

ORIGINAL ARTICLE

Development of Lifetime Comorbidity in the World Health Organization World Mental Health Surveys

Ronald C. Kessler, PhD; Johan Ormel, PhD; Maria Petukhova, PhD; Katie A. McLaughlin, PhD; Jennifer Greif Green, PhD; Leo J. Russo, PhD; Dan J. Stein, MD, PhD; Alan M. Zaslavsky, PhD; Sergio Aguilar-Gaxiola, MD, PhD; Jordi Alonso, MD, MPH, PhD; Laura Andrade, MD, PhD; Corina Benjet, PhD; Giovanni de Girolamo, MD; Ron de Graaf, PhD, MSc; Koen Demyttenaere, MD, PhD; John Fayyad, MD; Josep Maria Haro, MD, MPH, PhD; Chi yi Hu, MD, PhD; Aimee Karam, MD; Sing Lee, MB, BS, FRCPsych; Jean-Pierre Lepine, MD, HDR; Herbert Matchsinger, PhD; Constanta Mihaescu-Pintia, MD; Jose Posada-Villa, MD; Rajesh Sagar, MD; T. Bedirhan Üstün, PhD

Context: Although numerous studies have examined the role of latent variables in the structure of comorbidity among mental disorders, none has examined their role in the development of comorbidity.

Objective: To study the role of latent variables in the development of comorbidity among 18 lifetime DSM-IV disorders in the World Health Organization World Mental Health Surveys.

Design: Nationally or regionally representative community surveys.

Setting: Fourteen countries.

Participants: A total of 21 229 survey respondents.

Main Outcome Measures: First onset of 18 lifetime DSM-IV anxiety, mood, behavior, and substance disorders assessed retrospectively in the World Health Organization Composite International Diagnostic Interview.

Results: Separate internalizing (anxiety and mood disorders) and externalizing (behavior and substance disorders) factors were found in exploratory factor analy-

sis of lifetime disorders. Consistently significant positive time-lagged associations were found in survival analyses for virtually all temporally primary lifetime disorders predicting subsequent onset of other disorders. Within-domain (ie, internalizing or externalizing) associations were generally stronger than between-domain associations. Most time-lagged associations were explained by a model that assumed the existence of mediating latent internalizing and externalizing variables. Specific phobia and obsessive-compulsive disorder (internalizing) and hyperactivity and oppositional defiant disorders (externalizing) were the most important predictors. A small number of residual associations remained significant after controlling the latent variables.

Conclusions: The good fit of the latent variable model suggests that common causal pathways account for most of the comorbidity among the disorders considered herein. These common pathways should be the focus of future research on the development of comorbidity, although several important pairwise associations that cannot be accounted for by latent variables also exist that warrant further focused study.

Arch Gen Psychiatry. 2011;68(1):90-100

COMORBIDITY IS THE NORM among common mental disorders because more than 50% of people with a mental disorder in a given year meet criteria for multiple disorders.^{1,2} The structure of this comorbidity has been the subject of considerable interest. Beginning with an influential article by Krueger,³ numerous researchers have documented that bivariate associations among hierarchy-free anxiety, mood, behavior, and substance disorders can be accounted for by correlated latent predispositions to internalizing and externalizing disorders, with division of internalizing disorders into secondary dimensions of fear (eg, panic and phobia) and distress (eg,

major depressive episode and generalized anxiety disorder).⁴⁻⁹

For editorial comment see page 10

These results have been used to argue for a reorganization of the classification of mental disorders in the DSM and *International Classification of Disease* diagnostic systems.¹⁰⁻¹³ However, additional work is needed to evaluate the empirical support for such a reorganization because the framework has only recently been expanded to include additional forms of psychopathology, such as psychotic experiences.¹⁴ Moreover, additional research on the stability of

Author Affiliations are listed at the end of this article.

the structure across sociodemographic variables (eg, age, sex, and education) would be informative.

These results have also been used occasionally to investigate whether risk factors for individual disorders are more accurately conceptualized as risk factors for the latent dimensions underlying these disorders. Kramer and colleagues,¹⁵ for example, found that observed sex differences in several internalizing and externalizing disorders became statistically insignificant when controls were included for latent internalizing-externalizing dimensions. Such evidence can be valuable in distinguishing between specific and non-specific risk factors. The use of latent variable models in this way is only in its infancy. One obvious application is to the development of comorbidity itself. In particular, although the cross-sectional structure of comorbidity has been examined in a number of studies, we are unaware of attempts to investigate the role of latent dimensions in accounting for the development of comorbidity.

Although several studies used longitudinal data to determine whether the structure of internalizing and externalizing disorders is stable over time,^{9,16,17} none investigated whether this structure accounts for the associations between temporally primary disorders and the subsequent first onset of comorbid disorders. A number of other longitudinal studies examined temporal progression^{18,19} or sequencing²⁰⁻²³ between earlier and later mental disorders, documenting strong persistence of individual disorders over time and significant predictive associations between some but not other temporally primary and later disorders. For example, Fergusson and colleagues¹⁸ found that childhood conduct disorder but not attention-deficit/hyperactivity disorder (ADHD) predicted subsequent substance disorders. None of these studies, however, investigated whether associations of earlier disorders with onset of later disorders were mediated by latent variables.

Analysis of the latter sort could be useful in identifying potentially modifiable risk pathways by focusing attention on subsets of disorders with especially strong predictive associations that could subsequently be examined in more focused analyses.^{24,25} For example, clinical studies finding childhood impulse-control problems in a subset of patients with early-onset obsessive-compulsive disorder (OCD)^{26,27} and finding that impulse-control disorders continue to feature prominently in some cases of adult OCD^{28,29} have created interest in the importance of inhibitory dyscontrol in the pathogenesis of OCD.³⁰ However, the role of putative neurobiological markers of such dyscontrol in accounting for the associations of impulse-control disorders with subsequent OCD remains unstudied. The documentation in epidemiological data of special associations between a cluster of early-onset impulse-control disorders and subsequent OCD could help spur such research by suggesting that more focused prospective neurobiological studies of this cluster beginning in childhood might yield valuable information about an important OCD subtype.

The present report proposes a novel approach to investigate the role of latent variables in the development of comorbidity. We begin with a conventional survival analysis of epidemiological data collected in 14 countries in the World Health Organization (WHO) World Mental Health (WMH) Survey Initiative³¹ to study associations between earlier lifetime disorders and the subsequent first onset of

later disorders. We then elaborate these survival models using a new latent modeling approach to examine the extent to which the associations among observed disorders can be accounted for by the mediating effects of latent internalizing and externalizing variables.

METHODS

SAMPLES

The 14 WMH countries include 7 classified by the World Bank as developed (Belgium, France, Germany, Italy, the Netherlands, Spain, and the United States) and 7 classified as developing (Brazil, Colombia, India, Lebanon, Mexico, the Peoples' Republic of China, and Romania) (**Table 1**). Surveys were administered in multistage, clustered area probability household samples representative of specific regions within countries (Brazil, Colombia, India, Mexico, and the Peoples' Republic of China) or entire countries (the remaining countries). Respondents were interviewed face-to-face by trained lay interviewers who explained the purposes of the survey, made clear that participation was voluntary and that responses would be treated as confidential, and obtained informed consent before beginning interviews. These recruitment and consent procedures were approved by the local human subjects committee that monitored the study in each country. A total of 61 292 respondents were interviewed. Country-specific response rates ranged from 45.9% (France) to 98.6% (India). The weighted (by sample size) average response rate was 71.1%.

The interview was divided into 2 parts. Part 1 assessed core disorders and was completed by all respondents. Part 2 assessed additional disorders and numerous correlates and was completed by 100% of respondents who met criteria for any part 1 disorder plus a probability subsample of other part 1 respondents. Based on a concern about recall bias, disorders defined as beginning in childhood (ADHD, conduct disorder, oppositional defiant disorder [ODD], and separation anxiety disorder) were assessed only among respondents aged 18 to 44 years. This part 2 subsample, which ranges in size from 486 respondents in Belgium to 6218 in the Peoples' Republic of China and totals 21 229 respondents across countries, is the sample used in the present report. The part 1 samples were weighted to adjust for differential probabilities of selection and residual discrepancies between sample and census on sociodemographic and geographic variables. In addition, the part 2 samples were weighted to adjust for undersampling of part 1 respondents without part 1 disorders. A more detailed discussion of WMH sampling and weighting is presented elsewhere.³²

DIAGNOSTIC ASSESSMENT

Diagnoses were based on version 3.0 of the WHO Composite International Diagnostic Interview (CIDI),³³ a fully structured, lay-administered interview that generates diagnoses according to ICD-10 and DSM-IV criteria. The DSM-IV criteria are used herein. Translation and back-translation followed standard WHO procedures.³⁴ The 7-day interviewer training program was standardized across countries. Training culminated in an examination that had to be passed before the interviewer could begin production data collection. A more detailed discussion of WMH training and quality control is presented elsewhere.³⁵

The 18 lifetime diagnoses include mood disorders (bipolar I-II or subthreshold disorder [BPD] and major depressive episode/dysthymia), anxiety disorders (agoraphobia with or without panic disorder, generalized anxiety disorder [GAD], OCD, panic disorder with or without agoraphobia, posttraumatic stress

Table 1. WMH Survey Sample Characteristics

Country	Survey ^a	Sample Design	Field Dates	Age Range, y	Sample Size			Response Rate, % ^b
					Part 1	Part 2	Part 2 and Aged 18-44 y ^a	
Developed Countries								
Belgium	ESEMeD	Stratified multistage clustered probability sample of individuals residing in households from the national register of Belgium residents; NR	2001-2002	≥18	2419	1043	486	50.6
France	ESEMeD	Stratified multistage clustered sample of working telephone numbers merged with a reverse directory (for listed numbers); initial recruitment was by telephone, with supplemental in-person recruitment in households with listed numbers; NR	2001-2002	≥18	2894	1436	727	45.9
Germany	ESEMeD	Stratified multistage clustered probability sample of individuals from community resident registries; NR	2002-2003	≥18	3555	1323	621	57.8
Italy	ESEMeD	Stratified multistage clustered probability sample of individuals from municipality resident registries; NR	2001-2002	≥18	4712	1779	853	71.3
The Netherlands	ESEMeD	Stratified multistage clustered probability sample of individuals residing in households listed in municipal postal registries; NR	2002-2003	≥18	2372	1094	516	56.4
Spain	ESEMeD	Stratified multistage clustered area probability sample of household residents; NR	2001-2002	≥18	5473	2121	960	78.6
United States	NCS-R	Stratified multistage clustered area probability sample of household residents; NR	2002-2003	≥18	9282	5692	3197	70.9
Total					30 707	14 488	7360	63.8
Developing Countries								
Brazil	São Paulo Megacity	Stratified multistage clustered area probability sample of household residents in the São Paulo metropolitan area	2004-2007	≥18	5037	2942	1824	81.3
Colombia	NSMH	Stratified multistage clustered area probability sample of household residents in all urban areas of the country (approximately 73% of the total national population)	2003	18-65	4426	2381	1731	87.7
India	WMHI	Stratified multistage clustered area probability sample of household residents in Pondicherry region; NR	2003-2005	≥18	2992	1373	825	98.6
Lebanon	LEBANON	Stratified multistage clustered area probability sample of household residents; NR	2002-2003	≥18	2857	1031	595	70.0
Mexico	M-NCS	Stratified multistage clustered area probability sample of household residents in all urban areas of the country (approximately 75% of the total national population)	2001-2002	18-65	5782	2362	1736	76.6
PRC	Shenzhen	Stratified multistage clustered area probability sample of household residents and temporary residents in the Shenzhen area	2006-2007	≥18	7134	7134 ^c	6218 ^c	80.0
Romania	RMHS	Stratified multistage clustered area probability sample of household residents; NR	2005-2006	≥18	2357	2357	940	70.9
Total					30 585	19 580	13 869	80.2
Total for All Countries					61 292	34 068	21 229	71.1

Abbreviations: ESEMeD, European Study of the Epidemiology of Mental Disorders; LEBANON, Lebanese Evaluation of the Burden of Ailments and Needs of the Nation; M-NCS, Mexico National Comorbidity Survey; NCS-R, US National Comorbidity Survey Replication; NR, nationally representative; NSMH, Colombian National Study of Mental Health; PRC, People's Republic of China; RMHS, Romania Mental Health Survey; WMH, World Mental Health; WMHI, WMH India.

^aMost WMH surveys are based on stratified multistage clustered area probability household samples in which samples of areas equivalent to counties or municipalities in the United States were selected in the first stage followed by 1 or more subsequent stages of geographic sampling (eg, towns within counties, blocks within towns, households within blocks) to arrive at a sample of households, in each of which a listing of household members was created and 1 or 2 people were selected from this listing to be interviewed. No substitution was allowed when the originally sampled household resident could not be interviewed. These household samples were selected from census area data in all countries other than France (where telephone directories were used to select households) and the Netherlands (where postal registries were used to select households). Several WMH surveys (Belgium, Germany, and Italy) used municipal resident registries to select respondents without listing households. Ten of the 14 surveys are based on NR household samples. The others are representative of particular cities (Brazil and India) or the urbanized areas of the country (Colombia and Mexico).

^bCalculated as the ratio of the number of households in which an interview was completed to the number of households originally sampled, excluding from the denominator households known not to be eligible because of being vacant at the time of initial contact or because the residents were unable to speak the designated languages of the survey.

^cIn Shenzhen, all respondents received the part 2 interview and all respondents aged 18 through 44 years were used in the current analysis.

disorder [PTSD], separation anxiety disorder, social phobia, and specific phobia), behavior disorders (attention-deficit disorder [ADD], hyperactivity disorder [HD], conduct disorder with

covert symptoms [CD1; eg, lying, shoplifting], conduct disorder with overt symptoms [CD2; eg, bullying, being physically cruel to people], intermittent explosive disorder [IED], and

ODD), and substance disorders (alcohol and other drug abuse with or without dependence).

As detailed elsewhere,³⁶ blinded clinical reappraisal interviews found generally good concordance between DSM-IV diagnoses based on the CIDI and those based on the Structured Clinical Interview for DSM-IV Axis I Disorders.³⁷ Organic exclusions but not diagnostic hierarchy rules were used in making diagnoses. The CIDI included retrospective disorder age-at-onset reports based on a special question sequence that has been shown experimentally to improve recall accuracy.³⁸ Respondents were asked to date their age when they first had the full syndrome for each disorder, not the first symptom of the disorder.

ANALYSIS METHODS

Exploratory principal axis tetrachoric factor analysis with pro-max rotation was used to examine bivariate comorbidity. Clear internalizing (10 disorders) and externalizing (8 disorders) dimensions were found but no evidence of a third factor that distinguished fear from distress disorders. Discrete-time survival analysis³⁹ with person-year as the unit of analysis and a logistic link function⁴⁰ was then used to study associations of temporally primary lifetime disorders with subsequent first onset of later disorders. Each model predicted first onset of 1 of the 18 DSM-IV/CIDI disorders from information about prior lifetime occurrence of the other 17 disorders ($18 \times 17 = 306$ pairwise associations), which were treated as time-varying covariates, controlling for respondent age, sex, and country. Retrospective age-at-onset reports were used to define the predictor disorders as time varying and to define age at onset of the outcome disorders.

We then estimated a latent variable model that constrained the coefficients in the observed variable models to be mediated by hypothesized continuous time-varying latent internalizing and externalizing variables. The coefficients in the observed variable model were constrained in the sense that this model included 306 coefficients (Figure, A), whereas the latent variable model used only 36 independent coefficients to reproduce these same associations (Figure, B). These included 10 coefficients (1 of which was nonindependent because the 10 coefficients together perfectly predict the time t latent variable) for the time t lifetime internalizing disorders predicting the time t latent internalizing variable; 8 coefficients (1 of which was nonindependent because the 8 coefficients together perfectly predict the time t latent variable) for the time t lifetime externalizing disorders predicting the time t latent externalizing variable; 4 coefficients (2 of which were nonindependent because the pair of time t latent variables perfectly predict each of the 2 time $t + 1$ latent variables) for the time t latent internalizing and externalizing variables predicting the time $t + 1$ latent internalizing and externalizing variables; 10 coefficients for the time $t + 1$ latent internalizing variable predicting first onsets of the 10 time $t + 1$ internalizing disorders; and 8 coefficients for the time $t + 1$ latent externalizing variable predicting first onsets of the 8 time $t + 1$ externalizing disorders.

In interpreting the latent variable results, it is useful to note that the latent variables are actually weighted (by odds ratios [ORs] of disorders predicting latent variables) composites of all predictor disorders. The assumption that a single weighted composite can represent the effects of all predictor disorders is equivalent to assuming that the ratios of the ORs across predictors are constant across outcomes. These constraints are the key features of the model. The standard covariance structure analysis programs used in previous studies of the structure of comorbidity could not be used to impose these constraints because discrete-time survival analysis is based on a person-year data array that varies in size across the outcomes. An iterative maximum-likelihood method implemented in a SAS macro was consequently written to estimate the coefficients.⁴¹ This procedure sequentially estimated the

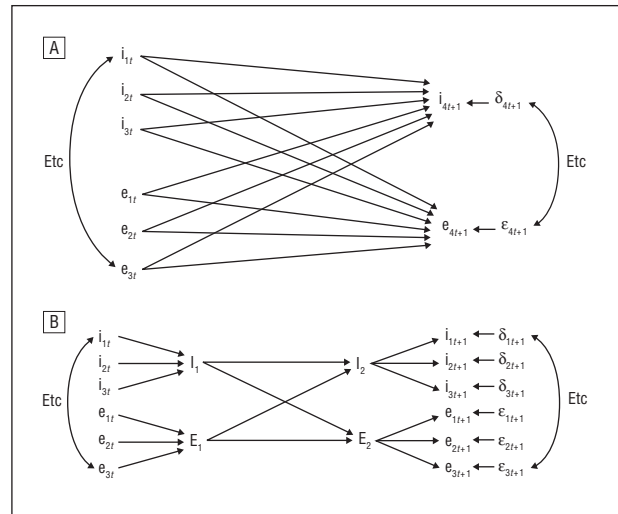


Figure. Model schematics. A, Schematic of the multivariate observed variable model. Only 3 observed lifetime time t internalizing disorders and externalizing disorders along with only 1 observed internalizing and 1 observed externalizing disorder at time $t + 1$ are shown to simplify the presentation, but there were 10 observed lifetime internalizing and 8 observed externalizing disorders in the actual survival model at each time point. First onset of each of these 18 disorders between times t and $t + 1$ was predicted by lifetime history of the other 17 disorders as of time t . Estimation was made in 18 separate survival equations, each with 17 predictors for history of the other disorders, for a total of 306 (18×17) pairwise time-lagged associations between earlier and later mental disorders. The 17 predictor disorders were treated as time-varying covariates in a discrete-time (person-year) survival framework. Controls were also included for respondent age at interview, sex, person-year, and country. B, Schematic of the multivariate latent variable model. Only 3 observed lifetime time t internalizing disorders and externalizing disorders and only 3 disorders of each set at time $t + 1$ are shown to simplify the presentation, but there were 10 observed lifetime internalizing and 8 observed externalizing disorders in the actual survival model. First onset of each of these 18 disorders between times t and $t + 1$ was predicted by latent internalizing or latent externalizing variables at time $t + 1$. These latent variables, in turn, were predicted by lifetime history of latent internalizing and externalizing variables as of time t . These time t latent variables, finally, were predicted by lifetime history of observed internalizing or externalizing variables as of time t . Estimation was performed using a 3-part iterative procedure. A total of 36 independent associations were estimated, 270 fewer than in the model for associations among observed disorders. As in the earlier observed variable model, the predictor disorders were treated as time-varying covariates in a discrete-time (person-year) survival framework, and controls were included for respondent age at interview, sex, person-year, and country. e indicates externalizing; i , internalizing. The Greek letters δ and ϵ represent measurement errors in observed i and e variables, respectively. Lowercase letters signify measured variables; and uppercase, latent variables.

coefficients in the 3 parts of the model (time t observed variables predicting time t latent variables, time t latent variables predicting time $t + 1$ latent variables, and time $t + 1$ latent variables predicting time $t + 1$ observed variables), each time holding constant the coefficients in the other 2 parts of the model to their values in the previous iteration, until estimates converged.

Once estimated, a likelihood-ratio χ^2 test was used to compare the fit of the latent variable model and the observed variable model with 270 ($306 - 36$) degrees of freedom. As described in the "Results" section, the latent variable model provided a better fit. We also investigated whether any of the 306 pairwise associations remained significant after controlling for the latent variables. Simple pairwise tests were inappropriate here because separate .05-level tests would generate more than a dozen false-positive results of 306 tests. The Bonferroni method and its extensions deal with this problem,⁴² but these are low-power tests that make it difficult to detect all but the largest true associations.⁴³ We consequently used an internal subsampling strategy to pinpoint pairwise associations for

Table 2. Prevalence and Rotated (Promax) Factor Pattern of Lifetime Disorders Separately in Developed and Developing World Mental Health Countries^a

Disorder	Estimated Lifetime Prevalence (SD), %			Standardized Regression Coefficient, Survey Part					
	Developed Countries	Developing Countries	Total	Developed Countries		Developing Countries		Total	
				1	2	1	2	1	2
Internalizing disorders									
Agoraphobia ^b	1.8 (13.0)	1.0 (9.9)	1.3 (11.0)	0.87	-0.11	0.74	-0.16	0.82	-0.14
Bipolar I-II disorder	4.4 (22.9)	2.0 (15.1)	2.8 (18.3)	0.37	0.31	0.54	0.20	0.46	0.27
Generalized anxiety disorder	4.9 (22.0)	1.4 (12.5)	2.6 (16.8)	0.67	0.04	0.72	-0.02	0.69	0.05
Major depressive episode/dysthymia	17.5 (40.9)	9.4 (33.1)	12.0 (36.5)	0.72	0.07	0.69	0.09	0.71	0.09
Obsessive-compulsive disorder	6.9 (29.7)	5.8 (32.6)	6.2 (31.7)	0.51	0.12	0.71	-0.17	0.63	-0.04
Panic disorder ^c	3.4 (16.6)	0.7 (8.0)	1.6 (11.8)	0.65	0.10	0.51	0.17	0.60	0.17
Posttraumatic stress disorder	4.4 (25.4)	1.6 (14.8)	2.6 (19.5)	0.57	0.18	0.43	0.18	0.52	0.21
Separation anxiety disorder	5.8 (25.3)	5.5 (24.2)	5.6 (24.6)	0.54	0.20	0.47	0.14	0.50	0.15
Social phobia	7.7 (30.4)	2.6 (18.5)	4.3 (23.7)	0.72	0.09	0.74	-0.04	0.71	0.09
Specific phobia	10.4 (35.4)	7.1 (32.3)	8.2 (33.3)	0.75	-0.13	0.78	-0.16	0.79	-0.16
Externalizing disorders									
Attention-deficit disorder	3.4 (23.5)	0.8 (9.5)	1.6 (15.8)	0.30	0.51	0.36	0.57	0.31	0.55
Hyperactivity disorder	2.7 (19.7)	0.6 (8.4)	1.3 (13.7)	0.19	0.58	0.32	0.60	0.22	0.61
Conduct disorder (overt) ^d	1.6 (15.3)	0.8 (9.2)	1.1 (11.6)	-0.09	0.94	-0.03	0.90	-0.08	0.93
Conduct disorder (covert) ^e	4.5 (31.1)	1.8 (15.6)	2.7 (22.1)	-0.04	0.90	0.05	0.84	-0.01	0.87
Intermittent explosive disorder	6.9 (32.5)	4.2 (28.1)	5.1 (29.9)	0.15	0.61	0.48	0.30	0.29	0.47
Oppositional defiant disorder	4.9 (34.0)	3.3 (20.9)	3.9 (26.1)	0.10	0.80	-0.02	0.73	0.02	0.78
Alcohol abuse ^f	9.7 (42.3)	8.0 (34.7)	8.5 (37.5)	0.01	0.76	-0.14	0.63	-0.06	0.73
Drug abuse ^e	6.4 (31.3)	2.7 (21.0)	3.9 (25.0)	-0.06	0.79	-0.15	0.69	-0.08	0.77
No. of respondents ^g	7360	13 869	21 229						

^aResults are based on principal axis factor analysis of tetrachoric correlation matrices estimated in person-year data sets. Disorders are defined by *DSM-IV* criteria and the Composite International Diagnostic Interview.

^bIndicates with or without panic disorder.

^cIndicates with or without agoraphobia.

^dIncludes, for example, bullying, fighting, and being physically cruel to people.

^eIncludes, for example, lying and shoplifting.

^fIndicates with or without dependence.

^gThe numbers of person-years (every year of life of the respondents beginning at 4 years to the age at interview) are 214 738 (developed countries), 376 961 (developing countries), and 591 699 (total).

further investigation by estimating observed variable survival models controlling for the latent variables in subsets of person-years. Rather than use random subsamples, which would simply have produced patterns determined by the rules of random sampling, we focused on meaningfully different subsamples defined by 4 independent life course stages (childhood, ages 4-12 years; adolescence, ages 13-19 years; young adulthood, ages 20-29 years; and middle adulthood, ages 30-44 years) and considered a given pairwise association substantively significant only if it was statistically significant at the .05 level in the total sample and in at least 2 independent subsamples with consistent sign patterns and ORs (exponentiated survival coefficients) greater than or equal to 2.0 or less than or equal to 0.5. Because the WMH data are clustered and weighted, the design-based method of jackknife repeated replications⁴⁴ was used to calculate standard errors and assess statistical significance. A SAS macro was used for this purpose.⁴¹

RESULTS

EXPLORATORY FACTOR ANALYSIS

Exploratory factor analysis of the 18 lifetime *DSM-IV*/CIDI disorders was performed separately in developed and developing countries. Only 2 meaningful factors were found, with unrotated eigenvalues of 8.0 and 1.8 (in developed countries) and 6.6 and 2.3 (in developing countries). Pro-

max-rotated factor loadings (standardized partial regression coefficients) showed that the factors correspond to internalizing and externalizing dimensions (**Table 2**). All the mood and anxiety disorders other than BPD loaded clearly on the internalizing factor (0.43-0.87 standardized regression coefficients). All the behavior and substance disorders other than IED loaded clearly on the externalizing factor (0.51-0.94 standardized regression coefficients). Bipolar disorder cross-loaded in developed countries (0.31-0.37) and IED in developing countries (0.30-0.48). However, country-level analyses found that BPD generally loaded more strongly on the internalizing factor and IED on the externalizing factor, leading us to classify them with these dimensions in further analyses. (Detailed results are not reported herein, but are available from the authors on request.) Separate factor analysis of only the internalizing disorders found no reliable secondary distinction between fear and other distress disorders (unrotated eigenvalues of 4.8 and 1.0 in developed countries and 4.3 and 1.3 in developing countries).

BIVARIATE AND MULTIVARIATE ASSOCIATIONS BETWEEN EARLIER AND LATER DISORDERS

As noted, we estimated 306 bivariate survival equations, each with the first onset of 1 disorder predicted by the prior

Table 3. Associations of Lifetime Disorders With Subsequent First Onset of Other Disorders Based on Bivariate and Multivariate Survival Models in the Total Sample^a

	Distribution of ORs				
	Median (Range)	IQR	Positive, %	Positive and Significant, %	No. of ORs
Internalizing predicting internalizing					90
Bivariate	3.6 (1.2-10.4)	3.0-4.3	100.0	97.8	
Multivariate	1.6 (0.4-5.5)	1.1-2.0	87.8	58.9	
Externalizing predicting internalizing					80
Bivariate	3.2 (1.7-7.5)	2.6-3.7	100.0	98.8	
Multivariate	1.3 (0.5-3.2)	1.0-1.6	80.0	28.8	
Internalizing predicting externalizing					80
Bivariate	3.0 (0.4-10.3)	2.4-3.9	96.3	90.0	
Multivariate	1.3 (0.1-3.2)	0.9-1.6	70.0	33.8	
Externalizing predicting externalizing					56
Bivariate	5.5 (0.5-30.0)	3.3-8.2	94.5	92.7	
Multivariate	1.6 (0.2-13.4)	1.2-2.9	81.8	50.9	
Total					306
Bivariate	3.4 (0.4-30.0)	2.7-4.3	98.0	95.1	
Multivariate	1.4 (0.1-13.4)	1.1-1.9	80.0	43.0	

Abbreviations: IQR, interquartile range; OR, odds ratio.

^aFirst lifetime onset of each of 18 *DSM-IV*/Composite International Diagnostic Interview disorders was predicted by a single dummy variable for lifetime history of 1 of the other disorders (bivariate model) or 17 dummy variables for history of each of the 17 other disorders (multivariate model) in discrete-time (person-year) survival models. The predictor disorders and latent variables were treated as time-varying covariates. Controls were included for respondent age at interview, person-year, sex, and country. Data include 21 229 respondents.

occurrence of 1 of the other 17 disorders. Of the 306 survival coefficients, 98.0% were positive and 95.1% were also significant (**Table 3**). (Detailed results are not reported herein, but are available from the authors on request.) The median (interquartile range) ORs were 3.4 (2.7-4.3). None of the negative ORs was significant. Within-domain ORs were generally larger than between-domain ORs, with within-domain median ORs of 3.6 to 5.5 compared with between-domain medians of 3.0 to 3.2.

This largely positive pattern persisted in attenuated form in multivariate models, with 80.0% of ORs positive and 43.0% positive and statistically significant (Table 3). The median (1.4) and interquartile range (1.1-1.9) of ORs were considerably lower than in bivariate models because of strong intercorrelations among predictor disorders. Nine of the 306 multivariate ORs were negative and significant (GAD predicting agoraphobia and specific phobia; HD, PTSD, and CD1 predicting OCD; CD2 predicting GAD and PTSD; and alcohol abuse predicting ADD and HD). Of the within-domain ORs, 50.9% to 58.9% were positive and significant compared with 28.8% to 33.8% of between-domain ORs. The median OR was higher within (1.6) than between (1.3) domains.

MULTIVARIATE ASSOCIATIONS IN THE LATENT VARIABLE MODEL

The latent variable model fit the observed data better than the observed variable model, as indicated by a lower Bayesian information criterion⁴⁵ of 7514.3 (latent) vs 7530.0 (observed) and an insignificant improvement in likelihood-ratio χ^2 of the observed variable model ($\chi^2_{270}=107.8$; $P=.99$). Latent variable coefficients were quite stable, as indicated by the Pearson correlations of model coefficients across 4 samples (the total sample and the 3

subsamples of all developed countries, all developing countries, and all countries excluding the 4 with survey response rates of less than 60% [Belgium, France, Germany, and the Netherlands]) of 0.88 to 0.97. (Detailed results are not reported herein, but are available from the authors on request.)

As noted, the latent variables are actually weighted (by ORs of disorders predicting latent variables) composites of all predictor disorders. The assumption that a single weighted composite can represent the effects of all the predictor disorders on all outcomes is equivalent to assuming that the ratios of the ORs across predictors are constant across outcomes. The good fit of the latent variable model shows that this assumption is generally consistent with the data, which means that the predictive effects of these disorders on each other can plausibly be assumed to be mediated by common internalizing and externalizing pathways.

The metric of the time t latent variables was set by fixing the slope of the latent variable on the strongest time t predictor to 1.0 and scaling other slopes relative to that value (**Table 4**). Within the internalizing domain, specific phobia was by far the most powerful predictor (1.00 by definition), followed by OCD (0.62) and other phobias (0.46-0.48) (Table 4). At the other extreme, GAD and panic disorder were insignificant predictors. The remaining internalizing disorders had ORs of intermediate strength (0.18-0.44). Within the externalizing domain, HD (1.00) and ODD (0.97) were the most powerful predictors. Alcohol and other drug abuse were insignificant, and the remaining externalizing disorders had ORs in the range of 0.43 to 0.77.

The ORs for the disorders as outcomes were much more consistent than for the disorders as predictors, with ranges of 0.68 to 1.00 (internalizing) and 0.44 to 1.00

Table 4. Parameter Estimates for Associations Between Observed Disorders and Latent Variables in the Latent Variable Model^a

Disorder	Estimate (SE)	
	Time <i>t</i> Disorders Predicting Time <i>t</i> Latent Variables	Time <i>t</i> + 1 Latent Variables Predicting Time <i>t</i> + 1 First Onset of Disorders
Internalizing		
Agoraphobia	0.48 (0.09) ^b	1.00 (0.09) ^b
Bipolar I/II disorder	0.18 (0.08) ^b	0.85 (0.05) ^b
Generalized anxiety disorder	0.02 (0.07)	0.72 (0.05) ^b
Major depressive episode	0.29 (0.06) ^b	0.68 (0.04) ^b
Obsessive-compulsive disorder	0.62 (0.07) ^b	0.87 (0.06) ^b
Panic disorder	-0.02 (0.10)	0.82 (0.05) ^b
Posttraumatic stress disorder	0.21 (0.08) ^b	0.68 (0.05) ^b
Separation anxiety disorder	0.44 (0.06) ^b	0.74 (0.05) ^b
Social phobia	0.46 (0.05) ^b	0.97 (0.05) ^b
Specific phobia	1.00 (0.09) ^b	0.86 (0.10) ^b
Externalizing		
Attention-deficit disorder	0.77 (0.24) ^b	1.00 (0.31) ^b
Hyperactivity disorder	1.00 (0.23) ^b	0.95 (0.16) ^b
Conduct disorder (overt)	0.43 (0.18) ^b	0.74 (0.16) ^b
Conduct disorder (covert)	0.57 (0.23) ^b	0.78 (0.16) ^b
Intermittent explosive disorder	0.77 (0.15) ^b	0.52 (0.08) ^b
Oppositional defiant disorder	0.97 (0.18) ^b	0.69 (0.15) ^b
Alcohol abuse disorder	-0.53 (0.35)	0.44 (0.08) ^b
Drug abuse disorder	0.51 (0.31)	0.38 (0.13) ^b

^aBased on an iteratively estimated pooled discrete-time (person-year) survival model with 17 dummy variables for history of each other disorder predicting subsequent first onset of each of the 18 disorders, assuming the existence of latent internalizing and externalizing disorders that explain the direct effects of the observed predictor disorders on the outcome disorders. The predictor disorders and latent variables were treated as time-varying covariates. Controls were included for respondent age at interview, person-year, sex, and country. Data include 21 229 respondents.

^bSignificant at the .05 level, 2-sided test.

(externalizing). Agoraphobia and social phobia were the most strongly predicted internalizing disorders, whereas ADD and HD were the most strongly predicted externalizing disorders. The relative importance of internalizing and externalizing disorders predicting each other was estimated in the set of 4 ORs between the latent variables at times *t* and *t* + 1 (**Table 5**). Weighted (by relative prevalence of disorders) within-domain ORs (1.6 for internalizing; 1.4 for externalizing) were higher than between-domain ORs (1.3 for time *t* internalizing predicting time *t* + 1 externalizing; 1.1 for time *t* externalizing predicting time *t* + 1 internalizing), but between-domain ORs were nonetheless statistically significant.

RESIDUAL ASSOCIATIONS NOT EXPLAINED BY THE LATENT VARIABLE MODEL

Only 13 of the 306 residual pairwise time-lagged associations between observed disorders passed our test of statistical significance. Nine of these were positive. Four involved within-disorder reciprocal ORs between CD1 and CD2 (3.2-4.8) and between ADD and HD (4.0-19.4). Two others involved asymmetrical associations between well-known disorder pairs (panic predicting agoraphobia [2.0-2.22] and depression predicting GAD [2.0-6.0], although the latter association was limited to child-adolescent onset). Two others might reflect diagnostic confusions, with agoraphobia predicting specific phobia (2.2-4.8) and HD (but, importantly, not ADD) predicting BPD (1.9-3.9). The final significant positive association was for IED predicting OCD (1.5-4.0). The 4 significant negative residual associations included PTSD predicting OCD (0.4-0.7), CD2

predicting BPD (0.2-0.5) and PTSD (0.2-0.4), and IED (0.5-0.6) predicting drug abuse.

COMMENT

Six limitations of this study are noteworthy. First, diagnoses were based on fully structured lay interviews. These typically produce more reliable (ie, reproducible across multiple interviewers) diagnoses than semistructured clinical interviews,⁴⁶ and their prevalence estimates typically correspond well with those based on clinical interviews.⁴⁷ However, fully structured interviews, unlike semistructured clinical interviews, are unable to clarify symptom responses or check questions across disorders to facilitate differential diagnosis, potentially leading to inflated estimates of comorbidity.

Second, disorders were assessed dichotomously rather than dimensionally, presumably reducing our ability to detect subtle aspects of structure in the data. This might help explain why we did not detect higher-order subfactors in the 2-factor exploratory factor analysis model.

Third, data were combined across countries with very different cultures and across surveys with very different response rates (which could have introduced variation in sample selection bias), different rates of sample exclusion (due to cross-national differences in rates of suicide, homelessness, and institutionalization), and different languages in which interviews were administered. Although every effort was made to make the translations as comparable as possible,³⁴ residual variation in meaning almost certainly contributed to cross-national variation in results.

Fourth, lifetime diagnoses were based on retrospective reports rather than prospective assessments, probably leading to recall bias that underestimated prevalence⁴⁸ and distorted age-at-onset estimates⁴⁹ despite the use of special memory-priming methods.³⁸ Bias in model coefficients might have varied across disorders as a function of age at onset and/or recency. Given the importance of this potential bias, it is noteworthy that the onset distributions based on these retrospective data are quite consistent with those based on prospective studies and studies performed at separate life course stages.⁵⁰ In addition, model coefficients in subsamples defined by life course stage are very consistent, suggesting that variation in recall across the sample age range does not influence results in any important way.

Fifth, models were based on the simplifying assumptions that the time-lagged associations among mental disorders are constant across countries and sex, stable across the life course, and unrelated to age at onset or time since onset of the predictor disorders. Preliminary analyses showed that these assumptions are a reasonable first approximation, but the investigation of these specifications needs to be a focus of ongoing WMH analysis.

Sixth, we did not take history of treatment into consideration even though early treatment, which varies in frequency across countries,⁵¹ might interrupt the progression of comorbidity and thereby distort estimates of predictive associations.

In the context of these limitations, our finding of a 2-factor internalizing-externalizing structure among WMH disorders is consistent with previous research^{4,9} but does not support the distinction in some previous studies between distress (eg, depression, GAD, and PTSD) and fear (eg, panic and phobias) disorders. As noted in the introduction, others also failed to find a distinction between distress and fear disorders.^{16,52} This less-differentiated structure in the WMH data might be due to our focus on lifetime disorders, whereas 12-month disorders were the focus of most studies that distinguished distress and fear disorders.

Our finding of significant time-lagged associations across virtually all pairs of the disorders considered herein is broadly consistent with evidence of associations between earlier and later disorders in previous longitudinal studies,¹⁸⁻²³ although most previous studies focused on prevalent cases, whereas we studied first onsets. We found, again consistent with previous studies, stronger and more consistent time-lagged associations within than between the internalizing and externalizing domains. However, again as in previous studies, we also found significant between-domain time-lagged associations.^{22,23}

Our analysis went beyond previous studies to investigate the role of latent variables in the development of comorbidity. We showed that most of the 306 pairwise time-lagged associations among the 18 disorders considered herein can be explained by a model that assumes the existence of mediating latent internalizing and externalizing variables. This finding extends previous cross-cultural work on the structure of comorbidity.⁵³ The fact that the predictive associations across this large number of disorders are mediated by 2 higher-order variables makes the internalizing and externalizing spectrum dimensions compelling targets for inquiry aimed at reducing the burden of men-

Table 5. Parameter Estimates for Associations Among Latent Variables in the Latent Variable Model^a

Time 1 Predictor Group	Time 2 Dependent Group, OR (95% CI) ^b	
	Internalizing	Externalizing
Internalizing	1.6 (1.5-1.6)	1.3 (1.2-1.3)
Externalizing	1.1 (1.1-1.2)	1.4 (1.3-1.4)

Abbreviations: CI, confidence interval; OR, odds ratio.

^aData include 21 229 respondents.

^bAll comparisons were significant at the .05 level, 2-sided test.

tal disorder around the world by interrupting the processes leading to the onset of comorbidity.

Specific phobia and OCD stood out as the most important internalizing predictors and HD and ODD as the most important externalizing predictors. The time-lagged associations involving these 4 predictors were largely mediated by the latent variables, with only 2 of the 13 significant residual associations involving these 4 strongest predictors (HD predicting ADD and BPD). Both of these were positive, showing that the comparatively high ORs of these 4 predictor disorders are relatively constant across the range of WMH outcomes. Although it is unclear why specific phobia and OCD should be the most important predictors among the internalizing disorders or HD and ODD among the externalizing disorders, the fact that all 4 are typically early-onset disorders⁵⁰ means they might be useful markers of youth at high risk for progression to later disorders. Even this possibility requires further analysis, however, because we did not investigate nonproportional hazards that might include differential predictive associations related to age at onset or time since onset. These more in-depth analyses go beyond the scope of this first report but will be pursued in ongoing WMH analyses.

Our finding of 13 significant residual associations shows that the latent variables do not explain all the comorbidity among the disorders considered. The 4 negative residual associations are most plausibly interpreted as suggesting the existence of more differentiated dimensions underlying internalizing and externalizing disorders. The negative association of IED with subsequent drug abuse, for example, could be due to externalizing disorders being made up of multiple dimensions, 1 or more of which is significantly more strongly related to drug abuse than to IED. Evidence consistent with this possibility exists in the literature.⁵⁴⁻⁵⁶ The negative residual association of CD2 (overt CD) with subsequent PTSD, in comparison, might be related to the findings that blunted psychophysiological and emotional reactivity to fear stimuli are predictors of CD,^{57,58} whereas heightened physiological reactivity to trauma-related stress cues is a predictor of PTSD.^{59,60} These observations suggest that a more differentiated latent variable model that includes internalizing and externalizing subdimensions might explain the significant negative associations found herein in the less differentiated WMH latent variable model.

The positive residual associations in the WMH data, in comparison, are most plausibly interpreted as disor-

der subtypes rather than comorbidities, including the reciprocal associations between CD1 (covert CD) and CD2 (overt CD) and between ADD and HD, or as a severity marker in the association between panic disorder and subsequent agoraphobia. At least 1 other association, between agoraphobia and subsequent specific phobia, could be due to diagnostic confusion in the CIDI. The same kind of confusion might account at least in part for the positive association between HD and subsequent BPD because differentiation between these 2 disorders can be difficult, especially within the constraints of a fully structured diagnostic interview,^{61,62} although a number of common neurobiological correlates have also been found for HD and BPD,^{63,64} arguing that ADHD might be a risk marker of BPD. The WMH finding that this association is specific to HD and does not apply to ADD has not, to our knowledge, been investigated previously.

It is important to caution that these few unique, significant residual pairwise associations should be treated as no more than preliminary owing to the problem of multiple testing and the limitations noted at the beginning of this section. Replication in other data sets, most importantly prospective data sets, is needed before these associations should be considered reliable. Furthermore, even if they are subsequently found to be reliable, their existence should not deflect attention from our main finding that the consistently significant comorbidities found among the 306 disorder pairs considered herein are likely due to common underlying processes that should be a major focus of future research on the development of comorbidity. One important implication of this finding is that future research on specific pairwise comorbid associations needs to guard against interpreting results as unique without first demonstrating, as we did herein, that they are specific rather than mere realizations of larger processes involving all internalizing and/or externalizing disorders. The fact that we found only 2 factors, finally, does not mean that only 2 underlying processes are at work because multiple processes could underlie each factor, and these diverse processes need to be studied to enrich our understanding of the causal influences leading to the higher-order structure found herein.

Submitted for Publication: February 3, 2010; final revision received July 13, 2010; accepted August 11, 2010.
Author Affiliations: Department of Health Care Policy, Harvard Medical School, Boston, Massachusetts (Drs Kessler, Petukhova, McLaughlin, Green, and Zaslavsky); Department of Psychiatry, University Medical Center Groningen, and Graduate Schools of Behavioural and Cognitive Neuroscience and for Experimental Psychopathology, University of Groningen, Groningen, the Netherlands (Dr Ormel); Shire Pharmaceuticals Research and Development, Chesterbrook, Pennsylvania (Dr Russo); Department of Psychiatry, University of Cape Town, Cape Town, South Africa (Dr Stein); School of Medicine, Center for Reducing Health Disparities, University of California, Davis (Dr Aguilar-Gaxiola); Health Services Research Unit, Institut Municipal d'Investigació Mèdica, Centro de Investigación Biomédica en Red (CIBER) en Epidemiología y Salud Pública, Barcelona, Spain (Dr Alonso); Section of Psychiatric Epidemiology, Depart-

ment and Institute of Psychiatry, School of Medicine, University of São Paulo, São Paulo, Brazil (Dr Andrade); National Institute of Psychiatry, Mexico City, Mexico (Dr Benjet); Istituto de Ricovero e Cura a Carattere Scientifico Centro S. Giovanni di Dio Fatebenefratelli, Brescia, Italy (Dr de Girolamo); Netherlands Institute of Mental Health and Addiction, Utrecht (Dr de Graaf); Department of Psychiatry, University Hospital Gasthuisberg, Leuven, Belgium (Dr Demyttenaere); St George Hospital University Medical Center, Balamand University, and Faculty of Medicine, Institute for Development, Research, Advocacy and Applied Care, Medical Institute for Neuropsychological Disorders, Beirut, Lebanon (Drs Fayyad and Karam); Parc Sanitari Sant Joan de Déu, Fundació Sant Joan de Déu, CIBER en Salud Mental, Sant Boi de Llobregat, Barcelona, Spain (Dr Haro); Shenzhen Institute of Mental Health and Shenzhen Kangning Hospital, Shenzhen, China (Dr Hu); The Chinese University of Hong Kong, Shatin, Hong Kong (Dr Lee); Hôpital Lariboisière Fernand Widal, Assistance Publique Hôpitaux de Paris, Institut National de la Santé et de la Recherche Médicale U 705, Centre national de la recherche scientifique Unité Mixte de Recherche, 7157 University Paris Diderot and Paris Descartes, Paris, France (Dr Lepine); Department of Psychiatry, University of Leipzig, Leipzig, Germany (Dr Matchsinger); National School of Public Health and Health Services Management, Bucharest, Romania (Dr Mihaescu-Pintia); Colegio Mayor de Cundinamarca University, Bogota, Colombia (Dr Posada-Villa); All India Institute of Medical Sciences, New Delhi (Dr Sagar); and Evidence and Information for Policy/Department of Health Financing and Stewardship, World Health Organization, Geneva, Switzerland (Dr Üstün).

Correspondence: Ronald C. Kessler, PhD, Department of Health Care Policy, Harvard Medical School, 180 Longwood Ave, Boston, MA 02115 (kessler@hcp.med.harvard.edu).

Author Contributions: Dr Kessler had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Financial Disclosure: Support for the WMH Surveys was obtained from a variety of government agencies, academic institutions, foundations, and private companies. In addition, Dr Andrade reports receiving partial research support for the São Paulo Megacity Mental Health Survey from Eli Lilly & Company, Brazil. Dr Kessler reports having been a consultant for GlaxoSmithKline, Kaiser Permanente, Pfizer, Inc, Sanofi-Aventis, Shire Pharmaceuticals, and Wyeth-Ayerst; having served on advisory boards for Eli Lilly & Company, Johnson & Johnson Pharmaceuticals, and Wyeth-Ayerst; and having received research support for his epidemiological studies from Bristol-Myers Squibb, Eli Lilly & Company, GlaxoSmithKline, Johnson & Johnson Pharmaceuticals, Ortho-McNeil, Pfizer, Inc, and Sanofi-Aventis. Dr Lepine reports having served on advisory boards for Wyeth Ayerst, Sanofi-Aventis, and Pope TBI and having received research support from Eli Lilly & Company and Pfizer, Inc. Dr Russo is an employee of Shire Pharmaceuticals. Dr Stein reports having received research grants and/or consultancy honoraria from AstraZeneca, Eli Lilly & Company, GlaxoSmithKline, Johnson & Johnson Pharmaceuticals, Lundbeck, Orion,

Pfizer, Inc, Pharmacia, Roche, Servier, Solvay, Sumitomo, Tikvah, and Wyeth-Ayerst.

Funding/Support: This study was supported by grant R01MH070884 from the US National Institute of Mental Health (NIMH); the John D. and Catherine T. MacArthur Foundation; the Pfizer Foundation; grants R13-MH066849, R01-MH069864, and R01 DA016558 from the US Public Health Service; grant FIRCA R03-TW006481 from the Fogarty International Center; the Pan American Health Organization; the Eli Lilly & Company Foundation; Ortho-McNeil Pharmaceutical, Inc; GlaxoSmithKline; Bristol-Myers Squibb; and Shire. The São Paulo Megacity Mental Health Survey is supported by thematic project grant 03/00204-3 from the State of São Paulo Research Foundation. The Colombian National Study of Mental Health is supported by the Ministry of Social Protection. The WMH Initiative is funded by the WHO (India) and helped by Ramamurthy Chandrasekaran, MD, Jawaharlal Institute of Postgraduate Medical Education and Research. The Lebanese National Mental Health Survey is supported by the Lebanese Ministry of Public Health; the WHO (Lebanon); Fogarty International; anonymous private donations to the Institute for Development, Research, Advocacy and Applied Care, Lebanon; and unrestricted grants from Janssen Cilag, Eli Lilly & Company, GlaxoSmithKline, Roche, and Novartis. The Mexican National Comorbidity Survey is supported by the National Institute of Psychiatry Ramon de la Fuente and by grant CONACyT-G30544-H from the National Council on Science and Technology, with supplemental support from the PanAmerican Health Organization. The Shenzhen Mental Health Survey is supported by the Shenzhen Bureau of Health and the Shenzhen Bureau of Science, Technology, and Information. The Romania WMH study projects "Policies in Mental Health Area" and "National Study Regarding Mental Health and Services Use" were performed by National School of Public Health and Health Services Management (formerly, the National Institute for Research and Development in Health), with technical support of Metro Media Transylvania, the National Institute of Statistics-National Centre for Training in Statistics, SC. Cheyenne Services SRL, Statistics Netherlands with funding by the Ministry of Public Health (formerly, the Ministry of Health) with supplemental support from Eli Lilly Romania SRL. The European Study of the Epidemiology of Mental Disorders (which includes surveys in Belgium, France, Germany, Italy, the Netherlands, and Spain) is funded by contracts QLG5-1999-01042 and SANCO 2004123 from the European Commission, the Piedmont Region (Italy); grant FIS 00/0028 from the Fondo de Investigación Sanitaria, Instituto de Salud Carlos III, Spain; grant SAF 2000-158-CE from the Ministerio de Ciencia y Tecnología, Spain; grants CIBER CB06/02/0046 and RETICS RD06/0011 REM-TAP from the Departament de Salut, Generalitat de Catalunya, Spain, Instituto de Salud Carlos III; by other local agencies; and by an unrestricted educational grant from GlaxoSmithKline. The US National Comorbidity Survey Replication is supported by grant U01-MH60220 from the NIMH with supplemental support from the National Institute of Drug Abuse, the Substance Abuse and Mental Health Services Administration, grant 044708 from the Robert Wood Johnson Foundation, and the John W. Alden Trust. Preparation of the present report was

funded by a grant from Shire Pharmaceuticals to investigate the long-term effects of ADHD on the later onset of secondary comorbid disorders.

Role of the Sponsors: The sponsors had no role in the design and conduct of the study; in the collection, management, analysis, and interpretation of the data; or in the preparation, review, or approval of the manuscript. Neither Shire nor any of the other funders of the larger WMH Survey Initiative played any role in defining the research question, performing the analysis, interpreting the results, writing the paper, or approving the paper for submission.

Additional Information: A complete list of WMH publications can be found at <http://www.hcp.med.harvard.edu/wmh/>.

Additional Contributions: The WMH staff assisted with instrumentation, fieldwork, and data analysis.

REFERENCES

1. Demyttenaere K, Bruffaerts R, Posada-Villa J, Gasquet I, Kovess V, Lepine JP, Angermeyer MC, Bernert S, de Girolamo G, Morosini P, Polidori G, Kikkawa T, Kawakami N, Ono Y, Takeshima T, Uda H, Karam EG, Fayyad JA, Karam AN, Mneimneh ZN, Medina-Mora ME, Borges G, Lara C, de Graaf R, Ormel J, Gureje O, Shen Y, Huang Y, Zhang M, Alonso J, Haro JM, Vilagut G, Bromet EJ, Gluzman S, Webb C, Kessler RC, Merikangas KR, Anthony JC, Von Korff MR, Wang PS, Brugha TS, Aguilar-Gaxiola S, Lee S, Heeringa S, Pennell BE, Zaslavsky AM, Üstün TB, Chatterji S; WHO World Mental Health Survey Consortium. Prevalence, severity, and unmet need for treatment of mental disorders in the World Health Organization World Mental Health Surveys. *JAMA*. 2004;291(21):2581-2590.
2. Kessler RC, Chiu WT, Demler O, Merikangas KR, Walters EE. Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication [published correction appears in *Arch Gen Psychiatry*. 2005;62(7):709]. *Arch Gen Psychiatry*. 2005;62(6):617-627.
3. Krueger RF. The structure of common mental disorders. *Arch Gen Psychiatry*. 1999;56(10):921-926.
4. Beesdo-Baum K, Höfler M, Gloster AT, Klotsche J, Lieb R, Beauducel A, Bühner M, Kessler RC, Wittchen HU. The structure of common mental disorders: a replication study in a community sample of adolescents and young adults. *Int J Methods Psychiatr Res*. 2009;18(4):204-220.
5. Cox BJ, Swinson RP. Instrument to assess depersonalization-derealization in panic disorder. *Depress Anxiety*. 2002;15(4):172-175.
6. Krueger RF, Markon KE. Reinterpreting comorbidity: a model-based approach to understanding and classifying psychopathology. *Annu Rev Clin Psychol*. 2006;2:111-133.
7. Lahey BB, Rathouz PJ, Van Hulle C, Urbano RC, Krueger RF, Applegate B, Garriock HA, Chapman DA, Waldman ID. Testing structural models of DSM-IV symptoms of common forms of child and adolescent psychopathology. *J Abnorm Child Psychol*. 2008;36(2):187-206.
8. Slade T, Watson D. The structure of common DSM-IV and ICD-10 mental disorders in the Australian general population. *Psychol Med*. 2006;36(11):1593-1600.
9. Vollebergh WA, Iedema J, Bijl RV, de Graaf R, Smit F, Ormel J. The structure and stability of common mental disorders: the NEMESIS Study. *Arch Gen Psychiatry*. 2001;58(6):597-603.
10. Andrews G, Goldberg DP, Krueger RF, Carpenter WT, Hyman SE, Sachdev P, Pine DS. Exploring the feasibility of a meta-structure for DSM-V and ICD-11: could it improve utility and validity? *Psychol Med*. 2009;39(12):1993-2000.
11. Goldberg DP, Krueger RF, Andrews G, Hobbs MJ. Emotional disorders: cluster 4 of the proposed meta-structure for DSM-V and ICD-11. *Psychol Med*. 2009;39(12):2043-2059.
12. Krueger RF, Markon KE. Understanding psychopathology: melding behavior genetics, personality, and quantitative psychology to develop an empirically based model. *Curr Dir Psychol Sci*. 2006;15(3):113-117.
13. Watson D. Rethinking the mood and anxiety disorders: a quantitative hierarchical model for DSM-V. *J Abnorm Psychol*. 2005;114(4):522-536.
14. Markon KE. Modeling psychopathology structure: a symptom-level analysis of Axis I and II disorders. *Psychol Med*. 2010;40(2):273-288.
15. Kramer MD, Krueger RF, Hicks BM. The role of internalizing and externalizing liability factors in accounting for gender differences in the prevalence of common psychopathological syndromes. *Psychol Med*. 2008;38(1):51-61.

16. Krueger RF, Caspi A, Moffitt TE, Silva PA. The structure and stability of common mental disorders (*DSM-III-R*): a longitudinal-epidemiological study. *J Abnorm Psychol.* 1998;107(2):216-227.
17. Wittchen HU, Beesdo-Baum K, Gloster AT, Höfler M, Klotsche J, Lieb R, Beauducel A, Böhner M, Kessler RC. The structure of mental disorders re-examined: is it developmentally stable and robust against additions? *Int J Methods Psychiatr Res.* 2009;18(4):189-203.
18. Fergusson DM, Horwood LJ, Ridder EM. Conduct and attentional problems in childhood and adolescence and later substance use, abuse and dependence: results of a 25-year longitudinal study. *Drug Alcohol Depend.* 2007;88(suppl 1):S14-S26.
19. Stein MB, Fuetsch M, Müller N, Höfler M, Lieb R, Wittchen HU. Social anxiety disorder and the risk of depression: a prospective community study of adolescents and young adults. *Arch Gen Psychiatry.* 2001;58(3):251-256.
20. Burke JD, Loeber R, Lahey BB, Rathouz PJ. Developmental transitions among affective and behavioral disorders in adolescent boys. *J Child Psychol Psychiatry.* 2005;46(11):1200-1210.
21. Copeland WE, Shanahan L, Costello EJ, Angold A. Childhood and adolescent psychiatric disorders as predictors of young adult disorders. *Arch Gen Psychiatry.* 2009;66(7):764-772.
22. Costello EJ, Mustillo S, Erkanli A, Keeler G, Angold A. Prevalence and development of psychiatric disorders in childhood and adolescence. *Arch Gen Psychiatry.* 2003;60(8):837-844.
23. Newman DL, Moffitt TE, Caspi A, Magdol L, Silva PA, Stanton WR. Psychiatric disorder in a birth cohort of young adults: prevalence, comorbidity, clinical significance, and new case incidence from ages 11 to 21. *J Consult Clin Psychol.* 1996;64(3):552-562.
24. Angold A, Costello EJ, Erkanli A. Comorbidity. *J Child Psychol Psychiatry.* 1999;40(1):57-87.
25. Jensen PS. Comorbidity and child psychopathology: recommendations for the next decade. *J Abnorm Child Psychol.* 2003;31(3):293-300.
26. Geller DA, Biederman J, Griffin S, Jones J, Lefkowitz TR. Comorbidity of juvenile obsessive-compulsive disorder with disruptive behavior disorders. *J Am Acad Child Adolesc Psychiatry.* 1996;35(12):1637-1646.
27. Thomsen PH, Jensen J. Latent class analysis of organic aspects of obsessive-compulsive disorder in children and adolescents. *Acta Psychiatr Scand.* 1991;84(4):391-395.
28. Hoehn-Saric R, Barksdale VC. Impulsiveness in obsessive-compulsive patients. *Br J Psychiatry.* 1983;143:177-182.
29. Matsunaga H, Kiriike N, Matsui T, Oya K, Okino K, Stein DJ. Impulsive disorders in Japanese adult patients with obsessive-compulsive disorder. *Compr Psychiatry.* 2005;46(1):43-49.
30. Chamberlain SR, Blackwell AD, FINEBERG NA, Robbins TW, Sahakian BJ. The neuropsychology of obsessive compulsive disorder: the importance of failures in cognitive and behavioural inhibition as candidate endophenotypic markers. *Neurosci Biobehav Rev.* 2005;29(3):399-419.
31. Kessler RC, Üstün TB, eds. *The WHO World Mental Health Surveys: Global Perspectives on the Epidemiology of Mental Disorders.* New York, NY: Cambridge University Press; 2008.
32. Heeringa SG, Wells EJ, Hubbard F, Mneimneh ZN, Chiu WT, Sampson NA, Berglund PA. Sample designs and sampling procedures. In: Kessler RC, Üstün TB, eds. *The WHO World Mental Health Surveys: Global Perspectives on the Epidemiology of Mental Disorders.* New York, NY: Cambridge University Press; 2008:14-32.
33. Kessler RC, Üstün TB. The World Mental Health (WMH) Survey Initiative Version of the World Health Organization (WHO) Composite International Diagnostic Interview (CIDI). *Int J Methods Psychiatr Res.* 2004;13(2):93-121.
34. Harkness J, Pennell BE, Villar A, Gebler N, Aguilar-Gaxiola S, Bilgen I. Translation procedures and translation assessment in the World Mental Health Survey Initiative. In: Kessler RC, Üstün TB, eds. *The WHO World Mental Health Surveys: Global Perspectives on the Epidemiology of Mental Disorders.* New York, NY: Cambridge University Press; 2008:91-113.
35. Pennell B-E, Mneimneh Z, Bowers A, Chardoul S, Wells JE, Viana MC, Dinkelmann K, Gebler N, Florescu S, He Y, Huang Y, Tomov T, Vilagut G. Implementation of the World Mental Health Surveys. In: Kessler RC, Üstün TB, eds. *The WHO World Mental Health Surveys: Global Perspectives on the Epidemiology of Mental Disorders.* New York, NY: Cambridge University Press; 2008:33-57.
36. Kessler RC, Abelson J, Demler O, Escobar JI, Gibbon M, Guyer ME, Howes MJ, Jin R, Vega WA, Walters EE, Wang P, Zaslavsky A, Zheng H. Clinical calibration of *DSM-IV* diagnoses in the World Mental Health (WMH) version of the World Health Organization (WHO) Composite International Diagnostic Interview (WMHCIDI). *Int J Methods Psychiatr Res.* 2004;13(2):122-139.
37. First MB, Spitzer RL, Gibbon M, Williams JBW. *Structured Clinical Interview for DSM-IV Axis I Disorders, Research Version, Non-patient Edition (SCID-I/NP).* New York: Biometrics Research, New York State Psychiatric Institute; 2002.
38. Knäuper B, Cannell CF, Schwarz N, Bruce ML, Kessler RC. Improving accuracy of major depression age-of-onset reports in the US National Comorbidity Survey. *Int J Methods Psychiatr Res.* 1999;8(1):39-48.
39. Efron B. Logistic regression, survival analysis, and the Kaplan-Meier curve. *J Am Stat Assoc.* 1988;83(402):414-425.
40. Willett JB, Singer JD. Investigating onset, cessation, relapse, and recovery: why you should, and how you can, use discrete-time survival analysis to examine event occurrence. *J Consult Clin Psychol.* 1993;61(6):952-965.
41. SAS Institute Inc. *SAS/STAT Software, Version 9.1 for Windows.* Cary, NC: SAS Institute Inc; 2002.
42. Shaffer JP. Multiple hypothesis testing. *Annu Rev Psychol.* 1995;46:561-584.
43. Perneger TV. What's wrong with Bonferroni adjustments. *BMJ.* 1998;316(7139):1236-1238.
44. Wolter KM. *Introduction to Variance Estimation.* New York, NY: Springer-Verlag; 1985.
45. Kass RE, Raftery AE. Bayes factors. *J Am Stat Assoc.* 1995;90(430):773-795.
46. Wittchen HU. Reliability and validity studies of the WHO-Composite International Diagnostic Interview (CIDI): a critical review. *J Psychiatr Res.* 1994;28(1):57-84.
47. Haro JM, Arbabzadeh-Bouchez S, Brugha TS, de Girolamo G, Guyer ME, Jin R, Lepine JP, Mazzi F, Reneses B, Vilagut G, Sampson NA, Kessler RC. Concordance of the Composite International Diagnostic Interview Version 3.0 (CIDI 3.0) with standardized clinical assessments in the WHO World Mental Health surveys. *Int J Methods Psychiatr Res.* 2006;15(4):167-180.
48. Moffitt TE, Caspi A, Taylor A, Kokaua J, Milne BJ, Polanczyk G, Poulton R. How common are common mental disorders? Evidence that lifetime prevalence rates are doubled by prospective versus retrospective ascertainment. *Psychol Med.* 2010;40(6):899-909.
49. Simon GE, VonKorff M. Recall of psychiatric history in cross-sectional surveys: implications for epidemiologic research. *Epidemiol Rev.* 1995;17(1):221-227.
50. Kessler RC, Amminger GP, Aguilar-Gaxiola S, Alonso J, Lee S, Üstün TB. Age of onset of mental disorders: a review of recent literature. *Curr Opin Psychiatry.* 2007;20(4):359-364.
51. Wang PS, Angermeyer M, Borges G, Bruffaerts R, Tat Chiu W, DE Girolamo G, Fayyad J, Gureje O, Haro JM, Huang Y, Kessler RC, Kovess V, Levinson D, Nakane Y, Oakley Brown MA, Ormel JH, Posada-Villa J, Aguilar-Gaxiola S, Alonso J, Lee S, Heeringa S, Pennell BE, Chatterji S, Üstün TB. Delay and failure in treatment seeking after first onset of mental disorders in the World Health Organization's World Mental Health Survey Initiative. *World Psychiatry.* 2007;6(3):177-185.
52. Krueger RF, Finger MS. Using item response theory to understand comorbidity among anxiety and unipolar mood disorders. *Psychol Assess.* 2001;13(1):140-151.
53. Krueger RF, Chentsova-Dutton YE, Markon KE, Goldberg D, Ormel J. A cross-cultural study of the structure of comorbidity among common psychopathological syndromes in the general health care setting. *J Abnorm Psychol.* 2003;112(3):437-447.
54. Farmer RF, Seeley JR, Kosty DB, Lewinsohn PM. Refinements in the hierarchical structure of externalizing psychiatric disorders: patterns of lifetime liability from mid-adolescence through early adulthood. *J Abnorm Psychol.* 2009;118(4):699-710.
55. Helfritz L, Stanford M. Personality and psychopathology in an impulsive aggressive college sample. *Aggress Behav.* 2006;32(1):28-37.
56. Sher KJ, Trull TJ. Personality and disinhibitory psychopathology: alcoholism and antisocial personality disorder. *J Abnorm Psychol.* 1994;103(1):92-102.
57. Herpertz SC, Mueller B, Qunaibi M, Lichterfeld C, Konrad K, Herpertz-Dahlmann B. Response to emotional stimuli in boys with conduct disorder. *Am J Psychiatry.* 2005;162(6):1100-1107.
58. Sterzer P, Stadler C, Krebs A, Kleinschmidt A, Poustka F. Abnormal neural responses to emotional visual stimuli in adolescents with conduct disorder. *Biol Psychiatry.* 2005;57(1):7-15.
59. Marshall RD, Garakani A. Psychobiology of the acute stress response and its relationship to the psychobiology of post-traumatic stress disorder. *Psychiatr Clin North Am.* 2002;25(2):385-395.
60. Orr SP, Roth WT. Psychophysiological assessment: clinical applications for PTSD. *J Affect Disord.* 2000;61(3):225-240.
61. Kim EY, Miklowitz DJ. Childhood mania, attention deficit hyperactivity disorder and conduct disorder: a critical review of diagnostic dilemmas. *Bipolar Disord.* 2002;4(4):215-225.
62. Wingo AP, Ghaemi SN. A systematic review of rates and diagnostic validity of comorbid adult attention-deficit/hyperactivity disorder and bipolar disorder. *J Clin Psychiatry.* 2007;68(11):1776-1784.
63. Galanter CA, Leibenluft E. Frontiers between attention deficit hyperactivity disorder and bipolar disorder. *Child Adolesc Psychiatr Clin N Am.* 2008;17(2):325-346, viii-ix.
64. Hegerl U, Himmerich H, Engmann B, Hensch T. Mania and attention-deficit/hyperactivity disorder: common symptomatology, common pathophysiology and common treatment? *Curr Opin Psychiatry.* 2010;23(1):1-7.