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Long-term mortality in young and middle-aged adults hospitalised with chronic disease: a Danish cohort study

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ABSTRACT

***Objectives*:** To examine the long-term outcomes for patients hospitalised with chronic diseases at age 30, 40, or 50 years.

***Design*:** Nationwide, population-based cohort study.

Setting: All Danish hospitals, 1979 to 1989, with follow-up through 2014.

Participants: All patients hospitalised during the study period with one, two, or three or more chronic diseases and age- and sex-matched unaffected persons from the general population: 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.

Main outcome measures: 25-year mortality risks based on Kaplan–Meier estimates, years-of-life-lost (YLLs), and mortality rate ratios based on Cox regression analysis.

***Results*:** 25-year mortality risks and YLLs increased steadily with increasing baseline morbidity burden and age, but the mortality risk difference compared with persons from the general population remained approximately constant across age cohorts. In the age-30 cohort, the risk differences for patients compared with unaffected comparators were 35.0% (95% confidence interval 32.5 to 37.5) with two diseases and 62.5% (54.3 to 70.3) with three or more diseases. In the age-50 cohort, these differences were respectively 48.4% (47.4 to 49.3) and 61.7% (60.1 to 63.0). We also found a steep socioeconomic gradient in estimated YLLs. Increasing morbidity burden augmented YLLs resulting from low income, unemployment, low education level, and psychiatric conditions. For example, in the age-30 cohort, YYLs attributable to low income were 2.4 for patients with one disease, 6.2 for patients with two diseases, and 11.5 for patients with three or more diseases.

***Conclusions*:** Among patients with multiple chronic diseases, the risk of death increases steadily with the number of chronic diseases and with age. Multimorbidity augments the already increased mortality among patients with low socioeconomic status.

Keywords: Multimorbidity, chronic disease, health disparities, epidemiology, mortality, cohort study

STRENGHTS AND LIMITATIONS OF THIS STUDY

- This nationwide, population-based cohort study examined the long-term mortality risks among patients of age 30, 40, or 50 years with and without hospital-diagnosed chronic disease.
- The study furthermore examined how number of chronic diseases impacts mortality and how socioeconomic factors and other psychiatric disease impacts these risks.
- The setting with long-term follow-up and accurate linkage within a uniform healthcare system eliminated selection and referral biases.
- Data on chronic and psychiatric diseases arose from inpatient hospitalisations and thus did not include conditions diagnosed and treated in the outpatient setting.
- Patients were identified based on 19 selected chronic diseases included in the Charlson Comorbidity Index, but other chronic conditions not listed here could potentially affect long-term outcomes.

INTRODUCTION

Multimorbidity, or the coexistence of two or more chronic conditions within the same individual,[1] is common among young and middle-aged adults.[2] A Scottish cross-sectional study established that despite a strong association of multimorbidity with increasing age, adults age 65 years or younger account for most of these patients in absolute numbers.[2] Multimorbidity is associated with fractionated healthcare and adverse health outcomes such as poor survival and reduced quality of life.[3-5]

Strong evidence exists that multimorbidity is associated with premature death; however, most previous studies examining this association have focused on older adults.[3 6-10] For example, in a recent meta-analysis of evidence pooled from 26 studies, risk of death was increased approximately 2-fold among multimorbid patients over age 60 years compared with those without multimorbidity.[3] In contrast, the long-term prognosis of young and middle-aged adults age 50 years or younger who have multimorbidity remains poorly understood. The lack of focus on this population is worrisome, considering their potentially long life expectancy and the huge personal and societal consequences of multimorbidity in this age group.[2 11] Furthermore, data increasingly indicate a strong socioeconomic gradient in the onset of multimorbidity, particularly among young and middle-aged adults,[2 12] with little information about how this gradient affects long-term prognosis.

To address these evidence gaps, we used nationwide health and administrative registries with virtually complete individual-level linkage and follow-up to examine 25-year mortality risks and expected years of life lost (YLLs) in three cohorts of patients age 30, 40, and 50 years hospitalised with one or more chronic diseases.

METHODS

Design and setting

We conducted a nationwide, population-based cohort study in Denmark covering 1979 to 1989, allowing for a 25-year follow-up period through 2014. The Danish National Health Service provides universal, tax-supported healthcare for all Danish residents to both general practitioners and hospital care.[13] Patient data are linkable at the individual-level across health and administrative registries through a unique 10-digit identifier, assigned by the Civil Registration System (CRS) to all residents at birth or upon immigration.[14]

Patient cohorts

We used the Danish National Patient Registry (DNPR) to construct three cohorts of different ages at baseline: We identified those ages 30, 40, or 50 years with a primary or secondary inpatient hospital diagnosis of at least one condition included in the Charlson Comorbidity Index (CCI).[15] We categorised the overall morbidity burden according to the number of diagnosed conditions (1, 2, or ≥3). Patients with at least two conditions were defined as having multimorbidities. The baseline was set as the date a patient reached age 30, 40, or 50 years. The cumulative source population during the inclusion period was 898 266 for people age 30 years; 871 658 for people age 40 years; and 627 826 for people age 50 years.

The DNPR has recorded non-psychiatric inpatient hospitalisations since 1977.[16] Records of hospitalisations in the DNPR include one primary and one or more secondary diagnosis, coded according to the *International Classification of Diseases* (ICD)–8th revision between 1977 and 1994 and 10th revision thereafter. The CCI is a commonly used index to identify comorbidities, and comprises a wide range of diseases, including cardiovascular, metabolic,

hepatic, and renal diseases, malignancies, dementia, peptic ulcer, and AIDS (Table S1).[15] Hospital diagnosis codes of CCI conditions have high validity in the DNPR, with positive predictive values for all CCI conditions exceeding 90% compared with medical records.[17]

General population comparison cohorts

We used the CRS to construct three general population comparison cohorts.[14] For this purpose, we matched, with replacement, up to five persons from the general population to each member of the patient cohorts on age and sex.[18] Persons were ineligible if they had one or more primary or secondary inpatient hospital diagnoses of any CCI conditions recorded in the DNPR any time before or at baseline. Diagnoses made after baseline were ignored.

Mortality

The primary outcome was time to death during 25 years of follow-up. Data on all-cause mortality were extracted from the CRS.

Covariables

To examine the impact of socioeconomic factors, we gathered information on socioeconomic factors 2 years before baseline: income level (low, intermediate, high, very high), employment status (early retirement, unemployed, employed), and education level (primary school, youth education/high school, higher education) from the Integrated Database for Labor Market Research.[19] We also gathered information on prevalent psychiatric conditions at baseline (schizophrenia, bipolar disorder/depression, schizotypal disorder, personality disorder, and other

mental illness) from the Psychiatric Central Research Registry (PCRR).[20] The PCRR contains data on all inpatient psychiatric admissions since 1969.

Statistical analysis

We characterised patients and their matched general population comparators according to age, sex, calendar year, morbidity burden, individual chronic diseases included in the CCI, income level, employment status, educational achievement, and psychiatric conditions. We followed cohort members from baseline until death, emigration, or 31 December 2014, whichever occurred first. Separately for each age cohort, we used the complement of the Kaplan–Meier estimator to compute and illustrate 25-year mortality risks for patients, stratified by their morbidity burden, and general population comparators.

As an additional method to assess survival in the patient and the general population cohorts, we computed expected YLLs as the mean survival difference between the two, *i.e.* the difference in the area between the mean Kaplan–Meier survival curves.[21] YLLs were computed for each morbidity level, as well as in strata of income, employment, and education, and for each psychiatric condition, without and with stratifying by morbidity level.

As a measure of the mortality rate ratio (MRR), we computed hazard ratios 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, stratified by number of morbidities. In multivariable analyses, we adjusted for income level, employment status, and education level. Because the proportionality assumption was violated, we applied a piecewise Cox regression, computing MRRs within 0-1 year, >1–5 years, >5–10 years, >10–20 years, and >20–25 years.

All statistical analyses were conducted using the SAS statistical software package, v. 9.4 (SAS Institute, Cary, NC). The study was approved by the Danish Data Protection Agency (record number: 2015-57-0002). Registry-based studies do not need ethical board approval in Denmark. Diagnosis codes are provided in Table S1.

Patient involvement

No patients were involved in setting the research question or the outcome measures, nor were they involved in developing plans for design or implementation of the study. No patients were asked to advise on interpretation or writing up of results. There are no plans to disseminate the results of the research to study participants or the relevant patient community.

RESULTS

We identified 13 857 patients and 69 285 age- and sex-matched general population comparators who were age 30 years; 24 129 patients and 120 645 age- and sex-matched comparators who were age 40 years; and 37 807 patients and 189 035 age and sex-matched comparators who were age 50 years (Table 1). The sexes were approximately equally distributed in each cohort. The prevalence of multimorbidity increased slightly with age. The most frequently hospital-diagnosed conditions were any tumour, peptic ulcer, chronic pulmonary disease, and type 1 and 2 diabetes. Socioeconomic status was generally lower in the patient cohorts, and across all age cohorts, low income, unemployment and early retirement, and less educational achievement was more frequent among patients than among general population comparators. Similarly, psychiatric conditions, such as personality disorder and other mental illness, were more common among the patients than among the comparators.

Absolute mortality risks

We observed 2999 deaths in the age-30 group, 8988 in the age-40 group, and 23 427 deaths in the age-50 group. The 25-year mortality risk increased steadily with increasing baseline number of morbidities and age (Figure 1). Among patients with one disease, the 25-year mortality risks were 19.4% (95% CI 18.7–20.1) in the age-30 group, 34.4% (95% CI 33.7–35.0) in the age-40 group, and 58.6% (95% CI 58.1–59.2) in the age-50 group. These risks increased respectively to 68.6% (95% CI 60.3–76.6), 82.3% (95% CI 78.0–86.3), and 92.4% (95% CI 90.6–93.9) among patients with three or more diseases at baseline. However, the mortality risk differences with matched comparators from the general population remained largely similar across age cohorts. For the age-30 patients at baseline, the risk differences with comparators were 13.3% (95% CI 12.8–13.8) with one disease, 35.0% (95% CI 32.5–37.5) with two diseases, and 62.5% (95% CI 54.3–70.3) with three or more diseases. For the age-40 patients, the risk differences with matched comparators were 21.3% (95% CI 20.9–21.7) with one disease, 46.8% (95% CI 44.9–48.6) with two, and 69.2% (95% CI 65.1–73.0) with three or more. Finally for the age-50 group, the risk differences from matched comparators were 28.0% (95% CI 27.6–28.3), 48.4% (95% CI 47.4–49.3), and 61.7% (95% CI 60.1–63.0) with one, two, and three-plus diseases, respectively.

Years-of-life-lost

We calculated expected YLLs by comparing the mean survival difference between the patient and general population cohorts. In line with the absolute mortality risks, expected YLLs during 25 years of follow-up increased with baseline age and with number of morbidities. For patients in the 30-year age group, the expected YLLs were 1.7, 5.2, and 10.4 with one, two, and three or

more diseases, respectively. For those in the 50-year group, the corresponding YLLs were 4.6, 9.3, and 13.4 (Table 2).

YLLs were greater among patients with low vs high income, for those on early retirement vs being employed, and for those with lower vs higher education level (Table 2). For example, YLLs for patients who were age 30 years and low income were as high as or higher than those for patients with very high income who were 10 years older. For psychiatric conditions, YLLs were substantial for the patient groups (*e.g.*, with schizophrenia, the YLLs were 3.6 in the age-30 cohort and 6.1 in the age-50 cohort).

YLLs in association with lower socioeconomic status and psychiatric conditions were more pronounced with increasing morbidity burden, regardless of age (Table 2). For example, in the age-30 cohort, YYLs because of low income were 2.4 for patients with one disease, 6.2 for patients with two diseases, and 11.5 for patients with three or more diseases. Similar trends were observed for most other socioeconomic factors and psychiatric conditions.

Mortality rate ratios

Compared with sex- and age-matched comparators from the general population, the relative risk of death during the first year was approximately 20–100-fold in patients with multimorbidity (Table 3). Although the MRRs decreased during follow-up, values ranging from approximately 2–10, depending on baseline age, persisted among patients surviving at least 20 years. We observed no consistent age gradient in the estimated MRRs. Estimates were largely similar regardless of adjustment for socioeconomic factors.

DISCUSSION

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 and with age. Although the mortality risk difference with persons from the general population increased among patients with more chronic conditions, it remained approximately constant across age cohorts. Increasing number of morbidities was linked to higher YLLs from low income, unemployment, low education level, and psychiatric conditions.

Our study should be viewed in light of several factors. Our setting with long-term follow-up and accurate linkage within a uniform healthcare system eliminated selection and referral biases. 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. Furthermore, we identified and categorised patients based on 19 selected chronic diseases included in the CCI, and other chronic conditions not listed here could potentially affect prognosis. In addition, prognoses associated with several of the included conditions, including myocardial infarction, stroke, some cancers, AIDS, and leukaemia, have improved considerably since the start of study period as a consequence of medical, diagnostic and treatment advances.[7 22]

Several previous studies have linked multimorbidity with increased mortality among older adults.[3 6-10] A meta-analysis including 26 studies of patients age 60 years or older reported a hazard ratio of 1.7 for patients with at least two diseases and 2.7 for those with at least three compared with people without multimorbidity.[3] Similarly, the Emerging Risk Factor Collaboration found a 4–7-fold increased risk of death among patients (mean age, 53 years) with cardiometabolic multimorbidity compared with a reference group without multimorbidity.[6] In

line with our study, a number of previous groups used the CCI to identify multimorbidity, either with[7 8] or without[9 10] an index disease. For example, Schmidt, *et al.*[7] found a 2.5-fold higher 5-year mortality rate among stroke patients with a weighted CCI score of 3+ compared with stroke patients with a weighted CCI score of 0.

In contrast to most previous literature on multimorbidity, we examined the prognosis in young- and middle-aged adults under age 50 years. In line with current understanding,[2] we found a steep socioeconomic gradient in YLLs attributable to multimorbidity, with YLLs because of low socioeconomic status increasing with the number of prevalent diseases. Although we compiled data on socioeconomic factors 2 years before baseline, reverse causality remains possible.[23] Given that YLLs for patients who were 30 years old and in the low-income category were as high as or higher than YLLs for very high-income patients a decade older, reducing disparities in healthcare is obviously crucial. We did not examine associations of modifiable risk factors linked to socioeconomic status, such as tobacco smoking, excessive alcohol consumption, poor diet, high body mass index, hypertension, and hyperlipidaemia.[24] We also could not evaluate whether socioeconomic status itself was acting directly through complex mechanisms involving upstream factors,[25] and both of these questions require further investigation.

Our study also evaluated YLLs in relation to psychiatric conditions, a poorly understood area in relation to somatic multimorbidity, particularly in young- and middle-aged adults. Psychiatric conditions increase in prevalence with increasing burden of physical ill-health.[2] Our findings that YLLs attributable to psychiatric conditions increased with an increasing number of prevalent diseases indicates an unmet need among those with these psychiatric conditions.

Healthcare systems lack an optimal infrastructure to properly care for patients with multimorbidity. Although these patients may be in contact with health services more frequently

than those who have a single disease, management of multimorbidity is usually fragmented, as medical professionals are becoming increasingly specialised in single diseases or organs.[2 26] Thus, improving coordination of care is a great challenge, particularly in light of the demographic changes that will lead to increasing numbers of patients with multiple conditions.[2]

In conclusion, young and middle-aged patients hospitalised with one or more chronic diseases had increased mortality risk during 25 years of follow-up, compared with age- and sex-matched unaffected persons from the general population. The risk of death grew steadily with the number of chronic diseases and with age. Multimorbidity also added to the increased mortality among patients with low socioeconomic status.

Contributions: AGO, NS, and HTS designed the study. EHP and HTS collected the data. NS and AGO reviewed the literature. AGO, NS, and HTS directed the analyses, which were carried out by BD. All authors participated in the discussion and interpretation of results. NS and AGO organized the writing and wrote the initial draft. All authors critically revised the manuscript for intellectual content and approved the final version. HTS is the guarantor.

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Competing interests: All authors have completed the ICMJE Uniform Disclosure at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare they have received no support from any organisation for the submitted work; no financial relationships in the previous three years with any organisations that might have an interest in the submitted work; and no other relationships or activities that could appear to have influenced the submitted work.

Ethics approval: Not needed.

Data sharing: No additional data available.

Transparency: The senior author, HTS, affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Table 1. Characteristics of Danish patients who had one or more chronic diseases when they reached age 30, 40, or 50 years and age- and sex-matched unaffected individuals from the general population during 1979–1989.

	Age 30 years		Age 40 years		Age 50 years	
	Patients N (%)	General population N (%)	Patients N (%)	General population N (%)	Patients N (%)	General population N (%)
Total	13 857 (100)	69 285 (100)	24 129 (100)	120 645 (100)	37 807 (100)	189 035 (100)
Sex						
Female	6861 (49.5)	34 305 (49.5)	11 566 (47.9)	57 830 (47.9)	18 058 (47.8)	90 290 (47.8)
Male	6996 (50.5)	34 980 (50.5)	12 563 (52.1)	62 815 (52.1)	19 749 (52.2)	98 745 (52.2)
Calendar year						
1979–1980	1434 (10.3)	7170 (10.3)	2102 (8.7)	10 510 (8.7)	4147 (11.0)	20 735 (11.0)
1981–1982	2016 (14.5)	10 080 (14.5)	3203 (13.3)	16 015 (13.3)	5679 (15.0)	28 395 (15.0)
1983–1984	2532 (18.3)	12 660 (18.3)	4630 (19.2)	23 150 (19.2)	6886 (18.2)	34 430 (18.2)
1985–1986	2986 (21.5)	14 930 (21.5)	5489 (22.7)	27 445 (22.7)	7838 (20.7)	39 190 (20.7)
1987–1989	4889 (35.3)	24 445 (35.3)	8705 (36.1)	43 525 (36.1)	13 257 (35.1)	66 285 (35.1)
Morbidity number (diseases in the CCI)						

No disease	69 285 (100.0)	120 645 (100.0)	189 035 (100.0)
One disease	12 464 (89.9)	21 514 (89.2)	32 013 (84.7)
Two diseases	1272 (9.2)	2291 (9.5)	4798 (12.7)
Three or more diseases	121 (0.9)	324 (1.3)	996 (2.6)
Specific conditions included in the CCI			
Myocardial infarction	89 (0.6)	973 (4.0)	4668 (12.3)
Congestive heart failure	103 (0.7)	225 (0.9)	864 (2.3)
Peripheral vascular disease	422 (3.0)	1117 (4.6)	2603 (6.9)
Cerebrovascular disease	545 (3.9)	1277 (5.3)	2908 (7.7)
Dementia	23 (0.2)	162 (0.7)	468 (1.2)
Chronic pulmonary disease	2425 (17.5)	3273 (13.6)	5447 (14.4)
Connective tissue disease	581 (4.2)	2232 (9.3)	2573 (6.8)
Ulcer disease	1462 (10.6)	4157 (17.2)	6055 (16.0)
Mild liver disease	581 (4.2)	1447 (6.0)	2039 (5.4)
Diabetes type 1 and 2	3560 (25.7)	4030 (16.7)	4835 (12.8)
Hemiplegia	178 (1.3)	202 (0.8)	270 (0.7)
Moderate to severe renal disease	990 (7.1)	1214 (5.0)	1475 (3.9)
Diabetes with end organ damage	892 (6.4)	994 (4.1)	1254 (3.3)

Any tumour	1690 (12.2)		4472 (18.5)		7733 (20.5)	
Leukaemia	51 (0.4)		104 (0.4)		117 (0.3)	
Lymphoma	318 (2.3)		457 (1.9)		383 (1.0)	
Moderate to severe liver disease	415 (3.0)		361 (1.5)		336 (0.9)	
Metastatic solid tumour	161 (1.2)		404 (1.7)		788 (2.1)	
AIDS	20 (0.1)		21 (0.1)		<5 (0.0)	
Income level						
Low	4551 (32.8)	16 273 (23.5)	8167 (33.8)	28 565 (23.7)	13 003 (34.4)	41 900 (22.2)
Intermediate	3400 (24.5)	16 070 (23.2)	6410 (26.6)	29 711 (24.6)	9615 (25.4)	46 968 (24.8)
High	3189 (23.0)	18 045 (26.0)	5099 (21.1)	29 717 (24.6)	8242 (21.8)	48 307 (25.6)
Very high	2672 (19.3)	17 938 (25.9)	4407 (18.3)	31 332 (26.0)	6869 (18.2)	50 175 (26.5)
Missing	45 (0.3)	959 (1.4)	46 (0.2)	1320 (1.1)	78 (0.2)	1685 (0.9)
Employment status						
Early retirement	2221 (16.0)	4636 (6.7)	5060 (21.0)	9477 (7.9)	11 814 (31.2)	23 921 (12.7)
Unemployed	1681 (12.1)	7077 (10.2)	1716 (7.1)	6465 (5.4)	1815 (4.8)	9177 (4.9)
Employed	9758 (70.4)	55 523 (80.1)	17 094 (70.8)	101 880 (84.4)	23 814 (63.0)	152 638 (80.7)
Missing	197 (1.4)	2049 (3.0)	259 (1.1)	2823 (2.3)	364 (1.0)	3299 (1.7)
Educational achievement						

Primary school	5525 (39.9)	22 463 (32.4)	10 320 (42.8)	41 956 (34.8)	20 708 (54.8)	93 209 (49.3)
Youth education/high school	5463 (39.4)	29 003 (41.9)	9288 (38.5)	48 889 (40.5)	12 091 (32.0)	62 774 (33.2)
Higher education	2153 (15.5)	13 369 (19.3)	3690 (15.3)	24 571 (20.4)	3879 (10.3)	26 664 (14.1)
Missing	716 (5.2)	4450 (6.4)	831 (3.4)	5229 (4.3)	1129 (3.0)	6388 (3.4)
Psychiatric conditions						
Schizophrenia	102 (0.7)	327 (0.5)	208 (0.9)	626 (0.5)	303 (0.8)	952 (0.5)
Bipolar disorder, depression, and recurrent depression	139 (1.0)	350 (0.5)	511 (2.1)	1210 (1.0)	1063 (2.8)	2629 (1.4)
Schizotypal disorder	56 (0.4)	126 (0.2)	69 (0.3)	212 (0.2)	39 (0.1)	122 (0.1)
Personality disorders	743 (5.4)	1411 (2.0)	2110 (8.7)	3476 (2.9)	3181 (8.4)	6182 (3.3)
Other mental illness	1430 (10.3)	2102 (3.0)	3400 (14.1)	4107 (3.4)	5096 (13.5)	6888 (3.6)

Abbreviation: CCI, Charlson Comorbidity Index

Table 2. Expected years-of-life-lost during 25 years of follow-up for patients who were age 30, 40, or 50 years during 1979–1986, by number of conditions and by socioeconomic factors and psychiatric conditions, overall and by number of chronic diseases.

		Expected years of life lost*		
		Age 30 years	**Age 40 years**	**Age 50 years**
	Morbidity			
	One disease	1.7	3.0	4.6
	Two diseases	5.2	7.5	9.3
	Three or more diseases	10.4	12.2	13.4
All patients	**Income**			
	Low	2.9	4.5	6.4
	Intermediate	1.8	3.4	5.2
	High	1.7	2.8	4.4
	Very high	1.6	2.4	4.4
	Employment			
	Early retirement	3.8	4.9	6.3
	Unemployed	1.6	3.4	4.3
	Employed	1.6	2.8	4.5
	Education			
	Primary school	2.4	3.6	5.4
	Youth education/high school	2.0	3.4	5.4
	Higher education	1.4	2.9	4.9
	Psychiatric conditions			
	Schizophrenia	3.6	3.5	6.1
	Bipolar disorder, depression, and recurrent depression	2.5	3.4	5.6
	Schizotypal disorder	2.2	2.1	5.1
	Personality disorders	3.2	3.7	5.0
	Other mental illness	3.5	4.0	5.0
One disease	**Income**			
	Low	2.4	3.7	5.4
	Intermediate	1.4	2.9	4.5
	High	1.4	2.4	3.9

	Very high	1.3	2.1	3.9
	Employment			
	Early retirement	3.1	4.0	5.2
	Unemployed	1.4	3.1	3.9
	Employed	1.3	2.4	3.9
	Education			
	Primary school	2.0	3.0	4.6
	Youth education, high school	1.6	2.9	4.6
	Higher education	1.0	2.4	4.1
	Psychiatric conditions			
	Schizophrenia	3.7	2.6	5.4
	Bipolar disorder, depression, and recurrent depression	2.3	2.6	4.6
	Schizotypal disorder	1.3	1.1	5.5
	Personality disorders	2.9	3.1	4.2
	Other mental illness	3.0	3.3	4.09
Two diseases	**Income**			
	Low	6.2	8.4	9.86
	Intermediate	5.1	7.8	9.16
	High	4.5	6.7	8.34
	Very high	4.1	5.7	7.97
	Employment			
	Early retirement	6.6	8.4	9.25
	Unemployed	4.3	7.0	7.65
	Employed	4.5	6.5	8.30
	Education			
	Primary school	5.5	8.0	9.07
	Youth education, high school	4.9	7.0	9.22
	Higher education	4.0	6.8	9.69
	Psychiatric conditions			
	Schizophrenia	5.6	11.2	8.94
	Bipolar disorder, depression, and recurrent depression	2.6	7.7	8.22

	Schizotypal disorder	11.4	15.7	2.31
	Personality disorders	4.1	7.1	7.59
	Other mental illness	6.0	7.0	7.13
Three or more diseases	**Income**			
	Low	11.5	12.7	13.4
	Intermediate	8.0	9.4	13.0
	High	2.8	13.3	12.0
	Very high	12.6	13.9	12.7
	Employment			
	Early retirement	7.3	10.9	12.2
	Unemployed	4.7	8.0	13.5
	Employed	5.0	11.8	12.3
	Education			
	Primary school	9.8	11.8	13.1
	Youth education, high school	11.5	12.5	13.4
	Higher education	7.5	11.3	13.6
	Psychiatric conditions			
	Schizophrenia	8.7	6.9	10.5
	Bipolar disorder, depression and recurrent depression	6.8	3.6	13.7
	Schizotypal disorder	-1.44	7.4	0.00
	Personality disorders	-12.6	8.0	9.6
	Other mental illness	12.7	9.0	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. Mortality rate ratios comparing patients with one or more chronic diseases at the time they reached age 30, 40, or 50 years with age- and sex-matched unaffected individuals from the general population, by follow-up time and number of chronic diseases.

		Age 30 years		Age 40 years		Age 50 years	
		Mortality rate ratios (95% CI)		Mortality rate ratios (95% CI)		Mortality rate ratios (95% CI)	
	Morbidity	Unadjusted	Adjusted*	Unadjusted	Adjusted*	Unadjusted	Adjusted*
0-1 year	1 disease	17.28 (11.98–24.91)	16.97 (10.75–26.80)	11.83 (9.72–14.41)	10.71 (8.63–13.30)	11.30 (10.06–12.69)	10.11 (8.94–11.43)
	2 diseases	127.50 (31.04–523.70)	Could not be estimated	37.19 (22.42–61.70)	44.12 (22.92–84.92)	26.13 (20.20–33.81)	23.45 (17.59–31.27)
	3+ diseases	20.00 (2.24–178.94)	Could not be estimated	41.25 (14.61–116.43)	92.15 (8.93–950.88)	87.14 (40.68–186.64)	83.08 (25.85–267.01)
>1–5 years	1 disease	6.29 (5.36–7.38)	5.60 (4.72–6.65)	6.74 (6.17–7.37)	5.92 (5.39–6.50)	4.93 (4.69–5.18)	4.31 (4.10–4.55)
	2 diseases	35.38 (19.34–64.73)	37.76 (16.91–84.35)	15.58 (12.40–19.58)	14.40 (11.15–18.59)	10.89 (9.69–12.24)	9.05 (7.98–10.25)
	3+ diseases	109.03 (14.70–808.93)	Could not be estimated	41.42 (19.90–86.22)	35.32 (12.69–98.25)	19.06 (14.71–24.71)	15.46 (11.28–21.20)
>5–10 years	1 disease	4.45 (3.88–5.11)	3.87 (3.34–4.48)	3.95 (3.67–4.26)	3.36 (3.11–3.64)	3.27 (3.14–3.41)	2.87 (2.74–3.00)
	2 diseases	12.34 (8.59–17.72)	12.58 (8.29–19.09)	10.18 (8.32–12.46)	8.55 (6.88–10.63)	7.01 (6.32–7.78)	5.80 (5.18–6.49)
	3+ diseases	23.54 (8.01–69.19)	56.10 (5.74–548.64)	21.66 (12.59–37.26)	13.74 (7.12–26.52)	11.23 (8.88–14.19)	8.45 (6.38–11.19)
>10–20 years	1 disease	2.99 (2.75–3.26)	2.60 (2.38–2.84)	2.77 (2.65–2.90)	2.41 (2.29–2.53)	2.30 (2.24–2.37)	2.08 (2.02–2.14)
	2 diseases	6.60 (5.30–8.22)	6.16 (4.86–7.81)	5.37 (4.69–6.16)	4.52 (3.90–5.23)	4.00 (3.70–4.32)	3.28 (3.02–3.57)
	3+ diseases	17.25 (8.25–36.07)	14.54 (6.54–32.35)	10.70 (6.96–16.44)	13.05 (6.62–25.70)	8.02 (6.49–9.91)	6.53 (5.16–8.28)

>20–25 years	1 disease	2.77 (2.51–3.05)	2.53 (2.28–2.80)	2.24 (2.12–2.38)	2.00 (1.89–2.13)	1.84 (1.77–1.91)	1.73 (1.66–1.81)
	2 diseases	5.12 (3.78–6.92)	4.37 (3.15–6.06)	4.33 (3.56–5.27)	3.86 (3.13–4.75)	2.54 (2.24–2.88)	2.29 (2.00–2.61)
	3+ diseases	3.82 (1.16–12.55)	4.72 (0.93–24.04)	16.12 (6.98–37.21)	9.29 (2.99–28.91)	2.98 (1.98–4.48)	2.04 (1.27–3.27)

Abbreviation: CCI, Charlson Comorbidity Index. *Adjusted for socioeconomic factors (income level, employment status, education level)

Figure 1. 25-year mortality risks for patients with one or more chronic diseases when they reached age 30, 40, or 50 years, stratified by number of chronic conditions, and age- and sex-matched unaffected individuals from the general population during 1979–1989 in Denmark.

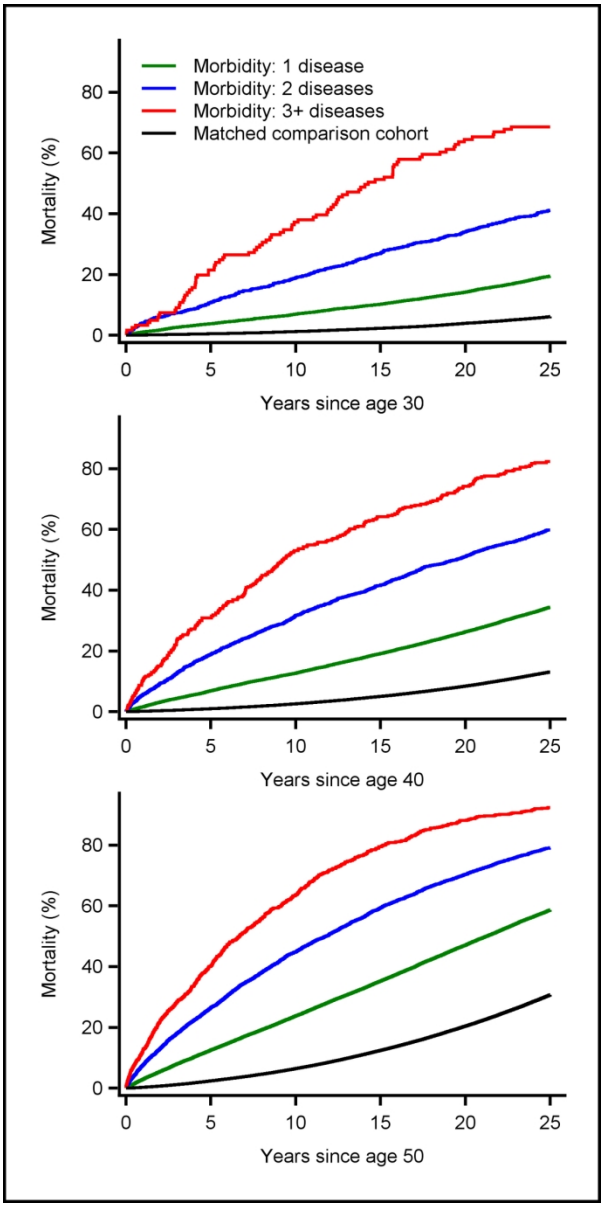

Figure 1. 25-year mortality risks for patients with one or more chronic diseases when they reached age 30, 40, or 50 years, stratified by number of chronic conditions, and age- and sex-matched unaffected individuals from the general population during 1979–1989 in Denmark.

49x99mm (600 x 600 DPI)

Table S1. *International Classification of Diseases* (ICD) codes used in the study.

	ICD-8 codes
Charlson Comorbidity Index	
Myocardial infarction	410
Congestive heart failure	427.09, 427.10, 427.11, 427.19, 428.99, 782.49
Peripheral vascular disease	440, 441, 442, 443, 444, 445
Cerebrovascular disease	430-438
Dementia	290.09-290.19, 293.09
Chronic pulmonary disease	490-493, 515-518
Connective tissue disease	712, 716, 734, 446, 135.99
Peptic ulcer	530.91, 530.98, 531-534
Mild liver disease	571, 573.01, 573.04
Diabetes type 1	249.00,249.06, 249.07, 249.09
Diabetes type 2	250.00,250.06, 250.07, 250.09
Hemiplegia	344
Moderate to severe renal disease	403, 404, 580-583,584,590.09, 593.19, 753.10-753.19, 792
Diabetes with end organ damage type 1	249.01-249.05, 249.08
type2	250.01-250.05, 250.08
Any tumour	140-194
Leukaemia	204-207
Lymphoma	200-203,275.59
Moderate to severe liver disease	070.00, 070.02, 070.04, 070.06, 070.08, 573.00, 456.00-456.09
Metastatic solid tumour	195-198, 199
AIDS	079.83
Psychiatric conditions	
Schizophrenia	295, 29719, 29799
Bipolar disorder, depression, and recurrent depression	296, 29809, 29819
Schizotypal disorder	30183
Personality disorders	300, 30100–30199 except 30183
Other mental illness (including all other psychiatric diagnoses, *e.g*., primary alcohol or substance abuse, organic disorders, anxiety disorders, adjustment disorders).	Remainder of 290-315 codes

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1-2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6-7
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	6-7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-8
Bias	9	Describe any efforts to address potential sources of bias	12
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8
		(*b*) Describe any methods used to examine subgroups and interactions	8
		(*c*) Explain how missing data were addressed	8
		(*d*) If applicable, explain how loss to follow-up was addressed	8
		(*e*) Describe any sensitivity analyses	8
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9
		(b) Indicate number of participants with missing data for each variable of interest	19
		(c) Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	Report numbers of outcome events or summary measures over time	9

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	9-11 NA 9-11
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	11-12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	15

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Long-term mortality in young and middle-aged adults hospitalised with chronic disease: a Danish cohort study

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ABSTRACT

***Objectives*:** To examine the long-term outcomes for patients hospitalised with chronic diseases at age 30, 40, or 50 years.

***Design*:** Nationwide, population-based cohort study.

Setting: All Danish hospitals, 1979 to 1989, with follow-up through 2014.

Participants: 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.

Main outcome measures: 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.

***Results*:** 25-year mortality risks and YLLs increased steadily with increasing number of morbidities leading to hospitalisation and age, but the risk difference with general population comparators remained approximately constant across age cohorts. In the age-30 cohort, the risk differences for patients compared with comparators were 35.0% (95% confidence interval 32.5 to 37.5) with two diseases and 62.5% (54.3 to 70.3) with three or more diseases. In the age-50 cohort, these differences were respectively 48.4% (47.4 to 49.3) and 61.7% (60.1 to 63.0). Increasing morbidity burden augmented YLLs resulting from low income, unemployment, low education level, and psychiatric conditions. In the age-30 cohort, YYLs attributable to low

income were 2.4 for patients with one disease, 6.2 for patients with two diseases, and 11.5 for patients with three or more diseases.

***Conclusions*:** Among patients with multiple chronic diseases, the risk of death increases steadily with the number of chronic diseases and with age. Multimorbidity augments the already increased mortality among patients with low socioeconomic status.

Keywords: Multimorbidity, chronic disease, health disparities, epidemiology, mortality, cohort study

STRENGHTS AND LIMITATIONS OF THIS STUDY

- This nationwide, population-based cohort study examined the long-term mortality risks among patients of age 30, 40, or 50 years with and without hospital-diagnosed chronic disease.
- The study furthermore examined how number of chronic diseases impacts mortality and how socioeconomic factors and other psychiatric disease impacts these risks.
- The setting with long-term follow-up and accurate linkage within a uniform healthcare system eliminated selection and referral biases.
- Data on chronic and psychiatric diseases arose from inpatient hospitalisations and thus did not include conditions diagnosed and treated in the outpatient setting.
- Patients were identified based on 19 selected chronic diseases included in the Charlson Comorbidity Index, but other chronic conditions not listed here could potentially affect long-term outcomes.

INTRODUCTION

Multimorbidity, or the coexistence of two or more chronic conditions within the same individual,[1] is common among young and middle-aged adults.[2] A Scottish cross-sectional study established that despite a strong association of multimorbidity with increasing age, adults age 65 years or younger account for most of these patients in absolute numbers.[2] Multimorbidity is associated with fractionated healthcare and adverse health outcomes such as poor survival and reduced quality of life.[3-5]

Strong evidence exists that multimorbidity is associated with premature death; however, most previous studies examining this association have focused on older adults.[3 6-10] For example, in a recent meta-analysis of evidence pooled from 26 studies, risk of death was increased approximately 2-fold among multimorbid patients over age 60 years compared with those without multimorbidity.[3] In contrast, the long-term prognosis of young and middle-aged adults age 50 years or younger who have multimorbidity remains poorly understood. The lack of focus on this population is worrisome, considering their potentially long life expectancy and the huge personal and societal consequences of multimorbidity in this age group.[2 11] Furthermore, data increasingly indicate a strong socioeconomic gradient in the onset of multimorbidity, particularly among young and middle-aged adults,[2 12] with little information about how this gradient affects long-term prognosis.

To address these evidence gaps, we used nationwide health and administrative registries with virtually complete individual-level linkage and follow-up to examine 25-year mortality risks and expected years of life lost (YLLs) in three cohorts of patients age 30, 40, and 50 years hospitalised with one or more chronic diseases.

METHODS

Design and setting

We conducted a nationwide, population-based cohort study in Denmark covering 1979 to 1989, allowing for a 25-year follow-up period through 2014. The Danish National Health Service provides universal, tax-supported healthcare for all Danish residents to both general practitioners and hospital care.[13] Patient data are linkable at the individual-level across health and administrative registries through a unique 10-digit identifier, assigned by the Civil Registration System (CRS) to all residents at birth or upon immigration.[14] The CRS is updated daily concerning changes in vital status and migration for the entire Danish population.

Patient cohorts

We used the Danish National Patient Registry (DNPR) to construct three cohorts of different ages at baseline: We identified those ages 30, 40, or 50 years with a primary or secondary inpatient hospital diagnosis of at least one condition included in the Charlson Comorbidity Index (CCI).[15] We categorised the overall morbidity burden according to the number of diagnosed conditions (1, 2, or ≥3). Patients with at least two conditions were defined as having multimorbidities. The baseline was set as the date a patient reached age 30, 40, or 50 years. The cumulative source population during the inclusion period was 898 266 for people age 30 years; 871 658 for people age 40 years; and 627 826 for people age 50 years.

The DNPR has recorded non-psychiatric inpatient hospitalisations since 1977.[16] Records of hospitalisations in the DNPR include one primary and one or more secondary diagnosis, coded according to the *International Classification of Diseases* (ICD)–8th revision between 1977 and 1994 and 10th revision thereafter. The CCI is a commonly used index to identify

comorbidities, and comprises a wide range of diseases, including cardiovascular, metabolic, hepatic, and renal diseases, malignancies, dementia, peptic ulcer, and AIDS (Table S1).[15] Hospital diagnosis codes of CCI conditions have high validity in the DNPR, with positive predictive values for all CCI conditions exceeding 90% compared with medical records.[17]

General population comparison cohorts

We used the CRS to construct three general population comparison cohorts.[14] For this purpose, we matched, with replacement, up to five persons from the general population to each member of the patient cohorts on date of birth and sex.[18] Persons were ineligible if they had one or more primary or secondary inpatient hospital diagnoses of any CCI conditions recorded in the DNPR any time before or at baseline. Diagnoses made after baseline were ignored.

Mortality

The primary outcome was time to death during 25 years of follow-up. Data on all-cause mortality were extracted from the CRS.

Covariables

To examine the impact of socioeconomic factors, we gathered information on socioeconomic factors 2 years before baseline: income level (low, intermediate, high, very high), employment status (early retirement, unemployed, employed), and education level (primary school, youth education/high school, higher education) from the Integrated Database for Labor Market Research.[19] We also gathered information on prevalent psychiatric conditions at baseline (schizophrenia, bipolar disorder/depression, schizotypal disorder, personality disorder, and other

mental illness) from the Psychiatric Central Research Registry (PCRR).[20] The PCRR contains data on all inpatient psychiatric admissions since 1969.

Statistical analysis

We characterised patients and their matched general population comparators according to age, sex, calendar year, morbidity burden, individual chronic diseases included in the CCI, income level, employment status, educational achievement, and psychiatric conditions. We followed cohort members from baseline until death, emigration, or 31 December 2014, whichever occurred first. Separately for each age cohort, we used the complement of the Kaplan–Meier estimator to compute and illustrate 25-year mortality risks for patients, stratified by their morbidity burden, and general population comparators.

As an additional method to assess survival in the patient and the general population cohorts, we computed expected YLLs as the mean survival difference between the two, *i.e.* the difference in the area between the mean Kaplan–Meier survival curves.[21] YLLs were computed for each morbidity level, as well as in strata of income, employment, and education, and for each psychiatric condition, without and with stratifying by morbidity level.

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.In multivariable analyses, we adjusted for income level, employment status, and education level. Because the proportionality assumption was violated, we applied a piecewise Cox regression, computing HRs within 0-1 year, >1–5 years, >5–10 years, >10–20 years, and >20–25 years.

All statistical analyses were conducted using the SAS statistical software package, v. 9.4 (SAS Institute, Cary, NC). The study was approved by the Danish Data Protection Agency (record number: 2015-57-0002). Registry-based studies do not need ethical board approval in Denmark. Diagnosis codes are provided in Table S1.

Patient involvement

No patients were involved in setting the research question or the outcome measures, nor were they involved in developing plans for design or implementation of the study. No patients were asked to advise on interpretation or writing up of results. There are no plans to disseminate the results of the research to study participants or the relevant patient community.

RESULTS

We identified 13 857 patients and 69 285 age- and sex-matched general population comparators who were age 30 years; 24 129 patients and 120 645 age- and sex-matched comparators who were age 40 years; and 37 807 patients and 189 035 age and sex-matched comparators who were age 50 years (Table 1). The sexes were approximately equally distributed in each cohort. The prevalence of multimorbidity increased slightly with age. The most frequently hospital-diagnosed conditions were any tumour, peptic ulcer, chronic pulmonary disease, and type 1 and 2 diabetes. Socioeconomic status was generally lower in the patient cohorts, and across all age cohorts, low income, unemployment and early retirement, and less educational achievement was more frequent among patients than among general population comparators. Similarly, psychiatric conditions, such as personality disorder and other mental illness, were more common among the patients than among the comparators.

Absolute mortality risks

We observed 2999 deaths in the age-30 group, 8988 in the age-40 group, and 23 427 deaths in the age-50 group. The 25-year mortality risk increased steadily with increasing number of morbidities leading to hospitalisation and age (Figure 1). Among patients with one disease, the 25-year mortality risks were 19.4% (95% CI 18.7–20.1) in the age-30 group, 34.4% (95% CI 33.7–35.0) in the age-40 group, and 58.6% (95% CI 58.1–59.2) in the age-50 group. These risks increased respectively to 68.6% (95% CI 60.3–76.6), 82.3% (95% CI 78.0–86.3), and 92.4% (95% CI 90.6–93.9) among patients with three or more diseases at baseline. However, the mortality risk differences with matched comparators from the general population remained largely similar across age cohorts. For the age-30 patients at baseline, the risk differences with comparators were 13.3% (95% CI 12.8–13.8) with one disease, 35.0% (95% CI 32.5–37.5) with two diseases, and 62.5% (95% CI 54.3–70.3) with three or more diseases. For the age-40 patients, the risk differences with matched comparators were 21.3% (95% CI 20.9–21.7) with one disease, 46.8% (95% CI 44.9–48.6) with two, and 69.2% (95% CI 65.1–73.0) with three or more. Finally for the age-50 group, the risk differences from matched comparators were 28.0% (95% CI 27.6–28.3), 48.4% (95% CI 47.4–49.3), and 61.7% (95% CI 60.1–63.0) with one, two, and three-plus diseases, respectively.

Years-of-life-lost

We calculated expected YLLs by comparing the mean survival difference between the patient and general population cohorts. In line with the absolute mortality risks, expected YLLs during 25 years of follow-up increased with baseline age and with number of morbidities. For patients

in the 30-year age group, the expected YLLs were 1.7, 5.2, and 10.4 with one, two, and three or more diseases, respectively. For those in the 50-year group, the corresponding YLLs were 4.6, 9.3, and 13.4 (Table 2).

YLLs were greater among patients with low vs high income, for those on early retirement vs being employed, and for those with lower vs higher education level (Table 2). For example, YLLs for patients who were age 30 years and low income were as high as or higher than those for patients with very high income who were 10 years older. For psychiatric conditions, YLLs were substantial for the patient groups (*e.g.*, with schizophrenia, the YLLs were 3.6 in the age-30 cohort and 6.1 in the age-50 cohort).

YLLs in association with lower socioeconomic status and psychiatric conditions were more pronounced with increasing morbidity burden, regardless of age (Table 2). For example, in the age-30 cohort, YYLs because of low income were 2.4 for patients with one disease, 6.2 for patients with two diseases, and 11.5 for patients with three or more diseases. Similar trends were observed for most other socioeconomic factors and psychiatric conditions.

Relative mortality risks

Compared with sex- and age-matched comparators from the general population, the relative risk of death during the first year was approximately 20–100-fold in patients with multimorbidity (Table 3). Although the HRs decreased during follow-up, values ranging from approximately 2–10, depending on baseline age, persisted among patients surviving at least 20 years. 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.

DISCUSSION

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. Although the mortality risk difference with persons from the general population increased among patients with more chronic conditions, it remained approximately constant across age cohorts. Increasing number of morbidities was linked to higher YLLs from low income, unemployment, low education level, and psychiatric conditions.

Our study should be viewed in light of several factors. Our setting with long-term follow-up and accurate linkage within a uniform healthcare system eliminated selection and referral biases. 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. 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. Furthermore, we identified and categorised patients based on 19 selected chronic diseases included in the CCI, and other chronic conditions not listed here could potentially affect prognosis. In addition, prognoses associated with several of the included conditions, including myocardial infarction, stroke, some cancers, AIDS, and leukaemia, have improved considerably since the start of study period as a consequence of medical, diagnostic and treatment advances.[7 22]

Several previous studies have linked multimorbidity with increased mortality among older adults.[3 6-10] A meta-analysis including 26 studies of patients age 60 years or older reported

a hazard ratio of 1.7 for patients with at least two diseases and 2.7 for those with at least three compared with people without multimorbidity.[3] Similarly, the Emerging Risk Factor Collaboration found a 4–7-fold increased risk of death among patients (mean age, 53 years) with cardiometabolic multimorbidity compared with a reference group without multimorbidity.[6] In line with our study, a number of previous groups used the CCI to identify multimorbidity, either with[7 8] or without[9 10] an index disease. For example, Schmidt, *et al.*[7] found a 2.5-fold higher 5-year mortality rate among stroke patients with a weighted CCI score of 3+ compared with stroke patients with a weighted CCI score of 0.

In contrast to most previous literature on multimorbidity, we examined the prognosis in young- and middle-aged adults under age 50 years. In line with current understanding,[2] we found a steep socioeconomic gradient in YLLs attributable to multimorbidity, with YLLs because of low socioeconomic status increasing with the number of prevalent diseases. Although we compiled data on socioeconomic factors 2 years before baseline, reverse causality remains possible.[23] Given that YLLs for patients who were 30 years old and in the low-income category were as high as or higher than YLLs for very high-income patients a decade older, reducing disparities in healthcare is obviously crucial. We did not examine associations of modifiable risk factors linked to socioeconomic status, such as tobacco smoking, excessive alcohol consumption, poor diet, high body mass index, hypertension, and hyperlipidaemia.[24] We also could not evaluate whether socioeconomic status itself was acting directly through complex mechanisms involving upstream factors,[25] and both of these questions require further investigation.

Our study also evaluated YLLs in relation to psychiatric conditions, a poorly understood area in relation to somatic multimorbidity, particularly in young- and middle-aged adults. Psychiatric conditions increase in prevalence with increasing burden of physical ill-health.[2] Our

findings that YLLs attributable to psychiatric conditions increased with an increasing number of prevalent diseases indicates an unmet need among those with these psychiatric conditions.

Healthcare systems lack an optimal infrastructure to properly care for patients with multimorbidity. Although these patients may be in contact with health services more frequently than those who have a single disease, management of multimorbidity is usually fragmented, as medical professionals are becoming increasingly specialised in single diseases or organs.[2 26] Thus, improving coordination of care is a great challenge, particularly in light of the demographic changes that will lead to increasing numbers of patients with multiple conditions.[2]

In conclusion, young and middle-aged patients hospitalised with one or more chronic diseases had increased mortality risk during 25 years of follow-up, compared with age- and sex-matched persons from the general population without chronic disease. The risk of death grew steadily with the number of chronic diseases and with age. Multimorbidity also added to the increased mortality among patients with low socioeconomic status.

Contributions: AGO, NS, and HTS designed the study. EHP and HTS collected the data. NS and AGO reviewed the literature. AGO, NS, and HTS directed the analyses, which were carried out by BD. All authors participated in the discussion and interpretation of results. NS and AGO organized the writing and wrote the initial draft. All authors critically revised the manuscript for intellectual content and approved the final version. HTS is the guarantor.

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Competing interests: All authors have completed the ICMJE Uniform Disclosure at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare they have received no support from any organisation for the submitted work; no financial relationships in the previous three years with any organisations that might have an interest in the submitted work; and no other relationships or activities that could appear to have influenced the submitted work.

Ethics approval: Not needed.

Data sharing: No additional data available.

Transparency: The senior author, HTS, affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Table 1. Characteristics of Danish patients with one or more chronic diseases leading to hospitalisation byage 30, 40, or 50 years and age- and sex-matched individuals from the general population without chronic disease during 1979–1989.

	Age 30 years		Age 40 years		Age 50 years	
	Patients N (%)	General population N (%)	Patients N (%)	General population N (%)	Patients N (%)	General population N (%)
Total	13 857 (100)	69 285 (100)	24 129 (100)	120 645 (100)	37 807 (100)	189 035 (100)
Sex						
Female	6861 (49.5)	34 305 (49.5)	11 566 (47.9)	57 830 (47.9)	18 058 (47.8)	90 290 (47.8)
Male	6996 (50.5)	34 980 (50.5)	12 563 (52.1)	62 815 (52.1)	19 749 (52.2)	98 745 (52.2)
Calendar year						
1979–1980	1434 (10.3)	7170 (10.3)	2102 (8.7)	10 510 (8.7)	4147 (11.0)	20 735 (11.0)
1981–1982	2016 (14.5)	10 080 (14.5)	3203 (13.3)	16 015 (13.3)	5679 (15.0)	28 395 (15.0)
1983–1984	2532 (18.3)	12 660 (18.3)	4630 (19.2)	23 150 (19.2)	6886 (18.2)	34 430 (18.2)
1985–1986	2986 (21.5)	14 930 (21.5)	5489 (22.7)	27 445 (22.7)	7838 (20.7)	39 190 (20.7)
1987–1989	4889 (35.3)	24 445 (35.3)	8705 (36.1)	43 525 (36.1)	13 257 (35.1)	66 285 (35.1)
Morbidity number (diseases in the CCI)						

No disease	69 285 (100.0)	120 645 (100.0)	189 035 (100.0)
One disease	12 464 (89.9)	21 514 (89.2)	32 013 (84.7)
Two diseases	1272 (9.2)	2291 (9.5)	4798 (12.7)
Three or more diseases	121 (0.9)	324 (1.3)	996 (2.6)
Specific conditions included in the CCI			
Myocardial infarction	89 (0.6)	973 (4.0)	4668 (12.3)
Congestive heart failure	103 (0.7)	225 (0.9)	864 (2.3)
Peripheral vascular disease	422 (3.0)	1117 (4.6)	2603 (6.9)
Cerebrovascular disease	545 (3.9)	1277 (5.3)	2908 (7.7)
Dementia	23 (0.2)	162 (0.7)	468 (1.2)
Chronic pulmonary disease	2425 (17.5)	3273 (13.6)	5447 (14.4)
Connective tissue disease	581 (4.2)	2232 (9.3)	2573 (6.8)
Ulcer disease	1462 (10.6)	4157 (17.2)	6055 (16.0)
Mild liver disease	581 (4.2)	1447 (6.0)	2039 (5.4)
Diabetes type 1 and 2	3560 (25.7)	4030 (16.7)	4835 (12.8)
Hemiplegia	178 (1.3)	202 (0.8)	270 (0.7)
Moderate to severe renal disease	990 (7.1)	1214 (5.0)	1475 (3.9)
Diabetes with end organ damage	892 (6.4)	994 (4.1)	1254 (3.3)

Any tumour	1690 (12.2)		4472 (18.5)		7733 (20.5)	
Leukaemia	51 (0.4)		104 (0.4)		117 (0.3)	
Lymphoma	318 (2.3)		457 (1.9)		383 (1.0)	
Moderate to severe liver disease	415 (3.0)		361 (1.5)		336 (0.9)	
Metastatic solid tumour	161 (1.2)		404 (1.7)		788 (2.1)	
AIDS	20 (0.1)		21 (0.1)		<5 (0.0)	
Income level						
Low	4551 (32.8)	16 273 (23.5)	8167 (33.8)	28 565 (23.7)	13 003 (34.4)	41 900 (22.2)
Intermediate	3400 (24.5)	16 070 (23.2)	6410 (26.6)	29 711 (24.6)	9615 (25.4)	46 968 (24.8)
High	3189 (23.0)	18 045 (26.0)	5099 (21.1)	29 717 (24.6)	8242 (21.8)	48 307 (25.6)
Very high	2672 (19.3)	17 938 (25.9)	4407 (18.3)	31 332 (26.0)	6869 (18.2)	50 175 (26.5)
Missing	45 (0.3)	959 (1.4)	46 (0.2)	1320 (1.1)	78 (0.2)	1685 (0.9)
Employment status						
Early retirement	2221 (16.0)	4636 (6.7)	5060 (21.0)	9477 (7.9)	11 814 (31.2)	23 921 (12.7)
Unemployed	1681 (12.1)	7077 (10.2)	1716 (7.1)	6465 (5.4)	1815 (4.8)	9177 (4.9)
Employed	9758 (70.4)	55 523 (80.1)	17 094 (70.8)	101 880 (84.4)	23 814 (63.0)	152 638 (80.7)
Missing	197 (1.4)	2049 (3.0)	259 (1.1)	2823 (2.3)	364 (1.0)	3299 (1.7)
Educational achievement						

Primary school	5525 (39.9)	22 463 (32.4)	10 320 (42.8)	41 956 (34.8)	20 708 (54.8)	93 209 (49.3)
Youth education/high school	5463 (39.4)	29 003 (41.9)	9288 (38.5)	48 889 (40.5)	12 091 (32.0)	62 774 (33.2)
Higher education	2153 (15.5)	13 369 (19.3)	3690 (15.3)	24 571 (20.4)	3879 (10.3)	26 664 (14.1)
Missing	716 (5.2)	4450 (6.4)	831 (3.4)	5229 (4.3)	1129 (3.0)	6388 (3.4)
Psychiatric conditions						
Schizophrenia	102 (0.7)	327 (0.5)	208 (0.9)	626 (0.5)	303 (0.8)	952 (0.5)
Bipolar disorder, depression, and recurrent depression	139 (1.0)	350 (0.5)	511 (2.1)	1210 (1.0)	1063 (2.8)	2629 (1.4)
Schizotypal disorder	56 (0.4)	126 (0.2)	69 (0.3)	212 (0.2)	39 (0.1)	122 (0.1)
Personality disorders	743 (5.4)	1411 (2.0)	2110 (8.7)	3476 (2.9)	3181 (8.4)	6182 (3.3)
Other mental illness	1430 (10.3)	2102 (3.0)	3400 (14.1)	4107 (3.4)	5096 (13.5)	6888 (3.6)

Abbreviation: CCI, Charlson Comorbidity Index

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			Age 40 years			Age 50 years		
		EYL in patients (95% CI)	EYL in general population (95% CI)	EYL lost	EYL in patients (95% CI)	EYL in general population (95% CI)	EYL lost	EYL in patients (95% CI)	EYL in general population (95% CI)	EYL lost
All patients	**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 (19.49-20.28)	23.68 (23.54-23.84)	3.8	17.68 (17.39-17.96)	22.61 (22.48-22.74)	4.9	14.42 (17.92-18.18)	20.70 (20.60-20.81)	6.3
	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
	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
One disease	**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 (23.42-23.89)	24.66 (24.68-24.77)	1.0	21.83 (21.62-22.15)	24.21 (24.15-24.26)	2.4	18.88 (18.54-19.20)	22.95 (22.87-23.03)	4.1
	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
Two diseases	**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 (15.80-18.24)	23.63 (23.22-24.21)	6.6	17.43 (16.87-17.98)	23.97 (23.88-24.06)	8.4	14.2 (13.77-14.64)	22.5 (22.41-22.59)	9.25
	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 (0.00-0.00)	8.71 (0.15-22.76)	8.7	5.47 (0.35-9.26)	12.32 (6.01-23.63)	6.9	5.16 (1.99-9.25)	15.68 (10.17-19.46)	10.5
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 disesae, by follow-up time and number of chronic diseases.

		Age 30 years				Age 40 years				Age 50 years			
				Hazard ratios (95% CI)				Hazard ratios (95% CI)				Hazard ratios (95% CI)	
	Morbidity	Deaths, N	PYs	Unadjusted	Adjusted*	Deaths, N	PYs	Unadjusted	Adjusted*	Deaths, N	PYs	Unadjusted	Adjusted*
0-1 year	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 years	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	117949.6	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 years	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	130893.8	3.27 (3.14–3.41)	2.87 (2.74–3.00)
	2 diseases	103	5392.4	12.34 (8.59–17.72)	12.58 (8.29–19.09)	292	8552.2	10.18 (8.32–12.46)	8.55 (6.88–10.63)	880	15298.8	7.01 (6.32–7.78)	5.80 (5.18–6.49)
	3+ diseases	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 years	1 disease	894	110446.6	2.99 (2.75–3.26)	2.60 (2.38–2.84)	2906	172727.6	2.77 (2.65–2.90)	2.41 (2.29–2.53)	7433	206509.4	2.30 (2.24–2.37)	2.08 (2.02–2.14)
	2 diseases	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+ diseases	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 years	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 diseases	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+ diseases	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)

Figure 1. 25-year mortality risks for patients with one or more chronic diseases when they reached age 30, 40, or 50 years, stratified by number of chronic conditions, and age- and sex-matched individuals from the general population without chronic disease during 1979–1989 in Denmark.

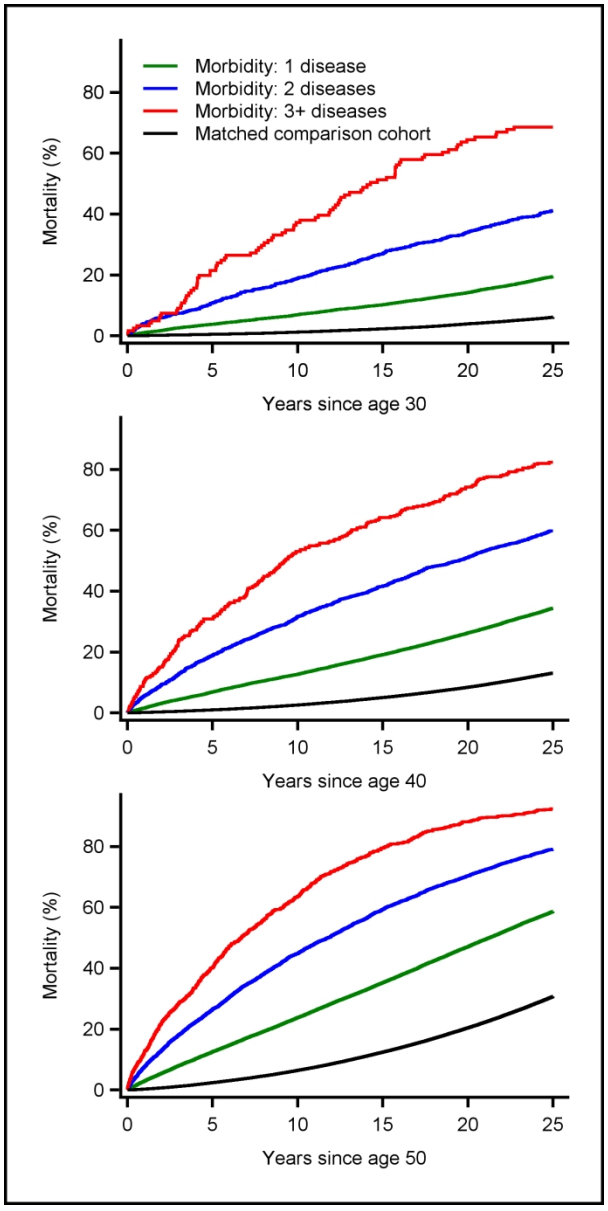

Figure 1. 25-year mortality risks for patients with one or more chronic diseases when they reached age 30, 40, or 50 years, stratified by number of chronic conditions, and age- and sex-matched unaffected individuals from the general population during 1979–1989 in Denmark.

50x100mm (800 x 800 DPI)

Table S1. *International Classification of Diseases* (ICD) codes used in the study.

	ICD-8 codes
Charlson Comorbidity Index	
Myocardial infarction	410
Congestive heart failure	427.09, 427.10, 427.11, 427.19, 428.99, 782.49
Peripheral vascular disease	440, 441, 442, 443, 444, 445
Cerebrovascular disease	430-438
Dementia	290.09-290.19, 293.09
Chronic pulmonary disease	490-493, 515-518
Connective tissue disease	712, 716, 734, 446, 135.99
Peptic ulcer	530.91, 530.98, 531-534
Mild liver disease	571, 573.01, 573.04
Diabetes type 1	249.00,249.06, 249.07, 249.09
Diabetes type 2	250.00,250.06, 250.07, 250.09
Hemiplegia	344
Moderate to severe renal disease	403, 404, 580-583,584,590.09, 593.19, 753.10-753.19, 792
Diabetes with end organ damage type 1	249.01-249.05, 249.08
type2	250.01-250.05, 250.08
Any tumour	140-194
Leukaemia	204-207
Lymphoma	200-203,275.59
Moderate to severe liver disease	070.00, 070.02, 070.04, 070.06, 070.08, 573.00, 456.00-456.09
Metastatic solid tumour	195-198, 199
AIDS	079.83
Psychiatric conditions	
Schizophrenia	295, 29719, 29799
Bipolar disorder, depression, and recurrent depression	296, 29809, 29819
Schizotypal disorder	30183
Personality disorders	300, 30100–30199 except 30183
Other mental illness (including all other psychiatric diagnoses, *e.g*., primary alcohol or substance abuse, organic disorders, anxiety disorders, adjustment disorders).	Remainder of 290-315 codes

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1-2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6-7
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	6-7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-8
Bias	9	Describe any efforts to address potential sources of bias	12
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8
		(*b*) Describe any methods used to examine subgroups and interactions	8
		(*c*) Explain how missing data were addressed	8
		(*d*) If applicable, explain how loss to follow-up was addressed	8
		(*e*) Describe any sensitivity analyses	8
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9
		(b) Indicate number of participants with missing data for each variable of interest	19
		(c) Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	Report numbers of outcome events or summary measures over time	9

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	9-11 NA 9-11
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	11-12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	15

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Long-term mortality in young and middle-aged adults hospitalised with chronic disease: a Danish cohort study

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ABSTRACT

***Objectives*:** To examine the long-term outcomes for patients hospitalised with chronic diseases at age 30, 40, or 50 years.

***Design*:** Nationwide, population-based cohort study.

Setting: All Danish hospitals, 1979 to 1989, with follow-up through 2014.

Participants: 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.

Main outcome measures: 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.

***Results*:** 25-year mortality risks and YLLs increased steadily with increasing number of morbidities leading to hospitalisation and age, but the risk difference with general population comparators remained approximately constant across age cohorts. In the age-30 cohort, the risk differences for patients compared with comparators were 35.0% (95% confidence interval 32.5 to 37.5) with two diseases and 62.5% (54.3 to 70.3) with three or more diseases. In the age-50 cohort, these differences were respectively 48.4% (47.4 to 49.3) and 61.7% (60.1 to 63.0). Increasing morbidity burden augmented YLLs resulting from low income, unemployment, low education level, and psychiatric conditions. In the age-30 cohort, YYLs attributable to low

income were 2.4 for patients with one disease, 6.2 for patients with two diseases, and 11.5 for patients with three or more diseases.

***Conclusions*:** Among patients with multiple chronic diseases, the risk of death increases steadily with the number of chronic diseases and with age. Multimorbidity augments the already increased mortality among patients with low socioeconomic status.

Keywords: Multimorbidity, chronic disease, health disparities, epidemiology, mortality, cohort study

STRENGHTS AND LIMITATIONS OF THIS STUDY

- This nationwide, population-based cohort study examined the long-term mortality risks among patients of age 30, 40, or 50 years with and without hospital-diagnosed chronic disease.
- The study furthermore examined how number of chronic diseases impacts mortality and how socioeconomic factors and other psychiatric disease impacts these risks.
- The setting with long-term follow-up and accurate linkage within a uniform healthcare system eliminated selection and referral biases.
- Data on chronic and psychiatric diseases arose from inpatient hospitalisations and thus did not include conditions diagnosed and treated in the outpatient setting.
- Patients were identified based on 19 selected chronic diseases included in the Charlson Comorbidity Index, but other chronic conditions not listed here could potentially affect long-term outcomes.

INTRODUCTION

Multimorbidity, or the coexistence of two or more chronic conditions within the same individual,[1] is common among young and middle-aged adults.[2] A Scottish cross-sectional study established that despite a strong association of multimorbidity with increasing age, adults age 65 years or younger account for most of these patients in absolute numbers.[2] Multimorbidity is associated with fractionated healthcare and adverse health outcomes such as poor survival and reduced quality of life.[3-5]

Strong evidence exists that multimorbidity is associated with premature death; however, most previous studies examining this association have focused on older adults.[3 6-10] For example, in a recent meta-analysis of evidence pooled from 26 studies, risk of death was increased approximately 2-fold among multimorbid patients over age 60 years compared with those without multimorbidity.[3] In contrast, the long-term prognosis of young and middle-aged adults age 50 years or younger who have multimorbidity remains poorly understood. The lack of focus on this population is worrisome, considering their potentially long life expectancy and the huge personal and societal consequences of multimorbidity in this age group.[2 11] Furthermore, data increasingly indicate a strong socioeconomic gradient in the onset of multimorbidity, particularly among young and middle-aged adults,[2 12] with little information about how this gradient affects long-term prognosis.

To address these evidence gaps, we used nationwide health and administrative registries with virtually complete individual-level linkage and follow-up to examine 25-year mortality risks and expected years of life lost (YLLs) in three cohorts of patients age 30, 40, and 50 years hospitalised with one or more chronic diseases.

METHODS

Design and setting

We conducted a nationwide, population-based cohort study in Denmark covering 1979 to 1989, allowing for a 25-year follow-up period through 2014. The Danish National Health Service provides universal, tax-supported healthcare for all Danish residents to both general practitioners and hospital care.[13] Patient data are linkable at the individual-level across health and administrative registries through a unique 10-digit identifier, assigned by the Civil Registration System (CRS) to all residents at birth or upon immigration.[14] The CRS is updated daily concerning changes in vital status and migration for the entire Danish population.

Patient cohorts

We used the Danish National Patient Registry (DNPR) to construct three cohorts of different ages at baseline: We identified those ages 30, 40, or 50 years with a primary or secondary inpatient hospital diagnosis of at least one condition included in the Charlson Comorbidity Index (CCI).[15] We categorised the overall morbidity burden according to the number of diagnosed conditions (1, 2, or ≥3). Patients with at least two conditions were defined as having multimorbidities. The baseline was set as the date a patient reached age 30, 40, or 50 years. The cumulative source population during the inclusion period was 898 266 for people age 30 years; 871 658 for people age 40 years; and 627 826 for people age 50 years.

The DNPR has recorded non-psychiatric inpatient hospitalisations since 1977.[16] Records of hospitalisations in the DNPR include one primary and one or more secondary diagnosis, coded according to the *International Classification of Diseases* (ICD)–8th revision between 1977 and 1994 and 10th revision thereafter. The CCI is a commonly used index to identify

comorbidities, and comprises a wide range of diseases, including cardiovascular, metabolic, hepatic, and renal diseases, malignancies, dementia, peptic ulcer, and AIDS (Table S1).[15] Hospital diagnosis codes of CCI conditions have high validity in the DNPR, with positive predictive values for all CCI conditions exceeding 90% compared with medical records.[17]

General population comparison cohorts

We used the CRS to construct three general population comparison cohorts.[14] For this purpose, we matched, with replacement, up to five persons from the general population to each member of the patient cohorts on date of birth and sex.[18] Persons were ineligible if they had one or more primary or secondary inpatient hospital diagnoses of any CCI conditions recorded in the DNPR any time before or at baseline. Diagnoses made after baseline were ignored.

Mortality

The primary outcome was time to death during 25 years of follow-up. Data on all-cause mortality were extracted from the CRS.

Covariables

To examine the impact of socioeconomic factors, we gathered information on socioeconomic factors 2 years before baseline: income level (low, intermediate, high, very high), employment status (early retirement, unemployed, employed), and education level (primary school, youth education/high school, higher education) from the Integrated Database for Labor Market Research.[19] We also gathered information on prevalent psychiatric conditions at baseline (schizophrenia, bipolar disorder/depression, schizotypal disorder, personality disorder, and other

mental illness) from the Psychiatric Central Research Registry (PCRR).[20] The PCRR contains data on all inpatient psychiatric admissions since 1969.

Statistical analysis

We characterised patients and their matched general population comparators according to age, sex, calendar year, morbidity burden, individual chronic diseases included in the CCI, income level, employment status, educational achievement, and psychiatric conditions. We followed cohort members from baseline until death, emigration, or 31 December 2014, whichever occurred first. Separately for each age cohort, we used the complement of the Kaplan–Meier estimator to compute and illustrate 25-year mortality risks for patients, stratified by their morbidity burden, and general population comparators.

As an additional method to assess survival in the patient and the general population cohorts, we computed expected YLLs as the mean survival difference between the two, *i.e.* the difference in the area between the mean Kaplan–Meier survival curves.[21] YLLs were computed for each morbidity level, as well as in strata of income, employment, and education, and for each psychiatric condition, without and with stratifying by morbidity level. 95% confidence intervals (CIs) were computed using bootstrapping on each of the matched pairs using 100 replicates.

As a measure of the mortality rate ratio we computed hazard ratios (HRs) of death and 95% confidence intervals 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. In multivariable analyses, we adjusted for income level, employment status, and education level.

Because the proportionality assumption was violated, we applied a piecewise Cox regression, computing HRs within 0-1 year, >1–5 years, >5–10 years, >10–20 years, and >20–25 years.

All statistical analyses were conducted using the SAS statistical software package, v. 9.4 (SAS Institute, Cary, NC). The study was approved by the Danish Data Protection Agency (record number: 2015-57-0002). Registry-based studies do not need ethical board approval in Denmark. Diagnosis codes are provided in Table S1.

Patient involvement

No patients were involved in setting the research question or the outcome measures, nor were they involved in developing plans for design or implementation of the study. No patients were asked to advise on interpretation or writing up of results. There are no plans to disseminate the results of the research to study participants or the relevant patient community.

RESULTS

We identified 13 857 patients and 69 285 age- and sex-matched general population comparators who were age 30 years; 24 129 patients and 120 645 age- and sex-matched comparators who were age 40 years; and 37 807 patients and 189 035 age and sex-matched comparators who were age 50 years (Table 1). The sexes were approximately equally distributed in each cohort. The prevalence of multimorbidity increased slightly with age. The most frequently hospital-diagnosed conditions were any tumour, peptic ulcer, chronic pulmonary disease, and type 1 and 2 diabetes. Socioeconomic status was generally lower in the patient cohorts, and across all age cohorts, low income, unemployment and early retirement, and less educational achievement was more frequent among patients than among general population comparators. Similarly, psychiatric

conditions, such as personality disorder and other mental illness, were more common among the patients than among the comparators.

Absolute mortality risks

We observed 2999 deaths in the age-30 group, 8988 in the age-40 group, and 23 427 deaths in the age-50 group. The 25-year mortality risk increased steadily with increasing number of morbidities leading to hospitalisation and age (Figure 1). Among patients with one disease, the 25-year mortality risks were 19.4% (95% CI 18.7–20.1) in the age-30 group, 34.4% (95% CI 33.7–35.0) in the age-40 group, and 58.6% (95% CI 58.1–59.2) in the age-50 group. These risks increased respectively to 68.6% (95% CI 60.3–76.6), 82.3% (95% CI 78.0–86.3), and 92.4% (95% CI 90.6–93.9) among patients with three or more diseases at baseline. However, the mortality risk differences with matched comparators from the general population remained largely similar across age cohorts. For the age-30 patients at baseline, the risk differences with comparators were 13.3% (95% CI 12.8–13.8) with one disease, 35.0% (95% CI 32.5–37.5) with two diseases, and 62.5% (95% CI 54.3–70.3) with three or more diseases. For the age-40 patients, the risk differences with matched comparators were 21.3% (95% CI 20.9–21.7) with one disease, 46.8% (95% CI 44.9–48.6) with two, and 69.2% (95% CI 65.1–73.0) with three or more. Finally for the age-50 group, the risk differences from matched comparators were 28.0% (95% CI 27.6–28.3), 48.4% (95% CI 47.4–49.3), and 61.7% (95% CI 60.1–63.0) with one, two, and three-plus diseases, respectively.

Years-of-life-lost

We calculated expected YLLs by comparing the mean survival difference between the patient

and general population cohorts. In line with the absolute mortality risks, expected YLLs during 25 years of follow-up increased with baseline age and with number of morbidities. For patients in the 30-year age group, the expected YLLs were 1.7 (95 CI: 1.6-1.8), 5.2 (95 CI: 4.7-5.6), and 10.4 (95 CI: 8.7-12.1)with one, two, and three or more diseases, respectively. For those in the 50-year group, the corresponding YLLs were 4.6 (95 CI: 4.5-4.7), 9.3 (95 CI: 9.1-9.6), and 13.4 (95 CI: 12.9-13.9) (Table 2).

YLLs were greater among patients with low vs high income, for those on early retirement vs being employed, and for those with lower vs higher education level (Table 2). For example, YLLs for patients who were age 30 years and low income were as high as or higher than those for patients with very high income who were 10 years older. For psychiatric conditions, YLLs were substantial for the patient groups (*e.g.*, with schizophrenia, the YLLs were 3.6 (95% CI: 1.8-5.5) in the age-30 cohort and 6.1 (95% CI: 5.0-7.2) in the age-50 cohort).

YLLs in association with lower socioeconomic status and psychiatric conditions were more pronounced with increasing morbidity burden, regardless of age (Table 2). For example, in the age-30 cohort, YYLs because of low income were 2.4 (95% CI: 2.2-2.6) for patients with one disease, 6.2 (95% CI: 5.3-7.2) for patients with two diseases, and 11.5 (95% CI: 8.2-14.8) for patients with three or more diseases. Similar trends were observed for most other socioeconomic factors and psychiatric conditions.

Relative mortality risks

Compared with sex- and age-matched comparators from the general population, the relative risk of death during the first year was approximately 20–100-fold in patients with multimorbidity (Table 3). Although the HRs decreased during follow-up, values ranging from approximately 2–

10, depending on baseline age, persisted among patients surviving at least 20 years. 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.

DISCUSSION

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. Although the mortality risk difference with persons from the general population increased among patients with more chronic conditions, it remained approximately constant across age cohorts. Increasing number of morbidities was linked to higher YLLs from low income, unemployment, low education level, and psychiatric conditions.

Our study should be viewed in light of several factors. Our setting with long-term follow-up and accurate linkage within a uniform healthcare system eliminated selection and referral biases. 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. 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. Furthermore, we identified and categorised patients based on 19 selected chronic diseases included in the CCI, and other chronic conditions not listed here could potentially affect prognosis. In addition, prognoses associated with several of the included conditions, including myocardial infarction,

stroke, some cancers, AIDS, and leukaemia, have improved considerably since the start of study period as a consequence of medical, diagnostic and treatment advances.[7 22]

Several previous studies have linked multimorbidity with increased mortality among older adults.[3 6-10] A meta-analysis including 26 studies of patients age 60 years or older reported a hazard ratio of 1.7 for patients with at least two diseases and 2.7 for those with at least three compared with people without multimorbidity.[3] Similarly, the Emerging Risk Factor Collaboration found a 4–7-fold increased risk of death among patients (mean age, 53 years) with cardiometabolic multimorbidity compared with a reference group without multimorbidity.[6] In line with our study, a number of previous groups used the CCI to identify multimorbidity, either with[7 8] or without[9 10] an index disease. For example, Schmidt, *et al.*[7] found a 2.5-fold higher 5-year mortality rate among stroke patients with a weighted CCI score of 3+ compared with stroke patients with a weighted CCI score of 0.

In contrast to most previous literature on multimorbidity, we examined the prognosis in young- and middle-aged adults under age 50 years. In line with current understanding,[2] we found a steep socioeconomic gradient in YLLs attributable to multimorbidity, with YLLs because of low socioeconomic status increasing with the number of prevalent diseases. Although we compiled data on socioeconomic factors 2 years before baseline, reverse causality remains possible.[23] Given that YLLs for patients who were 30 years old and in the low-income category were as high as or higher than YLLs for very high-income patients a decade older, reducing disparities in healthcare is obviously crucial. We did not examine associations of modifiable risk factors linked to socioeconomic status, such as tobacco smoking, excessive alcohol consumption, poor diet, high body mass index, hypertension, and hyperlipidaemia.[24] We also could not

evaluate whether socioeconomic status itself was acting directly through complex mechanisms involving upstream factors,[25] and both of these questions require further investigation.

Our study also evaluated YLLs in relation to psychiatric conditions, a poorly understood area in relation to somatic multimorbidity, particularly in young- and middle-aged adults. Psychiatric conditions increase in prevalence with increasing burden of physical ill-health.[2] Our findings that YLLs attributable to psychiatric conditions increased with an increasing number of prevalent diseases indicates an unmet need among those with these psychiatric conditions.

Healthcare systems lack an optimal infrastructure to properly care for patients with multimorbidity. Although these patients may be in contact with health services more frequently than those who have a single disease, management of multimorbidity is usually fragmented, as medical professionals are becoming increasingly specialised in single diseases or organs.[2 26] Thus, improving coordination of care is a great challenge, particularly in light of the demographic changes that will lead to increasing numbers of patients with multiple conditions.[2]

In conclusion, young and middle-aged patients hospitalised with one or more chronic diseases had increased mortality risk during 25 years of follow-up, compared with age- and sex-matched persons from the general population without chronic disease. The risk of death grew steadily with the number of chronic diseases and with age. Multimorbidity also added to the increased mortality among patients with low socioeconomic status.

Contributions: AGO, NS, and HTS designed the study. EHP and HTS collected the data. NS and AGO reviewed the literature. AGO, NS, and HTS directed the analyses, which were carried out by BD. All authors participated in the discussion and interpretation of results. NS and AGO organized the writing and wrote the initial draft. All authors critically revised the manuscript for intellectual content and approved the final version. HTS is the guarantor.

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Competing interests: All authors have completed the ICMJE Uniform Disclosure at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare they have received no support from any organisation for the submitted work; no financial relationships in the previous three years with any organisations that might have an interest in the submitted work; and no other relationships or activities that could appear to have influenced the submitted work.

Ethics approval: Not needed.

Data sharing: No additional data available.

Transparency: The senior author, HTS, affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Table 1. Characteristics of Danish patients with one or more chronic diseases leading to hospitalisation byage 30, 40, or 50 years and age- and sex-matched individuals from the general population without chronic disease during 1979–1989.

	Age 30 years		Age 40 years		Age 50 years	
	Patients N (%)	General population N (%)	Patients N (%)	General population N (%)	Patients N (%)	General population N (%)
Total	13 857 (100)	69 285 (100)	24 129 (100)	120 645 (100)	37 807 (100)	189 035 (100)
Sex						
Female	6861 (49.5)	34 305 (49.5)	11 566 (47.9)	57 830 (47.9)	18 058 (47.8)	90 290 (47.8)
Male	6996 (50.5)	34 980 (50.5)	12 563 (52.1)	62 815 (52.1)	19 749 (52.2)	98 745 (52.2)
Calendar year						
1979–1980	1434 (10.3)	7170 (10.3)	2102 (8.7)	10 510 (8.7)	4147 (11.0)	20 735 (11.0)
1981–1982	2016 (14.5)	10 080 (14.5)	3203 (13.3)	16 015 (13.3)	5679 (15.0)	28 395 (15.0)
1983–1984	2532 (18.3)	12 660 (18.3)	4630 (19.2)	23 150 (19.2)	6886 (18.2)	34 430 (18.2)
1985–1986	2986 (21.5)	14 930 (21.5)	5489 (22.7)	27 445 (22.7)	7838 (20.7)	39 190 (20.7)
1987–1989	4889 (35.3)	24 445 (35.3)	8705 (36.1)	43 525 (36.1)	13 257 (35.1)	66 285 (35.1)
Morbidity number (diseases in the CCI)						

No disease	69 285 (100.0)	120 645 (100.0)	189 035 (100.0)
One disease	12 464 (89.9)	21 514 (89.2)	32 013 (84.7)
Two diseases	1272 (9.2)	2291 (9.5)	4798 (12.7)
Three or more diseases	121 (0.9)	324 (1.3)	996 (2.6)
Specific conditions included in the CCI			
Myocardial infarction	89 (0.6)	973 (4.0)	4668 (12.3)
Congestive heart failure	103 (0.7)	225 (0.9)	864 (2.3)
Peripheral vascular disease	422 (3.0)	1117 (4.6)	2603 (6.9)
Cerebrovascular disease	545 (3.9)	1277 (5.3)	2908 (7.7)
Dementia	23 (0.2)	162 (0.7)	468 (1.2)
Chronic pulmonary disease	2425 (17.5)	3273 (13.6)	5447 (14.4)
Connective tissue disease	581 (4.2)	2232 (9.3)	2573 (6.8)
Ulcer disease	1462 (10.6)	4157 (17.2)	6055 (16.0)
Mild liver disease	581 (4.2)	1447 (6.0)	2039 (5.4)
Diabetes type 1 and 2	3560 (25.7)	4030 (16.7)	4835 (12.8)
Hemiplegia	178 (1.3)	202 (0.8)	270 (0.7)
Moderate to severe renal disease	990 (7.1)	1214 (5.0)	1475 (3.9)
Diabetes with end organ damage	892 (6.4)	994 (4.1)	1254 (3.3)

Any tumour	1690 (12.2)		4472 (18.5)		7733 (20.5)	
Leukaemia	51 (0.4)		104 (0.4)		117 (0.3)	
Lymphoma	318 (2.3)		457 (1.9)		383 (1.0)	
Moderate to severe liver disease	415 (3.0)		361 (1.5)		336 (0.9)	
Metastatic solid tumour	161 (1.2)		404 (1.7)		788 (2.1)	
AIDS	20 (0.1)		21 (0.1)		<5 (0.0)	
Income level						
Low	4551 (32.8)	16 273 (23.5)	8167 (33.8)	28 565 (23.7)	13 003 (34.4)	41 900 (22.2)
Intermediate	3400 (24.5)	16 070 (23.2)	6410 (26.6)	29 711 (24.6)	9615 (25.4)	46 968 (24.8)
High	3189 (23.0)	18 045 (26.0)	5099 (21.1)	29 717 (24.6)	8242 (21.8)	48 307 (25.6)
Very high	2672 (19.3)	17 938 (25.9)	4407 (18.3)	31 332 (26.0)	6869 (18.2)	50 175 (26.5)
Missing	45 (0.3)	959 (1.4)	46 (0.2)	1320 (1.1)	78 (0.2)	1685 (0.9)
Employment status						
Early retirement	2221 (16.0)	4636 (6.7)	5060 (21.0)	9477 (7.9)	11 814 (31.2)	23 921 (12.7)
Unemployed	1681 (12.1)	7077 (10.2)	1716 (7.1)	6465 (5.4)	1815 (4.8)	9177 (4.9)
Employed	9758 (70.4)	55 523 (80.1)	17 094 (70.8)	101 880 (84.4)	23 814 (63.0)	152 638 (80.7)
Missing	197 (1.4)	2049 (3.0)	259 (1.1)	2823 (2.3)	364 (1.0)	3299 (1.7)
Educational achievement						

Primary school	5525 (39.9)	22 463 (32.4)	10 320 (42.8)	41 956 (34.8)	20 708 (54.8)	93 209 (49.3)
Youth education/high school	5463 (39.4)	29 003 (41.9)	9288 (38.5)	48 889 (40.5)	12 091 (32.0)	62 774 (33.2)
Higher education	2153 (15.5)	13 369 (19.3)	3690 (15.3)	24 571 (20.4)	3879 (10.3)	26 664 (14.1)
Missing	716 (5.2)	4450 (6.4)	831 (3.4)	5229 (4.3)	1129 (3.0)	6388 (3.4)
Psychiatric conditions						
Schizophrenia	102 (0.7)	327 (0.5)	208 (0.9)	626 (0.5)	303 (0.8)	952 (0.5)
Bipolar disorder, depression, and recurrent depression	139 (1.0)	350 (0.5)	511 (2.1)	1210 (1.0)	1063 (2.8)	2629 (1.4)
Schizotypal disorder	56 (0.4)	126 (0.2)	69 (0.3)	212 (0.2)	39 (0.1)	122 (0.1)
Personality disorders	743 (5.4)	1411 (2.0)	2110 (8.7)	3476 (2.9)	3181 (8.4)	6182 (3.3)
Other mental illness	1430 (10.3)	2102 (3.0)	3400 (14.1)	4107 (3.4)	5096 (13.5)	6888 (3.6)

Abbreviation: CCI, Charlson Comorbidity Index

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			Age 40 years			Age 50 years		
		25-year EYL (95% CI)			25-year EYL (95% CI)			25-year EYL (95% CI)		
		Patients	General population	Difference (EYL lost)	Patients	General population	Difference (EYL lost)	Patients	General population	Difference (EYL lost)
All patients	**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)
	Psychiatric 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)

One disease	**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 (22.4-23.1)	24.2 (24.1-24.3)	1.4 (1.0-1.78)	20.0 (19.6-20.5)	23.1 (22.9-23.3)	3.1 (2.7-3.5)	17.1 (16.6-17.6)	21.0 (20.9-21.2)	3.9 (3.5-4.4)
	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)
Two diseases	**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 (6.2-21.7)	19.7 (15.4-22.4)	5.6 (-2.9-14.1)	9.7 (6.5-15.0)	20.9 (18.7-22.7)	11.2 (8.0-14.4)	9.4 (6.4-12.7)	18.3 (16.3-19.9)	8.9 (5.6-12.3)
	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)	7.7 (5.0-10.4)	11.6 (10.1-13.2)	19.8 (18.7-20.7)	8.2 (6.7-9.7)
	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 (12.6-18.3)	24.2 (24.1-24.7)	9.5 (7.0-12.1)	10.6 (9.2-12.2)	21.5 (20.7-23.6)	10.9 (8.9-12.9)	8.0 (7.3-8.8)	20.2 (19.5-21.0)	12.2 (11.3-13.2)
	Education									
	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)
	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)
	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)

Psychiatric conditions									
Schizophrenia	Could not be est.	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)
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)
Schizotypal disorder	1.4 (0.02-2.6)	Could not be est.	-1.4 (-3.1-0.2)	Could not be est.	7.4 (0.1-13.5)	7.4 (-0.2-15.1)	Could not be est.	Could not be est.	Could not be est.
Personality disorders	12.6 (7.0-19.9)	Could not be est.	-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)
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)

*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 disease, by follow-up time and number of chronic diseases.

		Age 30 years				Age 40 years				Age 50 years			
				Hazard ratios (95% CI)				Hazard ratios (95% CI)				Hazard ratios (95% CI)	
	Morbidity	Deaths, N	PYs	Unadjusted	Adjusted*	Deaths, N	PYs	Unadjusted	Adjusted*	Deaths, N	PYs	Unadjusted	Adjusted*
0-1 year	1 disease	128	12383.0	17.3 (12.0–24.9)	17.0 (10.8–26.8)	334	21325.6	11.8 (9.7–14.4)	10.7 (8.6–13.3)	931	31524.8	11.3 (10.1–12.7)	10.1 (8.9–11.4)
	2 diseases	51	1244.4	127.5 (31.0–523.7)	Could not be est.	127	2220.4	37.2 (22.4–61.7)	44.1 (22.9–84.9)	361	4599.4	26.1 (20.2–33.8)	23.5 (17.6–31.3)
	3+ diseases	< 5	< 5	Could not be est.	Could not be est.	33	305.0	41.3 (14.6–116.4)	92.2 (8.9–950.9)	122	927.2	87.1 (40.7–186.6)	83.1 (25.9–267.0)
>1–5 years	1 disease	342	48421.8	6.3 (5.4–7.4)	5.6 (4.7–6.7)	1139	82228.0	6.7 (6.2–7.4)	5.92 (5.4–6.5)	3063	117949.6	4.9 (4.7–5.2)	4.3 (4.1–4.6)
	2 diseases	86	4709.2	35.4 (19.3–64.7)	37.8 (16.9–84.4)	305	8015.4	15.6 (12.4–19.6)	14.4 (11.2–18.6)	905	15799.0	10.9 (9.7–12.2)	9.1 (8.0–10.3)
	3+ diseases	22	427.0	109.0 (14.7–808.9)	Could not be est.	67	1012.6	41.4 (19.9–86.2)	35.3 (12.7–98.3)	278	2879.2	19.1 (14.7–24.7)	15.5 (11.3–21.2)
>5–10 years	1 disease	387	58547.8	4.5 (3.9–5.1)	3.9 (3.3–4.5)	1240	96611.8	4.0 (3.7–4.3)	3.4 (3.1–3.6)	3596	130893.8	3.3 (3.1–3.4)	2.9 (2.7–3.0)
	2 diseases	103	5392.4	12.3 (8.6–17.7)	12.6 (8.3–19.1)	292	8552.2	10.2 (8.3–12.5)	8.6 (6.9–10.6)	880	15298.8	7.0 (6.3–7.8)	5.8 (5.2–6.5)
	3+ diseases	19	427.0	23.5 (8.0–69.2)	56.1 (5.7–548.6)	71	927.2	21.7 (12.6–37.3)	13.7 (7.1–26.5)	233	2330.2	11.2 (8.9–14.2)	8.5 (6.4–11.2)
>10–20 years	1 disease	894	110446.6	3.0 (2.8–3.3)	2.6 (2.3–2.8)	2906	172727.6	2.8 (2.7–2.9)	2.4 (2.3–2.5)	7433	206509.4	2.3 (2.2–2.4)	2.1 (2.0–2.1)
	2 diseases	191	9272.0	6.6 (5.3–8.2)	6.2 (4.9–7.8)	444	13322.4	5.4 (4.7–6.2)	4.5 (3.9–5.2)	1221	19800.6	4.0 (3.7–4.3)	3.3 (3.0–3.6)
	3+ diseases	33	585.6	17.3 (8.3–36.1)	14.5 (6.5–32.4)	68	1171.2	10.7 (7.0–16.4)	13.1 (6.6–25.7)	244	2159.4	8.0 (6.5–9.9)	6.5 (5.2–8.3)
>20–25 years	1 disease	645	51069.2	2.8 (2.5–3.1)	2.5 (2.3–2.8)	1736	74334.6	2.2 (2.1–2.4)	2.0 (1.9–2.1)	3700	75054.4	1.8 (1.8–1.9)	1.7 (1.7–1.8)
	2 diseases	89	3928.4	5.1 (3.8–6.9)	4.4 (3.2–6.1)	200	5063.0	4.3 (3.6–5.3)	3.9 (3.1–4.8)	417	5978.0	2.5 (2.2–2.9)	2.3 (2.0–2.6)
	3+ diseases	5	195.2	3.8 (1.2–12.6)	4.7 (0.9–24.0)	26	341.6	16.1 (7.0–37.2)	9.3 (3.0–28.9)	43	475.8	3.0 (2.0–4.5)	2.0 (1.3–3.3)

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

Figure 1. 25-year mortality risks for patients with one or more chronic diseases when they reached age 30, 40, or 50 years, stratified by number of chronic conditions, and age- and sex-matched individuals from the general population without chronic disease during 1979–1989 in Denmark.

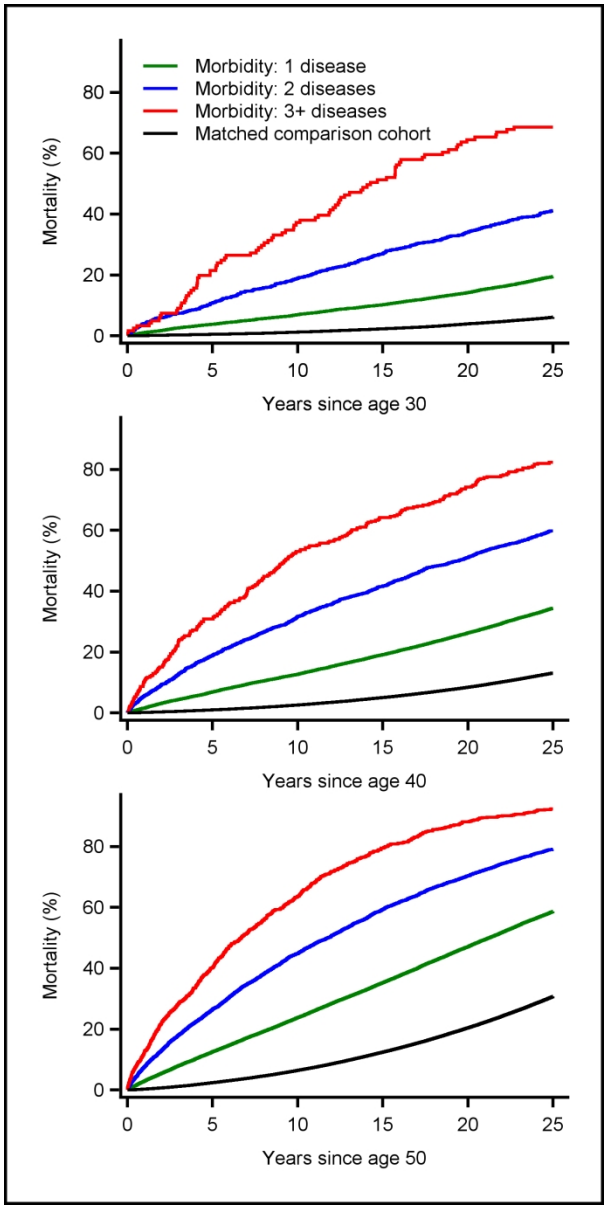

Figure 1. 25-year mortality risks for patients with one or more chronic diseases when they reached age 30, 40, or 50 years, stratified by number of chronic conditions, and age- and sex-matched unaffected individuals from the general population during 1979–1989 in Denmark.

50x100mm (800 x 800 DPI)

Table S1. *International Classification of Diseases* (ICD) codes used in the study.

	ICD-8 codes
Charlson Comorbidity Index	
Myocardial infarction	410
Congestive heart failure	427.09, 427.10, 427.11, 427.19, 428.99, 782.49
Peripheral vascular disease	440, 441, 442, 443, 444, 445
Cerebrovascular disease	430-438
Dementia	290.09-290.19, 293.09
Chronic pulmonary disease	490-493, 515-518
Connective tissue disease	712, 716, 734, 446, 135.99
Peptic ulcer	530.91, 530.98, 531-534
Mild liver disease	571, 573.01, 573.04
Diabetes type 1	249.00,249.06, 249.07, 249.09
Diabetes type 2	250.00,250.06, 250.07, 250.09
Hemiplegia	344
Moderate to severe renal disease	403, 404, 580-583,584,590.09, 593.19, 753.10-753.19, 792
Diabetes with end organ damage type 1	249.01-249.05, 249.08
type2	250.01-250.05, 250.08
Any tumour	140-194
Leukaemia	204-207
Lymphoma	200-203,275.59
Moderate to severe liver disease	070.00, 070.02, 070.04, 070.06, 070.08, 573.00, 456.00-456.09
Metastatic solid tumour	195-198, 199
AIDS	079.83
Psychiatric conditions	
Schizophrenia	295, 29719, 29799
Bipolar disorder, depression, and recurrent depression	296, 29809, 29819
Schizotypal disorder	30183
Personality disorders	300, 30100–30199 except 30183
Other mental illness (including all other psychiatric diagnoses, *e.g.*, primary alcohol or substance abuse, organic disorders, anxiety disorders, adjustment disorders).	Remainder of 290-315 codes

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1-2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6-7
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	6-7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-8
Bias	9	Describe any efforts to address potential sources of bias	12
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8
		(*b*) Describe any methods used to examine subgroups and interactions	8
		(*c*) Explain how missing data were addressed	8
		(*d*) If applicable, explain how loss to follow-up was addressed	8
		(*e*) Describe any sensitivity analyses	8
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9
		(b) Indicate number of participants with missing data for each variable of interest	19
		(c) Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	Report numbers of outcome events or summary measures over time	9

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	9-11 NA 9-11
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	11-12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	15

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.