

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Long-term mortality in young and middle-aged adults hospitalised with chronic disease: a Danish cohort study
AUTHORS	Skajaa, Nils; Ording, Anne Gulbech; Darvalics, Bianka; Horvath-Puho, Erzsebet; Sørensen, Henrik T. Toft

VERSION 1 – REVIEW

REVIEWER	Evangelos Kontopantelis University of Manchester UK
REVIEW RETURNED	23-Mar-2020

GENERAL COMMENTS	<p>The authors use National hospital data from Denmark to examine long-term mortality risk and years of life lost for those with chronic diseases (and multimorbidity) compared to persons from the general population. Overall this is good work and I will focus on methods and presentation.</p> <p>The abstract is well written and balanced. Two issues to consider. The immediate question mark that emerged when i read it was "the unaffected persons from the general population", and I was hoping that would become clearer later. The other issue is reporting results from analyses that are not previously mentioned (socio-economic analysis).</p> <p>The introduction is fine. Like i said regarding the abstract, the key issue for me is clarity on the "general population" and I don't think is provided. Do the author mean they are sampling from the whole population of Denmark, not hospitalised for one of the conditions of interest, or the whole hospitalised population, not hospitalised for one of the conditions of interest? If the former, which I think is what they imply, how did the linkage happen (i.e. how do they have survival data at the patient level for people not hospitalised? Is it though primary care data? do they cover the whole population?)</p> <p>Wouldn't cause-specific mortality rates (say from cardiovascular reasons) be of interest? there will be an issue with unmeasured confounding with all-cause deaths, with deprived populations having poorer health but dying because of deprivation primarily (i.e. alcohol, drugs etc) and not their poorer health.</p> <p>Deprivation changes little but it is a very long window this, to assume it is static at 2 years before baseline. So that's a pretty big limitation and i'd expect the role of deprivation to be somewhat</p>
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	<p>underestimated.</p> <p>is severity and/or years living with the conditions captured? probably not but be clear in terms of the limitations</p>
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REVIEWER	Yan Xie Clinical Epidemiology Center, Saint Louis VA health care system, U.S.
REVIEW RETURNED	01-Apr-2020

GENERAL COMMENTS	<p>In this study, Skajaa et al. used data from Denmark Civil Registration System and Danish National Patient Registry to estimate the association between number of morbidity and mortality. The research question is sound, and the results could be important. More detail about results and more careful interpretation of the results could help better understand and conclude the finding of the study.</p> <p>1\ The study focus on mortality difference in population with 0,1,2 and 3+ morbidities. Why the introduction only focus on multimorbidity? The authors could consider modifying the introduction to make it more related to the research question asked.</p> <p>2\ Please consider emphasis (in result, discussion, and abstract result section) that the number of morbidities in this study means primary or secondary hospitalization diagnosis. Morbidity associated with hospitalization could be much severe than morbidity in the community. Moreover, the occurrence of hospitalization itself is a predictor of death. It would be very important to make sure the results will not be misinterpreted.</p> <p>3\ Page 11, line 22 to 24. It is totally unclear how the authors interpreted the result and arrived at such conclusion. Please justify the conclusion, especially what is being compared and what is the definition of “largely similar”.</p> <p>4\ To give a better understanding of the data and the result, please provide 1-confidence interval for table 2, figure 1; 2-number of event along with event rate for each stratum in table 3; 3- the estimated life expectancy for general population and patient for each category in table 2.</p> <p>5\ Based on table 3, the unadjusted hazard of 3+ disease in year 0-1 is much lower than in 2 diseases in the age 30 group. Similarly, the adjusted hazard is not much different in the age 50 group during year 20-25. The finding is not concordant with the authors’ introduction and discussion, and should be explained. If this may due to low event rate and lack of power in the specific subgroup, treat the number of morbidity as spline instead of categorical variables could be considered.</p> <p>Minor points:</p> <p>1\ It is not clear to me how the hazard ratio transforms into MMR. If the MMR results are HRs, it may be better just report them as HRs.</p> <p>2\ Please clarify if the matching is based on age or date of birth.</p> <p>3\ page 8, line 40 to 47; how the regression was built is not clear.</p>
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	Please clarify does this means the regression was conditional on the matched paired and conducted separately in each morbidity subgroup?
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VERSION 1 – AUTHOR RESPONSE

REVIEWER 1

The authors use National hospital data from Denmark to examine long-term mortality risk and years of life lost for those with chronic diseases (and multimorbidity) compared to persons from the general population. Overall this is good work and I will focus on methods and presentation.

Response: We thank the Reviewer for the positive feedback on our work.

The abstract is well written and balanced. Two issues to consider. The immediate question mark that emerged when i read it was "the unaffected persons from the general population", and I was hoping that would become clearer later. The other issue is reporting results from analyses that are not previously mentioned (socio-economic analysis).

Response: We have changed the following in the Abstract, p. 2, l. 6-10:

“All patients hospitalised during the study period with one, two, or three or more chronic diseases and age- and sex-matched persons from the general population without chronic disease leading to hospitalisation: age-30 group, 13 857 patients and 69 285 comparators; age-40 group, 24 129 patients and 120 645 comparators; and age-50 group, 37 807 patients and 189 035 comparators.”

And p. 2, l. 11-14;

“25-year mortality risks based on Kaplan–Meier estimates, years-of-life-lost (YLLs), and mortality rate ratios based on Cox regression analysis. YLLs were computed for each morbidity level, as well as in strata of income, employment, education, and psychiatric conditions.”

Additionally, we have, throughout the manuscript, removed the word “unaffected” to describe the comparison cohort; instead, we describe this cohort as, “general population comparators without chronic disease”.

We hope these changes have enhanced the readability of the Abstract.

The introduction is fine. Like i said regarding the abstract, the key issue for me is clarity on the "general population" and I don't think is provided. Do the author mean they are sampling from the whole population of Denmark, not hospitalised for one of the conditions of interest, or the whole hospitalised population, not hospitalised for one of the conditions of interest? If the former, which I think is what they imply, how did the linkage happen (i.e. how do they have survival data at the patient level for people not hospitalised? Is it though primary care data? do they cover the whole population?)

Response: A unique 10-digit identifier is assigned to all Danish residents at birth or upon immigration. Records are kept and updated in the Danish Civil Registration System. Please see “*Schmidt M, Pedersen L, Sorensen HT. The Danish Civil Registration System as a tool in epidemiology. European journal of epidemiology 2014;29(8):541-49. doi: 10.1007/s10654-014-9930-3 [doi]*” for further reference.

The Reviewer is correct that we constructed the comparison cohorts by sampling from the entire Danish population. For each patient, we matched, with replacement, 5 persons from the general population on age and sex – comparators were ineligible if they were previously hospitalized for one of the conditions under study. Although not hospitalized, comparators are linkable at the individual-level through the unique

identifier created by the Civil Registration System. We agree that the Methods section lacks a description of the Civil Registration System. We have now added that, p. 6, l. 8-9:

“The CRS is updated daily concerning changes in vital status and migration for the entire Danish population.”

Wouldn't cause-specific mortality rates (say from cardiovascular reasons) be of interest? there will be an issue with unmeasured confounding with all-cause deaths, with deprived populations having poorer health but dying because of deprivation primarily (i.e. alcohol, drugs etc) and not their poorer health.

Response:

We agree that cause-specific mortality is of interest. We are currently planning another study taking this into account.

Deprivation changes little but it is a very long window this, to assume it is static at 2 years before baseline. So that's a pretty big limitation and i'd expect the role of deprivation to be somewhat underestimated.

Response: We thank the Reviewer for this important comment. We obtained data on socioeconomic factors two years before baseline to reduce any impact of early disease on socioeconomic status, that is, reverse causality. We agree that socioeconomic gradients are not static across the lifespan. For example, socioeconomic status differences are probably weaker during childhood and adolescence and greater during early adulthood and adulthood as factors (eg. smoking) contributing to disparities simultaneously grow. Nonetheless, we are not certain we fully understand why socioeconomic differences (deprivation) should be underestimated in this study as it is far from certain that differences would grow over the course of follow-up. Notwithstanding, the unadjusted relative risk estimates obtained in this study changed little when adjusting for socioeconomic factors.

Is severity and/or years living with the conditions captured? probably not but be clear in terms of the limitations

Response: Although severity is not directly measured, the number of morbidities probably serves as a proxy for severity. We agree with the Reviewer that our inability to capture years living with the conditions is a limitation. We have added the following to the Limitations section, p. 12, l. 16-18:

“It is possible that general population comparators were, in fact, living with chronic conditions not leading to hospitalization. This potential source of misclassification could have biased the HRs downwards.”

REVIEWER 2

Skajaa et al. used data from Denmark Civil Registration System and Danish National Patient Registry to estimate the association between number of morbidity and mortality. The research question is sound, and the results could be important. More detail about results and more careful interpretation of the results could help better understand and conclude the finding of the study.

Response: We thank the Reviewer for the careful review of our work.

The study focus on mortality difference in population with 0,1,2 and 3+ morbidities. Why the introduction only focus on multimorbidity? The authors could consider modifying the introduction to make it more related to the research question asked.

Response: We agree with the Reviewer that our study examined long-term outcomes in populations with both 0, 1, 2, and 3+ morbidities, i.e., not only those with multimorbidity. However, we believe the overarching topic of the paper is multimorbidity and its association with long-term outcomes, hence the focus on this topic in the Introduction and Discussion. In fact, the inclusion of populations with 0 and 1

morbidities serves as important reference groups. For these reasons, we prefer to keep the Introduction as displayed. If the Editors deem it necessary, we are of course willing to change it accordingly.

Please consider emphasis (in result, discussion, and abstract result section) that the number of morbidities in this study means primary or secondary hospitalization diagnosis. Morbidity associated with hospitalization could be much severe than morbidity in the community. Moreover, the occurrence of hospitalization itself is a predictor of death. It would be very important to make sure the results will not be misinterpreted.

Response: We agree that the inclusion of only hospitalized morbidities led to higher mortality risk estimates than would have been estimated had we included also outpatient or community morbidity. We described this limitation in the Limitations section of the Discussion, p. 12, l. 13-16:

“However, data on chronic and psychiatric conditions arose from inpatient hospitalisations and thus did not include conditions diagnosed and treated in the outpatient setting, including by general practitioners. Presumably, this selection yielded higher mortality risk estimates than would have resulted with inclusion of outpatient diagnoses.”

Moreover, we have added further emphasis on this selection in the Results sections of the Abstract, p. 2, l. 15-16:

“25-year mortality risks and YLLs increased steadily with increasing baseline number of morbidities leading to hospitalisation and age, but the mortality risk difference compared with persons from the general population remained approximately constant across age cohorts.”

Results in the main text, p. 10, l. 4-5:

“The 25-year mortality risk increased steadily with increasing baseline number of morbidities leading to hospitalisation and age (Figure 1)”

And in the Discussion, p. 12, l. 5-7:

“In this nationwide, population-based cohort study comprising patients age 30, 40, and 50 years, the 25-year mortality risk grew with increasing number of morbidities leading to hospitalisation and with age.”

Page 11, line 22 to 24. It is totally unclear how the authors interpreted the result and arrived at such conclusion. Please justify the conclusion, especially what is being compared and what is the definition of “largely similar”.

Response: We agree with the Reviewer that this description was not entirely clear. In fact, HRs tended to decrease with baseline age. Adjustment for socioeconomic factors did not change the associations materially. We have attempted to describe these issues clearer now, p. 11, l. 21-22 and p. 12, l. 1:

“HRs tended to decrease with increasing baseline age, irrespective of number of morbidities and follow-up period. Adjustment for socioeconomic factors did not change the unadjusted estimates materially”

To give a better understanding of the data and the result, please provide 1-confidence interval for table 2, figure 1; 2-number of event along with event rate for each stratum in table 3; 3- the estimated life expectancy for general population and patient for each category in table 2.

Response: We thank the Reviewer for this suggestion to improve the readability of the tables. We now provide the estimated life expectancies with corresponding confidence intervals for both cohorts in table 2, numbers of events and person-years in table 3. It was not possible to calculate confidence intervals for the estimated years of life lost. We include the updated tables here for reference.

Table 2. Expected years of life (EYL) and EYL lost during 25 years of follow-up for patients with one or more chronic diseases leading to hospitalisation by age 30, 40, or 50 years and age- and sex-matched individuals from the general population without chronic disease, by number of conditions and by socioeconomic factors and psychiatric conditions, overall and by number of chronic diseases.

	Age 30 years		EYL lost	Age 40 years		EYL lost	Age 50 years		
	EYL in patients (95% CI)	EYL in general population (95% CI)		EYL in patients (95% CI)	EYL in general population (95% CI)		EYL in patients (95% CI)	EYL in general population (95% CI)	EYL lost
Morbidity									
One disease	22.75 (22.63-22.87)	24.46 (24.44-24.49)	1.7	20.89 (20.77-21.00)	23.85 (23.82-23.88)	3.0	17.59 (17.48-17.70)	22.21 (22.17-22.24)	4.6
Two diseases	19.31 (18.79-19.87)	24.47 (24.39-24.55)	5.2	16.24 (15.79-16.69)	23.77 (23.68-23.86)	7.5	12.82 (12.52-13.14)	22.15 (22.06-22.24)	9.3
Three or more diseases	13.70 (12.33-16.24)	24.12 (24.06-24.63)	10.4	11.57 (10.38-12.80)	23.75 (23.58-24.05)	12.2	8.77 (8.17-9.40)	22.18 (21.98-22.36)	13.4
Income									
Low	21.28 (21.03-21.51)	24.18 (24.11-24.24)	2.9	19.01 (18.79-19.22)	23.50 (23.44-23.56)	4.5	15.15 (14.96-15.34)	21.60 (21.52-21.67)	6.4
Intermediate	22.73 (22.55-23.00)	24.49 (24.45-24.55)	1.8	20.48 (20.26-20.70)	23.84 (23.78-23.89)	3.4	17.17 (16.96-17.38)	22.37 (22.30-22.43)	5.2
High	22.82 (22.60-23.06)	24.55 (24.50-24.59)	1.7	21.12 (20.88-21.35)	23.93 (23.88-23.98)	2.8	17.67 (17.45-17.89)	22.15 (22.09-22.21)	4.4
Very high	23.03 (22.89-23.36)	24.61 (24.57-24.65)	1.6	21.65 (21.41-21.88)	24.09 (24.04-24.14)	2.4	18.19 (17.95-18.43)	22.61 (22.56-22.67)	4.4
Employment									
Early retirement	19.87 (19.49-	23.68 (23.54-	3.8	17.68 (17.39-	22.61 (22.48-	4.9	14.42 (17.92-	20.70 (20.60-	6.3

	20.28)	23.84)		17.96)	22.74)		18.18)	20.81)	
Unemployed	22.59 (22.24- 22.90)	24.18 (24.09- 24.28)	1.6	19.70 (19.34- 20.21)	23.09 (22.94- 23.23)	3.4	16.63 (16.15- 17.11)	20.98 (20.82- 21.14)	4.3
Employed	22.95 (22.82- 23.08)	24.57 (24.55- 24.60)	1.6	21.24 (21.11- 21.36)	24.01 (23.99- 24.04)	2.8	18.05 (17.92- 18.18)	22.53 (22.49- 22.56)	4.5
Education									
Primary school	21.92 (21.75- 22.15)	24.29 (24.24- 24.34)	2.4	19.98 (19.80- 20.16)	23.58 (23.53- 23.63)	3.6	16.61 (16.47- 16.76)	21.98 (21.94- 22.03)	5.4
Youth education/high school	22.57 (22.38- 22.75)	24.53 (24.50- 24.57)	2.0	20.53 (20.35- 20.71)	23.93 (23.89- 23.97)	3.4	16.85 (16.67- 17.04)	22.27 (22.22- 22.33)	5.4
Higher education	23.35 (23.11- 23.60)	24.72 (24.68- 24.77)	1.4	21.36 (21.15- 21.68)	24.21 (24.16- 24.26)	2.9	18.09 (17.76- 18.41)	22.96 (22.89- 23.03)	4.9
Psychiatric conditions									
Schizophrenia	18.07 (15.80- 19.82)	21.71 (20.76- 22.47)	3.6	16.94 (15.57- 18.39)	20.41 (19.69- 21.04)	3.5	12.32 (11.08- 13.53)	18.42 (17.81- 19.01)	6.1
Bipolar disorder, depression, and recurrent depression	20.35 (18.58- 21.69)	22.85 (22.29- 23.61)	2.5	18.00 (17.05- 18.84)	21.37 (20.93- 21.84)	3.4	14.43 (13.78- 15.08)	20.00 (19.65- 20.33)	5.6
Schizotypal disorder	19.13 (16.12- 21.50)	21.28 (19.51- 22.48)	2.2	18.43 (15.62- 20.48)	20.51 (19.16- 21.55)	2.1	13.94 (10.25- 17.44)	19.02 (17.29- 20.60)	5.1
Personality disorders	19.38 (18.68- 20.07)	22.54 (22.37- 23.06)	3.2	17.86 (17.40- 18.28)	21.51 (21.28- 21.81)	3.7	14.63 (14.25- 15.01)	19.63 (19.40- 19.86)	5.0
Other mental illness	18.72 (18.21- 19.24)	22.21 (21.90- 22.51)	3.5	16.42 (16.05- 16.77)	20.41 (20.15- 20.69)	4.0	13.01 (12.71- 13.31)	18.01 (17.78- 18.24)	5.0

One disease	Income									
	Low	21.79 (21.54-22.03)	24.17 (24.11-24.24)	2.4	19.77 (19.55-19.99)	23.51 (23.44-23.57)	3.7	16.19 (15.98-16.40)	21.61 (21.53-21.69)	5.4
	Intermediate	23.05 (22.88-23.32)	24.49 (24.45-24.55)	1.4	20.99 (20.77-21.20)	23.84 (23.79-23.90)	2.9	17.93 (17.72-18.15)	22.39 (22.32-22.45)	4.5
	High	23.15 (22.94-23.39)	24.55 (24.50-24.59)	1.4	21.53 (21.29-21.75)	23.93 (23.88-23.98)	2.4	18.31 (18.08-18.54)	22.16 (22.09-22.23)	3.9
	Very high	23.26 (23.13-23.59)	24.6 (24.57-24.65)	1.3	22 (21.77-22.24)	24.1 (24.05-24.14)	2.1	18.74 (18.49-18.99)	22.6 (22.54-22.66)	3.9
	Employment									
	Early retirement	20.52 (20.13-20.94)	23.66 (23.51-23.82)	3.1	21.66 (21.53-21.78)	24.02 (23.99-24.05)	4.0	18.64 (18.51-18.78)	22.53 (22.49-22.56)	5.2
	Unemployed	22.77 (22.42-23.08)	24.16 (24.07-24.27)	1.4	19.99 (19.62-20.52)	23.1 (22.94-23.25)	3.1	17.1 (16.60-17.60)	21.03 (20.85-21.20)	3.9
	Employed	23.26 (23.13-23.38)	24.57 (24.55-24.60)	1.3	18.6 (18.29-18.90)	22.63 (22.48-22.77)	2.4	15.51 (15.29-15.73)	20.72 (20.61-20.84)	3.9
	Education									
	Primary school	22.29 (22.12-22.52)	24.28 (24.23-24.33)	2.0	20.57 (20.39-20.75)	23.59 (23.54-23.64)	3.0	17.44 (17.29-17.59)	21.99 (21.94-22.04)	4.6
	Youth education, high school	22.97 (22.79-23.15)	24.53 (24.50-24.57)	1.6	21.07 (20.89-21.25)	23.93 (23.90-23.98)	2.9	17.67 (17.47-17.87)	22.28 (22.23-22.34)	4.6
	Higher education	23.65 (23.42-	24.66 (24.68-24.77)	1.0	21.83 (21.62-	24.21 (24.15-24.26)	2.4	18.88 (18.54-	22.95 (22.87-23.03)	4.1

	23.89)			22.15)			19.20)			
	Psychiatric conditions									
	Schizophrenia	18.17 (15.79- 19.98)	21.83 (20.83- 22.61)	3.7	17.69 (16.24- 19.19)	20.25 (19.47- 20.92)	2.6	13.02 (11.65- 14.34)	18.43 (17.77- 19.06)	5.4
	Bipolar disorder, depression, and recurrent depression	20.6 (18.74- 21.96)	22.93 (22.32- 23.71)	2.3	18.82 (17.80- 19.69)	21.37 (20.90- 21.87)	2.6	15.42 (14.69- 16.14)	19.98 (19.60- 20.34)	4.6
	Schizotypal disorder	19.91 (16.72- 22.23)	21.22 (19.36- 22.47)	1.3	19.43 (16.52- 21.39)	20.56 (19.06- 21.68)	1.1	13.48 (9.63- 17.77)	18.97 (17.05- 20.65)	5.5
	Personality disorders	19.62 (18.86- 20.34)	22.55 (22.37- 23.09)	2.9	18.41 (17.93- 18.86)	21.47 (21.23- 21.79)	3.1	15.41 (14.99- 15.82)	19.62 (19.37- 19.87)	4.2
	Other mental illness	19.21 (18.67- 19.76)	22.19 (21.86- 22.51)	3.0	17.16 (16.77- 17.54)	20.44 (20.16- 20.74)	3.3	13.95 (13.61- 14.29)	18.04 (17.78- 18.29)	4.09
	Income									
	Low	17.91 (16.97- 18.87)	24.16 (23.93- 24.35)	6.2	14.98 (14.25- 15.68)	23.36 (23.14- 23.57)	8.4	11.66 (11.19- 12.15)	21.52 (21.31- 21.73)	9.86
	Intermediate	19.43 (18.53- 20.73)	24.5 (24.33- 24.64)	5.1	15.99 (15.05- 16.87)	23.76 (23.57- 23.93)	7.8	13.07 (12.43- 13.71)	22.23 (22.05- 22.41)	9.16
	High	19.93 (18.78- 20.95)	24.46 (24.35- 24.64)	4.5	17.29 (16.33- 18.37)	23.94 (23.77- 24.10)	6.7	13.69 (12.96- 14.42)	22.04 (21.86- 22.21)	8.34
	Very high	20.56 (19.30- 21.71)	24.63 (24.48- 24.75)	4.1	18.23 (17.21- 19.36)	23.95 (23.85- 24.16)	5.7	14.67 (13.91- 15.53)	22.65 (22.51- 22.82)	7.97
	Employment									
	Early retirement	17.05	23.63 (23.22- 24.04)	6.6	17.43	23.97 (23.88- 24.06)	8.4	14.2 (13.77- 14.63)	22.5 (22.41- 22.59)	9.25

Two diseases

	(15.80-18.24)	24.21		(16.87-17.98)	24.06		14.64	22.59	
Unemployed	19.94 (18.15-21.69)	24.26 (23.89-24.50)	4.3	15.89 (13.98-17.73)	22.84 (22.36-23.35)	7.0	12.91 (11.25-14.54)	20.56 (20.06-21.02)	7.65
Employed	20.08 (19.46-20.71)	24.56 (24.48-24.64)	4.5	13.99 (13.15-14.80)	22.38 (21.90-22.83)	6.5	11.36 (10.90-11.83)	20.61 (20.30-20.91)	8.30
Education									
Primary school	18.83 (17.97-19.71)	24.34 (24.17-24.48)	5.5	15.5 (14.77-16.19)	23.47 (23.31-23.65)	8.0	12.84 (12.43-13.26)	21.9 (21.78-22.04)	9.07
Youth education, high school	19.62 (18.78-20.43)	24.49 (24.37-24.61)	4.9	16.83 (16.11-17.50)	23.86 (23.72-23.98)	7.0	12.97 (12.42-13.54)	22.19 (22.04-22.35)	9.22
Higher education	20.7 (19.33-21.93)	24.74 (24.57-24.84)	4.0	17.39 (16.32-18.57)	24.22 (24.05-24.37)	6.8	13.36 (12.28-14.41)	23.05 (22.85-23.24)	9.69
Psychiatric conditions									
Schizophrenia	14.09 (6.15-21.65)	19.69 (15.37-22.37)	5.6	9.73 (6.51-15.04)	20.91 (18.68-22.69)	11.2	9.37 (6.35-12.67)	18.3 (16.25-19.92)	8.94
Bipolar disorder, depression, and recurrent depression	16.69 (9.40-22.35)	19.33 (17.49-23.57)	2.6	13.47 (10.82-15.95)	21.12 (19.44-22.52)	7.7	11.6 (10.05-13.21)	19.82 (18.71-20.72)	8.22
Schizotypal disorder	8.94 (1.52-19.14)	20.3 (9.69-23.98)	11.4	3.68 (1.02-14.88)	19.41 (15.30-22.19)	15.7	12.92 (4.46-19.61)	15.23 (10.56-21.36)	2.31
Personality disorders	17.55 (15.41-19.76)	21.65 (20.56-23.20)	4.1	14.64 (13.31-15.95)	21.69 (20.81-22.51)	7.1	12.13 (11.17-13.07)	19.72 (19.04-20.32)	7.59
Other mental illness	15.75 (14.30-17.54)	21.76 (20.69-22.96)	6.0	13.04 (12.08-14.05)	20.08 (19.14-20.90)	7.0	10.67 (9.99-11.35)	17.8 (17.13-18.43)	7.13

Three or more diseases	Income									
	Low	12.26 (10.00-15.53)	23.76 (23.12-24.60)	11.5	10.56 (9.16-12.21)	23.31 (22.72-23.98)	12.7	7.85 (7.09-8.69)	21.22 (20.76-21.79)	13.4
	Intermediate	15.07 (11.54-19.34)	23.05 (23.38-24.76)	8.0	14.03 (11.17-16.57)	23.42 (22.97-24.06)	9.4	9.16 (7.79-10.57)	22.11 (21.67-22.49)	13.0
	High	13.07 (7.76-18.13)	15.88 (23.72-24.92)	2.8	10.48 (7.50-14.60)	23.81 (23.32-24.26)	13.3	10.22 (8.54-11.90)	22.17 (21.78-22.52)	12.0
	Very high	11.19 (7.37-19.95)	23.76 (22.96-24.53)	12.6	9.95 (6.30-14.63)	23.86 (23.55-24.35)	13.9	9.95 (8.11-12.07)	22.68 (22.37-23.00)	12.7
	Employment									
	Early retirement	11.43 (8.90-14.76)	23.18 (19.98-24.58)	7.3	12.08 (10.80-14.71)	23.89 (23.71-24.19)	10.9	10.16 (9.11-11.23)	22.51 (22.30-22.70)	12.2
	Unemployed	11.73 (8.64-21.78)	22.38 (21.79-24.54)	4.7	14.85 (6.93-20.58)	22.86 (21.17-23.93)	8.0	7.63 (4.32-12.84)	21.08 (19.92-22.02)	13.5
	Employed	14.67 (12.62-18.26)	24.19 (24.09-24.71)	5.0	10.57 (9.09-12.21)	21.46 (20.73-23.56)	11.8	8 (7.27-8.80)	20.21 (19.53-21.00)	12.3
	Education									
	Primary school	13.89 (11.07-17.45)	23.71 (23.31-24.51)	9.8	11.9 (10.21-13.57)	23.69 (23.26-24.12)	11.8	8.87 (8.06-9.71)	21.96 (21.66-22.24)	13.1
	Youth education, high school	12.79 (10.62-16.52)	24.26 (23.93-24.80)	11.5	11.09 (9.21-13.20)	23.55 (23.34-24.09)	12.5	8.84 (7.81-9.95)	22.26 (21.92-22.57)	13.4
	Higher education	13.92 (8.89-18.94)	21.42 (22.93-24.75)	7.5	12.59 (8.09-17.06)	23.87 (23.35-24.39)	11.3	8.95 (6.58-11.40)	22.6 (22.19-23.14)	13.6
Psychiatric conditions										
Schizophrenia	0 (0.00-	8.71 (0.15-	8.7	5.47 (0.35-	12.32 (6.01-	6.9	5.16 (1.99-	15.68 (10.17-	10.5	

	0.00)	22.76)		9.26)	23.63)		9.25)	19.46)	
Bipolar disorder, depression and recurrent depression	2.36 (0.36-19.86)	9.13 (3.20-24.01)	6.8	11.64 (5.91-18.44)	15.28 (11.00-22.45)	3.6	6.42 (4.46-8.95)	20.07 (18.01-22.26)	13.7
Schizotypal disorder	1.44 (0.02-2.63)	0 (0.00-0.00)	-1.44	0 (0.00-0.00)	7.42 (0.09-13.51)	7.4	0 (0.00-0.00)	0 (25.00-25.00)	0.00
Personality disorders	12.62 (6.99-19.85)	0 (25.00-25.00)	-12.6	13.21 (9.96-16.32)	21.21 (18.69-22.83)	8.0	9.09 (7.47-10.80)	18.64 (17.39-20.47)	9.6
Other mental illness	10.04 (6.03-15.11)	22.79 (16.34-24.64)	12.7	10.84 (8.74-12.88)	19.81 (17.15-21.70)	9.0	7.87 (6.88-8.94)	17.73 (16.26-19.15)	9.9

*Years of life lost were calculated as the difference in the area between the mean Kaplan–Meier survival curve in the patient and the general population cohorts.

Table 3. Hazard ratios comparing patients with one or more chronic diseases by age 30, 40, or 50 years with age- and sex-matched individuals from the general population without chronic diseases, by follow-up time and number of chronic diseases.

	Age 30 years				Age 40 years				Age 50 years				
	Morbidity	Deaths, N	PYs	Unadjusted	Adjusted*	Deaths, N	PYs	Unadjusted	Adjusted*	Deaths, N	PYs	Unadjusted	Adjusted*
0-1 yrs	1 disease	128	12383.0	17.28 (11.98–24.91)	16.97 (10.75–26.80)	334	21325.6	11.83 (9.72–14.41)	10.71 (8.63–13.30)	931	31524.8	11.30 (10.06–12.69)	10.11 (8.94–11.43)
	2 diseases	51	1244.4	127.50 (31.04–523.70)	Could not be estimated	127	2220.4	37.19 (22.42–61.70)	44.12 (22.92–84.92)	361	4599.4	26.13 (20.20–33.81)	23.45 (17.59–31.27)
	3+ diseases	< 5	< 5	20.00 (2.24–178.94)	Could not be estimated	33	305.0	41.25 (14.61–116.43)	92.15 (8.93–950.88)	122	927.2	87.14 (40.68–186.64)	83.08 (25.85–267.01)
>1-5 yrs	1 disease	342	48421.8	6.29 (5.36–7.38)	5.60 (4.72–6.65)	1139	82228.0	6.74 (6.17–7.37)	5.92 (5.39–6.50)	3063	11794.9.6	4.93 (4.69–5.18)	4.31 (4.10–4.55)
	2 diseases	86	4709.2	35.38 (19.34–64.73)	37.76 (16.91–84.35)	305	8015.4	15.58 (12.40–19.58)	14.40 (11.15–18.59)	905	15799.0	10.89 (9.69–12.24)	9.05 (7.98–10.25)
	3+ diseases	22	427.0	109.03 (14.70–808.93)	Could not be estimated	67	1012.6	41.42 (19.90–86.22)	35.32 (12.69–98.25)	278	2879.2	19.06 (14.71–24.71)	15.46 (11.28–21.20)
>5-10 yrs	1 disease	387	58547.8	4.45 (3.88–5.11)	3.87 (3.34–4.48)	1240	96611.8	3.95 (3.67–4.26)	3.36 (3.11–3.64)	3596	13089.3.8	3.27 (3.14–3.41)	2.87 (2.74–3.00)
	2 disease	103	5392.0	12.34 (8.59–)	12.58 (8.29–)	292	8552.0	10.18 (8.32–)	8.55 (6.88–)	880	15298.0	7.01 (6.32–)	5.80 (5.18–)

	s		4	17.72)	19.09)		2	12.46)	10.63)		.8	7.78)	6.49)
	3+ disease s	19	427.0	23.54 (8.01– 69.19)	56.10 (5.74– 548.64)	71	927.2	21.66 (12.59– 37.26)	13.74 (7.12– 26.52)	233	2330. 2	11.23 (8.88– 14.19)	8.45 (6.38– 11.19)
>10–20 yrs	1 disease	894	11044 6.6	2.99 (2.75– 3.26)	2.60 (2.38– 2.84)	2906	17272 7.6	2.77 (2.65– 2.90)	2.41 (2.29– 2.53)	7433	20650 9.4	2.30 (2.24– 2.37)	2.08 (2.02– 2.14)
	2 disease s	191	9272. 0	6.60 (5.30– 8.22)	6.16 (4.86– 7.81)	444	13322 .4	5.37 (4.69– 6.16)	4.52 (3.90– 5.23)	1221	19800 .6	4.00 (3.70– 4.32)	3.28 (3.02– 3.57)
	3+ disease s	33	585.6	17.25 (8.25– 36.07)	14.54 (6.54– 32.35)	68	1171. 2	10.70 (6.96– 16.44)	13.05 (6.62– 25.70)	244	2159. 4	8.02 (6.49– 9.91)	6.53 (5.16– 8.28)
>20–25 yrs	1 disease	645	51069 .2	2.77 (2.51– 3.05)	2.53 (2.28– 2.80)	1736	74334 .6	2.24 (2.12– 2.38)	2.00 (1.89– 2.13)	3700	75054 .4	1.84 (1.77– 1.91)	1.73 (1.66– 1.81)
	2 disease s	89	3928. 4	5.12 (3.78– 6.92)	4.37 (3.15– 6.06)	200	5063. 0	4.33 (3.56– 5.27)	3.86 (3.13– 4.75)	417	5978. 0	2.54 (2.24– 2.88)	2.29 (2.00– 2.61)
	3+ disease s	5	195.2	3.82 (1.16– 12.55)	4.72 (0.93– 24.04)	26	341.6	16.12 (6.98– 37.21)	9.29 (2.99– 28.91)	43	475.8	2.98 (1.98– 4.48)	2.04 (1.27– 3.27)

Abbreviation: PY, person-years. *Adjusted for socioeconomic factors (income level, employment status, education level)

Based on table 3, the unadjusted hazard of 3+ disease in year 0-1 is much lower than in 2 diseases in the age 30 group. Similarly, the adjusted hazard is not much different in the age 50 group during year 20-25. The finding is not concordant with the authors' introduction and discussion, and should be explained. If this may due to low event rate and lack of power in the specific subgroup, treat the number of morbidity as spline instead of categorical variables could be considered.

Response: The main conclusions of this study is that the 25-year mortality risks grew with increasing number of morbidities; the mortality risk difference with people from the general population without chronic disease also generally increased with increasing morbidity. It is correct that for some of the specific subgroups, e.g. those highlighted by the Reviewer, the relative risk estimates, that is, the hazard ratios comparing the patient cohorts with the general population, deviated slightly from the overall conclusions. However, as the Reviewer points out, for these subgroups, few events rates led to imprecise estimates. Hence, we do not believe that the specific results for these subgroups warrant further explanation in the main text. In fact, we have focused on the absolute mortality risks more so than the relative mortality risks.

It is not clear to me how the hazard ratio transforms into MMR. If the MMR results are HRs, it may be better just report them as HRs.

Response: We have changed all MMRs to HRs.

Please clarify if the matching is based on age or date of birth.

Response: The matching was based on date of birth. We have revised accordingly.

Page 8, line 40 to 47; how the regression was built is not clear. Please clarify does this means the regression was conditional on the matched paired and conducted separately in each morbidity subgroup?

Response: The regression was stratified Cox regression with the matched pairs being the stratas. The regression was then done separately for each morbidity subgroup. We have clarified in the statistical analyses (p. 8, l. 17-21):

“As a measure of the mortality rate ratio, we computed hazard ratios (HRs) of death and 95% confidence intervals (CIs) by means of stratified Cox proportional hazards regression within the sex- and age-matched strata, comparing the patient cohorts with the general population comparison cohorts. The regression was done separately in each morbidity subgroup.”

VERSION 2 – REVIEW

REVIEWER	Evangelos Kontopantelis University of Manchester UK
REVIEW RETURNED	15-Jul-2020

GENERAL COMMENTS	I am happy with the authors' responses and I don't have anything else to add
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REVIEWER	Yan Xie Clinical Epidemiology Center, VA Saint Louis Health Care System, USA
REVIEW RETURNED	09-Jul-2020

GENERAL COMMENTS	I appreciated the authors carefully considered and addressed my comments. Here I have a few additional comments hope could
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	<p>further help.</p> <p>1\ Difference in years of life lost (YLL) is one of the main outcomes of this paper, a confidence interval or uncertainty interval will better support the comparison and interpretation of the result. Ideally, CI could be estimated based on bootstrapping the cohort population before matching. If that is not flexible, authors could consider conduct bootstrapping on the matched pair to obtain the CI for YLL.</p> <p>2\ Results based on event number of 5, 26 etc. may not provide meaning information. Please consider removing the result from subgroups where the event number is too low.</p> <p>Minor:</p> <p>1\ Please verify the result in table 2 for psychiatric conditions in three or more diseases subgroup. What is the interpretation of the year of life lost as 0 (0, 0) / 0 (25, 25) ?</p> <p>2\ Also for table 2, Table legend may be needed to ensure readers will be clear that this is the estimated year of life in 25 years. Or an alternative may be showing the YLL in each subgroup based on 25-EYL instead. (so that result will not be misinterpreted in a way that life expectancy in the general population with age 30 is only 30+24 years).</p>
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VERSION 2 – AUTHOR RESPONSE

REVIEWER 1

I am happy with the authors' responses and I don't have anything else to add.

Response: Thank you.

REVIEWER 2

Difference in years of life lost (YLL) is one of the main outcomes of this paper, a confidence interval or uncertainty interval will better support the comparison and interpretation of the result. Ideally, CI could be estimated based on bootstrapping the cohort population before matching. If that is not flexible, authors could consider conduct bootstrapping on the matched pair to obtain the CI for YLL.

Response: We agree with and thank the Reviewer for this suggestion. We now include CIs for the YLLs implementing the Reviewer's suggestion to do bootstrapping on the matched pairs.

In the Methods section, we now state (p. 8, l. 16-17):

“95% confidence intervals (CIs) were computed using bootstrapping on each of the matched pairs using 100 replicates.”

Accordingly, we have added CIs in text where applicable and in Table 2.

Results based on event number of 5, 26 etc. may not provide meaning information. Please consider removing the result from subgroups where the event number is too low.

Response: In line with Danish legislation, we do not provide counts on less than 5. We agree with the Reviewer that hazard ratios from these subgroups should be removed. We have done so, stating that the hazard ratio “could not be estimated”.

Please verify the result in table 2 for psychiatric conditions in three or more diseases subgroup. What is the interpretation of the year of life lost as 0 (0, 0) / 0 (25, 25) ?

Response:We removed this result stating that the estimate could not be meaningfully obtained.

Also for table 2, Table legend may be needed to ensure readers will be clear that this is the estimated year of life in 25 years. Or an alternative may be showing the YLL in each subgroup based on 25-EYL instead. (so that result will not be misinterpreted in a way that life expectancy in the general population with age 30 is only 30+24 years).

Response:We agree. We have revised the table legend for improved interpretability. We attach the table here for reference.

Table 2. Expected years of life (EYL) and EYL lost during 25 years of follow-up for patients with one or more chronic diseases leading to hospitalisation by age 30, 40, or 50 years and age- and sex-matched individuals from the general population without chronic disease, by number of conditions and by socioeconomic factors and psychiatric conditions, overall and by number of chronic diseases.
*Years of life lost were calculated as the difference in the area between the mean Kaplan–Meier survival curve in the patient and the general population cohorts.

	Age 30 years			Age 40 years			Age 50 years		
	25-year EYL (95% CI)			25-year EYL (95% CI)			25-year EYL (95% CI)		
	Patient s	General populat ion	Differen ce (EYL lost)	Patient s	General populatio n	Differen ce (EYL lost)	Patient s	General populatio n	Differen ce (EYL lost)
Morbidity									
One disease	22.8 (22.6- 22.9)	24.5 (24.4- 24.5)	1.7 (1.6- 1.8)	20.9 (20.8- 21.0)	23.9 (23.8- 23.9)	3.0 (2.9- 3.1)	17.6 (17.5- 17.7)	22.2 (22.17- 22.24)	4.6 (4.5- 4.7)
Two diseases	19.3 (18.8- 19.8)	24.5 (24.4- 24.6)	5.2 (4.7- 5.6)	16.2 (15.8- 16.7)	23.8 (23.7- 23.9)	7.5 (7.2- 7.9)	12.8 (12.5- 13.1)	22.2 (22.1- 22.2)	9.3 (9.1- 9.6)

	Three or more diseases	13.7 (12.3-16.2)	24.1 (24.1-24.6)	10.4 (8.7-12.1)	11.6 (10.4-12.8)	23.8 (23.6-24.1)	12.2 (11.2-13.1)	8.8 (8.2-9.4)	22.2 (22.0-22.4)	13.4 (12.9-13.9)
Income										
	Low	21.3 (21.0-21.5)	24.2 (24.1-24.2)	2.9 (2.7-3.1)	19.0 (18.8-19.2)	23.5 (23.4-23.6)	4.5 (4.3-4.7)	15.2 (15.0-15.3)	21.6 (21.5-21.7)	6.4 (6.3-6.6)
	Intermediate	22.7 (22.6-23.0)	24.5 (24.5-24.6)	1.8 (1.6-2.0)	20.5 (20.3-20.7)	23.8 (23.8-23.9)	3.4 (3.2-3.5)	17.2 (17.0-17.4)	22.4 (22.3-22.4)	5.2 (5.0-5.4)
	High	22.8 (22.6-23.1)	24.6 (24.5-24.6)	1.7 (1.5-2.0)	21.1 (20.9-21.4)	23.9 (23.9-24.0)	2.8 (2.6-3.0)	17.7 (17.5-17.9)	22.2 (22.1-22.2)	4.5 (4.3-4.7)
	Very high	23.0 (22.9-23.4)	24.6 (24.6-24.7)	1.56 (1.4-1.8)	21.7 (21.4-21.9)	24.1 (24.0-24.1)	2.4 (2.3-2.6)	18.2 (18.0-18.4)	22.6 (22.6-22.7)	4.4 (4.2-4.6)
Employment										
	Early retirement	19.9 (19.5-20.3)	23.7 (23.5-23.8)	3.8 (3.5-4.2)	17.7 (17.4-18.0)	22.6 (22.5-22.7)	4.9 (4.7-5.2)	14.4 (17.9-18.2)	20.7 (20.6-20.8)	6.3 (6.1-6.5)
	Unemployed	22.6 (22.2-22.9)	24.2 (24.1-24.3)	1.6 (1.3-1.9)	19.7 (19.3-20.2)	23.1 (22.9-23.2)	3.4 (3.0-3.8)	16.6 (16.2-17.1)	21.0 (20.8-21.1)	4.4 (3.9-4.8)
	Employed	23.0 (22.8-23.1)	24.6 (24.6-24.6)	1.6 (1.5-1.7)	21.2 (21.1-21.4)	24.0 (24.0-24.0)	2.8 (2.7-2.9)	18.1 (17.9-18.2)	22.5 (22.5-22.6)	4.5 (4.4-4.6)
Education										
	Primary school	21.9 (21.8-22.2)	24.3 (24.2-24.3)	2.4 (2.2-2.5)	20.0 (19.8-20.2)	23.6 (23.5-23.6)	3.6 (3.4-3.8)	16.6 (16.5-16.8)	22.0 (21.9-22.0)	5.4 (5.3-5.5)
	Youth education/high school	22.6 (22.4-22.8)	24.5 (24.5-24.6)	2.0 (1.8-2.1)	20.5 (20.4-20.7)	23.9 (23.9-24.0)	3.4 (3.2-3.6)	16.9 (16.7-17.0)	22.3 (22.2-22.3)	5.4 (5.3-5.6)
	Higher education	23.4 (23.1-23.6)	24.7 (24.7-24.8)	1.4 (1.1-1.6)	21.4 (21.2-21.7)	24.2 (24.2-24.3)	2.9 (2.6-3.1)	18.1 (17.8-18.4)	23.0 (22.9-23.0)	4.9 (4.6-5.2)
Psychiat										

ric conditions									
Schizophrenia	18.1 (15.8-19.8)	21.7 (20.8-22.5)	3.6 (1.8-5.5)	16.9 (15.6-18.4)	20.4 (19.7-21.0)	3.5 (2.2-4.8)	12.3 (11.1-13.5)	18.4 (17.8-19.0)	6.1 (5.0-7.2)
Bipolar disorder, depression, and recurrent depression	20.4 (18.6-21.7)	22.9 (22.3-23.6)	2.5 (0.9-4.1)	18.0 (17.1-18.8)	21.4 (20.9-21.8)	3.4 (2.5-4.2)	14.4 (13.8-15.1)	20.0 (19.7-20.3)	5.6 (5.0-6.2)
Schizotypal disorder	19.1 (16.1-21.5)	21.3 (19.5-22.5)	2.2 (-0.6-4.9)	18.4 (15.6-20.5)	20.5 (19.2-21.6)	2.1 (-0.3-4.5)	13.9 (10.3-17.4)	19.0 (17.3-20.6)	5.1 (1.7-8.4)
Personality disorders	19.4 (18.7-20.1)	22.5 (22.4-23.1)	3.2 (2.5-3.9)	17.9 (17.4-18.3)	21.5 (21.3-21.8)	3.7 (3.2-4.1)	14.6 (14.3-15.0)	19.6 (19.4-19.9)	5.0 (4.5-5.3)
Other mental illness	18.7 (18.2-19.2)	22.2 (21.9-22.5)	3.5 (3.0-4.0)	16.4 (16.1-16.8)	20.4 (20.2-20.7)	4.0 (3.6-4.4)	13.0 (12.7-13.3)	18.0 (17.8-18.2)	5.0 (4.7-5.3)
Income									
Low	21.8 (21.5-22.0)	24.2 (24.1-24.2)	2.4 (2.2-2.6)	19.8 (19.6-20.0)	23.5 (23.4-23.6)	3.7 (3.5-4.0)	16.2 (16.0-16.4)	21.6 (21.5-21.7)	5.4 (5.3-5.6)
Intermediate	23.1 (22.9-23.3)	24.5 (24.5-24.6)	1.4 (1.2-1.6)	21.0 (20.8-21.2)	23.8 (23.8-23.9)	2.9 (2.7-3.0)	17.9 (17.7-18.2)	22.4 (22.3-22.5)	4.5 (4.3-4.7)
High	23.2 (22.9-23.4)	24.6 (24.5-24.6)	1.4 (1.1-1.7)	21.5 (21.3-21.8)	23.9 (23.9-24.0)	2.4 (2.2-2.6)	18.3 (18.1-18.5)	22.2 (22.1-22.2)	3.9 (3.7-4.0)
Very high	23.3 (23.1-23.6)	24.6 (24.6-24.7)	1.3 (1.2-1.5)	22.0 (21.8-22.2)	24.1 (24.1-24.1)	2.1 (1.9-2.3)	18.7 (18.5-19.0)	22.6 (22.5-22.7)	3.9 (3.7-4.1)
Employment									
Early retirement	20.5 (20.1-20.9)	23.7 (23.5-23.8)	3.1 (2.8-3.5)	21.7 (21.5-21.8)	24.0 (24.0-24.1)	4.0 (3.8-4.3)	18.6 (18.5-18.8)	22.5 (22.5-22.6)	5.2 (5.0-5.4)
Unemployed	22.8 (22.4-)	24.2 (24.1-)	1.4 (1.0-)	20.0 (19.6-)	23.1 (22.9-)	3.1 (2.7-)	17.1 (16.6-)	21.0 (20.9-)	3.9 (3.5-)

	23.1)	24.3)	1.78)	20.5)	23.3)	3.5)	17.6)	21.2)	4.4)
Employed	23.3 (23.1- 23.4)	24.6 (24.6- 24.6)	1.3 (1.2- 1.4)	18.6 (18.3- 18.9)	22.6 (22.5- 22.8)	2.4 (2.3- 2.5)	15.5 (15.3- 15.7)	20.7 (20.6- 20.8)	3.9 (3.8- 4.0)
Education									
Primary school	22.4 (22.1- 22.5)	24.3 (24.2- 24.3)	2.0 (1.8- 2.2)	20.6 (20.4- 20.8)	23.6 (23.5- 23.6)	3.0 (2.9- 3.2)	17.4 (17.3- 17.6)	22.0 (21.9- 22.0)	4.6 (4.4- 4.7)
Youth education, high school	23.0 (22.8- 23.2)	24.5 (24.5- 24.6)	1.6 (1.4- 1.7)	21.1 (20.9- 21.3)	23.9 (23.9- 24.0)	2.9 (2.7- 3.0)	17.7 (17.5- 17.9)	22.3 (22.2- 22.3)	4.6 (4.5- 4.8)
Higher education	23.7 (23.4- 23.9)	24.7 (24.7- 24.8)	1.0 (0.7- 1.3)	21.8 (21.6- 22.2)	24.2 (24.2- 24.3)	2.4 (2.1- 2.6)	18.9 (18.5- 19.2)	23.0 (22.9- 23.0)	4.1 (3.8- 4.4)
Psychiatric conditions									
Schizophrenia	18.2 (15.8- 20.0)	21.8 (20.8- 22.6)	3.7 (1.7- 5.6)	17.7 (16.2- 19.2)	20.3 (19.5- 20.9)	2.6 (1.2- 3.9)	13.0 (11.7- 14.3)	18.4 (17.8- 19.1)	5.4 (4.3- 6.6)
Bipolar disorder, depression, and recurrent depression	20.6 (18.7- 22.0)	22.9 (22.3- 23.7)	2.3 (0.7- 4.0)	18.8 (17.8- 19.7)	21.4 (20.9- 21.9)	2.6 (1.6- 3.5)	15.4 (14.7- 16.1)	20.0 (19.6- 20.3)	4.6 (3.9- 5.3)
Schizotypal disorder	19.9 (16.7- 22.2)	21.2 (19.4- 22.5)	1.3 (- 1.3-3.9)	19.4 (16.5- 21.4)	20.6 (19.1- 21.7)	1.1 (-1.2- 3.4)	13.5 (9.6- 17.8)	19.0 (17.1- 20.7)	5.5 (1.9- 9.1)
Personality disorders	19.6 (18.9- 20.3)	22.6 (22.4- 23.1)	2.3 (2.2- 3.7)	18.4 (17.9- 18.9)	21.5 (21.2- 21.8)	3.1 (2.6- 3.5)	15.4 (15.0- 15.8)	19.6 (19.4- 19.9)	4.2 (3.9- 4.6)
Other mental illness	19.2 (18.7- 19.8)	22.2 (21.9- 22.5)	3.0 (2.4- 3.5)	17.2 (16.8- 17.5)	20.4 (20.2- 20.7)	3.3 (2.8- 3.8)	14.0 (13.6- 14.3)	18.0 (17.8- 18.3)	4.1 (3.8- 4.4)

– 8 Income

Low	17.9 (17.0-18.9)	24.2 (23.9-24.4)	6.2 (5.3-7.2)	15.0 (14.3-15.7)	23.4 (23.1-23.6)	8.4 (7.7-9.1)	11.7 (11.2-12.2)	21.5 (21.3-21.7)	9.9 (9.5-10.3)
Intermediate	19.4 (18.5-20.7)	24.5 (24.3-24.6)	5.1 (4.1-6.0)	16.0 (15.1-16.9)	23.8 (23.6-23.9)	7.8 (7.0-8.5)	13.1 (12.4-13.7)	22.2 (22.1-22.4)	9.2 (8.7-9.6)
High	19.9 (18.8-21.0)	24.5 (24.4-24.6)	4.5 (3.6-5.5)	17.3 (16.3-18.4)	23.9 (23.8-24.1)	6.7 (5.8-7.5)	13.7 (13.0-14.4)	22.0 (21.9-22.2)	8.3 (7.7-9.0)
Very high	20.6 (19.3-21.7)	24.6 (24.5-24.7)	4.1 (3.1-5.1)	18.2 (17.2-19.5)	24.0 (23.9-24.2)	5.7 (4.8-6.6)	14.7 (13.9-15.5)	22.7 (22.5-22.8)	8.0 (7.4-8.6)

Employment

Early retirement	17.1 (15.8-18.2)	23.6 (23.2-24.2)	6.6 (5.2-8.0)	17.4 (16.9-18.0)	24.0 (23.9-24.1)	8.4 (7.6-9.2)	14.2 (13.8-14.6)	22.5 (22.4-22.6)	9.3 (8.8-9.7)
Unemployed	19.9 (18.2-21.7)	24.3 (23.9-24.5)	4.3 (1.4-7.2)	15.9 (14.0-17.7)	22.8 (22.4-23.4)	7.0 (5.5-8.4)	12.9 (11.3-14.5)	20.6 (20.1-21.0)	7.7 (6.3-9.0)
Employed	20.1 (19.5-20.7)	24.6 (24.5-24.6)	4.5 (3.9-5.0)	14.0 (13.2-14.8)	22.4 (21.9-22.8)	6.5 (6.1-7.0)	11.4 (10.9-11.8)	20.6 (20.3-20.9)	8.3 (7.9-8.7)

Education

Primary school	18.8 (18.0-19.7)	24.3 (24.2-24.5)	5.5 (4.6-6.4)	15.5 (14.8-16.2)	23.5 (23.3-23.7)	8.0 (7.4-8.5)	12.8 (12.4-13.3)	21.9 (21.8-22.0)	9.1 (8.8-9.4)
Youth education, high school	19.6 (18.8-20.4)	24.5 (24.4-24.6)	4.9 (4.1-5.6)	16.8 (16.1-17.5)	23.9 (23.7-24.0)	7.0 (6.4-7.6)	13.0 (12.4-13.5)	22.2 (22.0-22.4)	9.2 (8.8-9.7)
Higher education	20.7 (19.3-21.9)	24.7 (24.6-24.8)	4.0 (2.4-5.7)	17.4 (16.3-18.6)	24.2 (24.1-24.4)	6.8 (5.8-7.9)	13.4 (12.3-14.4)	23.1 (22.9-23.2)	9.7 (9.0-10.4)

Psychiatric conditions

Schizophrenia	14.1 (6.2-	19.7 (15.4-	5.6 (-2.9-14.1)	9.7 (6.5-15.0)	20.9 (18.7-	11.2 (8.0-	9.4 (6.4-	18.3 (16.3-	8.9 (5.6-12.3)
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	21.7)	22.4)			22.7)	14.4)	12.7)	19.9)	
Bipolar disorder, depression, and recurrent depression	16.7 (9.4-22.4)	19.3 (17.5-23.6)	2.6 (-4.7-10.0)	13.5 (10.8-16.0)	21.1 (19.4-22.5)		11.6 (10.1-13.2)	19.8 (18.7-20.7)	
Schizotypal disorder	8.9 (1.5-19.1)	20.3 (9.7-24.0)	11.4 (-5.6-28.3)	3.7 (1.0-14.9)	19.4 (15.3-22.2)	15.7 (10.8-20.6)	12.9 (4.5-19.6)	15.2 (10.6-21.4)	2.3 (-5.8-10.5)
Personality disorders	17.6 (15.4-19.8)	21.7 (20.6-23.2)	4.1 (0.9-7.3)	14.6 (13.3-16.0)	21.7 (20.8-22.5)	7.1 (5.8-8.3)	12.1 (11.2-13.1)	19.7 (19.0-20.3)	7.6 (6.8-8.4)
Other mental illness	15.8 (14.3-17.5)	21.8 (20.7-23.0)	6.0 (4.3-7.7)	13.0 (12.1-14.1)	20.1 (19.1-20.9)	7.0 (6.0-8.1)	10.7 (10.0-11.4)	17.8 (17.1-18.4)	7.1 (6.4-7.9)

Income

Low	12.3 (10.0-15.5)	23.8 (23.1-24.6)	11.5 (8.2-14.8)	10.6 (9.2-12.2)	23.3 (22.7-24.0)	12.7 (11.1-14.4)	7.9 (7.1-8.7)	21.2 (20.8-21.8)	13.4 (12.6-14.2)
Intermediate	15.1 (11.5-19.3)	23.1 (23.4-24.8)	8.0 (3.6-12.4)	14.0 (11.2-16.6)	23.4 (23.0-24.1)	9.4 (7.0-11.8)	9.2 (7.8-10.6)	22.1 (21.7-22.5)	13.0 (11.8-14.1)
High	13.1 (7.8-18.1)	15.9 (23.7-24.9)	2.8 (-12.0-17.6)	10.5 (7.5-14.6)	23.8 (23.3-24.3)	13.3 (10.8-15.9)	10.2 (8.5-11.9)	22.2 (21.8-22.5)	12.0 (10.6-13.3)
Very high	11.2 (7.4-20.0)	23.8 (23.0-24.5)	12.6 (8.7-16.4)	10.0 (6.3-14.6)	23.9 (23.6-24.4)	13.9 (10.4-17.4)	10.0 (8.1-12.1)	22.7 (22.4-23.0)	12.7 (11.1-14.4)

Three or more diseases

Employment

Early retirement	11.4 (8.9-14.8)	23.2 (20.0-24.6)	11.8 (2.2-21.3)	12.1 (10.8-14.7)	23.9 (23.7-24.2)	10.9 (8.9-12.9)	10.2 (9.1-11.2)	22.5 (22.3-22.7)	12.2 (11.3-13.2)
Unemployed	11.7 (8.6-21.8)	22.4 (21.8-24.5)	10.7 (5.8-15.5)	14.9 (6.9-20.6)	22.9 (21.2-23.9)	8.0 (-0.9-16.9)	7.6 (4.3-12.8)	21.1 (19.9-22.0)	13.5 (10.9-16.0)
Employed	14.7	24.2	9.5 (7.0-)	10.6	21.5	10.9 (8.9-)	8.0	20.2	12.2 (11.3-)

d	(12.6-18.3)	(24.1-24.7)	12.1	(9.2-12.2)	(20.7-23.6)	12.9	(7.3-8.8)	(19.5-21.0)	13.2)
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Educational

Primary school	13.9 (11.1-17.5)	23.7 (23.3-24.5)	9.8 (7.2-12.5)	11.9 (10.2-13.6)	237 (23.3-24.1)	11.8 (10.2-13.4)	8.9 (8.1-9.7)	22.0 (21.7-22.2)	13.1 (12.4-13.8)
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Youth education, high school	12.8 (10.6-16.5)	24.3 (23.9-24.8)	11.5 (7.5-15.4)	11.1 (9.2-13.2)	23.6 (23.3-24.1)	12.5 (10.7-14.2)	8.8 (7.8-10.0)	22.3 (21.9-22.6)	13.4 (12.7-14.2)
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Higher education	13.9 (8.9-18.9)	21.4 (22.9-24.8)	7.5 (-0.9-15.9)	12.6 (8.1-17.1)	23.9 (23.4-24.4)	11.3 (7.4-15.1)	9.0 (6.6-11.4)	22.6 (22.2-23.1)	13.6 (11.6-15.7)
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Psychiatric conditions

Schizophrenia	Could not beest.	8.7 (0.2-22.8)	8.7 (0.6-16.8)	5.5 (0.4-9.3)	12.3 (6.0-23.6)	6.9 (-2.7-16.4)	5.2 (2.0-9.3)	15.7 (10.2-19.5)	10.5 (6.2-14.9)
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Bipolar disorder, depression and recurrent depression	2.4 (0.4-19.9)	9.1 (3.2-24.0)	6.8 (-1.4-15.0)	11.6 (5.9-18.4)	15.3 (11.0-22.5)	3.6 (-3.9-11.2)	6.4 (4.5-9.0)	20.1 (18.0-22.3)	13.7 (11.8-15.5)
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Schizotypal disorder	1.4 (0.02-2.6)	Could not beest.	-1.4 (-3.1-0.2)	Could not beest.	7.4 (0.1-13.5)	7.4 (-0.2-15.1)	Could not beest.	Could not beest.	Could not beest.
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Personality disorders	12.6 (7.0-19.9)	Could not beest.	-12.6 (-17.7-7.6)	13.2 (10.0-16.3)	21.2 (18.7-22.8)	8.0 (4.8-11.3)	9.1 (7.5-10.8)	18.6 (17.4-20.5)	9.6 (8.0-11.1)
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Other mental illness	10.0 (6.0-15.1)	22.8 (16.3-24.6)	12.7 (-2.8-28.3)	10.8 (8.7-12.9)	19.8 (17.2-21.7)	9.0 (6.3-11.7)	7.9 (6.9-8.9)	17.7 (16.3-19.2)	9.9 (8.6-11.1)
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VERSION 3 – REVIEW

REVIEWER	Yan Xie Clinical Epidemiology Center, VA St. Louis Health Care System, St. Louis, MO, U.S.
REVIEW RETURNED	25-Aug-2020
GENERAL COMMENTS	All of my comments are well addressed by the authors.