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Impact of psychological distress on mortality in Spain. The importance of early detection and treatment of mental disorders.

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Abstract

Background. Mental health problems account for 14% of mortality worldwide. The aim of this study was to evaluate the association between psychological distress and mortality in the Spanish adult population.

Methods: Data came from a longitudinal study in population ≥15 years of age (n=21,005) who participated in the 2011-12 Spanish National Health Survey, which was linked to mortality records as of December 2020. Mental health was assessed with the GHQ-12, defining psychological distress as a dichotomous variable using a GHQ-12 score ≥3 as the cutoff point. Using Poisson regression, standardized mortality rate ratios (SRR) were estimated for all-cause, cardiovascular disease, and tumor-related mortality, adjusting for sociodemographic variables, lifestyles, and comorbidities.

Results: The standardized overall mortality rate in individuals with and without psychological distress was 14.58 and 10.90 per 1000 person-years, respectively, estimating an SRR of 1.34 (95%CI:1.19-1.50). The SRR for tumor-related mortality was 1.17 (95%CI:0.90-1.53), and cardiovascular-related mortality was related to higher distress (GHQ-12≥4): SRR of 1.22 (95%CI:0.98-1.51). Among psychological distressed individuals, the overall mortality SRR for those with a previous mental disorder diagnosis was 1.18 (95%CI:0.91-1.53) versus 1.34 (95%CI:1.18-1.54) for those without such diagnosis (p for interaction=0.067). Similarly, distressed participants taking prescription drugs for mental disorders had a lower mortality risk than those not taking them (p for interaction=0.016).

Conclusions: Individuals with psychological distress had a higher risk of overall-, cardiovascular disease- and tumor-related mortality. This association was higher among participants not previously diagnosed with a mental disorder and those not taking medication for mental issues.

Keywords: Psychological distress, diagnosis, treatment, mortality

Introduction

All types of mental illness are associated with premature mortality (Plana-Ripoll et al., 2019), especially with cancer and cardiovascular disease (Joukamaa et al., 2001). Further, an estimated 14.3% of overall global mortality may be attributed to mental health problems (Walker et al., 2015). In 2016, in the European Union, about 84 million people reported having a mental health problem, i.e., one in six people. The most frequent mental illnesses are anxiety and depression, affecting 5.4% and 4.5% of the population, respectively (OECD/EU, 2018).

Psychological distress, though not a mental health diagnosis, depicts symptoms of anxiety and depression, and can become a long-lasting and disabling disorder. There is ample published evidence associating psychological distress to an increased risk of mortality in general (Huppert and Whittington, 1995; Puustinen et al., 2011; Robinson et al., 2004; Yang et al., 2020), cancer- (Batty et al., 2017) and cardiovascular disease-related mortality in particular (Batty et al., 2016; Lee and Singh, 2020; Yang et al., 2020).

The importance of screening for early detection of mental health problems is widely recognize. Yet, much remains to learn about the mechanisms through which a prior mental illness diagnosis, either controlled with medication or not, may influence the association between psychological distress and mortality. In this study we chose the General Health Questionnaire (GHQ) (Goldberg et al., 1997), a widely used screening instrument to measure psychological distress, especially its 12-item version. The GHQ was originally designed as a screening tool for use in both clinical and community settings to detect cases of psychiatric morbidity or psychological distress in the population.

The aim of this study is to evaluate the association between psychological distress and all-cause-, cardiovascular disease-, and tumor-related mortality, according to whether the patient had a previous mental disorder diagnosis and whether the participant was taking a prescription drug for a mental health issue.

Methods

Design

This is a longitudinal study based on the 2011-12 Spanish National Health Survey data (ENSE, for its acronym in Spanish) (Ministerio de Sanidad, Servicios Sociales e Igualdad

/ Instituto Nacional de Estadística, 2013), linked to death registry data as of December 2020 *(Linking Mortality to the Spanish Health Surveys*, MESES study, for its Spanish acronym). The data, collected between July 2011 and June 2012, were provided by the Spanish National Institute of Statistics. ENSE´s sample design is multistage where all provinces are selected and within each province municipalities are selected and stratified by size. For each of the selected municipalities, a sample of census sections is chosen. Finally, the dwellings are sampled and an adult person ≥15 years of age, within each household, is selected to be interviewed face-to-face. The final sample consisted of 21,003 individuals and it is representative of the Spanish population.

Variables

The dependent variables were defined as all-cause mortality, mortality caused by circulatory system diseases (ICD-10: I00-I99) or caused by tumors (ICD-10: C00-D48), cumulative through December 31, 2020.

Mental health was estimated based on the 12-item General Health Questionnaire (GHQ-12) developed by Goldberg and colleagues (Goldberg et al., 1997) and validated in Spain (Sánchez-López and Dresch, 2008). The GHQ-12 assesses the incidence and severity of mental disorders during the recent weeks: ability to concentrate, loss of sleep over worry, playing a useful part, ability to make decisions, constantly feeling under strain, inability to overcome difficulties, ability to enjoy daily activities, ability to face problems, feelings of unhappiness and depression, loss of confidence, feeling worthless, and feeling reasonably happy. Responses are based on a four-point Likert scale: "much less than usual" and "usual" (assigned 0 points) vs. "more than usual" and "much more than usual" (assigned 1 point). The scores for positive items were reversed. Based on these dichotomized scores, a total score of 3 or more identifies individuals with a possible mental disorder(Goldberg et al., 1998).

Socio-demographic variables: sex; age (15-24, 25-44, 45-64, >64); cohabitation (living alone, with other members in the household); level of education (primary/no education, lower secondary, upper secondary, and university); area of residence (urban: ≥10,000 inhabitants, rural:<10,000 inhabitants).

Lifestyle variables: Sedentary leisure time was defined as either no exercise or spending leisure time almost completely sedentary. Average daily alcohol consumption was estimated from the frequency of habitual consumption of 6 types of alcoholic beverages

for each day of the week. Consumption was classified as: no consumption, low-risk consumption (≤20 g/day in men and ≤10 g/day in women) and average high-risk consumption (>20 g/day in men and >10 g/day in women). Binge drinking was defined as the consumption of 6 or more alcoholic drinks within 4 to 6 hours in the past month for men and 5 or more for women. Finally, based on their reported tobacco consumption, respondents were classified as never smoker, ex-smoker, smoker of 1 to 14 cigarettes, smoker of more than 14 cigarettes.

Comorbidity: This variable counts the number of diagnosed chronic diseases among these: hypertension, myocardial infarction, other heart diseases, osteoarthritis/arthritis/rheumatism, asthma, chronic bronchitis/emphysema/chronic obstructive pulmonary disease (COPD), diabetes, cirrhosis/liver dysfunction, stomach or duodenal ulcer, urinary incontinence, stroke/brain hemorrhage, malignant tumors, osteoporosis, and thyroid problems.

Self-reported mental health variables: These binary variables identify those diagnosed with mental disorders in the last 12 months (Have you been diagnosed by a doctor with anxiety, depression or other mental health problems?) (yes/no) and current consumption of prescribed drugs (Use of any of the following medications: tranquilizers, relaxants, sleeping pills, antidepressants, stimulants, prescribed by your doctor in the last two weeks) (yes/no).

Data analysis

We developed Poisson regression models, considering exposure time, for all-cause, cardiovascular, and tumor mortality, estimating standardized mortality rate per 1000 person-years (SR), standardized mortality rate ratios (SRR), and standardized mortality rate difference (SRD). The effect of psychological distress on mortality was estimated using 2 models: Model 1 adjusted for sociodemographic characteristics and lifestyles; and model 2 additionally adjusted for number of comorbidities. Performing sensitivity analyses we replicated these 2 models excluding individuals with tumors, myocardial infarction, or cerebrovascular disease.

The dose-response curve for the mortality SRR for the entire GHQ-12 score range (discrete variable) was estimated as a restricted cubic spline function (Greenland, 1995). We assessed interactions with variables for sex, age groups, educational level, and area of residence. In addition, possible interactions between positive GHQ-12 screening, a

mental disorder diagnosis, and current consumption of prescribed medication were explored. Finally, we repeated all analyses excluding proxy responses (i.e., the questionnaire is filled out by other than the selected individual) as sensitivity analysis.

Estimates were weighted by sampling weights to restore proportionality. All analyses were performed with Stata/MP 16.1 (StataCorp, College Station, USA), using the "survey" module to incorporate the complex sampling design features of the surveys, including weighting to ensure that the distribution of the sociodemographic characteristics of the sample mirror those of the population.

Ethical considerations

This study was approved by the Research Ethics Committee of the Spanish Institute of Health Carlos III. No: CEI PI 28_2019.

Results

The median follow-up time was 9 years, during which 2,346 deaths were recorded. Table 1 shows the sample distribution according to psychological distress (20.4% positive). Table 2 shows the association between psychological distress and overall mortality, cardiovascular disease-, and tumor-related mortality.

In terms of overall mortality, the SR for those suffering psychological distress was 16.07 per 1000 person-years (95%CI: 14.55-17.60), after adjusting for sociodemographic and lifestyle variables. In contrast, among those negative for psychological distress, the SR was 10.28 (95%CI: 9.57-10.99), with an SRD of 5.79 (95%CI: 4.18-7.40) and an SRR of 1.56 (95%CI: 1.40-1.75) (Model 1). Further adjusting for medical diagnoses, the overall mortality risk (SRR) for individuals with psychological distress was 1.34 (95%CI: 1.19-1.50) (Model 2). This is a similar result to what we observed when we excluded respondents with tumors and/or previous cardiovascular disease from the analyses.

In tumor-related mortality, those with distress had a fully adjusted SRR of 1.33 (95%CI: 1.06-1.67) (model 2). However, the strength of the association decreased to 1.17 (95%CI: 0.90-1.53) when respondents with a previous history of tumors were excluded.

Among those dying as a result of cardiovascular disease, the SRR for individuals positive for psychological distress was 1.11 (95%CI: 0.91-1.37). Further, excluding those with

previous cardiovascular pathology (SRR=1.06 (0.84-1.34)) did not have a significant impact. Finally, we failed to detect any significant interactions of psychological distress with sex, age, educational level, or area of residence.

Table 3 presents the association between psychological distress and overall mortality. First, the association is stratified by previous history of a mental disorder diagnosis, and by the consumption of medications related to these diseases, below. Individuals with a positive GHQ-12 and a previous diagnosis of mental illness had an SRR of 1.18 (95%CI: 0.91-1.53), whereas those with no previous diagnosis had a SRR of 1.34 (95%CI: 1.18-1.54), estimating an interaction approaching statistical significance (p=0.067). Also, respondents suffering from distress but being treated pharmacologically for mental illness had a SRR of 1.18 (95%CI: 0.96-1.45) versus those not receiving treatment (SRR: 1.41; 95%CI: 1.23-1.63). The interaction was statistically significant (p=0.016).

The dose-response relationship between psychological distress and all-cause mortality reveals a linear association when analyzing the entire range of GHQ-12 scores with a slope increase for scores ≥ 10 (Figure 1). For tumor-related mortality, the linear relationship is well-defined throughout the entire range of GHQ-12 scores. Regarding mortality caused by cardiovascular diseases, the association fails to be significant for GHQ-12 ≤3. For scores ≥4, i.e., higher levels of distress, the risk increases only for scores ≥10. The SRR for cardiovascular-related mortality for a GHQ ≥4 was 1.22 (95% CI:0.98-1.51) in individuals with no history of myocardial infarction and/or stroke.

Stratifying by previous history of mental health (yes/no) we observed that psychological distress and all-cause mortality were linearly related for the full range of GHQ-12 score. In addition, when we stratified for consumption prescription drugs for mental disorders (yes/no), the linear association was observed for GHQ-12 scores ≥ 8 points. (Figure S1)

Tables S1 and S2 (supplementary material) replicate the main analyses excluding responses provided by a proxy. Results confirm that these estimates are very similar to those obtained from the entire sample.

Discussion

To our knowledge, this is the first nation-wide study in Spain to analyze the impact of psychological distress on mortality using the GHQ-12. This population-based study with a 9-year follow-up suggests that psychological distress is associated with an increased

risk of all-cause, cardiovascular disease- and tumor-mortality, with a dose-response relationship. The strength of the association between distress and mortality weakens for those reporting a previous diagnosis of mental illness and/or taking related medication.

Our results support previous studies evaluating the impact of psychological distress, also assessed with the GHQ-12, on all-cause mortality. A study of 4,501 adults, between the ages of 18-75, followed for 7 years and selected from primary care registries, showed a dose-response association. Models adjusting for sociodemographic variables and smoking estimated an HR of 1.38 (1.06, 1.79) with a score of 1-3; increasing to 1.71 (1.32, 2.23) by raising the cutoff point to ≥4 (Robinson et al., 2004). Based on the Health Survey for England with 66 518 individuals aged 35 years or older (free of cancer and cardiovascular disease at baseline), for a mean follow-up of 8.2 years, using a score ≥4, the observed HR was 1.38 (Lazzarino et al., 2013).

Finding a linear dose-response relationship between psychological distress and mortality, with the risk of death increasing with increasing levels of distress, is noteworthy given the important clinical and public health implications as we discuss below. However, to our knowledge, only 2 studies have analyzed the dose-response pattern considering psychological distress as a discrete variable. Batty and colleagues (Batty et al., 2016) reported a dose-response relationship that was attenuated, though still significant, in models adjusting for 15 covariates. In the second study, Yang and colleagues analyzed data from 330,367 people over 18 years of age participating in the U.S. National Health Interview Survey (NHIS) and followed for 8 years. They found that psychological distress, measured with Kessler-6, was associated with a fairly linear dose-response pattern until near the end of the score range where the relationship tended to plateau (Yang et al., 2020). Finally, other studies approximating the dose-response relationship, by coding the psychological distress indicator into categories, also observe a gradient effect (Batty et al., 2016; Hockey et al., 2021; Lee and Singh, 2020; Ponizovsky et al., 2018).

The association between distress and tumor-related mortality observed in our work (SRR: 1.33) is also consistent with previous studies (Batty et al., 2017; Lee and Singh, 2021; Wang et al., 2020). However, this association was somewhat reduced (SRR: 1.17) after excluding individuals with a previous cancer diagnosis from the analysis. Longitudinal studies applying the same exclusion criteria, report inconclusive results regarding the association. An Israeli study reported a risk (HR) of mortality per one unit increase in

GHQ-12 score of 0.98, i.e., a null association (Ponizovsky et al., 2018). An English study based on 68,222 adults over 35 years of age, only found association between GHQ-12 scores and cancer mortality at very high levels of psychological distress (Russ et al., 2012). Finally, other association reported between GHQ-12 scores and cancer mortality was no longer significant once those with a previous history of cancer were excluded (Hamer et al., 2009).

These results could suggest reverse causality, i.e., that psychological distress does not impact the development of cancer or patient´s survival, but instead the distress is a consequence of the cancer. It is well documented that cancer patients are more likely to suffer depression and anxiety than the general population (Mitchell et al., 2011). However, the mechanisms through which psychological distress impact cancer are also well established (Batty et al., 2017), so the causal relationship is most likely bidirectional.

The observed association between distress and cardiovascular-disease mortality is also consistent with previous work using the GHQ-12 to measure psychological distress (Hamer et al., 2009; Robinson et al., 2004; Russ et al., 2012). The magnitude of the association is usually small in the low-to-moderate distress levels, and it increases when distress scores reach severe levels. Our risk estimates for GHQ-12 scores above 3 support previous findings (Hamer et al., 2009; Robinson et al., 2004; Russ et al., 2012).

Two of our main findings have important public health implications. Among distressed individuals, those with a previous diagnosis of a mental disorder or those currently under pharmacological treatment for a mental disorder have a lower mortality risk than individuals with neither diagnosis nor current treatment. These results may be notable because despite the high prevalence of mental health problems, many people do not seek professional help promptly, if at all, and, thus, treatment might be received late, if ever (Evans-Lacko et al., 2018; Kohn et al., 2004).

Our study´s main strengths reside in its population-based cohort design with a large sample followed for a median of 9 years and the use of personal identification for mortality record matching, reducing misclassification errors. Further, since the distress-mortality association could be influenced by health behaviors (e.g., tobacco and alcohol consumption) (Harris and Barraclough, 1998), the adjustment for lifestyle factors reduces the risk of residual confounding. Finally, to examine possible reverse causality, we ran

the analyses excluding respondents with previous serious pathologies as well as proxy respondents, as they often fill in for individuals too ill to respond themselves. In some cases, the strength of the associations is slightly or moderately reduced.

The main limitation of this study is the bias inherent to self-reported health data, a common issue in this type of studies. Also, our instrument for measuring psychological distress, the GHQ-12, does not provide a clinical diagnosis of anxiety or depression, but it has been widely used in population-based studies (Goldberg et al., 1997). Due to National Health Survey data limitations, we were unable to analyze the effects that receiving psychotherapy or some other intervention, as one more treatment for mental disorders, may have on our results. In addition, some stratified analyses have limited statistical power, the results of which should be confirmed by further research. Finally, psychological distress was recorded only at baseline. Given the dynamic nature of this mental issue, we cannot discount the possibility of individuals experiencing changes in their distress levels throughout the follow-up period.

Conclusions

Individuals experiencing psychological distress have a higher risk of all-cause, tumor-, and cardiovascular disease-mortality with a dose-response association. This relationship is stronger among individuals with no previous mental disorder diagnosis or with no prescriptions for treating mental health issues. These results underscore the importance of mental disorders early detection and treatment.

Author contributions

Teresa López-Cuadrado PhD, conceptualization, methodology, formal analysis, Writing - Original Draft, Writing - Review & Editing.

Cristina Ortiz MSc, data curation, methodology, Writing – Review & Editing.

Ana Ayuso-Álvarez, PhD, Writing - Review & Editing.

Iñaki Galán MD, PhD, conceptualization, data curation, methodology, validation, investigation, supervision, Writing - Review & Editing.

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Conflict of interest

The authors declare no conflicts of interest.

Table 1. Sample characteristics according to the presence of psychological distress as estimated by the GHQ-12. Spanish population ≥15 years of age

	N[a]	Psychological distress[b]	
		Yes	**No**
		%	**%**
N	20 382	4539	16 154
Sex			
Men	9373	40.1	51.1
Women	11009	59.9	48.9
Age (years)			
15 - 24	1608	7.0	12.6
25 44	6546	36.1	38.2
45 - 64	6575	33.3	29.9
≥ 65	5653	23.6	19.2
Educational level			
University	3048	11.4	17.1
Secondary school, 2nd cycle	5312	23.6	29.5
Secondary school 1st cycle	6539	35.8	32.9
Primary school or no studies	5483	29.1	20.5
Number of people in household			
Lives alone	4522	11.5	9.4
>1 person	15 860	88.5	90.6
Place of residence			
Urban area	15 558	79.9	78.8
Rural area	4824	20.1	21.2
Tobacco consumption			
Non-smoker	11 118	50.3	54.0
Ex-smoker	4083	19.5	19.7
1-14 cigarettes	3062	16.7	16.0
>14 cigarettes	2119	13.5	10.2
Alcohol consumption			
No consumption	11 122	60.4	51.8
Low-risk consumption	7420	31.5	39.2

High-risk consumption	1840	8.1	9.0
Binge drinking in the last month			
No	19 479	95.8	95.3
Yes	903	4.2	4.7
Leisure-time sedentarism			
No	11 312	45.1	58.5
Yes	9070	54.9	41.5
Body Mass Index			
Underweight	364	2.0	2.2
Normal weight	7977	37.7	42.8
Overweight	6978	31.8	33.8
Obesity	3265	18.7	14.5
No response	1798	9.8	6.7
Number of comorbidities			
0	10 096	39.8	60.3
1	4672	23.2	21.4
2	2724	15.0	10.1
>2	2890	22.1	8.2
Previous diagnosis mental disorder			
No	18 151	72.0	95.6
Yes	2,224	28.0	4.4
Consumption prescription drugs			
No	17 556	71.1	93.2
Yes	2 826	28.9	6.8
Deceased			
No	18 036	87.5	93.9
Yes	2346	12.5	6.1

[a]Unweighted sample size; [b]Weighted percentages

Table 2. Association between psychological distress, as estimated by the GHQ-12, and all-cause, cardiovascular disease-, and tumor-related mortality.

		Psychological Distress			
	N	**SR (95%CI) distressed**	**SR (95%CI) non-distressed**	**SRD (95%CI)**	**SRR (95%CI)**
All-cause mortality					
Model 1	20,382	16.07 (14.55, 17.60)	10.28 (9.57, 10.99)	5.79 (4.18, 7.40)	1.56 (1.40, 1.75)
Model 2	20,382	14.58 (13.15, 16.0)	10.90 (10.12, 11.67)	3.68 (2.11, 5.25)	1.34 (1.19, 1.50)
All-cause (excluding those with a history of myocardial infarction, cerebrovascular disease, or cancer)					
Model 1	19,019	12.10 (10.76, 13.44)	8.30 (7.68, 8.93)	3.80 (2.39, 5.20)	1.46 (1.28, 1.65)
Model 2	19,019	11.18 (9.99, 12.46)	8.59 (7.94, 9.24)	2.59 (1.21, 3.97)	1.30 (1.14, 1.48)
Tumors					
Model 1	20,382	4.41 (3.57, 5.26)	2.95 (2.61, 3.29)	1.46 (0.56, 2.36)	1.49 (1.20, 1.86)
Model 2	20,382	4.09 (3.28, 4.90)	3.07 (2.70, 3.43)	1.02 (0.14, 1.90)	1.33 (1.06, 1.67)
Tumors (excluding those with a cancer history)					
Model 1	19,673	3.22 (2.46, 3.99)	2.56 (2.24, 2.87)	0.67 (-0.15, 1.49)	1.26 (0.97, 1.64)
Model 2	19,673	3.07 (2.33, 3.80)	2.62 (2.29, 2.94)	0.45 (-0.35, 1.24)	1.17 (0.90, 1.53)
Cardiovascular diseases					
Model 1	20,382	4.50 (3.78, 5.21)	3.25 (2.88, 3.62)	1.25 (0.45, 2.04)	1.38 (1.14, 1.68)
Model 2	20,382	3.92 (3.27, 4.58)	3.51 (3.10, 3.93)	0.41 (-0.37, 1.19)	1.11 (0.91, 1.37)
Cardiovascular diseases (excluding those with a history of myocardial infarction and/or cerebrovascular disease)					
Model 1	19,679	3.60 (2.94, 4.27)	2.93 (2.57, 3.29)	6.67 (-0.06, 1.40)	1.23 (0.99, 1.52)
Model 2	19,679	3.38 (2.74, 4.03)	3.19 (2.78, 3.59)	0.19 (-0.56, 0.95)	1.06 (0.84, 1.34)

SR: Standardized mortality rate per 1000 person-years; SRD: Standardized mortality rate difference; SRR: Standardized mortality rate ratio. CI: Confidence Interval

Model 1: adjusted for sociodemographic characteristics (sex, age, cohabitation, educational level, and area of residence), and lifestyle factors (smoking, alcohol consumption, binge drinking, sedentary lifestyle, body mass index (BMI)).

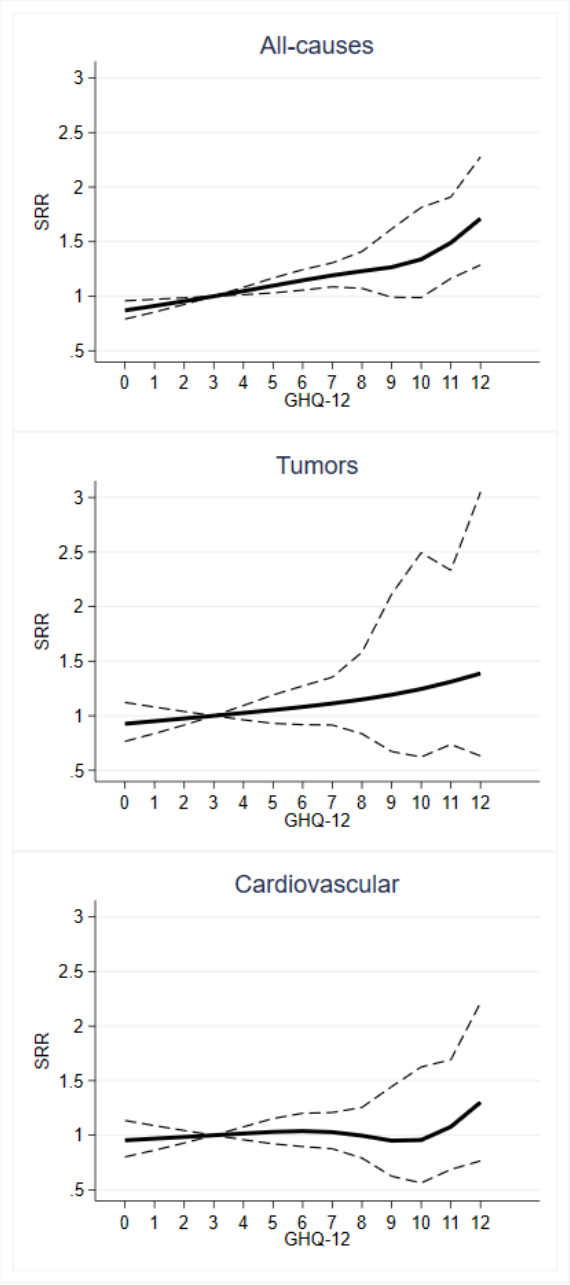
Model 2: adjusted for sociodemographic characteristics, lifestyle factors, and number of comorbidities.

Table 3. Association of psychological distress, as estimated by the GHQ-12, with all-cause mortality, stratified by mental health diagnosis and by prescription drug consumption.

	SRR (95% CI)	p for interaction
Previous diagnosis mental disorder		0.067
Yes	1.18 (0.91, 1.53)	
No	1.34 (1.18, 1.54)	
Consumption prescription drugs for mental disorders		0.016
Yes	1.18 (0.96, 1.45)	
No	1.41 (1.23, 1.63)	

SRR: Standardized mortality rate ratio, adjusted for sociodemographic characteristics (sex, age, cohabitation, educational level, and area of residence), lifestyle factors (smoking, alcohol consumption, binge drinking, sedentary lifestyle, body mass index), and number of comorbidities.
CI: Confidence Interval

Figure 1. Dose-response relationship of GHQ-12 scores and all-cause, tumor-, and cardiovascular disease-mortality.



Curves represent standardized mortality ratios (thick lines) and their 95% confidence intervals (thin lines) obtained from a design-based binary logistic regression for psychological distress based on restricted cubic splines for GHQ-12 index with knots at 4, 8, 10, and 12 points. The reference value (mortality ratio = 3). Mortality ratios were standardized to the overall distribution of sex, age, cohabitation, educational level, place of residence, lifestyle factors (smoking, alcohol consumption, binge drinking, sedentary lifestyle, body mass index), and number of comorbidities in the entire Spanish adult population (excluding those with a history of myocardial infarction, cerebrovascular disease, and/or tumors).

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