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Original Contribution

The Association Between Perceived Stress and Mortality Among People With Multimorbidity: A Prospective Population-Based Cohort Study

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Multimorbidity is common and is associated with poor mental health and high mortality. Nevertheless, no studies have evaluated whether mental health may affect the survival of people with multimorbidity. We investigated the association between perceived stress and mortality in people with multimorbidity by following a population-based cohort of 118,410 participants from the Danish National Health Survey 2010 for up to 4 years. Information on perceived stress and lifestyle was obtained from the survey. We assessed multimorbidity using nationwide register data on 39 conditions and identified 4,229 deaths for the 453,648 person-years at risk. Mortality rates rose with increasing levels of stress in a dose-response relationship (P-trend < 0.0001), independently of multimorbidity status. Mortality hazard ratios (highest stress quintile vs. lowest) were 1.51 (95% confidence interval (CI): 1.25, 1.84) among persons without multimorbidity, 1.39 (95% CI: 1.18, 1.64) among those with 2 or 3 conditions, and 1.43 (95% CI: 1.18, 1.73) among those with 4 or more conditions, when adjusted for disease severities, lifestyle, and socioeconomic status. The numbers of excess deaths associated with high stress were 69 among persons without multimorbidity, 128 among those with 2 or 3 conditions, and 255 among those with 4 or more conditions. Our findings suggested that perceived stress contributes significantly to higher mortality rates in a dose-response pattern, and more stress-associated deaths occurred in people with multimorbidity.

chronic disease; comorbidity; longitudinal studies; mental health; mortality; prognosis; stress, psychological

Abbreviations: CI, confidence interval; HR, hazard ratio; PSS, Perceived Stress Scale.

Multimorbidity (2 or more concurrent long-term health conditions) is common in the general population. The widespread prevalence of multimorbidity is primarily due to the growing incidence of chronic diseases in an increasingly aging population (1), and it is currently one of the most significant challenges faced by health care providers worldwide (2, 3). Moreover, a social pattern is seen: Multimorbidity is substantially more common in areas of socioeconomic deprivation, even in younger age groups (4). Multimorbidity is associated with impaired quality of life (5), increased health-care utilization (6), and high mortality rates (7).

Cross-sectional studies have shown that multimorbidity is associated with mental health conditions (4, 8, 9) and that the risk of depression increases with the number of physical conditions (10). Mental health conditions influence quality of life worldwide (11) and have been associated with a wide range of adverse health outcomes, including higher risk of cardiovascular events (12), metabolic syndrome (13), and death (14). An underlying physiological mechanism may explain the relationship between mental disorders and physical disorders, and neuroendocrine deregulation of the hypothalamic-pituitary-adrenal axis has been suggested because it may cause changes in the immune and inflammation system. These processes have been conceptualized as allostatic load (15–17), which may contribute to the development of multimorbidity and increased risk of chronic physical conditions in patients with mental health disorders (18, 19). Even subclinical perceived stress has been linked to changes in cortisol levels, the

immune system response, and cortical reactivity (20–23). Perceived stress may also lead to undesirable health behavior, such as a sedentary lifestyle, which might affect the prognosis of chronic diseases (24, 25).

Although high perceived stress levels are common in the Danish population (26) and the combination of perceived stress and multimorbidity may dim the prognosis, to our knowledge no previous studies have investigated this issue. Also, more prospective studies on multimorbidity are warranted (27). The purpose of this study was to investigate the association between perceived stress and mortality among people with multimorbidity in a large population-based cohort, which was followed for 4 years without loss to follow-up, while considering lifestyle factors, socioeconomic status, and morbidity burden.

METHODS

Study population

We performed a population-based cohort study based on data from participants in the mail- and Web-based Danish National Health Survey in 2010 (28). This nationally representative survey included both a random sample of all Danish citizens in the 5 regions of Denmark and an additional national sample. We included participants aged 25 years or older who had completed the questions on perceived stress (Figure 1); the Region of Southern Denmark did not include information on perceived stress in their survey. The cohort was accurately linked at the individual level to nationwide health registers through the unique 10-digit Danish personal identification number, which is assigned to all Danish citizens upon birth or immigration. All participants entered the study on May 1, 2010 (baseline), when all questionnaires were collected. All participants were followed until death, emigration, or the end of the study (latest time point with full register information; March 29, 2014), whichever came first.

The study was based on anonymized data located at Statens Serum Institut, a Danish governmental public health and research institution, and was approved by the Danish Data Protection Agency (record 2013-41-1719).

Information from the Danish National Health Survey

The primary exposure was perceived stress as measured by the Danish version of Cohen's 10-item Perceived Stress Scale (PSS) (29, 30), which is a self-report measure of subjective stress. Respondents indicate how often they have found their life unpredictable, uncontrollable, and overloaded in the past month. The instrument has demonstrated good validity and reliability (30, 31). Cronbach's α was 0.88 in our study population. All items were scored on a 5-point Likert scale (total sum scores: 0–40); high scores indicated high levels of stress. Because no standard cutoffs were predefined (29), we categorized all PSS sum scores into quintiles; scores in the highest quintile (>17) are generally considered abnormal (26).

Other baseline characteristics retrieved from the survey questionnaire included employment status and lifestyle factors such as physical activity, alcohol habits, smoking status, dietary habits, and body mass index (28).

Information from Danish national health registers

Study participants were categorized as having multimorbidity if they had 2 or more of 39 specific long-term conditions (Table 1). The composition of our multimorbidity index was based on recommendations in systematic reviews (32, 33), a large epidemiologic study by Barnett et al. (4), and other

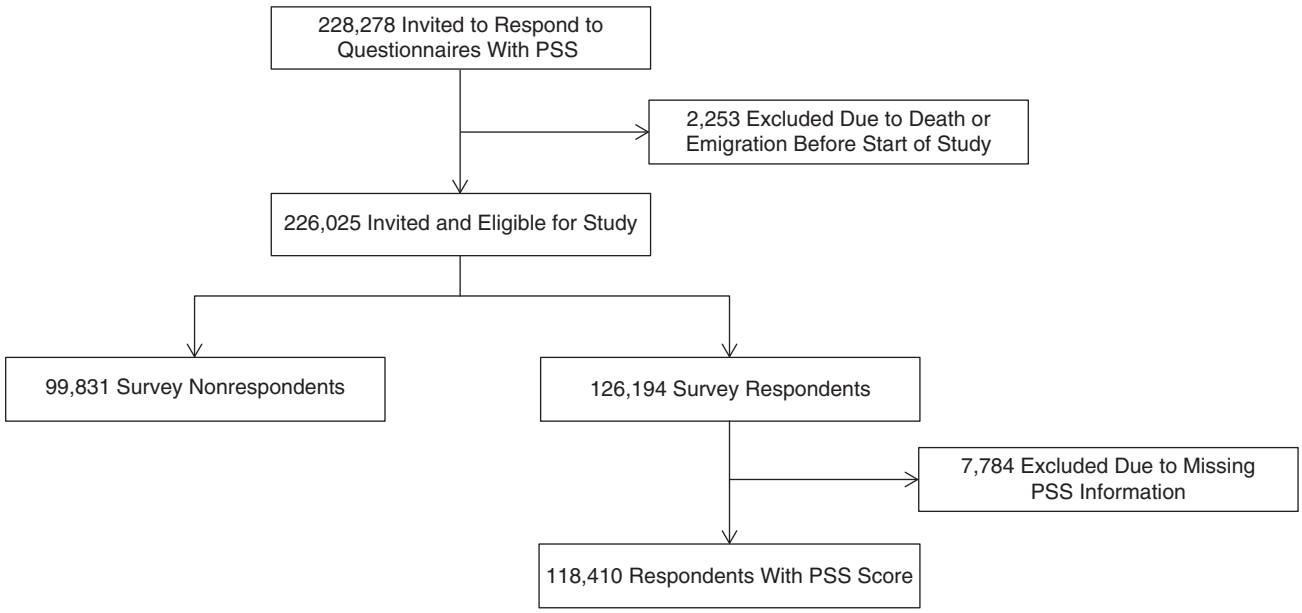

Figure 1. Selection of participants with Perceived Stress Scale (PSS) scores for an analysis of stress and mortality among people with multimorbidity, Danish National Health Survey, 2010–2014.

Table 1. List of Adverse Health Conditions in the Multimorbidity Index, Danish National Health Survey, 2010–2014

Category	Disease Group
Circulatory system	Hypertension
	Dyslipidemia
	Ischemic heart disease
	Atrial fibrillation
	Heart failure
	Peripheral artery occlusive disease
	Stroke
Endocrine system	Diabetes mellitus, types 1 and 2
	Thyroid disorder
	Gout
Pulmonary system and allergy	Chronic pulmonary disease
	Allergy
Gastrointestinal system	Ulcer/chronic gastritis
	Chronic liver disease
	Inflammatory bowel disease
	Diverticular disease of intestine
Urogenital system	Chronic kidney disease
	Prostate disorder
Musculoskeletal system	Connective tissue disorder
	Osteoporosis
	Painful condition
Hematological system	Anemia
	HIV/AIDS
Cancers	Cancer
Neurological system	Vision problem
	Hearing problem
	Migraine
	Epilepsy
	Parkinson disease
	Multiple sclerosis
	Neuropathy
Mental health conditions	Mood, stress-related, or anxiety disorder
	Psychological distress
	Alcohol problem
	Substance abuse
	Anorexia/bulimia
	Bipolar affective disorder
	Schizophrenia or schizoaffective disorder
	Dementia

Abbreviations: AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency virus.

established comorbidity indices (34–37). We reviewed the disease definitions to ensure good capture in Danish health registers and to accommodate the use of the Danish *International Classification of Diseases, Tenth Revision*, and Anatomical Therapeutic Chemical Classification System drug codes. The conditions were identified by combining diagnosis codes entered into Danish national registers by all Danish hospitals and outpatient clinics with data on redeemed prescriptions for medication within predefined time frames up to 15 years before baseline (38–42). Conditions were categorized as either physical conditions or established mental health conditions and were analyzed independently from the perceived stress score (algorithm presented in Web Table 1, available at http://aje.oxfordjournals.org/). We categorized study participants according to their multimorbidity status at baseline as having either no (at most 1 condition), moderate (2 or 3 conditions), or severe (4 or more conditions) multimorbidity. The survey included information on 18 self-reported chronic conditions (Web Table 2), which were not included in the multimorbidity index because the disease definitions in the questionnaire were not sufficiently specific and compatible with the multimorbidity index. The self-reported conditions were, however, included in a sensitivity analysis.

Information from the Danish Civil Registration System and Statistics Denmark

Our main outcome was all-cause mortality rates. Information on death, age, sex, and emigration during the study period was obtained from the Danish Civil Registration System, which holds updated records on the vital status of all Danish citizens (43). Individual socioeconomic factors (education, ethnicity, and cohabitation status) were obtained from Statistics Denmark (44).

Statistical analyses

For the main analyses, hazard ratios for all-cause mortality with 95% confidence intervals were calculated using a Cox proportional hazards model with age as the time axis. We tested the proportional hazards assumption using log(−log(survival)) plots.

We imputed missing data on lifestyle and socioeconomic factors in a chained equations model, including all covariates and pseudo-values for death, and generated 20 imputation sets (45, 46).

The PSS quintiles were compared using the first quintile (lowest stress level) as the referent. Covariates were selected a priori and were included successively in 4 models with increasing complexity. First, we adjusted the results for sex in addition to the intrinsic correction for age (used as the time scale). Second, we adjusted for the 31 physical conditions and then for the 8 mental health conditions as dummy variables. Third and fourth, adjustments for lifestyle and socioeconomic factors were added, respectively. Sensitivity models omitting adjustments for lifestyle and mental health conditions were fitted along with a model adjusting for self-reported conditions. PSS quintile was allowed to interact with level of multimorbidity; that is, analyses were stratified on the multimorbidity level, assuming an equal effect of correction factors across strata. A test for linear trend was performed in which we analyzed PSS quintile numbers as a continuous variable. We added a restricted cubic splines model with 5 knots over the full PSS score range using Harrell's default percentiles to evaluate the functional

Table 2. Distribution of Participant Characteristics (%)[a] According to Quintile of PSS Score ($n = 118,410$), Danish National Health Survey, 2010–2014

Characteristic	No. of Participants	% of Participants	Quintile of PSS Score				
			1 ($n = 26,636$)	2 ($n = 27,808$)	3 ($n = 21,256$)	4 ($n = 21,102$)	5 ($n = 21,608$)
Median PSS score (range)			4 (0–6)	9 (7–10)	12 (11–13)	15 (14–17)	21 (18–40)
Age at baseline, years[b]							
25–34	13,881	11.7	17.9	23.7	19.5	18.9	20.0
35–44	22,673	19.1	20.9	24.5	18.9	17.2	18.4
45–54	25,272	21.3	22.9	24.3	18.2	16.8	17.9
55–64	26,610	22.5	25.5	24.0	17.3	17.0	16.2
65–74	19,982	16.9	25.8	22.9	17.1	18.2	15.9
≥75	9,992	8.4	16.8	18.4	16.5	21.7	26.6
Sex[b]							
Male	54,968	46.4	26.1	24.8	17.7	16.5	14.8
Female	63,442	53.6	19.4	22.3	18.1	19.0	21.2
No. of comorbid conditions[b]							
0	58,718	49.6	25.6	26.3	18.9	16.5	12.7
1	25,755	21.8	22.2	22.9	17.8	18.1	18.9
2	14,677	12.4	21.1	21.5	17.3	18.6	21.6
3	8,999	7.6	17.9	19.9	16.4	19.5	26.3
≥4	10,261	8.7	11.7	15.0	15.0	22.0	36.4
Any mental health condition[b]							
No	109,137	92.2	23.8	24.6	18.4	17.7	15.5
Yes	9,273	7.8	7.3	10.9	12.3	19.5	50.0
Physical activity, type and hours/week							
Light or none, 0	16,818	14.2	13.1	16.2	15.2	20.4	35.1
Moderate, ≥4	70,357	59.4	22.3	23.8	18.5	18.3	17.1
Heavy, ≥4	28,980	24.5	29.1	27.4	18.3	14.8	10.4
Missing	2,255	1.9	15.4	17.3	15.6	22.9	28.9
Alcohol habits, drinks/week[c]							
<7/<14	76,894	64.9	23.9	24.8	18.4	17.2	15.7
7–14/14–21	15,768	13.3	24.0	24.4	18.8	17.7	15.2
>14/>21	11,110	9.4	21.9	22.3	17.5	18.0	20.2
Missing	14,638	12.4	13.8	16.3	15.1	21.3	33.5
Smoking status							
Never smoker	50,386	42.6	24.7	24.8	18.1	17.1	15.3
Former smoker	38,812	32.8	22.9	24.0	18.4	17.8	16.9
Current smoker	27,012	22.8	18.4	20.5	17.1	18.9	25.1
Missing	2,200	1.9	14.6	20.7	15.9	21.6	27.1

Table continues

form, and the results are presented graphically along with the PSS quintile estimates and a distribution histogram.

Absolute differences were reflected by cumulative incidence proportions. Excess deaths associated with stress were calculated using the PSS quintile hazard ratio relative to actual deaths within the multimorbidity status group (deaths × (hazard ratio (HR) − 1)/HR). We assessed effect modification by testing sex and multimorbidity status for multiplicative and additive

Table 2. Continued

Characteristic	No. of Participants	% of Participants	Quintile of PSS Score				
			1 (*n* = 26,636)	2 (*n* = 27,808)	3 (*n* = 21,256)	4 (*n* = 21,102)	5 (*n* = 21,608)
Dietary habits[d]							
Unhealthy	13,461	11.4	18.2	21.3	17.4	19.2	24.0
Medium	71,223	60.1	22.4	23.5	18.3	18.0	17.9
Healthy	29,854	25.2	25.5	25.2	17.6	16.4	15.2
Missing	3,872	3.3	16.2	18.2	15.6	21.0	28.9
Body mass index[e]							
Underweight (<18)	1,899	1.6	16.6	20.1	14.8	18.1	30.4
Normal weight (18–<25)	55,295	46.7	23.4	24.2	18.3	17.5	16.6
Overweight (25–<30)	41,957	35.4	23.5	24.1	18.0	17.6	16.9
Obese (≥30)	17,274	14.6	18.7	20.5	17.4	19.2	24.2
Missing	1,985	1.7	14.3	19.8	15.1	20.4	30.5
Working status							
Not working	45,573	38.5	19.9	20.0	16.3	18.8	24.9
Working	69,164	58.4	24.5	26.0	19.1	17.0	13.3
Missing	3,673	3.1	15.5	18.5	16.7	21.1	28.1
Education, years[b]							
<10	26,626	22.5	16.9	19.3	16.8	20.8	26.2
10–15	57,108	48.2	22.3	24.3	18.6	17.8	17.0
>15	32,392	27.4	27.9	26.0	17.9	15.3	12.9
Missing	2,284	1.9	14.5	16.2	16.0	20.1	33.2
Cohabitation status[b]							
Single	29,241	24.7	18.4	20.1	16.7	19.5	25.3
Cohabiting	89,169	75.3	23.8	24.6	18.4	17.3	15.9
Ethnicity[b]							
Danish	111,720	94.4	23.0	23.9	18.1	17.6	17.4
Other Western background	3,258	2.8	20.1	19.9	17.0	19.8	23.2
Other	3,432	2.9	7.1	12.8	13.5	24.2	42.5

Abbreviation: PSS, Perceived Stress Scale.

[a] Table shows data with missing values before multiple imputations. All data presented are percentages unless otherwise indicated.

[b] Variable was based on data from national registers. (Other variables were based on survey responses.)

[c] Number of alcoholic drinks consumed per week for females/males.

[d] Assessment of dietary habits was based on self-reported portions of meats, vegetables, fruit, and fat compared to national nutrition guidelines.

[e] Body mass index was calculated as weight (kg)/height $(m)^2$.

interactions (relative excess risk due to interaction) with the PSS quintile.

Point estimates and 95% confidence intervals of mortality rates in the PSS quintiles are presented graphically for the 3 multimorbidity status groups in a common graph. The results for the groups with multimorbidity were rescaled to ensure that the ratio between the depicted average relative mortality rates for these groups and the group without multimorbidity corresponded to the estimated mortality rate ratio between the groups when corrected for age, sex, socioeconomic factors, and lifestyle but not for conditions. Differences between points on the same curve were also corrected for number and type of condition, whereas level variations between curves reflected the actually observed differences in condition status in people from different multimorbidity status groups. The risk time-weighted average over the PSS quintiles was used.

In a subgroup analysis of people with mental health conditions, we assessed their relative mortality rates and absolute

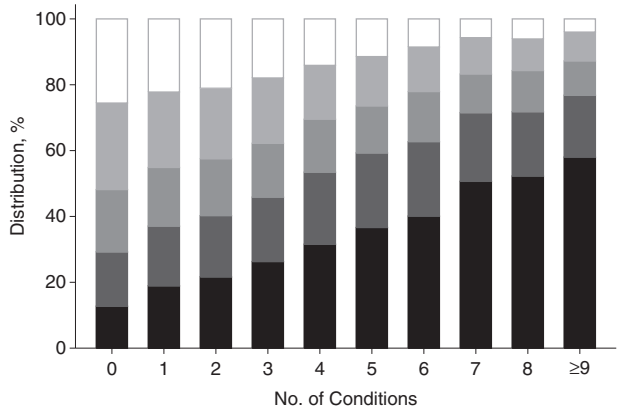

Figure 2. Distribution of quintiles of Perceived Stress Scale (PSS) score according to number of adverse health conditions, Danish National Health Survey, 2010–2014. White bars show quintile 1 (scores 0–6). Light gray bars show quintile 2 (scores 7–10). Medium gray bars show quintile 3 (scores 11–13). Dark gray bars show quintile 4 (scores 14–17). Black bars show quintile 5 (scores 18–40). No multimorbidity: ≤1 condition; moderate multimorbidity: 2–3 conditions; and severe multimorbidity: ≥4 conditions. *P*-trend < 0.0001 for mean PSS scores by number of conditions.

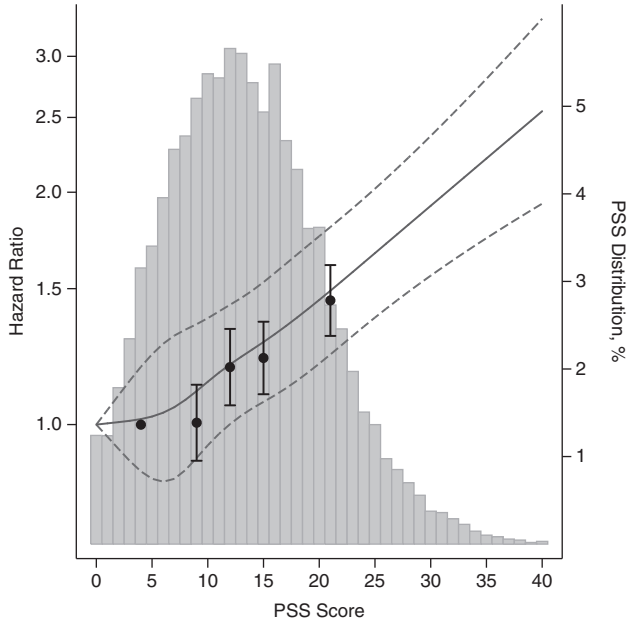

Figure 3. Overall association between Perceived Stress Scale (PSS) score and mortality hazard ratio displayed as PSS-quintile estimates and restricted cubic splines, Danish National Health Survey, 2010–2014. Circle with error bars shows hazard ratios with 95% confidence intervals for PSS quintiles adjusted for age, sex, 39 register-based health conditions, lifestyle, and socioeconomic factors, placed at the median within the quintile's range. Full line with dashed lines shows hazard ratios with 95% confidence intervals for restricted cubic splines of PSS scores adjusted for age, sex, 39 register-based health conditions, lifestyle, and socioeconomic factors. Gray columns represent the distribution of PSS scores (%) in the study population.

differences in the numbers of deaths compared with people with no mental health conditions. In a subgroup analysis of educational level, we stratified by dichotomized level of education (<10 years vs. ≥10 years).

Sensitivity analyses were performed to compare our main model with models using alternative ways of adjusting for multimorbidity, such as simple disease count, weighted Charlson comorbidity index scores (34), and complete-case analysis. Finally, we compared survey respondents and nonrespondents by using register data. All *P* values were 2-sided. Analyses were performed using Stata, version 13.1 (StataCorp LP, College Station, Texas).

RESULTS

We followed 118,410 individuals with PSS scores (Figure 1) for a total of 453,648 person-years at risk (mean follow-up time = 3.8 years). We identified 4,229 deaths, of which 3,224 (76%) occurred in participants with multimorbidity.

High levels of stress (cutpoint for the highest quintile of PSS score: ≥18) were associated with female sex, physical inactivity, high alcohol intake, smoking, unhealthy dietary habits, high or low body mass index, lower educational level, unemployment, non-Danish ethnic background, and living alone (Table 2). Half of all people with a mental health condition were categorized in the highest stress quintile, but in this quintile there were also nearly 4 times as many people without a mental health condition (16,970 vs. 4,638).

In our cohort, 20% of participants had moderate multimorbidity (2 or 3 conditions), and 9% had severe multimorbidity (4 or more conditions). Multimorbidity was associated with older age, physical inactivity, unhealthy dietary habits, high or low body mass index, lower educational level, unemployment, and living alone (Web Table 3). The proportion of people who reported high perceived stress rose consistently with increasing number of conditions (Figure 2).

The proportion of people with missing data on lifestyle and socioeconomic factors ranged from 1.7% (body mass index) to 12.4% (alcohol habits), and people with missing data tended to report higher levels of stress and multimorbidity.

The overall mortality rate rose with increasing stress levels; the study participants in the highest quintile of PSS score had a 3-fold higher mortality rate than those in the lowest quintile (age- and sex-adjusted HR = 2.95, 95% confidence interval (CI): 2.68, 3.25). The estimates were attenuated when adjusted for physical and mental health conditions, lifestyle, and socioeconomic factors, but the risk remained significant (adjusted HR = 1.45, 95% CI: 1.30, 1.61) (Figure 3). The fully adjusted cubic spline model showed a dose-response relationship between stress and mortality rate over the PSS score range, with no evident threshold levels (Figure 3). The overall mortality rate was higher in people with moderate multimorbidity (adjusted HR = 1.79, 95% CI: 1.65, 1.96) and severe multimorbidity (adjusted HR = 3.10, 95% CI: 2.83, 3.39) than in those without multimorbidity.

Stratification by multimorbidity status showed that stress was associated with higher mortality rates in all strata and adjustment models (Table 3). Fully adjusted mortality hazard ratios (highest vs. lowest quintile of PSS score) were 1.51

Table 3. Mortality Hazard Ratios for Quintiles of PSS Score According to Multimorbidity Status, Danish National Health Survey, 2010–2014

No. of Conditions and Quintile of PSS Score	No. of Deaths	CIP	Model 1[a]		Model 2a[b]		Model 2b[c]		Model 3[d]			
			HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	*P*-Trend[e]	No. of Excess Deaths Associated With Stress[f]
0–1 conditions												
1	223	0.011	1	Referent	1	Referent	1	Referent	1	Referent	<0.0001	Referent
2	218	0.010	1.10	0.91, 1.32	1.09	0.91, 1.32	1.09	0.90, 1.31	1.06	0.88, 1.28		12
3	171	0.011	1.23	1.01, 1.50	1.22	1.00, 1.49	1.22	1.00, 1.49	1.13	0.93, 1.38		20
4	188	0.013	1.43	1.18, 1.74	1.41	1.16, 1.72	1.40	1.16, 1.71	1.19	0.98, 1.45		30
5	205	0.017	2.16	1.79, 2.62	2.09	1.73, 2.53	2.06	1.70, 2.49	1.51	1.25, 1.84		69
2–3 conditions												
1	225	0.048	1	Referent	1	Referent	1	Referent	1	Referent	<0.0001	Referent
2	222	0.045	1.00	0.83, 1.20	0.96	0.80, 1.16	0.97	0.80, 1.16	0.95	0.79, 1.14		−12
3	230	0.057	1.34	1.11, 1.61	1.30	1.08, 1.56	1.30	1.08, 1.56	1.19	0.99, 1.43		37
4	285	0.063	1.39	1.16, 1.65	1.33	1.11, 1.58	1.31	1.10, 1.56	1.15	0.97, 1.38		37
5	456	0.082	2.19	1.86, 2.57	1.98	1.68, 2.32	1.88	1.60, 2.21	1.39	1.18, 1.64		128
≥4 conditions												
1	134	0.111	1	Referent	1	Referent	1	Referent	1	Referent	<0.0001	Referent
2	190	0.124	1.12	0.90, 1.40	1.08	0.86, 1.35	1.06	0.85, 1.32	1.01	0.81, 1.26		2
3	230	0.150	1.38	1.12, 1.71	1.32	1.06, 1.63	1.27	1.02, 1.57	1.21	0.98, 1.50		40
4	403	0.179	1.62	1.34, 1.98	1.50	1.23, 1.82	1.43	1.18, 1.75	1.26	1.04, 1.54		83
5	849	0.228	2.36	1.96, 2.83	2.00	1.66, 2.41	1.79	1.48, 2.16	1.43	1.18, 1.73		255

Abbreviations: CI, confidence interval; CIP, cumulative incidence proportion; HR, hazard ratio; PSS, Perceived Stress Scale.
[a] Results were adjusted for age and sex.
[b] Results were adjusted for age, sex, and 31 physical conditions.
[c] Results were adjusted for age, sex, 31 physical conditions, and 8 mental health conditions.
[d] Results were adjusted for age, sex, 31 physical conditions, 8 mental health conditions, and lifestyle and socioeconomic factors.
[e] *P* value from test for trend between PSS quintile numbers and mortality rate within the multimorbidity group.
[f] Absolute number of deaths associated with being in a PSS quintile above 1 within the multimorbidity group.

(95% CI: 1.25, 1.84), 1.39 (95% CI: 1.18, 1.64), and 1.43 (95% CI: 1.18, 1.73) for people with zero or 1, 2 or 3, and 4 or more conditions, respectively (Table 3). In all strata of multimorbidity, stress was associated with a comparably increased mortality rate in a dose-response pattern within each stratum (*P*-trend < 0.0001; Table 3).

We found no statistically significant effect of interactions between multimorbidity status and quintile of PSS score on the multiplicative or additive scales, or between sex and PSS quintile. The combined risk of stress and multimorbidity is shown in Figure 4, which indicates a high risk for those with high perceived stress and multimorbidity when considering the combination and relative severity of conditions between the multimorbidity groups. In absolute number of deaths, the association was even stronger in those with multimorbidity, as evidenced by the cumulative incidence proportions and excess deaths associated with stress (Table 3). The theoretical number of deaths—deaths that could have been prevented if the mortality rate in the highest quintile of PSS score had been reduced to that in the lowest quintile—was 69 for people with no multimorbidity, 128 for people with 2 or 3 conditions, and 255 for people with 4 or more conditions.

In a subgroup analysis, we studied the relationship between stress and mortality rate after stratifying by mental health conditions. We found that a dose-response relationship was present only in people without mental health conditions. Being in the highest quintile of PSS score without having a diagnosed mental health condition was comparable to actually having a mental health condition in terms of relative mortality, but more excess deaths occurred in persons with high perceived stress than in those with mental health conditions (328 deaths vs. 240 deaths) (Table 4).

A subgroup analysis of educational level revealed that the influence of stress and multimorbidity on mortality rates was similar for those with <10 years and ≥10 years of education, although people with more years of education and no multimorbidity seemed to have lower mortality rates than people with fewer years of education and no multimorbidity (Figure 5).

Our sensitivity analysis, which omitted adjustments for lifestyle, yielded higher hazard ratios, especially for those with multimorbidity. Excluding people with mental health conditions from the main analysis and the additional adjustments for self-reported conditions did not change the estimates significantly. In alternative adjustment models for multimorbidity and complete-case analysis, no systematic differences from the main analysis were found (Web Figure 1).

The overall response rate was 56%. Based on the data from national registers, nonrespondents were more likely to be

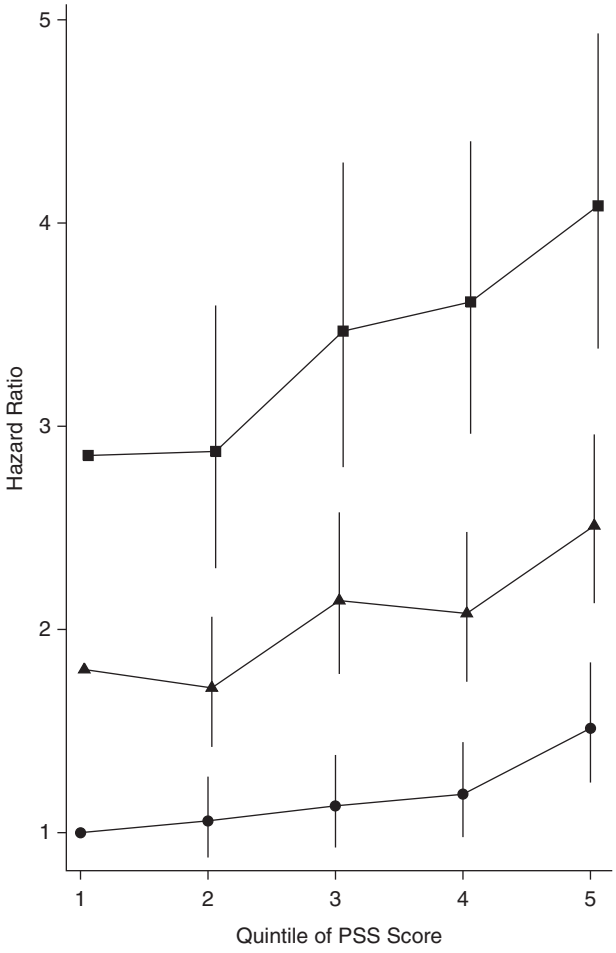

Figure 4. Hazard ratio for mortality according to multimorbidity status and quintile of Perceived Stress Scale (PSS) score, Danish National Health Survey, 2010–2014. Circles, ≤1 adverse health condition; triangles, 2–3 adverse health conditions; squares, ≥4 adverse health conditions. Associations between mortality rate and PSS score quintiles were adjusted for age, sex, 39 register-based health conditions, lifestyle, and socioeconomic factors. Associations between mortality rate and multimorbidity status groups were adjusted for age, sex, lifestyle, and socioeconomic factors. *P*-trend < 0.0001 in all multimorbidity status groups. Vertical lines, 95% confidence intervals.

male, to have more physical and mental health conditions, and to have fewer years of education. Furthermore, some variations (e.g., by age) were found in the response rates (Web Table 4). The overall mortality rate in nonrespondents during follow-up was higher than that in respondents when results were adjusted for age, sex, all register-based conditions, and socioeconomic factors (adjusted HR = 1.53, 95% CI: 1.10, 2.13). The association between mental health conditions, multimorbidity, and mortality rates was comparable in both respondents and nonrespondents (Web Table 5).

DISCUSSION

This large population-based cohort study showed that greater perceived stress and more severe multimorbidity were independently associated with a higher mortality rate and that perceived stress was associated with mortality rate in a dose-response manner with no evident threshold level. In absolute numbers, high perceived stress was associated with nearly 2–4 times more deaths, depending on the number of comorbid conditions, in people with multimorbidity than in people without it. These findings suggest that people with multimorbidity are a vulnerable patient group. Being in the highest stress quintile was comparable to having a mental health condition in terms of relative mortality, but high perceived stress with no mental health condition was associated with more deaths in absolute numbers.

Strengths and limitations of this study

A major strength of this study is the large population-based cohort and the combination of survey and register-based information. Our study extends previous knowledge on psychological stress and multimorbidity in several ways. We had prospectively collected data on the diagnoses and medication prescriptions of a homogeneous background population with detailed baseline information on individual lifestyle and socioeconomic factors. Our sample size allowed us to investigate mortality rates across graduated levels of stress and multimorbidity. The use of national registers ensured highly valid data on both deaths and migration with no loss to follow-up. However, the survey participation rate was 56%, which could limit the generalizability of our findings. Furthermore, selection bias may exist if the association between stress and mortality rate was different between respondents and nonrespondents. We found higher morbidity and mortality rates in nonrespondents than in respondents, but the association between mental health conditions, multimorbidity, and mortality rate was comparable in respondents and nonrespondents. We would expect higher levels of perceived stress in nonrespondents and have no reason to assume that the association found between stress and mortality rate depended on participation.

The PSS was chosen to measure stress in the Danish National Health Survey due to the qualities of this validated scale. The PSS measures the level of perceived chronic stress within the past month and seems to be stable over time (47). Even if a narrow stress construct is measured (29), the PSS correlates moderately or strongly with other measures of psychological distress and quality of life (e.g., the General Health Questionnaire, Beck's Depression Inventory, the Center for Epidemiologic Studies Depression Scale, the mental component of the 36-item Short Form Health Survey) (31) and other stress concepts (e.g., measurement of cortisol response and life-event scales) (20, 29). The correlation between the PSS score and mental health conditions was reflected by the high stress levels among the persons with mental illness included in our study. With no standard cutoffs, the PSS offers no threshold for diagnosable psychiatric disease (29).

There is no consensus in the literature about which conditions to include in a multimorbidity index (33). Multimorbidity status in our study was based on clinically acknowledged conditions from all Danish hospitals and outpatient clinics, including recommended key diseases (32). Because diagnoses from primary care were not available, our algorithm included redeemed

Table 4. Adjusted Mortality Hazard Ratios for Quintiles of PSS Score According to Number of Established Mental Health Conditions, Danish National Health Survey, 2010–2014

Quintile of PSS Score	No Mental Health Conditions ($n = 109,137$)				At Least 1 Mental Health Condition ($n = 9,273$)			
	No. of Deaths	HR	95% CI	No. of Excess Deaths Associated With Stress	No. of Deaths	HR	95% CI	No. of Excess Deaths Associated With Mental Health Conditions
Overall[a]	3,404	1	Referent	Referent	825	1.41	1.30, 1.54	240
1[b]	541	1	Referent	Referent	41	1	Referent	15
2[b]	564	0.99	0.88, 1.11	−6	66	1.13	0.76, 1.67	24
3[b]	554	1.19	1.05, 1.34	88	77	1.13	0.77, 1.65	29
4[b]	734	1.24	1.11, 1.39	142	142	1.00	0.70, 1.41	53
5[b]	1,011	1.48	1.32, 1.65	328	499	1.28	0.93, 1.77	185

Abbreviations: CI, confidence interval; HR, hazard ratio; PSS, Perceived Stress Scale.

[a] Hazard ratios were adjusted for PSS quintile, age, sex, all physical conditions, lifestyle, and socioeconomic factors.

[b] Hazard ratios were adjusted for any mental health condition, age, sex, all physical conditions, lifestyle, and socioeconomic factors.

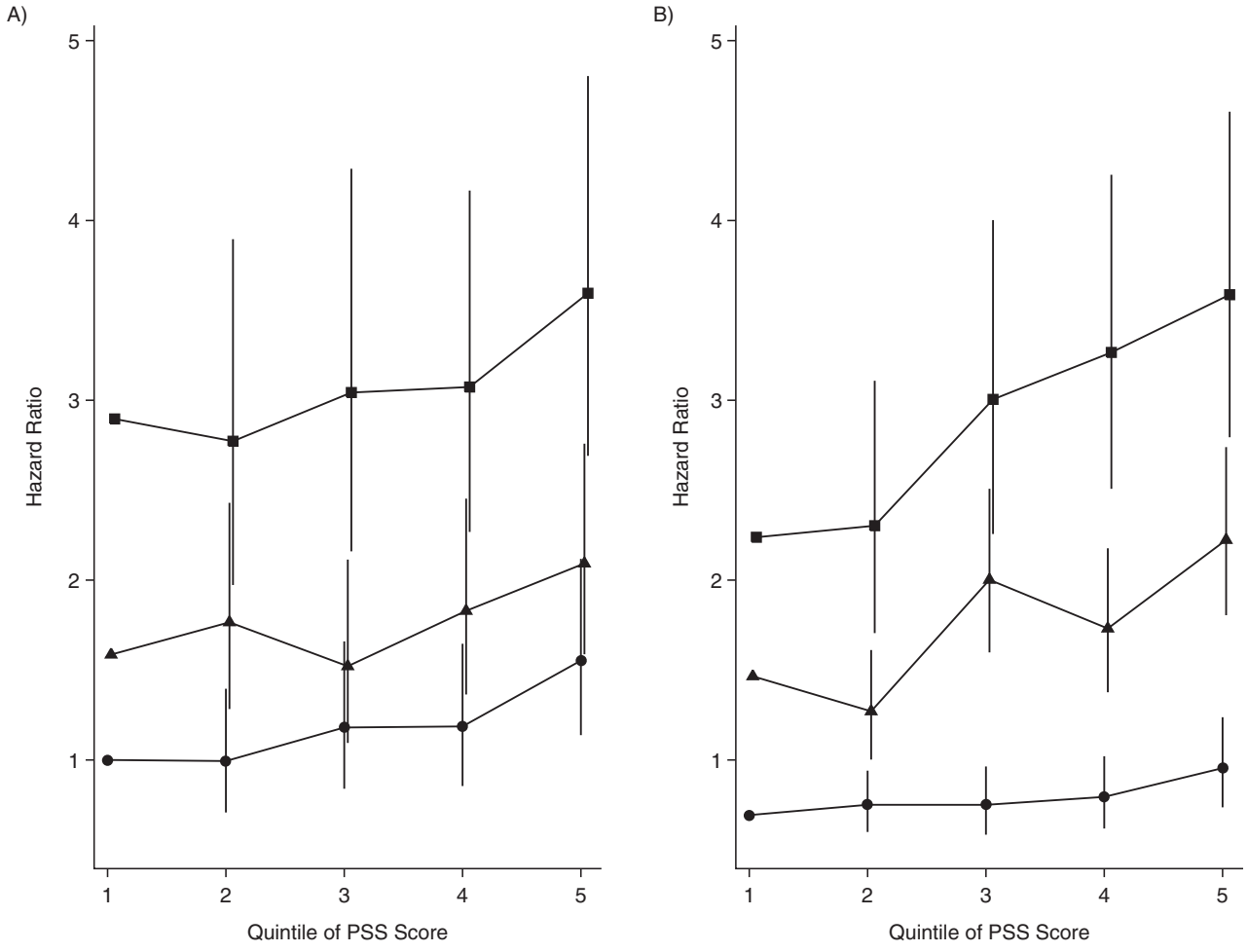

Figure 5. Hazard ratio for mortality according to multimorbidity status, quintile of Perceived Stress Scale (PSS) score, and educational level, Danish National Health Survey, 2010–2014. A) <10 years of education; B) ≥10 years of education. Circles, ≤1 adverse health condition; triangles, 2–3 adverse health conditions; squares, ≥4 adverse health conditions. Associations between mortality rate and PSS quintiles were adjusted for age, sex, 39 register-based health conditions, lifestyle, and socioeconomic factors, except level of education. Associations between mortality rate and multimorbidity status groups were adjusted for age, sex, and lifestyle factors. Vertical lines, 95% confidence intervals.

medication prescriptions from all pharmacies to capture conditions commonly treated in primary care, but this approach did not allow us to control for prescription compliance, untreated conditions, or stage and severity of disease in individuals for whom no data were available.

Multimorbidity studies often use simple disease-count models to estimate the morbidity burden. However, if the relative severity of disease combinations is not considered in the analysis, residual confounding may occur. To counter this, we adjusted our analyses for all conditions individually, which allowed us to establish the contribution of each individual condition to the mortality rate in addition to stratification for multimorbidity. Sensitivity analyses adjusting for disease count and the Charlson comorbidity index showed similar results.

We were able to control for a wide range of potential confounders at the individual level, including sex, physical and mental health conditions, lifestyle, and socioeconomic factors. However, some of these factors could be either upstream or downstream on the causal pathway and could act as intermediate variables; for example, exposure to stress may cause an unhealthy lifestyle, which may lead to increased mortality. Omitting adjustments for lifestyle yielded noticeably higher risks. Thus, our conservative approach of adjusting for all factors could have led to underestimation of the true association between stress and mortality rate. Although the association between stress and mortality rate remained significant after adjustments for confounding, such an association may not be causal; perceived stress could merely be a nonspecific marker for the severity of any underlying conditions, and treatment of stress would have an effect on mortality only if the association is causal.

Comparison with other studies

To our knowledge, this study was the first to assess mortality while accounting for the interplay between stress and multimorbidity. Previous studies have found a connection between mental health conditions and single-disease outcomes (12, 13), mortality (14), and multimorbidity (4, 9), but knowledge of how these factors interact and affect prognosis is lacking. Studies on mental-physical multimorbidity are often cross-sectional (4, 9, 10), and prospective studies on psychological distress do not necessarily address multimorbidity (13, 14). Barnett et al. (4) showed that mental-physical multimorbidity and socioeconomic status are closely related. Our results extend this finding; multimorbidity, mental health conditions, and fewer years of education were all factors impairing prognosis after mutual adjustments. Even though unstressed and healthy people with more years of education tended to have a lower baseline mortality rate, their mortality rate was comparable to that of people with fewer years of education when multimorbidity and higher stress levels were present. This could be interpreted as evidence that socioeconomic factors tend to predispose people to diseases that may eventually affect survival and thus make multimorbidity a key factor in well-documented health inequalities in terms of life expectancy (48).

Implications and conclusion

Our findings suggest that screening for depression or anxiety in patients with multimorbidity is not enough to capture the full association between mental health and mortality risk. We found that perceived stress was associated with more deaths than mental health conditions and thus also seems to play a key role in long-term prognosis. Our data do not suggest a critical point for intervention; even moderate stress was associated with increased mortality rates. These new findings call for greater clinical attention to psychological well-being and stress before the threshold for depression or anxiety diagnoses is reached. Stress could be a modifiable risk factor—possibly associated with lifestyle choices—but more research is required to further investigate the causal mechanisms between mental and physical health and substantiate physiological theories of stress and allostatic load (16). The single-disease paradigm has long been the standard in research and practice, but this approach is inadequate when treating people with multimorbidity, particularly when mental health problems are present. Thus, our study supports the adage that there is "no health without mental health" (3). Personalized care in a biopsychosocial context and a strong focus on mental health are essential when treating people with multimorbidity. Nevertheless, policies, guidelines, and practice structures to support people with multimorbidity are generally lacking. Although scientific evidence on stress management is limited, talk therapy, problem-solving therapy, and mindfulness-based stress reduction could play a role in reducing perceived stress in people with chronic conditions (49, 50). Furthermore, mounting evidence indicates that collaborative care models are effective in treatment of depression with comorbid medical conditions (51–53). Similar models, based on joint primary or secondary prevention targeting both mental and physical health, could prove efficient in people with stress and multimorbidity. More prospective studies are needed to further study this complex issue (54).

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