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Brief Report

Effect of SARS-CoV-2 incidence and immunisation rates on sporadic Creutzfeldt-Jakob disease incidence

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Short Title: Associations between sCJD and SARS-COV-2 incidence

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Abstract

Background

Recent case studies and media outlets have hypothesised an effect of SARS-CoV-2 infection and immunisation on the development or progression of neurodegenerative diseases such as Alzheimer's disease or sporadic Creutzfeldt-Jakob disease (sCJD).

Objectives

This study aims to identify potential associations of SARS-COV-2 infections and SARS-COV-2 immunisation with sCJD incidence, disease duration, and age of onset.

Method

We used data from a prospective sCJD surveillance study in Germany (2016 to 2022) and publicly available datasets of SARS-CoV-2 cases and vaccination numbers in Germany for the years 2020-2022. Associations of SARS-CoV-2 incidence and immunisation rates with sCJD incidence were assessed by comparing quarterly and annual cumulative sCJD incidences in the periods before (2016-2019) and during the pandemic (2020-2022).

Results

We could not identify any time-related effect of SARS-CoV-2 incidence or immunisation rate on the sCJD incidence. Moreover, we did not find any sCJD incidence alterations before and during the SARS-CoV-2 pandemic on a federal or state level. The overall sCJD incidence was within expected ranges in the years 2020 to 2022. There were no changes in age of onset and clinical disease duration in these years.

Conclusions

We found no evidence supporting a short-term effect of the pandemic on sCJD incidence. However, considering the extended pre-clinical phase of sCJD, continued surveillance is needed to identify potential future incidence alterations.

Introduction

Since the SARS-CoV-2 pandemic, researchers have hypothesised about a potential impact of the virus on neurological conditions. Various neurological complications of COVID-19 were described [1], and effects on onset or progression of neurodegenerative diseases were proposed [2]. These hypotheses were based on clinical considerations in Creutzfeldt-Jakob disease (CJD) cases with a close temporal relationship with SARS-CoV-2 infection [3,4] and on the identification of virus proteins that may induce protein misfolding or mediate spreading of misfolded protein in the brain [5,6]. SARS-CoV-2 infection may potentially accelerate prion diseases in many ways due to overlapping disease mechanisms [7]. However, prospective clinical studies or population-based epidemiological analyses are difficult to carry out and are not broadly available [8]. Sporadic Creutzfeldt-Jakob disease (sCJD) is a rapidly progressive and fatal neurological disorder with spongiform brain degeneration caused by misfolded prion protein; it is the most frequent form of human prion disease. In contrast to acquired and genetic prion diseases, no relevant causal factor has been identified [9]. Despite the potential transmissibility and general increase of sCJD incidence over the past decades [10], no epidemic spread or clearly defined spatiotemporal clustering was observed. Recently, media outlets have discussed a potential association between infection with or immunisation against SARS-CoV-2 and the appearance of sCJD cases. We aimed to investigate potential effects of SARS-CoV-2 incidence and/or immunisation rates on sCJD in Germany.

Materials and Methods

Study design and data sources

We performed an ecological study linking spatial and temporal resolved data on SARS-CoV-2 incidence and/or immunisation with sCJD incidence. Case numbers were provided by the German National Reference Center for the surveillance of Transmissible Spongiform Encephalopathies (NRZ-TSE) for the years 2016-2022 [11]. An sCJD diagnosis was based on clinical and neuropathological criteria and on cerebrospinal fluid (CSF) real-time quaking-induced conversion (RT-QuIC) positivity (i.e., standard in the German surveillance system since 2016) [11,12]. The date of CSF sample receipt or of first contacts with reporting institution (if no CSF was sent) was defined as the diagnosis date. We used publicly available datasets of SARS-CoV-2 cases and vaccinations provided by the Robert-Koch-Institute in Germany for the years 2020-2022 [13,14].

Data analysis

The datasets were merged so that information on sCJD and SARS-CoV-2 cases and vaccinations (i.e., basic immunisation with two doses) was available for each day from 2016 to 2022. We excluded SARS-CoV-2 cases and vaccinations of children since there is no rationale for short-term effects of infections and/or vaccinations of children on sCJD incidence in late adulthood. For calculating cumulative incidences for all endpoints, we used the German population as the population at risk [15]. We assessed the association of SARS-CoV-2 incidence with sCJD incidence by estimating and comparing quarterly and annual cumulative sCJD incidences before (2016-2019) and during (2020-2022) the pandemic. The annual cumulative incidences were summarised to compare the overall cumulative incidences between the pre-pandemic and the pandemic periods. We applied the same method to assess the association of sCJD incidence with SARS-CoV-2 immunisation rates but defined the pre-immunisation period as 2016-2020 and the immunisation period as 2021-2022. We performed stratified analyses for sex, age, and federal state for both associations (Appendix). Additionally, we estimated the relative risk (RR) of the effects of SARS-CoV-2 incidences and/or immunisations on sCJD incidence via a Poisson regression analysis using weekly data. For the evaluation of the effect on disease characteristics, we applied Kruskal-Wallis tests.

Results

Sporadic Creutzfeldt-Jakob disease in Germany in 2016 to 2022

Demographic characteristics of recorded sCJD cases are displayed in Table 1. In total, the NRZ-TSE recorded n=1.205 sCJD patients between 2016 and 2022. The median age at case notification was 69 years (IQR 62-76), the median total disease duration was 12.4 weeks (IQR 8.7-23.0), and the distribution of sexes was about equal (49.8% female, 50.2% male). The annual average incidence was 2.07 cases per million people. Regarding the age at notification and the total disease duration of sCJD patients, we found no relevant differences between the observed years (p=0.632 and p=0.976, respectively, Table 1).

Association of SARS-CoV-2 incidence and immunisation rates with sCJD incidence

The number of sCJD cases per day ranged between 0 and 4 (mean: 0.35) and remained constant before and throughout the SARS-CoV-2 pandemic (Fig. 1 and Table 2). The same is true for the quarterly sCJD incidence (Fig. 2 and Appendix); it was between 0.387 and 0.637 per 1 million people prior to the pandemic and remained stable during the pandemic (range: 0.368 to 0.637). When looking at SARS-CoV-2 vaccine administrations, the quarterly sCJD incidence ranged between 0.387 and 0.637 before and 0.368 and 0.589 during the vaccine administration periods. Quarterly sCJD incidences in the age group 60+ years (range: 1.027 to 1.993) were, as expected, higher than those in the age group 18-59 years (range: 0.051 to 0.201). However, no association of SARS-CoV-2 incidence and/or immunisation rates with sCJD incidence was observed in the main or the stratified analyses (for age, sex, and location; Appendix). Poisson regression analysis estimates confirmed that sCJD incidence was unrelated to the SARS-CoV-2 incidence (RR=1.00, 95%-CI 0.99-1.00, *P*-value=0.927) and/or immunisation rates (RR=1.00, 95%-CI 0.99-1.00, *P*-value=0.375) (Appendix).

Discussion/Conclusion

This study could not identify any relevant changes in sCJD incidence over the past seven years in Germany, and thus, there is no evidence that SARS-CoV-2 infections or vaccinations are associated with changes in sCJD incidence. Disease characteristics like age of onset or total disease duration did not change during the observation period. This is in contrast to individual case reports which have been picked up in media outlets over the past years.

Our study is the first one to show incidence patterns of SARS-CoV-2 and SARS-CoV-2 immunisation rates in relation to the incidence of a neurodegenerative/protein misfolding disease over time. The analysis of population-based data on the state and federal levels is a major strength of our study. Nonetheless, our study also has limitations. Overlooked/misdiagnosed sCJD cases might have influenced the results due to the overall rarity of the disease. However, this seems unlikely given the stability of the German CJD surveillance system, which has been established many years ago. The inclusion of clinically characterised and RT-QuIC positive cases from the only German centre that performs this test in routine diagnostics is most likely to have led to valid sCJD incidence figures. To further strengthen the stability of clinical assessment, we included only sCJD cases after 2015 because a comparison to the time before the broad application of the RT-QuIC assay might have been biased [11]. Stratified analyses for sCJD subtypes were not performed due to small subsets (Appendix Table 1) that did not suggest any distributional alternations in the period prior to or during the SARS-CoV-2 pandemic. Overall, small numbers—especially of the rarer (non-MM/MV1) subtypes [12]—may not allow identification of subtle changes. A recent study showed that environmental factors might have influenced the sCJD mortality in France [16] before 2016. In our study, we focused on SARS-CoV-2 and cannot exclude a potential effect of other environmental factors on the sCJD incidence in certain subgroups. In contrast to other studies [10,16], we could not identify any increase

of sCJD incidence over time. One reason for that could be the stability of the German surveillance program over several decades, resulting in homogeneously characterised patients (same laboratory test protocols and clinical criteria between 2016 and 2022) [11]. In this regard, we assume that the surveillance was robust despite potential disruptions due to the pandemic (e.g., "lockdowns") since the yearly incidence numbers in the pandemic years remained at levels comparable to those observed in the pre-pandemic years (Table 1 and Fig. 1). However, the most important limitation of this study is that we can only draw conclusions about the short-term effects of the pandemic. CJD has an exceedingly long pre-clinical disease phase of up to decades [9], so effects from the pandemic might occur in the future.

In conclusion, the SARS-CoV-2 pandemic and the vaccination programme against SARS-CoV-2 did not affect sCJD incidence or disease characteristics of sCJD in Germany. However, we cannot exclude that single disease courses may have been influenced by SARS-CoV-2 infections. Keeping in mind the prolonged incubation time of prion diseases, our study can also not answer the question whether SARS-CoV-2 might be able to induce protein misfolding in a clinically relevant way. We recommend ongoing attention to environmental factors in the framework of CJD surveillance.

Statements

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Statement of Ethics

The CJD surveillance study was conducted according to the revised Declaration of Helsinki and Good Clinical Practice guidelines and has been approved by the local ethics committee in the University Medical Center, Göttingen (No. 11/11/93). Informed consent for scientific analyses was obtained from the patient or the legal next of kin in autopsy-confirmed sCJD cases. Regarding other anonymously presented and aggregated data, the registration and scientific evaluation of sCJD is considered a matter of public health in Germany. In this context, the CJD Surveillance group has been tasked with diagnostic and epidemiological research by the Robert-Koch Institute and the German Federal Ministry of Health.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Peter Hermann, André Karch, and Inga Zerr contributed to the study conception and design. Data collection and analysis were performed by Peter Hermann, Julia Böhnke, Timothy Bunck, Stefan Goebel, Veronika Jäger, André Karch, and Inga Zerr. The first draft of the manuscript was written by Peter Hermann and Julia Böhnke. All authors read and approved the final manuscript.

Data Availability Statement

The sCJD dataset can be accessed via the NRZ-TSE, Germany, upon reasonable request. The SARS-CoV-2 datasets are publicly available via the Robert-Koch-Insitute, Germany. All analyses were performed in R version 4.3.1 (2023-06-16)

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Figure Legends

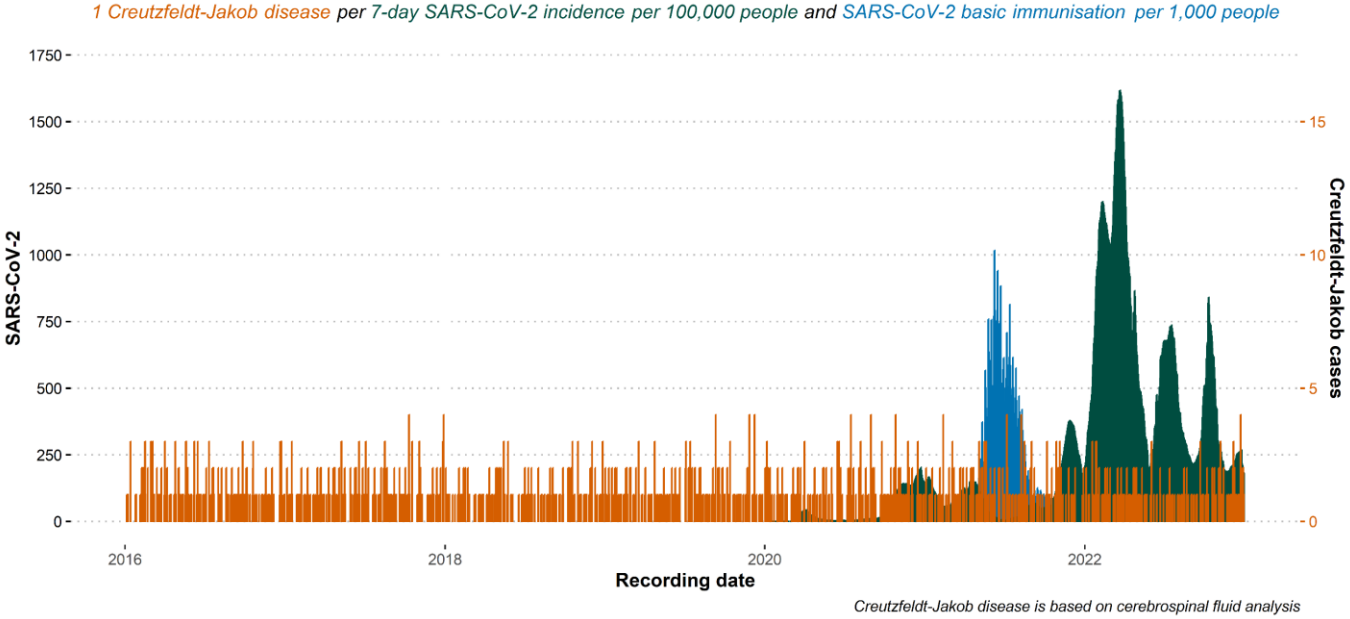
Fig. 1. sCJD cases, SARS-CoV-2 cases, and vaccinations against SARS-CoV-2, 2016-2022

Fig. 1 shows the absolute count of reported sCJD cases per day together with the SARS-CoV-2 incidence and immunisation numbers. The number of sCJD cases per day ranged between 0 and 4 (mean sCJD cases per day: 0.35).

Fig. 2. Quarterly incidence of CSF-confirmed sCJD per 1 million people in Germany.

Fig. 2 shows the quarterly incidence of reported sCJD cases in the period 2016 through 2022. Information on the periods of SARS-CoV-2 pandemic (see light grey box) and SARS-CoV-2 immunisation (see dark grey box) are marked.

Number of Creutzfeldt-Jakob cases, 7-day SARS-CoV-2 incidence per 100,000 people and number of SARS-CoV-2 basic immunisation per 1,000 people in Germany



Creutzfeldt-Jakob disease is based on cerebrospinal fluid analysis

Creutzfeldt-Jakob disease incidence per 1 million inhabitants in Germany

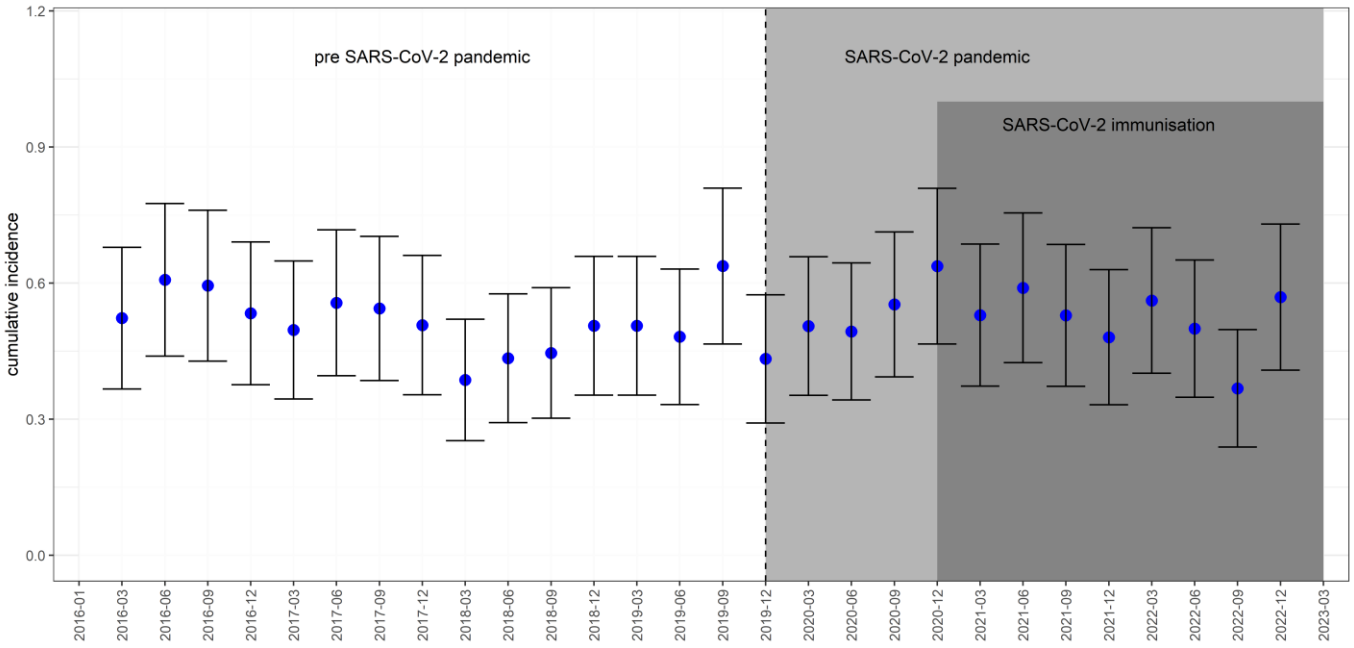


Table 1. sCJD cases in Germany, 2016-2022

Year	sCJD cases[1]: number	Sex: % female	Cumulative incidence: per million (95% CI)	Age[2]: median years (IQR)	Total disease duration: median days (IQR)/ available data
2016	186	46.8	2.254 (1.930, 2.578)	69 (61-76)	96 (64-159)/ n=93
2017	174	52.9	2.102 (1.789, 2.414)	69 (63-77)	84 (63-168)/ n=98
2018	147	44.9	1.771 (1.484, 2.057)	69 (63-76)	89 (57-161)/ n=103
2019	171	49.1	2.056 (1.748, 2.364)	69 (62-79)	89 (62-156)/ n=113
2020	182	47.8	2.189 (1.871, 2.507)	69 (64-76)	94 (62-182)/ n=121
2021	177	53.1	2.126 (1.813, 2.440)	71 (63-78)	83 (58-185)/ n=115
2022	168	53.6	1.991 (1.690, 2.293)	69 (61-76)	85 (67-149)/ n=86[3]

[1] Patients were classified as probable or definite CJD, or positive in the highly specific CSF Real-Time Quaking-Induced Conversion RT-QuIC assay without evidence for other diagnoses than CJD [Hermann et al. 2023]; [2]Age was observed at time point of CSF receipt or first telephone contact to medical institutions; [3]Data from 2022 may underlay a selection bias towards shorter disease duration, sCJD: sporadic Creutzfeldt-Jakob disease

Table 2. Pre-pandemic and pandemic cumulative sCJD incidence in Germany

	Cumulative incidence (95% Confidence Interval) per 1 million		
	Pre-pandemic period (2016-2019)	**Pandemic period (2020-2022)**	**Difference**
Overall analysis	2.046 (1.738, 2.353)	2.102 (1.791, 2.413)	0.057
Sex			
Female	1.953 (1.531, 2.375)	2.132 (1.693, 2.572)	0.179
Male	2.134 (1.687, 2.582)	2.071 (1.632, 2.510)	0.063
Unknown	0.024 (0.000, 0.072)	---	---
Age group			
18-59 years	0.507 (0.327, 0.686)	0.422 (0.258, 0.587)	0.084
60+ years	5.995 (5.000, 6.990)	6.166 (5.182, 7.149)	0.171
Federal state			
Baden Wurttemberg	2.011 (1.180, 2.842)	2.029 (1.195, 2.864)	0.018
Bavaria	2.112 (1.332, 2.892)	1.938 (1.188, 2.687)	0.174
Berlin	1.900 (0.511, 3.289)	1.887 (0.528, 3.246)	0.013
Brandenburg	3.067 (0.939, 5.195)	2.748 (0.716, 4.779)	0.319
Bremen	0.372 (0.000, 1.100)	2.458 (0.000, 6.147)	2.086
Hamburg	2.155 (0.043, 4.266)	2.128 (0.162, 4.093)	0.027
Hesse	2.149 (1.003, 3.295)	1.949 (0.872, 3.027)	0.200
Lower Saxony	2.127 (1.120, 3.134)	1.614 (0.740, 2.487)	0.513
Mecklenburg-West Pomerania	2.188 (0.000, 4.388)	2.895 (0.282, 5.508)	0.707
North Rhine-Westphalia	1.867 (1.236, 2.498)	1.946 (1.303, 2.589)	0.079
Rhineland-Palatinate	1.347 (0.236, 2.458)	2.102 (0.704, 3.500)	0.755
Saarland	2.560 (0.000, 5.601)	2.030 (0.000, 4.779)	0.530
Saxony	2.493 (0.953, 4.034)	3.218 (1.484, 4.951)	0.725
Saxony-Anhalt	2.562 (0.432, 4.693)	2.309 (0.292, 4.327)	0.253
Schleswig-Holstein	1.637 (0.221, 3.053)	2.622 (0.777, 4.466)	0.985
Thuringia	2.392 (0.351, 4.434)	3.002 (0.713, 5.292)	0.610

	Pre-immunisation period (2016-2020)	**Immunisation period (2021-2022)**	**Difference**
Overall analysis	2.074 (1.764, 2.384)	2.059 (1.752, 2.366)	0.015
Sex			
Female	1.976 (1.551, 2.400)	2.166 (1.723, 2.608)	0.190
Male	2.171 (1.720, 2.622)	1.949 (1.523, 2.375)	0.222
Unknown	0.024 (0.000, 0.072)	---	---
Age group			
18-59 years	0.483 (0.308, 0.658)	0.439 (0.272, 0.606)	0.044
60+ years	6.116 (5.115, 7.117)	5.949 (4.986, 6.911)	0.167
Federal state			
Baden Wurttemberg	2.059 (1.217, 2.900)	1.920 (1.109, 2.731)	0.139
Bavaria	2.099 (1.320, 2.877)	1.882 (1.145, 2.620)	0.217
Berlin	2.060 (0.614, 3.506)	1.479 (0.279, 2.680)	0.581
Brandenburg	3.085 (0.945, 5.224)	2.545 (0.590, 4.499)	0.540
Bremen	0.891 (0.000, 2.297)	2.202 (0.000, 5.679)	1.310
Hamburg	2.153 (0.043, 4.263)	2.118 (0.222, 4.014)	0.035
Hesse	2.068 (0.945, 3.191)	2.051 (0.951, 3.152)	0.017
Lower Saxony	2.050 (1.062, 3.039)	1.548 (0.695, 2.401)	0.502
Mecklenburg-West Pomerania	2.498 (0.140, 4.856)	2.473 (0.049, 4.897)	0.025
North Rhine-Westphalia	1.807 (1.186, 2.428)	2.136 (1.461, 2.810)	0.329
Rhineland-Palatinate	1.468 (0.309, 2.627)	2.177 (0.756, 3.598)	0.709
Saarland	2.660 (0.000, 5.784)	1.516 (0.000, 3.910)	1.143
Saxony	2.839 (1.205, 4.473)	2.715 (1.118, 4.311)	0.125
Saxony-Anhalt	2.607 (0.457, 4.757)	2.071 (0.160, 3.982)	0.536
Schleswig-Holstein	1.997 (0.438, 3.555)	2.215 (0.513, 3.917)	0.218
Thuringia	2.200 (0.243, 4.157)	3.788 (1.163, 6.412)	1.588