



BMJ Open Assessing relative COVID-19 mortality during the second wave: a prospective Swiss population-based study

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ABSTRACT

Objective During the first COVID-19 wave in Switzerland, relative mortality was at least eight times higher compared with the uninfected general population. We aimed to assess sex-specific and age-specific relative mortality associated with a SARS-CoV-2 diagnosis during the second wave.

Design Prospective population-based study.

Setting Individuals testing positive for SARS-CoV-2 after the start of the second wave on 1 October 2020 were followed up until death or administrative censoring on 31 December 2020.

Participants 5 179 740 inhabitants of Switzerland in fall 2018 aged 35–95 years (without COVID-19) and 257 288 persons tested positive for SARS-CoV-2 by PCR or antigen testing during the second wave.

Primary and secondary outcome measures The planned outcome measure was time to death from any cause, measured from the date of a SARS-CoV-2 diagnosis or 1 October in the general population. Information on confirmed SARS-CoV-2 diagnoses and deaths was matched by calendar time with the all-cause mortality of the general Swiss population of 2018. Proportional hazards models were used to estimate sex-specific and age-specific mortality rates and probabilities of death within 60 days.

Results The risk of death for individuals tested positive for SARS-CoV-2 in the second wave in Switzerland increased at least sixfold compared with the general population. HRs, reflecting the risk attributable to a SARS-CoV-2 infection, were higher for men (1.40, 95% CI 1.29 to 1.52) and increased for each additional year of age (1.01, 95% CI 1.01 to 1.02). COVID-19 mortality was reduced by at least 20% compared with the first wave in spring 2020.

Conclusion General mortality patterns, increased for men and older persons, were similar in spring and in fall. Absolute and relative COVID-19 mortality was smaller in fall.

Trial registration The protocol for this study was registered on 3 December 2020 at <https://osf.io/gbd6r>.

INTRODUCTION

An overwhelming body of research has been published since the start of the SARS-CoV-2 pandemic in early 2020. Many reports provide assessments of the burden of COVID-19 from multiple perspectives. The frequency of fatal

Strengths and limitations of this study

- Relative sex-specific and age-specific COVID-19 mortality rates for the second wave of fall 2020 comparing a cohort of COVID-19 patients with the general population are provided.
- A direct comparison with the relative mortality reported for the first wave in spring 2020 is possible, without confounding by differences in reporting systems, public health interventions or demographics.
- The present prospectively planned study replicates the main findings reported in a retrospective analysis of Swiss surveillance data from the first wave.
- The study excludes patients younger than 35 years and older than 95 years, as well as patients tested posthumously, and information on relevant comorbidities or sociodemographic information is not available at the population level.
- Fatal outcomes were studied exclusively, no assessment of the burden of COVID-19 in terms of hospitalisations or long COVID was possible.

outcomes is most commonly measured by case fatality rates,^{1–3} infection fatality rates^{4 5} or excess number of deaths.^{6 7} Early estimates have been challenged and updated^{8–11} during and after the first wave in spring 2020. Case and infection fatality rates have been criticised because interpretation depends on public health measures taken, testing and reporting systems, assessment of cause of death and underlying demographic characteristics, most importantly age distributions. Thus, fatality rates are hard to compare between different populations and in the same population over time^{12–15} and adjustment for the age composition and sex composition of the population is crucial.^{16–19}

Longitudinal assessments of the burden of disease became more important during the onset of second waves in summer and fall 2020. Comparisons of case fatality rates in the first and second wave have been published,^{20 21} indicating lower fatality rates



during the second wave, but contrary results have also been reported.²²

Excess mortality allows longitudinal patterns of COVID-19 mortality to be compared with the general population mortality without confounding by demographic characteristics and public health interventions.²³ Analysis of the all-cause mortality does not require the differentiation between deaths caused by COVID-19 or other reasons and might thus allow for a more comprehensive picture of the burden of disease.^{24–26}

An additional measure to assess the burden of disease is the relative mortality, which is defined as the ratio in absolute probabilities of death within a given time frame, across two different populations. The sex-specific and age-specific relative COVID-19 mortality was reported for the first wave of spring 2020 in Switzerland,²⁷ where mortality was at least eight times higher compared with the uninfected population. Sex and age had little impact on this relative risk.

In this study, we present sex-specific and age-specific relative COVID-19 mortality during the second wave in fall 2020 in Switzerland and based on these results compare relative COVID-19 mortality between the first and the second wave. In contrast to the first wave in Switzerland, which was characterised by strict public health interventions and moderate number of deaths,²⁸ the second wave caused local exceedances of hospital capacity and more than five times the number of COVID-19-related deaths, following late implementation of moderate public health interventions.

METHODS

Study design

This population-based study was planned prospectively (see study protocol) and includes information of two cohorts: individuals tested positive for SARS-CoV-2 in the second wave in Switzerland (Swiss Fall 2020 COVID-19 cohort) and the general Swiss population of fall 2018 (Swiss Fall 2018 cohort).

Data sources

The population-based data for Switzerland from 2014 to 2019 were obtained from the Swiss Federal Statistical Office, including daily death records and age-specific numbers of male and female inhabitants on 31 December of each year.

Records of individuals tested positive for SARS-CoV-2 from 1 October 2020 to 31 December 2020, including dates of tests and occurred deaths, were provided by the Swiss Federal Office for Public Health (FOPH). In Switzerland, SARS-CoV-2 tests were performed either by PCR and, since 2 November 2020, additionally with rapid antigen tests of lower and upper respiratory tract samples.²⁹ Test results were reported to the FOPH. Persons with positive SARS-CoV-2 tests were followed up. The testing recommendations in Switzerland during the second wave included testing of individuals with

Table 1 Study population

Criterion	Cohort	
	Swiss Fall 2018	Swiss Fall 2020 COVID-19
Alive 1 Oct	8 561 495	2 281 790*†
SARS-CoV-2 positive after 1 Oct		400 159*
35–95 years old	5 179 740	257 445*
Sex known		257 400
Not postmortem		257 288
Study population	5 179 740	257 288
Deaths	15 270	5077

Number of individuals in the Swiss Fall 2018 cohort as of 1 October 2018 and total number of 2 281 790 tests (PCR: 1 929 095 and antigen: 352 695) in Switzerland between 1 October 2020 and 31 December 2020. The table contains the number of individuals meeting the eligibility criteria in either cohort. ‘Study population’ refers to the number of observations in either cohort used for the final analysis.

*These numbers were retrieved from official FOPH reports on <https://www.covid19.admin.ch/>.

†The number of tests specifies the total counts of performed tests including multiple counts for individuals tested more than once. FOPH, Federal Office for Public Health; PCR, Polymerase Chain Reaction.

COVID-19 symptoms (respiratory illness symptoms, high temperature, sudden loss of sense of smell and/or taste, among others). In addition, persons suspected to have been in close contact with a person tested positive for SARS-CoV-2 were also recommended to be tested.

Study population

The Swiss Fall 2020 COVID-19 cohort included all men and women aged between 35 and 95 years, who tested positive for SARS-CoV-2 during the second wave in Switzerland, starting on 1 October 2020. Individuals who tested positive after their death only were excluded. The Swiss Fall 2018 cohort included all men and women of age 35–95 years alive on 1 October 2018, determined as the number of Swiss inhabitants on 31 December 2018 plus the number of deaths between 1 October 2018 and 31 December 2018 for women and men in the respective age group. This definition assumes that migration during the last 3 months of 2018 did not impact the estimation of mortality.

Eligibility criteria of both cohorts are described in [table 1](#). The Swiss Fall 2014–2017 and 2019 cohorts were defined analogously to the Swiss Fall 2018 cohort in order to assess robustness regarding the selected population in a sensitivity analysis.

Outcome measure

The outcome measure was time to death due to any cause, measured from a SARS-CoV-2 diagnosis or from 1 October 2018 in the general population.

Statistical analyses

In our primary analysis, we assessed the age-specific and sex-specific all-cause mortality of SARS-CoV-2-infected individuals (Swiss Fall 2020 COVID-19 cohort) relative to the general population of 2018 (Swiss Fall 2018 cohort) using survival analysis.

Mortality in both cohorts was analysed adjusted for seasonal effects, by using the same time scale, that is, the number of days after 1 October. For individuals in the Swiss Fall 2020 COVID-19 cohort, a delayed entry approach was used, as infected individuals do not become at risk of death until the date of the SARS-CoV-2 diagnosis. On 31 December, individuals alive in either cohort were administratively right censored.

Sex-specific and age-specific HRs with 95% CIs were estimated using a stratified Cox proportional hazards model, allowing for separate baseline hazards in the Swiss Fall 2020 COVID-19 and the Swiss Fall 2018 cohorts.

Women aged 65 years were defined as reference and the parameterisation of the linear predictor was chosen to quantify the effects of age and being male in the general population and the additional change in hazard attributable to age and being male in the COVID-19 cohort. P values and 95% CIs for the HRs were adjusted for multiplicity.

To provide a measure of absolute risk, sex-specific and age-specific probabilities of dying within 60 days after start of follow-up were predicted separately for the two cohorts based on estimates from a flexible parametric proportional hazards model.³⁰ The model for the Swiss Fall 2020 COVID-19 cohort allows estimation of the sex-specific and age-specific case fatality rate 60 days after a positive test. Relative COVID-19 mortality was defined as the ratio of the probabilities of death with 95% confidence bands estimated by taking only the uncertainty of the Swiss Fall 2020 COVID-19 cohort into account.³¹

The appropriateness of assuming proportional, linear, and additive effects of age and sex on the hazard function was investigated in three secondary analyses, contrasting the fitted model to models with time-varying sex and age effects, a non-linear additive effect of age on the log-hazard scale, or interaction effects of sex and age, respectively (online supplemental material S1). Additionally, we performed a sensitivity analysis by comparing the Swiss Fall 2020 COVID-19 cohort with the Swiss Fall 2014–2017 and 2019 cohorts, defined in an analogous way (online supplemental material S2).

Computational details

Computations were performed in R V.4.0.4.³² To estimate the log-HRs, semiparametric Cox proportional hazards models were fitted using the *survival*³³ package. Absolute mortalities were obtained from fully parametric models, parameterised with flexible log-cumulative baseline hazard functions, using the package *mlt*.^{30 34} Multiplicity-adjusted p values, CIs and confidence bands were computed using the *multcomp* package.³⁵ Analyses

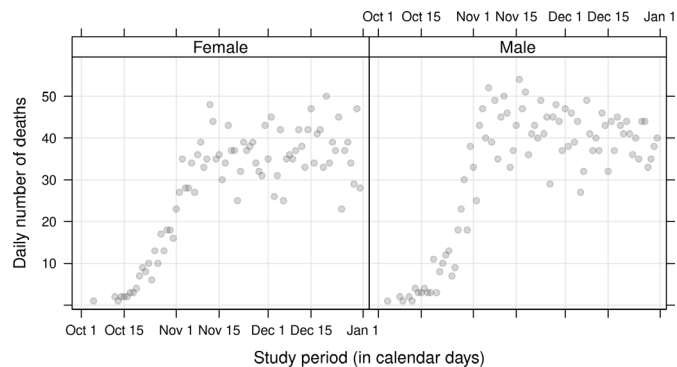


Figure 1 Swiss Fall 2020 COVID-19 cohort. Number of deaths from all causes reported between 1 October 2020 and 31 December 2020 of men and women (aged between 35 and 95 years), which were tested positive for SARS-CoV-2 as of 1 October (excluding postmortem tests).

were independently replicated in Stata³⁶ (V.16), using *stpm2*^{37 38} and *merlin*³⁹.

RESULTS

Overall, 257 288 persons were included in the Swiss Fall 2020 COVID-19 cohort and 5 179 740 persons in the Swiss Fall 2018 cohort. The second wave in Switzerland was characterised by a steep increase in daily number of deaths, starting from a daily maximum of 5 during the first half of October with peaks of 52–94 deaths in November and December. The daily numbers of deaths among men and women in the Swiss Fall 2020 COVID-19 cohort during the study period from 1 October to 31 December 2020 are shown in figure 1.

Sex and age characteristics of the Swiss Fall 2020 COVID-19 cohort, the Swiss Fall 2018 cohort and the additional Swiss population cohorts of other years (Fall 2014–2017 and 2019) are presented in table 2.

The age distribution of men in the Swiss Fall 2020 COVID-19 cohort matched the age distribution in the Swiss Fall 2018 cohort rather closely (figure 2, right panel), whereas women aged 65–75 years were slightly under-represented in the COVID-19 cohort (figure 2, left panel).

HRs for the effect of male sex and increasing age on all-cause mortality in the Swiss Fall 2018 cohort and additional hazards associated with a SARS-CoV-2 infection in the second wave (Swiss Fall 2020 COVID-19 cohort) are presented in table 3. In the general population, the all-cause hazard in men was 1.45 (95% CI: 1.39 to 1.51) times the hazard in women. Women aged 65 years experienced the same hazard as men 3.01 years younger. For each additional year of age, the hazard further increased by a factor of 1.13 (95% CI: 1.13 to 1.13).

The impact of a SARS-CoV-2 infection in the second wave was associated with an increased hazard for men and older patients. Being male with a SARS-CoV-2 infection increased the population hazard by a factor of 1.40 (95% CI: 1.29 to 1.52). Compared with women in the Swiss Fall 2018 cohort, the HR was $1.45 \times 1.40 = 2.02$ (95%

Table 2 Study populations

	Female		Male	
	N	Age	N	Age
Fall 2020 COVID-19	136 110 (52.90%)	57.21 (15.86)	121 178 (47.10%)	56.11 (14.42)
Fall 2018	2 660 812 (51.37%)	57.96 (14.93)	2 518 928 (48.63%)	56.30 (13.92)
Fall 2019	2 687 464 (51.34%)	58.05 (14.95)	2 547 327 (48.66%)	56.43 (13.99)
Fall 2017	2 635 579 (51.40%)	57.86 (14.92)	2 492 394 (48.60%)	56.16 (13.87)
Fall 2016	2 608 922 (51.42%)	57.79 (14.90)	2 464 644 (48.58%)	56.02 (13.81)
Fall 2015	2 578 897 (51.46%)	57.69 (14.89)	2 432 666 (48.54%)	55.88 (13.76)
Fall 2014	2 549 288 (51.52%)	57.62 (14.89)	2 398 899 (48.48%)	55.77 (13.72)

Number of individuals N (%) and mean age (SD) for women and men in the Swiss Fall 2020 COVID-19 cohort, the Swiss Fall population cohort of 2018, and earlier cohorts of 2014–2017 and 2019.

CI: 1.91 to 2.14), with more than half of this sex effect of SARS-CoV-2-positive men being attributable to the higher mortality risk of men in the general population ($\log\text{-HR } 0.37+0.34=0.70$). In comparison with the population age effect, the COVID-19-attributable age effect was very small (HR 1.01, 95% CI: 1.01 to 1.02), leading to a small increase in the total hazard for each additional year of age (HR: $1.13 \times 1.01 = 1.14$, 95% CI: 1.14 to 1.15). Hazards among men in the COVID-19 cohort were comparable with the mortality in women aged 5.24 years older.

The 60-day probability of death from any cause, shown in [figure 3](#) (top) and [table 4](#), was increased for SARS-CoV-2-positive individuals compared with the general population. In both cohorts, the 60-day probability of death increased log-linearly in age ([figure 3](#), top), with approximately the same slope, as explained by the very small additional age effect in the Swiss Fall 2020 COVID-19 cohort. Among 100 000 individuals, the estimated absolute mortality ranged from 16 (women 35 years old) and 32 (men 35 years old) to 27 267 (women 95 years old) and 48 002 (men 95 years old) in the Swiss Fall 2020 COVID-19 cohort ([table 4](#)). This absolute mortality in the COVID-19 cohort ([table 4](#), second column) can be interpreted as sex-specific and age-specific estimated case fatality rates. Relative COVID-19 mortality ranged from 6-fold to 9-fold for women and from 9-fold to 13-fold for

men compared with the general population of fall 2018 ([figure 3](#) (bottom panel), [table 4](#)), meaning that SARS-CoV-2-positive patients were associated with an at least 6-fold increase and an at most 13-fold increase of the mortality risk when compared with the Swiss Fall 2018 cohort.

Model diagnostics (online supplemental material S1) did not reveal relevant deviations from proportional hazards. The non-linear model indicated a non-linear age effect in the Swiss Fall COVID-19 cohort (online supplemental figures 1 and 2), showing a continuously and monotonically increasing hazard of age. A proportional hazards model allowing sex \times age interactions only marginally changed the HRs obtained from the main effects-only model ([table 3](#)), however, both the sex and age effects in the Swiss Fall 2020 COVID-19 cohort were attenuated in favour of a small sex \times age interaction (online supplemental table 1). Sensitivity analyses (online supplemental material S2) demonstrated that results reported for the Fall 2018 study population were very close to the results for the Fall 2014–2017 and 2019 study populations (online supplemental figures 3–12 and online supplemental table 2).

A direct comparison of the fall mortality patterns for Switzerland with the mortality pattern reported for spring²⁷ is possible due to the same study design, study area and statistical analyses techniques employed in both studies. The absolute mortality of men and women in the general population and the COVID-19 cohort of fall 2020 is compared with the corresponding spring cohorts in [figure 4](#).

In the general population of fall, the absolute mortality was approximately 87% of the general mortality in spring. Among patients with COVID-19, the reduction of absolute mortality of fall 2020 compared with spring was at least 20% for older patients and was further reduced for younger patients.

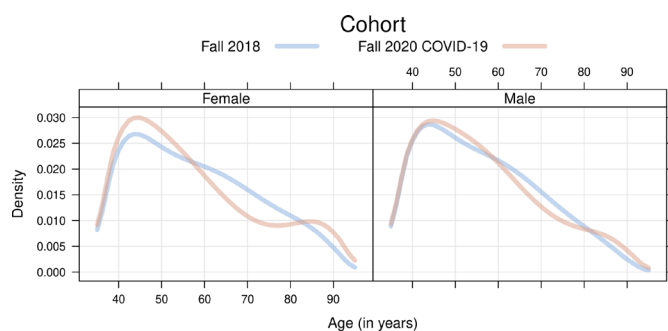


Figure 2 Swiss Fall 2018 and Swiss Fall 2020 COVID-19 cohorts. Comparison of age distribution of women and men in the Swiss Fall 2018 and Swiss Fall 2020 COVID-19 cohorts.

DISCUSSION

Comparing the all-cause mortality of SARS-CoV-2-positive individuals in the second wave in Switzerland with the

Table 3 Swiss Fall 2018 and Swiss Fall 2020 COVID-19 cohorts

Effect	log-HR	SE ×10	P value	HR	95% CI
Female	0			1	
Male	0.37	0.16	<0.001	1.45	1.39 to 1.51
Age 65	0			1	
Age – 65	0.12	0.01	<0.001	1.13	1.13 to 1.13
COVID-19 × Female	0			1	
COVID-19 × Male	0.34	0.33	<0.001	1.40	1.29 to 1.52
COVID-19 × Age 65	0			1	
COVID-19 × Age – 65	0.01	0.02	<0.001	1.01	1.01 to 1.02

Log-HRs and HRs reflecting the risk of being male ('Male') and each additional year of age ('Age – 65') compared with the baseline hazard among 65-year-old women. The interaction effects describe the additional risk attributable to the SARS-CoV-2 infection. Estimates of log-HRs are presented with SEs and HRs with 95% CIs. P values and CIs were adjusted for multiplicity.

general population of fall 2018, showed a 6-fold to 9-fold increase in short-term mortality attributable to a SARS-CoV-2 infection for women and 9-fold to 13-fold increase in men. Relatively speaking, all individuals aged between 35 and 95 years suffered roughly the same risk increase. Estimated sex-specific and age-specific case fatality rates ranged between 0.02% (women, 35 years) and 48.00%

(men, 95 years). In the general population not at risk of a SARS-CoV-2 infection, the hazard among men was 45% larger compared with women, and each additional year of age increased the hazard by 13%. The additional effect of being male in the SARS-CoV-2 positive cohort was 40%; the additional age effect, although statistically significant, was very small.

Our previous study reporting on relative COVID-19 mortality for the first wave in Switzerland in spring 2020²⁷ was based on the same study design and we are thus able to directly compare the different aspects of burden of COVID-19 between the spring and fall waves. Notably, the total number of deaths in the Swiss Fall 2020 COVID-19 cohort was much higher (with 5077 as compared with 894 in the first wave in spring 2020). The age distribution of infected men in fall 2020 closely matched the 2018 population, whereas larger discrepancies were observed for women in fall, and both sexes in spring.

HRs were almost equivalent to those estimated in the first wave, with a slightly more pronounced male COVID-19 effect and lower associated variability (HR 1.40, 95% CI: 1.29 to 1.52 instead of 1.21, 95% CI: 1.02 to 1.44 in spring).

Absolute mortalities for the spring and fall 2018 populations not at risk of a SARS-CoV-2 infection were slightly smaller in fall, reflecting well-known seasonal patterns of population mortality.⁴⁰ Absolute mortality in the SARS-CoV-2 positive cohort, indicated by estimated case fatality rates, decreased at least 20% compared with spring.

Relative COVID-19 mortalities were lower in fall compared with spring (at least six instead of eight). The much larger sample size in the Swiss Fall 2020 COVID-19 cohort and the larger number of deaths led to a substantial decrease in the variability and the upper confidence limits of the relative mortality.

Testing of more asymptomatic people and systematic mass SARS-CoV-2 testing in some parts of Switzerland may explain the decrease in absolute COVID-19 mortality compared with the first wave in spring 2020, at least in younger patients.

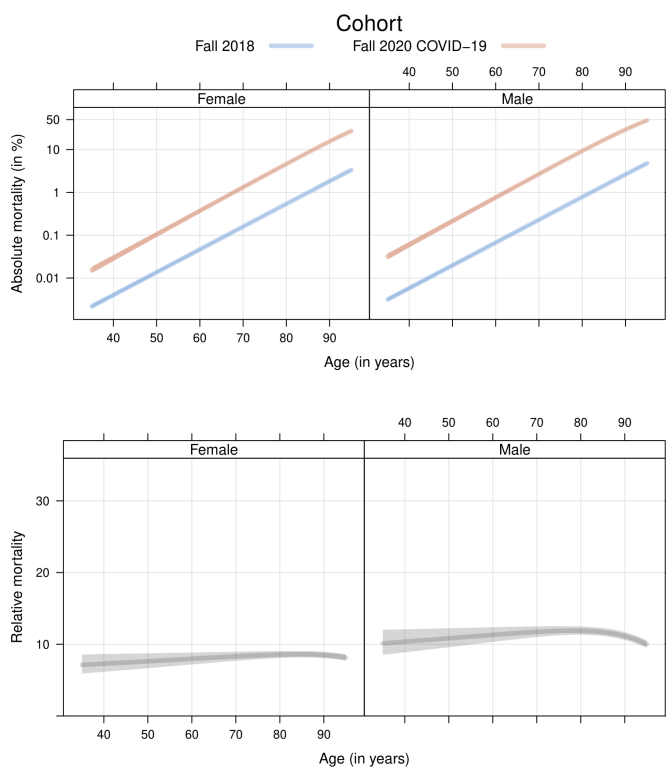


Figure 3 Swiss Fall 2018 and Swiss Fall 2020 COVID-19 cohorts. Absolute mortality, the probability of dying from any cause after 60 days, among women and men of different ages in the Fall 2018 and the Fall 2020 COVID-19 cohorts (top, shown on the logarithmic scale). Relative mortality, the ratio of absolute mortalities in the Fall 2020 COVID-19 and the Fall 2018 cohort, among women and men of different ages (bottom). All estimates are plotted with 95% confidence bands.

Table 4 Swiss Fall 2018 and Swiss Fall 2020 COVID-19 cohorts

Sex	Age	Mortality		
		Absolute Fall 2018	Absolute SARS-CoV-2	Relative
Female	35	2 (2–2)	16 (13–19)	7 (6–9)
	40	4 (4–4)	29 (25–35)	7 (6–9)
	45	7 (7–8)	55 (47–64)	7 (6–9)
	50	14 (13–15)	104 (91–119)	8 (7–9)
	55	25 (24–27)	197 (175–222)	8 (7–9)
	60	47 (44–49)	371 (335–412)	8 (7–9)
	65	86 (82–90)	700 (640–766)	8 (7–9)
	70	159 (152–165)	1318 (1222–1422)	8 (8–9)
	75	293 (282–303)	2474 (2320–2638)	8 (8–9)
	80	539 (522–558)	4620 (4368–4886)	9 (8–9)
	85	993 (960–1028)	8543 (8110–8999)	9 (8–9)
	90	1826 (1759–1895)	15 517 (14 722–16 350)	8 (8–9)
95	3344 (3206–3488)	27 267 (25 802–28 799)	8 (8–9)	
Male	35	3 (3–3)	32 (27–38)	10 (9–12)
	40	6 (5–6)	60 (52–70)	10 (9–12)
	45	11 (10–12)	113 (99–130)	11 (9–12)
	50	20 (18–21)	214 (190–242)	11 (10–12)
	55	36 (34–39)	404 (364–449)	11 (10–12)
	60	67 (64–71)	761 (696–833)	11 (10–12)
	65	124 (119–130)	1433 (1328–1546)	12 (11–12)
	70	229 (221–238)	2688 (2523–2865)	12 (11–12)
	75	423 (408–438)	5015 (4752–5292)	12 (11–13)
	80	779 (753–806)	9258 (8821–9716)	12 (11–12)
	85	1433 (1383–1485)	16 760 (15 979–17 574)	12 (11–12)
	90	2629 (2526–2736)	29 274 (27 852–30 751)	11 (11–12)
95	4798 (4584–5023)	48 002 (45 650–50 411)	10 (10–11)	

Absolute mortality estimated for the Swiss Fall 2018 (Absolute 2018) and the Swiss Fall 2020 COVID-19 cohort (Absolute SARS-CoV-2, the 60-day sex-specific and age-specific case fatality rate) among 100 000 women or men with corresponding age. Relative SARS-CoV-2 mortality (Relative) of the fall was computed as the ratio of the absolute mortalities in the Swiss Fall 2020 COVID-19 compared with the Swiss Fall 2018 cohort. Estimates are shown with CIs obtained from the 95% confidence bands given in figure 3.

The share of positive tests among all reported SARS-CoV-2 tests ranged between 0% and 35.9% during the spring wave and 4.9% and 30.5% during the fall wave,

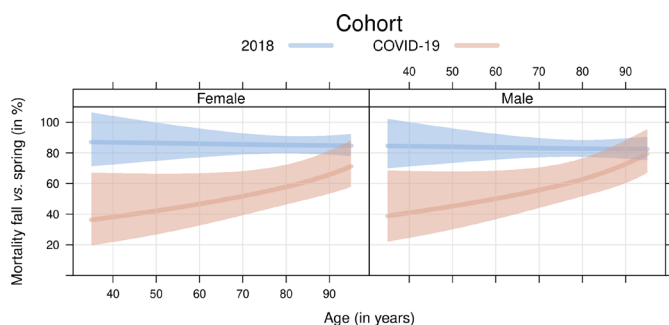


Figure 4 Ratio of absolute mortalities, fall versus spring. Comparison of the mortality of the fall and spring 2020 COVID-19 and general population cohorts. The mortality of men and women in fall compared with the corresponding mortality in spring in either cohort is shown.

with the daily trend being increased by 9% on average during the fall wave (online supplemental figure 13).

Estimates of infection rates from serosurveys indicate that the numbers of undiagnosed COVID-19 cases were larger in the first compared with the second wave with each confirmed SARS-CoV-2 case estimated to represent 2.7 infections in fall compared with 11.6 infections in spring 2020.⁴¹ Similarly, an analysis from Regensburg, Germany reported higher numbers of asymptomatic cases among the individuals tested positive for SARS-CoV-2 in fall 2020 (55.0% vs 14.4% in spring).⁴² The presence of undiagnosed infections, in spite of broader testing coverage in fall, would suggest an even lower mortality risk than assessed here.

The 20% reduction of the absolute mortality in fall when compared with spring could be partially explained by the broad use of dexamethasone in Swiss hospitals that has been shown to reduce mortality in severely ill patients with COVID-19.⁴³ In addition, also remdesivir

was used frequently in patients with severe COVID-19 pneumonia in the absence of invasive ventilation. In this group, this intervention also showed a reduction in mortality in one study.⁴⁴ Likely, other improvements in patient management developed based on experiences from the first wave may have also contributed to this finding.⁴⁵

Monitoring of viral variants confirmed that the variant B.1.1.7 (Alpha) constituted a small proportion (weekly average of maximum 2%) of the SARS-CoV-2 infections during the second wave in Switzerland. No other SARS-CoV-2 variants were detected during the study period.⁴⁶

Similar to the comparison of case fatality rates of the first and the second wave among many countries in August 2020,²¹ the decreased absolute and relative COVID-19 mortality reported for Switzerland here suggest a potential change in the epidemiological pattern. Broader testing coverage or improved treatment regimes are likely causes but, unfortunately, we can only speculate about their impact on absolute and relative measures of burden of COVID-19. Gaining a better understanding of potential causes and continuous monitoring of mortality might simplify comparisons across settings and allow to monitor the burden of the current pandemic more closely.

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Contributors SS, TH, MB and MC designed the study, acquired, preprocessed and analysed the data. SS and TH prepared an initial draft. HG, OK and CEW reviewed results and interpreted the data. All authors contributed to writing the manuscript and approved the final version.

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Competing interests TH has been paid for consulting, lectures or presentations from Novartis, Roche and PricewaterhouseCoopers. HG has received unrestricted research grants from Gilead Sciences and Roche; fees for data and safety monitoring board membership from Merck; consulting/advisory board membership fees from Gilead Sciences, Merck and Viiv Healthcare; and grants from SystemsX, and the National Institutes of Health. MC has been paid for consulting, lectures or presentations from Roche and Reinsurance Group of America UK Services Limited.

Patient consent for publication Not required.

Ethics approval Patient data were collected by the Swiss Federal Office of Public Health (Bundesamt für Gesundheit) under epidemic law.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data and the R and Stata code to reproduce all results are publicly available at https://gitlab.switch.ch/torsten.hothorn/relative_covid-19_mortality.

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