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

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Introduction

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 [1-7]. 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 [8]. 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 [9, 10]. 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 [11]. A higher Charlson Comorbidity Index correlated with increased COVID related risks across age groups and genders [12]. 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 [13]. Cardiovascular comorbidities had a modest effect on poor outcomes compared to other conditions [14]. 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 [15, 16].

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 [17]. 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 [18].

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. In our analysis, we take a similar approach, considering the entire population, not just hospitalized individuals. Our goal is to investigate how comorbidities interacted with COVID-19 and whether the mortality risk for individuals with comorbidities changed during the pandemic. We will examine both pandemic waves, 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.

Data and methods

We utilize comprehensive, nationwide individual Danish registry data, provided by Statistics Denmark. 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). Our analysis is specifically focused on 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 in the five years leading up to the pandemic (2015-2019), ensuring the associations are relevant to our study. As first step, we have decided to focus on specific severe chronic conditions, derived from a review of the scientific literature: Autoimmune diseases, Cancer, Cardiopathies, Chronic Kidney Disease, Chronic Obstructive Pulmonary Diseases, Dementia (and Alzheimer), Diabetes (type I and II), Digestive Diseases, High Blood Lipids, HIV, Hypertension, Neurologic Diseases, Organ Transplant, and Vasculopathies. Based on the presence of those conditions, each individual is then classified depending on the number of comorbidities they have: none, one, two or more. We will further explore alternative classifications of comorbidities.

In this preliminary phase, we have examined mortality risks for individuals with and without comorbidities using Kaplan-Meir curves. Our goal is to assess whether the pandemic had varying effects on different comorbidity profiles. To strengthen the first explorative analysis, we will perform log-rank tests. Subsequently, we'll delve deeper into our analysis by estimating relative risks. Our initial choice is a Cox regression, driven by our focus on understanding risk disparities rather than the exact hazard function shape. Should model diagnostics reveal inadequacies like a violation of the proportionality assumption, we remain open to alternative modeling strategies such as stratification, interaction with the time variable, or parametric survival models.

To gain a more comprehensive understanding of the interplay between COVID-19 and comorbidities, we'll further investigate how the risks of mortality from COVID-19 and other causes of death differ between individuals with and without comorbidities. This analysis will utilize a competing risk model, allowing us to explore the relationship between different comorbidity profiles and the occurrence of two distinct types of death: from COVID-19 and from other causes. This choice is crucial because

during the COVID-19 pandemic, healthcare resources were redirected to the emergency, impacting the healthcare system's ability to address other health concerns. Neglecting the interplay between the risks of these two types of death could lead to biased estimates of cause-specific hazards, particularly for individuals with chronic conditions, who may be more susceptible to increased mortality not only from COVID-19 but also from other causes of death.

First results

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.

It's important to acknowledge the limitations of this preliminary analysis, primarily the limited number of COVID-19 deaths in certain age, sex, and comorbidity combinations within a relatively small country like Denmark that experienced a comparatively milder impact from the pandemic than many other nations. Despite these limitations, our findings hold promise in revealing intriguing, health-status-specific, age-specific, and gender-specific COVID-19 patterns.
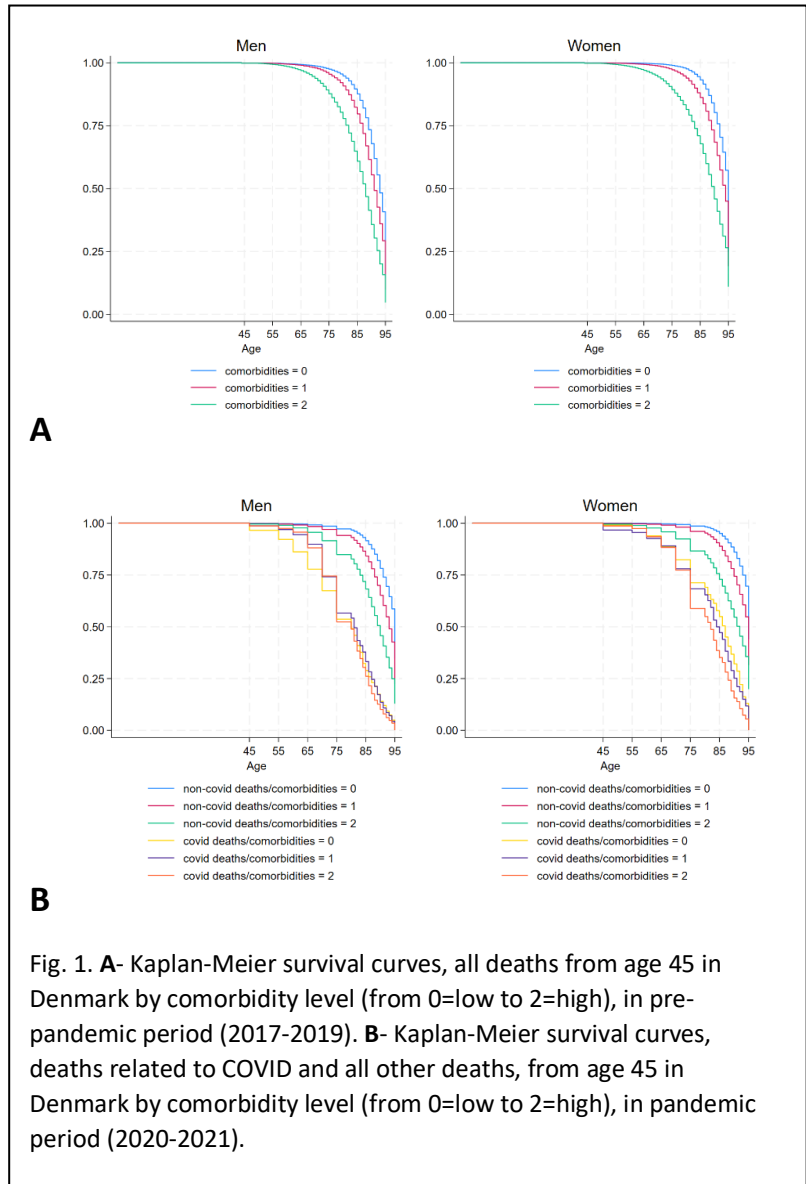

Fig. 1. **A**- Kaplan-Meier survival curves, all deaths from age 45 in Denmark by comorbidity level (from 0=low to 2=high), in pre-pandemic period (2017-2019). **B**- Kaplan-Meier survival curves, deaths related to COVID and all other deaths, from age 45 in Denmark by comorbidity level (from 0=low to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

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