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**The Association between Stress and Mortality among People with Multimorbidity:
A Prospective Population-Based Cohort Study**

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Abbreviations:

CI: Confidence interval

HR: Hazard ratio

PSS: Perceived Stress Scale

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ABSTRACT

Multimorbidity is common and 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 four years. Information on perceived stress and lifestyle was obtained from the survey. We assessed multimorbidity using nationwide register data on 39 condition categories 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 (trend $P < 0.0001$), independently of multimorbidity status. Mortality hazard ratios (highest versus lowest stress quintile) were 1.51 (95% confidence interval (CI): 1.25, 1.84) for no multimorbidity, 1.39 (95% CI: 1.18, 1.64) for two or three conditions, and 1.43 (95% CI: 1.18, 1.73) for four or more conditions when adjusted for disease severities, lifestyle, and socioeconomic status. Excess deaths associated with high stress were 69, 128, and 255, respectively. Our study suggests that perceived stress contributes significantly to higher mortality rates in a dose-response pattern, and more stress associated deaths occurred in people with multimorbidity.

MeSH keywords:

Stress, Psychological

Mental Health

Chronic Disease

Comorbidity

Mortality

Prognosis

Longitudinal Studies

Multimorbidity (two or more concurrent long-term health conditions) is common in the general population. The widespread prevalence is primarily due to the growing incidence of chronic diseases in an increasingly aging population (1) and is currently one of the most significant challenges faced by healthcare providers worldwide (2, 3). Moreover, a social pattern is seen as 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 healthcare 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 and physical disorders, and neuroendocrine deregulation of the hypothalamic pituitary adrenal axis has been suggested as this 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, the immune system response and cortical reactivity (20-23). Perceived stress may also lead to undesirable health behavior, such as 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 impair the prognosis, no former

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 four 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 five Danish regions 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 1 May 2010 (baseline) when all questionnaires were collected. All participants were followed until death, emigration, or end of study (latest time point with full register information; 29 March 2014), whichever came first.

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. Responding subjects 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 alpha was 0.88 in our study population. All items were scored on a 4-point Likert scale (total sum scores: 0–40); high scores indicated high levels of stress. As no standard cut-offs were predefined (29), we categorized all PSS sum scores into quintiles; scores in the highest quintile (≥ 15 –17) are generally considered abnormal (26).

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

Information from Danish national health registers

Study participants were categorized with multimorbidity if they had two 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 epidemiological study by Barnett et al. (4), and other 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, 10th version, and Anatomical Therapeutic Chemical 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 of drugs within predefined time frames up to 15 years

before baseline (38-42). Conditions were categorized as either “physical” or “established mental health” conditions and regarded independently from the perceived stress score (algorithm presented in Web Appendix, Web Table 1). We categorized study participants according to their multimorbidity status at baseline with either no (no or one condition), moderate (two or three conditions), or severe multimorbidity (four or more conditions). The survey included information on 18 self-reported chronic conditions (Web Appendix, 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 of 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 (HR) of all-cause mortality with 95% confidence intervals (CIs) were calculated using a Cox proportional hazard model with age as the time axis. We tested the proportional hazard assumption using $\log(-\log(\text{survival}))$ 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 reference. Covariates were selected a priori and included successively in four models with increasing complexity. First, we adjusted for sex besides the intrinsic correction for age used as time scale. Second, we adjusted for the 31 physical conditions and then for the eight 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 performed along with a model adjusting for self-reported conditions. PSS quintile was allowed to interact with level of multimorbidity, i.e. analyses were stratified on multimorbidity level assuming an equal effect of correction factors across strata. A test for linear trend was performed in which we analyzed PSS quintiles as a continuous variable. A restricted cubic splines model with five knots over the full PSS score range using Harrell's default percentiles was added to evaluate the functional form and is 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 HR relative to actual deaths within the multimorbidity status group ($\text{deaths} \times (\text{HR} - 1) / \text{HR}$). We assessed effect modification by testing sex and multimorbidity status for multiplicative and additive interactions (relative excess risk due to interaction) with the PSS quintile.

Point estimates (and 95% CIs) of mortality rates in the PSS quintiles are presented graphically for the three 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 non-multimorbid group 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. Risk time-weighted average over the PSS quintiles was used.

In a sub-group analysis of people with mental health conditions, we assessed their relative mortality rates and absolute differences in death compared to people with no mental health conditions. In a sub-group analysis of educational level, we stratified by dichotomized level of education (< 10 years versus \geq 10 years of education).

Sensitivity analyses were performed to compare our main model with models using alternative ways of adjusting for multimorbidity, i.e. simple disease count, weighted Charlson comorbidity index scores (34), and complete-case analysis. Finally, we compared survey respondents and non-respondents by using register data. All *P* values were two-sided. Analyses were performed in Stata 13.1 (StataCorp, TX).

RESULTS

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

High levels of stress (highest PSS quintile cut-off score: ≥ 18) were associated with female sex, physical inactivity, high alcohol intake, smoking, unhealthy dietary habits, high or low body mass index, shorter education, 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 this quintile also embraced nearly four times as many people without a mental health condition (16,970 versus 4,638).

In our cohort, 20% had moderate multimorbidity (two or three conditions) and 9% had severe multimorbidity (four or more conditions). Multimorbidity was associated with high age, physical inactivity, unhealthy dietary habits, high or low body mass index, shorter education, unemployment, and living alone (Web Appendix, 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 PSS quintile had a threefold higher mortality rate than those in the lowest quintile (age and sex-adjusted HR 2.95, 95% 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 with no multimorbidity.

Stratification by multimorbidity status showed that stress was associated with increased mortality rates in all strata and adjustment models (Table 3). Fully adjusted mortality HRs (highest versus lowest PSS quintile) was 1.51 (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 no or one, two or three, and four or more conditions, respectively (Table 3). In all strata of multimorbidity, stress was associated with an equally increased mortality rate in a dose-response pattern within each stratum (trend level: $P < 0.0001$, Table 3).

We found no statistically significant interactions between multimorbidity status and PSS quintile 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, which could have been prevented if the mortality rate in the highest PSS quintile had been reduced to that of the lowest PSS quintile, was 69 for people

with no multimorbidity, 128 for people with two or three conditions, and 255 for people with four or more conditions.

In a sub-group 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 PSS quintile 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 those with high perceived stress than in those with mental health conditions (328 versus 240) (Table 4).

A sub-group analysis of educational level revealed that the influence of stress and multimorbidity on mortality rates was similar for those with < 10 years and \geq 10 years of education, although people with longer education and no multimorbidity seemed to have lower mortality rates than people with shorter education and no multimorbidity (Figure 5).

Our sensitivity analysis, which omitted adjustments for lifestyle, yielded higher HRs, 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 Appendix, Web Figure 1).

The overall response rate was 56%. Based on the data from national registers, non-respondents were more likely to be male, to have more physical and mental health conditions, and to have shorter education. Furthermore, some variations (e.g. by age) were found in the response rates (Web Appendix, Web Table 4). The overall mortality rate in non-

respondents during follow-up was higher than in respondents when 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 non-respondents (Web Table 5).

DISCUSSION

This large population-based cohort study showed that stress and multimorbidity independently increased the mortality rate and that 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 two to four times more deaths in people with multimorbidity than in people without. 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 diagnoses and drug 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 non-respondents. We found higher morbidity and mortality rates in non-respondents than in respondents, but the association between mental health conditions, multimorbidity, and mortality rate was comparable in respondents and non-respondents. We would expect higher levels of perceived stress in non-respondents 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 in the cases with mental illness included in our study. With no cut-offs, 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). Our multimorbidity status was based on clinically acknowledged conditions from all Danish hospitals and outpatient clinics, including recommended key diseases (32). As

diagnoses from primary care were not available, our algorithm included redeemed drug 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 which no data was 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 as this allowed us to establish the contribution to the mortality rate from each individual condition 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 path and act as intermediate variables; exposure to stress may cause an adverse lifestyle, which may lead to increased mortality. Omitting adjustments for lifestyle yielded noticeably higher risks. Our conservative approach of adjusting for all factors could thus lead to an 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 association may not be causal; perceived stress could merely be an unspecific marker for the severity of any underlying conditions, and treatment of stress would only have an effect on mortality if the association is causal.

Comparison with other studies

To our knowledge, this study is the first to assess mortality while accounting for the interplay between stress and multimorbidity. Previous studies have reported 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 the 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. showed that mental-physical multimorbidity and socioeconomic status are closely related (4). Our results extend this finding; multimorbidity, mental health conditions, and shorter education were all factors impairing the prognosis after mutual adjustments. Even though unstressed and healthy people with longer educations tended to have a lower baseline mortality rate, their mortality rate was comparable to people with shorter educations when multimorbidity and higher stress levels were present. This could be interpreted as evidence that socioeconomic factors tend to predispose to diseases which eventually may affect the survival and thus make multimorbidity a key factor in the 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 effect of mental health; perceived stress also seems to play a key role for the long-term prognosis as it is associated with more deaths than mental health conditions. Our data do not suggest a critical point for intervention as even moderate stress was associated with increased mortality rates. These new findings call for increased

clinical attention to psychological wellbeing and stress, even before the threshold for depression or anxiety diagnoses is reached. Stress could be a modifiable risk factor, which is 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 handling 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, which are 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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Ethical approval:

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

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Tables and figures

Table 1. List of Condition 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
	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 disorders
Musculoskeletal system	Connective tissue disorders
	Osteoporosis
	Painful condition
Hematological system	Anemias
	HIV/AIDS
Cancers	Cancer
Neurological system	Vision problem
	Hearing problem
	Migraine
	Epilepsy
	Parkinson's disease
	Multiple sclerosis
	Neuropathies
Mental health conditions	Mood, stress-related, or anxiety disorders
	Psychological distress
	Alcohol problems
	Substance abuse
	Anorexia/bulimia
	Bipolar affective disorder
	Schizophrenia or schizoaffective disorder
	Dementia

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

Table 2. Participant Characteristics According to PSS Quintile, Danish National Health Survey, 2010-2014.

Characteristics ^a	Total No. (n=118,410)	Column %	Quintile of PSS Score (row %)				
			1 (n=26,636)	2 (n=27,808)	3 (n=21,256)	4 (n=21,102)	5 (n=21,608)
PSS score median (range)			4 (0-6)	9 (7-10)	12 (11-13)	15 (14-17)	21 (18-40)
Age at baseline ^b							
25-34 years	13,881	11.7	17.9	23.7	19.5	18.9	20.0
35-44 years	22,673	19.1	20.9	24.5	18.9	17.2	18.4
45-54 years	25,272	21.3	22.9	24.3	18.2	16.8	17.9
55-64 years	26,610	22.5	25.5	24.0	17.3	17.0	16.2
65-74 years	19,982	16.9	25.8	22.9	17.1	18.2	15.9
≥75 years	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
Number of 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	8.6	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							
Light or no weekly activity	16,818	14.2	13.1	16.2	15.2	20.4	35.1
Moderate activity ≥4 hours weekly	70,357	59.4	22.3	23.8	18.5	18.3	17.1
Hard activity ≥4 hours weekly	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 ^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
Dietary habits							
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 ^d							
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 ^a							
< 10 years	26,626	22.5	16.9	19.3	16.8	20.8	26.2
10-15 years	57,108	48.2	22.3	24.3	18.6	17.8	17.0
> 15 years	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 ^a							
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 ^a							
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

Abbreviations: PSS, Perceived Stress Scale. ^aTable shows data with missing values before multiple imputations. ^bVariable based on national registers (other variables based on survey). ^cDrinks per week for females/males. ^dBody mass index given as kg/m²

Table 3. Mortality Hazard Ratios for PSS Quintiles Stratified by Multimorbidity Status in Various Adjusted Models, Danish National Health Survey, 2010-2014.

No. of Conditions and Quintile of PSS Score	Deaths	CIP	Model 1 ^a		Model 2a ^b		Model 2b ^c		Model 3 ^d		P-value trend	Excess deaths associated with stress ^e
			HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI		
0–1 conditions												
1	223	.011	1	reference	1	reference	1	reference	1	reference	<0.0001	reference
2	218	.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	.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	.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	.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	.048	1	reference	1	reference	1	reference	1	reference	<0.0001	reference
2	222	.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	.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	.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	.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	.111	1	reference	1	reference	1	reference	1	reference	<0.0001	reference
2	190	.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	.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	.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	.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: PSS, Perceived Stress Scale; CIP, cumulative incidence proportion; HR, hazard ratio; 95% CI, 95% confidence intervals.

^aAdjusted for age and sex.

^bLike Model 1 with further adjustments for 31 physical conditions.

^cLike Model 2a with further adjustments 8 mental health conditions.

^dLike Model 2b with further adjustment for lifestyle and socioeconomic factors and a *P*-value for test for trend between PSS quintiles and mortality rate within each multimorbidity group.

^eAbsolute number of deaths associated with being in a PSS quintile above one within multimorbidity group.

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

Quintile of PSS Score	No mental health conditions (n=109,137)				One or more mental health conditions (n=9,273)			
	Deaths	HR	95% CI	Excess deaths associated with stress	Deaths	HR	95% CI	Excess deaths associated with mental health conditions
Overall ^a	3,404	1	reference	reference	825	1.41	1.30, 1.54	240
1 ^b	541	1	reference	reference	41	1	reference	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: PSS, Perceived Stress Scale. HR denotes hazard ratio. 95% CI denotes 95% confidence interval.

^aHRs adjusted for PSS quintile, age, sex, all physical conditions, lifestyle, and socioeconomic factors.

^bHRs adjusted for any mental health condition, age, sex, all physical conditions, lifestyle, and socioeconomic factors.

Figure titles and legends

Figure 1: Flow chart of participants. Danish National Health Survey, 2010-2014.

Abbreviations: PSS, Perceived Stress Scale.

Figure 2: Distribution of Perceived Stress Scale (PSS) quintiles according to number of conditions. Danish National Health Survey, 2010-2014.

White bars show PSS quintile 1 (scores 0–6). Light gray bars show PSS quintile 2 (scores 7–10).

Medium gray bars show PSS quintile 3 (scores 11–13). Dark gray bars show PSS quintile 4 (scores 14–

17). Black bars show PSS quintile 5 (scores 18–40). 0–1 conditions are no multimorbidity, 2–3

conditions are moderate multimorbidity, and 4 or more conditions are severe multimorbidity. Test

for trend: $P < 0.0001$ for mean PSS score over number of conditions. Abbreviations: PSS, Perceived

Stress Scale.

Figure 3: Overall association between Perceived Stress Scale (PSS) score and mortality hazard ratio according to PSS quintiles and restricted cubic splines. Danish National Health Survey, 2010-2014.

Circle with vertical caps shows hazard ratios with 95% confidence intervals for PSS quintiles adjusted for age, sex, 39 register-based conditions, lifestyle, and socioeconomic factors placed at the median within the quintile's range.

Full line with dotted range area shows hazard ratios with 95% confidence intervals for restricted cubic splines of PSS scores adjusted for age, sex, 39 register-based conditions, lifestyle, and socioeconomic factors.

Vertical bars represents the PSS distribution histogram in the study population in percent.

Abbreviations: PSS, Perceived Stress Scale.

Figure 4: Association between Perceived Stress Scale (PSS) score quintile, multimorbidity status, and mortality hazard ratio. Danish National Health Survey, 2010-2014.

Circle with vertical line shows hazard ratios with 95% confidence intervals for 0–1 conditions.

Triangle with vertical line shows hazard ratios with 95% confidence intervals for 2–3 conditions.

Square with vertical line shows hazard ratios with 95% confidence intervals for 4+ conditions.

Differences between mortality rate and PSS score quintiles adjusted for age, sex, 39 register-based conditions, lifestyle, and socioeconomic factors. Differences between mortality rate and multimorbidity status groups adjusted for age, sex, lifestyle, and socioeconomic factors. Test for trend: $P < 0.0001$ in all multimorbidity status groups. Abbreviations: PSS, Perceived Stress Scale.

Figure 5: Association between Perceived Stress Scale (PSS) score quintile, multimorbidity status, and mortality hazard ratio stratified by level of education. Danish National Health Survey, 2010-2014.

Panel A shows <10 years of education. Panel B shows >10 years of education. Circle with vertical line shows hazard ratios with 95% confidence intervals for 0–1 conditions. Triangle with vertical line shows hazard ratios with 95% confidence intervals for 2–3 conditions. Square with vertical line shows hazard ratios with 95% confidence intervals for 4+ conditions. Differences between mortality rate and PSS quintiles adjusted for age, sex, 39 register-based conditions, lifestyle, and socioeconomic factors, except level of education. Differences between mortality rate and multimorbidity status groups adjusted for age, sex, and lifestyle factors. Abbreviations: PSS, Perceived Stress Scale.