High variability of COVID-19 case fatality rate in Germany

Matthias Wjst (wjst@helmholtz-muenchen.de)
Helmholtz Zentrum München Deutsches Forschungszentrum für Gesundheit und Umwelt (GmbH)
Clemens Wendtner
München Klinik Schwabing Akademisches Lehrkrankenhaus Ludwig-Maximilians-Universität München

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Matthias Wjst [1 2], Clemens Wendtner [3]

[1]Institut für Lungenbiologie (iLBD)
Helmholtz Zentrum München Deutsches Forschungszentrum für Gesundheit und Umwelt (GmbH)
Ingolstädter Landstr. 1
85764 München-Neuherberg
Germany

[2]Institut für Medizinische Informatik, Statistik und Epidemiologie
Klinikum rechts der Isar
Grillparzerstr. 18
81675 München
Germany

[3]München Klinik Schwabing
Akademisches Lehrkrankenhaus
Ludwig-Maximilians-Universität München
Kölner Platz 1
80804 München
Germany

Abstract

During the first wave of the COVID-19 pandemic high case fatality rates (CFR) were noticed. Due to the dire consequences WHO guidelines recommended immediate intubation for patients with dyspnoea which has since been questioned after reviewing the initial clinical outcome.

Methods: PCR confirmed infection rates along with mortality data was obtained for all German districts from 27 Jan 2020 until 15 Feb 2021 using official data sources. A moving average CFRt was constructed by dividing disease related deaths two weeks after a given index days by the number of infections two weeks prior to that date. In addition to an international comparison, mortality data between the second and third largest German cities were also compared.

Results: Mean CFR is estimated to be 2.92 based on 71.965 fatalities and 2.465.407 cases. There was a large regional scattering of CFRs across the regional districts. Differences of the mortality pattern were observed also at state level and preserved across different sex and age groups while being largely independent of case numbers. Although Munich city had higher infection rates, more patients died during the first wave in Hamburg (OR 1.6, 95% CI 1.3-1.9). While the majority of Munich hospitals favoured a conservative management of hypoxemia including high flow nasal cannula (HFNC), Hamburg hospitals followed a more aggressive scheme of mechanical ventilation (MV). Austria and Switzerland experienced higher CFRs than Germany during the first wave but after changing treatment guidelines, both countries experienced lower CFRs during the second wave.

Conclusion: Different case fatality rates have been observed across Germany that are most likely caused by different treatment strategies.

Already at the beginning of the COVID19 pandemic, an exceptional high case fatality rate (CFR) was observed at many hotspots including Wuhan (China), Bergamo (Italy), and New York (US) (1). Due to the dire consequences, both WHO and German guidelines recommended immediate intubation and mechanical ventilation (MV), although as it turned out later, this recommendation was based on rather weak evidence (2).

The clinical picture of the COVID19 ARDS lung has been characterised by distinct phenotypes (3). Following an initial period of rather mild hypoxic respiratory distress, lung inflammation may either be either resolved or progress rapidly. Unfortunately the search for individual factors of disease progression in addition to age, sex, BMI, diabetes was not very successful, showing only minor effects by AB0 blood group and other gene variants (4). More relevant seem to be an impaired type 1 interferon activity that promotes an excessive inflammatory responses in severe COVID-19 illness (5).

The mortality in Germany has already been described from a population perspective (6) as until October 8.616 fatal cases had been hospitalized. Another study, more from a clinical perspective examined 10.021 cases admitted to German hospitals. This study reported an in-hospital mortality of 22% and a huge variation depending on type of ventilation (7) while 53% of the patients died under MV. While there was no major controversy about basic treatment recommendation (8), airflow management has undergone major changes since a first report[1] in April 2020 that raised doubts about the existing guidelines.

As the discussion how COVID-19 related ARDS should be treated is even ongoing - i.e. more aggressively by early intubation and MV or more conservative by applying non invasive ventilation (NIV) and high flow nasal cannula (HFNC) (9), we have now further analyzed regional CFR data in Germany and neighboring countries.¶

Methods

The analysis relies on public datasets and is a further result of a COVID-19 surveillance project (10) that started after the identification of the first European case in Munich, Germany on Jan 27, 2020 (11), (12). The end date for this analysis is 15 Feb 2021 during the upsurge of the new variant B.1.1.7. and soon after the emergency use authorisation of the first vaccines in December 2020. First and second waves were separated visually by the date 15 Aug 2020.

Regional GPS data were obtained from public.opendatasoft.com (28 March 2020), district data from www-genesis.destatis.de/genesis/online (29 March 2020) and hospital beds from https://www.landatlas.de/download/E/Krankenhausbetten.xlsx (2 Jan 2021). Worldwide COVID-19 case and death counts werde downloaded from https://github.com/owid/covid-19-data/tree/master/public/data (15 Feb 2021). Daily German COVID-19 case and death counts have been publicly released by Robert Koch Institute in Berlin https://opendata.arcgis.com/datasets/917fc37a709542548cc3be077a786c17_0.csv using the data freeze 6 March 2021. Two district codes have been corrected due to political reorganization while 12 areas of Berlin have ben combined into one large area resulting in 402 districts. All entries including error codes were deleted. Clinical data were obtained from the public DIVI register("Deutsche interdisziplinäre Vereinigung für Intensiv- und Notfallmedizin") that had been started by end of March 2020. Since the database was not fully functional before May 2020, only second wave data could be included here as downloaded from https://www.datawrapper.de/_/wwQvR starting on Oct 31, 2020. Neither RKI nor DIVI allowed direct database access despite numerous requests. Patient numbers of München hospitals were obtained from the local clinical management system (München Klinik Schwabing and LMU Koordination Pandemiemanagement) while data of Hamburg hospitals were retrieved from the literature (13) from 27 Jan 27 2020 until 3 June 2020.

The CFR is usually defined as the proportion of cases of a specified condition that are fatal within a specified time. This definition may lead to a paradox that more persons die of a disease than develop it during a given time period (14). CFRs therefore can be considered only final after the end of a pandemic although there is a need to calculate a CFRt even earlier as an evaluation parameter of non-pharmacological interventions clinical therapy. Analogously to

SIR infection models (15), CFRt has been constructed here by using a moving average where cases during the two weeks before the index day are used as reference to all fatalities during the two weeks following the index day (16), (17). Several models have been applied using various distance and time intervals while the finally used model seemed to capture best the disease course. Nevertheless, whenever infection rates are too low at start or end of a wave, CFR values are becoming unreliable.

As the current analysis is neither preregistered nor does it include any sample size calculation, no P-values are reported in accordance to recent recommendations (18). Marked as an explorative analysis it seems more appropriate to describe the epidemiological situation rather than to provide any statistical proof. Hence, graphical analysis is extensively used (19), (20), (21) and whenever possible, 95% confidence intervals, have been included. Odds ratios are calculated by Cochran–Mantel–Haenszel test. R Version 3.6.3. was used along with Rstudio 1.3.1093 along with packages ggplot2, rgdal, ggmap, openxlsx, ggrepel, gmodels, MASS, dplyr, grid, gridExtra, rgeos, sp, sf, openxlsx, rjson, tidyverse, stringr, magrittr and epitools). As only public data have ben included, no ethics committee has been involved.

Data and code is available from the corresponding author upon request; initial code and data of FIG 1 F and G is available at https://github.com/under-score/Covid-19-ICU

Results

Germany is divided into 16 federal states (Fig 1 A insert) and 402 districts (Fig 1 A main figure). The CFR is estimated to be 2.92 based on 71.965 fatalities and 2.465.407 cases. Following some irregular high values at the beginning of the pandemic the CFRt dropped to more realistic values but increased again during the second wave (Figure 1 B and supplemental Figure). Although the peak CFRt was identical during both waves, there was a large number of high values during the first wave (Figure 1 C). The highest CFR of all districts was observed in Sachsen / Görlitz including 957 deaths (CFR of 6.4), followed by Thüringen / Suhl including 85 deaths (CFR of 6.4) and Bayern /Schwabach including 100 deaths (CFR of 6.3).

Since case counts were much higher during the second wave it may be interesting to look for a possible correlation of CFR and case count (Fig 1 D, for individual state figures see the supplement S1). Most states did not show any correlation, except for a weak increase in Lower Saxony, Rhineland-Palatinate and North Rhine-Westphalia, which could indicate some capacity problems to deal with an increasing amount of patients. It may also be interesting to determine if there is a different age distribution by German states (Fig 1 E). The pattern is largely identical in all age groups, excluding any preferential effect on elderly people, whereas male sex is leading to a higher CFR (Fig 1 F).

Fig 1 G shows the relationship of CFR and MV patients at ICUs during the second wave in Germany. As there is no association at all, the high CFR variability must depends on pre ICU conditions. This is indeed shown in Fig 1 H where CFR steadily increases with the number of MV patients in relation to all COVID-19 infections in a district.

In a further step the individual time course of the COVID-19 related CFR is compared between Hamburg and Munich (Fig 2 A) as both cities followed different guidelines (Box). Although there are more cases in Munich, a higher CFR was found in Hamburg (OR 1.6; 1.3-1.9) during the first wave (Fig 2 B). According to official data by the Chamber of Physicians 2019, Hamburg has approx 50% less physicians working in private praxis which corresponds to a lower number of COVID-19 patients sent to hospitals (OR 0.7, 95% CI 0.7-0.8). While the number of beds was slightly higher, Hamburg had approx 20% fewer physicians working on general wards which corresponds to a higher number of patients transferred to the ICU (OR 1.9, 95% CI 1.5-2.3). Hence, disease severity may have been higher at Hamburg ICUs, leading to a higher death rate (OR 2.0, 95% CI 1.3-3.1).

In an international comparison Germany ranked slightly higher than the EU average and considerably higher than Austria and Switzerland (Fig 3 A). Both countries experienced higher CFRs than Germany during the first wave, but after changing treatment guidelines, both countries had lower CFRs during the second wave.

Discussion

COVID-19 related CFR was calculated initially for the passengers of the cruise ship "Princess Diamond" (23). It quickly became a central outcome parameter in national and international reports and in even more than 100 COVID-19 related mortality reviews (24) . More in depth analysis of case fatalities, however, remained rare. We now find that the CFR in Germany exceeds not only EU average but also that of neighbouring countries with comparable health care systems. Already during the first wave Swiss clinics moved to intermediate care to administer respiratory support including HFNC and NIV) that prevented ICU admission for a large proportion of patients (25). A rather similar development has been observed in Austria. Both countries changed initial treatment strategies and, according to a recent press report, cancelled the order of thousands of respirators that had been placed initially[2] This decision was not only based on local experience but also on new studies including a Canadian study that showed an increased hazard of death with each daily increment in driving pressure of mechanical ventilators (26). Rather similar results were obtained in a Dutch study where the 28-day-mortality significantly increased with tidal volume (27).

In contrast, CFRs in Germany remained high and also heterogenous during the second wave. This has been explained by different diagnostic thresholds whereas we find no consistent support for this view (Fig 1 D). Remarkably, the CFR is quite similar also in the younger age group which also argues against a higher affection of nursing homes or different prevalence of DNI/DNR orders. As most people die within hospitals (6) the main reason for the differences should be primarily sought by different medical care where early intubation and MV may lead to a worse outcome. Overall ICU fatalities in the comparison of the two cities account here for less fatalities than reported for Germany (6). The reasons for the discrepancy are not fully clear while there may be more patients dying at home or in nursing homes or there may be more unregistered case fatalities at non university hospitals. We may nevertheless assume (based on Fig 1 H and 2 B) that up to 50% of hospital deaths could have been avoided by more conservative treatment.

According to figures shown in (28) approximately 65% of ICU patients were ventilated in April during the peak of the first wave and about 55% during the peak of the second wave in December. The ICU outcome improved only slightly between the first and second wave (28) while the improvement in COVID-19 therapy certainly depends more on clinical management as transfer to ICU dropped from 30% to 14% (28). Although a positive effect of more frequent use of systemic steroids cannot be excluded another small scale study in Germany found also increased NIV and HFNC use during the second wave leading to an improved outcome (29).

A semi-ecological analysis like the one presented here may of course be influenced by various factors that could not be accounted for. Although consistent, some results may be distorted by improper definitions where standard, intermediate and intensive care are sometimes overlapping. There are many confounding factors: Regional outbreaks may inadvertently distort results or there might be different groups of the population being affected at different phases of the pandemic. There are also known issue with data quality and missing values. Although standardized, the exact definition of COVID-19, associated death may vary between states, and there are known differences in SARS-COV2 testing capacity which all may have influenced both numerators and denominators.

Without doubt there are structural differences also between clinical departments where highly specialized centres with the capacity of ECMO therapy may get more seriously ill patients. To exclude that distortion the two second largest cities in Germany have been chosen as comparable units. Munich favoured a more conservative management of Covid 19 associated hypoxemia, while Hamburg clinics followed a more aggressive scheme of mechanical ventilation (13). This may be concluded from numerous external and internal documents (BOX) while NIV or HFNC is seen more as a bridging therapy in Hamburg. Results obtained here show the advantage of a less aggressive approach, which accounts also for further aspects of pulmonology while anaesthesiology centers more on acute care and fixed blood gas thresholds. Patient centric NIV based therapy is also demanding, as it needs experience to be applied correctly (30). Although the ultimative goal of maintaining good oxygenation may be identical, fixed blood gas thresholds may be misleading in COVID-19 patients who have been described as "happy hypoxics" (31) who can tolerate lower pO_2 values than previously anticipated (32). In the beginning of the pandemic, patients were not intubated in their own interest only but also to reduce environmental virus contamination. Evidence is now accumulating that MV may have a negative effect of SARS-COV2 induced ARDS (33), (34) whereas detailed genetic and experimental studies are largely absent (35, 36).

Taken together, the results show a good agreement between the clinical and epidemiological approach (37) and provide further evidence that the high CFR in some German hospitals is caused by overtreatment (2), (38). As randomized clinical trials are largely impossible, also routinely collected data (39) are sufficient proof of the clinical observation that less invasive measures like HFNC could reduce the undoubtedly high CFR in ventilated COVID-19 patients.¶

Legend

Figure 1

1A. COVID-19 Case Fatality Rate (CFR) map by German districts. Germany is divided into 16 countries (insert) and 402 districts (main figure). The CFR is calculated for the whole period between 2020-01-27 and 2021-02-15. Categories are low (<2%), average (<4%) and high >4%. Data source: Official case and death counts by Robert Koch Institute Berlin.

B. Time course of COVID-19 CFRt in Germany. The CFRt is calculated in a moving window in each German district where all fatalities two weeks before the index day are divided by all new cases during the two preceding weeks. Following irregular high values at the beginning of the pandemic CFRt drops to more realistic values but increases again during the second wave. Weekly case fatalities are shown as vertical bars. For individual country figures see the supplement.

C. Distribution of COVID-19 CFR by German districts. While the peak CFR values are similar during both waves, there is a large tail to the right during the first wave indicating a high heterogeneity.

D. Correlation of COVID-19 CFR and case count by German states. Locally estimated scatterplot smoothing. Colour codes as in A, for individual state figures see the supplement. Most states do not show any correlation with case count, except Lower Saxony, Rhineland-Palatinate and North Rhine-Westphalia, which may indicate some capacity problems to deal with an increasing amount of patients. Thuringia shows an isolated peak for unknown reason.

E. Distribution of COVID-19 CFR and age group by German states. Colour codes as in A. CFR pattern are similar in all age groups, excluding any preference of the elderly in single states.

F. Distribution of COVID-19 CFR and sex by German states. Colour codes as in A. CFR pattern is largely identical in all states with the known higher prevalence in men.

G. COVID-19 CFR and MV ratio at ICU during the second wave in Germany. Locally estimated scatterplot smoothing. There is a slight CFR decrease from 4.0 to 3.6. The high CFR variability therefore depends probably on pre ICU conditions.

H. COVID-19 CFR and MV ratio to all COVID-19 cases in a district during the second wave. Locally estimated scatterplot smoothing. There is a steady increase in CFR from 3.6 to 5.1 in the indicated range.

Figure 2

A. Time course of COVID-19 CFRt in Hamburg and Munich, Germany. The CFRt is calculated as before in a moving window where all fatalities two weeks before the index day are divided by all new cases during the two preceding weeks. Hamburg always showed higher CFRt. Two weeks in July have been excluded from the display as case numbers dropped under 10 per day.

B. COVID-19 case fatalities in the cities Hamburg and Munich during the first wave until 3 June 2020. Data source Roedl et 2020. and pers. comm.

Figure 3

A. International CFR comparison. Using the OWID database Germany ranks slightly higher than the average EU CFR and considerable higher than Austria and Switzerland.

B Austria and Switzerland experienced higher CFRt than Germany during the first wave but when changing treatment guidelines, also had lower CFRs during the second wave. Data Source: Official government sources of all three countries.

Box

Munich Guideline (author translation) published online[3]

Michael Seilmaier, Joachim Meyer, Clemens Wendtner, Niklas Schneider

"Thus, for example we recommend that patients with COVID-19 and respiratory exhaustion in intensive care units first be stabilised by oxygen support via nasal cannula or high flow. The target is an oxygen saturation >90%. In particular, younger patients under 50 years of age and without severe pre-existing lung disease seem to benefit from the treatment. Invasive ventilations could therefore be avoided, ICU resources could be saved and the length of the stay in the ICU could be significantly shortened."

Hamburg Guideline (author translation) published online[4]

Stefan Kluge (Hamburg), Uwe Janssens, Tobias Welte,, Steffen Weber-Carstens, Gereon Schälte, Christoph D. Spinner, Jakob J. Malin, Petra Gastmeier, Florian Langer, Martin Wepler, Michael Westhoff, Michael Pfeifer, Klaus F. Rabe, Florian Hoffmann, Bernd W. Böttiger, Julia Weinmann-Menke, Alexander Kersten, Peter Berlit, Reiner Haase, Gernot Marx, Christian Karagiannidis

"The goal of the therapy for acute hypoxaemic respiratory insufficiency during COVID-19 is to ensure adequate oxygenation. The target should be SpO2 ≥ 90% (COPD patients >88%) or PaO_2>55 mm Hg. We suggest that for patients with COVID-19 and hypoxaemic respiratory insufficiency (PaO2/FiO2 = 100-300 mmHg), treatment with high flow oxygen therapy (HFNC) or non-invasive ventilation should be attempted under continuous monitoring and constant intubation standby. We suggest that intubation and invasive ventilation should be considered in patients with COVID-19 and more severe hypoxaemia (PaO2/FiO2 < 150 mm Hg) and respiratory rates > 30/min. Intubation and invasive ventilation should as a rule be performed when PaO2/FiO2 is < 100 mmHg."

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Conflicts of Interest

The authors declare that they have no conflicts of interest regarding the current manuscript.

Funding

The author declares that they had no external funding regarding the current analysis.

Ethics

see text

Data sharing

see text

Footnotes

[1] https://www.reuters.com/article/us-health-coronavirus-ventilators-specia-idUSKCN2251PE
[2] https://www.nzz.ch/wirtschaft/schweiz-ploetzlich-zu-viele-beatmungsgeraete-ld.1593268
https://www.addendum.org/coronavirus/beatmung/
[3] https://www.muenchen-klinik.de/covid-19/knowledge-sharing/
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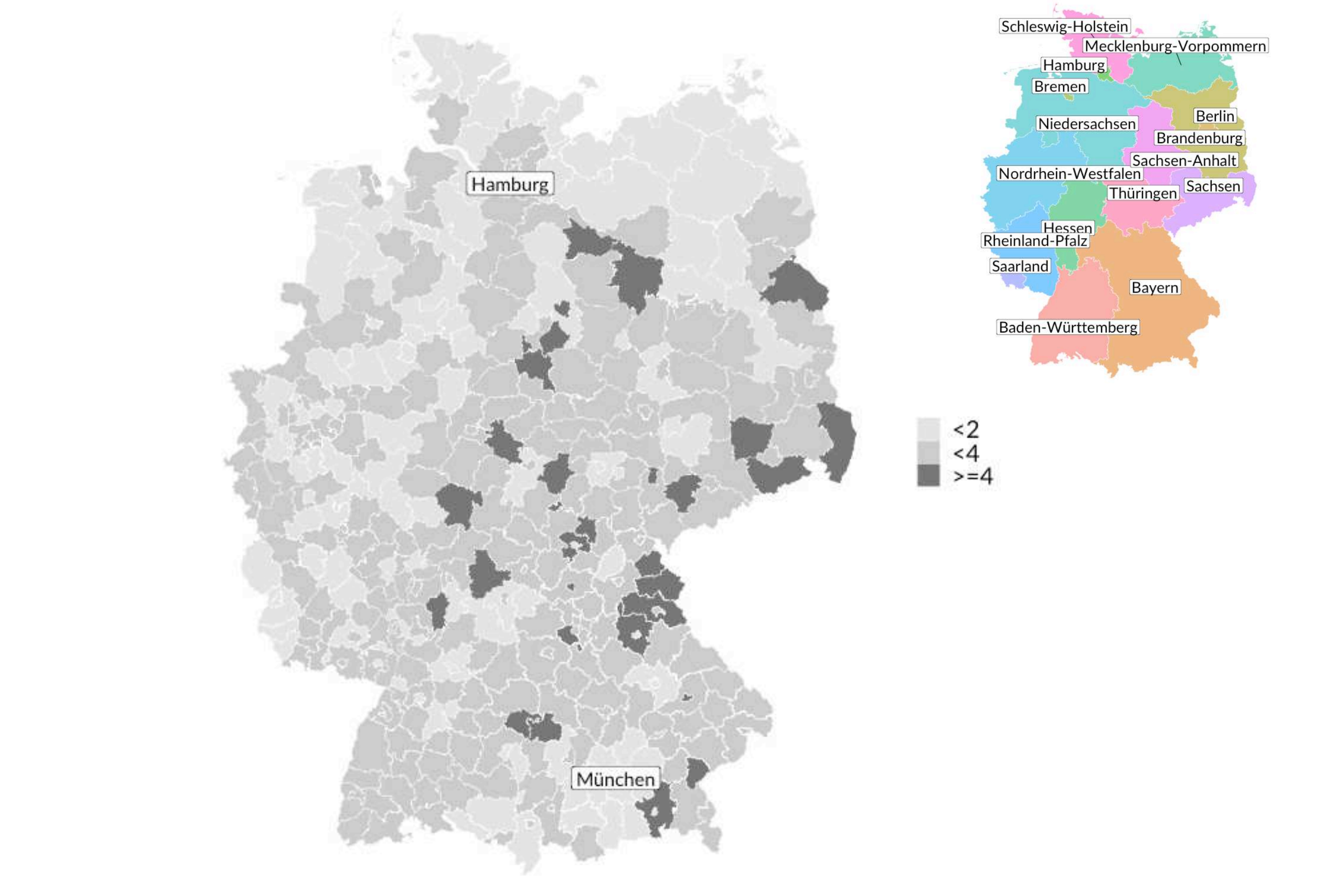

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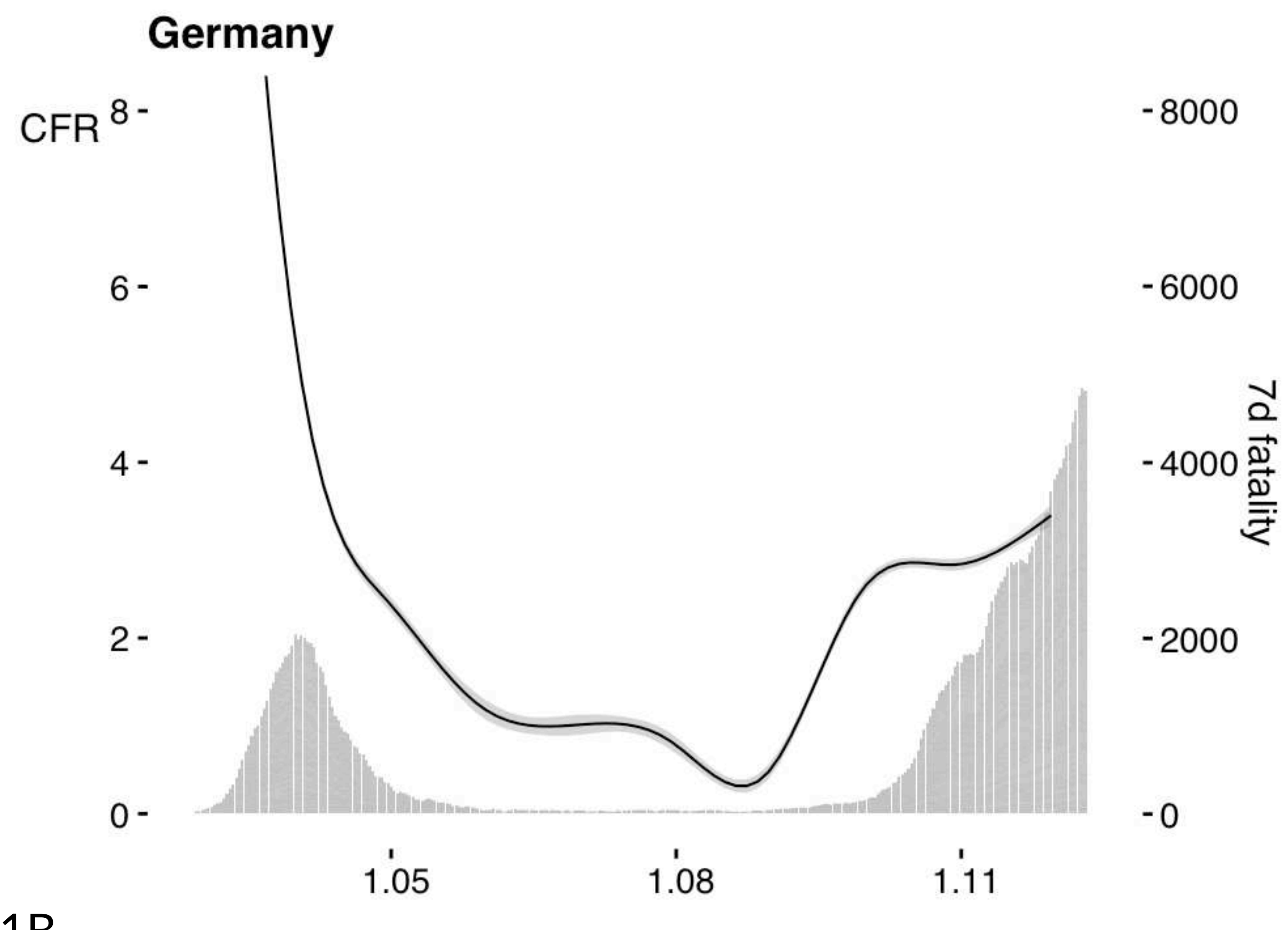

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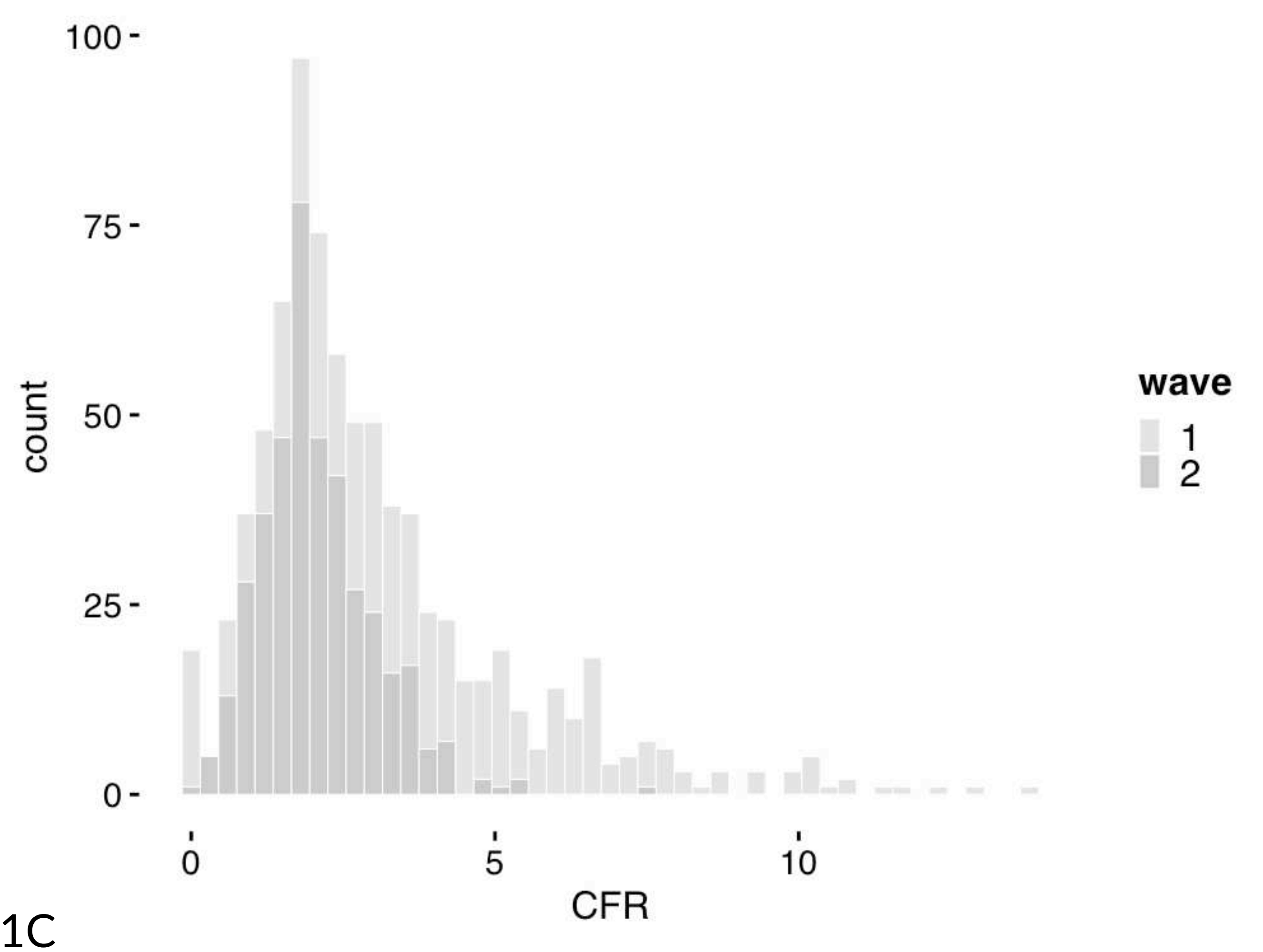

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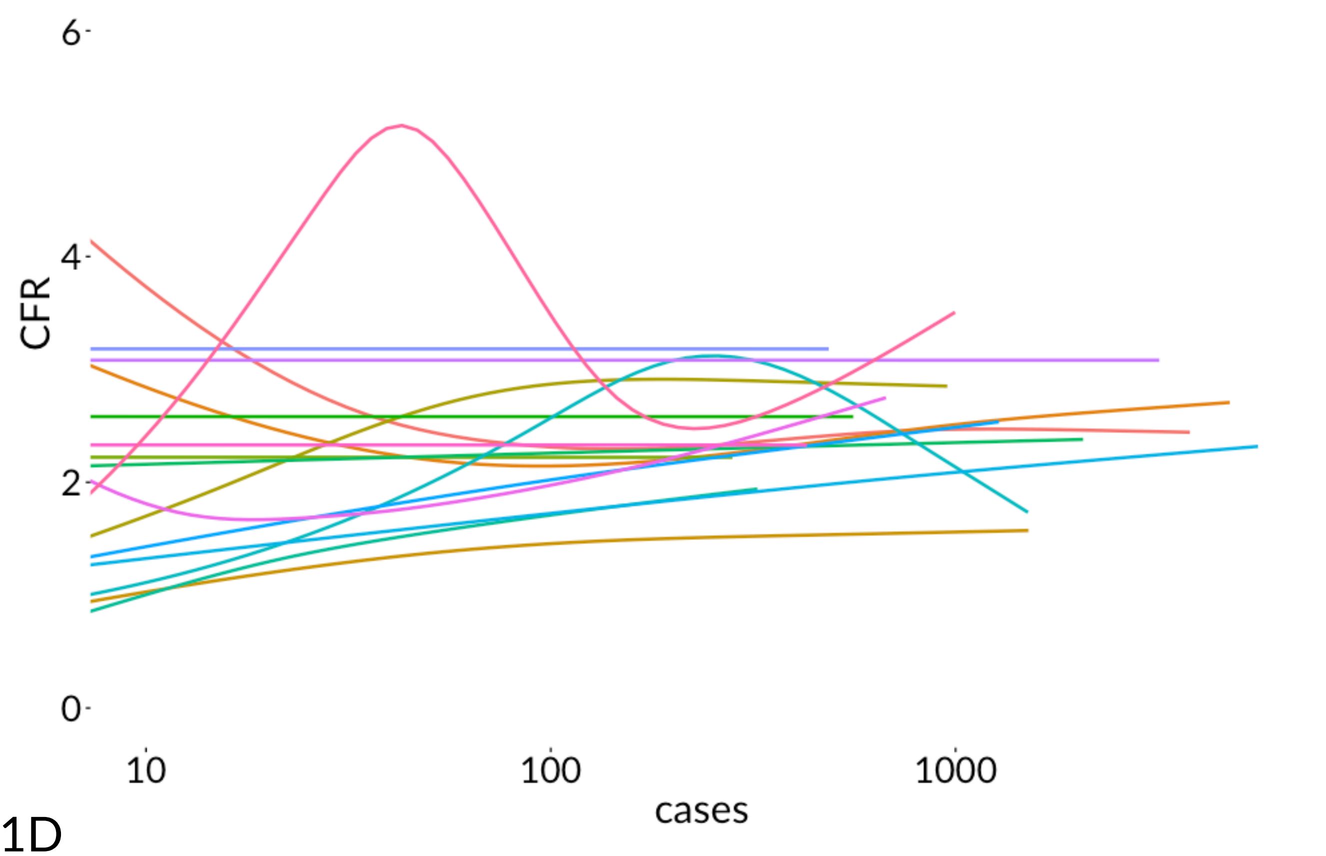

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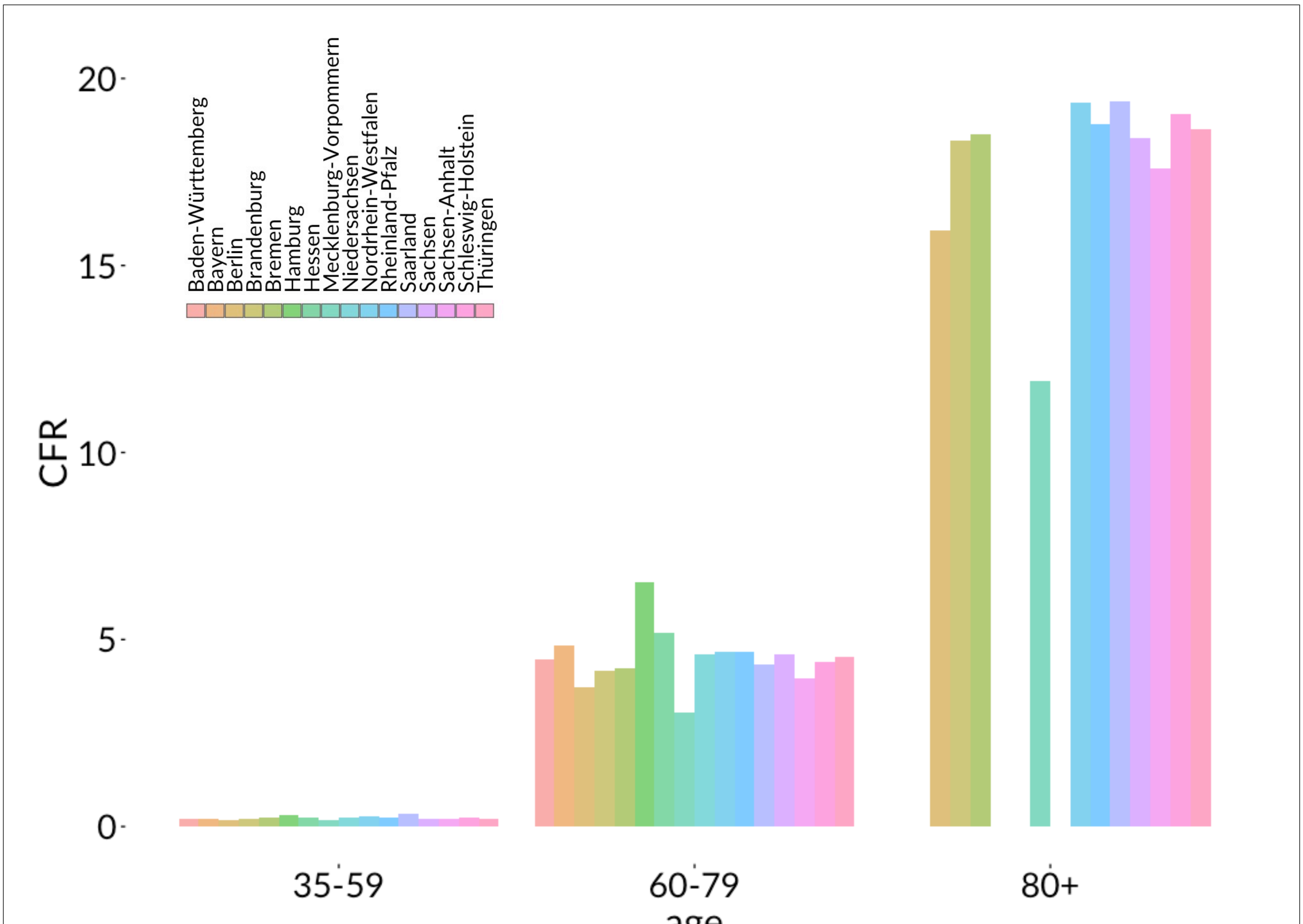

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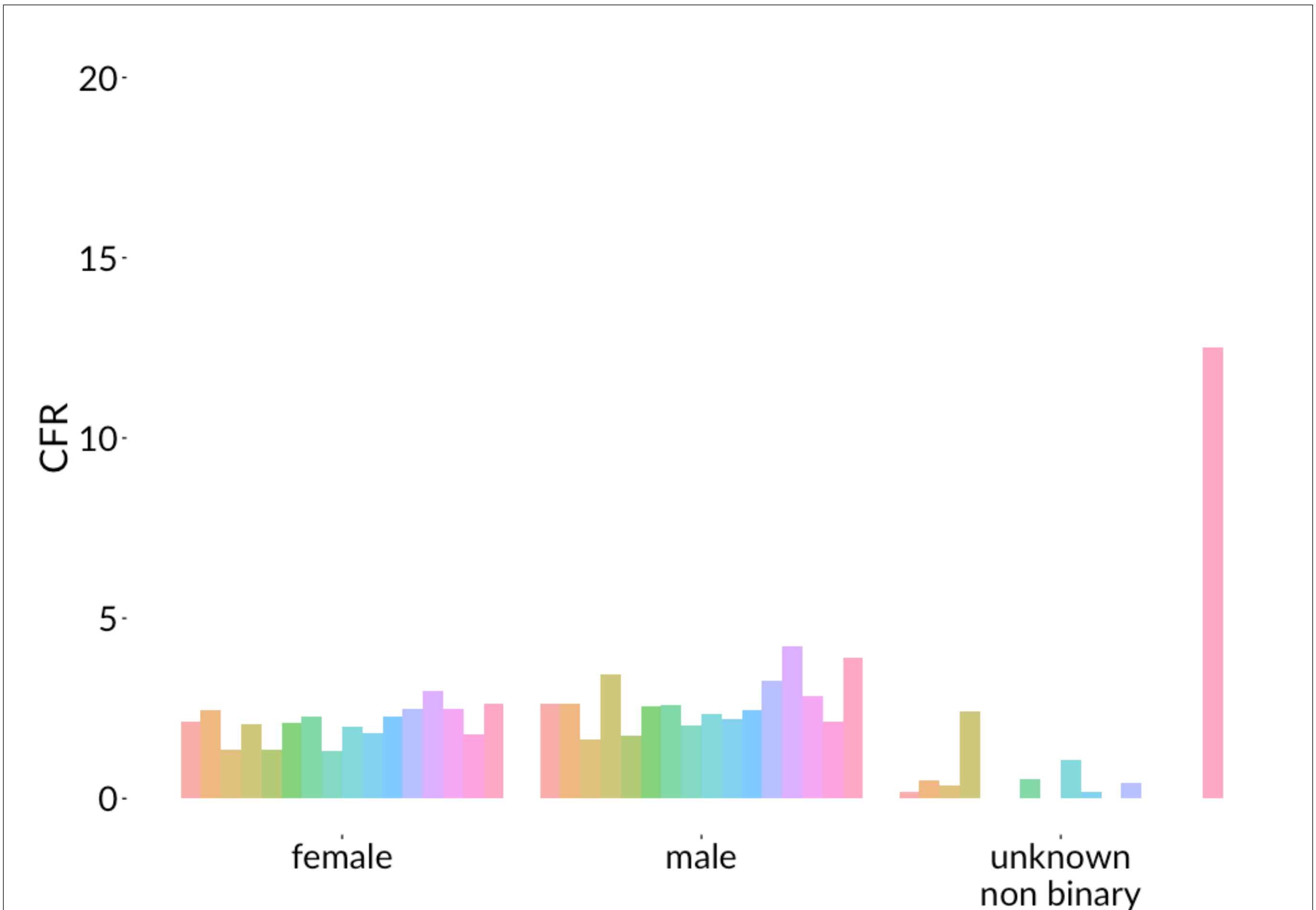
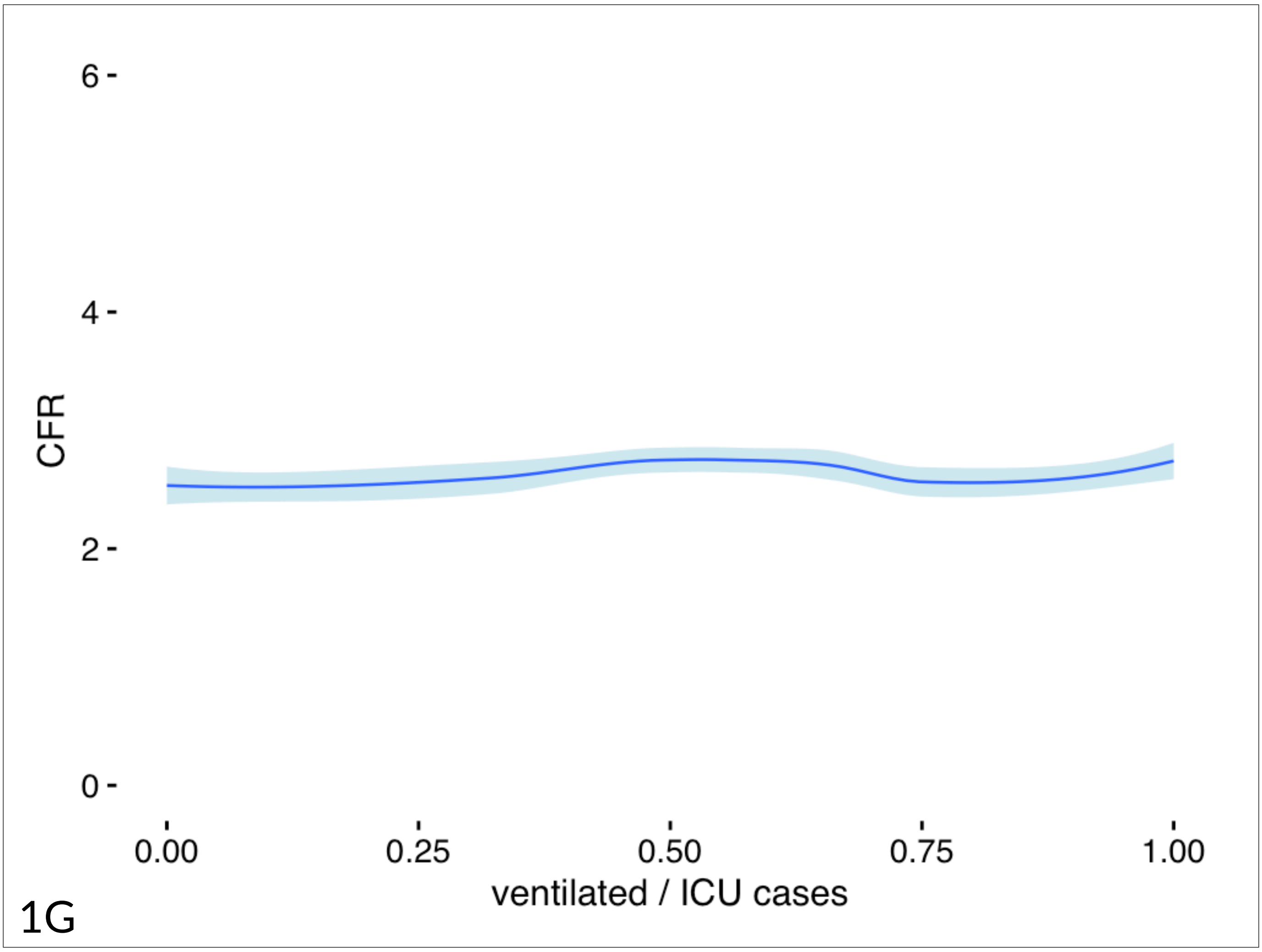
age

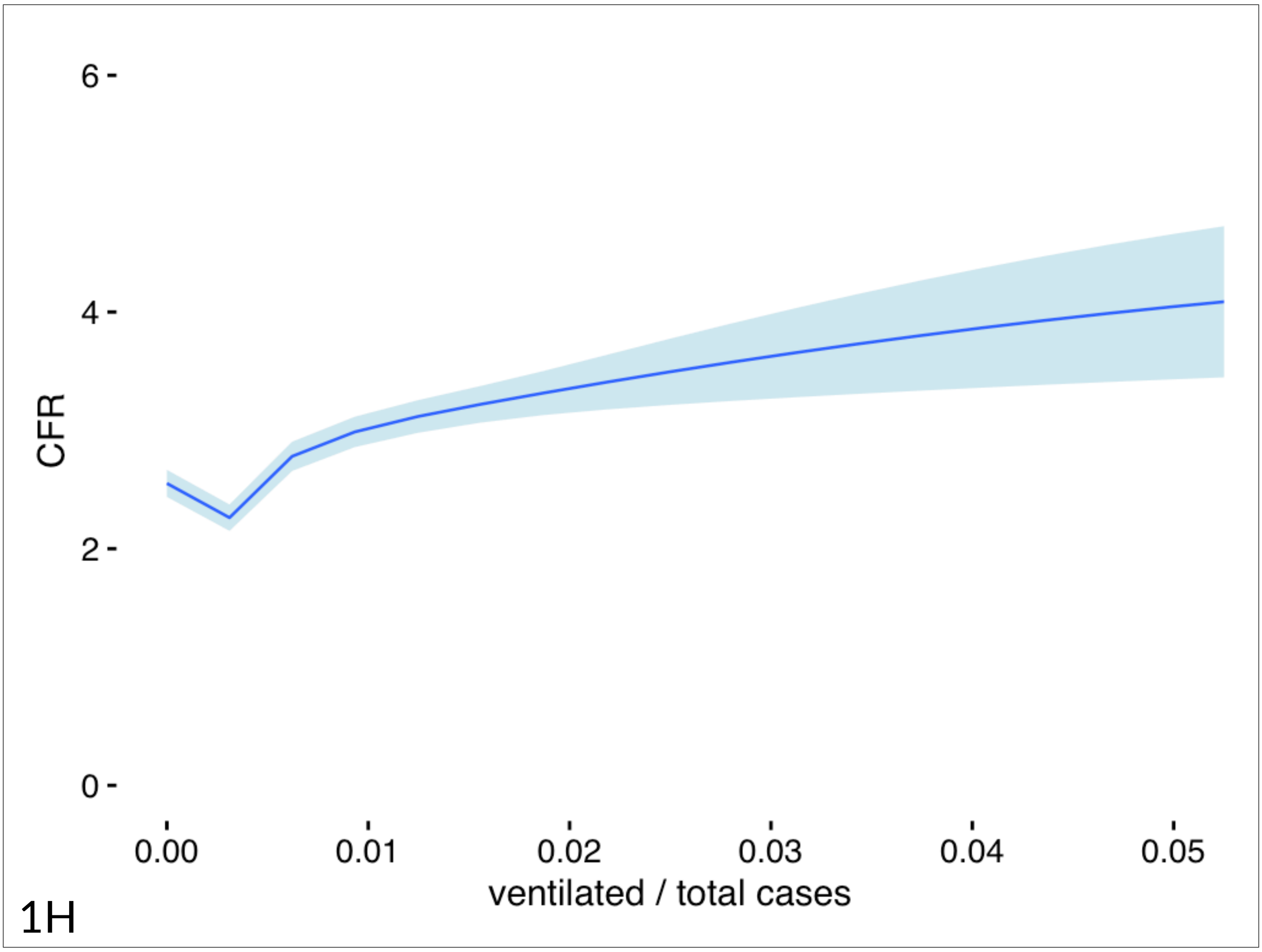
1E

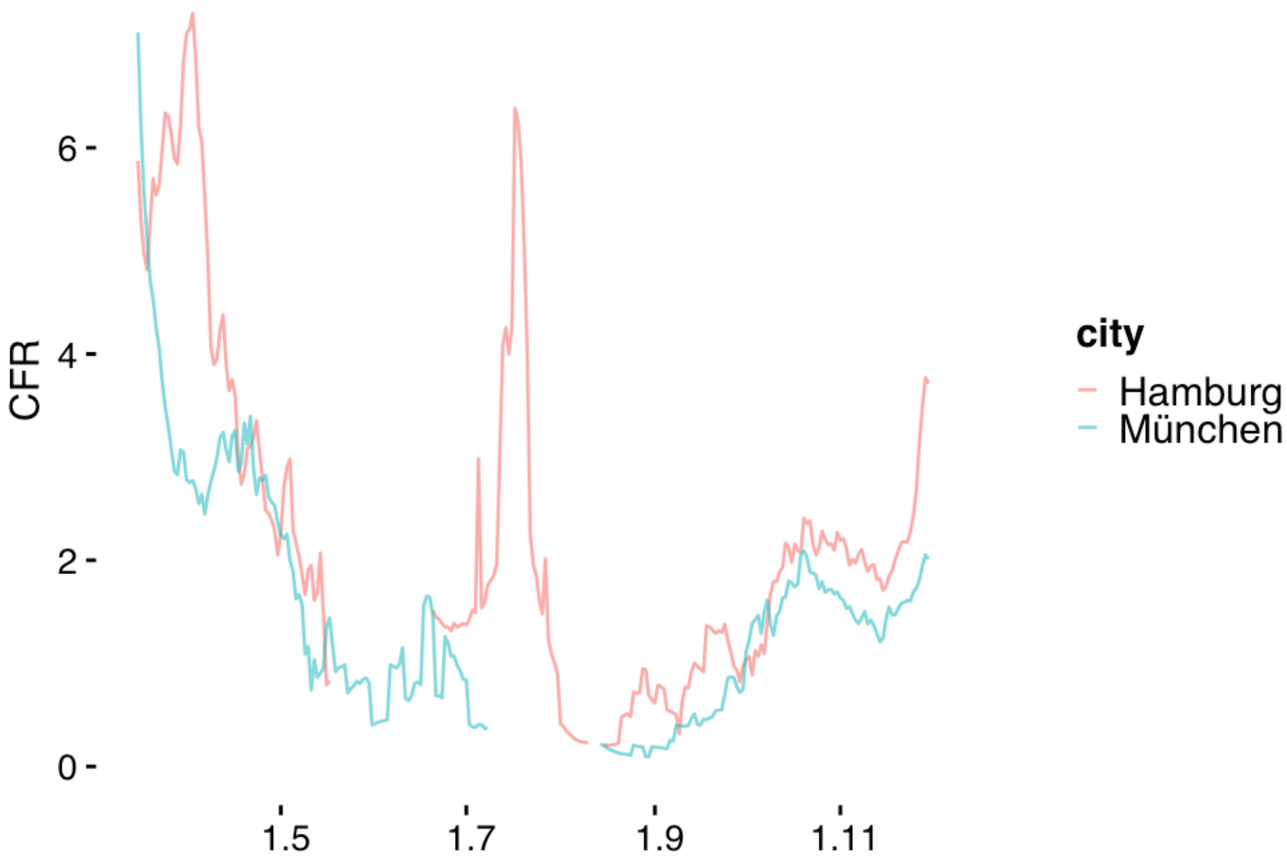


CFR
20
15
10
5
0
female
male
unknown
non binary
sex

1F


6
4
2
0
CFR
0.00
0.25
0.50
0.75
1.00
ventilated / ICU cases
1G


6
4
2
0
CFR
0.00
0.01
0.02
0.03
0.04
0.05
ventilated / total cases
1H



2A

COVID-19 epidemiology.

	Hamburg	München
death	265	219
survived	5.091	6.519
	5.356	6.738$

OR 1.5 (1.3-1.9)

hospitalization

	Hamburg	München
yes	996	1.631
no	4.360	5.107
	5.356	6.738

OR 0.7 (0.7-0.8)

transfer to ICU

	Hamburg	München
yes	261	259
no	735	1.372
	996	1.631

OR 1.9 (1.5-2.3)

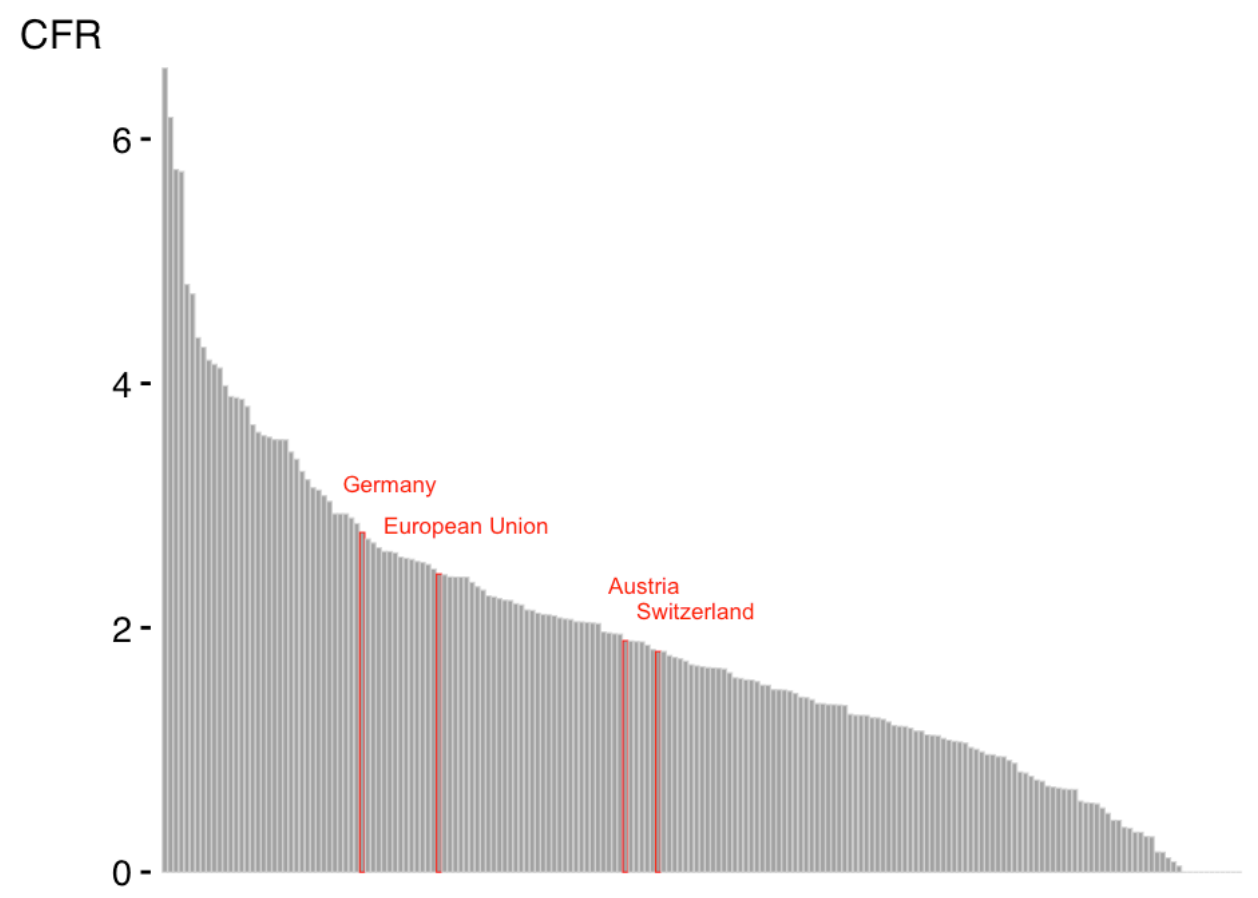
ICU fatality

	Hamburg	München
death	78	63
survived	145	196
	223&	259

OR 2.0 (1.3-3.1)

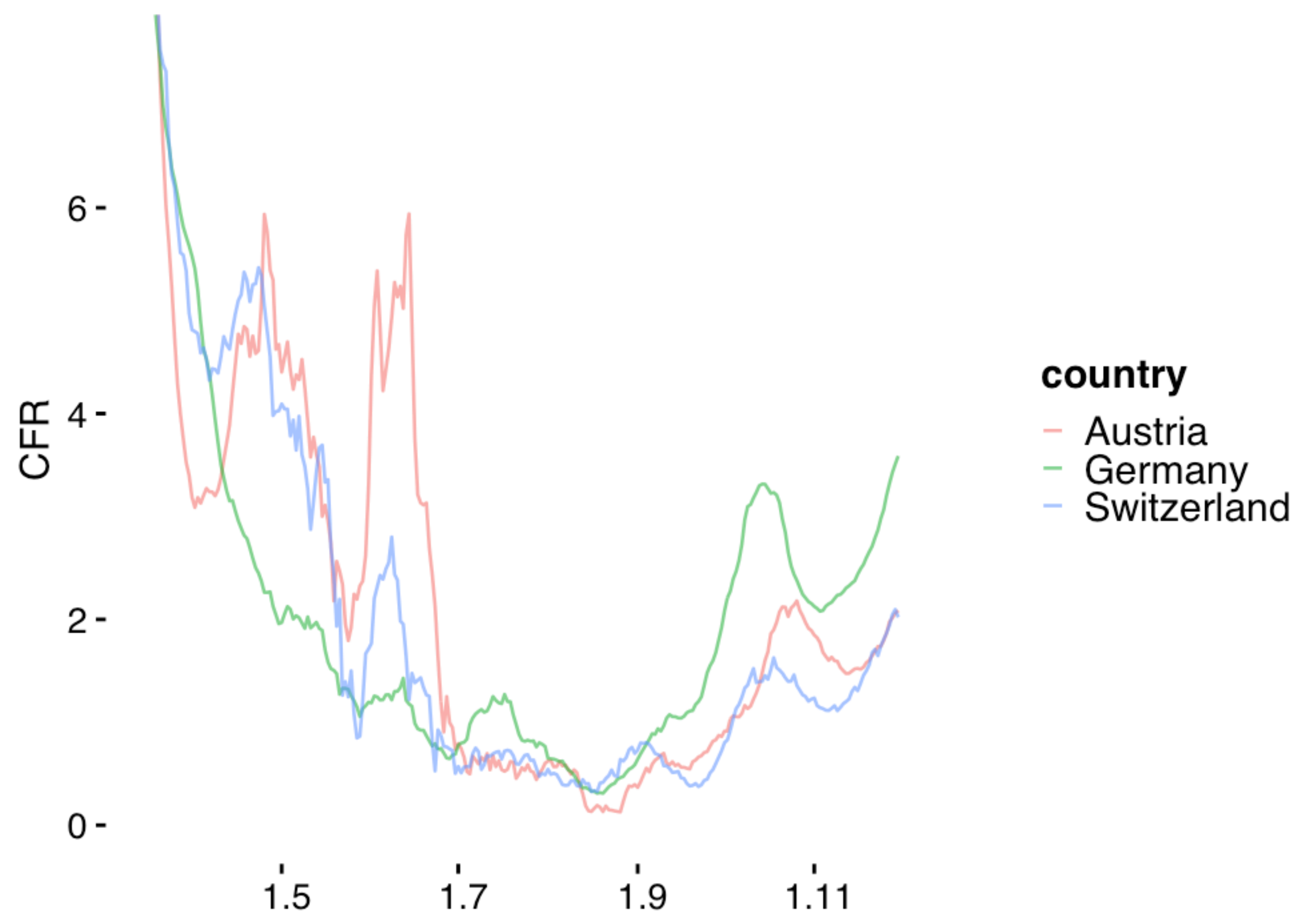
$ only TUM and LMU
& N=38 missing in Roedl et al 2020

2B



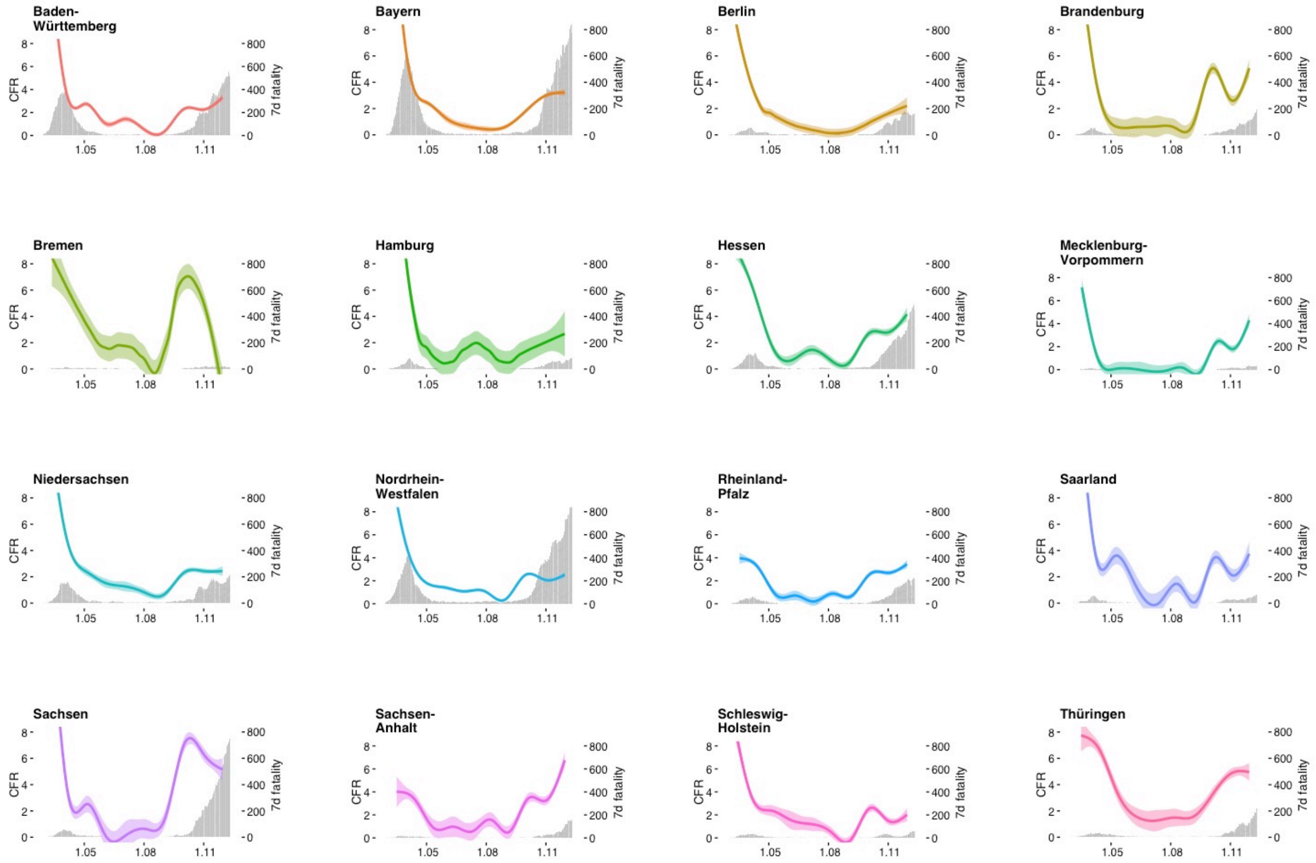
CFR
6
4
2
0
Germany
European Union
Austria
Switzerland

3A



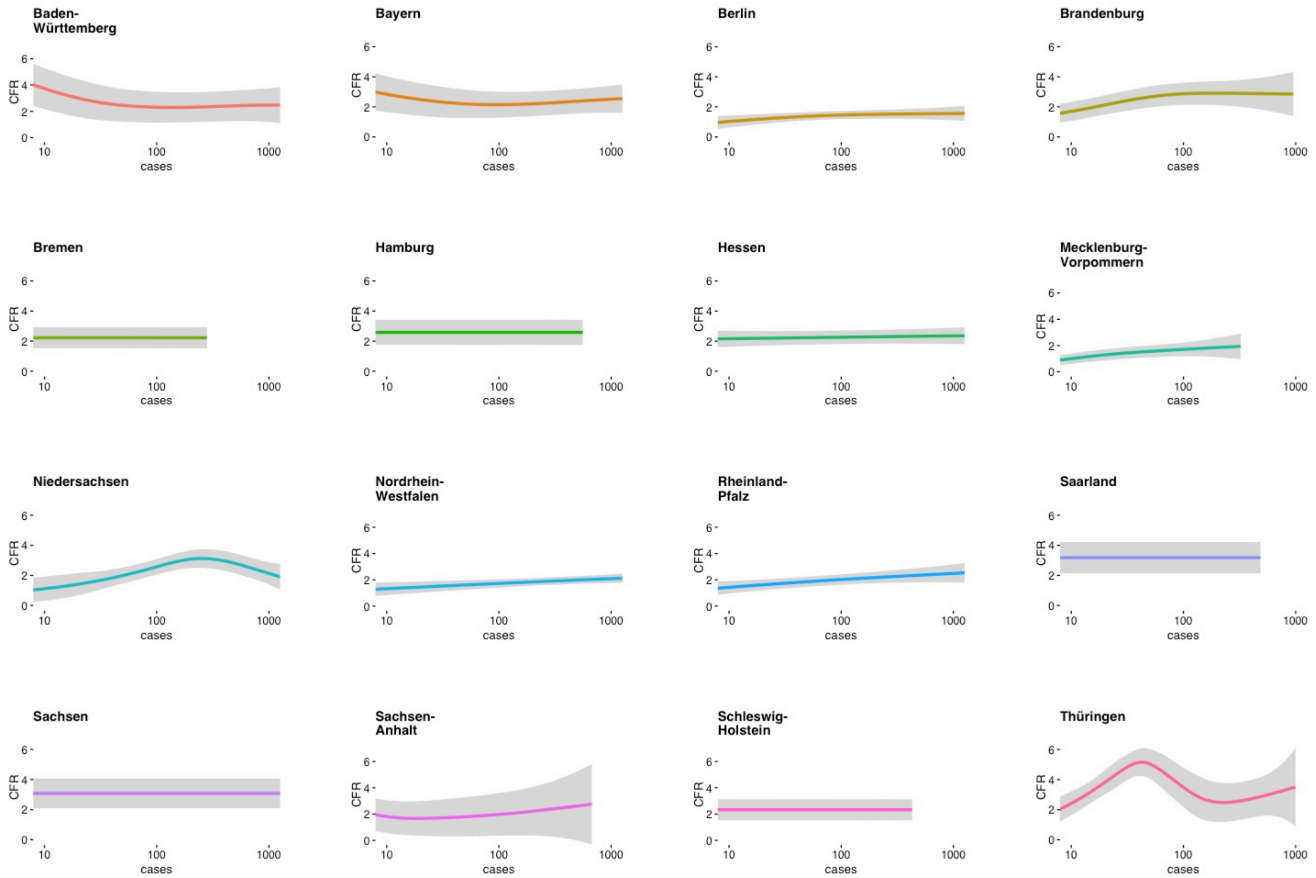
CFR
6
4
2
0
1.5
1.7
1.9
1.11
country
Austria
Germany
Switzerland

3B



Baden-Württemberg
Bayern
Berlin
Brandenburg
Bremen
Hamburg
Hessen
Mecklenburg-Vorpommern
Niedersachsen
Nordrhein-Westfalen
Rheinland-Pfalz
Saarland
Sachsen
Sachsen-Anhalt
Schleswig-Holstein
Thüringen
CFR
7d fatality
1.05
1.08
1.11

S1



Baden-Württemberg
Bayern
Berlin
Brandenburg
Bremen
Hamburg
Hessen
Mecklenburg-Vorpommern
Niedersachsen
Nordrhein-Westfalen
Rheinland-Pfalz
Saarland
Sachsen
Sachsen-Anhalt
Schleswig-Holstein
Thüringen
CFR
cases

S2