Anxiety and Depression Symptoms in a General Population and Future Risk of Bloodstream Infection: The HUNT Study

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ABSTRACT

Objective: We examined whether anxiety and depression symptoms constitute increased risk of bloodstream infection (BSI), as a proxy for sepsis.

Methods: A general population with self-reported anxiety and depression symptoms was followed prospectively for hospital-verified BSI. Using multivariable Cox regression analysis, we estimated hazard ratios (HR) with 95% confidence intervals (CI) of BSI and BSI mortality, with and without statistical adjustment for comorbidities, BMI, and life-style factors that may confound or mediate the associations.

Results: During 14.8 years median follow-up of 59,301 individuals, 1578 (2.7%) experienced BSI and 328 (0.55%) participants died within 30 days after a BSI. Severe depression symptoms were associated with a 38% increased risk of BSI, adjusted for age, sex, and education (HR = 1.38, 95% CI = 1.10–1.73). The HR was attenuated to 1.23 (0.96–1.59) after adjustment for comorbidities and to 1.15 (0.86–1.53) after additional adjustment for BMI and life-style factors. For severe anxiety symptoms, the corresponding HRs were 1.48 (1.20–1.83), 1.35 (1.07–1.70), and 1.28 (0.99–1.64). Moderate symptoms of depression and anxiety were not associated with increased BSI risk. The analysis of BSI mortality yielded imprecise results but suggested an increased risk of BSI mortality in participants with moderate depression symptoms.

Conclusions: Severe depression and anxiety symptoms were associated with a moderately increased risk of BSI. The association may, at least in part, be confounded or mediated by comorbidities, BMI, and life-style. Future research should investigate whether interventions targeting improved BMI and life-style may reduce the risk of BSI and sepsis in people with depression and anxiety symptoms.

Key words: anxiety, bloodstream infection, depression, epidemiology, sepsis.

INTRODUCTION

Bloodstream infection (BSI) is a common disease, with a reported incidence of 80 to 257 per 100,000 person-years, and is an important cause of morbidity and mortality worldwide. Annually, 1.2 million BSI episodes occur in Europe and 157,000 persons die from it. One fifth of these BSI episodes are hospital acquired (1). Most individuals with BSI fulfill the criteria for sepsis defined according to the 2001 definition, and BSI serves as a specific indicator for sepsis (2,3). Individuals with symptoms of depression and anxiety have a higher mortality and morbidity risk from somatic diseases like diabetes and cardiovascular disease compared with the general population (4–9). The pathogenic mechanisms linking these symptoms to somatic diseases are likely to involve neurohormonal stress and inflammation (10–15). These pathways are also proposed to influence the defense mechanisms against bacterial infections and could represent plausible links between symptoms of anxiety and depression and an increased risk of sepsis and BSI. Furthermore, anxiety and depression could

BMI = body mass index, **BSI** = bloodstream infection, **HADS** = Hospital Anxiety and Depression Scale, **HR** = hazard ratio, **HUNT** = Nord-Trøndelag Health Study, **IRR** = incidence rate ratio, **MSAD** = Mixed Symptoms of Anxiety and Depression

SDC Supplemental Content

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increase the risk of BSI through increased risk of somatic diseases, unhealthy life-style, and low adherence to treatment and medical advice (16–20). In a Danish nationwide cohort study, having a depression diagnosis was associated with a more than 2-fold increased risk of an International Classification of Diseases diagnosis of sepsis (21). A study of community dwelling US citizens reported that the association between psychological distress and increased long-term sepsis risk in part could be explained by depressive symptoms (16), which suggests that mental symptoms play a role in the susceptibility to sepsis. However, apart from these two studies, the association of depression and anxiety symptoms with risk and mortality of sepsis has not been examined. The large Norwegian population-based HUNT2 study cohort has prospective 15-year follow-up data on verified BSIs. In this cohort, we examined the associations between symptoms of depression and anxiety and the later risk and mortality of BSI.

METHODS

Study Population

All adult citizens 20 years or older in Nord-Trøndelag County, Norway, were invited to participate in the second survey (HUNT2) of the Nord-Trøndelag Health Study (HUNT) in 1995–1997 (22). In total, 93,898 persons received a postal invitation by surface mail and 65,236 (69.5%) participated. At least 97% of the participants were of European ancestry. Before participation, they signed an informed consent letter, which included the consent to link the HUNT study data with other health registries. The participants attended a clinical examination including blood sampling. The participants also self-reported on standardized questionnaires regarding a wide range of health-related topics (http://www.ntnu.edu/hunt/data/que). Our study excluded 43 participants (0.07%) with previous BSI, and 3521 (5.4%) participants died or moved out of the county before the start of follow-up in 1995–1999 (as detailed hereinafter). We included participants who answered a Norwegian version of the Hospital Anxiety and Depression Scale (HADS) questionnaire at HUNT2 (23), leaving 59,301 individuals for analysis. Figure 1 pictures the study recruitment and follow-up of the study population. The Regional Committee for Medical and Health Research Ethics approved the present study (REC Central, Reference Number 2012/153).

Symptoms of Anxiety and Depression

The HADS asks to report on core symptoms of anxiety (HADS-A) and depression (HADS-D) during the week before questioning (24). Seven questions regarding depression symptoms mirror anhedonia and loss of interest and seven questions about anxiety symptoms mirror mostly worry and tension. Missing scores on the HADS-A or HADS-D subscales were substituted based on the sum of completed items multiplied by 7/5 for those who had filled in five items and 7/6 for those who had filled in six items (25). All HADS questions have a four-point Likert scale ranging from 0 (no symptom) to 3 (highest symptom level); thus, the subscales range from 0 to 21 points (24). We used recommended cut-offs to categorize participants as having no (score ≤7), moderate (score 8–10), or severe symptoms (score ≥11) of depression or anxiety. The HADS, though not a diagnostic instrument and not assessing all aspects of depression, has proven to perform well in assessing severity and case of depression and anxiety disorders in different patient groups and in a general population (23,25). Valid HADS-A and HADS-D scores were summed up into HADS-total (HADS-T) scores, which mirror mixed symptoms of anxiety and depression (MSAD). We categorized the HADS-T scores into no (score <15), moderate (score 15–19), and severe (score ≥20) MSAD (25).

Repeated episodes of depression or anxiety symptoms may be more strongly associated with disease risk compared with single episodes (25–27). Among our 59,301 participants, previous symptoms of MSAD from the 4-item Anxiety and Depression Index (ADI-4) were available for 33,843 participants who also attended HUNT1 in 1984 to 1986 (all adult citizens ≥ 20 years living in Nord-Trøndelag county at the time of the survey were invited to participate in HUNT1) (Figure 1). The ADI-4 has a high correlation (0.83) with the HADS-T score used in HUNT2 and is an acceptable indicator for MSAD (sensitivity = 0.51, specificity = 0.93) (28). Two ADI questions have a 4-point Likert scale: one about calmness, ranging from almost all the time (1) to never (4); and the other about nervousness, ranging

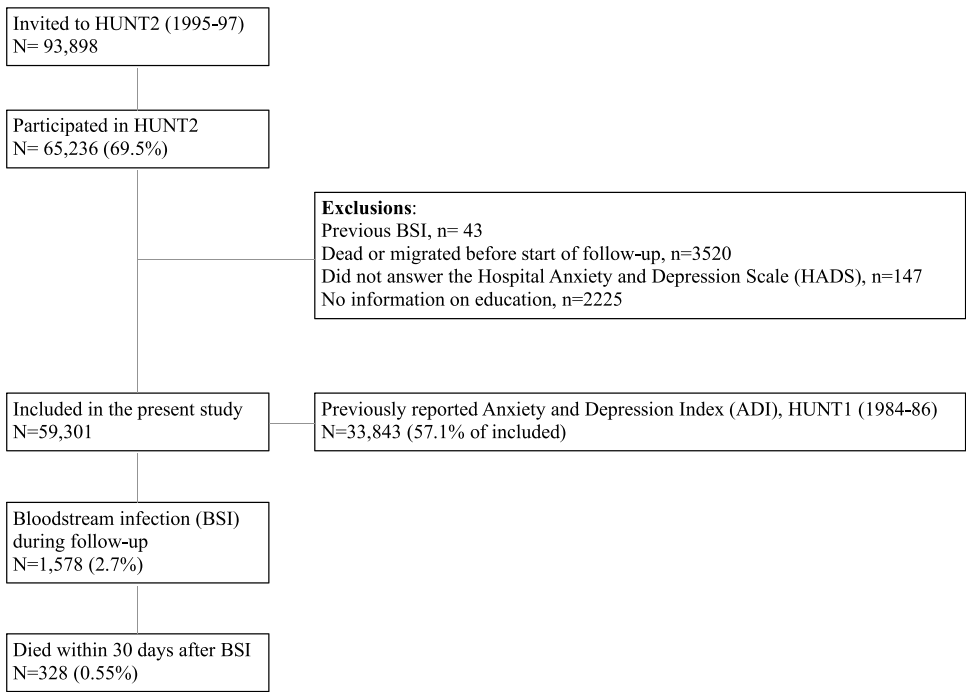

FIGURE 1. Study population.

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from never (1) to almost all the time (4). The last two ADI questions are about mood and vitality and have a 7-point Likert scale ranging from very happy/strong and fit (1) to very downhearted/tired and worn out (7). Thus, the subscales range from 4 to 22 points. In the analysis of repeated symptom episodes, we categorized participants as having symptoms of MSAD in HUNT1 if their score was higher than 14 (at the 96.4 percentile), and symptoms of MSAD in HUNT2 were defined as a score 20 or higher on the HADS-T subscale. Among participants of both HUNT1 and HUNT2, we categorized the combined burden of MSAD in HUNT1 and HUNT2 as no (MSAD symptoms in neither survey), one (MSAD symptoms in one survey), and two episodes (MSAD symptoms in both surveys) (25).

Outcome Ascertainment

Two community hospitals in Levanger and Namsos serve Nord-Trøndelag County, and St. Olavs Hospital in Trondheim serves as the tertiary referral center. We linked the information from the HUNT study to prospectively confirmed information on invasive pathogens in blood cultures taken at the hospitals on clinical indication for sepsis using the 11-digit unique personal identification number of Norwegian citizens. The BSI episodes were recorded as a part of the Mid-Norway Sepsis Study, at Levanger and St. Olavs Hospitals from 1 January 1995, whereas Namsos Hospital started their inclusion of BSI patients from September 1, 1999 (1,29). Isolates solely consisting of microorganisms commonly associated with skin contamination such as species of coagulase negative *Staphylococcus*, *Corynebacterium*, and *Propionibacterium* were not considered as BSI. In participants with multiple positive blood culture specimens, a new episode of BSI was defined as positive blood culture more than 30 days after the previous one. BSI mortality was defined as death within 30 days of detection of a BSI, and dates of death and migration were obtained from the Norwegian population register. In the analyses of risk of first-time BSI, participants were followed from the date of participation in HUNT2 (for participants having Levanger Hospital as their primary hospital) or September 1, 1999 (for participants having Namsos Hospital as their primary hospital) until their first BSI, migration out of Nord-Trøndelag, death, or end of follow-up at December 31, 2011, whichever occurred first. In the analyses of risk of BSI mortality, participants were followed until migration out of Nord-Trøndelag, death, or December 31, 2011, whichever occurred first.

Covariates

Body mass index (BMI) was calculated based on standardized measures of weight and height at participation in HUNT2. The HUNT2 questionnaires queried, among many items, smoking habits, leisure-time physical activity, education, and diseases. Smoking was categorized as current, previous, or never smoking. Participants were asked about their leisure time weekly amount of light (not sweaty or breathless) and vigorous (sweaty or breathless) physical activity during the last year (30). Leisure time physical activity was categorized as being nonactive (neither vigorous nor light activity), slightly active (<3 hours of light and no vigorous activity per week), moderately active (light activity ≥3 hours or <1 hour of vigorous activity per week), or highly active (≥1 hour of vigorous activity per week). The self-reported information on vigorous exercise in HUNT has been shown to correlate moderately well with oxygen uptake in healthy adults, whereas the association was less clear for self-report of light exercise (31). Education was categorized as 9 or less, 10 to 12, or greater than 12 years. Self-reported diseases included pulmonary disease (asthma or chronic obstructive pulmonary disease), diabetes, cardiovascular disease (a history of myocardial infarction, stroke, or angina), and cancer. A nonfasting whole blood sample was drawn from each participant at the HUNT2 clinical examination from which analysis of serum creatinine was performed (32). Prevalent kidney disease was categorized on basis of estimated glomerulus filtration rate, calculated with the Modification of Diet in Renal Disease formula (33), of less than 60 ml/min per 1.73 m^2.

Statistical Analysis

For each outcome (first-time BSI and BSI mortality), we used Cox regression analysis to estimate hazard ratios (HRs) with 95% confidence intervals (CIs) by categories of HADS. For test of trends, we assigned a numeric value of 0 (no symptoms) to 2 (severe symptoms) to the HADS categories and treated the categories as a continuous variable in the Cox model. In a separate analysis among individuals who participated in both HUNT1 and HUNT2, we estimated the risk of each BSI outcome associated with the presence of MSAD in both surveys. In a first model, we adjusted for age (by using age as the underlying time scale) (34), sex (by stratification), and education. In a second model, we also adjusted for comorbidities at HUNT2 (self-reported cardiovascular disease, pulmonary disease, kidney disease, cancer, and diabetes). These diseases may cause increased risk of BSI as well as anxiety and depression symptoms and thus represent plausible confounders (35,36). However, the causal pathway may also be directed from depression to increased risk of common chronic disease, suggesting a mediator role for common chronic disease between depression and risk of BSI (37,38). In a third model, we additionally included BMI and life-style factors (smoking and leisure time physical activity) at HUNT2. BMI and life-style factors may cause increased risk of BSI, but the associations with anxiety and depression symptoms are likely bidirectional, and thus, these factors may be either confounders or mediators in the association between anxiety and depression symptoms and risk of BSI (30,39). To quantify the influence of the adjustments on the risk estimates, we repeated all models among participants with no missing information on the covariates. All analyses were performed using STATA Version 13.1 (StataCorp).

RESULTS

Of the 59,301 participants, 1578 (2.7%) experienced at least one episode of BSI during 761,775 person-years of follow-up (median follow-up = 14.8 years), corresponding to an incidence rate of 207 per 100,000 person-years. Of the participants, 328 (0.55%) participants died within 30 days after a BSI during 767,368 person-years of follow-up for BSI mortality, corresponding to a mortality rate of 43 per 100,000 person-years. Participants who experienced BSI were more likely to be male, older, physical inactive, obese, and have higher depression symptom scores at baseline (Table 1).

Severe depression symptoms (HADS-D ≥11) were associated with a 38% increased risk of BSI (HR = 1.38, 95% CI = 1.10–1.73) after adjustment for age, sex, and education, compared with low symptom scores (HADS-D ≤7) (P trend = 0.009) (Table 2). The HR was attenuated to 1.23 (95% CI = 0.96–1.59, P trend = 0.205) after adjustment for comorbidities and to 1.15 (95% CI = 0.86–1.53, P trend = 0.815) after further adjustment for BMI and life-style factors. The association between MSAD and risk of BSI was similar to the association observed for HADS-D. Severe anxiety symptoms (HADS-A ≥11) were associated with a 48% increased risk of BSI (HR = 1.48, 95% CI = 1.20–1.83) after adjustment for age, sex, and education compared with low anxiety scores (HADS-A ≤7) (P trend = 0.003). The estimate was moderately attenuated after adjustment for comorbidities (HR = 1.35, 95% CI = 1.07–1.70. P trend = 0.118) and after additional adjustment for BMI and life-style factors (HR = 1.28, 95% CI = 0.99–1.64, P trend = 0.404). No similar association was seen for moderate depression or anxiety symptoms.

The analysis of BSI mortality yielded imprecise results, in particular for participants with severe anxiety or depression symptoms, because of the relatively low number of events (Table 3). However, the analysis suggested an increased risk of BSI mortality in participants with moderate depression symptoms; the HR (95% CI) was 1.51 (1.10–2.05) after adjustment for age, sex, and

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TABLE 1. Baseline Characteristics

Variable	Study Participants, *n* (%)	BSI During Follow-up, *n* (%)	No BSI During Follow-up, *n* (%)
Total *n* (%)	**59,301**	1578 (2.7)	57,723 (97.3)
Male sex	**27,943 (47.1)**	825 (52.3)	27,118 (47.0)
Age, M (SD), y	**59,301**	63.1 (13.9)	48.3 (16.7)
HADS-Depression Score	**59,301**		
0–7	53,024 (89.4)	1339 (84.9)	51,685 (89.5)
8–10	4455 (7.5)	160 (10.1)	4295 (7.4)
≥11	1822 (3.1)	79 (5.0)	1743 (3.1)
HADS-Anxiety Score	**58,410**		
0–7	49,462 (84.7)	1283 (84.7)	48,179 (84.7)
8–10	5908 (10.1)	136 (9.0)	5772 (10.1)
≥11	3040 (5.2)	96 (6.3)	2994 (5.2)
HADS-Total Score	**58,410**		
0–15	52,871 (90.5)	1335 (88.1)	51,536 (90.6)
16–19	2602 (4.5)	78 (5.2)	2524 (4.4)
≥20	2937 (5.0)	102 (6.7)	2835 (5.0)
Education	**59,301**		
≤9 y	21,175 (35.7)	890 (56.4)	20,285 (35.1)
10–12 y	26,143 (44.1)	523 (33.1)	25,620 (44.4)
>12 y	11,983 (20.2)	165 (10.5)	11,818 (20.5)
Smoking	**59,050**		
Never	26,624 (45.1)	582 (37.2)	26,042 (45.3)
Previous	15,323 (25.9)	546 (34.9)	14,777 (25.7)
Current	17,103 (29.0)	436 (27.9)	16,667 (29.0)
Leisure-time PA	**54,960**		
None	4206 (7.6)	179 (13.8)	4234 (7.5)
Slight	17,016 (31.0)	459 (35.2)	16,557 (30.9)
Moderate	18,629 (33.9)	421 (32.4)	18,208 (33.9)
High	15,109 (27.5)	242 (18.6)	14,867 (27.7)
BMI, M (SD), kg/m^2	**58,787**	27.5 (4.6)	26.3 (4.0)
Comorbidities (yes/no)	**58,421**		
Cardiovascular disease	4049 (6.9)	298 (18.9)	3751 (6.5)
Pulmonary disease	6524 (11.2)	246 (15.6)	6278 (10.9)
Diabetes	1534 (2.6)	125 (8.0)	1409 (2.5)
Malignant disease	2042 (3.5)	110 (7.7)	1932 (3.5)
Kidney failure	2215 (3.8)	117 (11.3)	2098 (3.6)

M (SD) = mean (standard deviation); HADS = Hospital Anxiety and Depression Scale; BMI = body mass index; PA = physical activity; BSI = bloodstream infection.

All variables, except HADS-Anxiety score, are statistically significant ($p < .05$) between those who experienced BSI during follow-up and those who did not experience BSI during follow-up.

education, with no attenuation after adjustment for comorbidities, but attenuated to 1.31 (0.89–1.93) after additional adjustment for BMI and life-style.

Among individuals who participated in both HUNT1 and HUNT2, those who reported MSAD in both surveys had a 51% increased risk of BSI, after adjustment for age, sex, and education (HR = 1.51, 95% CI = 1.04–2.20, *P* trend = 0.006) compared with those with no report of MSAD. The HR (95% CI) was attenuated to 1.39 (0.91–2.10, *P* trend = 0.236) after adjustment for comorbidities and to 1.30 (0.83–2.01, *P* trend = 0.504) after additional adjustment for BMI and life-style (Supplementary Table S1, Supplemental Digital Content 1, http://links.lww.com/PSYMED/A490). Repeated reports of MSAD were similarly associated with increased risk of BSI mortality but the low number of BSI deaths precluded precise estimates (Supplementary Table S2, Supplemental Digital Content 2, http://links.lww.com/PSYMED/A491).

Some participants were excluded from the second (comorbidity-adjusted) and third (comorbidity-, BMI-, and life-style-adjusted) Cox regression models because of missing information. In additional analyses, we repeated models 1 and 2 among participants with complete information on comorbidities and models 1 and 3 among participants with complete information on comorbidities, BMI, and life-style factors. In these analyses, we observed similar changes in HRs after adjustments as we did in the main analysis (data not shown). This indicates that the differences in HRs between the models were largely due to the statistical adjustment and not due to exclusion of participants with missing information.

DISCUSSION

In this large prospective cohort study, severe depression and anxiety symptoms were associated with a moderately increased risk of BSI. Repeated measurements of MSAD 10 years apart did not constitute any higher risk than one measurement at baseline only. The observed associations attenuated after adjustment for comorbidities, BMI, and life-style factors, indicating that these factors may either confound or mediate the associations of anxiety and depression symptoms with BSI risk.

To our knowledge, this is the first study to examine the association between anxiety and risk of BSI-related sepsis mortality and the second to analyze depression in this context. Although we did not have clinical information about the course of infection for all participants, a review of medical records of the patients with *Staphylococcus aureus* and *Streptococcus pneumoniae* BSI in this cohort has shown that approximately 98% met the 2001 sepsis criteria (2,3). Thus, we find it likely that our BSI patients had clinical sepsis. In line with our findings, a previous cohort study reported that depressive symptoms could explain part of the excess sepsis risk among people with psychological stress (16). Another more recent cohort study found that a diagnosis of depression constituted an increased risk of all infections (incidence rate ratio [IRR] = 1.64, 95% CI = 1.51–.79) and of an International Classification of Diseases diagnosis of sepsis (IRR = 2.39, 95% CI = 1.58–3.61) (21). From cardiovascular research, we know that studies using self-report of depression and anxiety symptoms consistently find smaller effects than studies relying on clinical diagnosis or psychiatric interviews, suggesting a dose-response effect (25).

One previous study of risk of future pneumonia and pneumococcal disease found that an anxiety diagnosis contributed to equally high relative risk estimates for infection as a depression diagnosis (2.2 versus 2.1) (40). Even though we found some difference in effect estimates of future BSI risk associated with HADS depression and anxiety scores, the confidence intervals were largely overlapping, suggesting that there may be no substantial difference in risk. The HADS does not include somatic symptoms of anxiety and depression (e.g., activation of the sympathetic nervous system, anorexia, and insomnia/hypersomnia) that are included in psychiatric diagnoses (24). On the other hand, the psychological items in HADS are not specific for anxiety and depression only. Thus, our data should be interpreted with care regarding

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TABLE 2. Hazard Ratios (95% CIs) of BSI During Follow-up According to HADS-D and HADS-A and MSAD (Measured by HADS-Total) in HUNT2 (1995–97)

	Adjusted for Age, Sex, and Education			Adjusted for Age, Sex, Education, and Comorbidities			Adjusted for Age, Sex, Education, Comorbidities, Leisure-Time Physical Activity, Smoking, and BMI		
	n = 59,301			*n* = 56,482			*n* = 52,485		
HADS-Score	Person-Years at Risk	BSI, *n*	HR, 95% CI	Person-Years at Risk	BSI, *n*	HR, 95% CI	Person-Years at Risk	BSI, *n*	HR, 95% CI
HADS-D	761,775	1578		730,170	1421		684,214	1189	
≤7	686,829	1339	Reference	661,842	1224	Reference	622,129	1036	Reference
8–10	53,880	160	1.07 (0.91–1.26)	49,650	135	1.00 (0.84–1.19)	45,027	102	0.91 (0.74–1.12)
≥11	21,065	79	1.38 (1.10–1.73)	18,676	62	1.23 (0.96–1.59)	16,690	51	1.15 (0.86–1.53)
P trend			0.009			0.205			0.815
HADS-A	752,841	1515		723,878	1386		680,090	1171	
≤7	637,952	1283	Reference	617,735	1192	Reference	581,049	1010	Reference
8–10	76,274	136	1.04 (0.88–1.24)	71,061	116	0.92 (0.76–1.11)	66,350	94	0.87 (0.70–1.07)
≥11	38,614	96	1.48 (1.20–1.83)	35,081	78	1.35 (1.07–1.70)	32,689	67	1.28 (0.99–1.64)
P trend			0.003			0.118			0.404
HADS-T	752,841	1515		723,878	1386		680,090	1171	
≤15	683,520	1335	Reference	660,651	1239	Reference	621,749	1053	Reference
16–19	32,946	78	1.07 (0.85–1.35)	30,575	66	0.98 (0.76–1.25)	27,947	50	0.88 (0.66–1.16)
≥20	36,374	102	1.38 (1.13–1.70)	32,651	81	1.23 (0.98–1.54)	30,392	68	1.13 (0.88–1.45)
P trend			0.002			0.126			0.582

MSAD = mixed symptoms of anxiety and depression; HADS = Hospital Anxiety and Depression Scale; BSI = bloodstream infection; HR = hazard ratio; CI = confidence interval; BMI = body mass index

TABLE 3. Hazard Ratios (95% CIs) of BSI Mortality (Indicated by Death Within 30 Days After a BSI) According to HADS-D and HADS-A and MSAD (Measured by HADS-Total) in HUNT2 (1995–1997)

	Adjusted for Sex, Age, and Education			Adjusted for Sex, Age, Education, and Comorbidities			Adjusted for Sex, Age, Education, Comorbidities, Leisure Time Physical Activity, Smoking, and BMI		
	n = 59,301			*n* = 56,482			*n* = 52,485		
HADS Score	Person-Years at Risk	No. BSI Deaths	HR (95% CI)	Person-Years at Risk	No. BSI Deaths	HR (95% CI)	Person-Years at Risk	No. BSI Deaths	HR (95% CI)
HADS-D	767,368	328		735,273	290		688,586	236	
≤7	691,656	266	Reference	666,306	234	Reference	625,966	196	Reference
8–10	54,421	48	1.51 (1.10–2.05)	50,086	45	1.62 (1.17–2.23)	45,389	30	1.31 (0.89–1.93)
≥11	21,289	14	1.16 (0.68–1.99)	18,879	11	1.06 (0.58–1.95)	17,231	10	1.06 (0.55–2.01)
P trend			0.052			0.061			0.368
HADS-A	758,267	311		728,892	278		684,419	228	
≤7	642,508	259	Reference	621,991	238	Reference	584,724	196	Reference
8–10	76,778	36	1.40 (0.98–1.98)	71,505	28	1.20 (0.81–1.77)	66,720	22	1.09 (0.70–1.70)
≥11	38,980	16	1.40 (0.84–2.32)	35,394	12	1.18 (0.66–2.12)	32,974	10	1.04 (0.55–1.99)
P trend			0.041			0.350			0.752
HADS-T	758,267	311		728,892	278		684,418	228	
≤15	688,312	274	Reference	665,123	249	Reference	625,625	205	Reference
16–19	33,184	20	1.33 (0.85–2.10)	30,779	16	1.15 (0.85–1.90)	28,103	13	1.14 (0.65–2.00)
≥20	36,770	17	1.18 (0.72–1.93)	32,989	13	1.03 (0.59–1.80)	30,690	10	0.83 (0.44–1.58)
P trend			0.261			0.761			0.745

MSAD = mixed symptoms of anxiety and depression; HADS = Hospital Anxiety and Depression Scale; BSI = bloodstream infection; HR = hazard ratio; CI = confidence interval; BMI = body mass index.

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effect of depression and anxiety on BSI and rather as an effect of psychiatric suffering in general.

The causal pathways between anxiety and depression symptoms and increased sepsis susceptibility are insufficiently known. Altered immune activity in depressed people may explain the excess sepsis risk in people with mental suffering (15,41–43). In addition, T cell function, which is paramount in the defense against bacteria that cause sepsis, is impaired by virtue of stress and depression (19). Several psychotropic medications are known to have immunomodulatory effects (e.g., SSRI and clozapine) and could interfere with the results (44). However, we had no data on these prescriptions to tease out their effects in the observed association between mental health and risk of BSI. The causal associations of chronic diseases, BMI, and life-style factors with anxiety and depression symptoms may be bidirectional, which means that these factors may be either confounders or mediators of the associations between anxiety and depression symptoms and risk of BSI. One possibility is that chronic diseases are confounders of the associations between poor mental health and somatic health outcomes such as BSI, because the chronic diseases can lead to both increased risk of somatic health outcomes (such as BSI) and poor mental health (i.e., chronic diseases are common causes of somatic health outcomes and poor mental health). Nonetheless, newer research also suggests the possibility for a causal link in the other direction, that is, from poor mental health to increased risk of a range of somatic chronic conditions (25,38,45), which means that somatic chronic conditions might mediate a causal association from poor mental health to increased BSI risk. The same ambiguity is true for obesity and unhealthy life-style; they could be confounders because they may be common causes of anxiety or depression symptoms and BSI risk. However, they could also be mediators because mental suffering may lead to unhealthier life-style and obesity (39), which in turn may increase the risk of BSI (30). If chronic diseases, BMI, and life-style factors are mediators in the association of anxiety and depression symptoms with risk of BSI, adjustments for these factors will lead to underestimation of the true effect (46).

Strengths and Limitations

Strengths of our study include the population-based design, the large sample size, and linkage to prospectively recorded information on BSI from all microbiology laboratories serving this population. The relatively low number of BSI deaths precluded precise estimates for BSI mortality. However, the ascertainment of mortality was complete because of registry linkage with the national population register. The limitations of the study include the observational (as opposed to randomized) design and the possibility of confounding in observational studies means that we cannot draw firm conclusions regarding causality. A HUNT2 nonparticipant study showed that health-related reasons for nonparticipation were evident 70 years or older. However, all our BSI events occurred after participation in HUNT2, making substantial selection bias less likely (32). For participants belonging to the catchment area of Namsos Hospital, we could not start the follow-up for BSI until the BSI recordings began in 1999, 2 to 4 years after the reporting of HADS. However, we observed no violation of the proportional hazards assumption for the association between HADS and BSI risk, and this delayed start of follow-up is not likely to have biased the results. Because of the geography of the region with no other hospitals nearby, it is not likely that BSI would have been recorded at other hospitals except for the rare cases when participants experienced BSI while on travel. Self-report of exposure could have led to nondifferential misclassification and therefore lower effect estimates than the true effect (47). Lastly, Norway is a country with high socioeconomic equality and access to health services, and the relation between mental health and BSI risk may be stronger in societies where patients with mental suffering have lower access to health care.

Implications

Both high HADS anxiety and depression scores are in a general population previously found to be associated with poor physical health and decreased adherence to standard life-style changing interventions (48). Persons with high scores on HADS tend to have decreased attention to physical health, be physical inactive, smoke, and eat unhealthily, and all these factors are found to increase the risk of sepsis (30,48). If behavioral factors are mediators in the relation between mental health and sepsis, this could therefore suggest that early focus on physical health and health behaviors are required to improve the adoption of healthy life-style in people with high HADS scores to reduce the burden of sepsis. If this association is causal, treatment of psychiatric symptoms might influence later morbidity and mortality of BSI. However, our findings need to be replicated in other populations and using other measures of depression and anxiety.

In conclusion, severe anxiety and depression symptoms as measured by HADS and MSAD were associated with a moderate increase in risk of BSI in this population-based cohort study. Comorbidities, obesity, and adverse life-style in individuals with psychiatric suffering explain at least some of the excess BSI risk.

The Nord-Trøndelag Health Study (The HUNT Study) is a collaboration between HUNT Research Centre (Faculty of Medicine and Health Sciences, NTNU, Norwegian University of Science and Technology), Nord-Trøndelag County Council, Central Norway Regional Health Authority, and the Norwegian Institute of Public Health.

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