# The Differential Influence of Distinct Clusters of Psychiatric Symptoms, as Assessed by the General Health Questionnaire, on Cause of Death in Older Persons Living in a Rural Community of Japan

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**OBJECTIVES:** To examine the influence of distinct clusters of psychiatric symptoms on subsequent cause-specific mortality in older persons living in the community.

**DESIGN:** A prospective cohort study over 7.5 years.

**SETTING:** Otsuki-town, Kochi prefecture, Japan.

**PARTICIPANTS:** Nine hundred eighty community-dwelling persons, aged 65 to 84 in 1991.

**MEASUREMENTS:** Psychiatric symptoms at baseline were measured using the 30-item version of the General Health Questionnaire (GHQ-30). A factor analysis was performed on the responses of all 980 subjects. The relationships between subscale scores on the identified factors and causes of deaths occurring over 7.5 years in 817 respondents with no physical disability at baseline were assessed using a proportional hazards model adjusted for age, gender, chronic conditions under treatment, regular physical activity, and availability of close or casual neighbors.

**RESULTS:** The factor analysis identified three clusters of psychiatric symptoms: depression, apathy/anergia, and anxiety. In the proportional hazards model, which included three GHQ subscales depicting these factors simultaneously, the depression subscale was associated with increased mortality from cerebrovascular disease (multivariate adjusted hazard ratio per unit increase in the standard score on the depression subscale = 2.04, 95% confidence interval (CI) = 1.17–3.55), and the apathy/anergia subscale was associated with increased mortality from noncancer and noncardiovascular causes (multivariate adjusted hazard ratio per unit increase in the standard score on the apathy/anergia subscale = 1.71, 95% CI = 1.25–2.34). The anxiety subscale was not associated with any cause of death.

**CONCLUSION:** Depressive symptoms and symptoms indicating apathy/anergia have differential influences on subsequent causes of death in older persons living in the community. Identification of specific psychiatric symptom clusters may contribute to the prevention of deaths from specific causes in older populations. **J Am Geriatr Soc 50:313–320, 2002.**

**Key words: affective symptoms; aged; cause of death; longitudinal study**

Mental and emotional health are attracting attention as important factors in subsequent health problems in older persons living in communities. Depression, especially, has been investigated in relation to overall mortality[1–9] and to mortality from and incidence of heart disease,[5,7,10–12] cerebrovascular disease,[5,10,11,13] and malignant neoplasms[7,14,15] and the onset of physical disability.[6,16,17] With a few exceptions,[1,2,4,13,14] a depressive symptom cluster, even when not meeting the criteria for a clinical depressive disorder,[6] is associated with adverse health consequences after adjustment for physical health status.[3,6,9,10,15–17] Some studies have reported that associations vary by gender,[5,11,12] physical health status,[8] duration of depressive symptoms,[10,11,15] and cause of death.[7]

Information on the adverse effects of other types of psychopathology on health consequences for community-dwelling older persons is sparse.[3,18] Further studies should evaluate both the independent effects of different psychopathologies and their comorbidity with depression. Instruments measuring depression and other types of psychopathology are suited to the conduct of such studies.

The General Health Questionnaire (GHQ) is a 60-item instrument that measures four categories of psychological distress and behavior alteration: depression, anxiety, social impairment, and hypochondriasis (somatic symptoms). Two abbreviated versions of the GHQ, a 28-item version (the GHQ-28) and a 30-item version (the GHQ-30), have widely been used as instruments to screen for current and diagnosable psychiatric disorders in community settings.[19,20]

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The GHQ-28 covers all four psychiatric symptom clusters assessed by the GHQ and has commonly been used to create four subscales corresponding to the respective elements. However, difficulties in interpreting the somatic symptom clusters have been recognized, in that the same somatic symptoms can be present in a person with an entirely physical illness as in one with a psychopathology. Depressed persons may overemphasize somatic symptoms simply because of their excessive insight into depressive state.[21] The correct attribution of somatic symptoms to a physical illness as opposed to a depressive mood is difficult. Interpretation of the second abbreviated version of the GHQ, the GHQ-30, is not plagued by this problem because items relevant to somatic symptoms are excluded. Subscales reflecting purely psychiatric symptoms can be created from responses to the GHQ-30.

The objective of the present study was to examine the relationships of distinct psychiatric symptom clusters with subsequent causes of death in older persons living in the community. Distinct psychiatric symptom clusters for community-dwelling older persons in Japan were identified, using the GHQ-30, and subscales depicting individual clusters were created. Their associations with specific causes of subsequent mortality were investigated in a 7.5-year prospective study.

## METHODS

### Study Sample

The present study was conducted in Otsuki-town, Kochi prefecture, which is located on the southwest coast of Shikoku Island, Japan. In this community of about 8,000 residents, 23% of persons were aged 65 and older in 1990. A questionnaire survey on health status and lifestyle characteristics of all noninstitutionalized residents aged 65 to 84 was conducted in February 1991. Of 1,494 residents meeting these requirements, 1,377 (92%) responded to the questionnaire survey. Reasons for nonresponse included absence during the survey period (n = 36) and refusal (n = 81). Of these 1,377 respondents, 980 completed the GHQ-30.

### Study Variables

The Japanese version of the GHQ-30[22] formed the baseline survey. The respondents evaluated their experience of each of 30 psychiatric symptoms over the past few weeks on a 4-point scale: "0, not at all; 1, no more than usual; 2, rather more than usual; and 3, much more than usual." Each symptom was scored according to the Likert scoring method for the response categories (0-1-2-3) to maximize the variability of the responses.

Physical health status at baseline was assessed in terms of activities of daily living (ADL) impairment and self-reported chronic conditions under treatment. ADL impairment was evaluated according to whether help was needed on six items derived from the Older Americans Resources and Services methodology:[23] walking, bathing, going to the toilet, dressing, grooming, and eating. Persons who needed help for at least one ADL item were regarded as impaired. Self-report of chronic conditions under treatment pertained to diseases of the circulatory system and included hypertension, heart disease, cerebrovascular disease, hypercholesterolemia, and diabetes mellitus.

The lifestyle characteristics surveyed at baseline comprised three health-related practices: smoking (present, past, and never), frequency of drinking (almost every day, sometimes, and never), and regular physical activity (performing spare-time physical activities regularly, taking the opportunity for increasing physical activity in the day time, and spending the daytime in a sedentary way) and three elements of social networks: marital status (married and not married), availability of close friends (having one or more close friends and having none), and availability of close or casual neighbors (having neighbors with whom one talks about personal matters, having casual neighbors to whom one says hello, and having neither type of neighbor).

### Follow-Up Status

Of the 980 persons who completed the GHQ-30, 817 were followed in the present analysis. Persons with ADL impairment (n = 113) and with missing values on the covariates used in the multivariate analysis (n = 50) were excluded.

The follow-up status of respondents was determined by inspecting the municipal records of movement and deaths filed under the family registration act of Japan. Under the act, all residents are required to notify the municipality of moves and vital events. A death certificate accompanies notifications of death. During the follow-up period of 7.5 years, from February 1991 to the end of August 1998, 23 subjects moved from the area and 138 died. The underlying cause of death as given on the death certificate was coded according to the *International Classification of Diseases, Ninth Revision* (ICD-9). After excluding two deaths from unknown causes, the numbers of deaths from specific causes were as follows: 20 deaths from cerebrovascular disease (ICD-9 codes 430–438); 26 deaths from heart disease (ICD-9 codes 390–392, 393–398, 401–405, 410–414, 415–429, 440–459); and 46 deaths from malignant neoplasms (ICD-9 codes 140–208). Of the remaining 44 deaths, 10 were from pneumonia and influenza (ICD-9 codes 480–486, 487), nine from accidents and injuries (ICD-9 codes 800–999), and 25 from all other causes. These 44 deaths were combined as noncardiovascular and noncancer causes.

### Statistical Analysis

A factor analysis with a varimax rotation was performed on the responses of the 980 persons who completed the GHQ-30. Initial factors were extracted using the principal components analysis, and a varimax rotation was performed on the initial factor solution. The resulting factor structure was interpreted, making reference to previous studies on factor structure of the GHQ-30 in community settings.[24–30] In accordance with previously employed criteria,[28] an item was defined as loading on a given factor if the factor loading was 0.5 or greater for that factor and less than 0.5 for other factors. A subscale for each GHQ factor was created by summing subject responses to the items that had loadings of 0.5 or greater on the corresponding factor. The score on each subscale was transformed as a standard score with mean and standard deviation for the 980 respondents.

To test for differences between the categories of the dichotomized study variables in the age- and gender-adjusted mean scores on the individual GHQ subscales, an analysis of covariance was performed.

A proportional hazards model was used to assess the association of each GHQ subscale with subsequent mortality for the 817 persons who had had no ADL impairment. The proportional hazards assumption for each GHQ subscale was checked using a model that included an interaction term between time and the score on the subscale. No GHQ subscale violated the assumptions in predicting all-cause or cause-specific mortality.

Analyses using a continuous measure of psychopathology may fail to ascertain an association between the psychopathology and subsequent mortality if the relationship is nonlinear.[31] Therefore, standard scores for individual GHQ subscales were tested in continuous and dichotomous versions ($<1$ vs $\geq 1$). Two models were fitted for each approach; one tested each of the three GHQ subscales separately and the other the three GHQ subscales simultaneously. In the latter case, the association of each GHQ factor with mortality was examined after adjustment for comorbidity of the other GHQ factors. In the analyses of cause-specific mortality, separate models were fitted for each cause of death, and persons who had died from other causes were treated as censored at the time of dying. In all models, the covariates of age, gender, chronic conditions under treatment, and lifestyle characteristics were adjusted for. The statistical analyses were performed using SPSS 10.0J for Windows.

## RESULTS

The mean age ± standard deviation at baseline of the subjects used in the factor analysis (n = 980) was 72.0 ± 5.4. Sixty-one percent were women, and 89% had no impairment on the six ADL items at that time.

As shown in Table 1, factor analysis with a varimax rotation identified five factors with eigenvalues exceeding unity. The five factors accounted for 53.9% of the total variance, whereas the first three factors accounted for 40.5%. Six items (items 19, 23, 24, 25, 29, 30) of the seven that loaded only on the first factor were interpreted as depression. All seven items (items 1, 3, 4, 6, 7, 8, 9) that loaded on the second factor were related to apathy and anergia (lack of energy). Two items relating to sleep disturbance (items 2, 5) and four items relating to anxiety (items 14, 15, 18, 21) defined the third factor. The combinations of items with loadings of 0.5 or greater on these three factors were similar to findings in other populations[24–30] and were labeled depression, apathy/anergia, and anxiety, respectively, for the purposes of this study. The fourth and the fifth factors were not interpreted, because the percentage of variance that each accounted for was relatively small ($<8\%$), and only two or three items in each had loadings of 0.5 or greater.

Table 2 presents descriptive and internal consistency statistics for the subscales corresponding to the three factors described. Item 22, which had loadings of 0.5 or greater on both the depression and the anxiety factor, was excluded when creating those two subscales. All reliability estimates (Cronbach's coefficient alpha) for the three subscales exceeded 0.8 and were acceptable.

Table 3 describes differences at baseline in the GHQ subscale scores between categories of age, gender, physical health status, and lifestyle characteristics. Scores on the depression and apathy/anergia subscales were higher in the older age group, and those on the depression and the anxiety subscales were higher in women. For five of the six cells resulting from the three GHQ subscales and two physical health variables, age- and gender-adjusted mean scores on the GHQ subscales were higher for persons with physical health impairment. The exception of no difference occurred for depression scores in relation to number of chronic conditions. For lifestyle characteristics, age- and gender-adjusted mean scores on the GHQ subscales were higher in persons not performing regular physical activity and in those having no close or casual neighbors. The two lifestyle characteristics were treated as potentially confounding variables in the survival analysis.

Table 4 shows the relationships between the individual GHQ subscales and subsequent all-cause and cause-specific mortality. Although the hazard ratios associated with the dichotomized subscales are higher than those associated with the continuous subscales, the two approaches give the same pattern of results. Therefore, only the results of the analysis using continuous subscales are described below.

When the individual GHQ subscales were examined separately, depression and apathy/anergia were found to be predictive of subsequent all-cause mortality, but, when all three GHQ subscales were included simultaneously, neither of these factors was associated with all-cause mortality. In the investigation of cause-specific mortality, in which the three GHQ subscales were included simultaneously, depression was found to be associated with an increased risk of cerebrovascular disease mortality (multivariate adjusted hazard ratio per unit increase in the depression subscale = 2.04, 95% confidence interval (CI) = 1.17–3.55), and apathy/anergia was found to be associated with an excess risk of dying from noncardiovascular and noncancer causes (multivariate adjusted hazard ratio per unit increase in the apathy/anergia subscale = 1.71, 95% CI = 1.25–2.34). No significant association was found between anxiety and mortality in the model that included all three GHQ subscales simultaneously.

The interactions of each of the GHQ subscales with age and gender were examined with respect to all-cause and cause-specific mortality. The only statistically significant interaction that occurred was between depression and gender, with regard to heart disease mortality ($P = .005$). To investigate this interaction further, gender-specific models using the depression subscale only were fitted for prediction of heart disease mortality. As seen in Table 5, depression was significantly associated with the risk of dying from heart disease in women only (multivariate adjusted hazard ratio per unit increase in the depression subscale in women = 2.03, 95% CI = 1.17–3.50).

## DISCUSSION

The burden of GHQ-derived psychiatric symptom clusters was found to be associated with subsequent mortality among community-dwelling older persons. These associations were observed in persons with no physical disability and could not be explained by comorbid physical illness.

**Table 1. Factor Loadings of 30 Items of the General Health Questionnaire (N = 980)**

| Item numbers and abbreviated items | Factor 1 | Factor 2 | Factor 3 | Factor 4 | Factor 5 |
|---|---|---|---|---|---|
| 25. Life entirely hopeless | 0.71* | 0.17 | 0.28 | 0.09 | 0.06 |
| 29. Life not worth living | 0.71* | 0.15 | 0.18 | 0.06 | 0.18 |
| 24. Thinking of yourself worthless | 0.70* | 0.23 | 0.05 | −0.02 | 0.08 |
| 30. Nerves too bad to do anything | 0.67* | 0.13 | 0.19 | 0.12 | 0.07 |
| 23. Losing confidence in yourself | 0.64* | 0.20 | 0.39 | 0.08 | 0.02 |
| 19. Scared or panicky | 0.61* | 0.02 | 0.31 | 0.22 | −0.08 |
| 28. Nervous and strung-up | 0.57* | 0.14 | 0.48 | −0.01 | 0.01 |
| 22. Unhappy and depressed | 0.52* | 0.18 | 0.51* | 0.09 | 0.04 |
| 6. Less busy and occupied | 0.13 | 0.73* | −0.01 | 0.11 | 0.13 |
| 8. Not managing as well as most people | 0.25 | 0.71* | 0.05 | −0.01 | 0.03 |
| 4. Not feeling energy | 0.07 | 0.67* | 0.19 | 0.24 | 0.06 |
| 1. Could not concentrate | 0.23 | 0.63* | 0.06 | 0.16 | 0.01 |
| 9. Not doing things well | 0.14 | 0.63* | 0.12 | 0.31 | 0.17 |
| 3. Not alert and awake | 0.09 | 0.60* | 0.18 | 0.14 | 0.05 |
| 7. Not getting out of house as usual | 0.02 | 0.57* | 0.14 | −0.02 | −0.05 |
| 2. Lost sleep over worry | 0.18 | 0.12 | 0.77* | −0.01 | 0.07 |
| 5. Restless, disturbed nights | 0.11 | 0.19 | 0.70* | −0.13 | 0.16 |
| 14. Constantly under strain | 0.21 | 0.19 | 0.67* | 0.03 | 0.01 |
| 18. Taking things hard | 0.46 | 0.01 | 0.58* | 0.15 | −0.03 |
| 15. Could not overcome difficulties | 0.37 | 0.09 | 0.55* | 0.15 | −0.01 |
| 21. Everything on top of you | 0.45 | 0.09 | 0.52* | 0.13 | −0.15 |
| 10. Not feeling warmth and affection | −0.01 | 0.01 | −0.10 | 0.73* | 0.09 |
| 11. Not easy to get on with others | 0.10 | 0.28 | 0.06 | 0.64* | 0.13 |
| 13. Could not make decisions | 0.12 | 0.46 | 0.19 | 0.55* | 0.02 |
| 26. Not hopeful about future | 0.13 | 0.13 | 0.08 | 0.17 | 0.81* |
| 27. Not feeling reasonably happy | 0.12 | 0.04 | 0.06 | 0.29 | 0.77* |
| 12. Not playing a useful part | 0.22 | 0.44 | −0.03 | 0.46 | 0.28 |
| 16. Life a struggle all the time | 0.24 | −0.13 | 0.41 | 0.18 | −0.36 |
| 17. Not enjoying normal activities | 0.21 | 0.33 | 0.28 | 0.49 | 0.18 |
| 20. Could not face problems | 0.36 | 0.23 | 0.10 | 0.39 | 0.11 |
| % variance explained | 14.8 | 13.2 | 12.5 | 7.8 | 5.6 |

*Items with factor loadings ≥0.5 on each factor are grouped together.

The reasons for excluding persons with ADL impairment should be clarified. Antecedent psychopathology is an independent predictor of physical disability,[16,17] and thus physical disability may represent an intermediate step in the causal pathway between a psychiatric symptom cluster and mortality in older populations. Therefore, control of physical disability as a confounding factor reduces the variability of the psychiatric symptom cluster[7,12] and underestimates the association of interest. By choosing subjects with no ADL impairment, the problem of overadjustment for physical disability can be avoided. In the present analysis, the number of chronic conditions under treatment was treated as a variable of physical health status that might confound the association of interest.

This study has several limitations. First, the findings could be biased because only persons who could complete the GHQ-30 were admitted as subjects. Of the 397 persons who were excluded from the present analysis because of incomplete responses to the GHQ-30, 302 had no ADL impairment. Compared with persons who were used in the

**Table 2. Descriptive Statistics, Intercorrelations, and Coefficient Alpha Reliability Estimates for Three General Health Questionnaire (GHQ) Subscales (N = 980)**

| GHQ Subscale | Numbers of Component Items | Range | Mean | Standard Deviation (±) | Correlation Coefficients | | |
|---|---|---|---|---|---|---|---|
| | | | | | Depression | Apathy/Anergia | Anxiety |
| Depression | 19, 23, 24, 25, 28, 29, 30 | 0–21 | 5.20 | 3.76 | 0.863* | | |
| Apathy/Anergia | 1, 3, 4, 6, 7, 8, 9 | 1–21 | 8.09 | 2.89 | 0.436 | 0.819* | |
| Anxiety | 2, 5, 14, 15, 18, 21 | 0–18 | 6.28 | 3.47 | 0.708 | 0.380 | 0.823* |

*Reliability estimates.

**Table 3. Adjusted Mean Scores on Three General Health Questionnaire Subscales by Age, Gender, Physical Health Status Variables, and Lifestyle Characteristics (n = 980)**

| Characteristic | General Health Questionnaire Subscales | | | | | |
|---|---|---|---|---|---|---|
| | Depression | | Apathy/Anergia | | Anxiety | |
| | Adjusted Mean | Standard Error (±) | Adjusted Mean | Standard Error (±) | Adjusted Mean | Standard Error (±) |
| Age† | | | | | | |
| 75–84 | 5.69** | 0.21 | 8.84** | 0.16 | 6.40 | 0.20 |
| 65–74 | 4.97 | 0.14 | 7.75 | 0.11 | 6.22 | 0.13 |
| Gender‡ | | | | | | |
| Female | 5.43* | 0.15 | 8.02 | 0.12 | 6.56** | 0.14 |
| Male | 4.84 | 0.19 | 8.20 | 0.15 | 5.85 | 0.18 |
| Physical health status§ | | | | | | |
| Physical activities of daily living | | | | | | |
| Impaired | 8.43** | 0.47 | 11.73** | 0.35 | 8.75** | 0.44 |
| Not impaired | 4.98 | 0.13 | 7.86 | 0.09 | 6.10 | 0.12 |
| Chronic conditions under treatment | | | | | | |
| ≥1 | 5.35 | 0.19 | 8.38** | 0.14 | 6.64* | 0.17 |
| 0 | 5.09 | 0.16 | 7.88 | 0.12 | 6.02 | 0.15 |
| Lifestyle characteristics§ | | | | | | |
| Smoking | | | | | | |
| Present | 5.01 | 0.29 | 8.08 | 0.22 | 5.93 | 0.27 |
| Never or past | 5.23 | 0.14 | 8.08 | 0.11 | 6.37 | 0.13 |
| Frequency of drinking | | | | | | |
| Sometimes or more | 4.81 | 0.36 | 7.84 | 0.28 | 5.97 | 0.34 |
| Never | 5.24 | 0.14 | 8.14 | 0.10 | 6.31 | 0.13 |
| Regular physical activity | | | | | | |
| Not performing | 6.48** | 0.29 | 10.04** | 0.21 | 6.86* | 0.27 |
| Performing or taking the opportunity | 4.97 | 0.13 | 7.71 | 0.10 | 6.18 | 0.13 |
| Marital status | | | | | | |
| Not married | 5.32 | 0.22 | 8.00 | 0.17 | 6.10 | 0.21 |
| Married | 5.05 | 0.16 | 8.14 | 0.12 | 6.40 | 0.15 |
| Close friends | | | | | | |
| Not having | 5.44 | 0.25 | 8.78** | 0.19 | 6.23 | 0.23 |
| Having | 5.09 | 0.14 | 7.84 | 0.11 | 6.25 | 0.13 |
| Close or casual neighbors | | | | | | |
| Not having either | 5.70** | 0.23 | 8.91** | 0.18 | 6.63* | 0.22 |
| Having either or both | 4.97 | 0.14 | 7.79 | 0.10 | 6.12 | 0.13 |

*$P < .05$; **$P < .01$, by analysis of covariance for difference in adjusted mean scores between categories.
†Adjusted for gender.
‡Adjusted for age.
§Adjusted for age and gender.

survival analysis (n = 817), they were older (mean age 73.1 vs 71.8; two-sample *t* test, equality of variances assumed, $P = .002$). There was no difference in the proportions of women and, of those with chronic conditions under treatment, between the two groups. If the persons excluded from the analysis had higher levels of psychiatric symptoms, associated with older age, then the present findings would underestimate the effect of the burden of psychiatric symptom clusters on subsequent mortality.[11]

Second, the GHQ might fail to identify some persons with chronic psychiatric symptoms in the target population. Because the response categories of the GHQ required assessment of whether each symptom was "worse than usual," this instrument might not identify the symptom in a person who had suffered it over a long period and had come to consider it usual.[20,32] The associations observed in the present study might, therefore, reflect only the effects of acute psychiatric symptoms.

Third, the loss of significant associations between the individual GHQ subscale scores and all-cause mortality, when all three GHQ subscales were included simultaneously, might indicate that the depression and the apathy/anergia subscales were not truly independent of each other but shared a variance that was the real correlate of all-cause mortality, this latent variance being imperfectly captured by either of the subscales. Alternatively, an independent influence of the GHQ subscales on specific causes of death might be diluted in the analysis for all-cause mortality, where relationships with insignificant causes of death were included.

**Table 4. Adjusted Hazard Ratios of All-Cause and Cause-Specific 7.5-Year Mortality Associated with Higher Scores on Each General Health Questionnaire (GHQ) Subscale Simultaneously Among Persons with no Physical Disability (n = 817)**

| | Using Continuous Subscales | | | | Using Dichotomized Subscales | | | |
|---|---|---|---|---|---|---|---|---|
| | Including GHQ Subscales Separately | | Including GHQ Subscales | | Including GHQ Subscales Separately | | Including GHQ Subscales | |
| GHQ factors | Hazard Ratio† | 95% CI | Hazard Ratio† | 95% CI | Hazard Ratio‡ | 95% CI | Hazard Ratio‡ | 95% CI |
| All causes | | | | | | | | |
| Depression | 1.23* | 1.04–1.45 | 1.15 | 0.90–1.47 | 1.72* | 1.12–2.64 | 1.44 | 0.85–2.45 |
| Apathy/Anergia | 1.26** | 1.06–1.49 | 1.18 | 0.98–1.43 | 1.81** | 1.19–2.76 | 1.59* | 1.01–2.51 |
| Anxiety | 1.18 | 0.99–1.40 | 1.00 | 0.77–1.29 | 1.35 | 0.89–2.06 | 1.02 | 0.62–1.68 |
| Cerebrovascular disease | | | | | | | | |
| Depression | 2.08** | 1.48–2.94 | 2.04* | 1.17–3.55 | 5.48** | 2.20–13.6 | 3.62* | 1.12–11.7 |
| Apathy/Anergia | 1.51* | 1.00–2.28 | 1.07 | 0.70–1.64 | 2.56 | 0.88–7.43 | 1.33 | 0.42–4.29 |
| Anxiety | 1.85** | 1.20–2.87 | 1.00 | 0.51–1.96 | 3.59** | 1.46–8.87 | 1.77 | 0.57–5.46 |
| Heart disease | | | | | | | | |
| Depression | 1.04 | 0.70–1.53 | 0.68 | 0.39–1.21 | 1.37 | 0.47–3.99 | 0.81 | 0.22–2.93 |
| Apathy/Anergia | 1.27 | 0.88–1.85 | 1.26 | 0.82–1.93 | 1.75 | 0.66–4.68 | 1.58 | 0.54–4.61 |
| Anxiety | 1.29 | 0.88–1.89 | 1.55 | 0.89–2.71 | 1.84 | 0.76–4.42 | 1.80 | 0.64–5.08 |
| Malignant neoplasms | | | | | | | | |
| Depression | 1.19 | 0.89–1.60 | 1.28 | 0.83–1.97 | 1.38 | 0.61–3.09 | 1.57 | 0.59–4.19 |
| Apathy/Anergia | 0.86 | 0.59–1.26 | 0.78 | 0.53–1.16 | 1.02 | 0.42–2.49 | 0.92 | 0.36–2.36 |
| Anxiety | 1.13 | 0.83–1.53 | 1.00 | 0.64–1.57 | 0.99 | 0.44–2.23 | 0.81 | 0.32–2.09 |
| Noncardiovascular-noncancer causes | | | | | | | | |
| Depression | 1.02 | 0.75–1.40 | 0.96 | 0.61–1.51 | 1.34 | 0.59–3.01 | 1.16 | 0.44–3.05 |
| Apathy/Anergia | 1.52** | 1.16–1.98 | 1.71** | 1.25–2.34 | 2.62** | 1.34–5.11 | 2.77** | 1.36–5.62 |
| Anxiety | 0.97 | 0.70–1.34 | 0.79 | 0.49–1.26 | 0.87 | 0.36–2.07 | 0.61 | 0.22–1.67 |

*$P < .05$, **$P < .01$

†A hazard ratio associated with a one-unit increase in the standard score on each GHQ subscale, adjusted for age, gender, chronic conditions under treatment, regular physical activity, and availability of close or casual neighbors.

‡A hazard ratio of ≥1 of the standard score on each GHQ subscale relative to <1, adjusted for the covariates described above.

CI = confidence interval.

Fourth, the subscales of the GHQ-30 have not been validated against a clinical diagnosis. The persons with higher scores on the subscales might include those who do not fit clinical criteria for psychiatric disorders. Depressive symptoms not meeting the criteria for clinical depressive disorders have been found to explain the discrepancy between a high prevalence of depressive symptoms and a low prevalence of clinically diagnosable depressive disorders in community populations.[33] Such symptoms have been identified as independent predictors of adverse health consequences.[6,34,35] A similar situation may exist for other clusters of psychiatric symptoms not meeting the criteria for clinical disorders but relevant to subsequent health events and should be explored.

Finally, the presence of persons with occult or unreported physical illnesses at baseline might have a residual confounding effect on the association of psychiatric symptoms with mortality. However, in the present study, the residual confounding effect seemed to be small. An analysis excluding the 10 persons who had died within 1 year of the baseline survey did not alter the findings.

**Table 5. Gender-Specific Adjusted Hazard Ratios of Heart Disease Mortality Over 7.5 years Associated with Higher Scores on the Depression Scale in Persons with no Physical Disability (n = 817)**

| | Using a Continuous Depression Scale | | Using a Dichotomized Depression Scale | |
|---|---|---|---|---|
| Gender | Hazard Ratio† | 95% CI | Hazard Ratio‡ | 95% CI |
| Men (17 deaths in 317 men) | 0.65 | 0.37–1.14 | 0.53 | 0.07–4.01 |
| Women (9 deaths in 500 women) | 2.03* | 1.17–3.50 | 3.05 | 0.76–12.3 |

*$P < .05$.

†A hazard ratio associated with a one-unit increase in the standard score on the depression scale, adjusted for age, chronic conditions under treatment, regular physical activity, and availability of close or casual neighbors.

‡A hazard ratio of ≥1 of the standard score on the depression scale relative to <1, adjusted for the covariates described above.

CI = confidence interval.

The specific relationships between distinct psychiatric symptom clusters and subsequent causes of death are worthy of notice. In the present study, depressive symptoms at baseline were associated with an increased risk of cerebrovascular disease mortality after adjustment for gender. This finding is consistent with the association between higher levels of depressive symptoms and increased risk of mortality from stroke in a 29-year prospective study of community-dwelling adults (mean age at baseline, 43 years) in Alameda County, the United States.[36] However, findings of prospective studies have been inconsistent for older populations with regard to the association between depression and cerebrovascular disease. The Established Population for the Epidemiologic Study for the Elderly (EPESE) in the United States, at its New Haven site, using all participants, found no relationship between initial scores on the Center for Epidemiologic Studies Depression Scale (CES-D) and stroke incidence across 7 years, after adjustment for gender and other potential confounding factors.[13] However, the depression score was associated with an increased incidence of stroke over 6 years, in both genders, when subjects were restricted to those with diagnosed hypertension.[5] At two other sites of the EPESE, the association between scores on the CES-D and stroke incidence was examined, by gender, in those with diagnosed hypertension, and a significant association was observed among men in East Boston but not in Iowa.[5]

As in the present study, subsequent increased risk of cardiovascular disease has been found to be associated with initial depressive symptom clusters in women only. At the New Haven site of the EPESE, a 9-year prospective study using all participants found an association between scores on the CES-D and coronary heart disease mortality in women with no physical disability.[12] In a 6-year prospective study, at three sites of the EPESE, which restricted subjects to those with diagnosed hypertension, an association was found for women at two of the three sites (New Haven and Iowa).[5]

By contrast, no epidemiological study has examined the relationship, found here, between a symptom cluster indicating apathy/anergia and the risk of dying from noncancer and noncardiovascular causes.

Depressive symptoms and apathy/anergia do not necessarily imply an affective disorder, and other explanations for the observed association between psychiatric symptom clusters and mortality need to be explored. For example, mood disturbance, fatigue, cognitive slowing, and anergia are associated with certain cytokines, notably α-interferon.[37,38] The neuropsychiatric changes associated with α-interferon are thought to reflect a disturbance in frontal lobe function[39,40] and may be mediated by neuroendocrine, neurotransmitter, or cytokine effects.[38,41] The neuroendocrine effects of α-interferon include disorders of thyroid function and stimulation of the adrenocorticotropic hormone/cortisol axis. The neurotransmitter effects of α-interferon include opioid-dopamine changes (underactivity of endogenous opioid systems, acting as a dopamine antagonist), serotonin depletion, and norepinephrine increases. Serotonin depletion is strongly associated with depressive symptoms. The cytokine effects of α-interferon include the secondary production of proinflammatory cytokines such as interleukin-6. Interleukin-6 has widespread neuroendocrine effects. It may affect the metabolism of lipoproteins and cause hypocholesterolemia,[42] which is thought to be associated with deaths due to noncardiovascular and noncancer causes.[43]

In their aggregate, the pathways evoked by α-interferon could be capable of contributing directly and indirectly to the development of, and the excess disability associated with, cardiovascular disease or cerebrovascular disease.[44] Thus, the "depressive" symptoms and apathy/anergia observed here could be either the direct result of underlying neuroendocrine or neuroimmunological responses to concurrent medical illnesses or a symptom of processes that affect the course of some illnesses. Neuroendocrine and neuroimmunological changes associated with medical illnesses should also be investigated in further studies on the relationship between psychiatric symptoms and subsequent health events.

The present study indicates that two of the three distinct psychiatric symptom clusters identified by the GHQ-30 have differential influences on subsequent causes of death in community-dwelling older persons. Persons with depressive symptoms and those with symptoms indicating apathy/anergia are at increased risk of death from differing causes. In Japan, public health services aimed at primary and secondary prevention of chronic diseases are provided at the municipality level for community-dwelling older persons, but psychiatric symptoms as influences on subsequent health events have not been well recognized in the preventive health services. Addressing the burden of psychiatric symptom clusters, even when they do not meet the criteria of clinically diagnosable disorders, could contribute to the prevention of mortality from specific causes.

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