period. In-hospital deaths declined in the period 2009-2019 (odds ratio (OR) per year, 0.954 [95% CI,0.950-0.958]), whereas deaths increased during the COVID-19 pandemic in 2020 (OR, 1.061 [95% CI 1.001-1.124] and in 2021 (OR, 1.164 [95% CI, 1.098-1.233]).

Conclusion: We found a stable IR of a first sepsis episode during the years 2009-2019. However, the increasing burden of all sepsis admissions indicates that sepsis awareness with updated guidelines and education must continue.

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Introduction

Sepsis is a dysfunctional immune response to infection that leads to acute life-threatening tissue damage and organ dysfunction.[1] With an estimated 50 million cases and 11 million sepsis-related deaths in 2017, sepsis remains a major cause of worldwide morbidity and mortality.[2] While sepsis may result from any infection, the majority of adult sepsis cases before the pandemic were attributed to bacterial infections, and viral sepsis was rare.[3-5] During the COVID-19 pandemic, an unprecedented number of patients developed viral sepsis,[6-9] with a high risk of co-infections and secondary infections that can aggravate the outcome.[10 11] It is likely that public health efforts to reduce the spread of SARS-CoV-2, such as lockdowns, may also have influenced the spread of other communicable diseases contributing to the risk of sepsis.[12 13] However, only one study has evaluated the impact of the pandemic on sepsis incidence rate and case fatality risk, using a few selected sepsis codes.[14] No previous study has focused exclusively on sepsis incidence rate using all sepsis codes, [2] and compared sepsis incidence rate and case fatality during the two first years of the COVID-19 pandemic with long-term historic trends.

Previous research on the incidence rates of sepsis before the COVID-19 pandemic has shown conflicting results.[2 15-17] However, the incidence rate and mortality rate are challenged, and more accurate quantification (i.e., correct identification and diagnosis coding) of sepsis are warranted.[18 19]

The overall aim of this study is therefore to describe temporal trends in sepsis incidence rate and case fatality using nationwide data on all adult hospital admissions from 2008 through 2021, and secondly to examine changes in hospital admission and mortality rates of sepsis during the first two COVID-19 pandemic years.

Methods

Data Source and Study Population

This nationwide longitudinal study used data from the Norwegian Patient Registry (NPR) and Statistics Norway.[20 21] NPR is an administrative database maintained by the Norwegian Directorate of Health that contains data with unique patient identifiers that allow follow-up of individual patients on every admission to public hospitals in Norway from 2008 onward. In addition, NPR contains admission and discharge dates, and the International Classification of Diseases 10th revision (ICD-10) discharge codes, while Statistics Norway contains demographic data on all citizens of Norway. In NPR, we identified all hospitalizations to public

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hospitals in Norway (2008–2021) aged ≥18 years with the ICD-10 discharge diagnosis code(s) for sepsis consistent with the Angus implementation refined by Rudd and colleagues.[2 22]

We treated each hospitalization as an individual entry, and within this entry, sepsis was defined as explicit or implicit sepsis. For explicit sepsis, we used the presence of one code (See Supplementary Table 1 for an overview of all ICD-10 codes to define sepsis). For implicit sepsis, we used the combination of one infection code with the presence of an acute organ dysfunction code. The strategy was used for the primary and up to 20 secondary co-existing ICD-10 discharge codes since there is no obligatory order for the secondary codes. We added COVID-19-related sepsis to the implicit sepsis category based on the presence of a diagnostic code for COVID-19 (U07.1, U07.2) and ≥one organ dysfunction code. Patients with a COVID-19 sepsis code and an explicit sepsis code were categorized as explicit sepsis. Figure 1 shows the selection of patients into the study.

Characteristics of Study Population

Patient characteristics were extracted from NPR, including sex, age, ICD codes for selected comorbidities,[23] as well as numbers of hospital stays from sepsis, readmissions, and in-hospital deaths (for details, see Supplementary Table 2). For sepsis admissions, we used ICD-10 codes to classify site(s) of infection into respiratory, genitourinary, intra-abdominal, extra-abdominal, endocarditis/myocarditis, soft tissue, infections following a procedure, and other (bone, joint, obstetric, ear, mouth, upper airway, central nervous system and unknown). The acute organ dysfunctions were classified by number and as circulatory, respiratory, renal, hepatic, coagulation, and/or other (acidosis, unspecific gangrene, central nervous system, and Systemic Inflammatory Response Syndrome (R65.1). A sepsis admission was defined as recurring sepsis admission if the patient was discharged with an explicit or implicit sepsis code and thereafter admitted with an explicit or implicit sepsis code, regardless of the time frame for the new admission. The number of sepsis admissions was categorized from one to five or more.

Statistical Analysis

Descriptive statistics are presented as frequencies, means, standard deviation, percent, and medians as appropriate, and are reported by sepsis or COVID-19 status. We calculated the crude sepsis incidence rate (IR) of a first and overall sepsis episode according to year (2008–2021) and ten-year age-groups as the number of sepsis admissions divided by the total number of inhabitants in Norway at the beginning of the year. The IRs for first and all sepsis were then standardized according to Segi's world standard population using ten-years age categories,[24 25] and reported per 100 000 person years.

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To evaluate the temporal trends of sepsis incidence rates and the impact of the COVID-19 pandemic on sepsis incidence rates we used Poisson regression to estimate incidence rate ratios (IRR) of sepsis using the number of sepsis admissions (total or first) as the dependent variable, population as exposure, the years 2009 to 2019 as a continuous variable, and the years 2008, 2020 and 2021 as separate indicator variables. The analyses were adjusted for sex (man, woman) and age (10-year categories). Since 2008 was the first observation year, we could not differentiate between a first and a recurrent episode, and 2008 thus was included as an indicator variable to account for a possibly inflated incidence rate of first sepsis. To account for overdispersion, we used the robust variance estimator.

Case fatality risk (CFR) was estimated based on first sepsis admissions with a discharge status of in-hospital death divided by all first sepsis hospitalizations. The calculation was performed on annual cases from 2008 to 2021 and by ten-years age groups in the same period. During 2020 and 2021 we also calculated the quarterly CFR and compared CFR for COVID-19-related sepsis and sepsis. To evaluate the trend of in-hospital mortality and the pandemic`s impact on hospital mortality, we used logistic regression to estimate odds ratios (ORs) for in-hospital death using the years 2009-2019 as a continuous variable, the years 2008, 2020, and 2021 as indicator variables, and adjusting for sex (man, woman) and age (10-year categories). We report 95% confidence intervals (CI) where relevant.

All analyses were conducted using STATA version 16.1 (Stata Corp).

Patient and public involvement

Two patient representatives from the user group at Nord-Trondelag Hospital Trust participated in the work with the research question and design of this study. In general, they are positive to use of health data for research purposes. They stress the importance of education regarding symptoms and signs of sepsis to prevent fatal outcome and gave advice that research results and information about sepsis should be published in newspapers and social media in order to reach the patients and relatives. According to this, we plan to distribute this research results on our social media to inform patients, sepsis charities, research funders and policy makers.

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Ethics

The study was approved by the Regional Committee for Medical and Health Research Ethics (REK) in Eastern Norway (2019/42772) and the Data Access Committee in Nord-Trøndelag Hospital Trust (2021/184). In accordance with the approval from the REK and the Norwegian law on medical research, the project did not require a written patient consent. This work was performed on TSD (Service for Sensitive Data) facilities owned by the University of Oslo, operated and developed by the TSD service group at the University of Oslo, IT Department (USIT). TSD is designed to store and post-process sensitive data in compliance with the Norwegian "Personal Data Act" and "Health Research Act."

Results

Characteristics of Study Population

Among 12.619.803 non-psychiatric adult hospitalizations during the study period (2008–2021), 317.705 (2.5%) met the criteria for sepsis, and of these, 222.832 (70%) were hospitalized with the first episode of sepsis. Patient characteristics according to a first episode of sepsis and COVID-19-related sepsis are presented in Table 1.

Table 1 Characteristic of the study population at first sepsis admission (2008-2021) and COVID-19-related sepsis (2020-2021)

Characteristics	**Sepsis**	**COVID-19-related sepsis**	**All first sepsis admissions**
	n (%)	n (%)	n (%)
First admission n (% of all sepsis admissions)	219 987 (69)	2845 (1)	222 832 (70)
Sex			
Male	118 580 (53.9)	1862 (65.5)	120 442 (54.1)
Age (years)			
Mean ± SD (Median)	71.2 ± 16.6 (74.4)	61.4±16.1 (61.8)	71.1 ± 16.6 (74.3)
Number of comorbidities			
0	66 869(30.4)	1 581(55.6)	68 450 (31.7)
1	97 894 (44.5)	909 (32.0)	98 803 (44 .3)
2	45 052 (20.5)	300 (10.5)	45 352 (20.4)
≥3	10 172 (4.6)	55 (1.9)	10 227 (4.6)
Comorbidities [a]			
Heart and vascular	99 360 (64.9)	702 (55.5)	100 062 (64.8)
Cancer	39 243 (25.6)	125(9.9)	39 368 (25.5)
Lung	35 859 (23.4)	306 (24.2)	36 165 (23.4)
Renal	8 873 (5.8)	76 (6.0)	8 949 (5.8)
Diabetes	24 030 (15.7)	386 (30.5)	24 416 (15.8)
Dementia	8 068 (5.3)	32 (2.5)	8 100 (5.3)
Immune	3 091 (2.0)	49 (3.9)	3 140 (2.0)
Liver	991 (0.7)	NA	994 (0.6)
Site of infection [b]			
Respiratory	79 290 (48.7)	2 528 (97.9)	81 818 (49.5)
Genitourinary	44 700 (27.5)	82 (3.2)	44 782 (27.1)

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Skin and soft tissue	8 260 (5.1)	5 (0.2)	8 265 (5.0)
Intra-abdominal	8 841(5.4)	29 (1.1)	8 870 (5.4)
Extra-abdominal	12 318 (7.6)	22 (0.9)	12 340 (7.5)
Infections following a procedure	8 277 (5.1)	13 (0.5)	8 290 (5.0)
Endocarditis/Myocarditis	2 522 (1.6)	8 (0.3)	2 530 (1.5)
Other [c]	28 836 (17.7)	152 (5.9)	28 997 (17.5)
Explicit sepsis	77 240 (35.1)	90 (3.2)	77 330 (34.7)
Number of Acute organ dysfunctions			
1	126 928 (84.5)	2 252 (81.2)	28 928(84.4)
2	17 869 (11.9)	427 (15.4)	18 296(12.0)
3	3 988 (2.7)	70 (2.5)	4 058 (2.7)
≥4	1 466 (1.0)	24 (0.9)	1490(1.0)
Organ system with acute organ dysfunction [d]			
Respiratory	59 465 (39.7)	2 399 (86.5)	61 864 (40.5)
Circulatory	14 824 (9.9)	68 (2.5)	14 892 (9.8)
Renal	66 809 (44.6)	433 (15.6)	67 242 (44.1)
Hepatic	3 192 (2.1)	17 (0.6)	3 209 (2.1)
Coagulation	6 428 (4.3)	43 (1.6)	6 471(4.2)
Other [e]	31 303 (20.9)	284 (10.3)	31 587 (20.7)
Number of hospital admissions for sepsis [f]			
1	168 904 (76.8)	2 714 (95.4)	171 618 (77.0)
2	33 097 (15.0)	4125 (4.4)	33 222 (14.9)
3	10 125 (4.6)	NA	10 129 (4.6)
4	40 010 (1.8)	NA	4 011 (1.8)
≥5	3 851 (1.8)	NA	3 852 (1.7)
Readmission [g]	54 967 (25.0)	474 (16.7)	55 441 (24.9)

If not mentioned otherwise, the percentage (%) is calculated from available data from the first admission with Sepsis or COVID-19-related sepsis.
Abbreviation: NA=Not Applicable (used when the number of admissions was ≤5).
[a] The proportion of all comorbidities is calculated as number of particular comorbidity over total number of comorbidities
[b] The proportion of all infections sites is calculated as number of individuals with particular infection site over total number of infections sites
[c] Other infection sites= Bone, obstetric, upper airway, central nervous system and unknown
[d] The proportion of organ dysfunctions is calculated based on n with any organ dysfunctions
[e] Other acute organ dysfunction= Acidosis, unspecific gangrene, central nervous system dysfunctions and Systemic Inflammatory Respons Syndrome.
[f] Number of hospital admissions= Calculated as new sepsis admission if admission with ICD-10 codes defining sepsis, regardless of time frame for the new sepsis admission. Follow up=14 years
[g] Readmission= admission within 30 days after discharge regardless of cause

In 2020 and 2021, 2.845 of 29.329 (9.7%) of first sepsis cases were identified as COVID-19 related sepsis. Men were overrepresented among patients with sepsis (53.9%) and COVID-19-related sepsis (65.5%). The sepsis patients were older than patients with COVID-19-related sepsis (mean age 71.1 vs. 61.4). The sepsis patients experienced renal acute organ dysfunction most often (44.6%). followed by respiratory failure (39.7%). The COVID-19-related sepsis patients experienced naturally most frequent respiratory failure (86.5%), followed by renal failure (15.6%). In total, 25.0% and 16.7% of the patients were readmitted within 30 days in the sepsis and

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COVID-19-related sepsis group, respectively. During the total study period (2008-2021), 24.2% of sepsis patients had ≥2 recurring sepsis hospitalization.

Sepsis Incidence Rates and Temporal Trends

The overall age-standardized IR of a first sepsis admission was 246/100.000 (95% CI, 245-247), whereas the age-standardized IR of all sepsis admissions was 352/100.000 (95% CI, 351-354) during the study period (Table 2).

Table 2 Standardized incidence rates for first and all sepsis admissions 2008-2021

Year	No. of persons	Incidence rate first sepsis admission per 100 000 person years		Incidence rate all sepsis admissions per 100 000 person years	
		Crude	Adjusted (95% CI)	Crude	Adjusted (95% CI)
2008	3 637 892	445	286 (281-291)	526	344 (338-350)
2009	3 697 780	401	257 (253-262)	544	342 (336-347)
2010	3 749 043	407	261 (257-266)	546	357 (351-362)
2011	3 805 931	402	260 (256-265)	545	356 (351-361)
2012	3 867 645	395	252 (247-256)	553	358 (353-364)
2013	3 928 378	380	240 (236-244)	533	343 (337-348)
2014	3 983 895	386	243 (238-247)	555	352 (346-357)
2015	4 040 198	401	250 (246-254)	576	361 (355-366)
2016	4 086 583	385	237 (233-241)	577	359 (353-364)
2017	4 127 266	409	246 (242-250)	599	361 (356-366)
2018	4 166 612	417	246 (242-250)	622	367 (362-372)
2019	4 205 704	409	240 (236-244)	631	368 (363-373)
2020	4 248 972	364	210 (206-213)	561	322 (317-326)
2021	4 279 679	390	226 (222-230)	602	343 (338-348)
Total	55 825 578	399	246 (245-247)	569	352 (351-354)

Abbrevation: CI = confidence interval

[a] Crude and age adjusted sepsis incidence rate was calculated by year (2008–2021) for first and all sepsis admissions by dividing sepsis admissions by the total number of inhabitants in Norway at beginning of the same years, using direct standardization weighted by 'Segi's world standard population.

The age-standardized IRRs for first and all sepsis admissions by year 2008-2021 is given in Table 3 and Figure 2. More detailed information on IRs in different age groups is given in Supplementary Figure 1, showing the highest occurrence in the older age groups.

Table 3 Poisson regression[a] for trends of first and all sepsis episode

	First sepsis admissions		All sepsis admissions	
	IRR	95% CI	IRR	95% CI
Per year 2009 to 2019	0.999	0.994-1.004	1.013	1.007-1.019
2008	1.110	1.021-1.210	1.007	0.920-1.102
2020	0.877	0.829-0.927	0.870	0.810-0.935
2021	0.929	0.870-0.992	0.908	0.840-0.980

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Female sex	0.688	0.669-0.707	0.677	0.656-0.699
Age group, years				
18-29	0.023	0.021-0.026	0.023	0.020-0.025
30-39	0.029	0.026-0.031	0.028	0.025-0.030
40-49	0.043	0.041-0.046	0.044	0.041-0.047
50-59	0.089	0.085-0.093	0.094	0.088-0.100
60-69	0.207	0.200-0.214	0.225	0.215-0.235
70-79	0.457	0.441-0.473	0.491	0.470-0.512
≥80	1.000	Reference	1.000	Reference
Constant[b]	0.031	0.030-0.033	0.040	0.038-0.042

Abbrevation: IRR = incidence rate ratio, CI = confidence interval
[a] The Poisson regression model was set up with cases as dependent variable, population as exposure, per year 2009-2019 as continuous covariate, and indicator variables as covariates for the years 2008, 2020 and 2021, and female sex and age groups.
[b] Constant = estimated incidence rate for men ≥80 in 2009

Poisson regression showed that from 2009 throughout 2019, the annual IRR of first sepsis episode was stable (IRR per year , 0.999; 95% CI, 0.994-1.004) , whereas the overall sepsis incidence rate increased (IRR per year increase, 1.013; 95% CI, 1.007-1.019), with a total increase in incidence rates of 15.5%. During the COVID-19 pandemic, the incidence rate was reduced compared to the previously 11-year period, with IRR of 0.877 (95% CI, 0.829-0.927) in 2020 and 0.929 (95% CI, 0.870-0.992) in 2021 for first sepsis cases, and 0.870 (95% CI, 0.810-0.935) in 2020 and 0.908 (95% CI, 0.840-0.980) in 2021 for all sepsis cases.

Case Fatality and Temporal Trends

The mean CFR was 13.7% over the fourteen years study period (Figure 3). In-hospital deaths declined during 2009 to 2019 (OR per year, 0.954 [95% CI, 0.950-0.958]), with a total decline of 43.1%. More information about the annual case fatality risk by ten years age-groups is shown in Supplementary Figure 2.

Hospital death increased during the COVID-19 pandemic with an OR 1.061 (95% CI, 1.001-1.124) in 2020 and an OR of 1.164 (95% CI, 1.098-1.233) in 2021 (Table 4).

Table 4 Logistic regression[a] with in-hospital deaths as dependent variable, 2008-2021.

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	First sepsis admission	
	OR	95% CI
Per year 2009 to 2019	0.954	0.950-0.958
2008	1.003	0.954-1.055
2020	1.061	1.001-1.124
2021	1.164	1.098-1.233
Female sex	0.898	0.876-0.920
Age group, years		
18-29	0.087	0.074-0.103
30-39	0.115	0.100-0.132
40-49	0.189	0.173-0.207
50-59	0.351	0.333-0.370
60-69	0.523	0.505-0.541
70-79	0.680	0.660-0.701
≥80	1.000	Reference
Constant[b]	0.327	0.317-0.338

Abbrevation: OR= odds ratio, CI=confidence interval
[a] The logistic regression is modelled with in-hospital death in as dependent variable, per year 2009-2019 as continuous covariate and indicator variables as covariates for the years 2008, 2020 and 2021, and female sex and age groups.
[b] Constant = estimated odds for men ≥80 in 2009

Quarterly calculations for the years 2020 and 2021 are given in Supplementary Table 3 and Supplementary Figure 3, illustrating that the hospital outcome in COVID-19-related sepsis varied across the pandemic. In contrast, patients with first sepsis admission experienced more stable outcomes over the same period.

Discussion

In this nationwide longitudinal registry study using all hospital data over fourteen years (2008-2021), we identify a stable trend in the incidence rate of a first sepsis episode but an increasing trend for all sepsis admissions. We also observed a decreasing trend in case fatality. Compared to the period 2009-2019, there was a substantial reduction in sepsis incidence rate during the first year of the COVID-19 pandemic that was somewhat attenuating towards pre-pandemic levels in 2021. Further, we demonstrate an increase in case fatality during the COVID-19 pandemic, most prominent in 2021.

Previously "The Global burden of Disease Study" by Rudd and colleagues (2020) registered an estimated reduction of 37% in the age-standardized incidence rate of sepsis from 1990 to 2017,[2] and the differences to our study could be due to heterogeneity between regions, the inclusion of low- and middle-income countries with less access to health care, inclusion of persons aged<18 and longer follow-up. Similarities with

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our study are the use of individual-level data and similar extraction of ICD-10 codes. Several other articles report increasing sepsis incidence rates,[15 17 22 26 27] i.e., the opposite of what we and Rudd and colleagues found. Martin et al. (2003) found an annual 8.7% increase in sepsis incidence rate using claimed-based data between 1979 and 2000.[26] Dombrovskiy et al. (2007) found almost doubled hospitalizations of severe sepsis from 1992 to 2003,[17] and Kumar et al. (2011) calculated an increase in sepsis incidence rate of 200/100 000 inhabitants from 2000 to 2007.[15] These results are difficult to compare with our analysis regarding first sepsis episodes because they report on all sepsis admissions and fail to stratify on individual entry. However, their results can be compared to our analysis of all sepsis admissions, where we find an increased age-and sex-adjusted incidence rate ratio before the current pandemic. Studies that include all sepsis admissions will naturally increase incidence rates because each person is possibly admitted multiple times, thus increasing the nominator without changing the denominator. Both Rudd and colleagues (2020) and our study go against the myth that the increase in sepsis incidence rates primarily is driven by more liberal practices in sepsis coding over time. It is more likely that previously reported increased incidence rates is caused by the failure to treat each case as an individual entry. Better treatment of medical conditions such as cancer and chronic diseases with increased use of immunosuppressives and invasive procedures [28 29] increases the number of patients at risk of developing more than one sepsis episode.[30] Further, sepsis survivors are prone to recurring sepsis due to new or worsened comorbidities and repeated infections and will thus drive the sepsis nominator.[31]

Previous studies of in-hospital sepsis mortality show in general a decreasing trend. Kaukonen et al. (2014) conducted a retrospective observational study over twelve years of sepsis patients admitted to ICU.[32] They reported annually decline in mortality throughout the study period with an odds ratio of 0.49 in 2012, with year 2000 as reference. In a European registry-based study of ICU sepsis patients, Yebenes et al. (2017) reported a odds ratio in 2012 with 2008 as reference of 0.77 in a multivariate analysis.[27] The higher decline than ours can possible be due to inclusion criteria regarding sepsis severity, and that new and updated guidelines, and more attention to the sepsis diagnosis have improved the recognition of the diagnosis, thus assisting clinicians in accurate and timely treatment of infections (i.e., early blood culture sampling and antibiotics), preventing illness severity and therefore reducing mortality.[33-37]

The sepsis incidence rate during the pandemic is previously studied by Bodilsen and colleagues (2021).[14] They compared hospital admissions for several diagnoses, one year prior to and 11 months after the COVID-19 pandemic and reported a significant reduction in sepsis incidence rate using a few selected sepsis codes and found elevated 30 days mortality.[14] These previous results are in line with our results. Explanations

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for the observed lower incidence of sepsis after the pandemic can be the lower incidence of other infections with lockdowns,[14 38] in addition to vaccination strategies prioritizing the elderly first and canceling elective surgeries.[39] Other explanations could be a higher threshold for hospitalization during the pandemic in order to avoid an overflow of ill patients to hospitals.

In the above-mentioned Danish study, the 30 days mortality for sepsis under and between the lockdowns was in line with our results.[14] The increased case fatality in first sepsis admission after the pandemic lockdown can be explained by the fatality of the novel SARS-CoV-2 virus. Further concerns are reluctance to seek health care because of the perceived risk of COVID-19 infection and negligence to report severe symptoms. Probably implications of these explanations are higher in-hospital mortality as those who were admitted with sepsis were more severely ill and thus had a higher baseline mortality risk.

There are several limitations to our study. First, the use of registry-based study design is dependent on ICD-code abstraction and the characteristics of registries.[40] However, it is mandatory for all Norwegian hospitals to report all activity to NPR and the NPR is a complete and unselected national hospital registry. Identifying sepsis by ICD-10 codes in register-based studies was first used by Angus,[22] and later modified by Rudd and colleagues to reflect the modern understanding of sepsis pathophysiology.[2] Different study designs have been investigated to find the most fitted design, with dividing results.[41-44] The method used by Rudd et al. (2020) has been criticized regarding code selecting strategies that does not fit all countries, and therefore most probable cause an overestimation of sepsis.[45] The ICD-10 codes are not static, and new specific codes for SIRS and septic shock were implemented in 2010.[46] We have during the follow-up used the Sepsis-3 definition, albeit the new definition first came in 2016.[1] However, the trends seem to be consistent across the follow-up period except for 2008 and the pandemic years. Second, the incidence rate of first episodes is probably inflated in 2008, but fitting 2008 as an indicator variable in the regression model will account for this. Third, retrieving organ dysfunction codes to identify implicit sepsis can generate false-positive outcomes since not all organ dysfunctions are caused by a specific infection. On the other hand, false-negative results can occur if the sepsis episode is inadequately documented. Fourth, this study is without an adjustment for illness severity. Our study adjusted for age, and the age differences in sepsis and COVID-19-related sepsis patients can indicate that other demographic characteristics and pathogenesis could affect the association between sepsis, COVID-19-related sepsis, and death. Finally, the influence of the pandemic was calculated from January 2020, although the first COVID-19 patients were first admitted in late February 2020, and thus, the estimated drop in incidence rate related to COVID-19 could be underestimated. It is important to note that the level of SARS-CoV-2 incidence in

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Norway has been relatively low and therefore, the interpretation of the analysis is primarily relevant to countries with the same burden.

The study also has several strengths, including the large sample size, the use of individual-based data, and a timespan of fourteen years, which makes it possible to detect trends over time. Another strength is that we, in one joint paper, report the burden of first sepsis admissions, all sepsis admissions and case fatality, including age-separated analyses. Since the patients at first admission are likely to be younger, have fewer comorbidities, and thus have less morbidity and mortality risk, stratifying on the first admission will avoid migrating the patient to the next stage, also known as Will Rogers Phenomenon," or stage migration.[40] To the best of our knowledge, this is the first study that provides nationwide hospital admissions-based epidemiological characteristics over fourteen years for sepsis and includes data outside the ICU as well as for severe COVID-19-related sepsis.

Our results have implications for health policymakers, clinicians, and researchers. The burden of sepsis is higher than previously described in comparable studies and requires further attention. More sepsis survivors put more pressure on skilled nursing facilities and in-home care. Surveillance and prevention should be assessed and implemented in primary health care. Side-effects of the pandemic, with a pressured healthcare system and a changed threshold for seeking health care, must be evaluated.

CONCLUSION

This nationwide register-based study over fourteen years reveals that the burden of sepsis still is high. Furthermore, the high incidence rates and decreasing mortality cause an increased number of sepsis survivors, with a growing impact on the healthcare system. Notably, the decreased incidence rates of sepsis hospitalizations together with increased mortality during the pandemics give a concern regarding different efforts that were made to stop the spread of SARS-CoV-2.

Ethics Approval

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Regional Committee for Medical and Health Research Ethics (REK) in Eastern Norway (2019/42772)

Data Access Committee in Nord-Trøndelag Hospital Trust (2021/184).

Contributorship statement

Study concept and design: Skei, Nilsen, Knoop, Prescott, Damås, Gustad

Acquisition of data: Skei, Gustad

Analysis and interpretation of data: Skei, Nilsen, Gustad

Drafting of the manuscript: Skei, Gustad

Funding acquisition: Gustad

Critical revision of the manuscript for important intellectual content: All authors

Statistical analysis: Skei, Gustad, Lydersen

Administrative, technical, or material support: Skei, Brkic, Gustad

Study supervision: Nilsen, Damås, Gustad

Competing interests

None of the authors have any conflicts of interest to declare.

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Role of the Funder:

The funding body had no role in the designs of the study, data collection, analysis, interpretation of data, or in writing the manuscript.

Data sharing statement:

No additional data available.

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Fig.1 Flowchart of the inclusion and exclusion process

Fig.2 Annual all and first sepsis incidence per 100.000 inhabitants

Fig.3 Annual Case Fatality Rate for first sepsis admission

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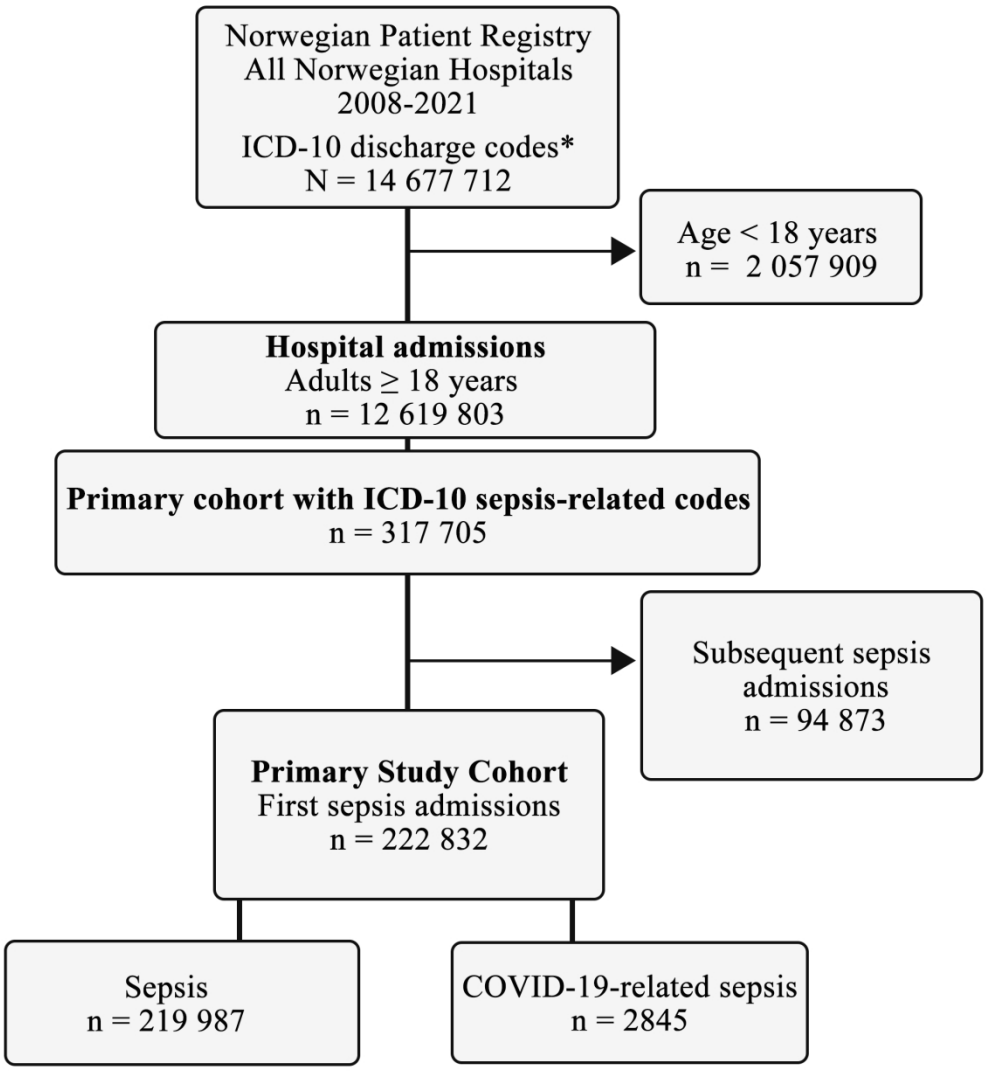

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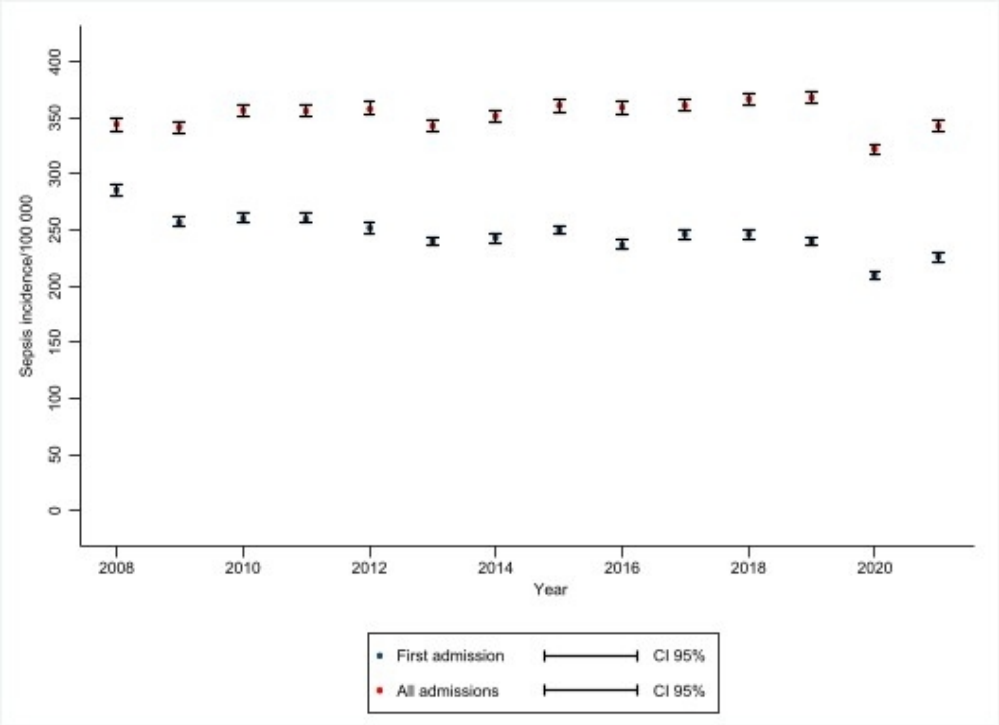

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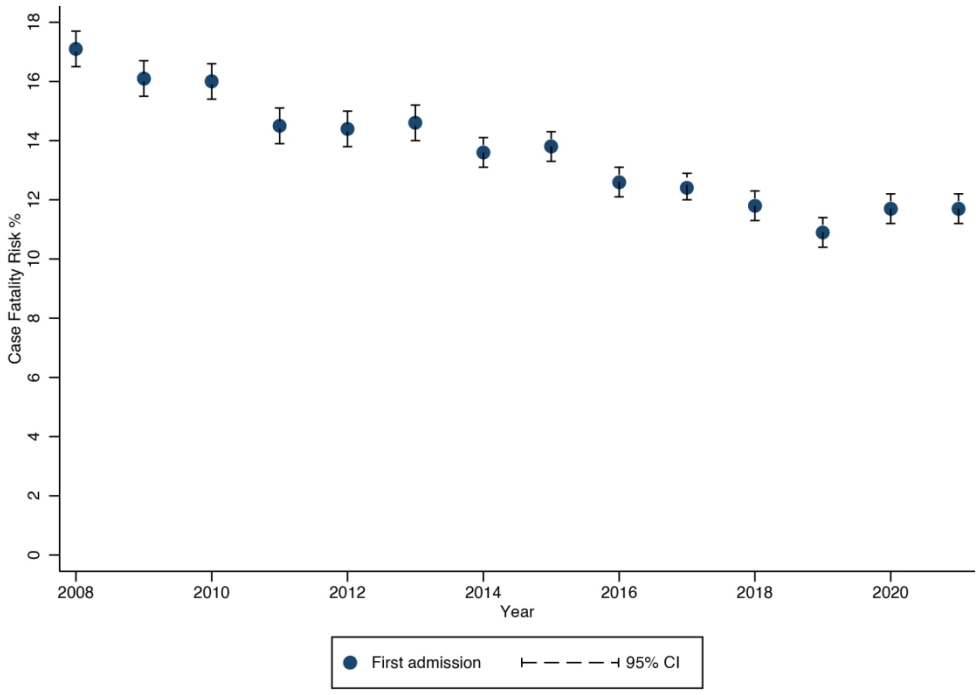

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Supplementary Table 1 Overview of ICD-10 codes identifying explicit and implicit sepsis

Explicit sepsis	A02.1, A20.7, A21.7, A22.7, A24.1, A26.7, A28.2, A32.7, A39.2, A39.4, A40, A41, A42.7, B00.7, B37.7
Implicit Sepsis[a,b]	**Infection** A00/09, A19/28, A30/32, A36/39, A42/44, A46, A48/49, A54, A59, A69.0, A69.1, A69.9, A70, A74/75, A77/81, A83/89, A92/99, B00/09, B25/27, B33/34, B37/46, B48/50, B54/55, B57/58, B60, B64, B67, B95/97, B99, G00/08, H05.0, H60.2, H70.0, I00, I33, I38/40.0, J01/06, J09/22, J36, J39.0, J39.1, J85, J86, K35/37, K61, K63.0/63.1, K65, K75.0, K81.0, K83.0, L02/04, L08, M00/01, M72.6, M86, N10, N15.1, N30, N39.0, N41.0, N41.2, N41.3, N45, N70/74, N98.0, N49, O03.0, O03.5, O04.5, O08.0, O23, O75.3, O85/86, O88.3, O91, O98, T80.2, T81.4, T82.6/82.7, T83.5/83.6, T84.5/84.7, T85.7, T88.0, U04, U07.1, U07.2 AND **Acute organ dysfunction** D65, D69.5, E87.2, G93.4, I46, I95.9, J80, J95.2, J96, K72.0, K72.9, N00, N17, N99.0, R02, R09.0, R09.2, R40.0/40.2, R41, R55, R57, R57.2, R65.1

Abbreviation: ICD= International Classification of Diseases

[a] Implicit sepsis was defined if one code of infection was present with at least one acute organ dysfunction within same hospital entry. Total sepsis estimates are calculated from both explicit and implicit cases.

[b] Explicit codes are excluded from infection codes

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Supplementary Table 2 ICD 10 codes identifying comorbidities and infection sites.

Comorbidities	**ICD-10** code
Chronic heart- and vascular disease	G45, H34, I00/31, I34/37, I42/45, I47/95.8, I97/99
Cancer	C00/97, D32/33, D35.2/35.4, D42, D43, D44.3/44.5, D45/47
Chronic lung disease	J41/47, J84, J98
Chronic renal disease	N18.3/18.5
Diabetes	E10/11
Dementia	F00/03, G30, G31.0, G31.2, G31.8
Chronic immune disease	D80/84, Z94.0/94.4, Z94.8
Chronic liver disease	K70.4, K72
Infection sites*	
Respiratory	J09/18, J20/22, J85/86, U04, U07.1, U07.2
Genitourinary	N10, N15.1, N30, N39.0, N41.0, N41.2/41.3, N45, N49, N70, N71/74, N98.0
Gastrointestinal infections	A00/09
Intra-abdominal	K35/37, K57, K61/61.1 K61.3, K63.0/63.1, K65, K75.0, K81.0, K83.0
Endocarditis/myocarditis	I33, I38/41
Skin/ Soft tissue	A46, B08/09, L02/04, L08, M72.6
Infection after procedure	T80.2, T81.4, T82.6/82.7, T83.5/83.6, T84.5/84.7, T85.7, T88
Other[a]	A19/28, A30/32, A36/39, A42/44, A48/49, A54, A59, A69.0, A69.1, A69.9, A70, A74/75, A77/80, A81, A83/89, A92/B06, B25/27, B33/34, B37/46, B48/50, B54/55, B57/58, B60, B64, B67, B95/97, B99, G00/08, H05.0, H60.2, H70.0, J01/06, J36, J39.0/39.1, M00/01, M86, O03.0, O03.5, O04.5, O08.0, O23, O75.3, O85/86, O88.3, O91, O98
Acute organ dysfunction	
Respiratory	J80, J95.2, J96, R09.0, R09.2
Circulatory	I46, I95.9, R57, R57.2
Renal	N00, N17, N99.0
Hepatic	K72.0, K72.9
Coagulation	D65, D69.5
Other acute organ dysfunctions	G93.4, R40.0/40.2, R41, R55, E87.2, R02, R65.1[b]

[a] Explicit codes are excluded from other infection sites.
[b] R65.1 was excluded in the count of acute organ dysfunctions if present in combination with R57.2, according to the Norwegian ICD-10 coding rules.

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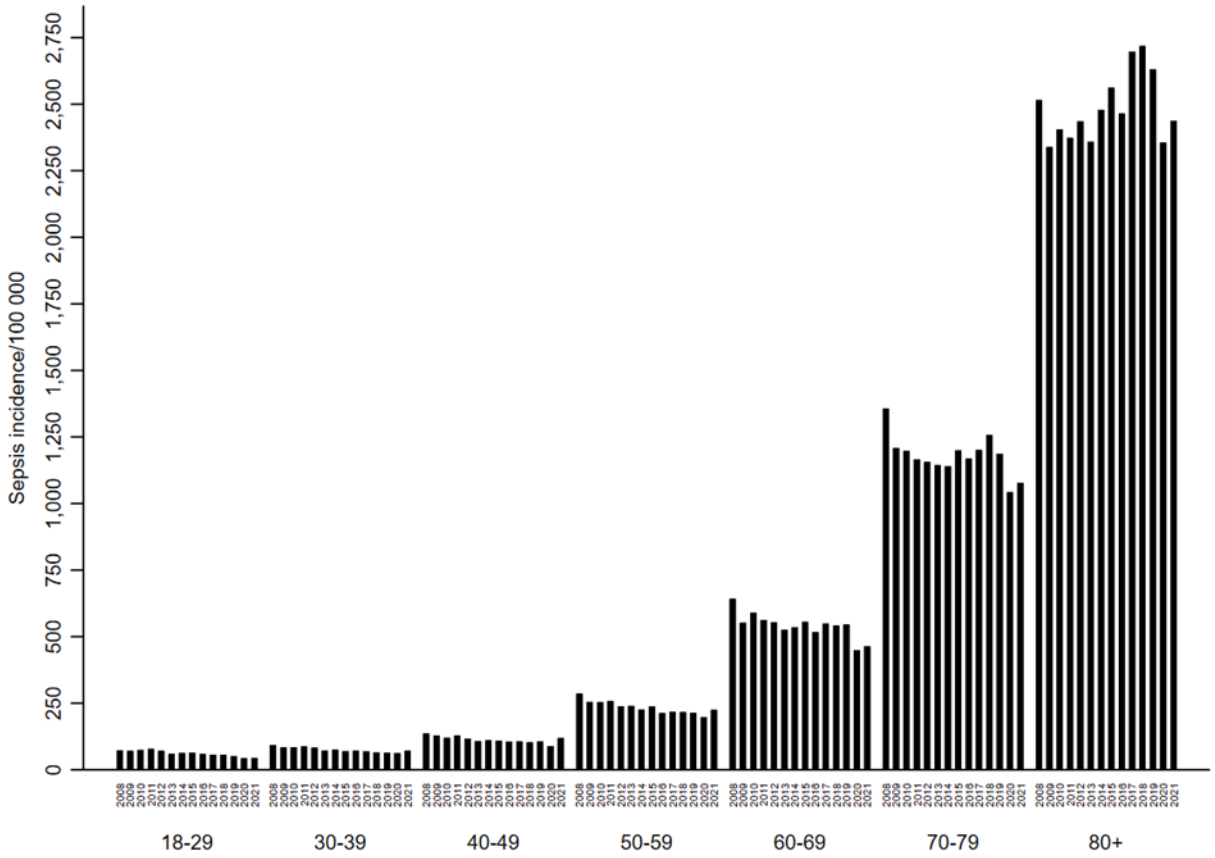

Supplementary Fig 1 Annual sepsis incidence rates for first admission by ten-years age groups

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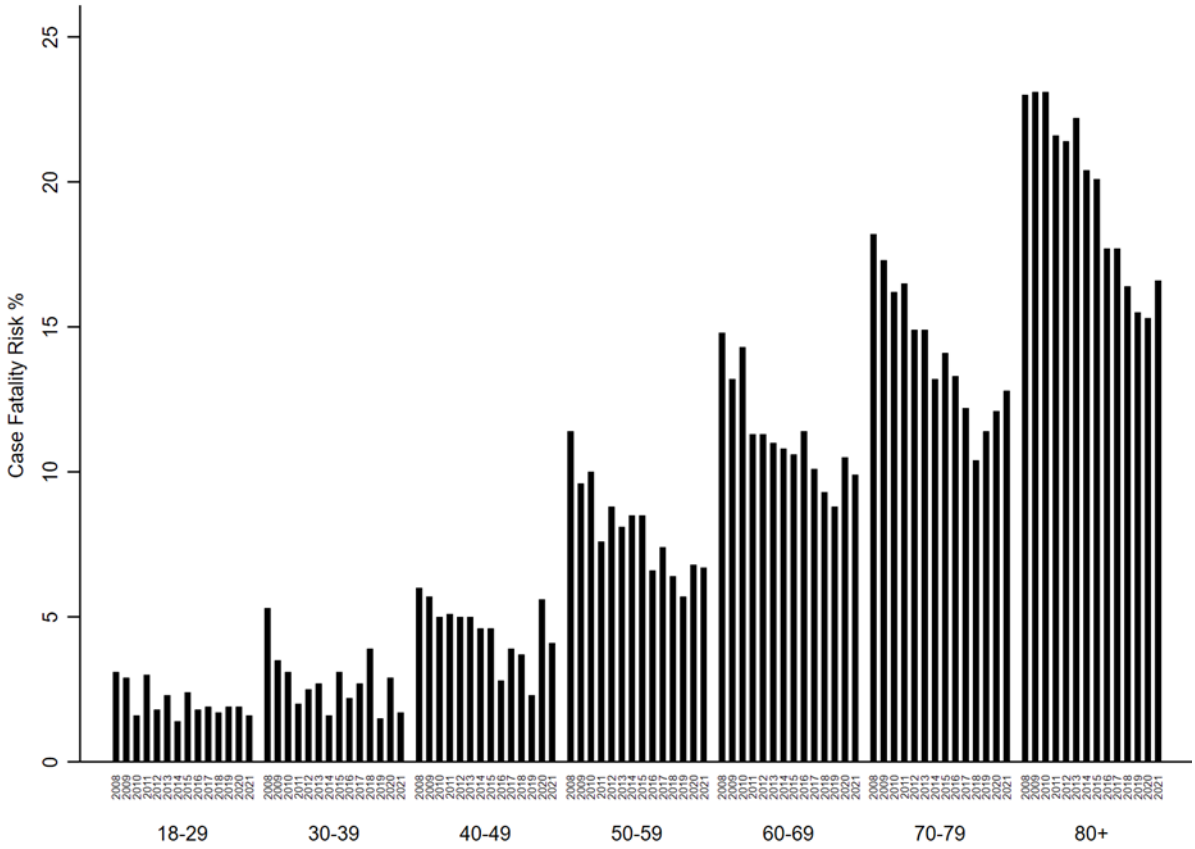

Suppl Fig 2 Annual case fatality risk in % for first sepsis admissions by ten years age-groups

Supplementary Table 3 First admissions, deaths, and CFR for sepsis and COVID-19-related sepsis patients in 2020 and 2021.

	2020						2021					
	Sepsis			COVID-19-related sepsis			Sepsis			COVID-19-related sepsis		
	N	Deaths	CFR %	N	Deaths	CFR %	N	Deaths	CFR %	N	Deaths	CFR %
Q1	4310	505	11.7	266	42	15.8	3335	415	12.4	655	58	8.9
Q2	3140	371	11.8	166	23	13.9	3336	401	12.0	389	25	6.4
Q3	3501	384	11.0	54	5	9.3	3734	446	11.9	225	32	14.2
Q4	3720	438	11.8	290	39	13.4	4233	505	11.9	800	128	16.0
Abbreviations: N = Number of cases, CFR= Case Fatality Risk calculated as in-hospital death divided by first sepsis admission in the quarter (Q). Q1 (January, February, March), Q2 (April, May, June), Q3 July, August; September, Q4 (October, November, December).												

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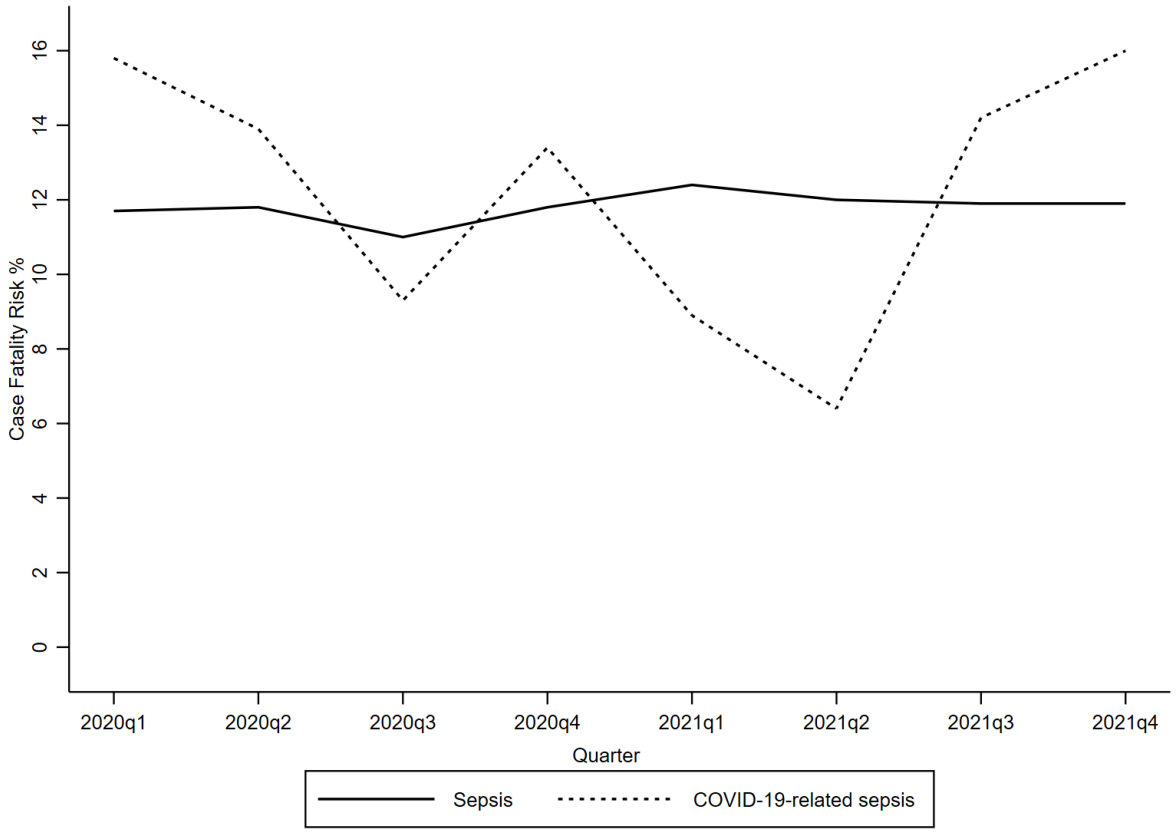

Note: Calculated as **Q1** (January 2020, February 2020, March 2020), **Q2** (April 2020, May 2020, June 2020), **Q3** (July 2020, August 2020, September 2020), **Q4** (October 2020, November 2020, December 2020), **Q1** (January 2021, February 2021, March 2021), **Q2** (April 2021, May 2021, June 2021), **Q3** (July 2021, August 2021, September 2021), **Q4** (October 2021, November 2021, December 2021).

Supplementary Fig 3 Quarterly mean case fatality risk in sepsis and COVID-19-related sepsis for first admission (2020 and 2021)

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The RECORD statement – checklist of items, extended from the STROBE statement, that should be reported in observational studies using routinely collected health data.

	Item No.	STROBE items	Location in manuscript where items are reported	RECORD items	Location in manuscript where items are reported
Title and abstract					
	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found	1 and 3	RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included. RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract. RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	1 3 No linkage
Introduction					
Background rationale	2	Explain the scientific background and rationale for the investigation being reported	4		
Objectives	3	State specific objectives, including any prespecified hypotheses	4		
Methods					
Study Design	4	Present key elements of study design early in the paper	4-6		
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4-6		

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Participants	6	*(a) Cohort study* - Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study* - Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study* - Give the eligibility criteria, and the sources and methods of selection of participants *(b) Cohort study* - For matched studies, give matching criteria and number of exposed and unexposed *Case-control study* - For matched studies, give matching criteria and the number of controls per case	4-6 4-6	RECORD 6.1: The methods of study population selection (such as codes or algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided. RECORD 6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided. RECORD 6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage.	Supplementary table 1 and 2 Figure 1 5 No linkage
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.	4-6	RECORD 7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided.	Supplementary table 2
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4-6		

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Bias	9	Describe any efforts to address potential sources of bias	5 10		5 10
Study size	10	Explain how the study size was arrived at			
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	4-6		
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) *Cohort study* - If applicable, explain how loss to follow-up was addressed *Case-control study* - If applicable, explain how matching of cases and controls was addressed *Cross-sectional study* - If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses	5-6 5-6 No missing data No loss to follow up		
Data access and cleaning methods		..		RECORD 12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population.	12

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				RECORD 12.2: Authors should provide information on the data cleaning methods used in the study.	
Linkage		..	No linkage	RECORD 12.3: State whether the study included person-level, institutional-level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided.	
Results					
Participants	13	(a) Report the numbers of individuals at each stage of the study (*e.g.*, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed) (b) Give reasons for non-participation at each stage. (c) Consider use of a flow diagram	Fig 1	RECORD 13.1: Describe in detail the selection of the persons included in the study (*i.e.,* study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.	Fig 1
Descriptive data	14	(a) Give characteristics of study participants (*e.g.*, demographic, clinical, social) and information on exposures and potential confounders (b) Indicate the number of participants with missing data for each variable of interest (c) *Cohort study* - summarise follow-up time (*e.g.*, average and total amount)	Table 1		
Outcome data	15	*Cohort study* - Report numbers of outcome events or summary measures over time *Case-control study* - Report numbers in each exposure	Supplementary Table 3 Table 2, 3 ,4		

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		category, or summary measures of exposure *Cross-sectional study* - Report numbers of outcome events or summary measures			
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Table 2, 3, 4 Supplementary Table 3		
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	5-6		
Discussion					
Key results	18	Summarise key results with reference to study objectives	2 8		
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	10	RECORD 19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported.	10
Interpretation	20	Give a cautious overall interpretation of results considering objectives,	11		

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		limitations, multiplicity of analyses, results from similar studies, and other relevant evidence			
Generalisability	21	Discuss the generalisability (external validity) of the study results			
Other Information					
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based			
Accessibility of protocol, raw data, and programming code		..		RECORD 22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.	Can be provided under Supplementary

*Reference: Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, Sørensen HT, von Elm E, Langan SM, the RECORD Working Committee. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. *PLoS Medicine* 2015; in press.

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Long-term temporal trends in incidence rate and case fatality of sepsis and COVID-19-related sepsis in Norwegian hospitals, 2008-2021: A nationwide registry study

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Long-term temporal trends in incidence rate and case fatality of sepsis and COVID-19-related sepsis in Norwegian hospitals, 2008-2021: A nationwide registry study

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Abstract

Objectives: To estimate temporal trends in incidence rate (IR) and case fatality during a 14-year period from 2008 through 2021, and to assess possible shifts in these trends during the COVID-19 pandemic.

Setting: All Norwegian hospitals 2008-2021.

Participants: 317.705 patients ≥ 18 year with a sepsis ICD-10 code retrieved from The Norwegian Patient Registry.

Primary and secondary measures: Annual age-standardized incidence rates with 95% confidence intervals (CI). Poisson regression was used to estimate changes in IRs across time, and logistic regression was used to estimate odds ratios (ORs) for in-hospital death.

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Results: Among 12.619.803 adult hospitalizations, a total of 317.705 (2.5%) hospitalizations in 222.832 (70.0%) unique patients met the sepsis criteria. The overall age-standardized IR of a first sepsis admission was 246/100.000 (95% CI, 245-247), whereas the age-standardized IR of all sepsis admissions was 352/100.000 (95% CI, 351-354). In the period 2009-2019, the annual IR for a first sepsis episode was stable (Incidence Rate Ratio (IRR) per year, 0.999; 95% CI, 0.994-1.004), whereas for all sepsis the IR increased by 15.5% (annual IRR, 1.013; 95% CI 1.007-1.019). During the COVID-19 pandemic, the IRR for a first sepsis was 0.877 (95% CI, 0.829-0.927) in 2020 and 0.929 (95% CI, 0.870-0.992) in 2021, and for all sepsis it was 0.870 (95% CI, 0.810-0.935) in 2020 and 0.908 (95% CI, 0.840-0.980) in 2021, compared to the previous 11-year period. Case fatality among first sepsis admissions declined in the period 2009-2019 (annual OR, 0.954 [95% CI, 0.950-0.958]), whereas case fatality increased during the COVID-19 pandemic in 2020 (OR, 1.061 [95% CI 1.001-1.124] and in 2021 (OR, 1.164 [95% CI, 1.098-1.233]).

Conclusion: We found a stable IR of a first sepsis admission during the years 2009-2019. However, the increasing burden of all sepsis admissions indicates that sepsis awareness with updated guidelines and education must continue.

Strengths and limitations of this study

- This study is based on complete data from all Norwegian hospitals during 14 years
- Sepsis was identified using the primary ICD-10 discharge diagnosis and up to 20 secondary ICD-10 diagnosis codes at discharge
- We used individual patient data enabling age and sex adjusted estimates and identification of first and recurrent sepsis.
- Implicit identification of sepsis based on diagnostic codes for acute organ dysfunction and infection may result in over-detection of sepsis in instances where acute organ dysfunction is unrelated to infection.

Introduction

Sepsis is a dysfunctional immune response to infection that leads to acute life-threatening tissue damage and organ dysfunction.[1] With an estimated 50 million cases and 11 million sepsis-related deaths in 2017, sepsis

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remains a major cause of worldwide morbidity and mortality.[2] While sepsis may result from any infection, the majority of adult sepsis cases before the COVID-19 pandemic were attributed to bacterial infections, and viral sepsis was thought to be rare.[3-5] During the COVID-19 pandemic, however, an unprecedented number of patients were diagnosed with viral sepsis (hereafter labelled COVID-19-related sepsis),[6-9] with a high risk of co-infections and secondary infections that can aggravate the outcome.[10 11] It is likely that public health efforts to reduce the spread of SARS-CoV-2, such as lockdowns, may also have influenced the spread of other communicable diseases contributing to the risk of sepsis.[12 13] However, few studies have assessed the impact of the pandemic on sepsis incidence rate and case fatality risk, using a few selected sepsis codes.[14] No previous study has focused exclusively on sepsis incidence rate using all sepsis codes, [2] and compared sepsis incidence rate and case fatality during the two first years of the COVID-19 pandemic with long-term historic trends.

Previous research on the incidence of sepsis before the COVID-19 pandemic has shown conflicting results. [2 15-17] However, precise incidence and mortality rates are difficult to measure, and a more accurate quantification (i.e., correct identification and diagnosis coding) of sepsis is warranted.[18 19]

The overall aim of this study is therefore to describe temporal trends in sepsis incidence rate and case fatality using nationwide Norwegian data on all adult hospital admissions from 2008 through 2021, and secondly to examine changes in hospital admission and mortality rates of sepsis during the first two COVID-19 pandemic years.

Methods

Data Source and Study Population

This nationwide longitudinal study used data from the Norwegian Patient Registry (NPR) and Statistics Norway.[20 21] NPR is an administrative database maintained by the Norwegian Directorate of Health that contains data with unique patient identifiers that allow longitudinal follow-up of individual patients for every admission to public hospitals in Norway from 2008 onward. In addition, NPR contains admission and discharge dates, and the International Classification of Diseases 10th revision (ICD-10) discharge codes, while Statistics Norway contains demographic data on all citizens of Norway. In NPR, we identified all hospitalizations to public hospitals in Norway (2008–2021) aged ≥18 years with the ICD-10 discharge diagnosis code(s) for sepsis consistent with the Angus implementation refined by Rudd and colleagues.[2 22]

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We treated each hospitalization as an individual entry, and within this entry, sepsis was defined as explicit or implicit sepsis. For explicit sepsis, we used the presence of one code (See Supplementary Table 1 for an overview of all ICD-10 codes to define explicit and implicit sepsis). For implicit sepsis, we used the combination of an infection code with the presence of an acute organ dysfunction code. The strategy was used for the primary and up to 20 secondary co-existing ICD-10 discharge codes since there is no obligatory order for the secondary codes. We added COVID-19-related sepsis to the implicit sepsis category based on the presence of a diagnostic code for COVID-19 (U07.1, U07.2) and ≥one organ dysfunction code. Patients with a COVID-19 sepsis code and an explicit sepsis code were categorized as explicit sepsis. Supplementary Figure 1 shows the flow chart of the selection of patients into the study.

Characteristics of Study Population

Patient characteristics were extracted from NPR, including sex, age, ICD codes for selected comorbidities based on diagnostic groups,[23] as well as numbers of hospital stays from sepsis, readmissions, and in-hospital deaths (for details, see Supplementary Table 2 ICD 10 codes identifying comorbidities and infection sites). For sepsis admissions, we used ICD-10 codes to classify site(s) of infection into respiratory, genitourinary, intra-abdominal, extra-abdominal, endocarditis/myocarditis, soft tissue, infections following a procedure, and other (bone, joint, obstetric, ear, mouth, upper airway, central nervous system and unknown). The acute organ dysfunctions were classified by number and as circulatory, respiratory, renal, hepatic, coagulation, and/or other (acidosis, unspecific gangrene, central nervous system, and Systemic Inflammatory Response Syndrome of infectious origin with organ dysfunction [R65.1]). A sepsis admission was defined as recurring sepsis admission if the patient was discharged with an explicit or implicit sepsis code and thereafter admitted with an explicit or implicit sepsis code, regardless of the time frame for the new admission. The number of sepsis admissions was categorized from one to five or more.

Statistical Analysis

Descriptive statistics are presented as frequencies, means, standard deviation, percent, and medians as appropriate, and are reported by sepsis or COVID-19-related sepsis. We calculated the crude sepsis incidence rate (IR) of a first, recurrent and all sepsis episode according to year (2008–2021) and ten-year age-groups as the number of sepsis admissions divided by the total number of inhabitants in Norway at the beginning of the year. The IRs for first and all sepsis were then standardized according to Segi's world standard population using ten-years age categories,[24 25] and reported per 100 000 person years.

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To evaluate the temporal trends of sepsis incidence rates and the impact of the COVID-19 pandemic on sepsis incidence rates we used Poisson regression to estimate incidence rate ratios (IRR) of sepsis using the number of sepsis admissions (total or first) as the dependent variable, population as exposure, the years 2009 to 2019 as a continuous variable, and the years 2008, 2020 and 2021 as separate indicator variables. Since our purpose was descriptive, we only adjusted for sex (man, woman) and age (10-year categories) in the analysis. Since 2008 was the first observation year, we could not differentiate between a first and a recurrent episode, and 2008 thus was included as an indicator variable to account for a possibly inflated incidence rate of first sepsis. To account for overdispersion, we used the robust variance estimator.

Case fatality risk (CFR) of a first sepsis admission was calculated as the number of first sepsis admissions with a discharge status of in-hospital death divided by all first sepsis hospitalizations. Similarly, CFR for recurrent sepsis was calculated as the number of recurrent sepsis admissions with a discharge status of in-hospital death divided by all recurrent sepsis hospitalizations. The calculation was performed on annual cases for first and recurrent sepsis admissions from 2008 to 2021 and by ten-year age groups in the same period. During 2020 and 2021 we also calculated the quarterly CFR and compared CFR for COVID-19-related sepsis and sepsis. To evaluate the trend of in-hospital mortality and the pandemic`s impact on hospital mortality, we used logistic regression to estimate odds ratios (ORs) for in-hospital death using the years 2009-2019 as a continuous variable, the years 2008, 2020, and 2021 as indicator variables, and adjusting for sex (man, woman) and age (10-year categories). We report 95% confidence intervals (CI) where relevant.

All analyses were conducted using STATA version 16.1 (Stata Corp).

Patient and public involvement

Two patient representatives from the user group at Nord-Trondelag Hospital Trust participated in developing the research question and design of this study and were supportive of the use of health data for research purposes. They stressed the importance of education regarding symptoms and signs of sepsis to prevent fatal outcome and gave advice that research results and information about sepsis should be published in newspapers and social media in order to reach the patients and relatives. According to this, we plan to distribute this research results on our social media to inform patients, sepsis charities, research funders and policy makers.

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Ethics

The study was approved by the Regional Committee for Medical and Health Research Ethics (REK) in Eastern Norway (2019/42772) and the Data Access Committee in Nord-Trøndelag Hospital Trust (2021/184). In accordance with the approval from the REK and the Norwegian law on medical research, the project did not require a written patient consent. This work was performed on TSD (Service for Sensitive Data) facilities owned by the University of Oslo, operated and developed by the TSD service group at the University of Oslo, IT Department (USIT). TSD is designed to store and post-process sensitive data in compliance with the Norwegian "Personal Data Act" and "Health Research Act."

Results

Characteristics of Study Population

Among 12.619.803 non-psychiatric adult hospitalizations during the study period (2008–2021), 317.705 (2.5%) met the criteria for sepsis, and of these, 222.832 (70%) were first hospitalizations with sepsis. Patient characteristics according to a first episode of sepsis and COVID-19-related sepsis are presented in Table 1.

Table 1 Characteristics of the study population at first sepsis admission (2008-2021) and COVID-19-related sepsis (2020-2021). Estimates represent n (%) unless otherwise stated.

Characteristics	**Sepsis[a]**	**COVID-19-related sepsis[b]**	**All first sepsis admissions**
First admission (% of all sepsis admissions)	219 987 (69.0)	2 845 (1.0)	222 832 (70.0)
Sex			
Male	118 580 (53.9)	1862 (65.5)	120 442 (54.1)
Female	101 407 (46.1)	983 (34.5)	102 390 (45.9)
Age (years)			
Mean ± SD (median)	71.2 ± 16.6 (74.4)	61.4 ± 16.1 (61.8)	71.1 ± 16.6 (74.3)
Number of comorbidities			
0	66 869(30.4)	1 581(55.6)	68 450 (31.7)
1	97 894 (44.5)	909 (32.0)	98 803 (44 .3)
2	45 052 (20.5)	300 (10.5)	45 352 (20.4)
≥3	10 172 (4.6)	55 (1.9)	10 227 (4.6)
Comorbidities[c]			
Heart and vascular	99 360 (64.9)	702 (55.5)	100 062 (64.8)
Cancer	39 243 (25.6)	125(9.9)	39 368 (25.5)
Lung	35 859 (23.4)	306 (24.2)	36 165 (23.4)
Renal	8 873 (5.8)	76 (6.0)	8 949 (5.8)
Diabetes	24 030 (15.7)	386 (30.5)	24 416 (15.8)
Dementia	8 068 (5.3)	32 (2.5)	8 100 (5.3)
Immune	3 091 (2.0)	49 (3.9)	3 140 (2.0)
Liver	991 (0.7)	NA	994 (0.6)

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Site of infection[d]			
Respiratory	79 290 (48.7)	2 528 (97.9)	81 818 (49.5)
Genitourinary	44 700 (27.5)	82 (3.2)	44 782 (27.1)
Skin and soft tissue	8 260 (5.1)	5 (0.2)	8 265 (5.0)
Intra-abdominal	8 841(5.4)	29 (1.1)	8 870 (5.4)
Extra-abdominal	12 318 (7.6)	22 (0.9)	12 340 (7.5)
Infections following a procedure	8 277 (5.1)	13 (0.5)	8 290 (5.0)
Endocarditis/Myocarditis	2 522 (1.6)	8 (0.3)	2 530 (1.5)
Other[e]	28 836 (17.7)	152 (5.9)	28 997 (17.5)
Explicit sepsis	77 240 (35.1)	90 (3.2)	77 330 (34.7)
Number of acute organ dysfunctions			
1	126 928 (84.5)	2 252 (81.2)	28 928(84.4)
2	17 869 (11.9)	427 (15.4)	18 296(12.0)
3	3 988 (2.7)	70 (2.5)	4 058 (2.7)
≥4	1 466 (1.0)	24 (0.9)	1490(1.0)
Organ system with acute organ dysfunction[f]			
Respiratory	59 465 (39.7)	2 399 (86.5)	61 864 (40.5)
Circulatory	14 824 (9.9)	68 (2.5)	14 892 (9.8)
Renal	66 809 (44.6)	433 (15.6)	67 242 (44.1)
Hepatic	3 192 (2.1)	17 (0.6)	3 209 (2.1)
Coagulation	6 428 (4.3)	43 (1.6)	6 471(4.2)
Other [e]	31 303 (20.9)	284 (10.3)	31 587 (20.7)
Number of hospital admissions for sepsis[g]			
1	168 904 (76.8)	2 714 (95.4)	171 618 (77.0)
2	33 097 (15.0)	4125 (4.4)	33 222 (14.9)
3	10 125 (4.6)	NA	10 129 (4.6)
4	40 010 (1.8)	NA	4 011 (1.8)
≥5	3 851 (1.8)	NA	3 852 (1.7)
Readmission[h]	54 967 (25.0)	474 (16.7)	55 441 (24.9)

If not mentioned otherwise, the percentage (%) is calculated from available data from the first admission with Sepsis or COVID-19-related sepsis.
Abbreviation: NA=Not Applicable (used when the number of admissions was ≤5).
[a] Sepsis included patients with implicit and/or explicit sepsis, but not patients with an ICD-10 code for COVID-19
[b] COVID-19-related sepsis included patients with COVID-19 combined with organ dysfunction or explicit code
[b] The proportion of all comorbidities is calculated as number of particular comorbidity over total number of comorbidities
[c] The proportion of all infections sites is calculated as number of individuals with particular infection site over total number of infections sites
[d] Other infection sites= Bone, obstetric, upper airway, central nervous system and unknown
[e] The proportion of organ dysfunctions is calculated based on n with any organ dysfunctions
[f] Other acute organ dysfunction= Acidosis, unspecific gangrene, central nervous system dysfunctions and Systemic Inflammatory Respons Syndrome.
[g] Number of hospital admissions= Calculated as new sepsis admission if admission with ICD-10 codes defining sepsis, regardless of time frame for the new sepsis admission. Follow up=14 years
[h] Readmission= admission within 30 days after discharge regardless of cause

In 2020 and 2021, 2.845 of 29.329 (9.7%) of first sepsis cases were identified as COVID-19 related sepsis. Men were overrepresented among patients with sepsis (53.9%) and COVID-19-related sepsis (65.5%). The sepsis patients were older than patients with COVID-19-related sepsis (mean age 71.1 vs. 61.4). The sepsis patients experienced renal acute organ dysfunction most often (44.6%). followed by respiratory failure (39.7%). The COVID-19-related sepsis patients experienced naturally most frequent respiratory failure (86.5%), followed by

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renal failure (15.6%). In total, 25.0% and 16.7% of the patients were readmitted within 30 days in the sepsis and COVID-19-related sepsis group, respectively. During the total study period (2008-2021), 24.2% of sepsis patients had ≥2 recurring sepsis hospitalization.

Sepsis Incidence Rates and Temporal Trends

Table 2 shows that from 2009 through 2019, the annual age-standardized IRR of first sepsis episode was stable (IRR per year, 0.999; 95% CI, 0.994-1.004), whereas the overall sepsis incidence rate increased (IRR per year increase, 1.013; 95% CI, 1.007-1.019), with a total increase in incidence rates of 15.5%. This is clearly illustrated in Figure 1. During the COVID-19 pandemic, the incidence rate was reduced compared to the previous 11-year period, with IRR of 0.877 (95% CI, 0.829-0.927) in 2020 and 0.929 (95% CI, 0.870-0.992) in 2021 for first sepsis cases, and 0.870 (95% CI, 0.810-0.935) in 2020 and 0.908 (95% CI, 0.840-0.980) in 2021 for all sepsis cases. The incidence rate for both first and recurrent sepsis increased exponentially from ages 50 and beyond, see Figure 2 for recurrent sepsis and Supplementary Figure 2 for first sepsis incidence.

Table 2 Poisson regression[a] for trends of first and all sepsis episodes

	First sepsis admissions		All sepsis admissions	
	IRR	95% CI	IRR	95% CI
Per year 2009 to 2019	0.999	0.994-1.004	1.013	1.007-1.019
2008	1.110	1.021-1.210	1.007	0.920-1.102
2020	0.877	0.829-0.927	0.870	0.810-0.935
2021	0.929	0.870-0.992	0.908	0.840-0.980
Female sex	0.688	0.669-0.707	0.677	0.656-0.699
Age group, years				
18-29	0.023	0.021-0.026	0.023	0.020-0.025
30-39	0.029	0.026-0.031	0.028	0.025-0.030
40-49	0.043	0.041-0.046	0.044	0.041-0.047
50-59	0.089	0.085-0.093	0.094	0.088-0.100
60-69	0.207	0.200-0.214	0.225	0.215-0.235
70-79	0.457	0.441-0.473	0.491	0.470-0.512
≥80	1.000	Reference	1.000	Reference
Constant[b]	0.031	0.030-0.033	0.040	0.038-0.042

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Abbrevation: IRR = incidence rate ratio, CI = confidence interval
[a] The Poisson regression model was set up with cases as dependent variable, population as exposure, per year 2009-2019 as continuous covariate, and indicator variables as covariates for the years 2008, 2020 and 2021, and female sex and age groups.
[b] Constant = estimated incidence rate for men ≥80 in 2009

The overall age-standardized IR of a first sepsis admission was 246/100.000 (95% CI, 245-247), whereas the age-standardized IR of all sepsis admissions was 352/100.000 (95% CI, 351-354) during the study period (Supplementary Table 3).

Case Fatality and Temporal Trends

The mean CFR was 13.7% for first sepsis admissions over the fourteen years study period and 12.6% among recurrent sepsis admissions In-hospital deaths for patients with a first sepsis admission declined during 2009 to 2019 (OR per year, 0.954 [95% CI, 0.950-0.958]), with a total decline of 43.1% (Table 3 an Supplementary Figure 3). Supplemental Figure 4 shows that this decline in CFR over the study period occurred in all ten-year age groups. The CFR for recurrent sepsis declined with an OR of 0.973 (95% CI, 0.966-0.980) per year in the same period, with a total decline of 28.0% (Table 3). Supplementary Table 4 displays the details for age standardizes CFR (%) for both first and recurrent sepsis episode per year

Hospital death increased during the COVID-19 pandemic with an OR 1.061 (95% CI, 1.001-1.124) in 2020 and an OR of 1.164 (95% CI, 1.098-1.233) in 2021 for first sepsis admissions, and for recurrent sepsis admissions in 2021 with an OR of 1.112 (95% CI, 1.027-1.205) (Table 3).

Table 3 Logistic regression[a] with in-hospital deaths as dependent variable, 2008-2021.	
First sepsis admission	Recurrent sepsis admission

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	OR	95% CI	OR	95% CI
Per year 2009 to 2019	0.954	0.950-0.958	0.973	0.966-0.980
2008	1.003	0.954-1.055	0.938	0.833-1.056
2020	1.061	1.001-1.124	0.985	0.909-1.067
2021	1.164	1.098-1.233	1.112	1.027-1.205
Female sex	0.898	0.876-0.920	0.863	0.830-0.900
Age group, years				
18-29	0.087	0.074-0.103	0.251	0.206-0.306
30-39	0.115	0.100-0.132	0.236	0.194-0.288
40-49	0.189	0.173-0.207	0.387	0.344-0.435
50-59	0.351	0.333-0.370	0.487	0.451-0.527
60-69	0.523	0.505-0.541	0.635	0.601-0.670
70-79	0.680	0.660-0.701	0.781	0.745-0.819
≥80	1.000	Reference	1.000	Reference
Constant[b]	0.327	0.317-0.338	0.247	0.234-0.261

Abbrevation: OR= odds ratio, CI=confidence interval
[a] The logistic regression is modelled with in-hospital death in as dependent variable, per year 2009-2019 as continuous covariate and indicator variables as covariates for the years 2008, 2020 and 2021, and female sex and age groups.
[b] Constant = estimated odds for men ≥80 in 2009

Quarterly calculations for the years 2020 and 2021 are given in Supplementary Table 5 and Supplementary Figure 5, illustrating that the hospital outcome in COVID-19-related sepsis varied across the pandemic. In contrast, patients with first sepsis admission experienced more stable outcomes over the same period.

Discussion

In this nationwide longitudinal registry study using all hospital data over fourteen years (2008-2021), we identify a stable trend in the incidence rate of a first sepsis episode but an increasing trend for all sepsis admissions. We also observed a decreasing trend in case fatality. Compared to the period 2009-2019, there was a substantial reduction in sepsis incidence rate during the first year of the COVID-19 pandemic that was somewhat attenuating towards pre-pandemic levels in 2021. Further, we demonstrate an increase in case fatality during the COVID-19 pandemic, most prominent in 2021.

Previously "The Global burden of Disease Study" by Rudd and colleagues (2020) registered an estimated reduction of 37% in the age-standardized incidence rate of sepsis from 1990 to 2017,[2] and the differences to our study could be due to heterogeneity between regions, the inclusion of low- and middle-income countries with less access to health care, inclusion of persons aged<18 and longer follow-up. Similarities with our study are the use of individual-level data and similar extraction of ICD-10 codes. Several other articles

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report increasing sepsis incidence rates,[15 17 22 26 27] i.e., the opposite of what we and Rudd and colleagues found. Martin et al. (2003) found an annual 8.7% increase in sepsis incidence rate using claimed-based data between 1979 and 2000.[26] Dombrovskiy et al. (2007) found almost doubled hospitalizations of severe sepsis from 1992 to 2003,[17] and Kumar et al. (2011) calculated an increase in sepsis incidence rate of 200/100 000 inhabitants from 2000 to 2007.[15] These results are difficult to compare with our analysis regarding first sepsis episodes because they report on all sepsis admissions not first sepsis admissions. However, their results can be compared to our analysis of all sepsis admissions, where we found an increased age-and sex-adjusted incidence rate ratio before the current pandemic. Studies that include all sepsis admissions will naturally increase incidence rates because each person may be admitted multiple times, thus increasing the numerator without changing the denominator. Both Rudd and colleagues (2020) and our study go against the myth that the increase in sepsis incidence rates primarily is driven by more liberal practices in sepsis coding over time. It is more likely that previously reported increased incidence rates is caused by the failure to treat each case as an individual entry.

The incidence of sepsis is higher among patients in the older age categories. Angus and colleagues (2001) investigated incidence of severe sepsis in the US in 1995 and reported that the incidence of sepsis increased exponentially from ages 50 years and beyond.[22] This was also confirmed in later studies,[15 17] and is in line with the data in our study. Plausible explanations include increased prevalence of comorbidities by age that make patients more prone to sepsis and age-related weakening in immune function.[28]. In addition, better treatment of medical conditions such as cancer and chronic diseases with increased use of immunosuppressives and invasive procedures [29 30] increases the number of patients at risk of developing more than one sepsis episode.[28] Further, sepsis survivors are prone to recurring sepsis due to new or worsened comorbidities and repeated infections and will thus drive the sepsis nominator.[31]

Previous studies of in-hospital sepsis mortality show in general a decreasing trend. Kaukonen et al. (2014) conducted a retrospective observational study over twelve years of sepsis patients admitted to ICU.[32] They reported annually decline in mortality throughout the study period with an odds ratio of 0.49 in 2012, with year 2000 as reference. In a European registry-based study of ICU sepsis patients, Yebenes et al. (2017) reported a odds ratio in 2012 with 2008 as reference of 0.77 in a multivariate analysis.[27] The higher decline than we observed can possible be due to different inclusion criteria of sepsis cases. While both Yebenes et al. and Kaukonen et al. stratified on all sepsis cases, the current study stratified on both first and all sepsis admissions. Other plausible explanations include different inclusion criteria regarding sepsis severity, and that new and updated guidelines, and more attention to the sepsis diagnosis have improved the recognition of the diagnosis,

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thus assisting clinicians in accurate and timely treatment of infections (i.e., early blood culture sampling and antibiotics), preventing illness severity and therefore reducing mortality.[33-37]

The sepsis incidence rate during the pandemic is previously studied by Bodilsen and colleagues (2021).[14] They compared hospital admissions for several diagnoses, one year prior to and 11 months after the COVID-19 pandemic and reported a significant reduction in sepsis incidence rate using a few selected sepsis codes and found elevated 30 days mortality.[14] These previous results are in line with our results. Explanations for the observed lower incidence of sepsis after the pandemic can be the lower incidence of other infections with lockdowns,[14 38] in addition to vaccination strategies prioritizing the elderly first and canceling elective surgeries.[39] Moreover, our study could only identify one-fourth of the reported deaths due to COVID-19 in Norway at the end of 2021, which suggest that the majority of deaths due to COVID-19 occurred outside the hospitals. A possible explanation for the low proportion of in-hospital deaths due to COVID-19-related sepsis could be a higher threshold for hospitalization during the pandemic in order to avoid an overflow of ill patients to hospitals[40].

In the above-mentioned Danish study, the 30 days mortality for sepsis under and between the lockdowns was in line with our results.[14] The increased case fatality in first sepsis admission after the pandemic lockdown can be explained by the fatality of the novel SARS-CoV-2 virus. Further concerns are reluctance to seek health care because of the perceived risk of COVID-19 infection and negligence to report severe symptoms. Probably implications of these explanations are higher in-hospital mortality as those who were admitted with sepsis were more severely ill and thus had a higher baseline mortality risk.

There are several limitations to our study. First, the use of registry-based study design is dependent on ICD-code abstraction and the characteristics of registries.[41] However, it is mandatory for all Norwegian hospitals to report all activity to NPR and the NPR is a complete and unselected national hospital registry. Identifying sepsis by ICD-10 codes in registry-based studies was first used by Angus,[22] and later modified by Rudd and colleagues to reflect the modern understanding of sepsis pathophysiology.[2] Different study designs have been investigated to find the most fitted design, with dividing results.[42-45] The selection strategies for ICD-10 codes used by Rudd et al. (2020) has been criticized for causing an overestimation of sepsis.[46] Further, recommended ICD-10 coding has changed throughout the period as new specific codes for SIRS and septic shock were implemented in 2010[47] and the Sepsis-3 definition was implemented in 2016[1] However, the trends seem to be consistent across the follow-up period except for 2008 and the pandemic years. Second, the

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incidence rate of first episodes is probably inflated in 2008, but we included 2008 as an indicator variable in the regression models to account for this. Third, the use of implicit sepsis can generate false-positive identification of sepsis since organ dysfunction concurrent to infection could be driven by other causes. On the other hand, false-negative results can occur if the organ dysfunction is inadequately documented. Fourth, as this was a descriptive study we did not adjust for illness severity, . or other characteristics and pathogenesis that could affect the association between sepsis, COVID-19-related sepsis, and death. As we presented age and sex adjusted results could mask possible age or sex specific differences in incidence and case fatality risks. Finally, the influence of the pandemic was calculated from January 2020, although the first COVID-19 patients were first admitted in late February 2020, and thus, the estimated drop in the incidence rate related to COVID-19 could be underestimated. It is important to note that the level of SARS-CoV-2 incidence in Norway has been relatively low and therefore, the interpretation of the analysis is primarily relevant to countries with the same burden.

The study also has several strengths, including the large sample size, nationwide data including all public hospitals, the use of individual-based data, and a timespan of fourteen years, which makes it possible to detect trends over time. Another strength is that we, in one joint paper, report the burden and case fatality of first sepsis admissions, recurrent and all sepsis admissions, including age-separated analyses. Since the patients at first admission are likely to be younger, have fewer comorbidities, and thus have less morbidity and mortality risk, stratifying on the first admission will avoid migrating the patient to the next stage, also known as Will Rogers Phenomenon," or stage migration.[41] To the best of our knowledge, this is the first study that provides nationwide hospital admissions-based epidemiological characteristics over fourteen years for sepsis and includes data outside the ICU as well as for severe COVID-19-related sepsis.

Our results have implications for health policymakers, clinicians, and researchers. The burden of sepsis is higher than previously described in comparable studies and requires further attention. More sepsis survivors put more pressure on skilled nursing facilities and in-home care. Surveillance and prevention should be assessed and implemented in primary health care. Side-effects of the pandemic, with a pressured healthcare system and a changed threshold for seeking health care, must be evaluated.

CONCLUSION

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This nationwide register-based study over fourteen years reveals that the burden of sepsis still is high. Furthermore, the high incidence rates and decreasing mortality cause an increased number of sepsis survivors, with a growing impact on the healthcare system. Notably, the decreased incidence rates of sepsis hospitalizations together with increased mortality during the pandemics give a concern regarding different efforts that were made to stop the spread of SARS-CoV-2.

Ethics Approval

Regional Committee for Medical and Health Research Ethics (REK) in Eastern Norway (2019/42772)

Data Access Committee in Nord-Trøndelag Hospital Trust (2021/184).

Contributorship statement

Study concept and design: Skei, Nilsen, Knoop, Prescott, Damås, Gustad

Acquisition of data: Skei, Gustad

Analysis and interpretation of data: Skei, Nilsen, Gustad

Drafting of the manuscript: Skei

Funding acquisition: Gustad

Critical revision of the manuscript for important intellectual content: Skei, Nilsen, Knoop, Mohus, Brkic, Liyanarachi. Prescott, Lydersen, Mohus, Solligård, Damås, Gustad

Statistical analysis: Skei, Gustad, Lydersen

Administrative, technical, or material support: Skei, Brkic, Gustad

Study supervision: Nilsen, Damås, Gustad

Competing interests

None of the authors have any conflicts of interest to declare.

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No additional data available.

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Fig.1 Annual all and first sepsis incidence per 100.000 inhabitants

Fig.2 Annual recurrent sepsis incidence rates by ten-year age groups

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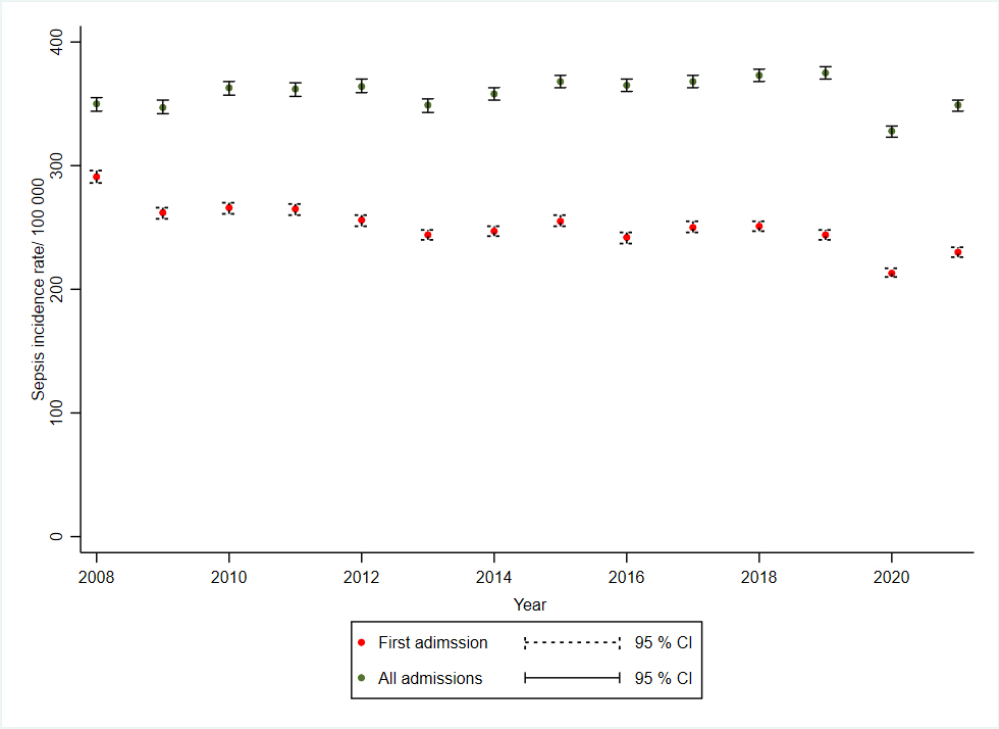

Fig.1 Annual all and first sepsis incidence per 100.000 inhabitants

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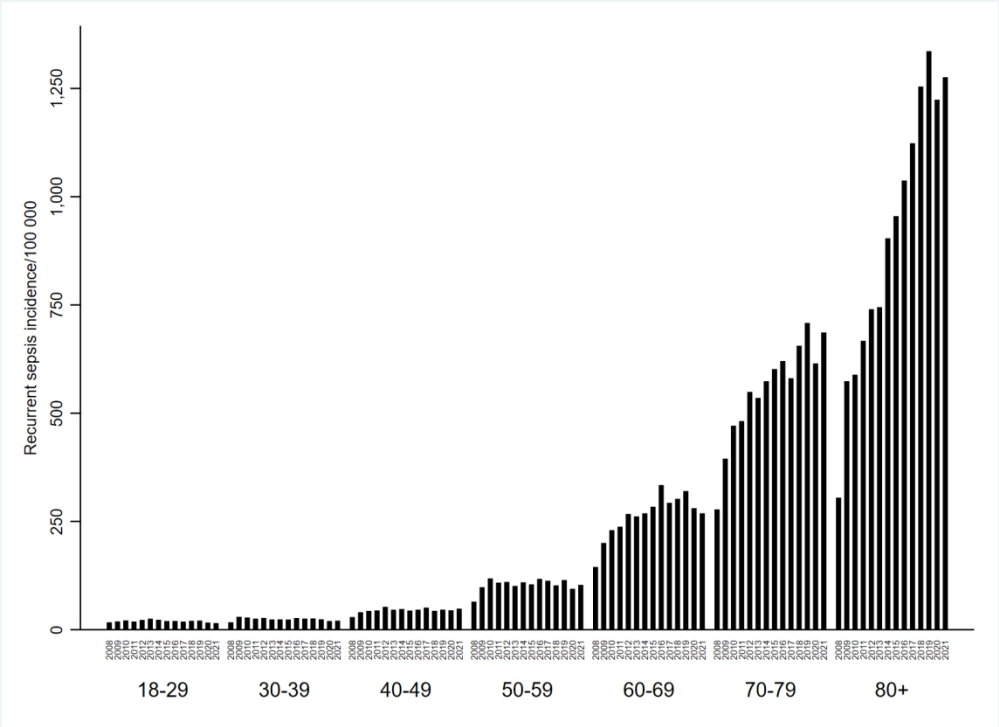

Fig.2 Annual recurrent sepsis incidence rates by ten-year age groups

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Supplementary

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Supplementary Table 1 Overview of ICD-10 codes identifying explicit and implicit sepsis

Sepsis, Explicit code strategy	A02.1, A20.7, A21.7, A22.7, A24.1, A26.7, A28.2, A32.7, A39.2, A39.4, A40, A41, A42.7, B00.7, B37.7
Sepsis[a,b] Implicit code strategy	**Infection** A00/09, A19/28, A30/32, A36/39, A42/44, A46, A48/49, A54, A59, A69.0, A69.1, A69.9, A70, A74/75, A77/81, A83/89, A92/99, B00/09, B25/27, B33/34, B37/46, B48/50, B54/55, B57/58, B60, B64, B67, B95/97, B99, G00/08, H05.0, H60.2, H70.0, I00, I33, I38/40.0, J01/06, J09/22, J36, J39.0, J39.1, J85, J86, K35/37, K61, K63.0/63.1, K65, K75.0, K81.0, K83.0, L02/04, L08, M00/01, M72.6, M86, N10, N15.1, N30, N39.0, N41.0, N41.2, N41.3, N45, N70/74, N98.0, N49, O03.0, O03.5, O04.5, O08.0, O23, O75.3, O85/86, O88.3, O91, O98, T80.2, T81.4, T82.6/82.7, T83.5/83.6, T84.5/84.7, T85.7, T88.0, AND **Acute organ dysfunction** D65, D69.5, E87.2, G93.4, I46, I95.9, J80, J95.2, J96, K72.0, K72.9, N00, N17, N99.0, R02, R09.0, R09.2, R40.0/40.2, R41, R55, R57, R57.2, R65.1
COVID-19-related sepsis, code strategy[c]	U04, U07.1, U07.2 AND Acute organ dysfunction (same codes as for implicit sepsis) OR one code from Explicit code strategy

Abbreviation: ICD= International Classification of Diseases

[a] Implicit sepsis was defined if one code of infection was present with at least one acute organ dysfunction within same hospital entry. Total sepsis estimates are calculated from both explicit and implicit cases.

[b] Explicit codes are excluded from infection codes

[c] Covid-19 related sepsis was defined if identified cause of hospitalization were SARS (U04) identified coronavirus (U07.1) or unidentified coronavirus (U07.2) and the patient had at least one organ dysfunction

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Supplementary Table 2 ICD 10 codes identifying comorbidities and infection sites.	
Comorbidities	**ICD-10** code
Chronic heart- and vascular disease	G45, H34, I00/31, I34/37, I42/45, I47/95.8, I97/99
Cancer	C00/97, D32/33, D35.2/35.4, D42, D43, D44.3/44.5, D45/47
Chronic lung disease	J41/47, J84, J98
Chronic renal disease	N18.3/18.5
Diabetes	E10/11
Dementia	F00/03, G30, G31.0, G31.2, G31.8
Chronic immune disease	D80/84, Z94.0/94.4, Z94.8
Chronic liver disease	K70.4, K72
Infection sites*	
Respiratory	J09/18, J20/22, J85/86, U04, U07.1, U07.2
Genitourinary	N10, N15.1, N30, N39.0, N41.0, N41.2/41.3, N45, N49, N70, N71/74, N98.0
Gastrointestinal infections	A00/09
Intra-abdominal	K35/37, K57, K61/61.1 K61.3, K63.0/63.1, K65, K75.0, K81.0, K83.0
Endocarditis/myocarditis	I33, I38/41
Skin/ Soft tissue	A46, B08/09, L02/04, L08, M72.6
Infection after procedure	T80.2, T81.4, T82.6/82.7, T83.5/83.6, T84.5/84.7, T85.7, T88
Other[a]	A19/28, A30/32, A36/39, A42/44, A48/49, A54, A59, A69.0, A69.1, A69.9, A70, A74/75, A77/80, A81, A83/89, A92/B06, B25/27, B33/34, B37/46, B48/50, B54/55, B57/58, B60, B64, B67, B95/97, B99, G00/08, H05.0, H60.2, H70.0, J01/06, J36, J39.0/39.1, M00/01, M86, O03.0, O03.5, O04.5, O08.0, O23, O75.3, O85/86, O88.3, O91, O98
Acute organ dysfunction	
Respiratory	J80, J95.2, J96, R09.0, R09.2
Circulatory	I46, I95.9, R57, R57.2
Renal	N00, N17, N99.0
Hepatic	K72.0, K72.9
Coagulation	D65, D69.5
Other acute organ dysfunctions	G93.4, R40.0/40.2, R41, R55, E87.2, R02, R65.1[b]
[a] Explicit codes are excluded from other infection sites. [b] R65.1 was excluded in the count of acute organ dysfunctions if present in combination with R57.2, according to the Norwegian ICD-10 coding rules.	

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Supplementary Table 3 Standardized incidence rates for first and all sepsis admissions 2008-2021

Year	No. of persons	Incidence rate first sepsis admission per 100 000 person years		Incidence rate all sepsis admissions per 100 000 person years	
		Crude	Adjusted (95% CI)	Crude	Adjusted (95% CI)
2008	3 637 892	445	286 (281-291)	526	344 (338-350)
2009	3 697 780	401	257 (253-262)	544	342 (336-347)
2010	3 749 043	407	261 (257-266)	546	357 (351-362)
2011	3 805 931	402	260 (256-265)	545	356 (351-361)
2012	3 867 645	395	252 (247-256)	553	358 (353-364)
2013	3 928 378	380	240 (236-244)	533	343 (337-348)
2014	3 983 895	386	243 (238-247)	555	352 (346-357)
2015	4 040 198	401	250 (246-254)	576	361 (355-366)
2016	4 086 583	385	237 (233-241)	577	359 (353-364)
2017	4 127 266	409	246 (242-250)	599	361 (356-366)
2018	4 166 612	417	246 (242-250)	622	367 (362-372)
2019	4 205 704	409	240 (236-244)	631	368 (363-373)
2020	4 248 972	364	210 (206-213)	561	322 (317-326)
2021	4 279 679	390	226 (222-230)	602	343 (338-348)
Total	55 825 578	399	246 (245-247)	569	352 (351-354)

Abbrevation: CI = confidence interval

[a] Crude and age adjusted sepsis incidence rate was calculated by year (2008–2021) for first and all sepsis admissions by dividing sepsis admissions by the total number of inhabitants in Norway at beginning of the same years, using direct standardization weighted by 'Segi's world standard population.

Supplementary Table 4 Age-standardized case fatality risks (%) for first and recurrent sepsis admissions 2008-2021

Year	CFR First sepsis admission			CFR Recurrent sepsis admission		
	N	Crude	Adjusted (95% CI)	N	Crude	Adjusted (95% CI)
2008	16 176	17.1	17.4 (16.8-18.0)	2 953	13.2	14.2 (12.9-15.6)
2009	14 993	16.1	16.3 (15.8-16.9)	4 398	13.1	13.9 (12.8-14.9)
2010	15 263	16.0	16.2 (15.6-16.8)	5 196	13.4	14.1 (13.1-15.1)
2011	15 309	14.5	15.0 (14.4-15.5)	5 426	13.5	13.9 (13.0-14.8)
2012	15 265	14.4	14.6 (14.0-15.1)	6 130	12.9	13.2 (12.3-14.0)
2013	14 887	14.6	14.7 (14.2-15.3)	6 055	13.2	13.4 (12.6-14.3)
2014	15 390	13.6	13.6 (13.1-14.2)	6 724	13.2	13.3 (12.5-14.1)
2015	16 205	13.8	13.8 (13.3-14.3)	7 056	12.8	12.8 (12.0-13.6)
2016	15 720	12.6	12.6 (12.1-13.1)	7 597	13.1	13.1 (12.3-13.8)
2017	16 873	12.3	12.2 (11.7-12.7)	8 026	12.5	12.3 (11.6-13.1)
2018	17 380	11.8	11.6 (11.1-12.0)	8 524	11.8	11.6 (10.9-12.2)
2019	17 217	10.9	10.7 (10.2-11.2)	9 312	11.2	10.9 (10.3-11.5)
2020	15 447	11.7	11.5 (11.0-12.0)	8 417	11.5	11.2 (10.5-11.8)
2021	16 707	12.0	11.9 (11.4-12.4)	9 050	12.5	12.0 (11.3-12.6)
Total	222 832	13.6	13.7 (13.5-13.8)	94 873	12.6	12.6 (12.4-12.8)

Abbrevation: CI = confidence interval, CFR= Case Fatality Risk

[a] Crude and age adjusted CFR was calculated by year (2008–2021) for first and recurrent sepsis admissions by dividing first and recurrent sepsis admissions by the total number of first and recurrent admissions of sepsis, using direct standardization.

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Supplementary Table 5 First admissions, deaths, and CFR for sepsis and COVID-19-related sepsis patients in 2020 and 2021

	2020						2021					
	Sepsis[a]			COVID-19-related sepsis[b]			Sepsis[a]			COVID-19-related sepsis[b]		
	N	Deaths	CFR %	N	Deaths	CFR %	N	Deaths	CFR %	N	Deaths	CFR %
Q1	4310	505	11.7	266	42	15.8	3335	415	12.4	655	58	8.9
Q2	3140	371	11.8	166	23	13.9	3336	401	12.0	389	25	6.4
Q3	3501	384	11.0	54	5	9.3	3734	446	11.9	225	32	14.2
Q4	3720	438	11.8	290	39	13.4	4233	505	11.9	800	128	16.0

Abbreviations: N = Number of cases, CFR= Case Fatality Risk calculated as in-hospital death divided by first sepsis admission in the quarter (Q). Q1 (January, February, March), Q2 (April, May, June), Q3 July, August; September, Q4 (October, November, December).
[a] Sepsis included patients with implicit and/or explicit sepsis, but not patients with an ICD-10 code for COVID-19
[b] COVID-19-related sepsis included patients with ICD-10 code for COVID-19 combined with organ dysfunction or explicit code.

Note: Calculated as **Q1** (January 2020, February 2020, March 2020), **Q2** (April 2020, May 2020, June 2020), **Q3** (July 2020, August 2020, September 2020), **Q4** (October 2020, November 2020, December 2020), **Q1** (January 2021, February 2021, March 2021), **Q2** (April 2021, May 2021, June 2021), **Q3** (July 2021, August 2021, September 2021), **Q4** (October 2021, November 2021, December 2021).

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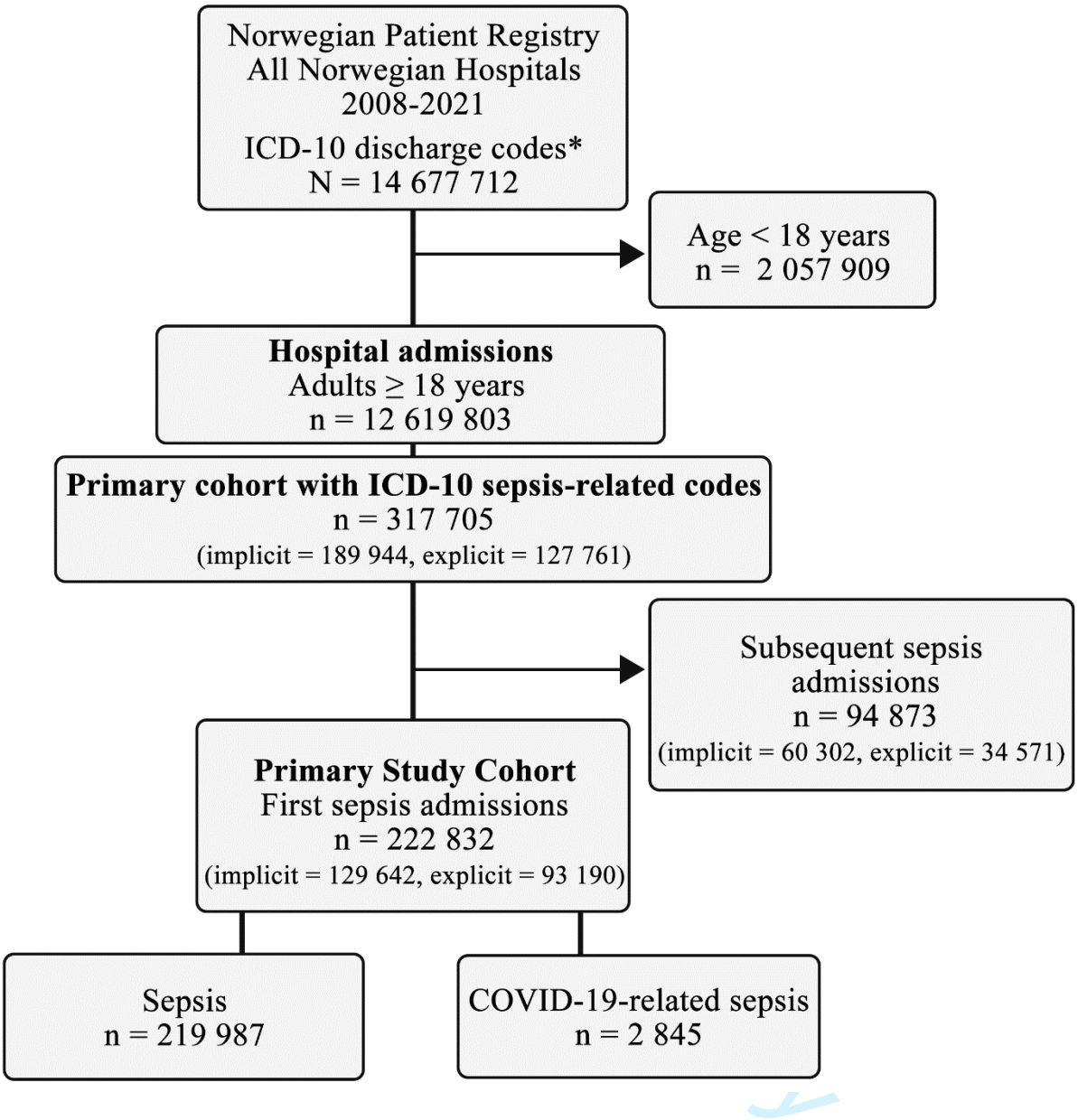
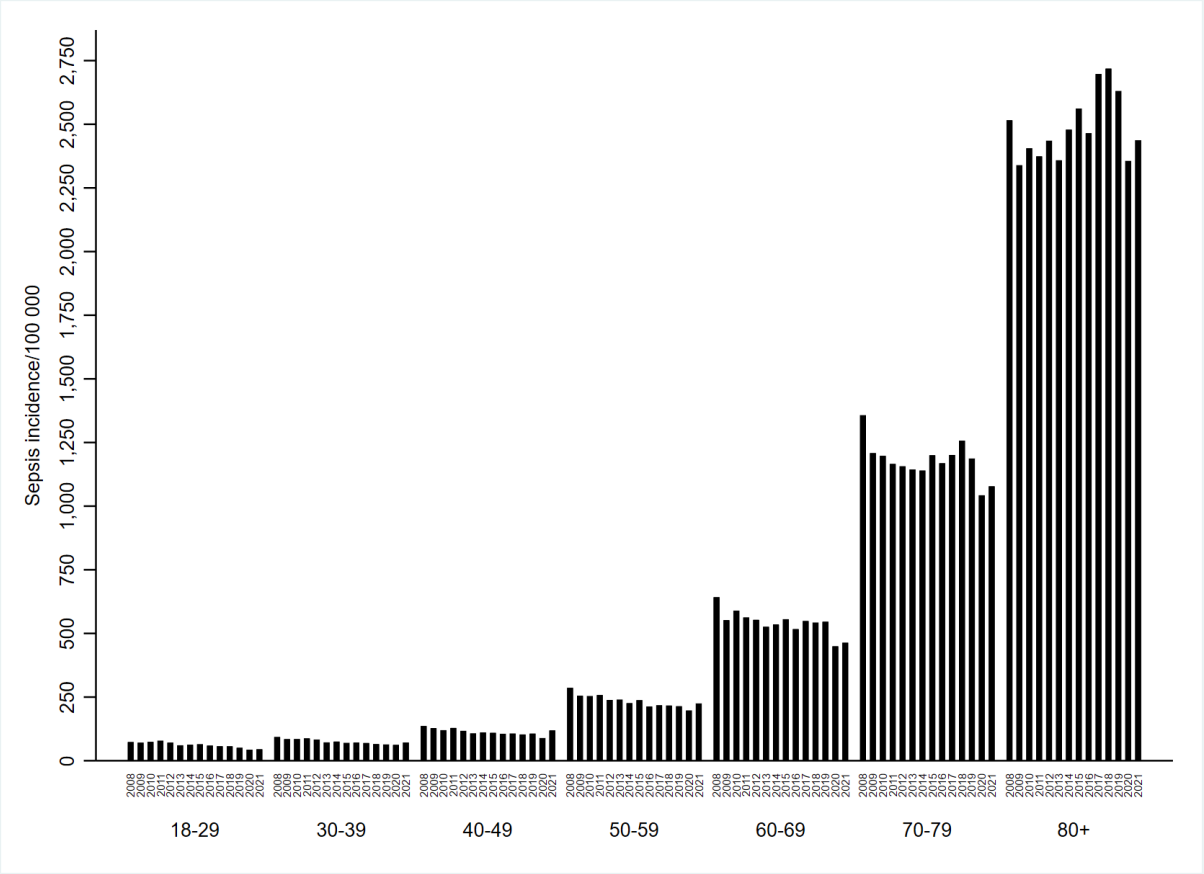
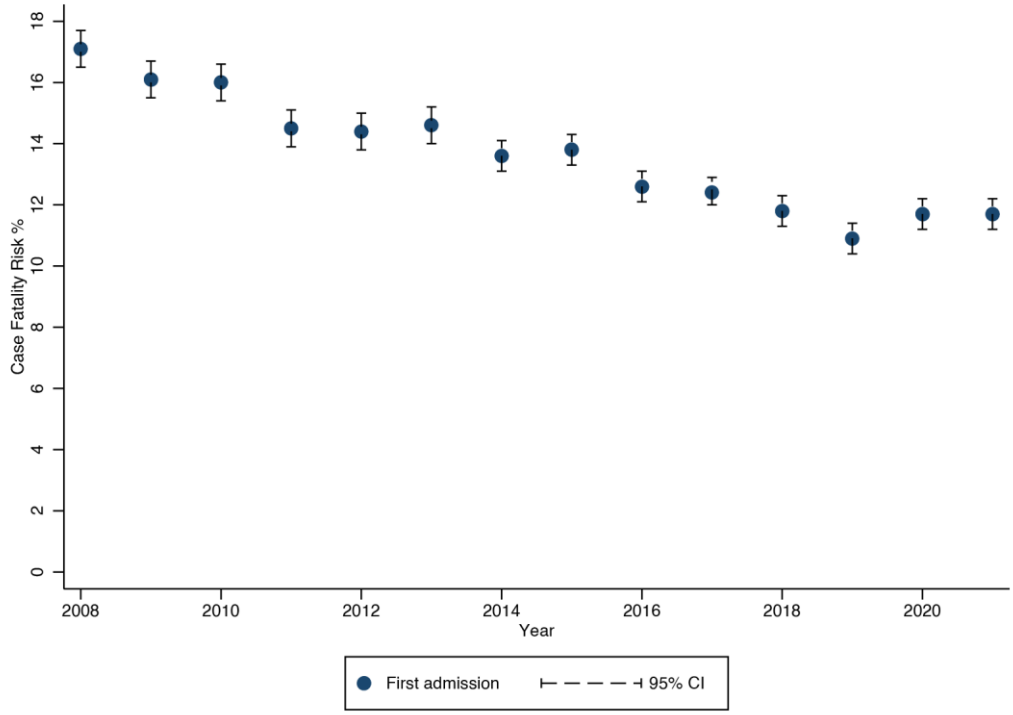


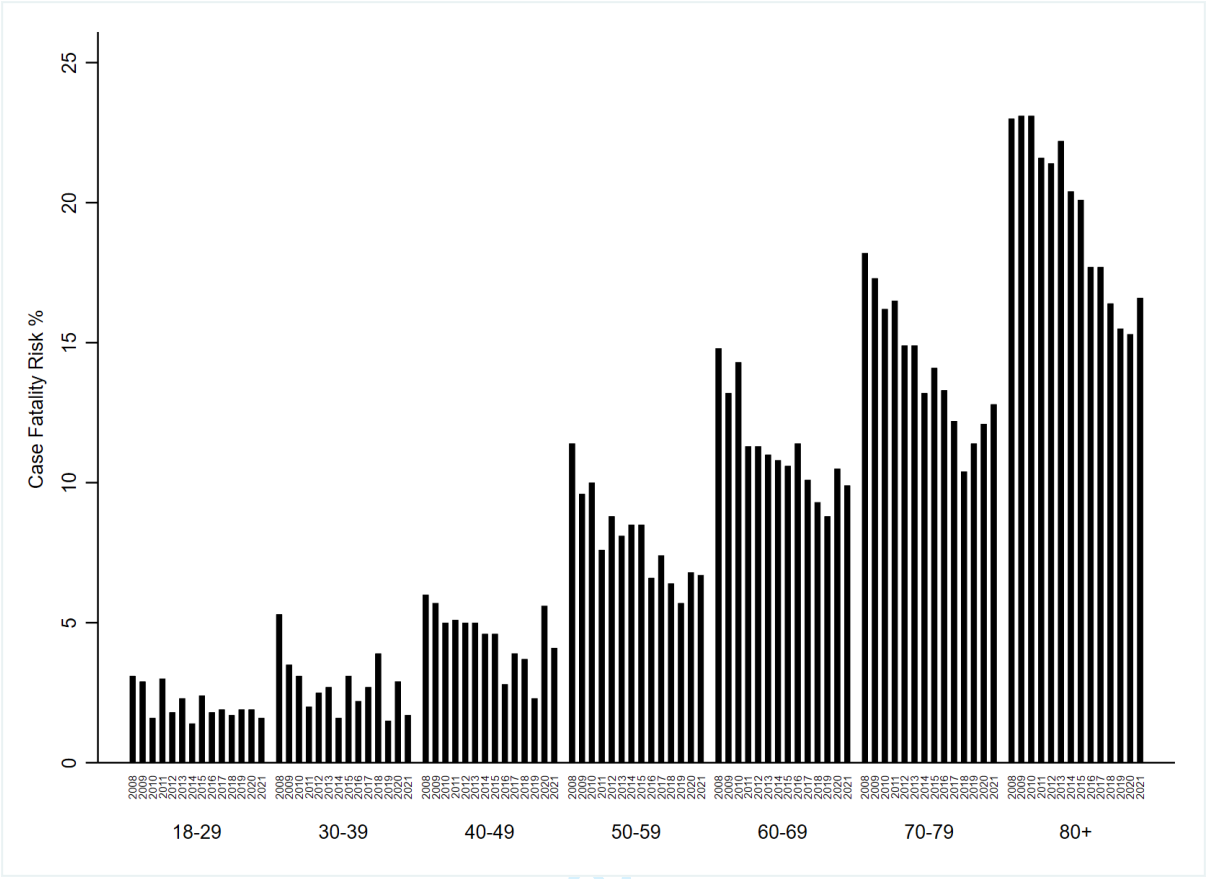
Supplementary Fig.1 Flowchart of the inclusion and exclusion process.



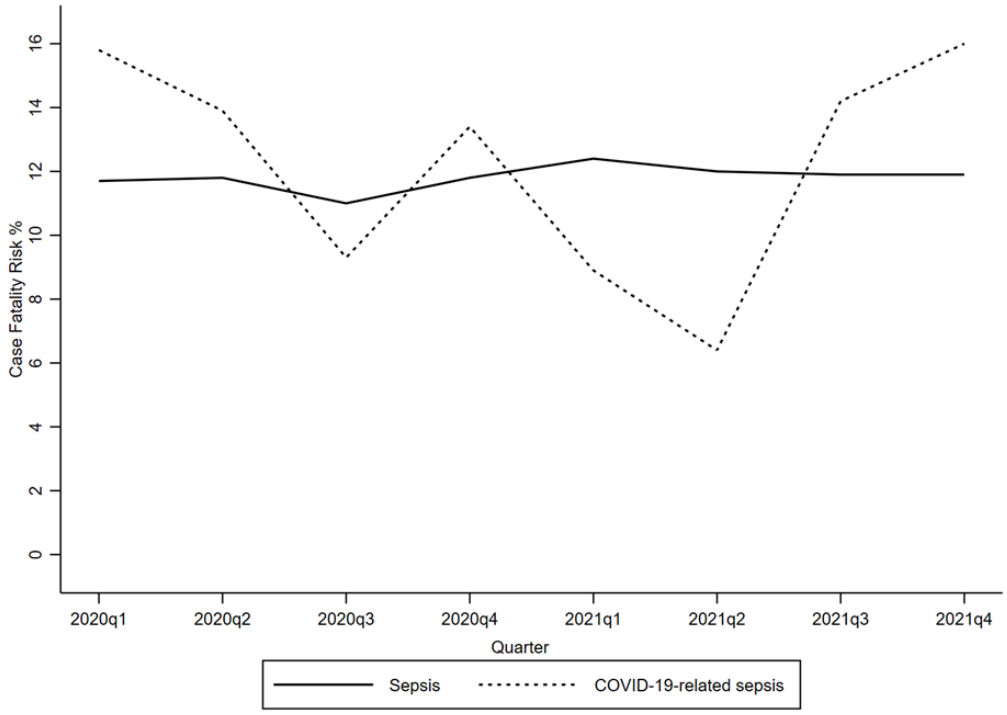
Supplementary Fig.2 Annual incidence rates for first sepsis admission per 100 000 Norwegian citizens by ten-year age groups



Supplementary Fig.3 Annual case fatality risk (CFR) in % for first sepsis admission



Supplementary Fig.4 Annual case fatality risk (CFR) in % for first sepsis admissions by ten-year age-groups



Supplementary Fig. 5 Quarterly mean case fatality risk (in %) in sepsis and COVID-19-related sepsis for first admission (2020 and 2021)

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The RECORD statement – checklist of items, extended from the STROBE statement, that should be reported in observational studies using routinely collected health data.

	Item No.	STROBE items	Location in manuscript where items are reported	RECORD items	Location in manuscript where items are reported
Title and abstract					
	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found	1 and 3	RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included. RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract. RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	1 3 No linkage
Introduction					
Background rationale	2	Explain the scientific background and rationale for the investigation being reported	4		
Objectives	3	State specific objectives, including any prespecified hypotheses	4		
Methods					
Study Design	4	Present key elements of study design early in the paper	4-6		
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4-6		

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Participants	6	*(a) Cohort study* - Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study* - Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study* - Give the eligibility criteria, and the sources and methods of selection of participants *(b) Cohort study* - For matched studies, give matching criteria and number of exposed and unexposed *Case-control study* - For matched studies, give matching criteria and the number of controls per case	4-6 4-6	RECORD 6.1: The methods of study population selection (such as codes or algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided. RECORD 6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided. RECORD 6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage.	Supplementary table 1 and 2 Figure 1 5 No linkage
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.	4-6	RECORD 7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided.	Supplementary table 2
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4-6		

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Bias	9	Describe any efforts to address potential sources of bias	5 10		5 10
Study size	10	Explain how the study size was arrived at			
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	4-6		
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) *Cohort study* - If applicable, explain how loss to follow-up was addressed *Case-control study* - If applicable, explain how matching of cases and controls was addressed *Cross-sectional study* - If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses	5-6 5-6 No missing data No loss to follow up		
Data access and cleaning methods		..		RECORD 12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population.	12

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				RECORD 12.2: Authors should provide information on the data cleaning methods used in the study.	
Linkage		..	No linkage	RECORD 12.3: State whether the study included person-level, institutional-level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided.	
Results					
Participants	13	(a) Report the numbers of individuals at each stage of the study (*e.g.*, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed) (b) Give reasons for non-participation at each stage. (c) Consider use of a flow diagram	Fig 1	RECORD 13.1: Describe in detail the selection of the persons included in the study (*i.e.,* study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.	Fig 1
Descriptive data	14	(a) Give characteristics of study participants (*e.g.*, demographic, clinical, social) and information on exposures and potential confounders (b) Indicate the number of participants with missing data for each variable of interest (c) *Cohort study* - summarise follow-up time (*e.g.*, average and total amount)	Table 1		
Outcome data	15	*Cohort study* - Report numbers of outcome events or summary measures over time *Case-control study* - Report numbers in each exposure	Supplementary Table 3 Table 2, 3 ,4		

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		category, or summary measures of exposure *Cross-sectional study* - Report numbers of outcome events or summary measures			
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Table 2, 3, 4 Supplementary Table 3		
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	5-6		
Discussion					
Key results	18	Summarise key results with reference to study objectives	2 8		
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	10	RECORD 19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported.	10
Interpretation	20	Give a cautious overall interpretation of results considering objectives,	11		

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		limitations, multiplicity of analyses, results from similar studies, and other relevant evidence			
Generalisability	21	Discuss the generalisability (external validity) of the study results			
Other Information					
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based			
Accessibility of protocol, raw data, and programming code		..		RECORD 22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.	Can be provided under Supplementary

*Reference: Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, Sørensen HT, von Elm E, Langan SM, the RECORD Working Committee. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. *PLoS Medicine* 2015; in press.

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Long-term temporal trends in incidence rate and case fatality of sepsis and COVID-19-related sepsis in Norwegian hospitals, 2008-2021: A nationwide registry study

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Long-term temporal trends in incidence rate and case fatality of sepsis and COVID-19-related sepsis in Norwegian hospitals, 2008-2021: A nationwide registry study

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Abstract

Objectives: To estimate temporal trends in incidence rate (IR) and case fatality during a 14-year period from 2008 through 2021, and to assess possible shifts in these trends during the COVID-19 pandemic.

Setting: All Norwegian hospitals 2008-2021.

Participants: 317.705 patients ≥ 18 year with a sepsis ICD-10 code retrieved from The Norwegian Patient Registry.

Primary and secondary measures: Annual age-standardized incidence rates with 95% confidence intervals (CI). Poisson regression was used to estimate changes in IRs across time, and logistic regression was used to estimate odds ratios (ORs) for in-hospital death.

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Results: Among 12.619.803 adult hospitalizations, a total of 317.705 (2.5%) hospitalizations in 222.832 (70.0%) unique patients met the sepsis criteria. The overall age-standardized IR of a first sepsis admission was 246/100.000 (95% CI, 245-247), whereas the age-standardized IR of all sepsis admissions was 352/100.000 (95% CI, 351-354). In the period 2009-2019, the annual IR for a first sepsis episode was stable (Incidence Rate Ratio (IRR) per year, 0.999; 95% CI, 0.994-1.004), whereas for recurrent sepsis the IR increased (annual IRR, 1.048; 95% CI 1.037-1.059). During the COVID-19 pandemic, the IRR for a first sepsis was 0.877 (95% CI, 0.829-0.927) in 2020 and 0.929 (95% CI, 0.870-0.992) in 2021, and for all sepsis it was 0.870 (95% CI, 0.810-0.935) in 2020 and 0.908 (95% CI, 0.840-0.980) in 2021, compared to the previous 11-year period. Case fatality among first sepsis admissions declined in the period 2009-2019 (annual OR, 0.954 [95% CI, 0.950-0.958]), whereas case fatality increased during the COVID-19 pandemic in 2020 (OR, 1.061 [95% CI 1.001-1.124] and in 2021 (OR, 1.164 [95% CI, 1.098-1.233]).

Conclusion: The overall IR of sepsis increased from 2009 through 2019, due to an increasing IR of recurrent sepsis, and indicates that sepsis awareness with updated guidelines and education must continue.

Strengths and limitations of this study

- This study is based on complete data from all Norwegian hospitals during 14 years
- Sepsis was identified using the primary ICD-10 discharge diagnosis and up to 20 secondary ICD-10 diagnosis codes at discharge
- We used individual patient data enabling age and sex adjusted estimates and identification of first and recurrent sepsis.
- Implicit identification of sepsis based on diagnostic codes for acute organ dysfunction and infection may result in over-detection of sepsis in instances where acute organ dysfunction is unrelated to infection.

Introduction

Sepsis is a dysfunctional immune response to infection that leads to acute life-threatening tissue damage and organ dysfunction.[1] With an estimated 50 million cases and 11 million sepsis-related deaths in 2017, sepsis remains a major cause of worldwide morbidity and mortality.[2] While sepsis may result from any infection, the

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majority of adult sepsis cases before the COVID-19 pandemic were attributed to bacterial infections, and viral sepsis was thought to be rare.[3-5] During the COVID-19 pandemic, however, an unprecedented number of patients were diagnosed with viral sepsis (hereafter labelled COVID-19-related sepsis),[6-9] with a high risk of co-infections and secondary infections that can aggravate the outcome.[10, 11] It is likely that public health efforts to reduce the spread of SARS-CoV-2, such as lockdowns, may also have influenced the spread of other communicable diseases contributing to the risk of sepsis.[12, 13] However, few studies have assessed the impact of the pandemic on sepsis incidence rate and case fatality risk, using a few selected sepsis codes.[14] No previous study has focused exclusively on sepsis incidence rate using all sepsis codes, [2] and compared sepsis incidence rate and case fatality during the two first years of the COVID-19 pandemic with long-term historic trends.

Previous research on the incidence of sepsis before the COVID-19 pandemic has shown conflicting results. [2, 15-17] However, precise incidence and mortality rates are difficult to measure, and a more accurate quantification (i.e., correct identification and diagnosis coding) of sepsis is warranted.[18, 19]

The overall aim of this study is therefore to describe temporal trends in sepsis incidence rate and case fatality using nationwide Norwegian data on all adult hospital admissions from 2008 through 2021, and secondly to examine changes in hospital admission and mortality rates of sepsis during the first two COVID-19 pandemic years.

Methods

Data Source and Study Population

This nationwide longitudinal study used data from the Norwegian Patient Registry (NPR) and Statistics Norway.[20, 21] NPR is an administrative database maintained by the Norwegian Directorate of Health that contains data with unique patient identifiers that allow longitudinal follow-up of individual patients for every admission to public hospitals in Norway from 2008 onward. In addition, NPR contains admission and discharge dates, and the International Classification of Diseases 10th revision (ICD-10) discharge codes, while Statistics Norway contains demographic data on all citizens of Norway. In NPR, we identified all hospitalizations to public hospitals in Norway (2008–2021) aged ≥18 years with the ICD-10 discharge diagnosis code(s) for sepsis consistent with the Angus implementation refined by Rudd and colleagues.[2, 22]

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We treated each hospitalization as an individual entry, and within this entry, sepsis was defined as explicit or implicit sepsis. For explicit sepsis, we used the presence of one code (See Supplementary Table 1 for an overview of all ICD-10 codes to define explicit and implicit sepsis). For implicit sepsis, we used the combination of an infection code with the presence of an acute organ dysfunction code. The strategy was used for the primary and up to 20 secondary co-existing ICD-10 discharge codes since there is no obligatory order for the secondary codes. We added COVID-19-related sepsis to the implicit sepsis category based on the presence of a diagnostic code for COVID-19 (U07.1, U07.2) and ≥one organ dysfunction code. Patients with a COVID-19 sepsis code and an explicit sepsis code were categorized as explicit sepsis. Supplementary Figure 1 shows the flow chart of the selection of patients into the study.

Characteristics of Study Population

Patient characteristics were extracted from NPR, including sex, age, ICD codes for selected comorbidities based on diagnostic groups,[23] as well as numbers of hospital stays from sepsis, readmissions, and in-hospital deaths (for details, see Supplementary Table 2 ICD 10 codes identifying comorbidities and infection sites). For sepsis admissions, we used ICD-10 codes to classify site(s) of infection into respiratory, genitourinary, intra-abdominal, extra-abdominal, endocarditis/myocarditis, soft tissue, infections following a procedure, and other (bone, joint, obstetric, ear, mouth, upper airway, central nervous system and unknown). The acute organ dysfunctions were classified by number and as circulatory, respiratory, renal, hepatic, coagulation, and/or other (acidosis, unspecific gangrene, central nervous system, and Systemic Inflammatory Response Syndrome of infectious origin with organ dysfunction [R65.1]). A sepsis admission was defined as recurring sepsis admission if the patient was discharged with an explicit or implicit sepsis code and thereafter admitted with an explicit or implicit sepsis code, regardless of the time frame for the new admission. The number of sepsis admissions was categorized from one to five or more.

Statistical Analysis

Descriptive statistics are presented as frequencies, means, standard deviation, percent, and medians as appropriate, and are reported by sepsis or COVID-19-related sepsis. We calculated the crude sepsis incidence rate (IR) of a first, recurrent and all sepsis episode according to year (2008–2021) and ten-year age-groups as the number of sepsis admissions divided by the total number of inhabitants in Norway at the beginning of the year. The IRs for first and all sepsis were then standardized according to Segi's world standard population using ten-years age categories,[24, 25] and reported per 100 000 person years.

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To evaluate the temporal trends of sepsis incidence rates and the impact of the COVID-19 pandemic on sepsis incidence rates we used Poisson regression to estimate incidence rate ratios (IRR) of sepsis using the number of sepsis admissions (total, recurrent or first) as the dependent variable, population as exposure, the years 2009 to 2019 as a continuous variable, and the years 2008, 2020 and 2021 as separate indicator variables. Since our purpose was descriptive, we only adjusted for sex (man, woman) and age (10-year categories) in the analysis. Since 2008 was the first observation year, we could not differentiate between a first and a recurrent episode, and 2008 thus was included as an indicator variable to account for a possibly inflated incidence rate of first sepsis. To account for overdispersion, we used the robust variance estimator.

Case fatality risk (CFR) of a first sepsis admission was calculated as the number of first sepsis admissions with a discharge status of in-hospital death divided by all first sepsis hospitalizations. Similarly, CFR for recurrent sepsis was calculated as the number of recurrent sepsis admissions with a discharge status of in-hospital death divided by all recurrent sepsis hospitalizations. The calculation was performed on annual cases for first and recurrent sepsis admissions from 2008 to 2021 and by ten-year age groups in the same period. During 2020 and 2021 we also calculated the quarterly CFR and compared CFR for COVID-19-related sepsis and sepsis. To evaluate the trend of in-hospital mortality and the pandemic`s impact on hospital mortality, we used logistic regression to estimate odds ratios (ORs) for in-hospital death using the years 2009-2019 as a continuous variable, the years 2008, 2020, and 2021 as indicator variables, and adjusting for sex (man, woman) and age (10-year categories). We report 95% confidence intervals (CI) where relevant.

All analyses were conducted using STATA version 16.1 (Stata Corp).

Patient and public involvement

Two patient representatives from the user group at Nord-Trondelag Hospital Trust participated in developing the research question and design of this study and were supportive of the use of health data for research purposes. They stressed the importance of education regarding symptoms and signs of sepsis to prevent fatal outcome and gave advice that research results and information about sepsis should be published in newspapers and social media in order to reach the patients and relatives. According to this, we plan to distribute this research results on our social media to inform patients, sepsis charities, research funders and policy makers.

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Ethics

The study was approved by the Regional Committee for Medical and Health Research Ethics (REK) in Eastern Norway (2019/42772) and the Data Access Committee in Nord-Trøndelag Hospital Trust (2021/184). In accordance with the approval from the REK and the Norwegian law on medical research, the project did not require a written patient consent. This work was performed on TSD (Service for Sensitive Data) facilities owned by the University of Oslo, operated and developed by the TSD service group at the University of Oslo, IT Department (USIT). TSD is designed to store and post-process sensitive data in compliance with the Norwegian "Personal Data Act" and "Health Research Act."

Results

Characteristics of Study Population

Among 12.619.803 non-psychiatric adult hospitalizations during the study period (2008–2021), 317.705 (2.5%) met the criteria for sepsis, and of these, 222.832 (70%) were first hospitalizations with sepsis. Patient characteristics according to a first episode of sepsis and COVID-19-related sepsis are presented in Table 1.

Table 1 Characteristics of the study population at first sepsis admission (2008-2021) and COVID-19-related sepsis (2020-2021). Estimates represent n (%) unless otherwise stated.

Characteristics	**Sepsis[a]**	**COVID-19-related sepsis[b]**	**All first sepsis admissions**
First admission (% of all sepsis admissions)	219 987 (69.0)	2 845 (1.0)	222 832 (70.0)
Sex			
Male	118 580 (53.9)	1862 (65.5)	120 442 (54.1)
Female	101 407 (46.1)	983 (34.5)	102 390 (45.9)
Age (years)			
Mean ± SD (median)	71.2 ± 16.6 (74.4)	61.4 ± 16.1 (61.8)	71.1 ± 16.6 (74.3)
Number of comorbidities			
0	66 869(30.4)	1 581(55.6)	68 450 (31.7)
1	97 894 (44.5)	909 (32.0)	98 803 (44 .3)
2	45 052 (20.5)	300 (10.5)	45 352 (20.4)
≥3	10 172 (4.6)	55 (1.9)	10 227 (4.6)
Comorbidities[c]			
Heart and vascular	99 360 (64.9)	702 (55.5)	100 062 (64.8)
Cancer	39 243 (25.6)	125(9.9)	39 368 (25.5)
Lung	35 859 (23.4)	306 (24.2)	36 165 (23.4)
Renal	8 873 (5.8)	76 (6.0)	8 949 (5.8)
Diabetes	24 030 (15.7)	386 (30.5)	24 416 (15.8)
Dementia	8 068 (5.3)	32 (2.5)	8 100 (5.3)
Immune	3 091 (2.0)	49 (3.9)	3 140 (2.0)
Liver	991 (0.7)	NA	994 (0.6)

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Site of infection[d]			
Respiratory	79 290 (48.7)	2 528 (97.9)	81 818 (49.5)
Genitourinary	44 700 (27.5)	82 (3.2)	44 782 (27.1)
Skin and soft tissue	8 260 (5.1)	5 (0.2)	8 265 (5.0)
Intra-abdominal	8 841(5.4)	29 (1.1)	8 870 (5.4)
Extra-abdominal	12 318 (7.6)	22 (0.9)	12 340 (7.5)
Infections following a procedure	8 277 (5.1)	13 (0.5)	8 290 (5.0)
Endocarditis/Myocarditis	2 522 (1.6)	8 (0.3)	2 530 (1.5)
Other[e]	28 836 (17.7)	152 (5.9)	28 997 (17.5)
Explicit sepsis	77 240 (35.1)	90 (3.2)	77 330 (34.7)
Number of acute organ dysfunctions			
1	126 928 (84.5)	2 252 (81.2)	28 928(84.4)
2	17 869 (11.9)	427 (15.4)	18 296(12.0)
3	3 988 (2.7)	70 (2.5)	4 058 (2.7)
≥4	1 466 (1.0)	24 (0.9)	1490(1.0)
Organ system with acute organ dysfunction[f]			
Respiratory	59 465 (39.7)	2 399 (86.5)	61 864 (40.5)
Circulatory	14 824 (9.9)	68 (2.5)	14 892 (9.8)
Renal	66 809 (44.6)	433 (15.6)	67 242 (44.1)
Hepatic	3 192 (2.1)	17 (0.6)	3 209 (2.1)
Coagulation	6 428 (4.3)	43 (1.6)	6 471(4.2)
Other [e]	31 303 (20.9)	284 (10.3)	31 587 (20.7)
Number of hospital admissions for sepsis[g]			
1	168 904 (76.8)	2 714 (95.4)	171 618 (77.0)
2	33 097 (15.0)	4125 (4.4)	33 222 (14.9)
3	10 125 (4.6)	NA	10 129 (4.6)
4	40 010 (1.8)	NA	4 011 (1.8)
≥5	3 851 (1.8)	NA	3 852 (1.7)
Readmission[h]	54 967 (25.0)	474 (16.7)	55 441 (24.9)

If not mentioned otherwise, the percentage (%) is calculated from available data from the first admission with Sepsis or COVID-19-related sepsis.
Abbreviation: NA=Not Applicable (used when the number of admissions was ≤5).
[a] Sepsis included patients with implicit and/or explicit sepsis, but not patients with an ICD-10 code for COVID-19
[b] COVID-19-related sepsis included patients with COVID-19 combined with organ dysfunction or explicit code
[b] The proportion of all comorbidities is calculated as number of particular comorbidity over total number of comorbidities
[c] The proportion of all infections sites is calculated as number of individuals with particular infection site over total number of infections sites
[d] Other infection sites= Bone, obstetric, upper airway, central nervous system and unknown
[e] The proportion of organ dysfunctions is calculated based on n with any organ dysfunctions
[f] Other acute organ dysfunction= Acidosis, unspecific gangrene, central nervous system dysfunctions and Systemic Inflammatory Respons Syndrome.
[g] Number of hospital admissions= Calculated as new sepsis admission if admission with ICD-10 codes defining sepsis, regardless of time frame for the new sepsis admission. Follow up=14 years
[h] Readmission= admission within 30 days after discharge regardless of cause

In 2020 and 2021, 2.845 of 29.329 (9.7%) of first sepsis cases were identified as COVID-19 related sepsis. Men were overrepresented among patients with sepsis (53.9%) and COVID-19-related sepsis (65.5%). The sepsis patients were older than patients with COVID-19-related sepsis (mean age 71.1 vs. 61.4). The sepsis patients experienced renal acute organ dysfunction most often (44.6%). followed by respiratory failure (39.7%). The COVID-19-related sepsis patients experienced naturally most frequent respiratory failure (86.5%), followed by

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renal failure (15.6%). In total, 25.0% and 16.7% of the patients were readmitted within 30 days in the sepsis and COVID-19-related sepsis group, respectively. During the total study period (2008-2021), 24.2% of sepsis patients had ≥2 recurring sepsis hospitalization.

Sepsis Incidence Rates and Temporal Trends

Table 2 shows that from 2009 through 2019, the annual age-standardized IRR of first sepsis episode was stable (IRR per year, 0.999; 95% CI, 0.994-1.004), whereas the incidence rate per year for recurrent sepsis increased with an IRR 1.048 (95% CI, 1.037-1.059) per year, with a total increase in overall incidence rates of 15.5%. This is clearly illustrated in Figure 1. During the COVID-19 pandemic, the incidence rate was reduced compared to the previous 11-year period, with IRR of 0.877 (95% CI, 0.829-0.927) in 2020 and 0.929 (95% CI, 0.870-0.992) in 2021 for first sepsis cases, and 0.870 (95% CI, 0.810-0.935) in 2020 and 0.908 (95% CI, 0.840-0.980) in 2021 for all sepsis cases. The incidence rate for both first and recurrent sepsis increased exponentially from ages 50 and beyond, and in individuals aged 80+ the incidence rates with recurrent sepsis were fivefold higher in 2021 than in 2008, see Figure 2 for first and recurrent sepsis and Supplementary Figure 2 for more detailed first sepsis incidence.

Table 2 Poisson regression[a] for trends of first, recurrent and all sepsis episodes

	First sepsis admissions		Recurrent sepsis admissions		All sepsis admissions	
	IRR	95% CI	IRR	95% CI	IRR	95% CI
Per year 2009 to 2019	0.999	0.994-1.004	1.048	1.037-1.059	1.013	1.007-1.019
2008	1.110	1.021-1.210	0.649	0.535-0.789	1.007	0.920-1.102
2020	0.877	0.829-0.927	0.844	0.746-0.964	0.870	0.810-0.935
2021	0.929	0.870-0.992	0.848	0.746-0.964	0.908	0.840-0.980
Female sex	0.688	0.669-0.707	0.652	0.615-0.691	0.677	0.656-0.699
Age group, years						
18-29	0.023	0.021-0.026	0.020	0.018-0.023	0.023	0.020-0.025
30-39	0.029	0.026-0.031	0.025	0.022-0.029	0.028	0.025-0.030
40-49	0.043	0.041-0.046	0.046	0.041-0.051	0.044	0.041-0.047
50-59	0.089	0.085-0.093	0.107	0.095-0.121	0.094	0.088-0.100
60-69	0.207	0.200-0.214	0.273	0.249-0.300	0.225	0.215-0.235

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70-79	0.457	0.441-0.473	0.581	0.536-0.631	0.491	0.470-0.512
≥80	1.000	Reference	1.000	Reference	1.000	Reference
Constant[b]	0.031	0.030-0.033	0.000[c]	0.000-0.000[c]	0.040	0.038-0.042

Abbrevation: IRR = incidence rate ratio, CI = confidence interval

[a] The Poisson regression model was set up with cases as dependent variable, population as exposure, per year 2009-2019 as continuous covariate, and indicator variables as covariates for the years 2008, 2020 and 2021, and female sex and age groups.

[b] Constant = estimated incidence rate for men ≥80 in 2009

[c] IRR=9.20e-44, 95% CI (5.09e-53-1.55e-34)

The overall age-standardized IR of a first sepsis admission was 246/100.000 (95% CI, 245-247), whereas the age-standardized IR of all sepsis admissions was 352/100.000 (95% CI, 351-354) during the study period (Supplementary Table 3).

Case Fatality and Temporal Trends

The mean CFR was 13.7% for first sepsis admissions over the fourteen years study period and 12.6% among recurrent sepsis admissions In-hospital deaths for patients with a first sepsis admission declined during 2009 to 2019 (OR per year, 0.954 [95% CI, 0.950-0.958]), with a total decline of 43.1% (Table 3 an Supplementary Figure 3). Supplemental Figure 4 shows that this decline in CFR over the study period occurred in all ten-year age groups. The CFR for recurrent sepsis declined with an OR of 0.973 (95% CI, 0.966-0.980) per year in the same period, with a total decline of 28.0% (Table 3). Supplementary Table 4 displays the details for age standardizes CFR (%) for both first and recurrent sepsis episode per year

Hospital death increased during the COVID-19 pandemic with an OR 1.061 (95% CI, 1.001-1.124) in 2020 and an OR of 1.164 (95% CI, 1.098-1.233) in 2021 for first sepsis admissions, and for recurrent sepsis admissions in 2021 with an OR of 1.112 (95% CI, 1.027-1.205) (Table 3).

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Table 3 Logistic regression[a] with in-hospital deaths as dependent variable, 2008-2021.

	First sepsis admission		Recurrent sepsis admission	
	OR	95% CI	OR	95% CI
Per year 2009 to 2019	0.954	0.950-0.958	0.973	0.966-0.980
2008	1.003	0.954-1.055	0.938	0.833-1.056
2020	1.061	1.001-1.124	0.985	0.909-1.067
2021	1.164	1.098-1.233	1.112	1.027-1.205
Female sex	0.898	0.876-0.920	0.863	0.830-0.900
Age group, years				
18-29	0.087	0.074-0.103	0.251	0.206-0.306
30-39	0.115	0.100-0.132	0.236	0.194-0.288
40-49	0.189	0.173-0.207	0.387	0.344-0.435
50-59	0.351	0.333-0.370	0.487	0.451-0.527
60-69	0.523	0.505-0.541	0.635	0.601-0.670
70-79	0.680	0.660-0.701	0.781	0.745-0.819
≥80	1.000	Reference	1.000	Reference
Constant[b]	0.327	0.317-0.338	0.247	0.234-0.261

Abbrevation: OR= odds ratio, CI=confidence interval
[a] The logistic regression is modelled with in-hospital death in as dependent variable, per year 2009-2019 as continuous covariate and indicator variables as covariates for the years 2008, 2020 and 2021, and female sex and age groups.
[b] Constant = estimated odds for men ≥80 in 2009

Quarterly calculations for the years 2020 and 2021 are given in Supplementary Table 5 and Supplementary Figure 5, illustrating that the hospital outcome in COVID-19-related sepsis varied across the pandemic. In contrast, patients with first sepsis admission experienced more stable outcomes over the same period.

Discussion

In this nationwide longitudinal registry study using all hospital data over fourteen years (2008-2021), we demonstrate a stable trend in the incidence rate of a first sepsis admission, while the recurrent sepsis incidence rate have at least doubled in all individuals aged 60 or above. Overall, the sepsis case fatality rates have declined substantially by approximately one third in all age groups, regardless of first or recurrent sepsis episode. During the COVID-19 pandemic in 2020 and 2021, the incidence rate of a first sepsis admissions decreased moderately compared to the pre-pandemic years, meanwhile the case fatality increased, most prominent in 2021.

Previously "The Global burden of Disease Study" by Rudd and colleagues (2020) registered an estimated reduction of 37% in the age-standardized incidence rate of sepsis from 1990 to 2017,[2] and the

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differences to our study could be due to heterogeneity between regions, the inclusion of low- and middle-income countries with less access to health care, inclusion of persons aged<18 and longer follow-up. Similarities with our study are the use of individual-level data and similar extraction of ICD-10 codes. Several other articles report increasing sepsis incidence rates,[15, 17, 22, 26, 27] i.e., the opposite of what we and Rudd and colleagues found. Martin et al. (2003) found an annual 8.7% increase in sepsis incidence rate using claimed-based data between 1979 and 2000.[26] Dombrovskiy et al. (2007) found almost doubled hospitalizations of severe sepsis from 1992 to 2003,[17] and Kumar et al. (2011) calculated an increase in sepsis incidence rate of 200/100 000 inhabitants from 2000 to 2007.[15] These results are difficult to compare with our analysis regarding first sepsis episodes because they report on all sepsis admissions not first sepsis admissions. However, their results can be compared to our analysis of all sepsis admissions, where we found an increased age-and sex-adjusted incidence rate ratio before the current pandemic. Studies that include all sepsis admissions will naturally increase incidence rates because each person may be admitted multiple times, thus increasing the numerator without changing the denominator. Both Rudd and colleagues (2020) and our study go against the myth that the increase in sepsis incidence rates primarily is driven by more liberal practices in sepsis coding over time. It is more likely that previously reported increased incidence rates is caused by the failure to treat each case as an individual entry.

The incidence of sepsis is higher among patients in the older age categories. Angus and colleagues (2001) investigated incidence of severe sepsis in the US in 1995 and reported that the incidence of sepsis increased exponentially from ages 50 years and beyond.[22] This was also confirmed in later studies,[15, 17] and is in line with the data in our study. Plausible explanations include increased prevalence of comorbidities by age that make patients more prone to sepsis and age-related weakening in immune function.[28] In addition, better treatment of medical conditions such as cancer and chronic diseases with increased use of immunosuppressives and invasive procedures [29, 30] increases the number of patients at risk of developing more than one sepsis episode.[28] Further, sepsis survivors are prone to recurring sepsis due to new or worsened comorbidities and repeated infections and will thus drive the sepsis nominator.[31]

Previous studies of in-hospital sepsis mortality show in general a decreasing trend. Kaukonen et al. (2014) conducted a retrospective observational study over twelve years of sepsis patients admitted to ICU.[32] They reported annually decline in mortality throughout the study period with an odds ratio of 0.49 in 2012, with year 2000 as reference. In a European registry-based study of ICU sepsis patients, Yebenes et al. (2017) reported a odds ratio in 2012 with 2008 as reference of 0.77 in a multivariate analysis.[27] The higher decline

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than we observed can possible be due to different inclusion criteria of sepsis cases. While both Yebenes et al. and Kaukonen et al. stratified on all sepsis cases, the current study stratified on both first and all sepsis admissions. Other plausible explanations include different inclusion criteria regarding sepsis severity, and that new and updated guidelines, and more attention to the sepsis diagnosis have improved the recognition of the diagnosis, thus assisting clinicians in accurate and timely treatment of infections (i.e., early blood culture sampling and antibiotics), preventing illness severity and therefore reducing mortality.[33-37]

The sepsis incidence rate during the pandemic is previously studied by Bodilsen and colleagues (2021).[14] They compared hospital admissions for several diagnoses, one year prior to and 11 months after the COVID-19 pandemic and reported a significant reduction in sepsis incidence rate using a few selected sepsis codes and found elevated 30 days mortality.[14] These previous results are in line with our results. Explanations for the observed lower incidence of sepsis after the pandemic can be the lower incidence of other infections with lockdowns,[14, 38] in addition to vaccination strategies prioritizing the elderly first and canceling elective surgeries.[39] Moreover, our study could only identify one-fourth of the reported deaths due to COVID-19 in Norway at the end of 2021, which suggest that the majority of deaths due to COVID-19 occurred outside the hospitals. A possible explanation for the low proportion of in-hospital deaths due to COVID-19-related sepsis could be a higher threshold for hospitalization during the pandemic in order to avoid an overflow of ill patients to hospitals.[40]

In the above-mentioned Danish study, the 30 days mortality for sepsis under and between the lockdowns was in line with our results.[14] The increased case fatality in first sepsis admission after the pandemic lockdown can be explained by the fatality of the novel SARS-CoV-2 virus. Further concerns are reluctance to seek health care because of the perceived risk of COVID-19 infection and negligence to report severe symptoms. Probably implications of these explanations are higher in-hospital mortality as those who were admitted with sepsis were more severely ill and thus had a higher baseline mortality risk.

There are several limitations to our study. First, the use of registry-based study design is dependent on ICD-code abstraction and the characteristics of registries.[41] However, it is mandatory for all Norwegian hospitals to report all activity to NPR and the NPR is a complete and unselected national hospital registry. Our study identified and extracted sepsis by ICD-10 discharge codes, first used in registry-based studies by Angus,[22] and later modified by Rudd and colleagues to reflect the modern understanding of sepsis pathophysiology.[2] In Norway, ICD-10 code reporting to NPR are mandatory, and undergoes quality controls

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by the National Service of Validation and completeness analysis, therefore our extraction of ICD-10 codes have minimal missing, incomplete or unknown discharge codes.[42] Different study designs have been investigated to find the most fitted design, with dividing results.[43-46] The selection strategies for ICD-10 codes used by Rudd et al. (2020) has been criticized for causing an overestimation of sepsis.[47] Further, recommended ICD-10 coding has changed throughout the period as new specific codes for SIRS and septic shock were implemented in 2010[48] and the Sepsis-3 definition was implemented in 2016.[1] However, the trends seem to be consistent across the follow-up period except for 2008 and the pandemic years. Second, the incidence rate of first episodes is probably inflated in 2008, but we included 2008 as an indicator variable in the regression models to account for this. Third, the use of implicit sepsis can generate false-positive identification of sepsis since organ dysfunction concurrent to infection could be driven by other causes. On the other hand, false-negative results can occur if the organ dysfunction is inadequately documented. Fourth, as this was a descriptive study we did not adjust for illness severity, or other characteristics and pathogenesis that could affect the association between sepsis, COVID-19-related sepsis, and death. As we presented age and sex adjusted results could mask possible age or sex specific differences in incidence and case fatality risks. Finally, the influence of the pandemic was calculated from January 2020, although the first COVID-19 patients were first admitted in late February 2020, and thus, the estimated drop in the incidence rate related to COVID-19 could be underestimated. It is important to note that the level of SARS-CoV-2 incidence in Norway has been relatively low and therefore, the interpretation of the analysis is primarily relevant to countries with the same burden.

The study also has several strengths, including the large sample size, nationwide data including all public hospitals, the use of individual-based data, and a timespan of fourteen years, which makes it possible to detect trends over time. Another strength is that we, in one joint paper, report the burden and case fatality of first sepsis admissions, recurrent and all sepsis admissions, including age-separated analyses. Since the patients at first admission are likely to be younger, have fewer comorbidities, and thus have less morbidity and mortality risk, stratifying on the first admission will avoid migrating the patient to the next stage, also known as Will Rogers Phenomenon," or stage migration.[41] To the best of our knowledge, this is the first study that provides nationwide hospital admissions-based epidemiological characteristics over fourteen years for sepsis and includes data outside the ICU as well as for severe COVID-19-related sepsis. Our findings argue against the view that sepsis incidence rate is declining and that reports of increasing sepsis incidence could largely reflect methodological difficulties and ICD-10 code attribution issues.

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Our results have implications for health policymakers, clinicians, and researchers. The burden of sepsis is higher than previously described in comparable studies and requires further attention. More sepsis survivors put more pressure on skilled nursing facilities and in-home care. There are few studies on longer-term recovery in sepsis patients, and more needs to be done prevent recurring sepsis, including early physical and cognitive rehabilitation, transition of care and follow up care.[31] Surveillance and prevention should be assessed and implemented in primary health care. Side-effects of the pandemic, with a pressured healthcare system and a changed threshold for seeking health care, must be evaluated.

CONCLUSION

This nationwide register-based study over fourteen years reveals that the burden of sepsis still is high, with increasing incidence rates of recurrent sepsis. Furthermore, the high incidence rates and decreasing mortality cause an increased number of sepsis survivors, with a growing impact on the healthcare system. Notably, the decreased incidence rates of sepsis hospitalizations together with increased mortality during the pandemics give a concern regarding different efforts that were made to stop the spread of SARS-CoV-2.

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Ethics Approval

Regional Committee for Medical and Health Research Ethics (REK) in Eastern Norway (2019/42772)

Data Access Committee in Nord-Trøndelag Hospital Trust (2021/184).

Contributorship statement

Study concept and design: Skei, Nilsen, Knoop, Prescott, Damås, Gustad

Acquisition of data: Skei, Gustad

Analysis and interpretation of data: Skei, Nilsen, Gustad

Drafting of the manuscript: Skei

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Funding acquisition: Gustad

Critical revision of the manuscript for important intellectual content: Skei, Nilsen, Knoop, Mohus, Brkic, Liyanarachi. Prescott, Lydersen, Mohus, Solligård, Damås, Gustad

Statistical analysis: Skei, Gustad, Lydersen

Administrative, technical, or material support: Skei, Brkic, Gustad

Study supervision: Nilsen, Damås, Gustad

Competing interests

None of the authors have any conflicts of interest to declare.

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Role of the Funder:

The funding body had no role in the designs of the study, data collection, analysis, interpretation of data, or in writing the manuscript.

Data availability statement:

No additional data available.

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Fig.1 Annual all and first sepsis incidence per 100.000 inhabitants

Fig.2 Annual first and recurrent sepsis incidence rates by ten-year age groups

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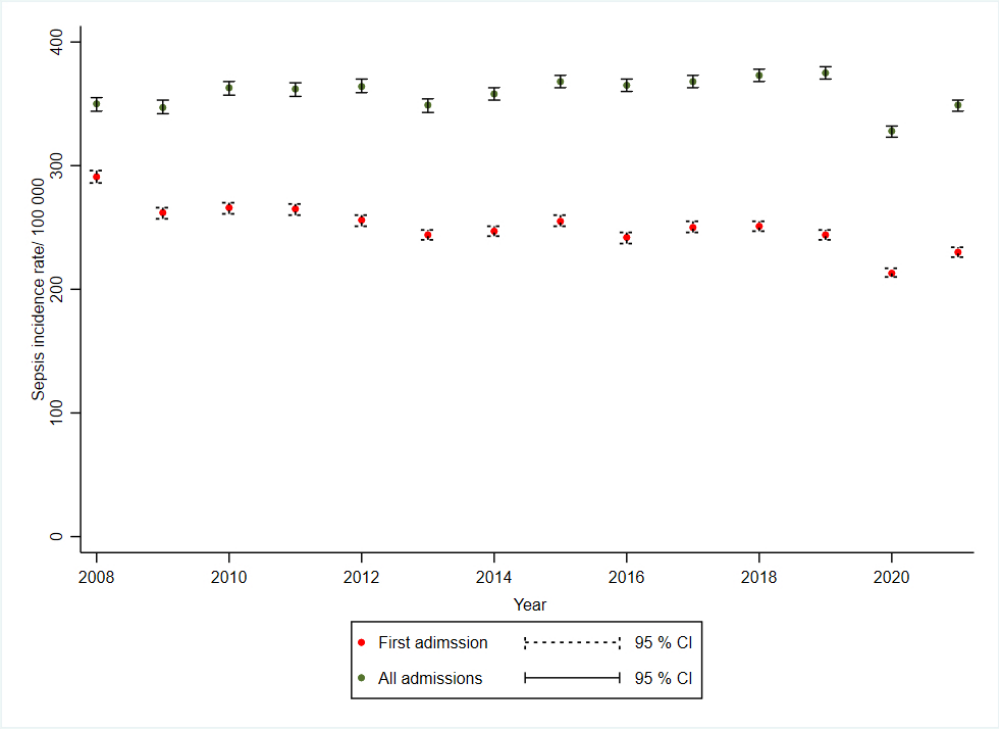

Fig.1 Annual all and first sepsis incidence per 100.000 inhabitants

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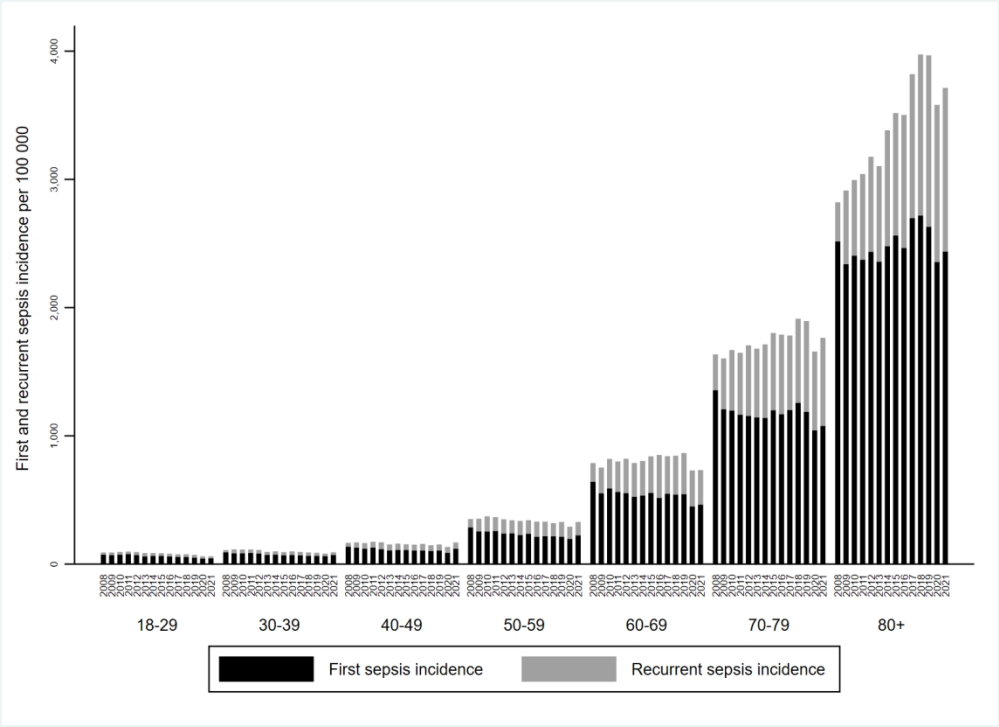

Fig.2 Annual first and recurrent sepsis incidence rates by ten-year age groups

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Supplementary

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Supplementary Table 1 Overview of ICD-10 codes identifying explicit and implicit sepsis

Sepsis, Explicit code strategy	A02.1, A20.7, A21.7, A22.7, A24.1, A26.7, A28.2, A32.7, A39.2, A39.4, A40, A41, A42.7, B00.7, B37.7
Sepsis[a,b] Implicit code strategy	**Infection** A00/09, A19/28, A30/32, A36/39, A42/44, A46, A48/49, A54, A59, A69.0, A69.1, A69.9, A70, A74/75, A77/81, A83/89, A92/99, B00/09, B25/27, B33/34, B37/46, B48/50, B54/55, B57/58, B60, B64, B67, B95/97, B99, G00/08, H05.0, H60.2, H70.0, I00, I33, I38/40.0, J01/06, J09/22, J36, J39.0, J39.1, J85, J86, K35/37, K61, K63.0/63.1, K65, K75.0, K81.0, K83.0, L02/04, L08, M00/01, M72.6, M86, N10, N15.1, N30, N39.0, N41.0, N41.2, N41.3, N45, N70/74, N98.0, N49, O03.0, O03.5, O04.5, O08.0, O23, O75.3, O85/86, O88.3, O91, O98, T80.2, T81.4, T82.6/82.7, T83.5/83.6, T84.5/84.7, T85.7, T88.0, AND **Acute organ dysfunction** D65, D69.5, E87.2, G93.4, I46, I95.9, J80, J95.2, J96, K72.0, K72.9, N00, N17, N99.0, R02, R09.0, R09.2, R40.0/40.2, R41, R55, R57, R57.2, R65.1
COVID-19-related sepsis, code strategy[c]	U04, U07.1, U07.2 AND Acute organ dysfunction (same codes as for implicit sepsis) OR one code from Explicit code strategy

Abbreviation: ICD= International Classification of Diseases

[a] Implicit sepsis was defined if one code of infection was present with at least one acute organ dysfunction within same hospital entry. Total sepsis estimates are calculated from both explicit and implicit cases.

[b] Explicit codes are excluded from infection codes

[c] Covid-19 related sepsis was defined if identified cause of hospitalization were SARS (U04) identified coronavirus (U07.1) or unidentified coronavirus (U07.2) and the patient had at least one organ dysfunction

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Supplementary Table 2 ICD 10 codes identifying comorbidities and infection sites.	
Comorbidities	**ICD-10** code
Chronic heart- and vascular disease	G45, H34, I00/31, I34/37, I42/45, I47/95.8, I97/99
Cancer	C00/97, D32/33, D35.2/35.4, D42, D43, D44.3/44.5, D45/47
Chronic lung disease	J41/47, J84, J98
Chronic renal disease	N18.3/18.5
Diabetes	E10/11
Dementia	F00/03, G30, G31.0, G31.2, G31.8
Chronic immune disease	D80/84, Z94.0/94.4, Z94.8
Chronic liver disease	K70.4, K72
Infection sites*	
Respiratory	J09/18, J20/22, J85/86, U04, U07.1, U07.2
Genitourinary	N10, N15.1, N30, N39.0, N41.0, N41.2/41.3, N45, N49, N70, N71/74, N98.0
Gastrointestinal infections	A00/09
Intra-abdominal	K35/37, K57, K61/61.1 K61.3, K63.0/63.1, K65, K75.0, K81.0, K83.0
Endocarditis/myocarditis	I33, I38/41
Skin/ Soft tissue	A46, B08/09, L02/04, L08, M72.6
Infection after procedure	T80.2, T81.4, T82.6/82.7, T83.5/83.6, T84.5/84.7, T85.7, T88
Other[a]	A19/28, A30/32, A36/39, A42/44, A48/49, A54, A59, A69.0, A69.1, A69.9, A70, A74/75, A77/80, A81, A83/89, A92/B06, B25/27, B33/34, B37/46, B48/50, B54/55, B57/58, B60, B64, B67, B95/97, B99, G00/08, H05.0, H60.2, H70.0, J01/06, J36, J39.0/39.1, M00/01, M86, O03.0, O03.5, O04.5, O08.0, O23, O75.3, O85/86, O88.3, O91, O98
Acute organ dysfunction	
Respiratory	J80, J95.2, J96, R09.0, R09.2
Circulatory	I46, I95.9, R57, R57.2
Renal	N00, N17, N99.0
Hepatic	K72.0, K72.9
Coagulation	D65, D69.5
Other acute organ dysfunctions	G93.4, R40.0/40.2, R41, R55, E87.2, R02, R65.1[b]
[a] Explicit codes are excluded from other infection sites. [b] R65.1 was excluded in the count of acute organ dysfunctions if present in combination with R57.2, according to the Norwegian ICD-10 coding rules.	

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Supplementary Table 3 Standardized incidence rates for first and all sepsis admissions 2008-2021

Year	No. of persons	Incidence rate first sepsis admission per 100 000 person years		Incidence rate all sepsis admissions per 100 000 person years	
		Crude	Adjusted (95% CI)	Crude	Adjusted (95% CI)
2008	3 637 892	445	286 (281-291)	526	344 (338-350)
2009	3 697 780	401	257 (253-262)	544	342 (336-347)
2010	3 749 043	407	261 (257-266)	546	357 (351-362)
2011	3 805 931	402	260 (256-265)	545	356 (351-361)
2012	3 867 645	395	252 (247-256)	553	358 (353-364)
2013	3 928 378	380	240 (236-244)	533	343 (337-348)
2014	3 983 895	386	243 (238-247)	555	352 (346-357)
2015	4 040 198	401	250 (246-254)	576	361 (355-366)
2016	4 086 583	385	237 (233-241)	577	359 (353-364)
2017	4 127 266	409	246 (242-250)	599	361 (356-366)
2018	4 166 612	417	246 (242-250)	622	367 (362-372)
2019	4 205 704	409	240 (236-244)	631	368 (363-373)
2020	4 248 972	364	210 (206-213)	561	322 (317-326)
2021	4 279 679	390	226 (222-230)	602	343 (338-348)
Total	55 825 578	399	246 (245-247)	569	352 (351-354)

Abbrevation: CI = confidence interval

[a] Crude and age adjusted sepsis incidence rate was calculated by year (2008–2021) for first and all sepsis admissions by dividing sepsis admissions by the total number of inhabitants in Norway at beginning of the same years, using direct standardization weighted by 'Segi's world standard population.

Supplementary Table 4 Age-standardized case fatality risks (%) for first and recurrent sepsis admissions 2008-2021

Year	CFR First sepsis admission			CFR Recurrent sepsis admission		
	N	Crude	Adjusted (95% CI)	N	Crude	Adjusted (95% CI)
2008	16 176	17.1	17.4 (16.8-18.0)	2 953	13.2	14.2 (12.9-15.6)
2009	14 993	16.1	16.3 (15.8-16.9)	4 398	13.1	13.9 (12.8-14.9)
2010	15 263	16.0	16.2 (15.6-16.8)	5 196	13.4	14.1 (13.1-15.1)
2011	15 309	14.5	15.0 (14.4-15.5)	5 426	13.5	13.9 (13.0-14.8)
2012	15 265	14.4	14.6 (14.0-15.1)	6 130	12.9	13.2 (12.3-14.0)
2013	14 887	14.6	14.7 (14.2-15.3)	6 055	13.2	13.4 (12.6-14.3)
2014	15 390	13.6	13.6 (13.1-14.2)	6 724	13.2	13.3 (12.5-14.1)
2015	16 205	13.8	13.8 (13.3-14.3)	7 056	12.8	12.8 (12.0-13.6)
2016	15 720	12.6	12.6 (12.1-13.1)	7 597	13.1	13.1 (12.3-13.8)
2017	16 873	12.3	12.2 (11.7-12.7)	8 026	12.5	12.3 (11.6-13.1)
2018	17 380	11.8	11.6 (11.1-12.0)	8 524	11.8	11.6 (10.9-12.2)
2019	17 217	10.9	10.7 (10.2-11.2)	9 312	11.2	10.9 (10.3-11.5)
2020	15 447	11.7	11.5 (11.0-12.0)	8 417	11.5	11.2 (10.5-11.8)
2021	16 707	12.0	11.9 (11.4-12.4)	9 050	12.5	12.0 (11.3-12.6)
Total	222 832	13.6	13.7 (13.5-13.8)	94 873	12.6	12.6 (12.4-12.8)

Abbrevation: CI = confidence interval, CFR= Case Fatality Risk

[a] Crude and age adjusted CFR was calculated by year (2008–2021) for first and recurrent sepsis admissions by dividing first and recurrent sepsis admissions by the total number of first and recurrent admissions of sepsis, using direct standardization.

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Supplementary Table 5 First admissions, deaths, and CFR for sepsis and COVID-19-related sepsis patients in 2020 and 2021

	2020						2021					
	Sepsis[a]			COVID-19-related sepsis[b]			Sepsis[a]			COVID-19-related sepsis[b]		
	N	Deaths	CFR %	N	Deaths	CFR %	N	Deaths	CFR %	N	Deaths	CFR %
Q1	4310	505	11.7	266	42	15.8	3335	415	12.4	655	58	8.9
Q2	3140	371	11.8	166	23	13.9	3336	401	12.0	389	25	6.4
Q3	3501	384	11.0	54	5	9.3	3734	446	11.9	225	32	14.2
Q4	3720	438	11.8	290	39	13.4	4233	505	11.9	800	128	16.0

Abbreviations: N = Number of cases, CFR= Case Fatality Risk calculated as in-hospital death divided by first sepsis admission in the quarter (Q). Q1 (January, February, March), Q2 (April, May, June), Q3 July, August; September, Q4 (October, November, December).
[a] Sepsis included patients with implicit and/or explicit sepsis, but not patients with an ICD-10 code for COVID-19
[b] COVID-19-related sepsis included patients with ICD-10 code for COVID-19 combined with organ dysfunction or explicit code.

Note: Calculated as **Q1** (January 2020, February 2020, March 2020), **Q2** (April 2020, May 2020, June 2020), **Q3** (July 2020, August 2020, September 2020), **Q4** (October 2020, November 2020, December 2020), **Q1** (January 2021, February 2021, March 2021), **Q2** (April 2021, May 2021, June 2021), **Q3** (July 2021, August 2021, September 2021), **Q4** (October 2021, November 2021, December 2021).

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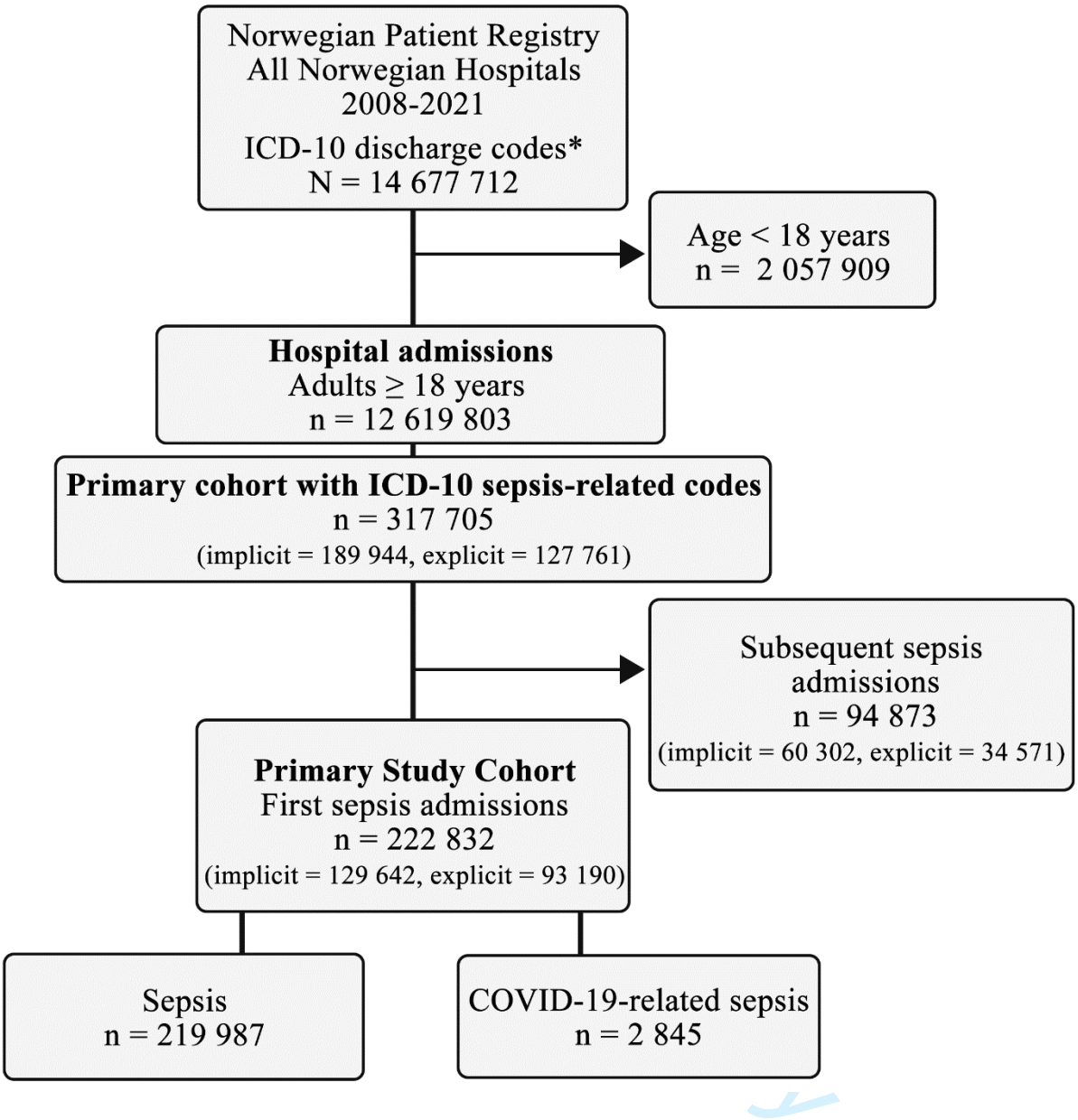
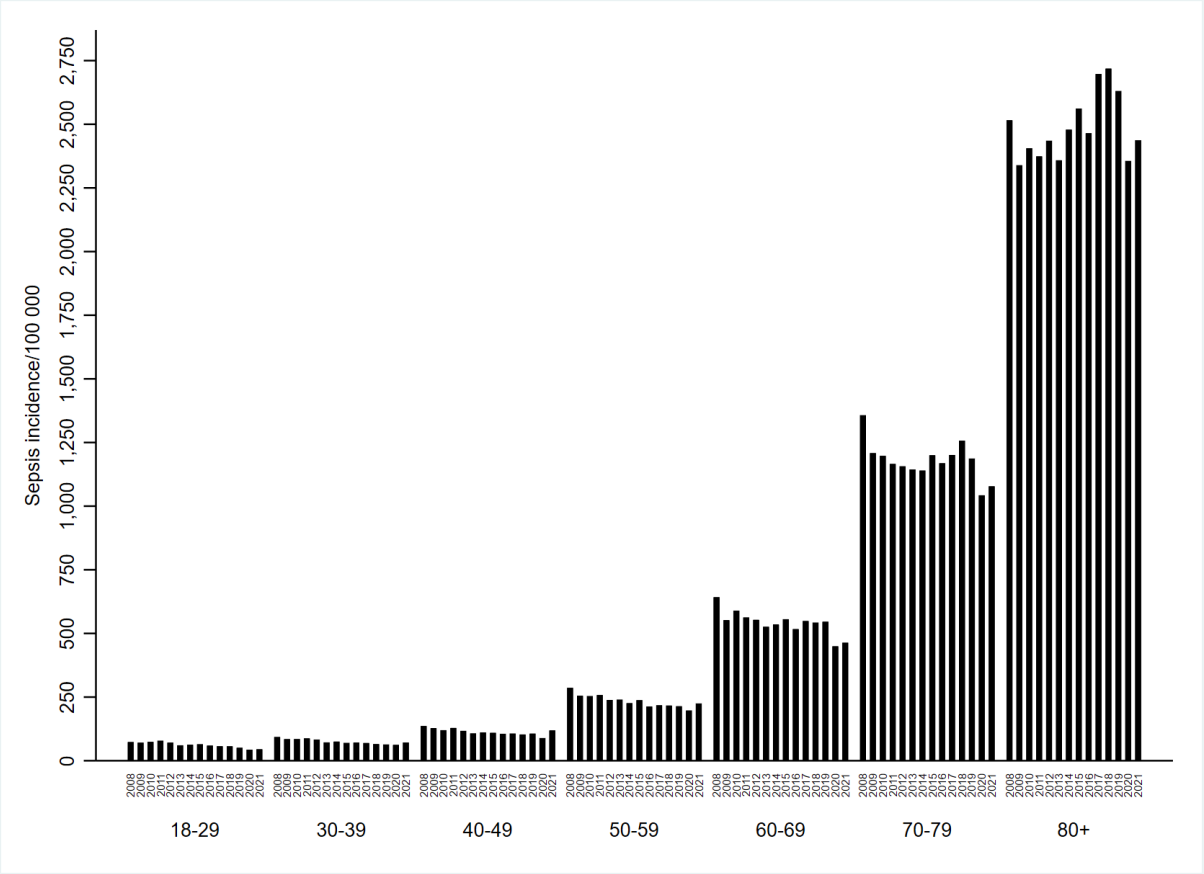
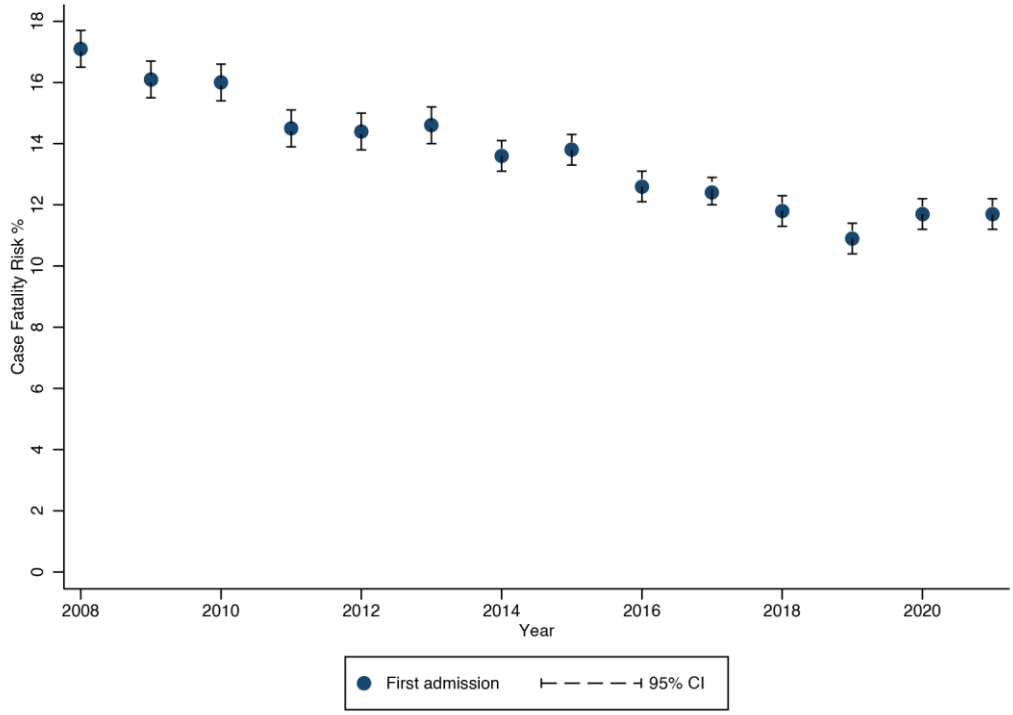


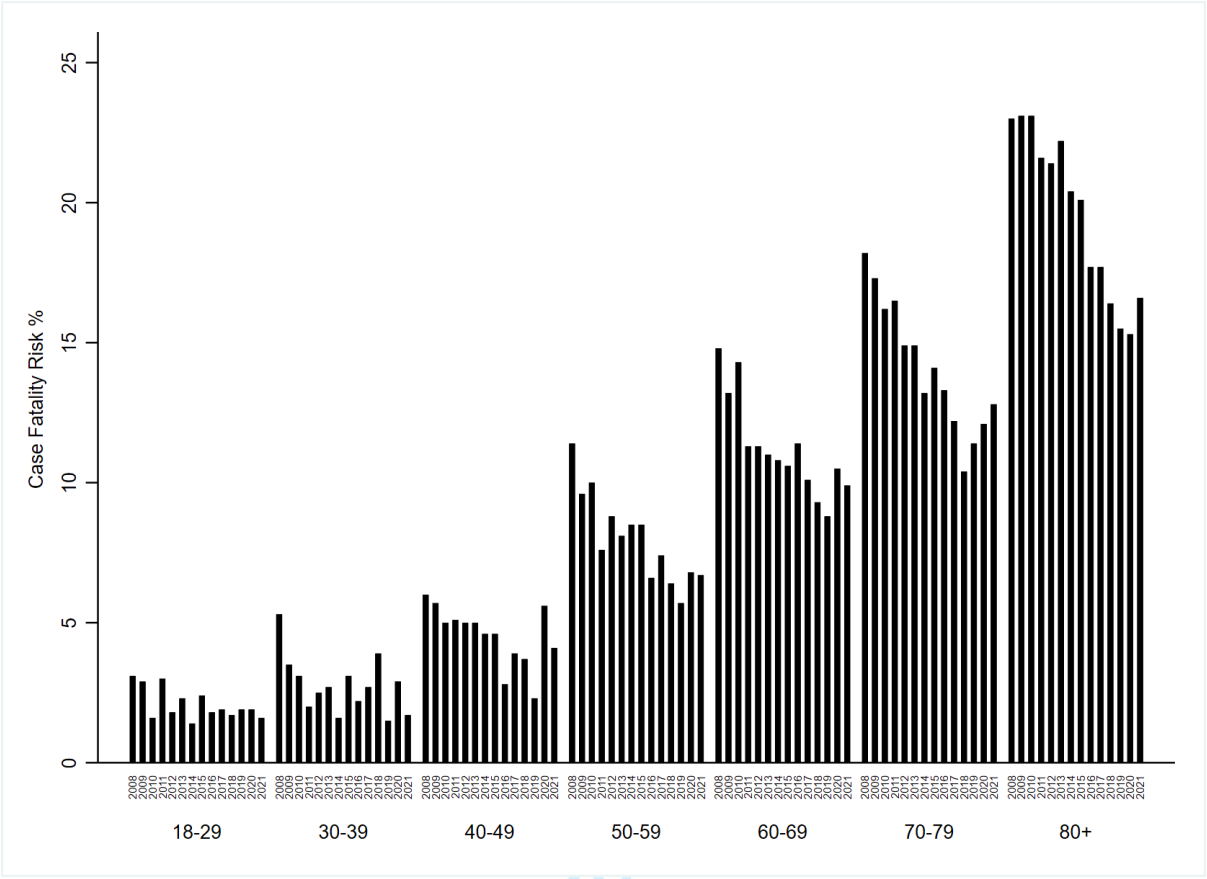
Supplementary Fig.1 Flowchart of the inclusion and exclusion process.



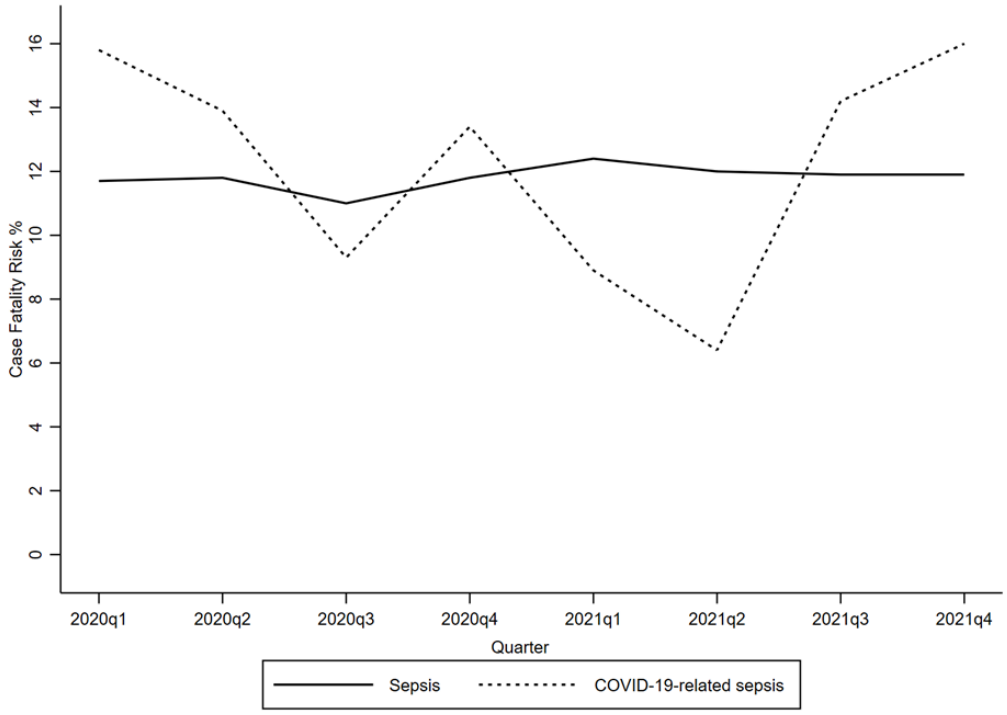
Supplementary Fig.2 Annual incidence rates for first sepsis admission per 100 000 Norwegian citizens by ten-year age groups



Supplementary Fig.3 Annual case fatality risk (CFR) in % for first sepsis admission



Supplementary Fig.4 Annual case fatality risk (CFR) in % for first sepsis admissions by ten-year age-groups



Supplementary Fig. 5 Quarterly mean case fatality risk (in %) in sepsis and COVID-19-related sepsis for first admission (2020 and 2021)

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The RECORD statement – checklist of items, extended from the STROBE statement, that should be reported in observational studies using routinely collected health data.

	Item No.	STROBE items	Location in manuscript where items are reported	RECORD items	Location in manuscript where items are reported
Title and abstract					
	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found	1 and 3	RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included. RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract. RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	1 3 No linkage
Introduction					
Background rationale	2	Explain the scientific background and rationale for the investigation being reported	4		
Objectives	3	State specific objectives, including any prespecified hypotheses	4		
Methods					
Study Design	4	Present key elements of study design early in the paper	4-6		
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4-6		

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Participants	6	*(a) Cohort study* - Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study* - Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study* - Give the eligibility criteria, and the sources and methods of selection of participants *(b) Cohort study* - For matched studies, give matching criteria and number of exposed and unexposed *Case-control study* - For matched studies, give matching criteria and the number of controls per case	4-6 4-6	RECORD 6.1: The methods of study population selection (such as codes or algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided. RECORD 6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided. RECORD 6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage.	Supplementary table 1 and 2 Figure 1 5 No linkage
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.	4-6	RECORD 7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided.	Supplementary table 2
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4-6		

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Bias	9	Describe any efforts to address potential sources of bias	5 10		5 10
Study size	10	Explain how the study size was arrived at			
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	4-6		
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) *Cohort study* - If applicable, explain how loss to follow-up was addressed *Case-control study* - If applicable, explain how matching of cases and controls was addressed *Cross-sectional study* - If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses	5-6 5-6 No missing data No loss to follow up		
Data access and cleaning methods		..		RECORD 12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population.	12

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				RECORD 12.2: Authors should provide information on the data cleaning methods used in the study.	
Linkage		..	No linkage	RECORD 12.3: State whether the study included person-level, institutional-level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided.	
Results					
Participants	13	(a) Report the numbers of individuals at each stage of the study (*e.g.*, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed) (b) Give reasons for non-participation at each stage. (c) Consider use of a flow diagram	Fig 1	RECORD 13.1: Describe in detail the selection of the persons included in the study (*i.e.,* study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.	Fig 1
Descriptive data	14	(a) Give characteristics of study participants (*e.g.*, demographic, clinical, social) and information on exposures and potential confounders (b) Indicate the number of participants with missing data for each variable of interest (c) *Cohort study* - summarise follow-up time (*e.g.*, average and total amount)	Table 1		
Outcome data	15	*Cohort study* - Report numbers of outcome events or summary measures over time *Case-control study* - Report numbers in each exposure	Supplementary Table 3 Table 2, 3 ,4		

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		category, or summary measures of exposure *Cross-sectional study* - Report numbers of outcome events or summary measures			
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Table 2, 3, 4 Supplementary Table 3		
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	5-6		
Discussion					
Key results	18	Summarise key results with reference to study objectives	2 8		
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	10	RECORD 19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported.	10
Interpretation	20	Give a cautious overall interpretation of results considering objectives,	11		

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		limitations, multiplicity of analyses, results from similar studies, and other relevant evidence			
Generalisability	21	Discuss the generalisability (external validity) of the study results			
Other Information					
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based			
Accessibility of protocol, raw data, and programming code		..		RECORD 22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.	Can be provided under Supplementary

*Reference: Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, Sørensen HT, von Elm E, Langan SM, the RECORD Working Committee. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. *PLoS Medicine* 2015; in press.

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