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SPECIAL ARTICLE

Anxious and non-anxious major depressive disorder in the World Health Organization World Mental Health Surveys

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Background. To examine cross-national patterns and correlates of lifetime and 12-month comorbid DSM-IV anxiety disorders among people with lifetime and 12-month DSM-IV major depressive disorder (MDD).

Method. Nationally or regionally representative epidemiological interviews were administered to 74 045 adults in 27 surveys across 24 countries in the WHO World Mental Health (WMH) Surveys. DSM-IV MDD, a wide range of comorbid DSM-IV anxiety disorders, and a number of correlates were assessed with the WHO Composite International Diagnostic Interview (CIDI).

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Results. 45.7% of respondents with lifetime MDD (32.0–46.5% inter-quartile range (IQR) across surveys) had one of more lifetime anxiety disorders. A slightly higher proportion of respondents with 12-month MDD had lifetime anxiety disorders (51.7%, 37.8–54.0% IQR) and only slightly lower proportions of respondents with 12-month MDD had 12-month anxiety disorders (41.6%, 29.9–47.2% IQR). Two-thirds (68%) of respondents with lifetime comorbid anxiety disorders and MDD reported an earlier age-of-onset (AOO) of their first anxiety disorder than their MDD, while 13.5% reported an earlier AOO of MDD and the remaining 18.5% reported the same AOO of both disorders. Women and previously married people had consistently elevated rates of lifetime and 12-month MDD as well as comorbid anxiety disorders. Consistently higher proportions of respondents with 12-month anxious than non-anxious MDD reported severe role impairment (64.4 *v.* 46.0%; $\chi^2_1 = 187.0$, $p < 0.001$) and suicide ideation (19.5 *v.* 8.9%; $\chi^2_1 = 71.6$, $p < 0.001$). Significantly more respondents with 12-month anxious than non-anxious MDD received treatment for their depression in the 12 months before interview, but this difference was more pronounced in high-income countries (68.8 *v.* 45.4%; $\chi^2_1 = 108.8$, $p < 0.001$) than low/middle-income countries (30.3 *v.* 20.6%; $\chi^2_1 = 11.7$, $p < 0.001$).

Conclusions. Patterns and correlates of comorbid DSM-IV anxiety disorders among people with DSM-IV MDD are similar across WMH countries. The narrow IQR of the proportion of respondents with temporally prior AOO of anxiety disorders than comorbid MDD (69.6–74.7%) is especially noteworthy. However, the fact that these proportions are not higher among respondents with 12-month than lifetime comorbidity means that temporal priority between lifetime anxiety disorders and MDD is not related to MDD persistence among people with anxious MDD. This, in turn, raises complex questions about the relative importance of temporally primary anxiety disorders as risk markers *v.* causal risk factors for subsequent MDD onset and persistence, including the possibility that anxiety disorders might primarily be risk markers for MDD onset and causal risk factors for MDD persistence.

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Introduction

The Global Burden of Disease (GBD) 2010 Study ranked major depressive disorder (MDD) as the 2nd leading cause of years lived with disability in the world (exceeded only by low back pain) and the 1st–4th leading cause (out of nearly 300 considered) in each region of the world (Vos *et al.* 2012). These high estimates are due to MDD having both high prevalence (estimated by the GBD 2010 investigators to be the 19th most common disease in the world) and high severity (indicated by higher ranking of MDD as a cause of disability than prevalent disease). However, MDD severity is highly variable (Birnbaum *et al.* 2010; Li *et al.* 2014). Indeed, severity is the most consistent discriminating characteristic in empirical studies of MDD symptom subtypes (van Loo *et al.* 2012).

One of the strongest predictors of MDD severity is comorbid anxiety disorder (Mineka & Vrshek-Schallhorn, 2008; Wu & Fang, 2014). Epidemiological studies show consistently that MDD is highly comorbid with numerous anxiety disorders (Andrade *et al.* 2003; Kessler *et al.* 2011*b*; Lamers *et al.* 2011) and more severe and persistent when accompanied by comorbid anxiety disorders (Ormel *et al.* 1994; Roy-Byrne *et al.* 2000; McLaughlin *et al.* 2006; Fichter *et al.* 2010). People with anxious MDD are also significantly more likely to seek treatment (Kessler *et al.* 2001; Jacobi *et al.* 2004) but significantly less likely to respond to treatment (Jakubovski & Bloch, 2014; Saveanu *et al.* 2014) than those with non-anxious MDD. Comorbid anxiety disorders have been found consistently to have earlier age-of-onset (AOO) than MDD both in cross-sectional surveys that assess AOO retrospectively (Kessler, 1995; Kessler *et al.* 2011*a*) and prospective studies that examine unfolding of comorbidity over time (Murphy *et al.* 1986; Bittner *et al.* 2004; Copeland *et al.* 2009; Klein *et al.* 2013).

Two noteworthy limitations of existing research on comorbid anxiety in MDD are that a narrow definition of comorbid anxiety is often used that either focuses on current (but not lifetime) comorbidity or examines only one anxiety disorder (typically generalised anxiety disorder or panic disorder) and that these studies are typically, although not always (Lin *et al.* 2014), carried out in high-income Western countries. We address both limitations here by presenting cross-national epidemiological data on comorbidities of DSM-IV anxiety disorders and MDD using a composite measure that includes a wide range of anxiety disorders in a coordinated series of 27 community epidemiological surveys carried out in 24 countries throughout the world. We estimate the proportions of survey respondents with lifetime and 12-month DSM-IV MDD who also met criteria for one or more lifetime and 12-month DSM-IV anxiety disorders. We examine cross-national consistencies in AOO priorities between comorbid anxiety disorders and MDD, whether anxious MDD is more severe and persistent than non-anxious MDD, and

whether people with anxious MDD are more likely than those with non-anxious MDD to obtain professional treatment for MDD. We also examine cross-national consistency in basic socio-demographic correlates of anxious and non-anxious MDD.

Methods

Sample

Data come from the WHO World Mental Health (WMH) Surveys, a series of community epidemiological surveys administered in ten countries classified by the World Bank (World Bank, 2009) as low or middle-income (Brazil, Bulgaria, Colombia, Iraq, Lebanon, Mexico, Nigeria, Peru, Peoples Republic of China (PRC) and Romania) and 14 high income (Australia, Belgium, France, Germany, Israel, Italy, Japan, Netherlands, New Zealand, Northern Ireland, Poland, Portugal, Spain and the USA). The majority of surveys (five in low/middle-income countries, 13 in high-income countries) were based on nationally representative household samples. Two were representative of all urban areas in their countries (Colombia, Mexico). Two were representative of selected regions in their countries (Japan, Nigeria). And a final five were representative of selected Metropolitan Areas in their countries (Sao Paulo in Brazil; Medellin in Colombia; Murcia in Spain; Beijing–Shanghai and Shenzhen in PRC).

Standardised interviewer training and quality control procedures were used in each survey (Pennell *et al.* 2008). Informed consent was obtained before administering interviews. The institutional review boards of the organisations coordinating the surveys approved and monitored compliance with procedures for informed consent and protecting human subjects. Interviews were administered face-to-face by trained lay interviewers in respondents' homes. A total of 138 602 adults (age 18+) completed interviews. The weighted (by sample size) average response rate was 68.7%. To reduce respondent burden, the interview was divided into two parts. Part I, which assessed core mental disorders, was administered to all respondents. Part II, which assessed additional disorders and correlates, was administered to all Part I respondents who met criteria for any Part I disorder plus a probability subsample of other Part I respondents. Part II interviews ($n = 74\,045$), the focus of the current report, were weighted by the inverse of their probabilities of selection into Part II and additionally weighted to adjust samples to match population distributions on the cross-classification of key socio-demographic and geographic variables. Further details about WMH sampling and weighting are available elsewhere (Heeringa *et al.* 2008).

Measures

Mental disorders

Mental disorders were assessed with the WHO Composite International Diagnostic Interview (CIDI) Version 3.0, (Kessler & Üstün, 2004), a fully structured lay-administered interview generating lifetime and 12-month prevalence estimates of 20 mood (major depressive, dysthymic, bipolar I–II and sub-threshold bipolar), anxiety (generalised anxiety, panic, agoraphobia, specific phobia, social phobia, post-traumatic stress, and separation anxiety), behaviour (attention-deficit/hyperactivity, oppositional-defiant, conduct, intermittent explosive) and substance (alcohol and drug abuse, alcohol and drug dependence with abuse) disorders. The WMH interview translation, back-translation and harmonisation protocol required culturally competent bilingual clinicians to review, modify, and approve key phrases describing symptoms (Harkness *et al.* 2008). However, no attempt was made to go beyond DSM-IV criteria to assess depression-equivalents that might be unique to the specific countries. The latter expansion might have led to a change in results, although previous research has shown that the latent structure of major depression is quite consistent across countries (Simon *et al.* 2002; Bernert *et al.* 2009; Schrier *et al.* 2010). Blinded clinical reappraisal interviews with the Structured Clinical Interview for DSM-IV (SCID; First *et al.* 2002) were carried out in four WMH countries. Good concordance was found with diagnoses based on the CIDI (Haro *et al.* 2006). AOO was assessed using a special probing sequence shown experimentally to yield more plausible distributions than conventional AOO questions (Knäuper *et al.* 1999).

MDD was defined as meeting lifetime DSM-IV/CIDI criteria for major depressive episode (MDE) and not meeting lifetime DSM-IV/CIDI criteria for broadly defined bipolar disorder (bipolar I–II or sub-threshold). As detailed elsewhere (Merikangas *et al.* 2011), our definition of sub-threshold bipolar disorder includes both hypomania without history of MDE and sub-threshold hypomania with history of MDE. Anxious MDD is defined as MDD in conjunction with any of the anxiety disorders assessed in the surveys. Comorbid anxiety is considered temporally primary if at least one lifetime anxiety disorder had an AOO earlier than that of MDD. MDD is considered temporally primary if MDD AOO is earlier than that of *all* lifetime comorbid anxiety disorders. A third category consists of respondents who reported that MDD AOO was the same as anxiety disorder AOO.

Impairment in role functioning

Severe role impairment in the 12 months before interview was assessed with a modified version of the

Sheehan Disability Scales (SDS; Leon *et al.* 1997) that asked respondents with 12-month MDD to think of the 1 month in the year when their depression was most severe and rate how much their depression interfered with their functioning in each of four role domains (home management, ability to work, social life and close relationships) during that month using a 0–10 response scale with labels of *None* (0), *Mild* (1–3), *Moderate* (4–6), *Severe* (7–9) and *Very Severe* (10) interference. Severe role impairment was defined as having any SDS score of 7–10. The SDS has excellent internal consistency reliability (Leon *et al.* 1997) and good concordance with objective measures of role functioning (Ormel *et al.* 2008). Suicide ideation was assessed with a single question that asked respondents whether there was ever a time in the 12 months before interview when they '*seriously thought about committing suicide*'.

Socio-demographics

We examined associations of MDD with respondent age (18–34, 35–49, 50–64, 65+), gender, current marital status (married, never married, previously married (combining separated, divorced and widowed)), current income (low, low-average, high-average and high based on country-specific quartiles of gross household income per family member) and education (none, some primary, completed primary, some secondary, completed secondary, some college or other post-secondary and completed college).

Treatment

Respondents with lifetime MDD were asked if they ever obtained professional treatment for their depression and, if so, if they did so in the past 12 months. Those with 12-month treatment were asked if they saw a mental health specialty treatment provider (psychiatrist, psychologist, other mental health professional in any setting, social worker or counsellor in a mental health specialty treatment setting, used a mental health hotline) general medical treatment provider (primary care doctor, other general medical doctor, any other health care profession seen in a general medical setting) or nonmedical treatment provider (religious or spiritual advisor, social worker or counsellor, any other type of healer) for a mental health problem. A more detailed description of WMH 12-month treatment measures is presented elsewhere (Wang *et al.* 2007).

Statistical analyses

Cross-tabulations were used to estimate lifetime and 12-month DSM-IV/CIDI MDD prevalence, the proportions of lifetime and 12-month cases with comorbid DSM-IV anxiety disorders, the proportions of lifetime comorbid cases with anxiety disorder or MDD temporally primary AOO, 12-month prevalence of severe role impairment and suicide ideation related to comorbid anxiety disorders among respondents with 12-month MDD, and 12-month MDD treatment as a function of comorbid anxiety disorders among respondents with 12-month MDD. Person-level logistic regression was used to examine multivariate associations of socio-demographic variables with lifetime and 12-month MDD in the total sample, lifetime anxious MDD among respondents with lifetime MDD, and 12-month anxious MDD among respondents with 12-month MDD. Time-varying socio-demographics (i.e., marital status, income and education) were defined as of the time of interview (rather than at time of disorder onset). Standard errors were estimated using the Taylor series linearisation method (Wolter, 1985) implemented in the SUDAAN software system (Research Triangle Institute, 2002) to adjust weighting and clustering. Multivariate significance of predictor sets was evaluated using Wald χ^2 tests based on design-corrected coefficient variance–covariance matrices. Statistical significance was evaluated using two-sided 0.05-level tests.

Results

Prevalence

Lifetime prevalence of DSM-IV/CIDI MDD averaged 11.2% across surveys, 8.1% in low/middle-income countries, and 13.0% in high-income countries. (Table 1) The inter-quartile range (IQR; 25th–75th percentiles) of lifetime prevalence estimates was 6.8–15.3%. The 45.7% of respondents with lifetime MDD (42.4% in low/middle-income countries, 46.9% in high-income countries, 32.0–46.5% IQR) also had one of more lifetime DSM-IV/CIDI anxiety disorders. A comparison of the ratios of (75th percentile – 25th percentile)/mean shows that lifetime prevalence varied much more across surveys than did the proportion of lifetime cases with lifetime comorbid anxiety disorders (0.75 *v.* 0.32).

Twelve-month MDD prevalence averaged 4.7% across surveys (4.0% in low/middle-income countries, 5.1% in high-income countries, 3.0–5.6 IQR), while 51.7% of respondents with 12-month MDD (48.0% in low/middle-income countries, 53.3% in high-income countries, 37.8–54.0% IQR) also had one or more lifetime DSM-IV/CIDI anxiety disorders. Only slightly lower proportions of respondents with 12-month MDD had 12-month comorbid anxiety disorders (41.6% in the total sample, 38.8% in low/middle-income countries, 42.9% in high-income countries, 29.9–47.2% IQR). As with lifetime prevalence, a comparison of the ratios of (75th percentile – 25th

Table 1. *Lifetime and 12-month prevalence of DSM-IV/CIDI MDD along with the proportions of respondents with lifetime and 12-month MDD who have comorbid DSM-IV/CIDI anxiety disorders[a] in the WHO WMH Surveys*

	Lifetime MDD				12-Month MDD						
	Lifetime MDD		Lifetime anxiety/ Lifetime MDD		12-month MDD		Lifetime anxiety/ 12-month MDD		12-month anxiety/ 12-month MDD		
	%	(S.E.)	%	(S.E.)	%	(S.E.)	%	(S.E.)	%	(S.E.)	(*n*)
I. Low/Middle Income											
Brazil – São Paulo	18.0	(0.8)	50.0	(2.2)	10.1	(0.6)	51.2	(2.9)	39.9	(2.8)	(2942)
Bulgaria	6.7	(0.5)	32.5	(3.3)	3.0	(0.3)	37.8	(5.0)	36.7	(4.9)	(2233)
Colombia	11.8	(0.7)	50.4	(3.0)	5.3	(0.5)	63.8	(4.1)	50.7	(4.4)	(2381)
Columbia – Medellin	9.9	(0.7)	51.4	(3.6)	3.8	(0.4)	54.0	(5.2)	47.3	(5.1)	(1673)
Iraq	7.2	(0.6)	46.1	(4.2)	3.9	(0.4)	50.7	(5.8)	42.1	(5.7)	(4332)
Lebanon	10.3	(0.8)	44.7	(3.6)	4.9	(0.5)	43.6	(5.3)	35.1	(5.0)	(1031)
Mexico	7.6	(0.5)	46.5	(2.9)	3.7	(0.3)	59.4	(3.9)	46.0	(4.1)	(2362)
Nigeria	3.2	(0.3)	19.1	(3.5)	1.1	(0.2)	20.3	(5.9)	18.7	(5.8)	(2143)
Peru	6.4	(0.4)	35.9	(3.3)	2.7	(0.3)	49.5	(5.4)	37.2	(5.1)	(1801)
PRC[b] – Beijing/Shanghai	3.8	(0.4)	25.3	(6.0)	2.0	(0.3)	36.8	(9.5)	33.6	(9.7)	(1628)
PRC[b] – Shenzhen	6.8	(0.6)	18.7	(3.4)	3.6	(0.4)	22.0	(3.8)	16.2	(3.4)	(2475)
Romania	2.9	(0.4)	27.0	(5.7)	1.5	(0.3)	31.5	(8.8)	25.9	(8.4)	(2357)
Total	8.1	(0.2)	42.4	(1.1)	4.0	(0.1)	48.0	(1.6)	38.8	(1.5)	(27 358)
II. High Income											
Australia	12.8	(0.5)	51.4	(2.1)	4.8	(0.3)	59.0	(3.5)	49.0	(3.4)	(8841)
Belgium	14.1	(1.1)	29.8	(3.3)	5.2	(0.7)	37.7	(6.3)	29.9	(5.6)	(1043)
France	20.4	(1.2)	41.6	(2.6)	5.6	(0.6)	51.0	(5.3)	41.8	(5.3)	(1436)
Germany	10.3	(0.7)	45.0	(3.1)	3.1	(0.4)	57.9	(5.6)	48.7	(5.7)	(1323)
Israel	9.8	(0.4)	21.9	(2.0)	5.9	(0.4)	23.7	(2.7)	18.1	(2.4)	(4859)
Italy	9.7	(0.5)	39.3	(2.6)	2.9	(0.3)	46.2	(5.1)	41.3	(5.0)	(1779)
Japan	6.8	(0.5)	27.6	(3.5)	2.4	(0.3)	42.2	(6.7)	29.1	(5.9)	(1682)
Netherlands	18.0	(1.3)	40.6	(3.3)	4.9	(0.7)	49.3	(6.6)	32.5	(5.9)	(1094)
New Zealand	15.8	(0.5)	52.4	(1.4)	5.7	(0.3)	60.3	(2.4)	49.5	(2.4)	(7312)
Northern Ireland	17.7	(1.0)	56.8	(2.8)	8.8	(0.7)	61.4	(4.4)	47.2	(4.3)	(1986)
Poland	3.8	(0.3)	32.2	(3.6)	1.6	(0.2)	36.7	(5.1)	27.8	(4.6)	(4000)
Portugal	17.4	(0.8)	45.3	(2.1)	7.0	(0.5)	49.8	(3.3)	42.5	(3.3)	(2060)
Spain	10.4	(0.6)	34.9	(2.6)	3.8	(0.3)	48.4	(4.5)	40.0	(4.3)	(2121)
Spain – Murcia	15.3	(1.0)	32.0	(3.0)	6.9	(0.7)	36.7	(4.8)	23.2	(3.8)	(1459)
US	16.6	(0.5)	62.6	(1.4)	6.7	(0.3)	71.9	(1.9)	58.5	(2.2)	(5692)
Total	13.0	(0.2)	46.9	(0.7)	5.1	(0.1)	53.3	(1.1)	42.9	(1.1)	(46 687)
III. Total	11.2	(0.1)	45.7	(0.6)	4.7	(0.1)	51.7	(0.9)	41.6	(0.9)	(74 045)

[a]Anxiety disorders include generalised anxiety disorder, panic disorder with or without agoraphobia, agoraphobia without a history of panic disorder, specific phobia, social phobia, separation anxiety and post-traumatic stress disorder.
[b]People's Republic of China.

percentile)/mean shows that 12-month prevalence varied more across surveys than did the proportion of 12-month cases with 12-month comorbid anxiety disorders (0.55 *v.* 0.42).

AOO priorities

Two-thirds (68.0%) of respondents with lifetime anxious MDD reported first onset of anxiety disorders at earlier ages than MDD (71.5% in low/middle-income countries, 66.9% in high-income countries, 69.6–74.7% IQR), (Table 2) while 13.5% reported earlier AOO of MDD than anxiety disorder (11.3% in low/middle-income countries, 14.2% in high-income countries, 10.2–15.6% IQR) and the remaining 18.5% (17.2% in low/middle-income countries, 18.9% in high-income countries, 10.6–23.7% IQR) reported the same AOO of anxiety disorders and MDD. The dominant temporal

Table 2. *Temporal priority in AOO distributions of lifetime DSM-IV/CIDI MDD and anxiety disorders[a] among respondents with lifetime and 12-month comorbid MDD and anxiety disorders in the WHO WMH Surveys*

	Among lifetime comorbid cases[b]					Among 12-Month comorbid cases[b]				
	Anxiety first		MDD first			Anxiety first		MDD first		
	%	(S.E.)	%	(S.E.)	(*n*)	%	(S.E.)	%	(S.E.)	(*n*)
I. Low/Middle Income										
Brazil – São Paulo	76.6*	(2.6)	12.8	(2.0)	(439)	75.6*	(3.4)	15.7	(3.0)	(205)
Bulgaria	62.8*	(5.6)	11.0	(3.1)	(145)	62.0*	(7.6)	13.1	(4.2)	(54)
Colombia	78.3*	(3.0)	8.2	(1.8)	(285)	84.4*	(3.3)	9.3	(2.7)	(110)
Columbia – Medellin	79.2*	(3.4)	10.1	(2.5)	(186)	87.4*	(4.1)	6.9	(3.0)	(73)
Iraq	44.4*	(6.3)	12.2	(3.5)	(167)	47.6*	(8.2)	11.0	(5.1)	(81)
Lebanon	68.1*	(4.8)	17.2	(4.1)	(128)	68.1*	(4.8)	18.8	(6.4)	(49)
Mexico	78.7*	(3.6)	13.4	(3.1)	(212)	77.8*	(4.1)	15.8	(3.7)	(101)
Nigeria	88.9*	(4.7)	5.2	(3.3)	(36)	86.1*	(9.1)	7.8	(7.9)	(12)
Peru	66.5*	(5.3)	15.6	(4.0)	(85)	69.3*	(6.9)	17.3	(5.6)	(37)
PRC[c] – Beijing/Shanghai	74.4*	(9.5)	5.1	(3.6)	(40)	70.0*	(13.1)	5.1	(4.5)	(21)
PRC[c] – Shenzhen	87.5*	(5.20	4.0	(2.2)	(70)	84.7*	(7.1)	2.9	(2.2)	(37)
Romania	89.9*	(5.70	3.9	(2.5)	(25)	97.2*	(3.0)	2.8	(3.0)	(11)
Total	71.5*	(1.5)	11.3	(1.0)	(1782)	72.9*	(2.0)	12.4	(1.4)	(791)
II. High Income										
Australia	62.8*	(2.6)	13.5	(1.8)	(623)	62.0*	(4.0)	16.2	(2.8)	(229)
Belgium	64.4*	(6.8)	14.2	(5.4)	(106)	65.9*	(10.1)	21.5	(10.0)	(39)
France	70.2*	(3.8)	15.6	(2.9)	(261)	64.1*	(7.3)	18.0	(5.4)	(68)
Germany	69.6*	(4.9)	17.1	(4.8)	(164)	72.8*	(8.0)	19.9	(8.0)	(55)
Israel	30.0	(4.8)	33.3	(4.7)	(104)	31.0	(6.1)	32.5	(5.9)	(48)
Italy	57.9*	(4.3)	12.8	(3.0)	(172)	56.9*	(7.4)	13.8	(5.8)	(51)
Japan	55.8*	(7.4)	5.4	(3.2)	(64)	59.1*	(10.4)	7.2	(5.3)	(25)
Netherlands	58.1*	(4.8)	18.7	(4.4)	(186)	52.8	(8.5)	31.4	(8.5)	(40)
New Zealand	70.2*	(1.8)	10.2	(1.3)	(1125)	71.1*	(2.8)	12.8	(2.3)	(370)
Northern Ireland	74.7*	(3.1)	17.1	(2.7)	(282)	77.2*	(4.0)	13.8	(3.2)	(110)
Poland	73.3*	(5.7)	17.5	(4.9)	(89)	71.1*	(8.2)	21.9	(7.9)	(36)
Portugal	69.5*	(2.8)	17.3	(2.3)	(338)	72.8*	(4.1)	17.9	(3.7)	(126)
Spain	56.8*	(4.4)	11.2	(2.5)	(217)	50.7*	(6.1)	14.5	(4.2)	(87)
Spain – Murcia	49.7*	(5.5)	22.3	(4.8)	(131)	44.7	(7.8)	31.5	(7.8)	(45)
US	75.6*	(1.6)	12.5	(1.3)	(957)	77.5*	(2.2)	13.2	(1.8)	(375)
Total	66.9*	(0.9)	14.2	(0.7)	(4818)	66.7*	(1.3)	16.5	(1.1)	(1704)
III. Total	68.0*	(0.8)	13.5	(0.6)	(6600)	68.5	(1.1)	15.3	(0.9)	(2495)

*Significant difference between the proportion of cases with anxiety temporally primary *v.* MDD temporally primary at the 0.05 level, two-sided test.

[a]Anxiety disorders include generalised anxiety disorder, panic disorder with or without agoraphobia, agoraphobia without a history of panic disorder, specific phobia, social phobia, separation anxiety and post-traumatic stress disorder.

[b]Percentages with MDD first and anxiety first sum to less than 100% because some respondents reported that their MDD and anxiety disorders started at the same age. In cases where respondents had multiple anxiety disorders, earliest AOO was used.

[c]People's Republic of China.

priority of anxiety disorders before MDD occurred in all surveys other than in Israel, where the proportions with temporally primary anxiety (30.0%) and MDD (33.3%) were virtually the same ($\chi^2_1 = 0.2$, $p = 0.62$).

Comparable proportions of respondents reporting temporally primary anxiety disorders were found for 12-month comorbid cases (68.5% in the total sample, 72.9% in low/middle-income countries, 66.7% in high-income countries, 62.0–72.8% IQR), again with the exception of Israel in addition to Murcia in Spain. It is noteworthy that rates of comorbid anxiety disorder among respondents with MDD (reported Table 1) were comparatively low in both Israel and Murcia (21.9–32.0% compared with IQR 32.0–46.5%).

Table 3. *Socio-demographic correlates of lifetime and 12-month DSM-IV/CIDI MDD and of comorbid anxiety disorders[a] given MDD in the WHO WMH Surveys[b]*

	Lifetime				12-Month			
	MDD		Anxiety disorder/ MDD		MDD		Anxiety disorder/ MDD	
	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)
Age								
18–34	1.4*	(1.25–1.52)	1.8*	(1.56–2.09)	2.1*	(1.78–2.42)	2.6*	(2.03–3.24)
35–49	1.9*	(1.73–2.06)	2.6*	(2.29–2.96)	2.5*	(2.16–2.84)	3.3*	(2.67–4.07)
50–64	1.7*	(1.55–1.85)	2.2*	(1.93–2.49)	1.9*	(1.68–2.21)	2.6*	(2.14–3.24)
65 +	1.0	–	1.0	–	1.0	–	1.0	–
χ^2_3	256.9*		247.2*		172.8*		126.0*	
Gender								
Male	1.0	–	1.0	–	1.0	–	1.0	–
Female	1.8*	(1.73–1.91)	2.1*	(1.97–2.28)	1.8*	(1.66–1.96)	2.1*	(1.83–2.36)
χ^2_1	536.0*		419.0*		199.5*		126.8*	
Marital status								
Married	1.0	–	1.0	–	1.0	–	1.0	–
Never Married	1.2*	(1.07–1.23)	1.2*	(1.04–1.27)	1.4*	(1.22–1.49)	1.4*	(1.23–1.69)
Sep/Wid/Divorced	2.0*	(1.90–2.19)	2.0*	(1.81–2.19)	2.2*	(1.97–2.42)	2.3*	(2.01–2.72)
χ^2_2	387.5*		203.1*		237.5*		128.5*	
Income[c]								
Low	1.1	(0.99–1.15)	1.3*	(1.16–1.43)	1.4*	(1.23–1.54)	1.6*	(1.36–1.89)
Low–Mid	1.1*	(1.05–1.22)	1.3*	(1.20–1.47)	1.3*	(1.19–1.49)	1.6*	(1.31–1.83)
Mid–High	1.1*	(1.05–1.20)	1.3*	(1.15–1.39)	1.2*	(1.05–1.30)	1.3*	(1.08–1.49)
High	1.0	–	1.0	–	1.0	–	1.0	–
χ^2_3	15.3*		36.6*		37.3*		36.5*	
Education level								
None	0.7*	(0.59–0.88)	0.7*	(0.51–0.93)	1.0	(0.75–1.37)	0.9	(0.58–1.40)
Some primary	0.9*	(0.79–0.98)	0.9	(0.79–1.08)	1.2*	(1.03–1.42)	1.2	(0.98–1.53)
Completed primary	0.7*	(0.64–0.80)	0.8*	(0.66–0.90)	0.9	(0.74–1.04)	1.0	(0.78–1.29)
Some secondary	0.8*	(0.72–0.85)	0.9*	(0.76–0.97)	0.9*	(0.76–0.99)	0.9	(0.77–1.16)
Completed secondary	0.8*	(0.70–0.82)	0.8*	(0.68–0.84)	0.8*	(0.72–0.91)	0.8*	(0.62–0.90)
Some College	1.0	(0.87–1.04)	1.0	(0.91–1.15)	1.0	(0.91–1.19)	1.1	(0.87–1.29)
Completed college	1.0	–	1.0	–	1.0	–	1.0	–
χ^2_6	85.3*		51.0*		46.2*		32.3*	
n	74 045		14 430		74 045		5898	

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

[a]Anxiety disorders include generalised anxiety disorder, panic disorder with or without agoraphobia, agoraphobia without a history of panic disorder, specific phobia, social phobia, separation anxiety and post-traumatic stress disorder.

[b]Based on person-level logistic regression models pooled across surveys. Time-varying socio-demographic variables were coded as of time of interview rather than as of AOO.

[c]Income was coded within country. Low = less than 50% of the median value of the ratio of before-tax income to number of family members; Low-average = 50–100% of the median value of the ratio of before-tax income to number of family members; High-average = more than 100% to 300% of the median value of the ratio of before-tax income to number of family members; High = more than 300% of the median value of the ratio of before-tax income to number of family members.

Socio-demographic correlates

Significantly higher rates of lifetime MDD were found among respondents in middle age (ages 35–64) compared with ages 65+ (OR = 1.7–1.9), women compared with men (OR = 1.8), the previously-married compared with currently-married (OR = 2.0), and those with less than high incomes compared with those with high incomes (OR = 1.1). (Table 3) Slightly *lower* lifetime prevalence of MDD was found among respondents with less than some college education compared with

those with at least some college education (OR = 0.7–0.9). Country-specific analyses (available online) showed that the most consistent of these associations were being female (significant in 23 surveys, OR IQR 1.6–2.2) and previously married (significant in 24 surveys, OR IQR 1.8–2.4). The elevated ORs associated with being middle-aged were significant in 13 surveys (OR IQR 1.7–2.9). The associations of income and education with lifetime MDD were inconsistent across surveys.

Significant associations of these same socio-demographic variables were found with comorbid anxiety disorders among respondents with lifetime MDD, but the ORs for age, sex and income were higher than in predicting lifetime MDD: OR = 1.8–2.7 for ages 18–44 compared with 65+; OR = 2.1 for women compared with men; and OR = 1.3 for low compared with high income. ORs associated with marital status and education were virtually identical to those predicting lifetime MDD. Country-specific analyses (results available online) showed that the most consistently elevated ORs predicting comorbid anxiety among people with MDD were being female (significant in 22 surveys, OR IQR 1.7–2.7) and previously married (significant in 15 surveys, OR IQR 1.5–2.1). The elevated ORs associated with being middle-aged were significant in 15 surveys (OR IQR 2.1–4.2), while the associations of income and education with lifetime anxious *v.* non-anxious MDD were inconsistent across surveys.

Socio-demographics were also significantly associated with 12-month MDD. The positive ORs of young age, not being married, low to high-average income, and less than college education were consistently somewhat larger than those of the same predictors with lifetime MDD. The OR associated with female gender, in comparison, was identical in predicting lifetime and 12-month MDD (OR = 1.8), indicating that women did not differ significantly from men in 12-month prevalence among lifetime cases. Broadly similar patterns were also found in predicting 12-month anxious MDD *v.* non-anxious MDD in that the ORs were all significant as a set (albeit with some ORs for specific education categories not significant even though education was significant overall [$\chi^2_6 = 32.3$, $p < 0.001$]) and either equal or higher in magnitude than those associated with MDD in the total sample. This means that these socio-demographics were all more strongly associated with persistence of anxious MDD than persistence of non-anxious MDD. The results of more detailed within-country analyses were unstable due to small numbers of cases (results available online).

Severity of anxious v. non-anxious MDD

The proportion of respondents with 12-month MDD who reported severe role impairment was significantly higher in the presence (64.4%) than absence (46.0%) of 12-month anxiety disorders ($\chi^2_1 = 187.0$, $p < 0.001$). (Table 4) Very similar overall patterns were found in low/middle-income countries (61.5% *v.* 41.9%; $\chi^2_1 = 97.5$, $p < 0.001$) and high-income countries (68.8% *v.* 49.6%; $\chi^2_1 = 128.0$, $p < 0.001$) although the pattern was less consistent in low/middle-income countries (7 of 12 surveys, 6 statistically significant) than high-income countries (all 15 surveys, 10 significant).

The proportion of respondents with 12-month MDD who reported suicide ideation was also significantly higher in the presence (19.5%) than absence (8.9%) of 12-month anxiety disorders ($\chi^2_1 = 71.6$, $p < 0.001$). Very similar patterns were found in low/middle-income countries (15.2% *v.* 9.4%; $\chi^2_1 = 7.9$, $p = 0.005$) and high-income countries (21.3 *v.* 8.7%; $\chi^2_1 = 72.8$, $p < 0.001$) overall, although consistency of the pattern was again somewhat lower in low/middle-income countries (9 of 12 surveys, 3 statistically significant) than high-income countries (14 of 15 surveys, 13 significant).

Treatment

Twelve-month treatment of MDD was significantly more common in the presence than absence of 12-month anxiety disorders (56.2% *v.* 37.3%; $\chi^2_1 = 21.8$, $p < 0.001$). (Table 5) Very similar *relative* treatment rates were found in low/middle income (30.3% *v.* 20.6%; $\chi^2_1 = 11.7$, $p < 0.001$) and high income (66.8% *v.* 45.4%; $\chi^2_1 = 108.8$, $p < 0.001$) countries (i.e., respondents with anxious MDD were roughly 50% more likely to receive treatment than those with non-anxious MDD). However, the *absolute* difference in treatment rates was much higher in high-income (a 23.4% higher treatment rate of anxious than non-anxious MDD [68.8–45.4%]) than low/middle-income (a 9.7% higher treatment rate of anxious than non-anxious MDD [30.3–20.6%]) countries due to the overall treatment rate being much higher in high income than low/middle-income countries. The pattern of higher treatment of anxious than non-anxious MDD was also more consistent in high-income (all 15 surveys, 10 significant) than low/middle-income (9 of 12 surveys, 3 significant) countries. Similarly significant patterns were found in separate treatment sectors other than the nonmedical sector in low/middle-income countries ($\chi^2_1 = 4.7$–7.5; $p = 0.030$–0.006) and in all sectors in high-income countries ($\chi^2_1 = 36.6$–77.1; $p < 0.001$).

Discussion

The above results are limited by between-survey differences in response rates and sample frames (most

Table 4. *Two indicators of severity (proportion of cases reporting severe role impairment due to depression and proportion of cases reporting suicide ideation) among respondents with 12-month DSM-IV/CIDI MDD depending on presence or absence of comorbid anxiety disorders*[a] *in the WHO WMH Surveys*

	Prevalence of severe role impairment[b] when comorbid anxiety disorders are …				Prevalence of suicide ideation[c] when comorbid anxiety disorders are …				Number of respondents with 12-month MDD where comorbid anxiety disorders are …	
	Present		Absent		Present		Absent		Present	Absent
	%	(S.E.)	%	(S.E.)	%	(S.E.)	%	(S.E.)	(n)	(n)
I. Low/Middle Income										
Brazil – São Paulo	57.0*	(3.5)	41.2	(2.9)	18.7*	(3.4)	7.1	(1.6)	(205)	(284)
Bulgaria	51.7*	(6.9)	41.5	(5.2)	8.7*	(4.5)	16.1	(6.7)	(54)	(91)
Colombia	49.3*	(4.8)	42.1	(4.8)	20.8*	(5.9)	13.5	(3.6)	(110)	(131)
Colombia – Medellin	51.0	(5.9)	51.1	(5.7)	21.3	(5.8)	18.5	(5.3)	(73)	(78)
Iraq	71.8*	(5.0)	36.3	(4.8)	11.8*	(5.9)	4.7	(1.8)	(81)	(101)
Lebanon	63.3	(7.0)	64.5	(5.5)	5.3*	(3.8)	9.2	(3.9)	(49)	(77)
Mexico	45.2*	(5.0)	38.6	(4.3)	16.4	(4.3)	15.9	(3.9)	(101)	(130)
Nigeria	8.0	(8.2)	16.2	(4.8)	20.8	(18.2)	17.7	(6.5)	(12)	(60)
Peru	35.3	(8.0)	39.7	(6.3)	6.9*	(4.7)	18.3	(5.0)	(37)	(62)
PRC[d] – Beijing/Shanghai	22.1	(9.3)	32.2	(5.8)	8.2	(5.8)	4.2	(2.8)	(21)	(66)
PRC[d] – Shenzhen	41.1*	(8.2)	19.4	(2.9)	5.0	(2.9)	3.2	(1.6)	(37)	(185)
Romania	46.9	(15.8)	40.8	(9.3)	5.0	(5.4)	4.6	(4.6)	(11)	(29)
Total	61.5*	(1.5)	41.9	(1.3)	15.2*	(1.8)	9.4	(1.0)	(791)	(1294)
II. High Income										
Australia	77.3*	(2.8)	52.4	(3.4)	24.9*	(3.9)	7.1	(1.7)	(229)	(217)
Belgium	66.0	(12.6)	52.4	(9.6)	12.7	(5.2)	10.9	(5.0)	(39)	(67)
France	67.2	(8.4)	49.3	(7.9)	19.3*	(6.3)	7.0	(2.8)	(68)	(89)
Germany	64.5	(9.6)	54.2	(8.7)	19.1*	(6.2)	2.1	(1.5)	(55)	(54)
Israel	70.8*	(6.6)	51.2	(3.3)	15.3*	(5.5)	9.7	(2.0)	(48)	(232)
Italy	59.8	(11.8)	53.6	(8.9)	10.8*	(4.4)	5.0	(2.4)	(51)	(67)
Japan	68.9*	(9.4)	28.5	(6.1)	32.7*	(11.0)	6.9	(3.6)	(25)	(56)
Netherlands	68.1	(14.7)	55.7	(9.4)	19.0	(7.2)	14.1	(9.0)	(40)	(81)
New Zealand	73.2*	(2.3)	56.2	(2.6)	28.9*	(3.3)	14.7	(2.3)	(370)	(365)
Northern Ireland	62.6*	(4.6)	51.1	(4.8)	14.7*	(3.7)	1.2	(0.9)	(110)	(109)
Poland	56.5*	(8.4)	41.7	(5.3)	18.5*	(7.0)	8.4	(3.3)	(36)	(87)
Portugal	59.3*	(4.4)	42.1	(3.9)	13.5*	(3.1)	8.7	(2.4)	(126)	(164)
Spain	61.8	(8.4)	52.6	(7.6)	6.8	(3.0)	7.3	(2.7)	(87)	(142)
Spain – Murcia	50.8*	(7.5)	36.4	(4.6)	15.2*	(6.0)	6.8	(2.9)	(45)	(109)
US	67.0*	(2.4)	46.0	(3.0)	21.5*	(2.4)	7.8	(1.7)	(375)	(271)
Total	68.8*	(1.2)	49.6	(1.2)	21.3*	(1.3)	8.7	(0.7)	(1704)	(2110)
III. Total	64.4*	(1.0)	46.0	(0.9)	19.5*	(1.1)	8.9	(0.6)	(2495)	(3404)

*Significant difference depending on whether comorbid anxiety disorders are present *v.* absent at the 0.05 level, two-sided test.
[a]Anxiety disorders include generalised anxiety disorder, panic disorder with or without agoraphobia, agoraphobia without a history of panic disorder, specific phobia, social phobia, separation anxiety and post-traumatic stress disorder.
[b]Ratings of *severe* or *very severe* on one or more SDS dimensions in the 1 month in the 12 before interview when the respondent's MDD was most severe.
[c]At any time in the 12 months before interview.
[d]People's Republic of China.

Table 5. *Treatment of 12-month DSM-IV/CIDI MDD in the presence* v. *absence of comorbid anxiety disorders*[a] *in the WHO WMH Surveys*[b]

	Any				Specialty Psychiatric[c]				General Medical[c]				Non-medical[c]			
	Present		Absent		Present		Absent		Present		Absent		Present		Absent	
	%	(S.E.)	%	(S.E.)	%	(S.E.)	%	(S.E.)	%	(S.E.)	%	(S.E.)	%	(S.E.)	%	(S.E.)
I. Low/Middle Income																
Brazil – São Paulo	43.9*	(4.5)	30.4	(3.5)	27.2	(4.0)	17.7	(2.8)	19.4	(3.7)	12.6	(2.6)	9.6	(2.9)	9.1	(2.3)
Bulgaria	39.7	(8.1)	27.8	(6.1)	13.9	(5.7)	8.7	(3.9)	34.6	(8.0)	22.7	(5.6)	0.5	(0.5)	0.9	(0.9)
Colombia	24.2	(5.9)	16.4	(3.7)	17.3	(5.6)	8.7	(2.7)	6.2	(2.2)	6.9	(2.5)	5.6	(3.9)	1.7	(1.1)
Colombia – Medellin	28.6	(6.1)	26.9	(6.1)	15.5	(4.9)	24.2	(5.9)	11.4	(4.1)	4.9	(2.8)	5.9	(2.9)	1.0	(1.0)
Iraq	16.5	(7.6)	8.4	(4.3)	7.0	(5.7)	5.8	(4.2)	2.6	(1.5)	0.5	(0.4)	7.0	(5.6)	2.1	(1.0)
Lebanon	18.2	(6.1)	26.0	(5.9)	7.4	(4.2)	13.0	(5.1)	11.8	(5.3)	13.1	(4.0)	2.0	(1.5)	1.8	(1.5)
Mexico	18.9	(4.6)	30.7	(4.7)	11.0	(4.0)	12.8	(3.4)	5.7*	(1.9)	13.8	(3.5)	6.1	(3.6)	5.8	(2.2)
Nigeria	58.5*	(18.1)	10.1	(5.7)	3.0	(3.2)	2.8	(2.1)	47.6*	(18.1)	8.3	(5.5)	8.0	(8.2)	1.7	(1.8)
Peru	25.9	(7.4)	33.2	(6.6)	6.7	(4.2)	19.6	(5.3)	12.5	(5.5)	12.0	(4.9)	12.8	(5.7)	8.7	(3.8)
PRC[d] – Beijing/Shanghai	56.2*	(18.5)	7.2	(4.4)	3.9	(4.1)	6.2	(4.4)	54.8*	(18.9)	0.6	(0.6)	37.5	(24.1)	0.5	(0.5)
PRC[d] – Shenzhen	14.1	(7.0)	5.9	(2.3)	9.9	(6.4)	0.2	(0.2)	9.5	(6.4)	0.7	(0.4)	2.5	(2.6)	5.3	(2.2)
Romania	48.5	(19.7)	12.0	(6.4)	30.4	(19.8)	7.5	(5.5)	25.1	(13.2)	8.3	(5.9)	–	–	1.2	(1.3)
Total	30.3*	(2.4)	20.6	(1.5)	16.1*	(1.9)	11.2	(1.2)	14.0*	(1.7)	8.6	(1.0)	7.5*	(1.7)	4.6	(0.7)
II. High Income																
Australia	80.2*	(2.6)	47.0	(3.4)	54.4*	(3.3)	22.6	(2.8)	61.9*	(3.2)	34.1	(3.2)	20.0*	(2.6)	6.9	(1.7)
Belgium	61.4	(10.1)	49.3	(8.6)	34.1	(9.1)	34.4	(8.5)	49.4	(10.1)	40.5	(8.6)	9.1	(6.2)	2.6	(2.0)
France	62.2*	(8.5)	36.4	(6.4)	28.7	(8.6)	14.7	(4.8)	49.7*	(8.1)	29.3	(5.7)	0.5	(0.6)	2.8	(1.6)
Germany	51.6	(7.5)	43.8	(8.5)	39.2*	(7.3)	17.6	(5.6)	21.2	(6.5)	33.8	(8.2)	10.4	(4.2)	5.9	(3.3)
Israel	55.8*	(7.5)	35.5	(3.3)	36.4*	(7.3)	19.7	(2.7)	35.0*	(7.3)	14.8	(2.4)	15.7	(5.6)	8.4	(1.8)
Italy	64.3*	(7.2)	20.2	(4.9)	21.8	(7.2)	9.9	(3.8)	61.4*	(7.4)	16.8	(4.7)	3.1	(2.2)	2.2	(1.6)
Japan	60.0*	(11.1)	32.4	(8.3)	46.6	(11.9)	20.4	(6.6)	18.1	(9.6)	9.7	(7.0)	34.0*	(11.7)	7.9	(4.3)
Netherlands	77.4*	(7.7)	36.8	(7.7)	52.7*	(10.5)	17.9	(4.5)	63.8*	(10.0)	27.3	(7.1)	10.3	(5.3)	3.7	(1.8)
New Zealand	64.7*	(3.3)	53.4	(3.5)	30.9*	(3.1)	21.7	(2.8)	46.8	(3.3)	42.1	(3.4)	19.9*	(2.8)	9.9	(1.9)
Northern Ireland	61.3*	(6.2)	41.0	(6.1)	25.2	(4.7)	11.4	(4.1)	59.6*	(6.2)	38.2	(6.0)	9.4	(3.2)	6.8	(3.6)
Poland	49.8	(9.7)	36.2	(6.0)	33.2	(8.8)	25.3	(5.1)	28.7	(9.4)	16.6	(4.7)	12.0	(5.6)	7.7	(3.5)
Portugal	60.8	(4.9)	55.4	(4.4)	32.8	(4.6)	25.2	(3.9)	41.0	(4.9)	36.6	(4.3)	6.9	(2.4)	3.5	(1.7)
Spain	70.2*	(6.1)	51.6	(5.6)	33.4	(6.5)	40.2	(5.3)	59.1*	(6.6)	24.8	(4.3)	6.2	(4.0)	2.3	(1.0)
Spain – Murcia	73.9	(7.8)	61.8	(5.9)	56.9*	(8.7)	33.6	(6.2)	21.0	(6.3)	33.0	(5.6)	4.9	(3.7)	1.1	(0.7)
US	63.5*	(2.8)	48.6	(3.3)	37.7*	(2.9)	26.0	(2.8)	38.0*	(2.9)	26.4	(3.0)	19.1	(2.3)	14.9	(2.3)
Total	66.8*	(1.5)	45.4	(1.4)	38.5*	(1.6)	22.6	(1.2)	47.7*	(1.6)	29.6	(1.3)	15.8*	(1.2)	7.4	(0.7)

Continued

Table 5. *Continued*

	Any				Specialty Psychiatric[c]				General Medical[c]				Non-medical[c]			
	Present		Absent		Present		Absent		Present		Absent		Present		Absent	
	%	(S.E.)	%	(S.E.)	%	(S.E.)	%	(S.E.)	%	(S.E.)	%	(S.E.)	%	(S.E.)	%	(S.E.)
III. Total	56.2*	(3.1)	37.3	(2.6)	32.0*	(3.0)	18.9	(2.1)	37.9*	(3.1)	22.7	(2.3)	13.4*	(2.2)	6.5	(1.3)

*Significant difference depending on whether comorbid anxiety disorders are present *v.* absent at the 0.05 level, two-sided test.
[a]Anxiety disorders include generalised anxiety disorder, panic disorder with or without agoraphobia, agoraphobia without a history of panic disorder, specific phobia, social phobia and post-traumatic stress disorder.
[b]See Table 3 for denominator sample sizes.
[c]See the text for definitions of specialty, general medical and non-medical treatments.
[d]People's Republic of China.

notably, underrepresentation of rural areas in developing countries), diagnoses being based on fully structured lay interviews rather than semi-structured clinician-administered interviews (although available evidence documents good concordance between the two types of diagnoses in WMH; Haro *et al.* 2006), the fact that we examined only a summary measure of any DSM-IV anxiety disorder rather than disaggregated disorder-specific measures, and the fact that the WMH surveys were cross-sectional. The latter limitation meant that both lifetime prevalence and AOO were assessed retrospectively. Previous methodological studies (Moffitt *et al.* 2010; Hamdi & Iacono, 2014; Takayanagi *et al.* 2014) suggest that use of retrospective recall probably led to underestimation of lifetime prevalence and overestimation of persistence. Long-term prospective studies are needed to resolve this problem.

Within the context of these limitations, we found a relatively narrow IQR across surveys (32.0–46.5%) in estimated rates of lifetime anxiety disorders among people with lifetime MDD, somewhat higher rates but an equally narrow IQR (37.8–54.0%) of lifetime comorbid anxiety disorders among respondents with 12-month MDD, and only slightly lower rates with a similarly narrow IQR (29.9–47.2%) of 12-month comorbid anxiety disorders among respondents with 12-month MDD. The fact that lifetime comorbid anxiety disorders were more prevalent among respondents with 12-month than lifetime MDD suggests that lifetime comorbid anxiety disorders predict MDD persistence, while the fact that 12-month comorbid anxiety disorders were only slightly less prevalent than lifetime comorbid anxiety disorders among respondents with 12-month MDD suggests that anxiety disorder persistence is positively associated with MDD persistence. These patterns are broadly consistent with previous epidemiological studies (Andrade *et al.* 2003; Kessler *et al.* 2011*b*; Lamers *et al.* 2011). We are unaware, although, of previous studies that examined either the differences we did in the magnitudes of lifetime comorbidity, 12-month comorbidity or comorbidity between lifetime anxiety disorders and 12-month MDD. Our results also go beyond previous studies in documenting considerable cross-national consistency in comorbidity between anxiety disorders and MDD.

The socio-demographic associations documented here are broadly consistent with previous studies in finding higher rates of both anxiety disorders and MDD among women (Parker & Brotchie, 2010; Altemus *et al.* 2014) and the previously married (Scott *et al.* 2010; Leach *et al.* 2013) along with less consistent inverse associations with age (de Graaf *et al.* 2013; McDowell *et al.* 2014). However, we are unaware

of prior systematic efforts to examine nested associations in the way we did here. It is noteworthy, although, that we did not examine disaggregated associations (e.g., the extent to which socio-demographics predict onset of secondary MDD among people with a history of temporally primary anxiety disorders). The strength and consistency of the associations we documented across nested outcomes suggest that more detailed studies of these specifications might be useful.

Our finding of higher role impairment and suicidality in anxious than non-anxious MDD is broadly consistent with previous findings (Roy-Byrne *et al.* 2000; McLaughlin *et al.* 2006; Ormel *et al.* 2008), although we showed that this pattern generalises to many more countries than in previous research. We found stronger and more consistent associations of comorbid anxiety disorders with elevated MDD treatment rates in high-income than low/middle-income countries. Previous studies of this pattern, which were limited to high-income Western countries (Kessler *et al.* 2001; Jacobi *et al.* 2004), found similar associations with those in the high-income WMH Surveys. The overrepresentation of anxious MDD in treatment populations is important because comorbid anxiety disorders predict both low MDD treatment persistence (Shippee *et al.* 2014) and low MDD treatment response (Stiles-Shields *et al.* 2014).

Our finding that the vast majority of WMH respondents with anxious MDD reported earlier AOO of anxiety disorders than MDD is consistent with previous research in both cross-sectional/retrospective (Kessler, 1995; Kessler *et al.* 2011*a*) and prospective (Murphy *et al.* 1986; Bittner *et al.* 2004; Copeland *et al.* 2009; Klein *et al.* 2013) samples. The narrow IQR of the proportion of respondents who reported earlier AOO of anxiety disorders than MDD (69.6–74.7%) is especially noteworthy. It is also striking, although, that these proportions are not higher among respondents with 12-month than lifetime comorbidity, as we might expect the latter rates to be higher if temporally primary comorbid anxiety was more important than temporally secondary comorbid anxiety in predicting MDD persistence. We are unaware of any previous research on this distinction. The finding that comorbid anxiety disorder is related to MDD persistence equally whether or not the anxiety is temporally primary might reflect influences of common underlying causes accounting for the lifetime comorbidities of MDD with anxiety disorders, although another possibility consistent with this pattern is that the causal processes accounting for the effects of anxiety disorders on MDD *onset* differ from the causal processes accounting for the effects of anxiety disorders on MDD *persistence*. We have no way to adjudicate between these competing possibilities with the WMH data.

If temporally primary anxiety disorders are causal risk factors for MDD, interventions to treat pure anxiety disorders would be expected to reduce subsequent onset of MDD. However, no well-controlled long-term treatment studies have evaluated this possibility despite calls to do so (Flannery-Schroeder, 2006; Garber & Weersing, 2010). Consistent with this possibility, although, two observational studies based on community epidemiological surveys found that individuals who received treatment for temporally primary panic disorder (Goodwin & Olfson, 2001) and generalised anxiety disorder (Goodwin & Gorman, 2002) were significantly less likely than others with these disorders to go on to develop temporally secondary MDD. Although selection bias into treatment is a possible explanation for these patterns, the most plausible type of selection bias (i.e., selection into treatment based on severity) would be expected to lead to the opposite association with subsequent MDD, arguing indirectly for the possibility that treatment of anxiety disorders might lead to a reduction in risk of subsequent MDD. Other results consistent with this possibility include those from controlled studies of focused psychotherapy for anxiety disorders that showed these treatments reduced concurrent symptoms of MDD (reviewed in Hofmann & Smits, 2008; Cuijpers *et al.* 2014), although this result is not entirely consistent (McLean *et al.* 1998; Woody *et al.* 1999). In addition, one small controlled study of CBT for social phobia among adolescent girls found that treatment reduced relapse of MDD among patients with a history of comorbid MDD over the subsequent year (Hayward *et al.* 2000).

Despite the suggestive evidence in the above studies, more definitive long-term controlled efficacy trials are needed to evaluate the impact of interventions to treat temporally primary anxiety disorders on the subsequent onset and persistence of MDD. An intriguing observation related to the need for this kind of definitive long-term controlled treatment study is that several epidemiological studies have found distinct risk factors for anxiety disorders that are not risk factors for MDD (Moffitt *et al.* 2007; Beesdo *et al.* 2010; Mathew *et al.* 2011; Asselmann *et al.* 2015). For example, an extensive literature shows that stressful life events associated with danger predict anxiety but not depression (Finlay-Jones & Brown, 1981; Kendler *et al.* 2003; Asselmann *et al.* 2015). This specificity should not exist if anxiety disorders caused MDD, as the latter causal process would lead to attenuated associations of the risk factors with MDD. To find that this is not the case suggests that something more complex is at work linking anxiety disorders with MDD and that common causes are involved in the comorbidity of anxiety disorders with MDD.

The existence of common causes would impose an upper bound on how much secondary MDD could be

prevented by successful treatment of temporally primary anxiety disorders. Common causes might also help account for the fact that concurrent comorbidity is associated with poor treatment response for both anxiety disorders (Rapee *et al.* 2013; Kelly *et al.* 2014) and MDD (Jakubovski & Bloch, 2014; Saveanu *et al.* 2014). Less is known, although, about the associations of *lifetime* comorbidity with treatment response among patients who do not have *concurrent* comorbid symptoms. An examination of this specification would be useful in helping distinguish differential treatment response associated with the amelioration of life stressors surrounding particular anxious-MDD episodes and risk factors associated with more fundamental causes of lifetime anxious-MDD.

The latter suggestion highlights the fact that little research has attempting to distinguish the determinants of first onsets from the determinants of the subsequent course of either anxiety disorders or MDD. Virtually all the research cited above on the association between treating anxiety disorders and subsequent change in depression as well as on the associations of comorbidity with differential treatment response implicitly focused on the course of depression, as only a small minority of MDD cases in clinical studies are first-onset cases. As noted above, it is quite possible that different processes are at work in bringing about lifetime comorbidity and episode comorbidity. Research is needed to investigate such differences explicitly.

It is noteworthy in this regard that epidemiological research assuming the existence of common causes has shown that the coefficients describing the cross-lagged prospective associations of temporally primary lifetime anxiety with subsequent first lifetime onset of MDD and vice versa can be parsimoniously described by assuming a latent intervening predisposition to all internalising disorders (Kessler *et al.* 2011*a*, *b*). Although some hypotheses have been advanced for asymmetries in these associations (Cummings *et al.* 2014), available evidence suggests that these asymmetries are weak. If this model is accurate, then temporally primary lifetime anxiety disorders might be risk markers rather than causal risk factors for the subsequent *first onset* of lifetime MDD even though anxiety disorders might have causal effects on the subsequent *persistence* of MDD. If this is the case, then successful intervention to treat early-onset primary anxiety disorders might not prevent the subsequent first onset of MDD even though it would reduce MDD persistence. A more consistent distinction between lifetime and concurrent comorbidity needs to be made in future observational and clinical studies of anxious MDD to shed light on these possibilities. As part of this increased focus, any attempt to carry out long-term controlled treatment studies to evaluate the effects of treating temporally primary anxiety on subsequent MDD should be designed to have a sufficiently large sample size and a sufficient duration of follow-up to examine effects on both MDD onset and MDD persistence and to include an assessment of plausible biomarkers. Our understanding of the causal determinants of the high comorbidity of MDD with anxiety disorders will remain at its current relatively primitive level until studies of this sort are carried out.

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Statement of Interest

In the past 3 years, Dr Kessler has been a consultant for Hoffman-La Roche, Inc., Johnson & Johnson Wellness and Prevention, and Sonofi-Aventis Groupe. Dr Kessler has served on advisory boards for Mensante Corporation, Plus One Health Management, Lake Nona Institute, and U.S. Preventive Medicine. Dr Kessler owns 25% share in DataStat, Inc. Dr Wilcox is an employee of Janssen Pharmaceuticals.

Ethical Standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

Supplementary materials and methods

The supplementary materials referred to in this article can be found at http://dx.doi.org/10.1017/S2045796015000189

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