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Associations between DSM-IV mental disorders and subsequent heart disease onset: beyond depression

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Abstract

Background—Prior studies on the depression-heart disease association have not usually used diagnostic measures of depression, nor taken other mental disorders into consideration. As a result, it is not clear whether the association between depression and heart disease onset reflects a specific association, or the comorbidity between depression and other mental disorders. Additionally, the relative magnitude of associations of a range of mental disorders with heart disease onset is unknown.

Methods—Face-to-face household surveys were conducted in 19 countries (n=52,095; person years=2,141,194). The Composite International Diagnostic Interview retrospectively assessed lifetime prevalence and age at onset of 16 DSM-IV mental disorders. Heart disease was indicated by self-report of physician's diagnosis, or self-report of heart attack, together with their timing (year). Survival analyses estimated associations between first onset of mental disorders and subsequent heart disease onset.

Results—After comorbidity adjustment, depression, panic disorder, specific phobia, post-traumatic stress disorder and alcohol use disorders were associated with heart disease onset (ORs 1.3–1.6). Increasing number of mental disorders was associated with heart disease in a dose-response fashion. Mood disorders and alcohol abuse were more strongly associated with earlier onset than later onset heart disease. Associations did not vary by gender.

Conclusions—Depression, anxiety and alcohol use disorders were significantly associated with heart disease onset; depression was the weakest predictor. If confirmed in future prospective studies, the breadth of psychopathology's links with heart disease onset has substantial clinical and public health implications.

Keywords

depression; anxiety disorders; alcohol abuse; heart disease; comorbidity

INTRODUCTION

An association between depressed mood and subsequent heart disease onset has been well documented ^{1–4}. However, an important limitation of most prior studies is that they have used symptom screening scales rather than diagnostic measures of depression. Symptom screening scales do not discriminate well between negative emotions ^{5,6} and do not always map well onto diagnostic categories ⁴. It is therefore unknown how much of the association observed in relation to depression may be explained by comorbid mental disorders such as anxiety disorders ^{5,6}, as anxiety has also been linked with subsequent heart disease ⁷. In fact, it has been suggested that anxiety might be more strongly associated with heart disease than depression ⁶, but we are not aware of a prior study including diagnostic measures of both depression and anxiety disorders that has been able to compare their relative strength of association with heart disease. Further mechanistic research into depression may be of

limited use unless it can be established that depression specifically is related to heart disease onset after taking comorbidity between all mental disorders into account.

A further consequence of the limited use of diagnostic measures of mental disorders in prior research is that it is unknown whether mental disorders other than depression and anxiety are associated with subsequent heart disease onset. Other mental disorders that could conceivably be linked with heart disease include bipolar affective disorder, alcohol use disorders, eating disorders, and intermittent explosive disorder (a disorder of anger dysregulation). Other gaps in our understanding of mental disorder-heart disease associations include whether experiencing more than one mental disorder further elevates risk of heart disease and whether associations vary by gender, or by age of onset (of either the mental disorder or of heart disease).

The present study uses the cross-national World Mental Health (WMH) Surveys dataset to examine associations between a wide range of DSM-IV mental disorders and subsequent heart disease onset. The WMH surveys are general population surveys that retrospectively assessed lifetime history of DSM-IV mental disorders and also obtained self-report of physician's diagnosis of chronic physical conditions including heart disease. The surveys are cross-sectional in design but collected information on age of onset of mental disorders and age at diagnosis of heart disease which allows the use of survival analysis to examine associations between temporally prior mental disorders and the subsequent onset of heart disease.

Our aims in this study were: (i) to investigate the association of the first onset of mood, anxiety, impulse control and substance use disorders with subsequent onset of heart disease, with and without adjustment for mental disorder comorbidity; (ii) to assess whether increasing number of mental disorders is associated with increasing risk of heart disease in a dose-response fashion; (iii) to examine whether associations vary by gender, or by age of mental disorder or heart disease onset.

METHOD

Samples and Procedures

This study uses data from 19 of the WMH surveys (see Table 1). A stratified multistage clustered area probability sampling strategy was used to select adult respondents (18 years+) in most WMH countries. Most of the surveys were based on nationally representative household (or population register) samples while Colombia, Mexico and Shenzhen were based on nationally representative household samples in urbanized areas. The central WMH staff trained bilingual supervisors in each country. The WHO translation protocol was used to translate instruments and training materials. Some surveys were carried out in bilingual form while others were carried out exclusively in the country's official language. In most countries, internal subsampling was used to reduce respondent burden and average interview time by dividing the interview into two parts. All respondents completed Part 1 which included the core diagnostic assessment of most mental disorders. All Part 1 respondents who met lifetime criteria for any mental disorder and a probability sample of respondents without mental disorders were administered Part 2 (at the same interview sitting) which assessed physical conditions and collected a range of other information related to survey aims. Part 2 respondents were weighted by the inverse of their probability of selection for Part 2 of the interview to adjust for differential sampling, resulting in an unbiased sample.

Analyses in this paper are based on the weighted Part 2 subsample ($n = 52,095$; person years $= 2,141,194$). The weighted (and unweighted) percentages of the Part 2 subsample with lifetime mental disorders are as follows: mood disorders 13.6% (24.7%); anxiety disorders

16.3% (25.7%); impulse control disorders 3.0% (4.9%); substance use disorders 8.2% (10.8%); any mental disorder 28.6% (44.0%). Additional weights were used to adjust for differential probabilities of selection within households, to adjust for non-response, and to match the samples to population sociodemographic distributions. Measures taken to ensure data accuracy, cross-national consistency and protection of respondents are described in detail elsewhere^{8,9}. All respondents provided written informed consent and procedures for protecting respondents were approved and monitored for compliance by the Institutional Review Boards in each country (see⁹ for details).

Measures

Mental disorders—All surveys used the WMH survey version of the WHO Composite International Diagnostic Interview (CIDI 3.0⁸), a fully structured interview, to assess lifetime history of mental disorders. Disorders were assessed using the definitions and criteria of the DSM-IV. The mental disorders included in this paper include *anxiety disorders* (panic disorder, agoraphobia without panic, specific phobia, social phobia, post-traumatic stress disorder, generalized anxiety disorder, obsessive compulsive disorder); *mood disorders* (major depressive disorder/dysthymia, bipolar broad (I, II and subthreshold)); *substance use disorders* (alcohol abuse and dependence, drug abuse and dependence); and *impulse control disorders* (intermittent explosive disorder, bulimia nervosa and binge eating disorder). Clinical reappraisal studies conducted in some of the WMH countries indicate that lifetime diagnoses of anxiety, mood and substance use disorders based on the CIDI have generally good concordance with diagnoses based on blinded clinical interviews¹⁰.

Heart disease status—In a series of questions adapted from the U.S Health Interview Survey, respondents were asked about the lifetime presence of selected chronic conditions. Respondents were asked: “*Did a doctor or other health professional ever tell you that you had any of the following illnesses....heart disease?*” Respondents were also asked: “*Have you ever had a heart attack?*” If respondents endorsed either of these questions they were classified as having a history of heart disease. Respondents were also asked how old they were when they were first diagnosed with heart disease or first had a heart attack (for those who endorsed both, the younger of the two ages was used). This year is referred to herein as the age of onset of heart disease, although it is recognized that the underlying pathology of heart disease develops over many years. Only adult-onset heart disease (onsets age 21+) was investigated in this paper.

Statistical Analysis

Discrete-time survival analyses¹¹ with person-year as the unit of analysis were used to investigate sequential associations between first onset of mental disorders and the subsequent onset of heart disease. A person-year data set was created in which each year in the life of each respondent up to and including the age of onset of heart disease or their age at interview (whichever came first) was treated as a separate observational record, with the year of heart disease onset coded 1 and earlier years coded 0 on a dichotomous outcome variable. Those reporting heart disease onset before age 21 ($n = 401$, 11.4% of the total number reporting heart disease) were excluded from the analyses. Mental disorder predictors were coded 1 from the year after first onset of each individual mental disorder. This time lag of 1 year ensured that first onsets of a mental disorder in the same year as heart disease onset did not count as a predictor. Only person-years up to the diagnosis of heart disease were analyzed so that only mental disorder episodes occurring prior to the onset of heart disease were included in the predictor set. Logistic regression analysis was used to estimate associations with the survival coefficients presented as odds ratios, indicating the relative odds of heart disease onset in a given year for a person with a specific mental disorder

compared to people without that disorder (including those without history of any mental disorder).

A series of bivariate and multivariate models were developed including the predictor mental disorder/s plus control variables. Models control for person-years, countries, gender, current age, and in the multivariate models, other mental disorders. Multivariate mental disorder type and number models were developed; other more complex non additive multivariate models were also estimated but model fit statistics did not indicate these provided a better fit for the data, so the simpler models are reported here (model fitting statistics available on request).

Our general approach was to not control for covariates that could be on the causal pathway between mental disorders and subsequent heart disease. However, we recognize that these variables may also confound associations so we re-estimated the multivariate model with adjustment for history of smoking (current/ever/never) and number of years of education. This made virtually no difference to associations (all previously significant associations remained significant and none reduced in magnitude – data available on request) so we report the results from the models unadjusted for smoking and education in this paper.

We examined whether early versus later onset mental disorders differed significantly in their associations with heart disease but no significant effects were found once mental disorder comorbidity was taken into account (results available on request). We also examined whether associations varied by age at heart disease onset by including interaction terms between person-years (coded as a continuous variable) and each type of mental disorder in the multivariate type model. Gender differences were examined by including interaction terms between gender and each mental disorder in the multivariate type model.

We investigated whether findings differed across countries by assessing whether there were interactions between any of the mental disorders and country income group (high versus low-middle income level). Two disorders (bulimia and drug dependence) could not be included in this analysis because there were no cases of these disorders comorbid with heart disease in low-middle income countries. Of the remaining 14 mental disorders, two showed significant interactions: alcohol abuse, with an interaction OR of 0.6 (0.3–1.0) indicating a stronger association between this disorder and heart disease in high income countries relative to low-middle income countries. The other significant interaction was with drug abuse which showed an interaction OR of 4.6 (1.6–13.6) suggesting a stronger association in lower-middle income countries. However, the small number of drug abuse-heart disease comorbid cases in low-middle income countries (resulting in wide confidence intervals for the OR) makes this finding potentially unreliable. Because there was so little indication of significant variation in associations between mental disorders and subsequent heart disease across country income groupings, further analysis were conducted on the pooled all-country dataset, with controls for country variation included in the models. In this context it is worth noting that our earlier studies of *concurrent* mental disorder-heart disease comorbidity in the WMH surveys also found that these associations were quite consistent cross-nationally¹², despite varying prevalence of mental disorders and heart disease.

As the WMH data are both clustered and weighted, the design-based Taylor series linearization¹³ implemented in version 10 of the SUDAAN software system was used to estimate standard errors and evaluate the statistical significance of coefficients.

RESULTS

Sample characteristics

The survey characteristics are shown in Table 1 together with information about the number of respondents reporting a history of adult onset heart disease (n=3197). Heart disease prevalence varies widely across countries, but as noted in the preceding paragraph our earlier work has found associations between mental disorders and heart disease to be much more stable across countries.

Number of years between first onset of mental disorder and heart disease onset

Table 2 shows that the median period of time between reported year of first onset of mental disorders and subsequent heart disease onset (the data in the 50th percentile column) ranged between 11.2 years for drug dependence and 37.5 years for specific phobia.

Type and number of mental disorders as predictors of heart disease onset

In the bivariate results presented in Table 3 all but two types of mental disorder were associated with heart disease onset with odds ratios (ORs) ranging between 1.4 and 2.5. After taking lifetime comorbidity (up until the age of onset of heart disease) into account, the mental disorders that remained significant in multivariate type model were depression/dysthymia, panic disorder, specific phobia, PTSD and alcohol abuse and dependence, with ORs from 1.3 to 1.6. The global chi square test for the joint effect of all mental disorders was significant ($\chi^2_{16} = 209.6$, $p < 0.05$), and the test for variation in ORs indicates that the associations differ significantly in magnitude ($\chi^2_{15} = 29.2$, $p < 0.05$).

The results from a multivariate model that considered number of mental disorders are presented in the final column in Table 3. A dose-response relationship is evident between the number of mental disorders experienced and heart disease onset, with ORs ranging from 1.5 for one mental disorder to 3.0 for 5+ mental disorders.

Variation by age of heart disease onset

The interaction tests between the majority (12/16) of mental disorders and person year were not significant, indicating that for these disorders variation in the timing of heart disease onset makes little difference to the strength of associations. For depression, bipolar disorder, GAD and alcohol abuse, however, there was a significant negative interaction with person year, shown in the first 3 data columns in Table 4. The results from the stratified models shown in the remainder of the table indicate that associations between these mental disorders and heart disease were stronger when the heart disease occurred earlier in life rather than later in life.

Gender differences

There were no significant interactions of gender with any of the mental disorders in associations with heart disease onset (results not shown, available on request), indicating that associations were similar for men and women.

DISCUSSION

These results should be considered within the context of the study limitations. The retrospective assessment of mental disorders is likely to have resulted in under-reporting of mental disorders¹⁴ and inaccuracies in the age of onset timing¹⁵, although the version of the CIDI used in the World Mental Health Surveys has been modified to improve accuracy in mental disorder onset reporting⁹. The other major limitation is the self-report of heart

disease. This is problematic for two reasons. First, because we do not know what proportion of those who reported heart disease in this study have coronary heart disease, the focus of the prior research in this area. Second, because methodological research on the validity of self-reported heart disease indicates that there can be quite substantial underreporting^{16–18}. It is important to note, however, that these same studies indicate that over-reporting of heart disease or heart attack is not common, and consistent with this other research has shown that while depression may bias the self-report of physical symptoms, it has not been found to bias the self-report of diagnosed physical conditions^{19,20}. What this methodological research suggests is that although misclassification of individuals with regard to the outcome in this study (heart disease) will undoubtedly have occurred, it is not likely to be related to the mental disorder predictors (and vice versa). This effect of this kind of ‘non-differential’ misclassification is usually to weaken associations, making the results we report here likely to be conservative. A further factor contributing to the probable conservative bias in these findings is that this study was conducted among heart disease (and depression) survivors. If these associations reflect causal mechanisms, then it may be that some of those most affected by an association between mental disorder and heart disease are not in the sample due to premature mortality. It is also possible that the relative strength of associations could be affected by this kind of survival bias.

Although these limitations are considerable, this study also has some significant strengths. Using a large general population sample it is the first study to be able to examine associations between a wide range of DSM-IV disorders with heart disease onset, and to thereby adjust for mental disorder comorbidity. It is noteworthy that both anxiety disorders and depression remained significant in comorbidity adjusted models, and that the associations with anxiety were greater in magnitude than those with depression. The possibility that anxiety might have stronger associations with heart disease than depression has been suggested previously^{6,21}, but this is the first study to examine this within a general population sample using diagnostic measures of depression and anxiety disorders. The association between panic disorder and heart disease found in this study is consistent with one earlier study using a diagnostic measure of panic disorder²², suggesting that panic disorder may have a specific link with increased risk of heart disease. The significant association we found between specific phobia and heart disease is consistent with earlier population studies using symptom-scale measures of phobic anxiety^{5,6}. Our finding that PTSD was associated with increased risk of heart disease onset extends the observations of this link found previously in war veteran samples^{23–25}, and in one general population sample of women²⁶, to general population samples of both sexes experiencing a wide range of triggering traumas. We did not find an association between GAD and heart disease, although such an association has been suggested in prior research²⁷ and GAD has been associated with heart disease prognosis independently of depression^{28,29}. This discrepancy may be explained by the fact that these prior studies have not controlled for history of other mental disorders. In the World Mental Health Surveys GAD has a later onset than most other disorders⁹ so it may be that the prior significant findings for GAD are due to the cumulative effects of prior mental disorder comorbidity.

Our results linking alcohol use disorders and heart disease are as would be expected given the extensive prior literature on heavy alcohol consumption and cardiovascular outcomes, but this is the first study to examine these associations after adjustment for a full range of comorbid mental disorders. It is notable that there was no association between intermittent explosive disorder and heart disease onset after comorbidity adjustment. This finding may have a bearing on interpretation of the research finding associations between anger or hostility and heart disease³⁰, where mental disorders are not typically taken into account.

We found that mood disorders and alcohol abuse were more strongly associated with earlier onset heart disease and we saw the same pattern with bipolar disorder. This might suggest that the effects of mood disorders in particular, if they are causally related to heart disease, are subtle compared to the effects of aging. Although this finding awaits confirmation in a prospective design, it is consistent with a large general practice database study that found that the strength of association between a history of serious mental illness and coronary heart disease mortality decreased with increasing age³¹.

The finding that both anxiety and mood disorders were related to subsequent heart disease after mutual adjustment suggests that they have additive effects. This is important given the common comorbidity of these conditions both in psychiatric samples (e.g., 54% of people with lifetime PTSD also have lifetime diagnoses of depression in this sample), and among people with heart disease³². Moreover, anxiety-depression comorbidity among those with heart disease has been associated with higher mortality relative to non-comorbid anxiety or depressive disorder³². It may therefore be important for future research to pay particular attention to potential causal mechanisms that mood and anxiety disorders have in common, rather than focusing on mechanisms that may be specific to depression (or to a particular anxiety disorder). Such mechanisms include certain pathophysiological features (sympathoadrenal hyper-reactivity, reduced heart-rate variability, heightened platelet activity and endothelial dysfunction)^{5,33,34}, as well as lifestyle factors and use of anti-depressant medications^{35–37}.

It also remains possible that non-causal (ie, common or confounding) factors may explain the associations we observed between mental disorders and heart disease (e.g., diet³⁸, genetics³⁹, fetal exposures^{40,41}, or personality⁴²). A further non-causal connection would be the possibility that treatment seeking for mental disorder earlier in life could result in earlier detection of heart disease.

Conclusions

In conclusion, this study offers new insights into the range of mental disorders associated with heart disease; the relative magnitude of associations; the increased risk associated with an increasing number of mental disorders experienced over the lifetime; the effect of age of heart disease onset and the similarity of associations across men and women. Future mechanistic research may need to take the breadth of psychopathology's association with heart disease into account and consider the implications of mental disorder comorbidity. It remains to be established whether these associations are causal, and the specific associations we report here require further confirmation in prospective studies. Notwithstanding these caveats, the associations observed in this global study of mood, anxiety and substance use disorders with increased risk of heart disease, associations that span over decades, are suggestive of a mental health-heart connection of substantial clinical and public health significance.

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Table 1

Characteristics of WMH samples and prevalence of self-reported history of physician-diagnosed heart disease (including self-reported heart attack) among those aged 21 years and over.

Country	Field Dates	Age Range	Weighted proportion of participants 45 years+ (%)	Sample Size		Response Rate (%)	History of Heart Disease	
				Part 1	Part 2 sub-sample		Number Unweighted (N)	Weighted (%)
Americas								
Colombia	2003	18–65	28.3	4426	2381	87.7	76	2.3
Mexico	2001–2	18–65	24.1	5782	2362	76.6	55	1.9
United States	2002–3	18+	47.6	9282	5692	70.9	353	6.7
Peru	2005–6	18–65	26.6	3930	1801	90.2	41	1.8
Asia and South Pacific								
Japan	2002–6	20+	62.0	4129	1682	55.1	102	5.0
PRC Shen Zhen	2006–7	18+	6.4	7132	2475	80.0	72	2.0
New Zealand	2003–4	18+	45.6	12790	7312	73.3	464	6.8
Europe								
Belgium	2001–2	18+	50.4	2419	1043	50.6	97	9.0
France	2001–2	18+	48.9	2894	1436	45.9	67	5.8
Germany	2002–3	18+	52.4	3555	1323	57.8	107	8.2
Italy	2001–2	18+	52.7	4712	1779	71.3	95	5.3
The Netherlands	2002–3	18+	47.4	2372	1094	56.4	96	8.0
Spain	2001–2	18+	47.6	5473	2121	78.6	117	4.6
Northern Ireland	2004–7	18+	47.0	4340	1986	68.4	106	4.9
Portugal	2008–9	18+	51.4	3849	2060	57.3	142	7.1
Romania	2005–6	18+	49.2	2357	2357	70.9	383	14.2
Poland	2010–11	18–64	40.7	10081	4000	50.4	234	5.4
Middle East								
Israel	2002–4	21+	45.6	4859	4859	72.6	445	8.3
Iraq	2006–7	18+	27.3	4332	4332	95.2	145	4.0
Weighted average response rate (%)					78.0			
Total sample size				98714	52095		3197	

Table 2

Number of years elapsing between reported year of first onset of DSM-IV mental disorders and reported year of subsequent heart disease onset*.

Type of Mental Disorders	Distribution of number of years between mental disorder first onset and heart disease onset		
	25th percentile	50th percentile	75th percentile
I. Mood disorders			
Major Depressive Episode/ Dysthymia	8.2	17.8	29.7
Bipolar Disorder (Broad)	13.2	18.5	24.9
II. Anxiety disorders			
Panic Disorder	8.2	16.9	34.6
Generalized Anxiety Disorder	6.7	17.2	29.7
Social Phobia	22.5	33.6	42.2
Specific Phobia	27.3	37.5	48.0
Agoraphobia without Panic	18.6	36.2	45.0
Post-Traumatic Stress Disorder	7.7	21.1	35.9
Obsessive Compulsive Disorder	10.3	22.5	31.6
III. Impulse-control disorders			
Intermittent Explosive Disorder	14.6	23.3	36.8
Binge Eating Disorder	3.7	22.7	31.2
Bulimia Nervosa	14.1	15.8	22.9
IV. Substance disorders			
Alcohol Abuse	10.5	19.3	27.5
Alcohol Dependence with Abuse	9.5	18.3	27.2
Drug Abuse	8.5	17.5	23.0
Drug Dependence with Abuse	7.6	11.2	18.8

* Cases are restricted to those whose heart disease onset occurred at the age of 21 years and above

Bivariate and multivariate associations (odds ratios) between DSM-IV mental disorders and the subsequent onset of heart disease.

Table 3

	Bivariate Models [†]		Multivariate Type Model [‡]		Multivariate Number Model [§]	
	OR	(95% C.I.)	OR	(95% C.I.)	OR	(95% C.I.)
I. Mood disorders						
Major Depressive Episode/Dysthymia	1.5*	(1.3–1.7)	1.3*	(1.1–1.4)	-	-
Bipolar Disorder (Broad)	1.6*	(1.1–2.4)	1.0	(0.6–1.5)	-	-
II. Anxiety disorders						
Panic Disorder	2.1*	(1.6–2.8)	1.5*	(1.1–1.9)	-	-
Generalized Anxiety Disorder	1.4*	(1.1–1.7)	0.9	(0.8–1.2)	-	-
Social Phobia	1.5*	(1.3–1.9)	1.1	(0.9–1.4)	-	-
Specific Phobia	1.9*	(1.6–2.2)	1.6*	(1.3–1.9)	-	-
Agoraphobia without Panic	1.3	(0.9–2.1)	0.9	(0.6–1.5)	-	-
Post-Traumatic Stress Disorder	2.0*	(1.5–2.5)	1.5*	(1.1–2.0)	-	-
Obsessive Compulsive Disorder	1.7*	(1.1–2.7)	1.3	(0.8–2.1)	-	-
III. Impulse-control disorders						
Intermittent Explosive Disorder	1.7*	(1.1–2.5)	1.2	(0.8–1.8)	-	-
Binge Eating Disorder	1.7	(1.0–3.0)	1.2	(0.6–2.2)	-	-
Bulimia Nervosa	2.1*	(1.0–4.3)	1.1	(0.5–2.5)	-	-
IV. Substance disorders						
Alcohol Abuse	1.8*	(1.5–2.1)	1.4*	(1.1–1.7)	-	-
Alcohol Dependence with Abuse	2.5*	(2.0–3.3)	1.5*	(1.1–2.1)	-	-
Drug Abuse	2.1*	(1.5–3.0)	1.3	(0.9–2.0)	-	-
Drug Dependence with Abuse	2.0*	(1.3–3.1)	0.7	(0.4–1.2)	-	-
Joint effect of all types of disorders, χ^2_{16}						
Difference between types of disorders, χ^2_{15}						
V. Number of disorders						
209.6*						
29.2*						

	Bivariate Models [†]		Multivariate Type Model [‡]		Multivariate Number Model [§]	
	OR	(95% C.I.)	OR	(95% C.I.)	OR	(95% C.I.)
Exactly 1 disorder	-	-	-	-	1.5*	(1.3–1.7)
Exactly 2 disorders	-	-	-	-	1.8*	(1.5–2.1)
Exactly 3 disorders	-	-	-	-	2.3*	(1.7–2.9)
Exactly 4 disorders	-	-	-	-	2.4*	(1.8–3.3)
5+ disorders	-	-	-	-	3.0*	(2.1–4.1)
Joint effect of number of disorders, χ^2_5						
						131.8*

* Significant at the 0.05 level, two-tailed test.

[†] Bivariate models: each mental disorder type was estimated as a predictor of the physical condition onset in a separate discrete time survival model controlling for age cohorts, gender, person-year and country.

[‡] Multivariate Type model: the model was estimated with dummy variables for all mental disorders entered simultaneously, including the controls specified above.

[§] Multivariate Number model: the model was estimated with dummy predictors for number of mental disorders without any information about type of mental disorders, including the controls specified above.

Table 4

Variations in associations between mental disorders and heart disease by timing of heart disease onset.

Type of Mental Disorders	Mental disorder*Person-year interaction [†]		Stratified Models [‡]			
	OR (95% C.I.)	χ^2_1 [p]	Up to Age 46 (95% C.I.)	Age 47–55 (95% C.I.)	Age 56–66 (95% C.I.)	Age 67+ (95% C.I.)
Major Depressive Episode/ Dysthymia	0.99* (0.98–0.99)	14.3* [0.000]	1.3* (1.0–1.7)	1.3* (1.0–1.8)	1.1 (0.8–1.4)	1.1 (0.8–1.5)
Bipolar Disorder (Broad)	0.98* (0.96–1.00)	4.8* [0.029]	1.3 (0.8–2.1)	0.6 (0.3–1.3)	0.7 (0.2–1.9)	0.4 (0.1–1.6)
Generalized Anxiety Disorder	0.98* (0.97–1.00)	7.1* [0.008]	1.0 (0.7–1.3)	1.1 (0.7–1.6)	0.9 (0.6–1.3)	0.7 (0.4–1.1)
Alcohol Abuse	0.98* (0.97–1.00)	6.0* [0.014]	1.9* (1.3–2.7)	1.2 (0.8–1.7)	0.9 (0.6–1.4)	0.5 (0.2–1.2)

* OR significant at the 0.05 level, 2-sided test

[†] A series of multivariate models were estimated. For example, the model for depression included the dummy variables for all mental disorders plus the cross-product term for depression and person-year, plus the controls specified for earlier models.

[‡] The multivariate model was estimated in the four person-year datasets corresponding to quartiles of the heart disease onset distribution. The fourth quartile (67 years +) did not include data from Colombia, Mexico, Peru and Poland as the upper age limit on participants in these countries was 65.