Association between psychological distress and liver disease mortality

Association between psychological distress and liver disease mortality: a meta-analysis of individual study participants

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ABSTRACT

Background & Aims: Risk factors for cardiovascular disease, such as obesity and hypertension, have been associated with non-alcoholic 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 elevated rates of liver disease. We investigated the relation of psychological distress (measured by the 12-item General Health Questionnaire; GHQ) with liver disease mortality.

Methods: We performed a meta-analysis of data from individual participants in 16 prospective studies of the general population of the UK, initiated from 1994 through 2008. We categorized GHQ score into four groups: zero (no distress), 1-3, 4-6, and 7-12.

Results: We used data from 166,631 individuals (55% women; 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 risk for liver disease mortality as GHQ score increased across categories ($p_{trend}<0.001$). The age- and sex-adjusted hazard ratio for the highest GHQ category (7-12) compared to those scoring zero was 3.48 (95% confidence interval, 2.68−4.52). After adjustment for health behaviors, socioeconomic status, body mass index, and diabetes, the hazard ratio was partially attenuated to 2.59 (95% confidence interval, 1.82–3.68).

Conclusions: Our novel finding that psychological distress was associated with liver disease mortality requires testing in other studies. Though results are unlikely to be causal, we provide further evidence for the deleterious effects of psychological problems on physical health.

KEYWORDS: death, steatosis, cirrhosis, mental health, GHQ-12

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is the hepatic manifestation of the metabolic syndrome. With an ageing 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 (e.g., 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 (liver failure, hepatocellular carcinoma and gastro-oesophageal varices). Already NAFLD as a primary cause represents the third commonest indication for liver transplantation in the USA (8.5%).[6]

With no disease-specific therapy, treatment for early NAFLD centres 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 prior to their developing significant disease and also 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 NAFLD population compared to the general population.[9, 10] The NAFLD and CVD association is biologically plausible given their shared causal pathways – dyslipidaemia, systemic inflammation and insulin resistance. The atherogenic liver theory (the liver-vessel axis hypothesis) is a further connection.[11]

It is also the case that psychological distress (anxiety and depression) is becoming recognized as a risk factor for CVD.[12-16] That liver disease has, at least in part, a shared aetiology 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 behaviours 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 the hepatic release of pro-inflammatory factors (e.g. interleukin-6, tumour necrosis factor alpha)[17] ultimately leading to the 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 data from 16 cohort studies in an individual participant meta-analysis. In contrast to the more traditional literature-based meta-analysis in which investigators may 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 three 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 four-point Likert scale (symptom present: 'not at all' or 'same as usual' scored zero; 'more than usual' or 'much more than usual' scored one point). A total GHQ-12 score of four or greater leads to individuals being defined as suffering from psychological distress and scores less than four are not considered to indicate substantial distress; this definition has been validated against standardised 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 cut-offs for further sub-dividing the group of people identified as suffering from psychological distress by a GHQ-12 score threshold. We therefore chose to divide individuals into four groups based on GHQ-12 score: asymptomatic (GHQ-12 score zero), sub-clinically 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 non-manual, 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 one 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 hospitalisation, and serum HbA_{1c} 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 gammaglutamyl transferase (gamma-GT) level, serum cholesterol (total and HDL-cholesterol), and serum C-reactive protein. All serum measurements were undertaken at the time of the second survey visit and analysed at local NHS 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*, Ninth (ICD-9) and Tenth (ICD-10) Revisions. Liver disease deaths were identified and categorised 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); 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 non-specific 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 sub-categories were defined: alcoholic liver disease (defined as any mention on the death certificate) and probable NAFLD (defined as any mention of fatty or other non-specific 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 gender (p=0.52) 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 standard errors in random effects meta-analyses in order to preserve within-study variation. Study members scoring zero on the GHQ-12 were regarded as being free of psychological distress and used as the reference group. In these analyses, we used four categories of psychological distress in order to allow us to explore dose-response associations. The group scoring zero was compared to the three groupings by GHQ-12 score mentioned above (1-3, 4-6, and 7-12) as well as the hazard ratio per one standard deviation increment (disadvantage) in GHQ-12 score (calculated with sex-specific standard deviations) being reported. Calendar time (months) was the time scale and, for participants with no record of an event, the data were censored at the first quarter of 2011. Models were adjusted for age (years), sex, health behaviours (frequency of alcohol consumption and smoking), socioeconomic status (age upon 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 (i) models including only individuals who did not consume alcohol or who had a normal BMI, (ii) additional covariates that had been measured only in specific years (physical activity, systemic arterial hypertension, gamma-GT, serum cholesterol, non-HDL cholesterol, C-reactive protein), and (iii) liver disease sub-categories: 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 two sensitivity analyses: (i) repeating the age- and sex- adjusted models including only individuals with complete data for all variables included in the multivariable models; and (ii) examining the effect of reverse

causality by dropping deaths occurring in the first five years of follow up. All analyses were conducted using R version 2.15.2[32] and the survival and metafor[33] packages.

RESULTS

Study member characteristics according to each of the sixteen studies featured in this pooling project are given 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). On comparing the characteristics of the analytical sample with study members who had been excluded (table 2), we found that, owing to the high numbers in the analyses, while absolute differences between the groups were very small, statistical significance at conventional levels was apparent. Thus, the exclusion of individuals from the present analyses is unlikely to have led to substantial selection bias. Indeed, we have previously examined this issue in another study and found no evidence that the relation of distress to both total mortality and cardiovascular disease 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 sixteen studies gave rise to 17,368 deaths, 457 of which were ascribed to liver disease. In supplementary figure 1 we depict the relation between psychological distress and liver disease mortality according to each study in the present meta-analysis. A standard deviation increase in distress score was almost invariably associated with an increased rate of liver disease mortality – exceptions were the HSE 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 sixteen 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 gender adjusted models (hazard ratio per standard deviation increase in GHQ-12 score: 1.40; 95% confidence interval 1.31-1.50), effects that were only marginally attenuated on full adjustment (1.26; 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 to those scoring zero on the GHQ-12. Disaggregating the distress categories further in order to explore the shape of the relation 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 BMI showed similar findings (table 5). We also repeated the analyses for the sub-categories of alcoholic liver disease and probable NAFLD which yielded similar results (supplementary tables 1 and 2 and supplementary figure 2), though the association was steeper for probable NAFLD.

Finally, we carried out the planned sub-group analyses including additional covariates and sensitivity analyses examining the effects of missing data and reverse causality: the strength of the distress-liver disease mortality relation 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 that was not completely explained by health behaviours (including alcohol consumption), diabetes mellitus, socioeconomic status, body mass index or inflammation. Indeed, the magnitude of the observed hazard ratios 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 one to two. Included within our analyses, we took into account the well-established observation of an unfavourable 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 if established risk factors for liver disease were shown in the present dataset. As anticipated, obesity (age- and sex-adjusted HR, 95% CI: 1.28, 0.97-1.70), diabetes (2.83, 1.83-4.41), and hypertension (1.94, 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

Whilst this type of study is not able to confirm direct cause and effect it can provide insights into relationships warranting further consideration. Indeed, a direct effect seems unlikely. The distress-liver disease relation 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 models dropping deaths occurring in the first five 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 (physical activity, systemic arterial hypertension, serum gamma-GT, serum cholesterol, and serum C-reactive protein). Furthermore, different liver diseases have markedly different underlying pathologies and so we examined sub-categories 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, i.e. together these diseases constituted the majority of the sample. For these two 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 pathological 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 sub-group 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 (e.g. copper) or other 'toxins' that are detrimental to both brain and liver.[37, 38] Indeed, raised serum transferrin saturation and greater dietary iron consumption has 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 may also drive liver disease.

Strengths and Limitations

This study used a very large sample of the general population, and over 17,000 participants died during follow-up, over 450 with liver disease related. 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 characterised, 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 variable for 65,464 (39%) of participants. However, our complete case analysis reported in supplementary Table 4 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 non-specific 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 4 or more, 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, third edition (revised).[41] A further 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 epidemiological 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. Since 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 disease 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 since it often does not exist in isolation but in combination with ALD or other diagnoses. Furthermore, in these cases, liver disease may not have been coded on the death certificate at all. There were insufficient numbers of deaths related to other causes of liver disease (e.g. viral hepatitis, haemachromatosis) to allow detailed analysis.

Public health implications and future research directions

Since this study is the first to identify this association, further work is required to confirm and build on the findings of the present study. Future work may involve Mendelian randomisation,[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 aetiological 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]

Conclusion

In conclusion, 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 which are not typically treated by specialists in mental health has particular relevance for general health professionals.

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Table 1. Characteristics of participants according to individual cohort studies: individual participant meta-analysis of sixteen prospective cohort studies

		Health Survey for England														Scottish Health Survey			
		1994	1995	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2008	**N**	1995	1998	2003	**N**
Adults irrespective of consent status	N	15804	16055	8582	15908	13947	11025	15647	10331	14836	12758	10303	14142	15102	**174440**	7932	9040	8092	**25064**
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	14709	14799	7794	14358	11593	7540	13352	8830	12454	8904	7866	11523	11659	**145381**	6640	7797	6813	**21250**
Follow-up duration (years)	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	**145381**	13.8	10.6	5.7	**21250**
	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	**145381**	52	49	10	**21250**
Age at baseline (years)	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	**145381**	40.7	45.8	49.8	**21250**
	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	**145381**	13.2	15.8	17.6	**21250**
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	**145381**	55.4	56.1	56.1	**21250**
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	**145381**	1.7	1.6	1.5	**21250**
	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	**128154**	68.0	68.1	67.5	**18869**
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	**144946**	37.2	34.9	26.4	**21120**
Left school ≥16[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**
Non-manual 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	**131570**	26.1	26.7	27.4	**19023**
	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	110355	4.0	5.5	5.6	21250

[a] Leaving school at the age of 16 years of younger approximates to completing only compulsory education, despite the changes in the minimum school leaving age in the UK during the twentieth century

[b] Comprising doctor-diagnosed diabetes, longstanding illness (diabetes), HbA_{1c}, and diabetes hospitalisation

Table 2. Characteristics of survey participants included and excluded from analyses: individual participant meta-analysis of sixteen prospective cohort studies

	Included	**Excluded**	***P***
N	166631	32873	-
Age (mean [SD])	46.6 (18.4)	50.9 (21.7)	<0.001
Female (%)	45.1	41.9	<0.001
GHQ-12 score (mean [SD])	1.5 (2.6)	1.4 (2.6)	<0.001
Drinks alcohol at least weekly (%)	69.5	64.7	<0.001
Current smoker (%)	26.2	26.7	0.095
Left school ≥16[a] (%)	67.5	62.8	<0.001
Non-manual occupational social class (%)	57.1	51.3	<0.001
Body mass index (mean [SD])	26.4 (4.8)	26.4 (5.0)	<0.001
Diabetes[b] (%)	5.5	7.2	<0.001

[a] approximates to compulsory education

[b] Comprising doctor-diagnosed diabetes, longstanding illness (diabetes), HbA_{1c}, and diabetes hospitalisation

Table 3. Psychological distress score according to baseline characteristics of study members: individual participant meta-analysis of sixteen prospective cohort studies

	Distress score			
	0	**1-3**	**4-6**	**7-12**
N (%)	98765 (59.3)	42446 (25.5)	13483 (8.1)	11937 (7.2)
Age (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 ≥16[a] (%)	68.4	67.7	66.0	61.3
Non-manual 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), HbA_{1c}, and diabetes hospitalisation

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 sixteen prospective cohort studies

			GHQ-12 score					
Model	**Liver disease deaths**	**N**	**0**	**1-3**	**4-6**	**7-12**	**Per SD disadvantage[a]**	**P_{trend}**
Age- and gender-adjusted (basic model)	457	166631	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)	<0.001
+ health behaviours[b]	451	16471	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)	<0.001
+ socioeconomic status[c]	437	158011	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)	<0.001
+ body mass index	403	150593	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)	<0.001
+ diabetes[d]	339	119520	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)	<0.001
Multivariable adjusted[e]	275	101167	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)	<0.001
Subgroup analyses[ŧ]								
+ physical activity[f]	307	114179	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)	<0.001
+ systemic arterial hypertension[g]	270	100320	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)	<0.001
+ gamma-GT[h]	121	21443	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)	<0.001
+ serum cholesterol[i]	190	64043	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)	<0.001
+ non-HDL cholesterol[j]	127	46963	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)	<0.001
+ C-reactive protein	78	36270	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)	<0.001

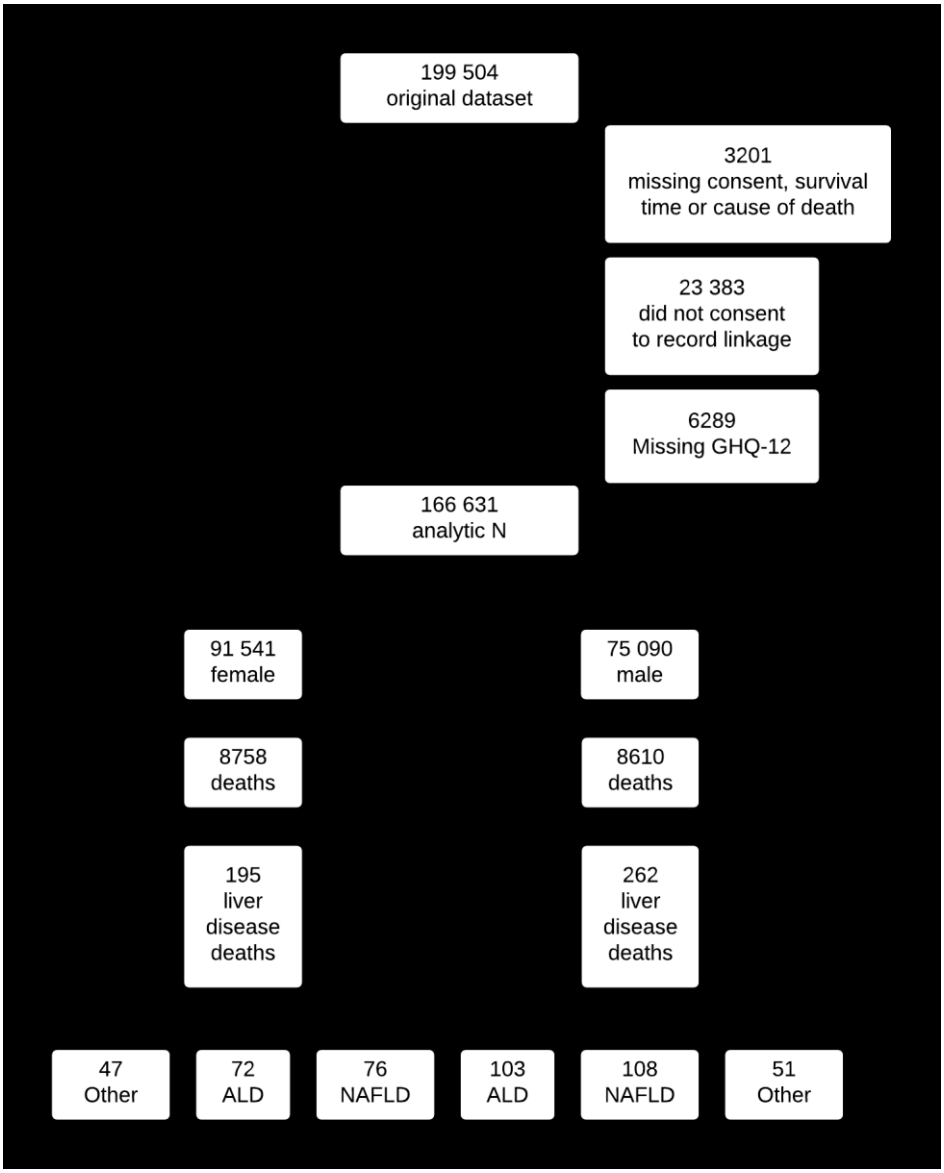
[a] GHQ-12 score standard deviation = 2.77 (women) and 2.43 (men)
[b] Health behaviours comprise frequency of alcohol consumption and smoking
[c] Socioeconomic status comprises age upon leaving full-time education and occupational social class
[d] Diabetes comprises doctor-diagnosed diabetes, longstanding illness (diabetes), HbA1c, and diabetes hospitalisation (not present in HSE 1994)
[e] Adjusted for all the variables in the upper half of the table
[f] Fewer than five average Weekly Sessions of moderate to vigorous physical activity including domestic (Walk/Domestic 30mins+, Sports/Exercise 15mins+) compared to five or more (UK government recommendations)
[g] Systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or on antihypertensive treatment (NICE guidance)
[h] Gamma-GT level >51 IU/L vs ≤51
[i] Serum total cholesterol ≥6.2 mmol/L or on lipid-lowering treatment versus other
[j] Non-HDL cholesterol (calculated by subtraction of HDL-C from total cholesterol, yielding a measure that encompasses low-, intermediate-, and very-low-density lipoprotein cholesterol)

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 non-drinkers and those with a normal BMI: individual participant meta-analysis of sixteen prospective cohort studies

			GHQ-12 score					
Model		**Liver disease deaths**	**0**	**1-3**	**4-6**	**7-12**	**Per SD disadvantage[a]**	**P_{trend}**
Age- and gender-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)	<0.001
	Non-drinkers[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)	0.002
	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)	<0.001
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)	<0.001
	Non-drinkers[b,e] (N=6395)	36	1	1.87 (0.70, 4.99)	–	3.97 (1.28, 12.3)	1.37 (1.00, 1.88)	0.052
	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)	<0.001

[a] GHQ-12 score standard deviation = 2.77 (women) and 2.43 (men)
[b] Non-drinkers defined as currently consuming no alcohol (based on self-report)
[c] Body mass index >18.5kg/m^2 and <25kg/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), HbA1c, and diabetes hospitalisation)
[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

Figure 1. Numbers of study members from induction through to analytic sample and subsequent mortality: individual participant meta-analysis of sixteen prospective cohort studies



ALD = Alcoholic liver disease; NAFLD = probable non-alcoholic fatty liver disease

Figure 2. Multivariable-adjusted hazard ratios (95% confidence intervals) for the association between increasing levels of psychological distress and liver disease mortality: individual participant meta-analysis of sixteen prospective cohort studies