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CLINICAL—LIVER

Association Between Psychological Distress and Liver Disease Mortality: A Meta-analysis of Individual Study Participants

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BACKGROUND & AIMS: Risk factors for cardiovascular disease, such as obesity and hypertension, have been associated with nonalcoholic fatty liver disease. Psychological distress (symptoms of anxiety and depression) is a risk factor for cardiovascular disease, so it might also be associated, directly or indirectly, with liver disease. We investigated the relationship between psychological distress (measured by the 12-item General Health Questionnaire [GHQ]) and liver disease mortality. **METHODS:** We performed a meta-analysis of data from individual participants in 16 prospective studies of the general population in the United Kingdom, initiated from 1994 through 2008. Subjects were assigned to groups based on GHQ score: 0 (no distress), 1−3, 4−6, or 7−12. **RESULTS:** We analyzed data from 166,631 individuals (55% women; mean ± SD age, 46.6 ± 18.4 years; range, 16−102 years). During a mean follow-up period of 9.5 years, 17,368 participants died (457 with liver disease). We found a significant increase in liver disease mortality with increase in GHQ score ($P_{trend} < .001$). The age- and sex-adjusted hazard ratio for the highest GHQ score category (ie, 7−12), compared with the 0 score category, was 3.48 (95% confidence interval: 2.68−4.52). After adjustment for health behaviors, socioeconomic status, body mass index, and diabetes, this hazard ratio decreased to 2.59 (95% confidence interval: 1.82−3.68). **CONCLUSIONS:** Based on a meta-analysis, psychological distress is associated with liver disease mortality, although this finding requires additional analysis. Although one is not likely to cause the other, we provide additional evidence for the deleterious effects of psychological problems on physical health.

Keywords: Steatosis; Cirrhosis; Mental Health; GHQ-12.

Nonalcoholic fatty liver disease (NAFLD) is the hepatic manifestation of the metabolic syndrome. With an aging and increasingly obese and diabetic population,[1,2] the prevalence of NAFLD is rising. Current estimates suggest the prevalence in the general population to be around one-third,[3] rising in high-risk populations (eg, those with type 2 diabetes mellitus) to as high as 70%.[4,5] The spectrum of NAFLD extends from simple steatosis through steatohepatitis (NASH) and fibrosis to cirrhosis and its complications (ie, liver failure, hepatocellular carcinoma, and gastroesophageal varices). NAFLD, as a primary cause, represents the third most common indication for liver transplantation in the United States (8.5%).[6]

With no disease-specific therapy, treatment for early NAFLD centers on weight management through lifestyle modification and, for later disease, surveillance for complications.[7,8] Given such limited treatments, it is imperative to develop strategies to identify high-risk individuals before they develop significant disease and to identify potentially modifiable risk factors.

There is growing evidence of links between NAFLD and cardiovascular disease (CVD). Several population-based studies have identified higher rates of CVD in the NAFLD population compared with the general population.[9,10] The NAFLD and CVD association is biologically plausible, given their shared causal pathways—dyslipidemia, systemic inflammation, and insulin resistance. The atherogenic liver theory (the liver−vessel axis hypothesis) is another connection.[11]

It is also the case that psychological distress (eg, anxiety and depression) is becoming recognized as a risk factor for CVD.[12−16] That liver disease has, at least in part, a shared etiology with CVD raises the suggestion of a predictive role for psychological distress in the occurrence of liver disease. Possible mechanisms include an indirect association via health behaviors, including alcohol intake, tobacco use, and poor diet. Psychological distress might also be linked to liver disease through stress-induced dysregulation of the hypothalamic−pituitary−adrenal axis, resulting in hepatic release of proinflammatory factors (eg, interleukin 6, tumor necrosis factor−α),[17] ultimately leading to development of NAFLD.[18]

Despite a plausible prima facie case for a link between distress and liver disease, to the best of our knowledge, it has yet to be tested. Therefore, we examined the association between distress and liver disease risk by pooling raw

Abbreviations used in this paper: CI, confidence interval; CVD, cardiovascular disease; GHQ-12, 12-item General Health Questionnaire; HR, hazard ratio; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis.

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data from 16 cohort studies in an individual participant meta-analysis. In contrast to the more traditional literature-based meta-analysis in which investigators might have to exclude publications that do not present results in a standard manner, the possibility of publication bias is reduced in an individual participant meta-analysis. Additionally, a literature-based meta-analysis cannot provide a consistent approach to statistical control for plausible covariates.

Methods

Study Samples

Participants were drawn from representative, general population-based health examination studies sampling household-dwelling individuals living in the United Kingdom: 13 Health Surveys for England[19] (conducted annually between 1994 and 2008) and 3 Scottish Health Surveys[20] (conducted in 1995, 1998, and 2003). Consenting study members were linked to National Health Service mortality records up to the first quarter of 2011. For these analyses, raw data for all these study years were used, with the exception of Health Surveys for England from 1996 and 2007, when psychological distress was not measured. Ethical approval was obtained from the London Research Ethics Council.

Measurement of Psychological Distress

During a household visit, interviewers collected information using computer-assisted personal interviewing modules. Psychological distress was measured using the 12-item version of the General Health Questionnaire (GHQ-12), a widely used measure of distress in population studies.[21,22] The GHQ-12 is generally considered to be a unidimensional scale of psychological distress,[23] consisting of items capturing symptoms of anxiety, depression, social dysfunction, and loss of confidence. Study members respond using a 4-point Likert scale (symptom present: "not at all" or "same as usual" scored 0 points; "more than usual" or "much more than usual" scored 1 point). A total GHQ-12 score of $\geq$4 leads to individuals being defined as suffering from psychological distress and scores $<$4 are not considered to indicate substantial distress; this definition has been validated against standardized psychiatric interviews and has been strongly associated with various psychological disorders, such as depression and anxiety.[24,25] Most previous studies of psychological distress have used such a dichotomy and few have examined associations across the full range of psychological distress. There are no standard cutoffs for further subdividing the group of people identified as suffering from psychological distress by a GHQ-12 score threshold. We therefore chose to divide individuals into 4 groups based on GHQ-12 score: asymptomatic (GHQ-12 score zero), subclinically symptomatic (GHQ-12 score 1−3), symptomatic (GHQ-12 score 4−6), and highly symptomatic individuals (GHQ-12 score 7−12). This is the approach we have taken in previous analyses.[16,26,27]

Measurement of Collateral Data

Alcohol consumption (units per week), smoking status (not a current smoker; or $<$5, 5−10, 10−15, 15−20, and $>$20 cigarettes per day), age upon leaving full-time education, current occupational social class (professional, managerial or technical, skilled nonmanual, skilled manual, partly skilled, and unskilled), and body mass index (based on directly measured height and weight) were ascertained during the interview using standard protocols.[19,20]

Where available, additional data recorded were: presence of diabetes mellitus at baseline (defined as 1 or more of the following indicators: self-reported, doctor-diagnosed diabetes mellitus; responding affirmatively to having a longstanding illness and identifying it as diabetes mellitus, diabetes mellitus hospitalization, and serum hemoglobin A1c level)[28]; number of weekly episodes of moderate to vigorous physical activity, including domestic[29]; and use of antihypertensive medication. Physical examination was undertaken by a nurse at a subsequent home visit and included systolic and diastolic blood pressure. Venous blood was also drawn to measure serum γ−glutamyl transferase level, serum cholesterol (total and high-density lipoprotein cholesterol), and serum C-reactive protein. All serum measurements were undertaken at the time of the second survey visit and analyzed at local National Health Service hospital laboratories using standard protocols.

Mortality Data

Vital status and, where applicable, causes of death were ascertained via linkage with national mortality records. All causes of death recorded on death certificates were coded using the International Classification of Diseases, 9th (ICD-9) and 10th (ICD-10) revisions. Liver disease deaths were identified and categorized using the following ICD codes (a modification of a previous approach[30]): alcoholic liver disease (ICD-9 571.0−571.3; ICD-10 K70), viral hepatitis (070; B15−B18); neoplastic disease (155; C22); fatty liver disease (571.8; K76.0) and other liver disease diagnoses (006.3, 275.0, 571.6, 572.0, 572.1; A06.4, E83.1, K71, K74.3, K75.0, K77.0, K77.8); and other nonspecific liver disease (456, 570, 571.4, 571.5, 571.9, 572.2−572.8, 573; K72, K73, K74 [not K47.3], K75 [not K75.0], K76 [not K76.0], I98.2−3). Two liver disease mortality subcategories were defined: alcoholic liver disease (defined as any mention on the death certificate) and probable NAFLD (defined as any mention of fatty or other nonspecific liver disease, but no mention of alcoholic liver disease, viral hepatitis, neoplastic disease, or other liver disease diagnosis).

Statistical Analyses

Preliminary analyses showed no evidence of effect modification by sex ($P = .52$) so data from men and women were pooled. After ascertaining that the proportional hazards assumption had not been violated, we used Cox proportional hazards models[31] to compute study-specific hazard ratios (HR) with accompanying 95% confidence intervals (CI) for the association of GHQ-12 score with liver mortality. We pooled the study-specific effect estimates and their SEs in random effects meta-analyses to preserve within-study variation. Study members scoring 0 on the GHQ-12 were regarded as being free of psychological distress and used as the reference group. In these analyses, we used 4 categories of psychological distress to allow us to explore dose−response associations. The group scoring 0 was compared with the 3 groupings by GHQ-12 score mentioned above (1−3, 4−6, and 7−12), as well as the HR per 1-SD increment (disadvantage) in GHQ-12 score (calculated with sex-specific SDs) being reported. Calendar time (months) was the time scale and, for participants with no record of an

Table 1. Characteristics of Participants According to Individual Cohort Studies: Individual Participant Meta-Analysis of 16 Prospective Cohort Studies

	Health Surveys for England														Scottish Health Surveys			
Characteristics	1994	1995	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2008	n	1995	1998	2003	n
Adults irrespective of consent status, n	15,804	16,055	8582	15,908	13,947	11,025	15,647	10,331	14,836	12,758	10,303	14,142	15,102	174,440	7932	9040	8092	25,064
Household response, %	77	78	76	74	76	75	74	74	73	72	74	68	64	—	—	77	67	—
Consented to mortality linkage, %	95.6	93.7	93.9	94.6	90.1	71.9	88.4	88.9	87.3	75.7	80.6	82.6	78.2	—	85.3	86.9	87.9	—
Included in analytic sample, n	14,709	14,799	7794	14,358	11,593	7540	13,352	8830	12,454	8904	7866	11,523	11,659	145,381	6640	7797	6813	21,250
Follow-up duration, *y*																		
Mean	15.1	14.2	12.6	11.8	11.2	9.4	9.2	8.4	7.4	6.4	5.4	4.5	2.5	145,381	13.8	10.6	5.7	21,250
SD	3.8	3.5	2.8	2.5	1.8	2.7	1.6	1.2	1.1	0.7	0.9	0.6	0.3	—	2.2	2.0	0.9	—
Deaths from liver disease, n	54	42	15	30	6	20	39	11	12	11	9	11	5	145,381	52	49	10	21,250
Age at baseline, *y*																		
Mean	45.8	46.2	46.0	46.5	43.7	51.1	47.1	39.1	47.5	45.2	54.3	49.1	48.7	145,381	40.7	45.8	49.8	21,250
SD	18.5	18.4	18.0	18.3	17.8	20.8	18.0	19.4	17.9	17.6	19.5	18.1	18.3	145,381	13.2	15.8	17.6	21,250
Female, %	54.2	54.2	54.0	54.7	53.9	55.7	54.7	55.7	55.3	56.0	54.7	55.0	55.2	145,381	55.4	56.1	56.1	21,250
GHQ-12 score																		
Mean	1.5	1.7	1.6	1.5	1.7	1.5	1.3	1.6	1.3	1.4	1.2	1.3	1.3	145,381	1.7	1.6	1.5	21,250
SD	2.6	2.7	2.6	2.6	2.8	2.7	2.4	2.6	2.5	2.6	2.4	2.5	2.6	—	2.8	2.8	2.8	—
Drinks alcohol at least weekly	68.6	70.5	72.3	72.7	68.4	69.2	72.1	71.4	71.1	63.8	69.1	68.1	67.4	128,154	68.0	68.1	67.5	18,869
Current smoker, %	27.3	27.5	28.2	28.0	25.5	24.9	25.4	27.7	24.6	21.5	21.0	22.0	21.5	144,946	37.2	34.9	26.4	21,120
Left school at ≥16 y,[a] %	62.3	61.6	63.7	64.6	70.1	63.2	68.4	77.5	70.7	75.9	63.8	72.6	73.7	145293	65.6	61.8	64.5	21233
Nonmanual occupational social class, %	54.6	56.0	55.6	55.3	55.4	57.7	58.0	57.8	60.0	60.6	69.6	61.2	61.3	137915	50.5	51.4	56.2	20171
Body mass index																		
Mean	25.9	26.0	26.3	26.4	26.1	26.6	26.9	26.0	26.9	26.7	27.2	27.2	27.5	131,570	26.1	26.7	27.4	19,023
SD	4.5	4.5	4.7	4.7	4.8	4.8	4.9	5.0	5.0	5.0	4.9	5.1	5.1	—	4.6	4.9	5.1	—
Diabetes[b]	—	5.0	5.3	2.8	5.4	9.0	6.7	5.6	4.7	5.4	6.7	6.3	8.0	110,355	4.0	5.5	5.6	21,250

[a] Leaving school at the age of 16 years or younger approximates to completing only compulsory education, despite the changes in the minimum school leaving age in the United Kingdom during the 20th century.
[b] Comprising doctor-diagnosed diabetes, longstanding illness (diabetes), hemoglobin A1c, and diabetes hospitalization.

event, the data were censored at the first quarter of 2011. Models were adjusted for age (years), sex, health behaviors (frequency of alcohol consumption and smoking), socioeconomic status (age on leaving full-time education and occupational social class), body mass index, and diabetes mellitus. The primary outcome was all liver-related mortality. Secondary analyses examined (1) models, including only individuals who did not consume alcohol or who had a normal BMI, (2) additional covariates that had been measured in specific years only (ie, physical activity, systemic arterial hypertension, γ−glutamyl transferase, serum cholesterol, non−high-density lipoprotein cholesterol, and C-reactive protein), (3) and liver disease subcategories: alcoholic liver disease and probable NAFLD. Details on the measurement protocols and data handling of these covariates can be found elsewhere.[19,20] Finally, we conducted 2 sensitivity analyses: repeating the age- and sex- adjusted models including only individuals with complete data for all variables included in the multivariable models and examining the effect of reverse causality by dropping deaths occurring in the first 5 years of follow-up. All analyses were conducted using R version 2.15.2[32] and the survival and metafor[33] software packages.

Results

Study member characteristics according to each of the 16 studies featured in this pooling project are provided in Table 1. There was some evidence of the expected secular changes in selected characteristics, such that the proportion of study members leaving school after the compulsory school-leaving age and mean body mass index increased, while survey response declined. There was no change in psychological distress score across the studies.

In Figure 1, we show the flow of participants from study induction through to analyses. After removing 32,873 participants (16.5%) who declined to be linked to mortality records and those who were missing psychological distress data, the analytic sample comprised 166,631 people (54.9% women; mean ± SD age 46.6 ± 18.4 years; range, 16−102 years). On comparing the characteristics of the analytical sample with study members who had been excluded (Table 2), we found that, because of the high numbers in the analyses, while absolute differences between the groups were very small, statistical significance at conventional levels was apparent. The exclusion of individuals from the present analyses is unlikely to have led to substantial selection bias. We have previously examined this issue in another study and found no evidence that the relationship of distress to both total mortality and CVD mortality differed according to whether participants agreed to respond to a resurvey questionnaire or not.[34]

Based on the 166,631 study members in the analytical sample, we examined baseline covariates according to categories of psychological distress (Table 3). Relative to people with lower distress levels, those who had higher scores were more likely to be female, have a basic education, to smoke, to be obese, and to have diabetes mellitus. Weekly intake of alcoholic beverages was less frequent in people reporting higher levels of distress.

A mean (SD) follow up of 9.5 (4.3) years across the 16 studies gave rise to 17,368 deaths, 457 of which were

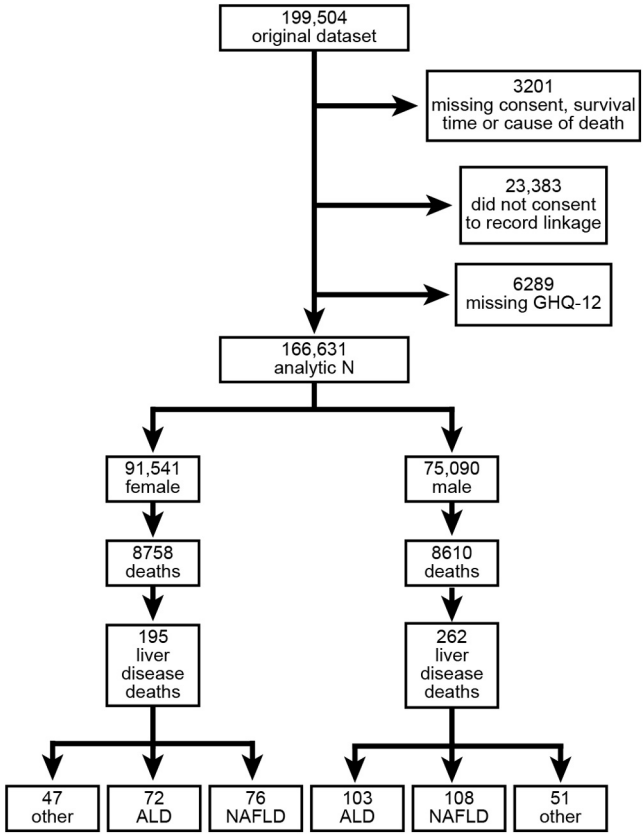

Figure 1. Numbers of study members from induction through to analytic sample and subsequent mortality: individual participant meta-analysis of 16 prospective cohort studies. ALD, alcoholic liver disease.

ascribed to liver disease. In Supplementary Figure 1, we depict the relationship between psychological distress and liver disease mortality according to each study in the present meta-analysis. An SD increase in distress score was almost invariably associated with an increased rate of liver

Table 2. Characteristics of Survey Participants Included and Excluded From Analyses: Individual Participant Meta-Analysis of 16 Prospective Cohort Studies

Characteristics	Included	Excluded	*P* value
n	166,631	32,873	—
Age, *y*, mean (SD)	46.6 (18.4)	50.9 (21.7)	<.001
Female, %	45.1	41.9	<.001
GHQ-12 score, mean (SD)	1.5 (2.6)	1.4 (2.6)	<.001
Drinks alcohol at least weekly, %	69.5	64.7	<.001
Current smoker, %	26.2	26.7	.095
Left school at age ≥16 y,[a] %	67.5	62.8	<.001
Nonmanual occupational social class, %	57.1	51.3	<.001
Body mass index, mean (SD)	26.4 (4.8)	26.4 (5.0)	<.001
Diabetes,[b] %	5.5	7.2	<.001

[a]Approximates to compulsory education.
[b]Comprising doctor-diagnosed diabetes, longstanding illness (diabetes), hemoglobin A1c, and diabetes hospitalization.

disease mortality—exceptions were the Health Surveys for England in 1997, 1999, and 2000—although statistical significance was not always apparent. This pattern of effect was highly consistent between studies, as evident from the I^2 statistics, which indicate low heterogeneity. Taking the 16 studies in aggregate, higher levels of distress were associated with a 26% greater risk of total liver disease mortality in multivariable-adjusted analyses.

Psychological distress was associated with increased liver disease mortality rates in age- and sex-adjusted models (HR per SD increase in GHQ-12 score: 1.40; 95% CI: 1.31−1.50), effects that were only marginally attenuated on full adjustment (HR = 1.26; 95% CI: 1.13−1.40; Table 4). Individuals with high levels of psychological distress (GHQ-12 score 7−12) were at substantially raised risk of liver disease mortality (multivariable-adjusted HR = 2.59; 95% CI: 1.82−3.68) compared with those scoring 0 on the GHQ-12. Disaggregating the distress categories further in order to explore the shape of the relationship with liver disease resulted in a suggestion of a dose−response pattern (Figure 2).

Models including only individuals who did not consume alcohol or who had a normal body mass index showed similar findings (Table 5). We also repeated the analyses for the subcategories of alcoholic liver disease and probable NAFLD, which yielded similar results (Supplementary Tables 1 and 2 and Supplementary Figure 2), although the association was steeper for probable NAFLD. Finally, we carried out the planned subgroup analyses, including additional covariates and sensitivity analyses examining the effects of missing data and reverse causality: the strength of the distress−liver disease mortality relationship was essentially unchanged (Table 4 and Supplementary Table 3).

Discussion

To our knowledge, this is the first population-based study to examine the association between psychological distress and liver disease−related mortality. In this large, general population sample, we found evidence of a dose−response relationship between increasing psychological distress (as measured by the GHQ-12) and increasing liver disease−related mortality, which was not completely explained by health behaviors (including alcohol consumption), diabetes mellitus, socioeconomic status, body mass index, or inflammation. The magnitude of the observed HRs at higher levels of distress (multivariable adjusted HR = 2.59; 95% CI: 1.82−3.68) is high by the standards of modern epidemiology, where the majority of HRs reported range from 1 to 2. Included within our analyses, we took into account the well-established observation of an unfavorable risk factor profile in people experiencing psychological distress, in particular, their higher prevalence of smoking and physical inactivity. Given the novelty of the distress−liver disease results, we also examined whether established risk factors for liver disease were shown in the present dataset. As anticipated, obesity (age- and sex-adjusted HR = 1.28; 95% CI: 0.97−1.70), diabetes (age- and sex-adjusted HR = 2.83; 95% CI: 1.83−4.41), and hypertension (age- and sex-adjusted HR = 1.94; 95% CI: 1.45−2.59) were all related to liver disease mortality. This gives us some confidence in the more novel results for psychological distress.

Plausible Mechanisms

Although this type of study is not able to confirm direct cause and effect, it can provide insights into relationships warranting additional consideration, but a direct effect seems unlikely. The distress−liver disease relationship was not fully explained by existing covariates in the present study, including alcohol consumption, smoking, socioeconomic status, body mass index, and diabetes mellitus. This suggests that other mechanisms underlying this association exist. It is possible that extant but hidden liver disease at baseline was associated with psychological distress and subsequent mortality. However, repeating the multivariable

Table 3. Baseline Characteristics of Study Members According to Psychological Distress Score: Individual Participant Meta-Analysis of 16 Prospective Cohort Studies

	Distress score			
Baseline characteristics	0	1−3	4−6	7−12
n (%)	98,765 (59.3)	42,446 (25.5)	13,483 (8.1)	11,937 (7.2)
Age, *y*, mean (SD)	47.2 (18.1)	45.7 (19.1)	45.3 (18.9)	47.0 (17.5)
Female, %	52.1	56.8	62.3	63.6
Drinks alcohol at least weekly, %	63.9	61.2	57.4	53.5
Current smoker, %	23.9	26.9	30.8	37.0
Left school age ≥16 y,[a] %	68.4	67.7	66.0	61.3
Nonmanual occupational social class, %	57.5	58.0	55.9	52.2
Obese,[b] %	20.5	20.6	21.3	23.6
Diabetes,[c] %	4.9	5.8	6.5	7.4

[a]Approximates to compulsory education.
[b]Body mass index ≥30 kg/m^2.
[c]Comprises doctor-diagnosed diabetes, longstanding illness (diabetes), hemoglobin A1c, and diabetes hospitalization.

Table 4. Hazard Ratios (95% Confidence Intervals) for the Association Between Psychological Distress (Measured by the 12-Item General Health Questionnaire) and Liver Disease Mortality: Individual Participant Meta-Analysis of 16 Prospective Cohort Studies

Model	Liver disease deaths	n	GHQ-12 score, HR (95% CI)					
			0	1–3	4–6	7–12	Per SD disadvantage[a]	P_{trend}
Age- and sex-adjusted (basic model)	457	166,631	1 (Ref)	1.18 (0.93–1.50)	2.09 (1.47–2.96)	3.48 (2.68–4.52)	1.40 (1.31–1.50)	<.001
Health behaviors[b]	451	16,471	1	1.17 (0.93–1.49)	1.96 (1.37–2.79)	3.08 (2.36–4.03)	1.35 (1.26–1.45)	<.001
Socioeconomic status[c]	437	158,011	1	1.17 (0.92–1.49)	1.90 (1.32–2.73)	3.52 (2.70–4.60)	1.39 (1.30–1.49)	<.001
Body mass index	403	150,593	1	1.17 (0.91–1.50)	2.21 (1.53–3.18)	3.36 (2.53–4.46)	1.40 (1.30–1.50)	<.001
Diabetes[d]	339	119,520	1	1.09 (0.82–1.45)	2.04 (1.37–3.03)	3.04 (2.25–4.11)	1.32 (1.19–1.46)	<.001
Multivariable adjusted[e]	275	101,167	1	1.02 (0.75–1.39)	2.01 (1.30–3.11)	2.59 (1.82–3.68)	1.26 (1.13–1.40)	<.001
Subgroup analyses								
Physical activity[f]	307	114,179	1	1.09 (0.81–1.45)	1.90 (1.22–2.95)	3.11 (2.27–4.26)	1.37 (1.26–1.50)	<.001
Systemic arterial hypertension[g]	270	100,320	1	1.37 (1.00–1.87)	2.20 (1.36–3.56)	4.42 (3.20–6.11)	1.50 (1.38–1.63)	<.001
γ-Glutamyl transferase[h]	121	21,443	1	1.01 (0.50–2.06)	1.23 (0.63–2.42)	3.06 (1.91–4.90)	1.40 (1.23–1.59)	<.001
Serum cholesterol[i]	190	64,043	1	1.46 (0.93–2.31)	2.04 (1.17–3.57)	4.27 (2.87–6.35)	1.49 (1.35–1.65)	<.001
Non-HDL cholesterol[j]	127	46,963	1	1.34 (0.71–2.54)	2.16 (1.08–4.32)	4.83 (3.03–7.72)	1.56 (1.38–1.77)	<.001
C-reactive protein	78	36,270	1	1.71 (0.99–2.96)	2.77 (1.03–7.48)	4.00 (2.09–7.66)	1.44 (1.22–1.71)	<.001

HDL, high-density lipoprotein.
[a]GHQ-12 score SD = 2.77 (women) and 2.43 (men).
[b]Health behaviors comprise frequency of alcohol consumption and smoking.
[c]Socioeconomic status comprises age upon leaving full-time education and occupational social class.
[d]Diabetes comprises doctor-diagnosed diabetes, longstanding illness (diabetes), hemoglobin A1c, and diabetes hospitalization (not present in the Health Survey for England 1994).
[e]Adjusted for all the variables in the upper half of the table.
[f]Fewer than 5 average weekly sessions of moderate to vigorous physical activity including domestic (walk/domestic 30 minutes+, sports/exercise 15 minutes+) compared with 5 or more (UK government recommendations).
[g]Systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or on antihypertensive treatment (National Institute for Health and Care Excellence guidance).
[h]γ-Glutamyl transferase level >51 IU/L vs ≤51 IU/L.
[i]Serum total cholesterol ≥6.2 mmol/L or on lipid-lowering treatment vs other.
[j]Non-HDL cholesterol (calculated by subtracting HDL cholesterol from total cholesterol, yielding a measure that encompasses low-, intermediate-, and very-low-density lipoprotein cholesterol).

models dropping deaths occurring in the first 5 years of follow-up did not alter our conclusions, suggesting that reverse causality did not materially bias our findings.

In an attempt to look more closely at potential risk factors, our subgroup analyses examined additional covariates (ie, physical activity, systemic arterial hypertension, serum γ−glutamyl transferase, serum cholesterol, and serum C-reactive protein). In addition, different liver diseases have markedly different underlying pathologies and so we examined subcategories of liver disease. In our study, we were able to attribute 40% of liver-related deaths to probable NAFLD and 38% to alcoholic liver disease, that is, together these diseases constituted the majority of the sample. For these 2 groups, there were stronger relationships with psychological distress than with all liver disease−related deaths combined. Both NAFLD and alcoholic liver disease result in similar pathologic changes in the liver, and both feature systemic inflammation as a prominent feature.[35,36] Given the argument of systemic inflammation as a shared risk factor between psychological distress and NAFLD, we would have expected to see the statistical relationship markedly attenuated after adjustment for C-reactive protein, however, this was not the case in the subgroup analysis. In addition, adjustment for factors related to CVD had only a small effect. This suggests that there is a mechanism at work beyond those we were able to study. Examples might include dysregulation of iron deposition or other trace elements (eg, copper), or other "toxins" that are detrimental to both brain and liver.[37,38] Indeed, raised serum transferrin saturation and greater dietary iron consumption have been linked to increased mortality.[39] In addition to the possibility of a causal relationship between psychological distress and liver disease, there is the possibility of a common cause; that is, factors that drive psychological distress can also drive liver disease.

Strengths and Limitations

This study used a very large sample of the general population, and >17,000 participants died during follow-up, >450 with liver disease. This large sample size allows detailed analyses to be conducted and the pattern of association between psychological distress and liver disease mortality to be examined. The cohort participants were well

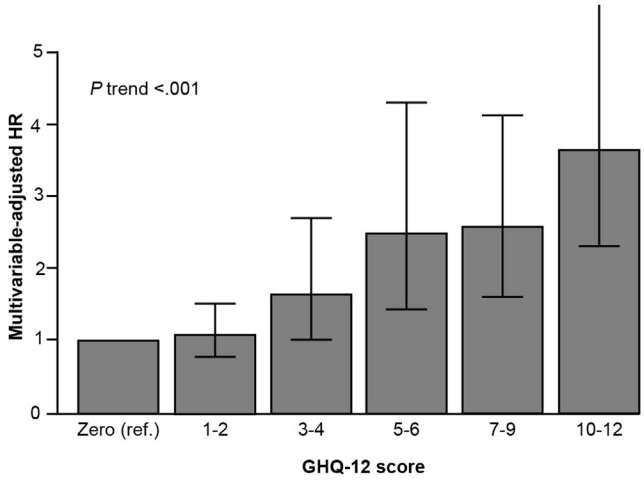

Figure 2. Multivariable-adjusted HRs (95% CIs) for the association between increasing levels of psychological distress and liver disease mortality: individual participant meta-analysis of 16 prospective cohort studies.

characterized, allowing relevant contextual variables to be incorporated into the statistical models, although the possibility of residual confounding remains. Certain relevant data were unavailable, specifically, the presence of liver disease or symptoms at baseline, iron status, and the subsequent occurrence of liver transplantation. Data were missing for one or more variables for 65,464 (39%) of participants. However, our complete case analysis reported in Supplementary Table 3 suggests that there was minimal bias resulting from missing data.

Using GHQ-12 score to estimate psychological distress, although widely used in population-based studies,[16,21,22,26,27] is not without limitations. The scale itself, with nonspecific questions about feelings of unhappiness and confidence, worry, and feelings of worthlessness, does not provide a clinical diagnosis of anxiety or depression, even though the 12 items do capture several aspects of these conditions. However, there is evidence that screening positive on the GHQ-12, defined here as scores of $\geq$4, is associated with anxiety and depression.[25,40] GHQ-12 has been shown to be a valid screening tool for anxiety and depression diagnosed according to the *Diagnostic and Statistical Manual of Mental Disorders*, 3rd ed, rev.[41] Another limitation is that GHQ-12 score was only recorded at baseline, and there was no reassessment of psychological distress via questionnaire.

Classifying cause of death according to death certification is a common methodology in epidemiologic studies.[26,42–46] In this study, we have included all cases of liver disease contributing to death, not just those defined as the underlying cause of death. Because causes of death are based on the certifying doctor's clinical assessment and knowledge of the deceased person, the use of this broad classification assists in capturing all deaths where liver disease played a role. Given that NAFLD is a diagnosis of exclusion and its natural history remains not fully understood, it is rarely coded in clinical practice on death certificates in the way that diseases such as CVD or diabetes mellitus are. As a result, the only way to identify NAFLD deaths is to create a probable group based on the exclusion of all known liver disease diagnoses. This is likely to underestimate the number of NAFLD-related deaths because it often does not exist in isolation but rather in combination with alcoholic liver disease or other diagnoses. In addition, in these cases, liver disease might not have been coded on the death certificate at all. There were insufficient numbers

Table 5. Hazard Ratios (95% Confidence Intervals) for the Association Between Psychological Distress (Measured by the 12-Item General Health Questionnaire) and Liver Disease Mortality in Nondrinkers and Those With a Normal Body Mass Index: Individual Participant Meta-Analysis of 16 Prospective Cohort Studies

		GHQ-12 score, HR (95% CI)					
Model	Liver disease deaths	0	1–3	4–6	7–12	Per SD disadvantage[a]	P_{trend}
Age- and sex-adjusted							
Full sample (N = 166,631)	457	1 (Ref)	1.18 (0.93–1.50)	2.09 (1.47–2.96)	3.48 (2.68–4.52)	1.40 (1.31–1.50)	<.001
Nondrinkers[b] (n = 11,898)	49	1	1.90 (0.87–4.12)	6.68 (1.34–33.3)	4.96 (1.99–12.3)	1.48 (1.16–1.89)	.002
Normal BMI[c] (n = 70,600)	176	1	1.29 (0.87–1.90)	2.46 (1.32–4.60)	4.13 (2.71–6.29)	1.47 (1.32–1.64)	<.001
Multivariable adjusted[d]							
Full sample (N = 101,167)	275	1	1.02 (0.75–1.39)	2.01 (1.30–3.11)	2.59 (1.82–3.68)	1.26 (1.13–1.40)	<.001
Nondrinkers[b,e] (n = 6395)	36	1	1.87 (0.70–4.99)	—	3.97 (1.28–12.3)	1.37 (1.00–1.88)	.052
Normal BMI[c,f] (n = 47,838)	123	1	1.37 (0.86–2.16)	2.58 (1.16–5.76)	2.88 (1.68–4.93)	1.32 (1.15–1.51)	<.001

BMI, body mass index.
[a]12-item GHQ score SD = 2.77 (women) and 2.43 (men).
[b]Nondrinkers defined as currently consuming no alcohol (based on self-report).
[c]Body mass index >18.5 kg/m^2 and <25 kg/m^2.
[d]Model adjusted for frequency of alcohol consumption, smoking, age upon leaving full-time education, occupational social class, body mass index, and diabetes (comprising doctor-diagnosed diabetes, longstanding illness (diabetes), hemoglobin A1c, and diabetes hospitalization).
[e]Model adjusted for all variables in multivariable adjusted model apart from frequency of alcohol consumption.
[f]Model adjusted for all variables in multivariable adjusted model apart from body mass index.

of deaths related to other causes of liver disease (eg, viral hepatitis, haemochromatosis) to allow detailed analysis.

Public Health Implications and Future Research Directions

Because this study is the first to identify this association, additional work is required to confirm and build on the findings of the present study. Future work might involve Mendelian randomization,[47] perhaps using a polygenic risk score for depression,[48,49] to shed light on the mechanism underlying the identified relationship between psychological distress and liver disease mortality. The next step would be an etiologic trial exploring the effect of treatment of psychological distress (talking therapy and/or medication) on liver function. This has already been done in the context of CVD outcomes.[50]

We add to the growing evidence of a detrimental impact of psychological distress on physical conditions by showing a new relationship with liver disease mortality. The raised risk evident at lower levels of distress that are not typically treated by specialists in mental health has particular relevance for general health professionals.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at http://dx.doi.org/10.1053/j.gastro.2015.02.004.

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The authors disclose no conflicts.

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Supplementary Table 1. Hazard Ratios (95% Confidence Intervals) for the Association Between Psychological Distress (Measured by the 12-Item General Health Questionnaire) and Alcoholic Liver Disease Mortality: Individual Participant Meta-Analysis of 16 Prospective Cohort Studies

Model	Alcoholic liver disease deaths	n	GHQ-12 score, HR (95% CI)					P_{trend}
			0	1–3	4–6	7–12	Per SD disadvantage[a]	
Age- and sex-adjusted (basic model)	175	166,631	1 (Ref)	0.89 (0.58–1.36)	1.43 (0.73–2.82)	4.58 (3.09–6.79)	1.55 (1.39–1.72)	<.001
Health behaviors[b]	171	153,140	1	0.87 (0.57–1.33)	1.29 (0.63–2.64)	3.74 (2.39–5.60)	1.45 (1.30–1.61)	<.001
Socioeconomic status[c]	166	146,991	1	0.91 (0.59–1.40)	1.49 (0.73–3.04)	4.40 (2.93–6.59)	1.52 (1.37–1.70)	<.001
Body mass index	158	142,758	1	0.95 (0.61–1.48)	1.44 (0.69–2.98)	4.94 (3.27–7.44)	1.56 (1.40–1.74)	<.001
Diabetes[d]	130	119,520	1	0.80 (0.47–1.37)	1.64 (0.76–3.54)	4.33 (2.75–6.83)	1.56 (1.38–1.77)	<.001
Multivariable adjusted[e]	109	84,285	1	0.83 (0.47–1.47)	1.43 (0.61–3.37)	3.46 (2.08–5.77)	1.41 (1.23–1.62)	<.001
Subgroup analyses								
Physical activity[f]	116	114,179	1	0.76 (0.44–1.31)	0.95 (0.40–2.24)	3.96 (2.47–6.36)	1.51 (1.33–1.72)	<.001
Systemic arterial hypertension[g]	103	92,820	1	1.02 (0.59–1.76)	1.45 (0.60–3.55)	5.14 (3.08–8.57)	1.64 (1.44–1.88)	<.001
γ-Glutamyl transferase[h]	59	21,443	1	0.90 (0.44–1.83)	0.78 (0.18–3.39)	4.76 (2.59–8.74)	1.59 (1.34–1.87)	<.001
Serum cholesterol[i]	68	53,308	1	1.02 (0.52–2.02)	0.94 (0.22–4.07)	6.63 (3.63–12.1)	1.73 (1.47–2.04)	<.001
Non-HDL cholesterol[j]	52	38,409	1	1.01 (0.44–2.33)	1.00 (0.23–4.34)	8.02 (4.06–15.8)	1.86 (1.55–2.22)	<.001
C-reactive protein	25	33,103	1	1.24 (0.42–3.66)	1.33 (0.16–10.8)	7.25 (2.42–21.8)	1.78 (1.35–2.34)	<.001

HDL, high-density lipoprotein.

[a]GHQ-12 score SD = 2.77 (women) and 2.43 (men).

[b]Health behaviors comprise frequency of alcohol consumption and smoking.

[c]Socioeconomic status comprises age upon leaving full-time education and occupational social class.

[d]Diabetes comprises doctor-diagnosed diabetes, longstanding illness (diabetes), hemoglobin A1c, and diabetes hospitalization (not present in Health Survey for England 1994).

[e]Adjusted for all the variables in the upper half of the table.

[f]Fewer than 5 average weekly sessions of moderate to vigorous physical activity, including domestic (walk/domestic 30 minutes+, sports/exercise 15 minutes+) compared with 5 or more (UK government recommendations).

[g]Systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or on antihypertensive treatment (National Institute for Health and Care Excellence guidance).

[h]γ-Glutamyl transferase level >51 IU/L vs ≤51 IU/L.

[i]Serum total cholesterol ≥6.2 mmol/L or on lipid-lowering treatment vs other.

[j]Non-HDL cholesterol (calculated by subtraction of HDL-cholesterol from total cholesterol, yielding a measure that encompasses low-, intermediate-, and very-low-density lipoprotein cholesterol).

Supplementary Table 2. Hazard Ratios (95% Confidence Intervals) for the Association Between Psychological Distress (Measured by the 12-Item General Health Questionnaire) and Probable Nonalcoholic Fatty Liver Disease Mortality: Individual Participant Meta-Analysis of 16 Prospective Cohort Studies

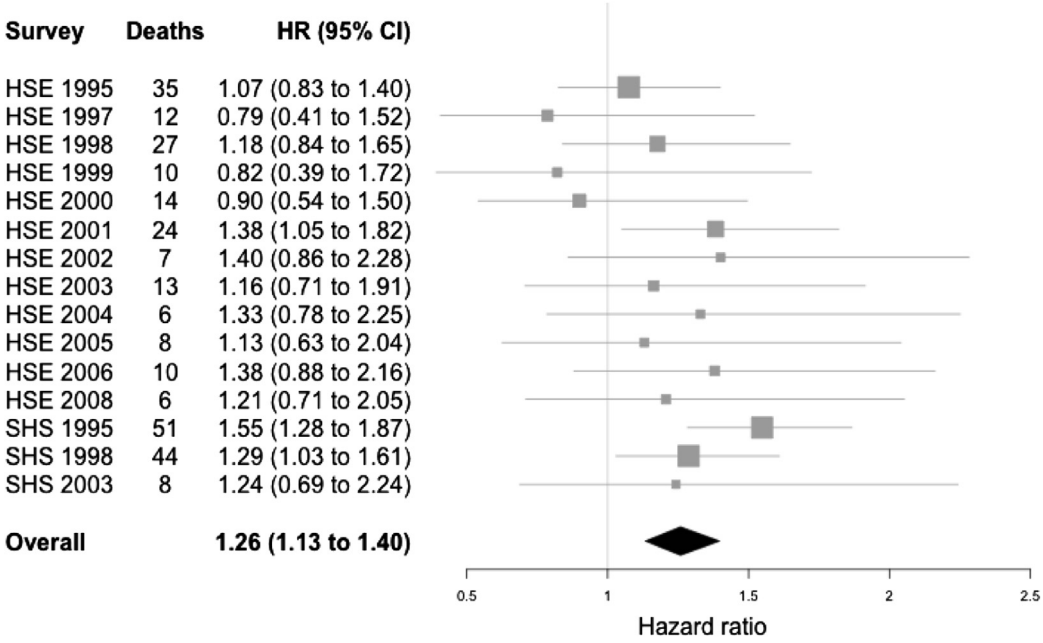
Model	Probable NAFLD deaths	n	GHQ-12 score, HR (95% CI)					P_{trend}
			0	1–3	4–6	7–12	Per SD disadvantage[a]	
Age- and sex-adjusted (basic model)	184	166,631	1 (Ref)	1.44 (0.98–2.09)	2.70 (1.58–4.64)	3.90 (2.53–6.02)	1.42 (1.27–1.58)	<.001
Health behaviors[b]	182	164,741	1	1.40 (0.96–2.05)	2.57 (1.49–4.41)	3.59 (2.30–5.60)	1.38 (1.23–1.54)	<.001
Socioeconomic status[c]	176	158,011	1	1.41 (0.95–2.08)	2.57 (1.49–4.45)	3.80 (2.43–5.93)	1.40 (1.25–1.56)	<.001
Body mass index	158	150,593	1	1.48 (0.98–2.24)	3.08 (1.77–5.37)	3.59 (2.20–5.85)	1.41 (1.25–1.59)	<.001
Diabetes[d]	138	119,520	1	1.39 (0.89–2.19)	2.79 (1.52–5.15)	3.58 (2.18–5.89)	1.37 (1.21–1.55)	<.001
Multivariable adjusted[e]	108	101,167	1	1.38 (0.80–2.40)	3.43 (1.77–6.65)	3.30 (1.85–5.90)	1.36 (1.18–1.57)	<.001
Subgroup analyses								
Physical activity[f]	128	114,179	1	1.47 (0.93–2.33)	1.90 (0.90–3.98)	3.60 (2.17–5.96)	1.38 (1.21–1.57)	<.001
Systemic arterial hypertension[g]	108	92,820	1	1.93 (1.13–3.28)	2.00 (0.80–5.02)	5.92 (3.32–10.6)	1.60 (1.40–1.82)	<.001
γ-Glutamyl transferase[h]	43	21,443	1	1.40 (0.68–2.86)	1.16 (0.33–4.01)	2.33 (0.90–6.06)	1.24 (0.97–1.58)	.091
Serum cholesterol[i]	79	50,169	1	2.17 (1.20–3.92)	2.97 (1.12–7.89)	4.61 (2.35–9.03)	1.45 (1.23–1.71)	<.001
Non-HDL cholesterol[j]	46	35,005	1	1.80 (0.59–5.51)	2.07 (0.55–7.72)	5.0 (2.07–12.1)	1.49 (1.17–1.89)	.001
C-reactive protein	29	29,384	1	2.80 (1.06–7.42)	—	6.21 (2.05–18.8)	1.42 (1.06–1.91)	.019

HDL, high-density lipoprotein.
[a]GHQ-12 score SD = 2.77 (women) and 2.43 (men).
[b]Health behaviors comprise frequency of alcohol consumption and smoking.
[c]Socioeconomic status comprises age upon leaving full-time education and occupational social class.
[d]Diabetes comprises doctor-diagnosed diabetes, longstanding illness (diabetes), hemoglobin A1c, and diabetes hospitalization (not present in Health Survey for England 1994).
[e]Adjusted for all the variables in the upper half of the table.
[f]Fewer than 5 average weekly sessions of moderate to vigorous physical activity including domestic (walk/domestic 30 minutes+, sports/exercise 15 minutes+) compared with 5 or more (UK government recommendations).
[g]Systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or on antihypertensive treatment (National Institute for Health and Care Excellence guidance).
[h]γ-Glutamyl transferase level >51 IU/L vs ≤51 IU/L.
[i]Serum total cholesterol ≥6.2 mmol/L or on lipid-lowering treatment vs other.
[j]Non-HDL cholesterol (calculated by subtraction of HDL cholesterol from total cholesterol, yielding a measure that encompasses low-, intermediate-, and very-low-density lipoprotein cholesterol).

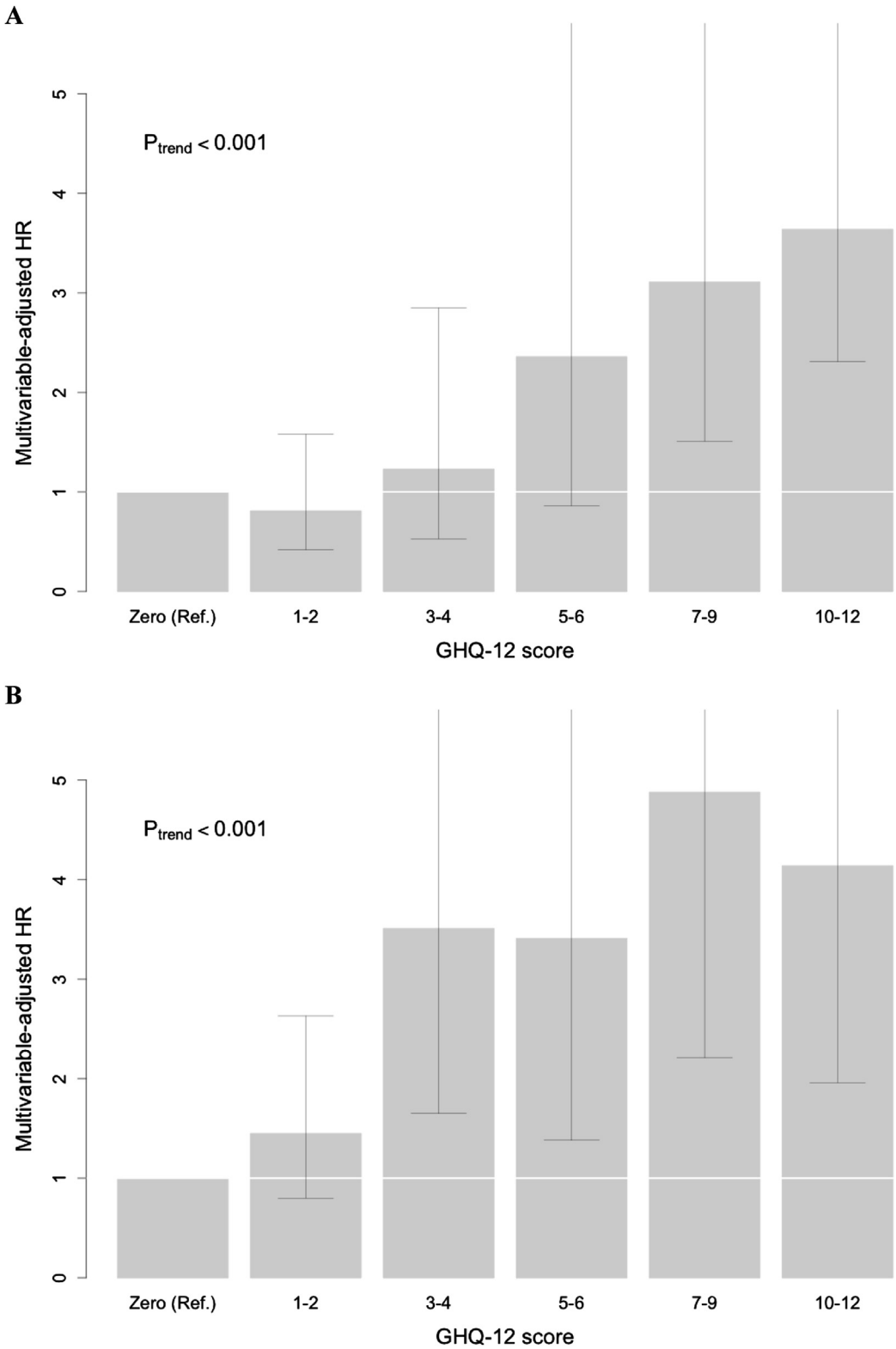
Supplementary Table 3. Hazard Ratios (95% Confidence Intervals) for the Association Between Psychological Distress (Measured by the 12-Item General Health Questionnaire) and Liver Disease Mortality in Participants With Complete Data for All Variables and With Deaths Occurring in the First 5 Years of Follow-Up Dropped: Individual Participant Meta-Analysis of 16 Prospective Cohort Studies

Model	Liver disease deaths	n	GHQ-12 score, HR (95% CI)					P_{trend}
			0	1–3	4–6	7–12	Per SD disadvantage[a]	
Age- and sex-adjusted	457	166,631	1 (Ref)	1.18 (0.93–1.50)	2.09 (1.47–2.96)	3.48 (2.68–4.52)	1.40 (1.31–1.50)	<.001
Complete data for all variables[b]	275	101,167	1	1.06 (0.78–1.45)	2.24 (1.46–3.45)	3.00 (2.13–4.24)	1.32 (1.19–1.46)	<.001
Multivariable adjusted[c]	275	101,167	1	1.02 (0.75–1.39)	2.01 (1.30–3.11)	2.59 (1.82–3.68)	1.26 (1.13–1.40)	<.001
Left censored[d]	163	80,173	1	1.03 (0.69–1.53)	1.72 (0.92–3.21)	2.21 (1.39–3.52)	1.23 (1.08–1.39)	.001

[a]GHQ-12 score SD = 2.77 (women) and 2.43 (men).
[b]Including only participants with no missing data for any variable included in the multivariable model (age- and sex-adjusted).
[c]Model adjusted for frequency of alcohol consumption, smoking, age upon leaving full-time education, occupational social class, body mass index, and diabetes (comprising doctor-diagnosed diabetes, longstanding illness (diabetes), hemoglobin A1c, and diabetes hospitalization).
[d]Deaths occurring in the first 5 years of follow-up dropped.



Supplementary Figure 1. Multivariable-adjusted HRs (95% CIs) per SD increase in psychological distress in relation to liver disease mortality according to study: individual participant meta-analysis of 16 prospective cohort studies. $I^2 = 13.7\%$. Health Survey for England 1994 is missing because it was excluded from the multivariable models due to missing data. The size of the boxes indicates the relative weights of the studies.



Supplementary Figure 2. Multivariable-adjusted HRs (95% CIs) for the association between increasing levels of psychological distress and (*A*) alcoholic liver disease mortality and (*B*) probable nonalcoholic liver disease mortality: individual participant meta-analysis of 16 prospective cohort studies.