

# Risk of death of individuals with different comorbidity profiles during the COVID-19 pandemic.

Virginia Zarulli<sup>1,2</sup>, Cosmo Strozza<sup>1</sup> and Silvia Rizzi<sup>1</sup>

1. CPop, Interdisciplinary Center for Population Dynamics, University of Southern Denmark (Odense, Denmark), Campusvej 25 - 5230 Odense (Denmark)
2. Department of Statistics, University of Padova (Padova, Italy), Via Cesare Battisti 241 – 35121 Padova (Italy)

Corresponding author: Virginia Zarulli, virginia.zarulli@unipd.it

## Abstract

During the COVID-19 pandemic chronic illnesses have been linked to a higher risk of hospitalization and mortality. Several studies have explored the connection between these comorbidities and the risk of hospitalization and health outcomes in patients hospitalized with COVID-19. However, the pandemic may have had differing effects on the mortality risk of comorbid individuals not hospitalized, either directly or indirectly.

In our analysis, we include the entire Danish population aged 45 years and older, not just the hospitalized individuals. Our goal is to investigate how comorbidities diagnosed prior to the pandemic interacted with COVID-19 and whether the mortality risk for individuals with comorbidities changed during the pandemic. We examine COVID-19-specific and non-COVID-19-related mortality during 2020 and 2021 to assess the direct and indirect effects of the pandemic on the mortality risk of individuals with and without comorbidities.

We utilize comprehensive, nationwide Danish registry data, and employ survival analysis techniques. Kaplan-Meier curves show a clear gradient in the risk of death based on comorbidity levels, with women exhibiting more pronounced differences. During the pandemic, the relationship between comorbidity and non-COVID related deaths appears similar, while with COVID-related deaths appears less distinct, especially among men, indicating intriguing gender-health-status-specific patterns.

## Keywords

Comorbidity, Mortality, COVID-19, Denmark

## Purpose

The COVID-19 pandemic has highlighted the critical role of underlying health conditions in shaping health disparities. Chronic illnesses have shown a clear link with a higher risk of hospitalization and mortality during this crisis, primarily due to shared characteristics with infectious diseases, such as heightened inflammation and weakened immune responses.

Numerous studies have explored the connection between comorbidities and hospitalization risk, focusing on post-hospitalization health outcomes in COVID-19 patients. Hypertension, diabetes, obesity, cardiovascular diseases, respiratory ailments, cancer, and acute kidney injury are among the prevailing comorbidities associated with increased risk [1-9]. Different comorbidities can have varying effects, as seen in a New York study where diabetic patients had a higher likelihood of invasive interventions, while hypertensive patients had a lower risk [10]. Age and age-comorbidity interactions also produce differing outcomes: younger adults with comorbidities faced higher risks, while older individuals' frailty reduced the relative impact of comorbidities on outcomes [11, 12]. This is consistent with the higher overall frailty of older individuals, which makes the effect of having a comorbidity compared to not having it, less determining for a negative health outcome, while having a comorbidity at early age is a much stronger discriminatory factor for poor health outcome.

In Denmark's initial COVID-19 wave, male patients, especially older individuals with comorbidities like hypertension, diabetes, and chronic pulmonary disease, had a higher risk of hospitalization and ICU admission. Those with chronic pulmonary disease, active cancer, and multiple comorbidities faced a significantly elevated risk of death [13]. A higher Charlson Comorbidity Index correlated with increased COVID related risks across age groups and genders [14]. Hypertension, coronary artery disease, and diabetes were common comorbidities among COVID-19 patients at North Zealand Hospital, with all ICU patients having at least one comorbidity [15]. Cardiovascular comorbidities had a modest effect on poor outcomes compared to other conditions [16]. Post-hospitalization studies yielded mixed results, with one study showing a higher risk for men and another identifying comorbidity, age, and gender as independent risk factors for death [17, 18].

Subsequently, a study found lower ICU admissions, reduced organ support usage, and shorter ICU stays among hospitalized COVID-19 patients, though mortality rates remained high, particularly among males, older individuals, and those with comorbidities [19]. A nationwide study involving blood donors aged 17-69 revealed a lower infection fatality rate among those under 51 without comorbidities, while older individuals without comorbidities had a higher infection fatality rate for men compared to women [20].

To summarize, comorbidities appear to play a potentially detrimental role in worsening COVID-19 outcomes in Denmark. Most studies have focused on the first wave, potentially impacted by issues in estimating infection fatality rates, and mostly on hospitalized individuals only. However, the pandemic may have had differing effects on the mortality risk of comorbid individuals not hospitalized, either directly or indirectly.

These challenges have prompted researchers to adopt an approach centered on excess death estimation, comparing pandemic to pre-pandemic mortality, rather than focusing solely on COVID-19 mortality [21]. In our analysis, we take a similar approach, focusing on the entire population, not just hospitalized individuals. Our goal is to investigate how comorbidities present prior to the pandemic interacted with COVID-19 and whether the mortality risk for individuals with comorbidities changed during the pandemic in Denmark. We will examine the first two pandemic years 2020 and 2021, including COVID-19-specific and non-COVID-19-related mortality, to assess the direct and indirect effects of the pandemic on the mortality risk of individuals with and without comorbidities.

## Methods

We utilize comprehensive, nationwide individual Danish registry data, provided by Statistics Denmark. Specifically, we retrieve information from the Danish Population Register, the Cause of Death Register, the National Patient Register, and the Education Register. We can link records from different registries for the same individual by using personal identifiers. Our study aims to compare mortality risks between individuals with and without comorbidities in the three years before (2017-2019) and during the pandemic (2020-2021), independently on whether they have been hospitalized or not after contracting COVID-19. In our analysis we include individuals aged 45 and older, as chronic conditions of concern are infrequently observed in younger age groups. We determine the presence of comorbidity based on diagnosed chronic conditions during hospitalization in the five years leading up to the pandemic (2015-2019), ensuring the associations are relevant to our study. We focused on specific severe chronic conditions derived from a review of the scientific literature: Neoplasms, Diabetes (type I and II), Chronic Rheumatic Heart Diseases, Angina Pectoris, Acute and Old Myocardial Infarction, Stroke, Parkinson's Disease, Alzheimer's Diseases, Chronic Respiratory Diseases, Cirrhosis, and Chronic Kidney Diseases. The list of chronic diseases and their respective ICD-10 codes is available in table A1 of Supplementary Materials (SI). Based on the presence of those conditions, each individual is then classified depending on the number of comorbidities they had: none, one, two or more. We also included information on the highest achieved educational attainment categorized – according to the International Standard Classification of Education (ISCED) – as low (less than high school diploma), middle (high school diploma) and high (university diploma).

The mortality follow-up started at age 45 and ended up either by death or censoring at the end of the observation period: 2017 to 2019 for the pre-pandemic period and 2020-2021 for the pandemic period. Our study population includes about 2.6 million individuals overall. During the pre-pandemic period, we observe over 105 thousand deaths. During the pandemic period, we separated the covid-related-deaths from the all the other deaths, and we observed respectively circa 2.5 thousand and 108 thousand deaths.

First, we examined mortality risks for individuals with and without comorbidities using Kaplan-Meier curves and performed log-rank tests to assess whether the pandemic had varying effects on different comorbidity profiles. Afterwards, we derived Nelson-Aalen estimates for the non-parametric cumulative hazard functions of men and women by level of comorbidity. Finally, we analyzed relative risks with Cox regression models, driven by our focus on understanding risk disparities rather than the exact shape of the hazard functions.

## Results

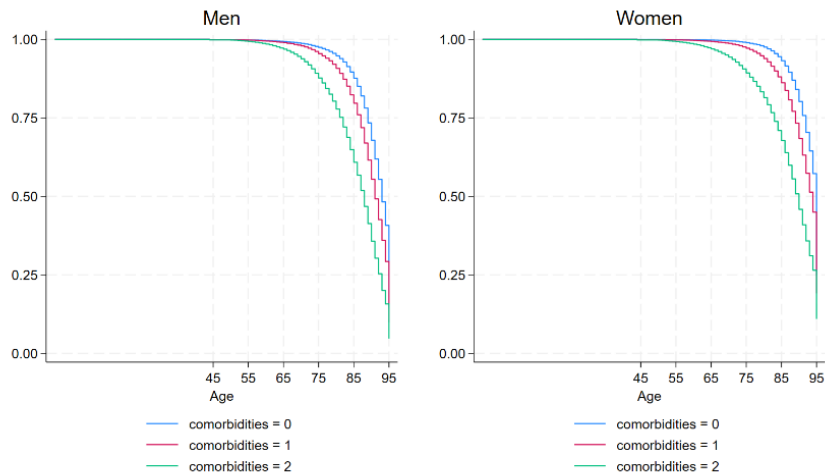
### *Kaplan-Meier survival curves*

In Figure 1, Panel A, we observe a clear and anticipated gradient in the risk of death, ranging from a lower risk for individuals without comorbidities to a higher risk for those with a greater burden of

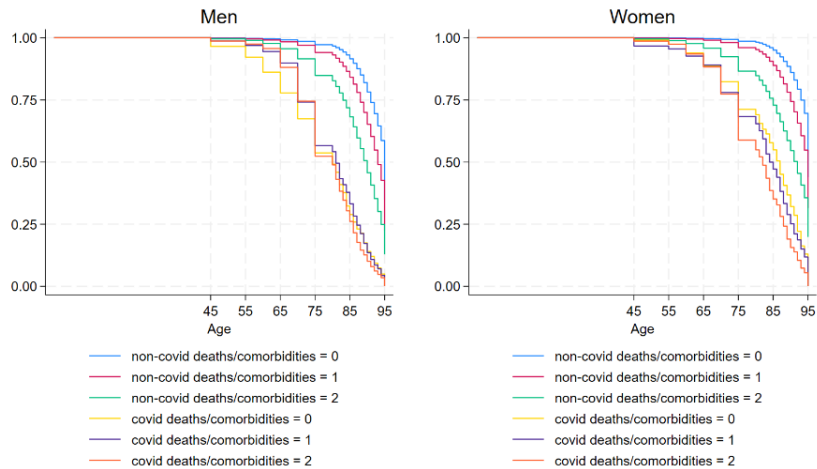
comorbidities. Notably, women exhibit a more pronounced separation among the curves representing varying comorbidity levels.

Turning our attention to Panel B, we can see that during the pandemic, deaths unrelated to COVID-19 maintain a consistent gradient corresponding to the pre-existing level of comorbidity. However, the relationship between comorbidity and COVID-related deaths appears less pronounced, particularly among men. In fact, the Kaplan-Meier survival curves for men almost completely overlap, and the gap between curves for non-COVID-related deaths is notably narrower compared to women.

Log-rank tests for the equality of the Kaplan-Meier survival curves, shown in Table A2 of SI, confirm this. In pre-pandemic times, the survival curves of the different comorbidity levels are significantly different for both men and women; during the pandemic, different comorbidity levels, in both sexes, still show significantly different survival for non-covid deaths, while for covid-related deaths, comorbidity survival rates are significantly different for women but not for men. This means that the risk of covid related death for women during the pandemic was significantly lower for individuals with no comorbidities compared to those with one or more comorbidities, but this was not the case for men.



A



B

Fig. 1. **Panel A-** Kaplan-Meier survival curves, all deaths from age 45 in Denmark by comorbidity level (from 0=low to 2=high), in pre-pandemic period (2017-2019). **Panel B-** Kaplan-Meier survival curves, deaths related to COVID and all other deaths, from age 45 in Denmark by comorbidity level (from 0=low to 2=high), in pandemic period (2020-2021).

### *Nelson-Aalen cumulative hazard*

Figure 2 shows the Nelson-Aalen estimate for the non-parametric cumulative hazard functions of men and women by level of comorbidity for all deaths in pre-pandemic period (panel A) and for covid-related and non-covid related deaths during the pandemic (panel B). As expected, the cumulative hazards of death for all combinations of comorbidities and type of deaths are higher for men than for women. When it comes to covid deaths, from age 70 the cumulative risk of death from covid clearly accelerates, for both sexes and for all the levels of comorbidities, indicating a strong impact of covid on the risk of death among the elderly. However, while for men, the risk of covid-death for individuals with no comorbidities (yellow line) is clearly higher than for all the other groups until age 70, it is not the case for women, whose hazard curves for the different groups practically overlap until age 65. After age 70, the risk of covid death becomes clearly higher than the risk of non-covid related death, but for men, the three levels of comorbidities don't have statistically different risks, while for women, those with two or more comorbidities are exposed to a significantly higher risk of death compared to those with one or no comorbidities, especially after age 80.

### *Cox regression*

We performed multiple regressions, progressively including additional variables and interaction terms in a stepwise approach. The model which offered the best fit of the data was selected based on the AIC criterion. The dependent variable is risk of death over age; independent variables are sex (male vs female), comorbidity level (having 1 or 2+ comorbidities vs zero comorbidities), education level (medium and high education level vs low education level). In the next sections we describe the

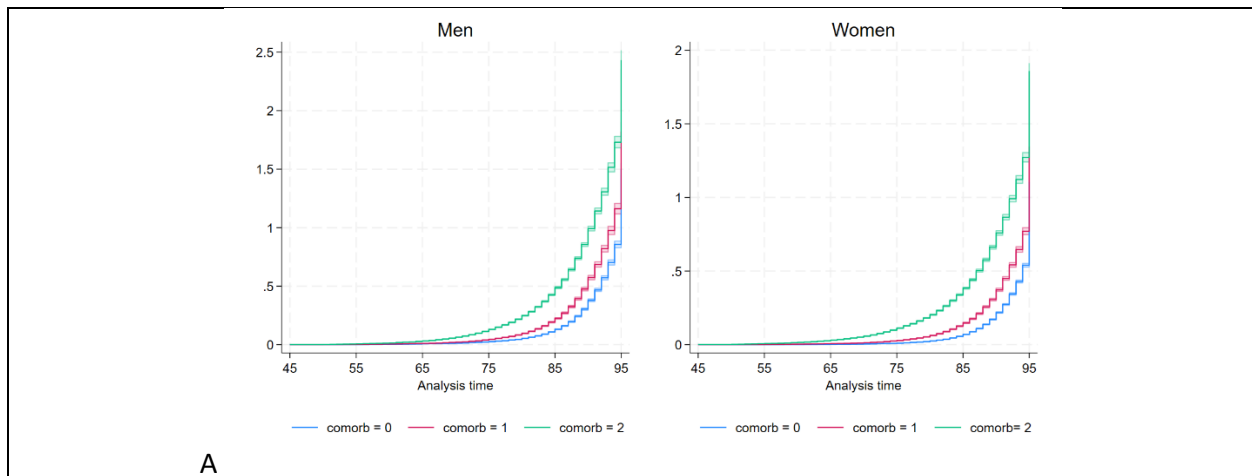
results for these models, for the pre-pandemic and the pandemic periods; for the pandemic period we included an additional covariate for type of death (covid-related vs non covid-related).

### Pre-pandemic period

Table A3 in SI shows the results of the Cox regression model applied to the pre-pandemic period; this model, which included interaction terms between all the included covariates, significantly improved the fit of the model compared to more the restricted models (those including fewer covariates and interaction terms), as indicated by the AIC statistic.

Not surprisingly, being a woman, having higher education and lower levels of comorbidity, in the pre-covid era significantly lowered the risk of death compared to men, lower education and higher comorbidity groups. The interpretation of the interaction effects, instead, is notoriously not straightforward from the regression coefficients. To ease the interpretation, we then used the command *margins*, available in Stata, to estimate and graph the interaction effects (results in table A3b in SI) which are shown in figure 3.

Among the individuals with no comorbidities, the category at the highest risk of death is less educated men, compared to which all the other combinations of sex and education levels, have significantly lower risk. Remarkably, lowly educated men with zero comorbidities display a higher risk than women with worse health condition (one comorbidity) at all levels of education and the same risk as highly educated men with one comorbidity. At comorbidity level 1, only men with middle and low education have higher risk of death with lowly educated men with no comorbidities. Only the individuals with two or more comorbidities (of both sexes and all levels of education) display a higher risk of death than men with low education and no comorbidity.



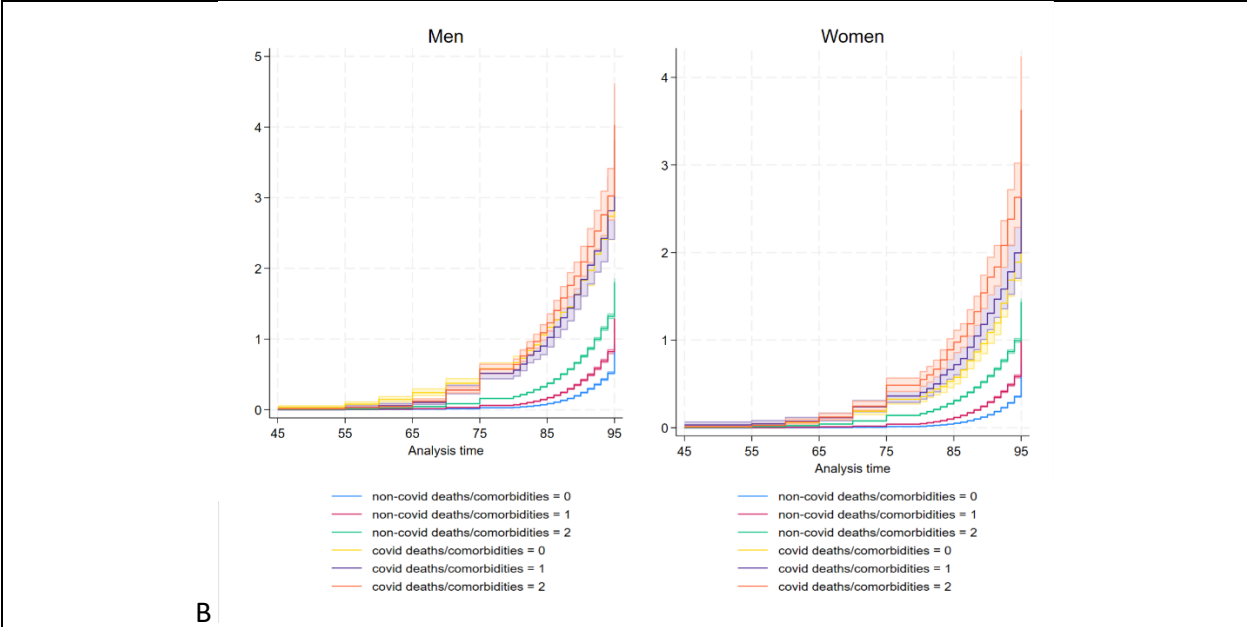


Fig. 2. **A-** Nelson-Aalen estimator for the hazard function, all deaths from age 45 in Denmark by comorbidity level (from 0=low to 2=high), in pre-pandemic period (2017-2019). **B-** Nelson-Aalen estimator for the hazard function, deaths related to COVID and all other deaths, from age 45 in Denmark by comorbidity level (from 0=low to 2=high), in pandemic period (2020-2021).

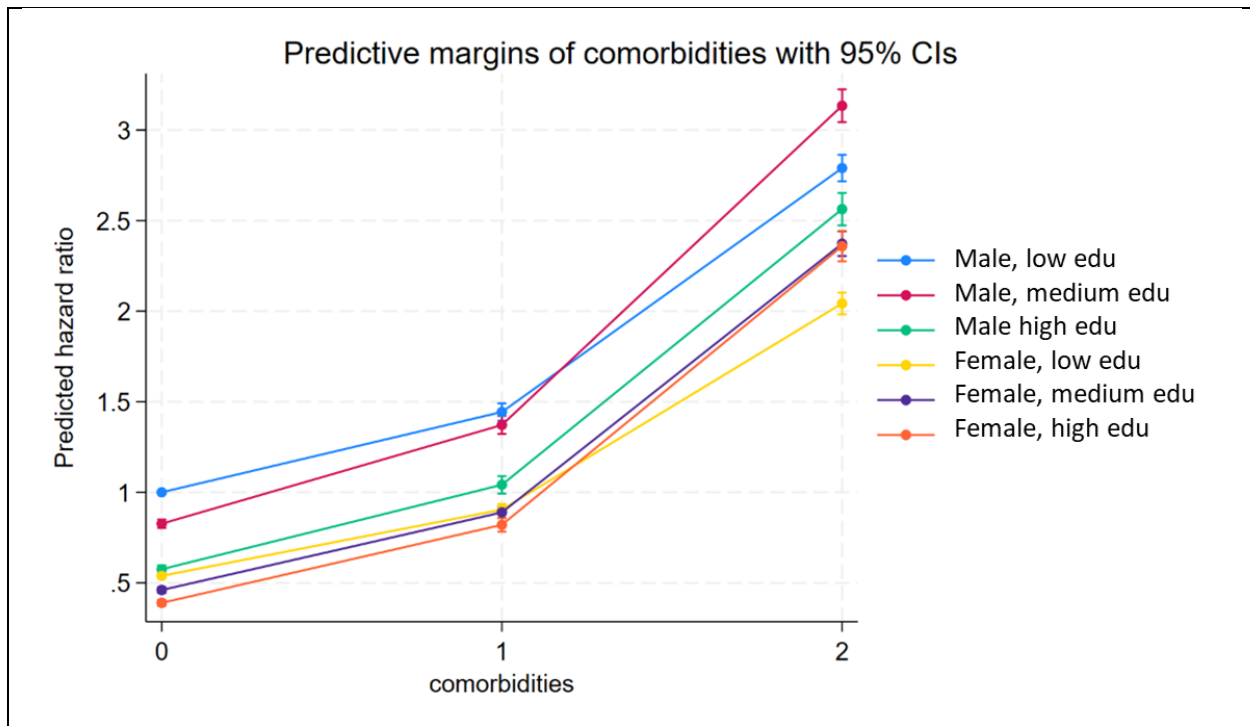


Fig. 3. Predictive margins of level of comorbidities, at different combinations of sex and education level, based on Cox regression model of risk of death in the pre-pandemic period (2017-2019).

### *Pandemic period*

We ran three separate analyses for the pandemic period: one with all the deaths pooled together and an additional covariate for the type of death (covid-related death vs non-covid-related), whose results are reported in table A4 and A4b and figure A1 in SI ; one only on the non-covid-related deaths (results in table A5 and A5b in SI and figure 4); and one only on covid-related deaths (results in figure A6 and A6b in SI and figure 5).

In the analysis with all the deaths pooled together, adding interaction terms between type of death (covid-related vs non covid-related) and the other covariates did not improve the fit of the model. The results of the best fitting model and the estimated interaction effects from *margins* are reported in table A4 and A4b in SI.

The results of the best fitting model and the predictive margins of the interaction terms for the analysis on non-covid-deaths during the pandemic are reported in table A5 and A5b in SI. Figure 4 offers a visual representation of the interaction between comorbidity and the other covariates in the analysis, which, even though with small differences, clearly resembles the patterns and the gradients observed during the pre-pandemic period.



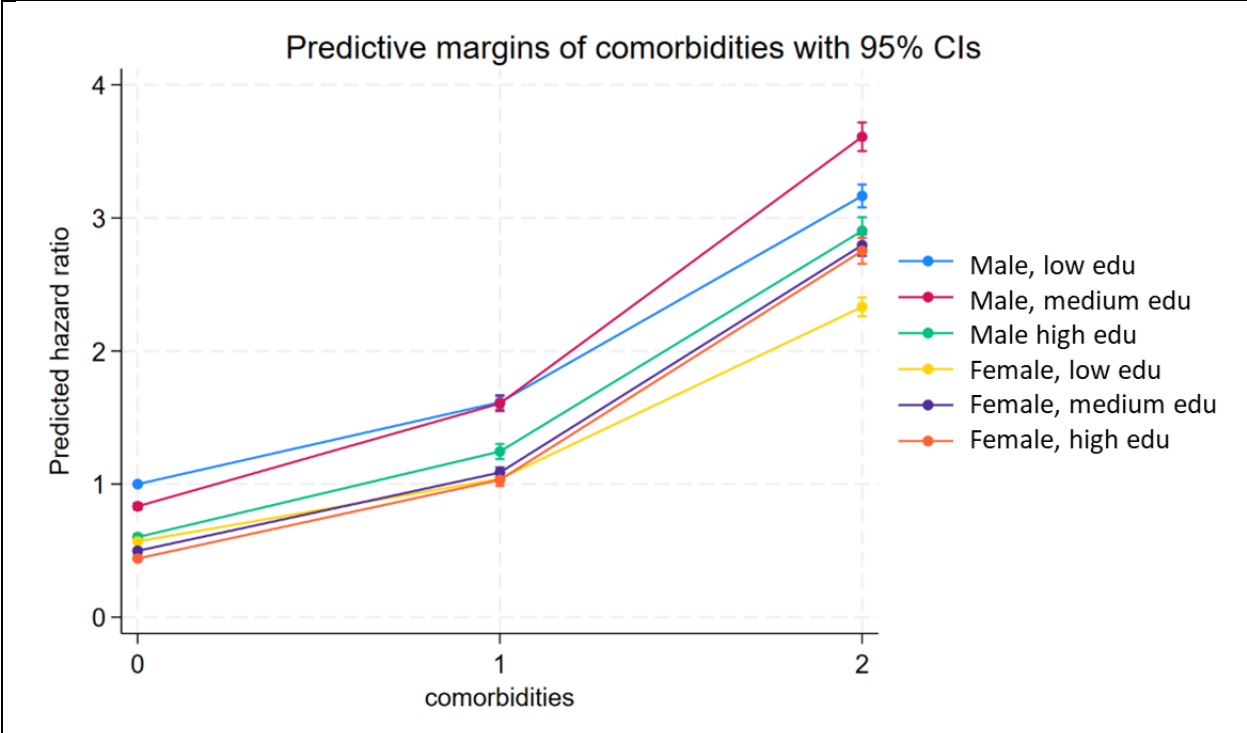


Fig. 4. Predictive margins of level of comorbidities, at different combinations of sex and education level for non-covid deaths, based on Cox regression model of risk of death in the pandemic period (2020-2021), non-covid deaths.

Finally, figure 5 depicts the interaction between comorbidity, education and sex for covid-related deaths during the pandemic, based on the results of the best fitting Cox model (whose results are reported in table A6 and A6b in SI). Even though the point estimates have high uncertainty, due to the small numbers of deaths from covid occurred in Denmark, an important change in the comorbidity-mortality pattern emerges. The pattern is strikingly different: the pre-existing comorbidity matters less, and all groups are more equally affected by covid-deaths. It is also important to notice how gender matters as, compared to the reference category (male, low education, healthy), women at all levels of education with 0 or 1 comorbidity had a significantly lower risk of death.

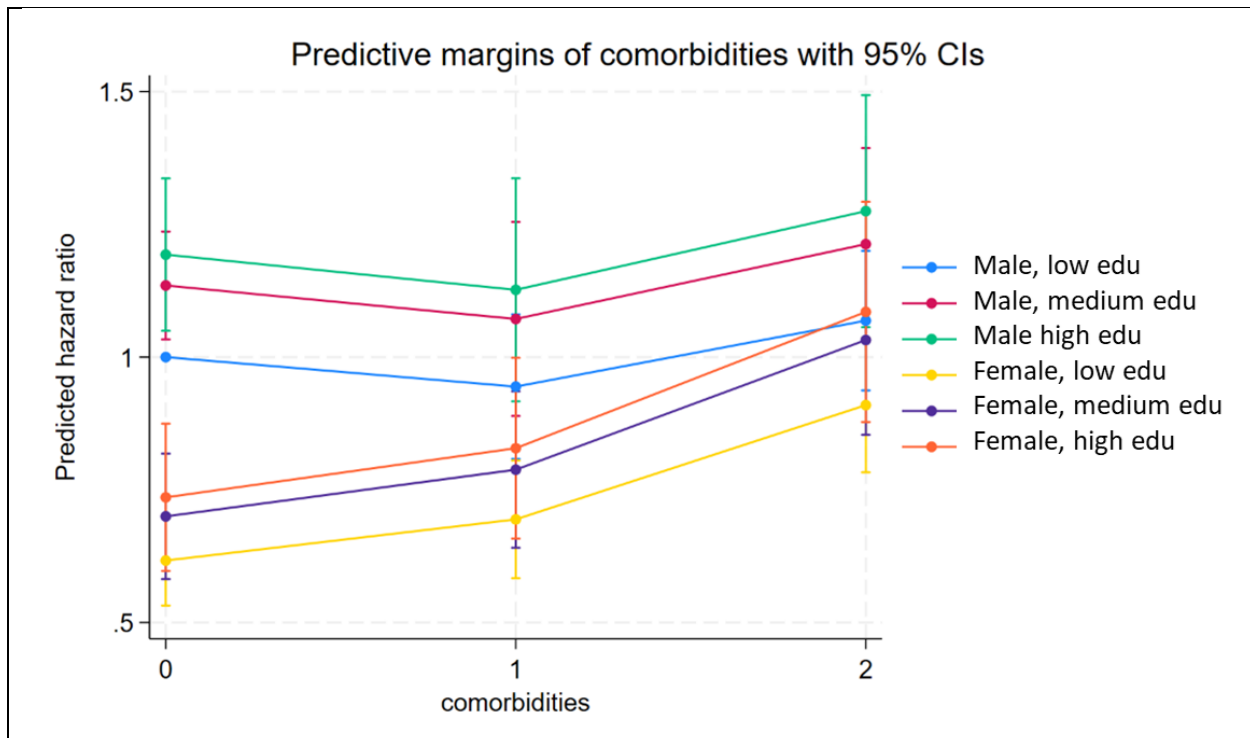


Fig. 5 Predictive margins of level of comorbidities, at different combinations of sex and education level for covid-deaths, based Cox regression model of risk of death in the pandemic period (2020-2021), covid deaths.

### Conclusions

Our analysis of mortality patterns in Denmark before and during the COVID-19 pandemic reveals several important findings regarding the interplay between comorbidities, sociodemographic factors, and COVID-19 mortality risk.

For non-COVID deaths during the pandemic, we observed a largely similar comorbidity-mortality pattern as in the pre-pandemic period. This suggests that the indirect effects of the pandemic did not substantially alter the relationship between pre-existing health conditions and mortality risk for causes other than COVID-19. However, one notable change was that the risk of non-COVID death for women with one comorbidity increased to a level comparable to that of lowly educated men without comorbidities. This may indicate that women with moderate health issues were more vulnerable to indirect pandemic effects, possibly due to disruptions in healthcare access or increased psychosocial stressors.

The most striking finding pertains to COVID-19 deaths, where we observed a significant shift in the comorbidity-mortality relationship. Contrary to expectations based on clinical studies of hospitalized patients, comorbidities appeared to play a less pronounced role in determining COVID-19 mortality risk across the entire population. All demographic and comorbidity groups were more equally affected by COVID-19 deaths than would be predicted based on pre-pandemic mortality patterns. This suggests that the virulence of SARS-CoV-2 may have partially overwhelmed the usual

protective effects of better health status, and this seems plausible particularly in the early stages of the pandemic before widespread vaccination.

Gender emerged as an important factor, with women of all education levels having significantly lower risk of COVID-19 death compared to men, even when accounting for comorbidity status. This aligns with global observations of higher COVID-19 mortality among men and suggests that biological sex differences may play a role in disease severity and outcomes.

The relative equalization of mortality risk across comorbidity groups for COVID-19 deaths has important implications for public health strategies. While protecting individuals with pre-existing conditions remains crucial, our findings suggest that pandemic mitigation efforts should target the entire population rather than focusing exclusively on those with known risk factors. The persistence of educational and gender disparities in COVID-19 mortality risk, even when accounting for comorbidities, also highlights the need for tailored interventions addressing social determinants of health [22, 23].

It is important to note that Denmark experienced low COVID-19 mortality compared to many other countries, likely due to early uptake of strong public health measures and a robust healthcare system [24, 25]. The generalizability of our findings may therefore be limited to countries with similar pandemic experiences and healthcare infrastructure. However, the fact that we detected these mortality patterns even in a country with relatively low impact underscores the profound effect of the pandemic on population health dynamics.

Our study has several limitations that warrant consideration. First, our classification of comorbidities relies on hospital discharge registries, potentially misclassifying individuals with chronic conditions managed exclusively in outpatient settings. However, this misclassification would be consistent across pre-pandemic and pandemic periods, minimizing the bias in our temporal comparisons. Second, our analysis considers the number of comorbidities rather than their severity or specific combinations, which may overlook nuanced relationships between certain health conditions and COVID-19 outcomes. Future studies incorporating more granular comorbidity data could provide additional insights.

Despite these limitations, our study has several strengths. The use of comprehensive, nationwide Danish registry data provides a uniquely complete picture of population-level mortality patterns. Unlike many COVID-19 studies focused solely on hospitalized patients, our inclusion of the entire adult population allows for a more holistic understanding of pandemic impacts across the health spectrum. The comparison of pre-pandemic and pandemic periods within the same population also provides valuable context for interpreting COVID-19 mortality patterns.

In conclusion, our findings reveal complex shifts in the relationship between comorbidities, sociodemographic factors, and mortality risk during the COVID-19 pandemic in Denmark. The relative equalization of COVID-19 mortality risk across comorbidity groups, combined with persistent educational and gender disparities, underscores the need for comprehensive public health approaches to pandemic preparedness and response.

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