younger respondents had a significantly greater risk of PTSD. After we limited the respondents to those who experienced at least one lifetime trauma event and adjusted for exposure to traumatic events, women had a significantly elevated risk of lifetime PTSD, which is consistent with previous findings in the US (Breslau et al., 1998; Kessler et al., 1995). On the other hand, younger age seems to be associated with PTSD, partly mediated by trauma exposure. Count of prior events, particularly prior network events, was associated with lifetime PTSD, as indicated by a previous study (Breslau et al., 1999).

4.4. Limitations

Several limitations should be considered in the interpretation of the data. First, our response rate was not high. The prevalence of trauma and PTSD may be over- or underestimated. Second, respondents may have not reported specific traumas due to fear of stigma or embarrassment associated with these ones (Dussich, 2001). Third, we did not consider comorbid mental disorders in analyzing the association between traumas and PTSD. Future studies may need to address impact of traumas on other mental disorders, such as depressive disorders. Fourth, our assessment of traumas and PTSD was based on self-reported retrospective data. Respondents may have not been able to recall their experience correctly, e.g., attributing a PTSD episode to a different trauma. Fifth, we combined PTSD associated with a worst event and that associated with a random event to increase PTSD cases, which was different from a previous study that used only a worst event (Kessler et al., 1995) and one which used only a random event (Breslau et al., 1998). The worst event approach is commonly used in epidemiological surveys but it makes it impossible to draw inferences about PTSD risk associated with *typical* traumas because *worst* traumas are atypical and associated with risk of PTSD presumably higher than for more typical traumas (Breslau et al., 1998; Kessler et al., 1995; Norris et al., 2003). With appropriate weighting of responses to random evens, we were able to estimate the population prevalence and distribution of lifetime PTSD associated with the wide range of traumas assessed in the survey. However, the use of different methods makes comparisons to prior publications difficult. Diagnoses, preparation of indicators, and analyses should be done in a standard way in future studies.

Despite of these limitations, the present community-based study confirmed that trauma exposures were prevalent in Japan as in other countries, but with a smaller risk of PTSD associated with these exposures. The lower prevalence of PTSD in Japan seems mainly attributable to lower conditional risks of PTSD following these events. The greater impact of events that occurred to loved ones rather than to oneself and that of "private events" on PTSD may reflect a Japanese cultural context in regard to family values and stigma and embarrassment associated with some traumatic events. The findings warrant further research of cross-cultural assessment of trauma exposure and cultural heterogeneity in the trauma-PTSD relationship.

Conflict of interests

Although there seems to be no actual conflict of interest, the potential conflict of interest is to be addressed as follows. N. Kawakami has been a consultant for Sekisui Chemical, Co., Ltd., Junpukai Health Care, Ds's Mental Health Labo, Ltd., and Riken Institute. He has had research support for his epidemiological studies from Fujitsu Infosoft Technologies, Ltd., Tak, Ltd., and NEC Soft, Ltd. R. Kessler has been a consultant for AstraZeneca, Analysis Group, Bristol-Myers Squibb, Cerner-Galt Associates, Eli Lilly & Company, GlaxoSmithKline Inc., HealthCore Inc., Health Dialog, Hoffman-LaRoche, Inc., Integrated Benefits Institute, John Snow Inc., Kaiser Permanente, Matria Inc., Mensante, Merck & Co, Inc., Ortho-McNeil Janssen Scientific Affairs, Pfizer Inc., Primary Care Network, Research Triangle Institute, Sanofi-Aventis Groupe, Shire US Inc., SRA International, Inc., Takeda Global Research & Development, Transcept Pharmaceuticals Inc., and Wyeth-Ayerst. He has served on advisory boards for Appliance Computing II, Eli Lilly & Company, Mindsite, Ortho-McNeil Janssen Scientific Affairs, Johnson & Johnson, Plus One Health Management and Wyeth-Ayerst. He has had research support for his epidemiological studies from Analysis Group Inc., Bristol-Myers Squibb, Eli Lilly & Company, EPI-Q, GlaxoSmithKline, Johnson & Johnson Pharmaceuticals, Ortho-McNeil Janssen Scientific Affairs, Pfizer Inc., Sanofi-Aventis Groupe, Shire US, Inc., and Walgreens Co. He owns 25% share in DataStat, Inc. None of the other authors have a conflict of interest.

Contributors

N. Kawakami designed the study, collected data, conducted the literature review and wrote the first draft of the manuscript. M. Tsuchiya conducted statistical analysis. M. Umeda conducted literature search. K. Koenen designed the study. R. Kessler designed the study and conducted statistical analysis. All author collected data, and contributed to and have approved the final manuscript.

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Associations between mental disorders and subsequent onset of hypertension

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ABSTRACT

Background: Previous work has suggested significant associations between various psychological symptoms (e.g., depression, anxiety, anger, alcohol abuse) and hypertension. However, the presence and extent of associations between common mental disorders and subsequent adult onset of hypertension remain unclear. Further, there are few data available on how such associations vary by gender or over life course.
Methods: Data from the World Mental Health Surveys (comprising 19 countries and 52,095 adults) were used. Survival analyses estimated associations between first onset of common mental disorders and subsequent onset of hypertension, with and without psychiatric comorbidity adjustment. Variations in the strength of associations by gender and by life course stage of onset of both the mental disorder and hypertension were investigated.

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Results: After psychiatric comorbidity adjustment, depression, panic disorder, social phobia, specific phobia, binge eating disorder, bulimia nervosa, alcohol abuse and drug abuse were significantly associated with subsequent diagnosis of hypertension (with odds ratios ranging from 1.1 to 1.6). Number of lifetime mental disorders was associated with subsequent hypertension in a dose–response fashion. For social phobia and alcohol abuse, associations with hypertension were stronger for males than females. For panic disorder, the association with hypertension was particularly apparent in earlier-onset hypertension.
Conclusions: Depression, anxiety, impulsive eating disorders and substance use disorders were significantly associated with the subsequent diagnosis of hypertension. These data underscore the importance of early detection of mental disorders, and of physical health monitoring in people with these conditions.

1. Introduction

Previous work has suggested significant associations between hypertension and psychological symptoms such as depression, anxiety and anger [1,2]. The existence of such associations would be consistent with work indicating that such symptoms are accompanied by alterations in peripheral and central neuroendocrine systems or may have a range of behavioral correlates, which may in turn have persistent adverse effects on physical health [3]. At the same time, there are few prospective data directly demonstrating a link between alterations in neurophysiology or behavior and subsequent hypertension, and it has also been suggested that being labeled as hypertensive itself leads to psychological symptoms [4].

Indeed, the presence and extent of associations between onset of common mental disorders and subsequent adult onset hypertension remain unclear. Much of the literature in this area has employed symptom screening scales, which may not discriminate well between different negative emotions, and little of the literature in this area has assessed common mental disorders [1,2]. Much work has focused on specific psychological domains rather than on the relative contributions of a range of symptoms or disorders, and no data are available on the effects of mental disorder comorbidity on subsequent hypertension. Further, there is little if any work examining the possibility that such associations may vary by gender or over the life course.

Assessing the nature of the associations between onset of common mental disorders and subsequent hypertension is important for several reasons. First, there is ongoing neuroscientific and behavioral interest in the potential mechanisms accounting for the adverse effects of psychological symptoms and mental disorders on physical health [5,6]. Second, given that common mental disorders are highly prevalent, often begin early in life and are treatable [7], an association between such conditions and subsequent hypertension would have important public health implications.

The cross-national World Mental Health Surveys (WMHS) provide a valuable data set for addressing questions about the presence and extent of associations between onset of common mental disorders and subsequent chronic medical conditions. In these population-based surveys, individuals from countries around the world have been assessed for lifetime history of a wide range of common mental disorders, as well as for self-reported physician's diagnosis of chronic medical conditions including hypertension [8]. Although the surveys are cross-section in design, information on the time of onset of these conditions was collected. Here, we examine the association between temporally prior common mental disorders and subsequent onset of hypertension in countries participating in the WMHS using survival analysis methods.

2. Method

2.1. Samples and procedures

Data are from 19 of the WMHS: Colombia, Mexico, Peru, United States, Shenzhen (China), Japan, New Zealand, Belgium, France, Germany, Italy, the Netherlands, Romania, Spain, Portugal, Israel, Iraq, Northern Ireland and Poland (Table 1). A stratified multistage clustered area probability sampling strategy was used to select adult respondents (18 years+) in most WMH countries. These surveys were based on nationally representative household samples, except for Colombia, Mexico and Shenzhen, which were based on representative household samples in urbanized areas.

In most countries, internal subsampling was used to reduce respondent burden and average interview time by dividing the interview, an expanded version of the WHO Composite International Diagnostic Interview (CIDI 3.0), into two parts. All respondents completed Part 1, which included the core diagnostic assessment of most common mental disorders. All Part 1 respondents who met lifetime criteria for any core mental disorder and a probability sample of other respondents were administered Part 2, which assessed physical conditions and collected a range of other information including sociodemographic data. Analyses in this paper are based on the weighted Part 2 subsample ($n=52,095$). Part 2 respondents were weighted by the inverse of their probability of selection for Part 2 of the interview to adjust for differential sampling. In other words, people with mental disorders were oversampled in the Part 2 subsample in order to boost sample size, but then downweighted in analyses, while people without mental disorders were undersampled in the Part 2 subsample, but then upweighted in analyses. The net effect of the weighting procedures is an unbiased sample. Additional weights were used to adjust for differential probabilities of selection within households, to adjust for nonresponse and to match the samples to population sociodemographic distributions. Measures taken to ensure interviewer and data accuracy and cross-national consistency are described in detail elsewhere [9]. All respondents provided informed consent, and procedures for protecting respondents' identity were approved and monitored for compliance by the Institutional Review Boards in each country.

2.2. Measures

2.2.1. Mental disorders

All surveys used the WMH survey version of the WHO Composite International Diagnostic Interview (now CIDI 3.0), a fully structured interview, to assess lifetime diagnosis of mental disorders. Disorders were assessed using the definitions and criteria of the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV) [10]. The mental disorders assessed for in this paper include *anxiety and related disorders* (panic disorder, agoraphobia without panic, specific phobia, social phobia, posttraumatic stress disorder, generalized anxiety disorder, obsessive compulsive disorder), *mood disorders* (major depressive disorder/dysthymia; bipolar disorders I, II and broad), *substance use disorders* (alcohol abuse and dependence, drug abuse and dependence) and *impulse control disorders* (intermittent explosive disorder, bulimia nervosa and binge eating disorder). The different impulse control disorders are classified in different sections of DSM-IV; intermittent explosive disorder is described in the section on impulse control disorders not elsewhere classified, while

Table 1
Characteristics of WMH samples and percent (and number) with self-reported physician's diagnosis of adult-onset hypertension

Country	Field dates	Age range	Sample size		Response rate (%)	History of hypertension diagnosis	
			Part 1	Part 2 subsample		Number unweighted (*N*)	Weighted (%)
Americas							
Colombia	2003	18–65	4426	2381	87.7	249	11.4
Mexico	2001–2	18–65	5782	2362	76.6	291	9.7
United States	2002–3	18+	9282	5692	70.9	1235	24.1
Peru	2005–6	18–65	3930	1801	90.2	169	8.3
Asia and South Pacific							
Japan	2002–6	20+	4129	1682	55.1	316	16.4
PRC Shenzhen	2006–7	18+	7132	2475	80.0	99	2.6
New Zealand	2003–4	18+	12,790	7312	73.3	1396	18.5
Europe							
Belgium	2001–2	18+	2419	1043	50.6	177	15.3
France	2001–2	18+	2894	1436	45.9	208	14.8
Germany	2002–3	18+	3555	1323	57.8	250	19.6
Italy	2001–2	18+	4712	1779	71.3	239	12.8
The Netherlands	2002–3	18+	2372	1094	56.4	166	15.6
Spain	2001–2	18+	5473	2121	78.6	374	15.3
Northern Ireland	2004–7	18+	4340	1986	68.4	353	17.6
Portugal	2008–9	18+	3849	2060	57.3	458	23.2
Romania	2005–6	18+	2357	2357	70.9	475	17.6
Poland	2010–11	18–64	10,081	4000	50.4	601	14.1
Middle East							
Israel	2002–4	21+	4859	4859	72.6	988	19.1
Iraq	2006–7	18+	4332	4332	95.2	378	9.3
Weighted average response rate (%)					78.0		
Total sample size			98,714	52,095		8422	

the impulsive eating disorders, bulimia nervosa and binge eating disorder, are found in the chapter on eating disorders. CIDI organic exclusion rules were applied in making diagnoses. 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 interviews [11].

2.2.2. Hypertension 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 ... high blood pressure?" If respondents endorsed this question, they were classified as having a history of hypertension for these analyses. Respondents were also asked how old they were when they were first diagnosed with high blood pressure. This year is referred to herein as the age of onset of hypertension, although it is recognized that the underlying pathophysiology of hypertension develops over many years. Only adult-onset hypertension (onsets age 21+) were investigated in this paper.

2.3. Statistical analysis

Discrete-time survival analyses [12] with person-year as the unit of analysis were used to test sequential associations between first onset of mental disorders and the subsequent onset of hypertension. For these analyses, 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 hypertension or their age at interview (whichever came first) was treated as a separate observational record, with the year of hypertension onset coded 1 and earlier years coded 0 on a dichotomous outcome variable. The small number of people who reported hypertension onset before age 21 was excluded from analysis. Mental disorder predictors were coded 1 from the year after first onset of each individual mental disorder. This time lag of 1 year in the coding of the predictors ensured that in cases where the first onset of a mental disorder and of hypertension occurred in the same year, the mental disorder would not count as a predictor. Only person-years up to the diagnosis of hypertension were analyzed so that only mental disorder episodes occurring prior to the onset of hypertension were included in the predictor set. Logistic regression analysis was used to analyze these data with the survival coefficients presented as odds ratios, indicating the relative odds of hypertension onset in a given year for a person with a prior history of mental disorder compared to a person without that mental disorder.

A series of bivariate and multivariate models was developed including the predictor mental disorder plus control variables. Models control for person-years, countries, gender, current age and, in the multivariate models, other mental disorders. Bivariate models investigated association of specific mental disorders with subsequent hypertension onset. The next model, a multivariate model, estimated the associations of each mental disorder with hypertension onset adjusting for mental disorder comorbidity (that is, for other mental disorders occurring at any stage prior to the onset of hypertension). A second multivariate model included a series of predictor variables for number of mental disorders (e.g., one such variable for respondents who experienced exactly one mental disorder, another for respondents who experienced exactly two mental disorders and so on) as well as the control variables. Other more complex non-additive multivariate models were also run, for example, including both type and number of mental disorders, but model fit statistics did not indicate a better fit for the data, so the simpler models are reported here.

Our general approach was to not control for covariates that could be on the causal pathway between mental disorders and subsequent hypertension. However, we recognize that these variables may also confound associations, so we reestimated the multivariate model with adjustment for history of smoking (ever/never) and educational attainment. This made virtually no difference to associations (all previously significant associations remained significant, with the one exception, namely, that between bulimia nervosa and hypertension, and none reduced in magnitude), so we report the results from the model unadjusted for smoking and education in this paper.

We examined life course variation in two ways. First, we examined whether early- versus late-onset mental disorders differed significantly in their associations with hypertension through creation of mental disorder-specific dummy variables for early-onset mental

disorder (≤21 years) and late-onset disorder (>21 years) (see table footnotes for model specification). Second, we assessed whether associations varied by when in the life course hypertension was diagnosed 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.

Our earlier studies of concurrent mental–physical comorbidity in the WMHS found that these associations are generally consistent cross-nationally, despite varying prevalence of mental disorder and physical conditions [13]. All analyses for this paper were therefore run on the pooled cross-national data set. We ran sensitivity analyses to test whether the associations between number of disorders and hypertension held in both lower- and higher-income countries, and we found that they did, but were slightly (but significantly) stronger in lower-income countries (data not shown, available on request). As the WMH data are both clustered and weighted, the design-based Taylor series linearization implemented in version 10 of the SUDAAN software system was used to estimate standard errors and evaluate the statistical significance of coefficients [14].

3. Results

3.1. Descriptive

The survey characteristics are shown in Table 1 together with information about the number of survey respondents reporting a history of hypertension (n=8422).

3.2. Type and number of mental disorders as predictors of hypertension onset

The associations between individual mental disorders and subsequent hypertension onset were investigated in a series of bivariate models (i.e., only one mental disorder considered at a time). In the results presented in Table 2, it is apparent that all but one type of mental disorder were found to predict adult hypertension onset with odds ratios (ORs) ranging between 1.4 and 2.5. The median number of years between onset of the predictor mental disorder and hypertension onset ranged from 11.7 (for bipolar disorder) to 34.2 (for specific phobia) (data not shown).

When lifetime comorbidity (that is, up until the age of onset of hypertension) was taken into account in the multivariate models, the magnitude of associations diminished slightly. The mental disorders that remained significant in the multivariate models were depression/dysthymia, panic disorder, social phobia, specific phobia, agoraphobia, binge-eating disorder, bulimia nervosa, alcohol abuse and drug abuse, with ORs from 1.1 to 1.6. The global χ^2 test for the joint effect of all mental disorders was significant (χ^2_{16}=304.7, $P\leq.05$), and the test for variation in ORs indicates that we can reject the hypothesis that the ORs are the same for all the mental disorders (χ^2_{15}=28.2, $P\leq.05$). This latter test allows more confident interpretation of the statistically significant mental disorders as having specific associations with hypertension onset (rather than indicating a generalized link between psychopathology and hypertension).

The results from a multivariate model that considered only number of mental disorders (i.e., not including information about type) are presented in the final column of data in Table 2. This suggests a dose–response relationship between the number of mental disorders

Table 2
Bivariate and multivariate associations (ORs) between DSM-IV mental disorders and the subsequent diagnosis of hypertension

	Bivariate models[a]		Multivariate type model[b]		Multivariate number model[c]	
	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)
I. Mood disorders						
Major depressive episode/dysthymia	1.4*	(1.3–1.5)	1.2*	(1.1–1.3)	–	–
Bipolar disorder (broad)	1.4*	(1.1–1.8)	0.9	(0.7–1.2)	–	–
II. Anxiety disorders						
Panic disorder	1.7*	(1.4–2.0)	1.2*	(1.1–1.5)	–	–
Generalized anxiety disorder	1.4*	(1.3–1.6)	1.1	(1.0–1.2)	–	–
Social phobia	1.5*	(1.3–1.6)	1.1*	(1.0–1.3)	–	–
Specific phobia	1.5*	(1.4–1.6)	1.3*	(1.2–1.4)	–	–
Agoraphobia without panic	1.5*	(1.2–2.0)	1.1	(0.8–1.5)	–	–
Posttraumatic stress disorder	1.4*	(1.2–1.6)	1.1	(0.9–1.2)	–	–
Obsessive compulsive disorder	1.4	(1.0–1.9)	1.1	(0.8–1.5)	–	–
III. Impulse control disorders						
Intermittent explosive disorder	1.6*	(1.3–1.9)	1.2	(1.0–1.5)	–	–
Binge-eating disorder	2.2*	(1.6–3.0)	1.6*	(1.2–2.2)	–	–
Bulimia nervosa	2.4*	(1.7–3.4)	1.5*	(1.0–2.2)	–	–
IV. Substance disorders						
Alcohol abuse	1.7*	(1.5–1.9)	1.4*	(1.2–1.6)	–	–
Alcohol dependence with abuse	1.9*	(1.6–2.2)	1.1	(0.9–1.3)	–	–
Drug abuse	2.1*	(1.7–2.4)	1.3*	(1.0–1.6)	–	–
Drug dependence with abuse	2.5*	(1.9–3.2)	1.1	(0.8–1.5)	–	–
Joint effect of all types of disorders, χ^2_{16}				304.7*		
Difference between types of disorders, χ^2_{15}				28.2*		
V. Number of disorders						
Exactly 1 disorder	–	–	–	–	1.4*	(1.3–1.5)
Exactly 2 disorders	–	–	–	–	1.7*	(1.5–1.9)
Exactly 3 disorders	–	–	–	–	1.7*	(1.4–2.0)
Exactly 4 disorders	–	–	–	–	1.6*	(1.4–2.0)
5+ disorders	–	–	–	–	2.5*	(2.0–3.0)
Joint effect of number of disorders, χ^2_5						212.6*

* Significant at the .05 level, two-tailed test.

[a] 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.

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

[c] 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.

experienced over the life course and subsequent onset of hypertension, with ORs ranging from 1.4 for 1 mental disorder to 2.5 for 5+ mental disorders. The global χ^2 test for the joint effect of the number of mental disorders was significant ($\chi^2_5=212.6$, $P\leq.05$). This model was a better fit for the data than either the multivariate type model just presented or a more complex model including information about number and type (model fitting results available on request).

Noting that the prevalence of hypertension was surprisingly low in our Chinese sample, we reanalyzed associations between individual mental disorders and subsequent hypertension onset, but with this sample excluded (data not shown). We found an increase in the strength of the associations, as reflected in the global χ^2 test for the joint effect of all mental disorders ($\chi^2_{16}=3154.7$, $P\leq.05$), the test for variation in ORs ($\chi^2_{15}=29.0$, $P\leq.05$) and the global χ^2 test for the joint of effect of number of disorders ($\chi^2_5=219.2$, $P\leq.05$).

3.3. Timing of mental disorder onset (early versus late onset)

We investigated whether early-onset mental disorders (first onset occurring prior to the age of 21) were more or less strongly associated with hypertension onset than later-onset mental disorders (Table 3). The first two columns of data in the table present the results from the bivariate models where early-onset and late-onset variants of each mental disorder were both included in the one model predicting subsequent onset of hypertension, with the usual control variables but with no adjustment for other mental disorders. Some early-onset mental disorders, such as panic disorder, agoraphobia and drug dependence, had quantitatively larger associations with hypertension than their later-onset counterparts, with the reverse being true for bulimia nervosa and alcohol dependence. However, in the second set of models which tested whether these apparent differences were statistically significant after accounting for the effect of having the mental disorder at all, no significant differences between early- and late-onset disorders were found in either the bivariate or multivariate models, with one exception, namely, that late onset depression/dysthymia [OR=1.3, 95% confidence interval (CI) 1.2–1.4] had a higher association than early-onset depression/dysthymia (OR=1.1, 95% CI 0.9–1.2) with hypertension in the multivariate model. Taken together, therefore, variation in the timing of the mental disorder predictor does not significantly affect the strength of association with subsequent hypertension onset.

3.4. Gender differences

There were few significant interactions of gender with any of the mental disorders in associations with hypertension onset (results not shown, available on request), with the exceptions of social phobia and in alcohol abuse (OR=1.3 in males and OR=1.0 in females for social phobia, OR=1.5 in males and OR=1.1 in females for alcohol abuse, when the multivariate models were employed).

3.5. Variation across the life course (timing of hypertension onset)

We then examined whether associations between mental disorders and hypertension onset varied as a function of when in the life course the hypertension onset occurred. These analyses were undertaken in multivariate models adjusting for other mental disorders. The interaction tests between the majority (11/16) of

Table 3
Associations (ORs) between early vs. late mental disorder onset and the subsequent diagnosis of hypertension

	Bivariate models[a]				Multivariate model[b]			
	Early	Late	Test of the difference between early and late		Early	Late	Test of the difference between early and late	
	OR (95% CI)	OR (95% CI)	χ^2_1	[P]	OR (95% CI)	OR (95% CI)	χ^2_1	[P]
I. Mood disorders								
Major depressive episode/dysthymia	1.4* (1.2–1.6)	1.4* (1.3–1.6)	0.5	[.485]	1.1 (0.9–1.2)	1.3* (1.2–1.4)	4.5*	[.034]
Bipolar disorder (broad)	1.5* (1.1–2.0)	1.3 (0.9–1.8)	0.5	[.482]	1.0 (0.7–1.3)	0.9 (0.7–1.3)	0.1	[.760]
II. Anxiety disorders								
Panic disorder	1.9* (1.5–2.3)	1.5* (1.2–2.0)	1.3	[.261]	1.3* (1.1–1.7)	1.2 (0.9–1.5)	0.9	[.347]
Generalized anxiety disorder	1.5* (1.3–1.8)	1.4* (1.2–1.6)	0.4	[.524]	1.1 (0.9–1.3)	1.1 (0.9–1.2)	0.0	[.965]
Social phobia	1.5* (1.3–1.7)	1.3 (1.0–1.8)	0.6	[.433]	1.2* (1.0–1.3)	1.0 (0.8–1.4)	0.5	[.494]
Specific phobia	1.5* (1.3–1.6)	1.7* (1.3–2.3)	0.7	[.402]	1.3* (1.2–1.4)	1.5* (1.1–2.0)	1.3	[.265]
Agoraphobia without panic disorder	1.8* (1.3–2.4)	1.1 (0.7–1.7)	3.5	[.063]	1.3 (0.9–1.8)	0.8 (0.5–1.2)	3.4	[.066]
Posttraumatic stress disorder	1.3* (1.1–1.6)	1.4* (1.1–1.7)	0.0	[.888]	1.0 (0.8–1.2)	1.1 (0.9–1.4)	0.5	[.474]
Obsessive compulsive disorder	1.3 (0.8–2.1)	1.5* (1.0–2.2)	0.2	[.691]	1.1 (0.7–1.7)	1.1 (0.8–1.7)	0.0	[.856]
III. Impulse control disorders								
Intermittent explosive disorder	1.6* (1.2–2.1)	1.5* (1.0–2.1)	0.2	[.659]	1.3 (1.0–1.6)	1.2 (0.9–1.8)	0.0	[.908]
Binge-eating disorder	2.3* (1.5–3.6)	2.1* (1.4–3.1)	0.1	[.711]	1.8* (1.2–2.8)	1.6* (1.1–2.3)	0.4	[.540]
Bulimia nervosa	1.9* (1.1–3.2)	3.5* (2.2–5.6)	2.9	[.089]	1.2 (0.7–2.0)	2.5* (1.5–4.2)	3.6	[.059]
IV. Substance disorders								
Alcohol abuse	1.6* (1.4–1.9)	1.7* (1.5–2.0)	0.3	[.618]	1.3* (1.1–1.6)	1.5* (1.2–1.7)	0.9	[.340]
Alcohol dependence with abuse	1.7* (1.3–2.2)	2.0* (1.6–2.5)	1.2	[.264]	0.9 (0.7–1.3)	1.2 (0.9–1.5)	2.0	[.159]
Drug abuse	2.1* (1.7–2.6)	2.0* (1.5–2.6)	0.2	[.702]	1.3* (1.0–1.7)	1.3 (0.9–1.9)	0.0	[.970]
Drug dependence with abuse	3.0* (2.1–4.3)	2.0* (1.3–2.9)	2.7	[.098]	1.5 (1.0–2.3)	0.9 (0.5–1.5)	2.5	[.114]
V. Joint effect of all early-onset disorders, χ^2_{16}					148.9*			
VI. Joint effect of all late-onset disorders, χ^2_{16}						125.3*		
VII. Joint effect of early-onset disorders independent of joint effect of any disorders, χ^2_{16}							28.9*	

* Significant at the .05 level, two-tailed test.

[a] Models include dummy variables for early-onset mental disorders (= first onset < 21 years of age) and for late-onset disorders, plus control variables (age cohort, person-years, gender and country). A second bivariate model was estimated to test the significance of the difference between early- and late-onset disorders. This model included the dummy variables for the early-onset disorder and the dummy variable for the disorder itself (i.e., having it at all), plus controls.

[b] Multivariate models paralleled the bivariate models in design but included dummy variables for all mental disorders entered simultaneously.

mental disorders and person-year were not significant, indicating that, for these disorders, variation in the timing of hypertension onset makes little difference to the strength of associations. For depression, bipolar disorder, panic disorder, posttraumatic stress disorder and alcohol dependence, however, there was a significant negative interaction with person-year, shown in the first three data columns in Table 4. To illustrate the nature of the interaction, the person-year data set was then stratified into quartiles of the hypertension onset distribution and the multivariate models reestimated in each of these quartiles. These results, shown in the remainder of Table 4, only partially support the possibility that the association with hypertension onset is strongest when the hypertension occurred at any particular stage of life. In panic disorder, however, the association between panic disorder and subsequent hypertension is significantly elevated (OR=1.5) for the younger person-year groups (up to age 40) but not for those in other age groups. This may be an important qualifying result of the main effect for panic disorder averaged across all person-years presented in Table 2.

4. Discussion

Several limitations of the current study deserve emphasis. First, retrospective assessment of mental disorders may lead to underestimations of prevalence and may also be associated with inaccuracies in age of onset timing [15]. Second, there were no clinical data to validate the diagnosis of hypertension or to characterize fully its duration, severity and sequelae. Nevertheless, self-reported hypertension is moderately associated with objective data on hypertensive status [16,17]. Estimates of sensitivity of self-report of hypertension range from 64% to 91% in several Western countries, although these may be lower in other locations [18] (as is apparent also in our own data). Further, while depression has been found to increase bias towards self-report of physical symptoms, it has not been found to increase bias towards self-report of diagnosed physical conditions [19].

Taken together, then, misclassification of individuals with regard to the predictor (i.e., common mental disorders) and outcome (e.g., adult onset of hypertension) in the WMHS is likely to be largely nondifferential. As a consequence, the strength of the associations between mental disorders and subsequent hypertension reported here is likely to be underestimated. Thus, for example, a reanalysis excluding the Chinese sample, in which there was very low prevalence of hypertension, yielded an increased strength of association between mental disorders and hypertension. An additional factor contributing to the likely conservative bias here is that the study was only conducted among hypertension (and mental disorder) survivors. It is possible that some of those individuals most adversely affected by an association between common mental disorders and subsequent hypertension are underrepresented in the sample due to premature mortality.

Epidemiological studies of hypertension are rarely able to obtain detailed data on common mental disorders, and the current study has several strengths, including the large number of respondents from across the globe and the rigorous assessment of a full range of common mental disorders. Indeed, this is the first study on the association of common mental disorders with hypertension to include a wide range of disorders and to adjust for comorbidity. It is therefore of interest that we found a modest but significant association between the onset of several mood, anxiety, impulse control and substance disorders with subsequent hypertension. These data are consistent with multiple reports that have focused on the association between single psychological domains and hypertension [1,2].

The fact that we found both major depression and anxiety disorders to be significantly associated with hypertension after mutual adjustment has implications for possible mechanisms. The majority of prior studies on this topic have focused on a single symptom domain or a narrow set of mental disorders; this focus can lead to mechanistic explanations that are overly specific to the variables studied. The findings here suggest that when considering how mental disorders may lead to hypertension, it may be useful to focus on potential causal mechanisms that mood and anxiety disorders have in common; these include altered sleep patterns, sympathoadrenal hyperreactivity, various neurotransmitter abnormalities and altered inflammatory processes [20,21]. At the same time, it is possible that various common factors, such as exposure to childhood adversity, may partially explain the associations between depression and anxiety disorders on the one hand and hypertension on the other hand [8].

Previous work on impulsive eating disorders has noted that while some individuals may develop hypotension due to bulimia, other individuals may develop metabolic syndrome including hypertension [21,23]. Although the WMHS asked about the presence of obesity, age of onset was not assessed, therefore precluding an analysis of the relative timing of obesity and hypertension. Hypertension in eating disorders may reflect a direct effect of binge eating, perhaps due to the large amount of food ingested, although further work is needed in order to elucidate the relevant mechanisms involved [22]. It is noteworthy that there was no association between intermittent explosive disorder and hypertension onset after comorbidity adjustment. Indeed, previous systematic reviews investigating the association between hostility, anger and hypertension have emphasized that findings are far from consistent and that they may be influenced by multiple confounders [4].

The association between alcohol, substances and hypertension reported here has long been recognized [23–25]. Animal experiments done more than a century ago showed that alcohol had vasoconstrictive and vasodilatory effects, and subsequent clinical work has suggested that regular alcohol consumption is associated with central sympathoadrenergic activation. A range of other mechanisms may

Table 4
Variations in associations between mental disorders and hypertension by life course timing of hypertension onset (diagnosis)

Type of mental disorders	Mental disorder*person-year interaction[a]			Stratified models[b]			
				Up to age 40	Age 41–50	Age 51–60	Age 61+
	OR (95% CI)	χ^2_1	[P]	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Major depressive episode/dysthymia	0.99* (0.98–0.99)	21.0*	[.000]	1.2* (1.0–1.4)	1.2 (1.0–1.4)	1.3* (1.1–1.5)	1.2 (1.0–1.4)
Bipolar disorder (broad)	0.98* (0.97–0.99)	7.1*	[.008]	1.2 (0.9–1.6)	0.8 (0.5–1.3)	0.8 (0.5–1.5)	0.8 (0.3–1.9)
Panic disorder	0.99* (0.98–1.00)	4.0*	[.047]	1.5* (1.2–2.0)	0.9 (0.6–1.2)	1.2 (0.9–1.7)	1.3 (0.8–2.0)
Posttraumatic stress disorder	0.99* (0.98–1.00)	5.9*	[.015]	1.0 (0.8–1.3)	1.1 (0.8–1.5)	1.2 (0.8–1.9)	0.8 (0.5–1.2)
Alcohol dependence with abuse	0.99* (0.97–1.00)	5.7*	[.017]	1.1 (0.8–1.5)	1.0 (0.7–1.4)	1.1 (0.7–1.7)	0.9 (0.3–2.9)

* OR significant at the .05 level, two-sided test.
[a] A series of multivariate models was estimated. For example, the model for depression included the dummy variables for all mental disorders plus the interaction term for depression and person-year (as a continuous variable), plus the controls specified for earlier models.
[b] The multivariate model was estimated in the four person-year data sets corresponding to quartiles of the hypertension onset distribution.

also be relevant. Similarly, use of sympathomimetic substances may lead to hypertension. Despite the important contributions of both alcohol and hypertension to the global burden of disease, the population attributable risk percentage for hypertension due to alcohol is estimated to be small [26], and this may contribute to the failure to observe associations between alcohol and drug dependence and hypertension in the current study.

It is notable that the strength of the associations of hypertension with impulsive eating disorders was the highest, followed in turn by the associations of hypertension with substance use disorders and then by those of hypertension with mood and anxiety disorders. This is the first study to examine these associations after adjustment for a full range of comorbid mental disorders, and it is relevant to emphasize that there is some evidence of a dose–response relationship between the number of common mental disorders and the subsequent onset of hypertension. This finding is potentially important insofar as it identifies specific potential intervention targets for reducing hypertension [27]. At the same time, it is consistent with other publications from the WMHS which emphasize the additive effects of comorbidity on a range of measures including psychosocial impairment as well as medical morbidity.

In general, our results reveal few significant differences in the patterns of associations for hypertension across gender. The finding that the association is stronger for alcohol abuse in males is, however, noteworthy and is consistent with previous work which has indicated that alcohol consumption may protect against hypertension at low doses in women, but that, as in men, there is a linear association between alcohol consumption and hypertension at higher doses [23,24]. This finding emphasizes the complexity of the relationships between common mental disorders and hypertension, and the care that needs to be taken when assessing the public health implications of findings. Speculatively, given the normative nature of mild but not more severe social anxiety in women in some societies, an analogous mechanism is at play in this condition.

Variation in the timing of the mental disorder predictor did not significantly affect the strength of association with subsequent hypertension onset. Panic disorder, however, may be more strongly associated with subsequent early-onset hypertension, a finding that is consistent with previous clinical work noting the association between panic attacks and an immediate increase in blood pressure [28] and with ongoing neuroscientific research on potential mechanisms which underlie this phenomenon [29,30]. The lack of associations between other disorders and hypertension and life course has implications for study design; for example, the effects of conditions such as depression on subsequent hypertension may be subtle compared to the effects of aging and so may not be manifest in studies with an average older age of participants.

Taken together, these data from the WMHS indicate modest but significant associations between a range of common mental disorders and hypertension. This study offers new insights into the nature of the association between common mental disorders and hypertension including the importance of mental disorder comorbidity, the relative magnitude of associations and the strength of associations by gender and by life course stage of onset of both the mental disorder and hypertension. The data here contribute to a growing literature on the importance of the relationship between mental disorders and chronic physical conditions and have clear public health import insofar as they underscore the importance of early detection of and intervention for mental disorders, and of physical health monitoring in people with these conditions. Although it remains to be established whether some of these associations are causal, the finding of associations with increased risk of hypertension in both men and women from developed and developing countries strengthens the need for further mechanistic work in this area [30].

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